Potential Causal Prophylactic Antimalarial Agents. Synthesis of Quinoxaline, Benzimidazole, and Alkoxybenzene Derivatives Containing a Novoldiamine Moiety

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Several quinoxaline, benzimidazole, and alkoxybenzene derivatives containing the novoldiamine function, either as a side chain or incorporated as a ring constituent, were synthesized as potential causal prophylactic antimalarial agents. 1-(5-Dimethylamino-2-pentyl)-5-methoxybenzimidazole (**2a**) was shown to have the desired prophylactic activity in the preliminary sporozoite-induced *Plasmodium gallinaceum* test.

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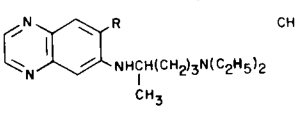
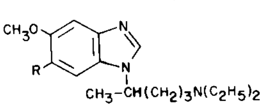
Several common structural features among different types of antimalarials have recently been postulated. For antimalarials acting mainly as blood schizontocides, two triangular features were noticed: One consists of a nitrogen atom, an oxygen atom, and the center of a six-membered planar (aromatic or heteroaromatic) ring. This feature is shared by quinine and related cinchona alkaloids, synthetic aminoalcohols, and a tetrahydrofuran derivative (1). The proposed triangular feature and its interatomic dimensions, which were substantiated by later studies (2-7), are interestingly similar to the reported structural features for α-adrenergic receptors among biologically active phenethylamines such as epinephrine and norepinephrine (8-10).

The other triangular feature for schizontocidal antimalarials consists of two nitrogen atoms and an electronegative atom (either an oxygen or a nitrogen atom). This feature is common in the alkaloid febrifugine and the synthetic 4-aminoquinolines (*e.g.*, chloroquine) and 9-aminoacridines (*e.g.*, quinacrine) (11).

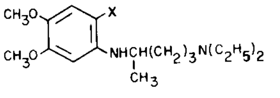
A structural feature, consisting of three electronegative atoms substituted around a benzene nucleus at positions 1, 2 and 4, has been observed among antimalarials acting mainly as causal prophylactic agents (12). Compounds such as 8-aminoquinolines, 6-aminoquinolines, 2-hydroxynaphthoquinones and 5-bromo-1,2-dimethoxy-4-[bis(diethylaminoethyl)amino]benzene (RC-12) belong to this class (13,14). This structural feature probably encompasses most antimalarial agents that participate in biological redox reactions *in vivo*. In order to further understand the scope and limitations of this feature, the following benzimidazole and quinoxaline derivatives, as well as RC-12 analogs containing the N',N'-diethyl-2,5-pentanediamine (novoldiamine) moiety (the side chain present in chloroquine, quinacrine, pamaquine and many other antimalarial agents) were synthesized. These compounds were so designed that each conforms to the 1,2,4-trisubstitution pattern but some may be less likely to undergo *in vivo* bioredox reactions.



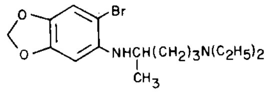
1a, R = H
b, R = OCH$_3$



2a, R = H
b, R = OCH$_3$



3a, X = H
b, X = Br



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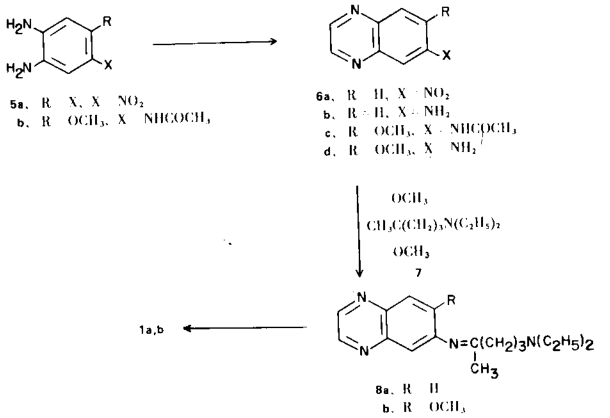
6-[(5-Diethylamino-2-pentyl)amino]quinoxaline (**1a**) was prepared as follows: Condensation of 4-nitro-*o*-phenylenediamine (**5a**) with glyoxal-sodium hydrosulfite adduct (15) yielded 6-nitroquinoxaline (16) (**6a**). Reduction of **6a** with stannous chloride gave the corresponding 6-amino derivative **6b**. The latter was condensed with 5-diethylamino-2,2-dimethoxypentane (13,18) (**7**) and the resulting anil **8a** was reduced with sodium borohydride to give the desired product **1a**.



