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BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE]

# CONSTITUENTS OF PYRETHRUM FLOWERS. XX. THE PARTIAL SYNTHESIS OF PYRETHRINS AND CINERINS AND THEIR RELATIVE TOXICITIES

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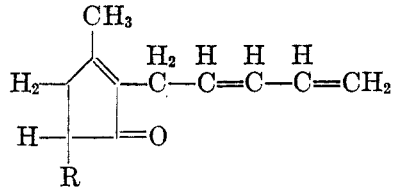
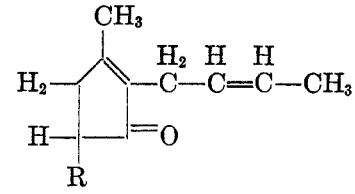
In the four preceding articles (1) it has been demonstrated that the methylcyclopentenolone esters of chrysanthemum monocarboxylic acid, previously designated as "pyrethrin I" and of monomethyl chrysanthemum dicarboxylic acid, designated as "pyrethrin II", consist not of homogeneous compounds but of mixtures of two constituents which differ from each other with respect to the nature of the side chain in the alcoholic-ketonic components.

These four constituents have now been designated as pyrethrins I and II (formula A) and cinerins I and II (formula B). Since the usual analytical

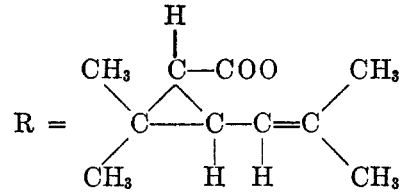


A

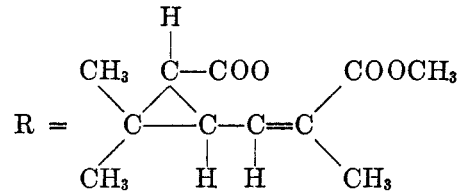


B

For pyrethrin I and cinerin I



For pyrethrin II and cinerin II



methods are based on the determination of the respective acids, the results refer to the content of the mixture of pyrethrin I with cinerin I and that of pyrethrin II with cinerin II in the sample. The proportions of the constituents in these mixtures may vary with different conditions of culture or breed of plant or, since the pyrethrins are less stable than the cinerins and may be lost by polymerization

or oxidation, their proportions may be changed during the process of extraction or on subsequent treatment. As a consequence of the demonstration of the heterogeneous nature of the chrysanthemum acid esters and the establishment of the structure of their respective constituents, the importance of establishing their relative toxicities is from several standpoints at once evident.

If there should be a marked difference in insecticidal properties between the pyrethrins and the cinerins, the plant breeder should aim to increase the content of the more effective one. Discrepancies between analytical and biological results might sometimes be due to the relative proportions of pyrethrins and cinerins present. Also with a view to an eventual synthesis, it is apparent that in case the cinerins are equal to or approach the pyrethrins in value they will be less difficult to prepare. It is also of interest to attempt to determine the toxicological effects produced by various structural modifications. By pursuing this line of research, it would be possible to determine which features of this class of compounds are essential to insect toxicity and which are nonessential.

For these studies it was decided to compare the insecticidal properties of the pure pyrethrins and cinerins prepared by esterification of chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid monomethyl ester with pyrethrolone formula A and cinerolone formula B (R = OH). Since both the optically active and the racemic forms of these compounds were available, it could be established whether or not optical activity in the alcoholic component is essential or important.

The effect of the reduction of points of unsaturation in the acid and in the alcoholic component could be determined by comparison of the two types of hydrogenated pyrethrins and cinerins.

The esterifications were carried out by the reaction of the hydroxy ketones and the chrysanthemum acid chlorides in benzene solution in the presence of pyridine. The acids employed were the natural dextro forms obtained by saponification of the mixture of semicarbazones of the "pyrethrins" and isolated by familiar procedures (2).

