

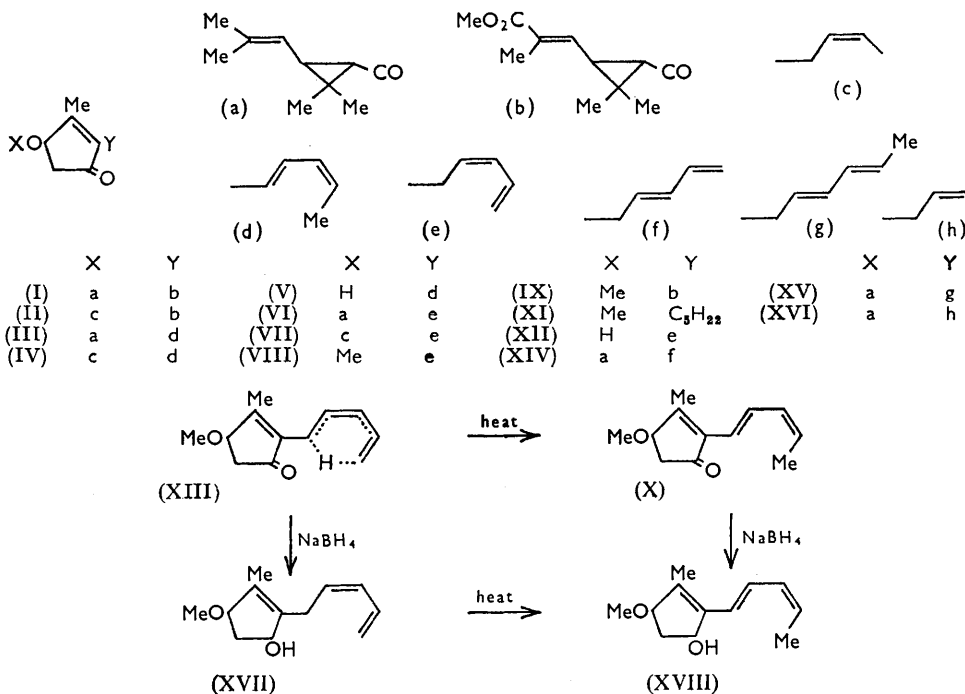
172. The Pyrethrins and Related Compounds. Part III.¹
 Thermal Isomerization of *cis*-Pyrethrolone and its Derivatives.

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When *cis*-pyrethrolone and related compounds are heated, new isomers are formed; these have *trans,cis*-diene side-chains in conjugation with the cyclopentenolone ring. *trans*-Pyrethrolone and compounds with mono-olefinic side-chains do not change in this way under the same conditions.

The infrared (i.r.) and ultraviolet (u.v.) spectra of the new, cross-conjugated isomers and of their ketonic derivatives are described and discussed.

BROWN and his co-workers² found that the mixture of naturally occurring pyrethrins (λ_{max} at 220–230 $\text{m}\mu$) are isomerized at *ca.* 200° to new compounds which absorb less at 220–230 $\text{m}\mu$ and have maxima at *ca.* 270 $\text{m}\mu$. By chromatographic separation and spectroscopic investigations of the fractions, they deduced that cinerin I (I) and cinerin II



(II) were unchanged and that new isomers [conveniently termed isopyrethrin I (III) and isopyrethrin II (IV), from the parent alcohol, isopyrethrolone (V)] were formed from pyrethrin I (VI) and pyrethrin II (VII) when the double bonds in the side-chain of the alcohol migrated into conjugation with the endocyclic olefinic centre.

In this Paper it is shown that such thermal rearrangements take place in all compounds of this group with a *cis*-penta-2,4-dienyl side-chain. When a mixture of (\pm)-pyrethrolone and -cinerolone methyl ethers³ (VIII and IX, respectively) (maximum at 225 $\text{m}\mu$) was heated at 210° *in vacuo* for 30 minutes, there was isolated a new compound (trough at 206 $\text{m}\mu$, neither maximum nor inflexion at 225 $\text{m}\mu$, maxima at 260 and 270 $\text{m}\mu$, shoulder at 279 $\text{m}\mu$) in 66% yield based on the pyrethrolone methyl ether present. This success in separating

¹ Part II, *J. Appl. Chem.*, 1961, 11, 19.

² Brown, Hollinshead, Phipers, and Wood, *Pyrethrum Post*, 1957, 4, No. 2, 13.

