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The synthesis is described of 1,4-diazabicyclo[2.2.2]octane and piperazine derivatives of potential interest for second-order NL optical activity.

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Non-linear optical (NLO) response in molecular materials arises from transient polarization of individual molecular electronic systems. Second order NLO effects arise from deviations from the parabolic electronic potential well induced by the substitution of donor and acceptor groups to give non-centrosymmetric molecules [1]. The choice of materials for NLO use is constrained by the requirement that there shall be no absorption of energy at the working frequencies.

Observable second order NLO effects require non-centrosymmetric ordering of the active molecular systems. Synthesis of asymmetric molecules, incorporating optically active substituents, appears to offer one of the more accessible routes to the formation of non-centrosymmetric media. The present paper describes the synthesis of compounds of two types. In the first, hydrogen bonding is utilized as a potential means for controlling molecular orientation in the solid state [2]. The second group com-

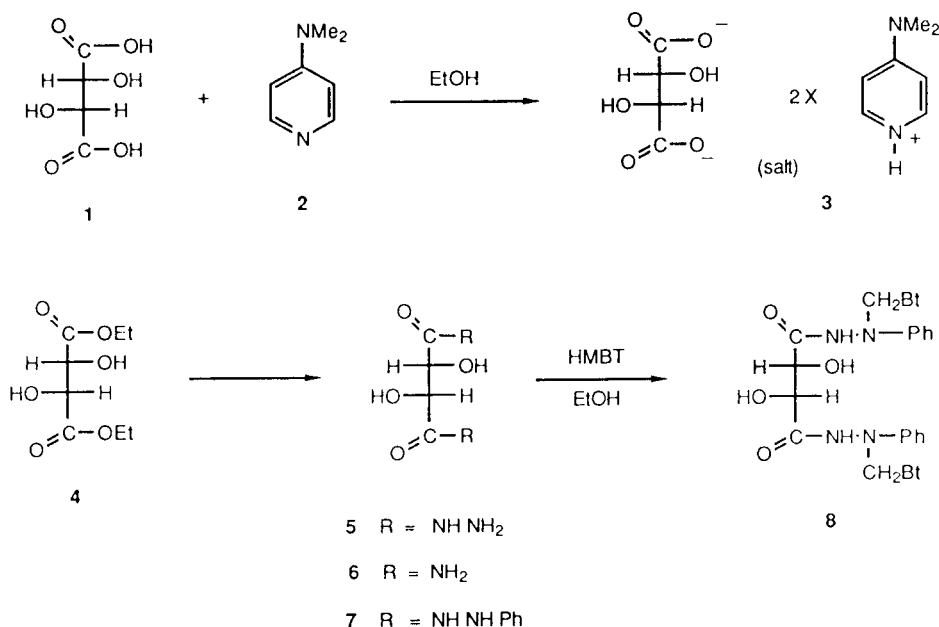
prises molecules with electron donor and acceptor groups attached to rigid sigma bond frameworks which should generate large excited state dipoles of interest in relation to second order non-linear optical effects [3].

#### Derivatives of Tartaric Acid.

Derivatives of tartaric acid are frequently crystalline solids with high melting points. They possess vicinal hydroxyl groups which take part in a cross-linking network of hydrogen bonds.

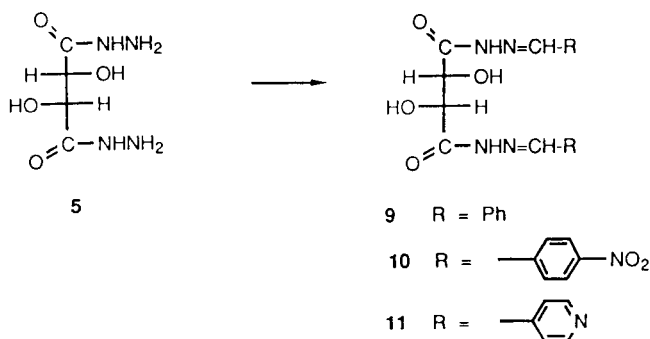
Ethanollic tartaric acid (**1**, 1 equivalent) with 4-*N,N*-dimethylaminopyridine (**2**, 2.1 equivalents) formed 4-*N,N*-dimethylaminopyridinium tartrate (**3**). Treatment of ethyl tartrate **4** with anhydrous hydrazine in ethanol afforded the tartaric hydrazide **5** [4]. Compound **4** with ethanolic ammonia gave tartramide **6** and with phenylhydrazine formed tartaric phenylhydrazide **7** [5]. Tartaric phenylhydrazide with hydroxymethylbenzotriazole in ethanol gave the bis adduct, **8**.

