Acta Poloniae Pharmaceutica

TOM XVII Rok założenia 1927 ZESZYT 6 1960

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OTRZYMYWANIE D,L-N-METYLO-β-(3,4-METYLENODWUOKSYFENYLO)-IZOPROPYLOAMINY I D,L-N-METYLO-β-(3,4-DWUMETOKSYFENYLO)-IZOPROPYLOAMINY

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W jednej z poprzednich prac *Biniecki* i *Muszyński* (1) opisali otrzymywanie siarczanu D,L-β(3,4-dwumetoksyfenylo) oraz D,L-β-(3,4-metylenodwuoksyfenylo)-izopropyloaminy.

Jako substancje wyjściowe we wspomnianej syntezie służyły eugenol i safrol. Korzystając z tych samych surowców i usprawnionego przez nas sposobu otrzymywania α-(3,4-dwumetoksyfenylo)-β-bromo- oraz α-(3,4-metylenodwuoksyfenylo)-β-bromo-propanu działaniem alkoholowego roztworu metyloaminy, zsyntetyzowaliśmy D,L-N-metylo-β-(3,4-dwumetoksyfenylo) oraz D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropyloaminę. Chodziło nam bowiem o rozstrzygnięcie, czy wprowadzenie grupy metylowej do azotu w D,L-β-(3,4-dwumetoksyfenylo)- i D,L-β(3,4-metylenodwuoksyfenylo)-izopropyloaminy wywierać będzie wpływ na właściwości farmakologiczne tych amin.

Zarówno D,L-N-metylo-β-(3,4-dwumetoksyfenylo) jak i D,L-N-metylo-β-3,4-dwumetylenodwuoksyfenylo)-izopropyloamina zostały zsyntetyzowane i opatentowane w 1914 r. przez Zakłady E. Mercka (2). Sposób otrzymywania jest jednak podany bardzo ogólnikowo i w opisie patentowym brak niektórych danych fizyko-chemicznych, jak t. t. chlorowodorku D,L-N-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloaminy.

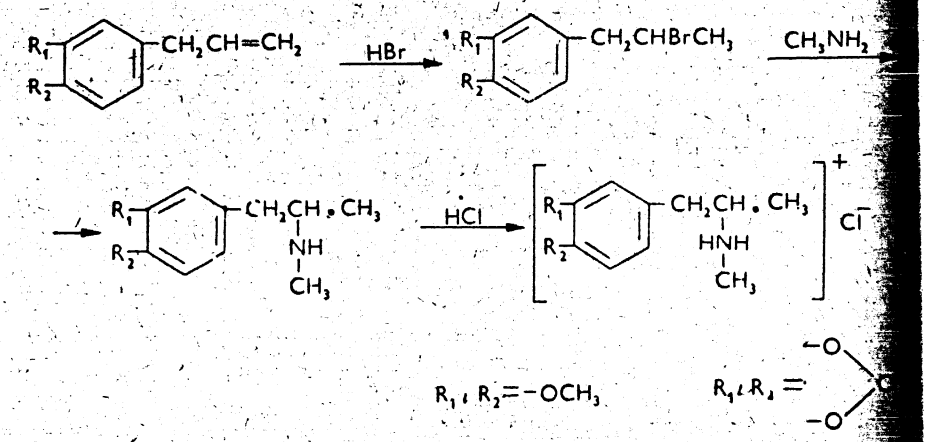
W pracy swej przy syntezie β-bromo-α-(3,4-metylenodwuoksyfenylo)-propanu opieraliśmy się częściowo na pracy *Yoshiaki* i *Sakakibara* (3) wprowadzając równocześnie własne modyfikacje, dzięki czemu udało nam się uzyskać lepszą wydajność. Wprowadzenie bromowodoru do metyloeugenolu wykonaliśmy sposobem analogicznym jak przy syntezie β-bromo-α-(3,4-metylenodwuoksyfenylo)-propanie.

Amonoliza zarówno β-bromo-α-(3,4-metylenodwuoksyfenylo)-propanu jak i β-bromo-α-(3,4-dwumetoksyfenylo)-propanu została przeprowadzona działaniem alkoholowego roztworu metyloaminy w temp. 130°—140°.

Ze względu na trudność w uzyskaniu chlorowodorku D,L-N-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloaminy bezpośrednio z zasady, przeprowadzono ostatnią najpierw w nadchloran, który oczyszczono przez kry-

stalizację. Z nadchloranu z kolei otrzymaliśmy czystą aminę i chloro dorek.

Niżej podany schemat przedstawia przebieg syntezy:



CZĘŚĆ DOŚWIADCZALNA

Do syntezy D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropy aminy i D,L-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloaminy uż safrol i eugenol firmy Riedel. Obydwa związki poddano uprzednio de lacji pod zmniejszonym ciśnieniem i zebrano frakcję safrolu w te 90°/2 mm i eugenolu w temp. 110°/4 mm. Safrol przedestylowany wy zywał refrakcję $n_D^{24}=1{,}5378$, eugenol $n_D^{24}=1{,}5405$.

70% wodny roztwór bromowodoru otrzymano według preparat Klimka (4). Potrzebny do amonolizy alkoholowy roztwór metyloam przyrządzono opierając się częściowo na podstawie przepisu podan w Organic Syntheses (5).

1. α-(3,4-Metylenodwuoksyfenylo)-β-bromopropan.

W kolbie 3-szyjnej, zaopatrzonej w mieszadło i termometr umieszczono 21 g wodnego roztworu HBr i po oziębieniu do temp. 0°, mieszając, wkroplono w ci 15 min. 5.3 g świeżo destylowanego safrolu. Zawartość kolby utrzymywano w ci 14 godzin o temp. 0°, po czym mieszaninę poreakcyjną wylano na drobno po czony lód. α-(3,4-Metylenodwuoksyfenylo)-β-bromo-propan ekstrahowano trzykr nie eterem (łącznie użyto 90 ml). Wyciąg eterowy wysuszono bezwodnym KHCO Po odpędzeniu eteru pozostałość destylowano z kolbki kołnierzowej pod zmniejsz nym ciśnieniem. Zebrano frakcję w temp. 130°—180°/2 mm (temp. łaźni). Otrzym 7,73 g (=97% wyd.) α-(3,4 metylenodwuoksyfenylo)-β-bromo-propanu w postaci tego oleju $n_D^{24}=1.5634$, co jest zgodne z danymi z piśmiennictwa (3). *Yoshiaki* i *kakibara* (3) otrzymali wspomniany związek z wydajnością 72,7%.

2. D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropyloamina.

Do 4,7 g α-(3,4-metylenodwuoksyfenylo)-β-bromo-propanu dodano 26 g 18 alkoholowego roztworu metyloaminy (1 mol + 4 mole). Mieszaninę reakcyjna topiono w rurze i ogrzewano w ciągu 3 godzin na łaźni olejowej (temp. łaźni 1

Następnie alkohol i nadmiar aminy oddestylowano pod zmniejszonym ciśnieniem. Do pozostałości w kolbie dodano 2 n HCl (do odczynu kwaśnego na papierek Kongo) i nieprzereagowany α-(3,4-metylenodwuoksyfenylo)-β-bromo-propan wyekstrahowano eterem (30 ml). Do wodnego roztworu chlorowodorku aminy dodano 10 g K_2CO_3 i wydzieloną D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropyloaminę ekstrahowano trzykrotnie eterem (ogółem zużyto około 40 ml). Wyciąg eterowy wysuszono K_2CO_3. Po odpędzeniu rozpuszczalnika pozostałą aminę przedestylowano pod zmniejszonym ciśnieniem. Zebrano frakcję przy ciśn. 16 mm wrzącą w temp. 130°—180° (temp. łaźni). Otrzymano 1,4 g jasnożółtej oleistej cieczy o $n_D^{19}=1.5311$. Ponadto zregenerowano 1,9 g nieprzereagowanego α-(3,4-metylenodwuoksyfenylo)-β-bromo-propanu. Po odliczeniu zregenerowanego α-(3,4-metylenodwuoksyfenylo)-β-bromo-propanu od 4,7 g substratu wydajność D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropyloaminy wynosi 63%.

Celem otrzymania chlorowodorku wyżej wymienionej aminy, 1,3 g zasady rozpuszczono w 1 ml bezwodnego etanolu a następnie dodano 4 ml alkoholowego roztworu HCl (do odczynu kwaśnego na papierek Kongo). Po dodaniu 14 ml bezwodnego eteru wydzieliły się kryształy, które odsączono po 3 godzinach. Osad wysuszono w eksykatorze próżniowym nad KOH i parafiną.

Otrzymano 1,2 g chlorowodorku D,L-N-metylo-β-(3,4-metylenodwuoksyfenylo)-izopropyloaminy (=73,2% wyd. w przeliczeniu na zasadę) o t. t. 148°—149°. Wg danych patentu E. Mercka (2) t. t. wyżej wspomnianego chlorowodorku wynosi 148°—150°.

3. α-(3,4-dwumetoksyfenylo)-β-bromo-propan.

Do 18,6 g 70% wodnego roztworu HBr wkroplono 5,73 g metyloeugenolu otrzymanego wg przepisu podanego w Organic Syntheses (6). Dodawanie metyloeugenolu jak i izolowanie α-(3,4-dwumetoksyfenylo)-β-bromo-propanu prowadzono w sposób analogiczny jak to podano przy otrzymywaniu α-(3,4-metylenodwuoksyfenylo)-β-bromo-propanu. Po odpędzeniu rozpuszczalnika pozostałą oleistą ciecz przedestylowano z kolby kołnierzowej pod ciśnieniem 2 mm i zebrano destylat przechodzący w temp. 135°—165° (temp. łaźni olejowej). Otrzymano 6,75 g α-(3,4-dwumetoksyfenylo-β-bromo-propanu (=81% wyd.) $n_D^{18}=1.5605$.

4. D,L-N-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloamina.

7,2 g α-(3,4-dwumetoksyfenylo)-β-bromo-propanu i 22,5 g (=30 ml) 38,2% roztworu alkoholowego metyloaminy umieszczono w rurze bombowej. Po zatopieniu rury mieszaninę reakcyjną ogrzewano przez 10 godzin na łaźni olejowej w temp. 140° (temp. łaźni). Następnie etanol i nieprzereagowaną metyloaminę oddestylowano pod zmniejszonym ciśnieniem. Do pozostałości w kolbie dodano 2 n HCl (do odczynu kwaśnego wobec papierka Kongo), po czym nieprzereagowany α-(3,4-dwumetoksyfenylo)-β-bromo-propan ekstrahowano eterem (zużyto około 60 ml). Pozostały roztwór wodny zawierający chlorowodorek aminy zalkalizowano 50% NaOH do $pH \sim 10$ (papierek uniwersalny) i ekstrahowano czterokrotnie chloroformem (ogółem zużyto około 100 ml). Wyciąg chloroformowy wysuszono bezwodnym K_2CO_3. Pozostałość po odpędzeniu rozpuszczalnika przedestylowano na łaźni parafinowej z kolby kołnierzowej pod ciśnieniem 2 mm i zebrano destylat w temp. 140°—200° (temp. łaźni). Otrzymano 2,35 g oleistej cieczy (=40,5% wyd.). $n_D^{22}=1.5265$.

Ponieważ nie udało się otrzymać chlorowodorku D,L-N-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloaminy bezpośrednio z aminy, przeprowadzono zasadę w nadchloran. Najpierw 1,39 g zasady rozpuszczono w 10 ml bezwodnego etanolu. Na-

stępnie dodano 10% roztwór $HClO_4$ do odczynu kwaśnego na papierek Kongo (1 40%-go $HClO_4$+3 cz. bezwodnego etanolu). Wydzielone kryształy nadchloranu po stawiono na 2 godziny w lodówce, po czym odsączono, przemyto etanolem i wy szono w eksykatorze próżniowym nad $CaCl_2$ i parafiną. Otrzymano 1,7 g (=82 wyd.) białych kryształów o t. t. 180°—181°.

Analiza: $C_{12}H_{19}O_2N.HClO_4$

obliczono	46,53% C	6,51% H
otrzymano	45,94% C	6,78% H

Celem otrzymania zasady, do 0,97 g nadchloranu dodano 10% roztwór NaOH odczynu alkalicznego na papierek uniwersalny (pH~10) i ekstrahowano chloro mem. Po wysuszeniu wyciągu chloroformowego bezwodnym K_2CO_3 i odpędze rozpuszczalnika pozostałość destylowano z kolby kołnierzowej i zebrano destylat ciśnieniem 3 mm w temp. 130°—180° (temp. łaźni). Otrzymano 0,64 g oleistej cie o n_D^{18} =1.5277.

Do 0,62 g oczyszczonej przez nadchloran aminy dodano około 1 ml bezwodn etanolu, po czym chłodząc z zewnątrz lodem, wysycono roztwór gazowym HCl. nieważ wydzielone w lodówce w ciągu 12 godz. kryształy chlorowodorku rozpu czały się w temp. pokojowej, oddestylowano alkohol wraz z nadmiarem HCl łaźni wodnej. Pozostały olej przeniesiono do eksykatora próżniowego nad Ca i KOH. Wydzielone kryształy chlorowodorku przemyto na gorąco dwukrotnie ete naftowym i wysuszono w eksykatorze. Otrzymano 0,6 g białych kryształów chlo wodorku D,L-N-metylo-β-(3,4-dwumetoksyfenylo)-izopropyloaminy o temp. 114°—119°.

C. Бинéцки, Е. Краевски

ПОЛУЧЕНИЕ D,L-N-МЕТИЛ-β-(3,4-МЕТИЛЕНДИОКСИФЕНИЛ)-ИЗОПРОПИЛ МИНА И D,L-N-МЕТИЛ-β-(3,4-ДИМЕТОКСИФЕНИЛ)-ИЗОПРОПИЛАМИНА

Содержание

Авторами описаны синтезы D,L-N-метил-β-(3,4-метилендиоксифенил)-изопр пиламина и D,L-N-метил-β-(3,4-диметоксифенил)-изопропиламина. Исходны соединениями являлись сафрол и метилэвгенол. Последние соединения действием 70% бромистого водорода переходят в α-(3,4-метилендиоксифенил -β-бромпропан и в α-(3,4-диметоксифенил)-β-бромпропан. Последующим де ствием алкогольного раствора метиламина получены D,L-N-метил-β-(3,4-метилен диоксифенил), а также D,L-N-метил-β-(3,4-диметоксифенил)-изопропиламин. Вы ше указанные амины переведены в хлористоводородные соединения.

St. Biniecki, E. Krajewski

PRODUCTION OF D,L-N-METHYL-β-(3,4-METHYLENEDIOXYPHENYL)-ISOPROPYLAMINE AND D,L-N-METHYL-β-(3,4-DIMETHOXYPHENYL)-ISOPROPYLAMINE

Summary

In their paper the authors describe the synthesis of D,L-N-methyl-β-(3,4-meth lenedioxyphenyl)-isopropylamine and D,L-N-methyl-β-(3,4-dimethoxyphenyl)-isop pylamine. As initial compounds they used saphrol and methyleugenol. By the ac

of a 70% bromohydride the latter was converted into α-(3,4-methylenedioxyphenyl)-β-bromopropane and α-(3,4-dimethoxyphenyl)-β-bromopropane. Subsequently they obtained, by the action of an alcoholic solution of methylamine, D,L-N-methyl-β-(3,4-methylenedioxyphenyl)-and D,L-N-methyl-β-(3,4-dimethoxyphenyl)-isopropylamine. The obove amines were converted into hydrochlorides.

Piśmiennictwo

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Otrzymano: 4. III. 1960.

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Warszawa ul. Przemysłowa 25.

Raney Ni, 0°, 3, 88; dioxane, $NiCl_2$, 35°, 3, 77; dioxane, $NiCl_2$, 35°, 24, 96; dioxane, $NiCl_2$, 65°, 3, 61; dioxane, $NiCl_2$, 101°, 24, 60; Et_2O, $NiCl_2$, 0°, 3, 68; tetrahydrofuran, $NiCl_2$, 0°, 3, 68; tetrahydropyran, $NiCl_2$, 35°, 3, 24; tetrahydropyran, $NiCl_2$, 85°, 24, 15. Addn. of $NiCl_2$ to $LiAlH_4$ in XI produced XII as a finely divided solid resembling Raney Ni, reacting vigorously with H_2O, apparently a Ni hydride or an active form of Ni with much adsorbed H. The effect of structure on hydrogenolysis of I was shown by comparison (ether, % hydrogenolysis in dioxane and in XI given): III, 77, 67; IV, 29, 5; V, 60, 69; VI, 55, 89; VII, 31, 80; VIII, 53, 65; IX, 12, 7; X, 41, 42; Ph_2O, 5, 4. The very sharp decrease in hydrogenolysis for IV and IX suggested that steric factors were equally or more important than the kind of substituent on the ring. To account for the observed effects of solvent, catalyst, temp., initial rapid reaction, and the reaction products it was proposed that I formed reversibly intermediate complexes with the solvent and the hydride or with the hydride which then underwent hydrogenolysis by excess hydride to yield product complexes from which the final products were liberated by H_2O. C. R. Addinall

Fries rearrangement of mononitrophenyl benzoates. I. Farka and T. Széll (Univ. Szeged, Hung.). *Acta Univ. Szegediensis, Acta Phys. et Chem.* 6, No. 1-4, 113-15(1960)(in English).—The Fries rearrangement of 2-nitrophenyl benzoate (I) and 4-nitrophenyl benzoate (II) in $PhNO_2$ in the presence of 1–1.25 moles $AlCl_3$ yielded, resp., 3-nitro-4-hydroxybenzophenone (III) (3.5%) and 5-nitro-2-hydroxybenzophenone (IV) (4%). 3-Nitrophenyl benzoate did not rearrange under these conditions. II (5 g.) was added to a soln. of 3.5 g. anhyd. $AlCl_3$ dissolved in 20 ml. $PhNO_2$, the mixt. heated 1 hr. at 170°, cooled, poured into dil. HCl and the mixt. stirred 1 hr. The $PhNO_2$ layer was treated with a mixt. of 20 ml. 10 *N* NaOH and 20 ml. 0.83 *M* NaF and steam-distd. until free of $PhNO_2$. The residue was filtered, acidified with concd. HCl, the aq. layer extd. 4 times with 40 ml. portions of CCl_4, the solid residue dissolved in EtOH and cooled overnight to yield IV, m. 122–4° (EtOH); phenylhydrazone m. 190–1° (EtOH); 2,4-dinitrophenylhydrazone m. 283–5°. The rearrangement of I was carried out in a similar manner to give III, m. 261° (ligroine). Kenneth L. Marsi

Action of boron trichloride on aryl allyl ethers; meta rearrangement of mesityl allyl ether. P. Fahrni, A. Habich, and H. Schmid (Univ. Zürich, Switz.). *Helv. Chim. Acta* 43, 448–52(1960)(in German).—The reaction of BCl_3 with aryl allyl ethers at 0–25° was studied. A mixt. of BCl_3–N_2 was passed through the ethers in presence or absence of PhCl or $PhNO_2$. The yield of the products varied with temp. and solvent. Phenyl allyl ether gave phenol, 2- and 4-allylphenol, and 2,6- and 2,4-diallylphenol. *p*-Tolyl allyl ether gave *p*-cresol, 2-allyl-4-methylphenol and 2,6- and 2,3-diallyl-4-methylphenol. 2,6-Dimethylphenyl allyl ether gave 2,6-dimethylphenol, m. 27.5°, 2,6-dimethyl-3-allylphenol, and 2,6-dimethyl-3,4-diallylphenol. Mesityl allyl ether gave a small amt. of mesitol and as main product 3-allylmesitol, m. 77°, also obtained in poor yield 2,4,6-trimethyl-*o*-quinol acetate and $CH_2{:}CHCH_2MgBr$. Allyl ethers were not rearranged with 33% H_2SO_4 at 20°. Treatment of a mixt. of 74.1% 2-allyl-2,4,6-trimethylcyclohexa-3,5-dien-1-one, 2.3% dimeric dienone, and 23.6% mesityl allyl ether with 33% H_2SO_4 at 20° gave 26.3% neutral products and 73.7% 3-allylmesitol. Mesityl benzyl ether gave with BCl_3 mesitol and putative 2,4,6-trimethyl-3-benzylphenol, m. 59–9.5°. K. Schoen

Irreversibility of the benzilic ester rearrangement. Jerome F. Eastham and Stanley Selman (Univ. of Tennessee, Knoxville). *J. Org. Chem.* **26**, 293–6(1961).—The benzilic acid and benzilic ester rearrangements were classified with a no. of related mol. rearrangements, each of which occurred through formation of a key intermediate of a structural type common to all of these base-induced rearrangements. Although this key intermediate could be formed from a benzilic acid ester, formation of it did not lead to a mol. rearrangement which would constitute reversal of the benzilic ester rearrangement discovered by Doering and Urban (*CA* 51, 2668*e*). Demonstration of this irreversibility of the benzilic ester rearrangement was done by showing the positional stability of labeling in Me anisilate-1-C^{14} (I) in the presence of strong base. Synthesis of the labeled ester involved the 1st successful alcoholysis of an aroyl cyanide to an imino ether. *o*-LiC_6H_4Me (from 8.6 g. *o*-BrC_6H_4Me) in 53 ml. Et_2O added dropwise to 10.5 g. Bz_2 in Et_2O and the mixt. hydrolyzed with dil. HCl gave 1.8 g. α-phenyl-2-methylbenzoin, m. 116–17° (alc.). Anisoyl chloride (9.5 g.) and 5 g. $CuC^{14}N$ heated 3.5 hrs. at 120–30° gave 5.7 g. anisoyl cyanide-1-C^{14} (II), m. 57–9° (C_6H_6-ligroine). II (3 g.) and 0.6 g. MeOH in 40 ml. Et_2O treated at 0° during 45 min. with dry HCl, and the mixt. refrigerated 3 hrs. gave *p*-methoxyphenylglyoxylimino Me ether-HCl (III). III stirred 5 min. in 50 ml. H_2O gave 1.74 g. Me *p*-methoxyphenylglyoxylate-1-C^{14} (IV), m. 50–1° (dil. alc.). III had an indefinite m.p. above 100° and the resolidified material m. 145–50°, identically with 4-methoxyphenylglyoxylamide (V). Anisoyl cyanide (9 g.) and 2.24 g. MeOH in 60 ml. Et_2O treated 1 hr. at 0° with anhyd. HCl gave crystals, m. 147–50°. This material stirred 0.5 hr. at room temp. with 60 ml. 2*N* HCl, heated to reflux, and cooled gave after extn. with 5% Na_2CO_3 and acidification 4-methoxyphenylglyoxylic acid (VI), m. 91–3°, and evapn. of the Et_2O soln. gave V, m. 148–9°. Anisoyl cyanide (10 g.) in MeOH treated 8 days in the refrigerator with dry HCl gave 9 g. Me anisate, m. 46–8° (aq. MeOH). Anisoyl cyanide (9 g.) and 200 ml. concd. HCl stirred 2 weeks at room temp. gave 4 g. VI. More vigorous hydrolytic conditions gave anisic acid. Grignard reagent from 4 g. *p*-bromoanisole and 0.52 g. Mg in Et_2O stirred 15 min. with 3.2 g. IV in 100 ml. Et_2O and the whole hydrolyzed gave 1.55 g. I, m. 109–10° (C_6H_6-ligroine). Labeled I mixed with 0.5 g. of unlabeled material and the solid recrystd. gave 1.9 g. product having 4.62 mc./mole. NaOMe (1.25 ml. of a mixt. of 0.6 mole NaOMe in 10 ml. MeOH and 2.5 ml. H_2O) heated 50 min. in a sealed vial with 100 mg. I gave 71.5 mg. crude anisilic acid-1-C^{14} (VII). VII in AcOH treated 0.5 hr. on the steam bath with 25 mg. CrO_3 in AcOH gave 26.5 mg. 4,4′-dimethoxybenzophenone (VIII), m. 142–4°. I (100 mg.) heated 2 days at 99° in a sealed vial with NaOMe in MeOH gave VIII, 0.02 mc./mole. I (200 mg.) heated 2 days at 200° in a sealed tube with 2 ml. soln. of NaOMe (from 10 ml. MeOH and 70 mg. Na) gave 163 mg. crude VII. VII oxidized with CrO_3 gave VIII, ~0.03 mc./mole. No rearrangement was found where anisyl and methoxy groups were present. B. K. Wasson

Preparation of DL-1-(3,4-methylenedioxyphenyl)-2-(methylamino)propane and DL-1-(3,4-dimethoxyphenyl)-2-(methylamino)propane. Stanisław Biniecki and Edmund Krajewski (Akad. Med., Warsaw). *Acta Polon. Pharm.* **17**, 421–5(1960)(in Polish).—Safrole (5.3 g.) added dropwise at 0° to 21 g. 70% HBr, the mixt. left 14 hrs. at 0°, poured on ice, extd. with Et_2O, and the ext. distd. *in vacuo* yielded 97% 3,4-$CH_2O_2C_6H_3CH_2CHBrMe$ (I), n_D^{25} 1.5634. Analogously, 5.73 g. 4-allylveratrole with 18.6 g. 70% HBr gave 81% 3,4-$(MeO)_2C_6H_3CH_2CHBrMe$ (II), n_D^{18} 1.5605. I (4.7 g.) with 26 g. 18.2% alc. $MeNH_2$ heated 3 hrs. at 130°, the solvent and excess amine distd., the residue acidified with HCl to Congo red, extd. with 30 ml. Et_2O to remove unchanged I, the aq. layer treated with 10 g. K_2CO_3, extd. with Et_2O, and the exts. distd. gave 1.4 g. 3,4-$CH_2O_2C_6H_3CH_2$-$CHMeNHMe$, n_D^{19} 1.5311, after 1.9 g. I was recovered; hydrochloride m. 148–9°. Similarly, 7.2 g. II and 22.5 g. $MeNH_2$ after 10 hrs. at 140° and similar working up (NaOH used instead of K_2CO_3 and $CHCl_3$ substituted for Et_2O in the last extn.) gave 2.35 g. 3,4-$(MeO)_2C_6H_3CH_2CHMeNHMe$, n_D^{25} 1.5265; prepn. of the hydrochloride, m. 114–19°, was not successful unless the base was purified via the perchlorate, m. 180–1°. Jerzy Lange

Anticancer agents. VI. Mechanism of desulfurization reaction of bis(*p*-nitrobenzyl) disulfide with hydrazine hydrate and the reaction of disulfide with various amines. Tetsuji Kametani, Seiichi Takano, Keiichiro Fukumoto, and Yuriko Takayanagi (Tohoku Univ., Sendai). *Yakugaku Zasshi* **81**, 83–8(1961); cf. *Bull. Chem. Soc. Japan* **33**, 1678 (1960).—*p*-$O_2NC_6H_4CH_2SH$ (1 g.) and 1 g. 80% $N_2H_4.H_2O$ in 5 ml. EtOH refluxed 5 hrs. in N and the soln. cooled yielded 96% *p*-$O_2NC_6H_4CH{:}NNH_2$, m. 133–4°. The above reaction with 0.5 mole equiv. of $N_2H_4.H_2O$ yielded 0.35 g. $(p\text{-}O_2NC_6H_4CH_2)_2S_2$ (I), m. 126.5° (MeOH), and 0.24 g. *p*-$O_2NC_6H_4CH{:}NNH_2$. I (3 g.) in 400 ml. EtOH treated dropwise with NH_2OH (from 3 g. of its HCl salt), refluxed 45 hrs., and the soln. concd. gave 2.3 g. *p*-$O_2NC_6H_4CH{:}$-NOH, m. 129°. I (0.1 g.) and $NH_2NHCONH_2$ (from 0.3 g. HCl salt) in 10 ml. EtOH refluxed 64 hrs. and the soln. concd. gave 50 mg. *p*-$O_2NC_6H_4CH{:}NNHCONH_2$, m. 198–9°. I (0.9 g.) in 100 ml. EtOH treated dropwise with 2.3 g. $MeNH_2$ in 15 ml. EtOH and the soln. refluxed 11 hrs. and concd. gave 0.3 g. *p*-$O_2NC_6H_4CH{:}NMe$, m. 173–5°, and

Die entsprechende Aethoxyverbindung krystallisirt in schönen grossen Tafeln vom Schmp. 89°.

0.2435 g Sbst.: 0.3082 g AgBr. — 0.1800 g Sbst.: 0.2298 g AgBr.

$C_{12}H_{13}O_3Br_3$. Ber. Br 53.91. Gef. Br 53.9, 54.3.

Abspaltbarkeit des β-Bromatoms in den Alkohol-Substitutionsproducten, R.CH(OR).CHBr.CH₃.

Propenyläther des Isosafrols, $(CH_2O_2:)C_6H_3.C(OC_2H_5):CH.CH_3$.

Die Abspaltung des β-Broms aus dem α-Aethoxy-β-brom-dihydroisosafrol erfolgt am besten durch mehrstündiges Erhitzen der alkoholischen Lösung mit einem Ueberschuss von Alkali in einem Autoclaven bei 100°. Die Verwendung von Natriumäthylat oder von Kaliumhydroxyd ergiebt dasselbe Resultat. In beiden Fällen wurden aus 20 g Aethoxyverbindung etwas mehr als 13 g des bei 10 mm Druck von 143—145° siedenden Propenyläthers erhalten, d. i. 94 pCt. der Theorie.

0.2163 g Sbst.: 0.5557 g CO_2, 0.1343 g H_2O.

$C_{12}H_{14}O_3$. Ber. C 69.90, H 6.79.
Gef. » 70.11, » 6.89.

Zur Umwandelung in das α-Keton, $(CH_2O_2:)C_6H_3.CO.CH_2.CH_3$, wurde der Propenyläther einige Zeit mit der dreifachen Menge 20-procentiger Salzsäure auf dem Wasserbade digerirt und dann so lange auf der Schüttelmaschine geschüttelt, bis sich alles in eine feste, krystallinische Masse verwandelt hatte. Dies Product zeigt bereits den Schmp. 38° und entsteht quantitativ: aus 7 g Aether 6 g Keton.

0.1562 g Sbst.: 0.3887 g CO_2, 0.0849 g H_2O.

$C_{10}H_{10}O_3$. Ber. C 67.42, H 5.62.
Gef. » 67.86, » 6.04.

Ueber die Einwirkung von 2 Mol. Gew. alkoholischem Natriumäthylat auf das Isosafroldibromid zur Darstellung des α-Ketons nach dem Verfahren von Wallach und Pond[1]), siehe S. 3473.

α-Aethoxy-β-brom-Dihydro-brom-isosafrol wurde mit überschüssigem, alkoholischem Kaliumhydroxyd im ganzen etwa 60 Stdn. gekocht, bis sich in der inzwischen mehrfach filtrirten Lösung kein Bromkalium mehr abschied. Das gewonnene Oel zeigte bei der Analyse zwar eine weitgehende, aber nicht vollständige Abspaltung des β-Bromatoms.

0.2163 g Sbst.: 0.1550 g AgBr.

$C_{12}H_{13}O_3Br$. Ber. Br 28.05. Gef. Br 30.5.

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[1]) Diese Berichte 28, 1719 [1895].

Das Oel wurde längere Zeit mit verdünnter Salzsäure stehen gelassen: es bildeten sich vorübergehend einige Krystalle, die aber wieder zerflossen. Aus der Schmiere konnte kein reines α-Keton abgeschieden werden.

Auch die Methoxy- und Aethoxy-Verbindungen des Dibrom-isosafrols wurden längere Zeit mit alkoholischem Kaliumhydroxyd und Natriumäthylat gekocht. Es schieden sich nur geringe Mengen Alkalibromid ab, die meiste Substanz wurde unverändert wiedergewonnen. Bei 100° im Druckrohr erfolgte wohl eine Einwirkung, doch konnten keine reinen Umsetzungsproducte isolirt werden, da neben unverändertem Ausgangsmaterial Bildung alkoholischer Producte unter theilweiser Verschmierung eintrat.

