[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Sodium Borohydride Reduction of Quaternary Schiff Bases and Alkaloids

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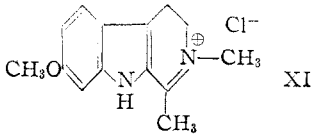
The reduction with sodium borohydride of quaternary bases and alkaloids containing a non-aromatic $-C=\overset{\oplus}{N}<$ bond leads to N-methyldihydro derivatives such as hydrocotarnine, N-methyldihydropeganine and N-methyltetrahydroyobyrine, whereas with C-Curarine-I formation of an ether-soluble base, apparently the so-called "dimeric ether base," is observed the infrared spectrum of which still shows the presence of the $>C=N-$ element.

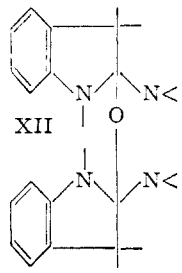
Whereas lithium aluminum hydride in some instances is capable of reducing tertiary heterocyclic bases to (more or less unstable) dihydro compounds,[2,3] the milder sodium borohydride requires quaternary open or cyclic Schiff bases.[4] Compared with analogous reductions using lithium aluminum hydride,[5] reductions with sodium borohydride offer the advantage of working in homogeneous methanolic solution as well as of selectivity, such as in the formation of arecoline from methyl nicotinate methiodide[6] and of methyl hexahydrosempervirine from sempervirine methiodide.[7] The latter type of reduction will be of great use whenever tetrahydropyridine and similar partially hydrogenated heterocyclic systems have to be prepared from the quaternary aromatic precursors as, *e.g.*, in the synthesis of lysergic acid.

In five- and six-membered quaternary heterocycles with only one double bond present, *i.e.*, in quaternary cyclic Schiff bases, the reduction products are, as expected, N-methyldihydro compounds.[4] The table lists a number of cases investigated so far. The absence of the characteristic infrared absorption band of the $>C=N-$ element in all normal reduction products is of diagnostic value. Whereas dihydroyobyrine (V) methiodide behaved normally, the analogous reduction of harmaline methochloride (XI) gave rise to complications (see Experimental). The reasons that led to the partial

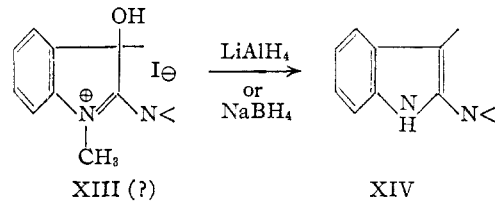


XI

and tentative formulation of C-Curarine-I chloride as a derivative of an α-aminoindole (IX) are presented elsewhere.[8] In this case the ether-soluble tertiary base obtained showed an infrared spectrum identical with that of the "dimeric ether base."[9] It is not likely that the ether base is formed according to XII, a type of compound discussed by Schlötzer,[10] since the infrared spectrum still contains the bands characteristic of the $>C=N-$ element. That the system present in IX behaves anomalously is shown by the lithium aluminum hydride reduction of β-hydroxyquebramidine methiodide (partial formula, presumably, XIII) which



XII



XIII (?) XIV

unexpectedly yields quebrachamine (assumed to be XIV).[11] The sodium borohydride reduction of C-Curarin-I chloride in aqueous acidic buffer solution,[12] the obvious modification to prevent formation of the ether base, has not been carried out yet because of the unavailability of the rare calabash alkaloid. C-Toxiferine-II and C-dihydrotoxiferine-I chlorides[13] on attempted reduction with sodium borohydride, have not yielded tertiary ether-soluble bases, a result suggesting the absence of a $>C=\overset{\oplus}{N}<$ element in these alkaloids.[14] Quaternary derivatives of tetrahydroquinoline, -isoquinoline and dihydroindole are not changed by the action of excess sodium borohydride (or lithium aluminum hydride) under a variety of conditions. An Emde cleavage[15] was never observed when tried with N-methyltetrahydro(iso)quinoline methiodide and similar compounds in many experiments.

(1) National Institute of Arthritis and Metabolic Diseases.

(2) F. Bohlmann, *Ber.*, **85**, 390 (1952); *cf.* W. G. Brown, *Organic Reactions*, **6**, 469 (1951).

(3) W. C. Wooten and R. L. McKee, THIS JOURNAL, **71**, 2946 (1949).

