tion which resulted was distilled after removal of volatile by-products to give a colorless liquid (8.30 g), bp 88–90° (13 mm). An identical product (2.2 g), *via* infrared, was obtained by warming at 110° for 5 hr a mixture of 1,1-dimethyl-2-crotonylhydrazine (2.56 g) and acetic anhydride (2.04 g). The infrared spectrum showed no NH absorption, strong absorption at 1700, and medium absorption at 1620 $cm^{-1}$. The diacylhydrazine was nonbasic, a characteristic of this class of compounds.

*Anal.* Calcd for $C_8H_{14}N_2O_2$: C, 56.47; H, 8.23; N, 16.47. Found: C, 56.51; H, 8.21; N, 16.29.

# Hydrobenzo[*b*]quinolizines. I. The Synthesis and Stereochemistry of Perhydrobenzo[*b*]quinolizines and Related Compounds[1,2]

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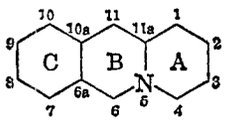
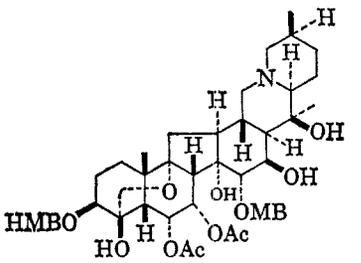
An approach to the synthesis of perhydrobenzo[*b*]quinolizine derivatives which starts from tricyclic aromatic compounds is described. Birch reduction of **9** afforded diene **8**, and strong acid hydrolysis gave a monophenol (**10**). Methylation of the phenol gave a methyl ether (**11**), and oxidation of the methyl ether yielded 4-methoxyphthalic acid. The latter sequence and nonidentity of the monophenol with **16** supported assignment of structure **10**. Mild acid hydrolysis of **8** gave a mixture of unsaturated ketones (**13** and **18**), and hydrogenation of the mixture afforded the diol monoether **19**. Birch reduction of **17** gave diene **20**, and mild acid hydrolysis afforded ketones **21** and **24**. Hydrogenation of the ketone mixture gave alcohol **22** and chromium trioxide oxidation of the alcohol gave the saturated ketone **25**. Birch reduction of **26** gave the diene **27**. Catalytic hydrogenation of **27** yielded **29**, and hydroxylation of the latter compound with 1 molar equiv of hydrogen peroxide in formic acid gave the diol **30**. An alternate preparation of **30** consisted of prior hydroxylation of **27** to **31**, followed by hydrogenation. Hydroxylation of **27** with excess hydrogen peroxide in formic acid yielded the tetrol **28**.

The perhydrobenzo[*b*]quinolizine (1,3,4,6,6a,7,8,9,10,-10a,11,11a-dodecahydro-2H-benzo[*b*]quinolizine) ring system (**1**) occurs in clinically useful hypotensive alkaloids of both the *Veratrum* [*e.g.*, protoveratrine A (**2**)] and *Rauwolfia* [*e.g.*, reserpine (**3**)] series. In each alkaloidal type, the ring designated C in **1** bears several oxygenated substituents. Only two simple derivatives of system **1** appear to have been described to date: **4**, synthesized as a model compound for the construction of the C–D–E ring skeleton of yohimbine,[3] and **5**, synthesized as a precursor of *dl*-alloyohimbane.[4]

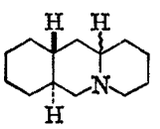



**1**

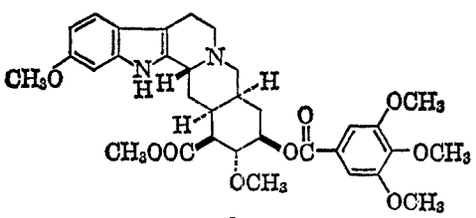



HMB = (+)-2-hydroxy-2-methylbutyryl
MB = (−)-2-methylbutyryl

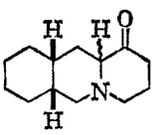
**2**



**4**




**3**



**5**

We describe herewith the first of a series of studies of synthetic approaches to perhydrobenzo[*b*]quinolizine derivatives. It is hoped that such synthetic sequences may lead ultimately to alkaloid analogs with enhanced or more specific pharmacological properties.

In the present work, an approach to derivatives of **1** which starts from known tricyclic aromatic compounds was selected. It was anticipated that selection of suitably substituted aromatic precursors might allow for the control of the stereochemistry during the reduction steps and facilitate the introduction of desired substituent groups. Several routes for the synthesis of 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-2H-benzo[*b*]-quinolizine (**9**) have been described previously.[5–7] Sugimoto proceeded *via* 2-pyridyl-3,4-dimethoxyphenylcarbinol, prepared by treatment of 3,4-dimethoxybenzaldehyde with 2-pyridylmagnesium bromide.[4] We found that a better yield of the carbinol (65%) could be obtained by use of 2-pyridyllithium in place of the Grignard reagent. Reduction of the carbinol to 2-piperidyl-3,4-dimethoxyphenylmethane was accomplished best with sodium and 1-butanol, and conversion to **9** was effected by treatment of the hydrochloride with formaldehyde under Pictet–Spengler reaction conditions. A modification of the approach of Bradsher and Dutta[7] *via* 8,9-dimethoxyacridizinium bromide (**7**) proved to be more satisfactory for the large-

(1) This investigation was supported, in part, by Public Health Service Research Grant No. HE-02275 from the National Heart Institute. The work was presented, in part, at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 9–13, 1963, Abstracts, p 35-O.

(2) All asymmetric synthetic products described are racemic mixtures. Only one optical antipode for each is drawn for convenience of representation and discussion. In the representation of the quinolizidine derivatives, the electron pair on nitrogen is understood to project downward, and a heavy-line bond to the 11a hydrogen indicates the *trans*-quinolizidine configuration.

