Experimental[18]

2-Aminoethylisoselenouronium Bromide Hydrobromide.—A solution of 5.78 g. (0.0282 mole) of 2-bromoethylamine hydrobromide and of 3.50 g. (0.0282 mole) of selenourea in 170 ml. of isopropyl alcohol was heated to reflux under a nitrogen atmosphere for 45 min. After cooling the product was removed by filtration. Recrystallization from a 10:1 mixture of ethanol and ethyl acetate yielded 6.20 g. (67%) of product melting at 200–204°.

The isoselenouronium salts shown in Table I were prepared in analogous fashion.

2-Selenoethylguanidine Flavianate.—A solution of 0.25 g. (0.00076 mole) of 2-aminoethylisoselenouronium bromide hydrobromide in 6.5 ml. of 0.2 *N* sodium hydroxide (pH 7.0–7.2) was left to stand at room temperature for 15 min. Addition of 1.0 ml. of 1 *M* aqueous flavianic acid resulted in the formation of a yellow precipitate which was washed successively with ice-cold water, ethanol, and ethyl acetate. Recrystallization from ethyl alcohol gave rise to a yield of 0.25 g. (68%) of material decomposing at 164°.

Anal. Calcd. for $C_{13}H_{15}N_5O_8Se$: C, 32.57; H, 3.12; N, 14.58. Found: C, 33.04; H, 3.26; N, 14.69.

2-Aminoselenazoline Hydrobromide.—A solution of 0.5 g. (0.0015 mole) of 2-aminoethylisoselenouronium bromide hydrobromide in 25 ml. of water was heated to reflux for 45 min. and then evaporated to dryness under reduced pressure. The residue was recrystallized twice from a 5:2 ethanol–ethyl acetate mixture to give a yield of 0.35 g. (70%) of product melting at 170–171°. A mixed melting point with an authentic sample[17] showed no depression.

(18) All melting points are uncorrected. Analyses were carried out at Midwest Microlab, Inc., Indianapolis, Indiana.

Synthesis and Anticholinergic Activity of Ester Derivatives of Substituted 3-Pyrrolidinols

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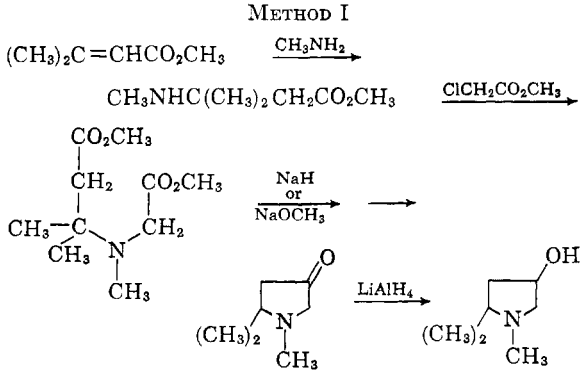
The preparation and preliminary pharmacological evaluation of eighteen ester derivatives of 3-pyrrolidinols are described.

A previous publication[1] recorded some ester derivatives of 2-substituted piperidines together with preliminary pharmacological data. In a similar fashion this paper reports esters of 3-pyrrolidinols[2] (Table I).

The N-alkyl-3-pyrrolidinols used were substituted monomethyl and dimethyl at positions 2, 4, and 5 and tetramethylene at 2 (Table II). The 3-pyrrolidinols other than 1,4,4-trimethyl-3-pyrrolidinol were prepared by lithium aluminum hydride reduction of the corresponding 3-keto compounds. The latter were formed *via* Dieckmann ring closure essentially according to the procedure of Leonard.[3]

The diesters used to prepare the dimethylpyrrolidinols and 1,5,5-trimethyl-3-pyrrolidinol were synthesized by the procedure illustrated below.

