Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.36; H, 8.01.

1-Ethoxymethyl-3,4-dihydroisoquinoline.—To a solution of 12 g. (0.06 mole) of N-(β-phenylethyl)-ethoxyacetamide in 150 cc. of refluxing xylene was added portionwise, over a period of fifteen minutes, 14 g. (0.1 mole) of phosphorus pentoxide. Reflux was maintained for another fifteen minutes. After decanting the xylene from the dark brown solid, 150 cc. of water was added and the mixture shaken until all had gone into solution. The water solution was extracted with two 50-cc. portions of ether to remove the xylene and any other ether-soluble material. The mixture which formed when the water solution was made strongly basic with alkali was extracted with four 50-cc. portions of ether. After drying the ether solution and removing the ether by distillation, the dark red-brown residue was distilled to give 4.9 g. (45%) of colorless liquid, b. p. 106–115° (1–1.5 mm.), $n^{22}D$ 1.5495. The liquid rapidly turned yellow on exposure to air.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99. Found: C, 75.48; H, 7.55. The sample had turned yellow before the analysis was made; oxidation could account for the low carbon–hydrogen values.

The picrate was obtained as yellow needles from ethanol, m. p. 138–139° with decomposition.

Anal. Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.68; H, 4.34. Found: C, 51.94; H, 4.38.

The hydrochloride precipitated when dry hydrogen chloride gas was bubbled through a dry ether solution of the distilled free base. It was very hygroscopic and difficult to handle, recrystallization from ethanol–ether giving colorless needles, m. p. 85–86° with darkening and decomposition.

Anal. Calcd. for $C_{12}H_{16}ClNO \cdot {}^1/_4H_2O$: C, 62.60; H, 7.22. Found: C, 62.84; H, 7.28.

1-Ethoxymethyl-1,2,3,4-tetrahydroisoquinoline (VII).—A solution of 3.6 g. (0.019 mole) of the distilled 1-ethoxymethyl-3,4-dihydroisoquinoline in 50 cc. of absolute ethanol, in the presence of about 1.0 g. of Raney nickel, was shaken for five hours at room temperature under hydrogen at 3.8 atmospheres. After removing the catalyst by filtration and the ethanol by distillation, the residue was distilled under reduced pressure to give 3.4 g. (94%) of colorless liquid, b. p. 90–103° (0.5–0.6 mm.), $n^{21}D$ 1.5360. The liquid turned light yellow on standing.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.97. Found: C, 74.66; H, 8.83. The colorless sample had turned light yellow before the analysis was run.

The picrate formed very slowly as tiny yellow needles from ethanol, m. p. 164–165°.

Anal. Calcd. for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.80. Found: C, 51.32; H, 4.50.

The hydrochloride was prepared by bubbling dry hydrogen chloride gas through an ethanol solution of the free base and adding ether to induce crystallization. Recrystallization from ethanol–ether gave colorless prisms, m. p. 155–156°.

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 63.28; H, 7.97. Found: C, 63.39; H, 7.80.

1-Ethoxymethyl-2-(3-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline (VIII).—To a solution of 1.9 g. (0.01 mole) of 1-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline in 30 cc. of 50% acetic acid was added 0.4 g. (0.05 mole) of 35% formaldehyde and 1.1 g. (0.01 mole) of indole. After the light yellow solution had stood at room temperature for seven hours, it was made basic with dilute sodium hydroxide, a light yellow oil separating. The mixture was extracted exhaustively with ether, and the ether removed from the combined extracts by distillation. The residue was taken up in 25 cc. of ethanol and a few cc. of water added dropwise until precipitation was complete. Recrystallization of the product from dilute ethanol gave 2.2 g. (69%) of tiny colorless needles, m. p. 100–102°. A small sample recrystallized again from dilute ethanol melted at 102–103°. Although the melting point was not changed, it was necessary to purify the product by chromatography (using chloroform–petroleum ether and a column of alumina) before a satisfactory analysis was obtained. Consistently high carbon values were obtained until this was done.

Anal. Calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.75. Found: C, 78.80; H, 7.50; N, 8.60.

Summary

A number of previously unreported 3-indolylmethylammonium salts, compounds which are analogous to the structures postulated for the calabash curare alkaloids, have been prepared. Some of these quaternary salts exhibit marked curariform activity, the most effective, N-(3-indolylmethyl)-N-methyl-1,2,3,4-tetrahydroisoquinolinium iodide, causing paralysis in mice in doses of 16 mg./kg.

