

**999. The Pyrethrins and Related Compounds.\* Part V.<sup>1</sup> Purification of (+)-Pyrethrolone as the Monohydrate, and the Nature of "Pyrethrolone-C."**

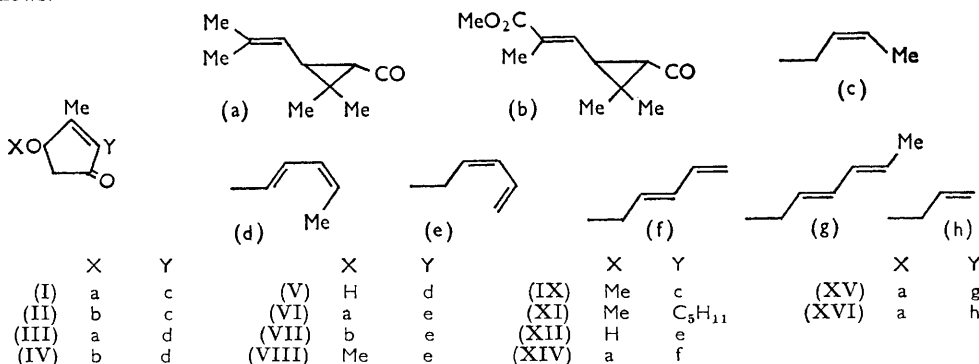
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(+)-Pyrethrolone forms a crystalline monohydrate from which the pure alcohol is obtained for the first time. The properties of the pure compound indicate that the hitherto unidentified pyrethrolone-C is pyrethrolone contaminated with thermally isomerized material.

A new procedure has been developed to obtain pure (+)-pyrethrolone (I).<sup>2</sup> First, dilute sulphuric acid liberated pyrethrolone and the related cinerolone (II) from their semicarbazones faster than aqueous potassium hydrogen sulphate.<sup>3</sup> Secondly, the first clear separation of (+)-pyrethrolone from (+)-cinerolone was achieved, because, although both ketols [and ( $\pm$ )-allethrolone (III)<sup>4</sup>] form monohydrates, only that from (+)-pyrethrolone was crystalline at room temperature and so recrystallization gave pure (+)-pyrethrolone hydrate, readily dehydrated to the pure alcohol.

(+)-Cinerolone (II) accumulated in the mother-liquors from recrystallization of pyrethrolone hydrate and was conveniently isolated thence by established procedures<sup>5,6</sup>

\* In Part III (*J.*, 1964, 888), formulæ (I)—(XVI) and the Table specifying them should be as follows.



<sup>1</sup> Part IV, Elliott, *J.*, 1964, 1854.

<sup>2</sup> Preliminary communication, Elliott, *Chem. and Ind.*, 1958, 685.

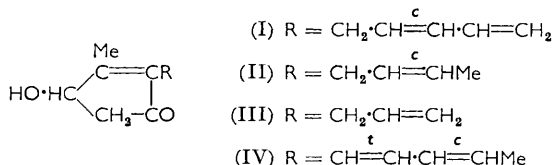
<sup>3</sup> For discussion, see (a) Elliott, *Chem. and Ind.*, 1960, 1142; (b) Crombie and Elliott, *Fortschr. Chem. org. Naturstoffe*, 1961, **19**, 120.

<sup>4</sup> Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1951, **73**, 3541.

<sup>5</sup> LaForge and Barthel, *J. Org. Chem.*, (a) 1944, **9**, 242; (b) 1945, **10**, 106, 114.

<sup>6</sup> West, *J.*, 1946, 463.

in which the first stage was the fractional distillation of the acetate mixture. When a stainless steel column packing was used, only (+)-cinerolone acetate distilled, pyrethrolone acetate being selectively polymerized. The cinerolone acetate was converted through the semicarbazone into (+)-cinerolone, whose physical constants agreed with those of synthetic <sup>7</sup> and optically resolved <sup>8</sup> samples.



Comparison of the properties now found for (+)-pyrethrolone ( $n_D^{20}$  1.5475,  $[\alpha]_D^{20}$  17.8°) with those of (+)-<sup>5</sup> and (±)-pyrethrolone-C <sup>6</sup> [ $n_D^{20}$  1.5520,  $\alpha_D^{25}$  5.6°] indicates that this unidentified alcohol, isolated by fractional distillation, was (+)- and (±)-pyrethrolone containing about 10% of isopyrethrolone (IV) <sup>9</sup> ( $n_D^{20}$  1.5894,  $[\alpha]_D^{20}$  -5.6) and was not closely related to cinerolone ( $n_D^{20}$  1.5169), to the alcohol from jasmolin II,<sup>10</sup> the racemic form of which has  $n_D^{20}$  1.506—1.508,<sup>7</sup> or to other constituents.<sup>11</sup>

The racemic forms of pyrethrolone and cinerolone<sup>5,6</sup> are probably formed during methanolysis of the ester semicarbazones with sodium methoxide, because, here, fractional precipitation with water after methanolysis gave some racemic semicarbazone. (+)-Pyrethrolone and (+)-cinerolone do not racemize when their semicarbazones are shaken with acids (contrary to an earlier view<sup>3a</sup>), and no racemic pyrethrolone acetate was obtained from (+)-pyrethrolone, either with acetic anhydride or with excess of acetyl chloride in pyridine.

