539. *Experiments on the Synthesis of the Pyrethrins. Part VI.* New Syntheses of the Cinerolones.*

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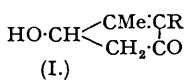
The fourteen-stage synthesis of (±)-*cis*-cinerolone (Part IV), involving *n*-pent-3-yn-1-ol as the key intermediate, is shortened to ten stages and improved in overall yield by the incorporation of a new sequence of reactions.

A superior ten-stage synthesis of (±)-*cis*-cinerolone is described, involving *n*-but-2-yn-1-ol as the key intermediate.

Synthetic (±)-*cis*-cinerolone is compared with naturally derived (±)-*cis*-cinerolone by means of their infra-red absorption spectra. It is shown that the latter is contaminated with (±)-pyrethrolone.

A homologue of *cis*-cinerolone, (±)-*cis*-*n*-pent-2-enylrethrolone is prepared and esterified with (+)-*trans*-chrysanthemic acid. The resultant ester is comparable with allethrin and the natural pyrethrins in toxicity towards houseflies.

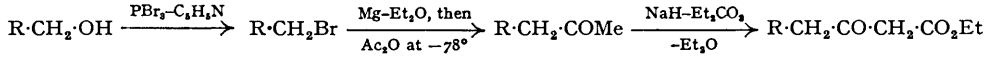
In Part IV two of us (Crombie and Harper, *J.*, 1950, 1152) described a fourteen-stage synthesis in 0·2% overall yield of (±)-*cis*-cinerolone (I*a*; " natural cinerolone "), following our route *B* (cf. Part V *). The essential feature of route *B* is a five-step process for proceeding



(I.)

(I*a*; R = CH_2·CH:CHMe-*cis*)
(I*b*; R = CH_2·CH:CHMe-*trans*)
(I*c*; R = CH_2·CH:CHEt-*cis*)

from R·CH_2·OH to R·CH_2·CO·CH_2·CO_2Me (where R is the alkenyl group ultimately becoming the side-chain of I). We now find that the following three-stage scheme (hereinafter referred to as route *E*), of which the second stage is based on the work of Newman and Booth (*J. Amer. Chem. Soc.*, 1945, **67**, 154), gives a better overall yield :

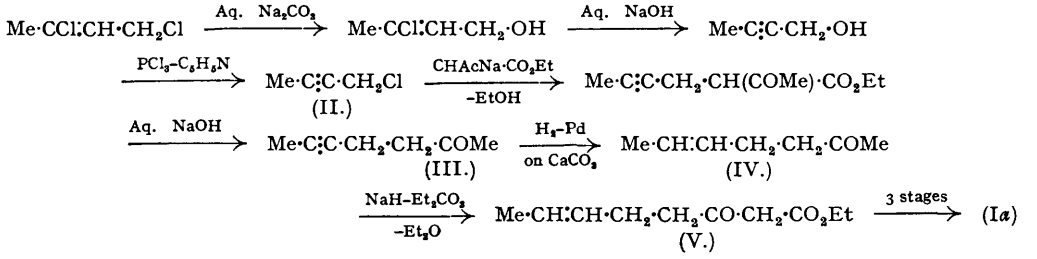


The bromide from the more accessible *trans*-*n*-pent-3-en-1-ol was converted into *trans*-*n*-hept-5-en-2-one (*trans*-crotylacetone) (60% yield), a ketone we had obtained earlier by the use of our route *D* (Part V *), and thence through ethyl *trans*-2-keto-*n*-hept-5-ene-1-carboxylate into (±)-*trans*-cinerolone (I*b*).

* Part V, *J.*, 1950, 3552.

