2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.80 (t, 1, J = 4 Hz, proton on C_5), 4.40 (2 q superposed, 4, J = 7 Hz, $-OCH_2-$), 3.15 (m, 2, protons on C_8), 2.05–1.60 (m, 4, protons on C_6 and C_7), 1.35 (2 t superposed, 6, $-CH_3$). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 68.57; H, 7.75; N, 5.71. Found: C, 68.42; H, 7.80; N, 5.60.

Diethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1,5-dicarboxylate (10). It was prepared in 70% yield from 2,6-piperidinedicarboxylic acid as described for **9**. An analytical sample was obtained by TLC (CH_2Cl_2): NMR ($CDCl_3$) δ 6.30 (s, 1, proton on C_2), 4.80 (m, 1, proton on C_5), 4.25 (q, 4, J = 7 Hz, $-OCH_2-$), 3.40–1.60 [m, 9, $-CH_3$ and $-(CH_2)_3-$], 1.35 (t, 6, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.52; H, 7.52; N, 5.01. Found: C, 64.60; H, 7.75; N, 5.10.

5,6,7,8-Tetrahydroindolizine-1-carboxylic Acid (11). A solution of 386 mg (2 mmol) of **6** and 700 mg of KOH in 9 ml of methanol–water (2:1) was refluxed for 3 h, cooled, diluted with water (20 ml), and acidified to pH 1. The precipitate was filtered and dried giving 300 mg (90%) of **11** as colorless crystals. After recrystallization from ethanol it showed mp 151–153 °C dec; NMR ($CDCl_3$) δ 11.00 (broad s, 1, exchangeable with D_2O= –COOH), 6.68 (AB quartet, 2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.08 (broad t, 2, protons on C_5), 3.23 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). Anal. Calcd for $C_9H_{11}NO_2$: C, 66.45; H, 6.66; N, 8.48. Found: C, 66.20; H, 6.69; N, 8.45.

5,6,7,8-Tetrahydroindolizine (12). A thin-walled glass tube containing 820 mg (5 mmol) of **11** was introduced in a bath at 240 °C until gas evolution ceased (5 min), leaving a brown oil. Chromatography on 60 g of silica gel using benzene as eluent afforded 520 mg (88%) of **12** as a colorless oil, which was homogeneous on TLC (benzene–ethyl acetate, 1:1): NMR ($CDCl_3$) δ 6.50 (d, 1, proton on C_1), 6.10 (t, 1, proton on C_2), 5.80 (d, 1, proton on C_3), 3.95 (broad t, 2, protons on C_5), 2.80 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). This compound was not stable enough to be analyzed.

Octahydroindolizine (δ-Coniceine, 13). A solution of 242 mg (2 mmol) of **12** in 20 ml of ethanol was hydrogenated for 24 hr at 3 atm using 200 mg of 10% palladium on carbon. The catalyst was filtered off and the filtrate evaporated, giving 240 mg (98%) of pure **13**. The picrate, recrystallized from methanol, had mp 225–228 °C (lit.[4] 224–228 °C). Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.20; H, 5.60; N, 15.7. Found: C, 47.30; H, 5.50; N, 15.8.

Registry No.—**1**, 54966-20-0; **2**, 61009-74-3; **3**, 61047-23-2; **4**, 61009-75-4; **5**, 61009-76-5; **6**, 61009-77-6; **7**, 61009-78-7; **8**, 61009-79-8; **9**, 61009-80-1; **10**, 61009-81-2; **11**, 61009-82-3; **12**, 13618-88-7; **13**, 13618-93-4; **13** picrate, 5210-66-2; 2-piperidinecarboxylic acid, 535-75-1; ethyl propiolate, 623-47-2; 3-carboxy-1,2,3,4-tetrahydroisoquinoline, 35186-99-3; 2,6-piperidinedicarboxylic acid, 499-82-1.

References and Notes

(1) This investigation was supported by grants from the National Research Council (Argentina).
(2) (a) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms", Part One, A. Weissberger, Ed., Interscience, New York, N.Y., 1961, p 239. (b) K. Matsumoto, *Yuki Gosei Kagaku Kyokai Shi*, **32**, 731 (1974); *Chem. Abstr.*, **82**, 72665 (1975).
(3) D. Cartwright, R. A. Gardiner, and K. L. Rinehart, *J. Am. Chem. Soc.*, **92**, 7615 (1970).
(4) B. Luning and C. Lundin, *Acta Chem. Scand.*, **21**, 2136 (1967).
(5) R. Cahill and T. R. Crabb, *Org. Magn. Reson.*, **4**, 259 (1972).
(6) J. E. Saxton, *Alkaloids (London)*, **4**, 84 (1974).
(7) R. Huisgen, *Chem. Soc., Spec. Publ.*, **No. 21** (1970).
(8) M. T. Pizzorno and S. M. Albonico, *J. Org. Chem.*, **39**, 731 (1974).
(9) C. J. Pouchart and J. R. Campbell in "The Aldrich Library of NMR Spectra", Vol. VIII, Aldrich Chemical Co., Milwaukee, Wis., 1974.
(10) P. L. Julian, W. J. Karpel, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, **70**, 180 (1948).
(11) N. E. Andersson and T. O. Soine, *J. Am. Pharm. Assoc.*, **39**, 460 (1950).

