ing to only 0.05 g. (6%) of 1,1-diphenylethylene. Acidification of the aqueous fraction with dilute sulfuric acid precipitated none of the chloro acid.

Methyl 2,2-Diphenyl-3-bromopropanoate.—Treatment of the corresponding carboxylic acid chloride[11] with excess dry methanol at room temperature for four hours gave, on fractionation *in vacuo*, a 94% yield of the methyl ester, b. p. 153–155° (0.9 mm.), $n^{25}D$ 1.5968. The distillate solidified and melted at 44–46°.

Anal. Calcd. for $C_{16}H_{15}BrO_2$: C, 60.20; H, 4.74. Found: C, 60.52; H, 4.66.

Treatment of Methyl 2,2-Diphenyl-3-bromopropanoate with Sodium Methoxide.—A solution of sodium methoxide (from 0.4 g. of sodium) in 50 cc. of dry methanol was treated with 2.80 g. of the methyl ester and refluxed for twenty-five hours. The solution remained colorless and no sodium bromide precipitated. The methanol was removed by distillation and the residue was shaken with an ether–water mixture. The aqueous layer was separated and acidified. No acidic product was precipitated. The neutral ether layer was washed with water and dried over anhydrous magnesium sulfate. Filtration and distillation of the ether gave 2.23 g. of an almost colorless oil, $n^{25}D$ 1.5940 which on distillation gave 1.3 g., b. p. 136° (0.3 mm.). The distillate solidified, m. p. 44–46°. Mixed with a sample of starting material it gave no depression of melting point.

Summary

1. The preparation of α,α-diphenyl-β-propiolactone is reported.

2. The formation of this β-lactone from 2,2-diphenyl-3-chloro, bromo and iodopropanoic acids has been studied together with formation of the by-product, 1,1-diphenylethylene. The re-formation of these β-halogen acids from the β-lactone on treatment with the corresponding hydrohalic acids is also described.

3. The reverse reactions of α,α-diphenyl-β-propiolactone with sodium chloride, bromide and iodide have been studied.

4. The reactivity of the halogen atoms in these β-halogen acids is contrasted with the lack of reactivity of the bromine atom in the methyl ester of 2,2-diphenyl-3-bromopropanoic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

α-Phenyltropic Acid and Basic Esters. Acid and Base-catalyzed Reactions of α,α-Diphenyl-β-propiolactone and of 2,2-Diphenyl-3-bromo- and Chloropropanoic Acids

BY HAROLD E. ZAUGG

During recent years a large number of basic esters of benzilic acid have been prepared by numerous workers[1,2] and many of them have been shown to exert a high order of antispasmodic and/or local anesthetic activity. Basic esters of α-phenyltropic acid (II) obviously would be of considerable interest in this connection since this acid approaches more nearly than does benzilic acid the structure of tropic acid of which the naturally occurring, potent antispasmodic, atropine, is a basic ester. Indeed, Burtner and Cusic[2] have already reported a basic ester of α-phenyltropic acid. The latter was prepared by the action of nitrous acid on the amino ester $(C_6H_5)_2C(COOCH_3)CH_2NH_2$, followed by saponification. They reported a melting point of 167–168° for this hydroxy acid.

In the present work, α,α-diphenyl-β-propiolactone (I)[3] was submitted to both acid and base hydrolysis with the expectation of arriving at the same acid II reported by Burtner and Cusic. However, this was not the case. An isomeric hydroxy acid melting at 157–158° was obtained. Since the method of preparation and the reactions of this acid, which are summarized in the accompanying flow-sheet, seemed to establish its structure as II, the work of Burtner and Cusic was repeated. The melting point (164.5–165.5°) found for their acid checked reasonably well; however, by a mixed melting point determination with an authentic specimen,[4] their acid proved to be identical with the isomeric α,β-diphenyllactic acid,[5] $C_6H_5CH_2C(OH)(C_6H_5)COOH$, m. p. 164.5–165.5°, formed by rearrangement of a phenyl group.

In retrospect the formation of this isomeric hydroxy acid is not surprising since a number of closely allied rearrangements under similar conditions are known.[6] On the other hand, it should be mentioned that tropic acid itself is formed by the action of nitrous acid on α-phenyl-β-alanine.[7] Thus the unpredictable nature of the Demyanov reaction is once more exemplified.