#### EXPERIMENTAL

For methods, see Part III.<sup>9</sup>

(+)-*Pyrethrolone hydrate*. The pyrethrins were extracted from 25% extract with nitromethane.<sup>12</sup> All traces of nitromethane were then removed at 65° *in vacuo*; this ensured a high yield of semicarbazone (below). The pyrethrins (101 g.) in 95% ethanol (1000 ml.) and pyridine (80 ml.) were set aside for 2 days at room temperature and 14 days at 0° with semicarbazide hydrochloride (72 g.) in water (360 ml.). Semicarbazone was separated and washed with water (1000 ml.). The washings were added to the filtrate from which more semicarbazone (38 g., total, 86%) separated after 24 hr. at 0°. Attempts to recrystallize semicarbazones at this stage and later depressed the yield of pyrethrolone. The dried semicarbazones (101 g.) were added to sodium (11.9 g.) dissolved in methanol (370 ml.); no water was added (cf. refs. 13—15). Undissolved solid was rapidly filtered off and the mother-liquor set aside at 0° for 20 days. The semicarbazones (27 g.) were separated and washed with water, which was added to the thick syrup obtained when methanol was removed from the filtrate on a steam-bath *in vacuo*, to precipitate a second crop of semicarbazone (21 g.). The combined crops (82%) had  $\lambda_{\text{max}}$  230 and 266  $\mu$  ( $\epsilon$  23,000 and 19,600),  $[\alpha]_D^{20}$  -168° (*c* 0.88 in pyridine), -124° (*c* 1.08 in glacial acetic acid).

In another experiment, the pyrethrin semicarbazones (200 g.) in methanol (1000 ml.) were set aside at 0° with sodium (25 g.) in methanol (500 ml.) for 5 days. After removal of the first crop of semicarbazone, successive portions (10 × 200 ml.) of water were added to the filtrate which was cooled to 0° for 20 hr., when the next crop was removed. All crops contained pyrethrolone and cinerolone (from ratio of  $\epsilon$  at 228 to that at 268  $\mu$ ), but nos. 1—3, 6, and 7

<sup>7</sup> Crombie, Harper, Stedman, and Thompson, *J.*, 1951, 2445.

<sup>8</sup> LaForge and Green, *J. Org. Chem.*, 1952, 17, 1635.

<sup>9</sup> Elliott, *J.*, 1964, 888.

<sup>10</sup> Godin, Sleeman, Snarey, and Thain, *Chem. and Ind.*, 1964, 371.

<sup>11</sup> Sawicki and Thain, *J. Sci. Food Agric.*, 1961, 12, 137; Chang, *Agric. Food Chem.*, 1961, 9, 390.

<sup>12</sup> Barthel, Haller, and LaForge, *Soap*, 1944, 20 (7), 121.

<sup>13</sup> Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, 7, 177.

<sup>14</sup> Haller and LaForge, *J. Org. Chem.*, 1936, 1, 38.

<sup>15</sup> West, *J.*, 1944, 51.

( $[\alpha]_D^{20}$  in glacial acetic acid  $-12$ ,  $-14$ ,  $-112$ ,  $-80$ , and  $-68^\circ$ , respectively) had lower rotations than the others ( $[\alpha]_D^{20} -124$  to  $-133^\circ$ ).

