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The synthesis of 1,2-diethyl-4-hydroxymethylpyrazolidine (**II**) was accomplished in two steps from 1,2-diethyl-4-ethoxycarbonylpyrazolidine (**I**). Also, 1,2-dimethyl-4-hydroxypiperidazine (**VI**) was prepared in three steps from 1,2-diethoxycarbonyl-1,2,3,6-tetrahydropyridazine (**IV**). The two alcohols were added to several aryl isocyanates and afforded fourteen new phenylurethan derivatives which showed moderate anticonvulsant activity in mice.

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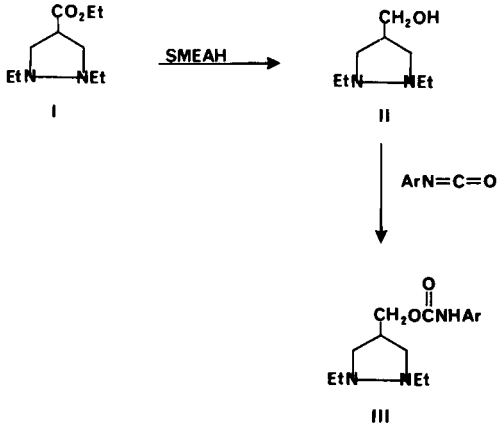
A recent report from these laboratories describes the synthesis and anticonvulsant testing of a series of arylurethans of 1,2-dimethyl-3-hydroxymethylpiperidazine [1]. Other earlier investigations [2] were concerned with several related series of phenylurethans. Key intermediates in all of these series are hydroxyl containing *N*-alkylated pyrazolidines and piperidazines. The present paper describes the synthesis of two related intermediates, 1,2-diethyl-4-hydroxymethylpyrazolidine (**II**) and 1,2-dimethyl-4-hydroxypiperidazine (**VI**) and their adduction to aryl isocyanates producing two new series of phenylurethans **III** and **VII**.

A Mannich reaction between malonic acid, formaldehyde and 1,2-diethylhydrazine with subsequent decarboxylation and esterification afforded **I** by modifying an earlier procedure [3]. Compound **I** was then reduced with sodium bis(2-methoxyethoxy)aluminum hydride to give the intermediate **II** (Scheme I).

Scheme I, SMEAH = $NaAlH_2(OCH_2CH_2OCH_3)_2$

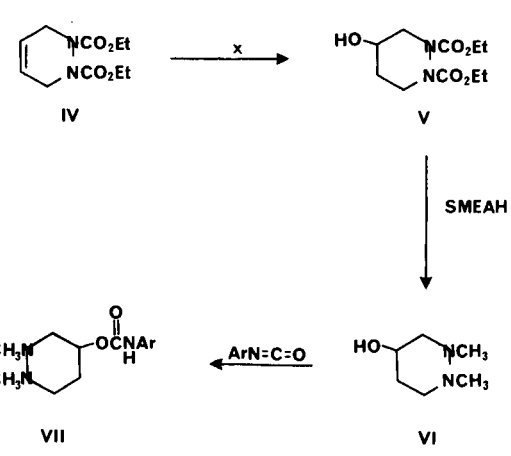


I II III

Synthesis of **VI** began by hydroboration-oxidation [4] of olefin **IV** producing the neutral alcohol **V** in 66% yield. Alternatively, **V** was obtained by oxymercuration-demercuration [5] of olefin **IV** in 75% yield. Reduction of **V** with sodium bis(2-methoxyethoxy)aluminum hydride gave alcohol **VI** in 80% yield (Scheme II). Initially lithium aluminum hydride/tetrahydrofuran was used in the reduction of **V**, but the yield of alcohol **VI** was poor. The advantages of sodium bis(2-methoxyethoxy)aluminum hydride over lithium aluminum hydride for the reduction of hydroxy substituted carbonyl compounds has been pointed out by others [6].

