THE SYNTHESIS AND REPELLENT PROPERTIES OF ESTERS OF N,N-DIALKYLPHTHALAMIC ACIDS

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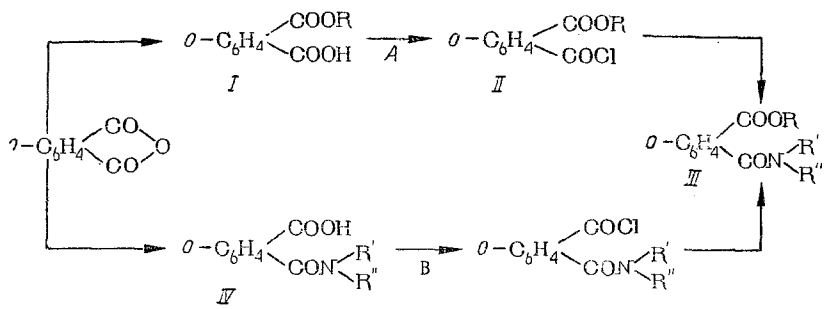
UDC 615.285.7:547.476.1

We have obtained a series of esters of N,N-dialkylphthalamic acid (III) during the course of investigations on the synthesis of repellents. We decided on this group of compounds since it is known that many dialkylamides of substituted benzoic acids are highly effective repellents [1, 2]. Esters of phthalic and certain other 1,2-dicarboxylic acids are also widely used as insect repellents [1]. Furthermore, good repellent properties have been reported for the propyl ester of succinic acid N,N-diethylamide [1, 3]. One of the compounds of type (III) (see Table 1, compound No. 5) was tested previously and displayed good repellent activity [3].

In the current work a simple method of synthesis (A) is described, permitting the preparation of compounds of type (III) in 50-80% yield (based on phthalic anhydride) starting from phthalic anhydride and without isolating or purifying the intermediate ester (I) or acid chloride (II).



The alternative method (B) was less versatile since secondary amines do not all react with phthalic anhydride giving N,N-dialkylphthalamic acids [4, 5].

The compounds (see Table 1) described in this work were synthesized by method A. Some of the esters of N,N-dimethyl- and N,N-diethylphthalamic acids were also obtained from the corresponding phthalamic acids (IV) by method B. The methyl ester of N,N-diethylphthalamic acid, described previously as a liquid [3], was a crystalline substance of mp 45-46°C.

Results on the laboratory testing of the compounds on mosquitos (Aedes aegypti) and fleas (Xenopsilla cheopsis) are presented in Table 1. The work was carried out using the olfactometers 0-21 [6] and 0-33 [7]. Samples of filter paper were impregnated with the preparations and were tested repeatedly in the presence of a standard repellent. Dimethyl phthalate served as standard in the experiments with mosquitos and m-toluic acid piperidide in the experiments with fleas. The effectiveness of compounds is expressed in indices in relation to one standard or the other (D/p) and (T/p). On the first day after impregnating the pieces of paper, values of the indices characterized substances according to their sharpness of repellent activity, and at the end of the test according to relative persistence.

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TABLE 1. Properties of N,N-Dialkylphthalamic Acid Esters: Indices of Repellency on Test in Olfactometers: I on Mosquitos; II on Fleas

