

Attempts at New Synthesis of 5,11-Dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

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Received March 19, 1982

Attempting some new approaches to 5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one (**6**), compounds **8**, **10** and **11** were prepared. Ring enlargement of **4** into **6** failed, as well as condensation of **10** and **11** into **10**, which is the potential precursor of pirenzepin (11-[2'-(4"-methylpiperazin-1"-yl)]acetyl derivative of **6**) via an envisaged intramolecular Diels-Alder reaction. Model compounds **5** and **13** were prepared and their behaviour in analogous reactions explained the failures of the intended transformations of **4**, as well as of condensation of **10** and **11**.

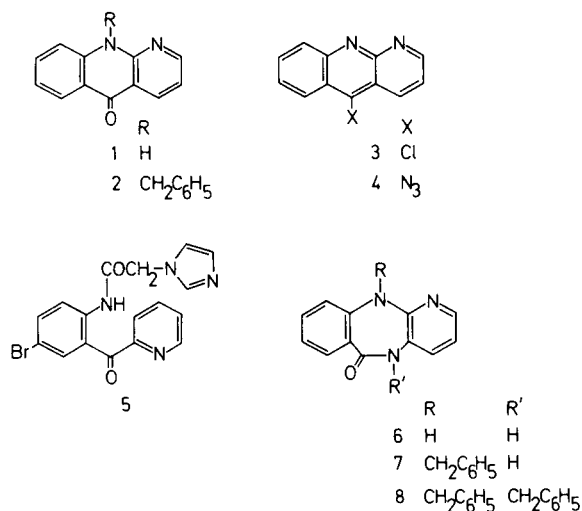
J. Heterocyclic Chem., **20**, 1335 (1983).

Introduction.

In the preceding paper (1) we describe the successful synthesis of the title tricyclic system **6**, while in the forthcoming paper (2) a new synthesis of its *N*-acyl derivatives is described and some other ring closures of **6** are reviewed. In this communication we describe some attempts at the formation of the title compound not covered by the methods described in the accompanying papers.

Results and Discussion.

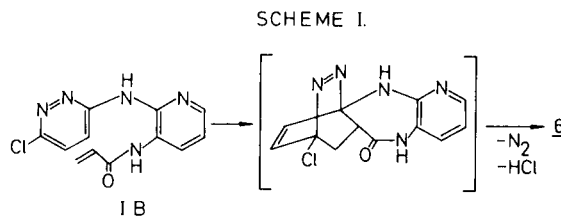
In the series of experiments we tried to accomplish ring enlargement in benzonaphthyridone derivatives **1-4**.



Since the starting compound **1** is readily available from 2-chloronicotinic acid (**3**), it was expected that its transformation into **4** via **3** followed by a regioselective Schmidt rearrangement (4,5) would represent a convenient approach to the basic tricycle **6**. All attempts to rearrange **1** or **2** into **6**, using sodium azide in trifluoroacetic acid, or in sulfuric acid/chloroform, and in polyphosphoric acid at various temperatures, failed. Since the model compound **5** also did not rearrange, it is obviously the strong vinylic-

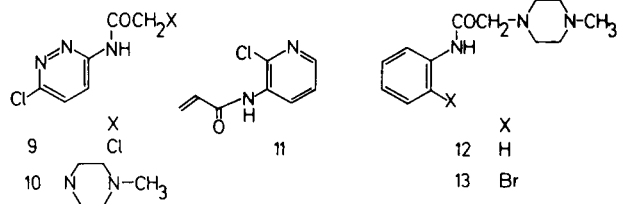
amide character of the carbonyl group in these compounds that prevents rearrangement. Compound **1** did not rearrange into **6** with freshly prepared sodium azide in liquid ammonia, although Bennet (6) succeeded in rearranging in high yield, a structurally related tricyclic ketone, thioxanthene-9-one 10,10-dioxide into the corresponding amide using the same reagent. Azide **4** did not rearrange into **6** on irradiation in potassium methoxide/methanol solution, rather it gave a mixture of products and in part was hydrolysed into **1**. It was reported (7) that β -azidoanthracene rearranges under such conditions into an *ortho*-fused naphthazepine system, on the other hand, it was repeatedly observed (8,9) that various azido acridines on irradiation give rise to a complex mixture of products. In compound **2** the tautomeric carbonyl character of **1** has been retained. All attempts at an acid catalysed rearrangement via ketoxime into **7**, which intermediate was independently prepared, failed. Compound **8** was isolated as a side product during the phase-transfer catalysed preparation of **7** according to the suggestion of Galy (10) who found that the use of such catalysts improves *N*- versus *O*-alkylation in the acridanone series.

