Synthesis of *p*-Aminobenzamides of Aminopiperidazines as Potential Antiarrhythmic Agents

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1,2-Dimethyl-4-aminopiperidazine (**4**), 1-(2-aminoethyl)-2-methylpiperidazine (**11**), 2-(2-aminoethyl)-3-methyl-2,3-diazabicyclo[2.2.1]heptane (**16**), and 1,2-dimethyl-3-aminomethylpiperidazine (**21**) have been synthesized. Amines **4**, **11**, and **16** were converted to the corresponding *p*-nitrobenzamides **7**, **12**, and **17**. Catalytic reduction of the latter nitro derivatives gave the corresponding *p*-aminobenzamides **8**, **13**, and **18**. For comparative studies, the acyclic analog, 4-amino-*N*-[2-(1,1,2-trimethylhydrazino)ethyl]benzamide (**25**) was also synthesized. Compounds **8**, **13** and **25** which are analogs of procainamide were evaluated in the isolated cardiac Purkinje fiber preparation by measuring their effects on the action potential upstroke velocity.

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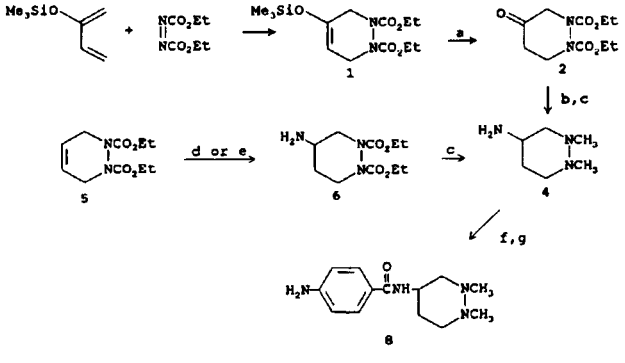
An earlier communication [2] from our laboratories described the synthesis and antiarrhythmic screening of *p*-aminobenzamides in which the basic moiety was contributed by a pyrazolidine ring. This report which is an extension of that previous work describes the synthesis of the *p*-aminobenzamides of several aminopiperidazines as well as their preliminary antiarrhythmic activity.

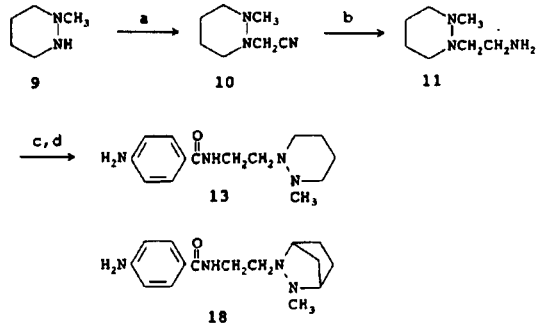
The necessary amino containing piperidazines and their corresponding *p*-aminobenzamides were prepared according to the pathways shown in Schemes I-IV. Diels-Alder reaction between 2-(trimethylsilyloxy)-1,3-butadiene and diethyl azodicarboxylate gave adduct **1** which was converted to the ketone **2** with methanol-trifluoroacetic acid. Conversion of **2** to its oxime followed by lithium aluminum hydride reduction gave the aminopiperidazine **4**. The latter was then converted *via* the *p*-nitrobenzamide in two steps to the *p*-aminobenzamide derivative **8** in the usual manner (Scheme I). Compound **4** was also synthesized in two steps

Scheme I



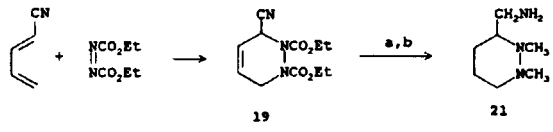
Reagents: a. CH_3OH, CF_3CO_2H; b. H_2NOH; c. SMEAH; d. BH_3, H_2NSO_3H; e. BH_3, NaOCl, NH_4OH; f. p-$O_2NC_6H_4COCl$; g. H_2, Pd-C.

