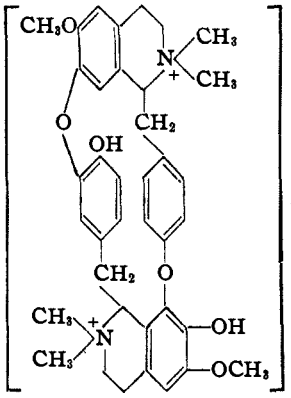
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Curariform Activity and Chemical Structure. II. Synthesis in the Benzyltetrahydroisoquinoline Series[1]

BY L. E. CRAIG AND D. S. TARBELL

One of the most effective of the curare alkaloids in causing paralysis of the peripheral nervous system (curariform paralysis) is *d*-tubocurarine chloride. This naturally occurring alkaloid was shown by King[2] to be of the bisbenzyltetrahydroisoquinoline type and to have structure I.



I

The present paper reports the syntheses of and the results of preliminary pharmacological tests on certain compounds analogous to half of the *d*-tubocurarine chloride molecule, that is, quaternary salts of benzyltetrahydroisoquinoline derivatives.

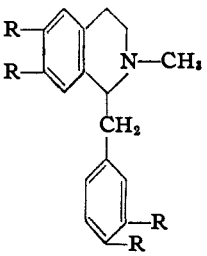
Numerous syntheses of laudanosine (II) have been reported in the literature. Pyman[3] treated tetrahydropapaverine with methyl iodide and obtained laudanosine hydroiodide in 5% yield, along with 21% of tetrahydropapaverine hydroiodide and 19% of laudanosine methiodide. Pictet and Finkelstein[4] prepared the methiodide of 3,4-dihydropapaverine, obtained from homoveratroylhomoveratrylamine by the Bischler–Napieralski reaction, converted it to the methochloride by stirring with silver chloride, and reduced the methochloride chemically with tin and hydrochloric acid. They obtained a 7% yield, based on the starting amide.

Several chemical reductions of N-methyl quaternary salts of papaverine have been reported,[5] in yields of 50–80%, but relatively long reaction periods were required and the necessary decomposition of the tin or zinc complex salts at the end of the reduction made the isolation of the product very inconvenient.

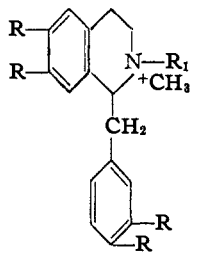
We have found that tetrahydropapaverine can be methylated to laudanosine very conveniently, and in excellent yield (89%), by the reductive methylation procedure,[6] using anhydrous formaldehyde in absolute alcohol, with Raney nickel and hydrogen under mild conditions.

N-Methyllaudanosinium iodide (III) and the previously unreported N-benzyllaudanosinium bromide (IV) were prepared by conventional methods.

The tetrahydropapaverine required for this synthesis was prepared by the hydrogenation of both papaverine and 3,4-dihydropapaverine, in the presence of Raney nickel, giving yields (greater than 80%) greatly improved over those reported in the literature.[7] A further advantage is that the 3,4-dihydropapaverine, which is very unstable, need not be isolated and purified after its formation by ring-closure of homoveratroylhomoveratrylamine, but may be hydrogenated in the crude form after transferring to the appropriate solvent.



(II) R = —OCH_3
(VII) R = —H



(III) R = —OCH_3, R_1 = CH_3
(IV) R = —OCH_3, R_1 = —$CH_2C_6H_5$
(VIII) R = —H, R_1 = —CH_3

A literature survey[8] on the types of compounds exhibiting curariform activity disclosed that certain compounds possessing a tertiary or quaternary nitrogen common to two saturated ring systems show marked curariform activity. Treatment of tetrahydropapaverine with formaldehyde gave such a compound, 2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine[9] (V), which was converted to the quaternary methiodide (VI) by treatment with methyl iodide.