5a, R = X, X = NO$_2$
b, R = OCH$_3$, X = NHCOCH$_3$

6a, R = H, X = NO$_2$
b, R = H, X = NH$_2$
c, R = OCH$_3$, X = NHCOCH$_3$
d, R = OCH$_3$, X = NH$_2$

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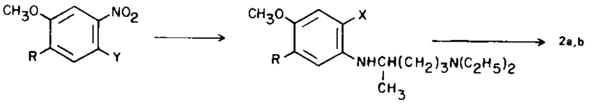
8a, R = H
b, R = OCH$_3$

The corresponding 7-methoxy compound **1b** was prepared by the following route. Catalytic hydrogenation of 4,5-dinitro-2-methoxyacetanilide (19) furnished the diamino compound **5b**. The latter, without purification, was immediately converted to the quinoxaline **6c** with glyoxal-sodium hydrosulfite. Compound **6c** was hydrolyzed with 5-*N* hydrochloric acid. The resulting aminoquinoxaline **6d** was condensed with **7** to give **8b**, which was reduced with sodium borohydride to yield **1b**.

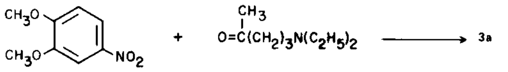
1-(5-Diethylamino-2-pentyl)-5-methoxybenzimidazole (**2a**) was prepared according to the method of Clemo and Swan (20) from 4-bromo-3-nitroanisole **9a** except that sodium bicarbonate rather than copper powder was used in the reaction. For the synthesis of the dimethoxy analog **2b**, 4-5-dinitroveratrole (**9b**) was used as the starting material. Treatment of **9b** with *N'*,*N'*-diethyl-2,5-pentanediamine under nitrogen gave 4-[(5-diethylamino-2-pentyl)-amino]-5-nitroveratrole (**10c**). Catalytic hydrogenation of the latter with platinum oxide gave the amino compound **10d**. Cyclization to the target compound **2b** was realized, albeit in low yield, by heating **10d** with formic acid at 165° in a closed vessel. Since a crystalline salt of **2b** could not be obtained in our hands, the free amine **2b** was purified by a short-path distillation.



9a, R = H, Y = Br
b, R = OCH_3, Y = NO_2

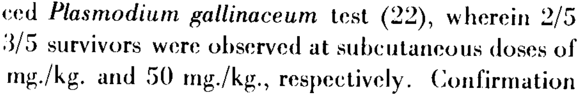
10a, R = H, X = NO_2
b, R = H, X = NH_2
c, R = OCH_3, X = NO_2
d, R = OCH_3, X = NH_2

4-[(5-Diethylamino-2-pentyl)amino]veratrole (**3a**) was prepared, in good yield, in one step by the platinum-catalyzed reductive alkylation reaction of 4-nitroveratrole (**11**) and 5-diethylaminopentan-2-one (**12**).



11 **12**

Catalytic hydrogenation of 4-bromo-5-nitroveratrol (21) (**13a**) followed by condensation of the resulting amino compound **13b** with 5-diethylamino-2,2-dimethoxypentane (7) gave the anil **14a**, which gave 4-bromo-5-[(5-diethylamino-2-pentyl)amino]veratrole (**3b**) upon reduction with sodium borohydride. In a similar manner, the methylenedioxy analog **4** was prepared from **13c** through the intermediates **13d** and **14b**.