Scheme II



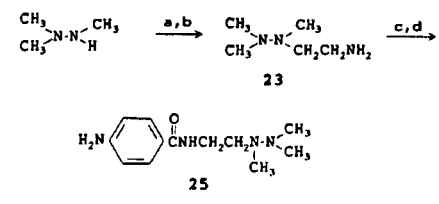
Reagents: a. NaCN, $NaHSO_3$, HCHO; b. LAH; c. p-$O_2NC_6H_4CO_2H$, $SiCl_4$; d. H_2, Pd-C.

Scheme III



Reagents: a. H_2, Pd-C; b. LAH.

Scheme IV



Reagents: a. NaCN, $NaHSO_3$, HCHO; b. LAH; c. p-$O_2NC_6H_4COCl$; d. H_2, Pd-C.

from 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine (**5**). Compound **5** was converted by borane to the corresponding organoborane which reacted with chloramine and gave 1,2-dicarbethoxy-4-aminopiperidazine (**6**) [3]. Alternatively, **6** was obtained from **5**, borane and hydroxylamine-*O*-sulfonic acid [4]. Reduction of **6** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) afforded 1,2-dimethyl-4-aminopiperidazine (**4**) (Scheme I).

Compound **13** was obtained in four steps from 1-methylpiperidazine (**9**). Cyanomethylation of **9** gave **10** which was reduced by lithium aluminum hydride to **11**. Conversion of **11** to **13** was similar to the transformation of **4** to **8** (Scheme II). The bicyclic *p*-aminobenzamide **18** was synthesized from 2-methyl-2,3-diazabicyclo[2.2.1]heptane (**14**) by a route analogous to that used for the conversion of **9** to **13** (Scheme II).

Diels-Alder reaction between 1-cyano-1,3-butadiene and diethyl azodicarboxylate gave adduct **19** in 58% yield. Reduction of the double bond in **19** produced **20**, but lithium aluminum hydride reduction of the latter compound gave a product mixture consisting of three components from which the picrate of **21** was obtained (Scheme III). Attempted conversion of impure **21** to the *p*-nitrobenzamide derivative, however, was unsuccessful.

The acyclic *p*-aminobenzamide **25** was prepared from 1,1,2-trimethylhydrazine [5] *via* a pathway (Scheme IV) similar to that used to transform **9** to **13**.

Compounds **8**, **13** and **25** were evaluated in the isolated cardiac Purkinje fiber preparation for their effects on the action potential upstroke velocity. All three were inactive at $10^{-4}M$ concentration whereas procainamide inhibited the upstroke velocity by $22 \pm 7\%$ (N = 4) at this concentration.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian EM-360 spectrometer as 10% w/v solutions in chloroform-d, using 1% v/v tetramethylsilane (TMS) as the internal standard.

Infrared spectra were recorded on a Perkin-Elmer model 567 grating infrared and model 1430 ratio recording infrared spectrophotometer, Perkin-Elmer Company, Norwalk, Connecticut.

Elemental analyses were performed by Desert Analytic, Tucson, Arizona, and by Baron Consulting Company, Orange, Connecticut.

1,2-Dicarbethoxy-4-(trimethylsilyloxy)-1,2,3,6-tetrahydropyridazine (**1**).

To a solution of 4.85 g (0.034 mole) of 2-(trimethylsilyloxy)-1,3-butadiene [6] in 15 ml of dry toluene was added dropwise 5.81 g (0.0334 mole) of diethyl azodicarboxylate in 5 ml of dry toluene. The mixture was stirred 2 hours at room temperature, and then heated to 120° for 20 hours. The solvent was evaporated under reduced pressure and yielded 10.96 g (theoretical, 10.57 g) of thick viscous yellow oil.

1,2-Dicarbethoxy-4-piperidazinone (**2**).

To 10.96 g (0.0334 mole) of **1** was added 30 ml of methanol. The mixture contained in a stoppered flask was stirred for 2 hours at room temperature. Then 25 drops of trifluoroacetic acid was added and stirring was continued for 1 hour. An additional 25 drops of trifluoroacetic acid was added and the mixture was stirred for another 22 hours. The solvent was evaporated under reduced pressure and gave 8.73 g (theoretical 8.15 g) of a viscous liquid. A small portion of the product was distilled, bp 121° (0.02 mm) (lit [7] bp 145-148°/1 mm); ir (film): 1705-1728 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.26 (t, 6H, two CH_3), 2.57 (t, 2H, $COCH_2$), 3.17-3.97 (m, 4H, two NCH_2), 4.23 (q, 4H, two OCH_2).

