The Arylaralkyloxazolidine System. 2-Phenyl-3-(*p*-methoxybenzyl)-oxazolidine (XXIII).—A solution of 24.5 g. (0.135 mole) of 2-(*p*-methoxybenzylamino)-ethanol[75,76] and 14.33 g. (0.135 mole) of benzaldehyde in 100 ml. of benzene was heated at reflux for 25 minutes in a Dean–Stark apparatus. The residue after removal of the benzene was distilled at 168° (0.45 mm.) to give 29 g. (80%) of 2-phenyl-3-(*p*-methoxybenzylamino)-oxazolidine, $n^{21.5}$D 1.5707. The infrared spectrum (carbon tetrachloride) showed no absorption in the O–H stretching region and exhibited maxima characteristic of oxazolidines[72,73] at 1168, 1057, 1041 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.74; H, 7.14; N, 5.46.

Hydrolysis.—Three grams of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine was hydrolyzed by shaking with 3.0 ml. of 6 *N* hydrochloric acid. Removal of the neutral material by methylene chloride extraction was followed by basification with potassium hydroxide. Extraction with methylene chloride followed by drying and evaporation gave 1.57 g. (90%) of pure 2-(*p*-methoxybenzylamino)-ethanol (infrared spectrum virtually identical with that of an authentic sample).

Isomerization Experiments.—(a) A solution of 3.0 g. of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine in 75 ml. of absolute methanol was heated at reflux for 24 hours. Evaporation of the methanol *in vacuo* was followed by the hydrolysis procedure above. 2-(*p*-Methoxybenzylamino)-ethanol was obtained in 99% yield (2.01 g.), with an infrared spectrum virtually identical with that of an authentic sample.

(b) A solution of 3.0 g. of 2-phenyl-3-(*p*-methoxybenzyl)-oxazolidine in 15 ml. of diethylene glycol monomethyl ether was heated at reflux under nitrogen for 24 hours. Upon hydrolysis, there was obtained 1.80 g. of basic material. The infrared spectrum of this material indicated that it was a mixture of 2-(*p*-methoxybenzylamino)-ethanol and 2-(benzylamino)-ethanol, in roughly equal amounts.

2-(*p*-Methoxyphenyl)-3-benzyloxazolidine (XXIV).—A solution of 25 g. (0.165 mole) of 2-(benzylamino)-ethanol[77] and 22.5 g. (0.165 mole) of anisaldehyde in 100 ml. of benzene was heated at reflux for 25 minutes in a Dean–Stark apparatus. The residue after removal of the benzene was distilled at 161–164° (0.35 mm.) to give 28.5 g. (64%) of 2-(*p*-methoxyphenyl)-3-benzyloxazolidine, $n^{21.5}$D 1.5717. The infrared spectrum (carbon tetrachloride) showed no absorption attributable to O–H stretching and exhibited bands characteristic of oxazolidines[72,73] at 1171, 1065 and 1043 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.53; H, 7.05; N, 5.06.

Hydrolysis.—Cleavage of 2-(*p*-methoxyphenyl)-3-benzyloxazolidine as described for the isomer gave pure 2-(benzylamino)-ethanol in 97% yield (1.96 g.), as shown by its infrared spectrum.

Isomerization Experiments.—(a) Treatment of 3.0 g. 2-(*p*-methoxyphenyl)-3-benzyloxazolidine in 75 ml. of refluxing methanol for 24 hours yielded 98% (1.66 g.) of 2-(benzylamino)-ethanol, as shown by its infrared spectrum.

(b) Repetition of the diethylene glycol monomethyl ether experiment on this isomer gave 1.81 g. of basic material which had an infrared spectrum indicative of a mixture of the two ethanolamines.

(75) W. S. Gump and E. J. Nikawitz, U. S. Patent 2,601,275 (1952); *C. A.*, **47**, 4908 (1953).

(76) C. W. Sondern and P. J. Breivogel, U. S. Patent 2,639,285 (1953); *C. A.*, **48**, 8266 (1954).

(77) L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey and L. W. Bannister, THIS JOURNAL, **72**, 745 (1950).

