200. *Experiments on the Synthesis of the Pyrethrins. Part III. Synthesis of Dihydrocinerin-I and Tetrahydropyrethrin-I; a Study of the Action of* N-*Bromosuccinimide on* 3-*Methyl*-2-n-*alkyl (and alkenyl)*-cyclo*pent*-2-*en*-1-*ones*.

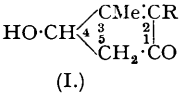
By Leslie Crombie, Michael Elliott, and Stanley H. Harper.

3-Methyl-2-*n*-alkyl*cyclo*pent-2-en-1-ones with one molecular proportion of *N*-bromosuccinimide undergo monosubstitution at the 4-position, together with some disubstitution (probably at the 4- and the 1′-position), and hence recovery of unchanged ketone. The bromoketone is converted into the acetoxyketone, which is hydrolysed to the (±)-4-hydroxy-3-methyl-2-*n*-alkyl*cyclo*pent-2-en-1-one. By this means are prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone (alkyl being butyl and amyl respectively), transformation products of cinerolone and of pyrethrolone, the alcoholic components of the natural pyrethrins. The bromoketones and silver (±)-*trans*-chrysanthemate give racemic dihydrocinerin-I and tetrahydropyrethrin-I which have very little insecticidal action.

The bromo-ketones readily eliminate hydrogen bromide, *e.g.*, with organic bases or sodium methoxide, to give *cyclo*pentadienones, characterised by high-melting derivatives but themselves probably existing only as dimers.

3-Methyl-2-*n*-alkenyl*cyclo*pent-2-en-1-ones undergo preferential side-chain substitution with *N*-bromosuccinimide, followed by elimination of hydrogen bromide and polymerisation. 3-Methyl-2-*n*-pent-4′-enyl*cyclo*pent-2-en-1-one undergoes very ready disubstitution, followed by elimination of hydrogen bromide. No monomeric product apart from unchanged ketone could be isolated and the method fails as a route to pyrethrolone or cinerolone and analogues containing alkenyl side chains.

The erroneous formulation of pyrethrolone (I*a*) as an α-ketol, with the hydroxyl group in the 5-position, was founded on its reducing properties and the isolation of a supposed *p*-nitrophenylosazone by Staudinger and Ruzicka (*Helv. Chim. Acta*, **1924**, **7**, 212). Subsequently, by analogy, cinerolone (I*b*) was also formulated as an α-ketol (LaForge and Barthel, *J. Org. Chem.*, **1945**, **10**, 114). However, LaForge and Soloway (*J. Amer. Chem. Soc.*, **1947**, **69**, 186, 2932) showed that synthetic (±)-5-hydroxy-3-methyl-2-*n*-butyl*cyclo*pent-2-en-1-one was not identical with naturally derived (±)-dihydrocinerolone and assigned the hydroxyl group to $C_{(4)}$, the only other vacant position in the ring. This structure (I*d*), with the hydroxyl group in an " allylic " position, accords well with the reactivity of the chloro-ketones obtained by the action of thionyl chloride on cinerolone, dihydrocinerolone, or tetrahydropyrethrolone, and with the ready hydrogenolysis of pyrethrolone acetate, pyrethrolone methyl ether, and the pyrethrins themselves. Further dihydrocinerolone possesses only feeble reducing power and does not yield a *p*-nitrophenylosazone, which excludes the α-ketol formulation.



(I.)

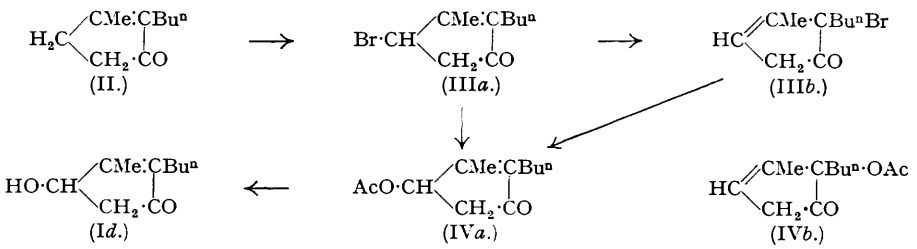
I*a*, R = $CH_2{\cdot}CH^{1'}{:}CH^{2'}{\cdot}CH{:}CH{\cdot}CH{:}CH_2$
I*b*, R = $CH_2{\cdot}CH{:}CHMe$
I*c*, R = $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Me$
I*d*, R = $CH_2{\cdot}CH_2{\cdot}CH_2Me$

Some confirmation of the correctness of the proposed structure was obtained by Soloway and LaForge (*ibid.*, p. 979) who synthesised a ketol by refluxing dihydrocinerone with *N*-bromosuccinimide in carbon tetrachloride for 18 hours and hydrolysing the crude bromo-ketone with an aqueous suspension of chalk. The semicarbazone and 3 : 5-dinitrobenzoate of this ketol were identical (mixed melting points) with those from naturally derived (±)-dihydrocinerolone. This work was reported briefly without experimental details and no amplification has yet been

published. Shortly afterwards Dauben and Wenkert (*ibid.*, p. 2075) described briefly the synthesis of the higher homologue, (±)-tetrahydropyrethrolone, by a similar route from tetrahydropyrethrone, but using only a 30-minutes reaction period and hydrolysing the bromo-ketone with an aqueous suspension of barium carbonate. They also prepared the acetoxy-ketone by reaction of the bromo-ketone with silver acetate.