13a, $R_1, R_2 = CH_3$; $X = NO_2$
b, $R_1, R_2 = CH_3$; $X = NH_2$
c, $R_1 + R_2 = CH_2$; $X = NO_2$
d, $R_1 + R_2 = CH_2$; $X = NH_2$

14a, $R_1, R_2 = CH_3$
b, $R_1 + R_2 = CH_2$

Available preliminary biological test data indicated that 1-(5-dimethylamino-2-pentyl)-5-methoxybenzimidazole (**2a**) possessed prophylactic activity in the sporozoite-induced *Plasmodium gallinaceum* test (22), wherein 2/5 and 3/5 survivors were observed at subcutaneous doses of 200 mg./kg. and 50 mg./kg., respectively. Confirmation tests have not yet been conducted. The corresponding dimethoxy analog **2b** had only 1/5 survivor at 400 mg./kg. and is considered inactive. Other compounds have not been evaluated in this prophylactic test system. In the blood-induced mouse tests against *P. berghei* (23), compounds **1b, 2b** and **3b** were inactive and compound **4** was toxic at 640 mg./kg. The biological testing work was conducted at Leo Rane Laboratories of the University of Miami under auspices of the U. S. Army Medical Research and Development Command Contract.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The nmr spectra were determined on a Varian HA-100 spectrophotometer. The mass spectral data were obtained with a Varian Mat CH-4B mass spectrometer. The infrared spectra were taken on a Perkin-Elmer Infracord and the untraviolet spectra were measured with a Beckman DK-2 spectrophotometer.

6-Nitroquinoxaline (**6a**).

Glyoxal-sodium hydrosulfite adduct (15) was prepared by mixing 150 ml. of 40% glyoxal (1.44 moles) and 218 g. (2.08 moles) of sodium hydrosulfite in 1l. of hot (60°) water and subsequent heating of the resulting solution at the same temperature for 30 minutes. This hot mixture, which contained the precipitated adduct, was added to a stirred suspension of 153 g. (1 mole) of 4-nitro-*o*-phenylenediamine (**5a**) and 2l. of hot (70°) water. The resulting mixture was heated at 70° until all solids dissolved (*ca.* 1 hour). After cooling to room temperature, 400 g. of sodium carbonate dihydrate was added with stirring. The precipitated product was collected by filtration and dried. It was then dissolved in 5.5l. of 95% ethanol and filtered while hot. The filtrate, on cooling, gave 62 g. (35% yield) of **6a**, m.p. 177-179° (lit. (16), m.p. 177°).

6-Aminoquinoxaline (**6b**).

This compound was prepared according to the method of Case and Brennan (17) from **6a** and stannous chloride in 41% yield, m.p. 152-155° (lit. (17), m.p. 157-158°).

5-Diethylamino-2,2-dimethoxypentane (**7**).

Although this compound was reported previously (13,18), a very high yield could be obtained by the following procedure: A mixture of 79 g. (0.5 mole) of freshly distilled 5-diethylaminopentan-2-one (**12**) in 400 ml. of methanol was saturated with dry hydrogen chloride until 18 g. of hydrogen chloride was absorbed. To it was added 63.5 g. (0.6 mole) of triethyl orthoformate and the mixture was refluxed for 30 minutes. After overnight standing, the reaction solution was poured into 1l. of saturated aqueous sodium carbonate solution and the mixture extracted with ether (3 x 400 ml.). The ether extract was dried (potassium carbonate), evaporated, and distilled to give 96.4 g. (98% yield) of **7** as a colorless liquid, b.p. 78-82°/3 mm (lit. (18), b.p. 106°/8 mm).

6-[(5-Diethylamino-2-pentyl)amino]quinoxaline (**1a**).

