61. *The Structure of Pyrethrolone and Related Compounds. Part II.*

By T. F. West.

The methyl ether obtained from pyrethrolone by means of methyl sulphate has $[a]_D^{20°}$ $-97\cdot3°$ (in alcohol), whereas that derived from pyrethrolone semicarbazone by treatment with methyl-alcoholic sulphuric acid is optically inactive (cf. Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 212). The corresponding semicarbazones have m. p. 183°, $[a]_D^{20°}$ $-82°$ (in pyridine), and m. p. 197°, $[a]_D \pm 0°$ (in pyridine), and the former on treatment with methyl-alcoholic sulphuric acid is converted into the optically inactive pyrethrolone methyl ether obtainable directly from pyrethrolone semicarbazone. Both compounds are shown by light-absorption measurements to contain similar chromophoric systems and are therefore probably stereoisomeric.

The failure of these and other pyrethrolone derivatives to undergo the Diels–Alder condensation is discussed, and an explanation is suggested by postulating a *cis*-configuration—similar to that present in *cis*-piperylene—for a conjugated side chain.

A fresh formulation for pyrethrolone is proposed which appears to be more in keeping with the chemical evidence than the structures previously advanced.

ALTHOUGH the absorption-spectra data appear to indicate that in the pyrethrolone fragment of the pyrethrin molecules two separate light-absorbing components are present, *viz.*, (*a*) an $a\beta$-unsaturated ketonic group in the *cyclo*pentenolone ring and (*b*) a conjugated system in the pentadienyl side chain (Gillam and West, *J.*, 1942, 671; this vol., p. 49; West, this vol., p. 51; cf. LaForge and Acree, *J. Org. Chem.*, 1942, **7**, 418), yet it has been pointed out by LaForge and his co-workers that the chemical evidence is inconclusive. For instance, LaForge and Haller (*ibid.*, 1938, **2**, 546) reported, amongst other divergences from the behaviour expected of a conjugated system, that neither pyrethrolone nor its deoxy-derivative pyrethrone forms addition products with α-naphthaquinone or gives normal adducts with maleic anhydride—the amorphous, resinous substance produced with the latter was considered to be due to the effect of traces of acids in polymerising pyrethrone.
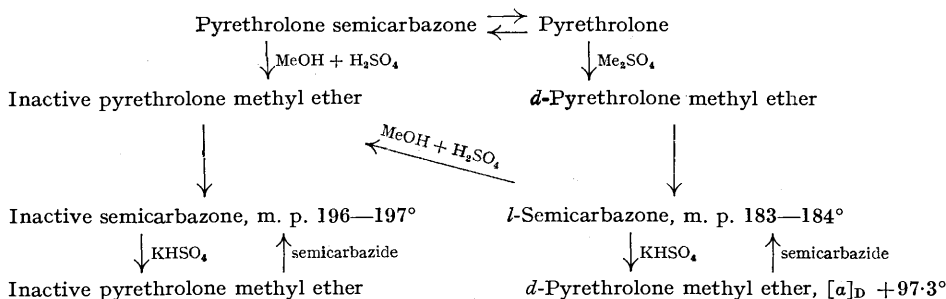
Pyrethrolone methyl ether is comparatively stable towards acids and less easily polymerised than pyrethrolone, and it has therefore been subjected to the action of maleic anhydride and other dienophiles. In the earlier experiments (commenced some years ago) the pyrethrolone methyl ether was prepared from pyrethrolone by treatment with methyl sulphate, as recommended by Staudinger and Ruzicka (*loc. cit.*, p. 224), but in confirmatory work it was decided to use, in addition, for comparison, samples of the methyl ether prepared by refluxing pyrethrolone semicarbazone with sulphuric acid and methyl alcohol (*idem, ibid.*, p. 222). These authors reported that each of these methods gave methyl ethers of which the semicarbazones (m. p. 183°) appeared to be identical. Gnadinger and Corl (*J. Amer. Chem. Soc.*, 1933, **55**, 1221) found that the sample of pyrethrolone methyl ether which they obtained from pyrethrolone semicarbazone yielded a semicarbazone, m. p. 187°, but stated that this high m. p. was " probably because of the presence of a small amount of pyrethrolone."

