237. *Experiments on the Synthesis of the Pyrethrins. Part IV. Synthesis of Cinerone, Cinerolone, and Cinerin-I.*

By Leslie Crombie and Stanley H. Harper.

(+)-Cinerolone of natural origin is ozonised and acetaldehyde together with a small proportion of formaldehyde obtained. It is considered that the formaldehyde is derived from pyrethrolone contaminant, whilst the isolation of acetaldehyde confirms the presence of a *n*-but-2-enyl side-chain in cinerolone.

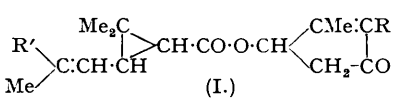
From consideration of the course of a previous synthesis of a stereoisomer of cinerone (Part II), it is concluded that the former is *trans*-cinerone and by exclusion the natural compounds have a *cis*-*n*-but-2-enyl side-chain.

Semi-hydrogenation of *n*-pent-3-yn-1-ol leads to *cis*-*n*-pent-3-en-1-ol, which is converted into *cis*-*n*-hex-3-enoic acid and thence by a thirteen-stage overall synthesis (see flow sheet) into *cis*-cinerone, identical with the naturally derived ketone.

Condensation of the intermediate methyl *cis*-2-keto-*n*-hept-5-ene-1-carboxylate (as the sodium salt) with pyruvaldehyde, and cyclisation, leads to (±)-*cis*-cinerolone, similarly identical with naturally derived (±)-cinerolone.

By esterification with (+)-*trans*-chrysanthemic acid (Part I) a total synthesis of cinerin-I, one of the active principles of natural pyrethrum, is achieved. This and the racemic ester from (±)-*trans*-chrysanthemic acid are insecticidally active.

The flower-heads of *Chrysanthemum cinerariifolium* (pyrethrum) are now considered to contain at least four compounds which are responsible for the remarkable insecticidal activity of pyrethrum powder and extract. These active principles are pyrethrin-I (I*a*), pyrethrin-II (I*b*) cinerin-I (I*c*), and cinerin-II (I*d*) (for a recent review of pyrethrum chemistry see Harper, *Ann. Reports*, 1948, **45**, 162).

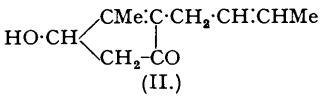


(I.)

(I*a*; R = $CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH_2$; R′ = Me.)
(I*b*; R = $CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH_2$; R′ = CO_2Me.)
(I*c*; R = $CH_2{\cdot}CH{:}CHMe$; R′ = Me.)
(I*d*; R = $CH_2{\cdot}CH{:}CHMe$; R′ = CO_2Me.)

With the probable exception of pyrethrin-II these keto-esters have not been isolated as such but only characterised in the form of their hydrolysis products. The presence of cinerin-I and

cinerin-II in pyrethrum extract was made likely when LaForge and Barthel (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106) isolated cinerolone (II) in both (+)- and (±)-forms, together with pyrethrolone, from the alcoholic products of hydrolysis. By analogy with pyrethrolone it was assumed that both cinerin-I and cinerin-II are present in pyrethrum extract. Their insecticidal effectiveness was demonstrated when LaForge and Barthel (*ibid.*, 1947, **12**, 199) re-formed cinerin-I and cinerin-II by esterifying both (+)- and (±)-cinerolone with naturally derived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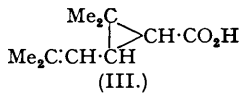
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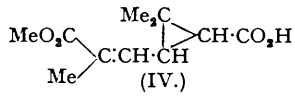
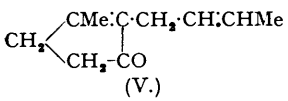

(IV.)

(+)-*trans*-chrysanthemic (chrysanthemum monocarboxylic) acid (III) and (+)-*trans*-pyrethric acid (the monomethyl ester of chrysanthemum dicarboxylic acid) (IV) respectively, and these were shown to be highly toxic to houseflies by Gersdorff (*J. Econ. Entomol.*, 1947, **40**, 878).

LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 114) treated cinerolone with thionyl chloride to give a chlorocinerone, containing highly reactive chlorine and giving the parent ketone cinerone on reduction with zinc. On the basis of terminal methyl value, the ultra-violet absorption of cinerolone, and analogy with pyrethrolone they assigned structure (V) to cinerone.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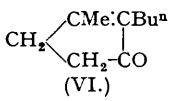
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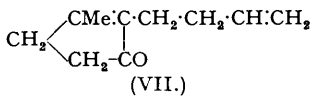
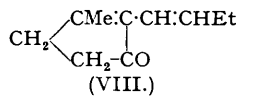

(VII.)


(VIII.)

Subsequently (*ibid.*, p. 222) they catalytically reduced cinerolone to dihydrocinerolone and converted this, *via* the chloro-compound, into dihydrocinerone, whose structure as 3-methyl-2-*n*-butyl*cyclo*pent-2-en-1-one (VI) was confirmed by comparison with a synthetic specimen.

