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]

Acknowledgment. The authors wish to thank Dr. J. R. Corrigan of these laboratories for his technical assistance and many useful suggestions. They are also indebted to Mr. Richard E. Miner of Metal Hydrides Incorporated, Beverly, Mass., for a sample of sodium aluminum hydride.

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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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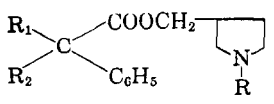
A series of 1-substituted 3-pyrrolidinylmethyl esters of disubstituted acetic and glycolic acids has been synthesized for antispasmodic screening. Different methods for the preparation of the highly active 1-methyl-3-pyrrolidinylmethyl esters of benzilic and phenylcyclohexylglycolic acids were studied. 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-



I

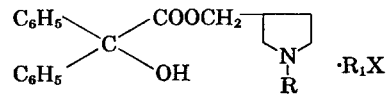
pyrrolidinylmethyl alcohols and chlorides[4] as intermediates. The acid moieties used were benzilic (R_1 = OH, R_2 = C_6H_5), diphenylacetic (R_1 = H, R_2 = C_6H_5), and phenylcyclohexylglycolic (R_1 = OH, R_2 = cyclohexyl) acids.

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.

(1) F. F. Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).
(2) R. R. Burtner, *Medicinal Chemistry*, Vol. 1, C. M. Suter, ed., Wiley, New York, 1951, p. 151.
(3) A. Burger, *Medicinal Chemistry*, Vol. 1, Interscience, New York and London, 1951, p. 417.
(4) Yao-Hua Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).
(5) A. Verley, *Bull. soc. chim.*, **41**, 788 (1927).
(6) R. F. Feldkamp, *J. Am. Chem. Soc.*, **74**, 3834 (1952).

TABLE I

1-Substituted 3-Pyrrolidinylmethyl Benzilates



R	R_1X	M.P.	Yield,[i] %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
H	—	127–131[a]	15	$C_{19}H_{21}NO_3$					4.50	4.28		
H	HCl	144.5–146.5[b]	80	$C_{19}H_{21}NO_3.HCl$	65.60	65.74	6.38	6.22			10.19[k]	10.08
CH_3	—	132–134[c]	60	$C_{20}H_{23}NO_3$								
CH_3	HCl	145–148[a]	89	$C_{20}H_{23}NO_3.HCl$	66.40	66.70	6.68	6.94			9.80[k]	9.89
CH_3	CH_3Br	177–178[d]	84	$C_{21}H_{26}BrNO_3$	60.00	60.10	6.24	6.13			19.01[l]	18.89
C_2H_5	—	73–74[c]	44	$C_{21}H_{25}NO_3$	74.31	74.39	7.42	7.26	4.13	4.20		
C_2H_5	CH_3Br	170–171[e]	88	$C_{22}H_{28}BrNO_3$	60.83	60.76	6.50	6.39			18.40[l]	18.16
n-C_3H_7	—	70–72[c]	57	$C_{22}H_{27}NO_3$	74.75	74.81	7.70	7.85	3.96	3.87		
i-C_3H_7	—	96–97[c]	45	$C_{22}H_{27}NO_3$	74.75	74.91	7.70	7.50	3.96	3.80		
i-C_3H_7	CH_3Br	167–169[a]	94	$C_{23}H_{30}BrNO_3$	61.60	61.53	6.74	6.68			17.82[l]	17.71
n-C_4H_9	—	67–68[c]	62	$C_{23}H_{29}NO_3$	75.17	75.26	7.95	7.70	3.81	4.15		
t-C_4H_9	—	71–73[c]	60	$C_{23}H_{29}NO_3$								
t-C_4H_9	HCl	193–195[f]	88	$C_{23}H_{29}NO_3.HCl$	68.38	68.20	7.48	7.61			8.78[k]	8.64
t-C_4H_9	CH_3Br	137–139[g]	45	$C_{24}H_{32}BrNO_3$	62.33	62.11	6.98	6.79			17.28[l]	17.25
$CH_2CH{=}CH_2$	—	86–88[c]	57	$C_{22}H_{25}NO_3$	75.18	75.32	7.17	7.31	3.99	3.72		
$CH_2CH{=}CH_2$	CH_3Br	153–154.5[h]	81	$C_{23}H_{28}BrNO_3$	61.88	61.75	6.32	6.22			17.91[l]	17.72
$CH_2C_6H_5$	—	90–91.5[i]	56	$C_{26}H_{27}NO_3$	77.77	77.79	6.78	6.95	3.49	3.42		
$CH_2C_6H_4$	CH_3Br	196–198[h]	61	$C_{27}H_{30}BrNO_3$	65.32	65.19	6.09	5.98			16.09[l]	16.32
	—	117–118[c]	62	$C_{25}H_{37}NO_3$	76.30	76.58	7.94	7.75	3.56	3.59		