The author was unable to raise above 184° the m. p. of the semicarbazone obtained from pyrethrolone methyl ether prepared from pyrethrolone and methyl sulphate, whereas samples of the semicarbazone from the ether obtained by treating pyrethrolone semicarbazone with methyl-alcoholic sulphuric acid melted as high as 197°. The two methyl ethers and their semicarbazones exhibited similar absorption spectra and therefore, presumably, contained similar chromophoric systems, but samples of the ether prepared with methyl sulphate had $\alpha_D +85°$, whereas the second compound was optically inactive. The semicarbazone (m. p. 183°) prepared from the dextrorotatory pyrethrolone methyl ether had $[\alpha]_D -82°$ (in pyridine), whereas that (m. p.

197°) derived from the optically inactive ether was itself inactive. During purification it was noticed that the active was more soluble than the inactive semicarbazone in organic solvents. Neither of the ethers could be reduced by the Pondorff–Meerwein method.

The active ether was recovered substantially unchanged after treatment with methyl-alcoholic sulphuric acid under the conditions used for the preparation of the inactive methyl ether from pyrethrolone semicarbazone. On the other hand, treatment of the lævorotatory pyrethrolone methyl ether semicarbazome in this manner gave an inactive pyrethrolone methyl ether of which the semicarbazone was shown to be identical with that prepared from the inactive methyl ether derived directly from pyrethrolone semicarbazone. Both the dextro-rotatory and the inactive pyrethrolone methyl ether were regenerated satisfactorily from the appropriate semicarbazones by treatment with aqueous potassium hydrogen sulphate in the presence of ether, but the inactive semicarbazone was hydrolysed much less rapidly. The compound regenerated from the semicarbazone of m. p. 183° had $[\alpha]_D$ +97·3° (in alcohol), and this was the highest value observed during the course of the work on these pyrethrolone derivatives.

The relationship between these compounds can be summarised as follows :

Pyrethrolone semicarbazone $\rightleftarrows$ Pyrethrolone

$\downarrow$MeOH + H₂SO₄ $\downarrow$Me₂SO₄

Inactive pyrethrolone methyl ether   *d*-Pyrethrolone methyl ether

$\xleftarrow{\text{MeOH} + \text{H}_2\text{SO}_4}$

Inactive semicarbazone, m. p. 196—197°   *l*-Semicarbazone, m. p. 183—184°

$\downarrow$KHSO₄ $\uparrow$semicarbazide $\downarrow$KHSO₄ $\uparrow$semicarbazide

Inactive pyrethrolone methyl ether   *d*-Pyrethrolone methyl ether, $[\alpha]_D$ +97·3°

Each of these ethers behaves abnormally in the Diels–Alder reaction. They were recovered unchanged after treatment under various conditions with α-naphthaquinone, *p*-benzoquinone, acetylenedicarboxylic esters, and maleic anhydride, although with the last considerable quantities of polymeric resinous substances were produced. The amount of resinous material was reduced when the reaction was carried out in the presence of phenyl-β-naphthylamine (Craig, *J. Amer. Chem. Soc.*, 1943, **65**, 1011), but although a larger proportion of unchanged methyl ether was recoverable no crystallisable adduct was obtained.