A mixture of 10.9 g. (0.075 mole) of **6b**, 20.8 g. (0.09 mole) of **7**, and 100 mg. of *p*-toluenesulfonic acid was stirred and heated at 160° for 3 hours. Methanol was removed by distillation during the reaction. The resulting mixture was diluted with 350 ml. of ether and washed successively with 5% sodium carbonate (50 ml.), water and saturated sodium chloride solution. After drying (potassium carbonate), the ether solution was evaporated to yield a dark red liquid **8a**. Its ir had a strong C=N absorption band at 1660 cm^{-1}. Without further purification, this liquid was dissolved in 270 ml. of absolute ethanol and treated, at 0°, with 7.5 g. of sodium borohydride in several portions. The resulting mixture was stirred at room temperature for 20 hours. It was then diluted with 500 ml. of water and extracted with ether (3 x 150 ml.). The ether extract was dried (potassium carbonate) and evaporated to give a viscous dark red liquid. Its ir spectrum had a strong NH absorption band at 3250 cm^{-1} and no C=N absorption was observed. The crude product was dissolved in 30 ml. of chloroform and column chromatographed twice on silica gel (Woelm, Act I), eluting with a 4:1 mixture of chloroform-methanol. The fraction containing the yellow colored eluant was collected and distilled by means of a Kügelrohr distillation apparatus at an oven temperature of 125 ± 3° (0.1 mm) to give 2.0 g. of analytically pure **1a**; nmr (deuteriochloroform): δ 8.52 and 8.36 (d, J = 2 cps, 2H, protons at C-2 and C-3) [assignment of the aromatic protons is based on a comparsion with 6-aminoquinoxaline (22)], 7.70 (d, $J_{7\text{-}8}$ = 9 cps, 1H, proton at C-8), 7.01 (q, $J_{7\text{-}8}$ = 9 cps, $J_{5\text{-}7}$ = 2.5 cps, 1H, C_7H), 6.83 (d, $J_{5\text{-}7}$ = 2.5 cps, 1H, C_5H), 3.55 (m, 1H methine H on the side chain), 2.56-2.22 (m, 6H, three CH_2), 1.70-1.40 (m, 4H, two CH_2 at the diethyl terminal), 1.22 (d, J = 6 cps, 3H, CH_3), 0.96 (t, J = 7 cps, 6H, two CH_3 at the diethyl terminal) and twin peaks at 5.05 and 4.98 (1H, NH).

Anal. Calcd. for $C_{17}H_{26}N_4$: C, 71.29; H, 9.15; N, 19.56. Found: C, 71.03; H, 9.09; N, 19.51.

6-Acetamido-7-methoxyquinoxaline (**6c**).

A mixture of 12.8 g. (0.05 mole) of 4,5-dinitro-2-methoxyacetanilide (19) and 1 g. of 10% palladium-on-carbon in 250 ml. of methanol was hydrogenated at 2.8 kg./cm^2 for 90 minutes. Catalyst was removed by filtration and the filtrate evaporated to give crude 4,5-diamino-2-methoxyacetanilide (**5b**) as an oil residue (which turned dark green in air). This was dissolved in 120 ml. of water and stirred with 14 g. of glyoxal-sodium hydrosulfite at 70° for 2 hours. The resulting yellow solid was collected by filtration to give 5.4 g. of **6c**. Addition of 20 g. of sodium carbonate to the filtrate precipitated another 4.4 g. of **6c**. The filtrate resulting from the second filtration was extracted with methylene chloride (4 x 50 ml.) to give an additional 0.4 g. of **6c**. The total yield of **6c** was therefore 10.4 g. (96%), m.p. 200°. Three recrystallizations from 2-propanol yielded an analytical sample, m.p. 200°; ir: 3300 and 1670 cm^{-1} (*N*-acetyl carbonyl).

Anal. Calcd. $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.59; H, 4.99; N, 19.18.

7-Amino-6-methoxyquinoxaline (**6d**).

A solution of 4.3 g. (0.02 mole) of **6c** in 21 ml. of 5 *N* hydrochloric acid was refluxed with stirring for 3 hours. Cooling of the reaction mixture in an ice water bath resulted in the precipitation of a dark brown solid. This was collected by filtration and washed with a small amount of 2-propanol to give 4.4 g. of a solid, which was stirred with 30 ml. of saturated sodium carbonate to yield 4.2 g. of crude **6d** as a yellow solid, m.p. 159-161°. Recrystallization from benzene gave 2.2 g. (63% yield) of **6d**, m.p. 162-164°; ir: 3400 and 3280 cm^{-1} (NH_2).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.49; H, 5.09; N, 24.05.

6-[(5-Diethylamino-2-pentyl)amino]quinoxaline (**1b**).

The intermediate anil **8b** was prepared from 6.6 g. of **6d**, 9.2 g. of **7** and 150 mg. of *p*-toluenesulfonic acid by essentially the same procedure as that for the preparation of **8a** and, in a similar manner to that for the preparation of **1a**, the anil **8b** was reduced with sodium borohydride in ethanol to give, after column and Kügelrohr (120-125°/0.3 mm) purification, 4.6 g. (39% yield) of **1b**. Its nmr spectrum was also in accord with the assigned structure.

