tion from water or ethanol gave a powder which did not melt below 340°.

Anal. Calcd. for $C_{25}H_{22}N_4O\cdot 2HCl$: C, 64.24; H, 5.18; N, 11.99. Found: C, 64.23; H, 5.25; N, 11.65.

From the acidic hydrolysis mixture, only a small amount of the amine (4.5%) was isolated as the hydrochloride.

4-Amino-2-cyclobutylquinoline.—This compound was prepared in a manner similar to that used for the 2-cyclopropyl analog, converting the isocyanate to the benzylcarbamate by heating with excess benzyl alcohol at 95° for 15 min. The carbamate was refluxed with 100 ml. of 1% hydrochloric acid, 50 ml. of 5% hydrochloric acid was added and the solution was distilled (300 ml.). Upon cooling, the carbamate hydrochloride, m.p. 123–125°, crystallized out. The mixture was filtered, the urethan refluxed with 50 ml. of 10% hydrochloric acid for 3 hr., and the acid solution was again steam-distilled and worked up. The colorless microcrystalline powder (yield, 45%) of **4-amino-2-cyclobutylquinoline hydrochloride** melted at 284–284.5° dec. after softening at *ca.* 250°.

Anal. Calcd. for $C_{13}H_{14}N_2\cdot HCl\cdot H_2O$: C, 61.77; H, 6.78. Found: C, 61.90; H, 6.91.

Acknowledgment.—We are grateful to the agencies which supported this research,[1a,c] and to Professor William Shive of the University of Texas for permission to quote his biological assay of β-cyclobutyl-α-alanine.

Synthesis of Phenethylamines Related to Mescaline as Possible Psychotomimetic Agents[1]

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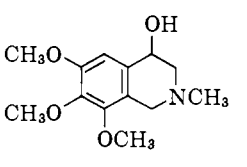
In order to determine the effect of particular structural modifications on the psychopharmacologic properties of mescaline, a series of β-substituted derivatives was synthesized for biologic testing.

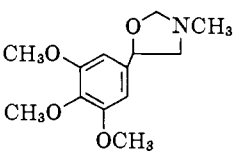
Mescaline, a well-known hallucinogenic agent, produces psychic effects only at very high dosages. Possibly, therefore, a metabolite of mescaline is the active agent. Creveling, *et al.*,[2] have reported that mescaline is converted by dopamine-β-oxidase to β-hydroxymescaline, a compound more closely related to the physiologically very active norepinephrine than is mescaline; and Axelrod[3] has reported that mescaline is N-methylated by an enzyme contained in rabbit lung, a transformation often associated with the formation of psychotomimetic products from naturally occurring compounds. In fact, although mescaline is of plant origin, metabolic products of the type suggested could conceivably be formed by mammals, including man, as abnormal products of tyrosine metabolism. In addition to the two enzymes referred to above, both of which act on a variety of phenethylamines other than mescaline, Axelrod[4] reported that 3,4,5-trihydroxyphenethylamine is transformed by O-methyltransferase to the 3,4-dimethoxy product. There is consequently, biochemical analogy for most of the transformations required.

In order to study their psychopharmacological properties, we have undertaken syntheses of metabolites of this type. We report here the synthesis of β-substituted compounds related to mescaline.

Hydroxymescaline (IV) which had previously been synthesized, was prepared by the reported procedure[5] from trimethoxybenzoic acid (I) through the acid chloride II condensed with cuprous cyanide to give the ketonitrile III which afforded IV on reduction with lithium aluminum hydride. Methylation of the primary amine (IV) with formaldehyde and formic acid by the Leuckart procedure did not give the expected dimethyl compound V.[6] The n.m.r. and infrared spectral data favor 2-methyl-4-hydroxy-6,7,8-trimethoxytetrahydroisoquinoline (XIX) as the structure for the reaction product. The finding of a singlet at 3.25 τ[7] in the aromatic hydrogen region with an intensity exactly one-ninth that of the peak at 6.17 τ produced by the nine methoxyl protons establishes the presence of only one aromatic hydrogen atom in the molecule and supports the assignment of structure XIX. The presence of hydroxyl, indicated by hydroxy proton signals in deuterochloroform which shifted characterically in position from 5.97–6.08–6.53τ with changes in concentration of solution, was confirmed by disappearance of the hydroxy proton signal when the sample was shaken with D_2O and the appearance of a new peak at 5.35τ due to the proton in H–OD formed in the exchange of the benzylic hydroxyl proton. The cyclization of the phenylethanolamine IV to a substituted tetrahydroisoquinoline XIX, postulated here, is analogous to that formulated[8] in the Pictet–Spengler synthesis. These observations rule out the other possible structure for the product, the oxazolidine XX, although cyclization to XX would otherwise seem improbable under these reaction conditions.[9]



XIX



XX

(1) Supported by a research grant (MY-3273) from the National Institutes of Health, U. S. Public Health Service.