In the original synthesis semi-hydrogenation of *n*-pent-3-yn-1-ol to *cis*-*n*-pent-3-en-1-ol was used as the means of introducing the *cis*-crotyl side-chain. The acetylenic alcohol was prepared by a bromination–dehydrobromination treatment of the mixed *cis*- and *trans*-*n*-pent-3-en-1-ols, themselves obtained through ring scission of the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans by sodium in ether (Crombie and Harper, *J.*, 1950, 873, 1715), but the yield over the bromination–dehydrobromination stages was poor (33%; 27% overall). We have sought, therefore, a more satisfactory preparation of *n*-pent-3-yn-1-ol. Miss J. Sandiford (Harper and Sandiford, unpublished observations) has found that the ring scission of the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans by sodamide in liquid ammonia yields *n*-pent-3-yn-1-ol directly, albeit in only 28% yield. According to an abstract (*Bull. Soc. chim.*, 1909, [iv], **6**, 98) Iotsitch prepared this alcohol in 95% yield by interaction of a prop-1-ynylmagnesium halide with ethylene oxide, but this is not described in Beilstein nor has the use of this method since been reported. We have found that reaction of the more accessible sodiopropyne in liquid ammonia with ethylene oxide gives a negligible yield. The use of route *E*, together with the shorter preparation of *n*-pent-3-yn-1-ol, provides a ten-stage synthesis of (±)-*cis*-cinerolone in about twice the overall yield of the original synthesis, but another route, described below, gives still better results.

In Part IV we envisaged an alternative synthesis of (±)-*cis*-cinerolone, by route *D*, requiring *n*-but-2-yn-1-ol as the key intermediate. Hitherto, this has been accessible only from propyne and paraformaldehyde in low yield (16%) [Yvon, *Compt. rend.*, 1925, **180**, 748; Hurd and Cohen, *J. Amer. Chem. Soc.*, 1931, **53**, 1068; though Iotsitch (*loc. cit.*) is stated to have obtained an 80% yield], but very recently Hatch and Nesbitt (*J. Amer. Chem. Soc.*, 1950, **72**, 727) have described an excellent preparation, from commercially available 1 : 3-dichlorobut-2-ene. Exploiting this we have investigated the following ten-stage route to (±)-*cis*-cinerolone:

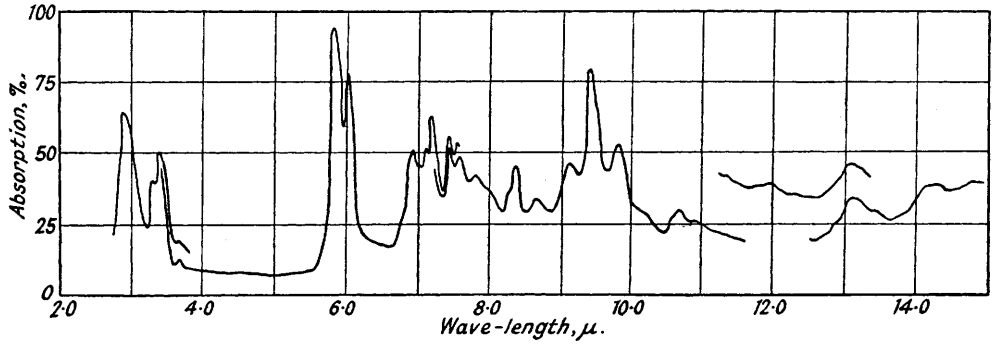


Conversion of *n*-but-2-yn-1-ol into the chloride gave a product of boiling point 102°, whereas Hurd and Cohen (*loc. cit.*) reported 81—84°. We observed, however, the distillation of a little water azeotrope at this lower temperature and these authors' product may well have been this azeotrope [this view has since been confirmed by Hatch and Chiola (*ibid.*, 1951, **73**, 360)]. Alkylation of ethyl sodioacetoacetate with this chloride (II) followed by ketonic fission gave *n*-hept-5-yn-2-one (III). Contrary to our usual experience of this reaction the neutral oil, removed before acidification and warming to liberate the ketone, contained *n*-hept-5-yn-2-one equivalent to a further 8% yield—formed by decarboxylation in alkaline solution. Semi-hydrogenation to *cis*-*n*-hept-5-en-2-one (IV; *cis*-crotylacetone) was carried out at this stage, as elimination of saturated or acetylenic ketonic contaminants by distillation was considered to be easier here than subsequently. This product was almost free from *trans*-isomer, for its infra-red spectrum showed only a slight hump at 10·3 μ., whereas the spectra of the specimens of *trans*-crotylacetone prepared by routes *D* and *E* both exhibited a strong band at this wave-length.