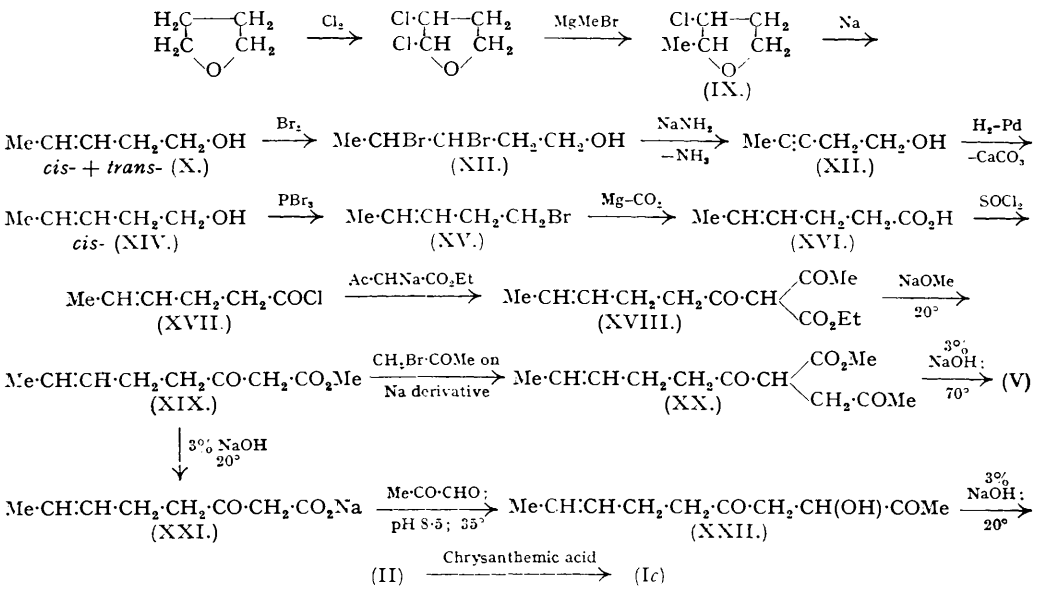
Since structure (VII) for cinerone was not excluded on spectroscopic grounds and assignment by terminal methyl values was rather uncertain, one of us attempted (Harper, Part II, *J.*, 1946, 892) to elucidate the structure of cinerone by direct synthesis. 3-Methyl-2-*n*-but-2′-enyl- and -2-*n*-but-3′-enyl-*cyclo*pent-2-en-1-one (V and VII respectively) were prepared but neither was identical with naturally derived cinerone. Since structure (VIII) was excluded on spectroscopic (cinerolone shows no absorption attributable to a cross-conjugated diene and αβ-unsaturated ketone system; cf. West, *J.*, 1946, 463) and other grounds it was concluded that naturally derived cinerone was the opposite geometrical isomer to the synthetic ketone (V).

We have ozonised (+)-cinerolone regenerated from a specimen of " cinerolone A-1 " semicarbazone, kindly provided by Dr. T. F. West (cf. *loc. cit.*). The volatile aldehydic product was converted into a heterogeneous dimedon derivative, which by conversion into the anhydride was shown to contain as the major component the anhydro-derivative of acetaldehyde, together with a small amount (~10%) of the derivative of formaldehyde. The source of the latter may well be a little pyrethrolone contaminant in this specimen of (+)-cinerolone. This conclusion is supported by the ultra-violet absorption of this and similar preparations of cinerolone semicarbazone (West, *loc. cit.*) which show appreciably more absorption at 2310 ± 10 A. than does tetrahydropyrethrolone semicarbazone (Gillam and West, *J.*, 1942, 671), due to the separate conjugated diene chromophore of the pyrethrolone side-chain. Likewise LaForge and Barthel's preparations of cinerolone (*J. Org. Chem.*, 1945, **10**, 114) may have contained pyrethrolone: they had refractive indices higher than would be expected for ketones of this type; further the (+)-cinerolone had $\varepsilon_{max.}$ 15,500 at $\lambda_{max.}$ 2275 A., whereas these trisubstituted αβ-unsaturated ketones normally have $\varepsilon_{max.}$ ~12,000 to 13,000 (cf. Gillam and West, *J.*, 1942, 486; Harper, *loc. cit.*; and data in this paper), the increased intensity being due to the superimposed absorption of the conjugated side-chain chromophore of the pyrethrolone side-chain. Although it seems probable that a pure specimen of (+)-cinerolone has not yet been isolated from pyrethrum extract, nevertheless this ozonisation confirms that cinerolone, in contrast to pyrethrolone, contains a terminal ethylidene group, *i.e.*, the but-2′-enyl side-chain.

The synthesis of 3-methyl-2-*n*-but-2′-enyl*cyclo*pent-2-en-1-one (V) started from crotonaldehyde which was reduced by the Meerwein–Ponndorf procedure to crotyl alcohol. This was converted by cold concentrated hydrochloric acid into crotyl chloride and thence by a malonic ester chain extension, into the pure crystalline malonic acid (m. p. 115°), and by decarboxylation into *n*-hex-3-enoic acid (this was described as Δ^4-hexenoic acid, but using the current *Journal* convention the carboxyl group is no longer numbered), identical with that made earlier by Eccott and Linstead (*J.*, 1929, 2163) from crotyl bromide using the same route. There is no doubt that commercial crotonaldehyde has the *trans*-configuration. Young (*J. Amer. Chem. Soc.*,

1932, **54**, 2498) obtained only *trans*-crotonic acid on oxidation with cold aqueous silver oxide, and studies of the Raman spectrum by Grédy and Piaux (*Compt. rend.*, 1934, **198**, 1235), of the ultra-violet absorption spectrum by Blacet, Young, and Roof (*J. Amer. Chem. Soc.*, 1937, **59**, 608), and measurement of the dipole moment by Bentley, Everard, Marsden, and Sutton (*J.*, 1949, 2957) have confirmed the exclusive *trans*-configuration. Likewise crotyl alcohol, chloride, and bromide, derived from commercial crotonaldehyde, have the *trans*-configuration. Grédy and Piaux (*loc. cit.*) suspected, on the evidence of Raman spectra, the presence of a small proportion (<10%) of *cis*-isomer in crotyl bromide, though crotyl chloride (*idem*, *Bull. Soc. chim.*, 1935, [v], **2**, 1029) was entirely *trans*. Winstein and Young (*J. Amer. Chem. Soc.*, 1936, **58**, 104, and subsequent papers), however, were unable to detect any *cis*-isomer by fractional distillation of the bromide and showed it to consist of *trans*-crotyl bromide together with some of the rearranged product, 1-methylallyl bromide. Lane, Fentress, and Sherwood (*ibid.*, 1944, **66**, 545) showed that such mixed crotyl chlorides or bromides interact with cuprous cyanide to give the same mixture of cyanides, in which the primary (91·5%) predominated and they suggested that reaction proceeded through the mesomeric ion, $CH_3\overset{+}{\frown}CH{=}CH{=}CH_2$. Recently, however, Kepner, Winstein, and Young (*ibid.*, 1949, **71**, 115) examined the reaction of both crotyl chloride and 1-methylallyl chloride with ethyl sodiomalonate. They showed conclusively that in the former case reaction proceeds by a normal bimolecular (S_N2) mechanism to give >99% of crotylmalonic ester. In the latter case the mechanism is again mainly S_N2, leading to 1-methylallylmalonic ester, though 6—10% crotylmalonic ester is formed by an abnormal bimolecular (S_N2') mechanism. A S_N1 mechanism is rejected. Clearly, the *n*-hex-3-enoic acid, prepared from *trans*-crotyl chloride, *via* a crystalline intermediate, and used in our earlier work, was pure *trans-n*-hex-3-enoic acid. Furthermore, we consider that the *trans*-configuration was maintained throughout the subsequent synthesis, the intermediate *trans-n*-hex-3-enoic acid leading to pure 3-methyl-2-*trans-n*-but-2′-enyl*cyclo*pent-2-en-1-one (hereinafter referred to as *trans*-cinerone). By exclusion, therefore, naturally derived cinerone has the *cis*-configuration.

