

89. The Structure of Pyrethrolone and Related Compounds. Part V.

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Using the method of LaForge and Barthel (*J. Org. Chem.*, 1945, **10**, 106) five semicarbazones have been obtained from the mixture of ketones known as "pyrethrolone" derived from Kenya pyrethrum flowers. By a modified procedure it was possible to isolate a sixth semicarbazone corresponding to the inactive modification of pyrethrolone C-1 and to offer an explanation for discrepancies in the melting points recorded for different samples of pyrethrolone B-1 semicarbazone. The absorption data for the semicarbazones and their hydrogenation products are in accord with the structures (I) and (II) proposed for the two ketones which are present in "natural pyrethrolone" as dextro and racemic forms (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 114).

SPECTROGRAPHIC study of the pyrethrins and related compounds (Gillam and West, *J.*, 1942, 671; 1944, 49) raised considerable difficulties in connection with the accepted ideas on the structure of these compounds and an explanation was sought for the anomalous chemical reactions of the cyclopentenolone fragment (West, *J.*, 1944, 51, 239, 642; 1945, 412). Meanwhile LaForge and Barthel subjected pyrethrolone to an exhaustive examination to detect heterogeneity and finally succeeded in isolating no fewer than five semicarbazones by combining a process of fractionation and acetylation before converting the fractions into semicarbazones (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106, 114, 222). These laevo-rotatory and inactive semicarbazones were considered to correspond to dextro and racemic forms of the ketone of empirical formula $C_{11}H_{14}O_2$ (pyrethrolone) with smaller quantities of *d*- and *dl*-forms of (II) (cinerolone). The semicarbazones A-1 and A-2 were derived from the *d*- and the *dl*-form respectively of cinerolone, B-1 and B-2 from the *d*- and the *dl*-form of one possible geometric isomer of pyrethrolone, and C from the *d*-form of the second possible geometric isomer of pyrethrolone. The preparation of the *dl*-form of the semicarbazone of pyrethrolone C is described below, and

now that all the possibilities (except the enantiomorphs of A-1, B-1 and "C") have been isolated the terms C-1 and C-2 are used in this paper to avoid misunderstanding.



Structure (I) was first suggested by Gillam and West (*loc. cit.*) for "pyrethrolone," but the production on ozonolysis of acetaldehyde with only small proportions of formaldehyde raised serious difficulties. LaForge and Barthel surmounted these difficulties by arguments based upon their discovery of the heterogeneous nature of pyrethrolone. By treatment with thionyl chloride, cinerolone was converted into the 5-chloro-derivative. This was reduced to the deoxy-derivative, cinerone, and dihydrocinerone was shown to be identical with synthetic 3-methyl-2-butylcyclopent-2-en-1-one. LaForge and Barthel (*loc. cit.*) considered that the terminal methyl values—which appear, however, to give results difficult to interpret (West, *J.*, 1945, 412)—and the absorption data confirmed that in cinerolone the side-chain double bond was in the 2:3 and not the 1:2 position, whilst for the pyrethrolone constituents (C₁₁H₁₄O₂) the evidence was considered to confirm formula (I).

In view of the repercussions involved in the discovery that pyrethrins I and II are such complex mixtures it appeared desirable to repeat this work and to supplement the absorption data recorded. Each of the five semicarbazones described by LaForge and Barthel has been prepared from "pyrethrolone" derived from pyrethrin concentrates including those predominating in pyrethrin I and pyrethrin II respectively, although the proportion of the various semicarbazones isolated showed some variation. From observations made in a number of experiments the semicarbazone of pyrethrolone B-1 has m. p. 210° (LaForge and Barthel, *J. Org. Chem.*, 1945, 10, 114) and the product m. p. 213—215° obtained by strict adherence to the LaForge and Barthel

