[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY]

# 4-Morpholinealkyl Esters and Amides Possessing Antispasmodic Activity*

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During recent years a number of synthetic antispasmodics have been introduced which are claimed to possess certain clinical advantages over the naturally occurring papaverine and atropine. Several investigators[1] have furnished excellent reviews and bibliographies relating to these compounds.

In this Laboratory a series (table) of morpholinealkyl esters and amides has been prepared. Several of these compounds have been found to exhibit pronounced antispasmodic activity, and, in general, they are less toxic than their diethylamino analogs. In contrast, the three N-alkylmorpholines investigated by Blicke and Zienty[1d] proved to be stimulants.

Since the inception of our morpholine series, several basic esters possessing a morpholine ring have been claimed as antispasmodics. Wolfes and Hromatka[2] have disclosed the preparation of β-4-morpholineëthyl 9-hydroxyfluorene-9-carboxylate and its hydrochloride. A recent British Patent[3] has mentioned β-4-morpholineëthyl α-phenylcyclohexaneacetate. Bockmühl and Ehrhart[4] have described the preparation of ethyl diphenyl-α-(β-4-morpholineëthyl)-acetate and its hydrochloride.

## Experimental

**Morpholine Alcohols and Amines.**—β-4-Morpholineethanol, 4-(β-aminoethyl)-morpholine and morpholine were used directly as supplied by Carbide and Carbon Chemicals Corporation. γ-4-Morpholinepropanol,[5] b. p. 147–149° (21 mm.), $n^{20}D$ 1.4762, $n^{25}D$ 1.4743, was obtained in 75.2% yield from trimethylene chlorohydrin and morpholine by the method (b) of Adams[6] for the preparation of dialkylaminoalkanols. Similarly, δ-4-morpholinebutanol,[7] b. p. 127–130° (2 mm.), $n^{20}D$ 1.4769, was prepared in 37.5% yield from tetramethylene chlorohydrin and morpholine.

**β-Methyl-β-4-morpholinepropanol.**—The procedure of Gardner and Haenni[5] for the preparation of γ-4-morpholinepropanol was essentially adopted. A mixture of 89.2 g. (1 mole) of 2-amino-2-methyl-1-propanol (Eastman Kodak Co.), 150 g. (1.05 moles) of β,β′-dichloroethyl ether and 150 g. (1.085 moles) of powdered anhydrous potassium carbonate, contained in a 1-liter flask provided with a reflux condenser and stirrer, was heated in an oil-bath to 170° before a vigorous reaction ensued. After removal of the bath to permit the evolution of carbon dioxide to moderate, the brown mixture was refluxed gently at 170° for 5.3 hours and then allowed to remain at room temperature for twelve hours. The semi-solid mass was warmed in a water-bath, pulverized and extracted with four 670-ml. portions of hot benzene. Fractionation from a modified Claisen flask gave 62.4 g. (39.1% yield) of colorless oil, b. p. 110–116° (2 mm.), which soon crystallized in the form of long glistening needles, m. p. 59–60°. Crystallization from petroleum ether did not alter the melting point.

*Anal.* Calcd. for $C_8H_{17}O_2N$: N, 8.80. Found: N, 8.95.

**α-Methyl-β-4-morpholineëthanol.**—This alcohol, b. p. 82–84° (1.5 mm.), $n^{20}D$ 1.4638, was obtained by the above method from isopropanolamine, β,β′-dichloroethyl ether and anhydrous potassium carbonate; yield, 42%.

*Anal.* Calcd. for $C_7H_{15}O_2N$: N, 9.65. Found: N, 9.66.

Later a sample with the same refractive index was furnished by Carbide and Carbon Chemicals Corporation.