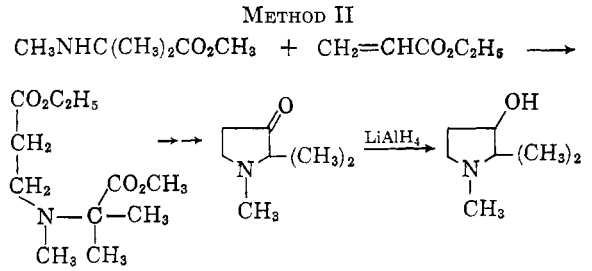
METHOD I



The method did not provide a synthetic route for the diester intermediates required for the 1,2,2- and 1,4,4-trimethyl-3-pyrrolidinols.

1,2,2-Trimethyl-3-pyrrolidinol and the corresponding spiro analog were prepared by the following scheme:

METHOD II



The methyl α-methylaminoisobutyrate was prepared essentially according to the procedure of Leonard and Barthel.[4]

1,4,4-Trimethyl-3-pyrrolidinol was prepared by an entirely different approach. α-Hydroxy-β,β-dimethyl-γ-butyrolactone[5] was converted to the

(1) C. W. Ryan and C. Ainsworth, *J. Org. Chem.*, **26**, 1547 (1961).

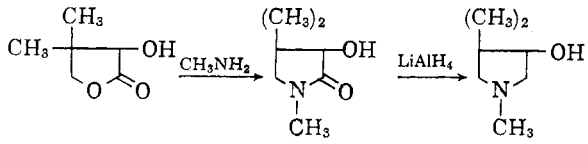
(2) Since this work was completed, three publications related to it have appeared: (a) R. E. Bowman, J. F. Cavalla, and J. Davoll, British Patent 821,436; [*Chem. Abstr.*, **56**, 2427 (1962)]. (b) B. V. Franko and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960). (c) J. F. Cavalla, *et. al.*, *ibid.*, **4**, 1 (1961).

(3) N. J. Leonard, *et al.*, *J. Am. Chem. Soc.*, **73**, 2371 (1951).

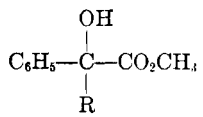
(4) N. J. Leonard and E. Barthel, Jr., *ibid.*, **72**, 3632 (1950).

(5) J. W. Lynn, U.S. Patent 2,863,878; [*Chem. Abstr.*, **53**, 7019 (1959)].

corresponding 1-methyllactam[6] and this was reduced with lithium aluminum hydride.



The methyl glycolic esters (the R group was cycloalkyl, aryl, and heteroaryl) were prepared by the addition of one mole of Grignard reagent to methyl phenylglyoxylate essentially according to the procedure of Martell.[7]



The basic esters described in Table I were prepared by the transesterification reaction[8] of the N-alkyl 3-pyrrolidinols and the methyl glycolic esters. Quaternization of some of the ester derivatives gave readily separable diastereoisomers that are listed as *a* and *b* in the table.

The compounds reported in this paper were examined by infrared and ultraviolet analyses and showed the expected absorption characteristics.

Several of the compounds were evaluated pharmacologically in animals in tests other than indicated in Table I. Those compounds with activity below 40 mg./kg. in the Shay rat test were administered to gastric fistula dogs. The quaternary compound X was among the most effective causing anacidity for two to four hours when given orally at 0.5 mg./kg. to meal stimulated innervated or denervated pouch dogs.

Experimental[9]

Preparation of the Pyrrolidinols. Method I. Methyl β-Methyl-β-methylaminobutyrate.—A solution of 27 g. (0.24 mole) of methyl β,β-dimethylacrylate,[10] 8 g. of methylamine, and 200 ml. of absolute alcohol was allowed to stand at room temperature for 1 week. It was then distilled; 16.4 g. (48% yield), of methyl β-methyl-β-methylaminobutyrate, b.p. 70–80° (20 mm.), $n^{25}D$ 1.4268, was obtained.

Anal. Calcd. for $C_7H_{15}NO_2$: N, 9.65. Found: N, 9.36.