Difficulty was experienced in characterising *cis*- and *trans*-crotylacetones. The 2 : 4-dinitrophenylhydrazones (*cis*-, m. p. 83·0—84·5°; *trans*-, m. p. 69—70°) proved more satisfactory than the semicarbazones (*cis*-, m. p. 124—125°), the derivatives of the *cis*-isomer being obtained more readily than those of the *trans*-isomer. Although the specimens of *trans*-crotylacetone prepared by routes *D* and *E* both gave the same 2 : 4-dinitrophenylhydrazone, a semicarbazone (m. p. 69—70°) could be isolated only from the former specimen. In contrast, von Braun and Gossel (*Ber.*, 1924, **57**, 373) recorded m. p. 97° for the semicarbazone of *trans*-crotylacetone prepared by the acetoacetic ester method, and Kimel and Cope (*J. Amer. Chem. Soc.*, 1943, **65**, 1992) reported m. p. 104·5—105·5° for the semicarbazone of a crotylacetone obtained by thermal rearrangement of 1-methylallyl acetoacetate. The latter may have been impure *cis*-crotylacetone, but it seems likely that *trans*-crotylacetone has not been obtained quite pure; certainly

the infra-red spectra of both of our preparations showed indications of the presence of contaminants. Nevertheless it is of interest that the *cis*-derivatives melt higher than those of *trans*-crotylacetone. Carbethoxylation of *cis*-*n*-hept-5-en-2-one (IV) gave ethyl 2-keto-*cis*-*n*-hept-5-ene-1-carboxylate (V), which was converted into (±)-*cis*-cinerolone in 1% overall yield by the same three stages of hydrolysis, condensation with pyruvaldehyde, and cyclisation as were used previously (Part IV, *loc. cit.*).

Comparison of the infra-red spectrum of the synthetic (see figure) with the recently published spectrum of naturally derived (±)-*cis*-cinerolone (Cupples, *J. Amer. Chem. Soc.*, 1950, **72**, 4522) shows excellent agreement: the peaks in the two spectra can be matched with only one significant exception, namely, a small peak at 11·1 μ. for the latter compound. The most likely impurity in the naturally derived material would be (±)-pyrethrolone and we have previously remarked (Part IV, *loc. cit.*) that ozonolysis, ultra-violet light absorption, and refractive index indicate that this is present in the specimens of naturally derived (±)-*cis*-cinerolone so far obtained. Examination of the infra-red spectrum of naturally derived (±)-pyrethrolone (B-2) (Crombie and Harper, unpublished observations) shows that it has a fairly strong absorption band at 11·1 μ. and comparison with the spectrum of naturally derived (±)-*cis*-cinerolone indicates that it is just this band which would be most clearly evident if pyrethrolone were present as an impurity. The spectrum of synthetic (±)-*cis*-cinerolone also shows the absence of anything more than traces of *trans*-isomer. The spectrum of (±)-*trans*-cinerolone (Cupples, *loc. cit.*) has a strong band at *ca.* 10·3 μ. in common with other *trans*-compounds of the type R·CH=CH·R′ (cf. Crombie and Harper, *J.*, 1950, 873; and references



cited therein). The wave-lengths (μ.) and assignments of the more important absorption bands of synthetic and naturally derived (±)-*cis*-cinerolone are listed in the Table.

