THE CHRYSANTHEMUMCARBOXYLIC ACIDS.

III.—Lactonization of the Chrysanthemic Acids *

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(±)-*cis*-Chrysanthemic acid is readily lactonized in boiling dilute sulphuric acid to the crystalline (±)-*cis*-dihydrochrysanthemo-δ-lactone. The lactone ring is opened by alkali hydrolysis and a derivative of the (±)-*cis*-δ-hydroxydihydrochrysanthemic acid is obtained. With methanolic sulphuric acid the lactone ring is opened to give mainly methyl (±)-*cis*-δ-methoxydihydrochrysanthemate together with methyl (±)-*cis*-chrysanthemate.

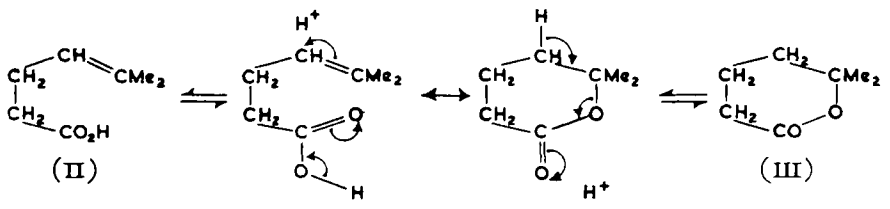
In contrast, (±)-*trans*-chrysanthemic acid is converted under similar conditions into the crystalline (±)-*trans*-δ-hydroxydihydrochrysanthemic acid.

The mechanisms of these reactions and their bearing on the Seil and the Wilcoxon–Holaday methods of pyrethrum assay are discussed.

On heating at 300° c. in sealed tubes (±)-*cis*- and (±)-*trans*-chrysanthemic acids and (±)-*cis*-dihydrochrysanthemo-δ-lactone are converted into an isomeric crystalline lactone, (±)-pyrocin. This is shown by oxidative degradation not to be a dihydrochrysanthemo-lactone but to be (±)-β-*iso*butenyl*iso*hexano-γ-lactone. These lactones are substantially non-toxic to houseflies.

Since (±)-*trans*-chrysanthemic acid, now readily available, together with (±)-*cis*-chrysanthemic acid, by the addition of ethyl diazoacetate to 2 : 5-dimethylhexa-2 : 4-diene (Campbell & Harper, 1945; Harper, Reed & Thompson, 1951), provides a model for the behaviour of natural chrysanthemum-monocarboxylic acid [(+)-*trans*-chrysanthemic acid], an investigation of the reactions of both (±)-*trans*- and (±)-*cis*-chrysanthemic acids has been undertaken. We now report an examination of the hydration and lactonization of these acids. These reactions have a bearing on the Seil and on the Wilcoxon–Holaday methods currently used for the assay of the pyrethrins and the consequences of this have already been pointed out by one of us (Harper, 1949, 1951).

The chrysanthemic acids (I) can be regarded as substituted Δ^{γ}-*iso*heptenoic acids, and it is relevant that it was for Δ^{γ}-*iso*heptenoic acid (II) that Linstead & Rydon (1933) demonstrated the existence of lacto-enoic tautomerism, involving the facile formation of the δ-lactone (III) in the presence of sulphuric acid or on heating alone at 216° c. The terminal methyl groups induce polarization of the double bond through inductive and hyperconjugative displacements as shown. We consider that this facilitates addition of a proton (as hydroxonium ion in aqueous media) to the γ-carbon atom and concomitant addition to the δ-carbon atom of the polarized carbonyl oxygen (as the un-ionized carboxyl group for ionization will be suppressed in the presence of sulphuric acid). Transfer of charge then occurs within the transition complex, followed by elimination of the carboxyl hydrogen as a proton (as hydroxonium ion in aqueous media) to form the lactone. We no longer consider that a free carbonium ion is formed but that the concomitant attack of the carbonyl oxygen gives a transition complex capable of mesomerism. This lowers the energy of the transition state, thereby making lactonization easier. In aqueous media too the energy requirement will be further reduced by solvation of both the attacking and departing protons. We consider it likely that the lactonization of olefinic acids in general proceeds by a mechanism of this type, exemplified for the case given above by the following scheme:



(II) (III)