This paper describes a study of the bromo-compounds obtained by the action of *N*-bromosuccinimide on dihydrocinerone, tetrahydropyrethrone, and related ketones, made in connection with the synthesis of racemic dihydrocinerin-I and tetrahydropyrethrin-I, during which we have prepared (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

We found that dihydrocinerone reacted to completion in a few minutes with *N*-bromosuccinimide in boiling carbon tetrachloride, neither benzoyl peroxide nor ultra-violet irradiation being necessary. After removal of succinimide and solvent, the undistilled bromo-ketone was refluxed with silver acetate in glacial acetic acid. Fractional distillation of the product gave the *acetoxyketone* [(±)-*dihydrocineronyl acetate*] in 60% overall yield from dihydrocinerone. Since there was also a forerun of dihydrocinerone and the recovery of succinimide had been quantitative, it was suspected that di- or poly-bromination had occurred. This suspicion was confirmed, for the highest-boiling fraction had a carbon and a hydrogen content tending towards that calculated for a diacetoxy-ketone. Further, distillation of the bromination product resolved it into unchanged dihydrocinerone, *monobromodihydrocinerone* (the main product), intermediate fractions, and a final fraction with a bromine content approaching that calculated for a dibromodihydrocinerone. Dibromination, which was not mentioned by Soloway and LaForge or by Dauben and Wenkert, is not surprising since two allylic methylene groups (the 4 and 1′) are available for free-radical substitution. Attempts to hydrolyse the acetoxy-ketone by prolonged refluxing with aqueous suspensions of barium carbonate were not successful (contrast Dauben and Wenkert above), but brief hydrolysis with methanolic potassium hydroxide gave (±)-dihydrocinerolone which was characterised as its semicarbazone and 3 : 5-dinitrobenzoate. The overall yield from ketone to ketol was 44%.



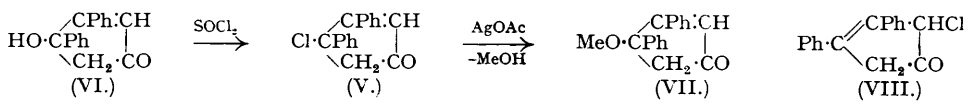
Similarly, tetrahydropyrethrone reacted rapidly and smoothly with one molecular proportion of *N*-bromosuccinimide, and the undistilled bromo-ketone gave, as above, tetrahydropyrethronyl acetate and (±)-tetrahydropyrethrolone, which was similarly characterised. This product did not react with lead tetra-acetate in acetic acid in the presence of water and is not therefore an α-ketol (cf. Baer and West, *J.*, 1949, 93). We also found that tetrahydropyrethrone reacted smoothly and completely with two molecular proportions of *N*-bromosuccinimide, without evolution of hydrogen bromide, and the dibromo-ketone so obtained reacted with yet another molecular proportion of *N*-bromosuccinimide in the presence of a trace of benzoyl peroxide.

Comparison of the physical properties and derivatives of our synthetic hydroxy-ketones with those of the corresponding naturally derived compounds shows satisfactory concordance (see *Nature*, 1948, **162**, 222) and in conjunction with the mixed melting points determined by Soloway and LaForge (*loc. cit.*) leaves no doubt as to the identity of our products with naturally derived (±)-dihydrocinerolone and (±)-tetrahydropyrethrolone.

In the communications of Soloway and LaForge (*loc. cit.*) and of Dauben and Wenkert (*loc. cit.*) no conclusive evidence or reasoned argument was given to support the assumption that bromination occurs in the 4-position of the ring and that the resultant ketols are 4-hydroxy-3-methyl-2-alkyl*cyclo*pent-2-en-1-ones. We have shown that substitution can occur in more than one position. Apart from the 4-methylene group, as pointed out above, the 1′-methylene group should be prone to substitution by free-radical reagents, while substitution at the 3-methyl group and at the 5-methylene group is conceivable though less likely. Strong evidence against the hydroxy-group derived from bromination with one molecular proportion of *N*-bromosuccinimide being elsewhere than at $C_{(4)}$ has been adduced (Harper, *Ann. Reports*, 1948, **45**, 162). The

4-hydroxy-structure of (±)-dihydrocinerolone has since been directly proved by synthesis : the cyclisation of (±)-3-hydroxy-*n*-decane-2 : 5-dione gives a product identical with the naturally derived material and with the ketol prepared by the *N*-bromosuccinimide route (mixed melting points of the 3 : 5-dinitrobenzoates) (Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 3165; Crombie, Edgar, Harper, and Lowe, forthcoming publication). Although this establishes that bromination occurs initially at the 4-methylene group, it does not follow that the following stages necessarily take the direct course (II ⟶ III*a* ⟶ IV*a* ⟶ I*d*) : there is a known tendency for the products of *N*-bromosuccinimide substitution to undergo allylic rearrangements (III*a* ⟶ III*b*), and for anionotropic rearrangement to occur (III*a* ⟶ IV*b*, or III*b* ⟶ IV*a*) on subsequent conversion into the acetoxy-ketones. That the acetoxy-ketone has the structure (IV*a*) is shown by its identity with naturally derived (±)-dihydrocineronyl acetate, prepared by catalytic reduction of (±)-cineronyl acetate which has been proved spectroscopically to contain an αβ-unsaturated carbonyl group (West, *J.*, 1946, 463). It is also known that in the alkaline hydrolysis of such esters, through acyl–oxygen fission, no rearrangement occurs. Any scheme involving (IV*b*) is therefore excluded.

