Synthesis of *p*-Aminobenzamides of Several Aminopyrazolidines: Potential Antiarrhythmic Agents Related to Procainamide

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Four heterocyclic amines including 1,2-diethyl-3-aminomethylpyrazolidine (**3**), 1-(2-aminoethyl)-2-methylpyrazolidine (**5**), 1,2-dimethyl-4-aminomethylpyrazolidine (**7**), and 1,2-diethyl-4-aminopyrazolidine (**9**) have been synthesized. Each was acylated with *p*-nitrobenzoyl chloride and afforded the corresponding *p*-nitrobenzamides **10**, **12**, **14**, and **16**. Catalytic reduction of these nitro intermediates gave the corresponding *p*-aminobenzamides **11**, **13**, **15**, and **17**. The latter compounds are analogs of procainamide and two of them, **15** and **17**, were evaluated in the isolated cardiac Purkinje fiber preparation by measuring their effects on the action potential upstroke velocity.

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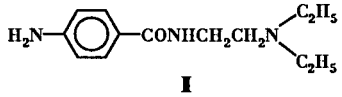
Our laboratories have previously reported the synthesis of procaine [1] and lidocaine [2] analogs as novel local anesthetic agents. In each of these two series of compounds, the alkylated amino group has been replaced by an alkylated pyrazolidine which serves as the basic group of the molecule. The activity observed in the above compounds warranted a similar investigation into the synthesis and pharmacological testing of several procainamide



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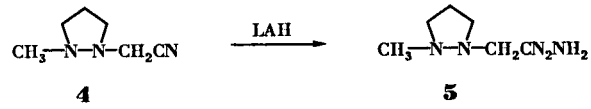
(**I**) analogs. In this report the synthesis of four procainamide analogs embodying an alkylated pyrazolidine ring is described.

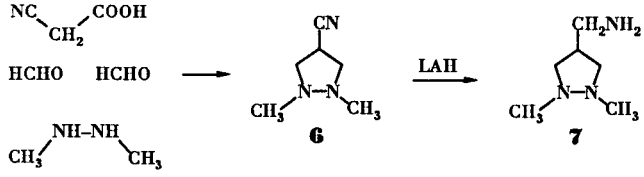
The requisite amino substituted pyrazolidines were obtained by the pathways shown in Schemes I-IV. Treatment of 1,2-diethyl-5-carbethoxy-3-pyrazolidinone (**1**) [1] with ethanolic ammonia gave the amide **2** which was reduced to the aminopyrazolidine **3** by lithium aluminum hydride (Scheme I). Aminopyrazolidine **5** was obtained by lithium aluminum hydride reduction of 1-cyanomethyl-2-methylpyrazolidine (**4**) [2] (Scheme II). A key first step in the synthesis of amine **7** involved a Mannich reaction between dimethylhydrazine, formaldehyde and cyanoacetic acid [3]. Subsequent decarboxylation produced 1,2-dimethyl-4-cyanopyrazolidine (**6**) which was also reduced by lithium aluminum hydride yielding the amine **7** (Scheme III). 1,2-Diethyl-4-aminopyrazolidine (**9**) was obtained according to a previously reported procedure [4]. 1,2-Diethylhydrazine was condensed with 1,3-dimorpholino-2-nitropropane [5] giving 1,2-diethyl-4-nitropyrazolidine. The latter was reduced with tin and hydrochloric acid producing amine **9** (Scheme IV).

