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]

S. MORRIS KUPCHAN AND C. GEORGE DEGRAZIA[3]

Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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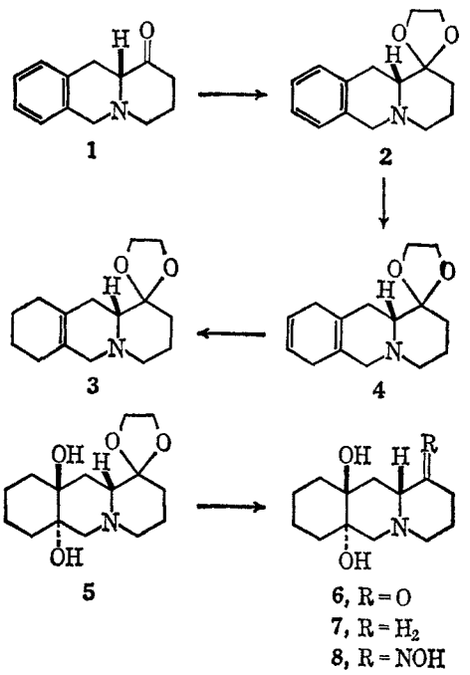
The ethylene ketal (2) derived from 3,4,11,11a-tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one (1) was reduced by the Birch procedure to the diene 4. Catalytic hydrogenation yielded 3, and hydroxylation with performic acid gave the diol 5. Ketal hydrolysis afforded 6, and Wolff–Kishner reduction led to 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).

(2) This investigation was supported, in part, by Public Health Service Grant No. HE-02275 from the National Heart Institute.

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

(4) S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

(5) G. A. Swan and G. R. Clemo, *J. Chem. Soc.*, 617 (1946).

(6) S. Archer, *J. Org. Chem.*, **16**, 430 (1951).

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

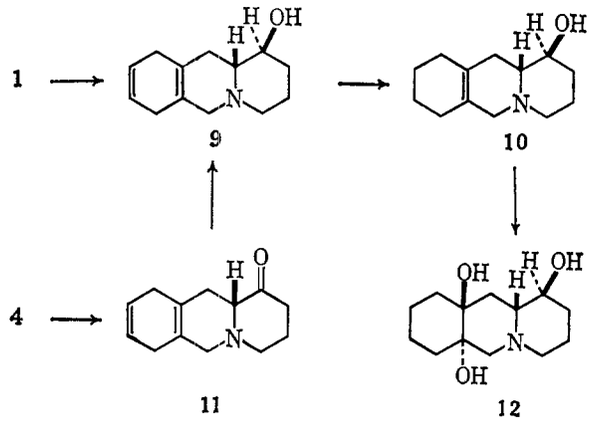
(8) E. J. Corey and G. A. Gregoriou, *J. Am. Chem. Soc.*, **81**, 3124 (1959).

(9) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953).

decahydro-2H-benzo[b]quinolizine-6a,10a-diol-1(6H)-one ethylene ketal (**5**). The infrared spectrum shows free hydroxyl stretching (2.75 μ) as well as hydrogen-bonded hydroxyl absorption (2.85–2.95 μ). The 6a,-10a-diol was shown to have the *trans*-diaxial configuration by interrelation with the diol **7**, described earlier.[4] Ketal hydrolysis of **5** was effected with hydrochloric acid at steam-bath temperature, whereby 3,4,6a,-7,8,9,10,10a,11,11a-decahydro-2H-benzo[b]quinolizine-6a,10a-diol-1(6H)-one (**6**) was obtained. Wolff–Kishner reduction of **6** gave 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-2H-benzo[b]quinolizine-6a,10a-diol (**7**).[4]

Lithium and alcohol in ammonia reduction[10] of **1** yielded 1,3,4,6,7,10,11,11a-octahydro-2H-benzo[b]quinolizin-1-ol (**9**) (see Scheme II). Alternatively, **9**

