rated, combined with the filtrate from the second crystallization, and recrystallized from EtOAc giving 0.22 g of yellow crystals, mp 237–239°. This was found by ir, nmr, and uv spectra to have the structure **15**. The principal spectral bands are: ir (Nujol mull) 1725, 1685 (C=O) and 1620, 1590, 1580 cm$^{-1}$ (C=N/C=O); uv (EtOH) 220 m$\mu$ ($\epsilon$ 32,050), 265 (13,250), 374 (5150); nmr ($CDCl_3$) $\delta$ 3.22 and 3.24 (2 s, 6, $NCH_3$), 6.42 (s, 1, 5-=CH), and between 6.75 and 7.55 (m's, 7, arom H's).

Column fractions 10–17 were evaporated giving 0.2 g of nearly white solid. This was recrystallized from *i*-PrOH yielding 0.18 g of white needles, mp 226–228.5°. Ir, nmr, and analysis showed this to have the structure **16**. The principal spectral bands are: ir (Nujol mull) 1740, 1675 (C=O) and 1610, 1590, 1570 cm$^{-1}$ (C=N/C=C); nmr ($CDCl_3$) $\delta$ 1.8 (d, 3, 5-$CH_3$), 3.39 (s, 3, $NCH_3$), 4.14 (q, 1, 5-CH), and between 7.05 and 7.65 (m's, 7, arom H's).

**7-(*o*-Chlorophenyl)-*s*-triazino[1,2-*a*][1,4]benzodiazepine-1,3(2*H*,5*H*)-dione 2-Methoxyethanol Solvate (17).** This was prepared from 5.39 g (0.02 mol) of **24** essentially as described for **13** using diethylene glycol–dimethyl ether as a solvent for the first step. The intermediate 1-carbethoxy-3-[5-*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]urea failed to crystallize but tlc ($SiO_2$, 5% MeOH in $CHCl_3$) showed mostly one spot. It was used in the second step without purification. Crude **17** crystallized from the xylene solution during reflux. It was collected and recrystallized first from MeOH and then from 2-methoxyethanol and dried at 100° (0.02 mm) for 6 hr giving 2.95 g of solid, mp 225–232°. This was found by nmr to contain one molecule of 2-methoxyethanol. The principal spectral bands are: ir (Nujol mull) 3250, 3060 (NH/OH), 1705 (C=O), and 1615, 1595, 1570 cm$^{-1}$ (C=N/C=C); nmr (DMSO-$d_6$) $\delta$ 3.25 (s, 3, $OCH_3$), between 3.0 and 3.8 (m's, 5, $OCH_2CH_2OH$), ab centered at 4.3 and 4.8 (2, $J$ = −11 Hz, 5-$CH_2$), and between 6.8 and 7.8 (m's, 8, arom H's).

**1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-2-imidazolidinone (18).** To a solution of 7.5 g (0.02 mol) of **8** in 100 ml of THF under $N_2$ was added portionwise with stirring 3.0 g (0.07 mol) of 56% NaH in mineral oil. After stirring at room temperature for 18 hr the mixture was concentrated *in vacuo*, mixed with water and pentane, and neutralized with AcOH. The solid was collected, washed ($H_2O$ and pentane), and dried giving 6.66 g of crystalline solid, mp 217–227° dec. Recrystallization from *i*-PrOH yielded 4.45 g (65.5%) of white crystals, mp 245–247.5°. The principal spectral bands are: ir (Nujol mull) 3220, 3120 (NH), 1710 (C=O), and 1605, 1580 cm$^{-1}$ (C=N/C=C); nmr ($CDCl_3$) $\delta$ 3.46 (t, 2, $CH_2$), 4.05 (t, 2, $CH_2$), 3-$CH_2$ too broad to locate, 6.23 (broad s, 1, NH), and between 7.1 and 7.7 (m's, 8, arom H's); mass spectrum $M\cdot^+$ 338 (1 Cl).

**1-[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]-2-imidazolidinone (19).** This was prepared as described for **18** from 4.1 g (0.01 mol) of **10**. The crude product was dissolved in EtOAc, treated with decolorizing charcoal, filtered, concentrated, and diluted with $Et_2O$ giving 1.16 g (31%) of white crystals, mp 197–199°. The principal spectral bands are: ir (Nujol mull) 3270, 3120 (NH), 1725 (C=), and 1605, 1580 cm$^{-1}$ (C=N/C=C); nmr ($CDCl_3$) $\delta$ 3.45 (t, 2, $CH_2$), 4.07 (t, 2, $CH_2$), 4.8 (broad s, 2, 3-$CH_2$), 6.5 (broad s, 1, NH), and between 7.0 and 7.6 (m's, 7, arom H's).

**1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-methylimidazolidin-2-one (20).** To a solution of 2.7 g (0.008 mol) of **18** in 50 ml of DMF, under $N_2$, was slowly added with stirring 0.602 ml (2.0 g, 0.008 mol) of TlOEt. After stirring for 15 min 0.62 ml (0.01 mol) of MeI was added dropwise. After stirring at room temperature for 18 hr the mixture was filtered and the solid TlI was extracted with DMF. The DMF solution was concentrated *in vacuo* and diluted with water. The resulting solid was collected, washed ($H_2O$), and dried giving 2.58 g of cream-colored solid showing only one spot on tlc ($SiO_2$, 5% MeOH in $CHCl_3$ or 60% EtOAc in cyclohexane). Recrystallization from *i*-PrOH yielded 2.32 g (82%) of light yellow crystals, mp 212–215° (after scintering at 195.5–199°). The principal spectral bands are: ir (Nujol mull) 1720 (C=O) and 1605, 1595, 1580 cm$^{-1}$ (C=N/C=C); nmr ($CDCl_3$) $\delta$ 2.9 (s, 3, $NCH_3$), 3.38 (t, 2, $CH_2$), 3.95 (t, 2, $CH_2$), 3-$CH_2$ too broad to locate, and between 7.22 and 7.7 (m's, arom H's).

**1-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-3-[2-(dimethylamino)ethyl]-2-imidazolidinone (21).** To a solution of 1.7 g (0.005 mol) of **18** in 25 ml of DMF, under $N_2$, was added with stirring 0.362 ml (0.005 mol) of TlOEt. A solid separated and 1.3 ml (0.65 g, 0.006 mol) of 4.6 *M* 2-(dimethylamino)ethyl chloride in xylene was added. After stirring at room temperature for 18 hr tlc ($SiO_2$, 20% MeOH in PhH) indicated the reaction was not complete so 1.3 ml more of the 2-(dimethylamino)ethyl chloride solution was added and stirring was continued for 4 days. The mixture was filtered, concentrated, diluted with $H_2O$, and extracted with $CHCl_3$. The extracts were washed ($H_2O$ + NaCl solution) and dried ($Na_2SO_4$). Evaporation of the solution gave light brown gum which was crystallized from cyclohexane–pentane and recrystallized from cyclohexane yielding 1.07 g (52%) of fluffy white needles, mp 129–130.5°. The principal spectral bands are: ir (Nujol mull) 1710 (C=O) and 1600, 1580 cm$^{-1}$ (C=N/C=C); nmr ($CDCl_3$) $\delta$ 2.22 [s, 6, $N(CH_3)_2$], 2.45 (t, 2, $CH_2$), 3.42 (t, 2, $CH_2$), 3.5 (t, 2, $CH_2$), 3.95 (t, 2, $CH_2$), 3-$CH_2$ too broad to locate, and between 7.1 and 7.7 (m's, arom H's); mass spectrum $M\cdot^+$ 409 (1 Cl).

**Acknowledgments.** The authors wish to thank the following people who contributed to this work: our Physical and Analytical Chemistry Unit for analytical and spectral data; Messrs. Bharat V. Kamdar, Alfred Koning, and Walter Friis for technical assistance.