The dimethylaminoethyl and diethylaminoethyl esters of α-phenyltropic acid (V, R = CH_3 and C_2H_5) were prepared. However, both the antispasmodic and local anesthetic activities of these compounds were disappointing, being much lower than those of the corresponding benzilic esters.

Best yields of α-phenyltropic acid (II) were obtained by acid hydrolysis of the β-lactone I

(1) Ford-Moore and Ing, *J. Chem. Soc.*, **55**, 952 (1947); King and Holmes, *ibid.*, 164 (1947); Holmes and Hill, U. S. Patent 2,399,736 and 2,430,116; Blicke, U. S. Patent 2,401,219; Northey and Hultquist, U. S. Patent 2,419,366; Chen, *et al.*, *J. Lab. Clin. Med.*, **30**, 700 (1945).

(2) Burtner and Cusic, THIS JOURNAL, **65**, 262 (1943).

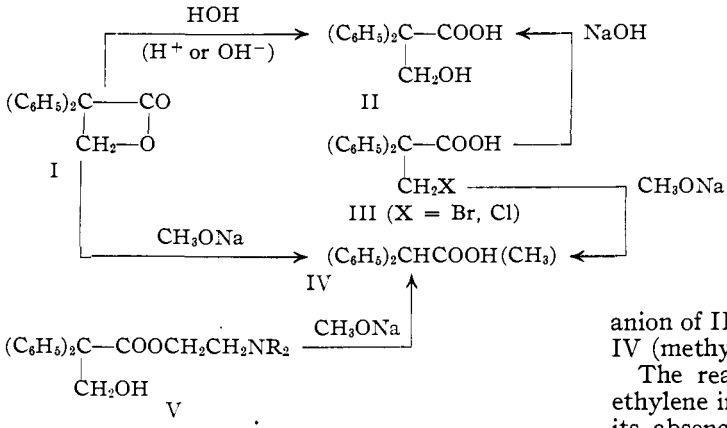
(3) Zaugg, *ibid.*, **72**, 2998 (1950).

(4) The author is indebted to Dr. A. W. Weston of these Laboratories for a sample of α,β-diphenyllactic acid prepared by the general method of Rohrmann, Jones and Shonle, *ibid.*, **66**, 1856 (1944).

(5) "Beilstein's Handbuch der org. Chem.," Suppl. Vol. X, p. 155.

(6) Levy and Gallais, *Bull. soc. chim.*, **43**, 862 (1928); Hickinbottom, "Reactions of Org. Compounds," 2nd ed., 313 (1948).

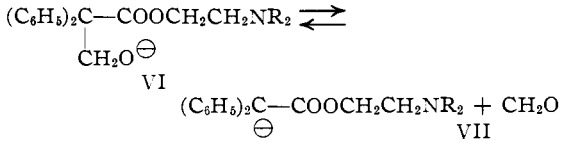
(7) Natarajan and Swaminathan, THIS JOURNAL, **69**, 2560 (1947).



in a mixture of water, sulfuric and acetic acids. Hydrolysis in excess aqueous alcoholic alkali gave the hydroxy acid II more rapidly even at room temperature but in poorer yield. Similarly, α-phenyltropic acid (II) was obtained rapidly in low yield directly from the bromo acid III (X = Br) by treatment with excess alkali at room temperature. The methyl ester of the bromo acid III reacted analogously on treatment with excess hot alkali. Both reactions were characterized by the concomitant formation of appreciable quantities of 1,1-diphenylethylene.[3] Alkaline hydrolysis of 2,2-diphenyl-3-chloropropanoic acid (III, X = Cl) likewise led to α-phenyltropic acid much more slowly than, but in approximately the same yield as, from the corresponding bromo acid. Practically no 1,1-diphenylethylene was formed as a by-product from the chloro acid.

The reaction of the bromo acid III (X = Br), the chloro acid III (X = Cl), the β-lactone I and the basic ester V (R = C_2H_5) with sodium methoxide in methanol led in each case to a mixture of diphenylacetic acid (IV) and a neutral ester (undoubtedly the methyl ester) saponifiable to diphenylacetic acid. The reactions with the bromo and chloro acids were the only ones in which concurrent formation of 1,1-diphenylethylene[3] could be detected.