Another approach to compound **6** has been envisaged as shown in Scheme I.

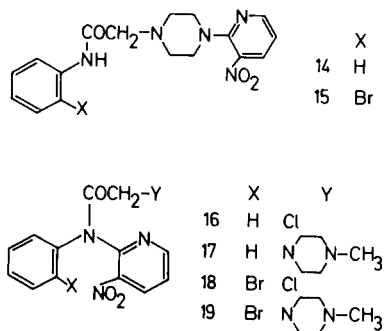


Compound IB was not available via arylation of 3-amino-6-chloropyridazine with **11**, instead of extensive decomposition of the former took place. Thereafter acidification of the N-H bond in this compound has been undertaken by acylation in order to attempt arylation of its conjugate base.

To this end compounds **9** and **10** were prepared in order to attempt to condense these compounds with 2-chloro-3-substituted-pyridines into bis(heteroaryl)amides **IC** and **ID**.



However, all attempts were unsuccessful since again the starting compound **10** decomposed. Even the *N*-deacyl congener **IA** was not available *via* condensation of 3-chloro-6-aminopyridazine and furthermore, even the more reactive 2-chloro-3-nitropyridine failed to react because of the instability of the first component under the harsh conditions required for amine arylation.



To establish the reactivity of the amide nitrogen as in **9** or **10**, *versus* 2-chloro-3-nitropyridine, the more stable model compounds **12** and **13** were prepared and allowed to react with the latter under various conditions. The only compounds isolated were **14** and **15** obtained on quaternization of the most basic nitrogen in **12** and **13** followed by subsequent elimination of methyl chloride. Compounds **17** and **19** could not be identified in the reaction mixtures while their standards were prepared by an independent route, *i.e.* *via* chloroacetyl intermediates **16** and **18**. Thus, the route to **6** *via* cycloaddition-elimination as in Scheme I was prevented at a very early stage. However, analogous cycloadditions to 3,6-disubstituted-pyridazines and subsequent elimination to form xanthenes has recently been reported by Jojima (11).

EXPERIMENTAL

For the general remarks see the preceding paper in this series (1).

Compound **1** has been prepared following the procedure described (3) and compound **9** *via* reference (12).

N-Benzylbenzo[*b*]-1,8-naphthyridin-10-one (**2**).

Compound **1** (0.835 g, 4.25 mmoles), benzyl chloride (1.35 g, 10.6 mmoles) and tributylbenzylammonium chloride (TBA) (590 mg, 2.13 mmoles) were added to a biphasic system of toluene (84 ml) and 50% potassium hydroxide (22 ml). The reaction mixture was stirred at room temperature for 1 hour and then heated at 60° for 20 hours. The mixture was allowed to cool to room temperature and then water (200 ml) was added. The organic layer was separated and the aqueous phase was extracted with toluene (2 × 50 ml), dried and evaporated. Crude **2** was crystallized from methanol to give 350 mg (30%) of **2**, mp 166-168°; ir: 1645, 1609, 1590, 1498, 1418, 1270 cm⁻¹; nmr (deuteriochloroform): 6.15 (s, 2H), 7.3 (s, 5H), 7.2-7.7 (m, 4H), 8.5-9.1 (m, 3H).

Anal. Calcd. for C₁₉H₁₄N₂O (286.32): C, 79.70; H, 4.93; N, 9.78. Found: C, 79.39; H, 4.89; N, 9.95.

9-Chlorobenzo[*b*]naphthyridine (**3**).

Compound **1** (985 mg, 5.0 mmoles) was slurried in thionyl chloride (5.0 ml) to which 5 drops of DMF had previously been added. On heating under reflux for 15 minutes a clear solution resulted to which toluene (10 ml, dried over sodium) was added and the solution evaporated to dryness and a sample of crude **3** crystallized from acetone, mp 182-185° dec; ir: 1610, 1590, 1565, 1432, 1375, 1322, 1285, 955 cm⁻¹; nmr (DMSO-*d*₆): 7.3-7.6 (m, 2H), 7.68 (d, J = 4 Hz, 1H), 7.88 (d, J = 6 Hz, 1H), 8.32 (dd, J = 4 Hz and J = 6 Hz, 1H), 8.8-9.0 (m, 2H).

