Hydrobenzo[b]quinolizines. II.[1] The Synthesis and Stereochemistry of Derivatives of 1,3,4,11a-Tetrahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11(6H)-one[2]

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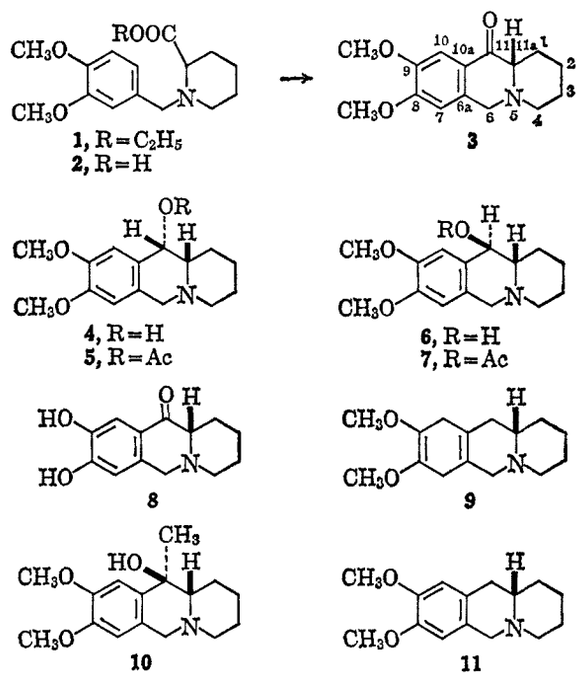
1,3,4,11a-Tetrahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11(6H)-one (**3**) was synthesized by polyphosphoric acid cyclization of the hydrochloride salt of 1-(3,4-dimethoxybenzyl)-2-carboxypiperidine (**2**). Catalytic hydrogenation of **3** with ruthenium yielded a mixture of epimeric alcohols **4** and **6**. Lithium aluminum hydride reduction of **3** gave only the β (equatorial) epimer **6**. Birch reduction of **3** yielded 1,3,4,6,7,10,11,11a-octahydro-8,9-dimethoxy-2H-benzo[b]quinolizine (**9**). Treatment of **3** with methylmagnesium iodide gave 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-11-methyl-2H-benzo[b]quinolizin-11-ol (**10**). Treatment of **3** under Leuckart reaction conditions gave 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-2H-benzo[b]quinolizine (**11**), and treatment of **3** or **6** with formic acid alone afforded the same product.

Our previous report[1] introduced our studies of the synthesis of hydrobenzo[b]quinolizine derivatives as alkaloid analogs. The present paper describes an approach to derivatives with an oxygen function at C-11, a position which corresponds to the hydroxyl-bearing C-20 in the ceveratrum alkaloids.[1]

The compound selected as a suitable precursor for the target compounds of the present investigation was 1,3,4,11a-tetrahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11(6H)-one (**3**). It was felt that the ketone function at C-11 in **3** might be advantageous in facilitating synthesis of derivatives stereoisomeric about C-10a, C-11, and C-11a.

The α-amino ketone **3** has been described[4] as a compound melting at 50–60°. In the present report, a more efficient synthesis of product melting at 136–137° is described. Condensation of 3,4-dimethoxybenzyl bromide[5] and 2-carbethoxypiperidine[6] was accomplished most effectively by treatment of the bromide in benzene with a twofold excess of the amine. As reaction proceeded, the hydrobromide salt of 2-carbethoxypiperidine separated from solution; 1-(3,4-dimethoxybenzyl)-2-carbethoxypiperidine (**1**) was isolated from the filtrate in almost quantitative yield. The use of polyphosphoric acid in the cyclization of aromatic esters is well documented.[7] However, in the case of **1**, attempts to cyclize the amine ester under a variety of conditions were unsuccessful. Saponification of **1** to **2** was effected with alcoholic potassium hydroxide. The hydrochloride salt of **2** was treated with polyphosphoric acid at 85° for 9 hr, to afford the desired ketone **3** in 73% yield (see Scheme I). The nmr spectrum supports assignment of structure **3**, rather than the possible 9,10-dimethoxy alternative, for the aromatic proton region shows singlets at τ 2.53 and 3.34, and no AB-type quartet expected for the C-7 and C-8 protons of the 9,10-dimethoxy isomer. The signal at τ 2.53 is assigned to the proton at C-10 in **3**, which is deshielded by the adjacent C-11 ketone;