SCHEME II



could be prepared by hydrolysis of **4** with hydrochloric acid to 3,4,7,10,11,11a-hexahydro-2H-benzo-[b]quinolizin-1(6H)-one (**11**), followed by lithium aluminum hydride reduction of **11**. It has been generally accepted that, with few exceptions,[11] alkali metal–alcohol reduction of cyclic ketones gives rise almost exclusively to the alcohol containing the thermodynamically more stable equatorial hydroxyl group.[12] Furthermore, it has been shown[13,14] that lithium aluminum hydride reduction of 1-ketoquinolizidine (**14**) yields a mixture of epimers (**13** and **15**) in which the equatorial epimer (**13**, *trans*-1,10-hydrogen configuration) predominates (see Scheme III). By analogy, β (equatorial) configuration is assigned to the hydroxyl group of **9**. The latter assignment is supported by the fact that the infrared spectrum of **9** shows an unassociated hydroxyl band at 2.77 μ.[14] In addition, the infrared spectrum of **9** shows bands for *trans*-quinolizidine (3.60, 3.71 μ) and unconjugated homoannular diene (5.82, 6.02 μ). Catalytic hydrogenation of **9** with platinum afforded 1,3,4,6,7,8,9,10,11,11a-decahydro-2H-benzo[b]quinolizin-1-ol (**10**), and hydroxylation of **10** with performic acid gave 1,3,4,6,6a,7,8,9,-

(10) W. S. Johnson, H. C. Dehm, and L. J. Chinn, *J. Org. Chem.*, **19**, 670 (1954); W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

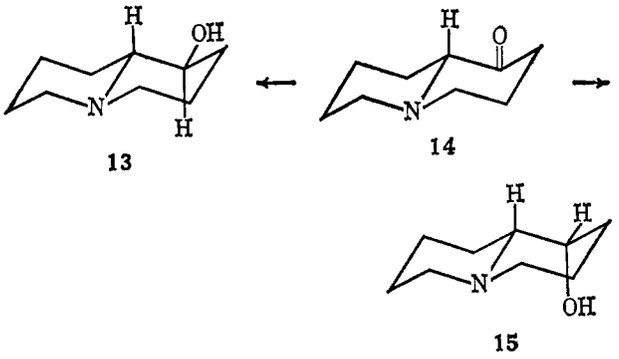
(11) *E.g.*, J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962).

(12) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(13) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955); N. J. Leonard and R. R. Sauers, *ibid.*, **79**, 6210 (1957); G. A. Swan, *J. Chem. Soc.*, 2051 (1958).

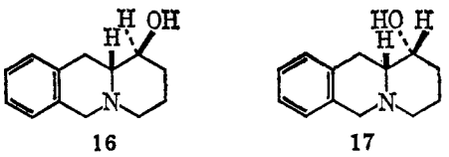
(14) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964); C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *ibid.*, **29**, 2252 (1964).

SCHEME III



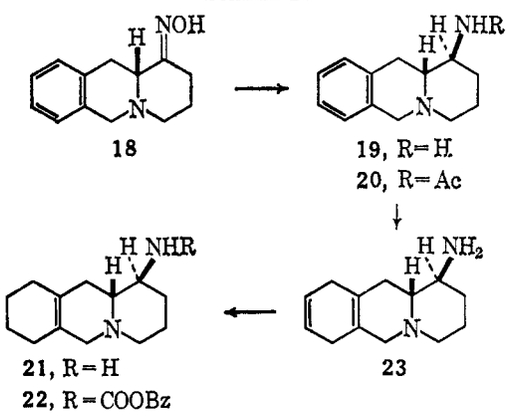
10,10a,11,11a-dodecahydro-2H-benzo[b]quinolizine-1,-6a,10-triol (**12**).

Reduction of **1** with lithium aluminum hydride afforded epimer A of 1,3,4,6,11,11a-hexahydro-2H-benzo[b]quinolizin-1-ol, whereas catalytic hydrogenation gave epimer B. Assignment of β (equatorial) configuration to the hydroxyl group of epimer A (**16**) is based on its synthesis by lithium aluminum hydride reduction and on the observation that its infrared spectrum shows an unassociated hydroxyl band at 2.75 μ.[14] The assignment is supported by the observation that epimer B (**17**) consumed chromic acid approximately twice as fast as epimer A (**16**).[15]



The general synthetic approach has been extended to the preparation of derivatives which possess an amino function at C-1. Reduction of 3,4,11,11a-tetrahydro-2H-benzo[b]quinolizin-1(6H)-one oxime (**18**) with lithium aluminum hydride in tetrahydrofuran gave 1,3,4,6,11,11a-hexahydro-1-amino-2H-benzo[b]-quinolizine (**19**) (see Scheme IV). The amine was

