solution with barium carbonate and removal of the excess barium carbonate and barium sulfate, the filtered solution strongly reduced Fehling solution. The solution was hydrogenated again at 140° over Raney nickel for fifteen hours under a pressure of 2600 pounds. The Raney nickel was separated and the non-reducing filtrate was concentrated *in vacuo* at 40°. The residue was extracted four times with boiling acetone and the combined extracts were dried over anhydrous calcium sulfate. After removal of the acetone and drying *in vacuo*, 2.4 g. of a sirupy product was obtained; $n^{20}D$ 1.4619. From the refractive index curve of known mixtures of glycerol and ethylene glycol prepared by Jayme and Sätre[9] this value approximately corresponds to a 74% (1.8 g.) glycerol–26% (0.6 g.) ethylene glycol. Based on 5 g. of sucrose the over-all yield of glycerol was thus 45%, and the yield of ethylene glycol was 66%. The product was distilled in a semi-micro fractionation apparatus consisting of a glass spiral column supported on an aluminum block, a heated jacket and a receiver of the rotating type described by Shrader and Ritzer.[11] At 3 mm. five fractions were collected from 80 to 165°. The main fraction distilled at 155–165°. The refractive indices at 20° of fractions 1 and 5, respectively, were 1.4326 and 1.4725. Fraction 1 gave a colorless solid upon shaking with benzoyl chloride and dilute sodium hydroxide in a typical Schotten–Baumann reaction. Recrystallization from alcohol yielded ethylene glycol dibenzoate, melting at 72–73°. A mixed melting point with a known product showed no depression. Fraction 5 under the same treatment yielded crystalline glycerol tribenzoate melting at 74–75°. A mixed melting point with a known sample also exhibited no depression.

(b) **Lead Tetraacetate.**—Five grams (0.0146 mole) of sucrose was suspended in 50 cc. of pyridine in a one-liter three-necked flask cooled to 0°. Twenty-two grams (0.049 mole) of lead tetraacetate in 650 cc. of pyridine was added slowly with motor stirring. Within four hours the original dark solution became clear. The solution was filtered and concentrated *in vacuo* at 40°. The concentrate was treated with 200 cc. of water containing 3.5 cc. of concd. sulfuric acid and the lead sulfate formed was separated with the aid of a centrifuge. The filtrate was neutralized with barium carbonate, filtered and concentrated *in vacuo* to a flaky solid. The solid was dissolved in 200 cc. of water and was concentrated to 65 cc., filtered twice through kieselguhr and treated with 10% sulfuric acid until no more barium sulfate precipitated. The filtered solution gave a strong Fehling test and a precipitate with 2,4-dinitrophenylhydrazine. The solution was neutralized with solid sodium bicarbonate and was then hydrogenated over fresh Raney nickel (4 g.) for twenty-two hours at 140° under a pressure of 2400 pounds. After removal of the Raney nickel, the filtrate did not reduce Fehling solution and gave no precipitate with 2,4-dinitrophenylhydrazine. The filtrate was then mixed with 3 cc. of concd. sulfuric acid carefully in the cold and was boiled under reflux for three and one-half hours. The solution was neutralized with barium carbonate and filtered. The filtrate showed strong reducing properties with Fehling solution and gave an immediate precipitate with 2,4-dinitrophenylhydrazine. The solution was hydrogenated over Raney nickel again as described. After removal of the catalyst, the filtrate was non-reducing to Fehling solution. The greenish solution was concentrated *in vacuo* at 40°, the residue was extracted with absolute ethyl alcohol three times, the combined extracts were dried over anhydrous calcium sulfate, filtered and concentrated. The residue was extracted with absolute ethyl alcohol, the extracts were filtered and concentrated *in vacuo* at 2 mm. to a colorless sirupy residue; $n^{20}D$ 1.4700; yield 1.0 g. Glycerol tribenzoate melting at 74–75° was isolated after benzoylation by the Schotten–Baumann reaction. Ethylene glycol was not identified. The yield of glycerol was about 25%.