This cleavage reaction of the basic ester V (R = C_2H_5) probably takes place through the intermediate formation of the anion VI which would exist in equilibrium with the diphenyl-



acetate anion VII and formaldehyde. This equilibrium would be forced almost completely to the right by the reaction of the anion VII with the more acidic methanol to give methoxide ion and diphenylacetic ester.[8] The analogous reaction of the β-lactone I likewise can be explained on similar grounds with the initial postulation of reaction with methoxide ion to give the ester anion VIII,[9] $(C_6H_5)_2C(CH_2O^-)-COOCH_3$, similar to VI. Finally, the same reaction of the bromo and chloro acids III is clarified by the reasonable assumption of primary β-lactone formation; and the over-all reaction mechanism can be represented by the following sequence: III → carboxylate anion of III → I → VIII → $(C_6H_5)_2C^{\ominus}COOCH_3$ → IV (methyl ester).[10]

The reason for the presence of 1,1-diphenylethylene in the reactions of the halogen acids and its absence in the other two reactions becomes apparent from the fact that this by-product originates from the carboxylate anion of III by a reaction concurrent with β-lactone formation.[3] The other two reactions both start at later stages in the above sequence.

The reason for the observed presence of free diphenylacetic acid in addition to its methyl ester in all of these cleavage reactions is not readily apparent. Traces of water could, perhaps, effect hydrolysis without leading to appreciable quantities of II. Another explanation might lie in the oxidation of the formaldehyde to formic acid by a Cannizzaro reaction[11] followed by ester interchange of the formic acid with methyl diphenylacetate to give the diphenylacetic acid. However, no efforts were made to establish the presence of methyl formate in the reaction mixtures.

Because of the size of the two phenyl groups in the α-position of α-phenyltropic acid (II), it was considered possible that cyclization could be effected to regenerate the β-lactone I.[12] However, attempts to bring about this lactonization were unsuccessful.

Acknowledgment.—The author is indebted to Mr. E. F. Shelberg, head of the Abbott Microanalytical Laboratory, for the elementary analyses.

Experimental

α-Phenyltropic Acid. A. By Acid Hydrolysis.—A solution of 11.95 g. of the β-lactone I[3] in a mixture of 195 cc. of glacial acetic acid, 43 cc. of concentrated sulfuric acid and 85 cc. of water was heated on the steam-bath for seven hours. The reaction mixture was diluted with

(8) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937).

(9) Compare Gresham, *et al.*, *ibid.*, **70**, 1004 (1948).

(10) Obviously, reaction of the β-lactone I with sodium hydroxide instead of with sodium methoxide would lead to the carboxylate anion $(C_6H_5)_2C(CH_2OH)-COO^{\ominus}$ which would be expected to show considerable reluctance to formation of the doubly charged anion necessary for cleavage of formaldehyde. This also accounts for the observed formation of α-phenyltropic acid by the action of sodium *hydroxide* on the halogen acids III, since the β-lactone is undoubtedly intermediate likewise in this transformation. This explanation is further substantiated by the observation that α-phenyltropic acid, once it is formed, is unchanged by the action of methanolic sodium methoxide.

(11) Geissman, "Organic Reactions," Vol. II, 98 (1944).

(12) Compare Bains and Thorpe, *J. Chem. Soc.*, 2742 (1923).

water to a volume of 1500 cc. and the oil which separated was taken up in ether. The ether layer was washed with water and then extracted with 150 cc. of 2 *N* sodium hydroxide. The aqueous extract was separated and acidified with concentrated hydrochloric acid. The precipitated oil was again taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave 12.7 g. of crude acid, m. p. 150–156°. This material was purified by dissolving in 60 cc. of hot 95% ethanol, adding 50 cc. of hot water, boiling with charcoal for a few minutes, filtering and adding hot water (180–200 cc.) to the hot filtrate until a faint cloudiness developed. Seeding and cooling gave 10.8 g. (83% yield) of α-phenyltropic acid (II), colorless needles, m. p. 156–158°. Further recrystallization for analysis gave m. p. 157–158°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.21; H, 5.63.