SCHEME IV



characterized as its acetamide derivative (**20**). The infrared spectra of **19** and **20** show characteristic bands for *trans*-quinolizidine. A previous investigation[16] has shown that lithium aluminum hydride reduction

(15) F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949); J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

(16) D. R. Smith, M. Maienthal, and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

of the oxime of 2-methylcyclohexanone yields *trans*-2-methylcyclohexylamine as the principal product. Furthermore, earlier investigations have demonstrated that such reductions generally afford equatorial amines.[12,17] By analogy the β (equatorial) configuration is suggested for primary amino function of **19**. Birch reduction of **19** gave a viscous oil with spectroscopic properties corresponding to the diene **23**. Catalytic hydrogenation led to consumption of 1 mole equiv of hydrogen and conversion to **21**, characterized as the crystalline carbobenzoxy derivative **22**. Oximation of **6** gave a crystalline derivative, **8**. Initial attempts to reduce **8** with lithium aluminum hydride led to intractable mixtures. Further studies of the potential usefulness of **22** and **8** in the synthesis of derivatives of 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-1-amino-2H-benzo[*b*]quinolizine are in progress.

Experimental Section[18]

3,4,11,11a-Tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one (1).—The α-amino ketone was prepared by procedures described previously[5,6] and was obtained as red-orange crystals (55%): mp 97–100° (lit.[5,6] mp 92–96°); λ_{max} 3.57 (*trans*-quinolizidine), 5.78 μ (ketone). The nmr spectrum shows four aromatic protons at τ 2.85.

3,4,11,11a-Tetrahydro-2H-benzo[*b*]quinolizin-1(6H)-one Ethylene Ketal (2).—In a 500-ml round-bottom flask, equipped with a Dean–Stark apparatus and water condenser with a drying tube, were placed **1** (6.0 g, 0.03 mole equiv, mp 97–100°) in anhydrous benzene (50 ml), ethylene glycol (200 ml), and *p*-toluenesulfonic acid (6.88 g, 0.04 mole equiv). The mixture was shaken thoroughly and additional benzene (150 ml) was added. The mixture was refluxed gently for 168 hr. The mixture was cooled, diluted with water (500 ml), neutralized with 20% sodium bicarbonate solution, and made distinctly basic with 20% potassium hydroxide solution. The benzene layer was separated from the aqueous layer, which was extracted four times with 100-ml portions of benzene. The benzene extracts were combined and washed with salt solution, dried over sodium sulfate, and evaporated under reduced pressure yielding a dark brown oil. After rubbing the sides of the flask, a semisolid formed. Water (25 ml) was added to the solid and the mixture was cooled. The pale brown solid was filtered, washed with water, and dried. The product was recrystallized from aqueous acetone, yielding white flaky crystals (5.6 g, 76%): mp 44–46°; λ_{max} 3.61 (*trans*-quinolizidine), 6.27, 6.67, 9.2–9.6 μ. The nmr spectrum shows four aromatic protons at τ 2.97.

The **methiodide of 2** was obtained as white needles, mp 260–263°. Recrystallization from ethanol–ether gave an analytical sample, mp 262–263° dec.

Anal. Calcd for $C_{16}H_{22}INO_2$: C, 49.62; H, 5.73; I, 32.77; N, 3.62. Found: C, 49.56; H, 5.87; I, 32.90; N, 3.70.

The nmr spectrum (formamide solution, tetramethylsilane as external standard) shows a singlet at τ 7.18 corresponding to the N-methylquinolizidinium cation.

3,4,7,10,11,11a-Hexahydro-2H-benzo[*b*]quinolizin-1(6H)-one Ethylene Ketal (4).—In a three-necked 500-ml flask was placed liquid ammonia (200 ml), and **2** (2.0 g, 0.0082 mole, mp 44–46°) dissolved in ether (20 ml) and lithium wire (5.0 g, 0.72 mole) were added in succession. Ethanol was added until the blue color disappeared. The excess ammonia was allowed to evaporate spontaneously overnight. Work-up in the usual manner[4] yielded a brown solid which was crystallized from acetone–Skellysolve B. Tan crystals (1.82 g, 90%), mp 85–86°, were obtained: λ_{max} 3.62, 3.71, 5.84, 6.03, 9.29–9.6 μ; λ_{max}^{EtOH} 267 mμ (ϵ 120). The nmr spectrum shows signals for vinylic protons at τ 4.30.