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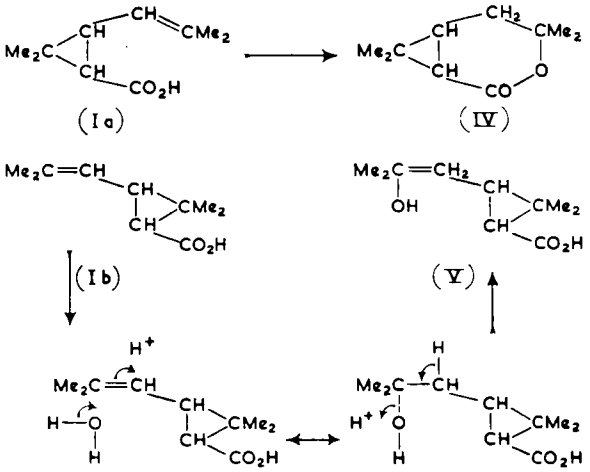
Whereas the carbon chain of Δ^{γ}-*iso*heptenoic acid is free to rotate into the most favourable position for lactonization (as shown), in the case of the chrysanthemic acids the incorporation of the α and β carbon atoms into a *cyclo*propane ring very considerably limits rotation of the carbon chain. Examination of molecular models of the chrysanthemic acids suggests that in the *cis*-acid (I*a*) the carboxyl and *iso*butenyl groups can approach each other closely enough to make the ready formation of *cis*-dihydrochrysanthemo-δ-lactone (IV) probable (purely geometrical considerations also permit of γ-lactone formation); whereas in the *trans*-acid (I*b*) these groups are so far apart as to make lactonization much less probable if not impossible (*trans*-dihydrochrysanthemo-γ- or -δ-lactones would have highly strained structures). It is relevant that neither *trans*-caronic acid nor *trans*-homocaronic acid form *trans*-anhydrides. Even if lactonization of *trans*-chrysanthemic acid (I*b*) is not possible, addition of a proton would still occur followed by attack by the carboxyl group of another molecule of acid to give eventually a polymeric ester-acid, alternatively, and more probably attack by the solvent (water) would occur to give *trans*-δ-hydroxydihydrochrysanthemic acid (V). This would proceed through the transfer of charge within the transition complex, as depicted, followed by elimination of the proton. Such hydrations will be subject to the same considerations as are discussed above for lactonization.

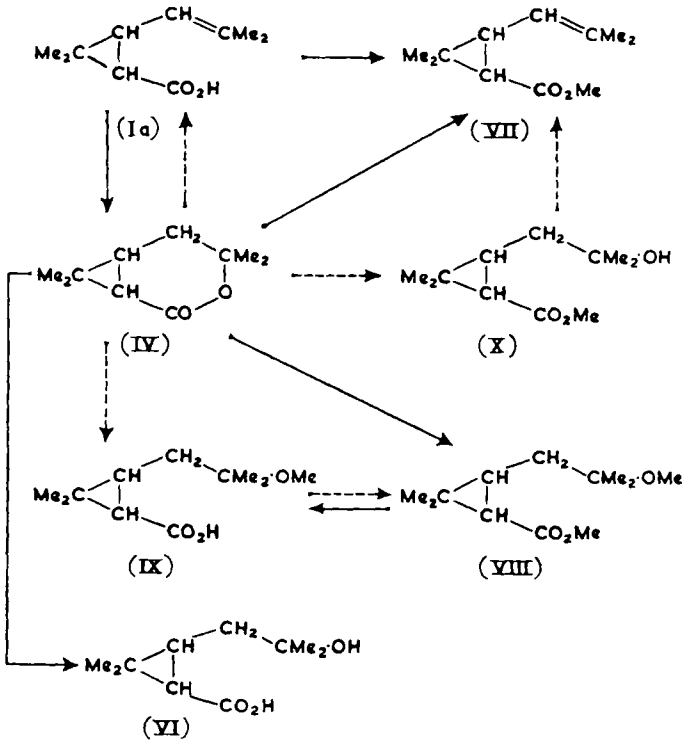


Boiling (±)-*cis*-chrysanthemic acid with 2N-sulphuric acid for 3 hours sufficed to effect a 60% conversion of the acid into an isomeric neutral substance, readily obtained as a superbly crystalline solid (m.p. 52–53° C.), which from the preceding argument should be (±)-*cis*-dihydrochrysanthemo-δ-lactone (IV). The alkali-soluble fraction yielded only unchanged (±)-*cis*-chrysanthemic acid, which together with the neutral product accounted for 95% of the starting acid in the form of isolated crystalline products. The neutral product was slowly hydrolysed by boiling 0·35N-ethanolic potassium hydroxide, being 92% complete in 2 hours. The product of hydrolysis, considered to be the salt of (±)-*cis*-δ-hydroxydihydrochrysanthemic acid (VI), yielded a crystalline *p*-bromophenacyl ester. This ester analysed correctly as the derivative of a hydroxydihydrochrysanthemic acid, thereby establishing the lactonic character of the neutral product.