Scheme II



4 **5**

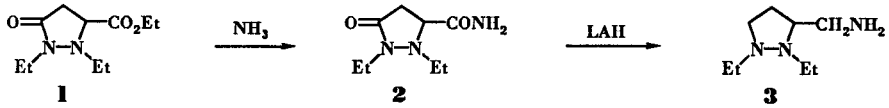
Scheme III



6 **7**

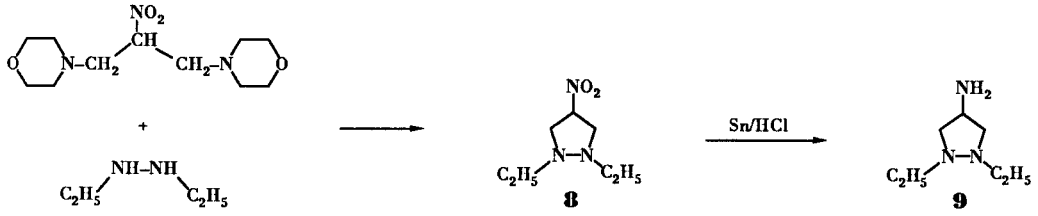
Acylation of amines **3**, **5**, **7** and **9** with *p*-nitrobenzoyl chloride afforded the corresponding *p*-nitrobenzamides **10**, **12**, **14** and **16**. These intermediates were then catalytically reduced using 5% palladium on carbon catalyst and formed the corresponding *p*-aminobenzamides **11**, **13**, **15** and **17** (Scheme V).

Scheme I

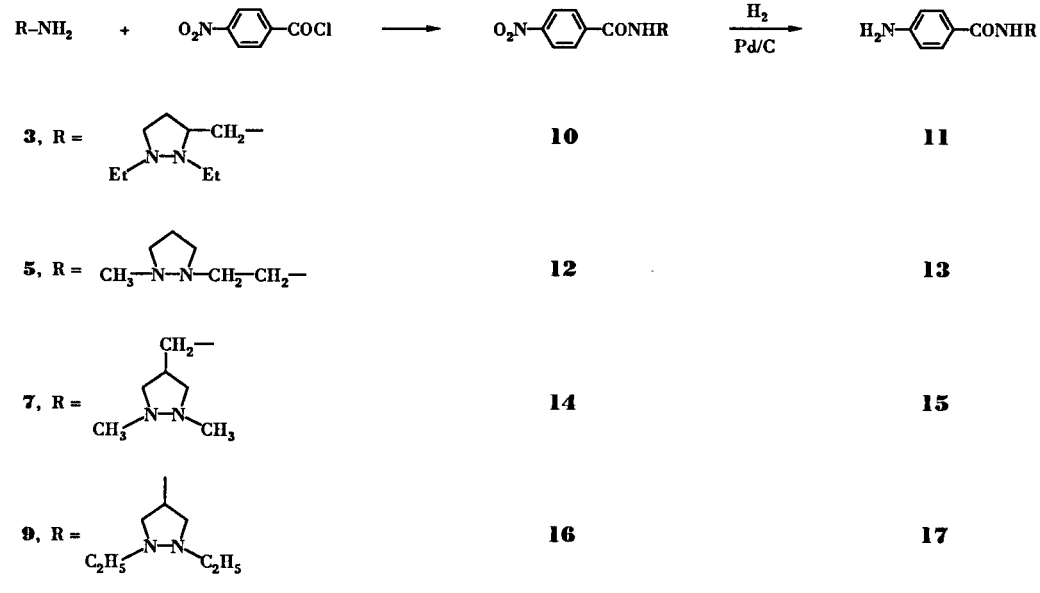


1 **2** **3**

Scheme IV



Scheme V



Compounds **15** and **17** were chosen for evaluation in the isolated cardiac Purkinje fiber preparation for their effects on the action potential upstroke velocity (an index of sodium channel activity). Procainamide (10^{-4} *M*) inhibited the upstroke velocity by 22 ±7% (N=4), whereas compounds **15** (N = 4) and **17** (N = 5) were inactive at this concentration. Procainamide acts as an antiarrhythmic agent primarily by virtue of its inhibition of the rapid sodium channel in cardiac tissues [6]. Therefore, to the extent that **15** and **17** would be dependent on the inhibition of the sodium channel for antiarrhythmic activity, these compounds would be expected to be much less active than procainamide.

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 Analytics, Tucson, Arizona, and by Baron Consulting Company, Orange, Connecticut.

1,2-Diethyl-5-carboxamido-3-pyrazolidinone (**2**).