**β,β-Dimethyl-γ-4-morpholinepropanol.**—This compound, b. p. 96–97° (2 mm.), $n^{20}D$ 1.4648, was prepared in 82.6% yield by the crossed Cannizzaro reaction[8] applied to β-4-morpholinepivalaldehyde which was synthesized by the method of Mannich.[9]

**Acids and Acid Chlorides.**—α-Chlorodiphenylacetyl chloride[10] and diphenylacetic acid[11] were readily obtained from benzilic acid.[12] Cinnamoyl chloride, triphenylacetic acid, dibenzylacetic acid, cyclohexanecarboxylic acid, phenylacetyl chloride, β,β-diphenylpropionic acid, N,N-diphenylcarbamyl chloride and benzoyl chloride were purchased from Eastman Kodak Company. *t*-Butylacetyl chloride and trimethylacetyl chloride were supplied by Dr. H. M. Crooks, Jr. 2-Camphanecarboxylic acid was prepared in accordance with the procedure of Rupe and Hirschmann.[13] α-Phenylcyclohexaneacetic acid[14,15] was obtained by alkaline hydrolysis of the intermediate nitrile.

* Presented before the Medicinal Division of the American Chemical Society, Atlantic City, September 8–12, 1941.

(1) (a) Slotta and Haberland, *Angew. Chemie*, **46**, 766 (1933); (b) Wagner-Jauregg, Arnold and Born, *Ber.*, **72**, 1551 (1939); (c) Blicke and Monroe, THIS JOURNAL, **61**, 91 (1939); (d) Blicke and Zienty, *ibid.*, **61**, 93, 771 and 774 (1939); (e) Blicke, Eighth National Organic Chemistry Symposium of the American Chemical Society, December 28–30, 1939, St. Louis, Missouri, p. 23; (f) Blicke, *J. Lab. Clinical Med.*, **26**, 133 (1940); (g) Külz and Rosenmund, *Ber.*, **72**, 19, 2161 (1939).

(2) German Patent 657,526 [*C. A.*, **32**, 6403 (1938)]; U. S. Patent 2,221,828 (1940).

(3) British Patent 532,943 (1941).

(4) U. S. Patent 2,230,774 (1941).

(5) Gardner and Haenni, THIS JOURNAL, **53**, 2763 (1931).

(6) Adams, *et al.*, *ibid.*, **59**, 2249 (1937).

(7) Anderson and Pollard, *ibid.*, **61**, 3440 (1939).

(8) Davidson and Weiss, "Organic Syntheses," Vol. 18, John Wiley and Sons, New York, N. Y., 1938, p. 79.

(9) (a) Mannich, British Patent 348,382 (1931); (b) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932); (c) experimental details are in press: presented by L. C. Cheney before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, Sept. 8–12, 1941.

(10) Bickel, *Ber.*, **22**, 1538 (1889).

(11) Marvel, Hager and Caudle, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1931, p. 219.

(12) Ballard and Dehn, *ibid.*, p. 82.

(13) Rupe and Hirschmann, *Helv. Chim. Acta*, **11**, 1180 (1928).

(14) Venus-Danilova and Bol'shukin, *J. Gen. Chem.* (U. S. S. R.), **7**, 2823 (1937) [*C. A.*, **32**, 2925 (1938)].

(15) Miescher and Hoffmann, *Helv. Chim. Acta*, **24**, 458 (1941).

**α-Phenylcyclohexaneacetonitrile.**—To 400 ml. of liquid ammonia, cooled in a carbon dioxide–acetone bath, was added 0.35 g. of finely pulverized ferric nitrate ($9H_2O$) (Baker C. P.). (The reaction was conducted under an atmosphere of nitrogen.) After stirring the resulting brown solution for ten to fifteen minutes, 1.7 g. of sodium was added. Dry air was then passed into the reaction flask for fifteen minutes (air dried over granular calcium chloride). This step is essential for the preparation of the catalyst. Clean dry sodium was then introduced through the neck of the reflux condenser until a total of 34.8 g. (1.51 moles) had been added. Hydrogen was evolved and the deep blue solution turned brown in color. After about one-third of the ammonia had evaporated, 400 ml. of sodium-dried xylene was introduced slowly; the bath was removed and the ammonia evaporated. The addition of 177.7 g. (1.51 moles) of phenylacetonitrile caused such an exothermic reaction that the mixture was cooled in an ice-bath. The stirrer was turned off and the mixture was allowed to stand overnight in an atmosphere of nitrogen.