(2) C. R. Creveling, J. Daly, B. Witkop, and S. Udenfriend, *Biochim. Biophys. Acta*, **64**, 125 (1962).

(3) J. Daly, J. Axelrod, and B. Witkop, *Ann. N. Y. Acad. Sci.*, **96**, 37 (1962).

(4) J. Axelrod, *Science*, **133**, 343 (1961).

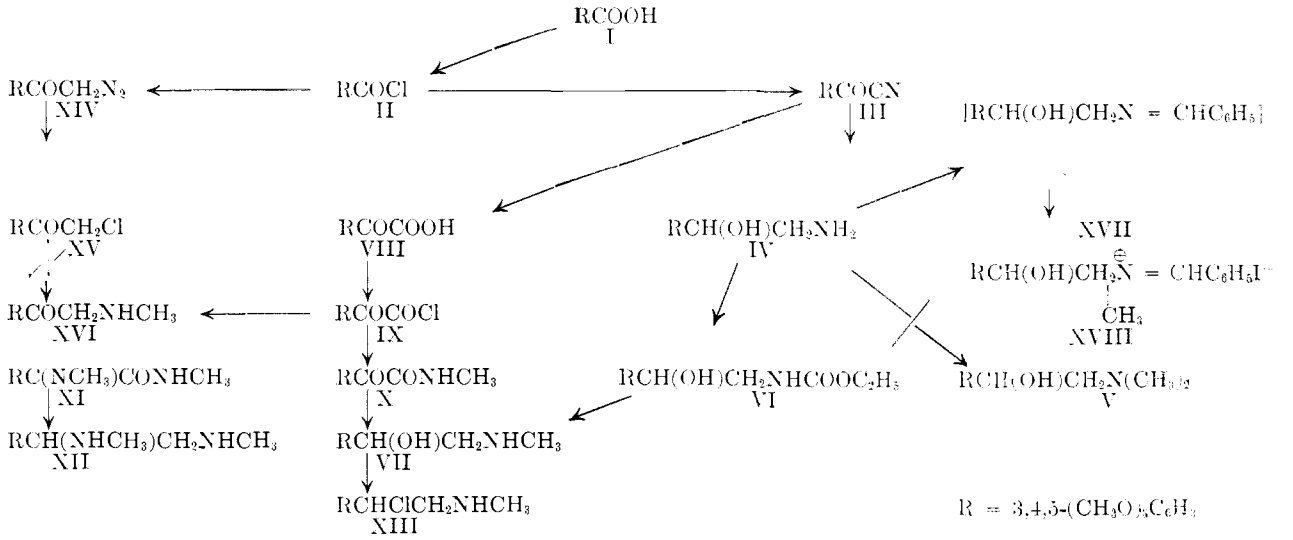
(5) A. Dornow and G. Petsch, *Arch. Pharm.*, **285**, 323 (1952).

(6) R. A. Heacock and O. Hutzinger, *Can. J. Chem.*, **40**, 128 (1962).

(7) The chemical shifts in τ values reported here are calculated using tetramethylsilane as the internal standard.

(8) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).

(9) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953). Also, the infrared spectrum of the product did not have the triplet of bands in the 1080–1200 cm.$^{-1}$ region characteristic of the O–C–N system in oxazolidines.



The synthesis of the secondary amine VII was effected by lithium aluminum hydride reduction of the urethane VI derived from the primary amine IV by condensation with ethyl chloroformate. This monomethyl derivative VII was also synthesized by a different route that involved hydrolysis of the ketonitrile III to the α-keto acid VIII; condensation of this acid as the acid chloride IX with methylamine to give the α-ketoamide X; and reduction of the amide with lithium aluminum hydride to VII. The over-all yield of the latter process was low because of the very poor yield in the reduction in the last step although a number of variations in procedure were tried. In the course of the latter preparation two other new products, N-methyl-β-methylaminomescaline (XII) and N-methyl-β-chloromescaline (XIII), which may be of interest for their possible psychotomimetic properties, also were formed. Compound XII was produced when the acid chloride IX was treated with excess methylamine and the intermediate, presumably XI, was reduced with lithium aluminum hydride. The chloroamine (XIII) formed when the corresponding β-hydroxy compound VII was warmed with hydrogen chloride.