(3) E. E. van Tamelen, D. L. Hughes, and C. W. Taylor, *J. Am. Chem. Soc.*, **78**, 4625 (1956).

(4) R. T. Rapala, E. R. Lavagnino, E. R. Shepard, and R. Farkas, *ibid.*, **79**, 3770 (1957).

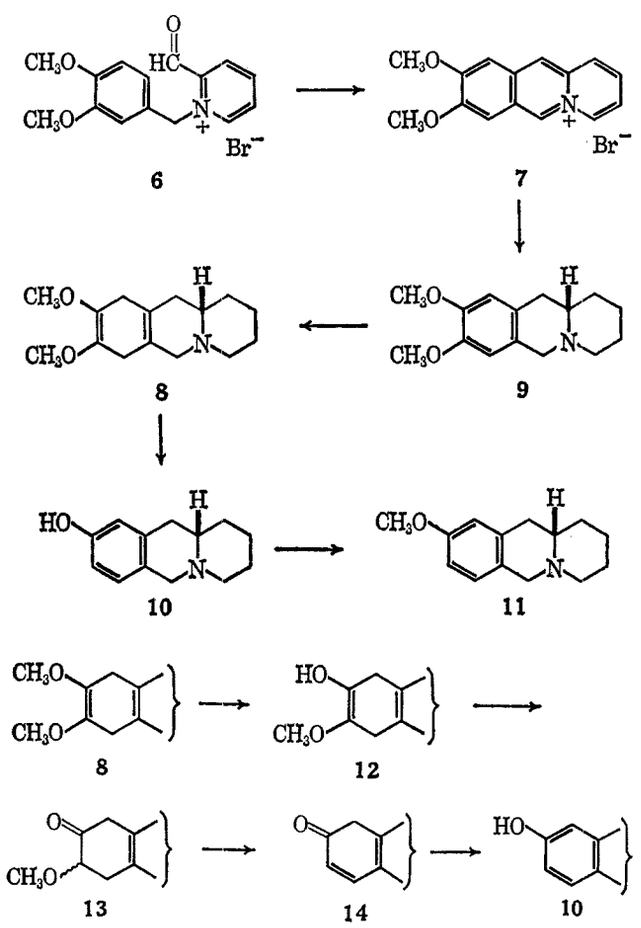
(5) N. Sugimoto, *J. Pharm. Soc. Japan*, **76**, 1045 (1956).

(6) C. Tani and K. Ishibashi, *ibid.*, **76**, 1064 (1956).

(7) C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).

scale preparation of **9**. Alkylation of pyridine-2-carboxaldehyde with 3,4-dimethoxybenzyl bromide in dimethylformamide gave **6**. Ring closure of **6** with hydrochloric acid, as described previously,[7] led to a moderate yield of **7**, accompanied by a considerable quantity of phenolic material formed by ether cleavage. A distinct improvement in the yield of **7** was effected by use of polyphosphoric acid as the catalyst for the ring closure, and the ether cleavage side reaction was avoided. The polyphosphoric acid catalyzed cyclization reaction mixture was neutralized and directly hydrogenated, whereupon **9** was obtained in 62% yield (see Scheme I).

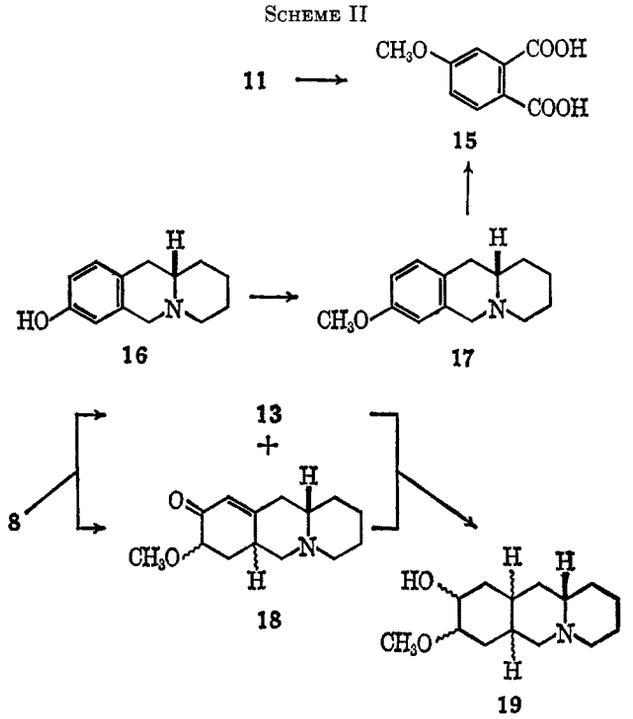
SCHEME I



Birch reduction of **9** under the conditions of Wilds and Nelson[8,9] smoothly afforded a reduction product which we formulate as 1,3,4,6,7,10,11,11a-octahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizine (**8**). The infrared absorption spectrum of **8** shows peaks at 5.82 and 5.92 $\mu$ but no absorption in the 6.2–6.3- or 6.6–6.7-$\mu$ aromatic regions. The ultraviolet absorption spectrum shows a peak of low intensity ($\epsilon$ 40) at 282 m$\mu$, and the nmr spectrum indicates the absence of vinyl protons. The formation of **8** is in accord with expectation based on the normal course of the Birch reduction.[8,9]

When **8** was subjected to hydrolysis with strong mineral acid, a monophenolic product was obtained. Assuming that hydrolysis had proceeded *via* the sequence **12**–**14**, the monophenolic product could be presumed to possess either the 1,3,4,6,11,11a-hexahydro-2H-benzo[*b*]quinolizin-9-ol structure (**10**) or the isomeric 8-phenol structure (**16**). 1,3,4,6,11,11a-Hexahydro-2H-benzo[*b*]quinolizin-8-ol (**16**), synthesized by the procedure of Bradsher and Yarrington,[10] proved to be different from the product of acid hydrolysis of **8**. An attempt to prepare **11** by the Bradsher procedure was unsuccessful. However, support for assignment of structure **10** for the acid hydrolysis product was obtained by permanganate oxidation of **11**, whereupon 4-methoxyphthalic acid (**15**) was obtained (see Scheme I). Permanganate oxidation of **17** yielded the same product. Since the 8-methoxybenzo[*b*]quinolizidine **17** and the 9-methoxy isomer **11** are the only isomers which would afford 4-methoxyphthalic acid upon oxidation, the nonidentity of **16** with the product of acid hydrolysis of **8** constitutes firm support for structure **10** for the acid hydrolysis product.