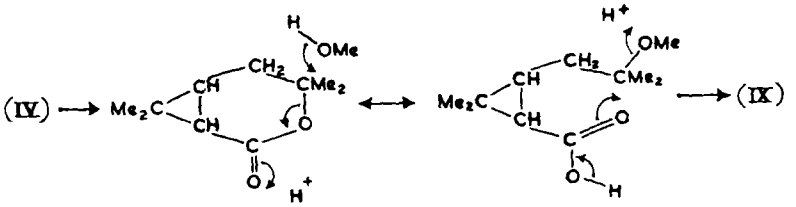
The lactone was saturated, for it did not decolorize bromine in carbon tetrachloride and was not reduced by hydrogen over Adams catalyst in glacial acetic acid. Hence the lactone is dicyclic, and monocyclic structures resulting from hydrolytic fission of the *cyclo*propane ring are excluded. Consistent with this conclusion the mildest condition for hydrolytic fission of the *cyclo*propane ring of caronic acid (to give the lactonic acid, terebic acid) is much more drastic—5% hydrochloric acid at 200° C.—than is required for the lactonization of *cis*-chrysanthemic acid. With Denigès reagent the lactone gave a positive test for a tertiary alcohol, presumably through prior hydrolytic fission to the hydroxy-acid. In the light of this evidence the lactone is clearly (±)-*cis*-dihydrochrysanthemo-δ-lactone (IV), in agreement with the course of lactonization predicted above.

(±)-*cis*-Dihydrochrysanthemo-δ-lactone was converted by boiling 1% methanolic sulphuric acid into a mixture of methyl esters through methanolytic fission of the lactone ring. Fractional distillation yielded, after a small forerun whose methoxyl content corresponded to that of methyl (±)-*cis*-chrysanthemate (VII), a methyl ester containing two methoxyl groups and giving, on analysis, figures corresponding to the empirical formula $C_{12}H_{22}O_3$, i.e. methyl chrysanthemate plus the elements of methanol, evidently methyl (±)-*cis*-δ-methoxydihydrochrysanthemate (VIII). Harper & Reed (1951) have observed the similar formation of a methyl methoxy-ester on direct esterification of (±)-*cis*-chrysanthemic acid with methanolic sulphuric acid. This ester was hydrolysed to a crystalline methoxydihydrochrysanthemic acid, which was further characterized by conversion into its *p*-phenylphenacyl ester. Hydrolysis of our methyl methoxy-ester yielded the same methoxydihydrochrysanthemic acid, evidently (±)-*cis*-δ-methoxydihydrochrysanthemic acid (IX), and *p*-phenylphenacyl ester, though not quite pure, being probably contaminated with (±)-*cis*-chrysanthemic acid.

Fission of a lactone ring by an alcohol to give an alkoxy-ester is rare, the product being generally the hydroxy-ester formed by ester-interchange. We are aware of only one other comparable fission of a lactone : that of the formation of ethyl γ-ethoxybutyrate from γ-butyrolactone with ethanol under pressure in the presence of sulphuric acid (Krzikalla & Dornheim, 1943). However, esters of *tert.*-butanol (e.g. the acetate and benzoate) react with methanol, in the absence of added acid, though by a mechanism that is probably acid-catalysed, to give *tert.*-butyl methyl ether, the carboxylic acid and its methyl ester, but no *tert.*-butanol (Cohen & Schneider, 1941). These alcoholyses clearly proceed by a mechanism involving alkyl–oxygen fission, the occurrence of which is facilitated by the electron-releasing properties of the *tert.*-butyl group, instead of by the more usual acyl–oxygen fission which would result in ester-interchange. As we have seen, the *gem*-dimethyl group of (±)-*cis*-dihydrochrysanthemo-δ-lactone exerts a powerful electron-releasing effect and we suggest that the methanolysis of (±)-*cis*-dihydrochrysanthemo-δ-lactone (IV) proceeds almost exclusively by alkyl–oxygen fission to give the methoxy-acid (IX), subsequently esterified to the methoxy-ester (VIII).



We consider that the alkyl–oxygen fission proceeds through a transition complex, exemplified for this methanolysis by the following scheme :



Alkyl–oxygen fission may also occur in the base-catalysed hydrolysis of (±)-*cis*-dihydrochrysanthemo-δ-lactone, which, qualitatively, was slower than we would have expected for the hydrolysis of a δ-lactone by the more usual acyl–oxygen fission mechanism.