Attempts to prepare VII by other syntheses were unsuccessful. Condensation of the chloroketone XV[10] prepared from the acid chloride II by way of the diazoketone XIV[11] did not give the expected ketoamine XVI. The only product that could be isolated from the reaction showed no carbonyl absorption in the infrared. Methylation with methyl iodide of the product[12] from the condensation of the primary amine (IV) with benzaldehyde did not yield the required quaternary amine XVIII which on hydrolysis would have afforded the desired product VII but gave other products not readily identifiable.

Some preliminary exploratory studies on the biological properties of the mescaline analogs have been made.[13] The acute toxicities and behavioral effects of mescaline·HCl, β-hydroxymescaline·HCl (IV), the tetrahydroisoquinoline·HCl (XIX), and N-methyl-β-hydroxymescaline·HCl (VII) were determined in male, albino Swiss mice. The approximate LD_{50} by the intraperitoneal route of VII is 410 mg./kg., that of XIX is 520 mg./kg., and that of IV is 440 mg./kg. The LD_{50} of mescaline is between 400–800 mg./kg. Grossly these compounds produce approximately the same effects which range from ataxia, to fine tremors to clonic convulsions. At certain doses there were differences in the responses within the group of compounds. Compound XIX produced effects most like mescaline; hydroxymescaline differed from mescaline in that animals on it were much more subdued. The monomethyl compound was quite different in that it produced a contraction of abdominal muscles and with hind leg rigidity.

The ability of these compounds to depress the spontaneous contractions of the isolated rabbit intestine were compared to epinephrine. In concentrations 10 to 20 times epinephrine these compounds did not produce any effect whereas epinephrine produced a maximum depression of the spontaneous contractions. In short, the substitutions on mescaline do not appear to have dramatically altered the biologic activity attributable to the parent compound in mice. If real but subtle differences have been produced by these substitutions much more refined biological tests must be performed. This study will be continued.

Experimental[14]

3,4,5-Trimethoxybenzoyl cyanide (III).—This compound was prepared from 3,4,5-trimethoxybenzoyl chloride[15] by the previously described procedure[5] with certain modifications. The yield of III was improved from 58 to 65% and the product more conveniently isolated by Soxhlet extraction of the crude nitrile with high boiling (60–110°) petroleum ether and recrystallization from benzene–petroleum ether in place in the more tedious sublimation procedure previously used.

β-Hydroxymescaline (IV).—The method adopted is essentially that of Dornow and Petsch[5] except for certain experimental modifications. Dry tetrahydrofuran was used instead of ether in the reaction and a reaction time of 6 hr. was found to give the best yield of product. The lithium aluminum hydride complex was decomposed conveniently by addition of 1 ml. of water,

(10) J. Michalsky and L. Sadilek, *Monatsh. Chem.*, **90**, 174 (1959).

(11) K. Banholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta*, **35**, 1577 (1952).

(12) The product presumed to be the Schiff base XVII may have been the corresponding oxazolidine (suggested by a referee) or possibly the isomeric tetrahydroisoquinoline.[8] Neither of the latter structures, however, would explain the apparent unreactivity toward methyl iodide noted.

(13) These studies were done at Arthur D. Little, Inc., Cambridge, Mass. We are indebted to this company for their interest in this project and for permission to publish these preliminary data.

(14) Microanalyses by Dr. Carol Fitz, Needham, Mass.; all melting points are corrected, and were determined using a Gallenkamp apparatus.

(15) E. Späth, *Monatsh. Chem.*, **40**, 129 (1919).

1 ml. of 15% sodium hydroxide solution, and 3 ml. of water per g. of lithium aluminum hydride used. The amine hydrochloride, precipitated from cold benzene by addition of benzene saturated with dry hydrogen chloride, was obtained after two recrystallizations from methanol–ether as white needles, m.p. 196–199° (40%).