Scheme II, SMEAH = $NaAlH_2(OCH_2CH_2OCH_3)_2$

x = BH_3, H_2O_2, ^-OH or $Hg(OAc)_2$, $NaBH_4$, ^-OH



Both **II** and **VI** added readily to substituted aryl isocyanates and formed **III** and **VII**, respectively, in good yields (Scheme I and II).

The two series of compounds (Tables I and II) were tested in the maximal electroshock (MES) seizure and pentylenetetrazol (sc Met) seizure threshold tests for anticonvulsant activity and neurotoxicity in mice [7] by known methods [8]. Among the pyrazolidine derived phenylurethans compounds **IIIc**, **IIIe**, **IIIf**, and **IIIg** displayed MES activity at 30 minutes. Compounds **IIIc**, **IIIe**, and **IIIf** were active at 100 mg/kg, but **IIIe** was also toxic at this dose. The most active compound **IIIg** exhibited protection but also toxicity at 30 mg/kg.

Compounds **VIIa**, **VIIc**, and **VIIg** were active members of the piperidazine-derived phenylurethans in the MES test at 30 minutes. All three showed activity at 100 mg/kg, however, **VIIc** and **VIIg** were also toxic at this dose. Neither series showed sc Met activity at doses up to 100 mg/kg. Compounds **VIIa** and **VIIg** were selected as candidates for Phase II studies with the following results.

Table I

Physical Properties of Arylurethans of 1,2-Diethyl-4-hydroxymethylpyrazolidine

Compound	Ar	Melting Point, °C	Yield [a] %	Formula	Analysis % Calcd./Found C	H	N
IIIa	*p*-$CH_3C_6H_4$	158-159 [b]	58	$C_{22}H_{28}N_6O_9$	50.77	5.42	16.15
					50.78	5.28	16.12
IIIb	*p*-$CH_3OC_6H_4$	151.5-153 [b]	85	$C_{22}H_{28}N_6O_{10}$	49.25	5.26	15.66
					49.50	5.23	15.84
IIIc	*p*-$C_2H_5OC_6H_4$	68-69 [c]	80	$C_{17}H_{27}N_3O_3$	63.53	8.47	13.07
					63.48	8.64	13.31
IIId	*p*-FC_6H_4	149-151 [b]	89	$C_{21}H_{25}FN_6O_9$	48.09	4.81	16.02
					47.81	4.56	16.33
IIIe	*p*-ClC_6H_4	89-90 [c]	97	$C_{15}H_{22}CNN_3O_2$	57.78	7.11	13.48
					58.02	7.35	13.70
IIIf	*p*-BrC_6H_5	98-99 [c]	89	$C_{15}H_{22}BrN_3O_2$	50.57	6.22	11.79
					50.79	6.29	12.06
IIIg	2,6-$(CH_3)_2C_6H_3$	66-68 [c]	75	$C_{17}H_{27}N_3O_2$	66.85	8.91	13.76
					66.45	9.19	14.04

[a] Yields are that of the free base. [b] Picrate, from 95% ethanol. [c] Tolulene-hexane.

Table II

Physical Properties of Arylurethans of 1,2-Dimethyl-4-hydroxypiperidazine

Compound	Ar	Melting Point, °C	Yield [a] %	Formula	Analysis % Calcd./Found C	H	N
VIIa	*o*-$CH_3C_6H_4$	72-73 [b]	80	$C_{14}H_{21}N_3O_2$	63.85	8.04	15.96
					63.99	8.10	16.06
VIIb	*o*-ClC_6H_4	182-183 [c]	76	$C_{13}H_{19}Cl_2N_3O_2$ [d]	48.76	5.98	13.12
					48.81	6.05	13.03
VIIc	*p*-$CH_3C_6H_4$	139-140 [e]	73	$C_{14}H_{21}N_3O_2$	63.85	8.04	15.96
					64.10	8.11	15.81
VIId	*p*-ClC_6H_4	123-124 [f]	78	$C_{13}H_{18}ClN_3O_2$	55.03	6.39	14.81
					54.84	6.30	14.83
VIIe	*p*-$CH_3OC_6H_4$	102-104 [f]	86	$C_{14}H_{21}N_3O_3$	60.20	7.58	15.04
					60.24	7.58	15.03
VIIf	*p*-$C_2H_5OC_6H_4$	135-136 [e]	65	$C_{15}H_{23}N_3O_3$	61.41	7.90	14.32
					61.46	7.96	14.33
VIIg	2,6-$(CH_3)_2C_6H_3$	98-99 [b]	87	$C_{15}H_{23}N_3O_2$	64.96	8.36	15.15
					64.97	8.39	15.22