B. **By Alkaline Hydrolysis.**—A suspension of 1.5 g. of the β-lactone I in 10 cc. of 95% ethanol was treated with 20 cc. of 20% sodium hydroxide. The mixture was allowed to stand at room temperature with occasional stirring until a clear solution formed (*ca.* thirty minutes). The mixture was then poured into ice-water and the clear solution thus obtained was acidified with concentrated hydrochloric acid. The precipitated oil solidified on standing overnight and was filtered off. Recrystallization first from the benzene–Skellysolve B solvent pair and then from water–alcohol gave 0.92 g. (57% yield) of α-phenyltropic acid (II), m. p. 156–158°.

α-Phenyltropic Acid from 2,2-Diphenyl-3-bromopropanoic Acid and Methyl Ester.—A suspension of 2.08 g. of the bromo acid (III)[13] in 10 cc. of 95% ethanol was treated with 20 cc. of 20% sodium hydroxide. The solution became clear almost immediately but was allowed to stand at room temperature for thirty minutes before diluting with water. The mixture was worked up in the usual manner and in addition to 0.36 g. of a neutral unsaturated oil, 0.52 g. (31% yield) of α-phenyltropic acid, m. p. 156–158°, was obtained. The neutral oil was shown to be 1,1-diphenylethylene by conversion to the dibromide,[14] m. p. 56–58°, which on heating characteristically evolved hydrogen bromide. Refluxing 6.4 g. of the methyl ester of the bromo acid for twenty-six hours with a mixture of 60 cc. of 20% sodium hydroxide and 30 cc. of 95% ethanol gave 1.90 g. of the neutral oil (1,1-diphenylethylene) but only 0.91 g. of α-phenyltropic acid, m. p. 156–158°.

α-Phenyltropic Acid from 2,2-Diphenyl-3-chloropropanoic Acid.—To a suspension of 13 g. (0.05 mole) of the chloro acid in 70 cc. of 95% ethanol was added 145 cc. of 20% sodium hydroxide. The solid acid dissolved rapidly. After standing at room temperature for sixty-eight hours, the solution was diluted with water to a large volume. Extraction with ether gave only 0.10 g. of a neutral oil consisting mainly of 1,1-diphenylethylene. Acidification of the aqueous solution gave 8.73 g. of acidic material, m. p. 135–150°. Recrystallization from 95% ethanol gave 4.2 g. (34% yield) of α-phenyltropic acid, m. p. 155–158°. Further impure crops were obtained which undoubtedly contained α-phenyltropic acid mixed with a persistent acidic contaminant of lower melting point. When this hydrolysis was stopped at the end of only forty-five minutes at room temperature, the product consisted mainly of starting material, with only a small amount of α-phenyltropic acid having been formed.

Attempted Lactonization of α-Phenyltropic Acid.—Refluxing 1 g. of the hydroxy-acid in 100 cc. of dry benzene containing two drops of concentrated sulfuric acid for three hours and then removing the benzene by distillation gave in addition to 0.26 g. of starting material only amorphous polymeric material. No β-lactone was formed.

Diethylaminoethyl Ester of α-Phenyltropic Acid (V, R = C_2H_5).—A solution of 2.42 g. (0.01 mole) of α-phenyltropic acid and 1.36 g. (0.01 mole) of freshly distilled diethylaminoethyl chloride in 20 cc. of dry isopropyl alcohol was refluxed for twelve hours and then cooled in ice. The hydrochloride which crystallized weighed 3.53 g. (93% yield) and melted at 152–154°. Recrystallization from 25 cc. of dry isopropyl alcohol gave 2.94 g., m. p. 154–155°. Further recrystallization of a sample for analysis raised the melting point to 154.5–156°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71. Found: C, 67.06; H, 7.17; N, 3.99.

