Table III—Effect of polysorbate 80 on the Permeability of Goldfish Membranes to 4-Aminoantipyrine, as Shown by Absorption, Exsorption, and Pharmacologic Effect Measurements

Type of Experiment[a]	Rate Constant with 0.01% Polysorbate min.$^{-1}$ ($\pm SD$) $\times 10^3$	Rate Constant without Polysorbate min.$^{-1}$ ($\pm SD$) $\times 10^3$	Ratio with : without Surfactant
Absorption	4.2 ($\pm$0.7)[b]	2.3 ($\pm$0.2)[b]	1.8
Exsorption	5.6 ($\pm$1.1)[c]	3.3 ($\pm$1.0)[c]	1.7
Overturn	—[d]	—[d]	1.5

[a] All experiments done at pH 7.0 at 20° ± 0.5°. [b] Mean of rate constants calculated from absorption data for each fish at each time. [c] Mean of individual rate constants. [d] Mean CT values, as g. min./l. ($\pm SD$): 61.2 ($\pm$10.2) with polysorbate; 91.5 ($\pm$10.2) without polysorbate.

probably not due (solely) to the leaching or extraction of membrane components.

The accidental death of one fish shortly after the start of an exsorption experiment, apparently due to an overdose of drug, provided a means of assessing the role of blood circulation on exsorption. The exsorption of 4-aminoantipyrine from the dead fish was much slower than from a living fish (Fig. 5). This is interpreted as being indicative of a change in the rate-limiting step in the exsorption process. Apparently, diffusion of drug through body tissues rather than through the external membranes becomes exsorption rate limiting when there is no blood circulation.

The results of these studies show that polysorbate 80 increases directly the permeability of biologic membranes of the goldfish to nonionized 4-aminoantipyrine. As shown in Table III, this effect is evident in absorption and exsorption studies involving chemical assays as well as in experiments in which absorption rate was determined indirectly on the basis of the time of onset of a pharmacologic effect. The ratio of rate constants with : without surfactant was similar in the three types of experiments.

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New Local Anesthetics II: Lidocaine Analogs Embodying Pyrazolidine as the Basic Moiety

MILTON J. KORNET and POO AN THIO

Abstract □ The synthesis of a number of novel pyrazolidinylacylanilides and their precursors is reported. In the course of molecular modification, the anilinocarbonyl or anilinocarbonylmethyl group has been attached to the 1-, 3-, and 4-positions of the pyrazolidine ring. These anilides exhibited varying degrees of local anesthetic activity.

Keyphrases □ Lidocaine analogs—local anesthetic □ Pyrazolidinylacylanilides and precursors—synthesis □ Anesthetic activity—lidocaine analogs □ IR spectrophotometry—identity □ NMR spectrometry—identity □ Vapor phase chromatography—separation, analysis

The local anesthetic activity of a series of esters containing the pyrazolidine ring has been reported by these laboratories (1). Subsequently, further testing of the compounds on the isolated nerve indicated that in general they were more potent than lidocaine.[1] These promising results prompted the authors to prepare a number of novel pyrazolidinylacylanilides and evaluate their local anesthetic activity, especially since the amide linkage possesses the special advantage of hydrolytic stability as compared with an ester bond.

Local anesthetics have been the subject of many reviews (2, 3) and it has been shown that the distance between the amide carbonyl and the basic amino group influences the activity to a very large extent. Maximum activity is generally observed when the two groups are separated by either one or two carbon atoms (4). With this in mind, efforts were directed to the synthesis of the several analogs in this series which would result

[1] Unpublished results from the Astra Research Laboratories.

from the attachment of the anilinocarbonyl or anilinocarbonylmethyl group to the 1-, 3-, and 4-positions of the pyrazolidine ring.

SYNTHESIS

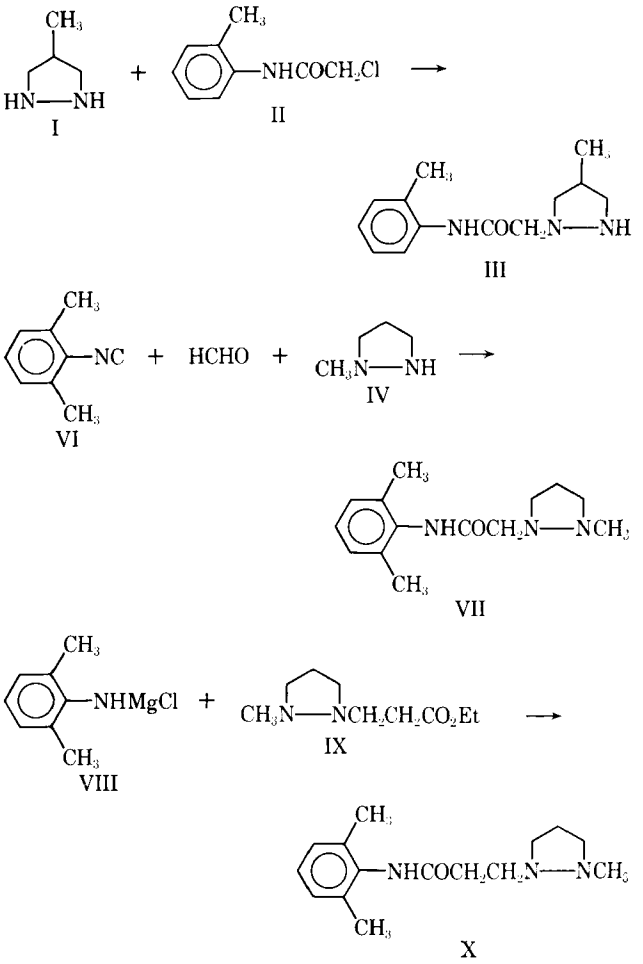
1-Pyrazolidinylacylanilides—1-(2′-Methylphenylcarbamoylmethyl)-4-methylpyrazolidine (III) was readily prepared by the alkylation of 4-methylpyrazolidine (I) (5) with *N*-chloroacetyl-2-methylaniline (II) (6) (Scheme I). This route cannot be used for the synthesis of the analog, 1-(2′,6′-dimethylphenylcarbamoylmethyl)-2-methylpyrazolidine (VII), because 1-methylpyrazolidine (IV) (7) is alkylated by *N*-chloroacetyl-2,6-dimethylaniline at the *N*-methyl nitrogen atom to give the corresponding quaternary salt (7).