ROCHESTER, N. Y. RECEIVED JULY 22, 1948

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

Curariform Activity and Chemical Structure. IV. Syntheses in the Piperidine Series[1]

BY L. E. CRAIG[2] AND D. S. TARBELL

Substituted 4-piperidones, 4-hydroxypiperidines and various piperidinium salts have been reported to exhibit rather intense curariform activity.[3,4] The present paper reports the syntheses of and the results of preliminary pharmacological tests on 4-piperidonium and 4-hydroxypiperidinium salts.

Di-β-carbomethoxyethylmethylamine (I), obtained by the addition of methylamine to methyl acrylate by the method of Mozingo and McCracken,[5] was treated with powdered sodium in xylene by the procedure of McElvain[6] to give 1-methyl-3-carbomethoxy-4-piperidone (III). Compound III, on acid hydrolysis, gave 1-methyl-4-piperidone (V), which was readily converted to 1-

(1) For the third paper of this series see Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).

(2) Aided by a Grant from the National Foundation for Infantile Paralysis. Present address: General Aniline and Film Corporation, Easton, Pennsylvania.

(3) Craig, *Chem. Revs.*, **42**, 360, 390 (1948).

(4) von Oettingen, "The Therapeutic Agents of the Pyrrole and Pyridine Group," Edwards Brothers, Inc., Ann Arbor, Michigan, 1936, p. 116.

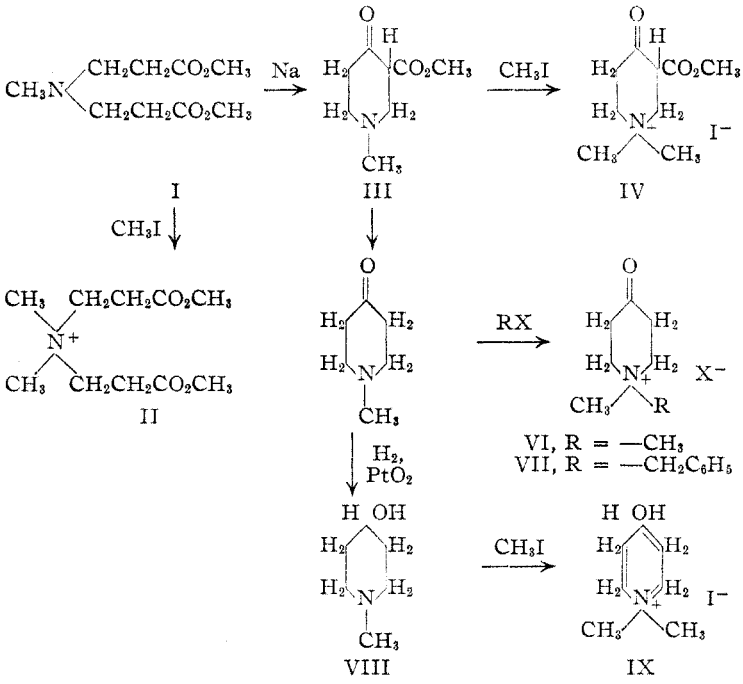
(5) Mozingo and McCracken, *Org. Syn.*, **20**, 35 (1940).

(6) McElvain, THIS JOURNAL, **46**, 1721 (1924).

methyl-4-hydroxypiperidine (VIII) by catalytic hydrogenation.

Previous workers[7,8,9] obtained a hydrochloride of 1-methyl-4-piperidone which melted at 94–95°. When dry hydrogen chloride gas was bubbled through a dry ether solution of distilled 1-methyl-4-piperidone, a hydrochloride was obtained which melted at 164–167°. It is probable that the hydrochloride melting at 94–95° contains water of crystallization (no analyses were reported). On distillation of the 1-methyl-4-piperidone, a considerable amount was left as a viscous residue in the distilling flask. As the distilled product also increased noticeably in viscosity on standing, it seems probable that it undergoes an aldol-type condensation.

The piperidone, hydroxypiperidine and the tertiary amine intermediates were converted into quaternary salts by conventional methods. The reactions carried out are summarized as



All of the quaternary salts, with the exception of compound II which produces a marked muscarinic action, cause curariform paralysis in mice. Compounds IV, VI, VII and IX are effective in doses of 180–280 mg./kg. when injected intraperitoneally. Compound IX is effective when given orally in doses of 1000 mg./kg.[10]

Experimental

Di-β-carbomethoxyethylmethylamine (I).—This compound was prepared by the procedure used by Mozingo and McCracken[5] for the preparation of the corresponding carbethoxy compound. In a typical experiment, 172 g. (2.0 moles) of methyl acrylate and 31 g. (1.0 mole) of methylamine gave 183 g. (90%) of colorless liquid, b. p. 108–112° (3–4 mm.).[11]