(4) R. Torossian and Ch. Sannié, *Compt. rend.*, **236**, 824 (1953); *cf.* R. Torossian, Étude de réduction partielle des sels d'ammonium quaternaires hétérocycliques à noyaux condensées, Thèse présentée a la faculté des Sciences de l'Université de Paris, 1953. In this thesis is described not only the potassium borohydride reduction of quaternary (iso)quinoline salts to dihydro [*cf.* W. M. Whaley and C. N. Robinson, THIS JOURNAL, **75**, 2008 (1953)] but also to tetrahydro derivatives, *e.g.*, the easy conversion of papaverine methiodide into laudanosine (Note added in proof).

(5) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).

(6) J. J. Panouse, *Compt. rend.*, **233**, 260, 1200 (1951).

(7) B. Witkop, THIS JOURNAL, **75**, 3361 (1953).

(8) B. Witkop, "Recent Investigations on Indole Alkaloids," lecture delivered before the Marburger Chemische Gesellschaft on July 24, 1953, abstracted in *Angewandte Chemie*, in press; *Experientia*, in preparation.

(9) Th. Wieland, H. J. Pistor and K. Bähr, *Ann.*, **547**, 140 (1941).

(10) A. Schlötzer, Dissertation, Univ. of Berlin, 1935.

(11) B. Witkop, in preparation.

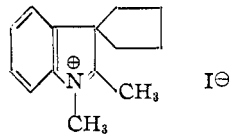
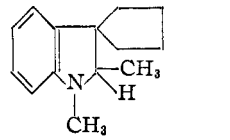
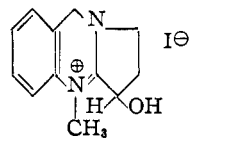
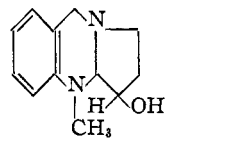
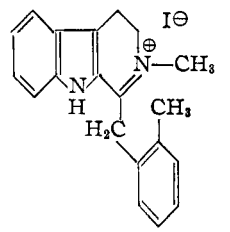
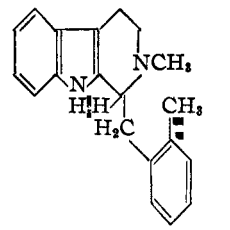
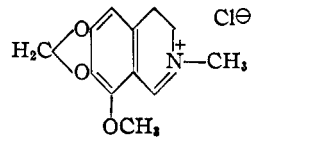
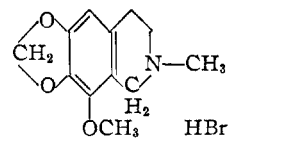
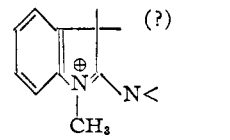
(12) *Cf.* M. L. Wolfrom and K. Anno, THIS JOURNAL, **74**, 5583 (1952).

(13) H. Wieland, K. Bähr and B. Witkop, *Ann.*, **547**, 156 (1941).

(14) J. Kebrle, H. Schmid, P. Waser and P. Karrer, *Helv. Chim. Acta*, **36**, 102 (1953).

(15) H. Emde and H. Krull, *Arch. Pharmaz.*, **274**, 173 (1936).

TABLE I

Compound	Formula	M.p., °C.	Infrared bands (in chloroform) $>C=\overset{\oplus}{N}<$	Infrared bands (in chloroform) Aromatic
spiro-(Cyclopentane-1,3′-*pseudo*-2′-methylindole) methiodide[a] (I)		204	6.07[s]	6.22 6.70
spiro-(Cyclopentane-1,3′-*pseudo*-1′,2′-dihydro-1′,2′-dimethylindole)[a] (II)		Oil (hydrochloride 129)	...	6.21[s] 6.74[s]
Peganine methiodide (III)		191–191.5[b]	5.97[m,f]	
N-Methyldihydropeganine (IV)		Oily	...	6.22[s] 6.70[s]
Dihydroyobyrine methiodide (V)		259–263[c]	6.15[s,g]	6.36[s] 6.43[s]
N-Methyltetrahydroyobyrine, (isolated as methiodide) (VI)		208–210[d] (methiodide 180–181)[d]	...	6.73[w] 6.85[s]
Cotarnine chloride (VII)		192	6.02[m,h]	6.18[s] 6.65[m] 6.70[s]
Hydrocotarnine hydrobromide (VIII)		229–230[e]	...	6.12 6.75
C-Curarine-I chloride (IX)		>300	6.04[s,i]	6.25[s] 6.73[s] 6.85[m]
"Dimeric ether base" (X)	$C_{40}H_{42}N_4O$	148	6.02[s]	6.26[s] 6.77[s] 6.86[s]