Dimethylaminoethyl Ester of α-Phenyltropic Acid (V, R = CH_3).—A solution of 3.59 g. of α-phenyltropic acid and 1.60 g. of freshly distilled dimethylaminoethyl chloride in 30 cc. of dry isopropyl alcohol was refluxed for two hours. After addition of 0.4 g. more dimethylaminoethyl chloride refluxing was continued for three hours. Since no product crystallized on cooling, the reaction mixture was diluted with water, acidified with hydrochloric acid and extracted with ether to remove insoluble by-products. From the ether extract was obtained 1.20 g. of unreacted α-phenyltropic acid. The aqueous solution was made basic with cold 20% sodium hydroxide and the free basic ester separated as a solid which was filtered off and recrystallized from methanol to give 1.87 g. (40% conversion and 54% yield, based on α-phenyltropic acid consumed), m. p. 140–142°. Further recrystallization from methanol did not raise the melting point.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.01; H, 7.29; N, 4.56.

Formation of Diphenylacetic Acid (IV) from the β-Lactone I.—A sodium methoxide solution was prepared by dissolving 0.17 g. (0.0074 mole) of sodium in 35 cc. of dry methanol. This was refluxed with 1.5 g. (0.0067 mole) of the β-lactone I for twenty-six hours. The methanol was removed by distillation and the residue was shaken with a mixture of water and ether. From the water layer on acidification was obtained after recrystallization from benzene–Skellysolve B, 0.57 g. of an acid, m. p. 140–144°. From the ether layer was recovered 0.71 g. of a neutral colorless oil which was saturated to bromine in carbon tetrachloride and which was saponified by refluxing for thirty minutes with a mixture of 15 cc. of 20% sodium hydroxide and 5 cc. of 95% ethanol. After recrystallization from benzene–Skellysolve B, the acid obtained from the saponification weighed 0.50 g. and melted at 140–144°. It proved to be identical with the acid fraction of the original reaction product. The two fractions were combined and recrystallized from dilute ethanol to give 0.86 g. of shiny flat needles, m. p. 143–145°. When mixed with an authentic specimen of diphenylacetic acid (m. p. 144–146°) it produced no depression of melting point. Similar treatment of α-phenyltropic acid with two moles of sodium methoxide in methanol gave only unreacted starting material (70% recovery). No diphenylacetic acid and no neutral ester was isolated.

Diphenylacetic Acid from 2,2-Diphenyl-3-bromopropanoic Acid.—A solution of 3.05 g. (0.01 mole) of the bromo acid (III) in 60 cc. of dry methanol containing sodium methoxide (formed from 0.46 g. (0.02 mole) of sodium) was refluxed for twenty-six hours. The methanol was removed by distillation and the residue treated as described above. The acidic fraction yielded 0.10 g. of material, m. p. 130–140°, which on purification proved to be diphenylacetic acid. The neutral fraction (1.64 g.) on saponification in the usual manner gave in addition to 0.71 g. of a non-saponifiable oil, unsaturated toward bromine in carbon tetrachloride (undoubtedly mainly 1,1-diphenylethylene), 0.65 g. of an acid, m. p. 142–145°. Several recrystallizations from dilute ethanol gave shiny flat needles, m. p. 144–145°. Elementary analysis and a mixed melting point with an authentic sample proved identity with diphenylacetic acid (IV). Also conversion to the corresponding amide, m. p. 165–166°, and mixing with an authentic specimen, m. p. 166–167°, produced no melting point depression.

Diphenylacetic Acid from 2,2-Diphenyl-3-chloropropanoic Acid.—Refluxing 5.2 g. (0.02 mole) of the chloro-acid III (X = Cl) for twenty-six hours in 120 cc. of dry

(13) Wegmann and Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(14) Lipp, *Ber.*, **56**, 567 (1923).

methanol containing sodium methoxide prepared from 0.92 g. (0.04 mole) of sodium, resulted in the formation of 0.8 g. of unsaponifiable oil (22% calculated as 1,1-diphenylethylene) and 2.7 g. (64%) of diphenylacetic acid, m. p. 143–146° (after saponification of the ester).

Diphenylacetic Acid from the Diethylaminoethyl Ester of α-Phenyltropic Acid.—A sodium methoxide solution prepared from 0.30 g. (0.013 mole) of sodium and 20 cc. of dry methanol was refluxed for twenty-six hours with 1.90 g. (0.005 mole) of the basic ester hydrochloride (V, R = C_2H_5). Working up the reaction mixture in the usual way gave 0.70 g. of diphenylacetic acid and 0.3 g. of a neutral oil which on saponification gave a further 0.22 g. of diphenylacetic acid. The total of 0.92 g. of acid obtained represents an 87% yield based on the ester hydrochloride.