[a] Recrystallized from isopropyl alcohol. [b] Recrystallized from acetone–isopropyl alcohol. [c] Recrystallized from n-heptane. [d] Recrystallized from methanol–isopropyl ether. [e] Recrystallized from ethanol–isopropyl ether. [f] Recrystallized from ethanol-ether. [g] Recrystallized from acetone-ether. [h] Recrystallized from ethanol. [i] Recrystallized from acetonitrile. [j] Based on the recrystallized products. [k] Chlorine analysis. [l] Bromine analysis.

In addition to the more general transesterification method, two other esterification procedures were specifically studied for the preparation of 1-methyl-3-pyrrolidinylmethyl benzilate.

The method of Horenstein and Pählicke[7], involving the interaction of equimolecular quantities of benzilic acid and 1-methyl-3-chloromethylpyrrolidine, was found to give no reaction when carried out in boiling isopropyl alcohol. However, the same reactants gave a 12% yield in higher boiling *n*-butyl alcohol and a 61% yield of 1-methyl-3-pyrrolidinylmethyl benzilate hydrochloride with no solvent at 153°.

The method of King and Holmes[8] involving the action of diphenylchloroacetyl chloride on 1-methyl-3-pyrrolidinemethanol followed by the hydrolysis of the resulting α-chloroester to the benzilate gave only a 12% yield.

A viscous oily 1-methyl-3-pyrrolidinylmethyl diphenylacetate was obtained when 1-methyl-3-pyrrolidinemethanol was treated with diphenylacetyl chloride. Attempts to prepare a crystalline acid addition salt were unsuccessful. The free base was converted to a crystalline methobromide.

1-Methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate was synthesized by either transesterification of 1-methyl-3-pyrrolidinemethanol with methyl or ethyl phenylcyclohexylglycolate, or selective catalytic hydrogenation of one phenyl ring of the corresponding benzilate. As expected from the two asymmetric centers present in the molecule, the distilled product was a mixture of two racemic bases. Conversion to hydrochloride salts provided an easy separation of the least soluble racemate salt (α-DL-isomer) in substantially pure form by fractional crystallization. The other isomer (β-DL-hydrochloride) could not be separated completely from the first racemate by conventional crystallization procedures. A precise and tedious adsorption chromatographic technique was resorted to in order to produce the first pure sample of the β-DL-isomer. Later an effective fractional precipitation method was devised by which pure β-DL-hydrochloride could be isolated from the racemic mixture by using the pure seed crystals available from the chromatographic separation.

The advantage of the selective hydrogenation method was the ready availability of the benzilate ester. The successful selective reduction of one ring in this work contrasts with the reported[9] unsuccessful attempts to selectively hydrogenate a single ring in the benzilate esters of 1-alkyl-4-piperidinol.

These 1-substituted 3-pyrrolidinylmethyl esters of disubstituted acetic and glycolic acids were submitted for pharmacological screening. 1-Methyl 3-pyrrolidinylmethyl benzilate and phenylcyclohexylglycolate were found to be potent antispasmodic agents. Detailed pharmacological reports on these compounds will be published elsewhere.