1,2-Dicarbethoxy-4-piperidazinone Oxime (**3**).

A mixture of 8.78 g (0.0334 mole) of **2** in 160 ml of absolute ethanol and 3.48 g (0.05 mole) of hydroxylamine hydrochloride and 30 ml of pyridine was refluxed for 3 hours (nitrogen atmosphere). After concentration, the residue was azeotroped with toluene *in vacuo*. The residue was dissolved in ether, extracted twice with water, and the ether layer was dried over magnesium sulfate. The solvent was evaporated under reduced pressure and produced 7.65 g (89%) of thick orange oil; ir (film); 3356 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.26 (t, 6H, two CH_3), 2.45 (t, 2H, CH_2), 2.77-3.87 (m, 4H, two NCH_2), 4.16 (q, 4H, two OCH_2), 8.4 (broad s, 1H, OH, deuterium oxide exchangeable).

1,2-Dimethyl-4-aminopiperidazine (**4**).

Method A.

To a suspension of 8.87 g (0.233 mole) of lithium aluminum hydride in 250 ml of anhydrous ether was added dropwise 4.65 g (0.018 mole) of **3** in 28 ml of anhydrous ether. The reaction mixture was refluxed for 28 hours, cooled with ice and decomposed with 60 g of 40% w/w of aqueous potassium hydroxide solution. The ether was decanted, and the residue was washed four times with ether. The combined ethereal extracts were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was distilled to give 1.4 g (60%) of colorless oil, bp 92-95° (10 mm); ^1H nmr (deuteriochloroform): δ 0.67-2.36 (m, 4H, CH_2 and NCH_2), 2.4 and 2.42 two (s, 3H, NCH_3), 2.6-3.84 (m, 3H, NCH_2, NCH).

A dipicrate derivative was made, mp 218-220° dec (90% ethanol).

Anal. Calcd. for $C_{18}H_{21}N_9O_{14}\cdot H_2O$: C, 35.71; H, 3.83; N, 20.82. Found: C, 35.57; H, 3.43; N, 20.58.

Method B.

To 35 ml of 70% sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in toluene and 40 ml of tetrahydrofuran was added dropwise a solution of 2.8 g (0.012 mole) of 1,2-dicarbethoxy-4-aminopiperidazine (**6**) in 20 ml of tetrahydrofuran under a nitrogen atmosphere. The reaction mixture was refluxed at 90° for 17 hours, cooled and added dropwise to an ice-bath cooled solution of 28 ml of 20% sodium hydroxide. The organic layer was separated and the aqueous layer was washed three times with tetrahydrofuran. The combined organic extract was dried over magnesium sulfate. The solvent was evaporated under reduced

pressure to give 0.24 g (15%) of oil. The ir and ^{1}H nmr were identical to the product **4** obtained under Method A.

1,2-Dicarbethoxy-4-aminopiperidazine (**6**).

Method A.

To 2 g (0.0087 mole) of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine (**5**) in 1.5 ml of tetrahydrofuran was added 2.9 ml of 1*M* borane in tetrahydrofuran. To this solution 0.73 g (0.0064 mole) of hydroxylamine-*O*-sulfonic acid was added and the reaction mixture was heated under reflux for 3 hours. The solution was cooled, acidified with 10% hydrochloric acid and extracted with ether which was discarded. The aqueous solution was cooled and basified to *p*H 11 wth 10% sodium hydroxide solution, and extracted twice with ether. The ether extract was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure and gave 0.2 g (10%) of oil, bp 145-150° (0.17 mm); ir (film): 3290 and 3350 cm^{-1} (NH_2), 1720 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 6H, two CH_3), 1.64 (s, 2H, NH_2, deuterium oxide exchangeable), 1.75-4.03 (m, 7H, cyclic CH_2, two NCH_2, and NCH), 4.3 (q, 4H, two OCH_2).