Anal. Calcd. for $C_{18}H_{28}N_4O$: C, 68.32; H, 8.92; N, 17.71. Found: C, 68.27; H, 8.67; N, 17.56.

4-[(5-Diethylamino-2-pentyl)amino]-3-nitroanisole (10a).

A mixture of 3.5 g. (0.015 mole) of 4-bromo-3-nitroanisole (**9a**), 2.5 g. (0.015 mole) of *N'*,*N'*-diethyl-2,5-pentanediamine and 1.3 g. of sodium bicarbonate was heated, with stirring, at 120° for 5 hours under nitrogen. The dark reaction mixture was cooled and extracted with ether (5 x 20 ml.). The ether extract was dried (sodium sulfate) and evaporated. The syrupy residue was chromatographed on silica gel. Elution with hexane gave a 66% recovery of the starting material **9a**. Continued elution with methylene chloride gave 1 g. (22% yield) of **10a** as a red liquid, b.p. 160-165°/0.03 mm (lit. (20), b.p. 195-200°/2 mm).

1-(5-Dimethylamino-2-pentyl)-5-methoxybenzimidazole (**2a**).

A mixture of 6.2 g. (0.02 mole) of **10a**, 75 ml. of ethanol and 0.2 g. of platinum oxide was hydrogenated at 4.2 kg./cm^2 for 5 hours. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. To the residue (**10b**) was added 50 ml. of 98% formic acid and the mixture heated in a stainless steel pressure vessel at 165° for 3 hours. The reaction mixture was cooled and excess formic acid removed. This was diluted with 25 ml. of water and made strongly basic with 20% sodium hydroxide. The resulting mixture was extracted with ether (5 x 30 ml.). The ether extract was dried (sodium sulfate), evaporated, and the residual oil distilled in a Kügelrohr to give 4.3 g. (74% yield) of **2a** as a pale yellow viscous liquid, b.p. 122-127°/0.05 mm (lit. (20), b.p. 190°/1.5 mm); λ max (ethanol): 250 (ϵ, 15,200), 292 nm (ϵ, 10,900); λ max (*p*H 1): 285 nm (ϵ, 12,600): m/e 289 (M^+).

Anal. Calcd. $C_{17}H_{27}N_3O.1.5\ H_2O$: C, 64.32; H, 9.56; N, 13.28. Found: C, 64.45; H, 9.55; N, 13.22.

4-[(5-Diethylamino-2-pentyl)amino]-5-nitroveratrole (**10c**).

A mixture of 11.4 g. (0.05 mole) of 4,5-dinitroveratrole (**9b**) and 8.7 g. (0.055 mole) of *N'*,*N'*-diethylpentanediamine was stirred and heated slowly to 85° under nitrogen, at which temperature the mixture became homogeneous. After being kept at 85° for 1 hour, it was heated at 110-115° for 6 hours and cooled. The thick, black syrup was dissolved in 15 ml. of methylene chloride and chromatographed through a neutral alumina column. Elution with hexane recovered 2 g. of **9b**. The adsorbent, which contained the product **10c**, was removed from the column and repeatedly extracted with chloroform to give 10 g. (62% yield) of **10c** as a deep orange oil; λ max (pH 1), 240 (ϵ, 18,400), 324 nm (ϵ, 8,100).

1-(5-Diethylamino-2-pentyl)-5,6-dimethoxybenzimidazole (**2b**).

This compound was prepared by catalytic hydrogenation of 6.4 g. (0.02 mole) of **10c** followed by condensation with formic acid in a similar manner as that for the preparation of **2a**. There was obtained 1.5 g. (23% yield) of **2b** after Kügelrohr purification, b.p. 150-155°/ 0.05 mm; λ max (pH 1): 292 nm (ϵ, 16,200): m/e: 319 (M^+).

Anal. Calcd. for $C_{18}H_{29}N_3O_2 \cdot 1.5\ H_2O$: C, 62.40: H, 9.31. N, 12.13. Found: C, 62.61; H, 9.47; N, 11.76.

4-[(5-Diethylamino-2-pentyl)amino]veratrole (**3a**).