(1) Aided by a Grant from the National Foundation for Infantile Paralysis. We are indebted to Dr. Virgil Boekelheide and R. Plato Schwartz D., for their interest in this work.

(2) King, *J. Chem. Soc.*, 1381 (1935); 265 (1948).

(3) Pyman, *J. Chem. Soc.*, 93, 1610 (1909).

(4) Pictet and Finkelstein, *Ber.*, **42**, 1979 (1909).

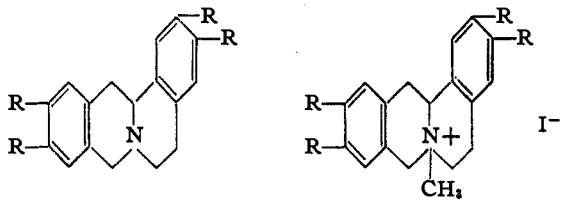
(5) (a) Awe[n]asescu, *ibid.*, *ibid.*, **70**, 472 (1937); (b) Pictet and Athanasescu, *ibid.*, 1900); (c) Pyman and Reynolds, *J. Chem. Soc.*, **97**, 1320

(6) For references related to the alkylation of aromatic and aliphatic amines with aldehydes and ketones, see (a) Clark, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1936), and (b) Emerson and Ringwald, *ibid.*, **63**, 2843 (1941), the last paper of a series.

(7) (a) Späth and Burger, *Ber.*, **60**, 704 (1927), obtained a 62% yield by electrolytic reduction of papaverine. Pyman[3] obtained a 39% yield by reduction of papaverine with tin and hydrochloric acid. (b) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934), reduced dihydropapaverine catalytically with palladium in 63% yield.

(8) Craig, *Chem. Rev.*, **42**, 285 (1948).

(9) This compound has appeared in the literature under the following names: norcoralydine, tetrahydropalmatine, and 2,3,11,12-tetramethoxyberbine. The "Ring Index" name has been used in this paper for clarity.



(V) R = —OCH_3 (VI) R = —OCH_3
(IX) R = —H (X) R = —H

The corresponding compounds without methoxyl groups were also prepared. 1-Benzyl-1,2,3,4-tetrahydroisoquinoline was prepared by catalytic hydrogenation (Raney nickel) of the 1-benzyl-3,4-dihydroisoquinoline formed in the Bischler–Napieralski synthesis. Here again the 3,4-dihydroisoquinoline was not isolated. Only chemical reductions have previously been reported.[10] The reductive methylation of the tetrahydroisoquinoline with formaldehyde gave 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII) in 66% yield. (VII) was converted into the quaternary methiodide (VIII).

Attempts to prepare 5,6,13,13a-tetrahydro-8-dibenzo(a,g)-quinolizine (IX) by treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde under both acidic and basic conditions were unsuccessful, but it was obtained by the method of Leithe[11] and converted to the quaternary methiodide (X).

Compounds III, IV, VI and VIII exhibited curare-like activity in mice, the two most effective, VI and VIII, being 1/70th to 1/75th as active as *d*-tubocurarine chloride. All four of the compounds showed vasodepression in dogs. Compounds V and X were convulsant poisons.[12]

Experimental[13]

Tetrahydropapaverine. A.—Ten grams of papaverine[14] in 250 cc. of ethanol was shaken with 1 g. of Raney nickel for four hours at 150° under hydrogen at 150 atm. The catalyst was removed by filtration and the filtrate reduced in volume to about 100 cc. An excess of dry hydrogen chloride gas was bubbled through the solution and ether added to precipitate the tetrahydropapaverine hydrochloride. Ten grams (89%) was obtained, m. p. 216–218°. The picrate after recrystallization from ethanol melted at 161–162°.[15]

