[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, RESEARCH DIVISION, MEAD JOHNSON AND CO.]

Pyrrolidines. I. 1-Substituted 3-Pyrrolidinylmethyl Alcohols and Chlorides[1]

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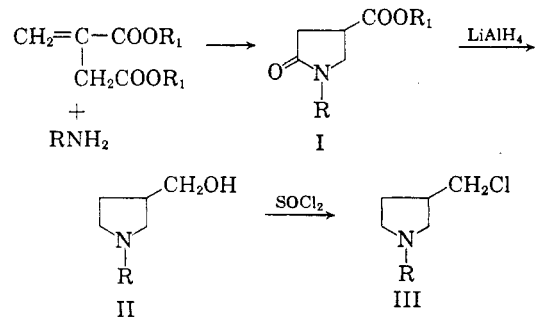
Dialkyl itaconate was condensed with various primary amines to form 1-substituted 5-oxo-3-pyrrolidinecarboxylates which were reduced to 1-substituted 3-pyrrolidinemethanols by lithium aluminum hydride. Treatment of these pyrrolidinemethanols with thionyl chloride yielded their corresponding chlorides. 1-Substituted 3-pyrrolidinylmethyl alcohols and chlorides are useful intermediates for the preparation of a number of physiologically active compounds. 1-Methyl-3-pyrrolidinemethanol was also prepared from diethyl 1,3-pyrrolidinedicarboxylate either by employing lithium aluminum hydride reduction directly or by Bouveault-Blanc reduction indirectly through ethyl 3-pyrrolidinecarboxylate as an intermediate.

The reaction of aniline with itaconic acid was studied by Gottlieb[2] in 1851 and by Michael and Palmer[3] in 1887. The structure of the product was established by Anschütz and Reuter[4] in 1889 to be 5-oxo-1-phenyl-3-pyrrolidinecarboxylic acid. Recently Paytash and his co-workers[5] used this reaction to prepare a large number of 1-substituted 5-oxo-3-pyrrolidinecarboxylic acids with various aryl, aralkyl, cycloalkyl, and heterocyclic amines in place of aniline. Itaconic acid has also been condensed with long chain alkylamines[6] and methylamine[7] to give the corresponding 1-substituted 5-oxo-3-pyrrolidinecarboxylic acids.

We have found that the lower alkyl esters of itaconic acid will condense with different primary amines in equimolecular quantities to form 1-substituted 5-oxo-3-pyrrolidinecarboxylates in good yields. The product obtained by condensing dimethyl itaconate with benzylamine was found to be identical with the esterification product of 1-benzyl 5-oxo-3-pyrrolidinecarboxylic acid prepared according to the procedure of Paytash.[5a] Ethyl 1-methyl - 5 - oxo - 3 - pyrrolidinecarboxylate has been prepared earlier by Uhle[8] and by Hardegger and Corrodi[9] from α-carboxysuccinic acid. The same compound was also formed by condensing diethyl itaconate with methylamine. The structure of these pyrrolidinones was further supported by the synthesis of butyl 1-*n*-octyl-5-oxo-3-pyrrolidinecarboxylate from dibutyl itaconate and *n*-octylamine by Knuth and Bruins[10] during the course of our work.

Sixteen 1-substituted 5-oxo-3-pyrrolidinecarboxylates (I) were synthesized. Their physical properties are summarized in Table I. These compounds were reduced by means of lithium aluminum hydride to 1-substituted 3-pyrrolidinemethanols (II). Treatment of the pyrrolidinemethanols with thionyl chloride converted them to the corresponding chlorides (III). The properties of 1-substituted 3-pyrrolidinemethanols and the chlorides are recorded in Tables II and III, respectively.



Unlike dialkylaminoalkyl halides,[11] which undergo ring formation as free bases, these chloromethylpyrrolidines are fairly stable and can be kept in an icebox for several months without deterioration.

1-Substituted 3-pyrrolidinemethanols and their corresponding chlorides are useful intermediates for the preparation of a number of physiologically active compounds of therapeutic value. Reports on these studies will be published in the future.

When sodium aluminum hydride[12] was used in place of lithium aluminum hydride for the reduction of methyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate, the yield of 1-methyl-3-pyrrolidinemethanol was slightly lower. 1-Methyl-3-pyrrolidinemethanol has also been synthesized by us from diethyl 1,3-pyrrolidinedicarboxylate either by em-

(1) R. F. Feldkamp and Y. H. Wu, U. S. Patent **2,826,588**, March 11, 1958. Presented in part at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

(2) J. Gottlieb, *Ann.*, **77**, 284 (1851).