Since semi-hydrogenation of an acetylenic link, using a supported palladium catalyst, is the most convenient synthetic method for the introduction of a *cis*-double bond (Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 90) the route to *cis*-cinerone detailed on the chart was explored. A preliminary account of this work was given in *Nature* (1949, **164**, 543).



The ring fission of the readily available mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofurans (IX) with sodium provides an excellent route for the preparation of *n*-pent-3-en-1-ol (X), which we have shown consists of a *cis-trans*-mixture, the latter predominating (Crombie and Harper, forthcoming publication). We have further shown that, when this mixture (X) is brominated in ether at low temperature and the 3 : 4-dibromopentanol (XI) is dehydro-

brominated with sodamide in liquid ammonia, *n*-pent-3-yn-1-ol (XII) is obtained (*J.*, 1950, 873). Much 3(or 4)-bromopent-3-enol was also formed: the reason for this is probably that the first stage of the dehydrohalogenation is the formation of 3(or 4)-bromopent-3-enol, which can exist in *cis*- and *trans*-forms (XIII*a*, *b*, *c*, and *d*). Subsequent *trans*-elimination of hydrogen bromide

Br·C·CH$_2$·CH$_2$·OH ‖ Me·CH	Br·C·CH$_2$·CH$_2$·OH ‖ HCMe	HC·CH$_2$·CH$_2$·OH ‖ Me·CBr	HC·CH$_2$·CH$_2$·OH ‖ Br·CMe
(XIII*a*.)	(XIII*b*.)	(XIII*c*.)	(XIII*d*.)

should be easy from (XIII*a*) and (XIII*c*) but difficult from (XIII*b*) and (XIII*d*). The by-product, 3(or 4)-bromopent-3-en-1-ol, hence probably has the *cis*-configuration. Recent similar cases of the recovery of the monobromo-compound in the dehydrobromination of a dibromide with alcoholic potassium hydroxide have been recorded by Stoll and Commarmont (*Helv. Chim. Acta*, 1949, **32**, 597) and by Normant (*Compt. rend.*, 1948, **226**, 1734). We have also encountered this difficulty in other cases of dehydrohalogenation with sodamide in liquid ammonia (cf. *Nature*, 1949, **164**, 1053). The *n*-pent-3-yn-1-ol was semi-hydrogenated by use of palladium on calcium carbonate, to give *cis*-*n*-pent-3-en-1-ol (XIV) in high yield. Conversion of the latter into the *bromide* (XV) with phosphorus tribromide in pyridine and carboxylation of the derived Grignard reagent gave cis-n-*hex*-3-*enoic acid* (XVI). The properties of this acid and of its derivatives are compared with those of what is clearly the pure *trans*-acid, made from crotyl chloride or bromide by malonic ester chain extension (Eccott and Linstead, *loc. cit.*; Letch and Linstead, *J.*, 1934, 1994; Harper, *loc. cit.*), in Table I.

TABLE I.

	M. p.	B. p.	n_D^{20}.	Anilide, m. p.	*p*-Bromophenacyl ester, m. p.
cis-*n*-Hex-3-enoic acid [1] ...	−35° to −34°	106°/14 mm.	1·4403	62°	55°
trans-*n*-Hex-3-enoic acid [1]	−1° to +1°	108—109/19 mm.	1·4387	87	82·5
,, ,, [2]	+1°	102/12 mm.	1·4367	87	—

[1] This work. [2] Letch and Linstead, *J.*, 1934, 1994.

Treatment of *cis*-*n*-hex-3-enoic acid (XVI) with thionyl chloride gave cis-n-*hex*-3-*enoyl chloride* (XVII) in high yield, which was condensed with ethyl sodioacetate in ether to yield ethyl *cis*-2 : 4-diketo-*n*-non-7-ene-3-carboxylate (XVIII). Without distillation this was treated with cold sodium methoxide in methanol to give *methyl* cis-2-*keto*-n-*hept*-5-*ene*-1-*carboxylate* (XIX) by ketonic fission. The sodio-derivative of this β-keto-ester in ether was treated with bromoacetone and the resultant methyl *cis*-2 : 5-diketo-*n*-dec-8-ene-4-carboxylate (XX) cyclised at once, without prior distillation, by stirring with 3% aqueous sodium hydroxide at 70°. The 3-*methyl*-2-cis-n-*but*-2′-*enyl*cyclo*pent*-2-*en*-1-*one* (V) (hereinafter referred to as *cis*-cinerone) was isolated by distillation and purified by conversion into the *semicarbazone* and regeneration with hot aqueous oxalic acid. The ketone was further characterised by formation of the p-*nitro*- and 2 : 4-*dinitro-phenylhydrazones*. Specimens of the first two derivatives of naturally derived cinerone were available from our previous work and their melting points were not depressed on admixture with the corresponding derivatives of synthetic *cis*-cinerone. On the other hand marked depressions of the melting points were observed when the corresponding derivatives of *trans*-cinerone were admixed with those of synthetic *cis*-cinerone, as had been observed with those of naturally derived cinerone (Harper, *loc. cit.*). The properties of synthetic *cis*- and *trans*-cinerone and naturally derived cinerone and of their derivatives are compared in Table II. The identity of naturally derived cinerone as 3-methyl-2-*cis*-*n*-but-2′-enyl*cyclo*pent-2-en-1-one is thus established.