N-Carbomethoxymethyl-N-(α,α-dimethyl-β-carbomethoxyethyl)methylamine.—A mixture of 16 g. (0.11 mole) of methyl β-methyl-β-methylaminobutyrate, 13 g. (0.12 mole) of methyl chloroacetate, 25 ml. of benzene, and 16 g. of anhydrous potassium carbonate was heated under reflux overnight. The solution was cooled, diluted with 100 ml. of water, and then made strongly basic with excess 50% sodium hydroxide solution. The benzene solution was dried with magnesium sulfate and distilled. After a forerun of starting material, 8.5 g. (36% yield) of product was collected, b.p. 125–135° (10 mm.). A small sample was used to prepare a hydrochloride salt, m.p. 78–80°.

Anal. Calcd. for $C_{10}H_{19}NO_4 \cdot HCl$: N, 5.52. Found: N, 5.28.

In a similar way the following crude esters were prepared: *N*-(carbomethoxymethyl)-*N*-α-methyl-β-carbethoxyethyl)-methylamine, b.p. 125–135° (10 mm.) from ethyl β-methylaminobutyrate[11] and methyl chloroacetate; N-(α-carbethoxyethyl)-N-(β-carbethoxyethyl)methylamine,[2c] b.p. 130–140 (10 mm.), from ethyl β-methylaminopropionate[12] and ethyl α-bromopropionate; and N-(carbomethoxymethyl)-N-(β-carbomethoxypropyl)methylamine, b.p. 120–125° (15 mm.) from methyl α-methyl-β-methylaminopropionate[13] and methyl chloroacetate.

1,2-Dimethyl-3-pyrrolidone.—A solution of 25 g. (0.11 mole) of N-(α-carbethoxyethyl)-N-(β-carbethoxyethyl)-methylamine in 50 ml. of toluene was added dropwise with stirring over a 45-min. period to 9 g. (0.22 mole) of 55% sodium hydride in oil dispersion suspended in 25 ml. of toluene. The reaction mixture was heated under reflux for 2 hr. It was then cooled and 10 ml. of ethanol and 50 ml. of water were added cautiously. The mixture was made strongly acidic by the addition of 6 *N* hydrochloric acid; the toluene layer was removed, and the aqueous layer was heated under reflux for 3 hr. After cooling, the solution was saturated with potassium carbonate and extracted with one 50-ml. and four 25-ml. portions of chloroform. The chloroform solution was dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was distilled and gave 8.0 g. (64% yield) of product,[2c] b.p. 60–80° (30 mm.), $n^{25}D$ 1.4422. This material, like the other ketones, was not purified but was used directly in the next step.

General Procedure for Reduction of 3-Pyrrolidones. 1,2-Dimethyl-3-pyrrolidinol (XIX, Table II).—The crude ketone described above (8.0 g., 0.07 mole) was added dropwise to a suspension of 4 g. of lithium aluminum hydride in 100 ml. of ether. After stirring for 15 min. the reaction mixture was treated successively with 4 ml. of water, 4 ml. of 20% sodium hydroxide solution, and 15 ml. of water. The ether was filtered and concentrated under reduced pressure. Distillation of the residue yielded 3.9 g. (48%) of 1,2-dimethyl-3-pyrrolidinol, b.p. 70–80° (10 mm.), $n^{25}D$ 1.4628.

Anal. Calcd. for $C_6H_{13}NO$: N, 12.16. Found: N, 12.43.

In a similar fashion XX, XXI, XXIII, XXIV, and XXV (Table II) were prepared from the corresponding crude ketones.

Method II. N-(α-Methyl-α-carbomethoxyethyl)-N-(β-carbethoxyethyl)methylamine.—A solution of 19.5 g. (0.15 mole) of methyl α-methylaminoisobutyrate,[4] 37 g. (0.37 mole) of ethyl acrylate, and 50 ml. of absolute ethanol was allowed to stand at room temperature for 4 days. It was then heated under reflux overnight. The reaction mixture was distilled, collecting 24.9 g. of crude product, b.p. 180–185° (10 mm.). This material was dissolved in 1 *N* hydrochloric acid and was extracted with two 100 ml. portions of benzene. The aqueous layer was made basic with potassium carbonate and was extracted with two 50-ml. portions of benzene. The benzene solution was dried with anhydrous magnesium sulfate, and distillation gave 16.4 g. (49% yield) of product, b.p. 180–185° (10 mm.).