The **methiodide of 4** crystallized from ethanol–ether as colorless needles, mp 278–279°.

Anal. Calcd for $C_{16}H_{24}INO_2$: C, 49.37; H, 6.22; I, 32.60; N, 3.60. Found: C, 49.22; H, 6.29; I, 32.57; N, 3.64.

The nmr spectrum (formamide solution, tetramethylsilane as external standard) shows a singlet at τ 7.17 corresponding to the N-methylquinolizidinium cation.

3,4,7,8,9,10,11,11a-Octahydro-2H-benzo[*b*]quinolizin-1(6H)-one Ethylene Ketal (3).—In a hydrogenation vessel was placed a solution of **4** (2.0 g, mp 85–86°) in ethanol (50 ml). The mixture was reduced with platinum oxide (0.5 g) at room temperature and atmospheric pressure. One mole equivalent of hydrogen was absorbed rapidly (1 hr). The catalyst was filtered and the filtrate was evaporated to yield a viscous colorless oil (1.74 g) which turned brown after exposure to the air. The oil was kept refrigerated. Attempts to crystallize the oil from a small volume of isopropyl ether yielded white crystals which melted at 38–41°. In subsequent reactions the crude oil was used: λ_{max} 3.61, 3.71, 9.2–9.6 μ.

The **methiodide of 3** crystallized from ethanol–ether as colorless needles, mp 124–125°.

Anal. Calcd for $C_{16}H_{26}INO_2$: C, 49.11; H, 6.70; I, 32.43; N, 3.58. Found: C, 48.88; H, 6.71; I, 32.37; N, 3.67.

The nmr spectrum (formamide solution, tetramethylsilane as external standard) shows a singlet at τ 7.21 corresponding to the N-methylquinolizidinium cation.

3,4,6a,7,8,9,10,10a,11,11a-Decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol-1(6H)-one Ethylene Ketal (5).—A solution of **3** (90 mg, 0.0036 mole) in 88% formic acid (1.3 ml) was treated with 30% hydrogen peroxide (0.15 ml, sp gr 1.11) dropwise, and the mixture was stirred at 40° for 3 hr. After cooling, the solution was treated cautiously with 20% potassium hydroxide solution to distinct basicity, whereupon a turbid solution formed. Ethanol was added dropwise until the cloudiness disappeared. The solution was gently boiled for 15–30 min, cooled, and extracted four times with 25-ml portions of chloroform. The chloroform extracts were dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude product was crystallized twice from acetone–Skellysolve B to yield colorless needles (40 mg, 39%): mp 207–208°; λ_{max} 2.75 (nonbonded hydroxyl), 2.85–2.95 (bonded hydroxyl), 3.53, 3.60 (*trans*-quinolizidine), 9.2–9.5 μ.

Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.41; H, 9.02; N, 4.98.

3,4,6a,7,8,9,10,10a,11,11a-Decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol-1(6H)-one (6).—A solution of **5** (50 mg, mp 207–208°) in 6 *N* hydrochloric acid (2 ml) was heated on the steam bath for 2 hr. The mixture was cooled in an ice bath and carefully made basic with 8 *N* ammonium hydroxide solution. The aqueous solution was extracted four times with 25-ml portions of benzene which were dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a colorless residue. Two recrystallizations from acetone–Skellysolve B yielded colorless needles (31 mg, 72%): mp 151–152°; λ_{max} 2.75 (nonbonded hydroxyl), 2.85 (bonded hydroxyl), 3.47, 3.55 (*trans*-quinolizidine), 5.80 μ (ketone).