From the ozonolysis evidence, CHR:CH·CH:CHMe appears to be a probable formulation for pyrethrolone (Gillam and West; West; *locc. cit.*), and if the *cis*-configuration is postulated for the pentadienyl side chain, the failure to react in the Diels–Alder condensation can be readily explained (Bachman and Goebel, *J. Amer. Chem. Soc.*, 1942, **64**, 787; Henne and Turk, *ibid.*, p. 826; Craig, *ibid.*, 1943, **65**, 1006). On the other hand, if the side chain –CH₂·CH:CH·CH:CH₂ for pyrethrolone and its derivatives is considered [the light-absorption data for the conjugated diene obtained by the methods described by Gillam and West (*loc. cit.*) do not allow of a clear differentiation between this structure and –CH:CH·CH:CHMe], this argument does not apply with the same force, although, from a consideration of models, the presence of the terminal substituted methyl group (·CH₂R) does seem to permit an explanation involving analogy with the behaviour of *cis*-piperylene. However, an alternative formulation (I) for pyrethrolone has arisen out of discussion of this anomalous behaviour towards dienophiles with Professor A. R. Todd, F.R.S.
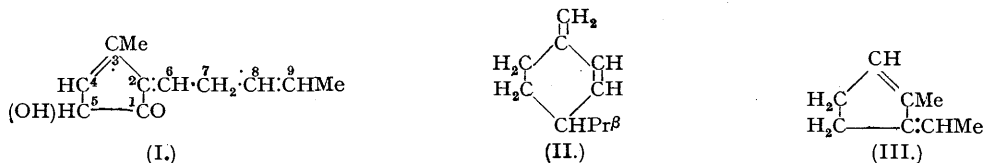
The failure of normal reactivity in the Diels–Alder condensation is then readily explained, since the conjugated diene system is locked in the *trans*-position and is analogous with that present in β-phellandrene (II), which gives only polymeric products with maleic anhydride (Goodway and West, *J. Soc. Chem. Ind.*, 1938, **57**, 37; *J.*, 1938, 2028), and in the hydrocarbon of probable formula (III) (King and Robinson, *J.*, 1941, 465) which did not yield an adduct. The formulation (I) explains the production of the main degradation products obtained from pyrethrolone by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 212) and obviates the interchange of >CO and >CH(OH) groups in the *cyclo*pentenolone ring which is necessary in accommodating the –CH:CH·CH:CHMe side chain. In addition, the behaviour of the pyrethrins on reduction (Haller and LaForge, *J. Org. Chem.*, 1936, **1**, 38; 1937, **2**, 49) and the anomalous behaviour of pyrethrolone derivatives with bromine (LaForge and Haller, *ibid.*, 1938, **2**, 546; Acree and LaForge, *ibid.*, 1940, **5**, 430) appears to find some explanation. If pyrethrone has the same structure as pyrethrolone (I), the fact that the former is optically inactive (LaForge and Haller, *loc. cit.*, 1938) is in agreement with the new formulation. Unfortunately, no light-absorption data are available for compounds containing the system involved in (I).

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of the d-*Pyrethrolone Methyl Ether.*—Pyrethrolone (6·5 g.) having b. p. 148—150°/0·8 mm., $n_D^{20°}$ 1·5384, $a_D^{25°}$ +8°, $d_{15·5°}^{15·5°}$ 1·051, methyl sulphate (19·5 g.), ether (39 ml.), and potassium hydroxide (19·5 g.) were mixed in this order, and the mixture stirred mechanically for 24 hours. By proceeding essentially as described by Staudinger and Ruzicka (*loc. cit.*, p. 224), the methyl ether obtained (5 g.) had b. p. 114—116°/0·8 mm., $n_D^{20°}$ 1·5130, $a_D^{25°}$ +85° (Found : OMe, 15·9. Calc. for $C_{12}H_{16}O_2$: OMe, 16·1%). A second sample of pyrethrolone (13·4 g.) having b. p. 164—167°/3 mm., $n_D^{20°}$ 1·5370, $d_{15·5°}^{15·5°}$ 1·052, $a_D^{25°}$ 14·1°, $\lambda_{max.}$ 2275 A., ε = 20,200, similarly treated, gave a methyl ether (8·6 g.) having b. p. 122—124°/2 mm., $n_D^{20°}$ 1·5113, $d_{15·5°}^{15·5°}$ 1·004, $a_D^{25°}$ 84·1° (Found : OMe, 15·4%), $\lambda_{max.}$ 2260 A., ε = 23,400. A third sample of the methyl ether prepared by this method had b. p. 104—106°/0·4 mm., $a_D^{20°}$ +85·4°, $d_{15·5°}^{15·5°}$ 1·004 (Found : OMe, 15·7%). Pyrethrolone methyl ether (1·5 g.) (a_D +85°) yielded a semicarbazone (1·83 g.), m. p. 173—176°; recrystallised from methyl alcohol (40 ml.), this (1·4 g.) had m. p. 179°, raised by one further recrystallisation to 183—184° (unchanged by further recrystallisation), $[a]_D$ −79° (*c*, 1·0 in pyridine) (Found : N, 16·7. Calc. for $C_{13}H_{19}O_2N_3$: N, 16·9%); $\lambda_{max.}$ 2320 A., ε = 17,300, and 2665 A., ε = 19,000. The methyl ether (a_D +84·1°) yielded a semicarbazone, m. p. 182—184°, $[a]_D$ −70° (*c*, 0·88 in pyridine), and the third sample (a_D +85·4°) a semicarbazone, m. p. 183—184°, $[a]_D$ −75° (*c*, 0·87 in pyridine). For the preparation of a regenerated d-pyrethrolone methyl ether, a mixture of the l-semicarbazone (2·8 g.), $[a]_D$ −70° (*c*, 0·76 in pyridine), m. p. 182—184°, potassium hydrogen sulphate (40 g.), water (90 ml.), and ether (90 ml.) in an atmosphere of carbon dioxide was shaken mechanically for 3 days, filtered from unchanged semicarbazone (washed and dried this weighed 1·75 g., m. p. 181—182°), and the ethereal solution washed with brine until neutral. The oil recovered by removing the ether was steam-distilled, and the volatile oil extracted from the distillate with light petroleum. Removal of the solvent gave 0·55 g. of oil which was distilled to give d-pyrethrolone methyl ether (0·5 g.), b. p. 87°/0·3 mm., $n_D^{20°}$ 1·5078, $d_{15·5°}^{15·5°}$ 1·001, $[a]_D$ +97·3° (*c*, 16·6 in alcohol) (Found : OMe, 16·7%), $\lambda_{max.}$ 2270 A., ε = 19·300. The semicarbazone prepared from this sample had m. p. 183—184° (after recrystallisation from methyl alcohol), $[a]_D$ −82° (*c*, 0·77 in pyridine).