To the efficiently stirred solution was added 246 g. (1.51 moles) of bromocyclohexane at such a rate that the temperature remained at 30–40°. After addition was complete, the red-brown mixture was heated, with stirring, in a boiling water-bath for three and one-half hours. Following the cautious addition of cold water, the xylene phase was washed twice with water and dried over anhydrous sodium sulfate. The solvent was removed under diminished pressure (water aspirator) whereupon the nitrile distilled as a yellow oil, b. p. 139–151° (4 mm.). [The major portion distilled at 149–151° (4 mm.).] The yield was 210 g. (70%). Upon standing in the cold, the oil crystallized as a colorless solid, m. p. 54–55.5° (cor.). Two recrystallizations from methanol produced small glistening needles, m. p. 56–57° (cor.).

**α-Phenylcyclohexaneacetic Acid.**—To a solution of 195 g. (0.98 mole) of α-phenylcyclohexaneacetonitrile, m. p. 54–55.5° (cor.), in 600 ml. of methanol contained in a high-pressure bomb, was added 140 g. (2.15 moles) of potassium hydroxide. The bomb was rocked and heated for seven hours at 185–195°. The contents of the cooled bomb were siphoned into a 2-liter round-bottomed flask and diluted with 800 ml. of warm water which had been used as a rinse. In order to remove most of the methanol, the brown solution was distilled until 675 ml. of distillate had been collected. The cooled solution was extracted with 500 ml. of ether in two portions, treated with "Darco," heated on the hot-plate to expel all ether, and filtered through a mat of "Super-Cel." Acidification of the warm, clear filtrate with concentrated hydrochloric acid, accompanied by efficient shaking and cooling, precipitated the acid as a fine granular solid. The acid was filtered, washed thoroughly with cold water and dried overnight at 60°. The yield of the crude acid, m. p. 152–153° (cor.), was 204.4 g. (95.5%). Recrystallization from dilute methanol yielded 197.1 g. or 92% of α-phenylcyclohexaneacetic acid melting at 152.5–153.5° (cor.).

**Esters, Amides and their Hydrochlorides.**—With the exception of the products described in the following sections of the experimental part, all of the compounds were prepared as follows. Conversion of the acid to the chloride was accomplished by refluxing a mixture of 30 ml. of thionyl chloride and 0.12 mole of acid for one hour or more, whereupon excess thionyl chloride was distilled *in vacuo*. To a cold solution of the acid chloride in 100 ml. of a suitable solvent (table), 0.1 mole of alcohol or amine was added in several portions with shaking. After standing overnight, protected by a calcium chloride tube, the mixture was refluxed (water- or wax-bath) for one to five hours. Subsequent to removal of solvent by distillation at reduced pressure, the residue was dissolved in water, and the cooled acidic solution was extracted with ether, rendered basic with sodium carbonate solution and again extracted with ether. The thoroughly washed ether solution of the amine was dried over anhydrous potassium carbonate, filtered and treated with a slight excess of absolute alcoholic hydrochloric acid. The precipitated salt was recrystallized to a constant melting point from a suitable anhydrous solvent. Yields of the purified compounds prepared by this procedure varied from 33–85% with two exceptions (β-4-morpholine triphenylacetate hydrochloride alcoholate, 16% and β-4-morpholine dibenzylacetate hydrochloride, 20%). For the reaction medium sodium-dried dioxane and chloroform (dried over Drierite) proved especially advantageous.

**β-4-Morpholineëthyl Benzilate Hydrochloride.**[16]—To a cold solution of 22.8 g. (0.1 mole) of benzilic acid in 80 ml. of anhydrous isopropanol was added 15.75 g. (0.105 mole) of 4-(β-chloroethyl)-morpholine.[17] After refluxing for four and one-half hours the mixture was cooled in ice and filtered. Recrystallization from isopropanol gave 18.1 g. (49% yield) of silky needles, m. p. 181.5–182.5°.