Absorption Spectra (Alcoholic Solutions) and Terminal Methyl Numbers for the Semicarbazones of Cinerolone A-1 and A-2 and Pyrethrolone B-1, B-2, C-1, and C-2 and Hydrogenated Products.*

| | λ_{\max} , A. | ϵ . | Me (C), %. | Terminal methyl number.* | M.W. used. |
|--|-----------------------------|----------------------|------------|--------------------------|------------|
| <i>Samples of semicarbazones derived by acetate method.</i> | | | | | |
| Cinerolone acetate A-1 | 2660 | 22,900 | 16.3 | 2.88 | 265 |
| Cinerolone acetate A-2 | 2660 | 20,250 | 16.4 | 2.90 | 265 |
| Pyrethrolone acetate B-1 | { 2290 2665 } | { 21,800 19,700 } | 12.9 | 2.38 | 277 |
| Pyrethrolone acetate B-2 | { 2295 2650 } | { 15,650 15,000 } | 13.5 | 2.49 | 277 |
| Pyrethrolone acetate C-1 | { 2310 2660 } | { 22,000 16,400 } | 11.8 | 2.18 | 277 |
| Pyrethrolone acetate C-2 | { 2310 2670 } | { 21,500 15,500 } | 11.4 | 2.10 | 277 |
| Cinerolone A-1 | { 2660 (2320) | { 18,300 10,900 } | 12.1 | 1.80 | 223 |
| Cinerolone A-2 | { no band 2660 (2320) | { 17,000 10,200 } | 12.2 | 1.82 | 223 |
| Pyrethrolone B-1 | { 2320 2665 } | { 18,700 17,600 } | 8.9 | 1.40 | 235 |
| Pyrethrolone B-2 | { 2310 2650 } | { 24,300 18,200 } | 9.2 | 1.44 | 235 |
| Pyrethrolone C-1 | { 2310 2665 } | { 25,350 19,800 } | 7.6 | 1.19 | 235 |
| Pyrethrolone C-2 | { 2310 2660 } | { 24,000 19,600 } | 8.0 | 1.25 | 235 |
| Dihydrocinerolone A-1 | 2650 | 21,800 | 13.2 | 1.98 | 225 |
| Dihydrocinerolone A-2 | 2650 | 17,700 | 12.2 | 1.83 | 225 |
| Tetrahydropyrethrolone B-1 | 2650 | 16,800 | 11.4 | 1.82 | 239 |
| Tetrahydropyrethrolone B-2 | 2650 | 22,000 | 12.9 | 2.05 | 239 |
| Tetrahydropyrethrolone C-1 | 2650 | 22,700 | 12.8 | 2.03 | 239 |
| Tetrahydropyrethrolone C-2 | 2650 | 22,000 | 12.5 | 1.99 | 239 |
| <i>Samples of semicarbazones derived by fractional distillation of natural pyrethrolone.</i> | | | | | |
| Cinerolone A-1 | { 2650 (2300) | { 19,600 9,030 } | 12.0 | 1.78 | 223 |
| Pyrethrolone B-1 | { 2300 2650 } | { 20,350 19,200 } | 9.3 | 1.46 | 235 |
| Pyrethrolone C-1 | { 2300 2655 } | { 24,900 18,900 } | 9.2 | 1.44 | 235 |
| Dihydrocinerolone A-1 | 2650 | 18,800 | 13.0 | 1.95 | 225 |
| Tetrahydropyrethrolone B-1 | 2650 | 20,600 | 12.1 | 1.93 | 239 |
| Tetrahydropyrethrolone C-1 | 2650 | 21,000 | 12.6 | 2.01 | 239 |

* Barthel and LaForge, *Ind. Eng. Chem. Anal.*, 1944, 16, 434.

method is a mixture of the semicarbazones of pyrethrolone B-1 and pyrethrolone C-1. The sixth semicarbazone (pyrethrolone semicarbazone C-2) corresponding to the racemic form of the dextrorotatory pyrethrolone C-1 was isolated by applying the acetate separation to an appropriate fraction, and a mixture of m. p. 213—214° corresponding to the impure B-1 semicarbazone was obtained as a by-product. By rigorous fractional distillation of "natural pyrethrolone" the three optically active forms of the semicarbazones were prepared without previous acetylation, so that no changes in the position of the double bonds in the molecules appeared to have taken place during treatment with acetic anhydride or subsequent conversion into the semicarbazones of the corresponding cyclopentenolones. The semicarbazones (A-1 and A-2) of cinerolone absorbed approximately one molecular proportion, and the semicarbazones of pyrethrolones B-1, B-2, C-1, and C-2 approximately two molecular proportions, of hydrogen to give dihydro- and tetrahydro-derivatives respectively of which the absorption spectra were typical of semicarbazones derived from $\alpha\beta$ -unsaturated ketones (Gillam and West, *J.*, 1942, 486; Evans and Gillam, *J.*, 1943, 565).

