Cyclization of 3-(*o*-Hydroxyphenyl)hexahydroindole 1-Oxides and 4-(*o*-Hydroxyphenyl)pyrroline 1-Oxides. Preparation of Hydrobenzofuro[3,2-*c*]indoles and Hydrobenzofuro[2,3-*c*]pyrroles

S. KLUTCHKO,* A. C. SONNTAG, M. VON STRANDTMANN, AND J. SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950

Received April 19, 1973

A novel synthesis of the hydrobenzofuro[3,2-*c*]indole and hydrobenzofuro[2,3-*c*]pyrrole ring systems is described. Stereochemistry is presented.

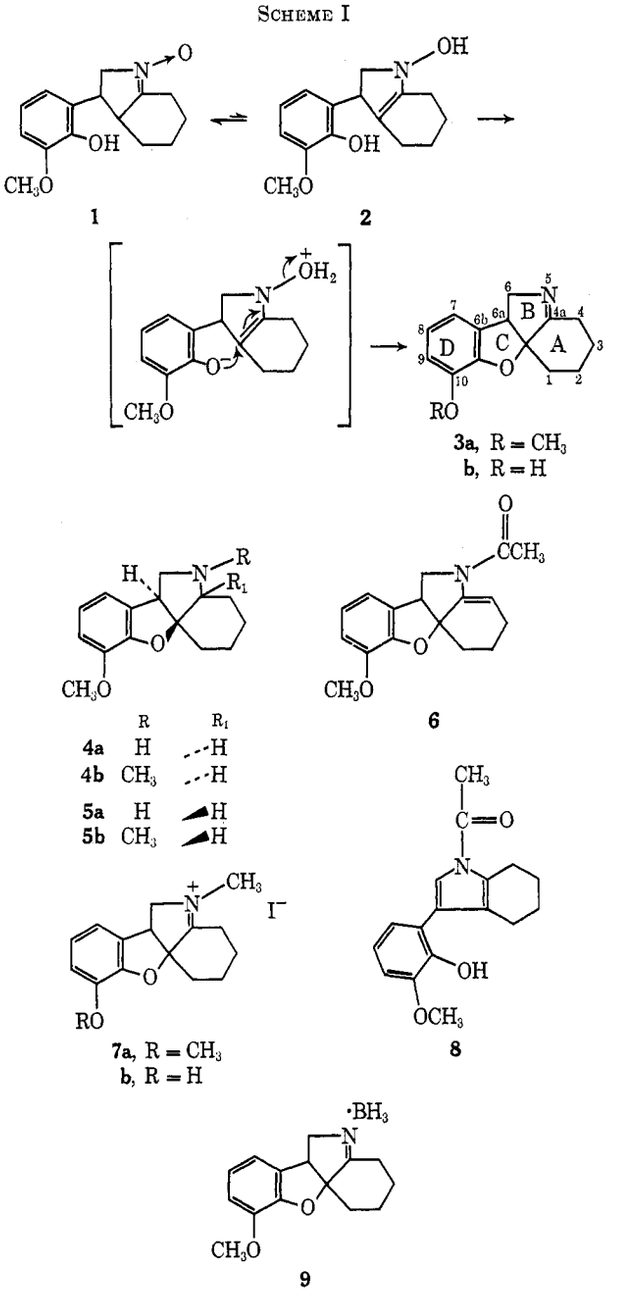
In the accompanying paper we discussed the preparation of various 3-(*o*-hydroxyphenyl)hexahydroindole 1-oxides and 4-(*o*-hydroxyphenyl)pyrroline 1-oxides by the reduction of 4-(nitromethyl)benzodihydropyran derivatives.[1] The present report describes the conversion of these phenolic nitrones to hydrobenzofuro[3,2-*c*]indoles (**3a** and **3b**) and hydrobenzofuro[2,3-*c*]pyrroles (**17**) *via* a novel thermal dehydrative cyclization.