(±)-*cis*-Cinerolone.	Bonded OH	Unsat. aliph. C—H	Satd. CH_3, CH_2, and C—H	C=O	C=C	Satd. CH_2	C—CH_3
Synthetic [1]	2·92	3·31	3·43	5·88	6·06	6·96	7·22
Naturally derived [2]	2·91	3·30	3·42	5·89	6·06	6·96	7·23

[1] This work. [2] Cupples, *loc. cit.*

We have also prepared a true homologue of *cis*-cinerolone, (±)-*cis*-*n*-pent-2-enylrethrolone (Ic) (for an exposition of this nomenclature, see Harper, *Chem. and Ind.*, 1949, 636) by route *C* (cf. Part V, *loc. cit.*). The starting material was "leaf alcohol," isolated from the tailings of Brazilian peppermint oil and shown by Crombie and Harper (*loc. cit.*) to be stereochemically pure *cis*-*n*-hex-3-en-1-ol. This was converted successively through the bromide and cyanide into *cis*-*n*-hept-4-enoic acid following Treff and Werner (*Ber.*, 1935, **68**, 640) and Hunsdiecker (*Ber.*, 1942, **75**, 460), though the modified procedure of LaForge, Green, and Gersdorff (*J. Amer. Chem. Soc.*, 1948, **70**, 3707) was used for the second stage. *cis*-*n*-Hept-4-enoyl chloride was converted into methyl *cis*-2-keto-*n*-oct-5-ene-1-carboxylate by *C*-acylation of acetoacetic ester (*loc. cit.*; cf. Part II, Harper, *J.*, 1946, 892; Part IV, *loc. cit.*). Hydrolysis of this ester and condensation of the sodium salt with pyruvaldehyde in aqueous solution gave *cis*-3-hydroxy-*n*-dec-8-ene-2 : 5-dione, cyclised by aqueous sodium hydroxide to (±)-*cis*-*n*-pent-2-enylrethrolone (Ic). This keto-alcohol was esterified with (+)-*trans*-chrysanthemoyl chloride (cf. Part V, *loc. cit.*) to give (±)-*cis*-*n*-pent-2-enylrethronyl (+)-*trans*-chrysanthemate, a true homologue of cinerin-I.

Dr. E. A. Parkin and Mr. A. A. Green of the Pest Infestation Laboratory have compared the insecticidal potencies of (±)-*cis*-*n*-pent-2-enylrethronyl (+)-*trans*-chrysanthemate and natural pyrethrins towards houseflies, over the concentration range 0·05—0·4% w/v in odourless distillate, by a modified Peet–Grady method (Parkin and Green, *Nature*, 1944, **154**, 16). Dr. Parkin reports that " there was no difference in toxicity between the two sets of corresponding solutions, either in knock-down in 10 minutes, or in kill in 24 hours." This homologue of cinerin-I, therefore, is comparable in toxicity towards houseflies to the (±)-allylrethronyl chrysanthemates, and the (±)-*n*-pent-2-enylrethronyl chrysanthemates are clearly worthy of further study.

Experimental.

Analyses are by micromethods. M. p.s are uncorrected. The infra-red absorption spectra were determined by one of us (L. C.) with a Grubb Parsons single-beam spectrometer coupled to a Brown recorder. Capillary films of pure liquid samples (*ca.* 5-μ. thickness) were used. We are indebted to Dr. W. C. Price for this facility.

trans-n-*Hept*-5-*en*-2-*one*.—*trans*-*n*-Pent-3-en-1-ol, b. p. 136—137°, n_D^{20} 1·4339, was prepared by the ring scission of *trans*-3-chloro-2-methyltetrahydrofuran in 73% yield and converted into its bromide (n_D^{20} 1·4696) as described previously (Crombie and Harper, *J.*, 1950, 1715).