C. Einwirkung von Wasser.

Von den α-Oxy-β-brom-Derivaten des Isosafrols und Anethols ist bisher nur dasjenige des Bromisosafrols[1]) beschrieben worden. Ihre Darstellung erfolgt bekanntlich durch Kochen der Dibromide mit wässriger Acetonlösung[2]). Ich habe es zweckmässig gefunden, durch Zusatz von gekörntem Marmor den entstehenden Bromwasserstoff zu binden. Da sich in diesem Falle alsbald eine concentrirte Bromcalciumlösung am Boden des Gefässes abscheidet, so muss dieselbe nach einiger Zeit entfernt und durch frisches Wasser ersetzt werden. Bei den schwerer reagirenden, kernbromirten Dibromiden muss zur Erzielung einer vollständigen Umsetzung lange Zeit erhitzt und eine möglichst wässrige Acetonlösung angewendet werden, damit auch eine genügend hohe Temperatur erreicht werden kann. Die nicht krystallisirenden Hydroxyl-Derivate können nur in der Weise isolirt werden, dass nach Verjagen des Acetons in Aether aufgenommen, die ätherische Lösung getrocknet und der Aether im Vacuum möglichst vollständig verdunstet wird.

α-Oxy-β-brom-dihydroisosafrol, $(CH_2O_2:)C_6H_3.CH(OH).CHBr.CH_3$.

Für die Darstellung dieser Verbindung geht man am besten direct vom Isosafrol aus. 200 g Isosafrol werden mit 400 g wasserfreiem Aether unter guter Kühlung und kräftigem Rühren allmählich mit 200 g Brom versetzt, sodann der Aether abgesaugt und das zurückbleibende Oel (406 g) in 800 g Aceton gelöst und mit 200 g Wasser und 65 g gekörntem Marmor versetzt. Es beginnt schon in der Kälte Kohlensäureentwickelung. Nach zweistündigem Erhitzen auf dem Wasserbade wurde die abgeschiedene Bromcalcium-Lauge entfernt, nochmals mit 150 g Wasser 2 Stunden erhitzt und das nach dem Abdestilliren des Acetons abgeschiedene Oel von der wässrigen Lösung ge-

[1]) Pond und Siegfried, Chem. Centralblatt 1903, I, 969.
[2]) Siehe auch Hell, diese Berichte 37, 1128 [1904].

trennt, mit Wasser gewaschen und im Vacuum getrocknet. Die Ausbeute betrug 312 g (ber. 320 g). Vom Marmor wurden etwa 50 g verbraucht. Eine weitere Reinigung der erhaltenen Oxy-Verbindung ist nicht möglich, da sie sich auch im Vacuum nicht destilliren lässt; deshalb konnten bei der Analyse keine scharf stimmenden Werthe erhalten werden.

0.2180 g Sbst.: 0.1489 g AgBr. — 0.2190 g Sbst.: 0.1486 g AgBr.

$C_{10}H_{11}O_3Br$. Ber. Br 30.88. Gef. Br 29.1, 28.9.

α-Oxy-β-brom-Dihydro-brom-isosafrol,
$(CH_2O_2:)C_6H_2Br.CH(OH).CHBr.CH_3$,

zeigte nach den Angaben von Pond und Siegfried den richtigen Schmp. 89°. Diese Autoren haben schon die Leichtabspaltbarkeit des β-Bromatoms in dieser Verbindung durch alkoholisches Kali beobachtet[1]).

α-Oxy-β-brom-Dihydro-dibrom-isosafrol,
$(CH_2O_2:)C_6HBr_2.CH(OH).CHBr.CH_3$.

Für die Darstellung dieser Verbindung bewährte sich am besten folgendes Verfahren: 30 g Dibromisosafroldibromid, 80 g Aceton und 40 g Wasser wurden bei Gegenwart von Marmor 8—9 Stunden erhitzt. Die Abnahme des Marmors beträgt dann 3.08 g (ber. 3.12 g). Nach dem Abdestilliren des Acetons, zuletzt im Vacuum, wird das Oel nochmals mit Aether aufgenommen, mit geglühtem Natriumsulfat getrocknet und der Aether im Vacuum wieder verdampft. Das Oxybromid hinterbleibt als eigenthümlich glasartige Masse, die trotz der bräunlichen Farbe vollkommen klar durchsichtig ist. Sie lässt sich eben noch mit dem Messer schneiden, springt dabei aber mitunter spröde aus einander. Lose, auf einen Haufen geschichtete Stücke waren nach 24 Stunden zu einem einzigen Klumpen zusammengesintert und nach 48 Stunden hatten sie wieder eine ebene, einheitliche Oberfläche angenommen. In gelinder Wärme wird die Masse dünnflüssig.

0.1704 g Sbst.: 0.2339 g AgBr.

$C_{10}H_9O_3Br_3$. Ber. Br 57.53. Gef. Br 58.4.

Der hohe Bromgehalt rührt vermuthlich von einer Beimengung an Isosafrolpentabromid[2]) her.

α-Oxy-β-brom-dihydroanethol, $CH_3O.C_6H_4.CH(OH).CHBr.CH_3$.

Diese Verbindung wurde in der üblichen Weise aus Anetholdibromid durch Erhitzen in wässriger Acetonlösung dargestellt und bildet ein schwach gelbgefärbtes Oel, das sich weder im Vacuum destilliren lässt, noch auch zum Krystallisiren gebracht werden konnte. Aus 20 g Dibromid wurden 15.3 g (15.9 g ber.) erhalten.

0.1925 g Sbst.: 0.1455 g AgBr.

$C_{10}H_{13}O_2Br$. Ber. Br 32.65. Gef. Br 32.19.

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[1]) Siehe diese Berichte 38, 2297 [1905].

[2]) Siehe S. 3466.

D. Einwirkung von Natriumacetat.

Die Einwirkung des Natriumacetats auf die Dibromide in Eisessiglösung erfolgt in der Hitze sehr leicht. Auch wenn genau ein Mol.-Gew. einwirkt, wird häufig auch das zweite Bromatom schon theilweise ersetzt. Hierbei bildet sich, wie später gezeigt werden wird, kein Glykoldiacetat, sondern das β-Acetylglykol. Selbst das sehr schwer reagirende Propenylbenzoldibromid[1]) kann durch Natriumacetat und Eisessig in eine Monacetylverbindung umgewandelt werden.

α-Acetoxy-β-brom-dihydroisosafrol, $(CH_2O_2:)C_6H_3.CH(O.C_2H_3O).CHBr.CH_3$.

64.4 g Isosafroldibromid wurden mit einer Lösung von 16.4 g Natriumacetat in 100 g Eisessig einige Zeit zum Sieden erhitzt. Das sich rasch abscheidende Bromnatrium wird dann abgesaugt (20.5 g), der Eisessig im Vacuum grösstentheils abdestillirt, der mit Aether aufgenommene Rückstand nach dem Waschen mit Wasser und Bicarbonatlösung im Vacuum vom Aether befreit. Es hinterblieben 55 g eines dicklichen Oels, das sich nicht weiter reinigen liess. Die Analyse der Acetylverbindung giebt keine gut stimmenden Zahlen, was wahrscheinlich darauf beruht, dass zum Theil auch eine Umsetzung des β-Bromatoms stattgefunden hat.

0.3467 g Sbst.: 0.1981 g AgBr.

$C_{12}H_{13}O_4Br$. Ber. Br 26.57. Gef. Br 24.31.

Beim Versuche, das Oel im Vacuum zu destilliren, trat Abspaltung von Essigsäure[2]) ein, und es wurde bei nochmaliger Destillation ein bei 12 mm Druck von 155—162° übergehendes Oel erhalten, das mit Isosafrol-β-bromid[3]), $(CH_2O_2:)C_6H_3.CH:CBr.CH_3$, identisch ist.

α-Acetoxy-β-brom-Dihydro-brom-isosafrol, $(CH_2O_2:)C_6H_2Br.CH(O.C_2H_3O).CHBr.CH_3$.

Eine kochende Lösung von 35 g Bromisosafroldibromid in 35 g Eisessig wurde mit der kochenden Lösung von 6.5 g Natriumacetat in 15 g Eisessig versetzt und einige Minuten im Kochen erhalten. Sehr rasch tritt Bromnatrium-Abscheidung ein. Nach einer Viertelstunde wurde in kaltes Wasser gegossen, und das abgeschiedene Oel ausgeäthert; aus dem Aether wurden nach der üblichen Reinigung beim Verdunsten 21.5 g Krystalle erhalten, die sofort nach dem Waschen mit etwas Aether-Petroläther den Schmp. 71—73° zeigten (Pond-Siegfried 73—74°). Die Mutterlauge hinterlässt 12 g eines nicht erstarrenden Oels, das bei der Verseifung mit alkoholischer Lauge statt des zu erwartenden öligen Oxyds[4]) ein Product lieferte, das nach der Destillation

[1]) Hell, diese Berichte 36, 206 [1903].
[2]) Vergl. Hell, diese Berichte 29, 681 [1896].
[3]) Dissertation Hoering, S. 49.
[4]) Vergl. die folgende Mittheilung.

im Vacuum krystallinisch erstarrte, nach wiederholtem Umkrystallisiren aus Alkohol den Schmp. 101—102° zeigte und durch Mischungsschmelzpunkt sich als Brom-isosafrol-β-keton erwies.

α-Acetoxy-β-brom-Dihydro-dibrom-isosafrol,
$(CH_2O_2)C_6HBr_2\,CH(O.C_2H_3O).CHBr.CH_3$.

Zu einer kochenden Lösung von 20 g Dibromisosafroldibromid in Eisessig wurde eine Lösung von 4 g Natriumacetat in 10 g Eisessig hinzugefügt und eine halbe Stunde im Sieden erhalten. Die Bromnatrium-Abscheidung beginnt nach 2–3 Minuten. Das beim Eingiessen in 100 ccm kaltes Wasser ausgeschiedene Oel erstarrt schnell zum grössten Theil und bildet nach dem Verrühren mit Aether eine feste, weisse Masse. Nach mehrmaligem Umkrystallisiren aus Benzin wurde ein Theil ganz rein, Schmp. 140—142°, ein Theil bleibt aber etwas unreiner vom niedrigeren Schmp. 135—140°. Die reine Verbindung ergab:

0.1542 g Sbst.: 0.1888 g AgBr.

$C_{12}H_{11}O_4Br_3$. Ber. Br 52.27. Gef. Br 52.1.

α-Acetoxy-β-brom-propyl-Benzol,
$C_6H_5.CH(O.C_2H_3O).CHBr.CH_3$.

55.6 g Propenylbenzoldibromid wurden mit 10 g Natriumacetat in Eisessiglösung eine Stunde erhitzt. Die Aufarbeitung erfolgte wie beim Isosafroldibromid. Das erhaltene Oel liess sich unter geringer Zersetzung (Abspaltung von Essigsäure) bei 13 mm Druck von 140—150° überdestilliren. Bei nochmaliger Destillation ging es bei 11 mm Druck von 142—145° farblos und klar über. Spec. Gewicht bei 19.5° = 1.388. Die Analyse ergab in Folge der schon früher erwähnten Essigsäureabspaltung einen etwas zu hohen Bromgehalt.

0.1943 g Sbst.: 0.1480 g AgBr.

$C_{11}H_{13}O_2Br$. Ber. Br 31.1. Gef. Br 32.4.

Austausch des β-Bromatoms in den Substitutionsderivaten.

In den α-Acetoxy-β-brom-Derivaten des Brom- und des Dibrom-Isosafrols konnte das β-Bromatom durch mehrstündiges Erhitzen mit Natriumacetat in Eisessiglösung durch die Acetylgruppe ersetzt werden; dabei wurde aber gleichzeitig die α-Acetylgruppe abgespalten, da die erhaltenen Reactionsproducte identisch mit den Eisessig-Additionsproducten der Propylenoxyde[1]) sind. Aus den Oxyverbindungen erfolgte eine Bromnatrium-Abspaltung überraschender Weise viel schwieriger. Die α-Methoxyverbindungen widerstanden der Einwirkung vom Natriumacetat in Eisessiglösung und auch in alkoholischer Lösung bei 120° im Rohr.

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[1]) Siehe Mittheilung V, S. 3483.

Aus Bromisosafrol-α-acetoxy-β-bromid wurde ein farbloses, dickes Oel erhalten.

0.1900 g Sbst.: 0.1123 g AgBr.

$C_{12}H_{13}O_5Br$. Ber. Br 25.22. Gef. Br 25.2.

Das Dibrom-isosafrol-Derivat lieferte Krystalle vom Schmp. 185—188°, die sich nach der Analyse und durch Mischungsschmelzpunkt mit dem Eisessig-Additionsproduct des Oxyds $(CH_2O_2:)C_6HBr_2.CH(OH).CH(O.C_2H_3O).CH_3$ (Schmp. 187—190°) identisch erwiesen.

0.1000 g Sbst.: 0.0941 g AgBr.

Monoacetat, $C_{12}H_{12}O_5Br_2$. Ber. Br 40.38.

Diacetat, $C_{14}H_{14}O_6Br_2$. Ber. Br 36.51. Gef. Br 40.0.

E. Einwirkung von Alkali.

Isosafrol-dibromid. 32.2 g Isosafroldibromid wurden in 50 ccm trocknem Aether mit einer Lösung von 2.3 g Natrium (1 Atomgew.) in 50 g absolutem Alkohol auf dem Wasserbade bis zur neutralen Reaction erwärmt. Bei der üblichen Aufarbeitung geht bei der Vacuumdestillation ein farbloses Oel bei 11 mm Druck von 155—165° über, das bei nochmaliger Destillation grösstentheils von 156—157° siedet. Ausbeute 21.1 g.

0.1922 g Sbst.: 0.1410 g AgBr.

$(CH_2O_2:)C_6H_3.CH(OC_2H_5).CHBr.CH_3$. Ber. Br 27.87. Gef. Br 31.22.

$(CH_2O_2:)C_6H_3.CH:CBr.CH_3$. Ber. Br 33.19.

Das Oel enthält nach diesem Analysenresultat 68 pCt. Isosafrol-β-bromid neben 32 pCt. der Aethoxyverbindung.

20 g Isosafroldibromid wurden in 50 g trocknem Aether mit aus 1.4 g Natrium bereitetem, trocknem Natriumäthylat 2 Stdn. auf dem Wasserbade erhitzt. Bei der Vacuumdestillation ging zwischen 147—153° bei 9 mm Druck ein farbloses Oel über, das, nochmals destillirt, bei 8 mm von 145—148° siedete.

0.1694 g Sbst.: 0.1287 g AgBr.

Gef. Br 32.33.

Aus diesem Resultat berechnet sich ein Gehalt von 83.8 pCt. Isosafrol-β-bromid und nur 16.2 pCt. Aethoxyverbindung.

Eine Nachprüfung der von Wallach und Pond beschriebenen Darstellung[1]) des α-Ketons aus dem Isosafroldibromid durch Einwirkung von überschüssigem, alkoholischem Natriummethylat gestaltete sich wie folgt:

35 g Isosafroldibromid wurden mit einer Auflösung von 10 g Natrium in 140 g wasserfreiem Methylalkohol 6 Stunden zum Sieden erhitzt, dann der Alkohol abdestillirt und der Rückstand mit Wasser-

[1]) Diese Berichte 28, 2719 [1895].

dampf abgeblasen. Das übergegangene farblose Oel wurde mit Aether aufgenommen, mit Chlorcalcium getrocknet und im Vacuum fractionirt. Es wurden folgende Fractionen erhalten:

I.	138—140°	bei 11 mm Druck	4.6 g
II.	140—142°		6.0 »
III.	142—147°		5.2 »
IV.	147—149°		1.7 »
	138—149°		17.5 g.

Keine dieser Fractionen wurde beim Stehen in einer Kältemischung fest. Oximbildung trat nicht ein, sodass also noch kein α-Keton zugegen war. Das Reactionsproduct war stark bromhaltig.

0.1872 g Sbst.: 0.4372 g CO_2, 0.0936 g H_2O. — 0.2168 g Sbst.: 0.0926 g AgBr.

II. Fract.: Gef. C 63.7, H 5.59, Br 8.36.

Diese Zahlen stimmen gut auf ein Gemisch von etwa 25 pCt. des Isosafrol-β-bromids mit 75 pCt. Propylenmethyläther $(CH_2O_2:)C_6H_3.C(OCH_3):CH.CH_3$. Beim Schütteln dieses Productes mit verdünnter Salzsäure schied sich daher das entstandene α-Keton nicht fest ab. Ueber die quantitative Gewinnung desselben aus dem Dibromid wurde schon im Vorhergehenden berichtet[1]).

Brom-isosafrol-dibromid. Bei der Einwirkung von 1 Mol.-Gew. Natriummethylat, gewonnen durch Auflösung von Natrium in möglichst wenig Methylalkohol, auf eine ätherische Lösung des Brom-isosafrol-dibromids wurde ein Oel erhalten, in welchem sich Krystalle bildeten. Dieselben zeigten nach zweimaligem Umkrystallisiren aus Methylalkohol den Schmp. 65°. Die Analyse stimmt auf die ungesättigte Verbindung $CH_2O_2:C_6H_2Br.CH:CBr.CH_3$.

0.1806 g Sbst.: 0.2143 g AgBr.

Gef. Br 50.5.

$C_{11}H_{12}O_3Br_2$. Ber. Br 45.44.

$C_{10}H_8O_2Br_2$. Ber. Br 49.98.

In dem Oele war noch die Methoxyverbindung enthalten, deren schwierige Reinabscheidung nicht weiter versucht wurde.

Bei der Wiederholung dieses Versuchs mit Natriumäthylat war der Verlauf ähnlich, nur bildete sich mehr schmierige Masse, und die ausgeschiedenen Krystalle konnten nach mehrmaligem Umkrystallisiren nur auf den Schmp. 57—65° gebracht werden.

Es wurden nun 10 g Bromisosafroldibromid in einen grossen Ueberschuss bereits im Kochen befindlichen alkoholischen Kalis auf einmal eingetragen und kurze Zeit weiter gekocht. Es tritt sofort

[1]) Siehe S. 3468.

lebhafte Abscheidung von Bromkalium ein. Ein grosser Theil des Alkohols wurde nun abdestillirt, dann wurde mit Wasser verdünnt, das ausgefallene Oel mit Aether aufgenommen, getrocknet und im Vacuum destillirt. Es ging bis auf einen geringen Rückstand bei 12 mm Druck von 178—185° über. Das Destillat (5.3 g) erstarrte in Eis. Aus Petroläther (27—35°) umkrystallisirt, zeigte es den Schmp. 52—55°, nach nochmaligem Umkrystallisiren 56—59°, blieb aber etwas schmierig. Die Analyse zeigt, dass das Allylenderivat $(CH_2O_2:)C_6H_2Br.C:C.CH_3$ entstanden ist.

0.1508 g Sbst.: 0.1218 g AgBr.

$C_{10}H_7O_2Br$. Ber. Br 33.45. Gef. Br 34.4.

Dibrom-isosafrol-dibromid. Dasselbe bleibt bei längerem Kochen mit trocknem Natriumäthylat in ätherischer oder Toluollösung unverändert. Es wurden nun 8 g des Dibromids fein gepulvert, auf einmal in überschüssiges, kochendes Natriummethylat eingetragen (1.5 g Natrium in 50 g Methylalkohol) und $1^1/_2$ Stunden gekocht. Das Dibromid geht nur schwer in Lösung, unter gleichzeitiger Abspaltung von Bromnatrium. Beim Erkalten schieden sich aus der filtrirten Lösung kleine Körnchen vom Schmp. 96—100° und feine Nadeln vom Schmp. 150—160° ab.

Die Körnchen wurden möglichst herausgesucht und nochmals umkrystallisirt. Sie behielten dabei ihren Schmp. 95—98°, reichten aber zur weiteren Untersuchung nicht aus. Die Nadeln sind in Methylalkohol sehr schwer löslich, lassen sich aber gut aus Chloroform umkrystallisiren. Sie kommen daraus in feinen, filzigen, lockeren Nadeln vom Schmp. 153—154° heraus.

0.1439 g Sbst.: 0.1612 g CO_2, 0.0260 g H_2O. — 0.1684 g Sbst.: 0.1875 g CO_2, 0.0290 g H_2O. — 0.1680 g Sbst.: 0.2383 g AgBr.

$C_{10}H_7O_2Br_3$. Ber. C 30.08, H 1.77, Br 60.13.
Gef. » 30.60, 30.40, » 2.00, 1.90, » 60.30.

Es ergiebt sich aus dieser Analyse, dass ein Bromatom abgespalten und die Verbindung $(CH_2O_2:)C_6H_2Br.CH:CBr.CH_3$ entstanden ist. Ausserdem zeigt dieser Versuch, dass das Propenylbromid gegen kochendes, alkoholisches Natriummethylat beständig ist.

Ein ähnlicher Versuch mit methylalkoholischem Kaliumhydroxyd ergab ebenfalls die Verbindung vom Schmp. 153—154° und eine Spur eines höher schmelzenden Körpers, der mit äthylalkoholischem Kaliumhydroxyd in grösserer Menge entsteht (das Allylenderivat). Die β-Bromverbindung hat ein Vierteljahr in einem bromwasserstoffhaltigen Exsiccator gestanden, ohne entsprechend dem von mir beim Dibromanethol-β-bromid beobachteten Vorgange[1]) durch Sauerstoffaufnahme in ein Keton $R.CO.CHBr.CH_3$ überzugehen.

[1]) Vergl. Boering, diese Berichte 37, 1557 [1904].

Bei der Einwirkung von kochendem alkoholischem Natriumäthylat im Ueberschuss entsteht aus dem Dibromisosafroldibromid das Allylenderivat $(CH_2O_2:)C_6HBr_2.C:C.CH_3$. Es scheidet sich aus der kochenden Lösung neben dem Bromnatrium allmählich ein dicker Krystallbrei ab, der sogleich den Schmp. 178—179° besitzt und nach dem Umkrystallisiren aus Benzin weisse Nadeln vom Schmp. 180—181° bildet. Auch bei der Einwirkung einer äthylalkoholischen Lösung von Kaliumhydroxyd bildet sich derselbe Körper, daneben entstehen aber auch geringe Mengen feiner, seidenartiger Nadeln vom Schmp. 150°, die das schon beschriebene Propylenderivat darstellen. Bringt man aber eine alkoholische Kaliumäthylatlösung zur Einwirkung, so bildet sich hauptsächlich die letzte Verbindung, während das Allylenderivat nur in geringer Menge entsteht. Bei allen diesen Versuchen wurde der schon früher erwähnte Körper vom Schmp. 95—100° gleichfalls in sehr geringer Menge beobachtet.

Analyse des Allylenderivats. (Schmp. 180—181°)

0.1445 g Sbst.: 0.2090 g CO_2, 0.0272 g H_2O. — 0.1273 g Sbst.: 0.1772 g CO_2, 0.0216 g H_2O. — 0.0880 g Sbst.: 0.1030 g AgBr. — 0.1220 g Sbst.: 0.1423 g AgBr.

$C_{10}H_6O_2Br_2$. Ber. C 37.74, H 1.90, Br 50.29.
Gef. » 37.70, 38.00, » 2.10, 1.90, » 49.80, 49.60.

Das Allylenderivat addirt in Schwefelkohlenstofflösung auch bei gelindem Erwärmen nur zwei Atome Brom; beim Allylenderivat des Isosafrols machte ich zuerst eine derartige Beobachtung, die inzwischen auch in anderen Fällen bekannt geworden ist. Die nach dem Verdunsten des Schwefelkohlenstoffs zurückbleibende graubraune Masse $(CH_2O_2:)C_6HBr_2.CBr:CBr.CH_3$(?) lässt sich durch Umkrystallisiren aus Benzin und Entfärben mit Thierkohle nur schwer reinigen. Der Schmelzpunkt steigt auf 126—128°.

0.1738 g Sbst.: 0.2691 g AgBr.

$C_{10}H_6O_2Br_4$. Ber. Br 66.94. Gef. Br 65.90.

Molekulargewichtsbestimmung:

1. Einwaage 0.0971 g Sbst: 0.105° Dep.
2. » 0.1004 g Sbst.: 0.10° Dep. in 12.70 g Benzol.

Gef. 1. 357, 2. 387. Mittel 372. Ber. 478.

Bei zweistündigem Erwärmen von Dibromisosafroldibromid mit Pyridin auf dem Wasserbade wurde das meiste Dibromid unverändert wiedergewonnen, der Rest war verharzt.

Zum Schluss möchte ich den HHrn. DDr. Grälert und Kippe für ihre Unterstützung bei dieser Arbeit meinen Dank aussprechen.

Dr. P. Hoering's Privatlaboratorium, Berlin NW. 87.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of 1,1,2-Trimethyl-5,6-methylenedioxyindane from Safrole

BY RUBY MURRAY ORCUTT AND MARSTON TAYLOR BOGERT

Supplementing our previous work in the indane group,[1] some experiments have been carried out with safrole (I) and isosafrole (VIII), which have led to a simple synthesis of 1,1,2-trimethyl-5,6-methylenedioxyindane by the following steps.

FLOW SHEET ($R = CH_2(O)_2C_6H_3-$)

(I) $RCH_2CH{=}CH_2 + HBr \longrightarrow$ (III) (IV)

(II) $RCH_2CHBrMe + Mg + H_2O \longrightarrow RCH_2CH(OH)Me + (RCH_2CHMe-)_2$

$RCH_2CHBrMe + Mg + AcMe \longrightarrow RCH_2CH(OH)Me + (RCH_2CHMe-)_2 +$

(V) $RCH_2CHMeC(OH)Me_2 \xrightarrow{+H_2SO_4}$

$\downarrow +H_2SO_4$

(VI) $RCH_2CMe{=}CMe_2 \xrightarrow{+H_2SO_4}$ $CH_2(O)_2C_6H_2(CH_2)(CMe_2)CHMe$ (VII)

(VIII) $RCH{=}CHMe + HBr \longrightarrow RCHBrEt$ (IX)

(X) $RCHO + EtMgBr \longrightarrow RCH(OH)Et + (RCHEt)_2O$

(XI) (XII)

Many of these compounds contain asymmetric carbon atoms and should therefore exist in optical isomers, but these stereochemical problems have not been attacked as yet.

Experimental

1-Piperonyl-1-bromoethane (II).—When a current of dry hydrogen bromide was led into carefully dried safrole, cooled to −5°, in a flask protected from access of moisture, there was a slow gain in weight up to 25% of that calculated for the addition of an equimolar quantity of hydrogen bromide. No further increase in weight occurred although the gas was passed in for several hours longer.

On working up the crude product, the yield of pure bromide (II), b. p. 145° at 9 mm., was 22%.

In another set of experiments, the safrole (25 g.) cooled to 0°, was mixed with an aqueous solution of hydrobromic acid (100 g.), saturated at 0° (or about 69% hydrogen bromide), and the mixture kept in a closed bottle at low temperature, with occasional shaking, for two or three days. The crude product was diluted with an ice-cold salt solution, the heavy bromide removed by extraction with ether, washed several times with the cold salt solution, dried over anhydrous potassium carbonate, the ether distilled off and the remainder fractionated under diminished pressure; b. p. 154–157° at 13 mm., 145° at 9 mm.; $n^{25}D$ 1.5614; yield 75%.

Anal. Calcd. for $C_{10}H_{11}O_2Br$: Br, 32.88. Found: Br, 32.82.

This process gave a very satisfactory product, with the by-products in the form of a decomposed residue easily eliminated. This secondary bromide was much more stable than the isomeric primary bromide, 2-piperonyl-1-bromoethane, described in a recent paper.[2]

In 1914, E. Merck took out a patent[3] for the manufacture of aromatic amines, in which this bromide, from safrole and aqueous hydrobromic acid, was an intermediate product, but was separated only in a crude state as a slightly colored heavy unstable oil, which decomposed when distilled *in vacuo* and was not analyzed.

1-Piperonylethanol-1 (III).—The bromide (II) was converted into the Grignard compound in the customary way, after activating the magnesium by a small crystal of iodine. The reaction, after starting rather slowly, proceeded satisfactorily, and the initial cloudiness disappeared as the reaction advanced. Due apparently to its sensitivity to oxygen, this Grignard compound tended to pass into the secondary alcohol (III) with surprising ease, even in a closed system from which all moisture had been carefully excluded, and this introduced complications in using it for the synthesis of other compounds as explained in the next section. No such difficulty was encountered[2] in the preparation of the isomeric $RCH_2CH_2CH_2MgBr$. At the close of the reaction, the mixture was warmed for thirty minutes, then cooled to 0°, stirred for two hours, hydrolyzed by acidulated ice water and worked up as usual. The crude product (8.5 g.) was distilled under reduced pressure, and yielded 4 g. of the alcohol (III) sought, b. p. 127–129° at 3 mm., 2.5 g. of a by-product of safrole-like odor and 0.5 g. of the butane derivative (IV).

In contradistinction to its primary isomer, 2-piperonylethanol-1, this alcohol showed no tendency whatever to crystallize.

Phenylurethan.—Colorless needles (from alcohol), m. p. 93–94° (uncorr.).

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.72. Found: C, 67.87; H, 5.75.

2-Methyl-3-piperonylbutanol-2 (V) was prepared by the Grignard reaction from the bromide (II) and acetone. Due to the sensitivity of the $RCH_2CH(MgBr)Me$, mentioned above, the preparation proved more troublesome than expected.

When the experiments were conducted in the air, there were obtained from 46 g. of the bromide (II), 16 g. of safrole, 10.4 g. of the secondary alcohol (III), 3 g. of the tertiary alcohol (V), and 1 g. of the 2,3-dipiperonylbutane (IV). The figures for the two alcohols are only approxi-

(1) (a) Bogert and Davidson, THIS JOURNAL, **56**, 185 (1934); (b) Roblin, Davidson and Bogert, *ibid.*, **56**, 248 (1934).

(2) Orcutt and Bogert, *ibid.*, **58**, 2055 (1936).

(3) Merck, German Patent 274,350; *Chem. Zentr.*, **85**, I, 2079 (1914).

mate, because of the difficulty of separating these alcohols quantitatively.

The secondary alcohol (III) isolated, b. p. 127–129° at 3 mm., was analyzed with the following results.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72. Found: C, 66.09; H, 6.69.

Its phenylurethan crystallized from alcohol in colorless needles, m. p. 93–94°. Mixed with the phenylurethan described in the foregoing section, the m. p. was unchanged.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.72. Found: C, 68.10; H, 5.77.

The tertiary alcohol (V), on account of the relatively small amount present, could not be isolated in satisfactory purity.

But when the experiments were carried out in an atmosphere of nitrogen, the same amount (46 g.) of initial bromide (II) gave 17 g. of safrole, none of the secondary alcohol (III), 11 g. of the tertiary alcohol (V), and 1.5 g. of the butane derivative (IV). From this mixture, the *tertiary alcohol* was easily isolated by fractional distillation as a colorless, very viscous liquid, b. p. 142–144° at 3 mm., which congealed in thick colorless needles, m. p. 49°, with some softening as low as 43°. The isomeric 2-methyl-4-piperonylbutanol-2 differs from it in persistently remaining liquid and refusing to crystallize.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 69.86; H, 8.37.

It did not form a phenylurethan. Phenyl isocyanate abstracted water from it, with separation of carbanilide.

2,3-Dipiperonylbutane (IV).—In the residues from the distillation of the crude products obtained in the preparation of both the secondary (III) and tertiary (V) alcohols, this by-product was found. It was purified by repeated crystallization, first from methyl and finally from ethyl alcohol, and then formed thick colorless needles or plates, m. p. 74°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.58; H, 6.79. Found: C, 73.26; H, 6.53.

1,1,2-Trimethyl-5,6-methylenedioxyindane (VII).—To 20 g. of well-cooled (7°) 85% sulfuric acid, there was stirred in gradually 7 g. of the tertiary alcohol (V). The resultant reddish mixture was diluted with ice water, extracted with ether, the ether extracts dried over fused potassium carbonate, the ether removed and the residue fractionated thrice over sodium. The indane so obtained was a colorless oil, b. p. 137° at 11 mm., of penetrating camphoraceous odor; yield about 65%. It did not decolorize an acetone solution of potassium permanganate.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.15; H, 8.20.