A mixture of 16.7 g. (0.1 mole) of 4-nitroveratrole (11), 18.8 g. (0.12 mole) of 5-diethylaminopentan-2-one (12), 100 mg. of platinum oxide, 10 ml. of acetic acid and 175 ml. of absolute ethanol was hydrogenated at 4.2 kg./cm^2 for 72 hours. Catalyst was removed from the mixture by filtration and the filtrate evaporated under reduced pressure to a dark oil. It was distilled *in vacuo* to give 22 g. (72% yield) of **3a** as a light red liquid, b.p. 147-152°/0.05 mm; ir: 3400 cm^{-1} (NH).

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.52. Found: C, 69.46; H, 10.51; N, 9.68.

4-Bromo-5-[(5-diethylamino-2-pentyl)amino]veratrole (**3b**).

A mixture of 10.5 g. (0.04 mole) of 4-bromo-5-nitroveratrole (21) (**13a**) and 1 g. of 5% platinum-on-carbon in 150 ml. of benzene was hydrogenated at 2 kg./cm^2. The hydrogenation was completed in 70 minutes. Catalyst was removed by filtration, and the filtrate evaporated under reduced pressure to yield crude **13b** as a light brown liquid, the ir of which had characteristic NH_2 absorptions at 3450 and 3350 cm^{-1}. The crude **13b** was mixed with 8.8 g. (0.044 mole) of **7** and 0.2 g. of *p*-toluenesulfonic acid and the mixture was heated with stirring at 160-165° for 2 hours, with a provision to distill the methanol formed during reaction. On cooling, the reaction mixture was diluted with 200 ml. of ether, washed with 30 ml. of 5% sodium carbonate and 30 ml. of saturated aqueous sodium chloride, and then dried (potassium carbonate). Removal of ether afforded crude **14a** as a light brown liquid, ir: 1660 cm^{-1} (C=N).

The crude **14a** was dissolved in 100 ml. of absolute ethanol and cooled to 0-5° in an ice bath. To the solution was added, in several portions, 5 g. of sodium borohydride. The resulting mixture was stirred at room temperature overnight. It was diluted with 400 ml. of water, extracted with ether (3 x 100 ml.) and dried (magnesium sulfate). Evaporation of the solvent yielded crude **3b** as a liquid. Kügelrohr distillation at 80-85°/0.3 mm first removed a lower-boiling component from the mixture and analytically pure **3b**, 9.6 g., was collected at 125-130°/0.3 mm. The overall yield of **3b** from **13a** was 65%; λ max (ethanol): 247 (ε, 14,200) and 312 nm (ε, 5,600); nmr (deuteriochloroform): 0.96 (6H, t, J = 6 cps, two terminal CH_3 of the diethyl group), 1.18 (3H, d, J = 6 cps, CH_3 attached to the C-1 of butyl group), 1.36-1.70 (4H, m, protons at C-2 and C-3 of the butyl group), 2.20-2.64 (6H, m, three CH_2 protons attached to the tertiary N), a broad peak at 3.40 (1H, methine proton at C-2 of the pentyl group), 3.68 and 3.74 (6H, s, two OCH_3), 6.22 and 6.88 (2H, s, two aromatic protons).

Anal. Calcd. for $C_{17}H_{29}BrN_2O_2$: C, 54.69; H, 7.83; N, 7.51. Found: C, 55.00; H, 7.95; N, 7.47.

2-Bromo-4,5-methylenedioxy-N-(5-diethylamino-2-pentyl)aniline (**4**).

This compound was prepared in a similar manner as that for the preparation of **3b** by catalytic reduction of 9 g. (0.038 mole) of 2-bromo-4,5-methylenedioxynitrobenzene (**13c**) followed by condensation with **7** and sodium borohydride reduction. The crude product was purified through column chromatography (silica gel, Woelm, Act I) eluting with chloroform-methanol followed by Kügelrohr distillation (110-115°/0.4 mm) to give 5.5 g. (40% overall yield from **13c**). Its ir and nmr were in accord with the expected structure.

Anal. Calcd. for $C_{16}H_{25}BrN_2O_2$: C, 53.78; H, 7.05; N, 7.84. Found: C, 53.50; H, 7.17; N, 7.81.

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