STUDIES IN THE FIELD OF PYRETHRINS AND RELATED COMPOUNDS.

XVII.* THE SYNTHESIS OF ESTERS OF DL-cis, trans-CHRYSANTHEMIC ACID AND N-HYDROXYMETHYL-3,4,5,6-TETRAHYDROPHTHALIMIDE AND N-HYDROXYMETHYPHTHALIMIDE

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The most effective insecticides for the control of harmful insects, which are carriers of infectious diseases, are the pyrethrins (and their synthetic analogues) which are the active principles of the camomiles Chrysanthemum cinerariaefolium Vis. (Dalmatian camomile) and Ch. coccineum Wildd. (Caucasus camomile). The latter compounds, as also certain pyrethrin constituents, are themselves esters of chrysanthemic monocarboxylic acid. Allethrin (allylretronyl dl-cis, trans-chrysanthemate), barthrin (6-chloropiperonyl dl-cis, trans-chrysanthemate), and dimethrin (2,4-dimethyl-benzyl dl-cis, trans-chrysanthemate) have found practical use. However, the overwhelming majority of the synthetic pyrethroids reported up to the present time, among them those enumerated above, yield to pyrethrin in insecticide activity and are comparable with the latter in price. As a consequence of this they are not able to compete with the natural insecticide.

Recently a new type of pyrethrin analog has been described by Japanese investigators [2], represented by the general formula (I):

\[
\begin{align*}
\text{R} & \equiv \text{CH}_3 \equiv \text{COOCH}_3 \\
\text{R} & \equiv \text{CH}_5 \\
\text{R} & \equiv \text{CH}_5
\end{align*}
\]

These substances possess powerful insecticide activity, the most interesting of them being N-(3,4,5,6-tetrahydrophthalimido) methyl dl-cis, trans-chrysanthemate (V), named neopinamine [3]. This substance is more effective than the natural pyrethrins on many species of insects [3-6].

The synthesis of chrysanthemate (V) was effected by us according to the following scheme. 1,2,3,6-Tetrahydrophthalic anhydride (II) was obtained by a Diels-Alder reaction between butadiene and maleic anhydride [7]. It was isomerized into 3,4,5,6-tetrahydrophthalic anhydride (III) at 200°C in the presence of phosphoric anhydride [8]. This was converted into the imide (IV) by reaction with ammonia, N-hydroxymethylation of which led to N-hydroxymethyl-3,4,5,6-tetrahydrophthalimide (VI). On interaction of alcohol (VII with a mixture of the acid chlorides of dl-cis and dl-trans-chrysanthemic acids (~ 1:1 ratio of geometrical isomers) [9], neopinamine (V) was obtained.

* Communication XVI see [1].

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The phthalimide derivative (VIII) was also obtained by N-hydroxymethylation of phthalimide by method [10] to N-hydroxymethylphthalimide (VII) and subsequent interaction with the acid chlorides of dl-cis, trans-chrysanthemic monocarboxylic acid.

\[\text{O} \quad \text{N-CH}_{2}-\text{O} \quad \text{N-CH}_{2}-\text{O} \quad \text{N-CH}_{2}-\text{O} \quad \text{N-CH}_{2}-\text{O}\]

In contrast to the pyrethroids known previously, (V) and (VIII) are crystalline substances; they possess a weak characteristic odor, are readily soluble in the usual organic solvents, among them hydrocarbons and freons (which is necessary for their use as aerosols), but these substances are practically insoluble in water.

The study of the insecticide properties of both compounds, in the form of aerosols, on house flies showed that neopinamine is 1.7 times more active and N-phthalimido-methyl dl-cis, trans-chrysanthemate is 0.86 times as active as natural pyrethrin.

**EXPERIMENTAL**

3,4,5,6-Tetrahydrophthalic Anhydride (III). To 37.1 g molten 1,2,3,6-tetrahydrophthalic anhydride [7] at 200° was added 0.56 g P2O5, the melt stirred at this temperature for 48 h and distilled in vacuum. Anhydride (III) (24.9 g; 81%) of bp 144-151° (4-5 mm), mp 69-70° was obtained. According to literature data [11] mp 72°.

3,4,5,6-Tetrahydrophthalimide (IV). To 56 ml 25% aqueous ammonia solution at 55-60° added 24.9 g anhydride (III) in several portions, after which the mixture was heated and kept at 110-115° for 2 h and then at 155-160° for 1½ h. The substance obtained was carefully powdered and washed in a funnel with 40 ml benzene. Imide (IV) (21.8 g : 88.5%) of mp 170°-170.5° was obtained. According to literature data [11], mp 172°.

N-Hydroxymethyl-3,4,5,6-tetrahydrophthalimide (IV). A mixture of 21.8 g imide (IV), 20.5 ml 40% formalin solution and 50 ml water was boiled for 4 h while slowly distilling. The residue was cooled, extracted with chloroform, the extract washed with NaHSO3 solution, then with NaCO3 solution, with water, and dried over MgSO4. After distilling off the solvent, the oil was rubbed with petroleum ether. Substance (VI) (19.4 g; 89%) of mp 78-80.5° (from toluene) was obtained. Found, %: N, 7.73; 7.74. C19H21NO4. Calculated, %: N, 7.73.

N-(3,4,5,6-Tetrahydrophthalimido)methyl dl-cis, trans-chrysanthemate (neopinamine) (V). To a stirred mixture of 19.4 g alcohol (VI), 1.1 g dry pyridine and 35 ml absolute benzene at 20° was added gradually a solution of 21.5 g dl-cis, trans-chrysanthemic monocarboxylic acid chloride in 60 ml benzene. The mixture was maintained at the same temperature for 12 h, poured into water, the benzene layer separated, and the aqueous layer twice extracted with benzene. The combined benzene solution was washed with 3% HCl solution, with saturated sodium hydrogen carbonate solution and with water, and dried over MgSO4. The solvent was distilled off, the residual oil rubbed with petroleum ether and placed in the refrigerator for 12 h, after which the crystals which had separated were filtered off. Chrysanthemate (V) (31.9 g; 89%) of mp 69-89° was obtained.

On analysis of the synthetic substance by the method of Sell [12], which was developed for the analysis of natural pyrethrins, it was found that it comprised 98% ester of chrysanthemic monocarboxylic acid.

N-Phthalimidomethyl dl-cis, trans-Chrysanthemate (VIII). To a solution of 4.74 g N-hydroxymethylphthalimide [10], 6.5 ml dry pyridine, and 50 ml absolute benzene was added gradually 5 g dl-cis, trans-chrysanthemic monocarboxylic acid chloride in 10 ml benzene. The mixture was stirred at 20° for 2 h, stood overnight and the reaction mixture subsequently treated as described above. Chrysanthemate (VIII) (8.3 g; 79%) of mp 82-103° was obtained. Found, %: N, 4.08, 4.17. C19H21NO4. Calculated, %: N, 4.25.

**LITERATURE CITED**