The Chemistry of Aporphines. III. The Mechanism of Carbon–Carbon Cleavage with Potassium Borohydride. Reduction Products of Nitrobenzylisoquinolinium Salts[1]

JOHN L. NEUMEYER, MONICA MCCARTHY, KLAUS K. WEINHARDT, AND PHILIP L. LEVINS

Arthur D. Little, Inc., Cambridge, Massachusetts 02140

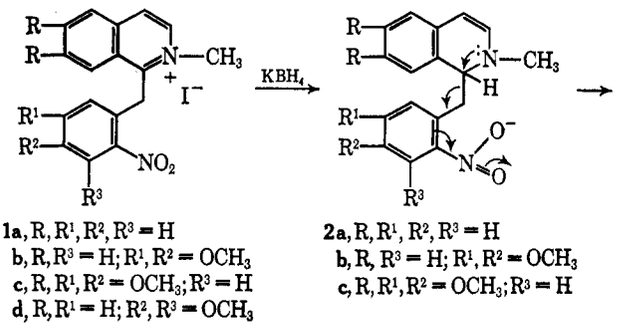
Received February 7, 1968

The recent synthesis of 1-nitrobenzylisoquinolinium salts has enabled a study of their reduction products with potassium borohydride. The unusual cleavage of a carbon–carbon bond in a number of these 1-benzylisoquinolinium salts **1** when treated with potassium borohydride was rationalized by a proposed mechanism. An intermediate (**2b**) in this mechanism was isolated and its structure was confirmed on the basis of its nmr, uv, and mass spectra, as well as by unequivocal synthesis. The structures of **2a**, which have been in dispute, and of similarly synthesized compounds are formulated as originally proposed by Gadamer, *et al.*

Our continued interest in the chemistry of aporphine and aporphine alkaloids led to the discovery of a novel method of preparing aporphine which can be similarly applied to the preparation of the related alkaloids.[2] Several recent reports have described other novel approaches to the synthesis of aporphines which are based either on a photocyclization of an aporphine precursor[3–5] or by a biogenetic-type oxidative coupling of a quaternary benzyltetrahydroisoquinoline[6] or of benzyltetrahydroisoquinoline followed by a dienol–benzene rearrangement.[7] We have not found these methods to be of general utility for the synthesis of naturally occurring or modified aporphine alkaloids.

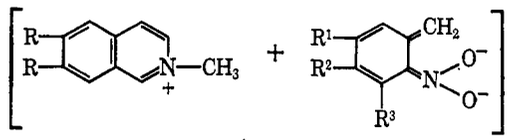
The classical methods used successfully for preparing aporphine types of structures have involved the Bischler–Napieralski cyclization–reduction–Pschorr cyclization sequence[8] or the Gadamer procedure[9] which involves the combination of a quaternary isoquinolinium salt with *o*-nitrotoluenes to form dihydroisoquinolines, reduction, and Pschorr cyclization. Our method,[2] which involved the alkylation of a Reissert compound with *o*-nitrobenzyl chloride, made available 1-(*o*-nitrobenzyl)isoquinoline, which could be readily converted into its quaternary salt **1a**. During the reduction of a number of these 1-benzylisoquinolinium salts (**1a**, **b**, or **c**) with potassium borohydride in refluxing ethanol, we observed the unusual cleavage of a carbon–carbon bond and suggested a mechanism for this reaction.[1] From the reduction of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1b**) the intermediate 1,2-dihydroisoquinoline **2b** was isolated and characterized. Further treatment of this 1,2-dihydroisoquinoline (**2b**) with borohydride in methanol yielded the expected cleavage products (**3a** and **4b**).