Since an anilide is easily accessible from a carboxylic acid or an appropriate derivative, and the latter may be obtained from a nitrile, 1-cyanomethyl-2-methylpyrazolidine (V) was considered a desirable intermediate. This nitrile was prepared in high yield by cyanomethylation of IV. Unexpectedly, however, the conversion of V into the corresponding carboxylic acid or ester has not been realized. The unsuccessful attempts included acid and base catalyzed hydrolysis and alcoholysis.[2] Compound VII was finally obtained by means of the Ugi reaction which normally involves the condensation of an isocyanide, aldehyde, and an amine (8) under aqueous acidic conditions. Recently this reaction has been applied to hydrazines (9). Condensation of IV with formaldehyde and 2,6-dimethylphenylisocyanide (VI) (10) gave an 80% yield[3] of VII (Scheme I). The reaction is easily carried out and furthermore it fits the principle of convergent synthesis (11).

The next higher homolog, X, was obtained from a Bodroux reaction (12) between 1-(2-ethoxycarbonylethyl)-2-methylpyrazolidine (IX) (7) and 2,6-dimethylanilinomagnesium chloride (VIII) (Scheme I). Compound X was isolated in pure form by column chromatography after it was learned that the *o*-tolyl and *o*-chlorophenyl analogs of X underwent an elimination reaction upon distillation under reduced pressure to give the corresponding acrylanilides.[4]

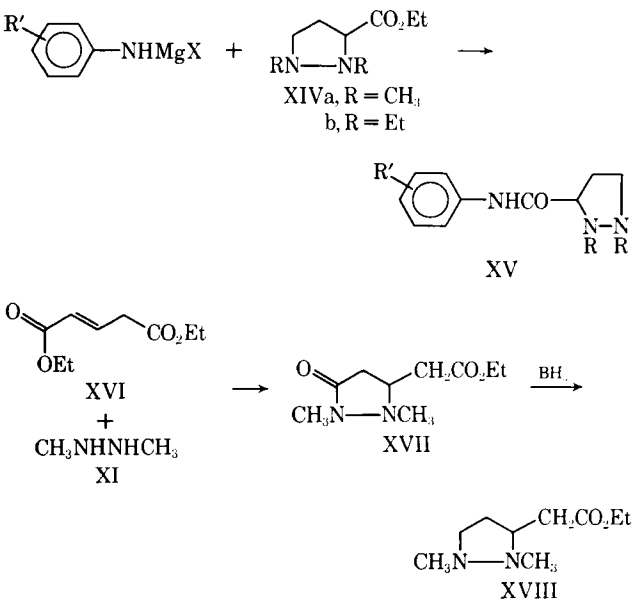
3-Pyrazolidinylacylanilides—These compounds were synthesized *via* the Bodroux reaction. The required ester intermediates, 1,2-dimethyl-(XIV*a*) and 1,2-diethyl-3-ethoxycarbonylpyrazolidine (XIV*b*) (13) were obtained from the selective borane reductions of 1,2-dimethyl- (XIII*a*) and 1,2-diethyl-3-ethoxycarbonyl-5-pyrazolidinone (XIII*b*), respectively. Pyrazolidinone XIII*a*, in turn, was prepared in high yield from 1,2-dimethylhydrazine (XI) and diethyl maleate (XII) by the same procedure (1) which afforded XIII*b*. Treatment of the esters XIV*a* and XIV*b* with several different Bodroux reagents resulted in a series of novel anilides (XV) bearing various substituents on the aromatic ring (Table I, Scheme II). This procedure which gave good yields of product from somewhat hindered reactants compares favorably with other methods of amide formation (14).