**β-4-Morpholineëthyl α-Chlorodiphenylacetate Hydrochloride.**—To a cold solution of 26.5 g. (0.1 mole) of α-chlorodiphenylacetyl chloride[10] in 100 ml. of dry dioxane was added 13.2 g. (0.1 mole) of β-morpholineëthanol in 25 ml. of dioxane. After being heated in the water-bath for fifteen minutes the solvent began to develop a red color. The mixture was refluxed in a wax-bath for two and one-half hours, cooled and diluted with a large volume of ether. The tan crystalline material which finally separated from solution was crystallized twice (Darco) from anhydrous ethyl acetate to obtain small white needles, m. p. 151.5–152.5°; yield, 6.2 g. (15.6%). The chlorine atom is readily replaced by hydroxyl by means of dilute sodium carbonate solution.

**γ-4-Morpholinepropyl Diphenylacetate Bromobenzylate.**—A solution of 15.4 g. (0.09 mole) of benzyl bromide in 40 ml. of anhydrous ether was poured into a cold solution of 27.9 g. (0.082 mole) of γ-4-morpholinepropyl diphenylacetate, b. p. 223–227° (1.25 mm.), in 100 ml. of ether. After refluxing the mixture for thirteen hours the ether was evaporated. Two crystallizations from acetone produced white needles, m. p. 137–138°, which were recrystallized from acetone–absolute alcohol without alteration of the melting point.

**ω-4-Morpholinehexyl Diphenylacetate Hydrochloride.**—A mixture of 26.5 g. (0.109 mole) of hexamethylene bromide (Eastman Kodak Co.), 27.5 g. (0.11 mole) of pulverized potassium diphenylacetate and 100 ml. of sodium-

(16) The general method is that of Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

(17) Mason and Block, THIS JOURNAL, **62**, 1443 (1940).