4-Hydroxy-2-methyl-6,7,8-trimethoxytetrahydroisoquinoline (XIX).—To a solution of 1.325 g. (0.005 mole) of IV hydrochloride in 1.3 ml. of 90% formic acid (0.025 mole) was added 1.25 ml. (0.015 mole) of a 37% formaldehyde solution. The reaction mixture was placed in an oil bath preheated to 90–95°. After a few minutes when gas evolution was observed the oil bath was removed until the carbon dioxide evolution noticeably subsided. The mixture was heated at 95–100° under a condenser for 8 hr. and then allowed to stand at room temperature overnight.[16] The solution was cooled, made alkaline with 2 *N* potassium hydroxide and diluted with ice cold water. The mixture was extracted 3 times each with ether and with chloroform. The combined organic extracts were washed successively with water and saturated sodium chloride and then dried over anhydrous magnesium sulfate. After removal of most of the solvent, the combined residues were dissolved in dry ether, cooled and treated with a cold ethereal solution saturated with dry hydrogen chloride. The precipitated crude amine hydrochloride salt was filtered, washed with ether and recrystallized repeatedly from methanol–ether–ethyl acetate to afford a pure product as white needles (28–30% yield), m.p. 189–191°.

Anal. Calcd. for $C_{13}H_{20}ClNO_4$: C, 53.88; H, 6.96; Cl, 12.24; N, 4.83. Found: C, 53.71; H, 6.98; Cl, 11.90; N, 5.00. ν_{max} in $CHCl_3$ (cm.$^{-1}$); 3400 (associated OH), 2900, 2790, 1605, 1460, 1357, 1120, and 1082.

3,4,5-Trimethoxyphenylglyoxylic acid (VIII).—This compound was prepared by hydrolysis of the keto nitrile III as described previously[17] without isolation of the intermediate keto amide. Hydrolysis was complete in 4 days affording VIII in 70% yield.

N-Methyl-3,4,5-trimethoxyphenylglyoxylamide (X).—To the keto acid VIII (10.0 g.), dissolved in freshly distilled thionyl chloride (150 ml.), was added 1.5 ml. of pyridine and the mixture allowed to stand at room temperature for 15 hr. The excess thionyl chloride was distilled at 30–35° (1–2 mm.). The crude yellow keto acid chloride that remained was dissolved in dry benzene, the solution filtered, and gaseous methylamine passed through the cooled filtrate for 4–5 min. Removal of the precipitated methylamine hydrochloride and evaporation of the filtrate gave crude keto amide (X). This product, dissolved in ethyl acetate, was washed twice with 2 *N* hydrochloric acid, once with water and then with saturated sodium chloride. The solution, after standing over anhydrous magnesium sulfate, gave on evaporation light yellow needles (yield 75–80%), m.p. 138–140° (chloroform–petroleum ether).

Anal. Calcd. for $C_{12}H_{15}NO_5$: N, 5.53. Found: N, 5.50. Principal ν_{max} in $CHCl_3$ (cm.$^{-1}$); 3395, 1705, and 1660.

N-[β-Hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl]-carbamate (VI).—To an ice-cold solution of 4.54 g. (0.02 mole) of β-hydroxymescaline (IV) in 100 ml. of water and 20–25 g. of chopped ice, 1.20 g. (0.011 mole) of ethyl chloroformate was added dropwise with vigorous stirring and external cooling to maintain the temperature between 5–10°. A solution of 0.022 mole of sodium hydroxide in 10 ml. of water then was added dropwise simultaneously with a second 1.2 g. portion (0.011 mole) of ethyl chloroformate, and the mixture was stirred for an additional 2 hr. at 5–10°.[18] The reaction mixture was extracted with ether and chloroform successively and the combined organic extracts were washed with water and dried. Evaporation of the solvent gave a white crystalline product (VI), yield 76%, m.p. 97–99° (benzene–petroleum ether).

Anal. Calcd. for $C_{14}H_{21}NO_6$: C, 56.19; H, 7.07; N, 4.68. Found: C, 55.83; H, 6.83; N, 4.81. Principal ν_{max} in $CHCl_3$ (cm.$^{-1}$); 3560, 3400, 1710.

