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Synthesis of *O*- and *N*-Methylated Derivatives of 5-Hydroxytryptamine

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Several new methylated derivatives of serotonin and bufotenine having potential physiological interest have been prepared. Convenient syntheses of 1-methylbufotenine, 5-methoxy-*N*,*N*-dimethyltryptamine, and 1-methyl-5-methoxy-*N*,*N*-dimethyltryptamine from 5-benzyloxyindole are described.

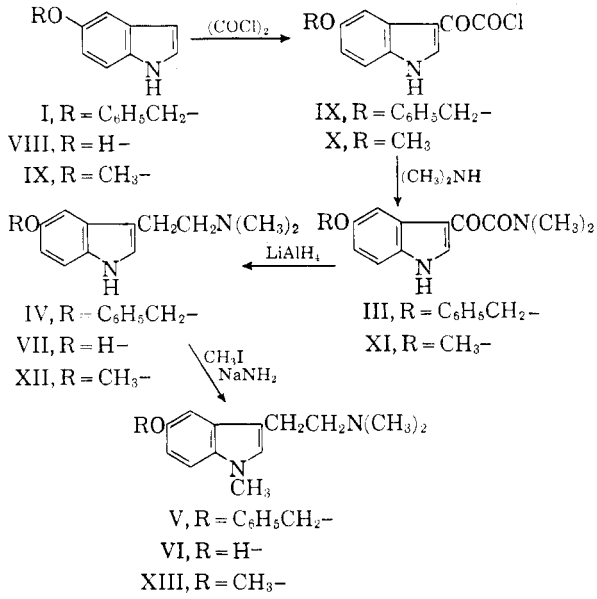
In a further investigation of indole compounds having potential psychotomimetic activity,[3] we undertook the synthesis of several new *O*- and *N*-methyl 5-hydroxytryptamine derivatives which are of interest because they are related structurally to 5-hydroxytryptamine (serotonin) and bufotenine (VII). The physiological significance of serotonin in the mammalian organism and its possible role in certain mental disorders has been a subject of wide study[4] during the past decade. The hallucinogenic activity of bufotenine(VII)[5] is also well documented and does not require further discussion here.

The general method described by Speeter and Anthony[6] was employed to introduce the β-dimethylaminoethyl side chain into the 3-position of various 5-substituted indoles. The individual steps in this reaction, which are shown in Chart I, use 5-benzyloxyindole (I) as a starting material. The conversion of I *via* intermediates II and III to *O*-benzylbufotenine (IV) has already been described.[6] Alkylation of IV in the 1-position was accomplished through the action of sodamide followed by methyl iodide on this compound dissolved in liquid ammonia;[7] a 92% yield of 1-methyl-5-benzyloxybufotenine (II) hydrochloride was obtained. Catalytic hydrogenolysis of V (HCl salt) in methanol solution in the presence of 10% palladium-on-charcoal catalyst gave 1-methylbufotenine (VI) hydrochloride in 85% yield. An exploratory attempt to *O*-methylate VI (free base) by means of methyl sulfate and alkali failed to give the desired 1,*N*,*N*-trimethyl-5-methoxytryptamine (XIII); instead, a water-soluble product was obtained which is thought to be a quaternary methosulfate of either XIII or its precursor VI.

Since alkylation of V by means of the sodamide–methyl iodide method did not result in quaternary salt formation, it was decided to attempt an *O*,*N*-dialkylation of bufotenine (VII) in this manner. A dry ethereal solution of the resulting alkylation product of VII was treated with anhydrous hydrogen bromide gas and the hydrobromide salt precipitated as a dark oil which could not be induced to crystallize by the usual methods. However, upon treating an ether solution of the crude base with picric acid, the monopicrate of the desired base XIII was obtained in low yield.