³ West, *J.*, 1944, 239.

the new compound from cinerolone methyl ether contrasted with earlier failures to isolate pyrethrolone methyl ether from its mixture with cinerolone methyl ether.⁴ The structure of the new product was deduced to be (\pm)-4-methoxy-3-methyl-2-(penta-1,3-dienyl)-cyclopent-2-enone (X) from the following evidence: (a) carbonyl (2,4-dinitrophenylhydrazone, semicarbazone; max. at 1703 cm^{-1}) and methoxyl (analysis) groups were present, (b) the infrared spectra of the starting material and of the product differed most significantly in the double-bond region, where the band at 907 cm^{-1} (conjugated vinyl¹) was suppressed and new bands emerged at 953 and 991 cm^{-1} , (c) acetaldehyde was formed on ozonolysis, (d) hydrogenation gave (\pm)-tetrahydropyrethrolone methyl ether (XI), identical with the product from hydrogenation of pyrethrolone methyl ether.

Optical activity at C-4 of the cyclopentenolone ring was retained when (+)-pyrethrolone (XII),^{5,6} (+)-pyrethrolone methyl ether (VIII), and (–)pyrethrin-I (VI),^{5,7} were thermally isomerized under the same conditions. (+)-Isopyrethrolone methyl ether (X) and (–)-isopyrethrolone (XII) were crystalline at room temperature and readily formed ketonic derivatives. Retention of optical activity during isomerization does not conflict with the suggested structures, because endocyclic double-bond migration cannot have taken place.

Thermal isomerization was readily detected by the increased absorption at *ca.* 270 $\text{m}\mu$, by the higher refractive indices, and by the decrease in positive rotations and increase in negative rotations of optically active compounds. The rate of thermal isomerization was such that small quantities of pyrethrolone^{5,6} (b. p. 124°/1.5 $\times 10^{-2}$ mm.) and of pyrethrin I^{5,7} (b. p. 146–148°/2 $\times 10^{-3}$ mm.) could be distilled rapidly without detectable isomerization; pyrethrin II^{5,7} (b. p. 196–197°/7 $\times 10^{-3}$ mm.) was appreciably rearranged in batch distillations but, with modern agitated thin-film apparatus, molecular distillation of the mixed pyrethrins without detectable isomerization is practicable.⁸ The recognition that pyrethrolone and its derivatives can undergo thermal isomerization bears on the question of the number of so-called pyrethrolone semicarbazones isolated; this is discussed elsewhere.^{9,6}

Thermal rearrangements of 1,3-dienes were considered by Wolinsky, Chollar, and Baird¹⁰ to take place by a mechanism involving 1,5-transfer of hydrogen in a cyclic transition state which was sterically possible when vinyl and alkyl groups were in *cis*-relation. Such a condition (XIII) is fulfilled in natural pyrethrolone and compounds related to it, where the presence of a *cis*-penta-2,4-dienyl side-chain is established.¹¹ Spectroscopic examination showed that the following compounds, in which cyclic intermediates could not form easily, did not undergo isomerization under conditions that permitted the rearrangement in *cis*-pyrethrolone and its derivatives to be easily detected: (a) *trans*-pyrethrin I^{12,13} (XIV), (b) *trans*-sorbylrethrin I^{13,14} (XV), (c) allethrin¹¹ (XVI), and (d) *cis*-crotylrethrin I (cinerin I) (I).¹¹ Methyl *trans*-chrysanthemate and methyl pyrethrate were also unchanged by heat.

The methoxy-alcohol (XVII), formed by reduction (sodium borohydride) of *cis*-pyrethrolone methyl ether, isomerized with heat to give a compound (XVIII) with identical spectra (u.v. and i.r.) to that obtained by reduction of isopyrethrolone methyl ether. Isomerization therefore did not depend on the presence of the keto-group.

⁴ LaForge and Barthel, *J. Org. Chem.*, 1944, **9**, 242.

⁵ Elliott, *Chem. and Ind.*, 1958, 685.

⁶ Elliott, to be published.

⁷ Sawicki, Elliott, Gower, Snarey, and Thain, *J. Sci. Food Agric.*, 1962, **13**, 172.

⁸ Elliott, Olejniczak, and Garner, *Pyrethrum Post*, 1959, **5**, No. 2, 8.

⁹ Elliott, *Chem. and Ind.*, 1960, 1142.

¹⁰ Wolinsky, Chollar, and Baird, *J. Amer. Chem. Soc.*, 1962, **84**, 2775.

¹¹ For a review and leading references see Crombie and Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 120.

¹² Crombie, Harper, and Thompson, *J.*, 1951, 2906.