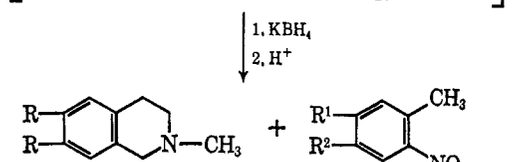
The reduction of pyridinium, quinolinium, and isoquinolinium ions to the dihydro- and the tetrahydro-N-substituted bases has been extensively investigated and recently reviewed.[10] The mechanism we proposed[1] for the reduction and cleavage of three 1-benzylisoquinolinium salts (**1a–c**) involves the initial nucleophilic attack of a hydride ion on the electrophilic 1 position of the isoquinoline nucleus to yield initially the 1,2-dihydro derivative **2** which we have now isolated in one instance (*viz.*, **2b**). The presence of



1a, R, R¹, R², R³ = H
b, R, R³ = H; R¹, R² = OCH₃
c, R, R¹, R² = OCH₃; R³ = H
d, R, R¹ = H; R², R³ = OCH₃

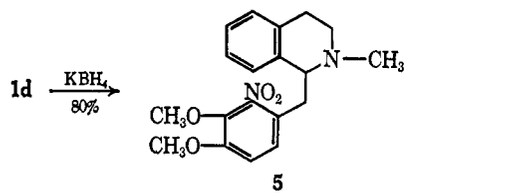
2a, R, R¹, R², R³ = H
b, R, R³ = H; R¹, R² = OCH₃
c, R, R¹, R² = OCH₃; R³ = H





3a, R = H
b, R = OCH₃

4a, R¹, R², R³ = H
b, R¹, R² = OCH₃; R³ = H



5

the nitrobenzyl group provides the necessary resonance stabilization of the benzyl anion to weaken the carbon–carbon bond, causing the cleavage reaction to occur. The aromaticity produced by the formation of the isoquinolinium salt further assists this cleavage. Both effects must be present in order

(1) A preliminary communication of part of this work has appeared. See part I: J. L. Neumeyer, M. McCarthy, and K. K. Weinhardt, *Tetrahedron Lett.*, 1095 (1967).

(2) Part II: J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *ibid.*, 3107 (1967).

(3) M. P. Cava, S. C. Havlicek, A. Lindest, and R. J. Spangler, *ibid.*, 2937 (1966).

(4) N. C. Yang, G. R. Lenz, and A. Shari, *ibid.*, 2941 (1966).

(5) S. M. Kupchan and R. M. Kanojia, *ibid.*, 5353 (1966).

(6) B. Frank and G. Schlingloff, *Ann. Chem.*, **659**, 123 (1962); B. Frank and G. Blaschke, *ibid.*, **695**, 144 (1966).

(7) M. Shamma and W. A. Slusarchyk, *Chem. Commun.*, 528 (1965).

(8) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

(9) J. Gadamer, M. Oberlin, and A. Schroeder, *Arch. Pharm.*, **263**, 81 (1925).

(10) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966); **6**, 68 (1966).

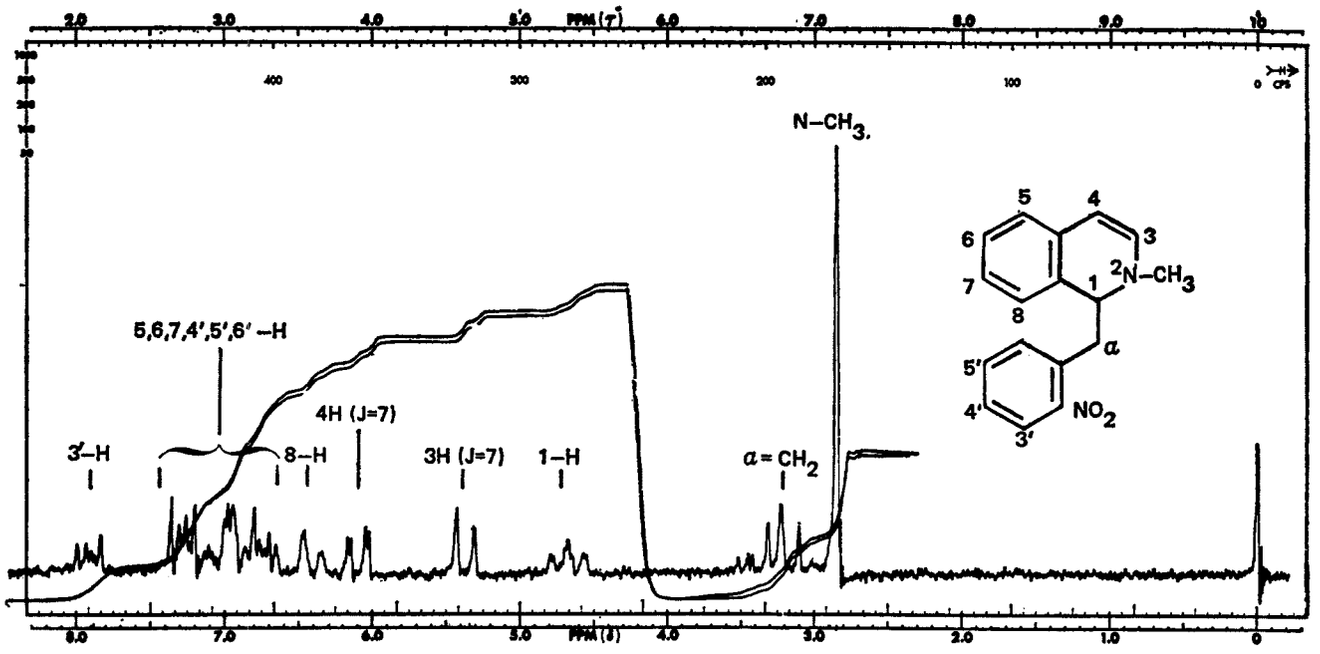
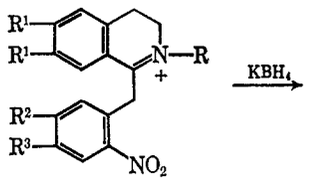
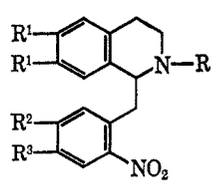