Preparation of the Inactive Pyrethrolone Methyl Ether (cf. Staudinger and Ruzicka, *loc. cit.*, p. 222).—Pyrethrolone semicarbazone (20 g.), m. p. 208°, was refluxed on the water-bath for 2½ hours with a solution of sulphuric acid (12 g.) in methyl alcohol (200 ml.), then water (400 ml.) was added, and the methyl alcohol removed by distillation under reduced pressure. The solution was cooled, and the solid material filtered off (6·3 g., dry). The filtrate was extracted with light petroleum, and the oil recovered by removing the solvent (7·5 g.) distilled to give a substantially inactive methyl ether (7·2 g.), b. p. 113—115°/0·8 mm., $n_D^{20°}$ 1·5149, $a_D^{25°}$ +0·1° (Found : OMe, 14·3, 14·5. Calc. for $C_{12}H_{16}O_2$: OMe, 16·1%), $\lambda_{max.}$ 2270 A., ε = 24,400. This methyl ether (0·5 g.) yielded a semicarbazone (0·63 g.), m. p. 194°, which recrystallised from methyl alcohol (35 ml.) to give 0·47 g., m. p. 195—196°, unchanged by further recrystallisation; $[a]_D$ ±0° (*c*, 1·0 in pyridine) (Found : N, 16·4. Calc. for $C_{13}H_{19}O_2N_3$: N, 16·9%); $\lambda_{max.}$ 2320 A., ε = 21,000, and 2655 A., ε = 19,000. Mixed with pyrethrolone semicarbazone (m. p. 205°), this had m. p. 182—188° (indef.), and mixed with the l-semicarbazone from d-pyrethrolone methyl ether (m. p. 183—184°) it had m. p. 182—193° (indef.). After extraction with light petroleum, the filtrate was extracted with ether to give only 0·7 g. of a semicrystalline mass which was added to the 6·3 g. of crystalline material obtained above, and the whole recrystallised from methyl alcohol (300 ml.) to give 5·3 g., m. p. 193—195°. This product was dissolved in methyl alcohol (350 ml.), and the solution filtered and concentrated to 70 ml., whereupon the first crop of crystals (4·5 g.) had m. p. 194—197°; after one recrystallisation from methyl alcohol (210 ml.) the semicarbazone (1·15 g.) had m. p. 195—197°, not depressed by admixture with the semicarbazone, m. p. 195—196°, obtained above; $[a]_D$ ±0° (*c*, 0·74 in pyridine). The filtrate was concentrated by distillation under reduced pressure to 70 ml., whereupon a second crop (2·55 g.) of the same compound, m. p. 195—197°, $[a]_D$ ±0° (*c*, 0·8 in pyridine), was obtained. The filtrate was combined with that from the first recrystallisation above, and the solution concentrated to 30 ml., a further 1·15 g. of crystalline material, m. p. 192° (sintering at 182°), being obtained. This third crop was not purified.