¹³ Crombie, Harper, and Newman, *J.*, 1956, 3963.

¹⁴ The nomenclature used is that suggested by Harper, *Chem. and Ind.*, 1949, 636.

Thus, only compounds containing *cis*-dienes isomerized, and, unless inversion of geometrical configuration occurred after emergence from the transition state (XIII), the new conformation of the side-chain should be *trans*-1,*cis*-3-dienyl. The infrared spectra of the isomerized compounds in the CH and CH₂ out-of-plane deformation regions agree with this because they correspond in form and position with those reported for the *cis,trans*- and *trans,cis*-hexa-2,4-dienols¹⁵ and the *cis,trans*- and *trans,cis*-deca-2,4-dienols¹⁶ (peaks in the regions 999—1003, 982—986, and 947—952 cm.⁻¹, respectively); the *trans,trans*- and *cis,cis*-dienols did not display these triplets of peaks. In particular, the spectrum of 1-hydroxy-4-methoxy-3-methyl-2-(penta-1,3-dienyl)cyclopent-2-ene (XVIII) contained three maxima, at 1005, 983, and 948 cm.⁻¹, of similar relative intensity to those in deca-*trans*-2,*cis*-4-dienol (at 1003, 983, and 948 cm.⁻¹),¹⁵ and corresponding combinations of bands were in the spectra of the unreduced isopyrethrolone derivatives. The endocyclic double bond, which bears no hydrogen atoms, can have little effect on the absorption bands attributed to the CH out-of-plane deformation in the conjugated diene side-chain. Thus mechanistic speculation and spectroscopic evidence support the *trans*-1,*cis*-3-conformation for the side-chain of isopyrethrolone and related compounds.

The compounds contain a unique system of cross-conjugated double bonds. In such situations, the ultraviolet spectrum is usually dominated by the more powerful chromophore; here, the *trans,cis*-diene in the side-chain conjugated with the double bond in the ring would be expected to have a greater influence than the shorter, alternative system, the α -unsaturated cyclopentenone. In agreement, the ultraviolet absorption spectra are characteristic of a conjugated triene (max. at 260 and 270, shoulder at 279 m μ) with rather low intensity (ϵ_{270} ca. 20,000). However, although there is neither maximum nor inflexion at the position of absorption of the α -unsaturated cyclopentenone chromophore (220—240 m μ), the carbonyl group does exert an appreciable influence. This was determined from the absorption of the reduced compound (XVIII) which was no longer cross-conjugated: the maxima at 260 and 270 m μ in (X) shifted to 268 and 277 m μ , respectively, and the shoulder at 279 m μ became a maximum at 289 m μ , whilst ϵ_{max} increased from 20,000 to 35,000. The maximum at 277 m μ is in the position calculated for a tetra-alkyl-substituted hexatriene (257 m μ + 4 \times 5 m μ increments = 277 m μ). The smaller intensity of absorption by the parent ketone is therefore associated partly with the influence of the keto-group; further, there is steric hindrance between the α -hydrogen in the diene side-chain and the ring-methyl group at C-3, which will lessen coplanarity and hence the intensity of absorption of the chromophore.

The triene chromophore dominates the spectra of the parent ketones. However, in the semicarbazones and 2,4-dinitrophenylhydrazones the influence of the triene is relatively smaller. The ultraviolet spectra are now characteristic of the whole system and cannot be described in terms of the sum of the absorptions of either of the separate chromophores (triene plus ketonic derivative or diene plus α -unsaturated ketonic derivative) from which they may be considered to be constituted. This is shown most clearly by the curves obtained by subtracting the spectra of the tetrahydropyrethrolone methyl ether derivatives from those of the isopyrethrolone methyl ether derivatives (see Experimental section).

EXPERIMENTAL

Ultraviolet spectra were measured in ethanol on a Unicam S.P. 500 spectrophotometer. Infrared spectra were determined for liquid films on a Grubb-Parsons double-beam spectrometer or a Perkin-Elmer Infracord spectrometer, model 137. The absorption bands noted are those significant for structural assignments or identification. Melting and boiling points are not corrected. Heating at 210° was by immersion in boiling nitrobenzene.

Thermal Isomerization of (\pm)-Pyrethrolone Methyl Ether.—A mixture of pyrethrolone and

¹⁵ Crombie, J., 1955, 1007.