SCHEME II



When **8** was subjected to dilute acid hydrolysis (5% hydrochloric acid), the crude oil obtained after treatment with alkali showed $\lambda_{max}^{EtOH}$ 229 m$\mu$ ($\epsilon$ 7500) and infrared absorption bands at 5.78 (m) and 5.94 (s) $\mu$. The latter absorption characteristics accord best with the view that the product consisted of a mixture of unconjugated ketone (**13**) and conjugated ketone (**18**). Hydrogenation of the mixture with palladium on carbon, and then with platinum, afforded a diol monoether for which structure **19** is suggested. Acetylation gave a monoacetate ester which shows *trans*-quinolizidine absorption[11] as a shoulder at 3.60 $\mu$ and acetate bands at 5.79, 8.0–8.3, and 9.05 $\mu$.

Birch reduction of **17**, under conditions similar to those used for **9**, afforded a good yield of 1,3,4,6,7,10,-11,11a-octahydro-8-methoxy-2H-benzo[*b*]quinolizine (**20**). The infrared spectrum shows absorption at 5.82 (w) and 5.94 (m) $\mu$, and absence of aromatic ab-

(8) A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958).

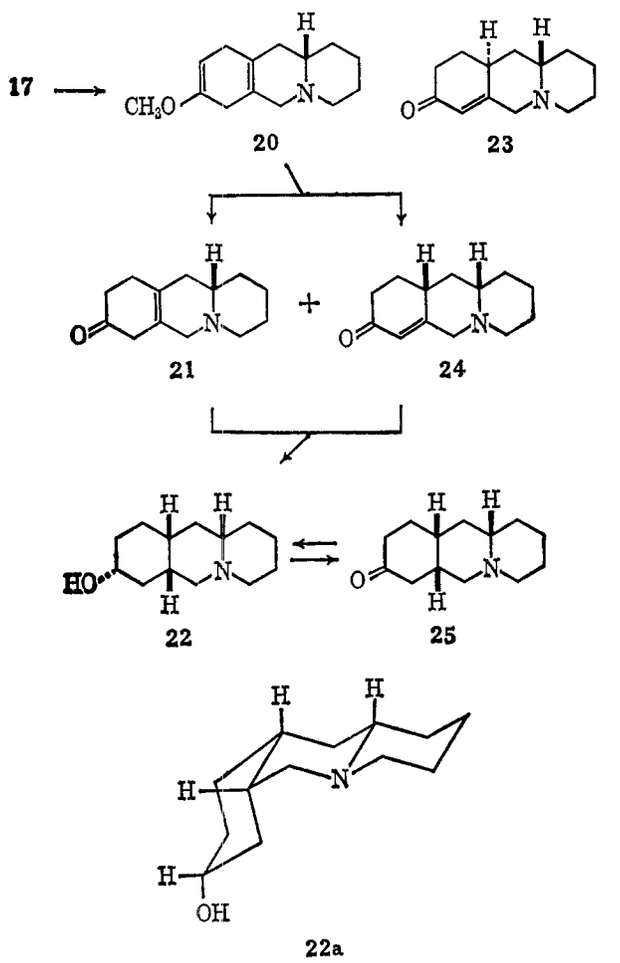
(9) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360, 5366 (1953). The authors reported $\lambda_{max}$ 5.90 and 6.02 $\mu$ for 2,5-dihydro-4-cyclohexylanisole and $\lambda_{max}$ 5.94 and 6.03 $\mu$ for 1,4-dihydro-17$\beta$-estradiol.

(10) C. K. Bradsher and N. L. Yarrington, *J. Org. Chem.*, **25**, 284 (1960).

(11) F. Bohlmann, *Ber.*, **91**, 2157 (1958).

sorption at 6.2–6.3 or 6.6–6.7 $\mu$. Furthermore, a peak at 3.63 $\mu$ indicates the presence of a *trans*-quinolizidine ring in **20**. In accord with the proposed structure, the ultraviolet absorption spectrum indicates the absence of conjugated double bonds or aromatic rings. Hydrolysis of **20** with dilute hydrochloric acid gave an oily product. The infrared spectrum of the product showed bands at 5.83 (s) and 5.99 (sh, m) $\mu$, in accord with the view that a mixture of conjugated ketone (**24**), and unconjugated ketone (**21**) was in hand (see Scheme III). Support for the latter view came from the ultra-