A method for obtaining chrysanthemum dicarboxylic acid monomethyl ester previously recommended (3), which is based on the cleavage of a pyrethrin II concentrate by hydrogenation, was found to result in the dihydro compound, contrary to the statement of Staudinger and Ruzicka that the double bond in the natural acid is stable to hydrogenation (2a). The dihydro acid obtained by this method served for the preparation of isodihydropyrethrin II and isodihydrocinerin II. Dihydrochrysanthemum monocarboxylic acid was obtained by hydrogenation of the natural chrysanthemum monocarboxylic acid. Hence, the prefix "isodihydro" in the names of all the isodihydropyrethrins and isodihydrocinerins indicates that the acid component is saturated. Natural pyrethrolone and cinerolone are dextrorotatory, as are also chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid monomethyl ester, but the pyrethrins and cinerins obtained by synthesis from these are all levorotatory.[1] When the

[1] In previous articles (1b, 1c), $[\alpha]_D$ of the semicarbazones of acetylpyrethrolone and acetylcinerolone were reported as +50° and +49°, respectively. The signs should read minus instead of plus.

prefix "active" or "racemic" is employed it refers to the optical characteristic of the alcoholic component. Active pyrethrin I and active cinerin I furnished crystalline semicarbazones in moderately good yields. The semicarbazones of the corresponding inactive compounds did not crystallize and no crystalline derivative was obtained from pyrethrin II or cinerin II.

TABLE I

ANALYTICAL AND PHYSICAL DATA FOR PYRETHRINS AND CINERINS

| COMPOUND | CALC'D | | FOUND | | METHOXYL | | REFRACTIVE INDEX $n^{25}_D$ | SPECIFIC ROTATION |
|---|---|---|---|---|---|---|---|---|
| | C | H | C | H | Calc'd | Found | | |
| Cinerin I, active | 75.94 | 8.86 | 75.35 | 8.45 | | | 1.5119 | $[\alpha]^{25}_D$ −27.4 |
| | | | 76.05 | 8.63 | | | | |
| | | | 75.42 | 8.75 | | | | |
| Cinerin I, racemic | | | 75.56 | 8.65 | | | 1.5110 | $[\alpha]^{27}_D$ −14.26 |
| Pyrethrin I, active | 76.83 | 8.53 | 75.83 | 8.47 | | | | $[\alpha]^{25}_D$ −26.3 |
| | | | 76.07 | 8.56 | | | | |
| Pyrethrin I, racemic | | | | | | | | $[\alpha]^{25}_D$ −14.66 |
| Cinerin II, active | 70.00 | 7.78 | 69.90 | 8.09 | 8.61 | 8.35 | 1.5175 | |
| Cinerin II, racemic | | | 69.83 | 7.76 | | 8.30 | 1.5181 | |
| Pyrethrin II, active | 70.97 | 7.53 | 69.72 | 7.59 | 8.33 | 8.82 | | |
| Pyrethrin II, racemic | | | 71.67 | 7.54 | | 8.13 | | |
| Isodihydrocinerin I, active | 75.47 | 9.43 | 75.45 | 9.14 | | | 1.4983 | |
| Isodihydropyrethrin I, active | 76.36 | 9.09 | 76.00 | 9.10 | | | 1.5081 | |
| Tetrahydropyrethrin I, active | 75.90 | 9.63 | 75.19 | 9.27 | | | 1.4917 | |
| Isodihydrocinerin II, active | 69.61 | 8.29 | 68.69 | 8.11 | 8.56 | 8.44 | 1.4958 | $[\alpha]^{28}_D$ −21.2 |
| | | | 68.72 | 8.20 | | | | |
| Isodihydropyrethrin II, active | 70.58 | 8.02 | 70.65 | 7.37 | 8.27 | 8.62 | 1.5110 | $[\alpha]^{28}_D$ −21.1 |
| | | | 69.78 | 7.62 | | 8.32 | | |
| | | | 68.25 | 7.85 | | | | |
| | | | 68.84 | 7.94 | | | | |
| Isodihydropyrethrin II, racemic | | | | | | 8.43 | | $[\alpha]^{28}_D$ −10.5 |
| Dihydrochrysanthemum dicarboxylic acid monomethyl ester | 61.68 | 8.41 | 61.99 | 8.20 | 14.5 | 13.95 | | |
| | | | 60.92 | 7.92 | | 13.40 | | |
| | | | | | | 13.80 | | |
| Pyrethrin I semicarbazone active | 68.57 | 8.05 | 67.46 | 7.75 | | | | |
| | | | 67.78 | 8.10 | | | | |

## EXPERIMENTAL

The following examples will illustrate the procedure employed for obtaining the synthetic pyrethrins and cinerins.