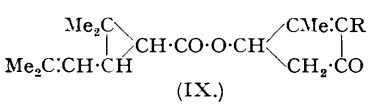
The evidence excluding the participation of (III*b*) is less conclusive. LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) converted (±)-dihydrocinerolone by thionyl chloride into a chloro-ketone, and dehalogenation of this with zinc in ethanol gave the unrearranged ketone, dihydrocinerone (II). If this is the reverse of the direct hydrolysis of the bromo-ketone to (±)-dihydrocinerolone (Soloway and LaForge, *loc. cit.*), then participation of (III*b*) is unlikely. No closely analogous system has been investigated in detail. Burton and Shoppee (*J.*, 1934, 201; cf. Allen and Spanagel, *J. Amer. Chem. Soc.*, 1932, **54**, 4338; Burton, Shoppee, and Wilson, *J.*, 1932, 720) carried out the reactions (VI ⟶ V ⟶ VII) and did not detect any tendency for reaction as the rearranged form (VIII), although conversion into the acetate was not investigated. Roberts, Young, and Winstein (*J. Amer. Chem. Soc.*, 1942, **64**, 2157) found that 1- and



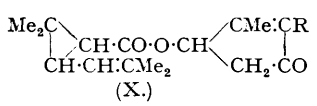
(VI.) (V.) (VII.) (VIII.)

3-methylallyl chlorides were converted by silver acetate in acetic acid, mainly by a S_N1 mechanism, into similar mixtures of acetates in which the primary acetate predominated. Subsequently Young and Andrews (*ibid.*, 1944, **66**, 421) found that on the alkaline hydrolysis in aqueous ethanol the primary chloride reacted mainly by a S_N2 mechanism to give predominantly the primary alcohol, whereas the secondary chloride reacted mainly by a S_N1 mechanism to give a mixed product. We consider that bromodihydrocinerone is predominantly (III*a*); this is consistent with the exclusive formation of (I*d*) on direct hydrolysis and with the deep-red colour of the 2 : 4-dinitrophenylhydrazone formed by bromotetrahydropyrethrone, indicative of αβ-unsaturation to the carbonyl group. Nevertheless the mechanism of the reaction with acetate ion, and presumably other carboxylate ions, is such that some (III*b*) could be present without detriment to the purity of the product.

Our main objective, the synthesis of racemic *dihydrocinerin*-I and *tetrahydropyrethrin*-I, was effected by refluxing bromodihydrocinerone and bromotetrahydropyrethrone respectively with silver (±)-*trans*-chrysanthemate (Campbell and Harper, *J.*, 1945, 283) in carbon tetra-



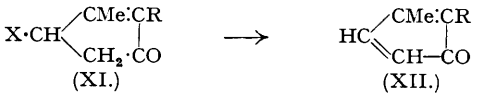
(IX.)



(X.)

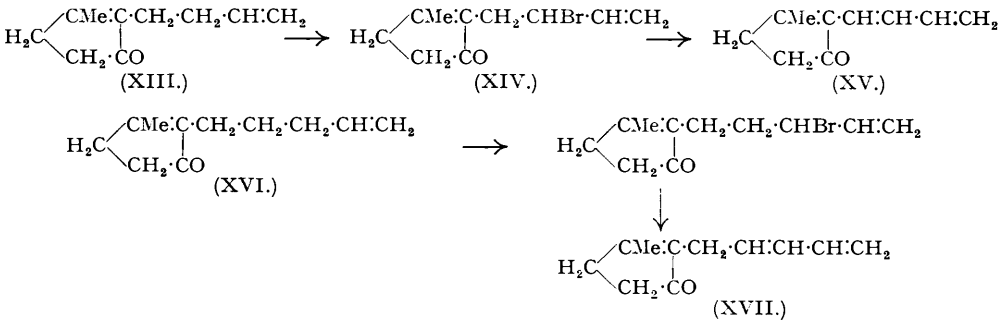
		% Knock-down, 10 minutes' exposure.	% Kill, 24 hours.
(±)-*n*-Butylrethronyl (±)-*trans*-chrysanthemate (racemic dihydrocinerin-I)	(IX; R = Bu^n)	25	3·6
(±)-*n*-Butylrethronyl (±)-*cis*-chrysanthemate	(X; R = Bu^n)	15	3·8
(±)-*n*-Amylrethronyl (±)-*trans*-chrysanthemate (racemic tetrahydropyrethrin-I)	(IX; R = C_5H_{11}-*n*)	0	0·9
(±)-*n*-Amylrethronyl (±)-*cis*-chrysanthemate	(X; R = C_5H_{11}-*n*)	0	2·9
Official Test Insecticide	—	100 (in 3 mins.)	56·0 (mean of 3)
Odourless distillate alone	—	0	2·0
Unsprayed control	—	—	0·6 (mean of 6)

chloride. In a similar manner esters from (±)-*cis*-chrysanthemic acid (Campbell and Harper, *loc. cit.*) were prepared (see Table) (for an exposition of the nomenclature for these esters, see Harper, *Chem. and Ind.*, 1949, 636). These esters at a concentration of 0·5% w/v in refined kerosene (" odourless distillate " used as a spray base) have been tested for insecticidal activity against house-flies by Dr. E. A. Parkin and Mr. A. A. Green of the Insecticides Section, Pest Infestation Laboratory, with the results summarised in the Table. The values are those of a single spraying, using a 10-minutes' exposure in the spray chamber, by the standardised procedure of the Pest Infestation Laboratory (Parkin and Green, *Nature*, 1944, **154**, 16) and comparison is made with the Official Test Insecticide containing 0·1% w/v natural pyrethrins. Although the esters derived from dihydrocinerolone show slight knock-down, all give negligible kill. Such results are in accord with the low toxicity observed by Haller and Sullivan (*J. Econ. Entomol.*, 1938, **31**, 276) for hydrogenated natural pyrethrin-I, by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 448) and by Gersdorff (*J. Econ. Entomol.*, 1947, **40**, 878) for (+)-*n*-amylrethronyl (+)-*trans*-chrysanthemate resynthesised from naturally derived acid and hydrogenated alcohol The double bonds in the side chains of the natural pyrethrins are therefore of great importance for insecticidal activity.