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# Compounds Affecting the Central Nervous System. 4. 3β-Phenyltropane-2-carboxylic Esters and Analogs

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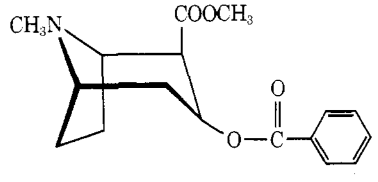
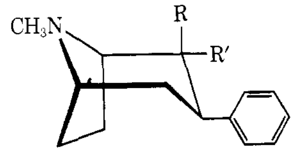
Modification of the structure of cocaine (**1**) by attachment of the aromatic ring directly to the 3 position of the tropane ring has resulted in a five- to sixtyfold increase in several biological parameters accompanied by a tenfold drop in local anesthetic activity and a fourfold lowering of intravenous toxicity.

Cocaine (**1**) has a variety of pharmacological actions, primary among them being strong CNS stimulation and local anesthetic action. These effects are accompanied by high toxicity and dependence liability. It was of considerable interest to see if modification of this molecule could result in a useful stimulant or antidepressant.



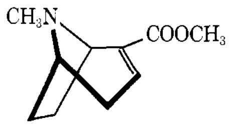
**1**



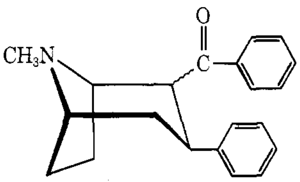
**2a**, R = COOCH$_3$; R′ = H
**b**, R = H; R′ = COOCH$_3$

The present paper describes modification **2a** and analogs. Formally, the phenyl group of cocaine has been attached directly to the tropane ring. The most active of these compounds are powerful stimulants which inhibit norepinephrine uptake in both heart and brain, reverse and prevent reserpine-induced eyelid ptosis, and produce only mild local anesthesia. The enantiomers of these compounds are devoid of stimulative activity.

Compound **2a** was prepared along with **2b** (1:3 ratio) by the reaction of phenylmagnesium bromide with (−)-anhydroecgonine methyl ester (**3**) at −20°. The 2-benzoyl derivatives **4a** and **4b** were formed in small quantity through reaction with a second molecule of Grignard reagent; the 2α configuration predominated. At room temperature, **4a** and **4b** were the principal products.[1] When 1 equiv of Cu$_2$Br$_2$ was used, only highly insoluble complexes resulted. A 5 mol % of cuprous salt produced troublesome complexes. Phenyllithium could not be substituted for the Grignard reagent owing to 1–2 addition with carbinol formation.[1] Most of the esters reported were prepared before optimum conditions were defined, and the low yields also reflect the early struggles with isomer separation.



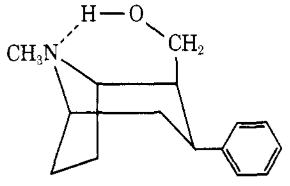
**3**



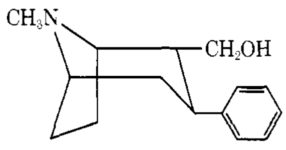
**4a**, 2β isomer
**b**, 2α isomer

Normally the 2-axial and 2-equatorial esters **2a** and **2b** were separated by column or plate chromatography. When it developed that the axial form **2a** was the epimer of interest, the equatorial epimer was removed from the reaction mixture by selective quaternization[†] with ethyl iodide at room temperature.

Configurational assignments for **2a** and **2b** were made on the basis of nmr and ir data.[3,4] The more polar (silica tlc) of the epimers showed an nmr coupling constant for the C-2 and C-3 hydrogens which indicated that they were in a trans-diaxial relationship. Therefore, it was the 3β-phenyl-2α-carboxylate **2b**. The nmr spectrum of the less polar of the epimers showed the C-2 and C-3 hydrogens to have a cis relationship. The functional groups at these positions then had to be β,β (as in **2a**) or α,α. This final distinction was made by reducing the epimer with LiAlH$_4$. The resulting alcohol **5** of necessity had the 2β configuration since its ir spectrum showed intramolecular hydrogen bonding. The less polar epimer is then properly represented by structure **2a**. As a confirmatory experiment, **2b** was reduced to **6** which showed only the expected intermolecular hydrogen bonding; it disappeared at high dilution. The acetates of **5** and **6** were also prepared, primarily for biological evaluation.



**5**

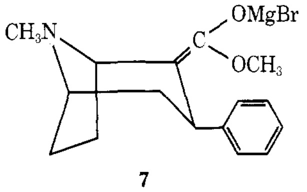


**6**

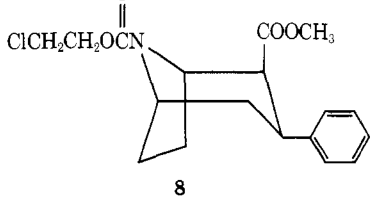
Nmr spectroscopy furnishes a convenient means for configurational assignment to these esters which are epimeric at C-2. The ester moiety in the axial (2β) position has a shielding effect on the NCH$_3$, producing a shift of 0.12–0.20 ppm upfield from that of the C-2 equatorial ester.[‡] There is a minor and unpredictable difference (±0.03 or less) in the COOCH$_3$ positions of these epimers.

Optical rotatory data are of questionable usefulness for configurational assignments to pairs of these C-2 epimeric compounds. Thus, cocaine (axial 2-COOCH$_3$) has a molar rotation value which is 17,570° more negative than that of pseudococaine (equatorial 2-COOCH$_3$). In the parallel case of ecgonine *vs.* pseudoecgonine, the difference is minus 12,580°. The difference for **2a** and **2b** is only minus 2670°. The 2-axial benzoyl compound **4a** is 31,110° more *positive* than equatorial compound **4b**.

There is indication that the equatorial configuration is the more stable at C-2. In experiments followed by tlc, NaOCH$_3$ in CH$_3$OH converted **2a** into **2b**, but accompanying decomposition destroyed the latter. Under the same conditions **2b** never produced any **2a** spot. On one sample of **2a**, heating for 30 min at 150° caused 10% conversion to **2b**; 30 min at 200° caused 50% conversion (followed by tlc). Subsequent samples were stable for 2 hr at 200° and began to decompose in a complex manner at 250°.



**7**



**8**

Attempts to influence the ratio of **2a** to **2b** in their initial formation were focused on the proton source for the hydrolysis of the Grignard adduct **7**. In order to increase the amount of the axial isomer **2a**, it appeared necessary to increase the amount of protonation at C-2 from the under or more hindered side of the molecule. The usual hydrolytic procedure of adding ice, followed by 2 *N* HCl, was varied by adding acetic acid in ether at both 0 and −50°, HCl gas, phenol in ether, BF$_3$·Et$_2$O, NH$_4$Cl, meth-

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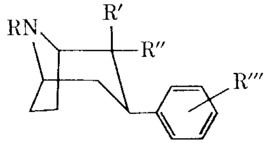
[†] Based on an observation of selective tropane quaternization by Weisz, *et al.*[2] Methyl iodide can be used where an isopropyl ester is present at C-2.

[‡] NCH$_3$ peak positions (ppm): **2a**, 2.22, **15**, 2.31, and **18**, 2.25 (2β-COOCH$_3$); **2b**, 2.42, **16**, 2.43, and **19**, 2.39 (2α-COOCH$_3$).