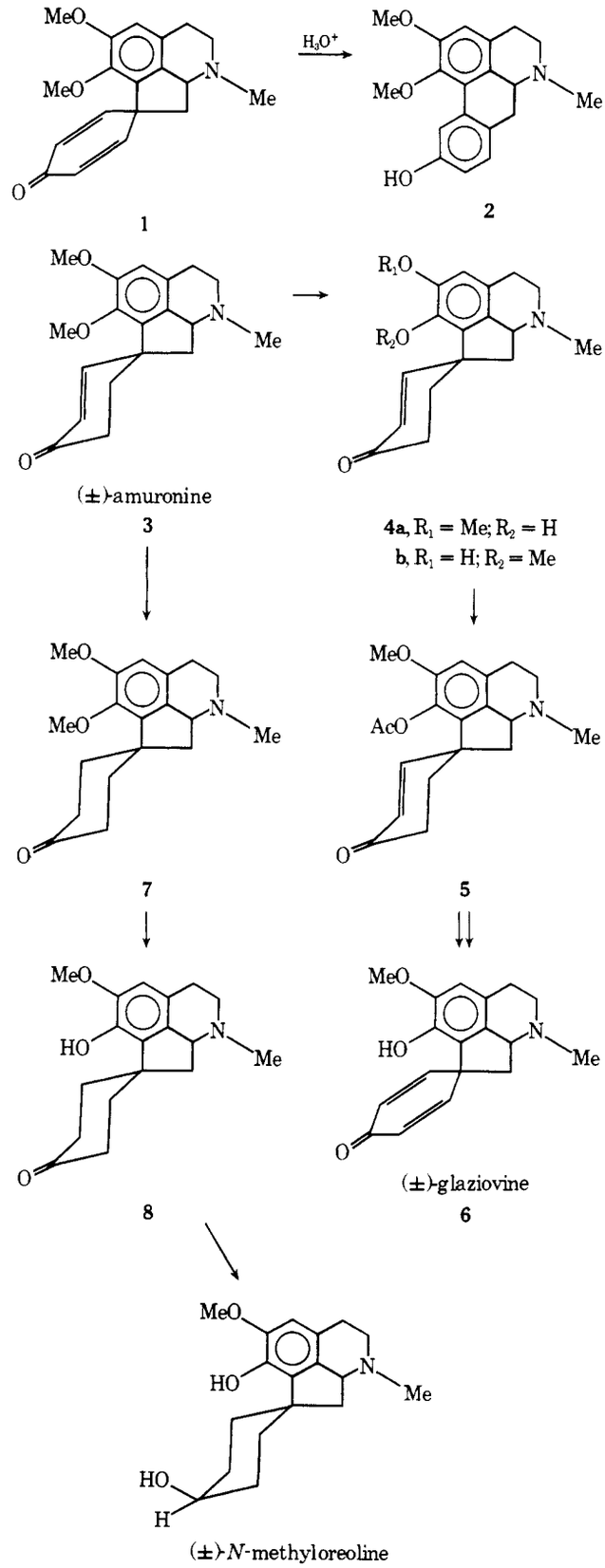
A Convenient Synthesis of (±)-Glaziovine and (±)-*N*-Methyloreoline

Jasjit S. Bindra* and Alex Grodski

Central Research, Pfizer Inc., Groton, Connecticut 06340

Received August 20, 1976

Preferential O-demethylation of isoquinolines with mineral acids under controlled conditions has provided access to a variety of phenolic isoquinoline alkaloids.[1] However, this process cannot be applied directly to proaporphine alkaloids containing a dienol or dienone system since these rearrange in the presence of strong acids to aporphines; e.g., pronuciferine (**1**) undergoes the dienone–phenol rearrangement in aqueous sulfuric acid to give 1,2-dimethoxy-10-hydroxyaporphine (**2**).[2] We have found that selective O-demethylation of amuronine (**3**) and tetrahydropronuciferine (**7**) proceeds smoothly in refluxing hydrochloric acid to furnish the corre-