Anal. Calcd. for C₁₆H₉ClN₂ (214.66): C, 67.14; H, 3.29; N, 13.05. Found: C, 66.85; H, 3.38; N, 13.22.

9-Azidobenzo[*b*]naphthyridine (**4**).

A slurry of 9-chlorobenzo[*b*]naphthyridine (**3**) (1.07 g, 5.0 mmoles) in methanol (10 ml) was cooled to 10° and then sodium azide (300 mg, 6.0 mmoles) was added. After 10 minutes stirring a deep-yellow colour appeared and the starting material dissolved completely. After stirring 1 hour at the same temperature, an inorganic precipitate was filtered off and the filtrate was evaporated to dryness. Crude **4** decomposed on attempted crystallizations from some common solvents; ir: 1665, 1630, 1608, 1590, 1530, 1476, 1462, 1438, 1310, 1282, 1250, 1235, 1200, 1158, 760, 670 cm⁻¹; nmr (DMSO-*d*₆): 7.5 (m, 2H), 7.92 (d, J = 8 Hz, 1H), 8.38 (d, J = 8 Hz, 1H); 8.7-9.0 (m, 2H), 9.85 (broad s, 1H).

N-(2'-Imidazo-1''-yl)acetyl-4-bromo-6-(pyrido-2''-yl)aniline (**5**).

N-(2'-Bromoacetyl)-4-bromo-6-(pyrido-2''-yl)aniline (prepared according to reference 13), (3.10 g, 7.7 mmoles) and imidazole (3.40 g, 50.0 mmoles) were dissolved in benzene (100 ml) and the resulting solution heated under reflux. After 10 minutes a brown oil separated and after 15 minutes the solvent was evaporated. The residual oil was slurried in water (100 ml), extracted with methylene chloride (3 × 100 ml) and the combined organic extracts were dried and evaporated. The crude product was crystallized from ethanol affording 2.1 g (71%) of pure **5**, mp 156-157°; ir: 3100-2800 (broad), 1665, 1580, 1475, 1305, 1285, 1235, 945, 682 cm⁻¹; nmr (deuteriochloroform): 4.85 (s, 2H), 7.1-8.0 (m, 5H), 8.5 (d, 1H), 11.05 (s, 1H).

Anal. Calcd. for C₁₇H₁₃BrN₄O₂ (385.23): C, 53.01; N, 3.40; O, 14.54. Found: C, 52.68; H, 3.39; N, 14.47.

5,11-Dihydro-11-benzyl-6H-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**7**) and Its 5-Benzyl Derivative **8**.

5,11-Dihydro-6H-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**6**) (3.0 g, 14.2 mmoles), benzyl chloride (4.43 g, 35.0 mmoles) and TBA (1.39 g, 5.0 mmoles) were added to a mixture of toluene (150 ml) and 50% potassium hydroxide (75 ml). The mixture was vigorously stirred at room temperature for 4 hours. Then 100 ml of water was added, the layers separated and the organic phase washed with water (2 × 100 ml). It was dried, evaporated and the residual oil purified on a 300 g silica gel column. Using 2-propanol as eluent, two main products were separated. Compound **8** emerged first (2.3 g, 41%) and on crystallization from 2-propanol it had mp 126-127°; ir: 1635, 1620, 1605, 1500, 1462, 1437, 1392, 1337 cm⁻¹; nmr (deuteriochloroform): 5.3 (s, 2H), 5.32 (s, 2H), 6.7-8.3 (m, 7H), 7.35 (s, 10H).

Anal. Calcd. for $C_{26}H_{21}N_3O$ (391.45): C, 79.77; H, 5.41; N, 10.73. Found: C, 79.39; H, 5.24; N, 10.48.

Compound **7** emerged as the second product (570 mg, 14%) and on crystallization from 2-propanol it had mp 157-158°; ir: 3250, 3180, 1630, 1615, 1468, 1450, 1325 cm^{-1} ; nmr (deuteriochloroform): 5.32 (s, 2H), 6.8-8.2 (m, 7H), 7.35 (s, 5H).

Anal. Calcd. for $C_{19}H_{13}N_3O$ (301.33): C, 75.73; H, 5.02; N, 13.95. Found: C, 75.44; H, 5.01; N, 14.05.