Anal. Calcd. for $C_{11}H_{21}NO_4$: N, 6.06. Found: N, 5.43.

1,2,2-Trimethyl-3-pyrrolidone.—N-(α-Methyl-α-carbomethoxyethyl)-N-(β-carbethoxyethyl)methylamine (16 g., 0.07 mole) was added dropwise with stirring to a hot sus-

(6) C. Shuster, German Patent 812,551 [*Chem. Abstr.*, **47**, 6986 (1953)] reported the preparation of α-hydroxybutyrolactam from the lactone and ammonia heated at 230°.

(7) M. T. Martell, Jr., Ph.D. thesis, University of Minnesota, 1958, p. 75.

(8) R. F. Feldkamp, *J. Am. Chem. Soc.*, **74**, 3834 (1952).

(9) The melting points were determined with a Fisher-Johns block and are uncorrected.

(10) R. B. Wagner and J. A. Moore, *J. Am. Chem. Soc.*, **72**, 974 (1950).

(11) K. Morsch, *Monatsh.*, **60**, 50 (1932); [*Chem. Abstr.*, **26**, 4030 (1932)].

(12) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).

(13) R. C. Smith and S. B. Binkley, *J. Org. Chem.*, **24**, 249 (1959).

TABLE I

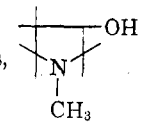
SUBSTITUTED 3-PYRROLIDINOL GLYCOLATES $R_1O-\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{CR_2C_6H_5}\cdot RX$