Scheme 1



Scheme 2 details the preparation of hydrazones from tartaric hydrazide (**5**) and aromatic aldehydes. Tartaric hydrazide underwent condensation with benzaldehyde, *p*-nitrobenzaldehyde and 4-pyridinecarboxaldehyde in aqueous solution to give the corresponding hydrazones **9** [**5**], **10** and **11** respectively.

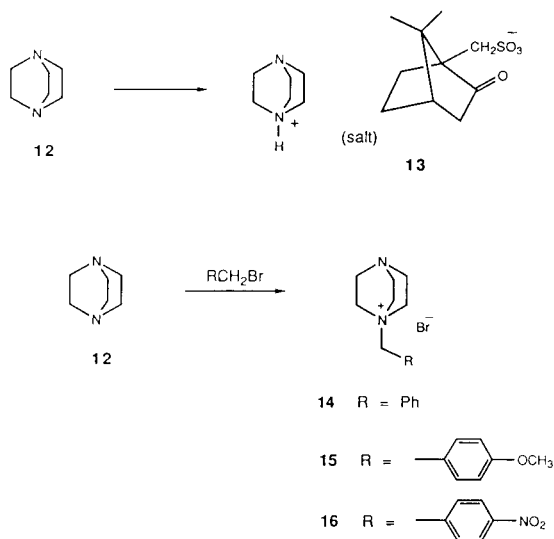
Scheme 2



### Dabconium Salts.

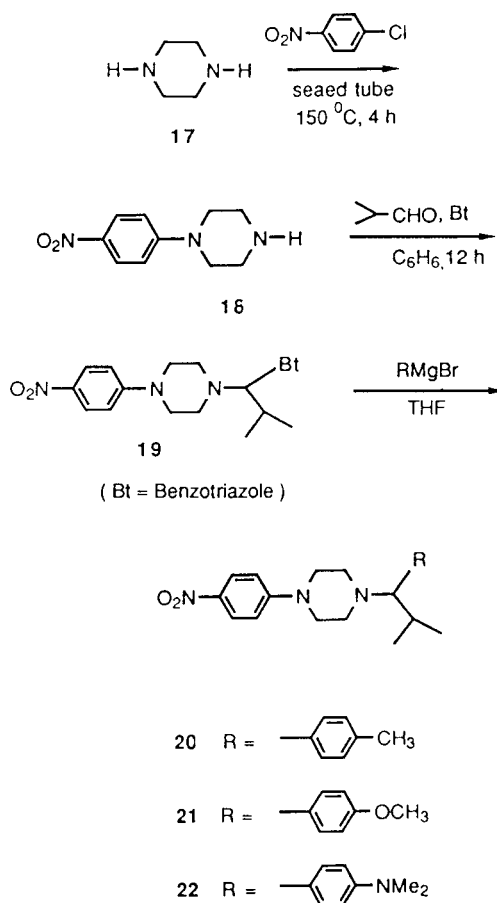
Monoquaternized dabconium cations, diamines in which the nitrogen atoms are separated by three dimethylene groups, allow the influence of a positively charged quaternized nitrogen atom on the donor properties of the free amine nitrogen atom to be probed [6].

Scheme 3



Scheme 3 describes the formation of the salt **13** of 1,4-diazabicyclo[2.2.2]octane (dabco, **12**) and 1*R*-,10-camphorsulfonic acid. Similar treatment of compound **12** with benzyl bromide or *p*-methoxybenzyl or *p*-nitrobenzyl bromide in acetone at room temperature formed dabconium salts **14** [7], **15**, and **16** respectively.