The trace of methyl (±)-*cis*-chrysanthemate (VII) also formed in the methanolysis of (±)-*cis*-dihydrochrysanthemo-δ-lactone (IV) could result from acyl–oxygen fission to give the hydroxy-ester (X), subsequently dehydrating to (VII), or from a reversal of the lactonization mechanism to give the acid (I*a*), then directly esterified to (VII).

We have also examined the behaviour of (±)-*trans*-chrysanthemic acid under conditions similar to those in which the *cis*-acid is lactonized, to find out which of the several reactions envisaged above takes place. After refluxing with 2N-sulphuric acid for 3 hours, unreacted acid and possible neutral products were removed by extraction with light petroleum. A 50% recovery of crystalline (±)-*trans*-chrysanthemic acid was obtained from this light petroleum solution by extraction with sodium carbonate and subsequent acidification. Evaporation of the extracted light petroleum solution left no appreciable residue, showing that no lactone had been formed. Continuous ether extraction of the original aqueous layer then gave, after concentration in a vacuum, a viscous liquid, which during the course of several weeks crystallized. The water-solubility of this product, obtained in 50% yield, and its glycerol-like behaviour before crystallization, pointed to its being a hydroxydihydrochrysanthemic acid rather than a polymeric ester-acid. This supposition was confirmed by the equivalent weight. With Denigès reagent, even at room temperature, this hydroxy-acid gave a positive test for a tertiary alcohol. Hydration of (±)-*trans*-chrysanthemic acid has therefore taken place with the formation of (±)-*trans*-δ-hydroxydihydrochrysanthemic acid (V) in agreement with the course of hydration envisaged above. Further description of the properties of this acid is reserved until a forthcoming communication on the hydration of the chrysanthemic acids.

In a study of the Seil method for the assay of the pyrethrins, Mitchell, Tresadern & Wood (1948) obtained only 40% recovery of (+)-*trans*-chrysanthemic acid after refluxing in 1% sulphuric acid for 75 minutes. From analogy with the behaviour of citronellal in the presence of acids they suggested that the loss of chrysanthemum-monocarboxylic acid was due ' to formation of a hydroxy-acid or a lactone or both.' Our work excludes formation of lactone from *trans*-chrysanthemic acid under the conditions of the Seil assay and demonstrates that the loss of the acid is due to hydration to the non-steam-volatile *trans*-δ-hydroxydihydrochrysanthemic acid.

The rapid sequence of colour changes observed on treating (±)-*trans*-δ-hydroxydihydrochrysanthemic acid with Denigès reagent is the same as that observed much more slowly in the stage of the Wilcoxon–Holaday method for the assay of the pyrethrins when the chrysanthemum-monocarboxylic acid is oxidized by Denigès reagent. We suggest that here, too, the initial reaction is one of hydration to *trans*-δ-hydroxydihydrochrysanthemic acid.

After much of the work described above had been completed we became aware of work done in Japan during and after World War II that was relevant to our investigation. Nagase (quoted by Matsui, 1950) and Nagase & Matsui (1944) obtained a laevorotatory crystalline lactone in low yield, isomeric with chrysanthemum-monocarboxylic acid, from the dry distillation of pyrethrum flowers and extract. This lactone was stated to be highly toxic to mosquitoes and to be responsible, in part at least, for the insecticidal effects of pyrethrum smoke. Subsequently Matsui (1950) prepared the same lactone—pyrocin—in 50% yield by heating chrysanthemum-monocarboxylic acid in a sealed tube at 400° C. Pyrocin was stated, though without supporting experimental details, to give *trans*-caronic acid and acetone on oxidation with potassium permanganate. On this evidence, together with a comparison of pyrocin with several synthetic lactones considered to be of comparable structure, Matsui concluded that pyrocin was (−)-*cis*-dihydrochrysanthemo-δ-lactone (IV). Furthermore, by similar heating of a mixture of (±)-*cis*- and (±)-*trans*-chrysanthemic acids he obtained (±)-pyrocin, m.p. 59–60° C., i.e. (±)-*cis*-dihydrochrysanthemo-δ-lactone, if Matsui's argument is correct. The discrepancy