¹⁶ Crombie, Harper, and Newman, J., 1957, 2754.

cinerolone methyl ethers (obtained directly from pyrethrolone and cinerolone semicarbazones³) was redistilled to give a fraction rich in (\pm)-pyrethrolone methyl ether [b. p. 84—86°/4 \times 10⁻³ mm.; n_D^{20} 1.5085; λ_{\max} . 225 m μ (ϵ 21,600); ν_{\max} . 1706, 1650, 993, 977, 907, and 800 cm.⁻¹; calculated content of pyrethrolone methyl ether, 47%]. This material was heated *in vacuo* at 210° for 30 min. and then distilled at 4 \times 10⁻² mm. After rejection of unchanged cinerolone and pyrethrolone methyl ethers (b. p. 64—92°; n_D^{20} 1.4972—1.5289), (\pm)-isopyrethrolone methyl ether (X) was isolated [1.23 g., 31% overall, 66% calc. on pyrethrolone methyl ether; b. p. 92—94°; n_D^{20} 1.5525; λ_{\max} . 260 and 270 m μ (ϵ 18,800 and 20,400), λ_{sh} 279 m μ (ϵ 17,500); ν_{\max} . 1706s, 1630m, 1587m, 991s, 953m, 926w, 860m, 746w, and 724m; Found: C, 74.0; H, 8.45; OMe, 17.4. C₁₂H₁₆O₂ requires C, 75.0; H, 8.4; OMe, 16.2%].

The semicarbazone (from aqueous ethanol) had m. p. 198° (decomp., introduced at 170°); λ_{\max} . 220 and 273 m μ (ϵ 17,100 and 31,700), λ_{inf} . 264 and 296 m μ (ϵ 28,400 and 23,300), λ_{sh} 286 m μ (ϵ 29,100) (Found: C, 61.8; H, 7.4; N, 16.8; OMe, 12.8. C₁₃H₁₉N₃O₂ requires C, 62.6; H, 7.7; N, 16.9; OMe, 12.5%).

The orange 2,4-dinitrophenylhydrazone (from 2,4-dinitrophenylhydrazine in 10% v/v sulphuric acid-methanol) had m. p. 189—191° after purification by passage in chloroform through a bentonite-kieselguhr column¹⁷ and two recrystallizations from ethanol [λ_{\max} . 232, 282, and 380 m μ (ϵ 25,000, 26,700, and 22,700), λ_{inf} . 262 and 308 m μ (ϵ 23,700 and 12,600); Found: C, 58.0; H, 5.4; N, 14.2. C₁₈H₂₀N₄O₅ requires C, 58.1; H, 5.4; N, 15.1%].

Ozonolysis of (\pm)-Isopyrethrolone Methyl Ether.—This compound (0.456 g.) in carbon tetrachloride (75 ml.) was treated with ozonized oxygen for 90 min. at 0°. After addition of ice, the volatile products were swept into saturated aqueous dimedone solution with nitrogen, and acetaldehyde was identified as the dimedone derivative (0.068 g.; m. p. and mixed m. p. 137—139.5°, after two crystallizations from aqueous ethanol).

Hydrogenation of (\pm)-Isopyrethrolone Methyl Ether.—(\pm)-Isopyrethrolone methyl ether (0.270 g.) in ethanol (35 ml.) with 5% palladium on calcium carbonate (0.080 g.) absorbed 69 ml. of hydrogen in 65 min. (Calc. for 2 mols. of hydrogen, 68 ml.). The product had b. p. 76—85°/4 \times 10⁻³ mm., n_D^{20} 1.4668; λ_{\max} . 230 m μ (ϵ 9680) [lit.,¹⁷ for tetrahydropyrethrolone methyl ether, b. p. 95—96°/1.7 mm., n_D^{20} 1.4732; λ_{\max} . 230.5 m μ (ϵ 10,600)]. The 2,4-dinitrophenylhydrazone, after chromatographic purification (bentonite-kieselguhr) and recrystallization (ethanol) had m. p. 143—145°; λ_{\max} . 217, 254, and 378 m μ (ϵ 16,400, 17,700, and 28,300). The m. p. was not depressed on admixture with the 2,4-dinitrophenylhydrazone (λ_{\max} . 216, 254, and 380 m μ (ϵ 17,300, 18,000, and 28,400)] of (\pm)-tetrahydropyrethrolone methyl ether obtained from (\pm)-pyrethrolone methyl ether (b. p. 81—89°/3 \times 10⁻³ mm., n_D^{20} 1.5146).