Hydrobenzofuro[3,2-*c*]indoles.—Heating a xylene solution of the phenolic nitrone **1** at reflux for a brief period resulted in the loss of 1 mol of water and the formation of a nonphenolic compound in 62% yield. The chemical behavior and the spectral properties of the dehydration product were compatible with the hexahydrobenzofuro[3,2-*c*]indole structure **3a**. The ir indicated the presence of a C=N moiety [1660 (base), 1690 cm^{-1} (hydrochloride)] and the lack of an OH group. The nmr spectrum of **3a** as the hydrochloride showed a 1 H quartet at δ 4.9 (H-6), a 2 H multiplet in the δ 4–4.3 region (H-6, H-4_{eq}), a 1 H quartet at δ 3.52 (H-6a), and a 1 H multiplet at δ 2.8 (H-4_{ax}).[2]

To substantiate the structure of **3a** its chemical properties were studied and found to be typical of such a cyclic imine. Treatment with strong acid or base failed to effect any reaction. Catalytic hydrogenation in the presence of acetic acid yielded the expected perhydroindole derivative **4a**. Quaternization of **3a** with methyl iodide gave a quaternary imine **7a** [ir 1695 cm^{-1} (C=N)] which could be catalytically reduced to a tertiary amine **4b**. Demethylation of **3a** gave **3b**. Acetylation of the imine gave the expected ene–acetamide **6**, the ir and nmr spectra of which verified the $CH_3CONC{=}CHR$ grouping. Treatment of the enacetamide with polyphosphoric acid gave the *N*-acetylpyrrole **8** [ir 3330 (OH), 1695 cm^{-1} (–CONC=C–); nmr δ 7.28 (1 H singlet, H-2), 2.98 (4 H multiplet, H-4 and H-7 methylenes)]. The isolation of the pyrrole was important in ruling out any gross structural rearrangements in the formation of **3a**.

The formation of **3a** may be rationalized by consideration of the nitrone **1** in its tautomeric ene–hydroxylamine form **2**. A similar tautomerism between an indolenine 1-oxide and an *N*-hydroxyindole has been observed.[3] Protonation of the hydroxylamine function in **2** by the phenol is followed by an addition–elimination process to give **3a**.[4]

SCHEME I



Stereochemistry of Octahydrobenzofuro[3,2-*c*]indoles.—The stereochemistry of the octahydrobenzofuro[3,2-*c*]indole ring system concerns only the con-

(1) S. Klutchko, A. Sonntag, M. von Strandtmann, and J. Shavel, Jr., *J. Org. Chem.*, **38**, 3049 (1973).

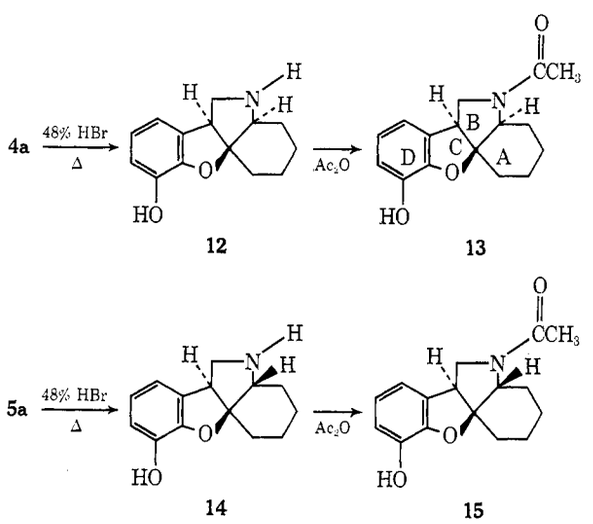
(2) The nmr of **3a** base showed no change in H-6a (δ 3.52) but the H-6 and H-4_{eq} moved upfield to form a 3 H multiplet in the δ 3.7–4.3 region.

(3) M. Mousseron-Canet and J. P. Boca, *Bull. Soc. Chim. Fr.*, 1296 (1967).