LaForge, Green, and Gersdorff (*J. Amer. Chem. Soc.*, 1948, **70**, 3707) have recently described the synthesis of a cinerone, preparing the intermediate ethyl 2-keto-*n*-hept-5-ene-1-carboxylate by an alternative route from crotyl chloride. Alkylation of ethyl sodioacetoacetate with crotyl chloride followed by ketonic fission yielded *n*-hept-5-en-2-one, which was carbethoxylated on the methyl group by use of ethyl carbonate and sodium hydride to give the required intermediate. This synthetic cinerone was not identical with naturally derived cinerone, but the melting points of the semicarbazone and *p*-nitrophenylhydrazone were lower than those of the derivatives of *trans*-cinerone, and it would appear to be a *cis*-*trans*-mixture in which the latter predominated. The origin of the crotyl chloride is not described, but commercial material prepared by chlorination of the but-2-enes may contain some *cis*-isomer (cf. Young and Andrews, *ibid.*, 1944, **66**, 421) although it is mainly *trans*-crotyl chloride. If this was used the heterogeneity of the starting material may afford some explanation of the final lack of identity. This tentative explanation

assumes that when either *cis*- or *trans*-crotyl chloride reacts with ethyl sodioacetoacetate the double bond maintains its configuration and there is little or no allylic rearrangement. This is so for *trans*-crotyl chloride, from the work described above, but whether *cis*-crotyl chloride behaves similarly is so far as we are aware unknown. If the reaction proceeds through a normal bimolecular (S_N2) mechanism, analogous to that with ethyl sodiomalonate (cf. Kepner, Winstein, and Young, *loc. cit.*), then retention of configuration would be expected. Because of this uncertainty we chose to start our synthesis of *cis*-cinerone from a *cis*-*n*-pent-3-enyl halide rather than from a *cis*-crotyl halide, although a synthesis of *n*-but-2-yn-1-ol and thence of *cis*-crotyl alcohol is in progress and it may thus be possible to examine this point.

TABLE II.

	B. p./mm.	n_D^{25}.*	Terminal methyl groups.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
cis-Cinerone [1]	120°/15	1·4982	1·52	2320	12,200
trans-Cinerone [1,2]	119/15	1·4983	1·67	2350	12,000
Natural cinerone [3]	—	1·5002	—	—	—

			Semicarbazone.			
	Nph,† m. p.	Dnph,† m. p.	M. p.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	Terminal methyl groups.
cis-Cinerone [1]	152·5°	138°	214°	2650	24,000	1·51
trans-Cinerone [1,2]	162	161	220	2660	21,800	1·38
Natural cinerone [3]	148	—	214—215	—	—	1·70

[1] This work. [2] Harper, Part II, *J.*, 1946, 892. [3] LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114. * *n* adjusted to 25° by using −0·0004 per degree.
† Nph = *p*-nitrophenylhydrazone; Dnph = 2 : 4-dinitrophenylhydrazone.

In a preliminary exploration of the above route to cinerone the mixed *cis-trans-n*-pent-3-en-1-ol, obtained directly from the ring fission, was employed as the starting material at the stage (XIV ⟶ XV). The semicarbazone of the cinerone was initially heterogeneous (m. p. 210—215°), but after recrystallisation the major and less soluble component had m. p. 222—223° and on admixture did not depress the melting point of pure *trans*-cinerone semicarbazone (Harper, *loc. cit.*). Further confirmation that this preparation of cinerone was predominantly of the unnatural configuration was obtained by preparing the *p*-nitrophenylhydrazone from the ketone regenerated from the semicarbazone of m. p. 210—215°. This *p*-nitrophenylhydrazone had initially m. p. 150—155°, but fractional crystallisation gave as the major component the less soluble form (m. p. 158—159°), which did not depress the melting point of the *trans*-derivative. From the mother-liquors a more soluble fraction, m. p. 147—150°, was isolated but this depressed the melting point (148—150°) of naturally derived cinerone *p*-nitrophenylhydrazone. It was evidently a *cis-trans*-mixture still on the *trans*-side of the eutectic. This additional preparation of unnatural cinerone, starting from predominantly *trans-n*-pent-3-en-1-ol, provides corroboration of the *trans*-configuration of this ketone and of the intermediate *n*-hex-3-enoic acid used in the original synthesis.

By utilising methyl *cis*-2-keto-*n*-hept-5-ene-1-carboxylate (XIX), prepared above as an intermediate in the synthesis of *cis*-cinerone, we have achieved the synthesis of (±)-cis-*cinerolone*. The acetoacetate was hydrolysed by shaking it with 3% aqueous sodium hydroxide at 20° for 3 days to give a solution of the sodium salt of the β-keto-acid (XXI). This salt was condensed with commercial aqueous pyruvaldehyde at 35° and pH 8·5 (cf. Henze, *Z. physiol. Chem.*, 1930, **189**, 121; Stöhr and Henze, *ibid.*, 1932, **206**, 1; Stöhr, *ibid.*, 1935, **235**, 265; Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 1517, 3165), then acidified and warmed to effect decarboxylation, and the resultant cis-3-*hydroxy*-n-*dec*-8-*ene*-2 : 5-*dione* (XXII) isolated by distillation. Cyclisation of this γ-diketone by shaking with 3% aqueous sodium hydroxide at 20° yielded (±)-4-*hydroxy*-3-*methyl*-2-cis-n-*but*-2′-*enyl*cyclo*pent*-2-*en*-1-*one* (II) [hereinafter referred to as (±)-*cis*-cinerolone]. The latter was characterised as its *semicarbazone* and as its *acetate semicarbazone*. These derivatives were identical with the corresponding derivatives of naturally derived (±)-cinerolone in melting point, and mixed melting points. Admixture with the corresponding derivatives of (±)-*trans*-cinerolone (prepared in collaboration with Mr. A. J. B. Edgar, forthcoming communication) gave the expected marked depressions of melting point. Similarly, naturally derived (±)-cinerolone semicarbazone and acetate semicarbazone depressed the melting points of the corresponding derivatives of (±)-*trans*-cinerolone. Comparison of the

properties of (±)-*cis*- and (±)-*trans*-cinerolone and their derivatives with naturally derived cinerolone is made in Table III.

TABLE III.