B.—A 10-g. sample of homoveratroylhomoveratrylamine, prepared from the hydrazide of β-(3,4-dimethoxyphenyl)-propionic acid and homoveratric acid by the method of Schöpf and Salzer,[16] was treated with phosphorus oxychloride in thiophene-free benzene according to the method of Kindler and Peschke,[7b] all operations being carried out under an atmosphere of nitrogen rather than carbon dioxide. The chloroform extract of the dihydroisoquinoline was evaporated to dryness, and the residue taken up in 75 cc. of ethanol. The solution was shaken for five hours at about 70° under hydrogen at 3.5 atm. in the presence of about 0.5 g. of Raney nickel. After removing the catalyst by filtration, the solution was reduced in volume to about 50 cc. and an excess of dry hydrogen chloride gas introduced. The tetrahydropapaverine hydrochloride was recrystallized from ethanol–ether, 8.7 g. (79%) of very light tan needles being obtained, m. p. 216°. The picrate melted at 161–162°.[15]

Laudanosine (II).—A 2-g. sample of tetrahydropapaverine hydrochloride was converted to the free base and dissolved in 50 cc. of absolute ethanol. An excess of anhydrous formaldehyde was introduced into the solution by passing a stream of dry nitrogen over dry paraformaldehyde, heated in a flask immersed in an oil-bath at 180–190°, and then into the cooled solution. About 0.5 g. of Raney nickel was added, and the solution shaken at room temperature for three and one-half hours under hydrogen at a pressure of 2.5 atm. The catalyst was removed by filtration, the ethanol solution reduced in volume to about 25 cc., and an excess of dry hydrogen chloride introduced. On adding ether, an oil separated and slowly crystallized. The product was dissolved in water and the cooled solution made basic with dilute alkali. The white amorphous solid (1.7 g., 89%, m. p. 111–113°) melted at 114–115° after recrystallization from dilute ethanol. The picrate was obtained as yellow needles from ethanol, m. p. 173–175°.[17]

N-Methyllaudanosinium Iodide (III).—This product was obtained in 69% yield by refluxing a dry benzene solution (50 cc.) of 3 g. of laudanosine and 1.5 cc. of methyl iodide for three hours, m. p. 212–214° without further purification. A small sample recrystallized from ethanol–ether with charcoal treatment melted at 214–215°.[18] This product was shown by mixed melting point to be identical with a product obtained in 15% yield from the treatment of tetrahydropapaverine with methyl iodide.

Anal. Calcd. for $C_{22}H_{30}INO_4$: C, 52.91; H, 6.10. Found: C, 52.98; H, 6.09.

N-Benzyllaudanosinium Bromide (IV).—This product was obtained in essentially quantitative yield by refluxing a benzene solution (25 cc.) of 1.2 g. of laudanosine and 0.5 cc. of benzyl bromide for six hours. After recrystallization from absolute ethanol, tiny needles were obtained, m. p. 157–165° with decomposition. No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{28}H_{34}BrNO_4$: C, 63.63; H, 6.49. Found: C, 63.50; H, 6.10. These analytical values were obtained after several analyses in which carbon percentages were consistently low.

2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine (V).[19]—Five grams of tetrahydropapaverine hydrochloride in 40 cc. of water was heated on a steam-bath while 10 cc. of 35% formaldehyde was added in small portions over a period of thirty minutes. Heating was continued for an additional thirty minutes. After concentrating the solution and cooling, 5.2 g. of the crude hydrochloride was obtained. The product was dissolved in a small amount of water and the free base liberated by the addition of an excess of dilute alkali, giving 3.8 g. (83%), m. p. 158–159°.

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09. Found: C, 70.98; H, 6.93.

The hydrochloride, prepared by passing dry hydrogen chloride gas through an ether solution, melted at 234–237° with decomposition.[20]

(10) (a) Leithe, *Ber.*, **63**, 1498 (1930); (b) Forsyth, Kelly and Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(11) Leithe, *Ber.*, **63**, 2343 (1930).