Figure 1.—Nuclear magnetic resonance spectrum of 2a

for the cleavage to take place. However, in the case of 1-(3,4-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1d**), where the nitro group is forced out of the plane of the benzene ring because of the additional steric interaction of the *o*-methoxy group, the "normal" reduction product, 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**), was isolated in 80% yield. Thus, the resonance stabilization of the benzyl anion was not provided, precluding the formation of the nitrotoluene. The reported "normal" reduction of the 3,4-dihydroisoquinoline derivatives as in **6a**[11] and **6b**[12] to **7a** and **b** with sodium borohydride can be rationalized on the basis of the above mechanism if one assumes initial attack of the borohydride ion at the 1 position to yield the tetrahydro derivatives **7** which are stable to further reduction in the isoquinoline ring. In the instance where the double bond resides in the 3,4 position, as in the dihydro derivative **2b** referred to above, cleavage occurs on treatment with boro-



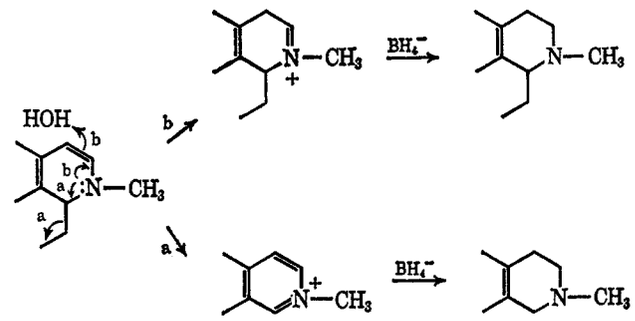
6a, R = CH_3, R^1 = OCH_3, R^2 = H, R^3 = OBz
b, R, R^2, R^3 = H; R^1 = —OCH_2—



7a, R = CH_3, R^1 = OCH_3, R^2 = H, R^3 = OBz
b, R, R^2, R^3 = H; R^1 = —OCH_2O—

hydride. This indicates that elimination occurs (Scheme I, pathway a) prior to protonation of the

SCHEME I



enamine system of the 3,4 double bond in the isoquinoline ring (Scheme I, pathway b) and a subsequent reduction to the tetrahydro derivative, as per the mechanism proposed by Anderson and Lyle[13] for the reduction of pyridinium salts.

In a strongly basic medium a hydrolytic cleavage involving a nucleophilic attack by hydroxide ion at the 1 position of the isoquinolinium salt was proposed[14] as an explanation of the observations of Pschorr,[15] who found that boiling nitropapaverine methiodide **1c** with 33% potassium hydroxide yielded methylnitroveratrole (**4b**) and a methoxycarbostyril.