To a saturated solution of ammonia in absolute ethanol (130 ml) cooled by an ice-bath was added dropwise 26.6 g (0.124 mole) of 1,2-diethyl-5-ethoxycarbonyl-3-pyrazolidinone (**1**) [1]. The mixture was stoppered and left for two days at room temperature. The solution was cooled in an ice-bath and ammonia gas was introduced in a slow stream for 1/2 hour. The crystals produced were filtered and washed with ether. Recrystallization from absolute ethanol afforded 18 g (79%) of product, mp 144-145°; ^{1}H nmr (deuteriochloroform): δ 1.17 (t, 3H, CH_3), 1.22 (t, 3H, CH_3), 2.93 (q, 2H, NCH_2), 3.1 (q, 2H, NCH_2), 2.98 (s, 1H, CHCO), 3.68-4.24 (m, 2H, CH_2CO), 7.06 and 7.33 (broad s, 2H, $CONH_2$, deuterium oxide exchangeable).

Anal. Calcd. for $C_8H_{15}N_3O_2$: C, 51.87; H, 8.16; N, 22.68. Found: C, 51.98; H, 8.32; N, 22.78.

1,2-Diethyl-3-aminomethylpyrazolidine (**3**).

To 35 ml of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene diluted with 8 ml of toluene under a nitrogen atmosphere was added a suspension of 4 g (0.021 mole) of **2** in 110 ml of tetrahydrofuran. The mixture was refluxed for 17 hours

cooled and added dropwise to 35 ml of 20% sodium hydroxide with stirring (magnetic) and ice-bath cooling. The organic layer was separated and the aqueous layer was extracted 5 x with ether. The combined organic layer was dried (magnesium sulfate) and the solvent was distilled through a glass column (1 x 30 cm). The residue was distilled and gave 2.44 g (72%) of a colorless liquid, bp 46° (0.4 mm); ir (film): 3350 and 3260 cm^{-1} (NH_2); ^1H nmr (deuteriochloroform): δ 1.09 (t, 6H, CH_3), 1.43 (s, 2H, NH_2, deuterium oxide exchangeable), 1.94 (m, 2H, CH_2), 2.69-3.92 (m, 9H, NCH_2 and NCH).

A dipicrate was prepared, mp 170-172° dec (95% ethanol).

Anal. Calcd. for $C_{20}H_{25}N_9O_{14}$: C, 39.03; H, 4.09; N, 20.48. Found: C, 39.12; H, 4.03; N, 20.39.

Reduction of **2** with lithium aluminum hydride in tetrahydrofuran gave **3** in 54% yield.

1-(2-Aminoethyl)-2-methylpyrazolidine (**5**).

A solution of 13.66 g (0.109 mole) of 1-cyanomethyl-2-methylpyrazolidine **4** [2] in 76 ml of anhydrous ether was added dropwise with stirring (mechanical) to a suspension of 7.62 g (0.2 mole) of lithium aluminum hydride in 680 ml of anhydrous ether. The mixture was refluxed overnight, cooled, and decomposed with 40% (w/w) aqueous potassium hydroxide. The ether layer was decanted, the inorganic sludge was extracted twice with ether, and the combined extracts were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was distilled and gave 9.45 g (67%) of colorless liquid, bp 86-94° (24 mm).

A dipicrate was prepared, mp 229° dec (95% ethanol).

Anal. Calcd. for $C_{18}H_{21}N_9O_{14}$: C, 36.80; H, 3.60; N, 21.46. Found: C, 36.90; H, 3.57; N, 21.25.

1,2-Dimethyl-4-cyanopyrazolidine (**6**).

To 15.96 g (0.12 mole) of 1,2-dimethylhydrazine dihydrochloride was added dropwise with cooling 16.58 g (0.12 mole) of potassium carbonate in 14 ml of water (nitrogen atmosphere). After stirring for 10 minutes at room temperature, 10.21 g (0.12 mole) of cyanoacetic acid in 16 ml of water was added dropwise, followed by 19.6 ml of 37% aqueous formaldehyde. The *p*H of the mixture was 5-6. A few drops of glacial acetic acid were added to make the *p*H 4-5. The mixture was stirred at room temperature for 52 hours and then decarboxylated by heating in an oil bath (100°) for 24 hours with a nitrogen purge. After cooling, sodium carbonate was added to *p*H 7-8 and the mixture was extracted with ether (48 hours) in a liquid-liquid extractor. The ether extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was distilled and afforded 3.7 g (25%) of a faint yellow liquid, bp 106° (20 mm); ir (film): 2240 cm^{-1} ($C\equiv N$); ^1H nmr (deuteriochloroform): δ 2.46 (s, 6H, NCH_3), 3.16 (m, 1H, CHCN), 3.21 (s, 4H, NCH_2).