Number[a]	R_1	R_2	RX	Yield, %	M.p.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Pharmacological data: Shay rat M.E.D.[b]	Pharmacological data: Antispasmodic effect atropine = 1.0[c]
I	$CH_2CH_2N(C_2H_5)CH_2CH$	C_6H_5	HCl	50	153–155[d]	$C_{20}H_{23}NO_3\cdot HCl$	66.38	66.14	6.69	6.48	3.87	3.57	>40	0.50
IIa	$CH_2CH_2N(C_2H_5)CH_2CH$	C_6H_5	CH_3Br		201–202	$C_{21}H_{26}BrNO_3$	60.00	60.41	6.23	6.35	3.33	3.25	>40	0.50
IIb	$CH_2CH_2N(C_2H_5)CH_2CH$	C_6H_5	CH_3Br		165–167	$C_{21}H_{26}BrNO_3$	60.00	59.81	6.23	6.22	3.33	3.34	20	0.50
III	$CH_2CH_2N(C_2H_5)CH_2CH$	C_6H_5	C_2H_5Br		203–204	$C_{22}H_{28}BrNO_3$	60.83	60.60	6.50	6.74	3.23	3.22	2.5	0.25
IV	$CH_2CH_2N[CH(CH_3)_2]CH_2CH$	C_6H_5	HCl	66	191–192[e]	$C_{21}H_{25}NO_3\cdot HCl$	67.10	66.97	6.97	6.82	3.73	3.75	>40	0.25
Va	$CH_2CH_2N[CH(CH_3)_2]CH_2CH$	C_6H_5	CH_3Br	31	201–203	$C_{22}H_{28}BrNO_3$	60.83	61.12	6.50	6.67	3.23	3.23	>40	0.50
Vb	$CH_2CH_2N[CH(CH_3)_2]CH_2CH$	C_6H_5	CH_3Br	38	173–178	$C_{22}H_{28}BrNO_3$	60.83	60.95	6.50	6.78	3.23	3.19	>40	0.20
VI	$CH_2CH_2N(CH_3)CH_2CH$	4-$CH_3C_6H_4$	CH_3Br	47	215–217	$C_{21}H_{26}BrNO_3$	60.00	59.77	6.23	5.79	3.33	3.33	>40	0.20
VII	$CH_2CH_2N(CH_3)CH_2CH$	4-ClC_6H_4	CH_3Br	45	201–203	$C_{20}H_{23}BrClNO_3$	54.50	54.33	5.26	5.44	3.18	3.13	20	1.0
VIIIa	$CH_2CH_2N(CH_3)CH_2CH$	C_6H_{11}[f]	CH_3Br	14[g]	257–259	$C_{20}H_{30}BrNO_3$	58.25	57.99	7.33	7.43	3.40	3.25	2.5	0.30
VIIIb	$CH_2CH_2N(CH_3)CH_2CH$	C_6H_{11}	CH_3Br	7	182–184	$C_{20}H_{30}BrNO_3$	58.25	58.54	7.33	7.38	3.40	3.32	2.5	0.25
IX	$CH_2CH_2N(CH_3)CH_2CH$	2-C_4H_3S[h]	HCl	46	150–152	$C_{17}H_{19}NO_3S\cdot HCl$	57.70	58.17	5.70	5.72	3.96	3.84	>40	1.0
X	$CH_2CH_2N(CH_3)CH_2CH$	2-C_4H_3S	CH_3Br	44	182–184	$C_{18}H_{22}BrNO_3S$	52.43	52.63	5.38	5.35	3.40	3.41	10	0.50
XI	$CH_2CH_2N(CH_3)CH(CH_3)CH$	C_6H_5	CH_3Br	63	228–231	$C_{21}H_{26}BrNO_3$	60.00	59.81	6.23	6.26	3.33	2.94	2.5	0.50
XII	$CH_2CH_2N(CH_3)C(CH_3)_2CH$	C_6H_5	CH_3Br	59	218–220	$C_{22}H_{28}BrNO_3$	60.83	60.59	6.50	6.62	3.23	3.36	5	1.0
XIII	$CH(CH_3)CH_2N(CH_3)CH_2CH$	C_6H_5	CH_3Br	19	150	$C_{21}H_{26}BrNO_3$	60.00	59.82	6.23	6.29	3.33	3.30	40	...
XIV	$C(CH_3)_2CH_2N(CH_3)CH_2CH$	C_6H_5	CH_3Br	32	257–258	$C_{22}H_{28}BrNO_3$	60.83	60.94	6.50	6.67	3.23	3.52	40	0.25
XV	$CH_2CH(CH_3)N(CH_3)CH_2CH$	C_6H_5	CH_3Br	48	231–233	$C_{21}H_{26}BrNO_3$	60.00	60.47	6.23	6.64	3.33	3.46	40	0.50
XVI	$CH_2C(CH_3)_2N(CH_3)CH_2CH$	C_6H_5	CH_3Br	64	234–236	$C_{22}H_{28}BrNO_3$	60.83	60.86	6.50	7.11	3.23	3.35	20	2.0
XVII	$CH_2CH_2N(CH_3)C(CH_2)_4CH$	C_6H_5	HCl	59	187–191	$C_{23}H_{27}NO_3\cdot HCl$	68.73	68.66	7.02	7.53	3.49	3.41	40	0.75
XVIII	$CH_2CH_2N(CH_3)C(CH_2)_4CH$	C_6H_5	CH_3Br	51	239–241	$C_{24}H_{30}BrNO_3$	62.61	62.43	6.57	6.70	3.04	3.32	10	1.0

[a] The letters a and b denote diastereoisomers. [b] Minimum effective dose in mg./kg. that reduced acid secretion of the Shay rat by at least 20% when the compound was administered orally. [c] Spasm induced in isolated guinea pig ileum with methacholine. [d] Franko and Lunsford (ref. 2b) reported m.p. 148–149°. [e] Reported (ref. 2b) m.p. 191.5–193°. [f] C_6H_{11} is cyclohexyl. [g] All yields are based on the starting amino alcohol. [h] C_4H_3S is thienyl.