The cinerolones appeared to be present to the extent of about 20—30% in the samples of "natural pyrethrolone" examined. The data recorded in the experimental part confirm the work of LaForge and Barthel, and the absorption data in the table are in accord with the structures which they propose for the two cyclopentenolones of empirical formulæ $C_{10}H_{14}O_2$ and $C_{11}H_{14}O_2$. The semicarbazones of the cinerolones showed maximum absorption at 2655 ± 5 A. (Evans and Gillam, *loc. cit.*), whilst the various pyrethrolone semicarbazones had maxima at 2655 ± 5 A. corresponding with the $>C=C-C=N$ linkage and in addition another band at 2310 ± 10 A. due to the separate conjugated diene chromophore system present in the side chain (Gillam and West, *loc. cit.*).

EXPERIMENTAL.

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

Separation of Pyrethrolones and Cinerolones through the Acetates.—Pyrethrum extract containing pyrethrin I 48.0%, pyrethrin II 43.8% (Seil method), acid value 2 (Barthel, Haller, and LaForge, *Soap*, 1944, 20, No. 7, 121), having λ_{max} 2295 A. with $E_{1\%}^{1cm}$ 765 (in alcohol) (370 g.), gave crude mixed pyrethrin semicarbazones (420 g.) containing some non-crystalline material. This yielded 230 g. of crude pyrethrolone semicarbazone, Me(C), 11.3%, which was recrystallized to give pyrethrolone semicarbazone (182 g.), m. p. 204—205°, Me(C), 9.2%, leaving a residue (31 g.) insoluble in methyl alcohol. The regenerated pyrethrolone (128 g.) had b. p. 131—150°/1.2 mm., n_D^{20} 1.5372, n_D^{25} 13.6°, Me(C), 13.2%. This was distilled to give two fractions: (a) (65 g.), b. p. 128—140°/1 mm., n_D^{20} 1.5366, n_D^{25} 13.8°, Me(C), 13.9%, (b) (26 g.), b. p. 140—147°/1 mm., n_D^{20} 1.5410, n_D^{25} 12.4°. Proceeding essentially as described by LaForge and Barthel (*J. Org. Chem.*, 1945, 10, 106) fraction (a) (61.5 g.) was acetylated and by distillation two fractions were obtained: (22.3 g.), b. p. 96—101°/0.35 mm., n_D^{20} 1.4978, n_D^{25} 24.8°, Me(C), 21.2%, and (37.5 g.), b. p. 110—118°/0.4 mm., n_D^{20} 1.5110, n_D^{25} 29.7°, Me(C), 17.5%. Cinerolone acetate semicarbazone A-1 had m. p. 148—151° (Found: C, 59.1; H, 7.1%). Cinerolone acetate semicarbazone A-2 had m. p. 150—152° (Found: C, 59.3; H, 7.1%). Pyrethrolone acetate semicarbazone B-1 had m. p. 122—124° (Found: C, 59.1, 59.2; H, 7.0, 6.75%). Pyrethrolone acetate semicarbazone B-2 had m. p. 168—170° (Found: C, 60.45; H, 7.0. Calc. for $C_{13}H_{19}O_2N_3$: C, 58.9; H, 7.2. Calc. for $C_{14}H_{19}O_2N_3$: C, 60.65; H, 6.9%). Cinerolone semicarbazone A-1 had m. p. 202—203°, $[\alpha]_D -186^\circ$ (c, 1 in pyridine) (Found: C, 59.8; H, 7.5%). Cinerolone semicarbazone A-2 had m. p. 199—200°, $[\alpha]_D \pm 0^\circ$ (c, 1 in pyridine) (Found: C, 59.5; H, 7.45%). Pyrethrolone semicarbazone B-1 had m. p. 213—215°, $[\alpha]_D -182^\circ$ (c, 1 in pyridine) (Found: C, 60.7; H, 7.4%). Pyrethrolone semicarbazone B-2 had m. p. 207—208°, $[\alpha]_D \pm 0^\circ$ (c, 0.5 in pyridine) (Found: C, 60.8; H, 7.3%). A pyrethrolone fraction b. p. 135—137°/0.5 mm., n_D^{20} 1.5530, n_D^{25} 11.2°, Me(C), 12.5%, was obtained by fractionating (b) above (LaForge and Barthel, *loc. cit.*) and was used to prepare the C-1 semicarbazone, m. p. 219—220° (decomp.), $[\alpha]_D -155^\circ$ (c, 0.2 in pyridine) (Found: C, 61.2; H, 6.7. Calc. for $C_{11}H_{17}O_2N_3$: C, 59.2; H, 7.6. Calc. for $C_{12}H_{17}O_2N_3$: C, 61.3; H, 7.2%). The data given in the table refer to these particular samples and to their hydrogenation products (LaForge and Barthel, *J. Org. Chem.