To a mixture of acetic anhydride (10 g.) and anhydrous ether cooled to −70° in a Dewar flask the similarly cooled Grignard reagent from *trans*-*n*-pent-3-enyl bromide (7·45 g.) and mangesium (1·22 g.) in ether (25 ml.) was added dropwise during 30 minutes with good stirring. A white solid separated and after a further 2 hours' stirring the mixture was decomposed with aqueous ammonium chloride. After isolation, distillation gave *trans*-*n*-hept-5-en-2-one (3·38 g., 60%), b. p. 148—152°, n_D^{20} 1·4309. The 2 : 4-*dinitrophenylhydrazone*, prepared in ethanol–hydrochloric acid, crystallised from ethanol as yellow needles, m. p. 69—70° (Found : C, 52·7; H, 5·6. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%).

The semicarbazone of a redistilled specimen of the ketone described in Part V was prepared in low yield in aqueous ethanol with semicarbazide hydrochloride and sodium acetate and on crystallisation from ethanol had m. p. 69—70°; no product was obtained by the use of semicarbazide hydrochloride and pyridine. The 2 : 4-dinitrophenylhydrazone, prepared as above and crystallised from ethanol and then from benzene–light petroleum (b. p. 60—80°), had m. p. 69—70°, not depressed on admixture with the above derivative (Found : C, 53·15; H, 6·1%).

n-*But*-2-*yn*-1-*ol*.—Technical grade 1 : 3-dichlorobut-2-ene (1 kg., 8 mols.; not redistilled) was added with stirring to boiling 2N-sodium carbonate (6 l.) and after refluxing for 6 hours the reaction mixture was steam-distilled. The product was separated from the distillate, dried (Na_2SO_4), and distilled to give 3-chlorobut-2-en-1-ol (62%, mean of several runs), b. p. 100—102°/70 mm., n_D^{15} 1·4673. Hatch and Ballin (*J. Amer. Chem. Soc.*, 1949, **71**, 1039) recorded a 72% yield from purified 1 : 3-dichlorobut-2-ene, but Hatch and Chiola (*ibid.*, 1951, **73**, 360) have since obtained only a 63% yield.

3-Chlorobut-2-en-1-ol (533 g., 5 mols.), flake sodium hydroxide (230 g.), and water (450 ml.) were refluxed with stirring for 2 hours. The reaction mixture was steam-distilled, and the product separated from the distillate, combined with those from several runs, dried (K_2CO_3), and fractionally distilled through a 100 × 2·5-cm. helices-packed total-reflux variable take-off column. Fractions having b. p. 140·0—142·0° and n_D^{20} 1·4538—1·4534 were united and represented a 38% yield of *n*-but-2-yn-1-ol. Hatch and Nesbitt (*ibid.*, 1950, **72**, 727) recorded a 40% yield.

n-*But*-2-*ynyl Chloride*.—Phosphorus trichloride (85·5 g.) was added during 1 hour to a stirred mixture of *n*-but-2-yn-1-ol (105 g.) and technical-grade pyridine (39 ml.) cooled to −5°. After being stirred for a further 3 hours, the last hour at room temperature, the product was distilled from the reaction mixture and had b. p. 58—74°/200 mm. The crude products from several such runs were bulked, washed successively with water, sodium carbonate, hydrochloric acid, and water, dried (Na_2SO_4), and distilled through the column described above. Fractions having b. p. 101·0—103·0° and n_D^{20} 1·4592 were united and represented a 56% yield of *n*-but-2-ynyl chloride.

n-*Hept*-5-*yn*-2-*one*.—By the procedure of Part V (*J.*, 1950, 3552), on a 1-mole scale, *n*-but-2-ynyl chloride yielded n-*hept*-5-*yn*-2-*one* (37%), b. p. 58—63°/10 mm., n_D^{20} 1·4495 (Found : C, 75·6; H, 9·05. $C_7H_{10}O$ requires C, 76·35; H, 9·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised as fine orange plates (from ethanol), m. p. 122·0—122·5° (Found : C, 54·0; H, 4·9; N, 19·05. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·8; N, 19·35%).