SCHEME I



the singlet at τ 3.34 is assignable to the aryl proton at C-7.[8] The infrared spectrum of **3** shows strong absorption at 3.57–3.62 μ, a fact which supports assignment of the *trans*-quinolizidine configuration indicated in formulation **3**.[9]

Catalytic reduction of 1,3,4,11a-tetrahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11(6H)-one (**3**) with ruthenium oxide at 2500 psi and 120° yielded a crystalline mixture of alcohols. Fractional crystallization separated epimer A (**4**), mp 205–206°, and epimer B (**6**), mp 158–159°, in a ratio of 4:1. Chemical reduction of **3**, with either sodium borohydride or lithium aluminum hydride, gave epimer B (**6**) as the predominant product. The latter fact and the unhindered nature of the 11-ketone support assignment of the equatorial (hence β) configuration to the hydroxyl group in epimer B.[10] In agreement with this assignment, the

(1) Part I in the series: S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

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(3) Recipient of 1964 Lunsford Richardson Pharmacy Award for a paper including part of this work.

(4) N. Sugimoto, *J. Pharm. Soc. Japan*, **64**, 27 (1944); **76**, 1045 (1956).

(5) R. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).

(6) W. A. Reckhow and D. S. Tarbell, *J. Am. Chem. Soc.*, **74**, 4960 (1952).

(7) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958).

(8) *Cf.* Spectra 187 and 339, N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962.

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

(10) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

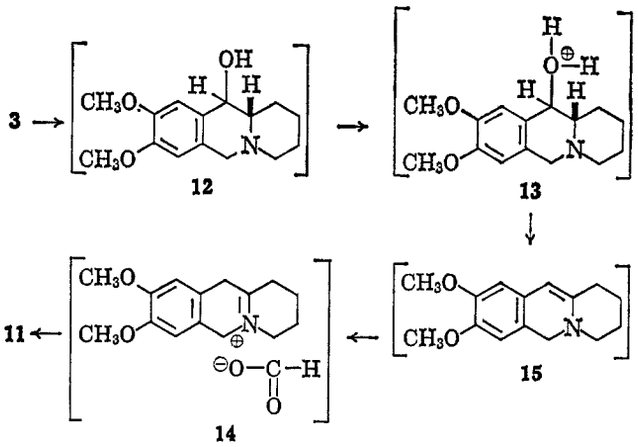
infrared spectrum of epimer B shows an unassociated hydroxyl band at 2.78 μ, and that of epimer A shows a broad hydrogen-bonded hydroxyl band at 2.85–3.15 μ.[11] Further corroboration came from the observation that epimer A (**4**, hydroxyl group axial) was oxidized by chromic acid in acetic acid twice as fast as epimer B.[12] The alcohols were readily acetylated to their respective acetates **5** and **7**. The infrared spectra of the epimeric alcohols and their acetate esters indicate that all contain *trans*-quinolizidine ring junctions.

Attempts at catalytic hydrogenation of the aromatic ring of the epimeric alcohols **4** and **6** at 300 atm and 180° with ruthenium oxide yielded intractable mixtures. Similarly, attempts at hydrogenating 1,3,4,11a-tetrahydro-2H-benzo[*b*]quinolizine-8,9-diol-11(6H)-one (**8**) (prepared by hydrobromic acid hydrolysis of the ether groups of **3**) under similar conditions led to intractable complex mixtures.

Birch reduction of **3** yielded 1,3,4,6,7,10,11,11a-octahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizine (**9**), characterized by comparison with a sample prepared by an alternate route.[1] Attempts to convert **3** to a ketal (by treatment with ethylene glycol and *p*-toluenesulfonic acid) or oxime (with hydroxylamine hydrochloride) were unsuccessful. Evidently the vinylogous ester character of the ketone rendered the compound unreactive to carbonyl reactions which are acid catalyzed.[13] On the other hand, the carbonyl group of **3** was quite susceptible to other nucleophilic reagents, as evidenced by hydride reductions already noted. Furthermore, treatment with methylmagnesium iodide gave 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-11-methyl-2H-benzo[*b*]quinolizin-11-ol (**10**). Assignment of β (equatorial) configuration to the hydroxyl group in **10** is supported by the observation that its infrared spectrum shows an unassociated hydroxyl bond at 2.77 μ.[11]