sponding 1-hydroxy-2-methoxy proaporphines in good yield, providing a convenient synthesis of (±)-glaziovine (**6**)[3] and (±)-*N*-methyloreoline (**9**).[4] The preferential O-demethylation at C-1 is presumably due to a crowding of the C-1 methyl out of plane of the aromatic ring. Thus, when synthetic[5] (±)-amuronine (**3**) was refluxed with 20% aqueous hydrochloric acid it afforded (±)-11,12-dihydroglaziovine (**4a**) in 60% yield. The IR, NMR, and mass spectra were identical with those reported in the literature.[6] Evidence that the methoxyl group in **4a** was at C-2 rather than C-1 was forthcoming from a comparison of the methoxyl signal in the NMR spectrum of the corresponding 1-methoxy-2-hydroxy isomer linearisine (**4b**).[2,7] The structure of **4a** was unequivocally established by conversion of this compound to glaziovine. Acetylation of **4a** with acetic anhydride in the presence of *N,N*-dimethyl-4-pyridineamine[8] gave (±)-1-*O*-acetyl-11,12-dihydroglaziovine (**5**), which was converted to (±)-glaziovine by bromination and dehydrobromination essentially as described by Casagrande et al.[6]

(±)-8,9,11,12-Tetrahydropronuciferine (**7**), prepared from amuronine by catalytic hydrogenation,[5] was refluxed with 20% hydrochloric acid to give (±)-8,9,11,12-tetrahydroglaziovine (**8**), mp 97 °C (ether) (Casagrande et al.[6] report mp 160–162 °C), in 55% yield. The structure of **8**, based on analytical and spectral data, was confirmed by comparison with a sample prepared by catalytic hydrogenation of **4a**. Reduction of **8** with lithium triethylborohydride followed by chromatography gave predominantly the axial alcohol, (±)-*N*-methyloreoline (**9**), identical with a sample prepared by hydrogenation of glaziovine over platinum oxide.[6]

Experimental Section[9]

(±)-11,12-Dihydroglaziovine (4a). A solution of 1.4 g (4.47 mmol) of (±)-amuronine in 50 ml of 20% HCl was refluxed for a 24-h period under a N_2 atmosphere. The resulting dark solution was cooled and concentrated under vacuum to yield a dark residue which was dissolved in 25 ml of distilled water. The acidic solution was neutralized carefully with solid $NaHCO_3$ and extracted with chloroform (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.9 g of a foam which crystallized from ether to yield (±)-11,12-dihydroglaziovine, mp 199–201 °C after further crystallization from ether (lit.[6] mp 199–200 °C), yield 60% (0.81 g): NMR δ_{CDCl_3} (Me_4Si) 2.4 (s, 3, *N*-methyl), 3.85 (s, 3, methoxyl), 6.09 (d, J = 10 Hz, 1, C-9 olefinic proton), 6.6 (s, 1, aromatic), 6.8 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1681 cm^{-1} (C=O); UV λ_{max} (EtOH) 227 nm (log ϵ 4.66), 278 (3.45); MS *m/e* 299 (M^+, 100), 298 (87), 257 (19), 256 (99).

(±)-1-*O*-Acetyl-11,12-dihydroglaziovine (5). To a solution of 0.168 g (0.56 mmol) of **4a** in 10 ml of CH_2Cl_2 stirred at room temperature under N_2 was added 0.75 ml of triethylamine, 0.07 g of *N,N*-dimethyl-4-pyridineamine, and 0.05 ml of acetic anhydride. The reaction mixture was stirred for 30 min, diluted with 20 ml of CH_2Cl_2, and washed with water (3 × 5 ml) and saturated $NaHCO_3$ solution (1 × 5 ml). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to yield 0.234 g of a foam which was crystallized from ether to yield (±)-1-*O*-acetyl-11,12-dihydroglaziovine, 0.18 g (95% yield): mp 176–178 °C (lit.[6] mp 178 °C); NMR δ_{CDCl_3} (Me_4Si) 2.15 (s, 3, *O*-acetyl), 2.4 (s, 3, *N*-methyl), 3.75 (s, 3, methoxyl), 6.0 (d, J = 10 Hz, 1, C-8 olefinic proton), 6.65 (s, 1, aromatic), 6.7 (d, J = 10 Hz, 1, C-8 olefinic proton); IR (KBr) 1754, 1672 cm^{-1} (C=O); UV λ_{max} (EtOH) 223 nm (log ϵ 4.36), 283 (3.4); MS *m/e* 341 (M^+, 66), 340 (56), 298 (100), 256 (47).

(±)-8,9,11,12-Tetrahydropronuciferine (7):[5] mp 124–126 °C; NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.85 (s, 6, methoxyls), 6.65 (s, 1, aromatic); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.38); MS *m/e* 315 (M^+, 28), 314 (100), 272 (55).