Table I



| Compd | R | R′ | R″ | R‴ | Mp, °C (base) | Mp, °C (salt) | Yield, % | Formula | Analyses$^{a}$ | $[\alpha]^{25}$D, deg |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | $CH_3$ | $COOCH_3$ | H | H | 62–64.5$^{b,e}$ |  | 16 | $C_{16}H_{21}NO_2$ | C, H, N | −5.3$^{c,d}$ |
| **2b** | $CH_3$ | H | $COOCH_3$ | H | 70–72$^{e,f}$ | 197–198$^{n,aa}$ | 46 | $C_{16}H_{21}NO_2 \cdot HCl$ | Cl, $OCH_3$ | +31.4$^{g,h,z}$ |
| **4a** | $CH_3$ | $COC_6H_5$ | H | H | 179–180$^{i}$ |  | <1 | $C_{21}H_{23}NO$ | C, H, N | +44.1$^{c}$ |
| **4b** | $CH_3$ | H | $COC_6H_5$ | H | 129–130$^{j}$ |  | <1 | $C_{21}H_{23}NO$ | C, H, N | −57.9$^{c}$ |
| **5** | $CH_3$ | $CH_2OH$ | H | H | 95–97$^{k,l}$ |  | 92 | $C_{15}H_{21}NO$ | C, H, N | −73.4$^{c}$ |
| **6** | $CH_3$ | H | $CH_2OH$ | H | 181–183$^{m,f}$ | 259–260$^{m,b}$ | 92$^{d}$ | $C_{15}H_{21}NO \cdot HCl$ | C, H, Cl | +25.0$^{g,h}$ |
| **11** | $CH_3$ | $CH_2OAc$ | H | H |  | 236.5–238.5$^{b,n}$ |  | $C_{17}H_{23}NO_2 \cdot HCl$ | C, H, Cl | −73.2$^{h}$ |
| **12** | $CH_3$ | H | $CH_2OAc$ | H |  | 227.5–230$^{m,o}$ |  | $(C_{17}H_{23}NO_2)_2C_{10}H_8S_2O_6$ | N, S | +31.1$^{h}$ |
| **13** | $CH_3$ | $COOCH_3$ | H | F$^{x}$ | 93–94.5$^{e}$ | 288–290 dec$^{m}$ | 5$^{g,p}$ | $(C_{16}H_{20}FNO_2)_2C_{10}H_8S_2O_6$$^{q}$ | C, H, S | −83.9$^{g,h}$ |
| **14** | $CH_3$ | H | $COOCH_3$ | F$^{x}$ | 70.5–73$^{e}$ | 85–93$^{bb}$ |  | $C_{16}H_{20}FNO_2 \cdot HCl \cdot H_2O$ | C, H, Cl | +23.7$^{g,h,r}$ |
| **15** | $CH_3$ | $COOCH_3$ | H | $OCH_3$$^{x}$ |  | 288 dec$^{k,m}$ | 1.2 | $(C_{17}H_{23}NO_3)_2C_{10}H_8S_2O_6$$^{q}$ | C, H, S | −92.0$^{h}$ |
| **16** | $CH_3$ | H | $COOCH_3$ | $OCH_3$$^{x}$ | 74.5–75.5$^{e}$ |  | 4 | $C_{17}H_{23}NO_3$ | C, H, N | +9.3$^{c}$ |
| **17** | $CH_3$ | H | $COC_6H_5$ | $OCH_3$$^{x}$ | 122–123$^{i}$ |  | 5 | $C_{23}H_{27}NO_3$ | C, H, N | −82.7$^{c}$ |
| **18** | $CH_3$ | $COOCH_3$ | H | $OCH_3$$^{y}$ | Oil |  | 4.5$^{d}$ | $C_{17}H_{23}NO_3$ | *dd* |  |
| **19** | $CH_3$ | H | $COOCH_3$ | $OCH_3$$^{y}$ | 81–82$^{l,aa}$ |  |  | $C_{17}H_{23}NO_3$ | C, H, N | +4.5$^{c}$ |
| **20** | $CH_3$ | $COOCH_3$ | H | OH$^{y}$ | Oil | 311 dec$^{k,ee}$ | 38$^{g}$ | $C_{16}H_{21}NO_3 \cdot HCl$ | C, H, Cl | −111.3$^{h}$ |
| **21**$^{v}$ | $CH_3$ | COO-*i*-Pr | H | H |  | 244–245 dec$^{n,aa}$ | 20 | $C_{18}H_{25}NO_2 \cdot HCl$ | C, H, N | −105.4$^{h}$ |
| **22**$^{v}$ | $CH_3$ | COO-*i*-Pr | H | F$^{x}$ | 110–112$^{e}$ | 224 dec$^{n}$ | 6$^{g,p}$ | $C_{18}H_{24}FNO_2 \cdot HCl$ | C, H, Cl | −97.3$^{g,h}$ |
| **23**$^{w}$ | H | $COOCH_3$ | H | H |  | 79–80$^{s,aa}$ |  | $C_{15}H_{19}NO_2 \cdot HCl \cdot H_2O$ | C, H, Cl | −110.0$^{h}$ |
| **24**$^{cc}$ | $CH_3$ | $COOCH_3$ | H | H | Oil | 272–274 dec$^{j,k}$ | 14$^{d}$ | $C_{16}H_{21}NO_2 \cdot C_{10}H_8O_6S_2$ | C, H, S | +85.2$^{h}$ |
| **25**$^{cc}$ | $CH_3$ | $COOCH_3$ | H | F$^{x}$ | 94–96$^{e,aa}$ | 292–294 dec$^{m,aa}$ | 9.5 | $(C_{16}H_{20}FNO_2)_2C_{10}H_8S_2O_6$$^{q}$ | C, H, S | +84.5$^{g,h}$ |
| **26**$^{cc}$ | $CH_3$ | H | $COOCH_3$ | F$^{x}$ | 71.5–73.5$^{e,aa}$ |  | 25 | $C_{16}H_{20}FNO_2$ | C, H, F | −1.2$^{t}$ |
| **27**$^{dd}$ | $CH_3$ | COOH | H | F$^{x}$ |  | 272–274$^{n}$ | 63 | $C_{15}H_{18}FNO_2 \cdot HCl$ | C, H, Cl | −105.3$^{h}$ |
| **28**$^{dd}$ | $CH_3$ | COOH | H | H |  | 273–274 dec$^{u}$ | 84 | $C_{15}H_{19}NO_2 \cdot HCl$ | C, H, N, Cl |  |

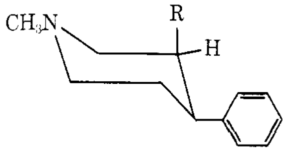
[a] Analytical results for indicated elements are within ±0.4% of the theoretical values. [b] Plates. [c] 1% in $CHCl_3$. [d] Free base. [e] From pentane. [f] Prisms. [g] Salt. [h] 1% in $H_2O$. [i] From ether. [j] From EtOH. [k] Heavy needles. [l] From hexane. [m] From $CH_3CN$. [n] From acetone. [o] Spherulites. [p] Poor reaction work-up. [q] Naphthalene-1,5-disulfonate salt. [r] $[\alpha]^{25}$D +1.1° (5% in $CHCl_3$) for free base. [s] From moist MeOH with ether added. [t] 5% in $CHCl_3$. [u] From MeOH with ether added. [v] Starting material described in Experimental Section. [w] Prepared from the *N*-(2-chloroethoxycarbonyl) derivative. See Experimental Section. [x] Para position. [y] Meta position. [z] $[\alpha]^{25}$D +4.6° (2% in $CHCl_3$) for the free base. [aa] Fine needles. [bb] From EtOAc–$Et_2O$–$H_2O$ mixture. [cc] **24**, **25**, and **26** are enantiomers of **2a**, **13**, and **14**, respectively. [dd] See Experimental Section. [ee] From MeOH.

anol, and trimethylamine. Dilute HCl was then added in each case. These variations had no effect on the ratio of isomers formed.

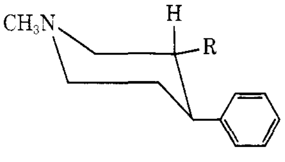
The absolute configuration of cocaine is known.[5] Since tropane ester **2a** was prepared from (−)-anhydroecgonine methyl ester derived from cocaine, it has the 1*R*,2*S*,3*S*,5*S* configuration. All other compounds reported here are related to this configuration with the exception of enantiomers **24–26** and piperidines **9** and **10.**

Table I summarizes the tropanes which were prepared in the course of defining the relationship between structure and CNS activity. The sole 8-nortropane, compound **23**, was prepared by treatment of **2a** with $ClCH_2CH_2O$-$COCl$[6] to form **8** which was then cleaved to the HN< compound **23** by treatment with chromous perchlorate.[7] Compounds **27** and **28** were prepared by simple acid hydrolysis of **13** and **2a**, respectively. Compounds **24–26** are enantiomeric with **2a**, **13**, and **14**, respectively. They were prepared from methyl (±)-3-oxo-1$\alpha$H,5$\alpha$H-tropane-2$\alpha$-carboxylate which was resolved according to the method of Findlay[8] with slight modification. The bitartrate salt of the unnatural (−) isomer was reduced (Pt, HOAc) to give methyl (+)-3$\alpha$-hydroxy-1$\alpha$H,5H-tropane-2$\alpha$-carboxylate which was dehydrated with $POCl_3$ to form (+)-anhydroecgonine methyl ester. This enantiomer of natural (−)-anhydroecgonine methyl ester (**3**) was then converted to **24–26** by the standard procedure.

