Antispasmodic Derivatives of Dialkylphenylacetic Acids *

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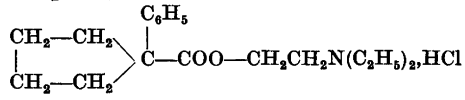
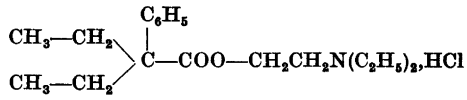
In 1947 Domenjoz *et al.*[1] investigated the spasmolytic activity of diethylaminoethyl 1-phenyl-cyclopentane-1-carboxylate (Parpanit):

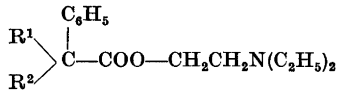


The application of this compound against parkinsonism [2] has made it especially well known.

Although it is known that the dimensions of drug molecules may be of great importance for their pharmacological activity it seemed to us to be doubtful that the cyclopentane ring should be of essential importance, since many similar compounds (Trasentin *etc.*) are known to possess antispasmodic activity. We therefore prepared the closely related compound diethylaminoethyl phenyldiethylacetate:

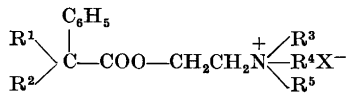


Actually this compound was very active, and other basic esters of dialkylphenylacetic acids of the type:



were similarly very active. The most active of these compounds was the diethylaminoethyl ester of methyl-ethyl-phenylacetic acid, the spasmolytic activity of which was found to be ten times as great as that of Trasentin with the toxicity only half as great. The corresponding quaternary compounds are even more active.

Table 1. Derivatives of dialkylphenylacetic acids:



R^1	R^2	$R^3=R^4$	R^5	X	Formula	M.p. °C	% N calc.	% N found	spasmolyt. act. (Trasentin = 1)
C_2H_5	C_2H_5	CH_3	H	Cl	$C_{16}H_{26}O_2NCl$	126	4.68	4.93 *	1.5
C_2H_5	C_2H_5	C_2H_5	H	Cl	$C_{18}H_{30}O_2NCl$	142	4.28	4.38	2.5
C_2H_5	CH_3	C_2H_5	H	Cl	$C_{17}H_{28}O_2NCl$	127	4.47	4.42	10.0
CH_3	CH_3	C_2H_5	H	Cl	$C_{16}H_{26}O_2NCl$	128	4.68	4.55	1.5
C_2H_5	C_2H_5	C_2H_5	CH_3	I	$C_{19}H_{32}O_2NI$	88	3.23	3.36	10.0
CH_3	C_2H_5	C_2H_5	CH_3	Br	$C_{18}H_{30}O_2NBr$	127	3.77	3.74	15
CH_3	C_2H_5	C_2H_5	C_2H_5	Br	$C_{19}H_{32}O_2NBr$	128	3.63	3.73	16
CH_3	C_2H_5	C_2H_5	CH_3	I	$C_{18}H_{30}O_2NI$	122	3.34	3.24	20
CH_3	CH_3	C_2H_5	C_2H_5	$CH_3C_6H_4SO_3$	$C_{25}H_{37}O_5NS$	66	3.02	3.05	—

* calc. C 64.20 H 8.68
found » 64.34 » 8.64

* Dan. Pat. 72436 and 73667 (1951).

The dialkylphenylacetic acids [3] were converted to the dialkylaminoethyl esters by reaction of their sodium or silver salts with β-dialkylaminoethyl chlorides, or alternatively by reaction of the acid chlorides with the dialkylaminoethanols in pyridine solution, the first method being the most convenient. The hydrochlorides were precipitated by passing dry hydrogen chloride thorugh etheral solutions of the esters. The quaternary compounds were prepared by addition of the alkyl bromides or iodides to ethanolic solutions of the basic esters; after standing of the solutions at 0° for some hours the quaternary salts were precipitated in almost quantitative yields by addition of ether and were recrystallized from acetone or acetone-ether. A toluenesulfonate was prepared by heating a solution of β-diethylamino ethyl dimethylphenylacetate (3 g) and ethyl toluenesulfonate (2.5 g) in benzene (25 ml) for 4 hours at 100°.

The compounds prepared are listed in the accompanying Table 1. The method applied will be illustrated by the following typical example:

Methyldiethyl-(methylethylphenylacetoxy-ethyl)-ammoniumbromide. Methylethyl-phenylacetic acid (56 g) was dissolved in ethanol and neutralized with a concentrated solution of sodium hydroxide. Ethanol and water were removed under reduced pressure and toluene was added to the residue and partly distilled off to remove last traces of water. Then a solution of 56 g of β-chloroethyldiethylamine (30 % excess) in 150 ml of toluene was added and the mixture boiled for 4—5 hours. The toluene was removed under reduced pressure and the residue distilled in vacuo. Yield 81 g (93 %) with b.p. 130—35° at 0.5 mm.

A solution of the ester (75 g) in ethanol (50 ml) was cooled at 0°, 75 ml of methyl bromide was added and the solution left for 24 hours in ice box. The bromide was precipitated by addition of 50 ml of ether, filtered and washed with ether. M. p. 127° after recrystallization from acetone. Yield 85 g (86 %).

1. Domenjoz, R. *Schweiz. med. Wochschr.* **76** (1946) 1282; Grünthal, E. *ibid.* **76** (1946) 1286; Hartmann, K. *ibid.* **76** (1946) 1289.
2. Schwab, R. S., and Leigh, D. *J. Am. Med. Assoc.* **139** (1949) 629.
3. Bodroux, F., and Taboury, F. *Bull. soc. chim. France* [4] **7** (1910) 666, 670, 732; Bodroux, F. *ibid.* [4] **7** (1910) 847; Blondeau, J. *Ann. chim.* [10] **2** (1924) 5; Haller, A., and Bauer, E. *Ann. chim.* [9] **9** (1918) 9.

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