1,2-Dimethyl-4-aminomethylpyrazolidine (**7**).

To a suspension of 2.78 g (0.0732 mole) of lithium aluminum hydride in 225 ml of anhydrous ether was added dropwise a solution of 5 g (0.04 mole) of **6** in 25 ml of anhydrous ether. The mixture was refluxed overnight (21 hours), cooled and decomposed with 40% (w/w) aqueous potassium hydroxide. The ether layer was decanted and the inorganic sludge was washed six times with ether. The combined ether extracts were dried over magnesium sulfate, and the solvent was distilled at atmospheric pressure. The residue was distilled giving 3.55 g (69%) of colorless liquid, bp 83-85° (29 mm); ir (film): 3350 and 3270 cm^{-1} (NH_2); ^1H nmr (deuteriochloroform): δ 1.32 (s, 2H, NH_2, deuterium oxide exchangeable), 2.46 (s, 6H, NCH_3), 2.59-3.21 (m, 7H, NCH_2 and CH).

4-Nitro-*N*-(1,2-diethyl-3-pyrazolidylmethyl)benzamide (**10**).

To a stirred solution of 3 g (0.019 mole) of **3** in 30 ml of dry pyridine and 30 ml of dry benzene was added dropwise a solution of 4.62 g (0.025 mole) of 4-nitrobenzoyl chloride in 30 ml of dry benzene (nitrogen atmosphere). The mixture was refluxed for 1.5 hours, cooled in an ice-bath and basified to *p*H 8 with 5% sodium carbonate 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 under reduced pressure leaving a thick reddish oil which was purified by dry column (1.5 x 22 in) chromatography. The silica gel (Woelm) column was developed with ethyl acetate and the product band was eluted with methanol. Removal of solvent gave a residue which was recrystallized from petroleum ether (bp 38-58°)-benzene. The crystals amounted to 3 g (51%), mp 63-64°; ^1H nmr (deuteriochloroform): δ 1.1 (t, 6H, CH_3), 2.1 (m, 2H, CH_2), 2.7 (m, 4H, NCH_2), 3.12-3.91 (m, 5H, NCH_2 and NCH), 7.16 (broad s, 1H, CONH, deuterium oxide exchangeable), 8.02 (d, 2H, ArH), 8.4 (d, 2H, ArH).

Anal. Calcd. for $C_{15}H_{22}N_4O_3$: C, 58.80; H, 7.23; N, 18.28. Found: C, 58.78; H, 7.19; N, 18.21.

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

This compound was prepared similarly to **10** from 5 g (0.038 mole) of **5** and 9.41 g (0.0507 mole) of 4-nitrobenzoyl chloride without the need for dry column chromatography. Workup afforded a brown solid which was recrystallized from ethyl acetate (Norit A charcoal) yielding 4.3 g (40%) of faint yellow needles, mp 152.5-153.5°; ^1H nmr (deuteriochloroform): δ 2.09 (m, 2H, CH_2), 2.5 (s, 3H, NCH_3), 2.92 (m, 6H, NCH_2), 3.71 (q, 2H, $CONCH_2$), 7.99 (d, 2H, ArH), 8.37 (d, 2H, ArH), 8.54 (broad s, 1H, CONH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.20; H, 6.54; N, 20.06.

4-Nitro-*N*-(1,2-dimethyl-4-pyrazolidylmethyl)benzamide (**14**).

To a cold solution of 1 g (0.00775 mole) of **7** in 5 ml of chloroform was added with stirring 1.44 g (0.00775 mole) of 4-nitrobenzoyl chloride in 5 ml of chloroform. The solution was stirred overnight and then basified with 5% sodium hydroxide to *p*H 8. The chloroform layer was separated, the aqueous layer was washed four times with chloroform, and the combined chloroform extracts were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was recrystallized from cyclohexane-toluene to give 1.61 g (75%) of crystals, mp 106.5-108°; ^1H nmr (deuteriochloroform): δ 2.52 (s, 6H, NCH_3), 2.63-3.76 (m, 7H, NCH_2 and CH), 7.89 (broad s, 1H, CONH, deuterium oxide exchangeable), 8.17 (d, 2H, ArH), 8.51 (d, 2H, ArH).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.02; H, 6.51; N, 19.97.