Method B.

To a cold (0°) solution of 2 g (0.0087 mole) of **5** in 7 ml of tetrahydrofuran was added 3 ml of 1*M* borane in tetrahydrofuran. The reaction mixture was stirred at 0° for 2 hours and allowed to warm to room temperature. Next, it was heated at 50° for 3 hours. The solution was cooled to 0° and 2.9 ml of 2*M* ammonium hydroxide solution was added, followed by the dropwise addition of 9 ml of 5% sodium hypochlorite solution. The mixture was stirred at 0° for 15 minutes, allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was acidified with 10% hydrochloric acid, and extracted twice with ether and the ether layer was discarded. The aqueous solution was basified with 5% sodium hydroxide, extracted five times with ether and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and produced 0.4 g (19%) of oil. The ir and ^{1}H nmr were identical to the product obtained in Method A.

4-Nitro-*N*-(1,2-dimethyl-4-piperidazyl)benzamide (**7**).

To a cold stirred solution of 1.4 g (0.0108 mole) of **4** in 7 ml of chloroform was added 2.01 g (0.0108 mole) of 4-nitrobenzoyl chloride in 7 ml of chloroform. After stirring overnight (nitrogen atmosphere) at room temperature, the mixture was neutralized with 5% sodium hydroxide solution to *p*H 8. The chloroform layer was separated and the aqueous layer was washed three times with chloroform. The combined organic layers were dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was recrystallized from toluene-cyclohexane to give 2 g (67%) of red-orange crystals, mp 152-152.5°; ^{1}H nmr (deuteriochloroform): δ 1.83 (m, 2H, CH_2), 2.47 (s, 6H, two NCH_3), 2.83 (m, 4H, two NCH_2), 4.3 (m, 1H, NCH), 6.9 (broad s, 1H, CONH, deuterium oxide exchangeable), 7.87 and 8.2 two (d, 2H, ArH).

A picrate derivative was made, mp 237-239° dec (aqueous dimethylformamide).

Anal. Calcd. for $C_{19}H_{21}N_7O_{10}$: C, 44.97; H, 4.17; N, 19.32. Found: C, 45.30; H, 3.96; N, 19.07.

4-Amino-*N*-(1,2-dimethyl-4-piperidazyl)benzamide (**8**).

To a solution of 1.12 g (0.0042 mole) of **7** in 80 ml of absolute ethanol was added 0.1 g of 5% Pd-C catalyst. The mixture was hydrogenated at an initial pressure of 57 psi for 1 hour in a Parr pressure reaction apparatus. The catalyst was filtered and the solvent was evaporated under reduced pressure to give 1.05 g (100%) of yellow solid; ^{1}H nmr (deuteriochloroform): δ 1.78 (m, 2H, CH_2), 2.41 (s, 6H, two NCH_3), 2.77 (m, 4H, two NCH_2), 4.28 (broad m, 3H, NCH and $ArNH_2$, deuterium oxide exchangeable), 6.52 (broad s, 1H, CONH, deuterium oxide exchangeable), 6.81 and 7.55 two (d, 2H, ArH).

A hydrochloride derivative was prepared, mp 101-102° (absolute ethanol-ether).

Anal. Calcd. for $C_{13}H_{20}N_4O\cdot HCl$: C, 54.83; H, 7.43; N, 19.67. Found: C, 55.20; H, 7.25; N, 19.49.

1-Cyanomethyl-2-methylpiperidazine (**10**).

This compound was prepared in a manner similar to **22** by the reaction of 8.51 g (0.082 mole) of sodium bisulfite in 20.5 ml of water, 6.1 ml of 37% aqueous formaldehyde solution, 8.2 g (0.082 mole) of 1-methylpiperidazine (**9**) [8] and a solution of 4.02 g (0.082 mole) of sodium cyanide in 11 ml of water. The product amounted to 5.27 g (46%) of colorless liquid, bp 128-132° (26 mm); ir (film): 2230 cm^{-1} (C≡N); ^{1}H nmr (deuteriochloroform): δ 1.66 (m, 4H, two CH_2), 2.53 (s, 3H, NCH_3), 2.86 (q, 4H, two NCH_2), 3.77 (s, 2H, NCH_2CN).