CHART I

Synthesis of 5-Hydroxytryptamine Derivatives



The general reaction scheme shown in Chart I also proved to be advantageous for a synthesis of both *O*-methylbufotenine (XII) and the *O*,*N*-dimethyl compound (XIII) from 5-methoxyindole. Hydrogenolysis of I in the presence of 10% palladium-on-charcoal catalyst was carried out in ethanol–acetic acid solution and also in ethanol alone. The resulting solutions of the labile 5-hydroxyindole (VIII) were found to have pronounced differences in their sensitivities to atmospheric oxygen; the product contained in the ethanol–acetic acid solution became dark blue-green upon very short exposure to air during filtration to remove the spent hydrogenolysis cata-

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(3) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **20**, 1454 (1955); *J. Org. Chem.*, **22**, 331 (1957); *J. Org. Chem.*, **23**, 19 (1958).

(4) G. P. Lewis, *5-Hydroxytryptamine*, 1st edition, Pergamon Press, New York (1958).

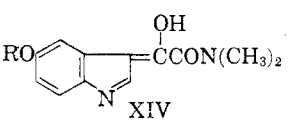
(5) U. L. Stromberg, *J. Chem. Soc.*, 1307 (1954); E. V. Evarts, *Ann. N. Y. Acad. Sci.*, **66**, 479, March 14, 1957.

(6) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(7) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

lyst, whereas solutions of VII in ethanol showed little or no tendency to form colored products during the filtration step. Alkylation of the 5-hydroxyindole preparations obtained from the two hydrogenolysis methods with methyl sulfate and alkali under identical conditions (nitrogen atmosphere) gave widely differing yields of 5-methoxyindole (IX). A 33% yield of IX was obtained from VII prepared in ethanol–acetic acid; the alkylation product obtained here required separation from relatively large quantities of dark resinous side products. In contrast, an 82% yield of IX was obtained from VII which was prepared in ethanol alone. Both yield values are based on the two reaction steps from I. The conversion of IX to 5 - methoxy - 3 - indole - *N,N* - dimethylglyoxalamide (XI) was effected in 75% yield *via* the intermediate glyoxalyl chloride (X) which was not characterized directly because of its sensitivity to moisture. Reduction of XIV with lithium aluminum hydride afforded *O*-methylbufotenine (XII) in nearly 92% yield, and subsequent alkylation of XII in liquid ammonia furnished the desired 1,*N*,-*N*-trimethyl-5-methoxytryptamine (XIII) in acceptable yield. The monopicrate obtained from this preparation of XIII was identical with the previously mentioned picrate prepared from impure XIII which resulted from the *O,N*-dimethylation of bufotenine (VII).

An exploratory attempt was made to *N*-methylate the glyoxalamide XI by the liquid ammonia method, since this could provide an additional route for obtaining XIII *via* the reduction of the expected *N*-alkylglyoxalamide. However, only unchanged XI was obtained at the end of the reaction. This apparent lack of reactivity may be associated with the possible tendency of XI to enolize strongly to the isoindole structure XIV which could form an *O*-sodio derivative in



XIV

sodamide–liquid ammonia. Since sodium alkoxides derived from vinyl-type alcohols are not easily alkylated under these conditions, the unchanged glyoxalamide XI would thus be regenerated in the course of treating the final reaction mixture with water.

Detailed results concerning the pyschopharmacology of these compounds will be published elsewhere.

EXPERIMENTAL[8]

5-Benzyloxy-1-methyl-N,N-dimethyltryptamine (V). 5-Benzyloxy-*N,N*-dimethyltryptamine was obtained from 5-benzyloxyindole in an over-all yield of 62% by the 3-step synthesis reported by Speeter and Anthony.[6] This compound was isolated and purified as the hydrochloride salt, m.p. 162–163° (reported,[6] 154–155°). Methylation at the 1-position was accomplished with $NaNH_2$ in liquid ammonia and methyl iodide by a procedure similar to that reported by Potts and Saxton[7] for methylation of tryptamine.

To an aqueous solution of 13.2 g. of 5-benzyloxy-*N,N*-dimethyltryptamine hydrochloride was added excess 10% NaOH to liberate the free base. The oil which separated was extracted with ether, dried over anhydrous $MgSO_4$, filtered, and added slowly and with stirring to a suspension of $NaNH_2$, prepared from 1 g. of clean sodium in about 150 ml. of liquid ammonia containing 0.1 g. of ferric nitrate. After stirring for 10 min., 3.5 ml. of methyl iodide was added dropwise, and the mixture was stirred 10 min. longer before allowing the ammonia to evaporate. The solid residue was treated with water and ether, and the ether layer was separated, washed with water, dried, and treated with an alcoholic HCl solution to precipitate the product as the hydrochloride salt; yield, 12.7 g. (92%); m.p. 182–183°, unchanged after recrystallization of a sample from alcohol-ether.