[a] Yeilds are that of free base. [b] Cyclohexane-hexane. [c] Ethanol-ether. [d] Hydrochloride. [e] Toluene. [f] Toluene-hexane.

Compound **VIIa** had ED_{50}: 55(43-68) mg/kg and TD_{50}: 123(102-135) mg/kg. Compound **VIIg** had ED_{50}: 31(25-37) mg/kg and TD $_{50}$: 117(96-140) mg/kg. Compounds **VII** are significantly more active than their five-membered ring homologs [9] reported earlier.

EXPERIMENTAL

Melting points were determined on either a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were taken on either a Perkin-Elmer 700 or Perkin-Elmer 1430 spectrophotometer as liquid films or potassium bromide pellets. The nmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained on an RMU-7 double focusing spectrometer by Hitachi/Perkin-Elmer. Elemental analyses were performed by Baron Consulting Co., Orange, CT and Micanal, Tucson, AZ.

1,2-Diethyl-4-ethoxycarbonylpyrazolidine (**I**).

This compound was prepared by modification of a previous procedure [3]. A mixture of 32.2 g (0.20 mole) of 1,2-diethylhydrazine dihydrochloride in 67 ml of water was neutralized with 27.6 g (0.20 mole) of potassium carbonate. Next, 20.8 g (0.20 mole) of malonic acid was added, followed by the dropwise addition of 32.6 ml of 37% aqueous formaldehyde under a nitrogen atmosphere. The mixture was stirred at room temperature for 36 hours

(carbon dioxide evolution), treated with 32 ml of concentrated hydrochloric acid and refluxed for 4 hours. After evaporation to near dryness the residue was treated with 530 ml of absolute ethanol and evaporated. The residue was suspended in 200 ml of absolute ethanol and 22 g of dry hydrogen chloride was passed in. The mixture was gently refluxed for 17 hours and evaporated *in vacuo*. The residue was carefully neutralized to *p*H 8-9 with 40% aqueous sodium hydroxide followed by extraction with ether (6 x 50 ml). Drying (magnesium sulfate) and evaporation gave 25.4 g of crude product which was distilled and produced 13 g (33%) of a colorless liquid, bp 70-75° (0.4 mm); ^{1}H nmr (deuteriochloroform): δ 0.82-1.48 (m, 9H), 2.15-3.92 (m, 9H, including q at 2.58), 4.10 (q, 2H).

1,2-Diethyl-4-hydroxymethylpyrazolidine (**II**).

A solution of the ester **I** in 20 ml of tetrahydrofuran was added dropwise to a mixture of 27 ml of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene and 30 ml of tetrahydrofuran. The mixture was stirred at room temperature for 17 hours and refluxed for 3 hours. The cooled reaction mixture was added dropwise to 44 ml of a stirred, cooled solution of 20% sodium hydroxide. The organic phase was separated and the aqueous phase was extracted four times with 55 ml portions of ether. After combining and drying (magnesium sulfate) the solution was evaporated *in vacuo*. The residue was distilled and afforded 6.8 g (66%) of a colorless liquid, bp 71° (0.15 mm); ^{1}H nmr (deuteriochloroform): δ 1.04 (t, 6H), 2.08-3.89 (m, 11H), 3.91 (s, 1H, deuterium oxide exchangeable).

1,2-Diethoxycarbonyl-4-hydroxypiperidazine (**V**) [10].

Method A.