Compound No.	R		Yield, %	bp in °C (mp in square brackets) BP in °C (mp in square brackets)	n_D^{20}	Found, %	Empirical formula	Calc., %	I				II		
									Index against dimethyl phthalate D/p				Index against m-toluic acid piperidide T/P		
									1st day	4th day	9th day	11th day	1st day	10th day	22nd day
1	CH_3	$N(CH_3)_2$	64	— [91-2]*	—	6,77	$C_{11}H_{13}NO_3$	6,76	0,4	—	0,4	—	0,5	0,6	0,4
2	C_2H_5	$N(CH_3)_2$	73	— [67—8]	—	6,26	$C_{12}H_{15}NO_3$	6,30	0,8	—	0,5	—	0,7	0,8	0,4
3	C_3H_7	$N(CH_3)_2$	53	176—8 (5 mm) —	1,5272	5,90	$C_{13}H_{17}NO_3$	5,95	1,0	—	0,6	—	0,6	0,8	0,4
4	C_4H_9	$N(CH_3)_2$	72	178—80 (5 mm) —	1,5180	5,37	$C_{14}H_{19}NO_3$	5,62	1,0	—	0,6	—	0,8	0,6	—
5	CH_3	$N(C_2H_5)_2$	64	145—6 (5 mm) [45-6]†	—	5,88	$C_{13}H_{17}NO_3$	5,95	0,2	0,3	0,7	0,4	0,7	—	—
6	C_2H_5	$N(C_2H_5)_2$	65	138—43 (5 mm) (43—4)	—	5,70	$C_{14}H_{19}NO_3$	5,62	0,2	0,4	0,5	0,3	0,7	—	—
7	C_3H_7	$N(C_2H_5)_2$	57	163—7 (6 mm) —	1,5170	5,64	$C_{15}H_{21}NO_3$	5,31	0,4	0,3	0,5	0,3	0,6	—	—
8	C_4H_9	$N(C_2H_5)_2$	71	173—6 (6 mm) —	1,5223	5,00	$C_{16}H_{23}NO_3$	5,04	0,3	0,2	0,4	0,2	0,6	—	—
9	CH_3	$N(CH_2)_5$	52	191—3 (5 mm) —	1,5517	5,91	$C_{14}H_{17}NO_3$	5,66	0,4	0,6	—	—	0,7	0,8	0,4
10	C_2H_5	$N(CH_2)_5$	70	196—8 (5 mm) —	1,5538	5,36	$C_{15}H_{19}NO_3$	5,36	0,2	0,3	1,1	0,5	0,7	—	—
11	C_3H_7	$N(CH_2)_5$	83	198—202 (4 mm) —	1,5389	5,22	$C_{16}H_{21}NO_3$	5,08	0,6	0,7	0,4	—	—	—	—
12	C_4H_9	$N(CH_2)_5$	82	216—8 (4 mm) —	1,5201	4,89	$C_{17}H_{23}NO_3$	4,83	0,4	0,6	0,3	—	0,6	—	—
13	CH_3	$N(CH_2)_6$	81	198—201(4 mm) [64—65]	—	5,40	$C_{15}H_{19}NO_3$	5,36	0,4	0,8	0,5	—	0,6	—	—
14	C_2H_5	$N(CH_2)_6$	65	210—2 (4 mm) —	1,5475	5,10	$C_{16}H_{21}NO_3$	5,08	1,0	0,5	0,5	—	0,6	—	—
15	C_3H_7	$N(CH_2)_6$	61	201—3 (2 mm) —	1,5415	5,07	$C_{17}H_{23}NO_3$	4,83	0,3	0,6	—	—	0,7	0,8	0,4
16	C_4H_9	$N(CH_2)_6$	72	225—7 (5 mm), —	1,5352	4,98	$C_{18}H_{25}NO_3$	4,61	0,5	0,6	—	—	0,7	0,8	0,4

* Literature data [8], mp 91-3°C.

†Literature data [3], bp 136-137°C (0.5 mm).

Compounds which give an index greater than 1 at the end of the test should be regarded as promising repellents. The data, presented in Table 1, indicate that compounds Nos. 3, 4, and 14 were not inferior to dimethyl phthalate in sharpness of repellent activity on mosquitos, but all the substances obtained were less persistent than the standards.

EXPERIMENTAL

N,N-Dialkylphthalamic Acid Esters

Method A. To 0.1 g-mole phthalic anhydride was added 0.5 g-mole of the corresponding alcohol and the mixture heated at the boiling point for 1 h. The excess of alcohol was removed in vacuum at 40°C, 0.2 g-mole thionyl chloride was added to the residue at 20°C, and the mixture kept overnight. Thionyl chloride was distilled off in vacuum at 40°C, the residue dissolved in 20 ml dry benzene and added to a solution of 0.1 g-mole secondary amine and 0.1 g-mole pyridine in 20 ml benzene at 0-5°C. The mixture was stirred for 3 h at 20-25°, the precipitate filtered off and washed with benzene (20 ml). The filtrate was washed with water, with 1% hydrochloric acid solution, with sodium bicarbonate solution, and once more with water. The solvent was removed and the residue distilled in vacuum. The results obtained are given in Table 1.

N,N-Diethylphthalamic Acid Propyl Ester

Method B. To 10 g N,N-diethylphthalamic acid was added 10 g thionyl chloride, the mixture boiled for 3 h, and the excess thionyl chloride removed in vacuum at less than 40°C. The residue was dissolved in a mixture of 20 ml benzene and 8 g pyridine and the solution obtained was added to 4 ml propyl alcohol in 10 ml benzene at 0-5° with stirring. After 12 h, treatment was as described in method A. Yield 6.7 g (57%). Other esters of N,N-diethylphthalamic and N,N-dimethylphthalamic acid could be obtained similarly.

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