(4) Cyclization of the phenol in **1** to the 2 position of the hydroindole moiety was also considered a possibility if the so-called Behrend rearrangement of the keto nitrone to the aldo nitrone occurred. This rearrangement, however, generally involved strong base catalysis: Behrend, *Justus Liebigs Ann. Chem.*, **265**, 238 (1891); A. Cope and A. Haven, *J. Amer. Chem. Soc.*, **72**, 4896 (1950). Spectral data was inconsistent with any of the benzofuro[2,3-*b*]indole structures that might have arisen from this sort of ring closure.

figuration at the A/B perhydroindole ring juncture, since the 5,5-fused ring system of the furoindole requires a cis fusion. The single product of catalytic reduction of the imine **3a** (Scheme I) was designated as the A/B-trans isomer **4a** on the basis of the expected preferential attack from the opposite side of the ether linkage. The A/B-cis isomer **5a** was isolated when the hydrochloride of **3a** was reduced with borohydride. In the formation of **5a** some of the relatively stable borane complex **9** was isolated. This compound could be converted to **5a** by acid treatment.

To confirm the above configuration assignments, the nmr spectra of the *N*-acetyl derivatives (**13** and **15**) of the demethylation products (**12** and **14**) were compared.[5] The spectrum of **15** displayed proton signals



12 13 14 15

at δ 4.1, whereas that of the corresponding **13**, except for aromatic resonance, did not exhibit any protons below δ 3.72. Consideration of the structure and models of these compounds indicated that in the case of the A/B-cis isomer (**15**) the proton at C-4a was in the equatorial conformation and in the plane of the amide carbonyl. This proton was therefore expected to resonate at lower field[6] than the corresponding proton of an A/B-trans compound which was limited to an axial conformation and appeared in the spectrum of **13** at δ 2.65.

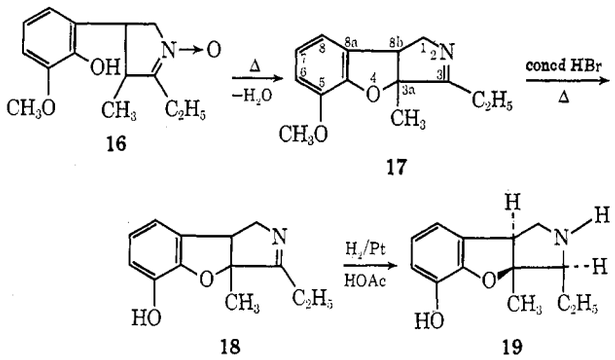
Hydrobenzofuro[2,3-*c*]pyrroles.—The hydrobenzofuropyrroles (**17, 18,** and **19**) were prepared in a fashion similar to that for the hydrobenzofuroindoles from the 4-(*o*-hydroxyphenyl)pyrroline 1-oxide derivative **16** (Scheme II).

Compound **19** was assigned the trans configuration at positions C-3 and C-3a by analogy to the octahydrobenzofuroindole stereochemistry described above.

(5) The N-acetylation and demethylation were carried out in order to shift the H-4a farther downfield and to remove the masking effect of the methoxy protons.

(6) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965), report a chemical-shift difference of 2.4 ppm for the geminal protons at C-6 of 4-oxoquinolizidine. The low-field resonance (4.63 ppm) of the equatorial proton at C-6 is attributed to its position in the plane of the amide carbonyl.

SCHEME II



16 17 18 19

Experimental Section[7]

1,2,3,4,6,6a-Hexahydro-10-methoxybenzofuro[3,2-*c*]indole Hydrochloride (3a).—A mixture of 60.0 g (0.23 mol) of **1** and 400 ml of xylene was heated with stirring to the boiling point. In a period of 0.5 hr, the theoretical amount of water (4.2 ml) was obtained. The cooled solution was diluted with 300 ml of ether, washed with 200 ml of 2 *M* KOH, dried over anhydrous potassium carbonate, filtered, and treated with HCl gas until complete precipitation of 48 g of the tacky salt. Recrystallization from 200 ml of absolute ethanol gave 40.9 g (62%) of **3a** hydrochloride, mp 224–226°, base mp 94–95°.

Anal. Calcd for $C_{15}H_{17}NO_2 \cdot HCl$: C, 64.40; H, 6.48; N, 5.01. Found: C, 64.31; H, 6.70; N, 5.17.