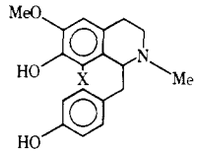
(±)-8,9,11,12-Tetrahydroglaziovine (8) was prepared as described for **4a**, in 55% yield: mp 97 °C (ether); NMR δ_{CDCl_3} (Me_4Si) 2.45 (s, 3, *N*-methyl), 3.9 (s, 3, methoxyl), 6.55 (s, 1, aromatic), 6.45–6.9 (bd, s, 1, phenolic OH); IR (KBr) 1718 cm^{-1} (C=O); UV λ_{max} (EtOH) 285 nm (log ϵ 3.42); MS *m/e* 301 (M^+, 34), 300 (100), 259 (13), 258 (75).

(±)-*N*-Methyloreoline (9). To a stirred solution of 0.098 g (0.325 mmol) of **8** in 10 ml of THF cooled to −70° under a nitrogen atmosphere was added dropwise 0.33 ml (0.33 mmol) of a 1 M solution of lithium triethylborohydride in THF. After addition, the reaction mixture was stirred for 0.5 h, warmed to room temperature, and acidified with acetic acid–water (6:1). The resulting solution was neutralized with saturated $NaHCO_3$ and extracted with chloroform (3 × 10 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to yield 0.083 g of a foam which was chromatographed on silica gel (eluted with chloroform) and crystallized from ether to give (±)-*N*-methyloreoline: mp 189–192 °C (lit.[6] mp 187–189 °C); NMR δ_{CDCl_3} (Me_4Si) 2.39 (s, 3, *N*-methyl), 3.98 (s, 3, methoxyl), 6.49 (s, 1, aromatic); UV λ_{max} (EtOH) 286 nm (log ϵ 3.37); MS *m/e* 303 (M^+, 40), 302 (100), 261 (16), 260 (85).

Registry No.—**3**, 19647-85-9; **4a**, 54274-43-0; **5**, 54169-67-4; **6**, 17127-48-9; **7**, 19647-93-9; **8**, 50300-14-6; **9**, 58166-04-4.

References and Notes

(1) Review: S. Teitel and A. Brossi, *Heterocycles*, **1**, 73 (1973).
(2) K. L. Stuart and M. P. Cava, *Chem. Rev.*, **68**, 321 (1968); for a recent review, see M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, N.Y., 1972, p 178.
(3) Glaziovine has been isolated from *Ocotea glaziovii* Mez, the Brazilian lauracea [B. Gilbert, M. E. A. Gilbert, M. DeOliveira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 694 (1964)], and no other abundant source of this pharmacologically interesting alkaloid is available. A biogenetic type synthesis, involving oxidation of *N*-methylcoclaurine (**10**) by ferricyanide, afforded a 1% yield of glaziovine [T. Kametani and H. Yagi, *J. Chem. Soc. C*, 2182 (1967)], while irradiation of 8-bromo-*N*-methylcoclaurine (**11**) in alkaline solution gave a 10% yield



10, X = H
11, X = Br

of the alkaloid [T. Kametani, S. Shibuya, T. Nakano, and F. Fukumoto, *J. Chem. Soc. C*, 3818 (1971)]. The latter synthesis has been reinvestigated and improved (26% yield) [C. Casagrande and L. Canonica, *J. Chem. Soc., Perkin Trans. 1*, 1647 (1975)]. Recently, Casagrande et al.[6] have reported extending Bernauer's synthesis[5] of amuronine to (±)-glaziovine.
(4) I. Mann and S. Pfeifer, *Pharmazie*, **22**, 124 (1967); S. Pfeifer and I. Mann, *ibid.*, **23**, 82 (1968); F. Šantavý and M. Maturová, *Planta Med.*, **16**, 311 (1967).
(5) K. Bernauer, *Helv. Chim. Acta*, **51**, 1119 (1968).
(6) C. Casagrande, L. Canonica, and G. Severini-Ricca, *J. Chem. Soc., Perkin Trans. 1*, 1652 (1975).
(7) L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *J. Chem. Soc. C*, 1676 (1966).
(8) W. Steglich and G. Hofle, *Angew. Chem., Int. Ed. Eng l.*, **8**, 981 (1969).
(9) Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. UV spectra were determined with a Cary 14 recording spectrometer.

An Improvement in the Doebner–Miller Synthesis of Quinaldines

Charles M. Leir

Riker Research Laboratories, 3M Company, St. Paul, Minnesota 55101

Received September 28, 1976

Since its discovery in 1881,[1] the Doebner–Miller reaction has found a great deal of synthetic utility for the preparation of substituted quinaldines (2-methylquinolines). Unlike the closely related Skraup synthesis of quinolines, the Doebner–Miller reaction is experimentally much simpler, and not nearly as hazardous to run.[2] However, the method does suffer from some major disadvantages. The yields reported are usually low owing to the many by-products formed in the reaction. Depending upon the particular conditions employed, a typical product mixture obtained from the reaction of an aniline with crotonaldehyde (or crotonaldehyde precursor) in strongly acidic solution consists of the desired quinaldine contami-