1-(2-Aminoethyl)-2-methylpiperidazine (**11**).

A solution of 5.25 g (0.0377 mole) of **10** in 25 ml of anhydrous ether was added dropwise with stirring to a suspension of 2.7 g (0.069 mole) of lithium aluminum hydride in 225 ml of anhydrous ether. The mixture was refluxed overnight, cooled and the complex was decomposed with 40% w/w aqueous potassium hydroxide solution. The ether layer was decanted and the inorganic sludge was extracted twice with ether. The combined ether layers were dried over magnesium sulfate and the solvent was distilled at atmospheric pressure. The residue was distilled and gave 3.5 g (65%) of colorless liquid, bp 53° (1 mm); ^{1}H nmr (deuteriochloroform): δ 1.48 (s, 2H, NH_2, deuterium oxide exchangeable), 1.58 (m, 4H, two CH_2), 2.47 (s, 3H, NCH_3), 2.74 (m, 8H, four NCH_2).

4-Nitro-*N*-[2-(2-methylpiperidazino)ethyl]benzamide (**12**).

To a mixture of 3.96 g (0.024 mole) of 4-nitrobenzoic acid and 3.4 g (0.024 mole) of **11** in 87 ml of anhydrous pyridine (cooled in an ice-bath) was added 2.41 g (0.014 mole) of silicon tetrachloride. A white precipitate formed immediately. The mixture was stirred at room temperature for 30 minutes and then refluxed for 2 hours under a nitrogen atmosphere. The mixture was poured onto crushed ice, and the precipitate (silica) was filtered and washed with hot ethanol. The washings were combined with the filtrate, and the resulting solution was concentrated and azeotroped with toluene. The residue was dissolved in chloroform and the solution was neutralized with sodium carbonate to *p*H 8. The organic layer was dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane and yielded 1 g (15%) of faint yellow crystals, mp 93-94°; ^{1}H nmr (deuteriochloroform): δ 1.68 (m, 4H, two CH_2), 2.57 (s, 3H, NCH_3), 2.94 (m, 6H, three NCH_2), 3.67 (q, 2H, $CONCH_2$), 7.98 and 8.36 two (d, 2H, ArH),

8.04 (broad s, 1H, CONH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{20}N_4O_3$: C, 57.52; H, 6.90; N, 19.16. Found: C, 57.85; H, 6.95; N, 18.93.

4-Amino-*N*-[2-(2-methylpiperidazino)ethyl]benzamide (**13**).

To a solution of 0.9 g (0.00308 mole) of **12** in 35 ml of absolute ethanol was added 0.09 g of 5% Pd-C catalyst. The mixture was hydrogenated at an initial pressure of 37 psi for 3 hours at room temperature. The catalyst was filtered and the filtrate was evaporated under reduced pressure and afforded 0.8 g (88%) of a thick yellow oil; ir (film): 3218 and 3335 cm^{-1} ($ArNH_2$), 1740 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.6 (m, 4H, two CH_2), 2.52 (s, 3H, NCH_3), 2.87 (m, 6H, three NCH_2), 3.63 (m, 4H, $CONCH_2$, and $ArNH_2$, deuterium oxide exchangeable), 6.67 (d, 2H, ArH), 7.43 (broad s, 1H, CONH, deuterium oxide exchangeable), 7.64 (d, 2H, ArH).

The acetyl derivative was prepared, mp 159-160° (chloroform-ether).

Anal. Calcd. for $C_{15}H_{24}N_4O_2$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.87; H, 8.02; N, 18.06.

2-Cyanomethyl-3-methyl-2,3-diazabicyclo[2.2.1]heptane (**15**).