An attempt to reductively aminate **3**, by Leuckart reaction[14] with formamide and 88% formic acid at 185°, yielded 1,3,4,6,11,11a-hexahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizine (**11**) rather than the sought-for amino derivative. It was found that **3** was reduced to **11** when heated with formic acid alone. A plausible route for the reduction proceeds in a manner analogous to that proposed by Leonard and Sauers[15] for the reduction of $\Delta^{1(10)}$-dehydroquinolizidine with formic acid. The first step in the reduction of **3** may involve hydride transfer from a formate ion to yield the alcohol **12** (see Scheme II). Support for the intermediacy of an alcohol such as **12** was adduced by the observation that treatment of **6** with 88% formic acid at 185° afforded a 78% yield of **11**.[1] Reduction of the benzylic alcohol may proceed *via* protonation to **13**, elimination to the enamine **15**, and hydride transfer *via* the ternary iminium formate (**14**).

SCHEME II



Experimental Section[16]

1-(3,4-Dimethoxybenzyl)-2-carbethoxypiperidine (**1**).—To a stirred solution of 2-carbethoxypiperidine[6] [18.8 g, 0.119 mole equiv, bp 80° (7.0 mm)] in anhydrous benzene (100 ml) was added dropwise a solution of 3,4-dimethoxybenzyl bromide[6] (13.75 g, 0.0595 mole equiv, mp 56–58°) in benzene (100 ml). During the addition of bromide, the hydrobromide salt of 2-carbethoxypiperidine began to precipitate from solution. The stirring was continued overnight at room temperature. The hydrobromide salt was filtered, washed with dry benzene, and dried (13.4 g). The filtrate was distilled under reduced pressure, yielding a viscous oil which was dissolved in 10% hydrochloric acid solution, extracted with ether, made basic with sodium carbonate, and extracted with ether several times. The extracts were dried over anhydrous sodium sulfate and distilled under reduced pressure to yield a viscous oil. Vacuum distillation gave a colorless oil (17.4 g, 95%), bp 195–198° (0.2 mm), lit.[4] bp 205–210° (1 mm).

1-(3,4-Dimethoxybenzyl)-2-carboxypiperidine Hydrochloride.—In a round-bottom flask equipped with a water condenser and drying tube, a mixture of **1** [20.0 g, bp 195–198° (0.2 mm)] and potassium hydroxide (3.7 g) in absolute ethanol (40 ml) was refluxed for 3 hr. The solvent was removed under reduced pressure and the residue was acidified with a 25% hydrochloric acid solution. The aqueous solution was evaporated to dryness *in vacuo*, and the residue extracted several times with hot absolute ethanol. The combined ethanol extracts were evaporated under reduced pressure. The solid was recrystallized from ethanol–ether to give the hydrochloride of 1-(3,4-dimethoxybenzyl)-2-carboxypiperidine (17.35 g, 85%), mp 222–223°, lit.[4] mp 222–223°.

1,3,4,11a-Tetrahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizin-11(6H)-one (**3**).—A suspension of 1-(3,4-dimethoxybenzyl)-2-carboxypiperidine hydrochloride (10 g, mp 222–223°) in polyphosphoric acid (50 g) was stirred at 85° under nitrogen for 9 hr. During the first 4 or 5 hr hydrochloric acid evolved steadily and was collected in a water trap. The reaction mixture turned from a colorless to dark red viscous oil. The mixture was cooled, water was added, and the solution was made alkaline with potassium carbonate. Extraction with benzene (four 50-ml portions) followed by drying over anhydrous sodium sulfate and evaporation of the solvent gave yellow crystals weighing 7.27 g. Recrystallization from methanol gave 3.85 g of yellow plates: mp 136–137° [second crop, 2.05 g, mp 133–134° (total, 73%)]; λ_{max} 3.61, 5.93, 6.20, 6.6, 7.75, 7.9 μ. The nmr spectrum shows 1H singlets at τ 2.58 (proton at C-10) and at 3.34 (proton at C-7), and a 6H singlet at 6.08 (methoxyl protons).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.53; H, 7.43; N, 5.48.