3-Chloro-6-(2'-methylpiperazin-1'-yl)acetylaminopyridazine (**10**).

To 3-chloro-6-chloroacetylaminopyridazine **9** (600 mg, 2.91 mmoles) dissolved in toluene (15 ml), *N*-methylpiperazine (380 mg, 3.79 mmoles) was added. The mixture was heated at reflux for 1 hour. Thereafter solvent was evaporated and the residual oil crystallized on addition of acetone. On recrystallization from ethanol 630 mg (81%) of pure **10** was obtained as yellow crystals, mp 154-156°; ir: 3180, 2800, 1740, 1570, 1540, 1395, 1360, 1200, 1145 cm^{-1} ; nmr (DMSO- d_6): 2.20 (s, 3H), 2.3-2.81 (m, 8H), 3.3 (s, 2H), 7.95 (d, $J = 8$ Hz), 8.5 (d, $J = 8$ Hz, 1H).

Anal. Calcd. for $C_{11}H_{13}ClN_5O$ (269.73): C, 48.98; H, 5.98; N, 25.97. Found: C, 48.91; H, 5.73; N, 26.11.

2-Chloro-3-*N*-propenylaminopyridine (**11**).

2-Chloro-3-aminopyridine (10.0 g, 77.8 mmoles) was dissolved in toluene (80 ml). To this vigorously stirred and cooled solution propenoyl chloride (7.04 g, 77.8 mmoles) dissolved in 50 ml of toluene was added dropwise. A white precipitate separated, the slurry was stirred for 1 hour at room temperature and then 6.3 ml (77.8 mmoles) of pyridine were added. After three additional hours of heating under reflux the reaction mixture was allowed to cool to room temperature and ice-water (150 ml) was added. The resulting slurry was extracted with ethyl acetate (3 × 100 ml), the combined organic extracts were washed with water (2 × 150 ml), dried and evaporated. The crude product was crystallized from diisopropyl ether affording 5.0 g (35%) of pure **11**, mp 76-77°; ir: 3300, 1665, 1630, 1515 cm^{-1} ; nmr (deuteriochloroform): 5.7-6.2 (m, 1H), 6.35-6.7 (m, 2H), 7.15-7.5 (m, 1H), 7.5-8.0 (broad s, 1H), 8.05-8.3 (m, 1H), 8.7-8.9 (m, 1H).

Anal. Calcd. for $C_8H_7ClN_2O$ (182.61): C, 52.62; H, 3.86; N, 15.34. Found: C, 52.33; H, 3.82; N, 15.74.

N-(4'-Methylpiperazin-1'-yl)acetylaniline (**12**).

A solution of *N*-bromoacetylaniline (21.4 g, 0.1 mole), and *N*-methylpiperazine (35.95 g, 0.1 mole) in toluene (300 ml) was refluxed for 4 hours. Then the solvent was evaporated to dryness and the glassy residue was dissolved in chloroform (300 ml). The organic solution was washed with water, dried and evaporated affording 15 g (64%) of crude **12** which on crystallization from ether-ethanol had mp 98-99°; ir: 3280, 3125, 1685, 1602, 1592, 1530, 1445, 1165, 1015, 755 cm^{-1} ; nmr (deuteriochloroform): 2.35 (s, 3H), 2.4-2.8 (m, 8H), 3.15 (s, 2H), 7.1-7.9 (m, 5H), 9.2 (broad s, 1H).

Anal. Calcd. for $C_{13}H_{19}N_3O$ (233.32): C, 66.91; H, 8.23; N, 18.00. Found: C, 67.18; H, 8.08; N, 17.81.

N-(4'-Methylpiperazin-1'-yl)acetyl-2-bromoaniline (**13**).

To the solution of *N*-bromoacetyl-2-bromoaniline (15.1 g, 51.5 mmoles) in dry toluene (250 ml), *N*-methylpiperazine (39.5 ml, 358 mmoles) was added. The suspension was heated under reflux for 3 hours and then evaporated. The brown residue was slurried in water (400 ml) and extracted with ethyl acetate (2 × 200 ml). Evaporation of the dried organic phase afforded 15.6 g (97%) of crude **13** which on recrystallization from diisopropyl ether had mp 87-88°; ir: 3240, 2940, 1690, 1590, 1570, 1510, 1435, 1420, 1290, 1160, 1010, 765 cm^{-1} ; nmr (deuteriochloroform): 2.3 (s, 3H), 2.45-2.85 (m, 8H), 3.18 (s, 2H), 6.8-7.65 (m, 3H), 8.4-8.7 (m, 1H), 10.0 (s, 1H).