(XI.) (XII.)

Structures of the type of (XI) would be expected to eliminate HX with ease to give compounds which are formulated tentatively as *cyclo*pentadienones (XII) or their dimers. Thus Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 226) record that pyrethronyl acetate eliminates acetic acid on pyrolysis, and on distillation the pyrethrins themselves give a lower-boiling fraction. When the synthetic esters described above were distilled, a forerun of chrysanthemic acid was obtained and characterised as its *p*-phenylphenacyl ester. This was not due to the presence of free acid in the crude product since the silver salt would not have hydrolysed under the conditions of the reaction and prolonged heating of the silver salt in a vacuum gave no volatile product. Treatment of bromodihydrocinerone with anhydrous trimethylamine in benzene and warming the quaternary salt thus formed with an aqueous suspension of magnesium oxide eliminated 90% of the bromine as trimethylammonium bromide. The resulting *cyclo*pentadienone (XII; R = Bu^n) would be expected to exist in a dimeric form but yield monomeric derivatives. A *semicarbazone* (m. p. 227°) and a deep-red 2 : 4-*dinitrophenylhydrazone* were isolated in good yield and gave analytical values consitent with their being derivatives of 3-methyl-2-*n*-butyl*cyclo*penta-2 : 4-dien-1-one. Similarly bromotetrahydropyrethrone with methanolic sodium methoxide gave no methyl ether but 83% of the bromine was eliminated as hydrogen bromide to give a product yielding a *semicarbazone* (m. p. 219°), presumably of



(XIII.) (XIV.) (XV.)

(XVI.) (XVII.)

3-methyl-2-*n*-amyl*cyclo*penta-2 : 4-dien-1-one. This semicarbazone is probably identical with that (m. p. 220°) which Staudinger and Ruzicka (*loc. cit.*) obtained from tetrahydropyrethrolone semicarbazone and regarded as being derived through heterocyclisation by elimination of water from the α-hydroxy-group.

Less success attended attempts to monobrominate, in the 4-position, *cyclo*pentenones related more closely to cinerone and pyrethrone in that they contained alkenyl side-chains. 3-Methyl-2-*n*-but-3′-enyl*cyclo*pent-2-en-1-one (XIII) reacted smoothly with one molecular proportion of *N*-bromosuccinimide, but after 15 minutes evolution of hydrogen bromide commenced. The sole product isolated by distillation was unchanged ketone (~15%) together with

a non-volatile polymeric residue. Evidently preferential substitution occurs at the 2′-methylene group adjacent to the side-chain double bond, together with some disubstitution, possibly at the 4-position. Elimination of hydrogen bromide from (XIV) would lead to a cross-conjugated trienone (XV) which might be expected to polymerise. Attention was then directed to 3-methyl-2-*n*-pent-4′-enyl*cyclo*pent-2-en-1-one (XVI) (the preparation of this ketone will be described in a forthcoming communication), for in this case preferential side-chain substitution at the 3′-position followed by elimination of hydrogen bromide could lead to pyrethrone (XVII) and thence, with substitution at the 4-position, possibly to pyrethrolone (I*a*) itself. After reaction with one molecular proportion of *N*-bromosuccinimide (again hydrogen bromide was evolved), only unchanged ketone (48%) could be isolated: no monosubstitution occurred, but all the ketone that reacted underwent dibromination. On the assumption that any bromopyrethrone present might polymerise on distillation, the undistilled bromo-ketone was treated with silver acetate in glacial acetic acid and the product converted into the semicarbazone; again only the derivative of the starting ketone was obtained, with no indication of the presence of pyrethronyl acetate semicarbazone. The side-chain double bond was blocked by the addition of bromine and the product treated with *N*-bromosuccinimide, but reagents used to eliminate vicinal bromine atoms also attacked the labile bromine at position 4. The *N*-bromosuccinimide route is therefore incapable of extension to the preparation of ketols containing alkenyl side chains.

Experimental.

Microanalyses, other than bromine determinations, were carried out by Drs. Weiler and Strauss, Oxford.

Reaction of Dihydrocinerone with N-Bromosuccinimide.—Dihydrocinerone (3·19 g.) (regenerated from the semicarbazone; b. p. 113°/15 mm., n_D^{25} 1·4802; cf. Harper, *J.*, 1946, 892) and *N*-bromosuccinimide (3·75 g., 1·0 mol.) were heated to boiling in carbon tetrachloride (10 ml.). Reaction commenced, as shown by a marked increase in the rate of reflux and succinimide floating to the surface, within 5 to 10 minutes and was completed by a further 15—30-minutes' refluxing. In other experiments neither the addition of catalytic quantities of benzoyl peroxide nor the use of freshly recrystallised *N*-bromosuccinimide caused any significant variation. The suspension was cooled to 0° and the succinimide collected (2·09 g., 99·5%). The carbon tetrachloride was removed from the filtrate by distillation through a short column at atmospheric pressure and the residue kept over paraffin wax in a vacuum desiccator, to give the crude bromo-ketone (5·52 g., 98%), n_D^{20} 1·5177. In another experiment the crude bromo-ketone (4·08 g.) was distilled at *ca.* 5×10^{-3} mm. through a plain column (220 × 6 mm.), both the flask and column being immersed in an oil-bath, to give the fractions: (i) b. p. 42—46° (0·21 g.); (ii) b. p. 47—56°, n_D^{25} 1·5132 (0·78 g.); (iii) b. p. 56—63°, n_D^{25} 1·5193 (1·69 g.) (Found: Br, 33·9. $C_{10}H_{15}OBr$ requires Br, 34·6%); (iv) b. p. 63—70° (0·62 g.); and (v) b. p. 85—88° (0·44 g.) (Found: Br, 45·4. $C_{10}H_{14}OBr_2$ requires Br, 51·5%). Fraction (i) consisted of unchanged ketone and the recovery of this together with the quantitative recovery of succinimide is consistent with the presence of dibromodihydrocinerone in (v). The spread of b. p. of fractions (ii)—(iv) of the *monobromodihydrocinerone* was caused, in part at least, by fluctuation of pressure but does not entirely exclude heterogeneity of the product.