TABLE II

3-PYRROLIDINOLS,



Number	Compound	Yield, %	$n^{25}D$	B.p., (mm.)	Empirical formula	Nitrogen Calcd.	Nitrogen Found
XIX	$CH_2CH_2N(CH_3)CH(CH_3)CHOH$	48	1.4628	70–80 (10)	$C_6H_{13}NO$	12.16	12.43
XX	$CH_2CH_2N(CH_3)C(CH_3)_2CHOH$	45	1.4698	80–85 (10)	$C_7H_{15}NO$	10.84	10.58
XXI	$CH(CH_3)CH_2N(CH_3)CH_2CHOH$	44	1.4560	75–80 (10)	$C_6H_{13}NO$	12.16	12.70
XXII	$C(CH_3)_2CH_2N(CH_3)CH_2CHOH$	46	1.4590	70–90 (10)	$C_7H_{15}NO$	10.84	10.01
XXIII	$CH_2CH(CH_3)N(CH_3)CH_2CHOH$	56	1.4580	70–80 (10)	$C_6H_{13}NO$	12.16	12.27
XXIV	$CH_2C(CH_3)_2N(CH_3)CH_2CHOH$	53	1.4648	82–85 (12)	$C_7H_{15}NO$	10.84	10.51
XXV	$CH_2CH_2N(CH_3)C(CH_2)_4CHOH$	59	1.4988	105–108 (5)	$C_9H_{17}NO$	9.02	9.00

pension of 7.6 g. (0.14 mole) of sodium methoxide in 100 ml. of toluene. The mixture was distilled slowly through a Vigreux column until the vapor temperature reached 110°. The reaction mixture was then cooled, and 100 ml. of water was added. The toluene layer was discarded, and the aqueous layer was heated for 4 hr. on a steam bath. It was then cooled, saturated with potassium carbonate, and extracted with one 50-ml. and three 25-ml. portions of chloroform. The chloroform solution was dried with anhydrous potassium carbonate and then was concentrated by heating on a steam bath. The residue was distilled, and there was obtained 3.2 g. (36% yield) of 1,2,2-trimethyl-3-pyrrolidone,[2c] b.p. 50° (10 mm.), $n^{25}D$ 1.4433.

Anal. Calcd. for $C_7H_{13}NO$: N, 11.02. Found: N, 10.73.

1-Methylaminocyclopentanecarbonitrile.—A solution of 170 g. (2.0 moles) of cyclopentanone and 140 g. (2.1 moles) of methylamine hydrochloride in 150 ml. of water was cooled, and a solution of 130 g. of potassium cyanide in 260 ml. of water was added with cooling to maintain the temperature at 15–20°. After stirring overnight at room temperature the reaction mixture was extracted with three 100-ml. portions of methylene chloride. The organic extract was dried with potassium carbonate, and then the solvent was removed by heating on a steam bath. The residue was distilled, and 204 g. (83% yield) of 1-methylaminocyclopentanecarbonitrile, b.p. 75–77° (7 mm.), was obtained.

Anal. Calcd. for $C_7H_{12}N_2$: N, 22.56. Found: N, 22.43.

Ethyl 1-Methylaminocyclopentanecarboxylate.—A solution of 50 g. (0.4 mole) of 1-methylaminocyclopentanecarbonitrile in 500 ml. of absolute alcohol saturated with hydrogen chloride was allowed to stand overnight. The reaction mixture was heated under reflux for 5 hr., cooled, and filtered. The filtrate was concentrated by heating under reduced pressure on a steam bath. The concentrate was cooled, and 200 g. of 50% potassium hydroxide was added. The mixture was extracted with four 100-ml. portions of ether. The ether extract was dried with potassium carbonate, concentrated on a steam bath, and the residue was distilled, yielding 39 g. (57%) of ethyl 1-methylaminocyclopentanecarboxylate, b.p. 68° (3 mm.), $n^{25}D$ 1.4475.

Anal. Calcd. for $C_9H_{17}NO_2$: N, 8.18. Found: N, 8.28.