Aromatic nitro and nitroso compounds are not normally reduced by sodium borohydride in aqueous or alcoholic solution; however, Neilson, *et al.*,[16] reported that aromatic nitro compounds could be smoothly reduced to the corresponding amines by sodium borohydride with palladized charcoal in aqueous methanol. In attempting to apply this method to the reduction of **1b** we obtained a highly colored crystalline compound, the structure of which was established to be the 1,2-dihydroisoquinoline **2b** on the basis of elemental analysis, nmr, uv, and mass spectroscopy, and

(11) W. H. Baarschers and R. R. Arndt, *Tetrahedron*, **21**, 2158 (1965).
(12) M. P. Cava and D. R. Dalton, *J. Org. Chem.*, **31**, 1281 (1966).
(13) P. S. Anderson and R. E. Lyle, *Tetrahedron Lett.*, 153 (1964).
(14) W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., N. Y., 1952, pp 479–480.
(15) R. Pschorr, *Ber.*, **37**, 1926 (1904).
(16) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

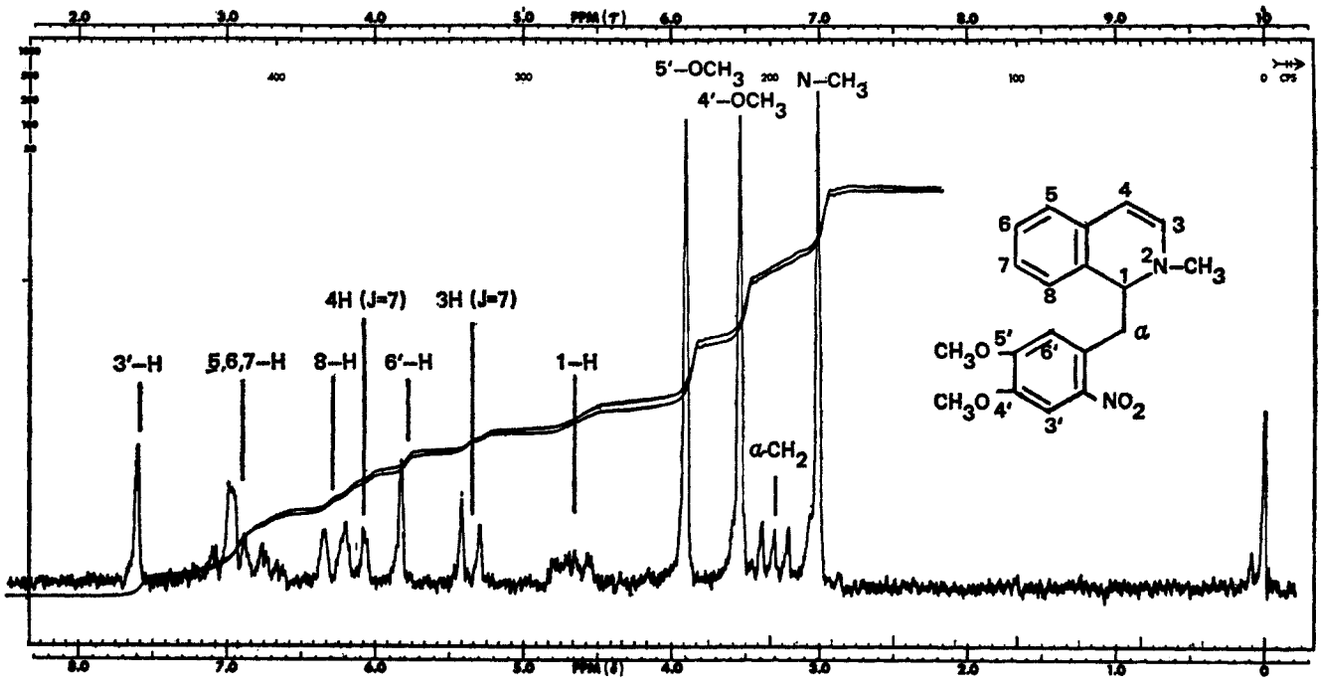
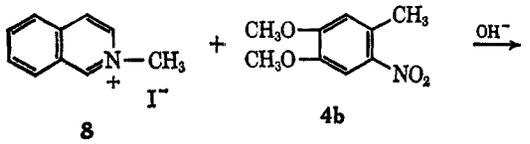
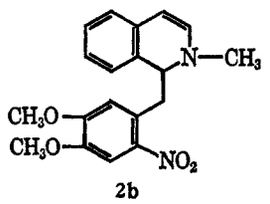


Figure 2.—Nuclear magnetic resonance spectrum of **2b**.