Hydrolysis of Bromodihydrocinerone.—In early experiments, carried out in 1946, direct hydrolysis of the undistilled bromo-ketone was attempted by refluxing it with aqueous potassium carbonate. This procedure yielded a bromine-free product, boiling in the correct range for dihydrocinerolone, which it was attempted to characterise as semicarbazone. However, only small quantities of impure derivative were obtained which could not be satisfactorily purified. Later experience showed that even when pure ketol is used the semicarbazone is formed and isolated with difficulty and only in low yield. It is likely therefore that (±)-dihydrocinerolone was actually obtained in these experiments.

The undistilled bromo-ketone (4·50 g.) and powdered silver acetate (7·5 g.) were refluxed in glacial acetic acid (25 ml.) for 4 hours. Next day the silver bromide was filtered off (3·08 g., after being washed with dilute nitric acid, equiv. to only 83·5% reaction) and the acetic acid removed by distillation through a short column under slightly reduced pressure. Distillation of the residue yielded, after a small forerun, *acetoxydihydrocinerone* [(±)-*dihydrocineronyl acetate*] (2·47 g., 60%), b. p. 100—103° (mainly 101°)/0·75 mm., n_D^{20} 1·4772 (Found: C, 68·2; H, 9·2. $C_{12}H_{18}O_3$ requires C, 68·2; H, 8·6%). The semicarbazone, prepared in the cold, had m. p. 148° not clearing until 163°, but could not be satisfactorily purified. The red 2 : 4-dinitrophenylhydrazone when prepared in cold alcoholic hydrochloric acid and crystallised from methanol had m p. 125—126°, but when prepared in boiling alcoholic hydrochloric acid and crystallised from ethanol or Cellosolve (methyl ether) had m. p. 136—137°. In another experiment, with 2·60 g. of undistilled bromo-ketone, the product was fractionally distilled at 0·3 mm. to give the fractions: (i) b. p. 63—69°, n_D^{20} 1·4810 (80 mg.) (Found: C, 75·9; H, 10·5. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%); (ii) b. p. 87—88°, n_D^{20} 1·4770 (760 mg.) (Found: C, 68·6; H, 8·9. $C_{12}H_{18}O_3$ requires C, 68·2; H, 8·6%); (iii) b. p. 89—92°, n_D^{20} 1·4775 (180 mg.) (Found: C, 68·2; H, 8·5%); (iv) b. p. 95°, n_D^{20} 1·4778 (310 mg.); and (v) b. p. 129—131° (210 mg.) (Found: C, 65·4; H, 8·2. $C_{14}H_{20}O_5$ requires C, 62·6; H, 7·5%). Fraction (i) contained unchanged ketone which it was shown above is present in undistilled bromo-ketone. Fractions (ii)—(iv) consisted of the *monoacetoxy-ketone*, there being no indication of heterogeneity. Fraction (v) contained *diacetoxydihydrocinerone* derived from the small proportion of dibromoketone formed in the initial substitution.

Acetoxydihydrocinerone (1·63 g.) was hydrolysed by being refluxed with excess of 0·5N-methanolic potassium hydroxide and following the course of the reaction by back-titration at 20-minute intervals.

After 60 minutes hydrolysis was 95% complete and the methanol was removed through a column. Ether-extraction of the oily suspension, drying, and distillation yielded, after a small forerun, (±)-dihydrocinerolone (0·95 g., 73%), b. p. 114—117°/0·8 mm., n_D^{20} 1·4942; Soloway and LaForge (*J. Amer. Chem. Soc.*, 1947, **69**, 979) record b. p. 110—114°/0·3 mm., n_D^{25} 1·4955, for their synthetic ketol; LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 222) record b. p. 115—117°/1 mm., n_D^{22} 1·4958, for "natural" material. The 3 : 5-dinitrobenzoate, triturated with light petroleum and crystallised twice from ethanol, had m. p. 110—110·5° (Found: C, 56·3; H, 5·0. Calc. for $C_{17}H_{18}O_3N_2$: C, 55·5; H, 4·9%); Soloway and LaForge (*loc. cit.*) record m. p. 111° for their synthetic derivative and m. p. 111° for the "natural" ester. The semicarbazone had m. p. 184—185°; Soloway and LaForge (*loc. cit.*) record m. p. 187° for their synthetic derivative; LaForge and Barthel (*loc. cit.*) record m. p. 185°; and West (*J.*, 1946. 463) records 184—185° for the naturally derived (±)-semicarbazone.

Reaction of Tetrahydropyrethrone with N-Bromosuccinimide.—Tetrahydropyrethrone (4·47 g.) (regenerated from the semicarbazone; b. p. 82·5°/0·7 mm., n_D^{25} 1·4764) was brominated, by the above procedure, to give the crude bromo-ketone (6·6 g.) (2 : 4-dinitrophenylhydrazone, deep-red needles, m. p. 128—130°, from methanol).