The picrate salt of **3** showed mp 167° dec (lit.[4] mp 50–60° of **3**; melting point of picrate, 170°).

Catalytic Reduction of 1,3,4,11a-Tetrahydro-8,9-dimethoxy-2H-benzo[*b*]quinolizin-11(6H)-one (**3**).—A solution of **3** (5.02 g, mp 136–137°) in methanol (250 ml) was hydrogenated over ruthenium oxide (1.0 g) at 2500 psi and 120° for 6 hr. The solution was filtered and the solvent was evaporated to yield a white solid. Crystallization from benzene gave a first crop of white

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

(12) *Cf.* J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955); F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(13) *Cf.* J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, pp 244, 250.

(14) F. S. Crossley and M. L. Moore, *J. Org. Chem.*, **9**, 529 (1944); K. G. Lewis, *J. Chem. Soc.*, 2249 (1950).

(15) N. J. Leonard and R. R. Sauers, *J. Am. Chem. Soc.*, **79**, 6210 (1957).

(16) General experimental procedures are given in the preceding article.

microcrystalline material (3.21 g, 64%), mp 202–205°; the mother liquor deposited 0.75 g of material melting over a wide range. Careful recrystallization of the first crop material from ethyl acetate gave epimer A of the alcohol (**4**, mp 205-205.5°). The infrared spectrum shows a broad hydrogen-bonded hydroxyl band at 2.85–3.15 μ, a strong *trans*-quinolizidine band at 3.63 μ, and aromatic bands at 6.20 and 6.63 μ.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.66; H, 7.89; N, 5.46.

Recrystallization of the second crop material gave epimer B of the alcohol **6**, mp 157–158°.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.22; H, 8.10; N, 5.17.

Metal Hydride Reduction of 1,3,4,11a-Tetrahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11(6H)-one (3). A. Reaction of 3 with Sodium Borohydride.—A solution of sodium borohydride (74 mg) in methanol (15 ml) was added dropwise to a stirred solution of **3** (0.50 g, mp 136–137°) in methanol (25 ml) under nitrogen and the resultant solution was kept overnight at room temperature. The solvent was removed under reduced pressure and the residue was suspended in water (10 ml) and extracted with benzene (three 30-ml portions). After drying the benzene extracts over anhydrous sodium sulfate, solvent was evaporated to yield a white solid residue. Crystallization from ethyl acetate gave epimer B (**6**), 352 mg, 70%, mp 158–159°. A second crop of crystalline material (44 mg), mp 175–192°, was obtained from the mother liquor and appeared to be mainly epimer A (**4**). The infrared spectrum (dichloromethane) of epimer B shows an unassociated hydroxyl peak at 2.78, and a *trans*-quinolizidine peak at 3.63 μ.

B. Reaction of 3 with Lithium Aluminum Hydride.—To a stirred suspension of lithium aluminum hydride (0.3 g) in anhydrous ether (30 ml) was added dropwise a solution of **3** (0.5 g, mp 136–137°) in anhydrous ether (50 ml). The mixture was stirred continuously with gentle heat for 6 hr. After cooling, water was carefully added to decompose the excess lithium aluminum hydride. Additional water was added, and the ether layer separated. The aqueous layer was extracted with two 30-ml portions of dichloromethane. The combined extracts were washed with water and dried over sodium sulfate, and then evaporated. The white solid which remained was crystallized from ethyl acetate. White needles of epimer B (0.267 g, 53%), mp 156–158°, were obtained.

Chromic acid oxidation of the epimeric alcohols was conducted by a modification of earlier procedures.[12] The alcohol (2 mg) was weighed in a colorimeter tube and dissolved in 1.5 ml of 90% acetic acid. Then, 0.5 ml of a freshly prepared solution containing 1 equiv of chromic acid was added and the disappearance of Cr^{VI} followed spectrophotometrically at 380 mμ using a Bausch and Lomb Spectronic 20. The sample tube was left in the colorimeter during the experiment; optical density readings were taken until they leveled off. Readings for **4** leveled off in 25 min and those for **6** in 50 min.