URBANA, ILL.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

The Reductive Cyclization of Indolylethylisoquinolinium Salts[1]

BY JOHN W. HUFFMAN

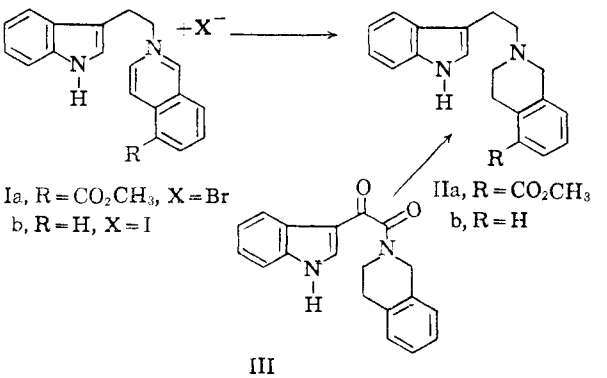
RECEIVED MAY 1, 1958

Sodium borohydride reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium salts has been shown to yield the corresponding 1,2,3,4-tetrahydroisoquinoline. Lithium aluminum hydride reduction, however, yields the 1,2-dihydroisoquinoline, which undergoes extremely facile ring closure to 5,7,8,13,13b,14-hexahydrobenzo[g]indolo[2,3a]quinolizine.

The great deal of attention which has been focused on the reductive cyclization of various 2-[2-(3-indolyl)-ethyl]-isoquinolinium salts,[2–4] and in particular the failures reported when sodium borohydride is used as a reducing agent prompted us to undertake a study of the mechanism of this interesting reaction. This reaction recently has taken on even greater significance with its use in the synthesis of alstonilol.[5]

We first turned our attention toward the nature of the sodium borohydride reduction of these systems. It has been reported[4] that 2-[2-(3-indolyl)-ethyl]-5-carbomethoxyisoquinolinium bromide (Ia) on reduction with sodium borohydride gave a material isomeric with, but not identical to, tetrahydroalstoniline, and also that reduction of Ib with potassium borohydride gives largely unidentified material.[2]

In our hands, reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium iodide (Ib) with sodium borohydride afforded a compound $C_{19}H_{20}N_2$. The



III

picrate of this material had a melting point which corresponded to that reported for 2-[2-(3-indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline.[2]

An authentic sample of the tetrahydroisoquino-

(1) Presented at the 35th Annual Meeting of the Georgia Academy of Sciences, Emory University, April 25, 1958.

(2) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

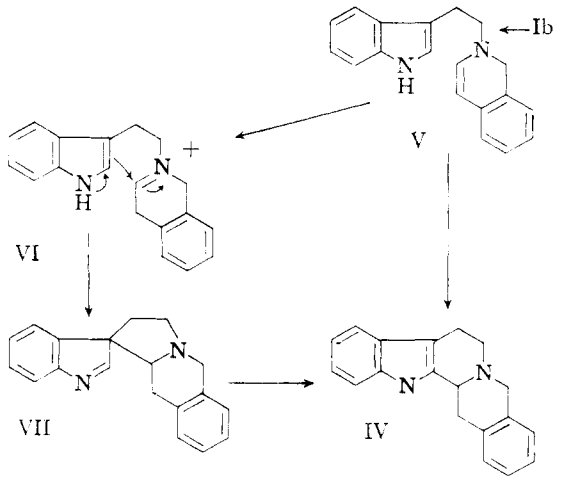
(3) R. C. Elderfield, B. A. Fischer and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(4) R. C. Elderfield, "Festschrift Arthur Stoll," Birkhäuser AG, Basel, 1957, p. 358.

(5) R. C. Elderfield and B. A. Fischer, *J. Org. Chem.*, **23**, 332 (1958).

line (IIb) was synthesized by treating 1,2,3,4-tetrahydroisoquinoline with indole-3-glyoxalyl chloride[6] to give the substituted glyoxamide III. This compound on reduction with lithium aluminum hydride gave the amine IIb, identical in all respects to that obtained by the direct reduction of the isoquinolinium salt Ib. It has been shown[7] recently that reduction of a number of isoquinolinium salts with sodium borohydride affords in all cases the corresponding 2-alkyl-1,2,3,4-tetrahydroisoquinoline. This evidence, coupled with our results, makes it apparent that the anomalous reduction product of the carbomethoxyisoquinolinium salt Ia is the tetrahydroisoquinoline IIa.