SCHEME III




violet absorption spectrum which showed $\lambda_{max}^{EtOH}$ 228 m$\mu$ ($\epsilon$ 2550). Acid treatment of the oily mixture, followed by exposure to alkali in the cold, evidently favored isomerization to conjugated ketone, because the resultant oily mixture then showed a band of low intensity at 5.83 and a strong band at 5.99 $\mu$; the ultraviolet absorption spectrum showed $\lambda_{max}^{EtOH}$ 228 m$\mu$ ($\epsilon$ 8500). Molecular models of **24** and of the C-10a epimer **23** support the view that **24** is thermodynamically more stable. In **24**, as in cyclohexene itself, one may assume that torsional forces require approximate coplanarity of the four carbon atoms associated with the olefinic system, and that ring C therefore exists in a half-chair conformation. In **23** only a half-boat conformation is possible, and the half-boat may be assumed to be less stable than the half-chair by at least 2.7 kcal/mole.[12] Since the isomerization of **21** to a conjugated ketone is an equilibration, and in view of the aforementioned spectral characteristics of the equilibrated mixture, it is reasonable to assume that **24** predominates in the mixture. Hydrogenation of the mixture with palladium on carbon, and then with platinum, yielded an alcohol which is assigned structure **22**. The infrared absorption spectrum shows bands at 2.79 and 2.96 (for nonbonded and hydrogen-bonded hydroxyl, respectively), and at 3.63 $\mu$ (for *trans*-quinolizidine). Assignment of configuration at C-6a is suggested by analogy to closely related steroid systems.[13] Acetylation with acetic anhydride gave a monoacetate ester which shows infrared absorption indicative of the absence of a hydroxyl group and the presence of an acetate ester (5.79, 7.95–8.15 $\mu$). Oxidation of **22** with chromium trioxide in glacial acetic acid gave 1,3,4,6a,7,9,10,10a,11,11a-decahydro-2H-benzo[*b*]quinolizin-8(6H)-one (**25**). The infrared absorption spectrum of **25** shows bands at 3.62 (*trans*-quinolizidine) and 5.87 $\mu$ (ketone) but no hydroxyl group absorption. Lithium aluminum hydride reduction of **25** gave **22** as the principal product. The latter observation supports assignment of equatorial (hence $\alpha$) configuration to the C-8 hydroxyl of **22** (*cf.* **22a**). In accord with this assignment, the nmr spectrum of **22** shows a signal at $\tau$ 6.42 attributable to the C-8 carbinol proton, which is a broad multiplet with half-width ($W_H$) equal to 20 cps, characteristic of an axial carbinol proton.[14]

Birch reduction of 1,3,4,6,11,11a-hexahydro-2H-benzo[*b*]quinolizine (**26**)[15] gave, in excellent yield, the diene **27**. The infrared absorption spectrum of **27** shows bands at 3.58 (*trans*-quinolizidine) and 6.03 $\mu$ (double bond) but no aromatic absorption in the 6.2–6.3-$\mu$ region. The ultraviolet absorption spectrum shows $\lambda_{max}^{EtOH}$ 265 m$\mu$ ($\epsilon$ 65), indicating the absence of a conjugated diene system. The nmr spectrum shows a signal at $\tau$ 4.31 for two vinyl protons, and absence of the aromatic proton signal at 2.93 in the spectrum of the precursor (**26**). When **27** was subjected to catalytic hydrogenation at room temperature and atmospheric pressure, 1 mole equiv of hydrogen was consumed. The product, a low-melting solid, shows no double bond absorption in the 6.03-$\mu$ region, in accord with expectation for structure **29** (containing only a tetrasubstituted double bond). The product was characterized in the form of its methiodide derivative. Hydroxylation of **29** with hydrogen peroxide and formic acid yielded a diol for which structure **30** is proposed. The infrared absorption spectrum shows bands at 2.77 (unbonded hydroxyl) and 2.90 $\mu$ (hydrogen bonded hydroxyl). The diol was found to be stable to periodic acid, indicating a rigid *trans*-diaxial configuration for the diol system in accord with expectation based on its formation by epoxide opening.[16] An alternate route to **30** proceeded *via* prior hydroxylation followed by hydrogenation. Hydroxylation of **27**

(12) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Am. Chem. Soc.*, **70**, 4227 (1948).

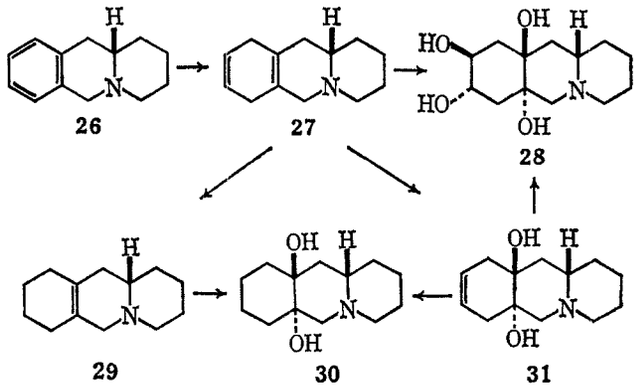
(13) W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister, and H. Wynberg, *ibid.*, **78**, 6289 (1956).

(14) *Cf.* H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.* **29**, 2248 (1964).

(15) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(16) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 296, 340.

SCHEME IV




with 1 molar equiv of hydrogen peroxide in formic acid yielded the unsaturated glycol **31**, and hydroxylation of **31** yielded tetrol **28** (see Scheme IV). Catalytic hydrogenation of **31** gave **30**. Hydroxylation of **27** with excess hydrogen peroxide in formic acid yielded tetrol **28**. The doubly *trans*-diaxial configuration was tentatively assigned to **28** on the basis of its formation by epoxide opening.[16] The tetrol consumed 1.15 molar equiv of periodic acid in 24 hr, in accord with the expectation that the rigid *trans*-diaxial glycol system at the B/C ring junction would be stable to periodic acid, whereas the flexible *trans*-diaxial 8,9-glycol would be sensitive to periodic acid.[17,18] Chemical, spectroscopic, and potentiometric evidence which strongly support the configurations shown for **27**, **28**, and **30** will be presented in a forthcoming publication.[19]

## Experimental Section[20]

**1,3,4,6,11,11a-Hexahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizine** (**9**).—The product (30.15 g) of quaternization of 3,4-dimethoxybenzyl bromide and pyridine-2-carboxaldehyde was treated with polyphosphoric acid (150 g), and the mixture was heated with a water bath at 80–85° for 8 hr. During the first 4 or 5 hr, hydrogen bromide evolved steadily and was collected in a water trap. The reaction mixture turned from yellow-brown to dark green and, finally, to a dark viscous oil. The oil was treated with 20% sodium hydroxide to a pH of 6. The resulting dark red solution was hydrogenated catalytically with platinum oxide (1.0 g) in a Parr apparatus until consumption of hydrogen ceased (12–18 hr). The mixture was filtered, made basic with 20% sodium hydroxide, and extracted with chloroform (three 500-ml portions). The combined extract was dried over anhydrous potassium carbonate and evaporated to dryness, and the crude product was crystallized from Skellysolve B. Two crops of crystals, 12.0 g, mp 104–106°, and 1.7 g, mp 103–105° (lit.[7] mp 108–108.5°), were obtained (over-all yield 62%). The infrared absorption spectrum of the product was identical with that of a sample prepared by the route described earlier.