Anal. Calcd. for $C_{20}H_{25}ClN_2O$: C, 69.7; H, 7.3; N, 8.1. Found: C, 69.6; H, 6.9; N, 8.0.

1-Methylbufotenine (VI). To a solution of V hydrochloride in 150 ml. of methanol in a Parr hydrogenation bottle was added 1 g. of 10% Pd-C catalyst. The mixture was shaken under 3 atmospheres of hydrogen for 6 hr. at room temperature, at which time one mole of H_2 had been absorbed. The catalyst was removed by filtration, and the filtrate concentrated under reduced pressure. The residual glassy product crystallized when warmed with a little methanol and carefully treated with ether to give 7 g. (83%) of 1-methylbufotenine hydrochloride, m.p. 191–192°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: C, 61.3; H, 7.5; N, 11.0. Found: C, 60.9; H, 7.3; N, 10.8.

Attempted O-methylation of 1-methylbufotenine. To a stirred mixture of 5.1 g. of 1-methylbufotenine hydrochloride, 5 ml. of alcohol, 5 ml. of water, and 4 ml. of dimethyl sulfate was added gradually 15 ml. of 20% aqueous NaOH. The mixture became warm during the addition and was further heated at 50–60° for an additional 15 min. When cooled and diluted with water, the alkaline mixture gave a clear, brown solution from which none of the desired product, XIII, could be obtained. Apparently, quaternization of the side-chain nitrogen had occurred to give only water-soluble products, and this method was not suitable for synthesis of XIII.

5-Methoxyindole (IX). To a solution of 29.7 g. of 5-benzyloxyindole in 250 ml. of alcohol in a Parr hydrogenation bottle was added 3 g. of 10% Pd-C catalyst, and the mixture was shaken under 3 atm. of hydrogen at room temperature. Eight hours were required to absorb one mole of hydrogen for debenzylation. The mixture was filtered to remove catalyst and concentrated under reduced pressure with a nitrogen bleed to a volume of about 50 ml. To this solution was added 28 ml. of dimethyl sulfate and 1.2 g. of sodium hydrosulfite, and while maintaining a nitrogen atmosphere over the reaction mixture, a solution of 12 g. of NaOH in 26 ml. of water was added slowly with stirring and cooling to keep the temperature of the reaction mixture at 20–25°. After heating the mixture to 70° for 0.5 hr., it was cooled and diluted with an equal volume of water to separate the crude 5-methoxyindole as a yellow oil. Extraction of the oil with ether-benzene, drying over anhydrous $MgSO_4$, filtration, concentration, and distillation of the residue under reduced pressure afforded 16 g. (82%) of pure 5-methoxyindole, b.p. 123–125°/0.5 mm., as a colorless solid, m.p. 57–57.5° (reported,[9] m.p. 55°).

5-Methoxy-3-indole-N,N-dimethylglyoxalamide (XI). To a solution of 16 g. of 5-methoxyindole in 200 ml. of dry ether was added 25 g. of oxalyl chloride slowly and with stirring

(8) All melting points uncorrected.

(9) R. H. Marchant and D. G. Harvey, *J. Chem. Soc.*, 1808 (1951).

while cooling with a water bath. After stirring for 10 min., the red-orange solid which had formed was quickly filtered, washed with dry ether, and at once returned to the reaction flask and suspended in a fresh 200-ml. portion of dry ether. To this mixture was added slowly and with stirring a solution of 12.5 ml. of anhydrous dimethylamine in 25 ml. of dry ether. After stirring for 0.5 hr., the solid product was collected by filtration, washed with ether, slurried with water, refiltered, washed with water and ether, and then recrystallized from tetrahydrofuran-ether; yield, 20 g. (75%) of white, cotton-like needles; m.p. 223–223.5°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.7; H, 6.0; N, 11.2.