By a similar sequence of reactions, starting with 1,2-dimethylhydrazine (XI) and diethyl glutaconate (XVI), 1,2-dimethyl-3-(2′,6′-dimethylphenylcarbamoylmethyl)pyrazolidine (XIX) was prepared. The yield and purity of the intermediate pyrazolidinone XVII was inferior to the analogous preparation of XIII*a*. This is due, in part, to the impure diethyl glutaconate[5] used and also to the apparent decreased ease of cyclization of the intermediate adduct, diethyl β-(*sym.*-dimethylhydrazino)glutarate (see *Experimental*). Selective borane reduction of the cyclic hydrazide functional group in the presence of the ester group (13) of XVII proceeded as expected and afforded the hydrazino ester XVIII (Scheme II). Reaction of XVIII with the Bodroux reagent VIII gave the desired xylidide XIX.



Scheme I

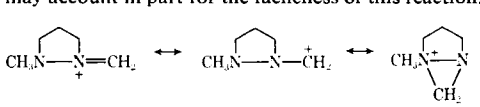
In order to prepare an anilide in which only one of the two nitrogen atoms of the pyrazolidine ring is alkylated, the preparation of 1-methyl-3-cyanopyrazolidine by the addition of hydrogen cyanide to 1-methyl-2-pyrazoline was attempted. Similar additions of hydrogen cyanide have been carried out on 5,5-dimethyl-1-pyrroline (15), phenylhydrazones (16), and azines (17). In the above



Scheme II

[2] By comparison, under identical reaction conditions, methanolysis of *N*-cyanomethylpyrrolidine afforded a 53% yield of methyl *N*-pyrrolidinoacetate.

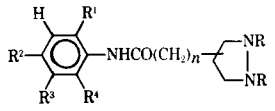
[3] The large degree of resonance stabilization of the intermediate iminium ion may account in part for the facileness of this reaction.



[4] M. J. Kornet, to be published.

[5] Distillation Products Industries, practical grade.

Table I—Physical Constants of



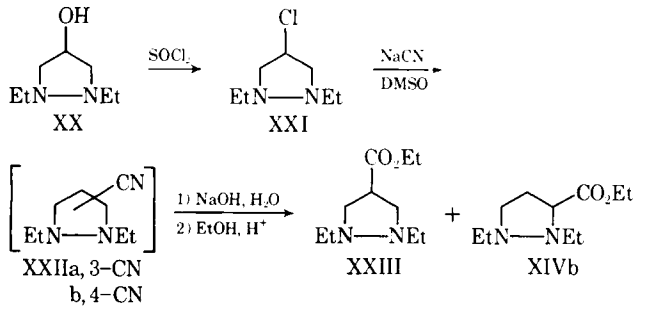
Compd.	Ring Position	n	R	R^1	R^2	R^3	R^4	B.p., °C M.p., °C	(mm.)	Yield, %	Formula	Anal., % Calcd.	Found
XV*a*	3	0	Et	H	H	H	H	119	(0.20)	38.2	$C_{14}H_{21}N_3O$	C, 67.98 H, 8.56 N, 16.99	C, 67.94 H, 8.54 N, 17.00
XV*b*	3	0	Et	Me	H	H	H	130	(0.19)	72.9	$C_{15}H_{23}N_3O$	C, 68.93 H, 8.87 N, 16.08	C, 68.57 H, 9.61 N, 15.72
XV*c*	3	0	Et	Me	H	Me	H	134	(0.28)	63	$C_{16}H_{25}N_3O$	C, 69.78 H, 9.15 N, 15.26	C, 69.84 H, 9.24 N, 15.27
XV*d*	3	0	Et	Me	H	H	Me	39–40[a]		60.7	$C_{16}H_{25}N_3O$	C, 69.78 H, 9.15 N, 15.26	C, 69.37 H, 9.58 N, 15.24
XV*e*	3	0	Et	Me	Me	H	Me	154.5	(0.28)	43.7	$C_{17}H_{27}N_3O$	C, 70.55 H, 9.40 N, 14.52	C, 69.97 H, 9.84 N, 14.53
XV*f*	3	0	Et	Cl	H	H	H	126–7	(0.22)	74	$C_{14}H_{20}ClN_3O$	C, 59.67 H, 7.15 N, 14.91	C, 59.99 H, 7.01 N, 14.95
XV*g*	3	0	Et	H	OEt	H	H	162	(0.30)	63.2	$C_{16}H_{25}N_3O_2$	C, 65.95 H, 8.65 N, 14.42	C, 66.08 H, 8.70 N, 14.35
XV*h*	3	0	Me	Me	H	H	Me	74–74.5[a]		55	$C_{14}H_{21}N_3O$	C, 67.98 H, 8.56 N, 16.99	C, 68.09 H, 8.66 N, 17.10
XIX	3	1	Me	Me	H	H	Me	108–109[b]		59.2	$C_{15}H_{23}N_3O$	C, 68.93 H, 8.87 N, 16.08	C, 69.04 H, 8.95 N, 16.14
XXIX	4	0	Et	Me	H	H	Me	101–104[c]		66.1	$C_{16}H_{25}N_3O$	C, 69.78 H, 9.15 N, 15.26	C, 70.00 H, 9.18 N, 15.32

[a] Recrystallized from hexane. [b] Recrystallized from a benzene–hexane mixture. [c] Recrystallized from benzene–cyclohexane (1:20).

case, however, only an insignificant amount of impure liquid was obtained which exhibited nitrile absorption in the IR at 4.5 μ.[6]

4-Pyrazolidinylacylanilides—The preparation of these compounds was not easily accomplished. Although numerous synthetic approaches were investigated, only two routes were successful. Even so, in both cases, the yield of the key intermediate, 1,2-diethyl-4-ethoxycarbonylpyrazolidine (XXIII) was low and its purification involved a gas chromatographic separation.