Fused with selenium for six hours at 266–270°, a strong odor of methyl mercaptan was noted, and from the tarry product there was isolated a small quantity of a clear yellow liquid, b. p. about 140° at 7 mm., which darkened rapidly and on re-distillation exhaled an odor resembling that of the original indane. It was not obtained in sufficient amount or purity for analysis or identification, nor could a picrate be prepared from it. These results are in accordance with our previous experience with indanes.[1b]

2-Methyl-3-piperonylbutene-2 (VI).—Occasionally this olefin was isolated from the crude product of the above indane synthesis, by fractional distillation of a cyclization product which was unsaturated to an acetone solution of potassium permanganate. It formed an oil, b. p. 120° at 7 mm., colorless when freshly distilled, which rapidly turned yellow, even in a tightly sealed bottle, possessed a citrous or alliaceous type of odor, quickly decolorized an acetone solution of potassium permanganate, and did not form a picrate. For analysis, it was freshly distilled.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.21; H, 8.06.

Subjected to the further action of sulfuric acid, it was rearranged to the isomeric indane (VII).

***alpha*-Ethylpiperonyl Bromide (IX).**—This bromide appeared to be formed in good yield by the action of aqueous hydrobromic acid (69%) upon isosafrole at 0°, as described for the preparation of its isomer (II) from safrole, but it was so unstable that it decomposed when distilled at a pressure of 2 mm.

The Merck patent,[3] already mentioned, refers also to the preparation of this bromide, in an impure state, from isosafrole and hydrobromic acid, and describes it as a slightly colored heavy unstable oil, which decomposed when distilled *in vacuo*, and was not analyzed.

This patent also claims the formation of the corresponding amine when the crude bromide is treated with ammonia. When we treated our product with alcoholic ammonia, even at low temperature, a vigorous reaction ensued, with immediate separation of ammonium bromide in an amount which indicated the presence of approximately 50% of the desired bromide (IX) in the original crude.

***alpha*-Ethylpiperonyl alcohol (XI)** was prepared from piperonal (X) and ethylmagnesium bromide, as recorded by Mameli.[4] Inasmuch as the compound obtained by us (yield 50%) showed a b. p. of 126–127° at 3 mm., whereas that reported by him was 172–175° at atmospheric pressure, our product was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72. Found: C, 66.77; H, 6.42.

No phenylurethan could be secured from this alcohol, because the phenyl isocyanate immediately withdrew from it the elements of water. In this respect it differed strikingly from the isomeric 1-piperonylethanol-1 (III). Nor could we prepare a benzoate from it, or convert it into the corresponding bromide by the action of phosphorus tribromide.

The pure alcohol, after standing for three months at laboratory temperature, turned cloudy and began to crystallize. Dried in an evacuated desiccator and analyzed, it proved to be the ether (XII); yield, equal to that calculated. Apparently this alcohol tends to split out a molecule of water on standing even at ordinary temperature. When warmed or distilled under reduced pressure, however, it loses water quite easily with formation of isosafrole, as found also by Mameli.[4]

Di-*alpha*-ethylpiperonyl Ether (XII).—The distillation residues from the preparation of the foregoing alcohol (XI), when crystallized from methyl alcohol, gave a 5% yield of this ether in colorless leaflets, m. p. 85°.

(4) Mameli, *Rend. Accad. Lincei*, [5] **13**, II, 315 (1904).

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 70.14; H, 6.48; mol. wt. (Rast), 342.2. Found: C, 70.04, 69.85; H, 6.21, 6.42; mol. wt. (Rast), 336.3.

Mameli,[5] who was the first to describe this ether, found that it was formed when an ether solution of the alcohol was left for many weeks in contact with traces of inorganic salts, and gave its m. p. as 88°.

Summary

1. By the addition of hydrobromic acid to safrole, 1-piperonyl-1-bromoethane has been prepared and from this the corresponding alcohol.

2. The Grignard reaction applied to the bromide, in the presence of acetone, yielded a mixture of 1-piperonylethanol-1, 2-methyl-3-piperonylbutanol-2 and 2,3-dipiperonylbutane.

3. This butanol has been converted by the action of sulfuric acid into the corresponding butene and 1,1,2-trimethyl-5,6-methylenedioxyindane.

4. From isosafrole and hydrobromic acid, *alpha*-ethylpiperonyl bromide has been obtained. The corresponding alcohol, from piperonal and ethylmagnesium bromide, has been shown to lose water on standing, with formation of the ether.

NEW YORK, N. Y. RECEIVED AUGUST 10, 1936

(5) Mameli, *Rend. Accad. Lincei*, [5] **13**, II, 612 (1904); *Gazz. chim. ital.*, **35**, II, 32 (1905).

[CONTRIBUTION FROM THE BURROUGHS WELLCOME AND CO., U. S. A., EXPERIMENTAL RESEARCH LABORATORIES]

Some N-Aryl Barbituric Acids. II

BY JOHANNES S. BUCK

The present work is a continuation of that described in an earlier paper.[1] Two further series of 1-aryl-5,5-dialkyl barbituric acids have been prepared, the aryl groups being, as before, phenyl, *o*-, *m*- and *p*-tolyl, *o*-, *m*- and *p*-anisyl, *o*-, *m*- and *p*-phenetyl, and *α*- and *β*-naphthyl, while the alkyl groups are now 5,5-ethyl-isobutyl and 5,5-ethyl-isoamyl. The alkyl groups were selected to allow comparison, pharmacologically, with a series of isoalkylaryl ureas at present under examination.

Since the sodium salts of the N-aryl barbituric acids show a tendency to hydrolyze in aqueous solution, a number of barbituric acids having a dialkylamino group on the phenyl ring was prepared. These compounds are soluble both in alkaline and in acid solution. The presence of the dialkylamino group should also facilitate the resolution of those barbituric acids which carry, in addition to this group, an asymmetric carbon atom.

The two phenyl compounds have been previously described by Hjort and Dox;[2] the others are new. The pharmacological data will be given later in another place.

Experimental

Ethyl isobutylethylmalonate[3] and ethyl isoamylethylmalonate[3] were prepared by the action of the isoalkyl iodide on ethyl ethylmalonate, in the presence of sodium ethylate. It was found advantageous to carry out the reaction as rapidly as possible and to shake the crude ester several times with 5% sodium hydroxide solution.[4] After fractionation under reduced pressure the isobutyl compound boiled at 128.5–130° (15 mm.) (yield 71%) and the isoamyl compound at 126–127° (7.5 mm.) (yield 64%).

The condensation of the ester with the aryl urea and the subsequent purification were carried out substantially as previously described.[1] The procedure was modified in the case of the dialkylamino compounds, the cold reaction mixture being diluted, extracted with ether when possible, and saturated with carbon dioxide to precipitate the product, which was purified by recrystallization from aqueous alcohol, and usually also from ethyl acetate–hexane. No particular trouble was encountered except with 1-*m*-phenetyl-5,5-ethyl-isoamyl barbituric acid which was very difficult to obtain crystalline.

The barbituric acids are tabulated below. They are all white, crystalline, tasteless compounds, soluble in cold 5% sodium hydroxide solution, practically insoluble in water, slightly soluble to insoluble in petroleum ether, soluble in ether, soluble in alcohol, moderately to readily soluble in benzene, and readily soluble in ethyl acetate. In addition, the dialkylamino compounds dissolve readily in 5% hydrochloric acid. The solvents used for purification are given in the order used. Three or more crystallizations were generally necessary. In the tables the appearance described is that of the bulk specimen, crystallized from the last solvent given. The appearance varies greatly with solvent, etc.

The ureas are the same as those previously used.[1] Dimethylaminophenyl urea and diethylaminophenyl urea were prepared by the action of potassium cyanate on the amine hydrochloride in aqueous solution.

(1) Buck, THIS JOURNAL, **58**, 1284 (1936).
(2) Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929).
(3) Shonle and Moment, THIS JOURNAL, **45**, 243 (1923).
(4) *Cf.* Michael, *J. prakt. Chem.*, [2] **72**, 537 (1905).

hydrate. This crude material contained 96% of the theoretical electropositive chlorine content. When it was distilled at 76–78° (10 mm.) this chlorine content was found to be 99% of theoretical. The distilled product melted at 4–4.5° cor., d^{20}_4 1.544. Since the crude material is sufficiently pure for most purposes, the distillation, which is dangerous, ought to be avoided.

i-Propyldichloramine was prepared by a modification of the above procedures. To an ice-cooled concentrated aqueous solution of 95 g. (1 mole) of *i*-propylamine hydrochloride (prepared *in situ*) was added slowly 2.25 moles of aqueous sodium hypochlorite (prepared by adding chlorine to cold 15% aqueous sodium hydroxide, 1.6 moles hypochlorous acid per liter). Simultaneously with this addition over two to three hours was added 6 *N* hydrochloric acid at such a rate that the acidity was maintained between *p*H 5.6 and 6.6. Brom cresol green and chlor phenol red papers can be used as criteria if the solution is allowed to creep into the paper so as to give an indicator zone ahead of the bleached zone. After two hours' subsequent stirring in the cold, the heavy oil was separated, washed once with 50 cc. cold water, twice with 50-cc. portions of 5% sodium thiosulfate, once with cold water, twice with cold 50% sulfuric acid and finally twice with cold water. The crude yield (97 g., 76% of theoretical) contained 94% of the theoretical electropositive chlorine content. Distillation at 41–43° (15 mm.) resulted in 70% recovery of yellow oil (d^{20}_4 1.165; $n^{23}D$ 1.4572) which contained 99.8% of the calculated electropositive chlorine content.

Anal. Calcd. for $C_3H_7NCl_2$: N, 10.9. Found: N, 10.6 (av.).

The authors are grateful for a grant from the National Research Council, Canada, which helped to defray the expenses of this investigation.

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TORONTO, CANADA RECEIVED FEBRUARY 21, 1947

A Modification of Wenker's Method of Preparing Ethyleneimine

BY PHILIP A. LEIGHTON, WILLIAM A. PERKINS AND MELVIN L. RENQUIST

The most convenient method for laboratory preparation of ethyleneimine is that of Wenker.[1] This is a two-step process involving the preparation of β-aminoethylsulfuric acid from monoethanolamine and sulfuric acid followed by treatment of the ester with alkali. An improved technique is suggested for the first step which involves less effort, gives a better quality of the intermediate ester, and leads to higher yields.

Six moles each of ethanolamine (b. p. 169.5–170.1°) and 95% sulfuric acid are separately diluted with half their weight of water and cooled in an ice-bath. The amine is added slowly to the acid with constant stirring in a round-bottom flask also cooled in an ice-bath. The mixture is then boiled under reduced pressure using a water aspirator attached to the flask. Bumping is prevented by the addition of glass beads and the use of a full flame to maintain vigorous boiling.

When the temperature of the liquid reaches 145°, only enough heat is applied to keep the solution boiling, and when a definite turbidity appears, usually between 155 and 160°, heating is stopped unless the temperature begins to fall. Quite suddenly crystallization takes place, causing the temperature to rise sharply to about 185°. After cooling, the cake is softened with 300 cc. of 95% ethanol, removed from the flask and ground with an additional 400 cc. of ethanol followed by filtering and drying.

The yield is 90–95%. The product is white, showing no evidence of charring as was the case when the heating was carried out in an open vessel according to Wenker's directions. Approximately one hour is required to remove the water from the above quantity of material. While Wenker was able to remove only 75% of the theoretical amount of water, in the above method a trap placed between the flask and aspirator collected virtually 100% of the amount expected.

(1) H. Wenker, THIS JOURNAL, 57, 2328 (1935).

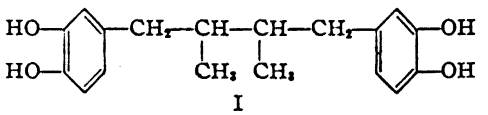
DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD UNIV., CALIFORNIA RECEIVED MAY 5, 1947

A Synthesis of Nordihydroguaiaretic Acid

BY S. V. LIEBERMAN, GEORGE P. MUELLER AND ERIC T. STILLER

Nordihydroguaiaretic acid or 2,3-*bis*-(3,4-dihydroxybenzyl)-butane [4,4¹-(2,3-dimethyltetramethylene)-dipyrocatechol] (I) is of practical interest as an antioxidant used in preserving edible fats and oils.[1] It is obtained for that purpose by the alkaline extraction of dried plants of the species *Larrea divaricata*.[2]

Schroeter and his co-workers first obtained this compound from the dimethyl ether of guaiaretic acid (II) by hydrogenation and subsequent demethylation.[3] The dimethyl ether of guaiaretic acid has since been synthesized by Haworth, *et al.*[4] These two syntheses constitute a proof of the structure of nordihydroguaiaretic acid.



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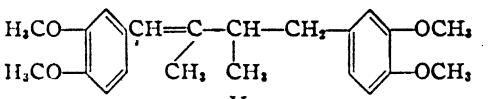
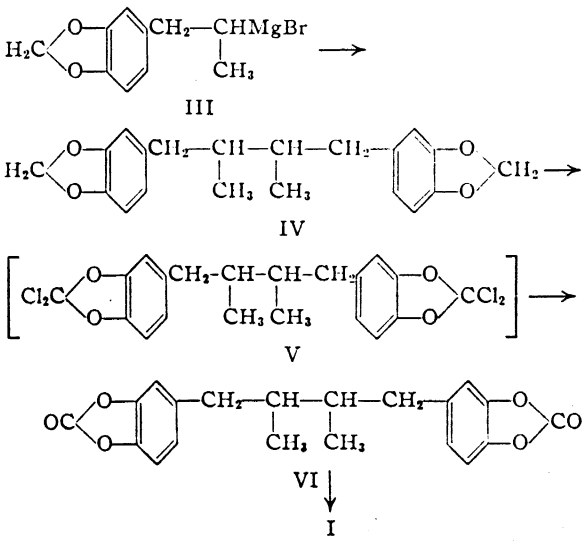


II

The new synthesis described here confirms this structure. The first step involves the coupling of two molecules of 1-piperonyl-1-bromoethane, yielding the corresponding dimethylene ether of nordihydroguaiaretic acid (IV), a compound reported by Orcutt and Bogert as a crystalline solid, m. p. 74°.[5] Apparently a mixture of the diastereoisomers of this compound is produced by the reaction of 1-piperonylethylmagnesium bro-

(1) U. S. Patent 2,373,192; Higgins and Black, *Oil & Soap*, 21, 277 (1944).
(2) U. S. Patent 2,382,475.
(3) Schroeter, Lichtenstadt and Irineu, *Ber.*, 51, 1587 (1918).
(4) Haworth, Mavin and Sheldrick, *J. Chem. Soc.*, 1423 (1934).
(5) Orcutt and Bogert, THIS JOURNAL, 58, 2057 (1936).

mide (III) in ethereal solution with one equivalent of iodine. While treatment with iodine gave a yield of 30%, the use of silver bromide instead of iodine gave a 21% yield. Our product was a heavy oil, b. p. 175–185° (0.1 mm.), having the correct analytical values for the dimethylene ether of nordihydroguaiaretic acid. Attempts to couple two molecules of the bromide with sodium or zinc dust in dry benzene, and with copper–bronze in decalin proved to be unsuccessful.



The dimethylene ether (IV) yielded nordihydroguaiaretic acid (I) by the following series of steps: the dimethylene ether (IV) was converted to the corresponding tetrachloro derivative (V), not isolated, which yielded the dicarbonic ester (VI) on mild hydrolysis; on saponification with acid, the dicarbonic ester (VI) yielded crystalline nordihydroguaiaretic acid (I). This product showed no depression of the melting point when mixed with an authentic sample of optically inactive nordihydroguaiaretic acid.[6]

1-(3,4-Dimethoxybenzyl)-1-bromoethane reacted with magnesium with difficulty and incompletely, yielding only 6% of the coupled product upon treatment with iodine. The phenylmagnesium bromide–cobaltous chloride free radical coupling method of Kharasch was applied.[7] None of the expected tetramethyl ether of nordihydroguaiaretic acid was obtained. The failure here, as compared to the success of this method when applied by Kharasch to the coupling of two molecules of anethole hydrobromide, may be attributed to the inactivity of the halogen in the β-position relative to its activity when adjacent to the benzene ring. The action of copper–bronze in decalin on 1-(3,4-dimethoxybenzyl)-1-bromoethane formed a small amount of heavy oil which was not further identified.

(6) Purchased from Nordigard Corporation, 2536 W. Monroe Street, Chicago 12, Ill.

(7) Kharasch and Kleiman, *ibid.*, **65**, 491 (1943).

Experimental

1-Piperonyl-1-bromoethane.—Safrole, 250 g., and 200 g. of 42% hydrobromic acid were mixed in a sintered disk gas-washing bottle immersed in an ice–salt-bath. A stream of hydrogen bromide was introduced, rapidly at first, and more slowly as saturation was approached. After four hours the gas inlet was removed and the mixture permitted to stand in ice overnight. It was poured into 500 cc. of cold brine. The organic layer was diluted with ether and removed. The ether solution, washed three times with cold brine, was dried with Drierite, then anhydrous magnesium sulfate and distilled. A fraction of 218 g., b. p. 154–158° (13–14 mm.), was collected; yield 62%.

Similarly, 250 g. of methyleugenol and 121 g. of hydrobromic acid gave 326 g. of 1-(3,4-dimethoxybenzyl)-1-bromoethane, b. p. 164–167° (9.5 mm.); yield 89.5%.

2,3-bis-(3,4-Methylenedioxybenzyl)-butane (IV).—A solution of 24.3 g. (0.1 mole) of 1-piperonyl-1-bromoethane in 75 cc. of anhydrous ether was added slowly to a stirred mixture of 2.43 g. (0.1 mole) of magnesium turnings and 50 cc. of ether contained under nitrogen in the conventional Grignard apparatus. A crystal of iodine and local heating initiated the reaction which continued with refluxing by the heat of reaction for thirty minutes. After an additional hour at reflux, the heat was removed and 12.7 g. (0.05 mole) of iodine in 75 cc. of ether added to the solution. The heat of the ensuing reaction caused refluxing to resume; the small amount of unreacted magnesium dissolved quickly. After an hour of heating following this addition, the solution was cooled below 15° and hydrolyzed by the slow addition of 4% hydrochloric acid. The organic material was separated with the aid of ether and dried. A viscous, amber-colored oil, 5.0 g., was collected by distillation, b. p. 175–185° (0.1 mm.); yield 31%.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.50; H, 6.94.

2,3-bis-(3,4-Carbonyldioxybenzyl)-butane (VI).[8]—2,3-bis-(3,4-Methylenedioxybenzyl)-butane, 3.5 g., was dissolved in 15 cc. of toluene and heated at reflux for three hours with 14 g. of phosphorus pentachloride. The reaction mixture was protected from moisture. The amber-colored solution was cooled and poured slowly into 300 cc. of a stirred mixture of saturated sodium carbonate and ice and the white precipitate collected, washed with cold water and dried at 50° *in vacuo;* the yield was 1.2 g. of product, m. p. 165–168°. An additional 0.25 g. was recovered by removing and evaporating the toluene layer. After two recrystallizations from toluene the compound melted at 171.5–173°.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.80; H, 5.08. Found: C, 67.53; H, 5.41.

Nordihydroguaiaretic Acid (I).—The product from the preceding reaction, 0.68 g., was heated at reflux in an atmosphere of nitrogen with 50 cc. of 1 *N* hydrochloric acid in 80% methanol. After two and one-half hours, during which the solid slowly dissolved, the solvent was removed under reduced pressure. The residual oil was taken up in ether and extracted with 15 cc. of a 5% sodium hydroxide–3% sodium hydrosulfite solution. The aqueous layer was separated, made just acid to litmus with dilute hydrochloric acid and permitted to stand; long colorless needles, 0.16 g., separated overnight, m. p. 185.0–186.5°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.52; H, 7.28. Found: C, 71.70; H, 7.43.

A mixture of this compound with a sample of nordihydroguaiaretic acid[6] melted at 185.0–186.5°. Neither the natural nor the synthetic phenol displayed any optical rotation.

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(8) *Cf. Organic Syntheses*, Coll. Vol. II, 1943, p. 549.

product was recovered by steam distillation as a colorless oil. Further purification was effected by steam distillation from an alkaline medium, and on cooling the distillate with ice the substance solidified to a mass of colorless needles, m. p. 25–26°; yield 3.25 g. (90%).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.79; H, 9.14. Found: C, 81.49; H, 9.32.

5-Hydroxy-4,7-dimethylhydrindene (VI).—The above ether (3.25 g.) was refluxed with 25 cc. of glacial acetic acid and 4 cc. of 48% hydrobromic acid for three hours in a nitrogen atmosphere, and on pouring the solution into water the hydroxy compound separated as a pink solid. It was taken up in dilute alkali, the solution was clarified with Norite and acidified, and the dried product was crystallized twice from petroleum ether; yield 2 g. (66%). The substance forms fine colorless needles melting at 111–112°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.32; H, 8.76.

The benzoyl derivative forms colorless plates, m. p. 72–73°, from dilute alcohol.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.80. Found: C, 80.82; H, 6.95.

5-Hydroxy-4,7-dimethyl-6-*p*-nitrobenzeneazohydrindene was obtained by coupling the components in 1% alkali at 0°. A red precipitate separated at once and it was unaffected by rendering the solution acidic and boiling the mixture to coagulate the material. Recrystallized from glacial acetic acid, in which it is sparingly soluble, the azo compound formed brownish-red needles, m. p. 220–222°, dec. It is insoluble in alkali.

Anal. Calcd. for $C_{17}H_{17}O_3N_3$: C, 65.58; H, 5.50. Found: C, 65.72; H, 5.85.

6-Methoxy-5,8-dimethyltetralin.—On condensing *p*-xylyl methyl ether and succinic anhydride with aluminum chloride in benzene solution as described by Clemo, Haworth and Walton,[12] the yield was even lower than that (70%) reported by these investigators, but the general procedure described by Fieser and Hershberg[17] proved very satisfactory. Using 0.2 mole of the ether, 0.21 mole of succinic anhydride, 200 cc. of tetrachloroethane, 50 cc. of nitrobenzene and 0.42 mole of aluminum chloride, stirring at 0° until solution was complete, and allowing the mixture to stand for four days at 0°, β-4-methoxy-2,5-dimethylbenzoylpropionic acid, recovered as usual and crystallized from dilute alcohol, was obtained as colorless crystals, m. p. 130–131°, in 86% yield. The reduction to γ-4-methoxy-2,5-dimethylphenylbutyric acid (m. p. 98–99°) by the Clemmensen–Martin method has been described[18] already. Cyclization was effected according to Clemo, Haworth and Walton[12] in 64% yield.

(17) Fieser and Hershberg, Part IV, in press.
(18) Martin, THIS JOURNAL, 58, 1438 (1936).

7-Methoxy-5,8-dimethyltetralone-1 (6 g.) was reduced by the ordinary Clemmensen method, refluxing for twenty-one hours, and the material extracted with ether after distillation (b. p. 116–125° at 12–13 mm.) was obtained as a solid, m. p. 36–38°; yield 4.25 g. (76%). Crystallization from petroleum ether gave colorless needles melting at 38–39°.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.52. Found: C, 82.36; H, 9.76.

6-Hydroxy-5,8-dimethyltetralin (IX).—For demethylation the ether (4.25 g.) was refluxed with glacial acetic acid (25 cc.) and 45% hydriodic acid (9.75 g.) for three hours. The crude product was precipitated from a clarified solution in dilute alkali and crystallized from petroleum ether, giving nearly colorless needles, m. p. 104–105°, yield 2.45 g. (62%). The substance dissolves in dilute alkali slowly on warming.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.79; H, 9.14. Found: C, 81.78; H, 9.48.

The benzoyl derivative forms very long, slender, colorless needles, m. p. 119–120°, from dilute alcohol.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.38; H, 7.18. Found: C, 81.44; H, 7.26.

6-Hydroxy-5,8-dimethyl-7-*p*-nitrobenzeneazotetralin was obtained by coupling as described above and crystallized from glacial acetic acid, in which it is sparingly soluble. The substance forms bronze-red needles, m. p. 229–231°. It is insoluble in alkali and stable to acids.

Anal. Calcd. for $C_{18}H_{19}O_3N_3$: C, 66.42; H, 5.90. Found: C, 66.50; H, 6.11.

Summary

β-Hydroxy derivatives of hydrindene and of tetralin with one ortho position blocked with a methyl group and the other free have been tested in the coupling reaction to determine if both ortho positions are capable of constituting enolic groups, or if there is any fixation of the bonds in the aromatic nucleus as the result of the spatial requirements of the attached alicyclic rings (Mills–Nixon effect). This test affords a more severe criterion of fixation than that of Mills and Nixon, based upon reactivities, and the results indicate that hydrindene has a rigid bond structure comparable with that of naphthalene, but that tetralin, like all ordinary benzene derivatives, can react in both Kekulé forms.

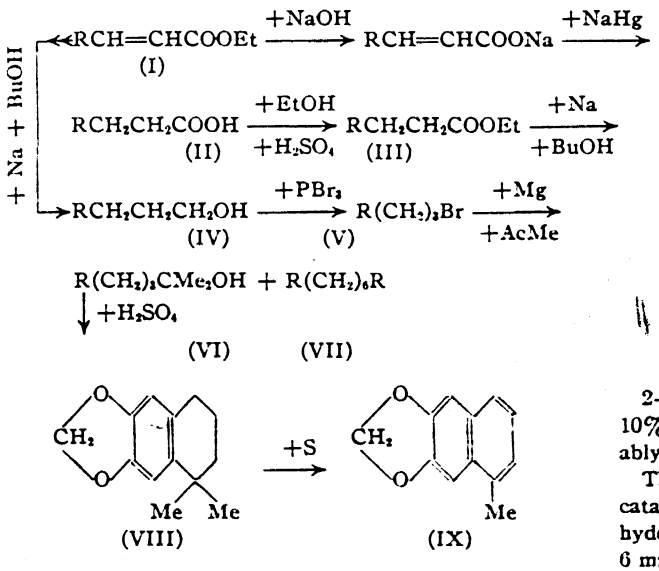
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED AUGUST 12, 1936

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of 1,1-Dimethyl-6,7-methylenedioxytetralin[1]

BY RUBY MURRAY ORCUTT AND MARSTON TAYLOR BOGERT

In continuation of our investigations in the ionene field,[2] and in the cyclodehydration of aromatic alcohols,[3] we have had occasion to synthesize a methylenedioxytetralin by the following steps, in which formulas R = $CH_2(O)_2C_6H_3$—



Experimental

Ethyl Piperonylacetate (III).—Ethyl piperonylideneacetate (I), prepared from piperonal and ethyl acetate, according to Hoering's directions,[4] was saponified by boiling with the calculated amount of 0.1 *N* sodium hydroxide. The solution was cooled quickly, to prevent the crystallization of the sodium salt, and a 10% excess of sodium amalgam was added slowly. When the reduction was complete, the mixture was filtered, the filtrate cooled with ice and acidified with hydrochloric acid. The precipitated piperonylacetic acid was washed, dried, and crystallized from ether, giving a colorless crystalline product, m. p. 87–90°, which did not decolorize a cooled 10% carbon tetrachloride solution of bromine; yield 75–80%.

Lorenz,[5] who prepared this acid by a similar method, differing only in certain details, gave its m. p. as 84°. Kaufmann and Radosević,[6] who obtained it by hydrolysis of its methylamide, also recorded the m. p. as 84°.

Warmed with absolute ethanol and a little sulfuric acid, the acid yielded the ethyl ester as a colorless transparent liquid, of pleasant odor, b. p. 184–185° at 14 mm., which did not decolorize a cooled 10% carbon tetrachloride solution of bromine; yield 83%.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.35. Found: C, 64.94; H, 6.64.

2-Piperonylethanol (IV), prepared from the foregoing ester by reduction with sodium and *n*-butyl alcohol, formed a colorless viscous liquid, b. p. 170–172° at 8 mm., 182–183.5° at 14 mm., 184–186° at 16 mm., and 186–188° at 19 mm.; yield 87%. Cooled to −10°, it slowly congealed to a crystalline mass. When the temperature of this solid was permitted to rise slowly, it began to melt at 28° and was completely liquefied at 29°. The m. p. of 2-piperonylidene ethanol is given in the literature[7] as 78–78.8° (corr.). Hence the product cannot be the unsaturated alcohol.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72. Found: C, 66.30; H, 6.75.

2-Piperonylethanol immediately decolorized a cooled 10% carbon tetrachloride solution of bromine, presumably being promptly oxidized thereby.

This saturated alcohol has been reported[8] as one of the catalytic reduction products of piperonylidene acetaldehyde, although the b. p. recorded (149–150°, uncorr., at 6 mm.) was lower than that given above.

Phenylurethan, m. p. 98–99°.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.72. Found: C, 67.97; H, 5.83.

A more direct and shorter road to the same goal (IV), was the reduction of the ethyl piperonylideneacetate (I) by sodium and *n*-butyl alcohol, as follows:

A 3-necked 2-liter flask, equipped with mercury-sealed stirrer, a reflux condenser, and a dropping funnel, protected with calcium chloride guard tubes, and containing 37.8 g. of sodium and 100 cc. of dry toluene, was heated above the m. p. of the sodium and then allowed to cool during vigorous stirring, so as to obtain the sodium in a finely divided state. To this mixture, there was added, as rapidly as possible, a solution of 36.2 g. of the ester (I) in 100 cc. of *n*-butyl alcohol. There ensued a vigorous reaction, with much foaming. When this subsided, more (150 cc.) *n*-butyl alcohol was added, to dilute the mixture, to aid in keeping the alcoholate in solution, and to react with any unattacked sodium.

The mixture was hydrolyzed by addition of water, the oily layer separated from the aqueous alkaline one, the latter extracted twice with *n*-butyl alcohol and the extracts added to the oily layer. This was distilled at ordinary pressure, to remove the toluene and butyl alcohol, and then under reduced pressure, to isolate the

(1) Presented in abstract before the Division of Organic Chemistry, at the New York meeting of the American Chemical Society, April 23, 1935.

(2) (a) Bogert and Fourman, THIS JOURNAL, **55**, 4670 (1933); (b) Bogert and Apfelbaum, *Science*, [N. S.], **79**, 280 (1934); (c) Bogert, Davidson and Apfelbaum, THIS JOURNAL, **56**, 959 (1934).

(3) (a) Bogert and Davidson, *ibid.*, **56**, 185 (1934); (b) Roblin, Davidson and Bogert, *ibid.*, **57**, 151 (1935).

(4) Hoering, *Ber.*, **40**, 2176 (1907).

(5) Lorenz, *ibid.*, **13**, 758 (1880).

(6) Kaufmann and Radosević, *ibid.*, **49**, 681 (1916).

(7) Bogert and Powell, THIS JOURNAL, **53**, 1609 (1931).

(8) Bogert and Powell, *ibid.*, **53**, 2757 (1931).

piperonylethanol (IV); b. p. 184–186° at 16 mm.; yield 62%.

From the aqueous alkaline layer there was obtained a small amount of piperonylideneacetic acid, $(CH_2O_2)C_6H_3CH{=}CHCOOH$, m. p. 237–238° (from acetic acid), agreeing with that in the literature.

Repeating the above experiment, with amyl in place of butyl alcohol, the results were much the same, except that the initial reaction was more vigorous, the yield somewhat lower (60%), and the by-product piperonylacetic acid, $(CH_2O_2)C_6H_3CH_2CH_2COOH$ (large, colorless crystals, m. p. 84°; m. p. in literature,[6] 84°).

In another series of experiments, replacing the toluene by xylene, the results were less satisfactory. The same alcohol (IV) was obtained and, as by-products, there were recovered both piperonylidene and piperonylacetic acids, in the ratio of 3:1. The former was reduced to the latter, in 80% yield, by sodium amalgam.[6]

1-Bromo-2-piperonylethane (V) could not be secured from the alcohol (IV) by the action of 48% aqueous hydrogen bromide, alone or with the addition of sulfuric acid, because of the decomposition which almost immediately ensued. It was obtained, however, by the following process.

The alcohol (28 g.), contained in a flask well protected from access of any moisture, was congealed in a freezing mixture and phosphorus tribromide (16 g.) added. After a few minutes' standing, the container was removed from the freezing mixture and allowed to come slowly to room temperature. The reaction began gradually, with evolution of hydrogen bromide, and accelerated considerably as the temperature approached that of the m. p. (28–29°) of the alcohol, so that some cooling occasionally was necessary at this point. The crude yellowish-brown product was poured into a mixture of dilute sodium bicarbonate solution and cracked ice, and the bromide (V) extracted with ether. The aqueous layer, containing some of the original alcohol as sodium alcoholate, was acidified and the alcohol recovered. The bromide obtained from the ether extracts, when freshly distilled and pure, was a colorless liquid, b. p. 163–165° at 7.5 mm., $n^{25}D$ 1.5599, but darkened rapidly on exposure to air and light; yield, 50–53%; original alcohol recovered, 20–25%.