Scheme 4



### 1,4-Disubstituted Piperazines.

Scheme 4 describes the preparation of 1,4-disubstituted piperazines, possessing an electron donating substituent at one nitrogen and the electron withdrawing substituent, *p*-nitrophenyl, at the other. 1-(*p*-Nitrophenyl)piperazine **18** [8] was prepared by heating anhydrous piperazine (**17**) and 1-chloro-4-nitrobenzene for 4 hours at 150° in a sealed tube. Refluxing compound **18** with isobutyraldehyde and benzotriazole in benzene using a Dean-Stark trap afforded the Mannich base **19** in 98% yield. In deuteriochloroform solution, the existence of the two expected positional isomers (benzotriazol-1-yl and -2-yl) was observed by <sup>1</sup>H nmr as a 1:1 mixture. Compound **19**, when subjected to Grignard reactions with *p*-tolylmagnesium bromide, *p*-anisylmagnesium bromide and *p*-dimethylaminophenylmagnesium bromide in dry THF afforded good yields of the compounds **20**, **21** and **22** respectively.

### Conclusions.

Results of the testing are given in Table 1. The poor results with the tartaric acid derivatives demonstrate that the degree of non-centrosymmetry of the acid is insuffi-

Table 1  
Results from Non-linear Optical Testing

Compound Generation Efficiency Relative to Urea	Second Harmonic
Bis-4- <i>N,N</i> -dimethylaminopyridinium tartrate (3)	< 0.0001
Tartaric-bis-(4-nitrophenyl)hydrazone (10)	< 0.0001
Tartaric-bis-(4-pyridyl)hydrazone (11)	< 0.0001
4-Aza-1-benzylazoniabicyclo[2.2.2]octane bromide (14)	< 0.0001
4-Aza-1- <i>p</i> -methoxybenzylazoniabicyclo[2.2.2]octane bromide (15)	< 0.0001
4-Aza-1- <i>p</i> -nitrobenzylazoniabicyclo[2.2.2]octane bromide (16)	< 0.0001
1-(4-Nitrophenyl)-4-(1-benzotriazol-1-yl-2-methyl)propylpiperazine (19)	1.71
1-(4-Nitrophenyl)-4-(1- <i>p</i> -methylphenyl-2-methyl)propylpiperazine (20)	0.004
1-(4-Nitrophenyl)-4-(1- <i>p</i> -methoxyphenyl-2-methyl)propylpiperazine (21)	0.0012
1-(4-Nitrophenyl)-4-(1- <i>p,N,N</i> -dimethylaminophenyl-2-methyl)propylpiperazine (22)	31.4

cient even with 4-nitroaniline as a substituent group. Clearly more extensive modeling is required to generate structured hydrogen bonding leading to a much larger projection of the molecular polarization moment on to the macroscopic polarization moment.

The results with the dabconium and piperazine derivatives are more interesting. The absence of any second order response for any of the diazabicyclooctane systems, shows that the molecules are probably dimerized in the crystal despite the three dimensional substituent group. Also these systems do not allow sufficient charge transfer by through bond interactions to create a significant change in molecular dipole in the excited state. In contrast, the piperazine derivatives show the effect of donor acceptor interactions through the sigma bond framework. The length of these systems in comparison with the dabconium derivatives indicates that the concept of a small charge separated by a long distance can give rise to NLO activity.

## EXPERIMENTAL

Melting points were determined with a Bristoline hot-stage microscope and are uncorrected. The ir spectra were recorded on a Perkin Elmer model 283B grating spectrophotometer. Proton and carbon nmr spectra were recorded on Varian XL-200 or VXR-300 spectrometers. All nmr spectra were recorded in deuteriochloroform, Me<sub>2</sub>SO-d<sub>6</sub> or deuterium oxide as solvent with tetramethylsilane or *p*-dioxane as internal reference.