TABLE I

MORPHOLINEALKYL ESTERS AND AMIDES

| Compound (R = β-4-morpholineethyl-) | Reaction medium | M. p., °C. (cor.) | Recrystallized from | Formula | N Analyses, %[a] Calcd. | Found | M. L. D.[b] mg./kg. | Activity[c] |
|---|---|---|---|---|---|---|---|---|
| Diphenylacetic acid R-amide | Benzene | 140–141 | AcOEt | $C_{20}H_{24}O_2N_2$ | 8.64 | 8.60 | | |
| β,β-Dimethyl-γ-4-morpholinepropyl diphenylacetate | Chloroform | 54.5–55.5 | Pet. ether | $C_{23}H_{29}O_3N$ | 3.82 | 3.86 | | |
| R N,N-diphenylcarbamate | Excess β-4-morpholineethanol | 63.5–64.5 | *i*-PrOH | $C_{19}H_{22}O_2N_2$ | 8.58 | 8.64 | | |
| α-Phenylcyclohexaneacetic acid R-amide | Dioxane | 152–153 | Dil. acetone | $C_{20}H_{30}O_2N_2$ | 8.48 | 8.32 | | |
| β,β-Dimethyl-γ-4-morpholinepropyl α-phenylcyclohexaneacetate | Dioxane | 77 | MeOH | $C_{23}H_{35}O_3N$ | 3.75 | 3.68 | | |
| β,β-Dimethyl-γ-4-morpholinepropyl benzoate | Chloroform | 55.5–56 | Pet. ether | $C_{16}H_{23}O_3N$ | 5.05 | 4.96 | | |
| | | | HYDROCHLORIDES[h] | | | | | |
| α-Chlorodiphenylacetic acid R-amide | Acetone | 139–140 | Acetone | $C_{20}H_{23}O_2N_2Cl\cdot HCl$ | 7.09 | 7.16 | 500 | 50 |
| Diphenylacetic acid R-amide | Benzene | 189–190 | EtOH–ether | $C_{20}H_{24}O_2N_2\cdot HCl$ | 7.76 | 7.74 | 300 | 20 |
| α-Phenylcyclohexaneacetic acid R-amide | Dioxane | 107.5–109 | Acetone | $C_{20}H_{30}O_2N_2\cdot HCl$ | 7.64 | 7.52 | 300 | 50 |
| R diphenylacetate | Dioxane | 137.5–138 | AcOEt | $C_{20}H_{23}O_3N\cdot HCl$ | 3.87 | 3.85 | 800 | 75 |
| Hydrobromide | | 119–120 | AcOEt | $C_{20}H_{23}O_3N\cdot HBr$ | 3.45 | 3.62 | 800 | 40 |
| R benzilate[d] | Isopropanol | 181.5–182.5 | *i*-PrOH | $C_{20}H_{23}O_4N\cdot HCl$ | 3.71 | 3.69 | 300 | 25 |
| R α-acetoxydiphenylacetate | Acetic anhydride | 186.5–187 | EtOH | $C_{22}H_{25}O_5N\cdot HCl$ | 3.34 | 3.48 | 300 | 25 |
| R α-chlorodiphenylacetate | Dioxane | 151.5–152.5 | AcOEt | $C_{20}H_{22}O_3N\cdot HCl$ | 3.54 | 3.42 | 200 | 75 |
| R β,β-diphenylpropionate | Dioxane | 127–128 | Acetone | $C_{21}H_{25}O_3N\cdot HCl$ | 3.73 | 3.92 | 500 | 50 |
| R dibenzylacetate | Benzene | 117–118 | AcOEt | $C_{22}H_{27}O_3N\cdot HCl$ | 3.59 | 3.49 | 600 | 60 |
| R α-phenylcyclohexaneacetate | Dioxane | 147–148 | AcOEt | $C_{20}H_{29}O_3N\cdot HCl$ | 3.84 | 3.89 | 400 | 100 |
| R triphenylacetate monoalcoholate | Benzene | 190.5–191.5 | EtOH–ether | $C_{26}H_{27}O_3N\cdot HCl\cdot C_2H_5OH$ | 2.89 | 2.91 | 400 | 25 |
| R N,N-diphenylcarbamate | Excess β-4-morpholineethanol | 160–161 | *i*-PrOH | $C_{19}H_{22}O_3N_2\cdot HCl$ | 7.72 | 7.78 | 350 | 30 |
| R phenylacetate[e] monohydrate | Acetone | 137–138 | EtOH | $C_{14}H_{18}O_3N\cdot HCl\cdot H_2O$ | 4.63 | 4.66 | 1500 | 10 |
| R cinnamate[e,f] | Acetone | 216.5–217 | EtOH–acetone | $C_{15}H_{19}O_3N\cdot HCl$ | | | 1500 | 40 |
| R cyclohexanecarboxylate monohydrate | Benzene | 144–145 | EtOH | $C_{13}H_{23}O_3N\cdot HCl.H_2O$ | 4.74 | 4.75 | 2500 | 10–20 |
| R 2-camphanecarboxylate | Dioxane | 202.5–203.5 | AcOEt | $C_{17}H_{29}O_3N\cdot HCl$ | 4.22 | 4.05 | 350 | 60 |
| R trimethylacetate picrate[g] | Acetone | 129.5–130.5 | EtOH | $C_{11}H_{21}O_3N\cdot C_6H_3O_7N_3$ | 12.61 | 12.54 | 1250 | 5 |
| R *i*-butylacetate | Acetone | 152–153 | EtOH–ether | $C_{12}H_{23}O_3N\cdot HCl$ | 5.27 | 5.27 | 1000 | 5–10 |
| γ-4-Morpholinepropyl diphenylacetate | Benzene | 119.5–120 | AcOEt | $C_{21}H_{26}O_3N\cdot HCl$ | 3.72 | 3.71 | 350 | 75 |
| γ-4-Morpholinepropyl diphenylacetate bromobenzylate | Ether | 137–138 | Acetone–EtOH | $C_{28}H_{32}O_4NBr$ | 2.74 | 2.80 | 40 | 50 |
| α-Methyl-R diphenylacetate | Acetone | 214.5–215 | EtOH | $C_{21}H_{25}O_3N\cdot HCl$ | 3.72 | 3.72 | 100 | 60 |
| δ-4-Morpholinebutyl diphenylacetate | Benzene | 118–119 | AcOEt | $C_{22}H_{27}O_3N\cdot HCl$ | 3.59 | 3.55 | 300 | 60 |
| β-Methyl-β-4-morpholinepropyl diphenylacetate | Benzene | 124.5–125.5 | AcOEt | $C_{22}H_{27}O_3N\cdot HCl$ | 3.59 | 3.64 | 700 | 60 |
| β,β-Dimethyl-γ-4-morpholinepropyl diphenylacetate | Chloroform | 149.5–150 | Acetone | $C_{23}H_{29}O_3N\cdot HCl$ | 3.47 | 3.48 | 1200 | 200 |
| Sulfate | | 140–141 | EtOH–ether | $(C_{23}H_{29}O_3N)_2\cdot H_2SO_4$ | 3.36 | 3.22 | 1000 | 200 |
| β,β-Dimethyl-γ-4-morpholinepropyl α-phenylcyclohexaneacetate | Dioxane | 127.5–128.5 | AcOEt | $C_{23}H_{35}O_3N\cdot HCl$ | 3.42 | 3.56 | 500 | 10 |
| β,β-Dimethyl-γ-4-morpholinepropyl benzoate | Chloroform | 161.5–162.5 | *i*-PrOH | $C_{16}H_{23}O_3N\cdot HCl$ | 4.46 | 4.55 | 900 | 40 |
| β,β-Dimethyl-γ-4-morpholinepropyl cinnamate | Chloroform | 149–150 | *i*-PrOH | $C_{18}H_{25}O_3N\cdot HCl$ | 4.12 | 4.06 | 1000 | 40 |
| ω-4-Morpholinehexyl diphenylacetate | Xylene | 113–114 | AcOEt | $C_{24}H_{31}O_3N\cdot HCl$ | 3.35 | 3.26 | 400 | 150 |