This compound was prepared in a manner similar to **22** by the reaction of 5.81 g (0.056 mole) of sodium bisulfite in 14 ml of water, 4 ml of 37% aqueous formaldehyde solution, 5.6 g (0.056 mole) of 2-methyl-2,3-diazabicyclo[2.2.1]heptane (**14**) [9], and a solution of 2.74 g (0.056 mole) of sodium cyanide in 7.5 ml of water. The product amounted to 4 g (51%) of a colorless liquid, bp 136-138° (24 mm).

2-(2-Aminoethyl)-3-methyl-2,3-diazabicyclo[2.2.1]heptane (**16**).

This compound was prepared in a manner similar to **11** by the reduction of 4 g (0.0287 mole) of **15** in 21 ml of anhydrous ether with 2.04 g (0.0538 mole) of lithium aluminum hydride in 184 ml of anhydrous ether. The complex was decomposed with 10 g of 40% w/w aqueous potassium hydroxide. Further workup and distillation gave 2.33 g (57%) of colorless liquid, bp 60° (0.8 mm).

A dipicrate derivative was prepared, mp 235° dec (95% ethanol).

Anal. Calcd. for $C_{20}H_{23}N_9O_{14}$: C, 39.16; H, 3.78; N, 20.55. Found: C, 39.18; H, 3.72; N, 20.46.

4-Nitro-*N*-[2-(2-methyl-3,6-endomethylenepiperidazino)ethyl]-benzamide (**17**).

This compound was prepared in a manner similar to **24** by the reaction of 2.33 g (0.0163 mole) of **16** in 26 ml of benzene and 26 ml of dry pyridine, and a solution of 3.93 g (0.0212 mole) of 4-nitrobenzoyl chloride in 26 ml of dry benzene. The product amounted to 1.5 g (32%) of yellow crystals, mp 168-169.5°; ^1H nmr (deuteriochloroform): δ 1.17-2.27 (m, 6H,three CH_2), 2.45 (s, 3H, NCH_3), 2.6-3.8 (m, 6H, two NCH and two NCH_2), 7.52 (broad s, 1H, CONH, deuterium oxide exchangeable), 7.95 and 8.34 two (d, 2H, ArH).

Anal. Calcd. for $C_{15}H_{20}N_4O_3$: C, 59.20; H, 6.62; N, 18.41. Found: C, 59.20; H, 6.65; N, 18.39.

4-Amino-*N*-[2-(2-methyl-3,6-endomethylenepiperidazino)ethyl]-benzamide (**18**).

To a solution of 1.24 g (0.0042 mole) of **17** in 150 ml of absolute ethanol was added 0.124 g of 5% Pd-C catalyst. The mixture was hydrogenated at an initial pressure of 35 psi for 1 hour in a Parr pressure reaction apparatus. The catalyst was filtered and the filtrate was evaporated under reduced pressure and furnished 1.11 g (100%) of yellow oil; ^1H nmr (deuteriochloroform): δ 1.5-2.25 (m, 6H, three CH_2), 2.45 (s, 3H, NCH_3), 2.78-3.55 (m, 6H, two NCH and two NCH_2), 4.06 (broad s, 2H, ArNH, deuterium oxide exchangeable), 6.7 and 7.67 two (d, 2H, ArH), 7.11 (broad s, 1H, CONH, deuterium oxide exchangeable).

A dihydrochloride salt was prepared, mp 164-166° dec (absolute ethanol-ether).

Anal. Calcd. for $C_{15}H_{22}N_4O \cdot 2HCl \cdot C_2H_5OH$: C, 51.91; H, 7.69; N, 14.24. Found: C, 51.66; H, 7.42; N, 14.68.

1,2-Dicarbethoxy-3-cyano-1,2,3,6-tetrahydropyridazine (**19**).

To 0.2 g (0.0025 mole) of 1-cyano-1,3-butadiene [10] in 1 ml of ether was added 0.49 g (0.0025 mole) of diethyl azodicarboxylate in 1 ml of ether. The reaction mixture was stirred at room temperature overnight and then heated to reflux for 2 hours. The solvent was evaporated under reduced pressure and the residue was distilled yielding 0.4 g (58%) of a viscous yellow oil, bp 142-148° (0.4 mm); ir (film): 2225 cm^{-1} (C≡N), 1708 and 1727 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.33 (t, 6H, two CH_3), 3.47-4.14 (m, 3H, NCH_2 and CHCN), 4.37 (q, 4H, two OCH_2), 5.51-6.44 (m, 2H, CH=CH).

