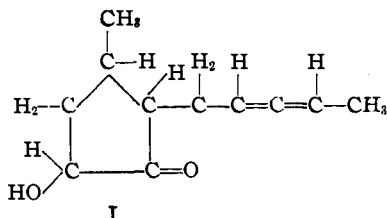


[CONTRIBUTION FROM DIVISION OF INSECTICIDE INVESTIGATIONS, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

## Constituents of Pyrethrum Flowers. VI. The Structure of Pyrethrolone<sup>1,2</sup>

BY F. B. LAFORGE AND H. L. HALLER

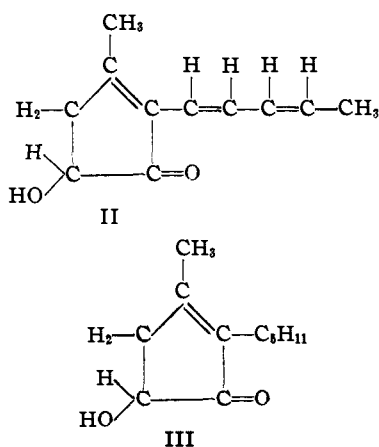
Pyrethrolone, the cyclic ketonic alcoholic component common to the two insecticidal constituents of pyrethrum flowers, has been assigned formula I by Staudinger and Ruzicka.<sup>3</sup>



The semicarbazone of pyrethrolone is obtained by saponification of the semicarbazones of either of the pyrethrins or mixtures of their semicarbazones.

In a previous communication<sup>4</sup> it has been shown that the semicarbazone of pyrethrolone should be represented by the empirical formula  $C_{12}H_{17}O_2N_3$ , and that of tetrahydropyrethrolone, which has a saturated side chain, by  $C_{12}H_{21}O_2N_3$ . It follows that pyrethrolone corresponds to formula  $C_{11}H_{14}O_2$  and tetrahydropyrethrolone to  $C_{11}H_{18}O_2$ . These formulas, which have been verified by numerous analyses, have two less hydrogen atoms than formula I and its tetrahydro derivative.<sup>5</sup>

This fact calls for a revision of formula I, and



(1) For article V of this series see *THIS JOURNAL*, **58**, 1061 (1936).  
 (2) We are indebted to F. Acree, Jr., and P. S. Schaffer for technical assistance throughout this investigation, and to W. G. Rose for the microcombustions.

(3) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 214 (1924).

(4) Haller and LaForge, *J. Org. Chem.*, **1**, 38 (1936).

(5) See also analytical figures for pyrethrin II, article II of this series, *THIS JOURNAL*, **57**, 1893 (1935).

it is suggested that pyrethrolone be assigned formula II and tetrahydropyrethrolone formula III.

In formula II a two-fold revision has been made. An additional double bond is placed in the 2,3-position in the nucleus, and following a later suggestion of Ruzicka and Pfeiffer the cumulated double-bond system has been replaced by a system of conjugated double bonds.<sup>6,7</sup>

Tetrahydropyrethrolone, having a saturated side chain, is better suited for study of the nuclear reactions than is pyrethrolone. It is best prepared by hydrogenation of pyrethrolone semicarbazone and subsequent hydrolysis of the hydrogenated compound.

When tetrahydropyrethrolone, prepared by hydrolysis of its semicarbazone (m. p. 196°), is again treated with semicarbazide, a mixture of semicarbazones that can be separated into two fractions is obtained. The larger part is the original semicarbazone melting at 196°, the other an isomer melting at 168°. This observation has been verified by us. When the semicarbazone of tetrahydropyrethrolone is hydrolyzed with potassium bisulfate solution at 100°, all the tetrahydropyrethrolone is obtained in the form which gives the semicarbazone melting at 168–170°.

The difference between the two tetrahydropyrethrolones derived from these semicarbazones, as suggested by Staudinger and Ruzicka,<sup>8</sup> is due merely to optical inactivation at the carbon atom to which the hydroxyl group is attached, the racemic compound being the one that yields the semicarbazone melting at 170°. This is true because the free ketone is optically inactive and for reasons that will immediately follow.

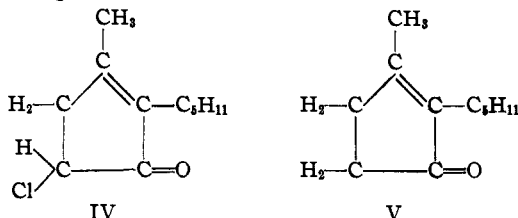
Preparations of pyrethrolone obtained from the semicarbazones are also without doubt mixtures containing more or less of the inactive form.