In the first route, 1,2-diethyl-4-pyrazolidinol (XX) (18) was chlorinated with thionyl chloride to give 1,2-diethyl-4-chloropyrazolidine (XXI). The chlorine atom of XXI was successively replaced by CN, COOH, and COOEt without isolation of the intermediates in an overall yield of 64% (Scheme III). The material

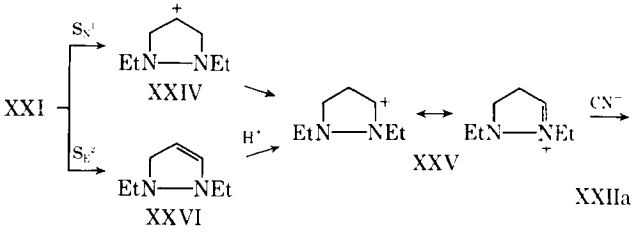


Scheme III

obtained from the esterification step showed typical ester carbonyl absorption in the IR; however, VPC analysis indicated the presence of two components in the ratio of 64:36 in order of increasing retention times. After collection, the major component was identified as XIV*b* by comparison of its VPC retention time, IR, and NMR spectra with an authentic sample. The minor component was the expected isomeric ester XXIII whose structural assignment is based on its elemental analysis, IR, and NMR spectra.

The formation of the unexpected ester XIV*b* may be visualized as arising from the corresponding 3-cyano intermediate XXII*a*. A mechanism explaining the formation of this nitrile involves as a first step the ionization of XXI to give the carbonium ion XXIV. Such an ionization may be anchimerically assisted by the hydrazine functional group. Once formed, XXIV could be expected to undergo an energetically favorable 1,2-hydride ion shift leading to the resonance-stabilized carbonium ion XXV. Nucleophilic attack on XXV by cyanide ion would give XXII*a*.

An alternate mechanism involves cyanide promoted dehydrohalogenation of XXI to give the enehydrazine XXVI, which is protonated to give XXV. The remainder of the reaction path is the same as the previous mechanism (Scheme IV). It is quite likely that both mechanisms are operating simultaneously.

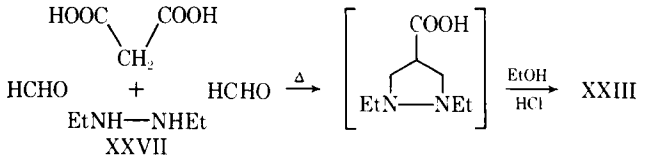


Scheme IV

A second approach to the synthesis of XXIII involved a Mannich reaction between 1,2-diethylhydrazine (XXVII) (19), formaldehyde, and malonic acid. Mannich and Kather (20), and later on Pelletier and Franz (21) have prepared bis-(dimethylaminomethyl)acetic

[6] If one assumes that nucleophilic attack by cyanide ion at the 3-position has to be preceded by protonation of the imine nitrogen, the observed lack of reactivity could be attributed to the presence of the more basic *N*-methyl nitrogen which is more readily protonated.

acid from dimethylamine, formaldehyde, and malonic acid. Utilizing a similar procedure with subsequent esterification, the ester XXIII was isolated in low yield by preparative gas chromatography (Scheme V). The product was identical in every respect to the minor



Scheme V

component obtained from XXI in the previous synthesis. Attempts to improve the yield by altering the molar proportions of the reactants, pH control by buffering, and preformation of 1,2-bis-(hydroxymethyl)-1,2-diethylhydrazine were to no avail. In additiion 1,2-dimethylhydrazine, formaldehyde, and malonic acid were condensed and following esterification with diazomethane gave a poor yield of 1,2-dimethyl-4-methoxycarbonylpyrazolidine (XXVIII).

Treatment of XXIII with VIII under the usual Bodroux conditions afforded the corresponding xylidide, 1,2-diethyl-4-(2′,6′-dimethylphenylcarbamoyl)pyrazolidine (XXIX) in 66% yield. Because of an insufficient amount of the *N,N′*-dimethyl ester intermediate XXVIII, the corresponding xylidide was not prepared.

Local Anesthetic Results[7]—Duration of local anesthetic activity was assessed by the method of Bülbring and Wajda in the guinea pig intradermal wheal (22) and in the rat sciatic block (23). The frequency performance of the compounds was evaluated in the rat sciatic block (23). Irritation liabilities were determined essentially by the method of Truant (23). Four of the 3-pyrazolidinylacylanilides (XV*b*, XV*c*, XV*e*, and XV*f*) in which ethyl groups are attached to the hydrazino nitrogens had durations equal to or greater than lidocaine and the frequencies in the rat sciatic blocks were similar to those of lidocaine. All however, were more irritating than lidocaine. Compound XV*h*, which is an *N,N′*-dimethyl analog in this series induced a nerve block of 119 min. compared to 136 min. by lidocaine (1%, with 1:100,000 epinephrine). This compound is about as irritating as lidocaine; however, durations in the guinea pig intradermal wheal were consistently shorter than those produced by lidocaine. The intravenous LD_{50} and 95% Fieller limits were determined to be 112 (106–118) mg./kg. and the intraperitoneal LD_{50} was 447 (398–502) mg./kg. Compound XIX exhibited rat sciatic nerve blocks of short duration and poor frequency and did not block the guinea pig wheals at all. Compounds VII, X and XXIX produced blocks of relatively short duration with both test methods. Both X and XXIX were about as irritating as lidocaine while VII was only slightly more irritating. The intravenous LD_{50}'s for the latter three compounds in female mice were determined to be as follows: VII, 151 (128–224) mg./kg.; X, 106 (92–138) mg./kg.; XXIX, 61 (47–72) mg./kg. Compound III was not tested because of solubility problems.