(11) Shrader and Ritzer, *Ind. Eng. Chem., Anal. Ed.*, 11, 54 (1939).

Summary

The rate-of-oxidation curve of sucrose by lead tetraacetate in dry acetic acid shows that oxidation occurs without appreciable cleavage of the glycosidic link. The oxidation of sucrose in pyridine yielded a colorless, amorphous powder with the properties of a tetraaldehyde. Oxidation of this substance by strontium hypobromite produced the strontium salt. The preparation of glycerol and ethylene glycol from the primary oxidation product of oxidation of sucrose by periodic acid or lead tetraacetate has been described.

NEW YORK 5, N. Y. RECEIVED NOVEMBER 11, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Curariform Activity and Chemical Structure. VI. Syntheses in the β- and γ-Carboline Series[1,2]

BY V. BOEKELHEIDE AND C. AINSWORTH[3]

In view of the suggestions that several of the calabash curare alkaloids probably contain the carboline nucleus[4,5] and since a model compound derived from 3-indolylmethylamine has been found to have fairly high curariform activity,[6] we have prepared a number of quaternary salts of 1,2,3,4-tetrahydro-β-carboline and 1,2,3,4-tetrahydro-γ-carboline for physiological testing.

For the synthesis of 2-methyl-1,2,3,4-tetrahydro-γ-carboline (I), the Fischer indole synthesis was employed using phenylhydrazine hydrochloride and N-methyl-4-piperidone hydrochloride in a modification of the method of Cook and Reed.[7] This was then converted to the corresponding salts, II and III, in the usual manner.

Since bromination of C-curarine-I chloride has been found to greatly intensify its activity,[8] the corresponding 8-bromo compounds (IV, V and VI) were prepared by utilizing the same reaction with *p*-bromophenylhydrazine instead of phenylhydrazine.

(1) Aided by a grant from the National Foundation for Infantile Paralysis.

(2) For paper V of this series, see Boekelheide and Rothchild, THIS JOURNAL, **71**, 879 (1949).

(3) Present address, Department of Chemistry, University of Colorado, Boulder, Colorado.

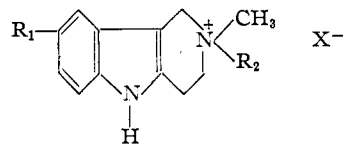
(4) Schmid and Karrer, *Helv. Chim. Acta*, **30**, 1162 (1947).

(5) Wieland, Witkop, and Bähr, *Ann.*, **558**, 144 (1947).

(6) Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).

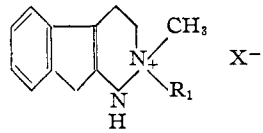
(7) Cook and Reed, *J. Chem. Soc.*, 399 (1945).

(8) Wieland, Pistor and Bähr, *Ann.*, **547**, 140 (1941).



I, R_1 = —H, R_2 = —H, X = —Cl
II, R_1 = —H, R_2 = —CH_3, X = —I
III, R_1 = —H, R_2 = —$CH_2C_6H_5$, X = —Cl
IV, R_1 = —Br, R_2 = —H, X = —Cl
V, R_1 = —Br, R_2 = —CH_3, X = —I
VI, R_1 = —Br, R_2 = —$CH_2C_6H_5$, X = —Cl

β-Carboline was prepared in a similar manner to that recently described by Speitel and Schlittler,[9] and it was then reduced to 1,2,3,4-tetrahydro-β-carboline by means of sodium and butanol. Reductive alkylation with formaldehyde proceeded in good yield to give the corresponding N-methyl derivative which was converted to VII and VIII in the usual way.



VII, R_1 = —CH_3, X = —I
VIII, R_1 = —$CH_2C_6H_5$, X = —Cl

Attempts to prepare 2-ethyl-1,2,3,4-tetrahydro-β-carboline by the cyclization of α-ethyltryptamine with formaldehyde were unsuccessful.