(3) A. Michael and G. M. Palmer, *Am. Chem. J.*, **9**, 199 (1887).

(4) R. Anschütz and F. Reuter, *Ann.*, **254**, 129 (1889).

(5) (a) P. L. Paytash, E. Sparrow, and J. C. Gathe, *J. Am. Chem. Soc.*, **72**, 1415 (1950). (b) P. L. Paytash, M. J. Thompson, and M. E. Fykes, *J. Am. Chem. Soc.*, **74**, 4549 (1952). (c) P. L. Paytash, M. J. Thompson, and W. B. Clarke, *J. Am. Chem. Soc.*, **76**, 3500 (1954).

(6) A. Mudrak, U. S. Patent **2,757,125**, July 31, 1956.

(7) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1092 (1956).

(8) F. C. Uhle, *J. Am. Chem. Soc.*, **73**, 2402 (1951).

(9) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **39**, 980 (1956).

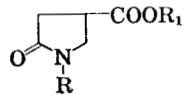
(10) C. J. Knuth and P. F. Bruins, *Ind. Eng. Chem.*, **47**, 1572 (1955).

(11) C. S. Marvel, W. H. Zartman, and O. D. Bluthardt, *J. Am. Chem. Soc.*, **49**, 2299 (1927).

(12) A. E. Finholt, E. C. Jacobson, A. E. Ogard, and P. Thompson, *J. Am. Chem. Soc.*, **77**, 4163 (1955).

TABLE I

1-SUBSTITUTED 5-OXO-3-PYRROLIDINECARBOXYLATES

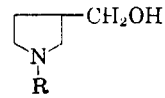


R	R_1	Procedure	B.P., Mm.	M.P.	n_D^{25}	Yield, %[f]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	A	160–161, 18.0		1.4742	84	$C_7H_{11}NO_3$	53.49	53.59	7.06	6.76
CH_3	C_2H_5	A	166–167, 19.0		1.4678	76	$C_8H_{13}NO_3$	56.13	56.68	7.65	7.82
C_2H_5	CH_3	A	104–106, 0.13		1.4702	89	$C_8H_{13}NO_3$	56.13	56.21	7.65	7.35
n-C_3H_7	CH_3	A	91.5–92, 0.08		1.4688	97	$C_9H_{15}NO_3$	58.36	57.82	8.16	7.82
i-C_3H_7	CH_3	A	86–88, 0.06		1.4665	91	$C_9H_{15}NO_3$	58.36	58.60	8.16	8.12
CH_2=$CHCH_2$	CH_3	A	178–179, 21.0		1.4829	96	$C_9H_{13}NO_3$	59.00	59.40	7.15	6.84
n-C_4H_9	CH_3	A	180–182, 18.0		1.4682	84	$C_{10}H_{17}NO_3$	60.28	60.80	8.60	8.63
t-C_4H_9[a]	CH_3	A	87–89, 0.3		1.4672	51	$C_{10}H_{17}NO_3$	60.28	60.41	8.60	8.64
Cyclohexyl	CH_3	B	122–124, 0.06	47–48	1.4944	81	$C_{12}H_{19}NO_3$	63.97	64.29	8.50	8.53
$C_6H_5CH_2$	CH_3	B	144–147, 0.06	64–65[b,c]	1.5358	79	$C_{13}H_{15}NO_3$	66.93	67.30	6.48	6.38
o-$ClC_6H_4CH_2$	CH_3	B	157, 0.045		1.5464	70	$C_{13}H_{14}ClNO_3$	58.32	58.70	5.27	4.91
$(C_6H_5)_2CH$[a]	CH_3	B		112–113[d]		17	$C_{19}H_{19}NO_3$	73.77	73.97	6.19	5.99
$C_6H_5CH_2CH_2$	CH_3	B		75–77[e]		89	$C_{14}H_{17}NO_3$	67.99	67.99	6.93	7.01
3,4-di$CH_3OC_6H_3CH_2CH_2$	CH_3	B	218–230, 0.06		1.5387	93	$C_{16}H_{21}NO_5$	60.52	60.90	6.89	6.68
C_6H_5	CH_3	C	152–154, 0.125	71–73[e]		43	$C_{12}H_{13}NO_3$	65.74	65.80	5.98	5.87
i-C_3H_7	n-C_4H_9	B	107–112, 0.06		1.4575	96	$C_{12}H_{21}NO_3$	63.41	63.55	9.31	9.24

[a] Prepared by Dr. J. R. Corrigan of these laboratories. [b] A mixed m.p. determination with methyl ester of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid prepared according to Paytash *et al.*[5a] showed no depression. [c] Recrystallized from *n*-heptane. [d] Recrystallized from methanol. [e] Recrystallized from 1:1 ethyl acetate-*n*-heptane mixture. [f] Based on purified products.