(12) The authors are indebted to Drs. J. A. Shannon, C. R. Linegar and J. C. Burke of the Squibb Institute for Medical Research for the pharmacological tests on these compounds.

(13) All melting points are corrected; analyses by Mrs. G. L. Sauvage and Dr. Carl Tiedcke.

(14) Obtained as the hydrochloride from Mallinckrodt Chemical Co.

(15) Pyman[3] reported 217–219° as m. p. of the hydrochloride and 161–162° for the picrate.

(16) Schöpf and Salzer, *Ann.*, **544**, 1 (1940).

(17) Pictet and Anthanasescu[5b] reported 115° as m. p. for the free base, and 174° for the picrate.

(18) Pyman[3] reported a m. p. of 123–215°. Pictet and Athanasescu[5b] reported a m. p. of 215–217°.

(19) Pictet and Chou, *Ber.*, **49**, 370 (1916).

(20) (a) Hayworth, Koepfli and Perkin, *J. Chem. Soc.*, 548 (1927), reported a m. p. of 147° for the free base. (b) *Arch. Pharm.*, **245**, 627 (1907), reported a m. p. of 145°. and Chou[19] reported a m. p. of 157–158° for the free base, for the hydrochloride.

7-Methyl-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizinium Iodide (VI).—This quaternary salt was obtained in essentially quantitative yield by refluxing a solution of 2 g. of 2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8-dibenzo(a,g)quinolizine and 1 cc. of methyl iodide in 50 cc. of benzene for three and one-half hours. The tiny white needles which precipitated melted at 244–249°.[21] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{22}H_{28}INO_4$: C, 53.12; H, 5.67. Found: C, 52.75; H, 5.71.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline.—A 20-g. sample of N-(β-phenylethyl)-phenylacetamide[22] was converted to 1-benzyl-3,4-dihydroisoquinoline by treatment with phosphorus pentoxide in boiling tetralin according to the procedure of Späth, Berger and Kuntara.[23] The light yellow oil (10 g., 54%) was dissolved in 75 cc. of ethanol, 1 g. of Raney nickel added, and the solution shaken for three hours at 70° under hydrogen at 3.5 atm. The catalyst was removed by filtration and the filtrate concentrated to about 40 cc. An excess of dry hydrogen chloride gas was introduced and ether added to facilitate precipitation. The 8.8 g. of colorless crystals obtained represent a 75% yield in the hydrogenation. A small sample after recrystallization from ethanol–ether melted at 172–173°.[24]

1-Benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VII).—The free base from 3.3 g. of 1-benzyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was dissolved in 75 cc. of absolute ethanol and an excess of anhydrous formaldehyde introduced as above. About 0.5 g. of Raney nickel was added and the solution shaken for three hours at room temperature under hydrogen at 3.3 atm. The catalyst was removed by filtration and the ethanol removed by distillation, leaving 2.3 g. (66%) of very light yellow oil. The picrate was obtained as tiny yellow needles from ethanol, m. p. 166.5–167°.[25]

(21) Osada, *J. Pharm. Soc.*, No. 547, 711 (1927), reported a m. p. of 245°. Haworth, Koepfli and Perkin, *J. Chem. Soc.*, 2263 (1927), reported a m. p. of 266° for the β-isomer, 230° for the α-isomer. Robinson and Sugasawa, *ibid.*, 789 (1932), reported a m. p. of 215°.

(22) Prepared by the method of Decker, *Ann.*, **395**, 282 (1912).

(23) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(24) Leithe (ref. 10a) reported a m. p. of 173°.

(25) Forsyth, Kelly and Pyman (ref. 10b) reported a m. p. of 165–167°.