Hydrolysis of Bromotetrahydropyrethrone.—The undistilled bromo-ketone (6·6 g.) was likewise treated with silver acetate (12·0 g.) in boiling glacial acetic acid (25 ml.), and the product fractionally distilled at 3 mm. to give the fractions: (i) b. p. 116·5—124°, n_D^{25} 1·4731 (0·24 g.); (ii) b. p. 124—129°, n_D^{25} 1·4755, (0·22 g.); (iii) b. p. 129—135°, n_D^{25} 1·4764 (0·33 g.); (iv) b. p. 135—140°, n_D^{25} 1·4750 (1·00 g.); (v) b. p. 140—144°, n_D^{25} 1·4745 (1·67 g.); (vi) b. p. 144—148°, n_D^{25} 1·4750 (0·86 g.); and (vii) b. p. 148—168°, n_D^{25} 1·4770 (0·38 g.). Fractions (iv)—(vi) were bulked and redistilled to give acetoxytetrahydropyrethrone [(±)-tetrahydropyrethronyl acetate] (3·01 g., 50% overall yield from tetrahydropyrethrone), b. p. 144—146°/3 mm., n_D^{25} 1·4747 (Found: C, 69·6; H, 9·5. Calc. for $C_{13}H_{20}O_3$: C, 69·6; H, 9·0%). Dauben and Wenkert (*J. Amer. Chem. Soc.*, 1947, **69**, 2075) record b. p. 120—123°/1 mm., n_D^{26} 1·4755, for their synthetic product; West (*J.*, 1945, 412) records b. p. 117°/1·3 mm., n_D^{20} 1·4761, for naturally derived (+)-acetate.

In another experiment, in an attempt to eliminate some of the manipulation, tetrahydropyrethrone (1·72 g.) was brominated with *N*-bromosuccinimide (1·85 g.) in carbon tetrachloride (15 ml.) and the separated succinimide filtered off. Silver acetate (1·0 g.) was added to the filtrate, and the suspension shaken at room temperature for 48 hours. After filtration and removal of the solvent the residue was fractionally distilled at 0·4 mm. to give the fractions: (i) b. p. 78—80°, n_D^{20} 1·4804 (120 mg.) (Found: C, 75·7; H, 10·0. Calc. for $C_{11}H_{18}O$: C, 79·4; H, 10·9%); (ii) b. p. 91—103°, n_D^{20} 1·4808 (150 mg.); (iii) b. p. 103°, n_D^{20} 1·4796 (260 mg.) (Found: C, 68·6; H, 9·0. Calc. for $C_{13}H_{20}O_3$: C, 69·6; H, 9·0%); (iv) b. p. 104°, n_D^{20} 1·4797 (130 mg.); and (v) b. p. 105°, n_D^{20} 1·4804 (140 mg.) (Found: C, 68·7; H, 9·15%). Fractions (i)—(ii) evidently contained unreacted tetrahydropyrethrone; fractions (iii)—(v) were pure acetoxytetrahydropyrethrone.

Although the acetoxy-ketone gave a deep-red 2 : 4-dinitrophenylhydrazone this could not be satisfactorily purified. The semicarbazone, which separated as an oil and only slowly solidified, had m. p. 132—132·5°, but there was insufficient for purification; Dauben and Wenkert (*loc. cit.*) record m. p. 85—86° for the semicarbazone, but this seems far too low, particularly as the naturally derived (+)-semicarbazone has m. p. 140—141° (West, *loc. cit.*).

In an attempt to hydrolyse acetoxytetrahydropyrethrone, the ester was recovered unchanged after 24 hours' refluxing with an aqueous-alcoholic suspension of barium carbonate. However, hydrolysis was achieved by refluxing the acetoxy-ketone (0·63 g.) with a slight excess of 0·5N-methanolic potasssium hydroxide for 1 hour. Extraction and distillation gave, after a small forerun, (±)-tetrahydropyrethrolone (0·25 g., 49%), b. p. 125—127°/0·4 mm., n_D^{25} 1·4882 (Found: C, 72·1; H, 9·9. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 10·0%); Dauben and Wenkert (*loc. cit.*) record b. p. 118—120°/0·3 mm., n_D^{25} 1·4921 for their synthetic ketol; West (*loc. cit.*) records b. p. 126—127°/0·8 mm., n_D^{20} 1·4932, for naturally derived (+)-ketol; LaForge and Barthel (*J Org. Chem.*, 1945, **10**, 114) record n_D^{25} 1·4900 and for (±)-tetrahydropyrethrolone, n_D^{28} 1·4892. The 3 : 5-dinitrobenzoate crystallised as needles with m. p. 105—106°; Dauben and Wenkert (*loc. cit.*) record m. p. 105—105·5° for the synthetic ester. The semicarbazone, crystallised from ethyl acetate, had m. p. 169°; Dauben and Wenkert (*loc. cit.*) record m. p. 170·2—170·6° for the synthetic semicarbazone; LaForge and Barthel (*loc. cit.*) record m. p. 172—173° and West (*J.*, 1946, 463) records m. p. 172—174° for the "natural" (±)-semicarbazone.

Preparation of Pyrethrins.—The (±)-*trans*-chrysanthemic acid used was prepared by Mr. H. W. B. Reed following the procedure of Campbell and Harper (*J.*, 1945, 283). When freshly prepared it had m. p. 54·0—54·5°, but when kept developed an unpleasant odour and softened before melting. This is characteristic of the *trans*-acid, whereas the (±)-*cis*-acid remains unchanged over a period of years. The (±)-*trans*-acid (2·02 g.) in alcohol was neutralised with approx. 0·1N-potassium hydroxide (phenolphthalein) and then rendered faintly acid with dilute nitric acid, a slight excess of aqueous ammonia added, and the solution boiled until neutral. The silver salt was precipitated with a slight excess of approx. 0·1N-silver nitrate, washed, and dried at 100° to a grey powder (3·02 g., 92%).