TABLE II

1-SUBSTITUTED 3-PYRROLIDINEMETHANOLS

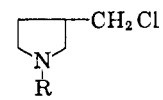


R	B.P., Mm.	n_D^{25}	Yield, %[d]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3[a]	94–96.5, 15.0	1.4662	79	$C_6H_{13}NO$	62.59	62.27	11.37	11.19
C_2H_5	110–111, 20.0	1.4693	74	$C_7H_{15}NO$	65.07	65.34	11.70	11.86
n-C_3H_7	122–126, 24.0	1.4669	79	$C_8H_{17}NO$	67.08	67.05	11.97	11.75
i-C_3H_7	122–122.5, 24.0	1.4713	76	$C_8H_{17}NO$	67.08	67.15	11.97	11.61
CH_2=$CHCH_2$	122–124, 21.0	1.4822	69	$C_8H_{15}NO$	68.04	68.22	10.71	11.01
n-C_4H_9	130–131, 19.0	1.4672	79	$C_9H_{19}NO$	68.74	69.39	12.18	12.14
t-C_4H_9[b]	139.5–149.5, 36	1.4744	81	$C_9H_{19}NO$	68.74	68.71	12.18	11.91
Cyclohexyl	97–101, 0.06	1.5023	88	$C_{11}H_{21}NO$	72.08	71.93	11.55	11.40
$C_6H_5CH_2$	166–168, 12.0	1.5431	69	$C_{12}H_{17}NO$	75.35	75.29	8.96	8.89
o-$ClC_6H_4CH_2$	114–122, 0.06	1.5541	70	$C_{12}H_{16}ClNO$	63.85	63.93	7.15	7.34
$C_6H_5CH_2CH_2$	114, 0.05	1.5380	91	$C_{13}H_{19}NO$	76.05	76.08	9.33	9.08
3,4-di$CH_3OC_6H_3CH_2CH_2$	144–148, 0.06	1.5446	93	$C_{15}H_{23}NO_3$	67.89	67.73	8.74	8.74
C_6H_5	130–135, 0.05 54–55[c]	1.5872	40	$C_{11}H_{15}NO$	74.54	74.56	8.53	8.39
$(C_6H_5)_2CH$[b]	150–154, 0.3 96–100[c]		70	$C_{18}H_{21}NO$	[e]			

[a] Methobromide: m.p. 254–256°. *Anal.* Calcd. for $C_7H_{16}BrNO$: C, 40.01; H, 7.68. Found: C, 40.19; H, 7.81. [b] Prepared by Dr. J. R. Corrigan of these laboratories. [c] Melting point. [d] Based on purified products. [e] Analyzed as hydrochloride, m.p. 238–239° dec. *Anal.* Calcd. for $C_{18}H_{22}ClNO$: Cl, 11.67. Found: Cl, 11.46.

TABLE III

1-SUBSTITUTED 3-CHLOROMETHYLPYRROLIDINES



R	B.P., Mm.	n_D^{25}	Yield, %[a]	Formula	Chlorine, % Calcd.	Chlorine, % Found
CH_3	75–76, 35	1.4608	83	$C_6H_{12}ClN$	26.53	26.86
C_2H_5	86–88, 36	1.4611	85	$C_7H_{14}ClN$	24.02	23.67
C_3H_7	89–90, 19	1.4611	86	$C_8H_{16}ClN$	21.93	22.03
i-C_3H_7	90–91, 24	1.4630	86	$C_8H_{16}ClN$	21.93	21.89
CH_2=$CHCH_2$	90–91, 14	1.4755	82	$C_8H_{14}ClN$	22.21	22.36
C_4H_9	108–110, 20	1.4625	81	$C_9H_{18}ClN$	20.18	20.14
$C_6H_5CH_2$	165–167, 19	1.5346	81	$C_{12}H_{16}ClN$	16.91	17.02
$C_6H_5CH_2CH_2$	97–102, 0.06	1.5319	94	$C_{13}H_{18}ClN$	15.85	15.06

[a] Based on purified products.