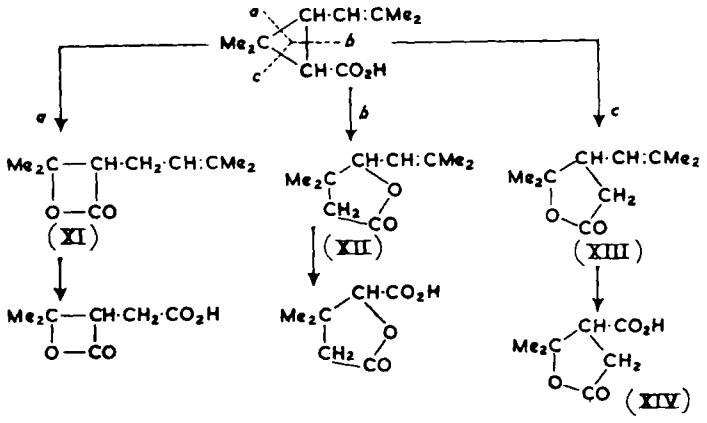
of melting point between (±)-pyrocin and our (±)-*cis*-dihydrochrysanthemo-δ-lactone, obtained by acid isomerization, appeared too large for them to be identical. In view of this uncertainty and the unsatisfactory character of Matsui's evidence for the structure of pyrocin, we have repeated relevant parts of his work and re-examined the properties of (±)-pyrocin.

In agreement with Matsui's observations [though using pure (±)-*trans*-chrysanthemic acid instead of a mixture with the (±)-*cis*-acid] heating of the acid at 400° C. in an evacuated sealed tube for 30 minutes caused little or no development of pressure and distillation of the neutral product, followed by crystallization from light petroleum, readily gave (±)-pyrocin, m.p. 59–60° C. In contrast, when heating pure (±)-*cis*-chrysanthemic acid to 400° C. our tubes invariably burst. We compromised by heating at 300° C. for 3 hours, for at 250° C. only a trace of lactone was formed. Even at 300° C. a high pressure developed, evidently due to carbon dioxide formed by concurrent decarboxylation. This surmise was confirmed by the isolation, on distillation of the lactone, of an unsaturated hydrocarbon forerun. The lactone, after crystallization, proved to be (±)-pyrocin, but was obtained in slightly lower yield than from (±)-*trans*-chrysanthemic acid.

It was immediately evident that (±)-pyrocin and (±)-*cis*-dihydrochrysanthemo-δ-lactone were not identical; the melting point discrepancy was real, the (±)-pyrocin was the much more soluble of the two in light petroleum, and on admixture a well marked depression of melting point was observed. In further contrast with (±)-*cis*-dihydrochrysanthemo-δ-lactone, (±)-pyrocin was recovered unchanged on attempted methanolysis in .1% methanolic sulphuric acid, but was hydrolysed to completion within 1 hour by 0·35N-ethanolic potassium hydroxide; we were unable to obtain a *p*-bromophenacyl ester from the hydrolysate. With Denigès reagent, too, (±)-pyrocin contrasted sharply with (±)-*cis*-dihydrochrysanthemo-δ-lactone in giving an immediate copious colourless crystalline precipitate and in the solution remaining colourless. We also found that (±)-*cis*-dihydrochrysanthemo-δ-lactone was converted into (±)-pyrocin by heating under similar conditions to those in which (±)-*cis*- and (±)-*trans*-chrysanthemic acid are isomerized into (±)-pyrocin.

With the exclusion of the *cis*-dihydrochrysanthemo-δ-lactone structure for pyrocin, we considered, but rejected for reasons that will be evident, the more immediate alternatives, *trans*-δ-, *cis*-γ-, and *trans*-γ-dihydrochrysanthemolactones, as being inconsistent with the behaviour of (±)-pyrocin. Further examination of (±)-pyrocin then revealed that it slowly absorbed bromine and the presence of an ethylenic link was confirmed by an uptake of about 1 mol. hydrogen on reduction over Adams catalyst in glacial acetic acid. That this uptake might be due to hydrogenolysis of the *cyclo*propane ring was excluded by the non-reduction of (±)-*cis*-dihydrochrysanthemo-δ-lactone under similar conditions. The presence of one double bond requires pyrocin to be monocyclic, clearly indicating that a profound structural rearrangement of the chrysanthemic acids occurs with fission of the *cyclo*propane ring.