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.26; H, 8.91; N, 5.79.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,10a-diol (7).—In a 10-ml round-bottom flask provided with a water condenser were placed **6** (30 mg, mp 151–152°), triethylene glycol (1.0 ml), and 97% hydrazine (0.1 ml), and the mixture was warmed at 125° in an oil bath for 2 hr. Anhydrous potassium hydroxide (0.1 g) was added and the mixture was heated to 180–185° for 45 min. The mixture was cooled and ice water (10 ml) was added. The solution was extracted three times with 20-ml portions of chloroform which were dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The oily residue crystallized upon treatment with Skellysolve B. The crystalline material was filtered, washed with water, and dried. Recrystallization from acetone–Skellysolve B yielded transparent crystals (15 mg, 55%): mp 116.5–117.5°; λ_{max} 2.75 (nonbonded hydroxyl), 2.87 (bonded hydroxyl), 3.48 and 3.55 μ (*trans*-quinolizidine). The mixture melting point was not depressed upon admixture with an authentic sample.[4]

1,3,4,6,7,10,11,11a-Octahydro-2H-benzo[*b*]quinolizin-1-ol (9).—In a three-necked 500-ml flask provided with a mechanical stirrer and a Dry Ice condenser capped with a soda-lime drying tube, a mixture of liquid ammonia (200 ml) and ether (15 ml) was stirred for 10 min. A solution of **1** (0.4 g, 0.002 mole, mp 97–100°) in ether (15 ml) was added to the stirred solution. Lithium wire (0.84 g, 0.092 g-atom) was added rapidly to the solution and the solution was stirred for 0.5 hr. Ethanol was added slowly over a period of 30 min until the dark blue solution gradually be-

(17) J. A. Mills, *J. Chem. Soc.*, 260 (1953).

(18) General experimental procedures are given in ref 4.

came colorless. After evaporating the ammonia, water was added to the brown cake which remained. The aqueous layer was extracted four times with 25-ml portions of chloroform, dried over sodium sulfate, and evaporated to dryness, yielding a dark brown residue. The crude product was recrystallized repeatedly from acetone–Skellysolve B to yield colorless transparent crystals (120 mg, 29%): mp 143–144°; λ_{max} 2.77 (nonbonded hydroxyl), 3.60, 3.71 (*trans*-quinolizidine), 5.82, 6.02 μ.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.22; H, 9.60; N, 6.88.

1,3,4,6,7,8,9,10,11,11a-Decahydro-2H-benzo[b]quinolizin-1-ol (10).—A solution of **9** (0.2 g, mp 143–144°) in ethanol (25 ml) was hydrogenated at atmospheric pressure and room temperature with platinum oxide (0.2 g). One mole equivalent of hydrogen was absorbed. After filtering the catalyst, the solvent was evaporated to dryness, yielding a colorless solid, which was recrystallized twice from acetone–Skellysolve B to yield colorless crystals (0.122 g, 60%): mp 137–138°; λ_{max} 2.77 (nonbonded hydroxyl), 3.60, 3.71 μ.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.13; H, 10.11; N, 7.01.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[b]quinolizine-1,6a,10a-triol (17).—A solution of **10** (30 mg, 0.00014 mole, mp 137–138°) in 88% formic acid (1.0 ml) was treated with 30% hydrogen peroxide (0.10 ml, sp gr 1.11) dropwise, and the mixture was stirred for 3 hr at 40°. After cooling, 20% potassium hydroxide solution was added carefully to pH 11, whereupon a milky solution formed. Ethanol was added to obtain a clear solution and the solution was boiled gently for 15–30 min. After cooling, the aqueous solution was extracted four times with 25-ml portions of chloroform, which were dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude solid was recrystallized twice from acetone–Skellysolve B to yield colorless, transparent plates (10 mg, 28%), mp 172–173°. The infrared spectrum (mineral oil mull) shows a shoulder at 2.83 (intramolecularly bonded hydroxyl), an intense peak at 2.98 (intermolecularly bonded hydroxyl), and a *trans*-quinolizidine peak at 3.58 μ.

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.84; H, 9.88; N, 6.09.

3,4,7,10,11,11a-Hexahydro-2H-benzo[b]quinolizin-1(6H)-one (11).—A solution of **4** (0.1 g, mp 85–86°) in 6 *N* hydrochloric acid (4.0 ml) was warmed on the steam bath for 2 hr, cooled in an ice bath, and made basic (pH 9) with 8 *N* ammonium hydroxide solution. Yellow crystals precipitated from solution, were filtered, washed with water, and dried. Recrystallization from aqueous ethanol yielded bright yellow clusters (54 mg, 67%, mp 94–95°): λ_{max} 3.57, 3.65, 5.82, 5.95 μ.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.97; H, 8.66; N, 6.86.