EXPERIMENTAL[10]

1-Substituted 3-pyrrolidinemethanols. The preparation of the 1-substituted 3-pyrrolidinemethanols, used in these syntheses, has been reported.[4]

3-Pyrrolidinemethanol. Anhydrous ammonia (17 g., 1 mole) was introduced at 10° to a solution of dimethyl itaconate (158 g., 1 mole) in 158 ml. of methanol. After standing overnight at room temperature, the reaction mixture was concentrated by evaporation in an air stream to remove the solvent. The residue was distilled under reduced pressure to collect 72 g. (50%) of methyl 5-oxo-3-pyrrolidinecarboxylate with b.p. 132–142° at 0.4–0.45 mm. The distillate solidified on standing, m.p. 62–64°. This compound was used directly for reduction without further purification.

A solution of methyl 5-oxo-3-pyrrolidinecarboxylate (30 g., 0.21 mole) in 75 ml. of tetrahydrofuran was added dropwise to a slurry of lithium aluminum hydride (16 g., 0.42 mole) in 150 ml. of tetrahydrofuran at such a rate that gentle refluxing was maintained. The addition took approximately 1 hr. After refluxing with stirring for 4.5 hr., the reaction mixture was carefully decomposed with 22.8 ml. of water, and filtered by suction. The filter cake was extracted with 150 ml. of a mixture of 1:1 tetrahydrofuran and isopropyl alcohol. The filtrate and extract were combined and the solvents removed by distillation. The oily residue was fractionated under reduced pressure to yield 10.1 g. (48%) of 3-pyrrolidinemethanol as a colorless oil, b.p. 74–76° at 0.5 mm., n_D^{25} 1.4898.

Anal. Calcd. for $C_5H_{11}NO$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.36; H, 10.97; N, 13.94.

1-Substituted 3-pyrrolidinylmethyl benzilates. A mixture of 1 mole of methyl benzilate, 1 mole of 1-substituted 3-pyrrolidinemethanol, 1 g. of metallic sodium, and 1 l. of *n*-heptane was placed in a suitable distilling flask. The flask was connected through a Dean and Stark apparatus to a condenser, and the suspension refluxed for about 4 hr. During this period methanol was removed from the reaction mixture as an azeotrope with *n*-heptane and separated in the lower part of the trap. The hot clear heptane reaction solution was decanted from insoluble material and cooled to room temperature. Usually the crude 1-substituted 3-pyrrolidinylmethyl benzilates crystallized readily and were collected by filtration. The esters were purified by recrystallization from hot *n*-heptane.

Hydrochlorides. A solution of 1-substituted 3-pyrrolidinylmethyl benzilate in an equivalent amount of 0.1*N* methanolic hydrochloric acid was diluted to cloudiness with anhydrous ether and placed at 0° overnight. The crystalline hydrochloride salts were collected by filtration and recrystallized from suitable solvents.

Methobromides. The methobromides of 1-substituted 3-pyrrolidinylmethyl benzilates were prepared by saturating a solution of the free base in acetone with methyl bromide. The precipitated crystalline quaternary salts were crystallized from suitable solvents.

Ten 1-substituted 3-pyrrolidinylmethyl benzilates, three hydrochlorides, and six methobromides with their corresponding physical constants are tabulated in Table I.

Preparation of 1-methyl-3-pyrrolidinylmethyl benzilate. I. Horenstein and Pählicke method. a. With n-butyl alcohol as solvent. A mixture of benzilic acid (11.4 g., 0.05 mole), 3-chloromethyl-1-methylpyrrolidine (6.7 g., 0.05 mole) and

(7) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).
(8) F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).
(9) S. B. Coan, B. Jaffe, and D. Papa, *J. Am. Chem. Soc.*, 78, 3701 (1956).