N-(1-Carbethoxycyclopentyl)-N-(β-carbethoxyethyl)-methylamine.—The reaction of ethyl 1-methylaminocyclopentanecarboxylate and ethyl acrylate in absolute alcohol (according to the earlier procedure) gave N-(1-carbethoxycyclopentyl)-N-(β-carbethoxyethyl)methylamine, b.p. 170–190° (1 mm.); yield 63%. The material was used directly in the next preparation.

1-Methyl-1-azaspiro[4.4]nonan-4-one.—A solution of 39 g. (0.15 mole) of N-(1-carbethoxycyclopentyl)-N-(β-carbethoxyethyl)methylamine in 75 ml. of toluene was added to a suspension of 15 g. of 55% sodium hydride in oil dispersion and 40 ml. of hot toluene. After heating under reflux for 3 hr., the reaction mixture was cooled, and 25 ml. of absolute alcohol, 50 ml. of water, and 100 ml. of 6 *N* hydrochloric acid were added. The mixture was heated under reflux for 5 hr., cooled, and made basic with potassium carbonate. It was extracted with three 50-ml. portions of chloroform. The chloroform was removed by heating on a steam bath, and the residue was distilled, yielding 7.8 g. (43%) of 1-methyl-1-azaspiro[4.4]nonan-4-one, b.p. 83–90° (5 mm.), $n^{25}D$ 1.4812. A small sample was used to prepare the hydrochloride salt, m.p. 124–126°.

Anal. Calcd. for $C_9H_{15}NO \cdot HCl$: N, 7.39. Found: N, 7.54.

3-Hydroxy-1,4,4-trimethyl-2-pyrrolidone.—A solution of 25 g. (0.19 mole) of α-hydroxy-β,β-dimethyl-γ-butyrolactone,[5] 12.5 g. (0.4 mole) of methylamine, and 50 ml. of methanol was heated for 4 hr. in a bomb at 250°. After cooling, the reaction mixture was dried with anhydrous magnesium sulfate and then was concentrated on a steam bath. The tarry residue was extracted with two 150-ml. portions of ether. The ether was removed, and distillation of the residue gave 8.5 g. (30% yield) of crude 3-hydroxy-1,4,4-trimethyl-2-pyrrolidone, b.p. 115–135° (10 mm.). The distillate crystallized on standing, and an analytical sample was obtained from ethyl acetate–petroleum ether, m.p. 75°.

Anal. Calcd. for $C_7H_{13}NO_2$: N, 9.78. Found: N, 9.80.

1,4,4-Trimethyl-3-pyrrolidinol.—A mixture of 8 g. (0.056 mole) of crude 3-hydroxy-1,4,4-trimethyl-2-pyrrolidone and 3 g. (0.08 mole) of lithium aluminum hydride in 100 ml. of dry ether was heated under reflux for 12 hr. Standard work-up of the reaction mixture yielded 3.4 g. (46%) of 1,4,4-trimethyl-3-pyrrolidinol (XXII, Table II).

Preparation of the Methyl Glycolates. Methyl 4-Methylbenzilate. General Procedure.—A Grignard solution was prepared by adding 94 g. (0.55 mole) of 4-methylbromobenzene in 500 ml. of dry ether to 13.2 g. (0.55 g.-atom) of magnesium. This was then added to a solution of 81 g. (0.50 mole) of methyl phenylglyoxylate and 500 ml. of dry ether at 0–5°. After stirring 1 hr. at this temperature the mixture was allowed to warm to room temperature. It was then hydrolyzed by the addition of 150 ml. of saturated ammonium chloride solution and 200 ml. of water. The ether solution was washed with three 100-ml. portions of water, dried with magnesium sulfate, and then was concentrated by heating on a steam bath under reduced pressure. The residue was induced to crystallize by the addition of petroleum ether. The crude product (78 g., m.p. 83–86°) was recrystallized

from 200 ml. of methanol to give 55 g. (43% yield) of methyl 4-methylbenzilate, m.p. 100–102°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.42; H, 6.27.

Methyl Phenyl-2-thienylglycolate.—The Grignard of 2-bromothiophene in the above procedure gave the ester in 33% yield, m.p. 57–58° (lit.,[7] m.p. 62–63°).