Summary

1. α-Phenyltropic acid has been prepared in good yield by hydrolysis of α,α-diphenyl-β-propiolactone. A product reported by previous workers to be α-phenyltropic acid has been found to possess the isomeric α,β-diphenyllacetic acid structure.

2. The reaction with sodium methoxide of 2,2-diphenyl-3-bromo and chloropropanoic acids, α,α-diphenyl-β-propiolactone and a basic ester of α-phenyltropic acid, has in each case been found to lead to a mixture of diphenylacetic acid and its methyl ester. The mechanism of this cleavage reaction is discussed.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

Basic Esters and Amides of α-Substituted Diphenylacetic Acids

BY HAROLD E. ZAUGG AND BRUCE W. HORROM

In a routine search for compounds possessing therapeutic activity, primarily analgetic, a number of basic esters and amides derived from acids of type $(C_6H_5)_2RCCOOH$ were prepared.[1] Five carboxylic acids were employed in which R was varied as follows: CH_3, C_2H_5, $CH_2{=}CHCH_2$, $ClCH_2$, and $BrCH_2$. In addition, several basic amides of 2-phenylbutanoic acid, $C_6H_5CH(C_2H_5)$-COOH were prepared. Of these six acids the 2,2-diphenyl-3-chloropropanoic acid was the only one not previously reported in the literature. It was made by the condensation of benzene with chloropyruvic acid in the presence of concentrated sulfuric acid according to the procedure of Wegmann and Dahn[2] for the preparation of the corresponding bromo acid.

The basic esters and amides were prepared by the reaction of the carboxylic acid chlorides with amino alcohols and diamines, respectively, in ether solution. The only new amine used in this work seems to be β-dimethylaminoisopropylamine. It was obtained by the reductive amination, with ammonia, of dimethylaminoacetone.

In every case but one, the diamine employed in the preparation of the amides possessed one tertiary amino group. The exception, N,N'-dimethylethylenediamine, contained two secondary amino groups and as expected gave considerable amounts of the bis-amide on treatment with the acid chloride. Although the desired basic mono-amide still predominated in this case, the corresponding reaction with ethylenediamine itself produced only the bis-amide and none of the basic amide.

All the esters and amides are listed in the table. During the course of the present work the dimethylaminoethyl[3] and diethylaminoethyl[4] esters of 2,2-diphenylpropanoic acid were reported by other workers.

Pharmacology.—The increase of pain threshold produced in dogs as summarized in the table was determined by a modification of the method of Andrews and Workman.[5] The authors are indebted to Dr. R. K. Richards and Mr. K. E. Kueter of the Abbott Pharmacological Research Laboratories for these tests. The symbols express the increase of pain threshold according to the following scale: 0 = none; ± = doubtful; + <10%; ++ = 10–20%; +++ = 20–30%; ++++ = 30–40%. Doses one-fifth to one-tenth of the LD_{50} were injected subcutaneously in the dogs. The toxicities were determined intraperitoneally in mice. Since a limited number of mice were used these values can be in error by as much as ±50%.

The most active compound proved to be the dimethylaminoethyl amide of 2,2-diphenyl-3-chloropropanoic acid. It induced the Straub phenomenon (tail erection) in mice, a characteristic of many narcotic drugs. However, it also produced considerable irritation at the site of subcutaneous injection, and by oral or intravenous administration it showed only a low order of activity. The same amide of the corresponding bromo acid suffered from the same defects. The values indicated in the table for the increase of pain threshold, therefore, do not reflect the true analgesic activities of these compounds. Some other property, possibly irritation, undoubtedly is responsible for the relatively high order of observed activity.

Several of these compounds were tested for

(1) For a discussion of the antispasmodic activity of certain derivatives of diphenylacetic acid, see Raymond, *J. Am. Pharm. Assoc.*, **32**, 249 (1943).

(2) Wegmann and Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(3) Larsen, Ruddy, Elpern and MacMullen, THIS JOURNAL, **71**, 532 (1949).

(4) British Patent Spec. 33,582, Dec. 19, 1947.

(5) Andrews and Workman, *J. Pharmacol.*, **73**, 99 (1941).