	B. p./mm.	n_D^{25}.*	Terminal methyl groups.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
(±)-*cis*-Cinerolone [1]	102—105°/<0·05	1·5100	1·34	2300	10,800
(±)-*trans*-Cinerolone [2] ...	116—118°/0·6	1·5124	1·53	—	—
Natural (±)-cinerolone [3]	—	1·5252	—	—	—
Natural (+)-cinerolone [3]	120—124°/1	1·5214	1·66	2275	15,500

	Semicarbazone.				
	M. p.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	Terminal methyl groups.	Acetate semicarbazone, m. p.
(±)-*cis*-Cinerolone [1]	197—199°	2650	25,200	1·47	147—148°
(±)-*trans*-Cinerolone [2] ...	208—209	2650	22,000	1·60	157—159
Natural (±)-cinerolone [3]	199—200	2650	21,000	1·45	151—152
,, ,, [4]	199—200	2660	17,000	—	150—152

[1] This work. [2] Crombie, Edgar, and Harper, unpublished. [3] LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 106, 114. [4] West, *J.*, 1946, 463.
* *n* adjusted to 25° by using −0·0004 per degree.

Utilising synthetic (±)-*cis*-cinerolone the first total synthesis of one of the active principles of pyrethrum flowers, that of cinerin-I, has now been accomplished by esterification with (+)-*trans*-chrysanthemic acid. The synthesis and resolution of (±)-*trans*-chrysanthemic acid was described by Campbell and Harper (Part I, *J.*, 1945, 283), who showed that the *p*-phenylphenacyl ester of the synthetic (+)-*trans*-acid was identical with that of the natural acid. Hence for convenience naturally derived acid was used for this esterification in the form of its chloride, which was treated with a pyridine solution of (±)-*cis*-cinerolone. This synthetic cinerin-I was isolated by distillation (b. p. ~132°/5 × 10^{-3} mm.) and consists of the diastereoisomeric pair of esters, (±)-cis-*cineronyl* (+)-trans-*chrysanthemate* (Ic) (for an explanation of this nomenclature, see Harper, *Chem. and Ind.*, 1949, 636). By a similar esterification with (±)-*trans*-chrysanthemic acid we have also prepared the fully racemic ester, (±)-cis-*cineronyl* (±)-trans-*chrysanthemate*. Preliminary examination of these esters against houseflies has shown them to be insecticidally active. When more material can be prepared a comprehensive comparison of relative toxicities between stereoisomers and with structural analogues will be made using several species of insects.

Since naturally derived (±)-*cis*-cinerolone has previously been converted into cinerin-II, using naturally derived (+)-*trans*-pyrethric acid (LaForge and Barthel, *J. Org. Chem.*, 1947, **12**, 199), this work also constitutes a partial synthesis of cinerin-II.

EXPERIMENTAL.

(Microanalyses and ultra-violet absorption spectra are by Drs. Weiler and Strauss, Oxford.)

cis-n-*Pent*-3-*enyl Bromide*.—*cis*-*n*-Pent-3-en-1-ol (37 g.), prepared as previously described (Crombie and Harper, *J.*, 1950, 873), mixed with dry pyridine (10 ml.) was cooled in ice, and phosphorus tribromide (47 g., 1·2 mol.) was added dropwise with stirring during 2 hours. The bromide was distilled by heating with a free flame and boiled mainly at 86—102°/210 mm. (59 g.). After being washed twice with cold 10% sodium hydroxide and twice with 10% sulphuric acid, a little light petroleum (b. p. 40—60°) being used to aid separation, the product was dried and distilled, to yield cis-n-*pent*-3-*enyl bromide* (40·7 g., 64%), b. p. 128—140°, n_D^{20} 1·4736. A portion, redistilled for analysis, had b. p. 95—97°/210 mm., n_D^{20} 1·4734 (Found : C, 40·3; H, 6·15; Br, 53·7. C_5H_9Br requires C, 40·3; H, 6·1; Br, 53·6%).

cis-n-*Hex*-3-*enoic Acid*.—A Grignard reagent was prepared from *cis*-*n*-pent-3-enyl bromide (40·5 g.) and magnesium (8·0 g.) in anhydrous ether (100 ml.). A further 100 ml. of ether were then added, the reagent was cooled in solid carbon dioxide and carboxylated by passage of dry carbon dioxide gas over the surface of the stirred solution. Finally a large excess of crushed solid carbon dioxide was added and the product set aside for 2 hours. Sulphuric acid (25%) was then added with stirring and cooling. The separated ethereal layer was extracted with 10% sodium hydroxide, the alkaline extract thoroughly washed with ether, and the acid liberated by acidification under a layer of light petroleum (b. p. 40—60°). Washing and distillation of the layer gave cis-n-*hex*-3-*enoic acid* (17·5 g., 56%), b. p. 110—112°/20 mm., n_D^{20} 1·4400 (Found : C, 63·4; H, 8·8. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%). In another experiment (see Table I) a yield of 62% was obtained. This acid was characterised by preparation of the *p*-*bromophenacyl ester*, colourless plates (from aqueous ethanol), m. p. 55° (Found : C, 54·25; H, 5·0. $C_{14}H_{15}O_3Br$ requires C, 54·1; H, 4·85%), and the *anilide*, colourless needles, m. p. 62°, from light petroleum (b. p. 60—80°) (Found : C, 76·25; H, 8·1. $C_{12}H_{15}ON$ requires C, 76·1; H, 8·0%).

trans-n-*Hex*-3-*enoic Acid*.—The acid prepared as in Part II (Harper, *J.*, 1946, 892) had m. p. −1° to +1°, b. p. 108—109°/19 mm., n_D^{20} 1·4387, and was characterised as the p-*bromophenacyl* ester, colourless needles (from aqueous ethanol), m. p. 81·5—82·5° (Found: C, 53·75; H, 5·0. $C_{14}H_{15}O_3Br$ requires C, 54·1; H, 4·85%), and as the anilide, colourless needles, m. p. 87°, from light petroleum (b. p. 60—80°).

cis-n-*Hex*-3-*enoyl Chloride*.—Thionyl chloride (21·8 g., 13·2 ml.) was added dropwise to *cis-n*-hex-3-enoic acid (16·7 g.), and the product set aside overnight. Distillation gave cis-n-*hex*-3-*enoyl chloride* (18·8 g., 97%), b. p. 52°/28 mm., n_D^{20} 1·4496 (Found: C, 54·1; 54·5; H, 7·25, 7·3; Cl, 25·8. C_6H_9OCl requires C, 54·4; H, 6·85; Cl, 26·7%).