Anal. Calcd. for $C_{13}H_{18}BrN_3O$ (312.21): C, 50.00; H, 5.81; N, 13.46. Found: C, 50.35; H, 5.89; N, 13.44.

N-(4'-3''-Nitropyrid-2''-yl)piperazin-1'-yl)acetylaniline (**14**).

Compound **12** (1.89 g, 8.1 mmoles) and 2-chloro-3-nitropyridine (1.28

g, 8.1 mmoles) were fused at 140° (oil bath) for 2 hours. On cooling the crude mixture was dissolved in acetone and purified on a 130 g silica gel column with methylene chloride-acetone (12:1) as eluent. In fractions 34-60 (5 ml per fraction), 490 mg (18%) of pure **14** was obtained which on crystallization from 96% ethanol melted at 124-125°; ir: 3180, 3060, 3040, 1665, 1600, 1550, 1505, 1315, 1240, 778, 760 cm^{-1} ; nmr (deuteriochloroform): 2.6-2.9 (t, 4H), 3.23 (s, 2H), 3.45-3.75 (t, 4H), 6.7-8.6 (m, 8H), 9.2 (broad s, 1H).

Anal. Calcd. for $C_{17}H_{21}N_5O_3$ (343.39): C, 59.48; H, 6.17; N, 20.04. Found: C, 59.18; H, 6.01; N, 20.02.

N-(4'-3''-Nitropyrid-2''-yl)piperazin-1'-yl)acetyl-2-bromoaniline (**15**).

Compound **13** (1.25 g, 4.0 mmoles) and 2-chloro-3-nitropyridine (635 mg, 4.0 mmoles) were fused at 170° (oil bath) for 3 hours. The mixture was allowed to cool to room temperature, then it was dissolved in methylene chloride and purified on a silica gel column (toluene-acetone 9:1 as eluent). There was obtained 440 mg (26%) of the pure **15**, mp 126-127°; ir: 3265, 1695, 1600, 1595, 1550, 1520, 1510, 1435, 1325, 1235 cm^{-1} ; nmr (deuteriochloroform): 2.65-2.95 (m, 4H), 3.28 (s, 2H), 3.5-3.8 (m, 4H), 6.70-6.75 (m, 4H), 8.1-8.7 (m, 3H), 10.0 (s, 1H).

Anal. Calcd. for $C_{17}H_{20}BrN_5O_3$ (420.27): C, 48.58; H, 4.32; N, 16.50. Found: C, 49.06; H, 4.32; N, 16.89.

2-(*N*-Chloroacetyl-*N*-phenyl)amino-3-nitropyridine (**16**).

2-Anilino-3-nitropyridine (1.1 g, 5.1 mmoles) in dioxane (20 ml) and chloroacetyl chloride (5.0 ml) were heated under reflux for 2.5 hours. After evaporation of the solvent and excess of chloroacetyl chloride, the residual mass was purified on a 60 g silica gel column with methylene chloride as eluent. In the fractions 10-23 (5 ml per fraction) 0.2 g of unreacted 2-anilino-3-nitropyridine was obtained, while in the fractions 37-70, 1.23 g (83%) of pure **16** was obtained. On dissolution in methylene chloride, addition of light petroleum and chilling with ice, pure **16** crystallized, mp 133-134°; ir: 1700, 1595, 1530, 1430, 1360, 1270, 1190, 850, 820, 780, 695 cm^{-1} ; nmr (deuteriochloroform): 4.1 (s, 2H), 7.3-8.2 (m, 6H), 8.43 (dd, $J_1 = 2$ Hz, $J_2 = 9$ Hz, 1H), 8.72 (dd, $J_1 = 2$ Hz, $J_2 = 9$ Hz, 1H).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_3$ (291.69): C, 53.52; H, 3.45; N, 14.40. Found: C, 53.18; H, 3.61; N, 14.09.

2-(*N*-(4'-Methylpiperazin-1'-yl)acetyl-*N*-phenyl)amino-3-nitropyridine (**17**).