Anal. Calcd. for $C_{10}H_{11}O_2Br$: C, 49.38; H, 4.56. Found: C, 49.41; H, 4.87.

1,4-Dipiperonylbutane (VII).—The Grignard reagent was prepared by mixing 48.8 g. of the above bromide, 8 g. of magnesium, and 50 cc. of dry ether, and adding 100 cc. more of dry ether when the reaction was well started. A final warming for an hour completed the reaction. After cooling the mixture to −5°, 14 g. of acetone in an equal volume of dry ether was slowly stirred in, and the stirring continued for a further half hour. It was then poured upon ice acidulated with the calculated quantity of sulfuric acid, extracted with ether, the ether extract dried over anhydrous potassium carbonate and the ether evaporated. As the residue cooled, crystals began to separate, and this separation was greatly hastened by the addition of some 95% ethanol. These crystals were colorless and their m. p. remained constant at 77–78.5° after six crystallizations from alcohol; b. p. about 240° at 3 mm.; yield, about 28%. Their analysis, however, indicated retention of some of the solvent alcohol. They were therefore fused for an hour at 120° and a pressure of 7.2 mm. (m. p. then 78°), and analyzed again.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.58; H, 6.79. Found: C, 73.79; H, 6.65.

2-Methyl-4-piperonylbutanol-2 (VI).—The mother liquors from the crystallization of the dipiperonylbutane (VII) were freed of solvent and distilled at 2 mm. pressure. Two fractions were thus obtained. One boiled at 65–75° and had a safrole odor. The other, b. p. 150–160°, consisted of the nearly pure tertiary alcohol (VI); yield 32%. Purified by two rectifications, it boiled at 145–148° at 2 mm. pressure.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 70.07; H, 8.50.

This alcohol was a very viscous pale yellowish liquid, which congealed to a glass, but did not crystallize, when cooled to −17°. No phenylurethan could be obtained from it, because phenyl isocyanate immediately withdrew the elements of water, with formation of carbanilide.

Attempts to isolate the olefin formed by this dehydration were not very successful, because the repeated rectifications to which it was subjected rearranged it to the tetralin, a change which takes place very easily, as shown by tests with potassium permanganate in acetone solution.

From the residue of the above distillation, more of the dipiperonylbutane was recovered.

1,1 - Dimethyl - 6,7 - methylenedioxytetralin (VIII).—Into 5 g. of vigorously stirred 85% sulfuric acid, there was dropped slowly 4 g. of the above alcohol (VI), maintaining the temperature at 10° or below. After all the alcohol had been added, the stirring was continued for thirty minutes. The mixture was poured upon ice, extracted with ether, to free it from insoluble tarry contaminants, the ether extract washed with dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate, the ether removed, and the residual liquid distilled twice over sodium. The tetralin was thus obtained as a colorless transparent liquid, of camphoraceous odor, b. p. 148–149° at 10 mm.; yield 70%.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.38; H, 7.76.

1 - Methyl - 6,7 - methylenedioxynaphthalene (IX).—Fusion of the tetralin (VIII) with sulfur gave such small yields of the expected naphthalene derivative (IX) that it could be satisfactorily characterized only by its *picrate*, which melted at 134–136°.

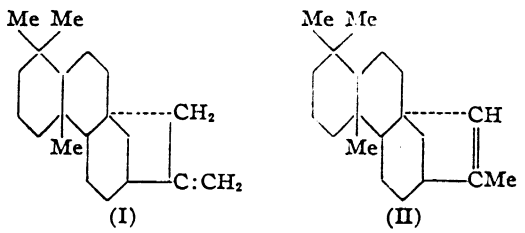
Anal. Calcd. for $C_{18}H_{13}O_9N_3$: N, 10.12. Found: N, 9.91.

Summary

Starting with ethyl piperonylideneacetate, the 1,1-dimethyl-6,7-methylenedioxytetralin has been synthesized by a series of steps analogous to those used by Bogert, Davidson and Apfelbaum[2c] for the preparation of ionene.

NEW YORK, N. Y. RECEIVED AUGUST 10, 1936

Treatment of IX with MeMgI, and decompn. with aq. NH_4Cl and ether extn. gave a cryst. product dehydrogenated to IV (picrate, m. 124°). Similarly II gives on oxidation a glycol $C_{20}H_{34}O_2$ (X), m. 235°, an oxo acid, $C_{20}H_{32}O_3$ (XI), m. 177–8° (semicarbazone, m. 212°), and an oxo acid, $C_{18}H_{28}O_3$ (XII), m. 182° (semicarbazone, m. 230°). XI is isomerized with 4% alc. HCl to an oxo acid, $C_{20}H_{32}O_3$ (XIII), m. 176° (semicarbazone, m. 207°), The mixed-m.ps. of XI and XIII and of their semicarbazones were depressed 10–15°. XI gives a pos. CHI_3 reaction and is dehydrogenated over Se to *1-methyl-7-ethylphenanthrene*, m. 84–5° (styphnate, m. 141–2°; trinitrobenzoate, m. 142–3°), which confirms the presence of the Ac group on C-7. Se dehydrogenation of the reaction product of the Me ester of XI and MeMgX gave a resin which was converted to V on heating over Pd-$BaSO_4$ 3 hrs. at 300–15°. XII gives a neg. CHI_3 reaction. The Me ester of XII with MeMgX gives a resinous soln. which dehydrogenates over Se to IV (picrate, m. 126°; styphnate, m. 152–3°). A MeOH soln. of the mother liquor residues from XI and XII gave on elution from an activated alumina column mixed acids, m. 160–75°, and an oxo acid, m. 215° (semicarbazone, m. 237–8°; 2,4-dinitrophenylhydrazone, m. 284–6°). Uota's (*C.A.* 31, 7416[5]) dicarboxylic acid, $C_{20}H_{30}O_4$, was not prepd. from XI. B. regards the following formulas as the structure of I and II.



(I) (II)

Chas. Burkhard

Attempt at the synthesis of antitubercular drugs analogous to DDT. A. Ercoli. *Farm. sci. e tec.* (Pavia) 2, 54(1947); *Excerpta Med.*, Sect. II, 1, 404–5(1948); cf. *C.A.* 41, 1797*g*.—On the basis of the structural resemblance between the insecticide $(p\text{-}ClC_6H_4)_2SO_2$ and the antitubercular drug $(p\text{-}H_2NC_6H_4)_2SO_2$ and on the fact that the insecticidal action of $(p\text{-}ClC_6H_4)_2CHCCl_3$ (DDT) is enhanced by the presence of the CCl_3 group, which increases the soly. in lipides, the di-Bz deriv. (I) of $(p\text{-}H_2NC_6H_4)_2CHCCl_3$ was prepd. I inhibits the growth of *Mycobacterium tuberculosis* at a concn. of 7–15 mg./l. *in vitro*, and is active against *Staphylococcus aureus*. The compd. $(p\text{-}O_2NC_6H_4)_2CHCCl_3$ shows a remarkable chemotherapeutic action in murine typhus. W. C. Tobie

Stereospecificity of hydrogen migration in the pinacol rearrangement. Kurt Mislow and Maurice Siegel (New York Univ., New York, N. Y.). *J. Am. Chem. Soc.* 74, 1060–1(1952).—Reduction of optically active 2-methylbenzilic acid (I) to $o\text{-}MeC_6H_4CPh(OH)CH_2OH$ (II), followed by acid-catalyzed rearrangement to optically active $Ph(o\text{-}MeC_6H_4)CHCHO$ (III) substantiates that H migration in the rearrangement is stereospecific. 2-Methylbenzil (2.8 g.) in 15 cc. hot EtOH made satd. by the addn. of water, the clear soln. treated with 3 g. KOH, refluxed 1 hr., adjusted to pH 8 with dil. HCl, filtered, the filtrate acidified, the oil shaken with 5% Na_2CO_3, and the soln. decanted and acidified yielded 50–68% I. I (60 g.) and 73 g. cinchonine yielded 68 g. *salt*, m. about 200°, $[\alpha]_D^{25}$ 117° (*c* 1.47, MeOH); the salt with dil. H_2SO_4 yielded I, m. 93–5°, $[\alpha]_D^{25}$ 11.4° (*c* 6.87, EtOH). I (11.2 g.) in 100 cc. Et_2O added dropwise to 2.1 g. $LiAlH_4$ yielded 7.8 g. II, m. 71–2°; I, $[\alpha]_D^{25}$ 7.2° (*c* 4.58, EtOH), yielded II, m. 61–9°, $[\alpha]_D^{25}$ 5.7° (*c* 4.94, EtOH); II (5.2 g.) in 15 cc. water contg. 3 drops H_2SO_4 refluxed 2 hrs. yielded 2.2 g. III, b_1 121–2°, n_D^{25} 1.5901, d_{25} 1.103, *MR* 64.34 (calcd. 64.28), $[\alpha]_D^{25}$ 1.36° (no solvent); 2,4-dinitrophenylhydrazone, m. 181–2° (decompn.). Felix Saunders

α,α-Disubstituted di-acids and their derivatives. II. 2,2-Diphenylglutaric acid and its principal functional derivatives. F. Salmon-Legagneur (Faculté sci., Rennes). *Bull. soc. chim. France* 1952, 994–9; cf. *C.A.* 47, 4868*h*.—Heating 19 g. Ph_2CHCN in 150 ml. C_6H_6 with 5.5 g. $NaNH_2$, then with 25 g. $Br(CH_2)_2CO_2Et$ gives 22 g. crude $Ph_2C(CN)(CH_2)_2CO_2Et$ (I), m. 61° after repeated crystns. from alc. Heating I with KOH gives $Ph_2C(CN)(CH_2)_2CO_2H$ (II), m. 158–9° (from 50% alc.); II Me ester, m. 57°. Slightly warming II in 80–5% H_2SO_4, and pouring over ice gives aq. Na_2CO_3 insol. $Ph_2C(CO.NH.CO.CH_2.CH_2)$ (III), m. 158–9° (from MeOH), insol. in aq. Na_2CO_3, and sol. $Ph_2C(CONH_2)(CH_2)_2CO_2H$ (IV), m. 142–4° (from 50% alc.). III Et ester, m. 143–5°. Heating III and IV 20 hrs. with 40% aq. KOH gives $Ph_2C(CO_2R^1)(CH_2)_2CO_2R^2$ (V) (R^1 = R^2 = H), m. 193–5° (from 40% AcOH). V gives the expd. thermal dissocn. consts. $K_1 = 12.4 \times 10^{-5}$ at 20° and K_2 = 4.1×10^{-6} at 20°. V (R^1 = H, R^2 = Me), m. 110–11° (from MeOH), is prepd. from the di-acid and 10 times its vol. of MeOH and 0.1 its wt. of concd. H_2SO_4; $K = 10.0 \times 10^{-5}$ at 20°. V (R^1 = R^2 = Me), m. 64–5°, prepd. from the di-acid and Me_2SO_4. V (R^1 = Me, R^2 = H) m. 129°, from the di-ester and alc. KOH, $K = 2.2 \times 10^{-5}$ at 20°. V (R^1 = H, R^2 = Et), m. 120–1°, V (R^1 = Et, R^2 = H), m. 107°. Treating V (R^1 = R^2 = H) with AcCl gives Ph_2C(CO.O.CO.CH_2.CH_2) (VI), m. 138–40°. II and $SOCl_2$, followed by NH_3, give $Ph_2C(CN)(CH_2)_2CONH_2$ (VII), m. 130–1°. VII and $SOCl_2$ give $Ph_2C(CN)(CH_2)_2CN$, m. 71–2°. Heating VI with $PhNH_2$ in C_6H_6 yields Ph_2C(CO.CH_2.CH_2), m. 150–1°. III. **The 2-phenyl-2-alkyl(or phenylalkyl)glutaric acids, and their principal derivatives.** F. Salmon-Legagneur and C. Neveu. *Ibid.* 1953, 70–5.—$PhCR(CN)(CH_2)_2CO_2H$ (I) are prepd. in 50–60% yields by heating PhCHRCN and $NaNH_2$ 2 hrs. in C_6H_6, with $Br(CH_2)_2CO_2Et$ and sapong. with alc. KOH. The following I were prepd. (R and m.p. given): Me, 77° (from CCl_4); Et, 92–3°; Pr, 63–5°; $PhCH_2$, 156°. Heating I with 85% H_2SO_4 1–2 min. gives almost quant. yields of the following $PhCR(CONH_2)(CH_2)_2CO_2H$ (II) [R and m.p. (from 30% alc.) given]: Me, 167–8°; Pr, 196–7°. I (R = Et) and 85% H_2SO_4 gives 70% II (R = Et) m. 157–8°, and 30% PhCR(CO.$(CH_2)_2$.CO.NH.CO) (III, R = Et) as hydrate, m. 68–9°; anhyd. m. 83–4° (from ether). II (R = Me or Pr) and 22 Bé. HCl give III (R = Me, m. 105°; Pr, m. 96–8°). I (R = $PhCH_2$) and 85% H_2SO_4 give only III (R = $PhCH_2$), m. 153–4°, which warmed with *N* NaOH yields II, m. 209–10°. Refluxing II or III or their mixt. 25–30 hrs. with 40% aq. KOH and adding HCl gives 60–70% yields $PhCR(CO_2H)CH_2CH_2CO_2H$ (IV) (R = Me), m. 130° (from ether-petr. ether) and $PhCMe(CO_2H)CH_2CH_2CO_2Me$, m. 83–4°. The following IV (R and m.p. given) were prepd.: Et, 130–2°; Pr, 112–13°; $PhCH_2$, 166°. Boiling IV with AcCl or Ac_2O gives the following PhCR(.CH_2.CH_2.CO.O.CO) (V) (R and m.p. given): Me, 77–8°; Et, Pr, oils; $PhCH_2$, 116–17°. Treating V (R = Me or Et) with $PhNH_2$ gives anilides (R = Me, m. 136°; Et, m. 171°) of uncertain structure which on heating with AcCl give PhCR(.CH_2.CH_2.CO.NPh.CO) (VI) (R = Me, m. 163°; Et, m. 115–17°; $PhCH_2$, m. 141–2°).

A new reaction of aliphatic diazo compounds. W. R. Bamford and T. S. Stevens (Univ. Sheffield, Engl.). *J. Chem. Soc.* 1952, 4675–8.—Aliphatic diazo compds. with some tertiary amines liberate N and give a base. A possible mechanism for the reaction is discussed. In each expt. the diazo compd. was added portionwise to the base at such a temp. (100–50°) that a steady reaction was maintained without outside heating. The following expts. are reported [diazo compd. used, base used, product, yield (%)]: *9-diazofluorene* (I), *N,N*-dimethyl-9-fluorenamine (II), *9-dimethylamino-9,9′-bifluorene*, m. 214–16° (picrate, m. 208–9°), 45; I, $PhCH_2NMe_2$ (III), 9-benzyl-9-(dimethylamino)-fluorene, 30; I, Ph_2CHNMe_2 (obtained in 94% yield from Ph_2CHBr, Me_2NH in $MeNO_2$), 9-dimethylamino-9,9′-bifluorene,—; Ph_2CN_2 (IV), II, 9-(α-dimethylaminobenzyl)-fluorene, m. 164° (picrate, m. 188–9°), 40; $PhMeCN_2$, III, $PhCOCH(CH_2Ph)NMe_2$, poor yield, mostly recovered III; $PhBzCN_2$, III, $Ph_2C{:}CO$,—; N_2CHCO_2Et, II, trace of amphoteric material, m. 205–10°; IV, $PhCH_2SMe$, indecisive results; IV, $PhCH_2OMe$, [Ph(MeO)CH]$_2$, and $(Ph_2CH)_2$, —. *4-(9-Fluorenyl)morpholine*, m. 149° [HBr salt, m. 241° (decompn.)], was prepd. from 9-bromofluorene and morpholine in Et_2O 15 hrs. 9-Bromo-2-nitrofluorene (V) with II in C_6H_6 gives *9-dimethylamino-2′-nitro-9,9-bifluorenyl*, 224° (decompn.) (picrate, m. 204–6°). Similarly V and III

give *9-benzyl-9-dimethylamino-2-nitrofluorene*, m. 174° (picrate, m. 235–8° (decompn.)). K. C. Schreiber

Some compounds related to hexestrol. D. A. Forss, W. Freund, and E. R. Stove (Univ. Melbourne, Australia). *J. Chem. Soc.* 1952, 5038–9.—*3,4-Diphenyl-2-hexanone*, m. 127°, is prepd. from EtCHPhCHPhCN and MeMgI in Et_2O. *β-(p-Methoxyphenyl)-α-phenylvaleronitrile* (I), m. 122°, is similarly prepd. from *p*-$MeOC_6H_4CH{:}C(CN)Ph$ (obtained from *p*-$MeOC_6H_4CHO$ and $PhCH_2CN$) and EtMgBr by the Soxhlet technique. Further reaction of I with MeMgI by the Soxhlet technique yields *4-(p-methoxyphenyl)-3-phenyl-2-hexanone*, m. 109–10°. *α,β-Bis(p-methoxyphenyl)valeronitrile*, m. 130–1°, obtained from $RCH{:}C(CN)R$ (R = *p*-$MeOC_6H_4$) and EtMgBr, yields on hydrolysis with concd. HCl both *α,β-bis(p-hydroxyphenyl)-valeric acid*, m. 188–91°, and another compd., m. 234–44°, which with AcCl gave *α,β-bis(p-acetoxyphenyl)valeric acid*, m. 215–16°. K. C. Schreiber

A simple synthesis of highly substituted ethanes. III. The probable reaction mechanism. E. Ziegler, W. Kaufmann, and N. Kreisel (Univ. Graz, Austria). *Monatsh.* 83, 1274–81(1952); cf. *C.A.* 47, 2728*a*.—$ClCH_2CO_2Ph$ is prepd. from $ClCH_2CCl_2OPh$ instead of $ClCH{:}CClOPh$ as erroneously reported in part II of this series (loc. cit.). *o*-Cresol (I) (37 g.) with 7.7 g. Na heated 2 hrs. in an autoclave at 145–50° with 100 cc. $Cl_2C{:}CHCl$ gave *o-MeC₆H₄OCCl:CHCl*, (II), b_{11} 105–6°. HCl gas passed 12 hrs. through 13 g. II gave 11 g. *o-MeC₆H₄OCCl₂CH₂Cl* (III), b_{13} 134–6°. $PhOCCl_2CH_2Cl$ (IV) (2 g.) and 3.8 g. I heated 3 hrs. at 50° and the melt triturated with Me_2CO, gave 3 g. *1,1,2,2-tetrakis(3-methyl-4-hydroxyphenyl)ethane* (V), m. 276–8° (from dil. alc. or dil. PrOH). II (sometimes with $AlCl_3$) or III (without $AlCl_3$) with I gave V. V in EtOH with Me_2SO_4 and NaOH gave the *tetra-Me ether* (VI), m. 159° (from dil. MeOH or EtOH or dil. HOAc). VI (1 g.) added in small amts. to 15 cc. hot HOAc contg. 1.4 g. CrO_3, and the mixt. heated 1 hr. and dild. with 40 cc. H_2O, gave *[3,4-Me(MeO)C₆H₂]₂CO*, m. 113° (from dil. alc.). II (2.6 g.), 3 g. PhOH, and some $AlCl_3$ warmed 1.5 hrs. to 40° and the residue triturated with Me_2CO gave 1.2 g. *1,1,2-tris(p-hydroxyphenyl)-2-(3-methyl-4-hydroxyphenyl)ethane* (VIII), m. 254° (from dil. Me_2CO or MeOH); *tripyridinium salt*, m. 145° (from C_5H_5N); VIII *tetra-Me ether*, m. 137° (from dil. alc. or HOAc). III and PhOH gave VIII. *$[(p\text{-}HOC_6H_4)_2CH]_2.4C_5H_5N$* m. 190°. V and *1,1,2,2-tetrakis(3,5-dimethyl-4-hydroxyphenyl)ethane* (IX) gave no pyridine salts. IV (4 g.), 8.8 g. 2,6-xylenol (X), and a small amt. of $AlCl_3$ warmed 4 hrs. at 50–60°, the mixt. triturated with Me_2CO, and the solid (66%) heated several times with HOAc gave a colorless, quite difficultly sol. *[3,5,4-Me₂(HO)C₆H₂]₂CH* (IX), plates from Me_2CO-H_2O, long needles from dioxane-H_2O, needles from C_5H_5N-H_2O, m. 338°; *tetra-Me ether* (XI), needles from dil. HOAc or alc., m. 211.5°; *tetraacetate* (XII), rods from alc., m. 297°. The HOAc soln. from the purification of IX with H_2O gave 5–25% vermilion needles of 2,6-dimethyl-4-[1,2,2-tris(4-hydroxy-3,5-dimethylphenyl)ethylidene]-2,5-cyclohexadien-1-one (XIII), m. 307° (decompn.) (clusters contg. 1 mol. HOAc, from HOAc), m. 319° (solvent-free crystals from C_5H_5N), sol. in dioxane, PhMe, $PhNO_2$, insol. in Et_2O, $CHCl_3$, and CCl_4. III, X, and $AlCl_3$ gave XIII. IX (1 g.) and 0.4 g. anhyd. $FeCl_3$ in 150 cc. HOAc warmed 4 hrs. at 90° gave 0.3 g. XIII. XIII kept 30 min. with Zn dust in HOAc and the soln. acidified and concd. gave IX. XIII (0.2 g.) in 25 cc. HOAc heated 1 hr. at 150° with anhyd. NaOAc, the soln. dild. with H_2O, and the ppt. (0.23 g.) taken up in dioxane and treated with a little H_2O, gave XII; addn. of more H_2O gave XIII *triacetate*, needles from dioxane-H_2O, m. 291.5°. XIII with Me_2SO_4 gave only XI. X and $PhOCCl{:}CHCl$ or IV reacted only in the presence of $AlCl_3$ and gave a product, m. 215°, contg. 14.3% Cl, of unknown structure. A mechanism is proposed. Jane C. Aycock

Syntheses of 3,4-diphenylhexane derivatives. II. Syntheses of 3,4-bis(*p*-methoxyphenyl)hexane, and 3,4-bis(3-methyl-4-methoxyphenyl)hexane. Shobun Tanabe and Sadao Onishi (Gohei Tanabe & Co., Tokyo). *J. Pharm. Soc. Japan* 73, 38–41(1953); cf. *C.A.* 45, 6174*h*.—$MeCH{:}CHCHEtOH$ (I) (6 g.) and 16.9 g. PhOMe (II) treated dropwise with 3 g. concd. H_2SO_4, the mixt. heated 6.5 hrs. at 13–18°, let stand 15.5 hrs., the product poured into water, the oily layer extd. with Et_2O, and the ext. distd. give 8.75 g. (76.6%) *p*-$MeOC_6H_4CHEtCH{:}CHMe$ (III), b_4 112–13°, and 9.8 g. recovered II. Oxidizing 1 g. III in 20 ml. 5% NaOH with 50 ml. 4% $KMnO_4$, adding 3 g. more $KMnO_4$, filtering the prod., concg. the filtrate, and acidifying with HCl give *p*-$MeOC_6H_4CO_2H$, needles, m. 184.3°. That III has 1 double bond is proved by the decolorization of 5% $KMnO_4$ by III in Me_2CO or of Br in CS_2 or by the absorption of the calcd. amt. of H on catalytic reduction. III (1.9 g.), 7.1 g. 74% HCO_2H, and 6.7 g. Me_2CO treated with 2.3 g. 31% H_2O_2, heated 7 hrs. at 40–5°, let stand 1 day at 25–35°, the excess H_2O_2 decompd. with KI, the liberated iodine removed with $Na_2S_2O_3$, and the residue hydrolyzed 1 hr. at 100° with 10% KOH gives an oil, 1.7 g. of which heated in 15 ml. C_6H_6 with 4 g. $(AcO)_4Pb$, gives AcH. III (4.1 g.) and 6 g. I treated with 3 g. concd. H_2SO_4, let stand 7 hrs. at 10° and 16.5 hrs. at room temp., the product poured into ice water, the oily layer extd. with Et_2O, and the ext. distd. give 2.6 g. *(p*-$MeOC_6H_4CHEt)_2$ (IV), b_{2-3} 180–90°, plates, m. 142–2.5° (from abs. alc.). Similarly, 5 g. I, 10 g. *o*-MeC_6H_4OMe (V), and 2 g. concd. H_2SO_4, allowed to react 6.5 hrs. at 20–3° and 15.5 hrs. at room temp., give 7.9 g. (74.8%) 3,4-Me(MeO)$C_6H_4CHEtCH{:}CHMe$ (VI), b_6 122°; 9 g. VI, 9 g. V, and concd. H_2SO_4, kept 7 hrs. at −2° to −3°, 15.5 hrs. at room temp., the product poured into water, the oily layer extd. with Et_2O and the ext. distd. give 7.5 g. of a fraction b_2 175–95°; recrystn. from Et_2O-EtOH gives 2.9 g. (25.8%) $[3,4\text{-}Me(MeO)C_6H_3CHEt]_2$ (VII), m. 124–5.5°. **III. Syntheses of the alkyl derivatives of 3,4-bis(*p*-methoxyphenyl)butane. 2.** *Ibid.* 41–5.—II (31 g.), 8 g. $MeCH{:}CHCHMeOH$ (XII), and 18 g. 97% H_2SO_4, heated 13.7 hrs. at 25°, let stand 17 hrs. at 15°, 30 g. water added, the oily layer extd. with Et_2O, and the ext. distd. give 11.2 g. of a fraction, b_3 190–200°, recrystn. of which from alc. give 1.3 g. (4.9%) *p-(p*-$ROC_6H_4CHEtCHMe)C_6H_4OR$ (VIII, R = Me) (IX), plates, m. 106–8°; demethylating 0.5 g. IX with 17 g. HI (d. 1.69) and 2 ml. AcOH 2 hrs. at 135–40°, cooling, filtering, and recrystg. from dil. AcOH give a quant. yield of (VIII, R = H) (X), needles, m. 186–7°; refluxing 0.25 g. X, 3 g. Ac_2O, and 0.2 g. AcONa, pouring the product into water, and recrystg. from alc. give 0.33 g. (VIII, R = Ac) (XI), m. 120–1°; XII (23 g.) and 45.5 g. II, treated 7 hrs. at 13° with 12.5 g. concd. H_2SO_4, let stand overnight, the product poured into water, extd. with Et_2O, and the ext. distd. give 35.8 g. (76.4%) *p*-$MeCH{:}CHCHMeC_6H_4OMe$ (XIII), b_{10} 110–16°; or treating 3.1 g. XIII and 4.1 g. II, and 2.2 g. concd. H_2SO_4 6.5 hrs. at 10°, letting the mixt. stand overnight, pouring into water, extg. with Et_2O, and distg., the ext. give 0.29 g. (5.8%) IX, m. 106–8°; 6.1 g. $MeCH{:}CHCH(OH)CH_2CH_2Me$ (XIVA), 14 g. II, and 14 g. concd. H_2SO_4 kept 14.3 hrs. at 23–5°, let stand overnight, poured into water, extd. with Et_2O, and the ext. distd. give 6.2 g. a fraction b_2 185–210°, recrystn. of which from abs. alc. gives 0.65 g. (3.89%) *p-(p*-$ROC_6H_4CHEtCHPr)C_6H_4OR$ (XIV, R = Me) (XV), leaves, m. 113–14°; demethylation of 0.5 g. XV with 7.5 ml. AcOH and 10 ml. 57% HI 2 hrs. at 135–40° and recrystn. of the product from alc. gives a quant. yield of (XIV, R = H) (XVI), needles, m. 170–3°, and acetylation of 0.5 g. XVI with 5 g. Ac_2O and 1 g. AcONa 30 min. at 100°, decompn. of the Ac_2O with water, and recrystn. of the product from dil. alc. give 0.53 g. (87%) (XIV, R = Ac) (XVII), m. 109–11°; 8.2 g. XIVA and 18.5 g. II, kept with 3.5 g. concd. H_2SO_4 7 hrs. at 10–20° and overnight at room temp., and the product worked up as usual give 12.1 g. (81.8%) *p*-$MeOC_6H_4CHPrCH{:}CHMe$ (XVIII), b. 115–18°; 4 g. XVIII, 7 g. II, and 6.3 g. concd. H_2SO_4 kept 8.7 hrs. at 12–6° and overnight at room temp. and the product treated as above give 0.29 g. (4.7%) XV, m. 113–14°; 32.4 g. II, 12.8 g. $MeCH{:}CHCHBuOH$ (XIX), and 18 g. concd. H_2SO_4 kept 18 hrs. at 23–5° and overnight at room temp., and the product treated as above gave 12.2 g. product (XXA), b_5 210–20°; 8 g. XXA demethylated with 46 g. 57% HI and 20 ml. AcOH by heating 2 hrs. at 135–40°, poured into water, and extd. with Et_2O give 6 g. *p,p'*-di-OH analog (XXB) of XXA; reaction of 3.2 g. XXB in 45 ml. 10% NaOH with 15 ml. BzCl and recrystn. of the product from abs. alc. give 0.9 g. *p-(p*-$BzOC_6H_4CHBuCHEt)C_6H_4OBz$ (XX), m. 179–83°; 7.2 g. XIX, 19.4 g. II and 5.3 g. concd. H_2SO_4 kept 6 hrs. at 10° and overnight at 10°, poured into water, extd. with Et_2O, and the ext. distd. give 8.1 g. (65%) *p*-$MeOC_6H_4CHBu{:}CHCHMe$, b_3 127–30°. **IV. Syntheses of the alkyl derivatives of 3,4-bis(*p*-methoxyphenyl)butane. 2.** *Ibid.* 46–8.—*p*-$MeCH{:}CHCHEtC_6H_3OMe$ (XXI) (4 g.), 7 g. *o*-MeC_6H_4OMe and 3.9 g. concd. H_2SO_4 kept 7 hrs. at 20–30° and overnight at room temp. and the product treated as above give $[3,4\text{-}Me(RO)C_6H_3CHEt]_2$ (XXII, R = Me) (XXIIA); reducing 0.5 g. XXIIA with 10 g. 57% HI and 5 ml. AcOH 2

hrs. at 135–40°, pouring the product into water, extg. with Et_2O, taking up in 10% NaOH, and acidifying give 3 g. (XXII, R = H) (XXIIB); 0.5 g. XXIIB in 5 ml. 10% NaOH and 1 ml. BzCl shaken well, and the product washed with water and recrystd. from alc. give 0.1 g. (XXII, R = Bz) (XXIII), needles, m. 175–8°; 3 g. *p*-MeCH:CHCHMeC$_6$H$_4$OMe (XXIV), 5 g. *o*-MeC$_6$H$_4$OMe, and 2.7 g. concd. H_2SO_4 kept 7 hrs. at 10–20° and overnight in ice, and the product poured into water and treated as usual give 2.3 g. oily 3,4-Me(RO)C$_6$H$_3$CHEtCHMeC$_6$H$_3$(OR)Me-4,3 (XXV, R = Me) (XXVI), b_2 195–200°; demethylation of 2.3 g. XXVI with 23 g. HI and AcOH by heating 1 hr., pouring into water, extg. with Et_2O, taking up in 5% KOH, acidifying with H_2SO_4, extg. with Et_2O, and distg. the ext. give 1.75 g. oily (XXV, R = H) (XXVA); 1.75 g. XXVA in 10% NaOH shaken with 10 ml. BzCl and the product recrystd. from alc. give 0.3 g. (XXV, R = Bz), m. 179–81°. *p*-MeOC$_6$H$_4$-CHPrCH:CHMe (4 g.), 6.5 g. *o*-MeC$_6$H$_4$OMe, and 1.3 g. concd. H_2SO_4 kept 7.5 hrs. at 10–20° and 16 hrs. at room temp. and the product treated as usual give 3.7 g. 3,4-Me(RO)C$_6$H$_3$CHEtCHPrC$_6$H$_3$(OR)Me-4,3 (XXVI, R = Me) (XXVIA), b_2 190–205°; 4.2 g. XXVIA, 46 g. 57% HI and a small amt. of AcOH, heated 2 hrs. at 135–40°, give 3.2 g. (XXVI, R = H) (XXVIB); 3.2 g. oily XXVIB and 15 ml. BzCl give 0.9 g. XXVI (R = Bz), m. 180–2° (from alc.). V. Condensation of alkyl-3-butene-1-ols with anisole. *Ibid.* 49–51.—CH_2:$CHCH_2OH$ (6 g.), 30 g. C_6H_6, and 10 ml. 92% H_2SO_4 kept 17 hrs. at 22–4° and 31 hrs. at room temp., the product poured into water, extd. with Et_2O, and the ext. washed with 10% NaOH and water, dried with $CaCl_2$, and distd. give 2 g. $PhCH_2CH$:CH_2; tribromide, m. 124.5–5°. Into *p*-MeOC$_6$H$_4$CHRCH:CHMe (XXVII) (2 g.) in 10 ml. $CHCl_3$ cooled with ice, $CHCl_3$ is passed in O contg. 5% O_3 for 1.5 hrs., the $CHCl_3$ removed, and the residue heated with 1 ml. water, sepg. into aq. and oily portion. The aq. portion is tested by paper chromatography; the product from XXVII is AcOH when R = Me, AcOH and $EtCO_2H$ when R = Et, AcOH and $PrCO_2H$ when R = Pr, and AcOH and $BuCO_2H$ when R = Bu. K. Kitsuta