Ethyl cis-2: 4-*Diketo*-n-*non*-7-*ene*-3-*carboxylate* [α-cis-n-*Hex*-3′-*enoylacetoacetate*].—Ethyl sodioacetoacetate was prepared from powdered sodium (3·6 g.) and ethyl acetoacetate (20·2 g.) in anhydrous ether. *cis-n*-Hex-3-enoyl chloride (18·2 g.) was added slowly and the suspension then refluxed for 5 hours. Water was added, the solution just acidified, and the ethereal layer removed, washed, and dried Evaporation of the ether gave crude ethyl α-*cis-n*-hex-3′-enoylacetoacetate which was used without distillation for the next stage. This simplification of procedure has since been adopted for the preparations described in Part II (*loc. cit.*).

Methyl cis-2-*Keto*-n-*hept*-5-*ene*-1-*carboxylat e*[γ-cis-n-*But*-2′-*enylacetoacetate*].—The crude ethyl α-*cis-n*-hex-3′-enoylacetoacetate (above) was added to cold sodium methoxide prepared by dissolving sodium (3·9 g.) in methanol (80 ml.). After 24 hours, the solution was diluted with much water, just acidified, and thoroughly extracted with ether. Distillation of the ethereal extract gave crude methyl *cis-n*-hex-3-enoate (6·2 g.), b. p. 55—60°/17 mm., n_D^{20} 1·4257, and *methyl* γ-cis-n-*but*-2′-*enylacetoacetate* (11·0 g., 47%), b. p. 62—66°/0·04 mm. In a second experiment the yield was 51%. For analysis a portion was redistilled, having b. p. 76—78°/0·6 mm., n_D^{20} 1·4507 (Found: C, 63·1; H, 8·45. $C_9H_{14}O_3$ requires C, 63·5; H, 8·25%). This ester gave an intense red colour with ferric chloride.

Methyl cis-2: 5-*Diketo*-n-*dec*-8-*ene*-4-*carboxylate* [α-cis-n-*Hex*-3′-*enoyl*-*lævulate*].—Sodium (0·24 g.) was powdered under xylene and then suspended in ether. Methyl γ-*cis-n*-but-2′-enylacetoacetate (1·47 g.) was added slowly and the suspension kept overnight to complete the formation of the sodio-derivative, which is partly soluble in ether. Freshly distilled bromoacetone (2·5 g.) was added and the suspension refluxed for 2 hours. Water was added, the aqueous layer acidified, and the product isolated from the ethereal layer by drying and evaporation. It was not distilled but used in the crude state for cyclisation.

3-*Methyl*-2-cis-n-*but*-2′-*enyl*cyclo*pent*-2-*en*-1-*one* [cis-*Cinerone*].—The crude methyl α-*cis-n*-hex-3′-enoyl-lævulate (above) was vigorously stirred with 3% sodium hydroxide solution (35 ml.) at 70° for 3 hours. The solution became brown and had a jasmone-like smell. It was cooled, acidified, and thoroughly extracted with ether. The extract was dried and distilled, to give 700 mg. of crude ketone, b. p. 69°/0·2 mm. to 79°/0·35 mm., which was purified by conversion into the semicarbazone. The crude ketone (680 mg.) in ethanol (2 ml.) was added, followed by pyridine (0·5 ml.), to a hot solution of semicarbazide hydrochloride (530 mg.) in water (0·5 ml.). The mixture was refluxed for 1 hour and then filtered, and the *semicarbazone* (600 mg.) washed with aqueous ethanol. On recrystallisation it formed colourless leaflets from ethanol (Found: C, 63·6; H, 8·3; N, 19·6. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3; N, 20·2%). Light absorption: $\lambda_{max.}$ 2650 A.; $\varepsilon_{max.}$ 24,000. The melting point and mixed melting point, determined simultaneously, showed this semicarbazone to be identical with that from naturally derived cinerone (cf. LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114):

	Synthetic.	1 : 1 Mixture.	Natural.
Put in bath	200°	200°	200°
Softened and becomes brown	210	209	209
M. p.	213—214 (decomp.)	213—214 (decomp.)	213—214 (decomp.)

When admixed with *trans*-cinerone semicarbazone (Harper, *loc. cit.*) and put in the bath at 190°, a 1 : 1 mixture softened and became brown at 200°, and was completely molten at 206°, thus demonstrating their non-identity.

Pure cis-*cinerone* was regenerated by refluxing the semicarbazone (300 mg.) with oxalic acid (600 mg.) in water (3 ml.) for 1 hour. The ketone was isolated by extraction with light petroleum (b. p. 40—60°) and distilled, having b. p. ~120°/15 mm., n_D^{20} 1·5002 (167 mg.). It had a pleasant jasmone-like odour. Light absorption: $\lambda_{max.}$ 2320 A.; $\varepsilon_{max.}$ 12,200 (Found: Me·C, 15·2%). *p*-Nitrophenylhydrazine (30 mg.) was suspended in methanol (2 ml.) and heated to boiling. A very small drop of concentrated hydrochloric acid was added, followed by *cis*-cinerone (30 mg.). After 15 minutes' refluxing, the derivative was allowed to separate overnight. The p-*nitrophenylhydrazone* formed orange-brown flattened needles (from methanol), m. p. 151·5—152·5° (Found: C, 67·0; H, 6·8. $C_{16}H_{19}O_2N$ requires C, 67·35; H, 6·7%). A 1 : 1 mixture with the *p*-nitrophenylhydrazone of naturally derived cinerone (m. p. 148—150°) (LaForge and Barthel, *loc. cit.*) also had m. p. 148—150°. A 1 : 1 mixture with *trans*-cinerone *p*-nitrophenylhydrazone (m. p. 160—162°) (Harper, *loc. cit.*) softened some degrees lower, before finally melting at 143°. The 2 : 4-*dinitrophenylhydrazone* was prepared in a similar fashion from *cis*-cinerone (20 mg.) and 2 : 4-dinitrophenylhydrazine (25 mg.). At first the derivative separated as a gel, but on recrystallisation gave superb dark red needles, m. p. 137—138° (Found: C, 58·0; H, 5·5; N, 16·7. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 16·9%). This depressed the melting point of *trans*-cinerone 2 : 4-dinitrophenylhydrazone (m. p. 161°) (Harper, *loc. cit.*) to 128—131°.