A solution of 1,2-diethoxycarbonyl-1,2,3,6-tetrahydropyridazine (**IV**) in 45 ml of tetrahydrofuran was added dropwise over a period of 15 minutes to a stirred solution of 25.1 ml of 1 *M* borane in tetrahydrofuran at 0°. After stirring at 0-5° for 2.5 hours, 50 ml of water was carefully added to hydrolyse excess borane. A cold solution of 3.4 ml of 30% hydrogen peroxide in 45 ml of 6 *N* sodium hydroxide was added with cooling while maintaining the temperature of the reaction at $<5°$. The mixture was stirred for 2 hours at 0-5°. The tetrahydrofuran layer was separated and the residue was extracted three times with 25 ml portions of tetrahydrofuran. The combined organic extract was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was distilled and gave 4.13 g (66%) of a thick liquid, bp 138-144° (0.30 mm); ^{1}H nmr (deuteriochloroform): δ 1.28 (t, 6H), 1.51-4.68 (m, 12H including deuterium oxide exchangeable H at 3.9).

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.38. Found: C, 48.82; H, 7.35; N, 11.63.

Method B [10].

To a solution of 4.78 g (0.015 mole) of mercuric acetate, 15 ml of water, and 15 ml of tetrahydrofuran was added 3.42 g (0.015 mole) of 1,2-diethoxycarbonyl-1,2,3,6-tetrahydropyridazine (**IV**). The initially yellow colored solution became colorless after 3 hours stirring at room temperature. After one more hour a solution of 15 ml of 3 *M* sodium hydroxide was added followed by 15 ml of 0.5 *M* sodium borohydride in 3 *M* sodium hydroxide. Precipitated mercury was allowed to settle and sodium chloride was added. The organic phase was separated and the residue was extracted two times with 10 ml portions of tetrahydrofuran. The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. Distillation afforded 2.77 g (75%) of product, bp 163-165° (1.5 mm) which was identical in all respects with Compound **V** obtained by Method A.

1,2-Dimethyl-4-hydroxypiperidazine (**VI**).

A solution of 35.7 g (0.145 mole) of **V** in 100 ml of tetrahydrofuran was added dropwise to a stirred (magnetic) mixture of 250 ml (1.74 moles) of 70% sodium bis(2-methoxyethoxy)aluminum hydride and 175 ml of tetrahydrofuran over a period of 1.25 hours. The mixture was refluxed for 18 hours. The cooled reaction mixture was added dropwise to a solution of 320 ml of 20% aqueous sodium hydroxide cooled by an ice-water bath (gas evolution). The organic phase was separated and the aqueous phase was extracted three times with 100 ml portions of ether. The combined organic layer was dried (magnesium sulfate) and concentrated *in vacuo* to 20 g of crude residue. Distillation gave 15 g (80%) of colorless oil, bp 62° (0.08 mm); ^{1}H nmr (deuteriochloroform): δ 1.27-4.09 (m, 14H, including singlets at 2.46 and 2.50 and exchangeable H at 3.35).

Phenylurethans of 1,2-Diethyl-4-hydroxymethylpyrazolidine (**III**) and 1,2-Dimethyl-4-hydroxypiperidazine (**VII**).

A mixture of 1.3 g (0.01 mole) of 1.2-dimethyl-4-hydroxypiperidazine (**VI**), 1.54 g (0.01 mole) of *p*-chlorophenyl isocyanate and 13 ml of dry toluene was refluxed for 19 hours. The cooled mixture was extracted with 30 ml of 2 *N* hydrochloric acid. The acidic extract was washed with 20 ml of benzene and filtered through a glass-sintered funnel. The clear filtrate was basified with solid sodium carbonate, extracted into chloroform and dried (magnesium sulfate). After filtering, the solvent was evaporated *in vacuo* and the residue was recyrstallized from toluene-hexane affording 2.2 g (78%) of product, mp 123-124°; ^{1}H nmr (deuteriochloroform): δ 1.5-2.21 (m, 2H), 2.53 (s, 6H), 2.7-3.25 (m, 4H), 4.78-5.31 (m, 1H), 7.09 (broad s, 1H), 7.4 (s, 4H).

Phenylurethans obtained as oils which could not be crystallized were converted to picrate or hydrochloride salts.

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