Acetylation of 1,3,4,6,11,11a-Hexahydro-8,9-dimethoxy-2H-benzo[b]quinolizin-11-ol. A. Acetylation of Epimer A (4).—A solution of epimer A (**4**, 0.5 g, mp 205–205.5°) in acetic acid (5 ml), acetic anhydride (3 ml), and 70% perchloric acid (0.1 ml) was allowed to stand overnight at room temperature. The solvents were evaporated under reduced pressure and the residue was dissolved in water which was made alkaline with 10% sodium hydroxide. Extraction with ether gave on evaporation a brown solid (0.52 g). Crystallization from Skellysolve B gave clusters of white crystals (0.367 g, 63%), mp 127–128°. Recrystallization gave an analytical sample of **5**: mp 127.5–128°; λ_{max} 3.63 (*trans*-quinolizidine), 5.83 μ (ester).

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.83; H, 7.59; N, 4.59. Found: C, 67.39; H, 7.86; N, 4.53.

B. Acetylation of Epimer B (6).—A solution of epimer B (**6**, 0.301 g, mp 157–158°) in pyridine (1.0 ml) and acetic anhydride (1.0 ml) was allowed to stand at 0° overnight. The reaction mixture was treated with sodium carbonate solution and extracted with ether, which on evaporation gave a solid residue (0.326 g). Crystallization from Skellysolve B gave a material melting at 71–78°. Further recrystallization gave pure product **7** (0.26 g, 77%): mp 90.5–91°; λ_{max} 3.61 (*trans*-quinolizidine), 5.81 μ (ester).

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.83; H, 7.59; N, 4.59. Found: C, 67.41; H, 7.77; N, 4.43.

1,3,4,11a-Tetrahydro-2H-benzo[b]quinolizine-8,9-diol-11(6H)-one (8).—In a 50-ml round-bottom flask equipped with a water condenser and drying tube were placed **3** (1.0 g, mp 135–136°), a solution of 30–32% hydrobromide gas in acetic acid (12 ml), and water (2 ml). The mixture was refluxed for 5 hr in an oil bath at 125°. The mixture was cooled, at which time crystals began to appear. These crystals were filtered, washed with glacial acetic acid, dried, and recrystallized from ethanol–ether. The hydrobromide salt (0.958 g, 80%) was obtained as white crystals, mp 245–248° dec.

Anal. Calcd for $C_{13}H_{16}BrNO_3$: C, 49.67; H, 5.13; Br, 25.44; N, 4.46. Found: C, 49.84; H, 5.49; Br, 24.51; N, 4.81.

The product (5 mg) was tested for the catechol group by dissolving in 95% methanol (0.5 ml) and adding 1 drop of 5% titanium trichloride solution. The solution turned from a purple to yellow immediately, indicating the presence of a catechol group.[17]

The free base was obtained by dissolving the hydrobromide salt (0.25 g, mp 245–248°) in water (5 ml). While cooling in an ice bath, a solution of 8% sodium bicarbonate was added dropwise until the solution was basic (pH 8). A pale yellow crystalline material precipitated from solution, was filtered, washed with water, and dried. The product (**8**) was crystallized from an ethanol–ether mixture, yielding fluffy yellow crystals (0.152 g, 81%), mp 200–203°.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.92; H, 6.48; N, 6.01. Found: C, 67.26; H, 6.40; N, 5.96.

1,3,4,6,7,10,11,11a-Octahydro-8,9-dimethoxy-2H-benzo[b]-quinolizine (9).—A three-necked 500-ml flask equipped with a mechanical stirrer and a liquid ammonia trap with a soda-lime drying tube was placed in an acetone–Dry Ice bath. Dried ammonia gas was induced into the flask to a volume of 200 ml of liquid ammonia. Anhydrous ether (10 ml) was added and the mixture was stirred for 10 min. To the mixture was added **3** (0.1 g, mp 135–136°) dissolved in anhydrous ether (25 ml). With stirring, lithium wire (0.28 g) which had been cut into small pieces was added to the solution over a period of 2 min. With each addition of the lithium, the liquid ammonia mixture turned from a yellow to a dark blue color. The solution was stirred for 1 hr. Ethanol was added dropwise until the solution became colorless. The reaction was left in the hood overnight until the solvents had evaporated. Water was added to dissolve the caked residue. The aqueous layer was extracted with four 30-ml portions of ether which were dried over sodium sulfate and evaporated to dryness under reduced pressure to yield a yellow residue. Crystallization of the crude product from aqueous ethanol yielded pale yellow crystals (40 mg, 40%): mp 82–84°; λ_{max}^{EtOH} 280 mμ (ϵ 60); λ_{max} 3.62, 5.83 (w), 5.95 (sh), 7.80, 7.90 μ. The melting point was not depressed upon admixture with an authentic sample of **9**.[1]