(10) Melting points and boiling points are uncorrected. Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

50 ml. of *n*-butyl alcohol was refluxed for 18 hr. The reaction mixture was concentrated to a gummy residue by evaporation of solvent in an air stream. A liberal amount of water and 1 ml. of 10% hydrochloric acid were added. After thorough stirring, the mixture was extracted with ether. The aqueous layer was separated and made basic with 10% sodium carbonate solution. The liberated base was extracted with chloroform and the extract dried with anhydrous magnesium sulfate. After filtration, the chloroform was removed by evaporation leaving a residual slurry that disintegrated into a white crystalline powder upon treatment with acetonitrile. The crude product was collected on a filter and recrystallized from 50 ml. of hot acetonitrile to yield 1.95 g. (12%) of 1-methyl-3-pyrrolidinylmethyl benzilate, m.p. 132–134°.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.80; H, 7.12; N, 4.31. Found: C, 73.54; H, 6.97; N, 4.52.

b. Without solvent. Benzilic acid (11.4 g., 0.05 mole) was mixed with 3-chloromethyl-1-methylpyrrolidine (6.7 g., 0.05 mole) and heated with stirring at an internal temperature of 153 ± 5° for 50 min. The reddish-brown gummy residue was dissolved in 40 ml. of isopropyl alcohol, decolorized with activated carbon, and diluted with 40 ml. of isopropyl ether. The crude product (13.4 g.) was recrystallized from 40 ml. of isopropyl alcohol to give 11.0 g. (61%) of 1-methyl-3-pyrrolidinylmethyl benzilate hydrochloride, m.p. 143–145°. A mixed melting point determination with an authentic sample showed no depression.

II. King and Holmes method. Diphenylchloroacetyl chloride. A stirred suspension of 20.9 g. (0.1 mole) of phosphorus pentachloride in 12.5 ml. of carbon tetrachloride was slowly treated over 30 min. with 11.4 g. (0.05 mole) of benzilic acid. Caution was exercised during the addition because of the vigorous evolution of hydrogen chloride. When addition was complete, the clear solution was refluxed for 1 hr. As much solvent and phosphorus oxychloride as possible were removed by distillation at 110–115° under partially reduced pressure. The residual oil solidified when it was stirred into an ice water mixture. The solid was extracted with benzene and the combined extract washed thoroughly with water and filtered. After removal of solvent, the solid residue was recrystallized from petroleum ether (b.p. 30–40°), collected and air dried at room temperature to give 9.3 g. (75%) of diphenylchloroacetyl chloride, m.p. 55–60°, reported[8] m.p. 50–51°.

1-Methyl-3-pyrrolidinylmethyl benzilate. A solution of 2.9 g. (0.025 mole) of 1-methyl-3-pyrrolidinemethanol[11] in 25 ml. of benzene[12] was slowly treated with 6.17 g. (0.023 mole) of diphenylchloroacetyl chloride with stirring. After being refluxed for 3 hr. the reaction mixture was heated for 30 min. with 3 ml. of water, cooled to room temperature, and treated with 50 ml. of water. Chloroform was added to dissolve any insoluble impurities. The aqueous layer was separated and made basic with 56% potassium hydroxide. The mixture was extracted with several portions of hot *n*-heptane. The combined *n*-heptane extract was filtered hot and the filtrate cooled in an icebox to yield 1.0 g. (12%) of crystalline 1-methyl-3-pyrrolidinylmethyl benzilate, m.p. 129–131°. A mixed melting point determination with an authentic sample showed no depression.

1-Methyl-3-pyrrolidinylmethyl diphenylacetate methobromide. A solution of 1-methyl-3-pyrrolidinemethanol (5.8 g., 0.05 mole) in 50 ml. of benzene was slowly added to a stirred solution of 11.5 g. (0.05 mole) of diphenylacetyl chloride in 50 ml. of benzene over a period of 1 hr. After stirring and refluxing for an additional hour, the reaction mixture separated into two layers. The upper benzene layer was decanted off and the lower viscous oily layer was dissolved in 15 ml. of water and the solution cooled in an ice bath. The cold solution was saturated with solid sodium carbonate, and extracted several times with isopropyl ether. The combined extract was dried over anhydrous magnesium sulfate, filtered, and concentrated to a viscous oily residue; yield, 16.0 g., n_D^{25} 1.5496. The crude oil was dissolved in 35 ml. of acetonitrile and the solution saturated with methyl bromide gas. An equal volume of ether was added with stirring and the reaction flask placed in the icebox overnight. The crystalline 1-methyl-3-pyrrolidinylmethyl diphenylacetate methobromide, that separated, was collected on a filter, washed with 1:1 acetonitrile-ether and dried; yield, 18.7 g., (92%), m.p. 146–148°. Recrystallization from isopropyl alcohol-ether did not change the melting point.