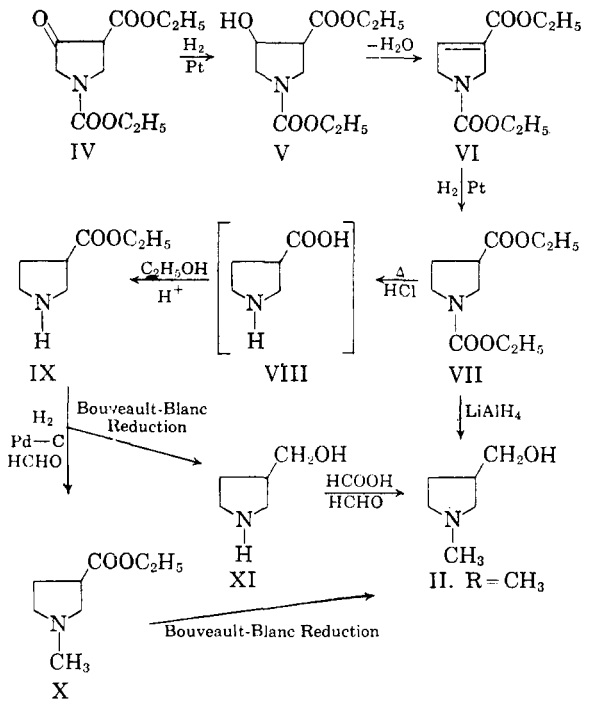
ploying lithium aluminum hydride reduction directly or by Bouveault-Blanc reduction indirectly through ethyl 3-pyrrolidinecarboxylate as an intermediate. The starting material, diethyl 1,3-pyrrolidinedicarboxylate (VII), was prepared by a series of reactions as described by Miyamoto,[13] *i.e.* diethyl 4-oxo-1,3-pyrrolidinedicarboxylate (IV), was catalytically reduced to diethyl 4-hydroxy-1,3-pyrrolidinedicarboxylate (V) which was dehydrated to diethyl 3-pyrroline-1,3-dicarboxylate (VI) and catalytically hydrogenated.

No pure product could be isolated when diethyl 1,3-pyrrolidinedicarboxylate (VII) was used directly in a Bouveault-Blanc reduction. Diethyl 1,3-pyrrolidinedicarboxylate was therefore hydrolyzed to 3-pyrrolidinecarboxylic acid (VIII) which was esterified, without isolating the pure product, to ethyl 3-pyrrolidinecarboxylate (IX). For the preparation of 1-methyl-3-pyrrolidinemethanol from ethyl 3-pyrrolidinecarboxylate, two routes were investigated. The first route comprised the *N*-methylation of ethyl 3-pyrrolidinecarboxylate using a similar procedure of Feldkamp *et al.*,[14] followed by a Bouveault-Blanc reduction of the ethyl 1-methyl-3-pyrrolidinecarboxylate (X) thus formed. The second route utilized the Bouveault-Blanc reduction first to obtain 3-pyrrolidinemethanol (XI), which was *N*-methylated by the formic

(13) M. Miyamoto, *Yakugaku Zasshi*, **77**, 568 (1957); *Chem. Abstr.*, **51**, 16422e (1957).

(14) R. F. Feldkamp, J. A. Faust, and A. J. Cushman, *J. Am. Chem. Soc.*, **74**, 3831 (1952).

acid–formaldehyde method of Clarke, *et al.*[15] This sequence of reactions may be illustrated as the following:



EXPERIMENTAL[16]

1-Benzyl-5-oxo-3-pyrrolidinecarboxylic acid. A mixture of itaconic acid (130.1 g., 1 mole) and benzylamine (107.2 g., 1 mole) was heated for 2 hr. The hot reaction mixture was poured into 500 g. of an ice water mixture to separate crude 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid as a crystalline solid. The crude product was dissolved in 200 ml. of 5*N* potassium hydroxide. The solution was decolorized with activated carbon, filtered, and the filtrate acidified with 100 ml. of concd. hydrochloric acid. The crystalline 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid (182.5 g., 83%) was collected on a filter, thoroughly washed with water, and dried, m.p. 143° (reported[5a] m.p. 143–144°).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98. Found: C, 65.87; H, 5.87.

Methyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate. A mixture of 1-benzyl-5-oxo-3-pyrrolidinecarboxylic acid (21.9 g., 0.1 mole) and 150 ml. of 20% hydrogen chloride in methanol was refluxed with stirring for 3 hr. The mixture was concentrated under reduced pressure to a syrup which was cooled in an ice bath and treated with 100 ml. of saturated sodium bicarbonate solution. The whole was extracted with three 150-ml. portions of ether. The combined ethereal extract was dried over anhydrous magnesium sulfate, filtered, and the solvent removed by distillation. The residue was fractionated under reduced pressure to collect a fraction with b.p. 205–215° at 18 mm. The distillate was dissolved in 10 ml. of methanol and the resulting solution scratched in a glass rod to initiate crystallization. The yield of methyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate was 16.0 g. (69%), m.p. 64–65°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48. Found: C, 67.06; H, 6.43.

Ethyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate. Similarly prepared in 73% yield was ethyl 1-benzyl-5-oxo-3-pyrrolidinecarboxylate, b.p. 223–226° at 13 mm., n_D^{25} 1.5267.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93. Found: C, 68.28; H, 6.89.

1-Substituted 5-oxo-3-pyrrolidinecarboxylates (I). Three procedures were employed. For lower alkylamines with low boiling points, condensation with itaconic esters was carried out at 5–10° and then allowed to stand at room temperature. For cycloalkylamines and aralkylamines with higher boiling points, the reaction was performed at room temperature and completed by refluxing the reaction mixture. For arylamines, elevated temperatures were used to effect the condensation.

Procedure A. Dialkyl itaconate (1 mole) was added with stirring to a solution of the alkylamine (1 mole) in 100 ml. of absolute methanol, cooled in an ice bath, at such a rate that a temperature of 5–10° was maintained. The addition usually took 30–60 min. The mixture was allowed to warm up to room temperature with stirring. After standing overnight, the solvent was removed by distillation and the residual oil fractionated under reduced pressure.

Procedure B. A mixture of dialkyl itaconate (1 mole), amine (1 mole), and 100 ml. of absolute methanol was prepared and stored at room temperature overnight. After being refluxed for 2–3 hr., the mixture was concentrated. The residue was fractionated under reduced pressure or crystallized from a suitable solvent.

Procedure C. A mixture of equimolecular amounts of methyl itaconate and the arylamine was heated at 180–195° for 3 hr. During the heating a nearly theoretical amount of methanol was collected as the distillate. The residue was then distilled under reduced pressure.

Sixteen 1-substituted 5-oxo-3-pyrrolidinecarboxylates were synthesized as listed in Table I.

1-Substituted 3-pyrrolidinemethanols (II). A solution of 1 mole of 1-substituted 5-oxo-3-pyrrolidinecarboxylate in 150 ml. of anhydrous ether was added slowly to a slurry of 54 g. (1.4 moles) of powdered lithium aluminum hydride in 700 ml. of absolute ether. The addition was made over a period of 4–5 hr. with efficient stirring so as to maintain a moderate reflux rate. When the addition was complete, refluxing and stirring was continued for 2 hr., after which the reaction mixture was left at room temperature overnight. The white lithium aluminum complex was decomposed by the slow addition of 77 g. of water and sufficient addition of ether to permit efficient stirring. The resulting slurry was stirred for 1 hr. and then filtered by suction. The ethereal filtrate was set aside while the cake was completely extracted in a Soxhlet type apparatus with absolute ethanol. After combining the ethereal and the ethanolic filtrates, the solvents were removed by distillation, and the thick oil fractionated under reduced pressure. Fourteen 1-substituted 3-pyrrolidinemethanols were prepared as listed in Table II.

1-Substituted 3-chloromethylpyrrolidines (III). A solution of 1 mole of 1-substituted 3-pyrrolidinemethanol in 300 ml. of chloroform was saturated with gaseous hydrogen chloride. The brown, two phase mixture was then heated to reflux and slowly treated with a solution of 240 g. (2 moles) of thionyl chloride in 300 ml. of chloroform. When the addition was complete, refluxing was continued for 1 hr. The excess thionyl chloride and solvent were partially removed by distillation. Two 250-ml. portions of absolute ethanol were successively added to the concentrate and removed by distillation. The residue was dissolved in 300 ml. of water and all insoluble material completely removed from the solution by extraction with isopropyl ether. This acidic aqueous solution was made strongly basic with 56% potassium hydroxide liberating the free basic chloride as an oil. The oil was extracted with ether, and the extract dried with anhydrous magnesium sulfate. After filtration, all solvent was removed by distillation and the residual oil fractionated under reduced pressure. Eight 1-substituted 3-chloromethyl-

(15) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(16) All melting points and boiling points are uncorrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill.

pyrrolidines were prepared. Their physical constants are listed in Table III.

1-Methyl-3-pyrrolidinemethanol. The physical properties, including refractive indices, infrared spectra, and boiling points, of the products from different syntheses were essentially the same.