*, 1945, 10, 114), the properties of which were: the A-1 semicarbazone (0.4 g.) hydrogenated in methyl alcohol using a platinum oxide catalyst absorbed 40 ml. of hydrogen at N.T.P. (Calc. for $C_{11}H_{17}O_2N_3$, one double bond: 40.2 ml.) and the recrystallised *l*-dihydrocinerolone A-1 semicarbazone had m. p. 196—197°, $[\alpha]_D -205^\circ$ (c, 1 in pyridine) (Found: C, 59.1; H, 8.4. Calc. for $C_{11}H_{19}O_2N_3$: C, 58.7; H, 8.4%). The A-2 semicarbazone (0.2 g.) absorbed 20.2 ml. of hydrogen at N.T.P. (Calc. 20.1 ml.) to give *i*-dihydrocinerolone A-2 semicarbazone, m. p. 184—185°, $[\alpha]_D \pm 0^\circ$ (c, 1 in pyridine) (Found: C, 59.5; H, 8.7%). The B-1 semicarbazone (0.4 g.) absorbed 76 ml. of hydrogen at N.T.P. (Calc. for $C_{12}H_{17}O_2N_3$, two double bonds: 76.3 ml.) to give the *l*-tetrahydrosemicarbazone, m. p. 195—197°, $[\alpha]_D -196^\circ$ (c, 1 in pyridine). The B-2 semicarbazone (0.2 g.) absorbed 38 ml. of hydrogen at N.T.P. to give the *i*-tetrahydrosemicarbazone, m. p. 172—174°, $[\alpha]_D \pm 0^\circ$ (c, 1 in pyridine). The C-1 semicarbazone (0.2 g.) absorbed 38 ml. at N.T.P. to give the *l*-tetrahydrosemicarbazone, m. p. 195—197° (not depressed on admixture with tetrahydropyrethrolone B-1 semicarbazone), $[\alpha]_D -209^\circ$ (c, 1 in pyridine). The process was repeated starting with a pyrethrum concentrate containing pyrethrin I, 76.0, pyrethrin II, 21.5% (Seil) to give the following semicarbazones: A-1, A-2, B-1, B-2, and C-1 with m. p. 202—203°, 199—200°, 207—208°, 207—208°, and 217—218°, and $[\alpha]_D$ (c, 1 in pyridine) —199°, +0.9°, —194°, —1.2°, and —167° respectively. Starting with a concentrate containing pyrethrin I, 12.7, pyrethrin II, 78.8% (Seil) the semicarbazones, A-1, A-2, B-1, B-2, and C-1 had m. p. 202—203°, 199—200°, 208—210°, 207—208°, and 217—219°, and $[\alpha]_D$ (c, 1 in pyridine) —201°, $\pm 0^\circ$, —186°, —1.4°, and —165° respectively. In another experiment a pyrethrum concentrate (345 g.) (pyrethrin I, 49.0%, pyrethrin II, 43.5%) gave semicarbazones as follows: A-1 (14.5 g.), A-2 (1.8 g.), B-2 (5 g.), m. p. 202—203°, 199—200°, and 207—208°, and $[\alpha]_D^{20}$ (c, 1 in pyridine) —192°, $\pm 0^\circ$, and —5° respectively. The pyrethrolone acetate fraction, n_D^{20} 1.5127, n_D^{25} 26.4°, corresponding to the B-1, B-2 mixture gave (after removing the B-2 semicarbazone) by evaporating the benzene liquors a product which was separated by recrystallisation from dry ether into a crystalline portion and a syrupy portion (obtained on evaporating the ether liquors to dryness) in about equal amounts. (The ether-insoluble resinous material was rejected.) The crystalline material had m. p. 118—120°. On saponification the pyrethrolone B-1 semicarbazone obtained had m. p. 210—211°, $[\alpha]_D -187^\circ$ (c, 1 in pyridine). The non-crystalline portion on saponification gave pyrethrolone B-1 semicarbazone, m. p. 206—207°, $[\alpha]_D -185^\circ$ (c, 1 in pyridine). Each of these semicarbazones absorbed 2 mols. of hydrogen to give tetrahydro-derivatives, m. p. and mixed m. p. 194—195°, and $[\alpha]_D -188^\circ$ and —208° (c, 1 in pyridine), respectively. (The constants for the B-1 semicarbazone appeared to depend upon the refractive index of the acetate fraction used. The B-1 pyrethrolone semicarbazone, m. p. 213—215°, obtained in the first experiment was derived from an acetate fraction n_D^{20} 1.5143.)