Lithium Aluminum Hydride Reduction of 11.—In a three-necked 100-ml round-bottom flask equipped with a mechanical stirrer, water condenser with drying tube, and equilibrating funnel were placed lithium aluminum hydride (0.3 g) and anhydrous ether (10 ml). To the stirred suspension was added **11** (0.3 g, mp 94–95°) in ether (25 ml), over a period of 15 min. The mixture was stirred at room temperature for 15 hr. Water was added cautiously to decompose the excess lithium aluminum hydride. Potassium hydroxide (10 *N*, 20 ml) was added, and the mixture was refluxed for 1 hr. After cooling the ether layer was separated and the aqueous layer was extracted three times with chloroform (25-ml portions). The extracts were combined, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized twice from acetone–Skellysolve B to yield colorless prisms (0.132 g, 43%), mp 143–144°. The mixture melting point was not depressed upon admixture with alcohol **9** obtained by lithium–ammonia reduction of **1**. The infrared spectra of the respective samples were found to be superimposable.

1,3,4,6,11,11a-Hexahydro-2H-benzo[b]quinolizin-1-ol (Epimer A, 16).—In a three-necked 100-ml round-bottom flask equipped with a mechanical stirrer, water condenser with drying tube, and equilibrating funnel were placed anhydrous ether (25 ml) and lithium aluminum hydride (0.5 g). To the stirred suspension was added **1** (0.7 g, mp 97–100°) in ether (20 ml) over a period of 15 min. The mixture was stirred at room temperature for 15 hr. Water was added carefully to decompose the excess lithium aluminum hydride, followed by 10 *N* potassium hydroxide (25 ml). The mixture was refluxed for 1 hr and cooled, and the ether layer was separated. The aqueous layer was extracted with three 25-ml portions of chloroform. The combined extracts were dried over sodium sulfate and evaporated to dryness under reduced pressure. The crude residue (mp 145–151°) was recrystallized from methanol–ether to yield colorless crystals (0.48 g, 70%), mp 152–153°. The infrared spectrum shows a sharp hydroxyl peak at 2.75 (nonbonded), a broad peak at 2.88–2.95 (hydrogen-bonded hydroxyl), *trans*-quinolizidine peaks at 3.55, 3.61, and 3.71, and aromatic absorption peaks at 6.30 and 6.68 μ.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.36; H, 8.65; N, 6.87.

The **acetate ester of 16** was prepared by treatment of **16** (0.1 g, mp 152–153°) in pyridine (1.0 ml) with excess acetic anhydride (0.5 ml) at room temperature overnight. Methanol was added to decompose excess acetic anhydride, followed by water. While cooling, the solution was made basic with dilute ammonium hydroxide. The aqueous layer was extracted three times with 20-ml portions of ether, which were dried over sodium sulfate and evaporated to dryness. To remove pyridine completely, anhydrous benzene was added, and distillation to dryness was repeated several times. The residue was recrystallized from Skellysolve B to yield clusters of colorless crystals (35 mg, 29%), mp 88–89°. The infrared spectrum shows strong *trans*-quinolizidine absorption at 3.56 and 3.61, and carbonyl (ester) absorption at 5.77 μ.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 72.87; H, 8.04; N, 5.96.

1,3,4,6,11,11a-Hexahydro-2H-benzo[b]quinolizin-1-ol (Epimer B, 17).—A solution of **1** (1.5 g, mp 97–100°) in ethanol (30 ml) was hydrogenated with platinum oxide (1.0 g) at atmospheric pressure and room temperature. One mole equivalent of hydrogen was absorbed after 2.5 hr. The catalyst was filtered, and the colorless filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from benzene to yield soft, fluffy crystals (0.83 g), mp 162–183°. Recrystallization from methanol–ether yielded colorless needles (0.8 g, 57%), mp 187–188°. The infrared spectrum shows a medium peak at 2.80–2.90 (hydroxyl stretching), a broad peak at 3.10–3.15 (hydrogen-bonded hydroxyl), *trans*-quinolizidine peaks at 3.57 and 3.61, and aromatic peaks at 6.3 and 6.6 μ.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.85; H, 8.51; N, 6.93.

Chromic Acid Oxidation of Epimeric Alcohols 16 and 17.—The chromic acid oxidation of epimeric alcohols **16** and **17** was carried out by a modification of earlier procedures.[15] The consumption of oxidant by alcohol **17** leveled off in 30 min and that of **16** in 50 min.