EXPERIMENTAL[8]

IR spectra were recorded on a spectrometer[9] and NMR spectra were recorded[10] with tetramethylsilane as the internal reference. Melting points[11] are corrected, while boiling points are uncorrected. The VPC analyses were obtained with a gas chromatograph[12] using a 6.09 m. × 0.93 cm. (20 ft. × 3/8 in.) aluminum column packed with 30% silicone gum rubber SE 30 on diatomite aggregate[13] (45–60 mesh); helium was used as the carrier gas and percentage compositions refer to the relative areas observed for the different components. Borane (1.0 *M*) in tetrahydrofuran (**THF**) solution was also used in this work.[14] Unless otherwise stated magnesium sulfate was employed as a drying agent.

Ethyl 1,2-dimethylpyrazolidine-3-carboxylate (XIV*a*), and ethyl 1,2-diethylpyrazolidine-3-carboxylate (XIV*b*) were prepared according to the published procedure (13).

1,2-Dimethyl-5-ethoxycarbonyl-3-pyrazolidinone (XIIIa)—A solution of 25.07 g. (0.155 mole) of diethyl maleate (XII) in 22 ml. of absolute ethanol was added dropwise with magnetic stirring and ice-bath cooling to a solution of 9.83 g. (0.164 mole) of 1,2-dimethylhydrazine (XI) (24) in 8 ml. of absolute ethanol. The reaction mixture, protected from moisture and CO_2 by a drying tube filled with $CaCl_2$ and sodalime, was refluxed overnight (14 hr.) on an oil bath. After removal of the ethanol under reduced pressure, the residue was fractionated to give 25.61 g. (89.5%) of product, b.p. 93–94° (0.33 mm.), IR (film) 5.77 μ (ester C=O), 5.92 μ (amide C=O).

Anal.—Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.05. Found: C, 51.53; H, 7.67; N, 15.18.

1,2-Dimethyl-3-ethoxycarbonylmethyl-5-pyrazolidinone (XVII)—Into a 250-ml. round-bottom flask equipped with a magnetic stirrer, a pressure-equalizing dropping funnel, and a reflux condenser protected by a tube filled with $CaCl_2$ and sodalime was placed a solution of 24.8 g. (0.411 mole) of 1,2-dimethylhydrazine (XI) (24) in 20 ml. of absolute ethanol. Next, a solution of 69.9 g. (0.376 mole) of diethyl glutaconate (XVI) in 40 ml. of absolute ethanol was added dropwise at room temperature over a period of 35 min. The mixture was refluxed overnight on an oil bath. After removal of the ethanol *in vacuo*, the residue was fractionated and gave 35.56 g. of Fraction 1, b.p. 90–98° (0.30 mm.) which was shown by VPC analysis to contain 24% of product, and 23.30 g. of Fraction 2, b.p. 98–100° (0.28 mm.) which was essentially product (92% pure by VPC analysis). The second major component in both fractions appears to be the uncyclized adduct, diethyl β-(*sym.* dimethylhydrazino)glutarate. When Fraction 1 was refluxed in hexane overnight with a catalytic quantity of sodium methoxide and subsequently distilled under reduced pressure, VPC analysis of the distillate indicated an increase in the content of XVII from the original 8 g. to 15 g. Considerable uncyclized adduct was also present. The analytical sample was collected by preparative VPC and exhibited: IR (film) 5.77 μ (ester C=O), 5.91 μ (amide C=O).

Anal.—Calcd. for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 54.15; H, 7.90; N, 13.88.

1,2-Dimethyl-3-ethoxycarbonylmethylpyrazolidine (XVIII)—Selective reduction of 22.19 g. (0.111 mole) of XVII (Fraction 2 of the previous preparation) in 100 ml. of **THF** with 166 ml. (0.166 mole) of 1.0 *M* borane in **THF** according to the described procedure (13) gave 13.60 g. of product, b.p. 95–112° (10 mm.) which was 85% pure by VPC analysis. The analytical sample was obtained by preparative VPC: IR (film) 5.76 μ (ester C=O), no amide C=O absorption, n_D^{29} 1.4503.

Anal.—Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.68; H, 10.53; N, 15.03.