**1,3,4,6,7,10,11,11a-Octahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizine** (**8**).—To a solution of **9** (2.60 g) in anhydrous ether (400 ml) in a three-necked flask equipped with a stirrer, a gas inlet tube, and a liquid ammonia trap with a soda-lime drying tube, was added liquid ammonia (600 ml). Under vigorous stirring, lithium metal (3.50 g) was added over the course of 2 min. After 5 min, absolute alcohol (50 ml) was added dropwise during a period of 20 min. The mixture was allowed to stand overnight, during which time the ammonia evaporated. The solution was heated on the steam bath to evaporate the alcohol, and the resulting cake was treated with water (200 ml) and ether (100 ml). The aqueous layer was extracted twice more with ether, and the combined ether extract was washed with saturated salt solution and dried over anhydrous potassium carbonate. Evaporation of the ether under a stream of nitrogen yielded 2.22 g of yellowish solid, mp 77–82°. Recrystallization from petroleum ether (bp 60–68°) gave a colorless crystalline product (1.90 g), mp 85–86°.

*Anal.* Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H 9.30; N, 5.72. Found: C, 72.19; H, 9.29; N, 5.49.

**1,3,4,6,11,11a-Hexahydro-2H-benzo[*b*]quinolizin-9-ol** (**10**).—A solution of **8** (2.22 g) in concentrated hydrochloric acid (9.5 ml) under an atmosphere of nitrogen was kept for 3 hr at room temperature, heated on the steam bath for 1 hr, and then kept at room temperature for an additional 3 hr. The reaction mixture was poured into 10% sodium hydroxide (100 ml) and extracted twice with ether. The alkaline solution was neutralized with excess carbon dioxide and the tan precipitate was collected (1.25 g, mp 214–220°). Ether extraction gave additional crude product (0.22 g, mp 210–222°). Recrystallization of the combined solids from absolute alcohol gave crystalline product, 0.98 g, mp 222–225° (second crop: 0.25 g, mp 217–223°).

*Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.23; H, 8.44; N, 7.14.

The **acetate ester of 10** was prepared with acetic anhydride–pyridine at steam-bath temperature; it was crystallized from Skellysolve B, mp 78–79°.

*Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.95; N, 5.71.

The **methyl ether 11** was prepared by treatment of **10** in methanol solution with an ethereal solution of diazomethane; crystallization from Skellysolve B gave colorless crystals, mp 47–49°.

*Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 76.79; H, 8.19; N, 6.55.

**Permanganate Oxidation of 11 to 4-Methoxyphthalic Acid** (**15**).—To a boiling solution of **11** (0.136 g) in water (15 ml) was added dropwise a solution of potassium permanganate (1.50 g) in water (40 ml), over a period of 3 hr. The solution was heated for an additional 3 hr. Sodium bisulfite (3 g) and concentrated hydrochloric acid (5 ml) were added, and the clear solution was extracted with ether (five 40-ml portions). The combined ether extract was dried over anhydrous sodium sulfate and evaporated to leave a greenish oily residue (0.086 g). The residue was triturated with dilute sodium bicarbonate solution and filtered; the filtrate was acidified with concentrated hydrochloric acid. The acidic solution was extracted with ether (six 10-ml portions) and the ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in water (10 ml), decolorized with Norit (0.05 g), filtered, and concentrated almost to dryness, whereupon a colorless crystalline solid separated. Filtration yielded 2.0 mg of colorless crystals, mp 166–168° (lit.[21] mp 168–170° for 4-methoxyphthalic acid). Upon cooling of the melting point sample to 70°, the melt solidified; reheating showed the melting point to be 91–94° (lit.[21] mp 93–96° for 4-methoxyphthalic anhydride). The melting point was not depressed by admixture of a sample of 4-methoxyphthalic acid prepared by permanganate oxidation of 1,3,4,6,11,11a-hexahydro-8-methoxy-2H-benzo[*b*]quinolizine (**17**).[10] The mixed sample showed the same behavior upon cooling and reheating, namely, solidification at 70° and melting at 91–94°.

**1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-8-methoxy-2H-benzo[*b*]quinolizin-9-ol** (**19**).—A solution of **8** (3.0 g) in 5% hydrochloric acid (30 ml) was kept in a refrigerator for 7 hr. A small aliquot was treated with sodium bicarbonate and extracted repeatedly with chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered, and evaporated to dryness under reduced pressure and gentle warming to yield a

(17) *Cf.*, *e.g.*, M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2119 (1958).

(18) The preference for diequatorial conformation for the alkyl aldehyde substituents in the product formed by cleavage of the 8,9-glycol system appears to favor strongly the *trans*-diaxial conformation of the tertiary glycol in the cleavage product.

(19) *Cf.* S. M. Kupchan, J. H. Block, and A. I. Isenberg, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 22–31, 1966, p K101.

(20) Melting points have been corrected for stem exposure. Ultraviolet absorption spectra were determined in 95% ethanol on a Cary recording spectrophotometer (Model 11-MS). Infrared absorption spectra were recorded in chloroform (unless otherwise stated) on a Beckman IR5 double-beam infrared recording spectrophotometer. Microanalyses were carried out by Dr. S. M. Nagy, Massachusetts Institute of Technology, and F. J. Alicino, P. O. Box 267, Metuchen, N. J. Nmr spectra were recorded on a Varian Associates recording spectrophotometer (A-60) at 60 Mcps in deuterated chloroform, tetramethylsilane internal standard, unless otherwise specified. Chemical shifts are recorded in $\tau$ values (parts per million) [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)]. Skellysolve B refers to petroleum ether fraction boiling at 60–68°, while Skellysolve C refers to the fraction boiling at 90–100°.