The "pyrethrolone C fraction" derived from the pyrethrin I concentrate had b. p. 133—134°/0.4 mm., n_D^{20} 1.5520, a_D^{25} 5.6°, whilst that from the pyrethrin II concentrate had b. p. 134—135°/0.4 mm., n_D^{20} 1.5511, a_D^{25} 9.3°. In an experiment the "pyrethrolone C-fraction" obtained by fractionation as described by LaForge and Barthel had b. p. 142—144°/0.8 mm., n_D^{20} 1.5520, a_D 10.2°, semicarbazone m. p. 218—219°, $[\alpha]_D^{20}$ -162° (c, 1 in pyridine). The fraction (12 g.) from which this was derived (b. p. 142—150°/1 mm., n_D^{20} 1.5415, a_D^{25} 13°) was acetylated. The acetylated product gave a semicarbazone (12 g.) which was accompanied by sticky material. The portion insoluble in cold benzene (3.1 g.) after two recrystallisations from hot benzene gave pyrethrolone C-2 acetate semicarbazone (1.3 g.), m. p. 163—165°, $[\alpha]_D \pm 0^\circ$ (c, 1.25 in methyl alcohol) (Found: C, 61.1; H, 6.7. Calc. for $C_{14}H_{19}O_3N_3$: C, 60.65; H, 6.9%). The portion (9.7 g.) recovered by evaporating the cold benzene solution, after recrystallisation from ether, gave pyrethrolone C-1 acetate semicarbazone (3 g.), m. p. 128—130°, $[\alpha]_D - 47.8^\circ$ (c, 2.5 in methyl alcohol), -32.6° (c, 1 in pyridine) (Found: C, 59.7; H, 6.9%). A resinous material (3.4 g.) insoluble in ether was rejected. From the ether filtrates a syrupy product (3.3 g.) was produced (cf. B-1, B-2 mixture). The inactive acetate semicarbazone on saponification in the usual manner gave pyrethrolone C-2 semicarbazone, m. p. 216—217° (rapid heating), $[\alpha]_D^{20} - 1^\circ$ (c, 1 in pyridine) (Found: C, 61.5; H, 7.2. Calc. for $C_{12}H_{17}O_2N_3$: C, 61.3; H, 7.2%). When hydrogenated in the presence of a reduced platinum oxide catalyst this semicarbazone (0.2 g.) absorbed 37.8 ml. of hydrogen at N.T.P. (Calc. for $C_{12}H_{17}O_2N_3$, two double bonds: 38.1 ml.) to give an inactive tetrahydro-derivative, m. p. 171—173° (not depressed on admixture with the semicarbazone of tetrahydro-pyrethrolone B-2), $[\alpha]_D \pm 0^\circ$ (c, 1 in pyridine) (Found: C, 60.5; H, 8.8. Calc. for $C_{12}H_{19}O_2N_3$: C, 60.25; H, 8.8%). The pyrethrolone C-1 acetate semicarbazone gave on saponification pyrethrolone C-1 semicarbazone, m. p. 219—220°, $[\alpha]_D^{20} - 159^\circ$ (c, 1 in pyridine), identical with the semicarbazone of pyrethrolone C-1 prepared from "pyrethrolone" by fractionation and (0.2 g.) absorbed 37.9 ml. of hydrogen at N.T.P. to give tetrahydro-pyrethrolone C-1 semicarbazone, m. p. 195—196°, $[\alpha]_D^{20} - 195^\circ$ (c, 1 in pyridine). The syrupy product on saponification gave a semicarbazone, m. p. 213—214°, not depressed by admixture with the semicarbazone B-1, m. p. 213—215°, obtained in the first experiment, $[\alpha]_D^{20} - 178^\circ$ (c, 1 in pyridine). (This suggests that the B-1 semicarbazone previously obtained by LaForge and Barthel was a mixture of pyrethrolone B-1 semicarbazone, m. p. 210—211°, and pyrethrolone C-1 semicarbazone, m. p. 219—220°.) This product (0.2 g.) absorbed 38.3 ml. of hydrogen at N.T.P. to give a tetrahydro-derivative, m. p. 195—196° (unchanged on admixture with tetrahydro-pyrethrolone B-1 semicarbazone), $[\alpha]_D - 208^\circ$ (c, 1 in pyridine).