1,2,3,4,6,6a-Hexahydrobenzofuro[3,2-*c*]indol-10-ol (3b).—A solution of 111.9 g (0.4 mol) of **3a** hydrochloride in 700 ml of 48% HBr was heated at reflux for 20 min. The cooled solution was diluted with 1.5 l. of ice water and concentrated ammonium hydroxide was added until pH 8.5 to precipitate 82 g (90%) of pure **3b**, mp 203–205°.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.46; H, 6.72; N, 6.34.

1,2,3,4,4aα,5,6,6aα-Octahydro-10-methoxybenzofuro[3,2-*c*]-indole Hydrochloride (A/B-trans) (4a).—A mixture of 5.5 g (0.027 mol) of **3a** base, 250 ml of absolute ethanol, 20 ml of glacial acetic acid, and 200 mg of PtO_2 was hydrogenated in a Paar apparatus for 6 hr. After filtration and concentration to remove most of the alcohol, 300 ml of water and then 10 *M* KOH was added to pH 10. The separated viscous oil was extracted into 600 ml of ether, and the solution was dried over K_2CO_3, filtered, and treated with HCl gas to precipitate 6.0 g (94%) of the salt, mp 268–270°. Recrystallization from 2-propanol gave pure **4a** hydrochloride, mp 277–279°.

Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl$: C, 63.94; H, 7.15; Cl, 12.58. Found: C, 64.10; H, 7.24; Cl, 12.35.

1,2,3,4,4aα,5,6,6aα-Octahydro-10-methoxy-5-methylbenzofuro[3,2-*c*]indole Hydriodide (A/B-Trans) (4b).—A solution of 6.5 g (0.017 mol) of **7a** in 250 ml of absolute ethanol was hydrogenated in a Paar apparatus for 16 hr using a mixture of 150 mg of PtO_2 and 200 mg of 10% Pd/C as a catalyst. After filtration and concentration to *ca.* 50 ml volume, 200 ml of ether was added to precipitate 6.1 g (93%) of **4b** hydriodide, mp 207–209°. Recrystallization from ethanol–ether gave pure crystals, mp 208–210°.

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HI$: C, 49.62; H, 5.73; N, 3.62. Found: C, 49.86; H, 5.85; N, 3.47.

1,2,3,4,4aβ,5,6,6aα-Octahydro-10-methoxybenzofuro[3,2-*c*]-indole Hydrochloride (A/B-cis) (5a) and Borane Complex of 3a (9).—Potassium borohydride, 5.4 g (0.1 mol), was added to a stirred solution of 24.3 g (0.1 mol) of **3a**, 100 ml of 1 *N* hydrochloric acid, and 200 g of ice water (containing ice chips). The temperature gradually rose to 25° as a tacky material separated. (Note: This material was shown by tlc to be a mixture of the complex **9** and the product **5a**.) In one run, **9** was isolated and purified from ethyl acetate: mp 165–168°; ir ($CHCl_3$) 2400 (borane complex), 1675 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{20}BNO_2$: C, 70.06; H, 7.84; N, 5.45. Found: C, 69.70; H, 7.73; N, 5.14.

(7) Melting points were determined with the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. Infrared spectra were determined with a Baird Model 455 double beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

The above tacky mixture was heated on the steam bath with 100 ml of methanol and 110 ml of 1 *N* hydrochloric acid until all material dissolved. Ice water (300 ml) and then excess 10 *M* KOH were added and the separated oil was extracted into ether. Treatment with hydrogen chloride gave 16.6 g (59%) of the salt **5a**, mp 207–209°.

Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl$: C, 63.94; H, 7.15; Cl, 12.58. Found: C, 64.12; H, 7.25; Cl, 12.57.

A/B-cis Isomer (5b) (*via* Eschweiler–Clarke Methylation of 5a).—A solution of 4.08 g (0.0167 mol) of **5a** base, 3.24 g (0.04 mol) of 37% formaldehyde, and 40 ml of 98% formic acid was heated on the steam bath for 1 hr, cooled, diluted to 150 ml with ice water, and made strongly alkaline with 10 *M* KOH. The separated base was extracted into ether. The dried (K_2CO_3) solution was treated with HCl gas to precipitate a tacky salt. Dissolution in 2-propanol and addition of ether yielded 4.0 g (81%) of pure crystalline **5b** hydrochloride, mp 208–210°.