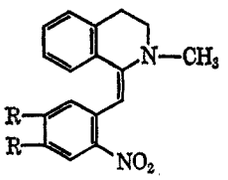
by an unequivocal synthesis. 4,5-Dimethoxy-2-nitrotoluene[1,15] (**4b**) was treated with isoquinoline methiodide (**8**) in alcoholic base by the procedure of Gadamer, *et al.*,[9] as applied to the synthesis of aporphine, to yield a product (**2b**) identical with that obtained by the borohydride reduction procedure. This compound became of considerable interest to us, since the location of the double bond of the adduct of 2-methylisoquinolinium iodide and *o*-nitrotoluene has recently been challenged. Weisbach, *et al.*,[17] on the basis of nmr and uv spectra, proposed that in the structure of this adduct, as well as a number of similar compounds, the double bond was located in the exocyclic position as in **9a** as opposed to the isomeric 3,4 positon in **2a** formulated earlier.[9,18]



8 **4b**



2b



9a, R = H
b, R = OCH_3

The formation of **9** from the potassium borohydride reduction was difficult to rationalize. This prompted us to study the structure of **2a** and **2b** in greater detail and to determine whether the 1,2-dihydroisoquinoline (as in **2a** and **b**) or a structure such as the 1-benzylidenetetrahydroisoquinoline (as in **9a** and **b**) properly described the product.[19]

The nmr spectra of **2a** and **2b** are shown in Figures 1 and 2. Although complete interpretation of the spectrum from **2a** was at first confusing, comparison of its spectrum with that obtained from **2b** led to a straightforward correlation of both structure and shift positions. The spectra may be clearly interpreted only in terms of the 1,2-dihydroisoquinoline structure. In both **2a** and **2b** there are two vinyl protons, exhibiting a normal 7-Hz *cis* coupling, as required by structure **2**, but not by **9**. The complexity of the resonance band at 3.2 and 4.67 ppm for **2a**, and 3.3 and 4.7 ppm for **2b** is due to the presence of the chiral center at carbon 1. The relative area of these two absorption signals is 2 to 1 in each case.

We conclude that the sample of **2a** prepared in our laboratories and that prepared by Weisbach, *et al.*,[17] were the same because of their identical melting points and their similar ultraviolet spectra (Figure 3). The formulation of the Gadamer product as **9** was based on its intense color and the electronic absorption spectrum which exhibited long tailing into the visible region having ϵ 323 at 470 mμ. It was believed unlikely that a compound with the alternative structure **2a** would have absorption of such intensity in the visible region.[17]

It seems reasonable to us that the long-wavelength absorption of **2a** and **2b** is due to a charge transfer band essentially established between the nitro aromatic nucleus and the dihydroisoquinoline ring. As expected,

(17) J. A. Weisbach, C. Burns, E. Macko, and B. Douglas, *J. Med. Chem.*, **6**, 91 (1963).

(18) M. Oberlin, *Arch. Pharm.*, **265**, 274 (1927); J. Muller, *Helv. Chim. Acta*, **31**, 1111 (1948).

(19) Schmid and Karrer [*ibid.*, **32**, 960 (1949)] obtained a dihydro compound from the reaction of papaverine methiodide with lithium aluminum hydride which was considered to be 1,2-dihydro-N-methylpapaverine. The location of the double bond in this instance has not been unambiguously established.