The following compounds were prepared according to previously known procedures: diethyl tartarate (4) [9], tartaric hydrazide (5) [4], tartramide (6) [5], tartaric phenylhydrazide (7) [5], tartaric diphenylhydrazone (9) [5], 4-aza-1-benzylazoniabicyclo[2.2.2]octane bromide (14) [7], 1-(*p*-nitrophenyl)piperazine (18) [8] and hydroxymethylbenzotriazole [10].

Bis-4-*N,N*-dimethylaminopyridinium Tartarate (3).

A solution of 4-*N,N*-dimethylaminopyridine (6.1 g, 50 mmoles) in hot (60-70°) ethanol (50 ml) was added dropwise to a solution of tartaric acid (3.5 g, 25 mmoles) in ethanol (50 ml). The product began to precipitate almost immediately. The reaction mixture was allowed to stir for 2 hours and the precipitate was filtered, washed with ethanol and dried to give 3 (7.7 g, 98%), mp 190°;

<sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>): δ 3.03 (s, 12 H), 3.97 (s, 2 H), 4.97 (br s, 4 H), 6.73 (d, 4 H, J = 6.8 Hz), 8.15 (m, 4 H); <sup>13</sup>C nmr (deuterium oxide): δ 40.1, 74.7, 107.6, 139.0, 158.3, 179.2.

Anal. Calcd. for C<sub>18</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub>: C, 54.81; H, 6.64; N, 14.20. Found: C, 54.75; H, 6.66; N, 14.22.

Tartaric-bis-(*p*-nitrophenyl)hydrazone (10).

A slurry of tartaric hydrazide (0.5 g, 2.8 mmoles) and *p*-nitrobenzaldehyde (0.85 g, 5.6 mmoles) in water (100 ml) was stirred at 80° in an oil bath for 2.5 hours. The product began to precipitate after a few minutes. The precipitate was filtered, washed with water (2 x 40 ml) and ethanol (40 ml) and dried. Recrystallization from pyridine-ethanol, to give 10 (1.2 g, 96%) as cream colored microcrystals, mp collapsed at 234-237°, slowly changed the crystalline form to transparent rectangular crystals at 260-265° and finally melted with dec at 287-288°; <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>): δ 4.57 (d, 2 H, J = 6 Hz), 6.03 (d, 2 H, J = 6 Hz), 7.9 (d, 4 H, J = 9 Hz), 8.24 (d, 4 H, J = 9 Hz), 8.56 (s, 2 H), 11.55 (s, 2 H); <sup>13</sup>C nmr (Me<sub>2</sub>SO-d<sub>6</sub>): δ 72.9, 127.1, 128.8, 130.0, 134.4, 148.0, 168.4; uv (ethanol): λ max 323 nm (log ε 3.8), 229 nm (3.6).

Anal. Calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>8</sub>: C, 48.65; H, 3.63; N, 18.91. Found: C, 48.49; H, 3.63; N, 18.83.

Tartaric-bis-(4-pyridyl)hydrazone (11).

The procedure was similar to that for the preparation of 10. The product 5 was recrystallized from acetic acid-ethanol, giving 11 (95%) as colorless needles, mp 216° dec; <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>): δ 4.54 (d, 2 H, J = 6 Hz), 6.0 (d, 2 H, J = 6 Hz), 7.6 (d, 4 H, J = 5 Hz), 8.47 (s, 2 H), 8.64 (d, 4 H, J = 5 Hz), 11.53 (s, 2 H); <sup>13</sup>C nmr (Me<sub>2</sub>SO-d<sub>6</sub>): δ 73.0, 121.0, 141.6, 145.6, 150.3, 168.8; uv (ethanol): λ max 290 nm (log ε 3.8), 210 nm (3.5).

Anal. Calcd. for C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.77; H, 4.23; N, 23.34.

4-Aza-1*H*-azoniabicyclo[2.2.2]octane 10-Camphorsulfonate (13).