[a] Micro-Dumas analyses conducted by Clark S. Chamberlain, Arthur Spang, and Leonard Doub. [b] For white mice intraperitoneally; M. L. D. for papaverine = 150; for Trasentin = 350. [c] Papaverine = 100. None of the bases was tested as such. [d] Blicke, Regional Meeting, American Chemical Society, Lafayette, Indiana, June 14, 1940; compound prepared for mydriatic studies. [e] Leffler and Brill, THIS JOURNAL, **55**, 365 (1933). [f] Gardner, Clark and Semb, *ibid.*, **55**, 2999 (1933). [g] Administered as the sulfate. Both hydrochloride and sulfate are extremely hygroscopic. [h] Unless otherwise indicated.

dried xylene was efficiently stirred and refluxed in a wax-bath maintained at 170–180° for 5.3 hours, whereupon the mixture was cooled and 19.2 g. (0.22 mole) of morpholine was introduced. The stirred mixture was refluxed for 2.3 hours, cooled and decanted. After extracting the residue with 100 ml. of boiling xylene, the combined xylene solutions were filtered, cooled and extracted with dilute hydrochloric acid. The acidic solution was cooled in ice, extracted twice with ether and then rendered basic with saturated sodium carbonate solution. The liberated base

was taken up in ether and the ether solution was washed thrice with cold water to remove all morpholine. Subsequent to drying the solution over anhydrous potassium carbonate, the addition of an excess of absolute alcoholic hydrochloric acid precipitated an oil. Cooling in an ice–salt-bath and rubbing with a glass rod finally induced crystallization. Two crystallizations from anhydrous isopropanol followed by recrystallization from ethyl acetate yielded 11.9 g. (25.9%) of white micro crystals, m. p. 113–114° (cor.).

In order to establish the structure definitely, 2 g. of the compound was refluxed for 1.3 hours with a solution of 2 g. of potassium hydroxide in 15 ml. of methanol. Following dilution with 60 ml. of water, the alkaline solution was extracted with ether, boiled, acidified and cooled to obtain 1.01 g. of colorless crystals, m. p. 147–148°, which did not depress the m. p. of authentic diphenylacetic acid.