3-Carbomethoxy-1-methyl-4-piperidone (III).—This compound was prepared by the procedure used by McElvain[6] for the corresponding carbethoxy compound. In one experiment, 41 g. (0.2 mole) of di-β-carbomethoxyethylmethylamine in 100 cc. of xylene was treated with 4.6 g. (0.2 mole) of powdered sodium to give 20.4 g. (60% crude yield) of light yellow oil. Attempts to distil this product resulted in considerable loss. The light yellow liquid rapidly became dark and viscous on heating and only 40–50% of the material distilled, b. p. 85–90° (1 mm.). It was found advisable to convert the entire crude product to the hydrochloride by bubbling dry hydrogen chloride gas through an ether solution (the conversion was essentially quantitative), m. p., after recrystallization from ethanol–ether, 164–165°.[12]

1-Methyl-4-piperidone (V).—This product was obtained by hydrolysis of 3-carbomethoxy-1-methyl-4-piperidone according to the procedure of Bolyard and McElvain.[7] The product was obtained by this procedure as the hydrochloride, m. p. 94–95°.[13] In one experiment, this crude hydrochloride was converted to the free base and the free base distilled, b. p. 54–56° (9 mm.), $n^{25}D$ 1.4588.[14] Much of the free base was not recovered on distillation and a viscous, dark residue was left in the distilling flask. The distilled product also increased noticeably in viscosity on standing. For this reason, the product was used immediately after distillation in subsequent reactions.

A stream of dry hydrogen chloride gas was bubbled through a benzene solution of the distilled free base. The hydrochloride so obtained was recrystallized from anhydrous chloroform–ether to give colorless crystals melting at 164–167°.

Anal. Calcd. for $C_6H_{12}ClNO$: C, 48.16; H, 8.09. Found: C, 48.11; H, 8.10.

A small amount of this hydrochloride was dissolved in water and the solution evaporated to dryness. The product so obtained melted at 94–95°. It is apparent that the hydrochloride previously reported contains water of crystallization.[15,15a]

4-Hydroxy-1-methylpiperidine (VIII).—The hydrochloride from 4.6 g. (0.004 mole) of freshly distilled 1-methyl-4-piperidone was dissolved in 75 cc. of ethanol and the solution shaken, in the presence of 0.3 g. of Adams platinum oxide catalyst, under hydrogen at 3.3 atm. at room temperature for eight hours. After removing the catalyst by filtration and the solvent by distillation, the residue was treated with a few cc. of concentrated alkali and the mixture exhaustively extracted with ether. The ether solution was dried over magnesium sulfate, the ether removed, and the residue distilled to give 3.1 g. (64%) of colorless

(7) Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929).

(8) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(9) Howton, *J. Org. Chem.*, **10**, 277 (1945).

(10) The authors are indebted to F. M. Berger, M.D., the University of Rochester School of Medicine and Dentistry, for the pharmacological tests on these compounds.

(11) Howton[9] reported a b. p. of 102–105° (4 mm.), and Cook and Reed, *J. Chem. Soc.*, 399 (1945), a b. p. of 137–140° (14 mm.).

(12) Howton[9] reported a m. p. of 163.7–164.5°.

(13) This m. p. agrees with that reported by other workers.[7,8,9]

(14) Prill and McElvain[8] reported a b. p. of 56–58° (11 mm.), $n^{25}D$ 1.4580.

(15) Keutel and McElvain, THIS JOURNAL, **53**, 2692 (1931), reported a m. p. of 92–94° for 4-piperidone hydrochloride containing one molecule of water of crystallization.

(15a) (Added in proof) modified procedures for the preparation of compounds V and VIII have been published recently by McElvain and Rorig, *ibid.*, **70**, 1820, 1826 (1948).

