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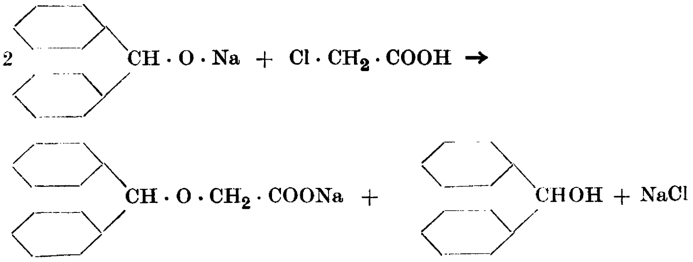
Diphenylmethoxyacetic Acid and Some Related Compounds

RICHARD DAHLBOM and LARS-ERIC ÖSTERBERG

Central Laboratories, Astra, Södertälje, Sweden

As starting materials for certain syntheses we required diphenylmethoxyacetic acid, diphenylmethylthioglycolic acid and the amides and ethyl esters of these acids. Among these compounds only diphenylmethylthioglycolic acid appears to have been reported in the literature [1]. This paper describes the syntheses of these new compounds and their properties.

Diphenylmethoxyacetic acid was prepared by treating the sodium salt of benzohydrol with chloroacetic acid.



The ethyl ester could be obtained by esterification with ethanol and sulfuric acid. It was, however, prepared more conveniently from ethyl bromoacetate and the sodium salt of benzohydrol.

In attempting to obtain the amide via the acid chloride, it was found that the acid was disintegrated by treatment with chlorinating agents such as thionyl chloride, phosphorus pentachloride and phosphorus oxychloride and only benzohydrol or diphenylmethyl chloride could be isolated.

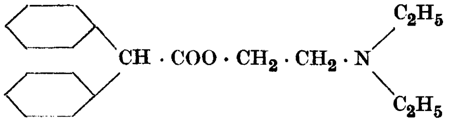
By reacting the acid with equimolar amounts of thionyl chloride and pyridine and treating the reaction product with ammonia by the method of Human and Mills [2], the acid amide was certainly obtained, but it was synthesized more conveniently and with a better yield by heating the ethyl ester with alcoholic ammonia in a sealed vessel at 100°.

As a starting material for heterocyclic compounds, especially imidazolines, we required diphenylmethoxyacetonitrile too. It proved, however, impossible to obtain this compound by dehydration of the amide. Distillation with phosphorus pentoxide caused cleavage of the molecule at the ether linkage, benzohydrol being formed. Treatment with thionyl chloride or phosphorus chlorides yielded diphenylmethyl chloride. We succeded, however, in producing the desired imidazoline in another way, by the action of 2-(chloromethyl)-imidazoline on the sodium salt of benzohydrol[3].

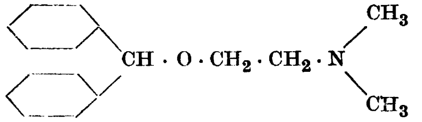
Diphenylmethylthioglycolic acid was prepared by the procedure of Holmberg[1]. The ethyl ester was obtained by esterification with ethanol and sulfuric acid in the usual way. The amide of this acid was prepared by heating the ester with alcoholic ammonia in a sealed vessel.

In this connection it seemed to us to be worth while investigating whether the β-dialkylaminoethyl esters of these two acids possessed any interesting pharmacological properties. These compounds bear a certain structural resemblance to Trasentin (I) and Benadryl (II), which are well known as an antispasmodic and an antihistamine agent, respectively.

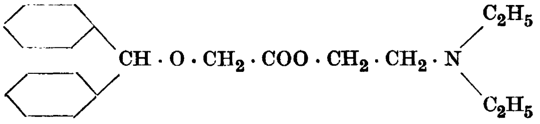
We therefore prepared the β-diethylaminoethyl esters of these acids (III, IV) by treating the acids with β-diethylaminoethyl chloride by the method of Miescher and Hoffmann[4].



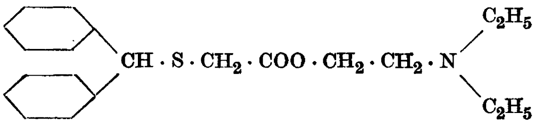
I. Trasentin.