1,2-Dicarbethoxy-3-cyanopiperidazine (**20**).

To a solution of 0.4 g (0.0015 mole) of **19** in 5 ml of absolute ethanol was added 0.04 g of 5% Pd-C catalyst. The mixture was hydrogenated for 26 minutes (initial hydrogen pressure was 41 psi) in a Parr pressure reaction apparatus. The catalyst was filtered and the filtrate was evaporated under reduced pressure and gave 0.4 g (99%) of an oil; ir (film): 2225 cm^{-1} (C≡N), 1704 and 1720 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.3 (m, 6H, two CH_3) 2.03 (m, 4H, two CH_2), 3.37-3.7 (m, 1H, CHCN), 3.35 (m, 6H, two OCH_2 and NCH_2).

1,2-Dimethyl-3-aminomethylpiperidazine (**21**).

This compound was prepared in a manner similar to **23** by the reduction of 0.5 g (0.00196 mole) of **20** in 4 ml of ether and 2 ml of THF with 1.18 g (0.03 mole) of lithium aluminum hydride. The reaction mixture was refluxed for 2.5 hours, cooled and decomposed with 11 g of 40% w/w aqueous potassium hydroxide solution. Further workup gave 0.18 g of colorless oil. Thin layer chromatography showed three components, and attempted separation was not successful.

A dipicrate derivative was prepared, mp 199-200° dec (95% ethanol).

Anal. Calcd. for $C_{19}H_{23}N_9O_{14}$: C, 37.94; H, 3.85; N, 20.96. Found: C, 38.00; H, 3.79; N, 20.69.

1,1,2-Trimethyl-2-cyanomethylhydrazine (**22**).

To a magnetically stirred solution of 40.42 g (0.389 mole) of sodium bisulfite in 97 ml of water was added 42.1 g (0.389 mole) of 37% aqueous formaldehyde solution. The temperature of the mixture rose to 54° and was immediately heated to 60° on the steam bath and allowed to cool to 35° over a period of 1 hour. Addition of 28.82 g (0.389 mole) of 1,1,2-trimethylhydrazine [5] to the stirred reaction mixture caused a temperature rise to 55°. The mixture was stored at room temperature for 2.5 hours and then treated with a solution of 19.08 g (0.389 mole) of sodium cyanide in 52 ml of water with efficient stirring so that the two layers became thoroughly mixed. After 3.5 hours the aqueous

mixture was extracted five times with ether. The ethereal extract was dried over magnesium sulfate and concentrated at 20°. Fractional distillation of the residue afforded 30 g (68%) of colorless liquid, bp 30° (0.4 mm); ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 6H, two NCH_3), 2.44 (s, 3H, NCH_3), 3.61 (s, 2H, NCH_2CN).

1,1,2-Trimethyl-2-(2-aminoethyl)hydrazine (**23**).

A solution of 17 g (0.15 mole) of **22** in 94.5 ml of anhydrous ether was added dropwise with stirring (mechanical) to a suspension of 10.46 g (0.275 mole) of lithium aluminum hydride in 933 ml of anhydrous ether. The mixture was refluxed overnight (17 hours), cooled, and the complex was decomposed with 47 g of 40% w/w aqueous potassium hydroxide solution. The ether layer was decanted, the inorganic sludge was extracted twice with ether, and the combined ether extracts were dried over magnesium sulfate. The solvent was evaporated at atmospheric pressure, and the residue was distilled to give 8 g (46%) of colorless liquid: bp 29-30° (1.4 mm).

A dipicrate derivative was prepared, mp 192-193° dec (70% ethanol).

Anal. Calcd. for $C_{17}H_{21}N_9O_{14}$: C, 35.49; H, 3.68; N, 21.91. Found: C, 35.61; H, 3.68; N, 21.80.

4-Nitro-*N*-[2-(1,1,2-trimethylhydrazino)ethyl]benzamide (**24**).