Methyl α-Cyclohexyl-α-phenylglycolate.—The Grignard reagent from cyclohexyl bromide treated according to the general procedure gave the ester in 31% yield, b.p. 170–175° (9 mm.).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 73.24; H, 8.45. Found: C, 72.90; H, 8.73.

Methyl 4-Chlorobenzilate.—The Grignard reagent derived from 4-chlorobromobenzene treated according to the general procedure gave the ester in 49% yield, m.p. 94–95°.

Anal. Calcd. for $C_{15}H_{13}ClO_3$: C, 65.10; H, 4.73. Found: C, 64.91; H, 4.73.

Preparation of the Substituted 3-Pyrrolidinol Glycolates (Table I). General Procedure.—A mixture of 0.07 mole of the 3-pyrrolidinol, 0.07 mole of the methyl glycolate, a trace of sodium methoxide, and 200 ml. of *n*-heptane was heated under reflux for 3 hr. using a Dean-Stark water separator to remove methanol as it was formed. The mixture was cooled and then was extracted with a 120-ml. and a 60-ml. portion of 1 *N* hydrochloric acid. The acid solution was washed with two 100-ml. volumes of benzene, and then it was made basic with potassium carbonate. The basic solution was extracted with two 50-ml. portions of benzene, the benzene solution was washed twice with 25-ml. volumes of water. The benzene solution was then dried with anhydrous potassium carbonate and concentrated by heating on a steam bath under reduced pressure. The residue dissolved in 50 ml. of ethyl acetate was treated with 50 ml. of hydrogen chloride-saturated ethanol. The crystalline hydrochloride that formed was collected and was recrystallized from ethanol–ethyl acetate or ethanol–ethyl acetate–isopropyl ether mixture.

Quaternary Salts.—When the quaternary salts were desired, the crude ester after solvent removal was dissolved in 50 ml. of methyl ethyl ketone and was treated with excess methyl bromide. The crystalline solid that formed was collected and recrystallized from the same solvent mixtures as the hydrochlorides.

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Potential Anticancer Agents. LXXV.[1] Analogs of Chlorambucil. X.[1] Sulfur-Containing Analogs

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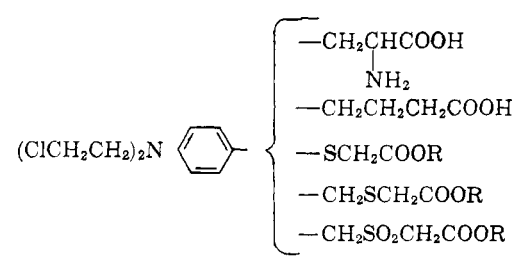
Conventional procedures for preparing aromatic nitrogen mustards have been successfully applied to the synthesis of *p*-mustards of (phenylthio)acetic acid and its methyl ester. Preparation of the benzyl homolog was prevented by the instability of derivatives of (benzylthio)acetic acid as intermediates. The *p*-mustard of methyl (benzylsulfonyl)acetate could be prepared under the same conditions, but resisted hydrolysis to the free acid.

Nitrogen mustards of cinnamic acid[3] and of phenoxyalkanoic acids[4] are active anticancer agents when tested on transplanted mouse tumors. Their animal tumor spectra resemble the spectrum of *p*-phenylalanine mustard (I), among clinically useful mustards, more than that of the structurally related chlorambucil (II). These facts suggested the synthesis of other alkylating agents related to chlorambucil, in which further significant changes in the character and oxidation level of the acidic side chain are made. Examples of such compounds which might show interesting biological activity and which might provide more insight into the relationship between structure and anticancer activity are the sulfur-containing acids III, V, and VII. This report describes a study of their preparation; success was encountered only in preparing III and the esters, IV and VIII.



I
II
III. R = H; IV. R = CH_3
V. R = H; VI. R = CH_3
VII. R = H; VIII. R = CH_3

The (phenylthio)acetic acid mustard III and the

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