We next considered the possible mechanisms for the intriguing reductive cyclization of 2-[2-(3-indolyl)-ethyl]-isoquinolinium bromide to 5,7,-8,13,13b,14 - hexahydrobenzo[g]indolo[2,3a]quinolizine IV using lithium aluminum hydride.[2] It has been suggested that the first step of this reaction is the normal reduction of an isoquinolinium salt to a 1,2-dihydroisoquinoline (V), and that this intermediate undergoes an acid-catalyzed cyclization, with lithium aluminum hydride behaving as a Lewis acid, or simply cyclizes spontaneously to the final product.



An alternate possibility was that the dihydroisoquinoline V isomerizes to the Schiff base VI, which then undergoes a base-catalyzed cyclization to the indolenine VII. This indolenine would be expected to undergo rearrangement thermally or on treatment with acid to the quinolizine IV.[8] This mechanism is similar to that which has been proposed for the conversion of 1-methyl-3-[2-N-(1,2,3,4-tetrahydroisoquinolylethyl)]-oxindole to a benzoindoloquinolizine by means of palladium dehydrogenation.[9,10]

A third possibility for the course of this reaction is the normal reduction of the isoquinolinium salt Ib to the 1,2-dihydroisoquinoline[11] V, which then undergoes cyclization to the quinolizine IV during the isolation of the product.

In order to ascertain which of these possibilities represented the actual mechanism of this reaction, we carried out the reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium bromide (Ib) with lithium aluminum hydride, and in order to avoid any acid-catalyzed rearrangements during the isolation of the product, the reaction was worked up using aqueous sodium hydroxide to decompose the precipitated aluminum salts. There was obtained in this manner a white solid which was unstable to both heat and atmospheric oxygen and which melted at 100°, with previous darkening. This material could not be completely characterized as it decomposed to a viscous red oil on attempted purification. A sample stored under nitrogen in the refrigerator for a period of two weeks also showed evidence of extensive decomposition. The ultraviolet spectrum of this material showed absorption in ethanol at 221, 278 (shoulder) 284, 293 and 336 mμ. This spectral evidence excluded the possibility (Table I) that this substance was either the indolenine VII or the cyclized product IV. The existence of absorption at 336 mμ suggested strongly that this material was indeed the dihydroisoquinoline V. Schmid and Karrer[11] have previously shown that 1,2-dihydroisoquinolines show absorption in this region, and in fact an equimolar mixture of 2-methyl-1,2-dihydroisoquinoline[11] and skatole showed ultraviolet absorption very similar to that of our isolated intermediate. On this basis we tentatively assigned the intermediate structure V.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Compound	EtOH λmax, mμ	log ε
Intermediate, m.p. 100° dec.	221	4.69
	278(s)	3.87
	284	3.88
	293	3.85
	336	3.83
Equimolar mixt. of skatole and 2-methyl-1,2-dihydroisoquinoline	224	5.22
	278(s)	4.04
	284	4.06
	293	4.05
	327	3.85
5,7,8,13,13b,14-Hexahydrobenzo[g]-indolo[2,3a]quinolizine (IV)	226	4.85
	274	3.97
	284	3.97
	292	3.86
11-Ethyltetrahydrocarbazolenine[8]	257	3.79

In order to confirm this structure and also the course of the over-all reaction this substance was reduced to [2-(3-indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline with sodium borohydride, and cyclized with aqueous hydrochloric acid to the quinolizine IV identical in all respects to an authentic sample, prepared by the method of Potts and Robinson.[2]

It should be pointed out that there are two paths open for this cyclization; the first is the direct acid-catalyzed cyclization of V to the final product, and the second is the isomerization of V to the Schiff

(6) (a) M. Giua, *Gazz. chim. ital.*, **54**, 593 (1924); (b) M. E. Speeter and W. C. Anthony, THIS JOURNAL, **76**, 6209 (1954).