Synthesis of 2,3-dipiperonylbutane. Yoshiaki Sakakibara (Yokohama Natl. Univ.). *J. Chem. Soc. Japan*, Pure Chem. Sect. 73, 235–6(1952).—Adding 25 g. cold safrole dropwise to 100 g. HBr (d. 1.8) at 0°, stirring 12 hrs., pouring into ice-salt, extg. with ether, and distn. gave 1-piperonyl-1-bromoethane (4-(2-bromopropyl)-1,2-methylenedioxybenzene) (I) in quant. yield. By the Grignard reaction with anhyd. $CoCl_2$ as catalyst (cf. Wilds and McCormack, *C.A.* 43, 3812*f*) I gave 14% 2,3-dipiperonyl butane (Orcutt and Bogert, *C.A.* 30, 8202[4]). K. Nakanishi

The condensation of biacetyl with substitutes benzaldehydes and with chloral. Hermann Schlenk (Univ. Würzburg, Ger.). *Chem. Ber.* 85, 901–4(1952); cf. *C.A.* 43, 187*a*.—Ac_2 condenses with aldehydes in the presence of piperidine (I) acetate, as described earlier, giving the following cinnamils, (*R*C$_6$H$_4$*CH:CHCO*)$_2$ (II), in 5–21% yield: *1,6-bis(p-chlorophenyl)-1,5-hexadiene-3,4-dione* (II, R = *p*-Cl), deep yellow crystals, m. 217°; *p-Br analog*, deep yellow, m. 225–6°; *o-MeO analog*, light orange, m. 177°; *p-isomer*, light orange, m. 168°; *o-EtO analog*, light orange, m. 120–1°; *3,4-CH$_2$O$_2$* analog, red-orange, m. 255°. Adding 1.8 g. I to 14.7 g. CCl_3CHO, 4.3 g. Ac_2, and 1.7 g. AcOH with cooling, and keeping the mixt. 2 weeks give 5.5 g. [*Cl$_3$CCH:CHC(OH)*$_2$]$_2$ (III), fine white needles, subliming 115–25°/0.1 mm., decompg. 199–200°. Heating 1.9 g. III 2 hrs. at 130° with 5 g. PCl_5 and 15 cc. $POCl_3$, pouring the mixt. on ice, and extg. with ether give 21 mg. *Cl$_3$CCH:CHC(OH)$_2$COCH$_2$CHClCCl$_3$*, cubelike crystals, m. 105–6°. Heating 3 g. III in 40 cc. AcOH with 15 cc. perhydrol 16 hrs. on a water bath and evapg. the mixt. *in vacuo* give 64 mg. $Cl_3CCH(OH)CH_2CO_2H$, m. 115°. F. E. Brauns

Polyyne compounds. III. A new synthesis of diphenyltetraacetylene. Masazumi Nakagawa, Akihide Nakamura, and Toshishige Inui (Osaka Univ.). *J. Chem. Soc. Japan*, Pure Chem. Sect. 73, 141–3(1952); cf. *C.A.* 46, 6603*b*; 47, 2740*e*.—PhC:CCHO (16.5 g.) in 40 cc. Et_2O added in 2 hrs. to (BrMgC:)$_2$ from C_2H_2 and EtMgBr (from 4.8 g. Mg and 22 g. EtBr), stirred 4 hrs., heated 1 hr. at 35°, left overnight, treated with stirring with 9 g. NH_4Cl in 25 cc. H_2O, the ether layer sepd., the residue extd. with ether, the combined ether solns. distd. *in vacuo*, and the solid residue kneaded with C_6H_6-petr. ether (3:1) and filtered yielded crude crystals, m. 130–2° (repeated recrystn. from the same solvent gave 6 g. product (I), m. 134–5°), and the filtrate yielded 3.2 g. of other crystals (II), m. 119–21° (121.5–2.5° after recrystn.); I and II are the *meso*- and *dl*-forms of [PhC:CCH(OH)C:]$_2$. To 2.6 g. II in 100 cc. C_6H_6-benzine (2:1) was added 4.1 g. PCl_5 portionwise during 1 hr. at 25° with stirring, the mixt. stirred 2.5 hrs. at 30–5°, poured onto ice, the aq. layer extd. with ether, the org. layer and the ether soln. combined, washed with aq. $NaHCO_3$ and H_2O, dried with $MgSO_4$, the solvent removed *in vacuo*, the residue extd. with 120 cc. petr. ether, and the petr. ether removed *in vacuo* to yield 3 g. crude [PhC:CCHClC:]$_2$ (III), pale yellow oil. I similarly gave III. III (3 g.) in 70 cc. ether added dropwise in the course of 2 hrs. to $NaNH_2$ (from 0.6 g. Na and 120 cc. liquid NH_3), the mixt. stirred 1 hr., the NH_3 evapd., the residue treated with 70 cc. ether and 70 cc. H_2O, filtered, the ether layer dried with $MgSO_4$, the ether removed *in vacuo*, the remaining crystals extd. with petr. ether at 45°, the petr. ether removed *in vacuo*, activated C added, and the product recrystd. from petr. ether yielded 0.57 g. [PhC:CC:C]$_2$, yellow needles, m. 113–14°; $\lambda_{max.}$ (log ϵ) at 397 (4.33), 366 (4.54), 340 (4.70), and 320 (4.31) mμ. IV. The synthesis of diphenylpentaacetylene. Masazumi Nakagawa and Toshishige Inui. *Ibid.* 143–5.—(HC:C)$_2$ (10 g.) in 150 cc. ether cooled to −60° added with vigorous stirring to EtMgBr (prepd. from 9.6 Mg and 44 g. EtBr in 75 cc. ether and cooled to −20°), the mixt. stirred 1 hr., boiled 30 min.; cooled with ice, 37.5 g. PhC:CCHO in 90 cc. ether added, the whole left overnight, boiled 30 min. with stirring, treated with 24 g. NH_4Cl and 61 cc. H_2O, the ether layer sepd., 2/3 of the ether removed at 45°, and the rest *in vacuo* (removals of solvents *in vacuo* were all carried out in a stream of H), and the residue kneaded with a little C_6H_6-PhMe (1:1) and filtered yielded crude crystals, decompn. 139° [repeated soln. in C_6H_6 at 50° and pptn. with petr. ether gave [PhC:CCH(OH)C:C]$_2$ (I), m. 144–5° (decompn.)], and, from the filtrate, other crystals (stereoisomer of I), decomp. 107–11.5° (m. 114.5–16° after purification); the combined yield of I and the stereoisomeric mixt. (II) was 15.9 g. II, treated with PCl_5 as described in part III, gave isomeric (PhC:CCHClC:C)$_2$ (III), m. 71–6° (decompn.) and 61–4° (decompn.), both very unstable, changing to a black tar. Crude III (4.2 g.) in 350 cc. ether added in a stream of H during 7 hrs. to $NaNH_2$ (from 0.8 g. Na and 450 cc. liquid NH_3) cooled with solid CO_2, the mixt. stirred 30 min., the NH_3 evapd., 100 cc. ether and 250 cc. H_2O added, the ether layer dried with $MgSO_4$ evapd. *in vacuo*, the residue extd. with petr. ether, and the ext. cooled with solid CO_2 yielded 0.54 g. (PhC:CC:CC:)$_2$, orange-yellow needles, m. 167–8°, $\lambda_{max.}$ (log ϵ) 431 (4.21), 397 (4.42), 268 (4.41), and 343 (4.36) mμ. (HC:C)$_2$ could be obtained in 80% yield by dropping (CH$_2$ClC:)$_2$ to a stirred soln. of 43 g. NaOH in 60 cc. H_2O kept at 130–5° in a stream of H. K. Nakanishi

The catalytic dehydrogenation of 5-substituted 1,2,3,4-tetrahydronaphthalene derivatives. Melvin S. Newman and Theodore S. Bye (Ohio State Univ., Columbus). *J. Am. Chem. Soc.* 74, 905–8(1952); cf. *C.A.* 44, 2961*b*.—All m. ps. cor. Purified 1-C$_{10}$H$_7$CO$_2$Et (1920 g.) hydrogenated as a 20% soln. in EtOH over Raney Ni at 50 atm. and 130–50° gave 1532 g. hydrogenated ester (I). I (365.7 g.) sapond. with alc. KOH yielded 283 g. *5,6,7,8-tetrahydro-1-naphthoic acid* (II), m. 150.7–1.9°. Other fractions of I (contg. some 1,2,3,4-tetrahydro-1-naphthoic acid) yielded 261 g. II, m. 150–1.5° (total yield 32.2%); *Me ester* (III) $b_{0.4-1.0}$ 93.5–6.5°, n_D^{25} 1.5431. III (110 g.) in 800 cc. Et_2O added dropwise to 13.5 g. $LiAlH_4$ in Et_2O yielded 91.5 g. of the *1-methanol* (IV), $b_{0.4-1.0}$ 105–7°; *1-naphthylurethan*, m. 136.7–7.7°; *acetate* (V), $b_{0.4-0.8}$ 102°, n_D^{25} 1.5325. II (20 g.) in 800 cc. Et_2O slowly added to 500 cc. Et_2O contg. 12.2 g. Li and 114 g. MeI the mixt. treated with water, and the neutral fraction distd. yielded 19.5 g. *5,6,7,8-tetrahydro-1-acetonaphthone* (VI), $b_{0.4-1.0}$ 95.5–9°, n_D^{25} 1.5550; *semicarbazone*, m. 221.5–3.5° (decompn.). IV (31.5 g.), 15.3 g. $SOCl_2$, pyridine, and 35 cc. PhMe treated slowly with 23 g. $SOCl_2$ and the mixt. heated 12 hrs. on the steam bath yielded 80% *chloride* (VII), $b_{0.4-1.0}$ 88–92°, m. 50–50.5°. The Grignard reagent from 30 g. VII added during 75 min. to 36 g. Ac_2O in 100 cc. Et_2O at −78° yielded 20.4 g. *1-(5,6,7,8-tetrahydro-1-naphthyl)-2-propanone* (VIIA), $b_{0.4-0.7}$ 115–19°, n_D^{25} 1.5496; *semicarbazone*, m. 214.8–17°. $AcCH_2CO_2Et$ (36.5 g.) added rapidly to 70 cc. abs. EtOH contg. 3.23 g. Na, then 25.3 g. VII in 90 cc. warm abs. EtOH, the mixt. heated 1 hr., 1–3 drops AcOH added, the soln. filtered, the filtrate evapd., the residual *ester* stirred overnight at room temp. with 280 cc. 10% NaOH, then 3 hrs. at 35–40° yielded 25.4 g. *4-(5,6,7,8-*

tetrahydro-1-naphthyl)-2-butanone (VIII), $b_{0.3}$ 108.5–10.5°, $n^{25}D$ 1.5388; *semicarbazone*, m. 138.5–9.5°. Me 5,6,7,8-tetrahydro-2-naphthoate with $LiAlH_4$ yielded 70% carbinol (IX); IX yielded 81.5% chloride (X). X processed as for VIII yielded 85% *4-(5,6,7,8-tetrahydro-2-naphthyl)-2-butanone* (XI), $b_{0.2-0.3}$ 105.5–10.5°, $n^{25}D$ 1.5348; *semicarbazone* m. 174–5°. The foregoing compds. were dehydrogenated over Pd-C (the compd., product (R' = 1-$C_{10}H_7$), yield (%), and m.p. are given): III, R'CO_2Me, 89.3, — (sapond. to the free acid, m. 161.4–2.4°); IV, R'H, 47.6, 79–80°, and R'Me, 45.5, $b_{0.5-1.0}$ 63–7° (picrate m. 140.5–2°); V, R'Me, 23.1, $b_{0.5-1.0}$ 61.5–7° (picrate, m. 141.2–2°), and 1,2,3,4-tetrahydro-5-methylnaphthalene, 12.2, —, and recovered V, 53.6, $b_{0.5-1.0}$ 105–10°; VI, R'COMe, 51.1, $b_{0.2-0.5}$ 95–9° (semicarbazone, m. 222.5–4°), and R'Et, 29.2, $b_{0.2-0.5}$ 66.5–71°; VIIA, R'CH_2COMe, 30.8, m. 91.5–2.5°, $b_{0.5-1.0}$ 128–32° [semicarbazone, m. 222.8–3.2° (decompn.)], and R'Me, 16.3, $b_{0.5-1.0}$ 63.5–5° (picrate, m. 139–41.5°); VIII, R'CH_2CH_2COMe, 90.2, $b_{0.5-1.0}$ 135–42° (semicarbazone, m. 177.2–8.2°); XI, 2-$C_{10}H_7CH_2CH_2$COMe, 68.0, m. 48.9–9.6°, $b_{0.3-0.5}$ 124–9° (oxime, m. 119.4–21°; semicarbazone, m. 171.8–3°). 1-$C_{10}H_7$MgCl chloride and Ac_2O at −78° yielded 34% R'CH_2COMe, m. 91.5–2.5°; semicarbazone, m. 223–4.2° (cf. *C.A.* 40, 2137[1]). Felix Saunders

The bromination of naphthalene. Frank R. Mayo and Wm. B. Hardy (Univ. of Chicago). *J. Am. Chem. Soc.* 74, 911–17(1952).—The bromination of $C_{10}H_8$ (I) was investigated in several solvents at 20–5°. In CCl_4 in the dark, about 15% addn. to the nucleus normally accompanies substitution. Both reactions are accelerated by ascaridole and retarded by air and iso-AmONO but the addn. reaction is more susceptible to acceleration and inhibition. Under illumination, more than 80% of the Br can react by addn. Substitution is accelerated by solvents of higher dielec. const. Addn. is less affected. In C_6H_6 and PhMe in the absence of light and catalysts, both addn. and substitution in I can occur without significant attack on the solvent. In PhMe, in the presence of light or ascaridole, side-chain substitution in the PhMe becomes the predominant reaction, and addn. to I is also accelerated, both at the expense of nuclear substitution in I. The ratio of side-chain substitution in PhMe to addn. in I increases as the Br concn. decreases. Conclusion: Substitution in I occurs by a polar or mol. mechanism, while addn. takes place by a free-radical mechanism. In contrast to C_6H_6 derivs., there is also a radical mechanism for substitution and a nonradical mechanism for addn., but these have not been fully identified and resolved. Br (20 g.) in 50 cc. CCl_4 added during 4–6 hrs. to 16 g. I and 3 mole-% ascaridole in 100 cc. CCl_4 under illumination and the solvent evapd. yielded 6.7 g. *1,2,3,4-tetrabromo-1,2,3,4-tetrahydronaphthalene* (II), m. 111–12° (decompn.). Some reactions of II are described. Felix Saunders

Bromination of 2-methylnaphthalene. N. B. Chapman and J. F. A. Williams (Univ. Southampton, Engl.). *J. Chem. Soc.* 1952, 5044–6.—2-$C_{10}H_7CH_2Br$ (II), m. 54°, was obtained in 95% yield by bromination of 2-$C_{10}H_7$Me with *N*-bromosuccinimide (I) in CCl_4. The yield depended greatly on the purity of the I used. The best results were obtained with I which had been washed free of Br, kept 8 hrs. over P_2O_5 at 0.5 mm., and immediately used. II is also obtained from 2-$C_{10}H_7$Me with Br in refluxing CCl_4 irradiated with a 500-w. bulb. The yield of crude product are 75–80%. K. C. Schreiber

The Bromination of aceto-2-naphthalide. F. Bell (Heriot-Watt Coll., Edinburgh, Scot.). *J. Chem. Soc.* 1952, 5046–7.—Bromination of *1,2-BrC$_{10}$H$_6$NHAc* with Br in $CHCl_3$ gave the hydrobromide of *N-(1,6-dibromo-2-naphthyl)acetamide* (I)-*HBr*, m. 220–30° (decompn.). I is also obtained from 2-$C_{10}H_7$NHAc with HBr and HNO_2. I could not be further brominated with Br and hot HOAc. Bromination of 1,2-$ClC_{10}H_6$NHAc with Br in cold HOAc yielded *N-(6-bromo-1-chloro-2-naphthyl)acetamide-HBr*, decompd. with NH_3 gave the free amide, m. 222°. K. C. Schreiber

The nitrochloronaphthalenes. II. The dinitration of 1-chloronaphthalene. H. F. Bassilios and M. Shawky (Univ. Farouk, Alexandria, Egypt). *Bull. soc. chim. France* 1952, 1022–9; cf. *C.A.* 47, 4316*i*.—Various conditions for the dinitration of 1-$C_{10}H_7Cl$ (I) with concd. HNO_3 (II), fuming HNO_3 (III), II + concd. H_2SO_4, III + concd. H_2SO_4, II + oleum, freshly prepd. HNO_3 (from $NaNO_3$ + H_2SO_4), and by II in CCl_4, HOAc or Ac_2O) are examd. The best yield (28%) of the only isolated dinitration product, 1,4,5-$ClC_{10}H_5(NO_2)_2$, m. 180° [Ullmann and Consonno, *Ber.* 35, 2802(1902)] is obtained with 4 moles III (d. 1.52) and I at 5° or with 2 moles II + 8 moles 100% H_2SO_4 for 1.5 hrs. at 5°, then 6 hrs. at 35°. In almost all runs large amts. of 1 or both of 2 mononitro compds., m. 61° (IV), and 85° (V), are found. It is claimed that both IV and V are 1,4-$ClC_{10}H_6NO_2$. A mixt. of equal parts of IV and V m. 67–72°, and the compds. cannot be sepd. by fractional crystn. On steam distn. IV distills before V. A mixt. of IV and V with $NH_2(CH_2OH)_2$ (VI) at 160° gives unchanged V and 1,4-$O_2NC_{10}H_6NH_2$ (VII), m. 194°. IV with Fe-MeOH-HCl gives 50% 1,4-$ClC_{10}H_6NH_2$ (VIII), m. 98°, which via diazotization gives 1,4-$C_{10}H_6Cl_2$ (IX), m. 67°. V, prepd. by an alternate route (*loc. cit.*) is similarly reduced to VIII which gives IX. V and VI give 78% VII, while IV and VI give 36%. The prepn. of I from 1-$C_{10}H_7NH_2$ in 71% yield is given. The best yield of IV (44%) is obtained with 5 moles II and I in 3 hrs. at 75°. No mixed-m.ps. with cmpds. of certain structure are given. David Todd

Preparation of 8-amino-1,3,5-naphthalenetrisulfonic acid (K-acid) and the identification of side-reaction products. F. Allisson, G. Brunner, and H. E. Fierz-David (Eidg. Tech. Hochschule, Zurich, Switz.). *Helv. Chim. Acta* 35, 2139–44 (1952); cf. *FIAT (Field Information Agencies Tech.) Final Rept.* 1016, p. 42.—8,1,3,5-$O_2NC_{10}H_4(SO_3H)_3$ (I) was reduced with NH_4SH to the 8-amino analog (II). Recrystd. com. 1,5-$C_{10}H_6(SO_3Na)_2$ (III) (332 g.) was gradually added with stirring to 800 g. $H_2SO_4.H_2O$ at 80° simultaneously with dropwise addn. of 470 g. 66% fuming H_2SO_4, and the turbid mixt. warmed 7 hrs. at 90° and another hr. at 99°; the soln. now became clear. Soln. was mixed, after it had cooled, slowly and with active stirring, with 250 cc. H_2O, with the temp. kept below 90°, then stirred 1 hr. at 99°, cooled to −5°, mixed with strong stirring (the temp. kept below 2°) with a mixt. of 68 g. HNO_3 (d:1.52) and 40 cc. concd. H_2SO_4, stirred 1 hr., the degree of nitration detd. in a Lunge nitrometer, the viscous clear orange soln. stirred into 4 l. H_2O and 2 kg. ice, stirred in a current of air 0.5 hr. to remove nitrous gases, neutralized with approx. 1.5 kg. chalk, sucked off over cryst. gypsum, and the combined filtrates (approx. 9 l.) from washing the residue 3 times with H_2O were evapd. to 4 l. at 50° *in vacuo* and sepd. from the cryst. gypsum; 2 l. of this soln. (contg. I), and 50 cc. 23% NH_3 warmed to 60° was treated dropwise with stirring with 320 cc. NH_4HS (prepd. from 600 g. 23% NH_3 and 276 g. H_2S), boiled 0.5 hr., made acid to Congo red with HCl, boiled another hr. with introduction of H_2S, allowed to stand 2 hrs. and filtered from the pptd. S. The total amine (68%) was detd. by titrating an aliquot with $NaNO_2$, and II sepd. by evapg. the soln. to 400 cc., filtering warm, heating to 80°, adding 50 g. NaCl, strongly acidifying with HCl, cooling, filtering, and purifying by dissolving in the calcd. quantity soda soln., and repptg. with HCl; 45% II was isolated, and the mother liquor, which was a fluorescent blue-green, contained another 22%. The reduction could also be carried out with H and Ni (cf. *C.A.* 46, 446*a*) under normal conditions and also under pressure at higher temps. Reduction under pressure with 80–6% H consumption gave a total amine of 56–62% (42% II isolated, with 16% in the mother liquor). The K salt of I, brown needles, decompg. in soln. above 60°, was prepd. pure from the K analog of III in an analogous manner and sepd. from the nitrated mixt. by adding a 20% soln. K_2CO_3 at 50° for complete pptn. of $CaCO_3$, evapg. to 1.6 l. at 50° *in vacuo*, filtering, and allowing to stand overnight. Most of a dinitro compound (IV) then crystd. out; the rest, on further evapn. to 1.1 l. [28 g. (5.5%) total yield]. On further evapn. 310 g. I crystd. The tri-K salt of 8,5,7,1,3-$HO(O_2N)_2C_{10}H_3(SO_3H)_2$ (IV) crystd. from H_2O as orange-yellow needles, turning red on heating, detonating when burned. The benzylthiuronium salt of IV contains 3 benzylthiuronium radicals. Dorothy L. Lesh

2-Naphthoic acid from 2-iodonaphthalene. S. I. Sergievskaya and N. P. Volynskiĭ (S. Ordzhonikidze All Union Chem.-Pharm. Inst., Moscow). *Zhur. Priklad. Khim.* 25, 898–9(1952).—To 0.5 l. concd. HCl and 1 l. boiling H_2O is added 430 g. 2-$C_{10}H_7NH_2$, the resulting suspension treated with 200 ml. concd. H_2SO_4, then cooled to 10–15°, finally to 2–3°, by addn. of ice, 210 g. $NaNO_2$ in H_2O added over 15 min. at 3°, the excess HNO_2 removed with concd. urea soln., the filtered soln. treated mixed with a concd. aq. soln. of 450 g. KI, the mixt. warmed to 90° after a brief period cooled, decanted, the 2-$C_{10}H_7I$ heated to 100–10° to remove moisture, and the molten product shaken with hot aq. $NaHSO_3$

sans espoir de reproductibilité rigoureuse d'une expérience à l'autre.

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N° 188. — Études sur les matières végétales volatiles CXLVII(1). Sur les cis et trans-isosafroles.

par Yves-René Naves et Pierre Ardizio.

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(*Manuscrit reçu le* 9.5.57.)

Le *cis*-isosafrole (α-isosafrole) et le *trans*-isosafrole (β-isosafrole) sont décrits et comparés.

Il règne dans la littérature chimique quelque confusion au sujet des isosafroles stéréoisomères. L'obtention du *cis*-isosafrole (α-isosafrole), affirmée par Hoering et Baum (2) et par Nagaï (3) a été niée par Watermann et Priester (4) et par Boeseken et Elser (5); la possibilité même de l'isoler a été mise en doute par Funakubo (6).

Nous venons d'isoler et nous décrivons le *cis*-isosafrole qui est non moins stable, à peu de choses près, que le *trans*-isosafrole. Il ne s'agit ni du produit décrit par Hoering et Baum, ni de celui dépeint par Nagaï.

Hoering et Baum ont situé la présence du *cis*-isosafrole dans les têtes de distillation peu importantes d'une grande quantité d'isosafrole brut. Ils en ont écarté le safrole par le complexe mercurique décrit par Balbiano, le *trans*-isosafrole par son picrate. Il est évident, comme nous le verrons, que ces soins ont été insuffisants pour l'obtention de *cis*-isosafrole pur mais il est tout aussi évident que les critiques adressées à Hoering et Baum par Watermann et Priester et par Boeseken et Elser sont, pour le moins, exagérées. Quant à Nagaï, il n'a visiblement obtenu aucune substance à l'état pur, les critiques que lui ont adressées Watermann et Priester sont parfaitement fondées mais ceux-ci ont eu tort d'affirmer que :
« Bei der Umlagerung von Safrol in Isosafrol mit alkoholischem Kaliumhydroxyd entsteht nur *eine* der geometrisch isomeren Formen, die möglich sind. Das in der Literatur beschriebene α-Isosafrol ist als eine Mischung von Safrol und β-Isosafrol zu betrachten. »

Nous savons isomériser le safrole de manière qu'il n'en demeure que fort peu à côté des isosafroles engendrés, mais on obtient de toute manière les deux stéréoisomères. Parmi ceux-ci, le *trans*-isosafrole est prédominant et c'est celui dont sont obtenus les meilleurs rendements en héliotropine. L'isosafrole récupéré au cours de l'isolement de celle-ci est plus riche en *cis*-isosafrole que la matière de départ.

Nous avons extrait l'isosafrole à partir d'un lot de 740 kg de fractions constituant les têtes de distillation (1,06 %) de 70 tonnes d'isosafrole brut (Hoering et Baum ont traité 1 kg de têtes provenant de 450 kg d'isosafrole brut). Cette extraction a été réalisée par la distillation à travers une colonne ayant une capacité de 70 plateaux théoriques. Les fractions considérées comme *cis*-isosafrole ne renfermaient, d'après leur spectre d'absorption infrarouge, ni *trans*-isosafrole, ni safrole. Leur transformation en dihydrosafrole a pu être réalisée avec un rendement sensiblement quantitatif.

Quant au *trans*-isosafrole, il a été obtenu, par la distillation dans des conditions analogues, de fractions prélevées en usine, au cœur de la distillation, d'une forte charge d'isosafrole brut, et nous l'avons éprouvé spectrographiquement comme son isomère.

En outre l'individualité de chaque préparation a été éprouvée par la chromatographie de la vapeur contre une phase liquide stationnaire. Le chromatographe a enregistré un seul pic dans chaque cas, mais deux pics accolés sensiblement égaux pour le mélange à poids égaux. Enfin, dans les mêmes conditions, l'addition de 1 % de stéréoisomère à chacune des préparations s'est laissée aisément reconnaitre.

Les deux isosafroles se distinguent entre eux et d'avec le safrole par les bandes d'absorption infrarouge fortes ci-après (nombre d'ondes en cm^{-1}) :

cis-isosafrole	*trans*-isosafrole	safrole
«	«	996
«	963	«
«	«	915
650	«	«
«	559	«
409)	«	—
396)		

Il est hors de doute que les bandes de 996 et 915 cm^{-1} du safrole caractérisent le groupement vinyle — CH = CH_2 (7, 8, 9, 10), toutes deux étant relatives à la vibration C — H la première pour — CH = C — et la seconde pour — C = CH_2.

La bande de 963 cm^{-1} correspond à δ(C — H) dans — CH = CH — *trans* tandis que celle de 559 cm^{-1} est une vibration de — C — C = C — *trans* (8, p. 40 et 9, 10). Les bandes de 650 cm^{-1} et de 409 et 396 cm^{-1} ont les mêmes origines respectives en structure *cis* (8, p. 42 et 9, 10).

Les *cis*- et *trans*-isosafroles et le safrole sont aisément distingués par leurs absorptions dans l'ultraviolet.

On trouve dans la littérature des opinions fort divergentes sur les possibilités de distinguer entre eux des isomères tels que les deux isosafroles par ces absorptions. Uyeo, Miwa et Nakanishi (11) ont constaté que les spectres des *cis*- et *trans*-isoeugénols sont très voisins, le *trans*- isoeugénol étant le plus absorbant. Pour Funakubo (12), qui prétend avoir décrit les stéréoisomères de plusieurs éthers de l'isochavibétol, les différences spectrales entre stéréoisomères sont très accusées. Mais il est évident que les préparations *cis* décrites par cet auteur n'ont pas les identités déclarées. Ni l'éther méthylique, ni l'éther *n*-propylique attribués à l'isochavibétol ne peuvent être retenus, ne serait-ce que parce que les réfractions moléculaires

sont inférieures de 3 à 4 unités aux valeurs correspondant aux structures escomptées. C'est bien à tort que le chimiste nippon explique les différences entre les caractères de sa préparation étiquettée comme éther méthylique du *cis*-isochavibétol et ceux de l'éther méthylique du *cis*-isoeugénol décrit par BOEDECKER et VOLK (13) par l'impureté de celui-ci.

Nos mesures montrent que les bandes B (benzénoïde) et K ($\pi\pi$ conjugaison et πp conjugaison) sont nettement séparées dans les spectres des isosafroles et du safrole par des minima prononcés.

Solvant : isooctane λ en mμ (ε)	*cis*-isosafrole	*trans*-isosafrole	safrole
Bandes B	297 297,5(4 700)	305(5 180)	289(3880) 285(3750)
Bandes K	259(9 700)	268(11 800) 259(12 300)	236,5(4 540)
Minima	281(3 100) 237(4 600)	283(3 950) 240(4 950)	254,5(600) —

On pourrait s'étonner de la qualification attachée ici à la bande de 236, 5 mμ du safrole. Nous la considérons comme la bande K benzénique (qui se trouve à 198 mμ chez le benzène) localisée ici par effet inductif.

Le spectre du safrole et celui de diverses préparations d'isosafroles ont été mentionnés par divers auteurs soit sans coordonnées numériques précises (14, 15) soit sans la mention du solvant utilisé (16). HILLMER et SCHORNING (17) donnent pour leur préparation d'isosafrole dissoute dans l'hexane $\lambda_{max} = 261$ mμ ($\varepsilon = 16\,200$) et 302 mμ ($\varepsilon = 6\,500$). Ces valeurs ε sont plus élevées que les plus élevées des nôtres (celles du *trans*-isosafrole) encore que les positions des bandes en longueurs d'ondes indiqueraient un mélange des deux isosafroles, mais des discordances analogues existent aussi entre les mesures rapportées par HILLMER et SCHORNING relatives à des substances voisines bien définies (safrole, eugénol) et nos mesures sur ces mêmes substances, tant en intensités qu'en longueurs d'ondes, et nous ne les interpréterons pas.

Le déplacement des absorptions entre le *cis*-isosafrole et le *trans*-isosafrole répond aux règles tirées de l'étude d'autres couples de stéréoisomères.