(21) M. Freund and E. Gäbel, *Ber.*, **30**, 1932 (1897).

dark brown oil. The infrared absorption spectrum showed strong carbonyl absorption at 5.95 $\mu$ and medium absorption at 5.78 $\mu$. The crude product (2.5 g) was subjected to catalytic hydrogenation with 30% palladium on carbon (600 mg), in ethanol (50 ml) containing potassium hydroxide (270 mg). After hydrogen consumption of about 66% of the expected amount, reaction had almost stopped. The reaction mixture was filtered and a small aliquot was removed for determination of the infrared absorption spectrum, which showed carbonyl absorption at 5.79 $\mu$. The rest of the solution was hydrogenated catalytically with platinum oxide (600 mg); after uptake of hydrogen of about 50% of the calculated amount, the mixture was filtered and evaporated to dryness under reduced pressure. The product was a viscous semisolid material which was dissolved in boiling Skellysolve B; the resulting solution was concentrated (to about 8 ml) and allowed to stand. Crystalline yellow-brown material (378 mg) separated. The crop was recrystallized from Skellysolve B, to give microcrystals (245 mg), mp 148–150°. A further recrystallization gave material which melted at 149–151°.

*Anal.* Calcd for $C_{14}H_{25}NO_2$: C, 70.23; H, 10.52. Found: C, 69.90; H, 10.08.

The **acetate ester of 19** was prepared with acetic anhydride–pyridine at 80°; it was crystallized from Skellysolve B, mp 76–78°.

*Anal.* Calcd for $C_{16}H_{27}NO_3$: C, 68.28; H, 9.69. Found: C, 68.22; H, 9.58.

**1,3,4,6,7,10,11,11a-Octahydro-8-methoxy-2H-benzo[b]quinolizine (20).**—A solution of 1,3,4,6,11,11a-hexahydro-8-methoxy-2H-benzo[b]quinolizine[10] (**17**, 8.0 g, mp 51–53°) in anhydrous ether (400 ml) and liquid ammonia (2.0 l.) was treated with lithium (16 g) over a 15-min period, and finally with 95% ethanol (250 ml). After evaporating to dryness, the residue was extracted with ether. The ether extract was dried with anhydrous potassium carbonate and evaporated to dryness. The microcrystalline product (7.9 g), mp 60–65°, was recrystallized from Skellysolve B. Several crops (total 5.69 g) of white scaly material, mp 71–74°, were obtained (total yield 71%). The infrared absorption spectrum (30% in $CS_2$) of pure product, mp 74–75°, shows a *trans*-quinolizidine band at 3.65, and bands at 5.80, and 5.95 $\mu$.

*Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.40. Found: C, 76.77; H, 9.62; N, 6.71.

**1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[b]quinolizin-8-ol (22).**—A solution of **20** (5.9 g, mp 74–75°) in 5% hydrochloric acid (800 ml) was refluxed under nitrogen in an oil bath for 2 hr. A small sample of the reaction mixture was neutralized with sodium bicarbonate and extracted with several portions of chloroform. The combined extracts were dried over anhydrous potassium carbonate and evaporated to a brown-red oil. The infrared absorption spectrum showed strong carbonyl absorption at 5.83 $\mu$, and a shoulder at 5.99 $\mu$. The ultraviolet absorption spectrum showed $\lambda_{max}^{EtOH}$ 228 m$\mu$ ($\epsilon$ 2550). The reaction mixture was made basic with 4% sodium hydroxide to pH 9–10. After 20 min the solution was extracted with chloroform (five 200-ml portions). The combined extracts were dried over anhydrous potassium carbonate, filtered, and evaporated to dryness under reduced pressure to yield a dark red-brown oil (3.55 g). An aliquot separated for infrared absorption spectrum showed a very strong conjugated carbonyl band at 5.99 and a weak shoulder at 5.83 $\mu$. The ultraviolet absorption spectrum showed $\lambda_{max}^{EtOH}$ 228 m$\mu$ ($\epsilon$ 8500). The crude oil (3.55 g) was hydrogenated catalytically in ethanol (300 ml) with potassium hydroxide (0.5 g) and 30% palladium on carbon (2.0 g). After an uptake of about 1 mole equiv of hydrogen, the mixture was filtered and evaporated to dryness under reduced pressure. From the dark brown oil obtained, an aliquot was removed to determine the infrared absorption spectrum, which showed strong absorption at 5.83 and a weak shoulder at 5.99 $\mu$. Without isolating the intermediate ketone, reduction of the crude product (3.55 g) was performed with platinum oxide (0.7 g). When the consumption of hydrogen ceased, the mixture was filtered, the solution was evaporated to dryness, and the semisolid residue was crystallized from Skellysolve B; yield 2.1 g, mp 128–130°. Recrystallization from acetone–Skellysolve B gave needles, mp 131–132°.

*Anal.* Calcd for $C_{13}H_{23}NO$: C, 74.58; H, 11.09; N, 6.69. Found: C, 74.65; H, 11.04; N, 6.74.

The **acetate ester of 22** was prepared with acetic anhydride–pyridine at 80° and was crystallized from Skellysolve B as prisms, mp 88–89°.

*Anal.* Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.40; H, 9.86; N, 5.48.