II. Benadryl.



III.



IV.

The compounds III and IV have been directly compared with Benadryl on isolated guinea-pig ileum *. They exerted a slight antihistamine action, and

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* The pharmacological investigations have been carried out at Astra's Biological Department by Dr. S. Wiedling.

their antispasmodic effect against barium chloride and acetylcholine was comparatively weak.

EXPERIMENTAL

Diphenylmethoxyacetic acid

184 g of benzohydrol was dissolved in 200 ml of dry toluene, and 23 g of powdered sodium added. The mixture was allowed to stand at room temperature overnight, and was then warmed with stirring for two hours at 100°. After cooling, a solution of 47 g of chloroacetic acid in 200 ml of toluene was added in portions, and the mixture was then refluxed for 7 hours. After cooling to room temperature, the mixture was extracted with 600 ml of 0.2 *N* sodium hydroxide. The alkaline solution was acidified with 5 *N* hydrochloric acid, whereupon the crude acid separated as an oil, which crystallized in a couple of days. The yield was 76 g. Extraction of the acidified solution with ether and evaporation of the ether yielded another 1.5 g of the acid. The total yield amounted to 64 %. From the toluene 85 g of benzohydrol could be recovered.

The crude acid was recrystallized from 50 % ethanol. M. p. 74—75°.

$C_{15}H_{14}O_3$ (242.3)	Calc.	C 74.5	H 5.78	Eq. wt. 242
	Found	» 75.0	» 5.67	» 242

For characterizing of the acid, its phenacyl ester was prepared.

A mixture of 3.1 g of the acid, 2.0 g of phenacyl bromide, 0.5 g of sodium carbonate and 30 ml of 66 % ethanol was refluxed for 1 hour. The mixture was then poured out into ice water, whereupon the ester separated as an oil, which soon crystallized. After recrystallization from ethanol it melted at 92—94°.

$C_{23}H_{20}O_4$ (360.4)	Calc.	C 76.7	H 5.58
	Found	» 76.7	» 5.60

Ethyl diphenylmethoxyacetate

A solution of the sodium salt of benzohydrol was prepared from 50 g of benzohydrol, 5.75 g of sodium and 225 ml of toluene along the lines of the preceding experiment. 42 g of ethyl bromoacetate was added, and the mixture was refluxed for 7 hours. After cooling, the mixture was washed with water in order to remove the separated sodium bromide. The toluene layer was dried over calcium chloride, and the toluene was distilled off on a water bath at 15 mm. The residue, 72 g, was distilled in high vacuum. The fraction boiling at 105—115° bath temperature at 0.002 mm was collected. Yield 30.0 g (41 %) of a colourless oil.

$C_{17}H_{18}O_3$ (270.3)	Calc.	C 75.6	H 6.71
	Found	» 76.0	» 6.70

This ester was very sensitive to alkaline hydrolysis. Thus it was saponified almost instantaneously at room temperature by means of ethanolic sodium hydroxide.

7.5 g of the ethyl ester was dissolved in 7.5 ml of ethanol, and 1.9 g of sodium hydroxide dissolved in 30 ml of ethanol was added. A vigorous reaction took place, and in a couple of minutes the solution had solidified. The precipitate was filtered off, dissolved in 200 ml of water and acidified with 2 N hydrochloric acid, whereupon 4.0 g of white crystals separated. After recrystallization from 50 % ethanol, m. p. 74—75° and eq. wt. 242.

Diphenylmethoxyacetamide

A. It proved advantageous to prepare this compound from the crude ethyl ester and not from the distilled product. 75.0 g of the crude ester, prepared as described above, was dissolved in 115 ml of ethanol, and the solution was saturated with dry ammonia gas in the cold. The mixture was heated in a sealed steel tube at 100° for sixteen hours. On cooling, 31 g of white crystals separated. The yield was 47 % calculated upon benzohydrol. The amide was recrystallized from 66 % ethanol. M. p. 134—135°.