It was of particular interest to determine if high rigidity in the molecule was a requirement for CNS activity. The unbridged (nonrigid) analog of **2a** is the cis ester **9a**. It and the trans isomer **10a** have been reported by Plati, *et al.*,[9] without configurational assignment. Reduction ($LiAlH_4$) of **9a** and **10a** has afforded alcohols **9b** and **10b**,[§] only one of which (**9b**, cis) showed intramolecular H bonding at high dilution. It was, therefore, possible to assign the cis and trans configurations respectively to the β and α compounds of Plati and coworkers. The corresponding acetate esters **9c** and **10c** were made for biological evaluation.



**9a**, R = $COOCH_3$
**b**, R = $CH_2OH$
**c**, R = $CH_2OAc$



**10a**, R = $COOCH_3$
**b**, R = $CH_2OH$
**c**, R = $CH_2OAc$

**Biological Studies.** Table II summarizes the overt behavioral effects produced by these 3β-aryltropane-2-carboxylates. The values reported are the lowest oral doses which produced an increase in locomotor activity. The most active compounds of the series are **13** and **23** which are some 64 times as active as cocaine. With a 4 mg/kg dose of **13**, stimulation was still evident at the end of 5 hr. Compound **25**, the enantiomer of **13**, is a mild depressant. Comparison of **2a** with **2b** and **13** with **14** shows that the 2-COOR group must have an axial configuration in order to be stimulative. Substitution of a 4-fluorine on the aromatic ring enhances activity (**13** *vs.* **2a**), whereas insertion of a 4-methoxy group reduces it (**15** *vs.* **2a**).

Reduction of the axial ester function on carbon 2 to a hydroxymethyl group (compound **5**) and acetylation of the resulting alcohol (compound **11**) did not lower the stimulative activity appreciably (compare with **2a**). However, removal of rigidity through removal of the ethylene bridge (compound **9a**) destroyed activity. Compound **9c**, the nonrigid analog of compound **11**, was only very weakly active. For all active compounds, the peak effect occurred at about 1 hr following medication. Further observations on stimulation are recorded in the ptosis study described below.

**Table II.** Effect of 3β-Aryltropanecarboxylate Esters on Locomotor Activity in Mice

| Compd | Min stimulative dose, mg/kg of base po | Compd | Min stimulative dose, mg/kg of base po |
|---|---|---|---|
| **Cocaine** | 64 | **12**[b] | >256 |
| **2a**[a] | 4 | **13**[b] | 1 |
| **2b**[b] | >256 | **14**[b] | >256 |
| **5**[a] | 4 | **15**[b] | 64 |
| **6**[b] | >256 | **16**[a] | >256 |
| **9a**[a] | >256 | **17**[a] | >256 |
| **9c**[b] | 256 | **21**[b] | 4 |
| **10c**[b] | <256 | **22**[b] | 4 |
| **11**[b] | 4 | **23**[b] | 1 |
| | | **25**[b] | 64[c] |

[a] The free base was administered. [b] The salt of the compound shown in Table I was administered. [c] Slight depressant.

Like cocaine,[10] the presently reported stimulants prevent as well as reverse reserpine-induced eyelid ptosis.[11] The most active compound, **13**, is more than five times as active as cocaine in the preventive test and 20 times as active in the reversal test. Table III summarizes the results. Again the enantiomer of **13** is inactive.

The local anesthetic action of these compounds was evaluated in parallel with cocaine using an intradermal anesthetic test in guinea pigs.[12] Compound **13** showed only about 15% of the local anesthetic activity produced by cocaine (after making allowance for the different salts involved). The activity of equatorial esters **2b** and **14** and the enantiomer **25** was not greatly different from that of compound **13**. Table IV summarizes these results.

Cocaine is known to inhibit the uptake of tritiated norepinephrine (NE-$^3$H) by heart, brain, and other adrenergically innervated tissues. For determination of this type of inhibition in heart tissue by some of the presently reported compounds, these compounds were injected subcutaneously into mice. After 15 min, 1 μCi of NE-$^3$H was injected into the tail vein. After 2 hr the animals were sacrificed, their hearts were incinerated, and the amount of NE-$^3$H therein was compared with that found in controls.[‡] Figure 1 shows the inhibitory effects of compounds **2a** and **15** and how they compare with cocaine and desmethylimipramine (DMI). Compound **2a** and DMI are about equiactive and some 15 times more active than cocaine.

The role which various substances play in influencing the normal action of norepinephrine in rat brain can be studied by introducing tritiated norepinephrine (NE-$^3$H) directly into the lateral ventricle of the brain.[13] This procedure circumvents the blood-brain barrier to norepinephrine and allows the tritiated material to equilibrate with endogenous stores. Thus, when a compound like cocaine inhibits the absorption of norepinephrine by the neuron, administration of the compound prior to the administration of the tritiated norepinephrine results in significantly lower levels of radioactivity in the brain tissue as compared to unmedicated controls.

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[§] Plati, *et al.*,[9] isolated a 1-methyl-4-phenylpiperidine-3-methanol of mp 107–109° by reduction of 5-carbethoxy-4-phenyl-2-pyridone with copper chromite catalyst. It probably is the trans isomer **10b** (our mp 111–113° as opposed to mp 99–100° of the cis isomer).

[‡] M. Levitt and W. R. Cumiskey, unpublished method.