(a) *From methyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate by using sodium aluminum hydride as a reducing agent.* A slurry of 12.1 g. (0.23 mole) of sodium aluminum hydride in 50 ml. of tetrahydrofuran was slowly treated with stirring over 1.5 hr. period with a solution of 23.6 g. (0.15 mole) of methyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate in 50 ml. of tetrahydrofuran. After being stirred and refluxed for an additional 1.5 hr., the reaction mixture was cooled in an ice bath and carefully treated with 12.1 ml. of water. The mixture was filtered and the filter cake extracted with two 150-ml. portions of boiling ethanol. The filtrate and the ethanolic extracts were combined. The solvents were removed by distillation under partial vacuum. The oily residue was fractionated under reduced pressure to yield 11.4 g. (66%) of 1-methyl-3-pyrrolidinemethanol as a colorless oil, b.p. 86–89° at 8 mm., n_D^{25} 1.4663.

(b) *From diethyl 1,3-pyrrolidinedicarboxylate. Diethyl 4-oxo-1,3-pyrrolidinedicarboxylate* (IV). The procedure of Kuhn and Osswald[17] was followed. Diethyl 4-oxo-1,3-pyrrolidinedicarboxylate melted at 60–62° (reported,[17] m.p. 59–62°.

Diethyl 4-hydroxy-1,3-pyrrolidinedicarboxylate (V). A solution of diethyl 4-oxo-1,3-pyrrolidinedicarboxylate (58.0 g., 0.25 mole) in 250 ml. of absolute ethanol was hydrogenated under 50 p.s.i. pressure of hydrogen using platinum oxide as the catalyst. The theoretical amount of hydrogen was absorbed in 16 hr. The catalyst was filtered off and the filtrate concentrated. The crude diethyl 4-hydroxy-1,3-pyrrolidinedicarboxylate (43.9 g.) was obtained by distilling the residue under reduced pressure, b.p. 134–164° at 0.2–0.3 mm., n_D^{25} 1.4730. The pure product (37.5 g., 65%) was collected as a colorless oil by redistilling the crude compound, b.p. 164–167° at 0.18 mm. (reported,[13] 176–178° at 2.5 mm.), n_D^{25} 1.4722.

Diethyl 3-pyrroline-1,3-dicarboxylate (VI). A mixture of diethyl 4-hydroxy-1,3-pyrrolidinedicarboxylate (23.1 g., 0.1 mole), acetic anhydride (69 ml.), and anhydrous sodium acetate (2.5 g.) was refluxed for 5.5 hr. The acetic anhydride was removed by distillation. The residual crystalline slurry was treated with 150 ml. of ether and the solid collected on a filter. The solid was dissolved in 50 ml. of water and the aqueous solution extracted several times with ether. The filtrate was mixed with the ethereal extracts, dried over anhydrous magnesium sulfate, and concentrated. The residual oil was distilled under reduced pressure to give 19.9 g. of a light colored distillate, b.p. 158° at 9 mm., n_D^{25} 1.4728. The pure diethyl 3-pyrroline-1,3-dicarboxylate (18.6 g., 87%) was obtained as a colorless oil by redistilling the crude compound, b.p. 155–160° at 9 mm. (reported,[13] 134° at 2 mm.), n_D^{25} 1.4748.

Diethyl 1,3-pyrrolidinedicarboxylate (VII). A solution of diethyl 3-pyrroline-1,3-dicarboxylate (17.1 g., 0.08 mole) in 75 ml. of absolute ethanol was hydrogenated under 50 p.s.i. pressure of hydrogen using platinum oxide as the catalyst. The theoretical amount of hydrogen was absorbed in 6 hr. The mixture was filtered. After removing the solvent the residual oil was distilled under reduced pressure to yield 16.3 g. (90%) of diethyl 1,3-pyrrolidinedicarboxylate as a colorless oil, b.p. 152–158° at 10 mm. (reported[13] 120–121° at 1.5 mm.), n_D^{25} 1.4582.

1-Methyl-3-pyrrolidinemethanol. A slurry of 2.0 g. (0.053 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether was slowly treated with a solution of diethyl 1,3-pyrrolidinedicarboxylate (4.3 g., 0.02 mole) in 25 ml. of anhydrous ether at such a rate that gentle refluxing was maintained. After being stirred and refluxed for an additional 5 hr., the reaction mixture was cooled in an ice bath and carefully treated with 2.9 ml. of water. The whole was filtered and the filter cake extracted with two 75-ml. portions of ethanol. The ethereal filtrate and the ethanolic extracts were combined and concentrated by distillation. The oily residue was distilled under reduced pressure to collect 1.50 g. (65%) of 1-methyl-3-pyrrolidinemethanol as a colorless oil, b.p. 85–90° at 10 mm., n_D^{25} 1.4662.