In view of the known propensity for the *cyclo*propane ring in analogous compounds to undergo hydrolytic fission in the presence of acids at high temperatures, it seemed likely that the formation of pyrocin from the chrysanthemic acids was due to direct fission of the *cyclo*propane ring through intramolecular attack by the carboxyl group. Formally this could occur in three ways:



Fission of (I) at *a* requires the unlikely formation of the β-lactone (XI), which would probably not survive the conditions of its formation but would lose carbon dioxide to give a diene hydrocarbon. Fission of (I) at *b* leading to (XII) involves attack at both asymmetric centres with the necessary racemization of one and the likely racemization of the other under the conditions of formation of pyrocin. The retention of optical activity when (±)-*trans*-chrysanthemic acid is converted into (−)-pyrocin makes this course of events improbable, as it does fission of (I) at *a* and thermal rupture of the *cyclo*propane ring to an open-chain diene-carboxylic acid which subsequently lactonizes. Although the fission of (I) at *c* to form (XIII) results in the racemization of one of the asymmetric centres the other is once removed from the reacting groups and might be expected to retain its activity during lactonization. Furthermore, the formation of (XIII) involves the theoretically more probable attack at the *gem*-dimethyl carbon atom with consequent formation of a *tert.*-γ-lactone.

Confirmation of the likely structure (XIII) for pyrocin was obtained by ozonization of (±)-pyrocin. This gave a 31% yield of acetone isolated as its 2 : 4-dinitrophenylhydrazone, together with a 33% yield of crystalline acid, whose identity as terebic acid (XIV) was established by mixed melting point with an authentic specimen. The isolation of terebic acid from this oxidation excludes structures (XI) and (XII) and unequivocally shows pyrocin to be β-*iso*butenyl*iso*hexano-γ-lactone (XIII).

In the light of this elucidation of the structure of pyrocin a number of structures put forward by Matsui (1950) are suspect. The formation of acetone on oxidation of (−)-pyrocin with potassium permanganate now receives an explanation, but not that of *trans*-caronic acid. It is possible that the latter was, in fact, the as yet unknown optically active form of terebic acid. Examination of molecular models of the chrysanthemic acids, having regard to the formation of pyrocin, suggests that in the *cis*-acid, in contrast with the *trans*-acid, the proximity of the *iso*butenyl group to the carboxyl group hinders the approach of the carboxyl group to the potential γ-carbon atom and hence that decarboxylation might preferentially occur—as, in fact, was observed.

In view of the Japanese statements of the high toxicity of (−)-pyrocin to mosquitoes and of (−)- and (±)-pyrocin to houseflies (Matsui, 1950), and before we realized that pyrocin was not a dihydrochrysanthemolactone, it appeared desirable to test (±)-*cis*-dihydrochrysanthemo-δ-lactone as well as (±)-pyrocin for insecticidal action. Over a concentration range of 0·05–0·4% (w/v) in odourless distillate, Dr. E. A. Parkin and Mr. A. A. Green found, using the Pest Infestation Laboratory procedure (Parkin & Green, 1944), that neither lactone gave more than 25% knock-down and 8% kill when tested against houseflies. A pyrethrin standard tested for comparison behaved normally in giving complete knock-down and 40–45% kill at 0·1% concentration. (±)-*cis*- and (±)-*trans*-Chrysanthemic acids, dissolved in odourless distillate containing 15% (v/v) *cyclo*hexanone, were similarly compared against the pyrethrin standard. Whereas the highest kill was only 16·9%, the acids showed moderate knock-down effect at 0·4% (45 and 48% respectively, against a knock-down of 12% for the solvent alone). Hence under our conditions of testing these four substances are substantially non-toxic to houseflies. The complete inactivity of (±)-pyrocin provides no support for Matsui's claims. Furthermore, from the description, his method of testing was rudimentary in the extreme, insecticidal efficiency being judged not by kill but by the percentage flies 'falling' during 20–50 minutes after volatilizing the substance into the chamber by heat.

We consider the (−)-pyrocin present in pyrethrum smoke is an artifact formed from the small amount of free chrysanthemum-monocarboxylic acid that is generally present in pyrethrum flowers or extract; we regard the claims of its high insecticidal activity with considerable reserve.

Experimental

(±)-cis-*Dihydrochrysanthemo-δ-lactone.*—(±)-*cis*-Chrysanthemic acid (4·0 g.; Harper *et al.*, 1951) was refluxed with 5% (v/v) sulphuric acid (80 ml.) under a double-surface condenser for 3 hours. Chrysanthemic acid tended to steam-distil into the condenser and crystallize on the walls; at intervals the crystals were melted down by stopping the flow of condenser water. The product was taken up in ether, washed three times with 5% sodium hydroxide, then with water, and the ether solution was dried over magnesium sulphate. Distillation then gave (±)-cis-*dihydrochrysanthemo-δ-lactone* (2·35 g.), b.p. 136° C./16 mm., 143° C./23 mm., n_D^{20} 1·4645. After dissolving in light petroleum (b.p. 40–60° C.) and setting aside, the lactone crystallized as large bipyramids, m.p. 52–53° C. (Found: C, 71·2; H, 9·55. $C_{10}H_{16}O_2$ requires C, 71·2; H, 9·55%). Washing with aqueous sodium hydroxide was more effective in removing unlactonized acid than washing with sodium hydrogen carbonate. Free acid in admixture with the

lactone could be determined by direct titration (sharp end-point to phenolphthalein) as the lactone was only slowly hydrolysed by aqueous alkali, even at the boiling point.