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.72; H, 7.43; N, 4.91.

5-Acetyl-1,2,3,5,6,6a-hexahydro-10-methoxybenzofuro[3,2-*c*]indole (6).—A quantity of 5.8 g (0.024 mol) of **3a** base was dissolved in 30 ml of acetic anhydride. After 5 min at reflux, 200 ml of water was added and the mixture was stirred for 0.5 hr to precipitate 6.1 g (90%) of **6**, mp 168–170°. Recrystallization from absolute ethanol gave pure crystals: mp 176–178°; ir (Nujol) 1682 (ene-amide C=O), 1650 cm^{-1} (vinyl C=C); nmr ($CDCl_3$) δ 6.72 (m, 3, aromatics), 5.4 (m, 1, H-4), 3.74 (s, 3, OCH_3), 3.3–3.75 (m, 3, H-6 and H-6a), 2.1 (s, 3, CH_3CO), and 1.3–2.4 (m, 6, methylene envelope).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.51; H, 6.85; N, 5.12.

1,2,3,4,6,6a-Hexahydro-10-methoxy-5-methylbenzofuro[3,2-*c*]indolinium Iodide (7a).—A solution of 4.0 g (0.017 mol) of **3a** base in 25 ml of methyl iodide was maintained at reflux for 1 hr. Most of the methyl iodide was distilled off and 50 ml of ether was added to give 6.0 g (95%) of yellow solid, mp 198–200°. Recrystallization from ethanol–ether gave pure **7a**: mp 200–202°; ir (Nujol) 1695 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{17}NO_2 \cdot CH_3I$: C, 49.88; H, 5.23; N 3.64. Found: C, 50.09; H, 5.30; N, 3.77.

1,2,3,4,6,6a-Hexahydro-10-hydroxy-5 methylbenzofuro[3,2-*c*]indolinium Iodide (7b).—Methyl iodide (25 ml) was added to a solution of 4.5 g (0.02 mol) of **3b** in 25 ml of dimethylformamide. After 1.5 hr reaction time, ether (200 ml) was added to precipitate an oil. The supernatant was decanted and the crude product was recrystallized from 50 ml of 2 propanol to give 5.3 g (73%) of **7b**: mp 200–202°; ir (Nujol) 3250 (OH) and 1685 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{15}NO_2 \cdot CH_3I$: C, 48.53; H, 4.89; H, 3.77. Found: C, 48.59; H, 4.86; N, 3.52.

1-Acetyl-4,5,6,7-tetrahydro-3-(2-hydroxy-3-methoxyphenyl)-indole (8).—A mixture of 7.3 g (0.0246 mol) of **6** and 60 g of polyphosphoric acid was heated with agitation at 50–60° for 15 min. The resulting reaction solution was poured into 500 ml of cold water to precipitate an orange solid. Recrystallization from 2 propanol gave 3.0 g (41%) of pure **8**, mp 121–123°.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.90. Found: C, 71.35; H, 6.90; N, 4.87.

1,2,3,4,4aα,5,6,6aα-Octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-Trans) (12) (*via* Demethylation of 4a).—A solution of 15.0 g (0.053 mol) of **4a** hydrochloride in 100 ml of 48% hydrobromic acid was maintained at reflux for 1 hr. On cooling 4.5 g (14%) of the HBr salt of **12** separated, mp 286–288°. Recrystallization from methanol–ether gave constant-melting hydrobromide, mp 292–294°. Treatment of an aqueous solution of the salt with ammonium hydroxide gave the pure base, mp 235–237°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.62; H, 7.42; N, 6.04.

Alternate Preparation of 12 (*via* Catalytic Reduction of 3b).—A solution of 46.0 g (0.3 mol) of **3b** in 150 ml of absolute ethanol and 100 ml of glacial acetic acid was hydrogenated at low pressure using a mixture of 1.0 g of PtO_2 and 1.0 g of 5% Pd/C. The catalyst was filtered, 1 l. of ice water was added to the filtrate, and concentrated ammonium hydroxide was added until complete precipitation of 40 g (87%) of tan solid, mp 220–225°. Recrystallization from absolute ethanol gave pure **12** base, mp 235–237°, hydrochloride mp 301–303°.