Anal. Calcd. for $C_{21}H_{26}BrNO_2$: C, 62.38; H, 6.48; Br, 19.77. Found: C, 62.93; H, 6.47; Br, 19.75.

Methyl and ethyl phenylcyclohexylglycolates. These intermediates were prepared by the procedure of Smith, *et al.*[13] The ethyl ester distilled at 174–178° at 13 mm., n_D^{25} 1.5121. (Smith, *et al.*,[13] report 172–173° at 10 mm., Coan, *et al.*,[9] 167–169° at 6 mm., n_D^{27} 1.5125.) The methyl ester boiled at 97–100° at 1 mm., n_D^{25} 1.5261. (Smith, *et al.*,[14] report a melting point of around 40° for material prepared by a different method.) The intermediate methyl phenylglyoxylate was most conveniently prepared by the oxidation of methyl mandelate with *N*-bromosuccinimide by the method of Kruse, Geurkink, and Grist.[15]

1-Methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate. I. Transesterification method. A mixture of 15.8 g. (0.06 mole) of ethyl phenylcyclohexylglycolate, 6.9 g. (0.06 mole) of 1-methyl-3-pyrrolidinemethanol, 0.1 g. of metallic sodium, and 150 ml. of *n*-heptane was gently refluxed under a Dean and Stark trap. As the trap filled with distillate of the ethanol-heptane azeotrope, it was drained and fresh *n*-heptane solvent added to the reaction solution. The reflux and slow distillation were continued for about 7 hr. The reaction mixture was filtered to remove a gelatinous solid and the filtrate concentrated by distillation. The residual liquid was fractionally distilled to give 8 g. (40%) of 1-methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate as a viscous yellow oil, b.p. 148–151° at 0.25 mm., n_D^{25} 1.5249.

Anal. Calcd. for $C_{20}H_{29}NO_3$: C, 72.87; H, 8.82; N, 4.22. Found: C, 72.49; H, 8.76; N, 4.04.

The same reaction was run using the methyl ester of phenylcyclohexylglycolic acid. The methanol resulting from transesterification separated readily from heptane in the Dean and Stark trap. The methyl ester is preferred over the ethyl ester because of the insolubility of methanol in heptane. From a 0.1-mole run, 4.8 ml. of methanol phase separated during a 3-hr. reflux period. Fractional distillation of the filtered reaction mixture gave a 74% yield of the product in two fractions: Fraction A, b.p. 113–143° at 0.16 mm., n_D^{25} 1.5226, weight 14.0 g. Fraction B, b.p. 146–155° at 0.16 mm., n_D^{25} 1.5246, weight 10.5 g. This product was used in the adsorption chromatographic procedure for the separation of diastereoisomers.

II. Selective hydrogenation method. A solution of 1-methyl-3-pyrrolidinylmethyl benzilate hydrochloride (18.1 g., 0.05 mole) in 150 ml. of glacial acetic acid was added to 10 g. of 10% platinum on alumina catalyst in a pressure bottle. The mixture was hydrogenated under 2–3 atm. pressure until 3.3 equivalents[16] of hydrogen had been absorbed. This amount of hydrogen is slightly over that required to saturate one of the phenyl rings. The reduction time was 6 hr. The hydrogenation mixture was filtered to remove the

(11) The hydrochloride of the amino alcohol has also been used successfully.

(12) The reaction has also been carried out in chloroform, carbon tetrachloride and without solvents.

(13) H. A. Smith, D. M. Alderman, Jr., C. D. Shacklett, and C. M. Welch, *J. Am. Chem. Soc.*, **71**, 3772 (1949).