In a similar preparation 8·4 g. (±)-*cis*-chrysanthemic acid gave 4·9 g. lactone (after crystallization: 4·4 g.) and 3·2 g. recovered crystalline unlactonized acid.

The lactone on boiling for 2 minutes with Denigès reagent gave a greenish-blue colour turning to green and a brown precipitate. (±)-*cis*-Chrysanthemic acid, similarly treated, gave successively cherry-red, purplish-red, blue, and finally green colours with a greenish-brown precipitate, just as the (±)-*trans*-acid did.

A solution of (±)-*cis*-chrysanthemic acid in excess sodium carbonate rapidly decolorized bromine water at 0° C. with precipitation of a neutral substance, presumed to be a bromo-lactone (cf. Harding, Haworth & Perkin, 1908). This product could not be obtained solid and was not further examined.

Hydrolysis of (±)-cis-*dihydrochrysanthemo-δ-lactone.*—The neutralized solution from the complete hydrolysis of (±)-*cis*-dihydrochrysanthemo-δ-lactone in ethanolic potassium hydroxide was evaporated to dryness. The residue was treated with a slight excess of *p*-bromophenacyl bromide in boiling aqueous ethanol during 1 hour and the solution was cooled and diluted to induce crystallization. The crude ester was discoloured and had m.p. 108–112° C.; hence it was treated with decolorizing carbon in ethanol, then percolated through a short column of activated alumina, and finally crystallized twice from ethanol to give p-*bromophenacyl* (±)-cis-*δ-hydroxydihydrochrysanthemate*, m.p. 115° C. (Found: C, 56·6; H, 6·1. $C_{18}H_{23}O_4Br$ requires C, 56·4; H, 6·05%).

Methanolysis of (±)-cis-*dihydrochrysanthemo-δ-lactone.*—(±)-*cis*-Dihydrochrysanthemo-δ-lactone (2·0 g.) was refluxed in 1% methanolic sulphuric acid (20 ml.) for 12 hours. Half the methanol was then distilled off, water was added to the residue, and the acid was neutralized with sodium hydrogen carbonate. The neutral products were extracted with ether and after drying were evaporated and fractionally distilled at 8 mm., to give the fractions: (*a*) b.p. 96–98° C. (0·21 g.), n_D^{20} 1·4556 (Found: C, 69·3; H, 10·0; OMe, 23·6%), (*b*) b.p. 98–99° C. (1·11 g.), n_D^{20} 1·4528 (Found: C, 67·9; H, 9·85; OMe, 27·8. $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3; OMe, 29·0%), (*c*) b.p. 99–100° C. (0·28 g.), n_D^{20} 1·4510. Fraction (*a*) was considered to contain about half its weight of methyl (±)-*cis*-chrysanthemate (Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 10·0; OMe, 17·0%), whereas fractions (*b*) and (*c*) were substantially *methyl* (±)-cis-*δ-methoxydihydrochrysanthemate.*

Part of fraction (*b*) (750 mg.) was hydrolysed by refluxing with 10% methanolic potassium hydroxide (5 ml.) for 5 hours. After distilling off half of the methanol, water was added to the residue and the liquid was extracted with ether to remove neutral material. On acidification of the aqueous layer an oil separated which was isolated with ether. This oil (650 mg.) crystallized completely on keeping in a vacuum desiccator and then had m.p. 61–73° C. One crystallization from a concentrated solution in ethyl acetate at 0° C. yielded somewhat impure (±)-*cis*-δ-methoxydihydrochrysanthemic acid, m.p. 84–85° C., whose melting point was raised to 85–88° C. on admixture with the pure acid (m.p. 89° C.) (cf. Harper & Reed, 1951). The *p*-phenylphenacyl ester of the acid (m.p. 84–85° C.) remained as an oil until seeded with the pure ester (cf. Harper & Reed, 1951). Two crystallizations from light petroleum (b.p. 40–60° C.) then gave material of m.p. 72–73° C., raised to 72–74° C. when mixed with pure *p*-phenylphenacyl ester of the same melting point.