1,2-Diethyl-4-chloropyrazolidine (XXI)[14]—A solution of 16.67 g. (0.116 mole) of 1,2-diethyl-4-pyrazolidinol (XX) (18) in 70 ml. of chloroform, cooled in an ice water bath and magnetically stirred was treated with anhydrous hydrogen chloride gas until the reaction mixture became acidic (pH ~ 3). Within 45 min., 15.2 g. (0.128 mole) of thionyl chloride was added dropwise and the resulting solution was refluxed for 4 hr. After removal of the solvent under reduced pressure, the residue was covered with 50 ml. of ether and cooled by means of an ice bath. The mixture was basified by the dropwise addition of 40% aqueous KOH to pH 8. The ether layer was separated and the residue was extracted three times with 25-ml. portions of ether. The combined ether extracts were dried and concentrated *in vacuo*. Distillation of the residue under reduced pressure afforded 6.12 g. (32.6%) of a nearly colorless liquid, b.p. 75–81° (15 mm.). The liquid deposited transparent crystals upon standing and was used immediately in the next step.

The picrate was prepared and recrystallized from absolute ethanol, m.p. 163–167.5°.

Anal.—Calcd. for $C_{13}H_{18}ClN_5O_7$: C, 39.85; H, 4.63; N, 17.87. Found: C, 40.19; H, 4.47; N, 17.94.

1,2-Diethyl-4-ethoxycarbonylpyrazolidine (XXIII) and 1,2-Diethyl-3-ethoxycarbonylpyrazolidine (XIVb)—A magnetically stirred

[7] The authors are grateful to Dr. Jack Adams, Astra Research Laboratories, for the local anesthetic data.

[8] Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerand.

[9] Beckman IR-8.

[10] Varian A-60.

[11] Fisher-Johns.

[12] Aerograph A-700 Autoprep.

[13] Chromosorb W, Johns-Manville Products Corp., New York, N. Y.

[14] These experiments were carried out by S. I. Tan.

mixture of 2.09 g. (0.0428 mole) of NaCN and 10 ml. of dry dimethyl sulfoxide was heated to approximately 115° and treated with 5.12 g. (0.0315 mole) of XXI which was added dropwise by means of a medicine dropper.[14] After completion of the addition the mixture was heated at 125–130° on an oil bath for 3 hr., cooled to room temperature, and treated with 2 g. of NaOH and 10 ml. of water. An oily layer separated whose IR spectrum exhibited absorption at 4.45 μ (C≡N). The mixture was stirred at room temperature for 2 hr., diluted with 10 ml. of water and heated at 90° for 38 hr., and finally refluxed for 6 hr. After removal of the solvents under reduced pressure (1.5–2.5 mm.), the residue was suspended in water and acidified to pH 3 with concentrated HCl. The solvents were distilled *in vacuo* (water pump) and the residue was rendered anhydrous by repeated distillations with absolute ethanol. The residue was dissolved in 75 ml. of absolute ethanol, saturated with anhydrous HCl gas, and stored overnight. After gentle refluxing for 3 hr. the mixture was evaporated *in vacuo* and the residue was covered with ether and basified with 40% aqueous KOH. The ether layer was separated and the aqueous phase was extracted twice with ether. The combined extracts were dried and concentrated *in vacuo*. The residue was distilled and afforded 4.05 g. of a colorless liquid, b.p. 113–118° (16 mm.). VPC analysis showed the presence of two components in the ratio of 64:36 in order of increasing retention times. Separation was achieved by preparative gas chromatography. The major component, $n_D^{24.6}$ 1.4459, was identical by several criteria (IR, NMR, VPC retention time) with authentic XIV*b* (13). The minor product is XXIII: $n_D^{24.6}$ 1.4497; IR (film) 5.80 μ (ester C=O); NMR ($CDCl_3$) δ 4.18 (q, 2, OCH_2), 3.20 (m, 5, ring protons), 2.60 (q, 4, NCH_2CH_3), 1.27 (t, 3, OCH_2CH_3), 1.08 (t, 6, NCH_2CH_3).

Anal.—Calcd. for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.97; H, 9.88; N, 14.05.

Alternatively, XXIII was obtained *via* a Mannich reaction in the following manner. To a solution of 20.8 g. (0.20 mole) of malonic acid in 27 ml. of water which was magnetically stirred and protected under a N_2 blanket was added dropwise a solution of 17.6 g. (0.20 mole) of 1,2-diethylhydrazine (XXVII) (19) in 10 ml. of water. Next, 32.6 ml. (0.40 mole) of 37% aqueous formaldehyde was added dropwise. The mixture was kept at room temperature under N_2 for 24 hr. and then heated in a slow N_2 stream overnight on a steam bath to effect decarboxylation. Water and other volatile material were removed by heating *in vacuo* until the mixture became a sirupy residue. The residue was treated with 40 ml. of concentrated HCl, evaporated to dryness and made anhydrous by repeated *in vacuo* evaporations with absolute ethanol. The anhydrous residue was suspended in 200 ml. of absolute ethanol, cooled in an ice bath, and saturated with dry HCl gas. The mixture was allowed to warm to room temperature over a period of 6 hr. and refluxed gently on an oil bath for 14 hr. After removal of solvent under reduced pressure, the residue was extracted three times with 50-ml. portions of ether. The residue was covered with 100 ml. of ether, cooled in an ice bath, and cautiously basified with 40% aqueous KOH. The ether layer was separated and the residue was extracted three times with 50-ml. portions of ether. The combined ethereal extracts were dried and concentrated *in vacuo*. The dark liquid residue was fractionated and afforded 10.99 g. of a pale yellow liquid, b.p. 115–140° (11 mm.) which contained 41% of XXIII as shown by VPC analysis. The pure product was obtained by preparative gas chromatography and was identical in every respect to the minor component described above.