(14) H. A. Smith, C. A. Buehler, T. A. Magee, K. V. Nayak, and D. M. Glenn, *J. Org. Chem.*, **24**, 1301 (1959).

(15) P. F. Kruse, Jr., N. Geurkink, and K. L. Grist, *J. Am. Chem. Soc.*, **76**, 5796 (1954).

(16) D. W. Adamson and S. Wilkinson, U. S. Patent **2,682,543** (1954).

catalyst and the clear filtrate diluted with 150 ml. of water. The aqueous solution was made basic with 300 ml. of 56% potassium hydroxide and the liberated amino ester extracted with three 100-ml. portions of *n*-heptane. The heptane solution was allowed to stand to permit the unreduced benzilate ester to crystallize, weight 1.5 g., m.p. 122–131°. The heptane filtrate was fractionally distilled and material boiling at 151–161° at 0.20 mm. was taken as product; yield, 11.9 g. (65%). The infrared spectrum of a fraction with b.p. 156–161° at 0.2 mm., n_D^{25} 1.5201, was consistent with the assigned structure and was very similar to that of 1-methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate prepared by transesterification.

Anal. Calcd. for $C_{20}H_{29}NO_3$: N, 4.22. Found: N, 4.43.

α-DL-1-Methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate hydrochloride (Racemate A). A solution of 4.2 g. (0.013 mole) of 1-methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate (mixture of two racemic bases) in 15 ml. of anhydrous ether was treated with 2.2 ml. (0.013 mole) of 5.92*N* ethanolic hydrogen chloride. An additional 85 ml. of dry ether was added to precipitate completely the mixed hydrochlorides as a yellow oil. After decanting the ether solution, the yellow oil was triturated with 25 ml. of ethyl acetate to produce a white solid which was then dissolved by adding ethanol dropwise with heating. The warm clear solution was further diluted with 50 ml. of ethyl acetate, stirred to initiate crystallization, and stored at 0°. A white crystalline hydrochloride was collected on a filter, washed with ethyl acetate, and dried at 70°, weight 1.5 g., m.p. 170–173°. Recrystallization from ethyl acetate–ethanol gave 1.0 g. of the α-form, Racemate A, m.p. 176–177°.

Anal. Calcd. for $C_{20}H_{29}NO_3$.HCl: C, 65.29; H, 8.22; N, 3.81. Found: C, 65.54; H, 8.24; N, 3.99.

β-DL-1-Methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate hydrochloride (Racemate B). I. Adsorption chromatographic method. A column of alumina[17] (782 g., 38 × 800 mm.) was prepared by sedimentation of the dry powder in a chromatographic tube partially filled with anhydrous benzene. Utilizing the discontinuous gradient elution technique, a 10.0-g. sample of 1-methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate, comprised of equal parts of two fractions previously obtained by the fractional distillation of the transesterification product, was dissolved in 50 ml. of dry benzene, introduced to the column head in the usual manner, developed with benzene, and eluted with benzene-ether, ether, ether-acetone, acetone, acetone-ethanol, and ethanol. The effluent was collected in test tubes (18 × 140 mm.) mounted on an automatic fraction collector turntable at a rate of 0.6 to 1.0 ml./min. The following number of fractions were collected: 359 fractions varying in volume from 20 to 25 ml. and 6 fractions in increments of 100 to 350 ml. The fractions were tested for the presence of amines by evaporating off the solvent from 5 drops, acidifying with 0.1*N* hydrochloric acid and adding 2 drops of Valser's reagent.[18] According to this test, fractions 1 to 134 were negative, fractions 135 to 235 were strongly positive but exhibited a detectable minimum and two maxima, fractions 236 to 249 were faintly positive, fractions 250 to 363 were positive, and fractions 364 to 365 were negative. The infrared spectra of fractions 250 to 363 showed insignificant absorption in the 13.5 to 14.5 μ region compared with fractions 135 to 235. Fraction 138 was concentrated under reduced pressure, the residual oil dissolved in anhydrous ether, and treated with ethanolic hydrogen chloride. After washing with anhydrous ether, the resulting white precipitate was found to have low solubility in ethyl acetate at room temperature. The hydrochloride crystallized in the form of small colorless platelets from ethyl acetate–ether, m.p. 178–180° dec., after two crystallizations. A mixed melting point determination with Racemate A showed no depression.