The results of preliminary testing with frogs showed that all of these quaternary salts had curariform activity.[10] Compounds III and VIII were the most active and their activity was of the order of one-fifth that of *d*-tubocurarine chloride. It is of interest that the bromine derivatives were less active than the bromine-free compounds.

Experimental[11]

2-Methyl-1,2,3,4-tetrahydro-γ-carboline.—A mixture of N-methyl-4-piperidone hydrochloride[12] (3.4 g., 0.02 mole) and phenylhydrazine hydrochloride (2.8 g., 0.02 mole) in 50 ml. of a saturated solution of ethanolic hydrogen chloride was heated under reflux for two hours and then stored overnight at 5°. The solution was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in water, the solution was made basic, and the precipitate was collected. After crystallization from aqueous methanol, there was obtained 2.0 g. (54%) of white plates, m. p. 169–170° (lit.,[7] m. p. 170–171°).

The **picrate** formed readily in alcohol and was obtained as yellow prisms, m. p. 130–131°.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13. Found: C, 51.86; H, 4.20.

2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carbolinium Iodide. II.—A solution of 1.86 g. of 2-methyl-1,2,3,4-tetrahydro-γ-carboline in 125 ml. of ether was treated with 1.0 ml. of methyl iodide. The solid, which precipitated, was recrystallized from water yielding 2.3 g. (70%) of colorless plates, m. p. 214–215°.

Anal. Calcd. for $C_{13}H_{17}N_2I$: C, 47.57; H, 5.22. Found: C, 47.28; H, 5.34.

2-Benzyl-2-methyl-1,2,3,4-tetrahydro-γ-carbolinium Chloride, III.—A solution of 1.86 g. of 2-methyl-1,2,3,4-tetrahydro-γ-carboline and 1.26 g. of benzyl chloride in 20 ml. of dioxane was allowed to stand at room temperature for two days. The precipitate was collected and crystallized from acetone to yield 1.9 g. (61%) of colorless prisms, m. p. 155–159°.

Anal. Calcd. for $C_{19}H_{21}N_2Cl \cdot H_2O$: C, 68.97; H, 7.01. Found: C, 68.76; H, 6.98.

8-Bromo-2-methyl-1,2,3,4-tetrahydro-γ-carboline, IV.—This was prepared by the same procedure as given for I. From 8.4 g. of N-methyl-4-piperidone hydrochloride and 11.2 g. of *p*-bromophenylhydrazine hydrochloride there was obtained 7.0 g. (52%) of coarse prisms, m. p. 185–186°, after crystallization from a water–methanol mixture.

Anal. Calcd. for $C_{12}H_{13}N_2Br$: C, 54.35; H, 4.94. Found: C, 54.31; H, 4.83.

The **picrate** of IV crystallized from alcohol as orange needles, m. p. 207–209°, with dec.

Anal. Calcd. for $C_{18}H_{16}N_5O_7Br$: C, 43.74; H, 3.26. Found: C, 43.59; H, 3.12.

8-Bromo-2,2-dimethyl-1,2,3,4-tetrahydro-γ-carbolinium iodide (V) was prepared in ether as described for II and was obtained, after crystallization from methanol, as colorless prisms, m. p. 241–243°.

Anal. Calcd. for $C_{13}H_{16}N_2BrI$: C, 38.35; H, 3.96. Found: C, 38.41; H, 3.88.

2-Benzyl-2-methyl-8-bromo-1,2,3,4-tetrahydro-γ-carbolinium chloride (VI) was prepared in dioxane as described for the preparation of III and, after crystallization from nitromethane, was obtained as colorless needles, m. p. 170–172°.

Anal. Calcd. for $C_{19}H_{20}N_2BrCl$: C, 58.25; H, 5.15. Found: C, 57.67, 58.78; H, 5.48, 5.45.