*Active pyrethrin I.* One and seven-tenths grams of pyrethrolone ($n^{25}_D$ 1.5433, $[\alpha]^{20}_D$ +11.7°) and 1.5 ml. of dry pyridine in 15 ml. of dry benzene were added to 2 g. of chrysanthemum monocarboxylic acid chloride in 15 ml. of benzene. The hydrochloride of pyridine separated in a short time, and the reaction mixture was allowed to stand for about 24 hours at room temperature. The crystalline material was filtered off, and the solution was extracted

with water and sodium bicarbonate solution. After removal of the solvent in vacuum, the residue was transferred to a small distilling flask with acetone, and the solvent was removed by evaporation. The distillation flask consisted of a specially constructed bulb with an inclined delivery tube of large diameter located about 1 cm. above the bulb leading to a receiving bulb connected to the vacuum line. The boiling bulb was provided with a very fine capillary, and the distillation was carried out under a vacuum of about 0.1 mm. and a bath temperature of about 170°. The time of heating was in all cases very short.

The semicarbazone was prepared in pyridine-alcohol solution. After recrystallization from ether it melted at 75–80°.

*Active cinerin I.* One and seven-tenths grams of active cinerolone ($n_D^{25}$ 1.5198 $[\alpha]_D^{25}$ +9.9°) in 15 ml. of benzene and 1.5 ml. of dry pyridine were added to 1.7 g. of chrysanthemum monocarboxylic acid chloride in 15 ml. of benzene. The reaction proceeded with separation of crystalline pyridine hydrochloride, and the product was treated in the same manner as described above.

The semicarbazone was prepared, and after recrystallization from ether melted at 67–70°.

*Active pyrethrin II and cinerin II.* The same conditions were observed as for pyrethrin I and cinerin I with substitution of methyl chrysanthemum dicarboxylic acid chloride (1.1 moles) for the monocarboxylic acid chloride. For the distillation of the ester a higher temperature was required and the oil-bath was heated to 200°. By the same procedure the following compounds were also prepared: Racemic pyrethrin I, racemic cinerin I, racemic pyrethrin II, racemic cinerin II, active isodihydropyrethrin I, active isodihydrocinerin I, active isodihydropyrethrin II, active isodihydrocinerin II, racemic isodihydropyrethrin II, active tetrahydropyrethrin I.

RELATIVE TOXICITIES OF PYRETHRINS AND CINERINS AND THEIR HYDROGENATED DERIVATIVES

Fourteen compounds were therefore made available for biological tests. The analytical data and physical constants for these compounds are presented in Table I.

The biological tests against houseflies, which were carried out by Gersdorff (4), gave results which may be briefly summarized as follows: Pyrethrin I is 1.5 times as toxic as cinerin I. Pyrethrin II is 1.3 times as toxic as cinerin II. Pyrethrin I is 4.0 times as toxic as pyrethrin II. Cinerin I is 4.0 times as toxic as cinerin II. Pyrethrin I is 2.0 times as toxic as isodihydropyrethrin I. Cinerin I is 2.0 times as toxic as isodihydrocinerin I. Isodihydropyrethrin I is about 1.75 times as toxic as isodihydrocinerin I. Tetrahydropyrethrin I is less than 0.03 times as toxic as pyrethrin I. The toxicity in all cases was independent of the presence of optical activity in the alcoholic ketone components, *i.e.*, whether the compound had been prepared from dextro or racemic pyrethrolone or cinerolone.

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