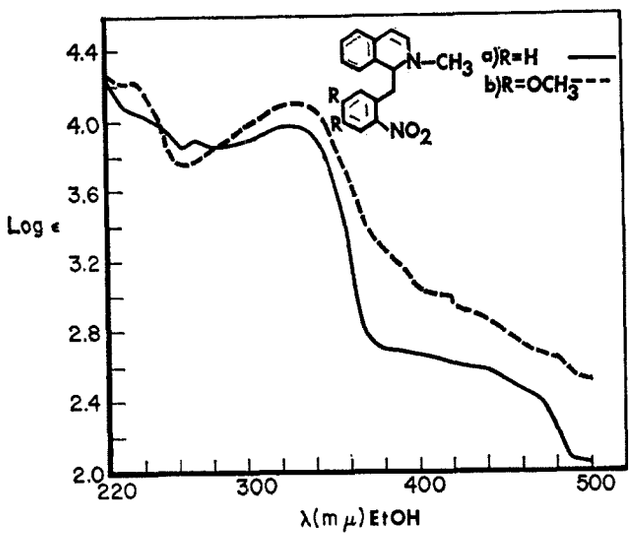
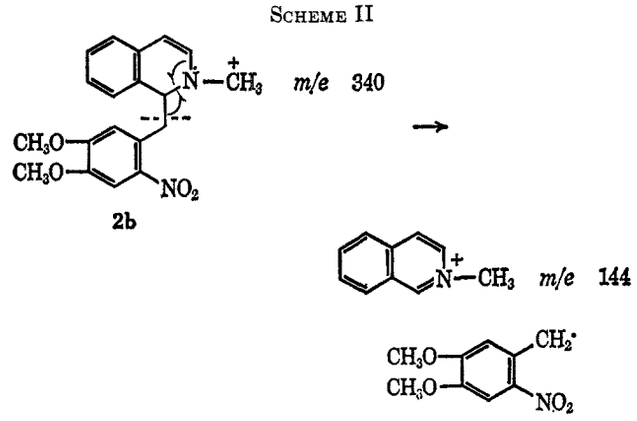


Figure 3.—Absorption spectra of **2a** and **2b**.

the absorption maximum at 470 mμ was shifted to a shorter wavelength as one examined the spectrum in less polar solvents, such as hexane.

Further proof of the structure of **2b** is afforded by its mass spectrum. The base peak in its spectrum occurs at *m/e* 144. All other peaks in the spectrum, including the parent at *m/e* 340, have less than 8% of the intensity of the *m/e* 144 peak. This may be readily explained in terms of simple cleavage of the bond on the carbon α to nitrogen, giving rise to the stable quinolinium ion and a stable radical species as shown in Scheme II.

SCHEME II



Experimental Section[20]

1-(2-Nitrobenzyl)isoquinoline Methodide (1a).—This compound was prepared from 1-(2-nitrobenzyl)isoquinoline[2] in 87% yield. The yellow needles were obtained from ethanol–acetone: dec pt 223°; uv, λ_{max}^{MeOH} 232 mμ (ε 44,000), 279 (s) (5000), 332 (4400), 342 (4400).

Anal. Calcd for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.25; H, 3.72; N, 6.79.

1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1b).—A mixture of 1 g of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline[2] and 20 ml of methyl iodide was stirred and heated under reflux for 48 hr. It was cooled and the crystals that separated were washed with dry ether and dried under vacuum to yield 1.28 g (89%) of the quaternary salt as a yellow powder, mp 211–212°.

Anal. Calcd for $C_{19}H_{19}IN_2O_4$: C, 49.20; H, 4.08; N, 6.04; I, 29.25. Found: C, 49.42; H, 4.14; N, 6.44; I, 28.98.

6′-Nitropapaverine Methiodide (1c).—A mixture of 1 g of 6′-nitropapaverine[15] and 20 ml of methyl iodide was heated under reflux for 25 hr. The bright yellow precipitate that formed on cooling was washed with ether and dried under vacuum to yield 1.37 g (100%) of the quaternary salt **1c**, mp 230° dec (lit.[15] mp 235° dec).

1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1d).—1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline[2] was converted quantitatively into the quaternary salt **1d** by heating under reflux with a 20- to 30-fold excess of iodomethane (without solvent) for 15–20 hr. The crude product, mp 190–193° dec, was recrystallized successively from water and from ethanol, but the melting point was unchanged.

Anal. Calcd for $C_{19}H_{19}IN_2O_4$: C, 48.94; H, 4.11; I, 27.22; N, 6.01. Found: C, 48.89; H, 4.10; I, 27.25; N, 6.14.