Le dihydrosafrole a été obtenu aussi bien du *cis*-isosafrole que du *trans*-isosafrole par hydrogénation sur nickel de Raney à 20° et à la pression atmosphérique. Le *cis*-isosafrole est le moins aisément hydrogénable. Le spectre d'absorption infrarouge du dihydrosafrole ne renferme aucune des bandes de 996, 963, 915, 650 cm^{-1} caractérisant le safrole ou l'un des isosafroles. Nous y trouvons par contre les bandes communes à tous ces produits, notamment la bande de 1 605 cm^{-1} du noyau aromatique, celle de 1 250 cm^{-1} de la vibration symétrique — C — O — C — et l'autre bande de 1 042 cm^{-1} d'origine oxydique. Le spectre du dihydrosafrole renferme avec 789 cm^{-1} une absorption intense caractéristique, très vraisemblablement, du radical *n*-propyle.

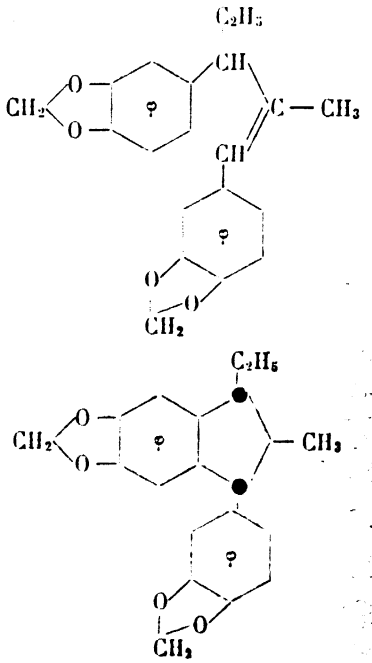
L'absorption du dihydrosafrole en solution dans l'isooctane présente à 235 mμ ($\varepsilon = 4\,000$) et à 288,5 mμ ($\varepsilon = 3800$) les bandes K et B correspondant sensiblement à celles du safrole.

On a annoncé que sous l'influence de réactifs protoniques l'isosafrole est aisément dimérisé en donnant des éthyl-1 méthyl-2 pipéronyl-3 méthylène-dioxy-6, 7 indanes fondant l'un à 145°, l'autre à 92°. En utilisant l'acide formique, GLICHITCH a eu celui F = 145° (18), tandis que BAKER, GOLDSELL, MCOMIE et ULBRICHT (19) n'ont eu, par ce même réactif, que l'isomère F = 92°.

Or nous avons constaté, avec la plus entière netteté, que le *cis*-isosafrole donne le dimère F = 145° auquel BAKER et ses collaborateurs attribuent la configuration *trans* (1*c*, 3*t*) tandis que le *trans*-isosafrole livre l'isomère F = 92° qui serait, d'après les mêmes auteurs, *cis* (1*c*, 3*c*), leurs configurations étant reliées avec les racémates respectivement *cis*, *trans* (γ) et *trans*, *trans* (α) de l'éther diméthylique du di-isoeugénol décrits par BAKER, HAKSAR, MCOMIE et ULBRICHT (23).

MAYER (24) aurait converti l'isomère F = 92° en isomère F = 145° en le chauffant. Pas plus que BAKER et ses collaborateurs (23), nous ne l'avons réalisé.

Il est probable que, comme on l'a déjà supposé, la formation des dimères cristallisés pentacycliques provient par l'intermédiaire des dimères tétracycliques (dimères liquides des isosafroles) dont les structures sont similaires à celles des isoanétholes [étudiées par PAILER (25), voir ég. BAKER et FELMONS, (26)].



L'addition de brome aux isosafroles a été étudiée par HOERING et BAUM (2) qui n'ont obtenu qu'un dérivé dibromé F = 51°, alors que NAGAÏ (3) aurait réalisé, de son côté, le bromure de *cis*-isosafrole $(\alpha)_D^{20} = +13°, 35$ et un bromure de *trans*-isosafrole $(\alpha)_D^{20} = +4°, 45$ (!) donnant par simple vement d'hydracide, des monobromures respectivement *trans* et *cis* car leur débromuration aurait livré l'isosafrole stéréoisomère de celui soumis à la bromuration. De même que HOERING et BAUM, nous n'avons obtenu que le dérivé dibromé F = 51-52°.

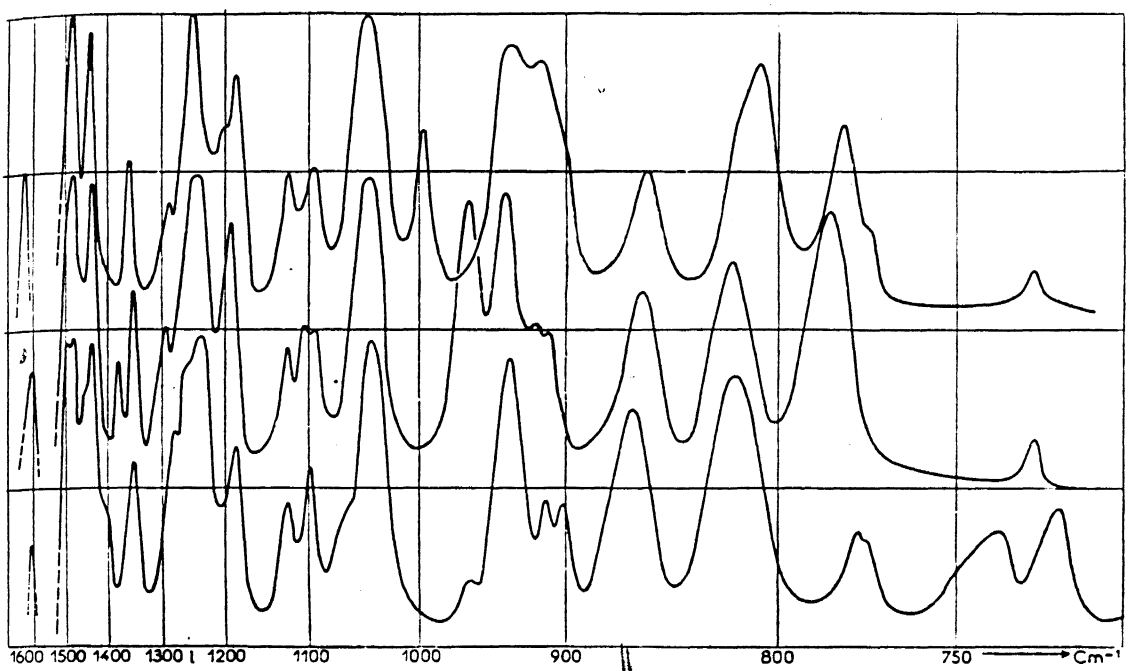
De même aussi que HOERING et BAUM, WATERMANN et PRIESTER, NAGAÏ, nous avons obtenu très aisément le picrate du *trans*-isosafrole F = 74-75°. Par contre le *cis*-isosafrole dont NAGAÏ a décrit un picrate F = ... ne nous a pas livré de dérivé. Contrairement au *trans*-isosafrole, le *cis*-isosafrole mélangé à l'acide picrique n'approfondit pas la teinte.

Nous comparerons les caractères de nos préparations d'isosafroles (I) avec les préparations décrites par HOERING et BAUM (II), après avoir ramené à 20° les valeurs originales.

	cis-isosafrole		*trans*-isosafrole	
	I	II	I	II
F	— 21°,5		+ 8°,2(*)	
d_4^{20}	1,1182	1,1061	1,1206	1,1085
n_D^{20}	1,56910	1,56281	1,57818	1,57189
ERM_D	+ 2,01	+ 2,18	+ 2,61	+ 2,78

(*) Watermann et Priester : + 6°,6 à 6°,7.

Il ressort de ceci que la préparation de *trans*-isosafrole de HOERING et BAUM était sensiblement pure tandis que leur préparation de *cis*-isosafrole renfermait encore, notamment,



Courbes, de haut en bas : Safrole, *trans*-isosafrole, *cis*-isosafrole. Les pourcentages d'absorption, en ordonnées, sont décalés de 50 %. Mesures sur les liquides homogènes, épaisseurs 25 μ.

du safrole. Il est intéressant de comparer les deux préparations d'isosafroles (I) à celles des isoeugénols *cis* et *trans* telles que les ont décrites BOEDEKER et VOLK (20), v. AUWERS (21) et JUNGE (22) :

	Isoeugénols.	
	cis	*trans*
d_4^{20}	1,0851 — 1,086	1,0852 — 1,087
n_D^{20}	1,5726 — 1,57002	1,5782 — 1,57862
ERM_D	+2,32/ + 2,10	+ 2,72/ + 2,66

Les caractères d'autres couples de stéréoisomères dans lesquels le chaînon benzénique est conjugué au cycle aromatique (ω-bromostyrolènes; stilbènes; α, β-diméthylstilbènes; β-méthyl-cinnamates d'éthyle; *o*-méthoxy α-méthyl-cinnamates de méthyle) ont été débattus par K. v. AUWERS (21).

Les stéréoisomères *trans* sont de façon générale les plus réfringents et montrent les plus fortes exaltations de la réfraction moléculaire; le *trans*-isosafrole satisfait aux règles. Il fond aussi plus haut que son stéréoisomère, ce que l'on constate pour la plupart des paires de substances évoquées.

PARTIE EXPÉRIMENTALE

Les microanalyses ont été effectuées par Mlle D. HOHL ou par Jean PLUMETTAZ. Les spectres d'absorption IR ont été mesurés jusqu'à 14 μ par Mlles A. GASSER et Y. SCHMIDELY sur spectromètre Perkin-Elmer 12 *c* avec optique de NaCl et au-dessus de 15 μ par Mlle Y. MORANDAT, sous la direction de J. LECOMTE, au Laboratoire de Recherches de Physique à la Sorbonne, sur spectromètre Perkin-Elmer 112, avec optiques de CsBr et de CsI. Les spectres UV ont été étudiés par A. Odermatt sur spectromètres Beckman DR et Unicam SP 500 et les chromatographies de vapeurs ont été réalisées par le même opérateur sur appareil de la Consolidated Electrodynamics Corp., type 26 — 201.

Les points de fusion sont corrigés; Δn représente $(n_F - n_C) \times 10^4$.

Préparation de safrole. — Le safrole a été obtenu à partir du produit technique F = 9,0-9°,5 extrait de l'essence de Sassafras brésilienne, traité par distillation dans une colonne adiabatique possédant une efficacité de l'ordre de 70 plateaux théoriques.

$Eb_{1,5} = 69\text{-}70°$; $F = 11°,0$; $d_4^{20} = 1,0993$;
$n_C^{20} = 1,53191$; $n_D^{20} = 1,53738$; $n_F^{20} = 1,55064$;
$\Delta n = 187,3$; $\Delta n/d = 170,4$; $ERM_D = +0,68$.

Spectre UV, solutions dans l'isooctane;

$\lambda_{max} = 285$ et 289 mμ ($\varepsilon = 3\,750$ et $3\,880$);
236,5 mμ ($\varepsilon = 4\,540$);
$\lambda_{min} = 254,5$ mμ ($\varepsilon = 600$).

Solutions dans l'alcool 96 % :

$\lambda_{max} = 285$ mμ ($\varepsilon = 3\,770$);
236 mμ ($\varepsilon = 4\,180$);
$\lambda_{min} = 256$ mμ ($\varepsilon = 700$).

Spectre IR : 1 634 (m); 1 486 (FF); 1 439 (F); 1 361 (m); 1 292 (f); 1 250 (FF); 1 200 (f); 1 187 (F); 1 123 (m); 1 096 (m); 1 043 (FF); 996 (mF); 932-915 (b. crénelée, F); 856 (m); 807 (F); 778 (mF).

Trans-isosafrole. — Le *trans*-isosafrole a été obtenu à partir des fractions principales de distillation d'isosafrole technique, par redistillation à travers la colonne mentionnée ci-dessus :

$Eb_{3,4} = 85\text{-}86°$; $F = +8°,2$; $d_4^{20} = 1,1206$;
$n_C^{20} = 1,57009$; $n_D^{20} = 1,57818$; $n_F^{20} = 1,59778$;
$\Delta n = 276,9$; $\Delta n/d = 247,1$; $ERM_D = +2,61$.

Spectre UV, solutions dans l'isooctane :

$\lambda_{max} = 305$ mμ ($\varepsilon = 5\,180$);
268 et 259 mμ ($\varepsilon = 11\,800$ et $12\,300$);
$\lambda_{min} = 283$ et 240 mμ ($\varepsilon = 3\,950$ et $4\,150$);

solutions dans l'alcool 96 % :

$\lambda_{max} = 305$ mμ ($\varepsilon = 5340$);
267 et 259,5 mμ ($\varepsilon = 11\,600$ et $12\,160$);
$\lambda_{min} = 284$ et 240 mμ ($\varepsilon = 4\,100$ et $5\,200$).

Spectre IR : 1 605 (mf); 1 489 (FF); 1438 (F); 1 453 (mF);

1 378 (mf); 1 298 (f); 1 250 (FF); 1 191 (F); 1 123 (mf); 1 105-1 091; (b. crenelée, m); 1 042 (FF); 963 (F); 939 (F); 917 (f); 910 (f); 860 (mF); 819 (mF); 782 (F); 603 (m); 559 (mF); 464 (m); 443 (mf); 424 (m); 348-325 (b. crénelée; m,) 268 (f)

Cis-isosafrole. — 2,2 kg pris sur un lot de 740 kg de têtes de distillations de 70 tonnes d'isosafrole technique ont été fractionnés à l'aide de la colonne mentionnée ci-dessus avec un prélèvement de 4 % sur le reflux total. Par reprises systématiques il a été obtenu 50 % environ de fractions sensiblement identiques.

$Eb_{3,5} = 77\text{-}79°$; $F = -21°,5$; $d^{420} = 1,1182$;
$n_C^{20} = 1,56169$; $n_D^{20} = 1,56910$; $n_F^{20} = 1,58706$;
$\Delta n = 253,7$; $\Delta n/d = 227,0$; $ERM_D = +2,18$.

Spectre UV, solutions dans l'isooctane :

$\lambda_{max} = 297,5$ mμ ($\varepsilon = 4\,700$);
259 mμ ($\varepsilon = 9\,700$);
$\lambda_{min} = 281$ et 237 mμ ($\varepsilon = 3\,100$ et $4\,600$).

Solutions dans l'alcool 96 % :

$\lambda_{max} = 296,5$ ($\varepsilon = 4\,450$);
259 mμ ($\varepsilon = 10\,000$);
$\lambda_{min} = 281$ et 237 mμ ($\varepsilon = 3\,100$ et $4\,800$).

Spectre IR : 1 605 (mf); 1 497-1 482 (b. crénelée, FF); 1 432 (F); 1 349 (mF); 1 260 (f); 1 239 (FF); 1 184 (mF); 1 122 (m); 1 098 (mF); 1 044 (FF); 966 (f); 937 (F); 912 (mf); 903 (mf); 865 (F); 816 (FF); 774 (mf); 770 (sh); 743 (mf); 734 (m); 650 (m); 598 (F); 441 (f); 427 (f); 409-396 (b. crénelée, m); 328 (f).

Chromatographies de vapeurs : Il a été fait usage de la charge de partition de faible polarité référence C de Perkin-Elmer, permettant de travailler jusqu'à 225°. Le tube de chromatographie avait 185 cm de long et 0,65 cm de diamètre. La température était de 200° ± 0,5; le courant d'azote, admis avec une supression de 1 atm., avait un débit de 40 ml/mn. Il a été injecté 20 μl de liquide; les substances pures ont donné une réponse d'environ 8 mV. Les pics des *cis*-et *trans*-isosafroles ont développé leurs sommets respectivement 13 mn 24 s et 15 mn 30 s après l'injection.

Dihydrosafrole.

25 g d'isosafrole *cis* ou *trans*, 50 ml d'alcool 96 % et 2 g de nickel de Raney ont été secoués dans l'hydrogène à 20° sous 730 mm. La vitesse d'hydrogénation a été dans chacun des cas relativement constante. 95 % de l'hydrogène théorique ont été absorbés en 102 mm dans le cas de l'isomère *cis*, en 39 mn dans celui de l'isomère *trans*.

Les produits d'hydrogénation distillés se sont révélés homogènes et sensiblement identiques par leurs caractères physiques et notamment spectraux. Voici ceux du produit de l'isomère cis :

$Eb_{2,2} = 67\text{-}68°$; $d_4^{20} = 1.0698$; $n_C^{20} = 1,51526$;
$n_D^{20} = 1,51984$; $n_F^{20} = 1,53094$; $\Delta n = 167,8$;
$\Delta n/d = 156,8$; $ERM_D = +0,76$.

$C_{10}H_{12}O_2$ (164,20) :

Calc. % : C 73,14 H 7,37
Tr. : 73,11 7,37

Spectre UV, solutions dans l'isooctane :

$\lambda_{max} = 288,5$ et 235 mμ ($\varepsilon = 3\,800$ et $4\,000$);
$\lambda_{min} = 254,5$ mμ ($\varepsilon = 350$);

Solutions dans l'alcool 96 % :

$\lambda_{max} = 287$ et 234 mμ ($\varepsilon = 3700$ et 3950);
$\lambda_{min} = 254,5$ mμ ($\varepsilon = 300$).

Spectre IR : 1 603 (m); 1 498 (FF); 1 450 (F); 1 360 (m); 1 250 (FF); 1 220 (f); 1 187 (m); 1 122 (f); 1 042 (FF); 941-927 (b. crénelée, F); 868 (f); 852 (m); 806 (FF); 789 (m); 772 (m).

Oxydation des isosafroles en acide pipéronylique.

2 g de *cis*- ou de *trans*-isosafrole et 18 ml d'eau émulsionnés et chauffés à 80-90° ont été additionnés en 1 h de 9,2 g de permanganate de potassium dissous dans 230 ml d'eau et le tout porté ensuite 30 mn à reflux. L'acide a été libéré par addition d'acide chlorhydrique au filtrat limpide froid du produit de la réaction. Recristallisé dans l'alcool 96 %, il fond à 229-230°. Le rendement a été de 80 % de la théorie sur le *trans*-isosafrole, de 70 % sur le *cis*-isosafrole. Les spectres d'absorption IR des deux préparations sont identiques.

$C_8H_6O_4$ (166,13) :

Calc. % : C 57,83 H 3,64
Tr. : 57,79 3,85

Spectre IR : 1 662 (FF); 1 605 (F); 1 500-1 492 (b. crénelée, F); 1 451 (FF); 1 415 (F); 1 368 (m); 1 297 (FF); 1 264-1 245 (b. crénelée, F); 1 187 (f); 1 167 (m); 1 115 (F); 1 076 (mF); 1 036 (FF); 932 (mF); 917 (F); 869 (m); 833 (mf); 812 (m); 782 (m); 772 (F); 740 (m).

3 g d'acide et 3 g de chlorure de thionyle ont été portés 1 h au bain-marie bouillant puis l'excès de réactif ayant été chassé au vide de la trompe à eau, le chlorure d'acide a été distillé.

F = 79,5-80°,5.

1 g de chlorure et 5 ml d'ammoniaque concentrée ont été chauffés jusqu'à homogénéisation. L'amide essorée après refroidissement et recristallisée dans le benzène F = 165-166°.

$C_8H_7O_3N$ (165,14) :

Calc. % : C 58,18 H 4,27 N 8,48
Tr. : 58,16 4,32 8,56

Spectre IR : 1646-1626-1597 (b. crénelée, F); 1 502 (m); 1 451 (FF); 1 380 (F); 1 351 (f) 1 244 (F) 1 189 (f); 1 164 (f); 1 126 (F); 1 068 (m); 1 034 (FF); 930 (F); 912 (m); 870 (m); 806 (m); 764 (m); 754 (mf).

Dibromoisosafrole F = 51-52°.

2 g de *trans* ou de *cis*-isosafrole dans 15 ml d'éther sec sont additionnés, entre — 10 et — 15°, de 2 g de brome on évapore l'éther par le vide et l'on recristallise le produit dans le pentane. Le rendement en produit F = 51-52° est de 70-80 % th. Il est analysé aussitôt obtenu.

$C_{10}H_{10}O_2Br_2$ (322,012) :

Calc. % : Br 49,64 Tr. % : Br 49,18.

Spectre IR : 1 490 (m); 1 450 (FF); 1 380 (F); 1 345 (f); 1 256 (FF); 1 202 (f); 1 176 (f); 1 150 (mF); 1 103 (m); 1 043 (F); 1 004 (m); 930 (FF); 904 (f); 858 (m); 827 (FF); 782 (F); 745 (m); 740 (m).

Dimères des isosafroles.

20 g de *trans*- ou de *cis*-isosafrole et 20 g d'acide formique à 90 % ont été portés 1 h à reflux. Le mélange a été refroidi, extrait par de l'éther et la fraction neutre a été distillée sous 0,2-0,3 mm (Eb = 180-200°) dans un ballon Claisen. Les distillats ont été recristallisés dans l'alcool 96 %.

Il a été obtenu, à partir du *trans*-isosafrole, 14 g du dimère F = 92° (I) et à partir du *cis*-isosafrole, 14, 6 g du dimère F = 145° (II).

$C_{20}H_{20}O_4$ (324,36) :

Calc. % : C 74,05 H 6,22
Tr. % : (I) 74,13 6,34
(II) 74,09 6,21

Spectres IR : (I)-1 474 (FF); 1 378 (m); 1 350 (m); 1 325 (m); 1 296 (f); 1 275-1 241 (b. crénelée, F); 1 214 (m); 1 188 (f); 1 137 (F); 1 085 (m); 1 080 (f); 1 042 (FF); 942 (FF) 923 (f); 895 (f); 883 (f); 862 (F); 838 (f); 816-807-799-792 (b. crénelée, F); 747 (F); 740 (m).

(II) — 1 463 (FF); 1 378 (F); 1 306 (m); 1 275 (f); 1 255 (F); 1 188 (m); 1 146 (F); 1 122 (f); 1 099 (m); 1 075 (f); 1 035 (F); 941 (FF); 897 (f); 883 (F); 873 (f); 858 (m); 832 (f); 816 (F); 800 (m); 790 (mf); 757 (f); 742 (f); 737 (f).

Picrate de trans-isosafrole.

1 g de *trans*-isosafrole et 1,4 g d'acide picrique dans 10 ml d'alcool absolu ont donné 1,3 g du dérivé recristallisé dans l'alcool absolu, F = 74-75°.

$C_{16}H_{13}O_9N_3$ (391,29) :

Calc. % :	C 49,11	H 3,35	N 10,74
Tr. :	48,99	3,60	10,93

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N° 189. — Action de l'acide perbenzoïque sur l'échinuline,

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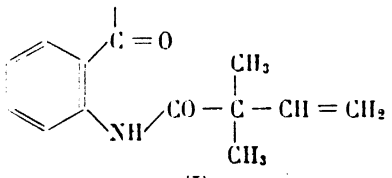
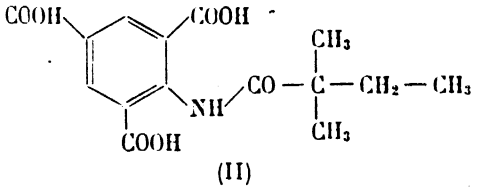
(*Manuscrit reçu le* 9.5.57.)

Avec l'acide perbenzoïque, l'échinuline donne une réaction caractéristique des indoles (I), la formation d'une amide de l'acide diméthylvinylacétique hydrolysable par l'acide benzènesulfonique.

La présence, dans l'échinuline, d'un enchaînement carbones-azote tel que celui de la formule (I), a été prouvée par QUILICO et ses collaborateurs (2) par l'isolement après oxydation permanganique de l'hexahydroéchinuline, de l'acide (II).



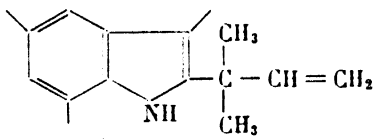
(I)



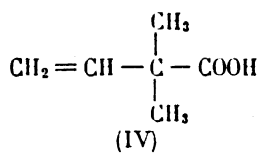
(II)

Les auteurs indiquent comme probable l'existence du système indolique (III) en se fondant sur cette dégradation, sur des analogies spectrales, des réactions colorées, l'absence de propriétés basiques et la possibilité de réaliser une copulation avec les diazoïques, aussi bien de l'échinuline et de l'hexahydroéchinuline que des bases qui en dérivent par pyrogénation (3, 4). *L'existence* d'un groupement vinyle est déduite du spectre infrarouge (bandes à 917 et 997 cm^{-1}) (4) et de la production de formol par ozonolyse (2). Sa *localisation* est déduite du fait qu'il n'est pas possible d'obtenir de l'acide 22-diméthyl-butyrique dans l'oxydation de l'échinuline, alors qu'il s'en forme dans celle de l'hexahydroéchinuline (5).

La réaction de l'acide perbenzoïque sur l'échinuline fournit un argument chimique direct en faveur de l'élément de structure III (I). Nous avons déjà rapporté brièvement, dans sa communication précédente, les réactions analogues sur l'hexahydroéchinuline et certains indoles (6).



(III)



(IV)

En présence d'un excès d'acide perbenzoïque à 0°, on observe la fixation de 3 atomes d'oxygène pendant le premier quart d'heure, d'un quatrième pendant le quart

(横濱國立大學學藝學部) (昭和 26 年 11 月 6 日受理)

2,3-ジピペロニル-ブタンの合成

榊　原　賢　明

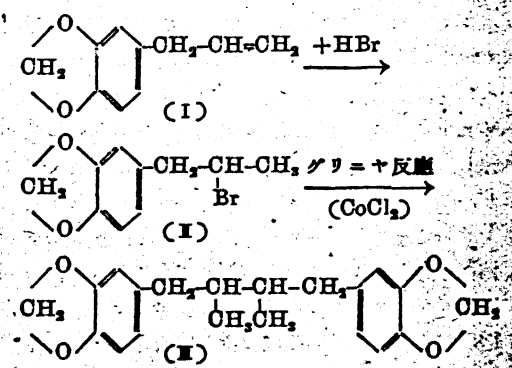
緒　言

本研究はピレトリンの共力剤の合成に關する研究の一部である。ピレトリンに胡麻油を少量混ぜると，ピレトリンの殺虫効果は，ピレトリンを單獨に用いた時よりも著しく增大することは，胡麻油中に含まれて居るセザミン($C_{20}H_{16}O_6$)の爲であることは Haller[1], Eagleson[2], Billing[3]等の研究に依つて明らかである。亦，Haller, La Forge[4]等はセザミンと同類關係の化合物についてピレトリンに對する共力効果を檢した結果，共力効果のあるためには，その分子中にメチレンジオキシフェニル基を有することが必要である旨を報告して居る。

我國では，松原弘道が[5] メチレンジオキシフェニル基を持つヒノキニン($C_{20}H_{16}O_6$)，及びエゴノール($C_{19}H_{18}O_5$)について共力効果のあることを報告し，亦，小野正夫[6]はサフロール及びその不飽和ケトン誘導體について共力効果のある旨を報告して居る。

ピレトリン劑は B.H.C. や D.D.T. の出現した今日に於いても，その速効性と家畜の脂肪組織への非貯藏性のため，現在に於いても重要な殺虫劑ではあるが，生産量少く且つ高價なため，共力劑を用いてその効力を發揮する必要がある。共力劑としては胡麻油を用いる事が一番簡單ではあるが，これは元來食用油であるから食用に供すべきである。現在の日本で，今メチレンジオキシフェニル基を持つ化合物で，一番安價に得られるのはサフロールであるが，これは分子が小さいため，長い間には揮發してしまうと思われる。そこで著者はサフロールを二つ結合させて，C數 20 の，丁度セザミンのC數と同數の 2,3-ジピペロニル-ブタンの合成を試みた。

即ち，サフロール(I)に臭化水素を添加して 1-ピペロニル-1-プロムエタン(II)を合成し，次に無水塩化コバルトを用いたグリニヤの變法を用いて 2,3-ジピペロニル-ブタン(III)を 14% の收量で合成することが出來た。



實驗の部

(1) 1-ピペロニル-1-ブロムエタンの合成　最初 Orcutt, Bogert 法[7]を追試してサフロールと 69% の臭化水素酸(比重 1.8)とを密閉器內で氷冷しながら 3 日間時々振盪を行つたが，收量はよくないので次の如く攪拌法に改良したところ收量はほとんど定量的となつた。

即ち，水銀シール付の三ツ口コルベンに比重 1.8 の臭化水素酸 100 g を入れ，外部より氷で冷却し，一方滴下漏斗より冷サフロール 25 g を攪拌しながら滴加すると，液は次第に青綠色となりやがて紫色となる。12時間後，コルベンの內容物を冷却しながら，尙猛烈に攪拌し續けると，內容物は紫色の泥狀となる。內容物を食鹽と氷水との混合物中に投じると，臭化物は下層に沈む。傾瀉して後エーテルにて抽出し，氷と食鹽水で 2 回洗滌し，無水炭酸カリで乾燥し，エーテル溜去後，減壓蒸溜して 5 mm, 130~135°C 附近にて 1-ピペロニル-1-プロムエタンが定量的に得られる。淡黃色の液體。$n_D^{15°}$ 1.5640

[比重 1.8 の臭化水素酸の調製]

實驗に使用した比重 1.8 の臭化水素酸 (69%) は次の如く調製した。

即ち，市販の臭化水素酸は比重 1.48 (47%)，或はこ

1) Haller *et al.*, *J. Econ. Entmol* 35, 247 (1942).
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6) 小野正夫, 防虫科學 15, 155 (1950).
7) R. M. Orcutt, M. T. Bogert, *J. Am. Chem. Soc.* 58, 2067 (1936).

れ以下なので一度蒸溜してから，これに臭素とテトラリンとで臭化水素を發生させ，生じた臭化水素をテトラリンで一度洗つて，伴つて來る臭素を除き，氷冷してある稀臭化水素酸に吸收させ濃度增加を行つた。

(2) **2,3-ジピペロニル-ブタンの合成**　この合成法は Wilds, Mccormack[8]のアネトールブロマイドよりヘクセストロールを合成したグリニヤの變法を應用したものである。

卽ち，ブロマイド(II)を原料として等モルの Mg 片を作用させて常法の如くグリニヤ試藥を作り，無水鹽化コバルト(ブロマイド 1 モルに對して 0.004 モル) を手早く加え，次に上記のブロマイドと等量のブロマイドのエーテル溶液を滴加しながら攪拌すると烈しく反應する。ブロマイドの滴加後，尙 1 時間程湯煎で加溫しながら攪拌し，內容物を氷水と鹽酸との混合物中に投入して分解し，エーテルで抽出し 2%鹽酸，水で 2 回洗い，鹽化カルシウムで乾燥後エーテルを溜去すると橙赤色の芳香ある液體が得られた。これを減壓蒸溜して 7 mm, 80～85°C 附近でサフロール臭ある多量の溜分 (グリニヤ反應物の 30%) と，135°C 附近で少量の未反應ブロマイドが得られたが，尙コルペン內に未溜分が多量殘つて居たので，後者を眞空蒸溜したところ，0.01～0.02 mm, 168～172°C にて無色の溜分を得た。このものは試驗管に入れて，さかさまにしても流出しない樣な粘稠な液體で，分析値は次の如くであつた。

2,3-ジピペロニル-ブタン ($C_{20}H_{22}O_4$)

	H%	C%
實驗値	6.51	72.55
計算値	6.79	73.60

尙，グリニヤ反應のためメチレンジオキシ環が開裂して居る虞があるため，鹽化第二鐵で呈色を檢したが，呈色しなかつたので 2,3-ジピペロニル-ブタンと斷定した。

この化合物は冬季放置して置いたところ結晶が析出し始めたので，石油エーテルにて再結晶を行つて短柱狀無色の結晶を得た。

融點　74°C, 收量　14%

本結晶の分析値は次の如くで，計算値とよく一致した。

$C_{20}H_{22}O_4$	H%	C%
實驗値	6.62	73.22
計算値	6.79	73.60

從つて得られた結晶は 2,3-ジピペロニル-ブタンである。

この場合，無水鹽化コバルトを使用しなければ，使用した場合に比して收量は 1/3 であつた。

結　語

以上の如く無水鹽化コバルトを觸媒としたグリニヤ變法を用いサフロールより 2,3-ジピペロニル-ブタンを合成したのであるが，この化合物は既に1936年 Orcutt, Bogert[9]により普通のグリニヤ反應により得られていることを，この化合物合成後知つた。分析値，融點より見て同一化合物と思われるが，本合成法の方が Orcutt, Bogert 法に比し，收量が 3 倍よい點で優れて居る。

尙，本化合物は松原弘道氏の御希望にもとづいて同氏に寄贈した。何れ他日同氏の許でその殺蟲共力劑としての生物試驗が行われるであろう。

本研究に當り終始御鞭撻を賜わつた東京文理科大學合眞一敎授，並びに色々と御助言下さいました岐阜大學農學部松原弘道氏，亦試料サフロールを御惠與下さつた日本香料の小野正夫氏に夫々厚く感謝する。尙，本研究費の一部は文部省科學研究費によるものである。

(昭和26年 4 月 6 日；日本化學會第 4 年會にて講演)

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Journal of Chromatographic Science, Vol. 29, June 1991

Gas Chromatographic and Mass Spectrometric Analysis of *N*-Methyl-1-aryl-2-propanamines Synthesized from the Substituted Allylbenzenes Present in Sassafras Oil

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Abstract

One method used for the synthesis of the illicit drug *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (methylenedioxymethamphetamine, MDMA) involves the treatment of safrole with HBr to form the intermediate 2-bromosafrole, followed by bromide displacement with methylamine. The starting material required for this synthesis, safrole, may be obtained from sassafras oil which is isolated from the roots of the sassafras plant. In addition to safrole, sassafras oil contains other allylbenzenes such as eugenol and 4-allyl-1,2-dimethoxybenzene. Gas chromatography–mass spectrometric (GC–MS) studies show that these allylbenzenes may also be brominated and undergo amine displacement to yield the corresponding *N*-methyl-1-aryl-2-propanamines. These studies also show that the regioisomeric 3-bromosafrole intermediate and 3-propanamine are not formed during this synthesis. Furthermore, the isomeric allylbenzenes isosafrole and isoeugenol that are generated in these reactions do not form stable bromo products and therefore no *N*-methyl-1-aryl-1-propanamine products are produced during the course of the bromination and amine displacement reactions.