Silver (±)-*trans*-chrysanthemate (2·83 g., 1·1 mols.) was added to the filtered solution of bromodihydrocinerone in carbon tetrachloride (25 ml.), freshly prepared from dihydrocinerone (1·45 g.). The reaction mixture was kept at room temperature overnight, then refluxed for 30 minutes, filtered, and evaporated, and the residue was distiled at 10^{-3} mm. in a small flask with a short distillation path. The following fractions were obtained: (i) b. p. 65—72° (660 mg.); (ii) b. p. 105—121° (880 mg.); and (iii) b. p. 121—130° (580 mg.). Fraction (iii) was yellow because of decomposition towards the end of the distillation. Redistillation of fractions (ii) and (iii), after a small forerun, yielded (±)-n-*butylrethronyl* (±)-trans-*chrysanthemate* (*dihydrocinerin*-I), b. p. 114—115°/1 × 10^{-3} mm., n_D^{20} 1·4992 (890 mg., 29% overall) (Found: C, 74·75; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%). An attempt to characterise this keto-ester as a 4-phenylsemicarbazone failed. When fraction (i) was cooled to −80°, crystallisation started. The solid had m. p. 42—52° (Found: C, 71·1; H, 9·4. Calc. for $C_{10}H_{16}O_2$ C, 71·4; H, 9·6%). Its identity as (±)-*trans*-chrysanthemic acid was confirmed by preparation of the *p*-phenylphenacyl ester, m. p. 113·5—115°, not depressed on admixture with an authentic specimen (Campbell and Harper, *loc. cit.*). Although silver (±)-*trans*-chrysanthemate became black and formed a mirror when heated to

240° at 10^{-3} mm., no distillation occurred. It is evident that the acid obtained above was formed by pyrolysis of the ester.

Tetrahydropyrethrin-I was prepared similarly by bromination of tetrahydropyrethrone (1·0 g.) and reaction with silver (±)-*trans*-chrysanthemate (1·90 g.). Fractional distillation of the crude product at 10^{-2} mm. gave (i) b. p. 86—87° (440 mg.) (Found: C, 71·0; H, 9·55. Calc. for $C_{10}H_{16}O_2$: C, 71·4: H, 9·6%), and (ii) b. p. 110—150° (770 mg.). Fraction (i) crystallised and was evidently (±)-*trans*-chrysanthemic acid. Redistillation of fraction (ii) with elimination of a small forerun (50 mg.), yielded (±)-n-*amylrethronyl* (±)-trans-*chrysanthemate* (*tetrahydropyrethrin-I*), b. p. 96°/7 × 10^{-4} mm., n_D^{20} 1·4970 (410 mg., 21% overall) (Found: C, 74·2; H, 9·6. $C_{21}H_{33}O_3$ requires C, 75·9; H, 9·7%). The keto-ester gave a brick-red 2 : 4-dinitrophenylhydrazone crystallising after many recrystallisations from ethanol, as prisms, m. p. 167°.

(±)-*cis*-Chrysanthemic acid (1·02 g.) was dissolved in a slight excess of 2·5N-sodium hydroxide, and rendered slightly acid with dilute nitric acid and then just alkaline with ammonia. The silver salt was precipitated by a slight excess of approx. 0·1N-silver nitrate, washed, and dried at 100° (1·41 g., 87%).

By a similar procedure dihydrocinerone (700 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·18 g.). The product boiled mainly at 133—144°/3 × 10^{-3} mm., and crystals of (±)-*cis*-chrysanthemic acid separated on storage. A light-petroleum solution was therefore washed with sodium hydrogen carbonate, and the residual ester re-distilled, to give (±)-n-*butylrethronyl* (±)-cis-*chrysanthemate*, b. p. 117—119°/3 × 10^{-4} mm., n_D^{20} 1·5000 (560 mg., 38% overall) (Found: C, 74·1, 74·2; H, 9·6, 9·5. $C_{20}H_{30}O_3$ requires C, 75·5; H, 9·5%).

Tetrahydropyrethrone (740 mg.) was brominated and then treated with silver (±)-*cis*-chrysanthemate (1·28 g.). Distillation at 10^{-2} mm. gave fractions: (i) b. p. 63—95° (40 mg.), and (ii) b. p. 120—153° (900 mg.). Both fractions deposited crystals when kept, which after being rinsed with light petroleum had m. p. 109—113°, not depressed on admixture with authentic (±)-*cis*-chrysanthemic acid. The light-petroleum solution was washed with sodium hydrogen carbonate, dried, evaporated, and distilled, to give (±)-n-*amylrethronyl* (±)-cis-*chrysanthemate*, b. p. 120—124°/2 × 10^{-3} mm., n_D^{20} 1·4980 (640 mg., 43% overall) (Found: C, 74·9; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·5%).

Immediately after distillation portions of these esters were sealed under nitrogen for analysis and for insecticidal assay. Portions kept for nearly 2 years show no signs of deterioration.

Elimination of Hydrogen Bromide from Bromodihydrocinerone.—Anhydrous trimethylamine vapour was passed into a solution of the bromo-ketone (850 mg.; b. p. 56°/6 × 10^{-4} mm., n_D^{25} 1·5178) in dry thiophen-free benzene (10 ml.). There was an immediate precipitate of white crystals. The suspension was kept for 12 hours, and then more trimethylamine vapour was passed in to complete the reaction. Benzene was removed in a vacuum at 40°, a suspension of magnesium oxide (400 mg.) in a little water was added, and the suspension boiled for 30 minutes. The organic material was extracted with ether, and the extract divided into two portions after being dried. One portion of the ethereal extract was evaporated and the residue converted into the 2 : 4-*dinitrophenylhydrazone* in boiling alcoholic hydrochloric acid. It separated in two forms from Cellosolve (methyl ether)—a dark red form crystallising almost at once and an orange modification which separated only on long storage of the mother-liquor. Both formed dark red blades, m. p. 236°, from alcohol–nitrobenzene (Found: C, 58·75; H, 5·4; N, 16·6. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 16·95%). The other portion of the extract yielded, after 5 minutes' refluxing with semicarbazide hydrochloride in pyridine–ethanol solution, a semicarbazone, m. p. 227° (decomp.) (from Cellosolve) (Found: C, 63·1; H, 8·0. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3%). Attempts to characterise the 3-methyl-2-*n*-butyl*cyclo*penta-2 : 4-dien-1-one as its dimer were unsuccessful.