For the preparation of regenerated i-pyrethrolone methyl ether, the inactive semicarbazone (2·85 g.), m. p. 195—196°, was shaken with a mixture of potassium hydrogen sulphate (40 g.), water (90 ml.), and ether (90 ml.) in an atmosphere of carbon dioxide mechanically for 10 days (the inactive semicarbazone was less easily hydrolysed than the l-semicarbazone, which was shaken for only 3 days to minimise possible change of the liberated active pyrethrolone methyl ether into the inactive form). The mixture was then filtered from unchanged semicarbazone, which was washed and dried (1·9 g., m. p. 192—193°), and the ethereal solution treated as described above to give 0·5 g. of steam-volatile oil, which was distilled to give 0·45 g. of the inactive pyrethrolone methyl ether, b. p. 85°/0·2 mm., $n_D^{20°}$ 1·5142, $d_{15·5°}^{15·5°}$ 1·015, $[a]_D$ ±0° (*c*, 14·11 in alcohol) (Found : OMe, 15·9%), $\lambda_{max.}$ 2270 A., ε = 25,000. The semicarbazone prepared from this sample had m. p. 196—197° after recrystallisation from methyl alcohol, $[a]_D$ ±0° (*c*, 0·52 in pyridine).

Conversion of the d- *into the* i-*Form.*—The l-semicarbazone (1 g.), m. p. 183—184°, was refluxed with methyl-alcoholic sulphuric acid as described above. After removal of the methyl alcohol there was no solid material in suspension, and accordingly the aqueous solution was extracted with light petroleum and the oil (0·3 g.) obtained was distilled to give 0·25 g., b. p. 99—100°/0·3 mm., $n_D^{20°}$ 1·5093, $[a]_D$ ±0° (*c*, 4·2 in alcohol) (Found : OMe, 16·9%), $\lambda_{max.}$ 2250 A., ε = 22,750. The semicarbazone prepared in the usual manner had m. p. 193° when crude, raised by two recrystallisations from methyl alcohol to 196—197°, not depressed by admixture with the semicarbazone (m. p. 195—196°) prepared directly from the methyl ether obtained from pyrethrolone semicarbazone by this method. (After extraction with light petroleum, the aqueous residue was extracted with ether to give only 0·15 g. of a dark, resinous product which was rejected.) When the d-pyrethrolone methyl ether itself (0·5 g.) was treated with methyl-alcoholic sulphuric acid, the ether recovered (0·41 g.) had b. p. 105—107°/0·8 mm., $n_D^{20°}$ 1·5075, $[a]_D$ +90° (*c*, 1·2 in alcohol) (Found : OMe, 17·6%), $\lambda_{max.}$ 2270 A., ε = 20,700. This recovered d-pyrethrolone methyl ether (0·17 g.), treated in the usual manner, yielded 0·19 g. of a semicarbazone, m. p. 176—179°, which recrystallised from methyl alcohol to give 0·11 g., m. p. 182—183°, not depressed by admixture with the semicarbazone derived from untreated d-pyrethrolone methyl ether.