Pyrethrolone and cinerolone semicarbazones (30 g., dried and ground finely to pass a 200-mesh sieve) were shaken at  $18^\circ$  in the dark for 7 weeks with potassium hydrogen sulphate (150 g.) in water (300 ml.) and ether (450 ml.) and a trace of quinol. Unreacted semicarbazone (6.2 g.) was filtered off and washed with ether. The combined ether layers were washed with saturated sodium chloride solution, and treated briefly with a little anhydrous sodium sulphate. Ether was removed *in vacuo* (water pump) without heating; the residue crystallized. The solid was washed with cold ether, to give (+)-*pyrethrolone hydrate* (10 g., colourless crystals) which was recrystallized by dissolution in warm ether (20 ml.) and cooling to  $-20^\circ$ . This gave pure hydrate (4.0 g.), m. p.  $38.8-39.6^\circ$  (sealed capillary), not raised by further crystallization (Found: C, 67.4; H, 7.9.  $C_{11}H_{16}O_3$  requires C, 67.3; H, 8.2%),  $[\alpha]_D^{20} +13.7^\circ$  (*c* 12.7 in ether) (equivalent to  $[\alpha]_D^{20} +15.1^\circ$  for the anhydrous compound),  $[\alpha]_D^{19} +12.5^\circ$  (*c* 13.1 in ethanol),  $\lambda_{max.}$  (in ethanol) 225  $m\mu$  ( $\epsilon$  33,800), (in ether) 226 ( $\epsilon$  33,400), (in water) 227 ( $\epsilon$  36,000).

Pyrethrolone and cinerolone (7.6 g., b. p.  $130-136^\circ/0.01$  mm.) recovered from the recrystallization liquors, together with crystalline hydrate, constituted a 75% yield of ketols, based on unrecovered semicarbazone.

(+)-Pyrethrolone,  $n_D^{20}$  1.5475,  $\lambda_{max.}$  225  $m\mu$  ( $\epsilon$  33,700),  $[\alpha]_D^{20} +17.8^\circ$  (*c* 10.4 in anhydrous ether), was obtained when the hydrate was evacuated to  $10^{-3}$  mm. over phosphoric oxide. Distillation of a small portion of the dehydrated material, rapidly to avoid thermal isomerization,<sup>9</sup> gave (+)-*pyrethrolone*, b. p.  $124^\circ/1.5 \times 10^{-2}$  mm.,  $n_D^{19}$  1.5479,  $\lambda_{max.}$  225  $m\mu$  ( $\epsilon$  33,500 in ethanol); corrected infrared absorption<sup>16</sup> (Found: C, 74.2; H, 8.1.  $C_{11}H_{14}O_2$  requires C, 74.1; H, 7.9%). The hydrate was stable in the dark at  $-20^\circ$ .

The hydrate (0.50 g.) in pyridine (2 ml.), with semicarbazide hydrochloride (0.50 g.) in water (2.5 ml.) during 16 hr. at room temperature, gave the *semicarbazone*, m. p.  $212-214^\circ$  (decomp.),  $[\alpha]_D^{20} -186^\circ$  (*c* 0.6 in pyridine) [West<sup>6</sup> found for pyrethrolone B1 semicarbazone, m. p.  $213-215^\circ$ ,  $[\alpha]_D^{20} -182^\circ$  (*c* 1 in pyridine)],  $\lambda_{max.}$  229 and 265  $m\mu$  ( $\epsilon$  27,300 and 21,800<sup>1</sup> (Found: C, 61.0; H, 7.3; N, 17.9.  $C_{12}H_{17}N_3O_2$  requires C, 61.3; H, 7.3; N, 16.9%).

The hydrate (0.5 g.), with 2,4-dinitrophenylhydrazine (0.5 g.) in aqueous sulphuric acid (50 ml.; 10% v/v), gave the bright orange 2,4-*dinitrophenylhydrazone* (0.88 g.). After thorough washing (water) and recrystallization (benzene) it had m. p.  $163-164^\circ$ ; correct ultraviolet absorption,<sup>1</sup>  $[\alpha]_D^{19} -157^\circ$  (*c* 0.46 in benzene) (Found: C, 56.9; H, 4.9.  $C_{17}H_{18}N_4O_5$  requires C, 57.0; H, 5.1%).

(+)-*Pyrethrolone with Sulphuric Acid*.—The finely powdered semicarbazones (50 g.) were shaken for 20 hr. with sulphuric acid (500 ml.; 10% v/v) and ether (250 ml.). The emulsified solid (dry weight, 31.5 g.) was separated by filtration and washed with water ( $2 \times 100$  ml.) and ether ( $3 \times 100$  ml.). Isolation as usual, gave pyrethrolone and cinerolone (13.4 g., 96%, based on unrecovered semicarbazone), b. p.  $128-147^\circ/5 \times 10^{-2}$  mm.,  $n_D^{20}$  1.5339—1.5442,  $[\alpha]_D^{20} +14.2^\circ$  (*c* 10.3 in ether, for a fraction of  $n_D^{20}$  1.5420). This material crystallized when homogenized with water (1.3 g.) and cooled to  $-20^\circ$ . Crystallization to constant m. p. and  $\epsilon_{max.}$  as before, gave (+)-pyrethrolone hydrate, identical with the product from potassium hydrogen sulphate.