The subtraction curve (see text) [(\pm)-isopyrethrolone methyl ether 2,4-dinitrophenylhydrazone minus tetrahydropyrethrolone methyl ether 2,4-dinitrophenylhydrazone] had λ_{\max} . 231 and 283 m μ (ϵ 9300 and 15,400). The corresponding curve for the semicarbazones had λ_{\max} . 220 and 290 m μ (ϵ 10,500 and 24,000).

Thermal Isomerization of (+)-Pyrethrolone Methyl Ether.—(+)-Pyrethrolone methyl ether [b. p. 106—108°/0.5 mm.; n_D^{20} 1.5217; $[\alpha]_D^{20}$ +99° (*c* 2.08 in methanol); λ_{\max} . 225 m μ (ϵ 31,600); (Found: C, 75.05; H, 8.25. Calc. for C₁₂H₁₆O₂: C, 75.0; H, 8.4%)] was made from pure (+)-pyrethrolone^{5,6} with dimethyl sulphate [lit.,³ b. p. 87°/0.3 mm.; n_D^{20} 1.5130, $[\alpha]_D$ +97.3°; λ_{\max} . 227 m μ (ϵ 19,300)]. (+)-Pyrethrolone methyl ether (1.9 g.) was heated *in vacuo* at 210° with a trace of quinol for 30 min. Distillation gave (+)-isopyrethrolone methyl ether [0.781 g., b. p. 103—106°/0.3 mm.; n_D^{20} 1.5592; $[\alpha]_D^{20}$ +92.7° (*c* 5.34 in methanol); Found: C, 74.2; H, 8.5%; λ_{\max} . 259 and 269 m μ (ϵ 18,700 and 21,000), λ_{sh} 279 m μ (ϵ 17,800); m. p. 23°, raised to 28° after one recrystallization from pentane; i.r. spectrum identical with that of (\pm)-isopyrethrolone methyl ether].

Reduction of (+)-Isopyrethrolone Methyl Ether.—This compound (0.534 g.) in methanol (10 ml.) was reduced during 16 hr. with sodium borohydride (1.0 g.). Isolation with ether after addition of saturated sodium chloride gave 1-hydroxy-4-methoxy-3-methyl-2-(penta-trans-1,cis-3-dienyl)cyclopent-2-ene (XVIII) [0.403 g.; b. p. 109—114°/0.2 mm.; n_D^{20} 1.5327; Found: C, 74.3; H, 10.1. C₁₂H₁₈O₂ requires C, 74.2; H, 9.4%; m. p., after two recrystallizations from pentane at -20°, 75.5—76.5°; λ_{\max} . 268, 278, and 288 m μ (ϵ 29,000, 35,000, and 28,000); ν_{\max} . 1720, 1670, 1640, 1004, 983, 958, 946, and 871 cm.⁻¹], identical (mixed m. p.

¹⁷ Linstead, Elvidge, and Whalley, "Modern Techniques of Organic Chemistry," Butterworths Scientific Publications, London, 1955, p. 5.

u.v. and i.r.) with the compound (XVIII) obtained by thermal isomerization of the methoxy-alcohol (XVII).

(+)-1-Hydroxy-4-methoxy-3-methyl-2-(penta-cis-2,4-dienyl)cyclopent-2-ene.—(+)-Pyrethrolone methyl ether (1.00 g.) in methanol (10 ml.) containing 2N-sodium hydroxide in methanol (2 drops) was reduced during one night with sodium borohydride (1.0 g.). After addition of water (10 ml.), the mixture was stirred for 1 hr., then neutralized (dilute hydrochloric acid) and extracted (ether). The ether extract was washed (saturated sodium chloride), dried (Na_2SO_4), evaporated, and distilled to give (+)-1-hydroxy-4-methoxy-3-methyl-2-(penta-cis-2,4-dienyl)cyclopent-2-ene (XVII) [0.66 g.; b. p. 102—103°/0.2 mm.; n_D^{20} 1.5172; m. p. 32°; $[\alpha]_D^{20}$ +112° (c 2.55 in methanol); no absorption at 1715 cm^{-1} (C=O); λ_{max} 230.5 μ (ϵ 22,800); Found: C, 73.8; H, 9.3. $\text{C}_{12}\text{H}_{18}\text{O}_2$ requires C, 74.2; H, 9.3%]. When this compound (0.245 g.) was heated *in vacuo* at 210° for 1 hr. and the residue recrystallized twice at -20° from pentane, 1-hydroxy-4-methoxy-3-methyl-2-(penta-1,3-dienyl)cyclopent-2-ene (XVIII) was obtained, identical (u.v., i.r., and mixed m. p.) with the product from reduction of isopyrethrolone methyl ether.