The neutral oils from several runs, removed before acidification and warming to liberate the ketone, were bulked, dried, and fractionally distilled to give further *n*-hept-5-yn-2-one (equivalent to an additional 8% yield), b. p. 59—75°/10 mm., n_D^{20} 1·4500, identified by its 2 : 4-dinitrophenylhydrazone, m. p. 122° (and mixed m. p.), together with *ethyl* αα-*di*-n-*but*-2-*ynylacetoacetate* (2-*acetyl*-2-n-*but*-2′-*ynyl*-n-*hex*-4-*ynoate*), b. p. 100—101°/0·1 mm., n_D^{20} 1·4757 (Found : C, 71·1; H, 7·5. $C_{14}H_{18}O_3$ requires C, 71·4; H, 7·7%).

cis-n-*Hept*-5-*en*-2-*one*.—*n*-Hept-5-yn-2-one (68 g.) was shaken in hydrogen over pre-reduced 5% palladium–calcium carbonate (5·5 g.) in ethyl acetate until 14 l. had been absorbed. Fractional distillation then gave cis-n-*hept*-5-*en*-2-*one* (54 g., 78%), b. p. 43—48°/10 mm., 148—151°, n_D^{20} 1·432 (Found : C, 75·4; H, 11·0. $C_7H_{12}O$ requires C, 75·0; H, 10·8%). The *semicarbazone*, prepared as described above, crystallised from ethanol in superb plates, m. p. 124—125° (Found : C, 57·4; H, 8·95. $C_8H_{15}ON_3$ requires C, 57·5; H, 8·95%), while the 2 : 4-*dinitrophenylhydrazone*, also prepared as described

above, crystallised from ethanol as orange needles, m. p. 83·0—84·5° (Found: C, 53·3; H, 5·5. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%).

(±)-cis-*Cinerolone*.—By the procedure of Part V *cis*-*n*-hept-5-en-2-one (48 g.) yielded *ethyl* cis-2-*keto*-n-*hept*-5-*ene*-1-*carboxylate* (56 g., 71%), b. p. 75—79°/0·1 mm., n_D^{20} 1·449 (Found: C, 65·15; H, 9·0. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). This ester (46 g.) was shaken with 3% aqueous sodium hydroxide (330 ml.) during 72 hours and then the sodium salt was condensed with aqueous pyruvaldehyde (67 ml.) as described in Part IV (*J.*, 1950, 1152). Fractional distillation of the product gave *cis*-3-hydroxy-*n*-dec-8-ene-2 : 5-dione (16·8 g., 36%), b. p. 108—120°/0·3 mm., n_D^{20} 1·465—1·472, of which 14·8 g. were cyclised by shaking it with 3% aqueous sodium hydroxide (115 ml.) for 1 hour. Isolation of the product as described gave (±)-*cis*-cinerolone (5·5 g., 41%), b. p. 116—130°/0·2 mm., of which the middle runnings had n_D^{20} 1·513 (Found: C, 72·2; H, 8·75. Calc. for $C_{10}H_{14}O_2$: C, 72·25; H, 8·5%). Uptake on micro-hydrogenation in glacial acetic acid over Adams's catalyst: 2·96 mols. ($2\,|\!=\! + 1\,C{:}O$); light absorption in ethanol: $\lambda_{max.}$ 2280 A., $\epsilon_{max.}$ 12,700. The semicarbazone had m. p. 199—201° (decomp.) when determined under the conditions previously described; a 1 : 1 mixture with naturally derived (±)-*cis*-cinerolone semicarbazone, m. p. 195—197° (decomp.), had m. p. 196—198° (decomp.).

Methyl cis-2-*Keto*-n-*oct*-5-*ene*-1-*carboxylate*.—*cis*-*n*-Hex-3-en-1-ol (186 g.), isolated as described by Crombie and Harper (*J.*, 1950, 873) from the same batch of tailings, was converted by Crombie and Harper's procedure (*J.*, 1950, 1715), with phosphorus tribromide (204 g.) at −25° to −30°, into *cis*-*n*-hex-3-enyl bromide (180 g., 60%), b. p. 138—140°, n_D^{20} 1·4729.