1-Benzyl-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (VIII).—A dry benzene solution (50 cc.) of 2.2 g. of 1-benzyl-2-methyl-1,2,2,4-tetrahydroisoquinoline and 2 cc. of methyl iodide was refluxed for three hours on a steam-bath. The light tan powder obtained on filtering the cooled reaction mixture amounted to 2.9 g. (83%). After recrystallization from absolute ethanol, 2.5 g. (72%) of tiny colorless needles were obtained, m. p. 242°.[26]

5,6,13,13a-Tetrahydro-8-dibenzo[a,g]quinolizine (IX).—Attempts to prepare 5,6,13,13a-tetrahydro-8-dibenzo-[a,g]quinolizine by treatment of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde in the presence of hydrochloric acid, or of sodium bicarbonate, were unsuccessful. It was prepared in 38% yield by the method of Leithe,[11] m. p. of the free base 84–85°, m. p. of the hydrochloride 231–232°.

7-Methyl-5,6,13,13a-tetrahydro-8-dibenzo[a,g]quinolizinium Iodide (X).—A dry solution of 0.6 g. of 5,6,13,-13a-tetrahydro-8-dibenzo[a,g]quinolizine and 2 cc. of methyl iodide in 50 cc. of dry benzene was refluxed for four hours. The light tan precipitate which formed was collected by filtration and dried. The 0.8 g. of product after recrystallization from ethanol–ether with charcoal treatment gave 0.7 g. (73%) of very light tan powder, m. p. 198–202°.[27] No attempt was made to separate the diastereoisomers.

Anal. Calcd. for $C_{18}H_{20}IN$: C, 57.30; H, 5.34. Found: C, 57.64; H, 5.36.

Summary

1-Benzyltetrahydroisoquinolines have been synthesized by improved methods. Quaternary salts of these compounds exhibited curare-like activity, the most effective being 1/75th as active as *d*-tubocurarine chloride.

(26) Leithe (ref. 10a) reported a m. p. of 242°. Freund and Bode, *Ber.*, **42**, 1763 (1909), reported a m. p. of 239–242°.

(27) Chakravarti, Haworth and Perkin, *J. Chem. Soc.*, 2275 (1927), reported a m. p. of 230–232° for the β-isomer, 212° for the α-isomer.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

Synthesis of Some Iodo-sugar Derivatives[1]

BY ALBERT L. RAYMOND AND ELMER F. SCHROEDER

The use of iodinated organic compounds as X-ray contrast agents in urography has become well established in recent years. However, the administration of such compounds by the intravenous route is attended by an element of danger because of occasional side effects. In a search for other suitable contrast agents of lower toxicity, a number of water soluble iodo-sugar derivatives have been prepared and subjected to preliminary tests. These include 6-iodo-6-desoxy-D-galactose (I), 6-iodo-6-desoxy-α-methyl-D-glucopyranoside (II), 6-iodo-6-desoxy-β-methyl-D-glucopyranoside (III) and 6-iodo-6-desoxy-1,4-sorbitan (IV).

The introduction of the iodine atom into the sugar residues was accomplished by the well-known procedure of Oldham and Rutherford[1a] by heating the corresponding 6-*p*-toluenesulfonyl (tosyl) derivative, suitably stabilized by substituent groups, with sodium iodide in acetone solution. Thus, 6-iodo-6-desoxy-D-galactose was obtained by the following series of reactions: 1,2,3,4-diisopropylidene-D-galactose[2] → 6-tosyl-1,2,3,4-diisopropylidene-D-galactose[3] → 6-iodo-6-desoxy-1,2,3,4-diisopropylidene-D-galactose[4] → 6-iodo-6-desoxy-D-galactose. The final step in this series was carried out by hydrolysis of the diisopropyli-

(1) Presented before the Division of Sugar Chemistry and Technology of the American Chemical Society at the Chicago meeting, April, 1948.

(1a) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(2) Van Grunenberg, Bredt and Freudenberg, *ibid.*, **60**, 1507 (1938).

(3) Freudenberg and Hixon, *Ber.*, **56**, 2119 (1923).

(4) Freudenberg and Raschig, *ibid.*, **60**, 1633 (1927).