3,4,11,11a-Tetrahydro-2H-benzo[b]quinolizin-1(6H)-one Oxime (18).—The oxime was prepared by the procedure of Swan and Clemo.[5] Recrystallization from methanol yielded colorless prisms (0.36 g, 70%), mp 206–207° (lit.[5] mp 207–208°).

1,3,4,6,11,11a-Hexahydro-1-amino-2H-benzo[b]quinolizine (19).—In a three-necked 250-ml round-bottom flask equipped with a mechanical stirrer, water condenser with a drying tube, and dropping funnel were placed anhydrous tetrahydrofuran (25 ml) and lithium aluminum hydride (4.95 g). To the stirred suspension was added **18** (10.62 g, mp 206–207°) in tetrahydrofuran (100 ml). The mixture was stirred and refluxed for 10 hr. After cooling, ethanol was added dropwise to decompose the excess lithium aluminum hydride. Potassium hydroxide (10 *N*, 25 ml) was added, and the solution was refluxed for 1 hr. The tetrahydrofuran was separated, and the aqueous layer was extracted with four 25-ml portions of ether. The combined extracts were dried over sodium sulfate and evaporated under reduced pressure to yield a brown oil. Vacuum distillation yielded a viscous yellow oil (6.3 g): bp 121–123° (0.25–0.3 mm); λ_{max} 2.95, 3.55, 3.61, 3.71, 6.3, 6.7 μ.

The **acetamide derivative 20** was prepared by treatment of **19** (0.23 g, bp 121–123° at 0.25–0.3 mm) with a 4–5-fold excess of acetic anhydride and work-up in the usual manner. Recrystallization from acetone–Skellysolve B gave colorless crystals (0.142 g, 53%): mp 195–196°; λ_{max} 2.90 (NH), 3.55, 3.60, 3.70, 6.00 (amide), 6.30, 6.45, 6.65 μ.

Anal. Calcd for $C_{15}H_{26}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.67; H, 8.19; N, 11.44.

1,3,4,6,7,10,11,11a-Octahydro-1-amino-2H-benzo[b]quinolizine (23).—A solution of **19** (0.25 g) in ether (20 ml) and liquid ammonia (150 ml) was treated with lithium wire (0.9 g) in the usual manner. Work-up yielded a viscous oil (0.22 g), which darkened on standing: λ_{max} 2.95, 3.55, 3.62, 5.98 μ. The crude product was used as such in subsequent hydrogenation reactions.

1,3,4,6,7,8,9,10,11,11a-Decahydro-1-amino-2H-benzo[*b*]quinolizine (21).—A solution of crude **23** (0.4 g) in ethanol (25 ml) was hydrogenated with platinum oxide (0.1 g) at atmospheric pressure and room temperature. One mole equivalent of hydrogen was absorbed. The catalyst was filtered and the solvent was distilled under reduced pressure to give a yellow oil (0.352 g) which could not be crystallized.

The product was characterized as the **carbobenzoxy derivative (22).** To a stirred and cooled solution of **21** (0.14 g) in anhydrous toluene (10 ml), 2 *N* sodium hydroxide (2.0 ml) was added. Carbobenzoxy chloride (0.12 g) was then added dropwise and the mixture was stirred in an ice bath for 1 hr. The toluene layer was separated and the aqueous layer extracted three times with 25-ml portions of chloroform. The extracts were combined, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The crude material was recrystallized twice from acetone–Skellysolve B to yield clusters of colorless crystals (78 mg, 33%), mp 167–169°. Recrystallization gave an analytical sample: mp 168–169°; λ_{max} 2.90 (NH), 3.55, 3.61, 5.78, 5.82, 6.51, 6.60 μ.

Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.90; H, 8.47; N, 7.88.