1,2,3,4-Tetrahydro-β-carboline.—This was obtained in 50% yield by the reduction of β-carboline[9] with sodium and butanol using the procedure employed by Ashley and Robinson[13] for the reduction of 4-keto-3,4-dihydro-β-carboline. Our product melted at 207–208° in accordance with that reported by Späth and Lederer.[14]

3-Methyl-1,2,3,4-tetrahydro-β-carboline.—A slow stream of dry nitrogen containing some formaldehyde vapor was passed into a cooled solution of 2.0 g. of 1,2,3,4-tetrahydro-β-carboline for thirty minutes. Raney nickel catalyst was added and the mixture was shaken at room temperature under three atmospheres pressure of hydrogen for three hours. After removal of catalyst and solvent, the residue was crystallized from alcohol yielding 1.5 g. (70%) of colorless needles, m. p. 217–218°.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58. Found: C, 77.06; H, 7.28.

The **picrate** of 3-methyl-1,2,3,4-tetrahydro-β-carboline crystallized from alcohol as bright yellow needles, m. p. 197–198°, with dec.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$: C, 52.05; H, 4.13. Found: C, 52.42; H, 4.16.

3,3-Dimethyl-1,2,3,4-tetrahydro-β-carbolinium Iodide, VII.—To a solution of 1.0 g. of 3-methyl-1,2,3,4-tetrahydro-β-carboline in 10 ml. of dry benzene there was added 1.0 ml. of methyl iodide and the mixture was boiled under reflux for thirty minutes. The fine white precipitate, which formed, was crystallized from absolute alcohol, yielding 1.1 g. (62%) of white needles, m. p. 265°.

Anal. Calcd. for $C_{13}H_{17}N_2I$: C, 47.57; H, 5.22. Found: C, 47.64; H, 5.01.

3-Benzyl-3-methyl-1,2,3,4-tetrahydro-β-carbolinium Chloride, VIII.—This was prepared in the same fashion as VII and was obtained as very hygroscopic white needles,

(9) Speitel and Schlittler, *Helv. Chim. Acta*, **32**, 863 (1949).

(10) We are indebted to Dr. Ernest Wright, Department of Physiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York, for the physiological testing.

(11) Microanalyses by Mrs. G. L. Sauvage and by the Micro-Tech Laboratories.

(12) Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).

(13) Ashley and Robinson, *J. Chem. Soc.*, 1376 (1928).

(14) Späth and Lederer, *Ber.*, **63**, 2102 (1930).

m. p. 165°, after crystallization from an alcohol–ether mixture. Even after it had been dried at 100° the product, on analysis, appeared to contain solvent of crystallization.

Anal. Calcd. for $C_{19}H_{21}N_2Cl\cdot 0.5H_2O$: C, 70.90; H, 6.89. Found: C, 71.12; H, 7.01.

α-Ethyltryptamine.—This was prepared according to the procedure of Snyder and Katz.[15]

The **picrate** of α-ethyltryptamine was obtained as scarlet prisms, m. p. 223–224°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.80; H, 4.59. Found: C, 52.18; H, 4.68.

(15) Snyder and Katz, THIS JOURNAL, **69**, 3140 (1947).

Attempts to effect cyclization by incubating α-ethyltryptamine with formaldehyde under various different conditions of *p*H and temperature similar to that employed by Späth and Lederer[14] gave no useful product.

Summary

A number of salts of β- and γ-carboline have been prepared and found to possess curariform activity.