N-Methyl-β-hydroxymescaline (VII).[19] **(a) By Lithium Aluminum Hydride Reduction of the Keto Amide (X).**—To a stirred suspension of 0.1 mole of lithium aluminum hydride in 60 ml. of dry ether was added dropwise a solution of 0.03 mole of the keto amide (X) in dry tetrahydrofuran with the reaction mixture at gentle reflux. After 70 hr. the mixture was cooled and decomposed as described above for the preparation of IV. The cooled ethereal solution of the amine was treated with ice-cooled ether saturated with dry hydrogen chloride and the crude solid that precipitated filtered. Repeated recrystallization from methanol–ether gave the product as a white crystalline solid, m.p. 169.5–172.5°, yield 12%.

Anal. Calcd. for $C_{12}H_{20}ClNO_4$: N, 5.04; Cl, 12.77. Found: N, 5.10; Cl, 12.90.

The hydrogen oxalate salt of VII was prepared from the crude amine as white platelets, m.p. 187–189° (ethanol–ethyl acetate).

Anal. Calcd. for $C_{14}H_{21}NO_8$: C, 50.57; H, 6.39; N, 4.23. Found: C, 50.82; H, 6.32; N, 4.73.

(b) By Lithium Aluminum Hydride Reduction of the Carbamate VI.—To a stirred suspension of 1.50 g. (0.04 mole) of lithium aluminum hydride in 150 ml. of dry ether was added a solution of 5.40 g. (0.018 mole) of the carbamate VI in 170 ml. of dry ether–tetrahydrofuran at a rate which produced controlled reflux. The mixture was refluxed for 65 hr., cooled and decomposed with water and 15% sodium hydroxide as described for the preparation of IV. The product crystallized from the concentrated ethereal extract as white platelets, m.p. 84–86°. The crude amine redissolved in cold ether and treated with a cold ether ethereal solution of hydrogen chloride gave a white crystalline hydrochloride (42% yield), m.p. 171–173° (methanol–ether). A mixture melting point with the product obtained by keto amide reduction above showed no depression. The infrared spectra of the two also were identical; ν_{max} in $CHCl_3$ (cm.$^{-1}$): 3355, 2925, 2725, 1600, 1460, 1335, 1128, and 1000.

N,N′-Dimethyl-(3,4,5-trimethoxyphenyl)ethylenediamine Dihydrochloride (XII·2HCl).—A solution of the keto acid chloride (IX) in benzene, saturated with methylamine gas without cooling, was warmed on a steam bath for 10 min. The crude product of this reaction, presumably the ketimine amide XI, on reduction with lithium aluminum hydride gave XII, an oil which was isolated as the crystalline dihydrochloride from cold benzene–methanol, m.p. 226–227.5° dec (8% yield).

Anal. Calcd. for $C_{13}H_{24}Cl_2N_2O_3$: N, 8.55; Cl, 21.8. Found: N, 8.6; Cl, 21.8.

N-Methyl-β-chloro-β-(3,4,5-trimethoxyphenyl)ethylamine Hydrochloride (XIII·HCl).—This product was derived from N-methyl-β-hydroxymescaline (VII) when crude base, isolated as an oily residue after the reduction of the keto amide X (procedure (a) above), was dissolved in benzene, with a trace of isopropyl alcohol, and treated with dry hydrogen chloride for 3 min. in the cold. The mixture was evaporated on the steam bath, and the oily residue, triturated with chloroform–acetone, yielded a solid, m.p. 164–165°. Two recrystallizations from the same solvent mixture raised the melting point to 170–171°.

Anal. Calcd. for $C_{12}H_{19}Cl_2NO_3$: C, 48.65; H, 6.74; N, 4.7; Cl, 23.9. Found: C, 49.28; H, 6.64; N, 5.06; Cl, 22.97.

Acknowledgments.—The authors are indebted to Mr. V. Grubliauskas for assistance in the preparation of certain of these derivatives in quantities sufficient for biological evaluation; and to Dr. Charles F. Hammer for his kind cooperation in determining and interpreting the n.m.r. spectra.

(16) Essentially the general method described by R. N. Icke and B. B. Wisegarver, "Organic Syntheses," Collective Vol. III, John Wiley and Sons, New York, N. Y., 1955, p. 723.

(17) F. Mauthner, *Ber.*, **41**, 921 (1908).

(18) The method is a modification of that of C. D. Gutsche and H. E. Johnson, *Org. Syn.*, **35**, 91 (1955).

(19) While this manuscript was in preparation, R. A. Heacock and O. Hutzinger[6] reported the preparation by a different route of the derivative VII.