In another methanolysis of (±)-*cis*-dihydrochrysanthemo-δ-lactone (500 mg.), the mixed esters were hydrolysed without isolation and the acidic product was isolated (190 mg.). This product deposited a few crystals, m.p. 80–102° C., from a solution in ethyl acetate; they were evidently impure (±)-*cis*-chrysanthemic acid. The remainder of the acid obtained by evaporation had m.p. 60–62° C. and was too soluble to permit of recrystallization. It was possibly a eutectic mixture of (±)-*cis*-chrysanthemic and (±)-*cis*-δ-methoxydihydrochrysanthemic acids.

(±)-β-iso*Butenyl*iso*hexano*-γ-*lactone* [(±)-*Pyrocin*].—(±)-*trans*-Chrysanthemic acid (2 × 1·0 g.) was heated at 300° C. for 3 hours in sealed tubes previously evacuated to 10^{-2} mm. After cooling and opening, the contents were rinsed out with ether, washed with aqueous sodium hydroxide, dried and distilled to give (±)-pyrocin (0·93 g., 46%), b.p. 116–119° C./9 mm., which solidified on cooling.

(±)-*cis*-Chrysanthemic acid (2 × 1·0 g.) similarly treated, though the tubes were opened with caution owing to the pressure of gaseous and dissolved carbon dioxide, gave (±)-pyrocin (0·70 g., 35%), b.p. 120–123° C./11 mm.

(±)-Pyrocin from either acid had m.p. 59–60° C. after crystallization from light petroleum (b.p. 40–60° C.), considerable loss occurring owing to its high solubility. A mixture with (±)-*cis*-dihydrochrysanthemo-δ-lactone melted at 30–35° C.

(±)-*cis*-Dihydrochrysanthemo-δ-lactone (0·75 g.) similarly treated, though at 275° C. for 4 hours, gave 350 mg. undistilled neutral product, which after dissolving in light petroleum (b.p. 40–60° C.) and cooling to − 20° C. deposited (±)-pyrocin (65 mg.), m.p. 57–59° C.

Mixed (±)-*cis*- and (±)-*trans*-chrysanthemic acids (5·0 g.) similarly treated, gave on distillation a forerun (0·20 g.), b.p. 38–39° C./12 mm., n_D^{20} 1·458 (Found: C, 84·8; H, 12·7%), followed by (±)-pyrocin (1·83 g., 37%), b.p. 127–129° C./10 mm., n_D^{20} 1·4708, together with 1·26 g. crude acid extracted in the sodium hydroxide. The forerun rapidly absorbed bromine from carbon tetrachloride solution and was evidently impure hydrocarbon formed by decarboxylation.

The rate of hydrolysis of (±)-pyrocin was compared with that of (±)-*cis*-dihydrochrysanthemo-δ-lactone by refluxing 84·0-mg. portions of each with 2-ml. portions of 0·35N-ethanolic potassium hydroxide, together with a blank, for various times and then back-titrating with 0·04N-hydrochloric acid to phenolphthalein (see Table I).

Table I

Time of hydrolysis, min.	0	30	60	120
(±)-Pyrocin hydrolysed, %	0	94·9	100·8	—
(±)-*cis*-Dihydrochrysanthemo-δ-lactone hydrolysed, %	0	62·3	77·8	91·9

On quantitative microhydrogenation over platinum oxide in glacial acetic acid (±)-pyrocin (15·30 mg.) absorbed 1·860 ml. hydrogen (at N.T.P.), equivalent to 0·91 mol.

Ozonization of (±)-*pyrocin.*—(±)-Pyrocin (1·0 g.) dissolved in carbon tetrachloride (25 ml.) was ozonized at 0° C., ozone approximating to the equivalent of one double bond being absorbed. The solvent was evaporated under reduced pressure and the residual ozonide was covered with water (40 ml.). Next day the solution was refluxed for 5 minutes and then distilled, three successive 5-ml. portions of distillate being collected. Treated with excess 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid these gave a large, a moderate, and a trace of precipitate respectively of acetone 2 : 4-dinitrophenylhydrazone (0·434 g., 31%), m.p. and mixed m.p. 124–125° C. On concentration of the remaining undistilled solution to 5 ml. a crystalline acid (0·310 g., 33%) separated, m.p. 174° C.; it was shown to be terebic acid by mixed m.p. (174° C.) with an authentic specimen of the same melting point, prepared by the method of Birch, Gough & Kon (1921).

Microanalyses are by Drs. Weiler & Strauss, Oxford; the semi-micro equivalents are by the authors.

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