5-Methoxy-N,N-dimethyltryptamine (XII). To a stirred mixture of 11.7 g. of lithium aluminum hydride and 250 ml. of dry ether was added portionwise and cautiously a suspension of 18.5 g. of XI in 200 ml. of hot dry benzene, using additional dry ether to transfer the last of the solid. The reaction mixture was stirred and refluxed for 1.5 hr. longer, cooled in an ice bath, and cautiously treated with water to hydrolyze excess $LiAlH_4$ and the reaction complex. The ether-benzene solution of the product was filtered from the insoluble inorganic matter, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a residue of crude XII, which solidified on cooling; yield, 15 g. (91%). A portion of the crude product was converted to its hydrochloride salt, which was recrystallized from alcohol-ether; m.p. 145–146°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: Cl, 13.9. Found: Cl, 14.0.

1-Methyl-5-methoxy-N,N-dimethyltryptamine (XIII). *From* XII. A suspension of $NaNH_2$ in liquid ammonia was prepared from 1 g. of clean sodium, 150 ml. of liquid ammonia, and 0.1 g. of ferric nitrate. To this mixture was added portionwise 6 g. of crude XII dissolved in 20 ml. of dry ether. After stirring for 5 min., 3 ml. of methyl iodide was added slowly, and the ammonia was allowed to evaporate. The residue was treated with water, and the product extracted from this mixture with ethyl acetate and chloroform. After drying over anhydrous $MgSO_4$ and filtration, treatment with dry HCl precipitated crude XIII as its HCl salt. Recrystallization from alcohol-ether afforded 3.7 g. of 1-methyl-5-methoxy-*N,N*-dimethyltryptamine hydrochloride (50%), m.p. 196–196.5°, unchanged after one more recrystallization from alcohol-ether.

Anal. Calcd. for $C_{14}H_{21}ClN_2O$: Cl, 13.2; N, 10.4. Found: Cl, 13.1; N, 10.0.

From bufotenine (VII). To a suspension of $NaNH_2$ in 150 ml. of liquid ammonia prepared from 1.6 g. of clean sodium was added 6.1 g. of bufotenine, which had been obtained by hydrogenolysis of *O*-benzylbufotenine hydrochloride with hydrogen and 10% Pd-C.[6] After stirring for several minutes, 5 ml. of methyl iodide was added slowly, and the ammonia allowed to evaporate. The dark brown residue was treated with water and ether, the ether extract was separated and dried, and treated with anhydrous HBr. A very dark oil separated; attempts to purify it were futile. Finally, a sample was converted to the free base and a picrate obtained, which melted at 206–207° (dec.) after several recrystallizations from acetone-water; this picrate was identical to a specimen prepared from the product obtained from XII, m.p. 206–207° (dec.), no depression on mixed melting point.

Anal. Calcd. for $C_{26}H_{23}N_5O_8$: C, 52.0; H, 4.99; N, 15.19. Found: C, 52.0; H, 4.99; N, 15.17.

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Psychopharmacological Activity of Ring- and Side Chain-Substituted β-Phenethylamines[1]

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Synthesis of a number of ring-substituted β-phenethylamines containing alkyl, halogen, and alkoxy substituents by various methods is described. The influence of these ring substituents on the psychotomimetic activity of substituted β-phenethylamines was examined by observing the effect of these compounds on cat behavior.

To obtain additional information on the influence of both the nature and position of substituents on ring- and side chain-substituted β-phenethylamines on the psychotomimetic activity of this class of compounds, a series of β-phenethylamines containing a variety of substituents in the 3, 4, and 5 positions was synthesized. Substituents which were examined included alkyl, phenyl, halogen, and alkoxy in varying positions on the benzene ring in β-phenethylamine; a few compounds were also made with hydroxy or methyl groups in the side chain which are related to epinephrine and amphetamine. The effect of these compounds on normal cat behavior[4] was used as an index to the changes in psychochemical activity induced by the various substituents.

Synthesis. Most of the *p*-alkyl and halogen-substituted β-phenethylamines studied were obtained by chloromethylation of the appropriately substituted benzene, conversion of the resulting sub-

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(4) S. Norton and E. J. deBeer, *Ann. N. Y. Acad. Sci.*, 65, 249 (1956).