(c) *From ethyl 3-pyrrolidinecarboxylate (Bouveault-Blanc reaction). Ethyl 3-pyrrolidinecarboxylate* (IX). A stirred mixture of diethyl 1,3-pyrrolidinedicarboxylate (10.8 g., 0.05 mole) and 50 ml. of water was slowly treated (10–15 min.) with 50 ml. of concd. hydrochloric acid. After refluxing for 7 hr. the resulting clear solution was cooled to room temperature and thoroughly shaken with 50 ml. of ethyl acetate. The aqueous layer was separated and concentrated under reduced pressure to a viscous oily residue which was extracted twice with liberal amounts of absolute ethanol. The combined ethanol solutions were concentrated by distillation to give crude 3-pyrrolidinecarboxylic acid hydrochloride as a yellow viscous oil. A solution of dry hydrogen chloride (35 g.) in 130 ml. of absolute ethanol was added, and the mixture was refluxed for 20 hr. After concentrating the ethanolic reaction mixture by distillation under reduced pressure, the greenish yellow viscous residue was cooled in an ice bath, covered with 75 ml. of ether, and made strongly basic with 10 ml. of 40% sodium hydroxide. The aqueous layer was separated and thoroughly extracted with two 75-ml. portions of ether. The combined ethereal extract was dried over anhydrous magnesium sulfate, filtered, concentrated, and fractionated under reduced pressure to collect 3.65 g. (51%) of ethyl 3-pyrrolidinecarboxylate as a colorless, very mobile liquid, b.p. 92–94° at 17 mm., n_D^{25} 1.4531.

Ethyl 1-methyl-3-pyrrolidinecarboxylate (X). A mixture of ethyl 3-pyrrolidinecarboxylate (3.45 g., 0.024 mole), formaldehyde (37%, 2.0 g., 0.024 mole), acetic acid (2.9 g., 0.048 mole), and 25 ml. of water was hydrogenated under 50 p.s.i. pressure of hydrogen using 0.2 g. of 10% palladium on charcoal as the catalyst. The theoretical amount of hydrogen was absorbed in 30 min. The catalyst was removed by filtration and the filtrate concentrated by distillation. The oily residue was cooled in an ice bath, covered with 100 ml. of ether, and made strongly basic with 10 ml. of 40% sodium hydroxide. The aqueous layer was separated and extracted with two 50-ml. portions of ether. The combined ethereal extract was dried over anhydrous magnesium sulfate, filtered, and concentrated by distillation. The residue was fractionated under reduced pressure to yield 2.75 g. (73%) of ethyl 1-methyl-3-pyrrolidinecarboxylate as a colorless oil, b.p. 80–82° at 15 mm., n_D^{25} 1.4400. Redistillation of the crude product gave 2.54 g. (67.3%) of the pure product, b.p. 102–103° at 38 mm., n_D^{25} 1.4401.

Anal. Calcd. for $C_8H_{15}NO$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.13; H, 9.66; N, 9.28.

1-Methyl-3-pyrrolidinemethanol. Freshly cut sodium metal (1.5 g., 0.065 g.-atom) was covered with 8 ml. of dry toluene and the mixture heated to slow reflux with efficient stirring, while a combined solution of ethyl 1-methyl-3-pyrrolidinecarboxylate (2.50 g., 0.016 mole), 4-methylpentanol-2 (3.40 g., 0.033 mole), and 12 ml. of dry toluene was added dropwise over a 2 hr. period. After being stirred and refluxed for 3 hr., the reaction mixture was cooled to 50–60°, and carefully treated with 5 ml. of water. The organic layer was separated. The aqueous layer was extracted with two 25-ml. portions of toluene and one 25-ml. portion of ether. The combined toluene and ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The oily residue was distilled under reduced pressure to give 1.28 g. (70%) of 1-methyl-3-pyrrolidinemethanol as a light straw colored distillate, b.p. 112–114° at 38 mm., n_D^{25} 1.4656. The pure product (1.17 g., 64.9%) was obtained as a colorless liquid by redistillation under reduced pressure, b.p. 112–114° at 38 mm., n_D^{25} 1.4661.

(17) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).