**Table III.** Effect of 3β-Aryltropanecarboxylate Esters on Reserpine-Induced Ptosis in Mice

| Compd | Dose, mg/kg ip | Prevention test MPS[a] | Prevention test PV[b] | Reversal test MPS[a] | Reversal test PV[b] | Overt behavior |
|---|---|---|---|---|---|---|
| **2a** | 0.1 | | | 3.0 | NS[d] | 0.5 and 1 mg/kg controls questionable stim, 0.5 hr; 10, 30, and 50 mg/kg controls stim, running, jumping, biting, squeaking, hyperexcitable at 0.5 and 3 hr; mild stim at 5 hr; reversal 10, 30, and 50 mg/kg stim, running, biting, squeaking, vasodilation, some salivation at 0.5 hr |
| | 0.5 | | | 2.9 | NS | |
| | 1 | 2.6 | NS | 2.4 | 0.038 | |
| | 10 | 2.1 | 0.038 | 1.8 | 0.002 | |
| | 30 | 1.4 | 0.000 | 1.3 | 0.000 | |
| | 50 | 0.75 | 0.000 | 1.1 | 0.000 | |
| | G.T.[e] | 3.1, 3.1 | | 3.5, 3.4, 3.3 | | |
| **2b** | 30 | 3.4 | NS | 2.6 | NS | 30 and 50 mg/kg controls mild stim, some biting, squeaking; reversal, 30 and 50 mg/kg, moving about at 0.5 hr |
| | 50 | 2.6 | NS | 2.5 | 0.038 | |
| | $H_2O$[f] | 3.1 | | 3.4 | | |
| **5** | 1 | 3.4 | NS | 3.3 | NS | 10, 30, and 50 mg/kg stim, running, jumping, biting, squeaking, tearing, salivation, hyperexcitable at 0.5 hr; moderate stim at 3 hr; reversal, 10, 30, and 50 mg/kg, stim, running, biting, squeaking at 0.5 hr; prevention, 1/8 dead at 30 and 3/8 dead at 50 mg/kg before reserpine |
| | 10 | 2.5 | NS | 1.8 | 0.002 | |
| | 30 | 2.3 | 0.054 | 1.8 | 0.002 | |
| | 50 | 1.6 | 0.018 | 1.8 | 0.002 | |
| | G.T.[e] | 3.3, 3.3 | | 3.3, 3.4 | | |
| **6** | 30 | 3.1 | NS | 3.0 | NS | |
| | 50 | 2.9 | NS | 2.8 | NS | |
| | $H_2O$[f] | 3.4 | | 3.4 | | |
| **11** | 0.1 | | | 3.4 | NS | 10, 30, and 50 mg/kg controls stim, running, jumping, biting, squeaking, hyperexcitable at 0.5 and 3 hr; mild stim at 5 hr; 0.5 and 1 mg/kg control questionable mild stim at 0.5 hr |
| | 0.5 | | | 2.6 | 0.064 | |
| | 1 | | | 2.1 | 0.006 | |
| | 10 | | | 1.1 | 0.000 | |
| | 30 | 2.6 | 0.064 | 1.3 | 0.002 | |
| | 50 | 2.2 | 0.030 | 1.6 | 0.000 | |
| | $H_2O$[f] | 3.4 | | 3.4, 3.5, 3.3 | | |
| **12** | 30 | 3.4 | NS | 2.8 | 0.038 | |
| | 50 | 3.4 | NS | 2.8 | 0.064 | |
| | $H_2O$[f] | 3.4 | | 3.5 | | |
| **13** | 0.1 | | | 3.1 | NS | 0.5 and 1 mg/kg controls stim, running, jumping; 10, 30, and 50 mg/kg stim, running, jumping, biting, squeaking, some salvation, still stimulated at 3 and 5 hr; reversal, 10, 30, and 50 mg/kg stim, running, jumping, vasodilation, mild stimulation at 3 hr; prevention, 30 and 50 mg/kg, vasodilation |
| | 0.5 | | | 2.4 | 0.010 | |
| | 1 | 2.5 | 0.064 | 2.4 | 0.004 | |
| | 10 | 2.1 | 0.006 | 1.1 | 0.000 | |
| | 30 | 1.4 | 0.000 | 1.8 | 0.002 | |
| | $H_2O$[f] | 3.4, 3.1 | | 3.6, 3.3, 3.5 | | |
| **23** | 1 | 3.0 | NS | 2.4 | 0.050 | Stim, running, jumping, biting, squeaking at 10, 30, and 50 mg/kg; still stimulated at 3 and 5 hr |
| | 10 | 1.8 | 0.006 | 1.5 | 0.002 | |
| | 30 | 0.9 | 0.000 | 1.3 | 0.000 | |
| | 50 | 0.9 | 0.000 | 1.0 | 0.000 | |
| | $H_2O$[f] | 3.3, 3.1 | | 3.3, 3.4 | | |
| **25** | 30 | 3.1 | NS | 2.8 | NS | No changes obsd at 30 and 50 mg/kg |
| | 50 | 3.0 | NS | 3.0 | NS | |
| | $H_2O$[f] | 3.4 | | 3.5 | | |
| **27** | 30 | 3.5 | NS | 3.1 | NS | |
| | 50 | 3.1 | NS | 3.1 | NS | |
| | $H_2O$[f] | 3.3 | | 3.4 | | |
| **Cocaine** | 1 | 3.5 | NS | 3.4 | NS | 50 and 100 mg/kg controls excitement, convulsions; reversal, 50 and 100 mg/kg, convulsions, complete recovery from reserpine; at 100 mg/kg 1/8 dead at 0.5 hr |
| | 10 | 3.4 | NS | 2.1 | 0.010 | |
| | 30 | 2.9 | NS | 1.5 | 0.002 | |
| | 50 | 2.4 | 0.010 | 0.5 | 0.000 | |
| | $H_2O$[f] | 3.6 | | 3.4 | | |

[a] Mean ptosis score. [b] Probability values (PV) were calculated on "two-tailed" probabilities. Values of 0.05 are considered significant. [c] Effect of compound alone unless otherwise specified as "reversal" or "prevention" test. [d] NS denotes "not significant." [e] 1% gum tragacanth mucilage controls. [f] $H_2O$ control.

Table V shows the results of such a study wherein graded doses of compound **13** were administered subcutaneously. Cocaine was run in parallel for comparison, but higher doses of the latter were not practical owing to toxicity. **13** appears to be about 22 times more active than cocaine and apparently crosses the blood-brain barrier easily. Whereas **13** and DMI are about equiactive in the mouse heart, **13** is about 20 times more active than DMI in rat brain. This comparison is based on a report by Schildkraut, *et al.*,[14] that 25 mg/kg of DMI caused a 30 ± 3% drop in NE-$^3$H concentration in rat brain.

Toxicity studies on compounds **2a** and **13** in mice gave 24-hr $LD_{50}$ values of 63 (48–73) and 71 (64–78) mg/kg iv, respectively, compared with 18 (17–19) mg/kg for cocaine. Both of these 3-aryltropanes showed about the same oral toxicity as that of cocaine, the values being in the 200–400 mg/kg range. Further indications of toxicity are contained in the notes on overt behavior in Table III.

## Conclusions

Attachment of the benzene ring of cocaine directly to carbon 3 of the tropane moiety produced strongly enhanced stimulant activity. Using structure **2a** as a point of reference, replacement of the *N*-methyl group by a hydrogen atom (**23**) or substitution of a fluorine for hydrogen in the para position of the benzene ring (**13**) enhanced

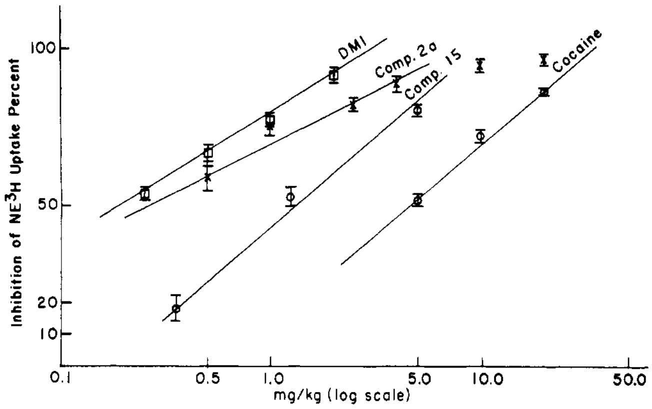

Figure 1. Inhibition of NE-$^3$H uptake in mouse heart.

**Table IV.** Local Anesthetic Activity in Guinea Pigs

| Drug[a] | Concn,[b] % | No. positive/no. tested | Mean anesthetic score | TAC$_5$, % (g/ml) | Activity ratio[c] |
|---|---|---|---|---|---|
| Cocaine | 0.125 | 4/4 | 32 | | |
| | 0.06 | 4/4 | 14 | 0.033 | |
| | 0.03 | 4/4 | 5 | | |
| **2a** | 1 | 4/4 | 27 | | 0.13 |
| | 0.5 | 4/4 | 11 | 0.25 | |
| | 0.25 | 4/4 | 7 | | |
| Cocaine | 0.125 | 4/4 | 24 | | |
| | 0.06 | 4/4 | 17 | 0.035 | |
| | 0.03 | 2/4 | 1.5 | | |
| **2b** | 1 | 4/4 | 19 | | 0.2 |
| | 0.5 | 4/4 | 13 | 0.16 | |
| | 0.25 | 4/4 | 9 | | |
| Cocaine | 0.125 | 4/4 | 35 | | |
| | 0.06 | 4/4 | 21 | 0.03 | |
| | 0.03 | 3/4 | 5 | | |
| **13** | 1 | 4/4 | 27 | | 0.11 |
| | 0.5 | 4/4 | 18 | 0.27 | |
| | 0.25 | 2/4 | 2 | | |
| Cocaine | 0.125 | 4/4 | 27 | | |
| | 0.06 | 4/4 | 14 | 0.031 | |
| | 0.03 | 3/4 | 5 | | |
| **14** | 1 | 4/4 | 23 | | 0.10 |
| | 0.5 | 4/4 | 15 | 0.30 | |
| | 0.25 | 2/4 | 1 | | |
| Cocaine | 0.125 | 4/4 | 31 | | |
| | 0.06 | 4/4 | 25 | 0.03 | |
| | 0.03 | 7/8 | 3 | | |
| **21** | 1 | 4/4 | 21 | | 0.2 |
| | 0.5 | 4/4 | 19 | 0.15 | |
| | 0.25 | 4/4 | 11 | | |
| | 0.125 | 1/4 | 1 | | |
| Cocaine | 0.125 | 4/4 | 29 | | |
| | 0.06 | 4/4 | 14.5 | 0.034 | |
| | 0.03 | 3/4 | 4 | | |
| **25** | 1 | 4/4 | 22 | | 0.11 |
| | 0.5 | 4/4 | 11 | 0.3 | |
| | 0.25 | 2/4 | 3 | | |