Treatment of d-*Pyrethrolone Methyl Ether with Maleic Anhydride and Other Dienophiles.*—In a typical experiment, pyrethrolone methyl ether (10 g.), $a_D^{20°}$ +85·4°, maleic anhydride (5 g.), and benzene (67 ml.) were mixed, divided into 10 equal portions, heated in sealed tubes in an atmosphere of nitrogen for 6 hours at 100°, and set aside overnight. The benzene was poured from the resin (which, recovered by dissolving in acetone, weighed 4·5 g. when dried in a vacuum desiccator) deposited in the tubes. The benzene solution was washed with hot water—the first wash causing the liberation of an insoluble, sticky, resinous scum (0·3 g. when dry) from the benzene solution—until the aqueous washings were no longer acid to litmus. The benzene was removed by distillation, and the residual oil steam-distilled. The oil extracted from the distillate with light petroleum was distilled, giving 6 g. of unchanged pyrethrolone methyl ether, b. p. 102—103°/0·3 mm., $n_D^{20°}$ 1·5118, a_D +86°, $d_{15·5°}^{15·5°}$ 1·003 (Found : OMe, 15·6%); its semicarbazone had m. p. 183—184° after recrystallisation from methyl alcohol, not depressed by admixture with that obtained from the methyl ether not subjected to the action of maleic anhydride. The non-steam volatile portion was obtained by cooling the water and filtering off the solid material, which was dried in a vacuum desiccator (0·6 g.). This was extracted with methyl alcohol

to leave 0·12 g. of insoluble resin.   The methyl alcohol was allowed to evaporate at room temperature, but left only sticky, non-crystalline, resinous material which could not be induced to crystallise by treatment with other solvents. This experiment is typical of a number in which the time of heating was varied, the residue obtained from the benzene solution after washing with water was subjected to vacuum distillation, and the benzene solution was distilled without treatment with water, but in each case only unchanged methyl ether was obtained, yielding the semicarbazone, m. p. 183°, and the resinous higher-boiling material could not be crystallised and decomposed on attempted vacuum distillation. When acetone was employed in place of the benzene as solvent, all the reaction products were retained in the solution, which became viscous, but on distillation, although a smaller proportion of the unchanged methyl ether was recovered, the resinous reaction product could not be distilled or crystallised.   When benzene was used as solvent, the deposition of resin in the tubes during heating could be avoided by adding phenyl-β-naphthylamine to the reaction mixture, but in spite of a number of experiments no crystallisable or volatile products (other than unreacted methyl ether) could be obtained.   In these experiments the $[\alpha]_D$ of the recovered pyrethrolone methyl ether varied between 85° and 95° (in alcohol), and in each case identification was completed by preparation of the semicarbazone and mixed m. p. determination.

When the ether was heated with methyl acetylenedicarboxylate at 145—150° for 5 hours in an atmosphere of nitrogen, only a small amount of brown resinous material was obtained after removal of unreacted pyrethrolone methyl ether and unchanged ester by distillation.   Similar results were obtained with the ethyl ester.

The active pyrethrolone methyl ether was recovered practically quantitatively after being heated with p-benzoquinone or α-naphthaquinone in alcoholic solution for periods up to 6 hours in sealed tubes at 100°.

Treatment of Inactive Methyl Ether with Maleic Anhydride.—In a typical experiment the inactive pyrethrolone methyl ether (1·5 g.), maleic anhydride (0·75 g.), phenyl-β-naphthylamine (0·37 g.), and benzene (10 ml.) were heated in sealed tubes in a nitrogen atmosphere at 100° for 6 hours.   No resin separated in the tube, but on shaking the benzene solution with water a gummy scum separated.   After repeated washing with hot water, the benzene was removed, and the oily residue steam-distilled.   The oil (0·9 g.) recovered from the distillate by extraction with light petroleum had b. p. 100—101°/0·5 mm., $n_D^{20°}$ 1·5121, $[\alpha]_D + 0·76°$ (c, 5 in alcohol), $d_{15·5°}^{15·5°}$ 1·001, and its identity as unreacted pyrethrolone methyl ether was confirmed by the preparation of the semicarbazone, m. p. 196—197°, not depressed by admixture with semicarbazone prepared from the original ether.   The non-steam volatile portion was collected, and distilled at 0·3 mm., but only a further small quantity (0·2 g.) of unreacted methyl ether (yielding the appropriate semicarbazone) was obtained (with some phenyl-β-naphthylamine), leaving a resin which decomposed and darkened on attempted distillation.   Similar results were obtained in the absence of the phenyl-β-naphthylamine, except that deposition occurred in the tube during heating of the reactants and the amount of pyrethrolone methyl ether recovered was slightly reduced.   The use of acetone instead of benzene did not lead to any crystallisable products.

Determinations of absorption spectra were made in ethyl alcohol solution on a Hilger E_3 quartz spectrograph in conjunction with a Spekker photometer.