Introduction

The various *N*-substituted derivatives of 1-(3,4-methylenedioxyphenyl)-2-propanamine (3,4-methylenedioxyamphetamine, MDA) have been popular drugs of abuse in the past decade (1–3). The *N*-methyl derivative, 3,4-methylenedioxymethamphetamine (MDMA, Ecstacy, or XTC) is perhaps the most widely abused drug of this series. MDMA is reported to have the unique ability to facilitate interpersonal communication by reducing the anxiety and fear that normally accompanies the discussion of emotionally painful events (4). In recent years, other designer drug analogs of MDA including the *N*-ethyl (MDE) and *N*-hydroxy (NOHMDA) derivatives have also been encountered in forensic samples and appear to possess pharmacological activities comparable to MDA and MDMA (5). The continued designer drug exploration of the MDA series has resulted in legislation in recent years to upgrade the penalties associated with the clandestine synthesis and abuse of these compounds.

A variety of methods have been reported for the synthesis of MDA, MDMA, and related compounds (5,6). The most direct approach involves treatment of the commercially available ketone 1-(3,4-methylenedioxyphenyl)-2-propanone (3,4-methylenedioxyphenylacetone) with ammonia or methylamine under reducing conditions as shown in Scheme 1. Based on this synthetic strategy, the availability of the ketone was controlled by the Drug Enforcement Administration under the Chemical Diversion and Trafficking Act in March of 1989. The restricted availability of the key ketone precursor has forced clandestine laboratory operators to seek alternative approaches for the synthesis of MDA and MDMA. One such alternate method employs the natural product safrole, which is commercially available or can be obtained by extraction or distillation of the sassafras plant native to the United States. Safrole may be brominated with hydrobromic acid to yield 2-bromosafrole, which can be converted to MDA or MDMA by direct displacement with ammonia or methylamine, respectively (Scheme 2). It appears that this latter approach was being employed by the operator of a clandestine laboratory seized recently. In this laboratory, safrole was obtained by steam distillation of the roots of the sassafras plant, and then treated with HBr to generate 2-bromosafrole. In an earlier study we found that in addition to safrole, sassafras oil contains other allylbenzenes such as eugenol (4-allyl-2-methoxyphenol) and 4-allyl-1,2-dimethoxybenzene (Scheme 3). In the present study, gas chromatographic–mass spectral (GC–MS) methods were used to determine if the other allylbenzenes present in sassafras oil also undergo the bromination and amine displacement reactions to yield the corresponding *N*-methyl-1-aryl-2-propanamines.

Experimental

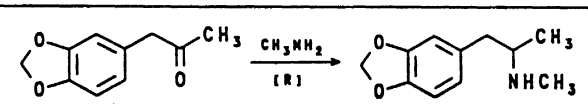
Gas chromatographic–mass spectrometric analysis. These analyses were performed using a Hewlett-Packard 5970B mass selective detector with sample introduction into the mass spectrometer via a gas chromatograph equipped with a 12-m × 0.20-mm i.d. fused-silica column with a 0.33-μm thickness of methylsilicone (HP1). The column temperature was programmed from 70° to 150°C at a rate of 15°/min and from 150° to 250° at a rate of 25°/min.

Bromination reactions. Samples of the individual substituted allylbenzenes (5.0 g of safrole, isosafrole, eugenol, isoeugenol, etc.) in 48% HBr (25 mL) were stirred at room temperature for 7 days. The reactions were then quenched with the addition of crushed ice (25 mL) and extracted with ether (2 × 50 mL). The ether extracts were evaporated to dryness under reduced pressure and the resultant product oils analyzed directly.

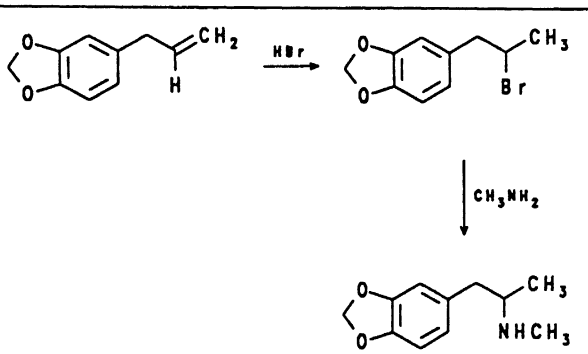
Amination reactions. The crude bromination products (2.0 g) were dissolved in methanol (100 mL) containing 40% aqueous methylamine (20 mL) and stirred at room temperature for 4 days. The reaction mixture was evaporated to dryness and the resultant oil dissolved in 10% HCl (50 mL). The aqueous acidic solution was washed with ether (2 × 50 mL) and then made basic (pH 12) by the addition of NaOH pellets. The aqueous base solution was extracted with ether (2 × 50 mL) and the combined ether extracts evaporated to dryness under reduced pressure. The resulting oil was analyzed directly.

Synthesis of the standard N-*methylaryl-2-propanamines.* A solution of the appropriate ketone (10 mMol), 1-(3,4-methylenedioxyphenyl)-2-propanone or 1-(3,4-dimethoxyphenyl)-2-propanone, aqueous methylamine (100 mMol), and sodium cyanoborohydride (25 mMol) in methanol (25 mL) was stirred at room temperature for 24 h. The reaction mixture was then evaporated to dryness under reduced pressure and the residue suspended in dichloromethane (50 mL). The dichloromethane suspension was extracted with 3 N HCl (2 × 75 mL) and the combined acid extracts made basic (pH 12) with sodium hydroxide. The basic aqueous suspension was then extracted with dichloromethane (2 × 100 mL) and the combined organic extracts dried over anhydrous sodium sulfate. Filtration followed by evaporation of the filtrate solvent gave the product amines in the free base form. Treatment of the bases with ethereal HCl (50 mL) afforded the amine hydrochlorides which were isolated by filtration and recrystallized from mixtures of anhydrous ether and absolute ethanol. The structure of the products were confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the product was established by GC–MS.

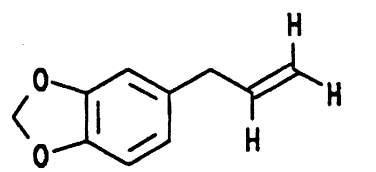
Synthesis of N-*methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine.* Aqueous methylamine (20 mMol) was added dropwise to a stirred solution of 1-(3,4-methylenedioxyphenyl)-3-propionyl chloride (10 mMol) in chloroform (50 mL) and the mixture stirred at room temperature for 1 h. The mixture was then stirred at reflux for ca. 15 min and the solvent evaporated under reduced pressure to yield an oil. The oil was partitioned between 20% potassium carbonate (50 mL) and chloroform (50 mL), and the chloroform layer separated. The chloroform solution was then washed with 10% HCl (50 mL) and evaporated under reduced pressure to yield the intermediate amide. A solution of the amide in THF (40 mL) was added dropwise to a suspension of lithium aluminum hydride (1 g) in THF (10 mL) stirred under a nitrogen atmosphere. After the addition was complete, the mixture was stirred at reflux overnight. The mixture was then cooled to room temperature, filtered, and the filtrate solvent evaporated under reduced pressure to yield the crude amine as an oil. The oil was partitioned between 10% HCl (50 mL) and chloroform (50 mL) and the aqueous layer separated and made basic (pH 12) with aqueous sodium hydroxide. The aqueous base suspension was extracted with chloroform (50 mL) and the chloroform removed under reduced pressure to yield the product amine in free base form. Treatment of the base with ethereal HCl afforded the desired amine hydrochloride. The structure of the product was confirmed by IR (KBr) and ^{1}H-NMR (deuterated DMSO). The purity of the product was established by GC–MS.



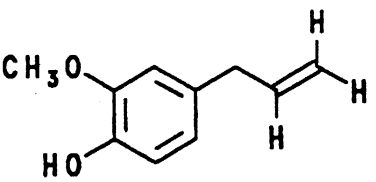
Scheme 1. Synthesis of *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA) by reductive amination.



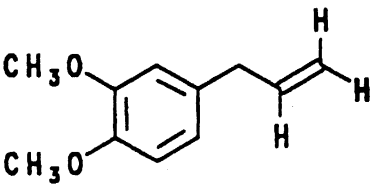
Scheme 2. Synthesis of 1-(3,4-methylenedioxyphenyl)-2-propanamine (MDMA) from safrole.



SAFROLE



EUGENOL



4-ALLYL-1,2-DIMETHOXY-BENZENE

Scheme 3. Allylbenzenes present in sassafras oil.

Results and Discussion

In a recent report (7), three allyl-substituted benzenes were identified as components of the volatile organic fraction from the steam distillation of the roots of the sassafras plant. The major component was safrole (4-allyl-1,2-methylenedioxybenzene); however, appreciable quantities of eugenol (4-allyl-2-methoxyphenol) and 4-allyl-1,2-dimethoxybenzene were also identified (Scheme 3). This mixture of allylbenzenes was obtained from a clandestine laboratory involved in the synthesis of aryl-2-propanamines via the addition of HBr to the double bond of the allyl group followed by amine displacement of the bromide. The major aryl-2-propanamine obtained from treating the brominated sassafras oil with methylamine would be 3,4-methylenedioxymethamphetamine (MDMA, Ecstacy, or XTC). This method for the preparation of MDMA circumvents the need for controlled precursor chemicals by obtaining the key intermediate, safrole, from the plant material.

In this study, authentic samples of each of the three allyl-substituted benzenes found in the sassafras distillate were subjected to the bromination–amination procedure. The goal of this work was to determine if these allyl benzenes would yield amine products similar to MDMA. The amine product from the treatment of safrole in this manner would be 3,4-methylenedioxymethamphetamine, MDMA (Scheme 2). The chromatogram resulting from the GC analysis of the amine from safrole is shown in Figure 1. The chromatogram shows one major component eluting at 7.2 min and displaying a base peak at *m/z* 58 and a molecular weight of 193. The chromatogram does not show any other major components in the amine product prepared from safrole. This mass spectrum is consistent with that obtained from an authentic sample of MDMA prepared from 3,4-methylenedioxyphenyl-2-propanone and methylamine via reductive amination with sodium cyanoborohydride (Scheme 1).

The bromination of the isolated double bond in safrole could yield the 3-bromo intermediate as well as the 2-bromo regioisomer. The bromination at the terminal carbon to give 1-(3,4-methylenedioxyphenyl)-3-bromopropane, followed by displacement of bromide by methylamine, would yield the 3-methylaminopropane regioisomer of MDMA. Although no 3-methylamino isomer was observed in the GC–MS analysis of the amination product from safrole following treatment with HBr, an authentic sample of *N*-methyl-1-(3,4-methylenedioxyphenyl)-3-propanamine was prepared to validate the specificity of the analytical method. This amine was prepared from 1-(3,4-methylenedioxyphenyl)propionic acid via methylamide formation followed by amide reduction with lithium aluminum hydride to yield the corresponding amine (Scheme 4). These two amines were subjected to GC–MS analysis yielding the chromatograms and spectra in Figure 2. This analysis was done under the same con-

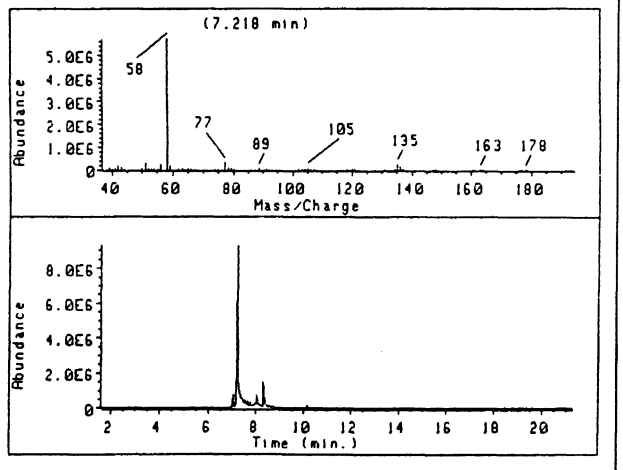


Figure 1. GC–MS analysis of the amines isolated after treatment of bromosafrole with methylamine.

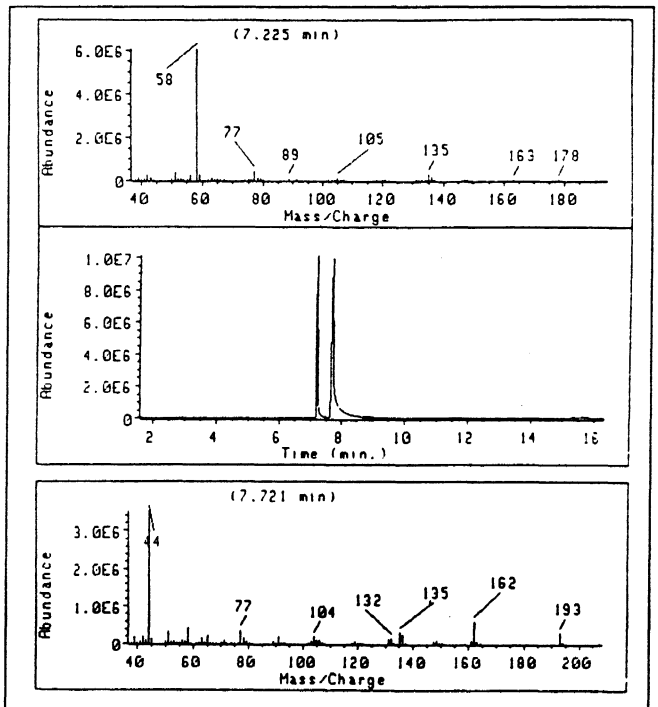
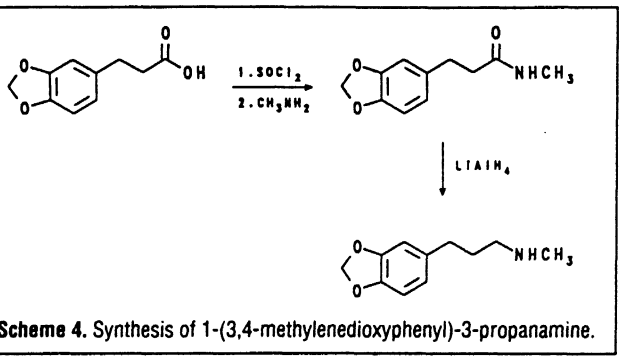
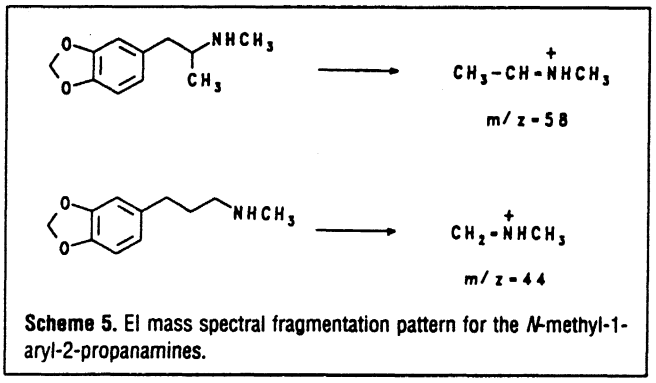


Figure 2. GC–MS analysis of the regioisomeric *N*-methyl-1-(3,4-methylenedioxyphenyl)-2- and 3-propanamines.



Scheme 4. Synthesis of 1-(3,4-methylenedioxyphenyl)-3-propanamine.



Scheme 5. EI mass spectral fragmentation pattern for the *N*-methyl-1-aryl-2-propanamines.

ditions as described for the chromatogram in Figure 1. The two regioisomeric amines are well resolved in the chromatogram (Figure 2) and the peak at 7.225 min for MDMA matches the elution properties for the major component in the safrole-derived amines in Figure 1. The base peak in this spectrum at *m/z* 58 is consistent with the 2-methylaminopropane side chain and is likely the result of the amine-dominated fragmentation illustrated in Scheme 5. The peak eluting at 7.721 min and yielding a base peak at *m/z* 44 is the 3-methylaminopropane isomer. The *m/z* 44 fragment arises from a similar fragmentation reaction from the 3-methylaminopropane as shown in Scheme 5.

The results of this experiment show that only the 2-aminopropane (MDMA) is produced in significant quantities via the treatment of safrole with HBr followed by methylamine as in Scheme 2. Furthermore, the gas chromatographic conditions used for the analysis of amines (as in Figure 1) are clearly capable of resolving the regioisomeric 2- and 3-propanamines (Figure 2).

The second allyl-substituted benzene identified in the plant distillate was eugenol. This compound was subjected to the same analogous reaction conditions as safrole, i.e., treatment with HBr followed by methylamine. The amine fraction from the reaction mixture was subjected to GC–MS analysis to yield the chromatogram and accompanying spectrum in Figure 3. Again, one major amine component was identified which, based upon the fragmentation data, is the 2-propanamine (*m/z* 58) product. This 2-propanamine is the result of bromide ion displacement from the major bromine addition site, the 2-position. Thus, this experiment shows that the 2-propanamine product of eugenol is a likely component of the amine fraction obtained from HBr and methylamine treatment of sassafras oil

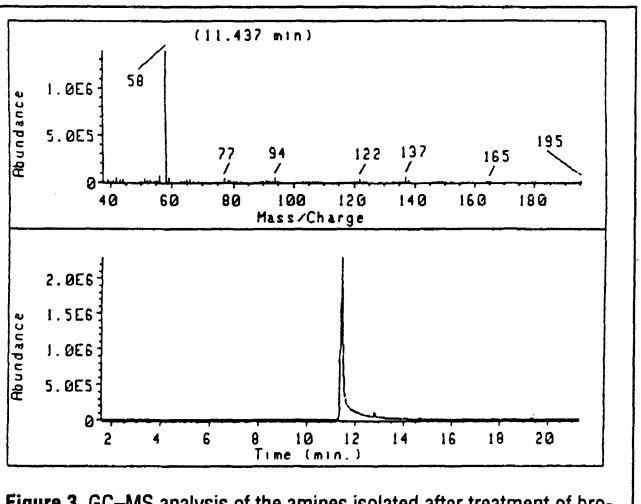


Figure 3. GC–MS analysis of the amines isolated after treatment of bromoeugenol with methylamine.

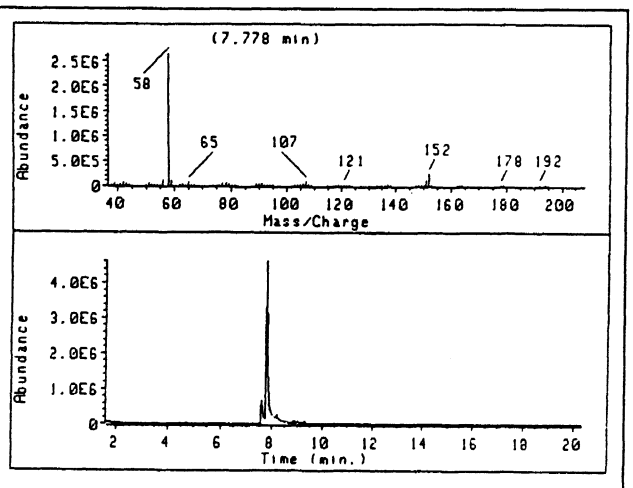
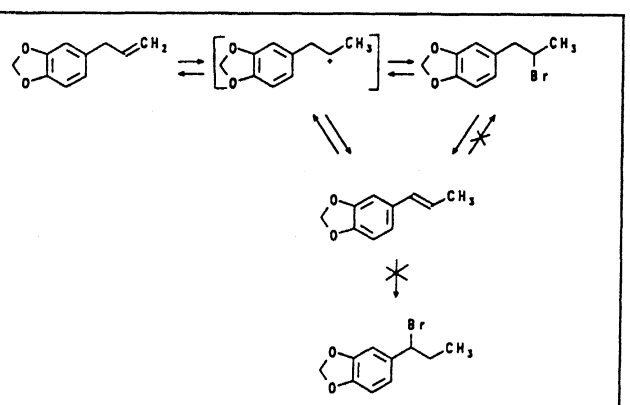


Figure 4. GC–MS analysis of the amines isolated after treatment of brominated 4-allyl-1,2-dimethoxybenzene with methylamine.

The third substituted allylbenzene, 4-allyl-1,2-dimethoxybenzene, was subjected to the same synthetic procedure as described previously. Analysis of the amine fraction yielded the chromatogram and spectrum in Figure 4. The product is composed primarily of one amine which appears to be the *N*-methyl-2-propanamine based on the characteristic amine dominated fragmentation pattern with a base peak of *m/z* 58. Independent synthesis of this amine from 3,4-dimethoxyphenylacetone via reductive amination confirmed the identity of the major component in Figure 4 as *N*-methyl-1-(3,4-dimethoxyphenyl)-2-propanamine.

In a previous report (7), the analysis of HBr-treated sassafras oil showed the presence of isosafrole, which was not identified in the original oil prior to HBr treatment. It was theorized that this product formed from elimination of HBr from 2-bromosafrole as shown in Scheme 6. The readdition of HBr to this compound could yield the 1-bromosafrole intermediate and the 1-propanamine product upon treatment with methylamine. Although this product was not identified in the amine fraction from sassafras oil, the failure to identify such a product could be because of a lack of necessary instrument sensitivity or of the complexity of the sample. In a effort to determine the reactivity of this isomeric olefin, isosafrole was subjected to treatment with HBr under the reaction conditions outlined in Scheme 2. Analysis of the product solution showed only the presence of the starting material isosafrole; no bromine-containing organic compounds were detected. Thus the conjugated double bond in isosafrole does not add HBr under the same conditions as safrole. Therefore, any isosafrole generated via HBr elimination would not undergo readdition and should accumulate in the reaction mixture. Similar studies were conducted with isoeugenol which may have formed from eugenol in the original sassafras oil. The reaction of HBr with isoeugenol was also unsuccessful under the conditions used for HBr-addition to the unconjugated double bond in eugenol.

In summary, these experiments show that HBr treatment of the various substituted allylbenzenes found in sassafras oil yields predominantly the 2-bromopropane intermediates. Methylamine displacement reactions with these bromo intermediates yields the *N*-methyl-1-aryl-2-propanamines as the major components. The



Scheme 6. Formation of isofarole from safrole.

2-propanamines of eugenol and 1-allyl-3, 4-dimethoxybenzene are likely components of MDMA samples prepared from sassafras oil.

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Manuscript received March 4, 1991.

alc. and glacial AcOH give 91 g. *o*-$C_6H_4(CO)_2NCH_2C_6H_4F$-*p* (**XIV**), m. 132–4°; 70 g. **XIV** heated with 65 g. 40% NaOH, cooled, stirred with 140 g. 34% HCl 2 hrs. with heating, dild. with 1 l. water, filtered, the filtrate evapd. to dryness, and the product recrystd. from alc. give 37 g. (**XI**, R^4 = F) (**XV**), m. 265–8°; 20 g. **XII**, 8 g. NH_4SCN, and 35 ml. PhBr heated on an oil bath 1.5 hrs. at 145–50°, cooled, filtered, dild. with water, filtered, and the product washed with water and dried give 18.5 g. *p*-$R^5C_6H_4CH_2NHCSNH_2$ (**XVI**, R^5 = Br) (**XVII**), leaves, m. 157–8° (from H_2O); 30 g. **XIII**, 15 g. NH_4SCN, and 50 ml. PhBr heated 1 hr. at 145–50° and treated as above give 28 g. (**XVI**, R^5 = Cl) (**XVIII**), leaves, m. 139–9.5°; 25 g. **XV**, 13 g. NH_4SCN, and 40 ml. PhBr heated 45 min. at 150–5° and treated as above give 24.3 g. (**XVI**, R^5 = F) (**XIX**), leaves, m. 125–7°; 12 g. **XVII** in 30 ml. water treated with 8 g. **IIA** dropwise, stirred 2 hrs. with heating, dild. with water, filtered with C, neutralized with NaOH, and the ppt. filtered, washed with water, and recrystd. from alc. give 6.3 g. S.C($NHCH_2C_6H_4R^6$-*p*):N.CH:CH (**XX**, R^6 = Br) (**XXI**), m. 130–1°; 20 g. **XVIII** and 15 g. **IIA** similarly give 12 g. (**XX**, R^6 = Cl) (**XXII**), m. 129.5–131°; 18 g. **XIX** and 15 g. **IIA** give 11.6 g. (**XX**, R^6 = F) (**XXIII**), m. 130.5–2.0°. **XXI** (13 g.) in 120 ml. dry C_6H_6 heated 30 min. with 3 g. $NaNH_2$, treated with the free base of **VA** (10 g. **VA** neutralized with NaOH and extd. with C_6H_6), refluxed 4 hrs., water added, the product washed with water, extd. with dil. HCl, the ext. made alk. with NaOH, extd. with C_6H_6, and the ext. dried with K_2CO_3 and distd. give 11.3 g. (69%) R^7(*p*-$R^8C_6H_4CH_2$)-$NCH_2CH_2NMe_2$ [**XXIV**, R^7 = S.CH:CH.N:C— (**XXV**), R^8 = Br], $b_{6.5}$ 203–4° (HCl salt, m. 164–5°); 12 g. **XXII**, 3 g. $NaNH_2$, and 12 g. **VA** give 11.2 g. (70.6%) (**XXIV**, R^7 = **XXV**, R^8 = Cl), $b_{6.5}$ 192–4° (HCl salt, m. 157.5–8°); 10 g. **XXIII**, 3 g. $NaNH_2$, and 10 g. **VA** give 9.6 g. (71.4%) (**XXIV**, R^7 = **XXV**, R^8 = F), $b_{6.5}$ 172–4° (HCl salt, m. 156–6.5°; maleic acid salt, m. 112–12.5°. K. Kitsuta

Utilization of safrole as a medical raw material. V. **Syntheses of imidazole and thiazole compounds.** Masao Ohara (Inst. Pharmaceutical Resources, Koganei, Tokyo). *J. Pharm. Soc. Japan* **72**, 936–8(1952); cf. *C.A.* **46**, 11206*h*. —3,4-$CH_2O_2C_6H_3CH(OMe)CH(NH_2)Me$ (I) (1 g.), 1.3 g. $PhCH_2C(OEt):NH.HCl$, and 0.5 g. Na_2CO_3 in 10 ml. Et_2O mixed well, allowed to stand overnight, water and Et_2O added, the Et_2O layer distd., the sirupy residue dissolved with alc. HCl, filtered, and the filtrate cooled give 1.1 g. 3,4-$CH_2O_2C_6H_3CH(OMe)CHMeNHC(:NH)CH_2Ph$ (II), white plates, decomp. 250–1° (from dil. alc.). 3,4-$CH_2O_2C_6H_3$-$COCHBrMe$ (III) (2 g.), 1 g. $MeC(:NH)NH_2.HCl$, and 3 g. Na_2CO_3 fused 2 hrs. at 160°, cooled, heated with dil. HCl, filtered, the filtrate made alk. with NH_4OH, the oily layer extd. with AcOEt, the AcOEt removed, and the residue treated with MeOH-HCl give 2,5-dimethyl-4-(3,4-methylenedioxyphenyl)imidazole (IV); **IV**.HCl, decomp. 227–9°. **III** (3 g.), 3 g. $PhCH_2C(:NH)NH_2.HCl$, and 4 g. AcONa heated 4 hrs. at 150–60°, cooled, dil. HCl added, the mixt. filtered, the filtrate made alk. with NH_4OH, the oily layer extd. with C_6H_6, the C_6H_6 removed, and the residue treated with MeOH-HCl give 4-(3,4-methylenedioxyphenyl)-5-methylimidazole (V); V.HCl.0.5H_2O, white needles, decomp. 227–30°. **III** (10 g.) and 3 g. $(NH_2)_2CS$ in 100 ml. hot alc. allowed to stand overnight give 2-amino-4-(3,4-methylenedioxyphenyl)-5-methylthiazole as its HBr salt (**VI**), m. 207–10°, which, dissolved in a large amt. of water, made alk., and the ppt. filtered and recrystd. from alc. gives 7.6 g. of the free base (**VII**), plates, m. 185–6°; **VII**.HCl, needles, decomp. 224–5°. **VII** (3 g.) in 30 ml. C_5H_5N treated with 3 g. *p*-$AcNHC_6H_4SO_2Cl$ portionwise, boiled 10 hrs. on an oil bath, the solvent removed *in vacuo*, the residue treated with dil. NaOH in excess, the insol. portion filtered, acidified, and the ppt. filtered, washed with water, and recrystd. from C_5H_5N-EtOH gives 3 g. 2-(*p*-$AcNHC_6H_4SO_2NH$) analog (**VIII**) of **VII**, granules, m. 216–17°; 2 g. **VIII** in 40 ml. EtOH-H_2O (1:1) contg. 10% NaOH, boiled on a water bath 2 hrs., water added, the alc. removed, the residue filtered, the filtrate made to pH 5 with dil. AcOH, and the product filtered and recrystd. from alc. give 15 g. 2-(*p*-$H_2NC_6H_4SO_2NH$) analog (**IX**) of **VIII**, needles, m. 219–21°. **VII** (2 g.) in 20 ml. xylene heated 7 hrs. with 3 g. Et_2NCH_2-CH_2Cl on an oil bath, the xylene removed *in vacuo*, the residue treated with dil. AcOH, filtered, the filtrate made alk., the oily layer extd. with C_6H_6, and the C_6H_6 removed give a sirupy 2-$Et_2NCH_2CH_2NH$ analog (**X**) of **VII** (picrolonate, decomp. 156–7°; picrate, m. 94–7°; methiodide, gelatinous). **VI. Syntheses of isoquinoline compounds having a dialkylaminoethyl radical.** Masao Ohara, Kozo Mochizuki, and Yoshio Deguchi. *Ibid.* 939–41.—*o*-$PhCH_2OC_6H_4COCl$ (**XI**) (prepd. from $SOCl_2$ and the acid) condensed with **I** to sirupy *o*-[3,4-$CH_2O_2C_6H_3CH(OMe)$-$CHMeNHCO]C_6H_4OCH_2Ph$-*o* (**XII**); 5 g. **XII** in 30 ml. xylene boiled 1 hr. with 9 g. $POCl_3$, cooled, petr. ether added, the clear upper layer decanted, the residue dissolved in MeOH, filtered with C, and the filtrate made alk. with NH_4OH gives sirupy 1-(*o*-benzyloxyphenyl)-3-methyl-6,7-methylenedioxyisoquinoline (**XIII**); 1-(*m*-benzyloxyphenyl) isomer (**XIV**), m. 115–17°. **XIII** (2.5 g.) in 30 ml. 20% HCl with a small amt. of MeOH heated on a water bath 4 hrs., filtered with C, the filtrate treated with Na_2CO_3, the ppt. filtered, treated with dil. NaOH, the insol. portion filtered off, the filtrate treated with satd. NH_4Cl, and the ppt. filtered and recrystd. from alc. give 1 g. 1-(*o*-HOC_6H_4) analog (**XV**) of **XIII**, plates, m. 146°; 1-(*m*-HOC_6H_4) isomer, plates, m. 268°. **XV** (0.7 g.), 3.5 g. 2% EtONa, and Et_2-NCH_2CH_2Cl with a trace of NaI boiled on a water bath 4 hrs., cooled, the ppt. filtered off, the filtrate concd. *in vacuo*, the oily layer extd. with C_6H_6, the ext. treated with dil. HCl, the HCl layer made alk., the oily layer taken up with C_6H_6, and the C_6H_6 removed give 0.6 g. sirupy 1-(*o*-Et_2-$NCH_2CH_2OC_6H_4$) analog (**XVI**) of **XV**; picrate, needles, m. 184–6°; methiodide, gelatinous. 1-(*m*-$Et_2NCH_2CH_2$-OC_6H_4) analog (**XVII**), sirupy; **XVII** picrate, m. 161–2°; **XVII**.MeI, granules, m. 75°; **XVII**.MeBr, gelatinous. 1-(*p*-$Et_2NCH_2CH_2OC_6H_4$) analog (**XVIII**) of **XV**, sirupy; picrate, decomp. 238–9°; methiodide, needles, m. 120°. Similarly, 0.7 g. **XV** and 0.3 g. $Me_2NCH_2CH_2Cl$ give a sirupy 1-(*o*-$Me_2NCH_2CH_2OC_6H_4$) analog (**XIX**) of **XV**; picrate, needles, m. 158–61°; methiodide, gelatinous. 1-(*m*-$Me_2NCH_2CH_2OC_6H_4$) analog (**XX**) of **XV**, sirupy; picrate, m. 190–2°; methiodide, leaves, m. 140°. 1-(*p*-Me_2-$NCH_2CH_2OC_6H_4$) analog (**XXI**) of **XV**, solid; picrate, m. 207–11°. Me 1-methyl-6,7-methylenedioxy-3-isoquinolinecarboxylate (**XXII**) (1 g.) and 1 g. $Et_2NCH_2CH_2OH$ heated on an oil bath 6 hrs. at 150°, the volatile substance removed *in vacuo*, the residue taken up in 3% AcOH, filtered, the filtrate made alk., and the free base filtered and recrystd. from Me_2CO give the $Et_2NCH_2CH_2$ ester of **XXII**, $C_{18}H_{22}$-$O_5N_2.0.5H_2O$, white needles, m. 69–71°. K. Kitsuta