[a] B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 2572 (1953). [b] Reported 189–190°: F. Konek, *Math. Nat. Anz. ung. Akad. Wiss.*, **54**, 452 (1936); *Chem. Z.*, **107**, II, 1353 (1936). [c] B. Witkop, THIS JOURNAL, **75**, 3361 (1953). [d] The free base, reported by P. Karrer and P. Waser, *Helv. Chim. Acta*, **32**, 420 (1949), was not obtained crystalline and, therefore, converted to the methiodide, reported by Karrer (ref. 5) to melt at 232°; perhaps there are two different crystalline modifications of this methiodide. [e] The literature records 236–237°; C. R. A. Wright, *J. Chem. Soc.*, **32**, 525 (1877). [f] The position of this band in peganine hydrochloride is at 5.95 (saturated chloroform solution), at 5.90 (mulled in nujol). The >C=H— band in free peganine is at 6.10 μ (chloroform). [g] These measurements were taken in nujol. The >C=N— band in dihydroyobyrine hydrochloride is at 6.13 (in chloroform) and at 6.12 (in nujol); in the free base there is a weak band

at 6.14. [h] This distinct band is missing in the infrared spectrum of free cotarnine (m.p. 132–133°) mulled in nujol, confirming the carbinol amine structure assigned to the free base. [i] The spectrum was taken of the complex of C-Curarine-I chloride with one mole of chloroform (B. Witkop, unpublished) which unlike all other quaternary alkaloids from Calabash Curare is soluble in chloroform.

Experimental[16]

Peganine Methiodide (III).—Peganine (300 mg.), 1 cc. of methyl iodide, and 10 cc. of methanol were refluxed for 1.5 hours. Evaporation left a brown fragrant oil which crystallized overnight. Washing with acetone and drying left 355 mg. (69.5%; theory = 525 mg.) of a pinkish powder. Recrystallization from methanol gave two types of crystals: A, the main product, colorless needles, and B, a very few small red polyhedra. The crystals were separated and each group crystallized twice from methanol. A, the methiodide, produced clusters of birefringent needles, m.p. 191–191.5° (reported 189–190°)[17] (local melting 184°; brown-black melt). B forms glass-like brownish cubes, dec. 183–213.5° (darkening starts 176°, black viscous melt). Comparison of the infrared and ultraviolet spectrum of B with that of peganine hydrochloride strongly indicated that B is peganine hydriodide.

N-Methyldihydropeganine (IV).—Peganine methiodide (85 mg.) in 10 cc. of methanol was cautiously treated with 80 mg. of powdered sodium borohydride. When vigorous gas evolution subsided, the mixture was refluxed for an hour and evaporated to dryness. The residue was taken up in 1.5 cc. of warm 2 *N* hydrochloric acid, made basic with 2 cc. of 2 *N* potassium hydroxide, and extracted with ether. The extract, after drying over magnesium sulfate and evaporating, left a perfectly colorless oil whose infrared spectrum, compared to that of peganine, showed it to be N-methyldihydropeganine. The picrate, hydrochloride and perchlorate were all gummy. The material was treated with 0.1 cc. of benzoyl chloride in 0.3 cc. of pyridine, heated 5 minutes on the steam-bath, and worked up in the usual fashion. The product was a colorless oil, the infrared spectrum of which showed it to be O-benzoyl-N-methyldihydropeganine. The hydrochloride and oxalate were both gummy, although a few crystals of oxalate, m.p. 163°, were obtained. The material was insufficient for analysis.

N-Methyltetrahydroyobyrine (VI) Methiodide.—When 200 mg. of dihydroyobyrine methiodide (V, m.p. 259–263°)[18] in 20 ml. of methanol was treated with 200 mg. of sodium borohydride, strong effervescence occurred and the yellow color became much lighter. The mixture was refluxed for 45 minutes and worked up as usual. The residue was treated with 3 cc. of 2 *N* HCl and extracted with ether and chloroform. The combined extracts amounted to 140 mg. of non-crystalline material which dissolved in water to form a yellow solution. Addition of 2 *N* potassium hydroxide precipitated a white oily deposit which was extracted with ether. After drying and evaporation the extract left a yellow oil which was chromatographed on 5 g. of Florisil. Methanolic chloroform (50%) eluted a yellow non-crystalline fraction. The hydrochloride was crystalline but strongly deliquescent, the hydriodide was crystalline but turned dark and oily on standing. The oil in ether solution was treated with methyl iodide to yield the methiodide as slightly yellow birefringent needles, m.p. 180–181° (clear melt).