Constituents from "Pyrethrolone" by Fractionation.—"Natural pyrethrolone," on rigorous fractional distillation at 0.5 mm., gave (i) b. p. 122—124°/0.7 mm., n_D^{20} 1.5221, $[\alpha]_D$ 12.6°, Me (C), 15.7%; (ii) b. p. 135—137°/0.7 mm., n_D^{20} 1.5402, $[\alpha]_D$ 14.6°, Me (C), 12%; (iii) b. p. 140—142°/0.9 mm., n_D^{20} 1.5505, $[\alpha]_D$ 11.4°, Me (C), 12.4%. (During the fractionation the refractive index of intermediate fractions rose steadily with rise in b. p. whilst the optical rotation rose to a maximum and then decreased.) The semicarbazones derived from fractions (i), (ii) and (iii) correspond with the cinerolone A-1, pyrethrolone B-1 (contaminated with pyrethrolone B-2) and pyrethrolone C-1 semicarbazone obtained by the acetate method and had the following properties: A-1, m. p. 200—201°, $[\alpha]_D - 180^\circ$ (c, 1 in pyridine) (Found: C, 59.4; H, 7.6%). B-1, m. p. 208—209°, $[\alpha]_D - 167^\circ$ (c, 1 in pyridine) (Found: C, 60.9; H, 7.2%). C-1, m. p. 218—219°, $[\alpha]_D - 152^\circ$ (c, 0.16 in pyridine) (Found: C, 61.1; H, 7.25%). Cinerolone A-1 semicarbazone (0.2 g.) absorbed 22.2 ml. of hydrogen at N.T.P. to give dihydrocinerolone A-1 semicarbazone, m. p. 196—197°, $[\alpha]_D^{20} - 220^\circ$ (c, 1 in pyridine). Pyrethrolone B-1 semicarbazone (0.4 g.) absorbed 76.1 ml. of hydrogen at N.T.P. to give the tetrahydro-derivative, m. p. 195—197°, $[\alpha]_D^{20} - 196^\circ$ (c, 1 in pyridine), and pyrethrolone C-1 semicarbazone (0.2 g.) absorbed 38.2 ml. of hydrogen at N.T.P. to give the tetrahydro-derivative, m. p. 195—197°, $[\alpha]_D^{20} - 207^\circ$ (c, 1 in pyridine). The m. ps. were not depressed on admixture with the corresponding derivatives obtained *via* the acetates.

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