This bromide was stirred with potassium cyanide (120 g.) in ethylene glycol (500 ml.) for 2 hours at 100°, the reaction mixture poured into water, and the cyanide taken up in ether, dried (Na_2SO_4), and distilled to give *cis*-*n*-hex-3-enyl cyanide (112 g., 85%), b. p. 84—86°/25 mm., n_D^{20} 1·4352. The cyanide was refluxed in 20% aqueous potassium hydroxide (500 ml.) during 18 hours, the reaction mixture cooled, extracted with ether, and the aqueous layer acidified. The acid that separated was taken up in ether, dried (Na_2SO_4), and distilled to give *cis*-*n*-hept-4-enoic acid (108 g., 83%), b. p. 130—136°/30 mm., n_D^{20} 1·4416.

By the procedure of Part II (*J.*, 1946, 892) *cis*-*n*-hept-4-enoyl chloride (121 g.), b. p. 72—76°/35 mm., n_D^{20} 1·4500, prepared from the above acid in 89% yield by the use of thionyl chloride, was condensed with ethyl sodioacetoacetate (from 123 g. of acetoacetic ester) in ether, and then without distillation treated with cold methanolic sodium methoxide (550 ml., from 27 g. of sodium) to give methyl *cis*-2-keto-*n*-oct-5-ene-1-carboxylate (43 g., 33% for the two stages), b. p. 131—137°/30 mm., n_D^{20} 1·4524 (Found: C, 65·5; H, 9·3. Calc. for $C_{10}H_{16}O_3$: C, 65·2; H, 8·8%).

4-*Hydroxy*-3-*methyl*-2-cis-n-*pent*-2′-*enyl*cyclo*pent*-2-*en*-1-*one* [(±)-cis-n-*Pent*-2-*enylrethrolone*].—By procedure *A* of Part V methyl *cis*-2-keto-*n*-oct-5-ene-1-carboxylate (30 g.) was shaken with 10% aqueous sodium hydroxide (150 ml.) during 48 hours and the resulting solution of sodium salt condensed with aqueous pyruvaldehyde (35 ml.) at 35° during 6 hours. Isolation as described then gave cis-3-*hydroxy*-n-*undec*-8-*ene*-2 : 5-*dione* (9·0 g., 26%), b. p. 95—104°/0·1 mm., n_D^{20} 1·461—1·463. This was stirred with 10% aqueous sodium hydroxide (50 ml.) during 1 hour and the product isolated by the procedure of Part V. Distillation at 0·1 mm. gave several fractions, of which those having b. p. 100—114° and n_D^{20} 1·503—1·511 were bulked (2·16 g.) and redistilled to give (±)-*cis*-*n*-pent-2-enylrethrolone (1·60 g., 20%), b. p. 89—95°/0·03 mm., n_D^{20} 1·506—1·508.

(±)-cis-n-*Pent*-2-*enylrethronyl* (+)-trans-*Chrysanthemate*.—Following the procedure of Part V the reaction product from (±)-*cis*-*n*-pent-2-enylrethrolone (1·60 g.), (+)-*trans*-chrysanthemoyl chloride (1·60 g.), and pyridine (1·3 g.) in benzene (27 ml.) was distilled at 3×10^{-3} mm. and, after elimination of a forerun (0·20 g.), the *ester* was collected (0·66 g., 23%), b. p. 99·5—100·5°, n_D^{20} 1·4992—1·5003, of which the middle runnings had n_D^{20} 1·5000 (Found: C, 74·5; H, 9·05. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·1%). Light absorption in ethanol: $\lambda_{max.}$ 2270 A.; $\epsilon_{max.}$ 17,700.

One of us (D. T.) gratefully acknowledges a maintenance grant from the County Durham Education Committee. We are indebted to the Agricultural Research Council, the Central Research Fund of the University of London, and the Chemical Society for grants which have defrayed the expenses of this investigation, and to Dr. E. A. Parkin for the biological tests.

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[*Received, April 23rd*, 1951.]