1,2-Dimethyl-4-methoxycarbonylpyrazolidine (XXVIII)—The carboxylic acid precursor was prepared by the Mannich condensation of malonic acid, formaldehyde, and 1,2-dimethylhydrazine (24) by essentially the same method which was used for the carboxylic acid precursor of XXIII. Esterification was accomplished with diazomethane. Workup afforded a low yield of impure distillate from which an analytical sample was obtained by preparative gas chromatography: IR (film) 5.76 μ (ester C=O); NMR ($CDCl_3$) δ 3.75 (s, 3, OCH_3), 3.17 (m, 5, ring *H*), 2.48 (s, 6, NCH_3).

Anal.—Calcd. for $C_7H_{14}N_2O_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.00; H, 9.38; N, 17.57.

Anilide Formation via the Bodroux Reaction—*General Method*—Into a flame-dried, nitrogen-flushed 500-ml. three-necked flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, a gas inlet tube, and a condenser (the outlet end was attached to a tube leading to a mercury bubbler) was placed 34.5 ml. of 2.9 *M* MeMgCl in THF (0.100 mole) and 35 ml. of THF. All of the operations described below were carried out with continuous stirring and, up to the addition of the NH_4Cl solution, in a dry nitrogen atmosphere. A solution of 0.100 mole of the aniline in 25 ml. of THF was added dropwise to the dark Grignard reagent over a period of 30 min. Gas was evolved, the mixture heated up spontaneously, the liquid changed color, and some solid was formed which remained in suspension. After the vigorous reaction subsided, a solution of 0.050 mole of an appropriate ester in 25 ml. of THF was added over a 10-min. period. The mixture changed color and was refluxed on an oil bath for 2 hr. Anhydrous ether (25 ml.) was added and the Grignard complexes were decomposed by the careful addition of approximately 19 ml. of saturated aqueous NH_4Cl without cooling. After separation of the ether phase, the residue was extracted twice with 100-ml. portions of ether and finally once with 50 ml. of ether. The combined ethereal extract was dried and concentrated *in vacuo*. The residue was fractionated under reduced pressure. In some cases the product solidified spontaneously and was purified further by recrystallization from a suitable solvent. The IR spectra of the products showed very strong absorption maxima varying from 5.9–6.1 μ (amide C=O). For physical and analytical data see Table I.

The reaction was also successfully carried out with self-prepared MeMgI in anhydrous diethyl ether instead of the commercially obtained MeMgCl in THF, however, with this method a sticky precipitate formed after the addition of the ester to the reaction mixture which made efficient stirring very difficult.

1-(2′,6′-Dimethylphenylcarbamoylmethyl)-2-methylpyrazolidine (VII)—A solution of 2.58 g. (0.030 mole) of 1-methylpyrazolidine (IV) (7) in 5 ml. of distilled water was titrated (bromocresol purple indicator) with concentrated HCl (approximately 2.5 ml.) to a pH of 6. By means of a pipet, 2.44 ml. of 37% aqueous formaldehyde solution (0.030 mole) was added, followed by 3.52 g. (0.0268 mole) of 2,6-dimethylphenylisocyanide (VI) (10) and 1 ml. of water. The mixture was cooled with an ice water bath and 10 ml. of acetone was added, whereupon all of the isocyanide dissolved with heat evolution. The flask containing the mixture was flushed with N_2 and kept at room temperature for 63 hr. after which time the isocyanide odor was no longer discernible. The solution was concentrated under reduced pressure, cooled in an ice bath, and acidified with concentrated HCl. The acidified mixture was extracted twice with 20-ml. portions of toluene, covered with 40 ml. of ether, cooled in an ice bath, and basified with 40% aqueous KOH. The ether layer was decanted and the residue was extracted twice with 30-ml. portions of ether. The combined ether extract was dried and concentrated under reduced pressure. The residue, which solidified on standing, was fractionally distilled and gave 5.30 g. (80%) of a viscous yellow liquid, b.p. 152–153° (0.23 mm.). The distillate solidified and was recrystallized from hexane and gave 4.20 g. (63.3%) of colorless needles: m.p. 70–72°; IR (film) 6.05 μ (amide C=O).

Anal.—Calcd. for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.17; H, 8.42; N, 17.14.

4-Methylpyrazolidine (I)—To a suspension of 56.7 g. (1.49 moles) of $LiAlH_4$ in 1 l. of THF was added dropwise a solution of 80.0 g. (0.807 mole) of 4-methyl-3-pyrazolidinone (25, 26) in 400 ml. of THF. After refluxing overnight, the reaction mixture was cooled in an ice-salt bath and decomposed by cautiously adding dropwise a 40% aqueous KOH solution until a clear separation was observed. The THF layer was separated, the residue was extracted several times with ether, and the combined extracts were dried. The solution was acidified with saturated ethanolic HCl to give colorless needles which were collected on a Büchner funnel and washed with absolute ethanol and then ether. The crystals (81.4 g.) were covered with ether and basified with a minimum amount of 40% aqueous KOH. The ether layer was separated and the aqueous phase was extracted in a liquid-liquid extractor for 48 hr. The combined ether extracts were dried and distilled through a short Vigreux column in order to remove the ether and THF. Distillation of the residue through the same column afforded 36.47 g. (52.5%) of colorless liquid, b.p. 67–72° (37 mm.), lit. (5) b.p. 69–70° (40 mm.).