(7) R. Mirza, *J. Chem. Soc.*, 4400 (1957).

(8) B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 1558 (1951).

(9) (a) P. L. Julian and A. Magnani, *ibid.*, **71**, 3207 (1949); (b) P. L. Julian, A. Magnani, J. Pikl and E. W. Karpel, *ibid.*, **70**, 174 (1948).

(10) B. Belleau, *Chemistry & Industry*, 229 (1955).

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

base VI, which can then undergo a Pictet–Spengler reaction to give the final product.[12]

It is also worthy of comment that in the several instances where Lewis acid action of lithium aluminum hydride may be invoked[2,9] this behavior can be explained on the grounds that the precipitated aluminum salts were decomposed by mineral acid. In fact, there appears to be in the literature no *bona fide* examples of lithium aluminum hydride itself behaving as a Lewis acid.

Experimental

All melting points were determined on a Kofler hot-stage, and are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratory, Knoxville, Tenn.

2-[2-(3-Indolyl)-ethyl]-isoquinolinium Bromide.—To a solution of 0.91 g. of 2-(3-indolyl)-ethyl bromide[13] in 15 ml. of ethanol was added 0.8 ml. of isoquinoline. The reaction mixture was allowed to stand at room temperature in an atmosphere of nitrogen for one week. It was then concentrated to a small volume. On cooling, 0.80 g. (55%) of yellow crystals, m.p. 208–210°, was obtained. Recrystallization from methanol afforded yellow needles, m.p. 211–212°.

Anal. Calcd. for $C_{19}H_{17}N_2Br$: C, 64.59; H, 4.85; N, 7.93; Br, 22.62. Found: C, 64.42; H, 4.76; N, 8.18; Br, 22.77.

2-[2-(3-Indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline.—To a solution of 0.10 g. of [2-(3-indolyl)-ethyl]-isoquinolinium iodide[2] in 10 ml. of methanol and 3 ml. of water was added 0.30 g. of sodium borohydride. The solution was refluxed two hours, cooled, and cautiously acidified with dilute hydrochloric acid. The reaction mixture was washed three times with ether, made basic with 10% sodium hydroxide, and extracted with ether. The ethereal solution was dried and the solvent removed at reduced pressure affording 0.030 g. (44%) of yellow oil. Trituration with cyclohexane afforded white crystals, m.p. 114–116°. Repeated recrystallization from cyclohexane gave white needles, m.p. 121–122°.

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.56; H, 7.29; N, 10.14. Found: C, 82.37; H, 7.19; N, 10.17.

The picrate was formed in the usual manner and was isolated from aqueous acetone as red-orange rosettes, m.p. 170–171°. Potts and Robinson[2] report a m.p. of 171° for this compound.

Anal. Calcd. for $C_{25}H_{23}N_5O_7$: C, 59.40; H, 4.58; N, 13.86. Found: C, 59.02; H, 4.34; N, 13.40.

2-[1,2-Dioxo-2-(3-indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline.—To a suspension of 3.51 g. of indole-3-glyoxylyl chloride[6] in 100 ml. of dry benzene was added 3.9 g. of 1,2,3,4-tetrahydroisoquinoline and 3.9 ml. of dry pyridine. The mixture was allowed to stand at room temperature for one hour. The reaction mixture was washed with water, dilute hydrochloric acid, and finally with sodium bicarbonate. The benzene solution was dried over magnesium sulfate, and the solvent removed at reduced pressure, affording 1.39 g. (25%) of white powder, m.p. 180–182°. Recrystallization from ethyl acetate gave white crystals, m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.17; H, 5.47; N, 9.22.