To a stirred solution of 7 g (0.059 mole) of **23** in 85 ml of dry benzene and 85 ml of dry pyridine was added dropwise a solution of 14.42 g (0.077 mole) of 4-nitrobenzoyl chloride in 115 ml of dry benzene (under a nitrogen atmosphere). The resulting mixture was stirred at room temperature for 17 hours, cooled, and basified to *p*H 8 with 5% sodium bicarbonate solution. The organic layer was separated and the aqueous layer was washed three times with chloroform. The combined organic extracts were dried over magnesium sulfate. After concentrating, the residue was azeotroped with toluene *in vacuo*. The residue was decolorized with activated carbon (neutral Norit A) and gave a yellow solid residue. Recrystallization from cyclohexane-benzene afforded 4 g (25%) of pale yellow crystals, mp 86-87.5°; ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3H, NCH_3), 2.45 (s, 6H, two NCH_3), 2.8 (t, 2H, NCH_2), 3.76 (q, 2H, $CONCH_2$), 8.14 and 8.53 two (d, 2H, ArH), 8.25 (broad s, 1H, CONH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{12}H_{18}N_4O_3$: C, 54.12; H, 6.81; N, 21.04. Found: C, 54.15; H, 6.88; N, 21.00.

4-Amino-*N*-[2-(1,1,2-trimethylhydrazino)ethyl]benzamide (**25**).

To a solution of 1.93 g (0.0072 mole) of **24** in 120 ml of absolute ethanol was added 0.2 g of 5% Pd-C catalyst. The mixture was hydrogenated at an initial pressure of 45 psi for 1 hour in a Parr pressure reaction apparatus and produced 1.65 g (97%) of yellow viscous oil; ^{1}H nmr (deuteriochloroform): δ 2.27 (s, 3H, NCH_3), 2.32 (s, 6H, two NCH_3), 2.62 (t, 2H, NCH_2), 3.53 (q, 2H, $CONCH_2$), 4.26 (broad s, 2H, ArNH, deuterium oxide exchangeable), 6.54 and 7.48 two (d, 2H, ArH), 7.24 (broad s, 1H, CONH, deuterium oxide exchangeable).

The acetyl derivative was prepared by dissolving the compound in excess acetic anhydride. After remaining overnight at room temperature, the product obtained was recrystallized from chloroform-ether and gave a white solid, mp 156-158°.

Anal. Calcd. for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.69; H, 7.70; N, 19.87.

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REFERENCES AND NOTES

[1] Abstracted in part from the Ph.D. thesis submitted by K. Abdul-Nabi Ali to the Graduate School of the University of Kentucky, 1989.

[2] M. J. Kornet, K. A.-N. Ali and M. I. Steinberg, *J. Heterocyclic Chem.*, **30**, 109 (1993).

[3] G. W. Kabalka, K. A. R. Sastry, G. W. McCollum and H. Yoshioka, *J. Org. Chem.*, **46**, 4296 (1981).

[4] M. W. Rathke, N. Inoue, K. R. Varma and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 2870 (1966).

[5] J. B. Class, J. G. Aston and T. S. Oakwood, *J. Am. Chem. Soc.*, **75**, 2937 (1953).

[6] M. E. Jung and C. A. McCombs, *Org. Synth. Coll Vol* **VI**, John Wiley and Sons, Inc, New York, 1988, p 445.

[7] R. S. Vartanyan, A. L. Gyul'budagyan, A. Kh. Khanamiryan and S. H. Vartanian, *Arm. Khim. Zh.*, **40**, 596 (1987); *Chem. Abstr.*, **110**, 23824a (1989).

[8] M. J. Kornet and J. Chu, *J. Heterocyclic Chem.*, **18**, 293 (1981).

[9] M. J. Kornet and J. Y. Chu, *J. Pharm. Sci.*, **72**, 94 (1983).

[10] T. Katagire, T. Nito, K. Takabe and J. Tanka, *Nippon Kagaku Kaishi*, **12**, 2370 (1974); *Chem. Abstr.*, **82**, 155249e (1975).