This procedure was repeated, but 10 ketol fractions were isolated in succession after shaking each for 1 hr., and unreacted semicarbazone was re-processed. The optical rotations of the fractions did not vary significantly from the mean,  $[\alpha]_D^{20} +13.6^\circ$  (ether), and semicarbazone remaining had  $[\alpha]_D^{20} -184^\circ$  (pyridine).

Pyruvic acid in glacial acetic acid<sup>17</sup> gave a lower yield of less pure ketols.

*Cinerolone Acetate*.—Pyrethrolone and cinerolone (175 g., in mother-liquors from recrystallization of pyrethrolone hydrate) were heated on steam for 8 hr. with acetic anhydride (500 g.). The residue after removal of excess reagent (151 g., b. p.  $120-136^\circ/4 \times 10^{-2}$  mm.,  $n_D^{20}$  1.5127,  $\alpha_D^{20} +28.3^\circ$ ) contained pyrethrolone acetate ( $n_D^{20}$  1.5180; pip at 1600 and strong absorption at 909  $cm^{-1,16}$ ) and cinerolone acetate ( $n_D^{20}$  1.4915), and was fractionated on a column ( $50 \times 1.5$  cm.) packed with Dixon stainless steel gauze rings at a reflux ratio of 1 : 5, jacket temperature  $122^\circ$ , and an oil-bath temperature slowly raised from 220 to  $240^\circ$ . Twenty fractions (each *ca.* 2.0 g.), b. p.  $105-120^\circ/0.04-0.1$  mm., were collected, for which  $n_D^{20}$ ,  $\alpha_D^{20}$ ,  $\epsilon_{max.}$  at 227  $m\mu$ , %C, and %H varied insignificantly from the following mean values: 1.4915,

<sup>16</sup> Elliott, *J. Appl. Chem.*, 1961, **11**, 19.

<sup>17</sup> Hershberg, *J. Org. Chem.*, 1948, **13**, 542.

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+35.6°, 12,900, 69.3, 7.8; (Calc. for cinerolone acetate: C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>; C, 69.2; H, 7.7%. Calc. for pyrethrolone acetate, C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>: C, 70.9; H, 7.3%). Infrared spectra confirmed the identity of the fractions and excluded the presence of pyrethrolone acetate.

For comparison, pyrethrolone hydrate was converted into the acetate (b. p. 124°/0.1 mm.,  $n_D^{20}$  1.5180,  $\alpha_D^{20}$  +34.5°) with excess of acetic anhydride. With excess of acetyl chloride (3 ml.) in pyridine (10 ml.), pyrethrolone (1.86 g.) gave the acetate, b. p. 126—128°/0.2 mm.,  $n_D^{20}$  1.5192,  $\alpha_D^{20}$  +35.5°.

(+)-Cinerolone acetate was converted<sup>5b,6</sup> into (–)-cinerolone semicarbazone, m. p. 200° (decomp.),  $[\alpha]_D^{18}$  –143° (*c* 0.4 in glacial acetic acid) (lit.,<sup>8</sup>  $[\alpha]_D^{25}$  –144, –152°), and thence by agitation with dilute sulphuric acid into (+)-cinerolone, b. p. 106—114°/2.5—3.5 × 10<sup>–3</sup> mm.,  $n_D^{20}$  1.5160,  $[\alpha]_D^{20}$  +14.3° (*c* 12.9 in ether),  $[\alpha]_D^{15}$  +11.5° (*c* 10.6 in ethanol),  $\lambda_{max}$  225 m $\mu$  ( $\epsilon$  12,900); correct infrared absorption<sup>16</sup> (Found: C, 72.5; H, 8.8. Calc. for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: C, 72.25; H, 8.5%).

Esterification of pyrethrolone and cinerolone with (+)-chrysanthemic and (+)-pyrethric acids gave pyrethrins I and II and cinerins I and II, identical in biological activity with naturally derived samples.<sup>18</sup>

The red 2,4-dinitrophenylhydrazone of (+)-cinerolone (cf. pyrethrolone) had m. p. 160—163°,  $[\alpha]_D^{20}$  –165° (*c* 0.5 in benzene),  $\lambda_{max}$  215, 250, and 380 m $\mu$  ( $\epsilon$  16,300, 17,000, and 27,600),  $\lambda_{infl}$  282.5 m $\mu$  ( $\epsilon$  9450) (Found: C, 56.2; H, 4.9; N, 15.3. C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub> requires C, 55.5; H, 5.2; N, 16.2%).

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<sup>18</sup> Sawicki, Elliott, Gower, Snarey, and Thain, *J. Sci. Food Agric.*, 1962, **13**, 172.