1,3,4,6,11,11a-Hexahydro-8,9-dimethoxy-11-methyl-2H-benzo-[b]quinolizin-11-ol (10).—In a three-necked 100-ml flask equipped with a water condenser with a drying tube and equilibrating funnel were placed dry magnesium turnings (96 mg), anhydrous ether (15 ml), and one crystal of iodine. Methyl iodide (0.6 g) dissolved in anhydrous ether (10 ml) was added dropwise over a period of 30 min. After gentle heating on the steam bath, the reaction became vigorous. The yellow color produced by the iodine disappeared and after 1.5 hr, **3** (1.0 g, mp 135–136°) dissolved in ether (50 ml) was added dropwise over a period of 1 hr. The mixture was refluxed for 2 hr on the steam bath. The ethereal solution and insoluble precipitate were treated with a 25% sulfuric acid solution until the mixture was distinctly acid. The aqueous acid layer was washed with several portions of ether and made alkaline with potassium carbonate. The aqueous alkaline solution was extracted three times with ether–benzene and the extract was dried over sodium sulfate and distilled under reduced pressure. The pale yellow residue was recrystallized twice from ethyl acetate to yield a white crystalline product (0.293 g, 28%): mp 184–185°; λ_{max} 2.77, 3.60, 6.20, 6.60 μ.

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.35; N, 5.05. Found: C, 69.04; H, 8.27; N, 5.11.

1,3,4,6,11,11a-Hexahydro-8,9-dimethoxy-2H-benzo[b]quinolizine (11). A. Formamide–Formic Acid Reduction of 3.—In a Claisen flask fitted with a water condenser set for downward distillation were placed **3** (0.5 g, mp 135–136°), formamide (4 ml), and 88% formic acid (4 ml). The homogeneous mixture was heated slowly in an oil bath until the temperature reached 185°, at which time several drops of the distillate were collected (colorless, pH 5). The mixture was heated continuously for 3 hr at 180–185°.

(17) F. Weygand and E. Csendes, *Ber.*, **85**, 45 (1952).

The reaction mixture was cooled and treated with water (10 ml). An 8 *N* ammonium hydroxide solution was added dropwise to pH 9. The turbid aqueous layer was extracted with chloroform (three 50-ml portions) which were dried over sodium sulfate and distilled under reduced pressure. The crude solid was crystallized from aqueous ethanol, yielding pale yellow plates (0.27 g, 57%): mp 105–106°; λ_{max} 3.61, 3.71, 6.20, 6.60 μ. The mixture melting point was not depressed upon admixture with an authentic sample of 11.[1]

B. Reduction of 6 with 88% Formic Acid.—In a 50-ml Claisen flask fitted with a water condenser set for downward distillation was added epimer B (6, 85 mg, mp 157–158°) and 88% formic acid (3 ml). The mixture was heated in an oil bath slowly until the temperature reached 185°. The mixture was heated for 1.5 hr at 185°. While cooling, water (3 ml) was added and the mixture was treated with sodium carbonate until distinctly basic. The aqueous layer was extracted with ether (three 25-ml portions), which was dried over sodium sulfate. Removal of the solvent under reduced pressure gave a crude yellow solid which was crystallized from aqueous ethanol, yielding pale yellow platelets (61 mg, 77%), mp 104–105°. This product was identical (by infrared and mixture melting point comparison) with an authentic sample of 11 and the compound prepared by the attempted Leuckart reduction of 3.