To a stirred solution of 1,4-diazabicyclo[2.2.2]octane (1.5 g, 13 mmoles) in ethanol (40 ml) was added a solution of 1*R*-(-)-10-camphorsulfonic acid (3.1 g, 13 mmoles) in ethanol (40 ml) in small portions at room temperature. After 6 hours the solvent was distilled off under reduced pressure to give 13 (4.6 g, 100%) as colorless microcrystals, mp slow melting at 260-265° was accompanied by a change in the crystalline form to needles. Slow dec began at 295°, but was incomplete even at 330°; <sup>1</sup>H nmr (deuterium oxide): δ 0.58 (s, 3 H), 0.79 (s, 3 H), 1.2-1.4 (m, 2 H), 1.68-1.9 (m, 3 H), 2.1-2.2 (m, 2 H), 2.6 (d, 1 H, J = 15 Hz), 3.0 (d, 1 H, J = 15 Hz), 3.1-3.53 (m, 12 H); <sup>13</sup>C nmr (deuterium oxide): δ

19.6, 19.8, 25.4, 27.1, 43.1, 43.4, 44.7, 48.0, 49.0, 59.3, 222.5; uv (ethanol):  $\lambda$  max 282 nm (log  $\epsilon$  1.9), 204 nm (3.3).

*Anal.* Calcd. for  $C_{16}H_{28}N_2O_4S$ : C, 55.79; H, 8.19; N, 8.13. Found: C, 55.29; H, 8.45; N, 8.02.

#### 4-Aza-1-*p*-methoxybenzylazoniabicyclo[2.2.2]octane Bromide (15).

A solution of *p*-methoxybenzylbromide (5.38 g, 26.7 mmoles) in dry ether (60 ml) was added dropwise to a solution of 1,4-diazabicyclo[2.2.2]octane (3 g, 26.7 mmoles) in dry ether (150 ml). The product began to precipitate almost immediately. The reaction mixture was allowed to stir for 2 hours and the product was filtered, washed with dry ether (2 x 30 ml) and dried to give **15** (8.2 g, 98%) as colorless microcrystals; mp 177-178°;  $^1H$  nmr (deuteriochloroform):  $\delta$  3.19 (t, 6 H, J = 7 Hz), 3.76 (t, 6 H, J = 7 Hz), 3.81 (s, 3 H), 4.99 (s, 2 H), 6.91 (d, 2 H, J = 9 Hz), 7.6 (d, 2 H, J = 9 Hz);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  45.1, 51.2, 55.1, 66.3, 114.2, 117.9, 134.4, 160.8; uv (methanol):  $\lambda$  max 270 nm (log  $\epsilon$  3.03), 235 nm (4.13).

*Anal.* Calcd. for  $C_{14}H_{21}N_2OBr$ : C, 53.68; H, 6.76; N, 8.94. Found: C, 53.33; H, 6.75; N, 8.72.

#### 4-Aza-1-*p*-nitrobenzylazoniabicyclo[2.2.2]octane Bromide (16).

The procedure was similar to that for the preparation of **15**. The product was washed with dry ether (3 x 40 ml) and dried to give **16** (97%) as colorless microcrystals, mp slow melting with dec began at 220°, but was incomplete even at 310°;  $^1H$  nmr ( $Me_2SO-d_6$ ):  $\delta$  3.04 (t, 6 H, J = 7 Hz), 3.43 (t, 6 H, J = 7 Hz), 4.85 (s, 2 H), 7.87 (d, 2 H, J = 9 Hz), 8.34 (d, 2 H, J = 9 Hz);  $^{13}C$  nmr ( $Me_2SO-d_6$ ):  $\delta$  44.6, 51.5, 64.5, 123.7, 134.5, 134.81, 148.5; uv (methanol):  $\lambda$  max 254 nm (log  $\epsilon$  5.1); hrms: for  $C_{13}H_{18}N_3O_2Br$ : Theoretical/found molecular weight for the corresponding dab-conium cation: 248.13990/248.13799.