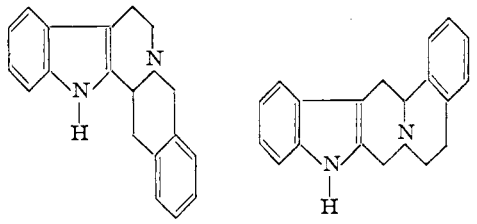
ROCHESTER, NEW YORK RECEIVED SEPTEMBER 14, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Curariform Activity and Chemical Structure. VII. Some 1-Skatylisoquinoline Derivatives and a Novel Method for their Synthesis[1,2]

BY V. BOEKELHEIDE AND C. AINSWORTH[3]

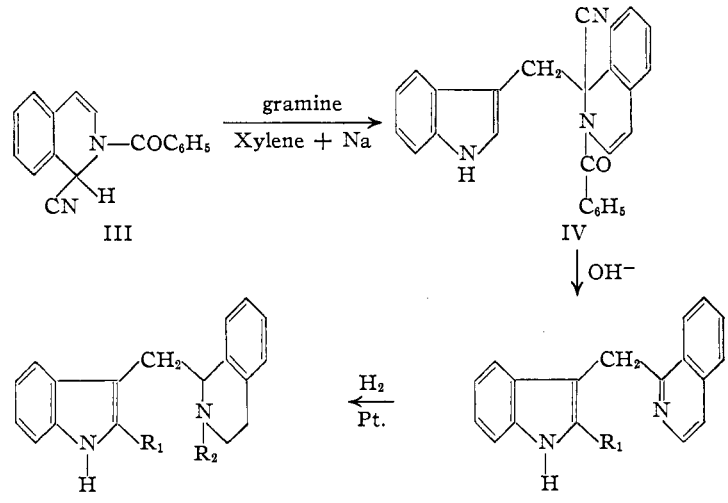
Investigation of the highly potent calabash curare alkaloids has led to speculation that certain of these alkaloids may contain a hexahydrobenzoindoloquinolizine nucleus.[4a,b,5] The only simple hexahydrobenzoindoloquinolizine known is I, which was prepared by Clemo and Swan in their investigation of yobyrine.[6] However, as yet, nothing has been reported on the curariform activity of the quaternary salts of I. Because of the desirability of having synthetic samples of hexahydrobenzoindoloquinolizines for physiological testing and for comparison studies, we have prepared some 1-skatylisoquinoline derivatives and attempted their conversion to II.



I II

For the synthesis of 1-skatylisoquinoline a new method has been employed. Reissert's compound[7] (III), which is well known for its acid hydrolysis to benzaldehyde and isoquinaldinic acid,[8] was alkylated with gramine in the presence of sodium to give IV in fair yield. On basic hydrolysis IV was readily converted to 1-skatylisoquinoline (V) in quantitative yield. The two-step combination of alkylation and basic hydrolysis appears to have promise as a general method for preparing 1-substituted isoquinolines.

In the hydrolysis of IV with dilute sodium hydroxide the other products formed in addition to V were sodium cyanide and sodium benzoate. To explain the formation of these products and the ease of hydrolysis we suggest that the reaction



VII, R_1 = —H, R_2 = —H
VIII, R_1 = —H, R_2 = —CH_2OH
IX, R_1 = —CO_2Et, R_2 = —H
X, R_1 = —CH_2OH, R_2 = —H
XI, R_1 = —H, R_2 = —CH_3

V, R_2 = — H
VI, R_1 = —CO_2Et

proceeds by attack of a hydroxyl ion or a water molecule at the amide linkage which results in the shift of a pair of electrons and loss of a cyanide ion

(1) Aided by a grant from the National Foundation for Infantile Paralysis.

(2) For paper VI of this series, see Boekelheide and Ainsworth, THIS JOURNAL, **72**, 2132 (1950).

(3) Present address, Department of Chemistry, University of Colorado, Boulder, Colorado.

(4) For leading references on the chemistry of calabash curare, see (a) Schmid and Karrer, *Helv. chim. acta*, **30**, 2101 (1947); (b) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

(5) For speculation on the presence of the hexahydrobenzoindoloquinolizine nucleus in certain C-curare alkaloids, see ref. 4b and Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).

(6) Clemo and Swan, *J. Chem. Soc.*, 617 (1946).

(7) Reissert, *Ber.*, **38**, 3427 (1905).

(8) Padbury and Lindwall, THIS JOURNAL, **67**, 1268 (1945).