2-[2-(3-Indolyl)-ethyl -1,2,3,4-tetrahydroisoquinoline.—To a suspension of 1.0 g. of lithium aluminum hydride in 50 ml. of dry ether was added 0.40 g. of 2-[1,2-dioxo-2-(3-indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline in small portions over the period of an hour and the reaction mixture stirred overnight at room temperature. The excess lithium aluminum hydride was decomposed with a solution of ethyl acetate in dry ether and the reaction mixture made strongly basic with 10% sodium hydroxide. The aqueous layer was drawn off, and extracted three times with ether. The ethereal extracts were combined, and extracted twice with 10% hydrochloric acid. The extracts were combined, made basic with 10% sodium hydroxide, and extracted with three portions of ether. The ethereal extracts were dried and the solvent removed at reduced pressure affording 0.14 g. (39%) of a pale yellow glass which slowly crystallized on standing. Recrystallization from cyclohexane afforded white crystals, m.p. 121–122°; mixed m.p. with material obtained by the borohydride reduction of 2-[2-(3-indolyl)-ethyl]-isoquinolinium iodide, 120–121°. The picrate was formed in the usual manner and had m.p. and mixed m.p. 169–170°.

2-[2-(3-Indolyl)-ethyl]-1,2-dihydroisoquinoline.—To a suspension of 0.40 g. of lithium aluminum hydride in 50 ml. of dry ether was added 0.45 g. of 2-[2-(3-indolyl)-ethyl]-isoquinolinium bromide. The reaction mixture was allowed to stand overnight at room temperature, and the excess lithium aluminum hydride then decomposed with ethyl acetate. The reaction mixture was made strongly basic with 10% sodium hydroxide, and the aqueous layer drawn off, and extracted with ether. The ethereal solutions were combined, washed with water, and dried. The solvent was removed at water-pump pressure and room temperature, affording 0.30 g. (86%) of a white powder, m.p. 100–105° dec. All attempts to purify this material for analysis resulted in extensive decomposition.

2-[2-(3-Indolyl)-ethyl]-1,2,3,4-tetrahydroisoquinoline.—To a solution of 0.067 g. of 2-(3-indolyl)-ethyl-1,2-dihydroisoquinoline in 7 ml. of aqueous methanol was added 0.40 g. of sodium borohydride. The solution was refluxed one hour, cautiously acidified, and washed with ether. The acid solution was made basic with sodium hydroxide and extracted twice with ether. The ethereal solution was washed with water, dried, and the solvent removed at reduced pressure, affording 0.045 g. (67%) of a viscous oil. This oil was dissolved in a small quantity of ethanol, and treated with a few drops of saturated ethanolic picric acid solution, giving small rosettes of orange crystals, m.p. 162–167°. Recrystallization from aqueous acetone afforded material of m.p. and mixed m.p. 169–170°. Decomposition of 0.016 g. of the picrate with base afforded 0.005 g. of white crystals, m.p. and mixed m.p. 115–118°.

5,7,8,13,13b,14-Hexahydrobenzo[g]indolo[2,3a]quinolizine.—A solution of 0.2 g. of 2-(3-indolyl)-ethyl-1,2-dihydroisoquinoline was dissolved in 15 ml. of 30% aqueous hydrogen chloride and the solution warmed on the steam-bath for 10 minutes. The reaction mixture was made basic with 10% sodium hydroxide and extracted three times with chloroform. The chloroform extracts were washed with water, dried, and the solvent removed at the water-pump, giving 0.089 g. (45%) of pale tan powder, m.p. 176–178° dec. Recrystallization from cyclohexane–ethyl acetate gave white needles, m.p. 185–187° dec. The melting point was undepressed on mixing with a sample prepared by the method of Potts and Robinson.[2]

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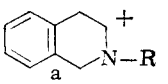
(12) In either case the carbonium ion (a) would be the same, and, formally, these reductive cyclizations may be regarded as modifications of the Pictet–Spengler isoquinoline synthesis. Battersby



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and Binks, *J. Chem. Soc.*, 2888 (1955), have proposed that the conversion of papaverine methiodide to N-methylpavine with tin and hydrochloric acid occurs *via* a mechanism similar to that which we have demonstrated for the conversion of indolylethylisoquinolinium salts to the dehydroyohimbane skeleton. We wish to thank Professor R. B. Woodward of Harvard University for calling this work to our attention.

(13) T. Hoshino and K. Shimodaira, *Ann.*, **520**, 25 (1935). We wish to thank Dr. K. T. Potts of Harvard University for the generous gift of a quantity of 2-(3-indolyl)-ethyl alcohol used to prepare this compound.