The hydrochloride salt of the material present in fraction 167 was prepared in the same manner. Virtually all of the salt dissolved in ethyl acetate at room temperature. The first crop of colorless platelets which crystallized from ethyl acetate–ether melted at 163–167° dec., a second crop from ethyl acetate–heptane, small white needles, melted at 128–130°, and a third crop from the same solvents melted at 129–130°. Recrystallization of the third crop yielded small white needles of the β-compound (Racemate B), melting at 129–130° with no decomposition. Circular paper chromatograms (Eaton-Dikeman No. 7) of this material employing as the mobile phase the chloroform-rich layer prepared by shaking 750 ml. of chloroform, 200 ml. of 1% hydrochloric acid, and 7.5 ml. of *n*-propyl alcohol, revealed only one fluorescent zone under ultraviolet light with an R_f value approaching 1. In contrast, the R_f value of the higher melting Racemate A is virtually zero.

II. Fractional precipitation method. 1-Methyl-3-pyrrolidinylmethyl phenylcyclohexylglycolate (5.0 g.) was dissolved in 50 ml. of anhydrous ether. Cold ethanolic hydrogen chloride (4.87*N*, 3.1 ml.) was added dropwise to the chilled and continuously stirred ethereal solution. An initial white precipitate became gummy when addition was complete. The solvents were removed under reduced pressure, and the resultant orange syrupy residue triturated with three 25-ml. portions of anhydrous ether. The ether decantates were discarded. Ethyl acetate (10 ml.) was added to the residue and the suspension warmed to reflux temperature. The resultant clear orange solution began to deposit crystalline material as it cooled to room temperature. After further cooling in an ice bath for 1 hr., the white crystalline material (1.73 g.) was collected by filtration, washed dropwise with ethyl acetate (10 ml.), and air dried, m.p. 163–168° dec.

An attempt to obtain a second crop from the combined mother liquor and washings by addition of *n*-heptane, warming the cloudy solution until clear, and slow cooling with scratching was unsuccessful. The cloudy solution was then stirred for 15 min. during which time an orange oil was deposited. The slightly opaque decantate was filtered through Celite and the clear light orange filtrate was again made cloudy by the addition of *n*-heptane. A light orange viscous oil settled out leaving a colorless liquid phase which was again decanted through a filter. This process was repeated three more times to precipitate additional oily fractions from the liquid phase.

Fraction IV, a clear colorless viscous oil, was dissolved in hot ethyl acetate-*n*-heptane, allowed to cool slowly to room temperature and seeded with a few crystals of Racemate B obtained from the third crop of chromatographic fraction 167. The small white needles which formed during a standing period of 72 hr. at room temperature melted at 129–130°. Recrystallization of this crop from ethyl acetate-*n*-heptane and drying of the crystalline material for 12 hr. over phosphorus pentoxide at 0.5 mm. did not change the melting point. A mixed melting point determination with the seeding material showed no depression. The infrared spectrum (potassium bromide) was found to be consistent with the assigned structure, showing absorption maxima at 2.90 μ, 3.40 μ, 3.75 μ, 5.75 μ, 13.45 μ, and 14.10 μ.

Anal. Calcd. for $C_{20}H_{29}NO_3$.HCl: C, 65.29; H, 8.22; Cl, 9.64. Found: C, 65.98; H, 8.00; Cl, 9.48.

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(17) Brockmann Activity Grade 1, Analytical Grade, 100–200 mesh, AG-7, pH 7.5–8.0; Bio-Rad Laboratories, 800 Delaware, Berkeley, Calif.

(18) *Pharmacopoeia of the United States of America*, 15th revision, Mack Printing Co., Easton, Pa., 1955, p. 1096.