[a] The free base **2a** was dissolved in dilute lactic acid for test. The remainder of the compounds were tested in the form of salts as listed in Table I. Cocaine was tested as its HCl salt. [b] The concentrations shown are those of salts used except for that of base **2a**. [c] Activity of cocaine = 1.

**Table V.** Effect of Compound **13** and Cocaine on NE-$^3$H Concentrations in Rat Brain

| Compd | Dose, mg/kg (base) | nCi/g of brain ± S.E. | % reduction of NE-$^3$H |
|---|---|---|---|
| **13** | 21 | 5.3 ± 0.5 | 61 |
| **13** | 5.3 | 5.7 ± 0.3 | 59 |
| **13** | 1.3 | 9.2 ± 0.7 | 33 |
| Cocaine | 28.5 | 10.3 ± 1.2 | 25 |
| Control | | 13.7 ± 0.5 | |

stimulant action even further. Other modifications of **2a** tended to diminish this activity. The enantiomer of **13** was not a stimulant. Removal of the ethylene bridge (**9a**) also destroyed activity. Moving the 2-carbomethoxy group from an axial to an equatorial configuration gave a compound (**2b**) which was inactive in the locomotor screen (>256 mg/kg) but appeared to produce slight stimulation as judged by the operator of the ptosis test.

The general activity profile of these 3β-phenyltropane-2β-carboxylic esters appeared to parallel that of cocaine. Compound **13**, the most broadly studied member of the series, was about five times more active than cocaine in preventing reserpine-induced ptosis and some 20 times more effective in reversing it. Concurrently, the level of local anesthetic activity dropped to about 15% of that of cocaine. Finally, the inhibitory action of cocaine on uptake of norepinephrine in adrenergically ennervated tissues was observed with **2a** and **13** in mouse heart and rat brain, these 3-phenyltropanes being some 15-20 times more active than cocaine.

## Experimental Section**

**General Method for 3β-Aryltropanecarboxylic Esters.** The best method for preparing these compounds became apparent near the end of this work and is given in general terms here. Specific details follow under the appropriate compound heading with additional data in Table I. To an efficiently stirred solution of 1.0 mol of the Grignard reagent in 1.0 l. of $Et_2O$ under $N_2$ and maintained at −20° (±3°) was added a solution of 0.5 mol of (−)-anhydroecgonine methyl ester in 300 ml of $Et_2O$. Stirring was continued at this temperature for 1 hr and then the mixture was poured onto 500 g of ice. This mixture was acidified with 2 *N* HCl to dissolve all solid and the $Et_2O$ layer was then separated and discarded. The $H_2O$ layer was made basic with concentrated $NH_4OH$ and saturated with NaCl. Three extractions with $Et_2O$ separated the product which was then distilled (0.4 mm). A minor amount of unchanged anhydroecgonine ester distilled first, followed by an unseparable mixture of the 2α- and 2β-carboalkoxy isomers. The 2-benzoyl-3-phenyltropane by-products, exemplified by **4a** and **4b**, remained in the still pot.

If isolation of both the 2α and 2β epimers was desired, the mixture of these isomers was chromatographed on silica gel (40 g/g of compound) using *i*-$PrNH_2$-$Et_2O$-pentane (3:30:67) for elution. The 2β epimer was eluted first. If only the biologically interesting 2β epimer was wanted, the mixture was heated under reflux for 5 hr with 4 vol of acetone and 1.1 equiv of EtI. Removal of acetone and excess EtI *in vacuo* and partition of the residue between $Et_2O$ and $H_2O$ gave the pure β epimer in the $Et_2O$ layer and the quaternary salt of the α epimer in the $H_2O$.

Chromatography of the still pot residue above on silica gel afforded the 2β-aroyl-3-aryltropane (such as **4a**) as a quickly eluted material and the 2α-aroyl isomer (such as **4b**) as a more polar component.

**Compounds 2a and 2b** were formed in 75% yield, bp 128-134° (0.4 mm). Epimers were separated by chromatography. **2a** showed $M^+$ 259; $\lambda_{max}$ (oil) 5.72 and 5.82 μ; $\lambda_{max}$ (KBr) 5.70 μ; nmr on HCl salt (10% in DMSO-$d_6$) $J_{2,3}$ = 6.5 Hz. **2b** showed $\lambda_{max}$ (oil) 5.76 μ; nmr on HCl salt (10% in DMSO-$d_6$) $J_{2,3}$ = 11-12 Hz, $J_{3,4}$ = 5.5, 12 Hz.

**Compound 4a:** $\epsilon_{254\,nm}$ (EtOH) 11,200; $\lambda_{max}$ (KBr) 5.93 μ; nmr $J_{1,2}$ and $J_{2,3}$ *ca.* 1.5 and 3 Hz but unassigned (axial benzoyl).

**Compound 4b:** $\epsilon_{246\,nm}$ (EtOH) 13,800; $\lambda_{max}$ (KBr) 5.97 μ; nmr $J_{2,3}$ = 11 Hz, $J_{1,2}$ = 2 Hz (equatorial 2-benzoyl).

**3β-Phenyl-1αH,5αH-tropane-2β-methanol (5).** A solution of 2.96 g (11.4 mmol) of **2a** in 15 ml of $Et_2O$ was added dropwise

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** All melting points are uncorrected. Nmr spectra were measured in $CDCl_3$ unless otherwise noted using TMS as an internal standard. Where water was used, the TMS was external. Brinckmann Instruments silica gel grade $PF_{254}$ was used in 1-mm thickness for preparative plate chromatography. Analytical results for indicated elements are within ±0.4% of the theoretical values.

with stirring to 0.47 g (12.4 mmol) of $LiAlH_4$ in 25 ml of $Et_2O$. The mixture was stirred at room temperature for 2 hr, treated with 1.1 ml of $H_2O$, and filtered. Concentration of the filtrate and recrystallization of the residue from pentane gave 2.43 g (92%) of needles, mp 94–96.5°. A further recrystallization from hexane gave 2.10 g of compound **5** of Table I: ir ($CCl_4$) broad OH bond at 3231 $cm^{-1}$ not diluted out in 0.001 *M* solution.

The acetate ester of **5** ($Ac_2O$-pyridine, 1 hr, 100°) was an oil whose crystalline hydrochloride salt is compound **11** of Table I.

**3β-Phenyl-1αH,5αH-tropane-2α-methanol (6).** This alcohol was prepared from **2b** and $LiAlH_4$ in the manner described immediately above except that the cake resulting from hydrolysis had to be extracted thoroughly with $CHCl_3$. The basic product was recrystallized to give compound **6** of Table I: ir ($CCl_4$) single sharp peak at 3648 $cm^{-1}$ in 0.001 *M* solution.

The HCl salt of **6** is described in Table I. The acetate ester of **6** ($Ac_2O$-pyridine, 2.5 hr, 100°) was an oil whose crystalline naphthalene-1,5-disulfonate salt is compound **12** of Table I.