#### 1-Benzotriazol-1-yl-2-methyl-1-[4-(4-nitrophenyl)piperazin-1-yl]propane (19).

A solution of 1-(*p*-nitrophenyl)piperazine (6 g, 29 mmoles), benzotriazole (3.45 g, 29 mmoles) and isobutyraldehyde (2.1 g, 29 mmoles) in benzene (200 ml) was refluxed under stirring for 24 hours using a Dean-Stark trap. The reaction mixture was cooled and the solvent was distilled off under reduced pressure. The precipitate was recrystallized from ethyl acetate-petroleum ether (40-60) to give **19** (10.8 g, 98%) as yellow microcrystals; mp 169-170°;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.66 (d, 3 H, J = 6.3 Hz), 0.7 (d, 3 H, J = 6.6 Hz), 1.23 (d, 3 H, J = 6.6 Hz), 1.27 (d, 3 H, J = 6.9 Hz), 2.67-2.81 (m, 8 H), 2.96-3.12 (m, 2 H), 3.31-3.47 (m, 8 H), 5.14 (d, 1 H, J = 10.8 Hz), 5.19 (d, 1 H, J = 10.8 Hz), 6.68-6.71 (m, 4 H), 6.72-7.62 (m, 6 H), 7.87-8.12 (m, 6 H);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  19.1, 19.2, 19.3, 19.9, 28.9, 29.0, 47.0, 47.1, 47.7, 48.1, 85.1, 92.0, 109.5, 112.5, 112.6, 118.2, 119.9, 123.9, 125.7, 125.8, 126.2, 127.5, 128.2, 134.4, 138.3, 138.4, 143.5, 145.3, 154.51, 154.6; uv (methanol):  $\lambda$  max 378 nm (log  $\epsilon$  4.30), 276 nm (3.88), 234 nm (4.13).

*Anal.* Calcd. for  $C_{20}H_{24}N_6O_2$ : C, 63.14; H, 6.36; N, 22.09. Found: C, 62.89; H, 6.39; N, 22.17.

#### 2-Methyl-1-(4-methylphenyl)-1-[4-(4-nitrophenyl)piperazin-1-yl]propane (20).

A Grignard reagent prepared from magnesium turnings (0.1 g, 3.9 mmoles) and 4-bromotoluene (0.5 ml, 3.9 mmoles) in dry THF (20 ml) was added in small portions to the cooled (0-5°) and stirred solution of the compound **19** in dry THF (20 ml). The

reaction mixture was stirred at 0-5° for 4 hours and at room temperature for 3 hours and poured onto a mixture of crushed ice and 5 g of ammonium chloride. The product was extracted with ether (3 x 30 ml). The combined ether extract was washed with 5% sodium carbonate solution (2 x 40 ml) followed by water (40 ml) and dried (anhydrous sodium carbonate). The product was chromatographed on silica gel with ethyl acetate-hexane (1:5 mixture) followed by recrystallization from methanol to give **20** (4.2 g, 90%) as pale yellow microcrystals, mp 90-91°;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.74 (d, 2 H, J = 6.6 Hz), 0.99 (d, 2 H, J = 6.3 Hz), 2.25-2.3 (m, 1 H), 2.32 (s, 3 H), 2.39-2.52 (m, 4 H), 3.04 (d, 1 H, J = 8.7 Hz), 3.33-3.37 (m, 4 H), 6.7 (d, 2 H, J = 9.6 Hz), 7.02 (d, 2 H, J = 8.1 Hz), 7.11 (d, 2 H, J = 7.8 Hz), 8.04 (d, 2 H, J = 9.6 Hz);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  18.9, 20.6, 21.0, 27.7, 47.2, 49.1, 75.5, 112.1, 125.8, 128.4, 129.0, 133.9, 136.4, 137.9, 155.8; uv (methanol):  $\lambda$  max 385 nm (log  $\epsilon$  4.34), 218 nm (4.25).

*Anal.* Calcd. for  $C_{21}H_{27}N_3O_2$ : C, 71.36; H, 7.70; N, 11.89. Found: C, 71.55; H, 7.78; N, 11.94.