1,2,3,4,4aβ,5,6,6aα-Octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-cis) (14).—A solution of 10.5 g (0.037 mol) of **5a** hydrochloride in 40 ml of concentrated HBr was maintained at reflux for 1 hr and diluted with ice water to 200-ml volume. Concentrated ammonium hydroxide was added to precipitate 7.4 g (80%) of pure base **14**, mp 234–236°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.80; H, 7.40; N, 6.31.

5-Acetyl-1,2,3,4,4aα,5,6,6aα-octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-trans) (13).—A quantity of 7.2 g (0.031 mol) of **12** was dissolved in 50 ml of acetic anhydride with stirring. After *ca.* 15 min the separated product was filtered, stirred with water for 15 min, and filtered again to give 6.5 g (77%) of **13**, mp 221–224°. Recrystallization from 2-propanol gave **13**, mp 225–227°.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.23; H, 6.98; N, 5.24.

A/B-cis Isomer (15).—The 5-acetyl cis isomer **15** was prepared from **14** by the same procedure used to prepare **13**, mp 204–205°.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.54; H, 7.05; N, 5.33.

3-Ethyl-3a,8b-dihydro-5-methoxy-3a-methyl-1*H*-benzofuro-[2,3-*c*]pyrrole Hydrochloride (17).—A solution of 10.0 g (0.04 mol) of 2-ethyl-4-(2-hydroxy-3-methoxyphenyl)-3-methyl-1-pyrroline 1-oxide (**16**) in 150 ml of xylene was maintained at reflux under nitrogen for 45 min. The calculated amount of water was measured after 15 min. Work-up was similar to that for **3a**, giving 8.2 g (76.7%) of pure **17** hydrochloride, mp 193–195°.

Anal. Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.50; H, 6.81; N, 5.09.

3-Ethyl-3a,8b-dihydro-3a-methyl-1*H*-benzofuro[2,3-*c*]pyrrol-5-ol (18).—A solution of 5.0 g (0.019 mol) of **17** hydrochloride in 30 ml of 48% hydrobromic acid was maintained at reflux under nitrogen for 15 min. Ice water (50 ml) was added and the solution was basified with ammonium hydroxide to precipitate 3.9 g (96%) of **18**, mp 171–173°.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.15; H, 6.91; N, 6.25.

3-Ethyl-2,3,3a,8b-tetrahydro-3a-methyl-1*H*-benzofuro[2,3-*c*]-pyrrol-5-ol (19).—A solution of 2.0 g (0.009 mol) of **18** in 150 ml of absolute ethanol and 3 ml of glacial acetic acid was hydrogenated in a Paar apparatus with platinum oxide, giving 1.9 g (95%) of pure base, mp 239–241°.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.38; H, 7.73; N, 6.36.

Acknowledgment.—The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular, we wish to thank Dr. C. Greenough for the spectral data and Mrs. U. Zeek for analytical determinations. We also wish to thank the Chemical Development Department under the supervision of Dr. A. W. Ruddy for the large-scale preparation of intermediates.

Registry No.—**1**, 40682-18-6; **3a**, 40682-19-7; **3a** HCl, 36860-43-2; **3b**, 36860-37-4; **4a** HCl, 40682-22-2; **4b** HI, 40682-23-3; **5a**, 40682-24-4; **5a** HCl, 40682-25-5; **5b** HCl, 40682-26-6; **6**, 36860-39-6; **7a**, 36860-41-0; **7b**, 36860-36-3; **8**, 40682-30-2; **9**, 40682-31-3; **12**, 40682-32-4; **12** HBr, 40682-33-5; **12** HCl, 40682-34-6; **13**, 40682-35-7; **14**, 40682-36-8; **15**, 40682-37-9; **16**, 40682-38-0; **17** HCl, 40682-39-1; **18**, 40682-40-4; **19**, 40682-41-5.