TABLE I

QUATERNARY SALTS

Compound	M. p.,[a] °C.	Yield, %	Formula	Analyses,[b] % Calcd. C	Calcd. H	Found C	Found H
II[c]	146 dec.	65	$C_{10}H_{20}INO_4$	34.79	5.84	34.71	5.96
IV[d]	127–128 dec.	60	$C_9H_{16}INO_3 \cdot 0.5H_2O$	33.60	5.27	33.81	5.17
VI[e,f]	174–179 dec.	82	$C_7H_{14}INO$	32.95	5.53	32.60	5.41
VII[e]	182 dec.	67	$C_{13}H_{18}BrNO$	54.94	6.38	54.86	6.20
IX[d]	309–311 dec.	82	$C_7H_{16}INO$	32.70	6.27	32.74	6.15

[a] All melting points are corrected. [b] Analyses by Mrs. G. L. Sauvage. [c] Recrystallized from ethanol. [d] Recrystallized from methanol–ether. [e] Not recrystallized. [f] Howton[9] obtained a quaternary salt which analyzed for one molecule of methanol of crystallization, m. p. 187.6–188°.

liquid, b. p. 80–87° (5–6 mm.), $n^{21}D$ 1.4718.[16] The hydrochloride melted at 155–156°.[16]

Preparation of Quaternary Salts.—The tertiary amines prepared in the above experiments were converted into quaternary salts by allowing benzene solutions of the distilled amine and excesses of the alkyl halide to stand at room temperature for twenty-four hours, the quaternary salts precipitating as they formed. The salts prepared are listed in Table I.

(16) Mills, Parkin and Ward, *J. Chem. Soc.*, 2613 (1927), reported a b. p. of 105° (18 mm.) and a m. p. for the hydrochloride of 157–158°. Riegel and Reinhard, THIS JOURNAL, **48**, 1334 (1926), reported a b. p. of 116–118° (36 mm.).

Summary

A number of previously unreported 4-piperidonium and 4-hydroxypiperidinium salts have been prepared. They were found to exhibit mild curariform activity, and one was found to be effective when administered orally.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Isomeric Dihydroxanthopterins[1]

BY GEORGE H. HITCHINGS AND GERTRUDE B. ELION

Dihydroxanthopterin (2-amino-4,6-dihydroxydihydropteridine) has been prepared by three routes[2,3,4] involving the reduction of a pteridine. Purrmann[2] reduced xanthopterincarboxylic acid catalytically and found the resultant dihydro-acid to be readily decarboxylated to dihydroxanthopterin. Totter[3] was able to isolate the same compound from the reduction of leucopterin (2-amino-4,6,7-trihydroxypteridine) by sodium amalgam, and O'Dell, *et al.*,[4] obtained it directly by the catalytic reduction of xanthopterin (III). The latter were the first to assign a structure to the compound. They made the logical suggestion that the two hydrogen atoms might add across the 7,8 double bond to give 7,8-dihydroxanthopterin (V). The synthesis of (V) by an apparently definitive method, however, has led to a dihydroxanthopterin distinct from that formed by reductive methods. For convenience the compound produced by reductive methods will be called α-dihydroxanthopterin and the synthetic compound, β-dihydroxanthopterin.

The existence of two dihydroxanthopterins where a single substance would have been expected recalls the suggestion (not clearly established) that stable tautomers of certain dihydropyrazines may exist.[5] The establishment of this instance of isomerism has important implications in the field of pteridine chemistry; the resistance of the β-dihydroxanthopterin structure to oxidation may have some bearing on the role of oxidative reactions in the synthesis of folic acid.

β-Dihydroxanthopterin was prepared in these laboratories several years ago as a possible intermediate in the synthesis of xanthopterin, which at that time was believed to have a number of important biological functions.[6,7,8] This compound is, indeed, convertible to xanthopterin but in poor yield (20%) and only under relatively drastic conditions (concentrated sulfuric acid at 210° for fifteen minutes). The α-isomer, on the other hand, can be converted to xanthopterin by a wide range of oxidative procedures, quantitatively by exposure to oxygen in alkaline solution with[2] or without platinum catalyst or by alkaline permanganate oxidation at room temperature.[9] Other properties of the two are compared in Table I. In addition to the observed differences in oxidizability the difference in stability to acid and alkali is noteworthy. The α-isomer is gradually decomposed by acid, giving unidentified colored

(1) Presented before the Division of Organic Chemistry at the New York meeting of the American Chemical Society, September 16, 1947.

(2) Purrmann, *Ann.*, **548**, 284 (1941).

(3) Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(4) O'Dell, Vandenbelt, Bloom and Pfiffner, THIS JOURNAL, **69**, 250 (1947).

(5) D'Albe, translator, "Richter's Organic Chemistry," Vol. III, P. Blakiston's Son and Co., Philadelphia, 1923, p. 284.

(6) Tschesche and Wolf, *Z. physiol. Chem.*, **248**, 34 (1937).

(7) Totter and Day, *J. Biol. Chem.*, **147**, 257 (1943).

(8) Simmons and Norris, *J. Biol. Chem.*, **140**, 679 (1941).

(9) Elion, Light and Hitchings, forthcoming publication.