4-Amino-*N*-(1,2-diethyl-3-pyrazolidylmethyl)benzamide (**11**).

To a solution of 1.3 g (0.0042 mole) of **10** in 50 ml of absolute ethanol was added 0.13 g of 5% Pd-C catalyst. The mixture was hydrogenated at an initial pressure of 45 psi for 3 hours at room

temperature. The catalyst was filtered and the filtrate was evaporated under reduced pressure leaving a viscous oil which solidified overnight. Recrystallization from petroleum ether (bp 38-58°)-benzene afforded 0.8 g (68%) of product, mp 94-96°; ^{1}H nmr (deuteriochloroform): δ 1.1 (t, 6H, CH_3), 2.00 (m, 2H, CH_2), 2.71 (m, 4H, NCH_2), 3.03-4.32 (m, 7H, NCH_2, NCH, and $ArNH_2$), 6.7 (d, 2H, ArH), 7.7 (d, 2H, ArH), and 6.78-7.00 (broad s, 1H, CONH).

Anal. Calcd. for $C_{15}H_{24}N_4O$: C, 65.18; H, 8.75; N, 20.27. Found: C, 64.91; H, 8.84; N, 20.12.

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

A mixture of 0.75 g (0.0027 mole) of **12**, 0.075 g of 5% Pd-C in 50 ml of absolute ethanol was hydrogenated for 1 hour in a manner similar to the preparation of **11**. Workup gave 0.58 g (87%) of a viscous oil; ^{1}H nmr (deuteriochloroform): δ 2.09 (m, 2H, CH_2), 2.47 (s, 3H, NCH_3), 2.86 (m, 6H, NCH_2), 3.66 (q, 2H, $CONCH_2$), 4.15 (broad s, 2H, $ArNH_2$, deuterium oxide exchangeable), 6.66 (d, 2H, ArH), 7.64 (d, 2H, ArH), 7.83 (broad s, 1H, CONH, deuterium oxide exchangeable).

A dipicrate was prepared, mp 173.5-174.5° (95% ethanol).

Anal. Calcd. for $C_{25}H_{26}N_{10}O_{15}$: C, 42.50; H, 3.71; N, 19.82. Found: C, 42.47; H, 3.75; N, 19.67.

4-Amino-*N*-(1,2-dimethyl-4-pyrazolidylmethyl)benzamide (**15**).

Hydrogenation was similar to **11** starting from 2 g (0.00719 mole) of **14**, and 0.2 g of 5% Pd-C in 120 ml of absolute ethanol for 30 minutes. Workup produced 1.6 g (90%) of a low melting solid; ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 6H, NCH_3), 2.55-3.27 (m, 5H, NCH_2, CH), 3.48 (t, 2H, $CONCH_2$), 4.01 (broad s, 2H, $ArNH_2$), 6.61 (d, 2H, ArH), 7.58 (d, 2H, ArH), 6.81 (broad s, 1H, CONH).

An acetamide was prepared, mp 72-75° (ethanol-ether).

Anal. Calcd. for $C_{15}H_{22}N_4O_2 \cdot 0.5C_2H_5OH$: C, 61.32; H, 8.04; N, 17.88. Found: C, 60.95; H, 7.59; N, 17.80.

4-Amino-*N*-(1,2-diethyl-4-pyrazolidyl)benzamide (**17**).

Hydrogenation (30 minutes) was carried out similar to **11** starting from 3 g (0.0103 mole) of 4-nitro-*N*-(1,2-diethyl-4-pyrazolidyl)-benzamide (**16**) [7] and 0.22 g of 5% Pd-C in 20 ml of absolute ethanol. Workup afforded 2.4 g (89%) of solid, mp 118-120° (lit [7] mp 119-121°).

Acknowledgement.

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