**1,3,4,6a,7,9,10,10a,11,11a-Decahydro-2H-benzo[b]quinolizin-8(6H)-one (25).**—To a magnetically stirred solution of **22** (491 mg, mp 130–131°) in 90% acetic acid (10 ml), a solution of chromic oxide (0.605 g) in 90% acetic acid (15 ml) was added dropwise over a period of 5 min. A dark thick oil formed in the bottom of the reaction flask. The supernatant solution was transferred to another reaction flask, and the thick oil was dissolved in water (2 ml) and combined with the original solution. Stirring was continued for 2 hr. The mixture was treated with cracked ice and enough 20% potassium hydroxide solution to bring the pH to 10–11. The mixture was extracted with chloroform (four 20-ml portions), dried over anhydrous potassium carbonate, filtered, and evaporated to dryness to yield a brownish crystalline solid (243 mg), mp 60–61°. The infrared absorption spectrum shows a strong carbonyl band at 5.87 $\mu$, and *trans*-quinolizidine absorption at 3.58–3.62 $\mu$.

*Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.30; H, 10.23; N, 6.75. Found: C, 75.06; H, 10.44; N, 7.07.

**Lithium Aluminum Hydride Reduction of 1,3,4,6a,7,9,10,10a,-11,11a-Decahydro-2H-benzo[b]quinolizin-8(6H)-one (25).**—To a lithium aluminum hydride (20 mg) suspension in ether (15 ml) was added a solution of (6H)**25** (49 mg, mp 60–61°) in ether (5 ml), and the resulting suspension was refluxed for 3 hr. The suspension was treated with water and extracted with ether (four 20-ml portions). The ether solution was dried with anhydrous potassium carbonate and evaporated to dryness to yield yellow-white microcrystalline material (35 mg). Recrystallization from acetone–Skellysolve B gave needles (27 mg), mp 128–130°, characterized as **22** by mixture melting point and infrared spectral comparison with an authentic sample.

**1,3,4,6,11,11a-Hexahydro-2H-benzo[b]quinolizine (26).**—The free base, mp 50–52°, was prepared in crystalline form by treatment of its hydrobromide salt[15] with aqueous alkali and ether, and evaporating the ethereal solution to dryness.

The **methiodide of 26**, crystallized from ethanol–ethyl acetate, showed mp 296–297°. The nmr spectrum in trifluoroacetic acid shows a signal for $NCH_3$ at $\tau$ 6.29.

*Anal.* Calcd for $C_{14}H_{20}IN$: C, 51.08; H, 6.12; I, 38.55; N, 4.25. Found: C, 50.90; H, 6.41; I, 39.02; N, 4.35.

**1,3,4,6,7,10,11,11a-Octahydro-2H-benzo[b]quinolizine (27).**—A solution of **26** (7.50 g) in ether (500 ml) and liquid ammonia (1500 ml) was treated with lithium (15.78 g) over a 15-min period, and finally with ethanol (200 ml). After evaporation to dryness the residue was extracted with ether. The ether extract was dried with anhydrous potassium carbonate and evaporated to dryness. The crude product (7.45 g) was microcrystalline and showed mp 59–61°. Recrystallization from ethanol–water gave crystals with mp 62–63°, $\lambda_{max}^{EtOH}$ 264 m$\mu$ ($\epsilon$ 65), $\lambda_{max}$ 6.03 $\mu$.

The **methiodide of 27**, recrystallized from ethanol–ether, showed sintering at 226–228° and mp 252–254°. The nmr spectrum in trifluoroacetic acid shows a signal for $NCH_3$ at $\tau$ 6.90.

*Anal.* Calcd for $C_{14}H_{22}IN$: C, 50.76; H, 6.70; I, 38.31; N, 4.23. Found: C, 50.69; H, 6.79; I, 38.74; N, 4.31.

**1,3,4,6,7,8,9,10,11,11a-Decahydro-2H-benzo[b]quinolizine (29).**—A solution of **27** (0.203 g, mp 59–61°) in ethanol (50 ml) was hydrogenated using platinum oxide (21 mg) catalyst. The hydrogenation was stopped after 1.01 mole equiv had been consumed (1 hr). Filtration of the catalyst and evaporation of the solvent to dryness gave a very low-melting crystalline material (*ca.* 20–25°). The compound crystallized at low temperatures in the refrigerator and partially melted at room temperature. It was distilled under reduced pressure (bp 92–96° at 0.9 mm). The distillate melted at 20–25°. The infrared absorption spectrum shows disappearance of the weak band at 6.03 $\mu$ which was present in the starting material.

The **methiodide of 29**, recrystallized from ethanol–ether, showed mp 281–282°.

*Anal.* Calcd for $C_{14}H_{24}IN$: C, 50.45; H, 7.27; N, 4.21. Found: C, 50.56; H, 7.34; N, 4.35.

**1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[b]quinolizine-6a,10a-diol (30).**—A solution of **29** (3.023 g, mp 20–25°) in 88% formic acid (15 ml) was treated with 30% hydrogen peroxide (1.71 ml, sp gr 1.11). After 4 hr at 40°, 12% sodium hydroxide (150 ml) was added, whereupon a milky suspension developed. Ethanol (200 ml) was added to clarify the suspension, and the resulting solution was extracted with chloroform (four 100-ml por-

tions), dried over anhydrous potassium carbonate, and chromatographed on silicic acid (20 g). Elution with chloroform (100 ml) and ether (100 ml) gave a semisolid product with $R_f$ higher than the principal product. The material eluted with methanol (400 ml) was recrystallized from Skellysolve B to give colorless prisms (0.866 g): mp 115–117°; $\lambda_{max}$ 2.77, 2.90 $\mu$.

*Anal.* Calcd for $C_{13}H_{23}NO_2$: C, 69.40; H, 10.30; N, 6.22. Found: C, 69.75; H, 9.99; N, 6.38.

The **methiodide of 30**, recrystallized from methanol–ether, showed mp 250–254°. The nmr spectrum in 10% aqueous solution with a dioxane internal standard shows a signal for $NCH_3$ at $\tau$ 6.86.

*Anal.* Calcd for $C_{14}H_{26}INO_2$: C, 45.77; H, 7.15; N, 3.81. Found: C, 45.92; H, 7.35; N, 3.49.