**Compounds 13 and 14.** $Cu_2Cl_2$ (7 mol %) was used in this preparation. The reaction was run at −10°. On a small scale they were separated by thick-layer plate chromatography (silica gel). On a large scale, epimer **13** was separated from **14** by selective quaternization of the latter with EtI.

**Compounds 15 and 16.** The unsaturated ester was added at 0° but the reaction was allowed to warm to 25° during the stirring period. Epimers were distilled together and then separated on silica preparative plates. The still pot residue crystallized and yielded compound **17**. A repeat run at −20° with quenching at that temperature gave a 43.5% yield of the distilled mixture of esters **15** and **16**, bp 164–179° (0.8–1.5 mm).

**Compounds 18 and 19.** The standard procedure gave 38% recovery of starting material and 34% of the **18–19** mixture, bp 150–170° (0.5 mm). Nmr indicated a 3:1 ratio of 2α:2β esters. Reflux of this mixture with 2 equiv of benzyl chloride in $CH_3CN$ for 27 hr left most of the 2β epimer **18** unchanged (4.5%). It was purified finally by plate chromatography (nmr compatible, $NCH_3$ 2.25 ppm; $\epsilon_{273\ nm}$ 1980, $\epsilon_{280\ nm}$ 1810) and the oily base was used in the preparation of **20** without further characterization.

The benzyl quaternary of the 2α epimer was debenzylated (Pd/C catalyst plus 1 equiv of HCl in 95% EtOH with $H_2$ under 3.5 $kg/cm^2$) to give the crystalline 2α epimer. Preparative plate chromatography gave the analytical sample, compound **19** of Table I: nmr $NCH_3$ 2.39 ppm; $\epsilon_{273\ nm}$ 2070, $\epsilon_{280\ nm}$ 1900.

**Compound 20.** A solution of 5.2 g of methoxy ester **18** in 25 ml of 48% HBr was refluxed for 1 hr and chilled, and the crystalline 3β-(*m*-hydroxyphenyl)-1αH,5αH-tropane-2β-carboxylic acid hydrobromide was collected (3.62 g, 66%). It was mixed with 80 ml of MeOH and gaseous HCl was bubbled in to saturation. The resulting solution was refluxed gently for 6 hr with a slow stream of HCl passing through. The solvent was removed, concentrated $NH_4OH$ was added, and the basic ester product was extracted with ether. Conversion of the oily base to its HCl salt gave compound **20** of Table I.

**Isopropyl esters 21** and **22** were prepared from the isopropyl ester of (−)-anhydroecgonine which is described immediately below.

**(−)-Anhydroecgonine Isopropyl Ester.** A mixture of 50 g of natural ecgonine hydrochloride and 100 ml of $POCl_3$ was refluxed for 1 hr and the excess $POCl_3$ was removed by warming *in vacuo*. The residue was treated with 350 ml of *i*-PrOH and let stand for 65 hr. Removal of the solvent, basification with 35% NaOH, and fourfold extraction with $Et_2O$ gave 45.8 g of oil. Distillation gave 42 g (90%) of product, bp 87–96° (0.8 mm). A center cut furnished the analytical sample: $[\alpha]^{25}{}_D$ −33.1° (1% in $CHCl_3$); $n^{25}{}_D$ 1.4860; $\epsilon_{218\ nm}$ (EtOH) 9217; ir and nmr spectra compatible with structure. *Anal.* ($C_{12}H_{19}NO_2$) C, H, N.

**Methyl 8-(2-Chloroethoxycarbonyl)-3β-phenyl-1αH,5αH-nortropane-2β-carboxylate (8).** A mixture of 5.40 g (2.08 mmol) of the 2-axial ester **2a** and 4.3 ml (5.9 g, 4.16 mmol) of 2-chloroethyl chloroformate was heated at 100° for 1.25 hr. Gas evolution ceased after 40 min. The excess chloroformate was removed by warming *in vacuo* and the residual oil in $Et_2O$ was percolated through 200 g of silica gel. The 4.8 g (65%) of oil in the first 400 ml of eluate showed a single spot by tlc and its spectra (ir and nmr) were completely compatible with the structure for the expected product. This material was used without further treatment.

**Methyl 3β-Phenyl-1αH,5αH-nortropane-2β-carboxylate (23).** All solutions and the apparatus were flushed with argon. A stirred solution of 10 ml of $(CH_2NH_2)_2$ in 800 ml of DMF was treated with 100 ml (83 mequiv) of 0.83 *N* $Cr(ClO_4)_2$.[6] The temperature rose to 42°. It was brought back to 25° and 4.80 g (1.36 mmol) of the chloroethylurethane **8** in 20 ml of DMF was added. This mixture was stirred for 2 hr, allowed to stand overnight, and then poured into ice–water. $(NH_4)_2CO_3$ (10 g) was added and the weakly basic mixture was extracted three times with $CHCl_3$-EtOH (2:1). The extracts were treated with an excess of 2 *N* HCl and concentrated to a pasty residue by warming *in vacuo*.

The pasty residue was treated with excess cold 2 *N* NaOH and the product was extracted with $Et_2O$. The oil obtained from the extracts was chromatographed on eight 20 × 40 cm preparative silica chromatoplates with development by *i*-$PrNH_2$-$Et_2O$ (3:97). The crystalline solid (2.05 g) from the principal product band was converted to its HCl salt, compound **23** of Table I.

**3β-(*p*-Fluorophenyl)-1αH,5αH-tropane-2β-carboxylic Acid (27).** A solution of 1.23 g (4.4 mmol) of ester **13** in 60 ml of 2 *N* HCl was heated under reflux for 24 hr and concentrated to give a crystalline residue. Two recrystallizations from acetone furnished 0.83 g of compound **27** of Table I.

**3β-Phenyl-1αH,5αH-tropane-2β-carboxylic Acid (28).** A solution of 4.6 g (0.018 mol) of ester **2a** in 75 ml of 2 *N* HCl was refluxed for 20 hr and concentrated to a residual oil by warming *in vacuo*. Trituration with acetone produced a solid which was recrystallized to give compound **28** of Table I. Nmr (5% in $D_2O$) showed the C-3 hydrogen at 3.5 ppm with a pattern ($J_{3,4}$ = 12 Hz, $J_{3,4}$ and $J_{2,3}$ = 6 and 6.5 Hz) supportive of the structure assigned.

**Resolution of Methyl (±)-3-Oxo-1αH,5αH-tropane-2α-carboxylate.** The method of Findlay[8] was used on his crude keto ester which, incidentally, crystallized quickly and completely upon addition of 2 equiv of $H_2O$. In the original precipitation of bitartrate salt only 1.2 ml of $H_2O$ was used for each gram of keto ester dihydrate and the warm, homogeneous mixture was *treated with charcoal* before allowing the salt to crystallize. Slow cooling and proper seeding gave an easily filterable mass of needles. One recrystallization from an equal weight of $H_2O$ then gave adequately pure bitartrate dihydrate [$[\alpha]^{25}{}_D$ +16.4°, mp 100–103° (lit.[8] $[\alpha]^{25}{}_D$ +15.4°, mp 91–94°)] in 66% yield (11% reported[8]).

Following isolation of roughly an equal quantity of the enantiomer from the processed mother liquors using (−)-tartaric acid, the filtrates were brought to pH 8 and the remaining basic material was extracted with $CHCl_3$. Short-path distillation of this basic residue at 0.2 mm using steam heat afforded substantial recovery of white, crystalline, unresolved keto ester which could be reprocessed.