2-Mercapto-4,5-diphenylimidazole derivatives as possible sympathomimetics. M. Vivekananda Bhatt, Balakrishna Harihara Iyer, and Praphulla Chandra Guha. *J. Indian Inst. Sci.* **31A**, Pt. 4, 43–50(1949); cf. *C.A.* **42**, 8799*b*.—The compds. listed in *C.A.* **42**, 8799*b*, were synthesized to study the pharmacol. effect of a phenethylamine structure, an alkylthiopseudourea residue, and an imidazole ring in the same compd. and to test the effect of different alkyl or aryl groups attached to the S of the mercapto group. There are discrepancies in the m.ps. reported in the 2 papers for the following *4,5-diphenylimidazole derivs.* (earlier values given in parentheses): 2-(2-hydroxyethylthio) 178° (167°); 2-(2,4,6-trinitrophenylthio), m. 250° (186°); 1-(*p*-methoxyphenyl), m. 297° (given as 1-*p*-tolyl in the earlier abstr.); 2-benzylthio-1-(*p*-methoxyphenyl), m. 161.2° (191–2°). D. K. Emory

Synthesis of β-aminocyclohexanepropionic acid and some derivatives. V. M. Rodionov and T. S. Kiseleva (D.I. Mendeleev Chem. Tech. Inst., Moscow). *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* **1952**, 278–88.—Cyclohexanone (49 g.), 61 g. $ClCH_2CO_2Et$, and 100 ml. dry C_6H_6 treated gradually with EtONa (dry) under 15° (amt. of EtONa unstated), stirred 4 hrs., and heated 48 hrs. on a steam bath, gave, after diln. with H_2O, washing the org. layer with 3% AcOH, and distn., 73% Et α,1-epoxycyclohexaneacetate (Et 1-oxospiro[2.5]-octane-2-carboxylate) (I), b_{10} 115–16°; with $NaNH_2$ catalyst the yield is 50%. I (67 g.) added to 9.2 g. Na in 220 ml. abs. EtOH, cooled to 15°, and dild. with 8 ml. H_2O gave 90% corresponding *Na salt*. This (250 g.) in 150 ml. H_2O is treated gradually with 150 ml. 1:1 H_2SO_4 with simultaneous passage of a stream of steam through the soln., giving a distillate of *hexahydrobenzaldehyde* which is collected in ice water; the upper layer of the distillate is sepd., taken up in 50 ml. EtOH, satd. with NH_3 with shaking and cooling, the suspension of the aldehyde-NH_3 ppt. allowed to stand 10–12 hrs. *in situ*, filtered, and the filter cake washed with EtOH

$N_2H_4.H_2O$ refluxed 0.75 hr. in 20 cc. $O(CH_2CH_2OH)_2$, the temp. raised to 200° by removing the H_2O, the mixt refluxed 4 hrs., cooled, poured into H_2O, acidified, extd. with EtOAc, and the product crystd. gave 1.2 g. $RCH_2CH_2CHMeCO_2H$ (XIII), m. 77–8° (ligroine). XIII (0.9 g.) cyclized as described above with PCl_5 and $SnCl_4$ gave 1,2,3,4-tetrahydro-2,5,6,7,8-pentamethyl-1-oxonaphthalene (XIV), m. 57–8° (ligroine). XIV (0.56 g.) in 5 cc. Et_2O added under N to a soln. prepd. from 7 g. MeI and 0.7 g. Li, most of the Et_2O removed after 6 hrs., 20 cc. C_6H_6 added, and the mixt. refluxed 3 hrs. and decompd. in ice and HCl gave 1,2-dihydro-3,4,5,5,7,8-hexamethylnaphthalene (XV), m. 89–90° (alc.). XV (0.11 g.) and 0.6 g. 30% Pd-C heated in refluxing $C_6H_3Cl_3$ under CO_2 required 7 hrs. for completion of the reaction; *b* the product, isolated through its picrate and distd., gave 60 mg. I, m. 48–50° (MeOH); *s*-$C_6H_3(NO_2)_3$ complex, m. 186–9°; picrate, m. 155–7°, unstable. IVa (5 g.), 3.5 g. EtCOCl, and 5 g. $AlCl_3$ in CH_2Cl_2 gave 7 g. 5-propionylprehnitene (XVI), $b_{0.2}$ 104°, n_D^{13} 1.5345. XVI (6.4 g.) and 5.4 g. Br in CCl_4 as above gave 7.7 g. α-bromo-5-propionylprehnitene (XVII), m. 36.5–7.5° (ligroine). XVII oxidized with NaOBr gave X. $CH_2(CO_2Et)_2$ (4.6 g.) added to 0.66 g. Na in 15 cc. alc., left 2 hrs. with 7.7 g. XVII in 10 cc. alc. at 60°, *c* the alc. removed, and the product isolated in the usual manner gave 6.4 g. of the ketol ether (XVIII), $b_{0.1}$ 104–10°; XVIII reduced Fehling soln., and with refluxing aq.-alc. KOH gave X. Methylsuccinic anhydride (4.3 g.) and 10 g. $AlCl_3$ in 30 cc. $PhNO_2$ added at 0° to 5 g. IVa in 5 cc. $PhNO_2$, the mixt. kept 1 hr. at room temp., decompd. with ice and HCl, and the $PhNO_2$ steam-distd. gave 2 g. XII; no other pure component was isolated from the residual mixt. Reaction in $(CH_2Cl)_2$ as described by Abadir (loc. cit.) gave *d* 85% $RCOCHMeCH_2CO_2H$, m. 112°, reduced by the Clemmensen method to the butyric acid, m. 106–7°. CH_2:CHCH$_2$CHMeAc (7.3 g.) left 4 hrs. at 35° with 8.2 g. IVa and 12.8 g. $AlCl_3$ and the product sepd. as usual gave 11.2 g. III, colorless oil, b_3 159°, n_D^{19} 1.5188; semicarbazone, m. 183–4°. III oxidized with concd. HNO_3 at 175–80° gave VI. III (2 g.) in 10 cc. Et_2O refluxed 2 hrs. with 0.31 g. $LiAlH_4$ in Et_2O gave $MeCHRCH_2CHMeCH(OH)Me$ (XIX), $b_{0.07}$ 112°. XIX (1.5 g.) added at 10° to 2 g. concd. H_2SO_4, *e* stirred 3 hrs. at room temp., and ice added gave an oil, b. 122–3°, with no OH max. in the infrared spectrum. III (11.2 g.) added dropwise at room temp. to IV (from 125 g. P_2O_5 and 50 cc. concd. H_3PO_4), the mixt. heated 5 hrs. at 125–30°, cooled, dild. with H_2O, extd. with Et_2O, and the product distd. gave 2 fractions: 4.2 g., $b_{0.07}$ 100–3°, and 3.2 g., $b_{0.07}$ 125–30°. The 2nd fraction gave 1,2,3,4,6,7-$C_{10}H_7Me_6$, m. 143–4°, λ 237, and 293, log ε 4.90, 3.81; picrate, m. 194–5°; 2,4,7-trinitrofluorenone complex, m. 205–6°. The 1st fraction was redistd. and collected as an oil, $b_{0.8}$ 140°, *f* n_D^{13} 1.5441, λ 220, 255(295) mμ, log ε 4.24, 3.60 (2.96), decolorizing Br in H_2O and $KMnO_4$ soln. and giving a yellow-brown color with $C(NO_2)_4$, with dil. HNO_3 at 175–80° it yielded VI; it was recovered after being heated 100 hrs. at 310° in a sealed tube with Se; at 360° (70 hrs.) charring occurred. IX (18.5 g.) refluxed 3 hrs. with 4 g. $LiAlH_4$ in 20 cc. Et_2O gave 14 g. 5-(1-hydroxyethyl)prehnitene (XX), b_1 121°, m. 53–4° (ligroine). XX (5 g.) and 0.5 g. C_5H_5N in 250 cc. Et_2O treated dropwise at −25° with 3.2 g. PBr_3 in *g* 250 cc. Et_2O, the mixt. stirred 0.5 hr. at −25°, poured the next morning into ice H_2O, and the Et_2O layer sepd., washed with $NaHCO_3$ soln., and distd. gave 4.8 g. 5-(1-bromoethyl)-prehnitene (XXI), m. 48° (ligroine), $b_{0.05}$ 90°. In one expt. in which crude XXI from 10.6 g. XX was distd. at 120°/0.15 mm., HBr was evolved, and, in addn. to a small amt. of XXI, 6.8 g. of a hydrocarbon, $b_{0.15}$ 200°, m. 169–70°(C_6H_6), was obtained; its ultraviolet absorption was very similar to that of 9,10-dihydroanthracene and it may possibly be 9,10-dihydro-1,2,3,4,5,6,7,8,9,10-decamethylanthracene, formed by condensation of 2 mol XXI; it was recovered after heating with Se at 310°; at 340° for 50 hrs. the product was charred. MeCHRMgBr (from 0.49 g. of the above bromide and 0.05 g. Mg) in 20 cc. Et_2O added dropwise to 0.25 g. $MeCHAc_2$ (XXII) in 20 cc. Et_2O at −80°, the suspension added slowly after 4 hrs. to a cold soln. of NH_4Cl, and the mixt. extd. with Et_2O, gave 0.25 g. MeCHRCMe:CRMe, prisms, m. 220–3°, λ 270, 279 mμ, ε 2.98, 2.94. XXII (32 g.), 18.5 g. $(CH_2OH)_2$, *i* and 100 mg. *p*-$MeC_6H_4SO_3H$ in 400 cc. C_6H_6 refluxed 20 hrs. gave 25.6 g. of the ketal, $b_{0.1}$ 60°, n_D^{20} 1.4411. XXII (21 g.) and 16 g. $HSCH_2CH_2OH$ gave 16 g. of the hemithioketal, $b_{0.1}$ 56°, n_D^{13} 1.4860. B. K. Wasson

Nitration of 1-ethylnaphthalene, 4-nitro- and 4,5-dinitro-1-ethylnaphthalene. S. I. Sergievskaya, T. S. Safonova, and G. Ya. Uretskaya. *J. Gen. Chem. U.S.S.R.* **27**, 823–6 (1957)(English translation).—See *C.A.* **51**, 16376*c*. B. M. R.

Antispasmodics. X. Syntheses of aralkylamines. Yutaka Kasuya and Kyo Fujie (Univ. Tokyo). *Yakugaku Zasshi* **78**, 551–3(1958); cf. *C.A.* **50**, 7309*h*.; **52**, 16587*g*.—$MeCO(CH_2)_2NEt_2$ (I) (1 g.) in 20 ml. Et_2O treated dropwise with 1 g. MeI, kept overnight, the ppt. filtered off, taken up in 3:1 Me_2CO-EtOH, and Et_2O added gave I.MeI, m. 161°; similarly is prepd. I.EtI, m. 185°. $Bz(CH_2)_2NEt_2$ (II) gave II.HCl, m. 108–10°, II.MeI, m. 160°, and II.EtI, m. 191°. A mixt. of 40 g. 2-acetyl-5,6,7,8-tetrahydronaphthalene, 25 g. $Et_2NH.HCl$, 14 g. $(CH_2O)_n$, and 105 ml. EtOH refluxed 2 hrs., then 2 more hrs. with 3 g. addnl. $(CH_2O)_n$, the soln. concd., the residue in dil. HCl washed with Et_2O, made alk. with K_2CO_3, the product extd. with Et_2O, dry HCl gas passed in, and the mixt. held at 0° gave 35 g. *2-diethylaminoethyl 5,6,7,8-tetrahydro-2-naphthyl ketone* (III), m. 107°. PhMgBr (0.81 g. Mg and 5.23 g. PhBr in Et_2O) treated dropwise with 5 g. III, kept overnight, refluxed 2 hrs., cooled at 0°, the product decompd. with *c* H_2O contg. 1.78 g. NH_4Cl, the Et_2O layer stirred with 10% HCl, and the HCl layer made alk. with Na_2CO_3, extd. with Et_2O, and treated with dry HCl gas yielded 21% *1-phenyl-1-(5,6,7,8-tetrahydro-2-naphthyl)-3-diethylamino-1-propanol HCl* (IV), m. 222° (MeOH-Et_2O). Similarly are prepd. $RR^1C(OH)CH_2CH_2R^2$ (V) (R, R^1, R^2, m.ps. of the HCl salt, methiodide, and ethiodide given): *Ph, Ph, NEt_2*, 202°, 190°, 207–8°; *Ph, Ph* piperidino, 238°, 214–15°, 204–5°. V (R,R^1,R^2, and b.p./mm. of free base given): *H, Ph, NEt_2*, 118–20°/5; *Me, H, NEt_2*, 68.5°/7. $HCONH_2$ [from 192 g. $(NH_4)_2CO_3$ and 230 g. HCO_2H] and 5 g. Ph_2CHCH_2Ac heated 12 hrs. at 182–5° yielded 60% $Ph_2CHCH_2CHMeNH_2$; HCl salt, m. 175°; picrate, m. 178°. HCONHMe (from 30 g. $MeNH_2$ and 50 g. HCO_2H) and 7.5 g. Ph_2CHCH_2Ac heated 18 hrs. at 180°, cooled, H_2O added, the product extd. with Et_2O, the ext. concd., the residue and 80 ml. concd. HCl heated 3 hrs., kept overnight, and the ppt. filtered off and recrystd. from H_2O yielded 70% *$Ph_2CHCH_2CHMeNHMe$* (VI) as HCl salt, m. 172–3°; free base, b_7 170°. Or, 1.5 g. Ph_2CHCH_2Ac in Et_2O, 1.2 g. 35% $MeNH_2$, and 0.5 g. Al-Hg heated 15 hrs. at 50–60°, the $Al(OH)_3$ filtered off, the filtrate concd., and the residue treated with HCl yielded 67% VI.HCl, m. 172–3°. VI (1.2 g.), 0.2 g. 90% HCO_2H, and 0.4 g. 38% formalin heated 20 hrs. at 100°, cooled, and the product treated with 10 ml. 5% HCl, washed with Et_2O, made alk. with NaOH, and extd. with Et_2O gave *$Ph_2CHCH_2CHMeNMe_2$* (VII); VII picrate, m. 128.5°; VII.HCl, m. 128°; VII.HI, m. 193°; VII.MeI, m. 203°. XI. Syntheses of aralkylamines and their quaternary ammonium derivatives. Yutaka Kasuya. *Ibid.* 509–11.—$Ph_2C(OH)CH_2CHMeR$ (I) and R^1X refluxed, the excess R^1X removed, and the residue washed with Et_2O and recrystd. from MeOH-Et_2O gave I.R^1X (II). II [R,R^1, X, and m.p. (decompn.) given]: *NMe_2, Me, I*, 254°; *NMe_2, Et, I*, 217°; *NEt_2, Me, I*, 205°; *NEt_2, Et, I*, 187°; *piperidino, Me, I*, 237°; *piperidino, Me, Cl*, 230°. $Ph_2C(OH)CH_2CHRMe$ (III) (1 g.) in 10 ml. C_6H_6 and 1 g. $SOCl_2$ refluxed 90 min., the soln. evapd. to dryness, and the residue in H_2O made alk. with NaOH, and extd. with Et_2O gave Ph_2C:CHCHRMe (IV). IV (R, m.ps. of salt, methiodide, and ethiodide given): *NMe_2, HCl*, 95°, 208°, 181°; *NEt_2, tartrate*, 103°, 152°, 122-3°; *piperidino, HCl salt*, 139°, 182°, 150°. The warm MeOH soln. of III (R = piperidino) (V) and an equimolar amt. of D-tartaric acid in warm MeOH held at room temp. for sepn. of cryst. *l*-V D-tartrate (VI), the mother liquor concd., and the residue treated with Et_2O gave *d*-V D-tartrate (VII). VI, m. 205°, $[\alpha]_D^{18}$ −38.2°; *l*-V, m. 96°, $[\alpha]_D^{20}$ −64.6°; *l*-V.HCl, m. 234°, $[\alpha]_D^{18}$ −53.1°. VII, m. 161°, $[\alpha]_D^{18}$ 43.3°; *d*-V, m. 96°, $[\alpha]_D^{20}$ 53.5°; *d*-V.HCl, m. 234°, $[\alpha]_D^{18}$ 52.1°. PhMgBr (34.3 g. PhBr, 5.4 g. Mg, and Et_2O) at 0° treated dropwise with 11 g. 2-$EtO_2CC_5H_4N$ in 50 ml. Et_2O, held overnight, the product decompd. with H_2O contg. 11.7 g. NH_4Cl, the Et_2O layer extd. with 10% HCl, made alk. with K_2CO_3, and the product extd. with Et_2O yielded 21% $Ph_2C(x\text{-}C_5H_4N)OH$ (VIII, x = 2), m. 105°; methiodide, m. 175°. Similarly are prepd. VIII (x, m.p., and m.p. of methiodide given): *3*, 115°, 250°; *4*, 235°, 230°. [3,4-$CH_2O_2C_6H_3CH_2CH_2Ac$ (1.5 g.) in 11 g. 94% EtOH treated with 1.2 g. 35% $MeNH_2$ and 0.5 g. Al-Hg, heated 5 hrs. at 50–60°, the Al(OH)$_3$ filtered off, the filtrate concd., and the residue in 5% HCl washed with Et_2O, made alk. with NaOH, and extd. with

$_2O$ yielded 78% 3,4-$CH_2O_2C_6H_3CH_2CHMeNHMe$ (IX); X.HCl, m. 124°. Similarly is prepd. 3,4-$CH_2O_2C_6H_3CH_2$-$H_2CHMeNMe_2$ (X); X.HI, m. 121°; X.MeI, m. 176°.
K. Kitsuta

Synthesis of naphthalimide and its derivatives. A. P. *a* arishin and D. M. Kustol (State Pedagog. Inst., Polva). *Zhur. Obshchei Khim.* 28, 692–5(1958).—Heating 0 g. naphthalic anhydride and 80 ml. 16% NH_4OH 30 min. a steam bath (final temp. 90°), and dilg. with H_2O gave 0% *naphthalimide*, m. 299–300°; with 16% NH_4OH at 60° — is forms a soln. of NH_4 salt of naphthalic acid monoamide, hich with aq. KOH gave a ppt. of the mono-K salt of aphthalic monoamide. Similarly prepd. were 98% *4-hloronaphthalimide*, m. 302–3°, 98% *4-bromonaphthalimide*, *b* n. 296–7°, and 97.5% *4-nitronaphthalimide*, m. 289–90°. eating 20 g. 4,5-dichloronaphthalic anhydride with 20 ml. $PhNO_2$ and 160 ml. 16% NH_4OH 2 hrs., boiling the residue ith 150 ml. 3% NaOH to distil the $PhNO_2$, and filtering ave an insol. Na deriv. which refluxed with 10% HCl and — ooled gave 88% *4,5-dichloronaphthalimide*, m. 372–3° rom $PhNO_2$). Similarly prepd. were 65% *4-bromo-5-hloronaphthalimide*, m. above 365°, and 95% *4,5-dibromo-aphthalimide*, m. 343–4° (from $PhNO_2$). In the above re- *c* ctions heating of the anhydrides with NH_4OH should be radual to avoid the loss of NH_3 at the early stage of reaction.
G. M. Kosolapoff

Synthesis and transformations of *cis*- and *trans*-1-ethynyl derivs. of 1-decalols. I. N. Nazarov, G. V. Aleksandrova, — nd A. A. Akhrem (N.D. Zelinskiĭ Inst. Org. Chem., Moscow). *Doklady Akad. Nauk S.S.S.R.* 119, 708–11(1958); . *C.A.* 50, 13846*b*.—*trans*-1-Decalone reacted with C_2H_2 in iquid NH_3-Na in the presence of powd. KOH yielding mixed *d* *isomeric trans-1-ethynyl derivs. of 1-decalol*, which by freezing nd chromatography on Al_2O_3 gave *epimeric forms*, m. 4–5° (I), and b_1 86–7° (II), n_D^{20} 1.5044, d_{20} 1.0041. Reaction f *cis*-1-decalone with Na and C_2H_2 in liquid NH_3 gave 60% *is-1-ethynyl deriv. of 1-decalol* (III), m. 55–6°, and only 10% — the ketone isomerized to the trans isomer in the reaction; olation of the latter ketone excludes the enol mechanism of cetylenic synthesis and confirms the purely organometallic oute (*C.A.* 48, 927*c*). Acetylation of the above 3 alcs. with Ac_2O gave, resp. the *acetates*, b_2 106–8°, n_D^{20} 1.4940, d_{20} *e* .0344; m. 79–80°; and m. 65–7°. The difficulty of esterification of the 1st alc. suggests that its HO group is axially located. Hydration of I in aq. MeOH with $HgSO_4$ gave *rans-1-acetyl deriv. of 1-decalol*, b_2 106–7°, 1.4970, 1.0502, nly on heating to 65°. II reacted at 20° to yield *trans-1-cetyl deriv. of 1-decalol isomer*, b_1 80–2°, 1.4898, 1.0337, which forms a semicarbazone and 2,4-dinitrophenylhydra- one, while its isomer yields only the semicarbazone indicat- ing a hindrance by Ac group in this isomer. III was hy- *f* drated only at 65° yielding *cis-1-acetyl deriv. of 1-decalol*, m. 6–7°, which formed only the semicarbazone, indicating teric hindrance by the cyclohexane ring. Oxidation of the omeric acetyldecalols with NaOBr gave, resp., *isomeric hydroxydecahydronaphthalene-1-carboxylic acids*, m. 149–50° *cetate*, m. 164–5°), m. 115–16° (*acetate*, unisolated), and . 134–6° (*acetate*, m. 141–2°). Thus II and III carry the O group in equatorial position, while I has an axial HO roup, this configuration being preserved in the hydroxy cids above.
G. M. Kosolapoff

Inner complex salts of azo compounds. V. Reactions — **coppering of *o*-hydroxy-*o'*-alkoxy azo compounds with simultaneous dealkylation.** V. I. Mur. *Zhur. Obshchei Khim.* 28, 998–1002(1958); cf. *C.A.* 52, 15460*c*.—Dealkyla- — ion caused by reaction of *o*-hydroxy-*o'*-alkoxy azo compds. ith $CuSO_4$ and pyridine proceeds just as readily as that of 1 Cu complex of the azo compound; the 1:2 complexes e much more resistant. In a series of arylazonaphthols it as shown that the substituent in *p*-position of aryl group *h* ffects the ease of such dealkylation in descending series: O_2, H, MeO, Me and Cl. *m*-NO_2 group hinders dealkyla- on. Possible mechanism is discussed.
G. M. K.

Synthesis and ultraviolet absorption spectra of certain — **sulfur-containing derivatives of naphthalene.** Arthur H. einstein and Robert M. Pierson (Goodyear Tire & Rubber esearch Lab., Akron, O.). *J. Org. Chem.* 23, 554–60 958).—Certain mercaptans, sulfides, and disulfides of aphthalene, such as the 1- (I) and 2-thionaphthols (II), *i* heir respective disulfides (III) (IV) and mixed Ph sulfides, s well as 2-naphthyl benzyl sulfide (V), 1-naphthyl allyl sul- de (VI), the 1- (VII) and 2-naphthylmethanethiols (VIII), naphthylmethyl benzyl sulfide (IX), and 1-(α-naphthyl)-2-methylpropane-2-thiol (X) were either synthesized or purified, and their ultraviolet absorption spectra recorded and correlated. Syntheses of 2-naphthylmethyl β-hydroxyethyl sulfide (XI), and 1,5-bis(β-naphthylmethylthio)pentane (XII) are also described. Com. II preëxtd. with hot MeOH treated with aq. KOH, addn. of mineral acid pptd. the thiol, the collected, washed, and dried ppt. was recrystd. gave II, m. 81.8–2.4° (alc.). II (64 g.) in 260 ml. alc. filtered through a medium porosity sintered glass funnel, the residue discarded, the filtrate refluxed 1 hr. with 50.4 g. iodine with 800 ml. MeOH, the ppt. washed with 95% alc., then with H_2O, oven dried, and recrystd. gave 51.5 g. IV, m. 141.8–2.6° ($CHCl_3$). II K salt (0.086 mole) in aq. alc. refluxed 2 hrs. with 12.7 g. $PhCH_2Cl$ in 50 ml. alc., unreacted II removed by extg. with hot 10% KOH, the residual sulfide washed with H_2O and crystd. gave 10.6 g. V, m. 89.8–90.5° (alc.). 1-Naphthylmethyl benzyl sulfide (XIII), XI, XII, and VI were prepd. by the same general procedure as that — used to prep. V. The following results were obtained (sulfide, m.p., recrystn. solvent, % crude yield, reactant thiol, halide given): V, 89.8–90.5°, alc., 49, II, $PhCH_2Cl$; 1-naphthyl phenyl sulfide (XIV), 39–40.5°, 95% alc., 12, II, PhI; 2-naphthyl phenyl sulfide (XV), 50.7–1.7°, abs. alc., 18, II, PhI; XIII, 57–7.3°, 95% alc., 85, VII, $PhCH_2Cl$; XI, 52–3.5°, 65% alc., 100. VIII, $HOCH_2CH_2Cl$; XII, 97.6-8.6°, $CHCl_3$-C_6H_{14}, 34, pentamethylene disulfide, 2-bromomethylnaphthalene; VI, —, —, 78, II, CH_2:-$CHCH_2Br$. II Na salt (25 g.) refluxed 3 hrs. at 188° with 8.4 g. PhI and 1 g. Cu powder, mixt. cooled, dild. with C_6H_6, filtered, C_6H_6 distd. together with the PhI, and the residual product fractionally distd. gave the following fractions: (*1*) 0.5 g. orange oil, $b_{0.25}$ 125–37° (Ph_2S); (*2*) 12.4 g. yellow oil, $b_{0.25}$ 144–56°, m. 47.5–50°; (*3*) 5.0 g. yellow oil, $b_{0.25}$ 154–65°, m. 38–41°; (*4*) 3.6 g., amber oil, $b_{0.25}$ 170–223° (dinaphthyl sulfide); (*5*) 2 g. black greasy solid residue. Recrystn. of fraction *2* gave 5.7 g. XV. Recrystn. of fraction *3* from 93% aq. alc. gave 3.3 g. XIV. Extg. 10 g. crude II with several 100 ml. portions of $CHCl_3$, and removing the solvent from the ext. gave 7.4 g. II, m. 73–7°. The $CHCl_3$ insol. residue was primarily a metallic powder which decompd. with mineral acid. II (4 g.) treated with 5.06 g. *e* 2,4-$(O_2N)_2C_6H_3Cl$ in alc. gave 6.57 g. dinitrophenyl sulfide (XVI). Careful repeated fractional recrystn. from hot 2:1 alc.-C_6H_6 gave 5.21 g. XVI, yellow solid, m. 149–50°, and 0.33 g. IV, m. 141.5–2.5° and about 1 g. of a solid, m. 103–35°, believed to be a mixt. of IV and XVI. No trace of the — α-2,4-dinitrophenyl sulfide could be found. 1-Chloromethylnaphthalene (XVII) was converted to VII by the method of Urquhart, *et al.* [*Org. Syntheses Collective Vol.* III, 363(1955)]. XVII (19.4 g.) refluxed 7 hrs. with 8.4 *f* g. $CS(NH_2)_2$ and 60 ml. 98% aq. alc., treated with 6.8 g. NaOH and refluxed another 2 hrs., most of the alc. removed, the residue acidified, treated with brine, and extd. with C_6H_6, the ext. washed and distd. gave 17.5 g. of yellow oil consisting of the desired VII of 91.2% purity. Distn. gave 15.1 g. VII, $b_{0.6}$ 142–3°, n_D^{20} 1.6628. VIII was similarly prepd. 2-Methylnaphthalene gave 2-bromomethylnaphthalene; this was converted to 79.9% crude VIII and purified to 9.5 g. good VIII, m. 47.2–7.7° (alc.). Hydrosulfurating crude 1-methylallylnaphthalene (XVIII) gave X. A *g* Grignard reagent obtained by the interaction of 104 g. 1-bromonaphthalene (XIX) with 12.2 g. Mg in 500 ml. Et_2O under N treated, first, with 50 ml. anhyd. Et_2O and 200 ml. anhyd. C_6H_6, then, with 0.500 mole quantity of β-methallyl — chloride during 0.5 hr., the system refluxed 2 hrs., hydrolyzed with 330 ml. 10% H_2SO_4, the layers sepd., Et_2O, β-methallyl chloride, and C_6H_6 removed, and the 89.4 g. residual oil distd. gave 57.9 g. crude XVIII, $b_{6.9}$ 128–32°. XVIII contained some XIX but was used without further purification. Crude XVIII treated at −78° in a glass-lined *h* steel autoclave with 10 ml. 48% BF_3 in Et_2O and 90 g. liquid H_2S, the sealed autoclave allowed to warm to room temp. and stand for 88 hrs., the vessel opened, product — poured into H_2O, extd. with Et_2O gave 60.5 g. of a brown oil which contained 83.2% X. X could not be purified by formation of the Pb mercaptide and liberation of X with mineral acid. By distn. 27.4 g. crude X under N the following fractions were obtained: (*1*) 8.6 g. yellow oil, b_5 152–5° (contg. 94.5% X); (*2*) 10.2 g. yellow fluorescent oil, b_5 155.7–60.0°, n_D^{20} 1.6162 (contg. 97.1% X). The over-all yield of fairly pure X from XIX was 34.8%. Fraction *2* was used for detn. of ultraviolet absorption spectrum and for element analysis. III was prepd. in 2 ways. Diazotized 1-