**1,3,4,6,6a,7,10,10a,11,11a-Decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol (31).**—To a solution of **27** (2.0 g, 0.106 mole equiv, mp 59–61°) in 88% formic acid (26 ml), 30% hydrogen peroxide (1.08 ml, sp gr 1.11, 0.106 mole equiv) was added, and the mixture was maintained at 40° for 3 hr. A 20% solution of sodium hydroxide was added to pH 11–12. To the cloudy suspension, 95% ethanol (150 ml) was added, and the resulting solution was boiled for 20 min. Extraction with chloroform (four 100-ml portions), followed by drying over anhydrous potassium carbonate and evaporation to dryness, gave an amorphous crude material (2.0 g). Chromatography on silicic acid–Celite 545 (3:2 ratio, 15 g) with chloroform yielded, in the first eluates (250 ml of chloroform), a product which crystallized from Skellysolve C as prisms (745 g): mp 90–91°; $\lambda_{max}$ 2.79, 2.89, 6.06 $\mu$.[1]

*Anal.* Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.74; H, 9.51; N, 6.25.

The fractions eluted from the column with methanol yielded material which crystallized from methanol–acetone to yield a product (30 mg) of mp 198–202°, characterized as tetrol **28**.

**Catalytic Hydrogenation of 31 to 30.**—A solution of 1,3,4,6,6a,7,10,10a,11,11a-decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol (**31**, 0.490 g, mp 86–88.5°) in ethanol (15 ml) was reduced at atmospheric pressure and room temperature using platinum oxide catalyst (307 mg). After 1 hr, uptake was quantitative. Filtration of the solution and evaporation to dryness gave a crystalline material which was recrystallized from Skellysolve B–acetone yielding a first crop (284 mg), mp 115–116°, and a second crop (166 mg), mp 115–116°, for a total yield of 91%. The mixture melting point of this product with **30** showed no depression. The infrared absorption spectrum of the product and that of **30** were found to be identical.

**Hydroxylation of 1,3,4,6,6a,7,10,10a,11,11a-Decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol (31).**—A formic acid (1.3 ml) solution of **31** (0.100 g, 0.00045 mole equiv, mp 86–88°) was warmed to 40° on a water bath. A 30% hydrogen peroxide solution (0.15 ml, sp gr 1.11, 0.0015 mole equiv) was added and the temperature kept constant (40°) for 3.5 hr. The solution was made basic with 20% potassium hydroxide to pH 11–12, ethanol (20 ml) was added to dissolve the cloudy suspension, and the resulting solution was boiled (15 min). After cooling, the solution was extracted with chloroform, dried with anhydrous potassium carbonate, and evaporated to dryness. The brownish crystalline material (118 mg), mp 186–196°, was recrystallized from acetone to yield a first crop (32 mg), mp 200–203°, and a second crop (28 mg), mp 199–202°, characterized as tetrol **28** by mixture melting point and infrared spectral comparison.

**1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol (28).**—A solution of **27** (8.674 g, 0.0459 mole equiv, mp 60–61°) in 88% formic acid (114 ml) was treated with 30% hydrogen peroxide (13.05 ml, sp gr 1.11, 0.128 mole equiv). The mixture was kept at 40° with a water bath. After 3 hr the mixture was treated with 20% potassium hydroxide to pH 11–12. Ethanol was added to dissolve the milky suspension formed and the resulting solution was boiled for 0.5 hr. After cooling, the solution was extracted with chloroform (five 300-ml portions); the extract was dried over anhydrous potassium carbonate and evaporated to dryness. The crude product (8.030 g) was a brown crystalline solid. Chromatographic separation was accomplished with silicic acid–Celite 545 (4:1 ratio, 250 g), using chloroform and chloroform–methanol mixtures of increasing polarity as eluents. The material eluted with 60% methanol in chloroform and with methanol was crystallized from methanol–acetone to give a product (3.796 g) of mp 199–203°. Recrystallization from the same solvents gave colorless scaly crystals, mp 202–203°.

*Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.66; H, 9.02; N, 5.44. Found: C, 60.84; H, 8.93; N, 5.49.

The **methiodide of 28**, crystallized from ethanol–ethyl acetate, showed mp 241–242°. The nmr spectrum in deuterium oxide with sodium 2,2-dimethyl-2-silapentane-5-sulfonate internal standard shows a signal for $NCH_3$ at $\tau$ 6.79.

*Anal.* Calcd for $C_{14}H_{26}INO_4$: C, 42.12; H, 6.56; I, 31.79; N, 3.51. Found: C, 41.84; H, 6.62; I, 31.55; N, 3.55.

**1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 8,9-Diisobutyrate.**—To a solution of **28** (1.563 g, 0.0061 mole equiv, mp 200–202°) in anhydrous pyridine (3 ml), isobutyryl chloride (sp gr 1.41, 1.563 ml, 0.0183 mole equiv) was added slowly while cooling with an ice bath. The clear solution was allowed to come to room temperature and then to stand for 98 hr. The mixture was cautiously treated with a few drops of methanol, while cooling in an ice bath. The mixture was treated with cracked ice and dilute ammonium hydroxide to pH 8 and extracted with chloroform (four 50-ml portions); the combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness with the aid of anhydrous benzene. The resulting oil was dissolved in acetone–Skellysolve C and the hot solution was filtered. Concentration yielded solid material (0.341 g), mp 114–120°. A second crop was obtained (101 mg), mp 110–117°. Both crops were combined and recrystallized from the same solvents to yield crystalline product (161 mg), mp 119–120° [second crop (118 mg), mp 116–119°], $\lambda_{max}$ 2.80, 2.90, 5.76, 8.10–8.30 $\mu$.

*Anal.* Calcd for $C_{21}H_{35}NO_6$: C, 63.43; H, 8.89. Found: C, 63.70; H, 8.54.