Hydrobenzo[*b*]quinolizines. III.[1] The Synthesis and Stereochemistry of Derivatives of 3,4,11,11a-Tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one[2]

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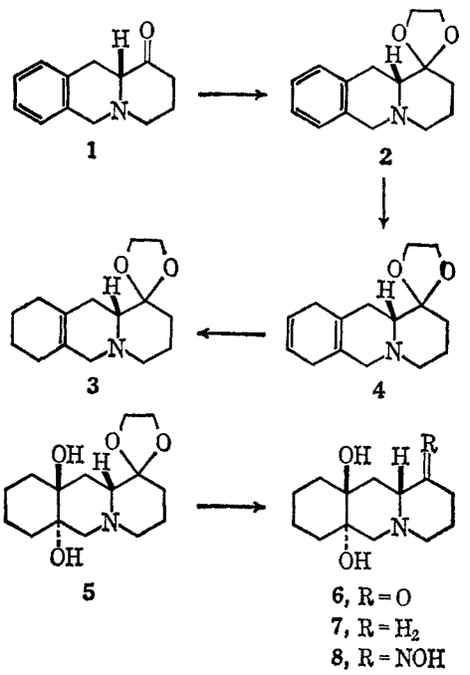
The ethylene ketal (2) derived from 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one (1) was reduced by the Birch procedure to the diene 4. Catalytic hydrogenation yielded 3, and hydroxylation with performic acid gave the diol 5. Ketal hydrolysis afforded 6, and Wolff–Kishner reduction led to 1,3,4,6,6a,7,8,9,10,10a,-11,11a-dodecahydro-2H-benzo[*b*]quinolizine-6a,10a-diol (7). Lithium and alcohol in ammonia reduction of 1 yielded homoannular diene 9, and the latter product was obtained, alternatively, by hydrolysis of 4 to 11 followed by lithium aluminum hydride reduction of 11. Arguments are advanced for assignment of β (equatorial) configuration to the hydroxyl group in 9. Catalytic hydrogenation of 9 yielded 10 and hydroxylation with performic acid gave the triol 12. Reduction of 1 with lithium aluminum hydride gave 16; catalytic hydrogenation of 1 yielded 17. Reduction of oxime 18 with lithium aluminum hydride gave the primary amine 19, characterized as its acetamide derivative 20. Birch reduction of 19 gave diene 23. Catalytic reduction of 23 yielded the unsaturated amine 21, which was characterized as its carbobenzoxy derivative 22.

Our previous reports[1,4] have introduced our studies on the synthesis of hydrobenzo[*b*]quinolizine derivatives as alkaloid analogs. The present paper describes an approach to derivatives substituted at C-1, a position which corresponds to the indole–nitrogen-substituted C-2 of reserpine.[4]

The compound selected as a suitable precursor for the desired compounds was 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one (1), readily available by routes described earlier.[5,6] The infrared spectrum of 1 shows a sharp peak at 3.57 μ, characteristic of *trans*-quinolizidines.[7] Treatment of 1 with ethylene glycol and *p*-toluenesulfonic acid in benzene[8] effected ketalization at C-1, affording 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one ethylene ketal (2) (see Scheme I). In accord with the assigned structure, the infrared spectrum shows bands at 3.61 (*trans*-quinolizidine), 6.27 and 6.67 (aromatic), and 9.2–9.6 μ (ketal ether), and the nmr spectrum indicates the presence of four aromatic protons. Birch reduction of ketal 2 according to the procedure of Wilds and Nelson[9] yielded 3,4,7,10,11,11a-hexahydro-2H-benzo[*b*]quinolizin-1(6H)-one ethylene ketal (4). The

SCHEME I



infrared spectrum shows bands at 3.62 and 3.71 (*trans*-quinolizidine)[7] and at 5.84 and 6.03 μ (unconjugated homoannular diene),[4] and λ_{max}^{EtOH} 267 mμ (ϵ 120). Catalytic hydrogenation of 4 led to consumption of 1 mole equiv of hydrogen and yielded 3,4,7,8,9,-10,11,11a-octahydro-2H-benzo[*b*]quinolizin-1(6H)-one ethylene ketal (3).

Treatment of 3 in 88% formic acid with 30% hydrogen peroxide yielded 3,4,6a,7,8,9,10,10a,11,11a-

(1) Part II in the series: S. M. Kupchan, A. D. J. Baron, and C. G. DeGrazia, *J. Org. Chem.*, **31**, 1713 (1966).

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