trans-*Cinerone*.—In a preliminary investigation the above route to *cis*-cinerone was tested using the *cis-trans-n*-pent-3-en-1-ol mixture (b. p. 138—141°; n_D^{20} 1·4374) obtained directly from the ring fission of the mixed *cis*- and *trans*-3-chloro-2-methyltetrahydrofuran (Crombie and Harper, unpublished). This *n*-pent-3-en-1-ol (112 g.) yielded successively: *n*-pent-3-enyl bromide (142 g., 73%; b. p. 89—97°/225 mm., n_D^{20} 1·4720), *n*-hex-3-enoic acid (64·5 g., 65%; b. p. 117—119°/24 mm., n_D^{20} 1·4380), *n*-hex-3-enoyl chloride (65 g., 91·5%; b. p. 60°/24 mm.), methyl γ-*n*-but-2′-enylacetoacetate (41 g., 50%; b. p. 84—

91°/3 mm., n_D^{25} 1·4475), and crude cinerone (22·5 g., 64%; b. p. 128—138°/25 mm.). The crude cinerone was converted into the semicarbazone (29 g., 94%) which had m. p. 210—215° after stirring with methanol (Found: C, 64·0; H, 8·5; N, 19·6%) (Light absorption: $\lambda_{max.}$ 2650 A., $\varepsilon_{max.}$ 23,800). Fractional crystallisation from methanol yielded as the less soluble major component material, m. p. 222—224°, after softening and becoming brown at 216°, which when admixed with *trans*-cinerone semicarbazone (m. p. 223—224°, after softening at 214°, when determined simultaneously) showed no depression of the m. p. The cinerone regenerated from the semicarbazone, m. p. 210—215°, had b. p. 130°/27 mm., n_D^{20} 1·5002 (Found: C, 78·6; H, 9·4%; Me·C, 16·7%). This ketone gave a *p*-nitrophenylhydrazone, as orange-red needles, m. p. 150—155°, which on fractional crystallisation from methanol gave as the less soluble major component material, m. p. 158—159°. This did not depress the m. p. of *trans*-cinerone *p*-nitrophenylhydrazone (159—160°). From the mother-liquors a small amount of more soluble material, m. p. 147—150°, was obtained, which when admixed with naturally derived cinerone *p*-nitrophenylhydrazone (of m. p. 147—150°) was depressed to m. p. 140—142°.

cis-3-*Hydroxy*-n-*dec*-8-*ene*-2 : 5-*dione*.—Methyl *γ-cis-n*-but-2′-enylacetoacetate (6·0 g.) was shaken with 3% sodium hydroxide (50 ml.) for 3 days at 20°. A little unhydrolysed material was removed with light petroleum, and the solution of sodium *γ-cis-n*-but-2′-enylacetoacetate used directly. To this solution a measured volume of commercial pyruvaldehyde (35% w/v aqueous solution containing sulphuric acid) was added dropwise until the mixture became acid. Enough further pyruvaldehyde to make the total quantity 7·25 ml. (1·0 mol.) was then neutralised with 10% sodium hydroxide and added. This final solution was adjusted to pH 8·5 (narrow-range indicator paper). This solution was kept at 35° (thermostat) for 6 hours and then overnight at room temperature. It was then acidified and heated to 50° to bring about decarboxylation. The product was isolated by saturating the mixture with salt and extraction with ether. The heating and extraction were repeated several times. After the bulked extracts had been washed with acid and water the product was distilled. A low-boiling pale yellow fraction, b. p. 61—67°/0·2 mm., n_D^{20} 1·444—1·448, was collected and then the deeper yellow cis-3-*hydroxy*-n-*dec*-8-*ene*-2 : 5-*dione* (2·5 g., 39%), b. p. 106—110°/0·2 mm., n_D^{20} 1·4745. On redistillation it had b. p. 92—93°/0·05 mm., n_D^{20} 1·4731 (Found: C, 65·4; H, 8·75. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%).

(±)-4-*Hydroxy*-3-*methyl*-2-cis-n-*but* 2′-*enyl*cyclo*pent*-2-*en*-1-*one* [(±)-cis-*Cinerolone*].—3-Hydroxy-*cis-n*-dec-8-ene-2 : 5-dione (1·6 g.) was shaken with 3% sodium hydroxide (30 ml.) at 20° for 6 hours. The oily suspension was then acidified and thoroughly extracted with ether, washed, dried, and distilled. The majority of the product (500 mg.) had b. p. 115—125°/0·08 mm., and on redistillation gave (±)-cis-*cinerolone* (370 mg.), b. p. 102—105°/<0·05 mm., n_D^{20} 1·5120 (Found: C, 71·25; H, 8·9, 8·5; Me·C, 12·1. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%). Light absorption: $\lambda_{max.}$ 2300 A.; $\varepsilon_{max.}$ 10,800.

(±)-*cis*-Cinerolone (55 mg.) was diluted with ethanol (0·2 ml.) and added to semicarbazide hydrochloride (30 mg.) in water (0·04 ml.). Pyridine (0·03 ml.) was added and the mixture heated in a sealed tube at 100° for 40 minutes. Cooling, filtering off, and washing the product with aqueous alcohol gave the semicarbazone (46 mg.), m. p. 195—196°, after previous darkening. Recrystallisation from 5 : 3 ethyl acetate–ethanol gave (±)-cis-*cinerolone semicarbazone* as colourless crystals, m. p. 197—199° (decomp.) (Found: C, 59·3; H, 8·1; N, 18·1; Me·C, 9·9%. $C_{11}H_{18}O_2N_2$ requires C, 58·9; H, 8·1; N, 18·7%). Light absorption: $\lambda_{max.}$ 2650 A.; $\varepsilon_{max.}$ 25,200. A 1 : 1 mixture with naturally derived (±)-cinerolone semicarbazone [m. p. 196—198° (decomp.); cf. West, *J.*, 1946, 463] also had m. p. 196—198° (decomp.). The actual m. p.s observed depended on the rate of heating and values between 192—200° were obtained by varying it. Several m. p.s were determined, always with the three samples side by side in the bath, and no depressions were observed. (±)-*cis*-Cinerolone semicarbazone depressed the m. p. of (±)-*trans*-cinerolone semicarbazone [m. p. 208—209° (decomp.)] (prepared with Mr. A. J. B. Edgar, unpublished) to 192°, with some solid persisting to 195°.