Potassium Borohydride Reductions. A. 6′-Nitropapaverine Methiodide (1c).—In a typical run 3 g of potassium borohydride was added slowly to a mixture of 2 g of 6′-nitropapaverine methiodide (**1c**), 30 ml of ethanol, and 14 ml of water. The mixture was stirred and heated at reflux for 7 hr and then was allowed to stand at room temperature for 30 hr. On work-up 0.51 g (68%) of 4,5-dimethoxy-2-nitrotoluene (**4b**) was isolated as yellow crystals, mp 117.5–119° (lit.[15] mp 118°). An nmr spectrum and elemental analysis further confirmed the structure. Also isolated by acid extraction of the reaction mixture and neutralization of the extract was 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3b**), mp 64–74°. A picrate, mp 160–161° (lit.[21] mp 158–159°), was prepared in ether solution and recrystallized from ethanol. An authentic sample of the tetrahydroisoquinoline **3b**[22] was converted into its picrate, mp 160–162°. A mixture of the authentic sample and prepared picrates had mp 157.5–159.5°.

B. 1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1b).—Similarly reduced with 1.5 g of potassium borohydride was 1 g of the methiodide **1b** in 18 ml of ethanol and 8 ml of water. From the reaction mixture 0.29 g (72%) of 4,5-dimethoxy-2-nitrotoluene (**4b**), mp 117.5–118.5° (lit.[15] mp 118°), was isolated. Also isolated by acid extraction of the reaction mixture and neutralization was 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**), a brown oil that was characterized by conversion into a picrate, which did not depress the melting point of the picrate made from an authentic sample of 2-methyl-1,2,3,4-tetrahydroisoquinoline, mp 148–150° (lit.[23] mp 148–150°).

The above reduction was attempted using buffered conditions. Thus, 1.29 g of potassium borohydride was added slowly to a mixture of 0.83 g of the methiodide **1b**, 1 g of sodium acetate, 1.93 ml of glacial acetic acid, 21 ml of ethanol, and 12 ml of water. The reaction mixture was stirred and heated at 84° for 2 hr and allowed to cool overnight. Potassium borohydride (1.29 g), 1 g of sodium acetate, and 1.93 ml of acetic acid were added and the reaction was stirred and heated at reflux for an additional 7 hr. On work-up, only the cleavage product **4b** was isolated.

C.—Under identical conditions as in A above, **1-(2-nitrobenzyl)isoquinoline methiodide (1a)** was reduced with potassium borohydride in refluxing aqueous ethanol to yield the tetrahydroisoquinoline **3a**, picrate mp 156° dec (lit.[23] mp 146°).

D. 1-(3,4-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (1d).—An aqueous solution of 550 mg of potassium borohydride was added to a solution of 1.7 g of the methiodide **1d** in a mixture of 150 ml of ethanol and 100 ml of water, and the mixture was stirred for 45 min at 30°. The temperature of the mixture was raised slowly and finally the mixture was allowed to reflux for 1 hr.

(20) All melting points were recorded on a Thomas–Hoover melting point apparatus and were uncorrected; the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were recorded on a Perkin-Elmer grating spectrophotometer, Model 521; the nmr spectra were determined on a Varian A-60 spectrophotometer with tetramethylsilane as the internal standard; ultraviolet spectra were recorded with a Beckman Model DK-1A; and mass spectra were obtained with a CEC-21-110B spectrometer.

(21) R. Forsyth, C. I. Kelley, and F. L. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(22) Kindly supplied by Dr. A. Brossi, Hoffmann-La Roche Laboratories, Nutley, N. J.

(23) J. v. Braun and K. Wirz, *Ber.*, 60B, 102 (1927).