3-Pyrrolidinemethanol (XI). Freshly cut sodium metal (1.15 g., 0.05 g.-atom) was covered with 5 ml. of dry toluene and the mixture heated to slow reflux with efficient stirring, while a combined solution of ethyl 3-pyrrolidinecarboxylate (1.4 g., 0.01 mole), 4-methylpentanol-2 (2.62 g., 0.025 mole), and 15 ml. of dry toluene was added dropwise over a 1-hr. period. After being stirred and refluxed for 2 hr., the reaction mixture was cooled to 50–60° and carefully decomposed with 10 ml. of water. The organic layer was separated. The aqueous layer was saturated with solid potassium hydroxide and extracted several times with toluene. The toluene extracts were combined and dried over anhydrous magnesium sulfate. The oily residue which was obtained after filtering and concentrating the toluene solution was distilled under reduced pressure to collect 0.30 g. (30%) 3-pyrrolidinemethanol as a colorless distillate, b.p. 122° at 15 mm., n_D^{25} 1.4851.

1-Methyl-3-pyrrolidinemethanol. A mixture of 3-pyrrolidinemethanol (300 mg., 3 mmoles), formic acid (380 mg., 8 mmoles), and formaldehyde (37%, 270 mg., 3 mmoles) was refluxed for 6.5 hr. Concentrated hydrochloric acid (600 mg., 7 mmoles) was added and the refluxing continued for 30 min. The residue, obtained by concentrating the mixture in a partial vacuum, was cooled in an ice bath, made strongly basic with 0.5 ml. of 40% sodium hydroxide, and extracted thoroughly with ether. The ethereal extract was dried over anhydrous magnesium sulfate, filtered, and concentrated to an oily residue. 1-Methyl-3-pyrrolidinemethanol (120 mg., 35%) was obtained as a colorless oil by fractional distillation, b.p. 93–95° at 16 mm., n_D^{25} 1.4682.

1-Methyl-3-pyrrolidinemethanol methobromide. A solution of 1-methyl-3-pyrrolidinemethanol (120 mg., 1 mmole) in 0.5 ml. of acetonitrile was cooled in an ice bath and saturated with methyl bromide. 1-Methyl-3-pyrrolidinemethanol methobromide separated as white crystals which were filtered and washed with a 0.5–1 ml. amount of isopropyl alcohol. After drying at 60° for 1 hr., 1-methyl-3-pyrrolidinemethanol methobromide (110 mg., 52%) melted at 250–253°. A mixed melting point determination with an authentic sample showed no depression.[18]

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(18) See Table II, footnote *a*.

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, RESEARCH DIVISION, MEAD JOHNSON AND CO.]

Pyrrolidines. II. 1-Substituted 3-Pyrrolidinylmethyl Esters of Disubstituted Acetic and Glycolic Acids

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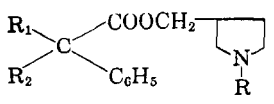
A series of 1-substituted 3-pyrrolidinylmethyl esters of disubstituted acetic and glycolic acids has been synthesized for antispasmodic screening. Different methods for the preparation of the highly active 1-methyl-3-pyrrolidinylmethyl esters of benzilic and phenylcyclohexylglycolic acids were studied. A separation of two possible racemic forms of 1-methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate was accomplished by the combined use of fractional crystallization, adsorption chromatography, and fractional precipitation.

A large number of basic alkyl esters of disubstituted acetic and glycolic acids has been synthesized in the past. Some of them have been shown to possess useful antispasmodic action.[1–3]

In a search for more physiologically acceptable antispasmodic agents we have synthesized a series of esters of structure (I) using 1-substituted 3-



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pyrrolidinylmethyl alcohols and chlorides[4] as intermediates. The acid moieties used were benzilic (R_1 = OH, R_2 = C_6H_5), diphenylacetic (R_1 = H, R_2 = C_6H_5), and phenylcyclohexylglycolic (R_1 = OH, R_2 = cyclohexyl) acids.

The 1-substituted 3-pyrrolidinylmethyl benzilates were most readily prepared by the transesterification[5,6] of the 1-substituted 3-pyrrolidinemethanols with methyl benzilate using *n*-heptane as the reaction medium, a catalytic amount of metallic sodium, and a Dean and Stark apparatus to trap the methanol formed. The reaction went smoothly and generally was completed after a three to four hour reflux period. The volume of the methanol phase separated in the Dean and Stark trap was a good indication of the extent of the reaction. The free 1-substituted 3-pyrrolidinylmethyl benzilates prepared were crystalline solids that could be recrystallized from *n*-heptane. Their hydrochloride and methobromide salts were prepared by the usual procedures. The physical properties of the free bases, hydrochlorides, and methobromides are recorded in Table I.

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(3) A. Burger, *Medicinal Chemistry*, Vol. 1, Interscience, New York and London, 1951, p. 417.
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(5) A. Verley, *Bull. soc. chim.*, **41**, 788 (1927).
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