#### 1-(*p*-Nitrophenyl)-4-(1-*p*-methoxyphenyl-2-methyl)propylpiperazine (21).

The procedure was similar to that for the preparation of **20**. The crude product was chromatographed on silica gel with chloroform-hexane (4:1 mixture) followed by recrystallization from methanol to give **21** (88%) as yellow microcrystals, mp 94-95°;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.75 (d, 3 H, J = 6.6 Hz), 0.98 (d, 3 H, J = 6.6 Hz), 2.23-2.26 (m, 1 H), 2.43-2.53 (m, 4 H), 3.03 (d, 1 H, J = 8.7 Hz), 3.34-3.79 (m, 4 H), 3.71 (s, 3 H), 6.72 (d, 2 H, J = 9.6 Hz), 6.85 (d, 2 H, J = 9.0 Hz), 7.07 (d, 2 H, J = 8.7 Hz), 8.06 (d, 2 H, J = 9.3 Hz);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  18.8, 20.6, 27.9, 47.2, 49.2, 55.1, 75.1, 112.2, 113.0, 125.8, 129.2, 130.1, 137.9, 154.8, 158.5; uv (methanol):  $\lambda$  max 385 nm (log  $\epsilon$  4.37), 227 nm (4.39).

*Anal.* Calcd. for  $C_{21}H_{27}N_3O_3$ : C, 68.27; H, 7.37; N, 11.37. Found: C, 68.32; H, 7.44; N, 11.29.

#### 1-(*p*-Nitrophenyl)-4-(1-*p*-*N,N*-dimethylaminophenyl-2-methyl)propylpiperazine (22).

The procedure was similar to that for the preparation of **20**. The crude product was chromatographed on neutral alumina with chloroform followed by recrystallization from chloroform-petroleum ether (40-60°) to give **22** (92%) as pale yellow plates, mp 159-160°;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.75 (d, 3 H, J = 6.6 Hz), 0.99 (d, 3 H, J = 6.6 Hz), 2.23-2.25 (m, 1 H), 2.39-2.53 (m, 4 H), 2.92 (s, 6 H), 2.98 (d, 1 H, J = 8.7 Hz), 3.33-3.37 (m, 4 H), 6.67 (d, 2 H, J = 7.8 Hz), 6.7 (d, 2 H, J = 8.4 Hz), 7.0 (d, 2 H, J = 8.7 Hz), 8.05 (d, 2 H, J = 9.3 Hz);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  19.0, 20.7, 27.9, 40.5, 47.2, 49.1, 75.2, 111.6, 112.0, 124.9, 125.8, 129.8, 137.8, 149.5, 154.8; uv (methanol):  $\lambda$  max 385 nm (log  $\epsilon$  4.07), 255 nm (4.13).

*Anal.* Calcd. for  $C_{22}H_{30}N_4O_2$ : C, 69.08; H, 7.91; N, 14.65. Found: C, 69.28; H, 8.01; N, 14.68.

## REFERENCES AND NOTES

- [1] S. J. Lalama and A. F. Garito, *Phys. Rev.*, **A20**, 1179 (1979).
- [2] T. W. Panunto, Z. Urbanczyk-Lipkowska, R. Johnson and M. C. Etter, *J. Am. Chem. Soc.*, **109**, 7786 (1987).
- [3] J. W. Verhoeven, *Pure Appl. Chem.*, **58**, 1285 (1986).
- [4] R. V. Rothenburg, *Chem. Ber.*, **26**, 2053 (1893).
- [5] P. F. Frankland and A. Slatore, *J. Chem. Soc., Trans.*, 1349 (1903).

[6] J. V. Quagliano, A. K. Banerjee, V. L. Goedken, and L. M. Vallarino, *J. Am. Chem. Soc.*, **92**, 482 (1970).

[7] S. D. Ross, J. J. Bruno, and R. C. Petersen, *J. Am. Chem. Soc.*, **85**, 3999 (1963).

[8] A. G. Kalle, German Offen. 1,239,940 (1967); C.A. **67**, 101031z

(1967).

[9] T. M. Lowry and J. O. Cutter, *J. Chem. Soc.*, **121**, 532 (1922).

[10] J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.*, **74**, 3868 (1952).