1-(2′-Methylphenylcarbamoylmethyl)-4-methylpyrazolidine (III)—In a flask protected from the atmosphere by a drying tube filled with $CaCl_2$ and sodalime was placed 4.22 g. (0.023 mole) of *N*-chloroacetyl-2-methylaniline (II) (6), 30 ml. of sodium-dried benzene and 4.92 g. (0.058 mole) of I. The mixture heated up spontaneously and was refluxed for 2.75 hr. After standing at room temperature overnight, refluxing was resumed for 1.5 hr. The benzene layer was separated and the residue was extracted twice with 10-ml. portions of

benzene. The combined benzene solution was extracted with 35-, 15-, and 10-ml. portions of 2 *N* HCl. The acidic aqueous extract was basified with 40% KOH and extracted four times with 25-ml. portions of $CHCl_3$. The chloroform solution was dried and concentrated. Fractional distillation of the residue gave 3.45 g. (64.6%) of a yellow liquid, b.p. 161–162° (0.27 mm.), IR (film) 5.95 μ (amide C=O).

Anal.—Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.00; H, 8.19; N, 18.10.

1-[2-(2′,6′-Dimethylphenylcarbamoyl)ethyl]-2-methylpyrazolidine (X)—This compound was obtained from 8.29 g. (0.0446 mole) of 1-(2-ethoxycarbonylethyl)-2-methylpyrazolidine (IX) (7) *via* the Bodroux reaction. Since similar anilides derived from *o*-chloroaniline and *o*-toluidine underwent an elimination to 1-methylpyrazolidine and the corresponding acrylanilide upon distillation, the workup was modified in the following way. The residue remaining after drying and concentration was distilled in order to remove the majority of the 2,6-dimethylaniline, b.p. 40–42° (0.3 mm.), bath temperature 65–75°. The distillation residue was dissolved in 40 ml. of ether and extracted twice with 15-ml. and once with 20-ml. portions of 10% aqueous HCl. The combined aqueous extract was washed with two 15-ml. portions of ether, covered with 35 ml. of ether and basified in the cold with 40% aqueous NaOH. After separation of the ether layer, the aqueous phase was extracted three times with 35-ml. portions of ether. The combined ether extract was dried, concentrated *in vacuo*, and chromatographed on 200 g. of silica gel (28–200 mesh). Elution was effected with a series of pure solvents and mixtures thereof of increasing polarity (petroleum ether, benzene, ether, and methanol). The eluant was monitored by TLC and the desired product began to be eluted when ether–methanol (50:50) was used. The elution was completed with 600 ml. of methanol. After drying, the combined eluant was concentrated and afforded 4.8 g. (41.4%) of a very pale yellow oil: NMR ($CDCl_3$) δ 7.26 (s, 3, aromatic *H*), 2.56 (s, NCH_3), 2.32 (s, benzylic *CH*), 1.93–3.32 (m, aliphatic *CH*).

The picrate was prepared and recrystallized from absolute ethanol, m.p. 119–122°.

Anal.—Calcd. for $C_{21}H_{26}N_6O_8$: C, 51.42; H, 5.34; N, 17.14. Found: C, 51.73; H, 5.17; N, 17.30.

1-Cyanomethyl-2-methylpyrazolidine (V)—In view of possible HCN formation, all operations were carried out in the hood. To a magnetically stirred solution of 11.63 g. (0.112 mole) of $NaHSO_3$ in 28 ml. of water was added 8.4 ml of a 36.9% aqueous formaldehyde solution (0.103 mole). The temperature of the mixture rose spontaneously to 50° and was immediately heated to 60° on the steam bath and allowed to cool to 35° over a period of 1 hr. Addition of 9.65 g. (0.112 mole) of IV (7) to the stirred water-clear mixture caused a temperature rise to 55°. The mixture was stored at room temperature for 2.25 hr. and then treated with a solution of 5.48 g. (0.112 mole) of NaCN in 15 ml. of water with efficient stirring so that the two layers became thoroughly mixed. After 3.5 hr., enough solid NaCl was added to saturate the aqueous mixture which was extracted five times with 60-ml. portions of ether. The ethereal extract was dried and concentrated at 20°. Fractional distillation of the residue afforded 11.43 g. (90%) of a water-clear liquid, b.p. 101° (14 mm.), IR (film) 4.47 μ (C≡N).

Anal.—Calcd. for $C_6H_{11}N_3$: C, 57.57; H, 8.86; N, 33.57. Found: C, 57.75; H, 8.87; N, 33.80.

A picrate was prepared and recrystallized from absolute ethanol, m.p. 138.5–141°.

Anal.—Calcd. for $C_{12}H_{14}N_6O_7$: C, 40.67; H, 3.98; N, 23.72. Found: C, 40.80; H, 3.98; N, 23.56.

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