**β-4-Morpholineëthyl α-Acetoxydiphenylacetate Hydrochloride.**—A mixture of 3.8 g. (0.01 mole) of β-4-morpholineëthyl benzilate hydrochloride, 20 ml. of acetic anhydride and 4 g. of freshly fused sodium acetate was refluxed in a wax-bath at 150–160° for two hours, then cooled, covered with ether, diluted with water and made basic to litmus with ammonium hydroxide. The ether layer was washed with water and dried over "Drierite." The hydrochloride, obtained by adding an excess of absolute alcoholic hydrochloric acid to the filtered solution, was crystallized twice from absolute alcohol. The yield of white platelets was 1 g. or 23.8%.

**α-Chlorodiphenylacetic Acid β-4-Morpholineëthylamide Hydrochloride.**—To 15 g. (0.0568 mole) of α-chlorodiphenylacetyl chloride dissolved in 100 ml. of anhydrous acetone was added 16.3 g. (0.125 mole) of β-4-morpholineethylamine (Carbide and Carbon Chemicals Corporation) dissolved in 25 ml. of dry acetone, while the solution was cooled with tap water. The solution was then refluxed for one and one-half hours after adding 2.8 g. of anhydrous sodium carbonate. Upon concentrating to half the original volume, a mixture was obtained which was taken up in 150 ml. of benzene and washed with 50 ml. of water, two 50-ml. portions of 5% sodium bicarbonate solution and finally with two 50-ml. portions of water. After drying the benzene solution it was saturated with dry hydrogen chloride. The resulting brown solid was collected and fractionally extracted with boiling benzene and acetone. The residue was then thrice recrystallized from a large volume of boiling acetone to obtain 2.2 g. (6.8%), melting at 139–140°.

Investigation of this series of compounds is being extended.

## Pharmacology

Preliminary pharmacological studies have been made in these laboratories by Mr. L. W. Rowe, who will report on their antispasmodic activity elsewhere.[18] A summary of the activity is presented in the table. Each compound was tested upon rabbit and guinea pig non-antagonized intestinal strips immersed in Locke–Ringer's solution and checked at least once. For comparative purposes, papaverine was usually employed as a standard reference compound and was applied to the same strips employed to evaluate the new compounds. The strips were washed free of antispasmodic and allowed to return to equilibrium before further treatment.

A study of the data reveals that all of the morpholinealkyl esters included in this series possess antispasmodic activity, although some exert it only to a slight degree. Several of the compounds approach papaverine, while others equal or exceed papaverine in activity. We have concluded from our work with this series that it is essential to have a di-substituted acetic acid derivative wherein at least one group is aryl, inasmuch as mono-aryl, di- and tri-alkyl and monoalicyclic acid esters are relatively inactive. Substitution of a cyclohexyl group for a phenyl group increased the activity slightly in one instance (compare β-4-morpholineëthyl α-phenylcyclohexane acetate hydrochloride with the corresponding diphenylacetate hydrochloride) while reduction of one phenyl group of β,β-dimethyl-γ-4-morpholinepropyl diphenylacetate hydrochloride caused a decrease in activity. The latter result was unexpected in view of the work of others. In general, branching of the alkyl chain and lengthening of the long straight chain in the alcohol portion of the ester lead to more active compounds within certain limits of solubility. Three of the compounds deserve further investigation.

The 4-morpholinealkyl amides included in the table are less active antispasmodics than the corresponding esters.

## Summary

1. Twenty-five 4-morpholinealkyl esters and three 4-morpholinealkyl substituted amides have been prepared in the form of their salts and tested for antispasmodic activity. In addition, several of the bases have been isolated and their properties determined.

2. The three most active compounds in this series are β,β-dimethyl-γ-4-morpholinepropyl diphenylacetate hydrochloride, ω-4-morpholinehexyl diphenylacetate hydrochloride and β-4-morpholineëthyl-α-phenylcyclohexaneacetate hydrochloride.

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(18) Presented at the Am. Ph. Assoc. meeting, Detroit, Michigan, August 18–22, 1941; Rowe, *J. Am. Pharm. Assoc.*, in press.