(±)-*cis*-Cinerolone (30 mg.) was dissolved in benzene and a slight excess over the theoretical amounts of pyridine and acetyl chloride was added. After 2 hours at room temperature and then 15 minutes at 50°, the solution was cooled, and water and ether were added. The ethereal layer was washed and dried and the solvent removed under partial vacuum, finally heating to 50° to remove excess of pyridine. Semicarbazide hydrochloride (25 mg.) in water (0·02 ml.) was then added and the mixture heated to 80°. Pyridine (0·02 ml.) and ethanol (0·15 ml.) were then run in and the mixture was heated for 2 hours at 100° in a sealed tube. To the product water was added with stirring. After being kept overnight the crude acetate semicarbazone (5 mg.) was isolated and recrystallised. This (±)-cis-*cineronyl acetate semicarbazone* was identical with naturally derived " cinerolone A-2 acetate " semicarbazone (West, *loc. cit.*), mixtures showing no depression of the m. p.:

	Synthetic.	1 : 1 Mixture.	Natural.
Slow heating: softening	144°	144°	144°
m. p.	146—147	146—147	146—147
Faster heating: m. p.	147—148	147—148	149

Synthetic (±)-*cis*-cineronyl acetate semicarbazone depressed the m. p. of (±)-*trans*-cineronyl acetate semicarbazone (m. p. 157—159°), prepared by a method similar to that described above, to 135—140°, after softening when being placed in the bath at 128°.

(±)-cis-*Cineronyl* (+)-trans-*Chrysanthemate* (*Cinerin-I*).—Synthetic (±)-*cis*-cinerolone (84 mg.) was dissolved in benzene (1 ml.) containing pyridine (0·08 ml.). (+)-*trans*-Chrysanthemoyl chloride (90 mg.) (prepared by the action of thionyl chloride on the naturally derived acid, and having b. p. 104°/20 mm., n_D^{25} 1·4825) was added. Immediate reaction ensued and the product was set aside for 24 hours. It was washed with saturated sodium hydrogen carbonate solution and then with water. After drying and evaporation of the benzene and pyridine at 15 mm., the residue was distilled. A small forerun was collected, n_D^{20} 1·4917, and then the remainder as the required *ester* collected as one fraction (85 mg.), b. p. ~132°/5 × 10^{-3} mm., n_D^{20} 1·5049. Redistillation at 6 × 10^{-3} mm. yielded *cinerin-I* having n_D^{20} 1·5043

(Found: C, 75·0; H, 9·25. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). LaForge and Barthel (*J. Org. Chem.*, 1947, **12**, 199) record n_D^{25} 1·5110 for (±)-*cis*-cineronyl (+)-*trans*-chrysanthemate re-synthesised from the naturally derived components. The forerun was not examined for the presence of free (+)-*trans*-acid (cf. Part III, *J.*, 1950, 971).

(±)-trans-*Chrysanthemoyl Chloride*.—To (±)-*trans*-chrysanthemic acid (4·0 g.) (prepared by Mr. H. W. B. Reed; cf. Campbell and Harper, Part I, *J.*, 1945, 283) in light petroleum (b. p. 40—60°) thionyl chloride (2·3 ml.) was added and the mixture kept overnight. Evaporation and distillation gave (±)-trans-*chrysanthemoyl chloride* (3·6 g., 81%), b. p. 100—101°/17·5 mm., n_D^{20} 1·4851 (Found: C, 64·3; H, 8·1; Cl, 19·0. $C_{10}H_{15}OCl$ requires C, 64·55; H, 8·1; Cl, 19·6%).

(±)-cis-*Cineronyl* (±)-trans-*Chrysanthemate*.—(±)-*cis*-Cinerolone (65 mg.) was esterified with (±)-*trans*-chrysanthemoyl chloride (70 mg.) as above and distilled, to give the required *ester* (85 mg.), b. p. ~130°/1 × 10^{-4} mm., n_D^{20} 1·5000 (Found: C, 73·7, 73·75; H, 9·0, 9·3%). No attempt was made to purify this ester further.

Naturally Derived (±)-*Cinerolone*.—" Cinerolone A-2 " semicarbazone (100 mg.) (West, *loc. cit.*) was shaken with 0·5N-sulphuric acid (2 ml.) under light petroleum (b. p. 40—60°; 2 ml.) for several days at room temperature. Separation of the light petroleum layer, evaporation, and distillation of the residue at 0·05 mm. yielded (±)-cinerolone, having n_D^{20} 1·5156.

Ozonolysis of Naturally Derived (+)-*Cinerolone*.—" Cinerolone A-1 " semicarbazone (542 mg.) (West, *loc. cit.*) was shaken intermittently for 3 months with saturated potassium hydrogen sulphate solution under ether freed from peroxides and in a nitrogen atmosphere. Although a few mg. of semicarbazone remained unhydrolysed the ethereal layer was separated and evaporated, and the residual (+)-cinerolone (assumed to be 400 mg.) dissolved in carbon tetrachloride (25 ml.). This solution was ozonised at 0°, the exit gases being passed through aqueous dimedon, until excess of ozone emerged. Water was added to the ozonide suspension, and air aspirated overnight through and into the aqueous dimedon. The separated derivative had m. p. 127—131°, not raised above 130—132° by crystallisation from 50% aqueous ethanol [126 mg., 17% yield as the acetaldehyde derivative; cf. the 29% yield of pure derivative obtained on ozonolysis of *trans*-cinerone (Harper, *loc. cit.*) with the same apparatus and technique]. 89 Mg. of this mixed derivative in glacial acetic acid were heated at 100° for 12 hours and then diluted, and the precipitate was leached with sodium hydroxide solution. The insoluble acetaldehyde-dimedon " anhydride," crystallising from 50% aqueous ethanol as plates, had m. p. 174°. Acidification of the alkaline extract yielded the formaldehyde-dimedon derivative (12 mg.), which, crystallising from 50% aqueous ethanol as needles, had m. p. 188°, not depressed on admixture with an authentic specimen (189°).

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