3,4,6a,7,8,9,10,10a,11,11a-Decahydro-2H-benzo[*b*]quinolizine-6a,10a-diol-1(6H)-one Oxime (8).—In a 50-ml round-bottom flask provided with a water condenser and drying tube were placed **6** (0.1 g, mp 151–152°), hydroxylamine hydrochloride (0.1 g), anhydrous sodium acetate (0.2 g), and anhydrous methanol (10 ml). The mixture was refluxed for 3 hr, cooled, and evaporated to dryness under reduced pressure. Water was added to the residue, followed by several drops of concentrated ammonium hydroxide to pH 9. Upon cooling, the oxime crystallized from solution, was filtered, washed with water, and dried. Several recrystallizations from methanol–ether yielded colorless transparent crystals (68 mg, 67%), mp 242–246° dec. Recrystallization from methanol–ether gave an analytical sample, mp 245–246° dec. The infrared spectrum (mineral oil mull) shows a sharp peak at 2.93 (OH stretching of oxime), a peak at 3.02 attributed to hydrogen-bonded hydroxyl, a *trans*-quinolizidine peak at 3.61, and a sharp peak at 6.09 μ (C=N).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.49; H, 8.59; N, 11.10.

The Synthesis of 1,2,4-Triazine

WILLIAM W. PAUDLER AND JERRY M. BARTON

Department of Chemistry, Ohio University, Athens, Ohio

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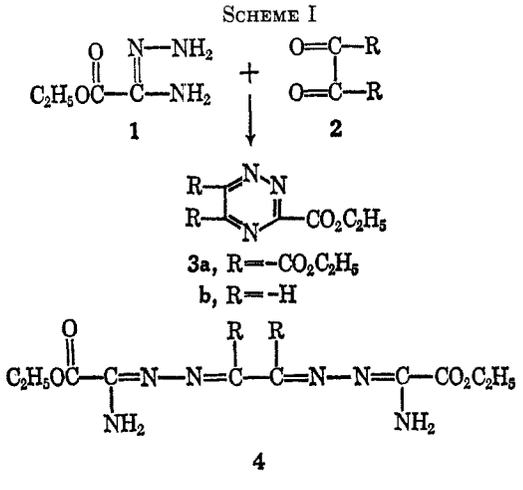
The condensation of glyoxal with ethyl oxalamidrazonate (1) yields ethyl 1,2,4-triazine-3-carboxylate (**3b**). This compound was converted to 1,2,4-triazine by saponification of **3b**, followed by decarboxylation. The nmr spectra of the various triazines are reported.

We have recently[1] been concerned with the study of various heteroaromatic systems, and now wish to report the synthesis of 1,2,4-triazine (*as*-triazine).

During the past few years several attempted syntheses of 1,2,4-triazine have been reported.[2-5] One of these attempts[4] involved the condensation of ethyl oxalamidrazonate (1) (Scheme I) with diethyl diketosuccinate (2, R = $-CO_2C_2H_5$) to yield the triester of 1,2,4-triazine-3,5,6-tricarboxylic acid (**3a**). Hydrolysis to the tricarboxylic acid followed by thermal decarboxylation yielded the anhydride of 1,2,4-triazine-5,6-dicarboxylic acid. Similarly, 5,6-diphenyl-1,2,4-triazine-3-carboxylic acid is readily decarboxylated to 5,6-diphenyl-1,2,4-triazine.[6] These reactions clearly demonstrate the lability of a 3-carboxylate grouping on 1,2,4-triazines.

SCHEME I



Previous attempts[4] to obtain 1,2,4-triazine-3-carboxylic acid by condensing ethyl oxalamidrazonate (1) with glyoxal (2, R = –H) did not afford the expected ester **3b**. The only materials obtained were compound **4** (R = –H) and a viscous, presumably polymeric, substance.

It is certainly reasonable to expect that the ester **3b** should be formed in this reaction, especially under the conditions of fairly high dilution as described by Ratz and Schroeder.[4] We consequently repeated this synthesis and examined the nmr spectrum of the crude reaction mixture resulting from the condensation of **1** with glyoxal. This spectrum revealed the presence of a material (A) which shows an AB pattern with H_A and H_B at τ 0.48 and 1.07, respectively. These chemical shifts are typical for H_6 and H_5 in other 1,2,4-triazines (Table I). It thus became clear that an attempt at isolating compound A from the crude reaction mixture would be eminently worthwhile.

Chromatography on neutral alumina afforded material which was considerably enriched in compound A. This substance was finally obtained pure by distillation, followed by recrystallization from a mixture of benzene and hexane. Elemental analysis and molecular weight determination agreed with the formula $C_6H_7N_3O_2$. The nmr spectrum indicates the presence of an ethyl group and of two strongly deshielded, coupled protons (Table I). These data are in agree-

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