Thermal Isomerization of (+)-Pyrethrolone.—(+)-Pyrethrolone [b. p. 125.5—135°; n_D^{20} 1.5461; $[\alpha]_D^{20}$ +15.1° (c 12.7 in ether); 4.07 g.; from pyrethrolone hydrate^{5,6}] was heated *in vacuo* at 210° for 30 min. The viscous residue was transferred with benzene and distilled. After rejection of fractions b. p. 120—140°/5 × 10⁻² mm., n_D^{20} 1.5613—1.5770, (-)-isopyrethrolone [0.722 g.; b. p. 140°/4 × 10⁻² mm.; n_D^{20} 1.5894; $[\alpha]_D^{20}$ -5.6° (c 4.82 in ether); λ_{max} 261, 270, and 279 μ (ϵ 18,000, 19,800, and 16,900); ν_{max} 1686s (C=O), 1603s, 1513s, 1066s, 1011s, 992s, 954m, 927m, 861m, 831m, 763m, 728m, and 706m cm^{-1}] was isolated. After one crystallization from ether this had m. p. 63—64.5° (Found: C, 73.0; H, 8.1%).

The 2,4-dinitrophenylhydrazone [from ketone (0.28 g.) and a solution of 2,4-dinitrophenylhydrazine (0.2 g.) in 20 ml. of 10% sulphuric acid] had m. p. 198—200° (decomp.) (from benzene); $[\alpha]_D^{19}$ -130° (c 0.111 in benzene); λ_{max} 233, 282, and 380 μ (ϵ 26,700, 27,500, and 24,100) (Found: C, 56.8; H, 5.4; N, 15.2. $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_5$ requires C, 57.0; H, 5.1; N, 15.6%).

Thermal Isomerization of (-)-Pyrethrin I.—The ester⁷ (5.50 g.; $[\alpha]_D^{20}$ -14.5°, in iso-octane) was heated *in vacuo* for 30 min. at 210°. Isolation by distillation gave, after rejection of fractions of low b. p., (-)-isopyrethrin I [1.38 g.; b. p. 170—178°/5 × 10⁻² mm.; $[\alpha]_D^{20}$ -74.8° (c 6.94 in hexane); λ_{max} 261 and 270 μ (ϵ 18,000 and 18,900); λ_{inf} 280 μ (ϵ 16,200); Found: C, 76.1; H, 8.7. $\text{C}_{21}\text{H}_{28}\text{O}_3$ requires C, 76.8; H, 8.6%].

Spectroscopic Investigation of Thermal Isomerizations.—Petroleum distillate was purified for spectroscopy in the region 200—300 μ by stirring it in succession with chromic acid solution and concentrated sulphuric acid (2 portions). The product was washed (sodium hydrogen carbonate, then sodium chloride solutions), dried (Na_2SO_4), and distilled. The fraction b. p. 210—220° was used. The compound (1—5 mg., depending on ϵ_{max}) was dissolved in *ca.* 3 g. of this distillate, and the ultraviolet spectrum determined. The solution (*ca.* 2 ml.) was heated *in vacuo* for 1 hr. at 210°, and the ultraviolet spectrum then redetermined on cooling. The following are listed: compound, decrease in $E_{1\text{cm}}^1\%$ at approximate position of maximum of unheated compound, increase in $E_{1\text{cm}}^1\%$ at 270 μ . Natural pyrethrins¹⁸ 538, 221; pyrethrin I⁷ 654, 306; pyrethrin II,⁷ 508, 353; cinerin II,⁷ 29, 39; allethrin,¹¹ 0,0; (\pm)-*trans*-sorbyl-rethrin I,¹³ 18, 50; (\pm)-*trans*-pyrethrin I,¹² 310, 122 (increase at 270 μ due to general absorption only; no specific absorption at 260, 270, and 280 μ , as obtained with *cis*-diene derivatives).

Methyl (\pm)-*trans*-chrysanthemate¹⁹ [from (\pm)-*trans*-chrysanthemic acid by the action of diazomethane] and methyl (\pm)-*trans*-pyrethrate²⁰ showed no change in absorption after 1 hr. *in vacuo* at 210°.

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¹⁸ Barthel, Haller, and LaForge, *Soap*, 1944, 20, No. 7, 121.

¹⁹ Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, 7, 201.

²⁰ Crombie, Harper, and Sleep, *J.*, 1957, 2743.