Anal. Calcd. for $C_{21}H_{25}N_2I$: C, 58.33; H, 5.83; N, 6.48. Found: C, 58.30; H, 6.04; N, 6.51.

Hydrocotarnine (VIII).—When 1 g. of cotarnine chloride (VII) in 20 cc. of methanol was treated at 0° with 1 g. of sodium borohydride, there was a vigorous effervescence and the yellow color of the solution faded. The cloudy colorless solution was refluxed for an hour, then taken to dryness *in vacuo* at 100°. The residue was dissolved in 2 *N* HCl, filtered with Celite, made basic with 2 *N* alkali and extracted with ether. The extract was washed with saturated salt solution, dried over magnesium sulfate, and evaporated to leave 675 mg. of a light yellow oil which was chromatographed over alumina. The purest fraction was treated with hydrogen bromide in ether to yield a crystalline hydrobromide, m.p. 229–230°.

Anal. Calcd. for $C_{12}H_{15}NO_3 \cdot HBr$: C, 47.69; H, 5.34; N, 4.64. Found: C, 47.70; H, 5.44; N, 4.61.

Reaction of Harmaline Methochloride with Sodium Borohydride.—When 18 mg. of harmaline methochloride (m.p. 277°)[19] in 20 cc. of methanol was refluxed with 18 mg. of sodium borohydride, the yellow color of the solution vanished at first and reappeared during the refluxing. After 1.5 hours of refluxing, the mixture was treated with another 18 mg. of sodium borohydride, whereupon the color again vanished. The mixture was taken to dryness *in vacuo* at 100°. The white fluffy residue, having an odor reminiscent of iodoform, was worked up in the usual way. There were obtained colorless birefringent prisms, m.p. 176–178° (sublimation from 133°). The chloroform solution of the substance turned yellow with green fluorescence on standing. Found: C, 67.15; H, 7.70; a compound $C_{14}H_{18}N_2O \cdot H_2O$ would require C, 67.74; H, 8.14.

The infrared spectrum of the reduction product and the starting material showed the following bands in chloroform:

Harmaline methochloride	6.11^s (6.22^w)	6.34^m	6.67^s	6.84^s
Reduction product	6.13^s	—	6.34^s	6.43^s 6.85^s

The reduction product had a strong and narrow band at 2.86 μ characteristic of an indole imino group; the ultraviolet absorption showed λ_{max} (log ϵ): 298 (3.74); 2.72 (3.65); 228 (4.51). The comparison with the spectrum of 6-methoxyindole[20] [λ_{max} (log ϵ): 287 (3.63); 265 (3.66)] shows, as does the infrared spectrum, that the compound m.p. 176–178° cannot be a straightforward reduction product but may have been formed *via* an autoxidation process.[21]

Reaction of C-Curarine-I Chloride (Tentative Partial Formula IX) with Sodium Borohydride.—A solution of 50 mg. of C-curarine-I chloride in 10 cc. of methanol was treated with 50 mg. of sodium borohydride in 5 cc. of methanol, followed by another portion of 50 mg. of sodium borohydride. The mixture was refluxed for one hour. The reaction product was worked up in the usual way. The infrared spectrum of the ether-soluble base was identical with that of the so-called "dimeric ether base" (X).

Acknowledgment.—We are indebted to Dr. Roger Adams for his kind donation of peganine.

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(16) All melting points are corrected.

(17) F. Konek, *Chem. Zentr.*, **107**, II, 1353 (1936), Table I, ref. b.

(18) B. Witkop, THIS JOURNAL, **75**, 3361 (1953).

(19) B. Witkop, *Ann.*, **554**, 126 (1943).

(20) F. Pruckner and B. Witkop, *Ann.*, **545**, 127 (1943).

(21) The formation of N^{α},N^{β}-diphenyl-N^{β}-anisalanis-hydrazidine in the reaction of anisalphenylhydrazone with lithium aluminum hydride is another example of the participation of molecular oxygen in a metal hydride reduction, *cf.* B. Witkop and H. M. Kissman, THIS JOURNAL, **75**, 1975 (1953).