Elimination of Hydrogen Bromide from Bromotetrahydropyrethrone.—Undistilled bromo-ketone (500 mg.) was added to a cold solution of sodium (47 mg., 1 g.-atom) in methanol (5 ml.) and kept for 12 hours at room temperature. The orange solution was acidified and extracted with ether. The ethereal extract was evaporated and the residue converted into the *semicarbazone*, which formed micro-crystalline needles (from Cellosolve), m. p. 219° (Found: C, 65·0; H, 8·95; N, 18·1. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·65; N, 19·0%), and was evidently the derivative of 3-methyl-2-*n*-amyl*cyclo*penta-2 : 4-dien-1-one and not the methyl ether semicarbazone ($C_{13}H_{23}ON_3$ requires C, 61·6; H, 9·15; N, 16·5%)

Undistilled bromo-ketone (from 197 mg. of tetrahydropyrethrone) was refluxed with zinc dust (160 mg.) in ethanol (2 ml.) for 45 minutes. Addition of water and extraction with ether yielded a viscous product which was converted into the semicarbazone. This derivative separated quickly and after recrystallisation from Cellosolve had m. p. 221—223° not depressed on admixture with the above semicarbazone, m. p. 219°. Evidently elimination of hydrogen bromide occurred instead of reductive replacement of bromine to give tetrahydropyrethrone (semicarbazone, m. p. 177°), although LaForge and Haller (*J. Org. Chem.*, 1936, **1**, 38) were able to reduce chlorotetrahydropyrethrone to tetrahydropyrethrone by this method.

The bromo-ketone liberated iodine from potassium iodide in boiling ethanol.

Reaction of 3-*Methyl*-2-n-*but*-3′-*enyl*cyclo*pent*-2-*en*-1-*one with* N-*Bromosuccinimide.*—The ketone (1·20 g.) (regenerated from the semicarbazone; b. p. 129—133°/25 mm., n_D^{25} 1·4928; cf. Harper, *loc. cit.*) reacted smoothly with *N*-bromosuccinimide (1·42 g., 1·0 mol.) in boiling carbon tetrachloride (30 ml.). After 15 minutes evolution of hydrogen bromide was observed, and refluxing was continued until this was complete (*ca.* 1 hour). After filtration and evaporation of the solvent the viscous residue was distilled. The sole volatile product (160 mg.) had b. p. 50°/7 × 10^{-2} mm. and gave a 2 : 4-dinitrophenylhydrazone, crystallising from ethanol in red needles, m. p. 145°, not depressed on admixture with the 2 : 4-dinitrophenylhydrazone of the original ketone (Harper, *loc. cit.*). This derivative occasionally exhibits dimorphism, having then m. p. *ca.* 160°.

Reaction of 3-*Methyl*-2-n-*pent*-4′-*enyl*cyclo*pent*-2-*en*-1-*one with* N-*Bromosuccinimide.*—The ketone (1·64 g.) (regenerated from the semicarbazone; b. p. 127—129°/20 mm., n_D^{20} 1·4948) reacted with *N*-bromosuccinimide (1·78 g., 1·0 mol.) in warm carbon tetrachloride (10 ml.). Refluxing was continued until the evolution of hydrogen bromide commenced. The suspension was then quickly cooled, filtered (0·91 g. of succinimide, 88%), and evaporated. Distillation of the residue gave, as the sole volatile

product, unchanged ketone, b. p. 82—91°/0·35 mm., n_D^{20} 1·4997 (0·95 g.), and a polymeric residue. The distillate was converted into the semicarbazone (1·07 g., 48%), which had m. p. 172—173° after one crystallisation and did not depress the m. p. of the original ketone semicarbazone. The ketone reacted with 2 molecular proportions of *N*-bromosuccinimide but required the addition of benzoyl peroxide after 30 minutes' refluxing to complete the reaction.

In another experiment refluxing was continued until evolution of hydrogen bromide was complete. Without distillation the product was refluxed with silver acetate in glacial acetic acid. The suspension was filtered, the acetic acid removed in a vacuum, and the residue converted directly into the semicarbazone. The product had, however, m. p. 171—172° which was not depressed on admixture with the semicarbazone of the original ketone.

Addition of 10% bromine in carbon tetrachloride (1 mol.) to the ketone below 0° required illumination for decolorisation to occur. The 3-methyl-2-(4′ : 5′-dibromo-*n*-amyl)*cyclo*pent-2-en-1-one so formed was characterised by a 2 : 4-*dinitrophenylhydrazone*, m. p. 123—124° (Found: C, 41·3; H, 3·8. $C_{17}H_{20}O_4N_4Br_2$ requires C, 40·5; H, 4·0%). Without isolation the dibromo-ketone was treated with *N*-bromosuccinimide (1 mol.); reaction took place rapidly, with some evolution of hydrogen bromide towards the end. Refluxing of the tribromo-ketone with potassium iodide in ethanol effected only partial removal of the vicinal bromine atoms. This was confirmed by re-examination of the dibromo-ketone which likewise reacted only slightly with potassium iodide in ethanol.

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