$C_{15}H_{15}NO_2$ (241.3)	Calc.	C 74.7	H 6.28	N 5.81
	Found	» 74.7	» 6.27	» 5.79

B. To a solution of 7.3 g of diphenylmethoxyacetic acid and 2.4 g of pyridine in 75 ml of ether, 3.58 g of thionyl chloride was added, drop-wise with stirring. The mixture was left at room temperature for an hour, 75 ml of pyridine was then added, and the mixture was saturated with dry ammonia gas and was allowed to stand overnight. The mixture was then poured out into ice water, and the precipitate was collected. Yield 3.1 g (42 %). After recrystallization from 66 % ethanol m. p. 134—135°.

β-Diethylaminoethyl diphenylmethoxyacetate

12.1 g of diphenylmethoxyacetic acid, 8.6 g of β-diethylaminoethyl chloride hydrochloride[5] and 13.5 g of dried potassium carbonate were suspended in 50 ml of acetone and refluxed with stirring for 24 hours. The mixture was filtered, and the chilled filtrate acidified with a solution of dry hydrogen chloride in acetone. The resulting precipitate was collected, the yield was 6.7 g. After recrystallization from ethyl acetate the pure hydrochloride melted at 143—144°.

$C_{21}H_{27}NO_3 \cdot HCl$ (377.9)	Calc.	Cl 9.39	N 3.70
	Found	» 9.31	» 3.65

The free base could be obtained by dissolving the hydrochloride in water and precipitating with sodium carbonate solution. This yielded an oil, which was extracted with ether. The ether was died over calcium chloride and distilled off. The residue distilled at 0.002 mm at 160° in the bath giving a colourless oil.

$C_{21}H_{27}NO_3$ (341.4) Calc. N 4.12 Found N 4.11

Diphenylmethylthioglycolic acid

Holmberg[1] prepared this compound by heating equivalent parts of benzohydrol and thioglycolic acid for 4 hours on the water bath either suspended in 2 *N* hydrochloric acid or without any diluent. We prepared it by a slight modification of the latter method.

If a drop of conc. hydrochloric acid was added to the reaction mixture, a vigorous reaction commenced, and in a few minutes the crude acid crystallized.

Ethyl diphenylmethylthioglycolate

A mixture of 5.0 g of diphenylmethylthioglycolic acid, 5 ml of conc. sulfuric acid and 50 ml of ethanol was refluxed for 5 hours. The solution was poured out into 300 ml of ice water, and the crude ester was then extracted with ether. The ether layer was washed with sodium carbonate solution and water, dried over calcium chloride and evaporated. Distillation of the residue at 0.001 mm at 125° in the bath yielded 4.4 g of a colourless oil (79.5 %).

$C_{17}H_{18}O_2S$ (286.4)	Calc.	C 71.3	H 6.33	S 11.2
	Found	» 71.0	» 6.26	» 11.2

Diphenylmethylthioglycolamide

28.8 g of the ethyl ester was dissolved in 100 ml of ethanol, and the solution was saturated, at a low temperature with ammonia gas. It was then heated in a sealed steel tube at 100° for 16 hours. On cooling, 17.1 g of the amide separated. Recrystallization from ethanol gave white crystals with the m. p. 110—112°.

$C_{15}H_{15}NOS$ (257.3)	Calc.	N 5.45	S 12.5
	Found	» 5.42	» 12.3

β-Diethylaminoethyl diphenylmethylthioglycolate

A mixture of 13.0 g of diphenylmethylthioglycolic acid, 8.6 g of β-diethylaminoethyl chloride hydrochloride, 13.5 g of potassium carbonate and 50 ml of acetone was refluxed with stirring for 24 hours. The solution was filtered and acidified with a solution of dry hydrogen chloride in acetone. The precipitated hydrochloride amounted to 6.1 g. After recrystallization from acetone it melted at 164—165°.

$C_{21}H_{27}NO_2S \cdot HCl$ (394.0)	Calc.	Cl 9.02	N 3.56
	Found	» 9.03	» 3.56

SUMMARY

The preparation of diphenylmethoxyacetic acid and a number of derivatives of this acid and diphenylmethylthioglycolic acid has been described.

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