A thin layer chromatogram on Adsorbosil-2 from ethyl acetate showed one spot at the base line (potassium iodide or the methiodide or a mixture of them) and one spot each at R_f 0.9 and 0.85. Solid potassium borohydride was added in small portions to the boiling reaction mixture. Additional chromatograms showed a decrease in the upper spot (R_f 0.9). Potassium borohydride addition was continued until this spot (presumably the 1,2-dihydro compound) disappeared completely. The solution was refluxed for an additional 1 hr and allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was brought to pH 9 by addition of 20% sodium hydroxide and extracted with ether. The combined ether extracts were dried over magnesium sulfate in the presence of a little charcoal. The ether was removed under reduced pressure to yield 1.0 g (80%) of 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**) as a nearly colorless solid, mp 90–93°. A portion was recrystallized from *n*-hexane and then from petroleum ether–ethanol (25:0.3) to give yellow-green crystals, mp 97–98.5°. The infrared and nmr spectra were consistent with the assigned structure. The ultraviolet spectrum showed bands at λ_{max}^{MeOH} 208 mμ (ε 26,000), 265 (2300), and 272 (2300).

Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.74; H, 6.40; N, 8.15.

1-(4,5-Dimethoxy-2-nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (2b). Method A. Borohydride Reduction of 1b.—To 0.05 g of 10% palladium on charcoal in 24 ml of water, through which nitrogen was bubbled, were added 0.15 g of potassium borohydride and 10 ml of water. A solution of 0.5 g of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline methiodide (**1b**) in 13 ml of ethanol and 13 ml of water was slowly added; the mixture was stirred 20 min more. An orange solid formed on the sides of the flask. The reaction mixture was extracted with ether and the ether was washed with 5% acetic acid and then was extracted with 1 *N* hydrochloric acid. The acid extract was made basic with potassium hydroxide and extracted into ether. The ether was evaporated yielding 0.37 g (75%) of an orange solid, which was recrystallized in methanol to give **2b**, mp 138–141°.

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.19; H, 5.84; N, 8.34.

The nmr spectrum and the uv spectrum of **2b** are shown in Figures 2 and 3, respectively.

Method B. Treatment of Isoquinoline Methiodide and 4,5-Dimethoxy-2-nitrotoluene in Sodium Methoxide.—The method of Weisbach, *et al.*,[17] was used for the preparation of **2b**. Thus, 0.83 g of 4,5-dimethoxy-2-nitrotoluene (**4b**)[1,14] and 0.55 g of isoquinoline methiodide were added to a warm, stirred solution of sodium (0.15 g) in 15 ml of absolute methanol. The reaction mixture was stirred overnight, cooled to 0°, and filtered to yield 2 g of a yellow-orange solid. Recrystallization from methanol yielded **2b**, mp 140–141°. A mixture melting point with the sample of **2b** prepared by the borohydride reduction of **1b** was not depressed. All spectra (infrared, uv, nmr) were identical with those from the previously prepared sample.

1-(2-Nitrobenzyl)-2-methyl-1,2-dihydroisoquinoline (2a).—This compound was prepared from 2-nitrotoluene and isoquinoline methiodide by the procedure of Weisbach, *et al.*,[17] to give **2a**, mp 88–91°; (lit. mp 90°,[9] 95–96°[17]). The nmr spectrum of this compound is shown in Figure 1, the uv spectrum is shown in Figure 3.

Reduction of 2b with Potassium Borohydride.—To a suspension of 0.075 g of **2b** in 10 ml of ethanol and 5 ml of water was added 0.12 g of potassium borohydride. The mixture was heated at reflux and stirred overnight. The ethanol was evaporated and water was added. The reaction mixture was extracted with ether. The ether was extracted with 0.1 *N* hydrochloric acid, the acid extract was made basic with potassium hydroxide pellets, and the basic solution was extracted with ether, which was dried over potassium carbonate. Evaporation of the ether yielded 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) which was characterized by conversion into the picrate, mp 150–152°. Also isolated from the acid-washed ether solution was a yellow solid, mp 115–118°, previously identified as **4b**.

Registry No.—**1a**, 16472-48-3; **1b**, 16622-51-8; **1c**, 16620-92-1; **1d**, 16472-49-4; **2a**, 16620-94-3; **2b**, 16620-95-4; **3b**, 16620-96-5; **5**, 16472-50-7; potassium borohydride, 1303-72-6.

Acknowledgment.—We wish to thank Professor Robert E. Lyle, Jr., for many helpful discussions and Mr. Bernard R. Neustadt for the preparation of a number of compounds. We also wish to acknowledge the financial support of Arthur D. Little, Inc.