**(+)-Methyl 3α-Hydroxy-1αH,5αH-tropane-2α-carboxylate [(+)-Pseudoalloecgonine Methyl Ester].** A solution of 7.00 g (0.0183 mol) of methyl (−)-3-oxo-1αH,5αH-tropane-2α-carboxylate (−)-bitartrate dihydrate in 100 ml of $H_2O$ was diluted with 200 ml of HOAc.[††] 1.0 g of $PtO_2$ was added, and the mixture was hydrogenated at room temperature under 4.2 $kg/cm^2$ for 19 hr. The catalyst and solvent were removed and the residual oil was treated with $CHCl_3$ and an excess of cold 35% NaOH. The aqueous layer was extracted twice with $CHCl_3$ and the combined $CHCl_3$ layers were concentrated to give an oil. This oil was dissolved in 100 ml of $Et_2O$, the solution was filtered to remove a powdery impurity, and the solvent was evaporated to give an oil which solidified (3.05 g, 82.5%).

This (+)-pseudoalloecgonine methyl ester was recrystallized twice from hexane (small amount of insoluble brown powder)[‡‡] to give massive prisms: mp 82.5–84.5°; $[\alpha]^{25}{}_D$ +38.2° (1% in $CHCl_3$); ir curve superimposable on that of its enantiomer; nmr peaks appeared in expected positions[3] but the coupling constants, $J_{2,3}$ = 3–4 Hz and $J_{3,4}$ = 3–4. 1 Hz, are lower in value than those reported by Sinnema, *et al.*[3] Supple, *et al.*,[4] attribute this to a flattening of the piperidine ring caused by the 3α-OH group. *Anal.* ($C_{10}H_{17}NO_3$) C, H, N.

**(+)-Anhydroecgonine Methyl Ester (Unnatural).** A mixture of 15.7 g (0.079 mol) of (+)-allopseudoecgonine methyl ester and 50 ml of $POCl_3$ was refluxed for 2.5 hr and concentrated to a residual oil by warming *in vacuo*. The oil was poured onto ice and the mixture made basic with 35% NaOH. The product was extracted with two portions of $Et_2O$ and four portions of $CHCl_3$ and distilled, practically all (8.72 g, 61%) boiling at 67–74° (0.1 mm). A center cut showed $n^{26}{}_D$ 1.5011; $[\alpha]^{25}{}_D$ +38.3° (1% in $CHCl_3$); ir $\lambda_{max}$ 1712 (C=O) and 1633 $cm^{-1}$ (C=C). *Anal.* ($C_{10}H_{15}NO_2$) C, H, N.

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[††] When the keto ester was dissolved in an $H_2O$-HOAc mixture using heat to aid dissolution, considerable enol acetate was formed.

[‡‡] Recrystallization requires about 12 ml of hexane/g but considerably more hexane is necessary to extract all the product from the brown powder.

**Compound 24.** The standard procedure using phenylmagnesium bromide and (+)-anhydroecgonine methyl ester (**3**) and no Cu salt gave a mixture isomeric at C-2: 42.6 g (72%); bp 129–135° (0.5–0.6 mm); isomer ratio 18:82 2β:2α (by vpc, 160° isothermal, OV-17). Reflux of the mixture (0.16 mol) with 0.20 mol of benzyl chloride in 100 ml of $CH_3CN$ for 5 hr, addition of $Et_2O$, and filtration separated most of the quaternary salt of the 2α-ester. The filtrate was extracted with 2 *N* HCl and the extracts were made basic with concentrated $NH_4OH$. Extraction with $Et_2O$ gave 8.2 g (14%) of the 2β-ester whose 1,5-naphthalenedisulfonate salt is compound **24** of Table I.

**Compounds 25 and 26.** $Cu_2Cl_2$ (6 mol %) was used in this reaction. The temperature was held at 0 to −5° during addition of (+)-anhydroecgonine methyl ester and subsequent stirring. The epimers were separated on a silica gel column (50:1 ratio) using *i*-$PrNH_2$–$Et_2O$–pentane (0.5:69.5:30) for elution.

***cis*-1-Methyl-4-phenylpiperidine-3-methanol (9b).** Plati, *et al.*,[9] report a mixture of *cis*- and *trans*-methyl (±)-1-methyl-4-phenylpiperidine-3-carboxylates from which they removed most of what is shown here to be the trans isomer as the HBr salt. The enriched cis isomer (Plati's β isomer) (10.6 g, 0.046 mol) was reduced with $LiAlH_4$ in the manner described for the preparation of **5** above. The crude product was recrystallized twice from EtOAc to give 6.12 g of massive prisms: mp 99–100°; ir ($CCl_4$) broad OH band at 3322 $cm^{-1}$ not diluted out in 0.001 *M* solution. *Anal.* ($C_{13}H_{19}NO$) C, H, neut equiv.

The acetate ester of **9b** ($Ac_2O$-pyridine, 3 hr, 100°) was an oil, the HCl salt of which formed long prisms, mp 191–194° ($CH_3CN$). *Anal.* ($C_{15}H_{21}NO_2 \cdot HCl$) C, H, Cl.

***trans*-1-Methyl-4-phenylpiperidine-3-methanol (10b).** The α isomer of methyl (±)-1-methyl-4-phenylpiperidine-3-carboxylate reported by Plati, *et al.*,[9] (5.4 g) was reduced with $LiAlH_4$ in the manner described for the preparation of **5** above. Recyrstallization of the product from EtOAc gave 3.9 g of prism clusters, mp 109–111°, which probably is the same material as that isomer of unknown configuration reported by Plati, *et al.*,[9] with mp 107–109°. The present material showed a single sharp ir peak at 3647 $cm^{-1}$ (nonbonded OH) in 0.005 *M* solution ($CCl_4$). The ir and nmr spectra were compatible with the expected structure.

The acetate ester **10c** of **10b** ($Ac_2O$-pyridine, 2 hr, 100°) was an oil, the HCl salt of which formed needles, mp 213.5–215° ($CH_3CN$). *Anal.* ($C_{15}H_{21}NO_2 \cdot HCl$) C, H, Cl.

**Biological.** The studies on locomotor activity (Table II), ptosis reversal and prevention (Table III), norepinephrine uptake inhibition in mouse heart (Figure 1), and acute toxicity were done using male Swiss-Webster mice (20 ± 2 g). The norepinephrine uptake inhibition experiments on brain tissue were done with male Sprague-Dawley strain rats (220 ± 20 g) and the local anesthetic determinations were made on Hartley strain guinea pigs (250–370 g). When compounds were administered as suspensions in 1% gum tragacanth, a volume of 0.1 ml was given per 10 g of animal body weight.

For the locomotor activity determinations the compounds were administered orally as suspensions in 1% gum tragacanth. The lowest doses which produced an increase in locomotor activity were gauged by visual observation of a group of six mice at the various dose levels beginning 30 min after medication. The results were confirmed with the aid of actophotometers.[15]

The ptosis prevention and reversal tests were done as described by Aceto and Harris.[11] In Table III where the controls are recorded as G.T. (1% gum tragacanth), the compounds in free base form were given as suspensions in that vehicle. Otherwise, the compounds were administered in salt form in aqueous solution. Each value for a mean ptosis score (MPS) represents observation of eight mice. The doses reported are in terms of the salts when used.

The local anesthetic activity was measured by the intradermal method of Bülbring and Wajda using guinea pigs. The average threshold anesthetic concentration ($TAC_5$) was obtained from the dose-effect curve (semilogarithmic plot of duration in minutes *vs.* dosage) as described by Luduena and Hoppe.[16]

In the mouse heart norepinephrine uptake inhibition experiments, aqueous solutions of DMI and cocaine hydrochlorides were used, as was an aqueous solution of compound **15**·1,5-naphthalenedisulfonate. Compound **2a** was dissolved in lactic acid. The dosage plotted is that of the salt used except for **2a** which was a free base. Each point in Figure 1 represents the mean ± S.E. obtained from six individual mouse hearts.

In the rat brain norepinephrine uptake inhibition studies, aqueous solutions of compound **13**·1,5-naphthalenedisulfonate and cocaine·HCl were used. The compounds were administered sc 45 min before intraventricular injection of 1 μCi of NE-$^3$H in a weakly acidic and buffered solution of 0.01-ml volume. The rats were sacrificed 2 hr after the NE-$^3$H injection. Each value in Table V represents the mean from six individual rat brains. Doses have been recalculated to a free amine basis.

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