Compound **16** (4.50 g, 15.5 mmoles) was dissolved in dry toluene (150 ml) and 6.85 ml (6.2 g, 62.0 mmoles) of *N*-methylpiperazine was added. The mixture was heated at 80° (oil bath) for 5 hours. Then the solvent and excess of reagent were evaporated. The residual mass was dissolved in chloroform (400 ml), washed with water, the organic phase was dried and evaporated leaving 5.5 g of the crude **17**. It was purified on a 130 g silica gel column using acetone-methanol (6:1) as eluent. In the fractions 45-128 (5 ml per fraction), 3.81 g (70%) of pure **17** was obtained which on crystallization from 2-propanol had mp 151-152° dec; ir: 1690, 1590, 1530, 1350, 1250, 1170, 1015, 850, 760, 700, 610 cm^{-1} ; nmr (deuteriochloroform): 2.25 (s, 3H), 2.45 (broad s, 8H, 4CH₂), 3.2 (s, 2H), 7.3-7.7 (m, 6H), 8.38 (dd, $J_1 = 4$ Hz, $J_2 = 8$ Hz, 1H), 8.7 (dd, $J_1 = 4$ Hz, $J_2 = 8$ Hz, 1H).

Anal. Calcd. for $C_{18}H_{21}N_5O_3$ (355.39): C, 60.82; H, 5.95; N, 19.70. Found: C, 60.37; H, 6.02; N, 19.98.

2-(*N*-Chloroacetyl-*N*-2'-bromophenyl)amino-3-nitropyridine (**18**).

2-(2'-Bromophenyl)amino-3-nitropyridine (1.47 g, 5.0 mmoles) was dissolved in methylcellosolve (20 ml) and 5 ml of chloroacetyl chloride was added. The mixture was heated under reflux for 7 hours. After evaporation of the solvent and the excess reagent, the crude product was dissolved in chloroform (150 ml), washed with water (150 ml) and the organic layer was dried, evaporated and the residue placed on a column (10 g) of silica gel and eluted with methylene chloride. In fractions 5-15 (5 ml per fraction), 1.85 g (87%) of pure **18** was obtained which on crystallization from ethanol melted at 208-209°; ir: 1703, 1595, 1536, 1410, 1362, 860, 815, 690 cm^{-1} ; nmr (deuteriochloroform): 4.12 (s, 2H), 7.2-8.2 (m, 5H), 8.40 (dd, $J_1 = 2$ Hz, $J_2 = 10$ Hz, 1H), 8.80 (dd, $J_1 = 2$ Hz, $J_2 =$

10 Hz, 1H).

Anal. Calcd. for $C_{13}H_8BrClN_3O_3$ (370.56): C, 42.13; H, 2.47; N, 11.33. Found: C, 42.60; H, 2.20; N, 11.09.

2-(N-(4'-Methylpiperazin-1'-yl)acetyl-N-2'-bromophenyl)amino-3-nitropyridine (**19**).

Compound **18** (1.48 g, 4.0 mmoles) was dissolved in dry toluene (40 ml) to which 1.8 ml (16.0 mmoles) of N-methylpiperazine was added and the mixture was heated at 80° (oil bath) for 6 hours. After evaporation of the solvent and excess reagent, the crude product was dissolved in chloroform (150 ml), washed with water (150 ml), the organic phase dried and evaporated leaving 1.8 g of crude **19**, which was purified on a column (60 g) of silica gel with acetone-methanol (4:1) as eluent. In fractions 1-23 (5 ml per fraction) 0.50 g of unreacted **18** was separated while the fractions 32-94 contained 0.75 g (34%) of pure **19**, which on crystallization from acetone had mp 158-159° dec; ir: 2940, 1695, 1590, 1300, 1225, 1170, 1010, 850, 760, 720, 640 cm^{-1} ; nmr (deuteriochloroform): 2.30 (s, 3H), 2.5 (broad s, 8H, 4CH₂), 3.25 (s, 2H), 7.35-8 (m, 5H), 8.44 (dd, J₁ = 4 Hz, J₂ = 8 Hz, 1H), 8.66 (dd, J₁ = 4 Hz, J₂ = 8 Hz, 1H).

Anal. Calcd. for $C_{18}H_{20}BrN_5O_3$ (434.29): C, 49.77; H, 4.64; N, 16.13. Found: C, 49.55; H, 4.76; N, 16.29.

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