(6) Ruzicka and Pfeiffer, *Helv. Chim. Acta*, **16**, 1208 (1933).

(7) With the suggested change in the nucleus, a reinterpretation of the results of the oxidation and ozonization experiments of Staudinger and Ruzicka from which the arrangement of the double bonds in the side chain of formula I was deduced might indicate that the conjugated system so common in natural products is not excluded. We wish to state emphatically, however, that at present no positive evidence for either the conjugated or the cumulated system is available. This phase of the investigation is now in progress.

(8) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 226 (1924).

The hydroxyl group in tetrahydropyretrolone is readily replaced by chlorine, and the resulting chloro derivative of formula IV yields on reduction an optically inactive ketone of structure V, which gives a semicarbazone that melts at 176°.

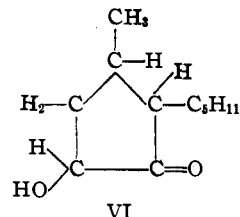


Structure V is the one that on the basis of degradation and synthesis has been assigned to dihydrojasmonone,<sup>6,9</sup> the semicarbazone of which also melts at 176°. Through the courtesy of Dr. W. Treff, of Heine and Co., Leipzig, Germany, we have obtained a sample of authentic dihydrojasmonone semicarbazone. It melted at 176° and a mixture of it with our tetrahydropyretrolone semicarbazone likewise at 176°. The two compounds are therefore identical. The optically inactive tetrahydropyretrolone, the semicarbazone of which melts at 170°, also yields a chloro compound which on reduction gives the same compound of formula V as that obtained from active tetrahydropyretrolone. Its semicarbazone also melts at 176°, and a mixture of it with the corresponding derivative obtained from the active substance likewise melts at 176°. The *p*-nitrophenylhydrazone melts at 107°. The two substances are therefore identical, and the proof is established that both active and inactive tetrahydropyretrolone are to be represented by formula III.

With the assumption that tetrahydropyretrolone corresponds to formula III, its characteristic reactions are readily explained. In agreement with the recorded observation, it should yield caproic acid on oxidation. The location of the double bond where only carbon-to-carbon linkages are present would render it difficult to hydrogenate, which is also in agreement with experience. Formula III, in fact, not only satisfies all the recorded properties of tetrahydropyretrolone, but in addition it explains all the recorded divergences from the expected.

The formula VI, which has been proposed by Staudinger and Ruzicka<sup>8</sup> for tetrahydropyretrolone, has the same nucleus as formula I, but it has a saturated side chain. From analogy with

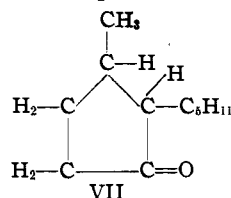
compounds having the same nucleus, a compound of that structure would be expected to yield



1-amyl-2-methylglutaric acid upon mild oxidation with permanganate. The experiment, however, gave a negative result.<sup>10</sup>

The formation of malonic acid, which has been regarded as a degradation product of the side chain in the oxidation of pyretrolone (of formula I), may possibly be as an oxidation product of the nucleus (of formula II), and hence could not be regarded as proof of the grouping —CHCH<sub>2</sub>CH— in the side chain.

Although the ethers and acetates of cyclopentanones of known structure are stable on hydrogenation, pyretrolone and its methyl ether and acetate are in part hydrogenated to the completely saturated compound of formula VII.<sup>11,12</sup>



This compound was also prepared synthetically by Staudinger and Ruzicka, and its identity established with the reduction product of pyretrolone. (The compound of formula V was an intermediate product in this synthesis.)

It is possible that the presence of a double bond, situated as in formulas II and III, might induce a cleavage such as is observed with the pyretrolone derivatives, with the formation of hexahydropyretrolone of formula VII. The hydrogenation of the pyretrolone derivatives does not, however, proceed simply or with quantitative yields.

It was in this phase of their investigations that the discontinuity in the reasoning of Staudinger and Ruzicka occurred.

Pyretrolone and also tetrahydropyretrolone

(10) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 228 (1924).

(11) Staudinger and Ruzicka, *ibid.*, **7**, 237 (1924).

(12) This compound has been called "tetrahydropyretrolone" by Staudinger and Ruzicka. In view of the introduction of a double bond in the nucleus of the revised formulas it should be designated as hexahydropyretrolone.

have been found to be very sensitive compounds. Both, although nearly insoluble in water, are probably hygroscopic, and for this reason it is unusually difficult to obtain satisfactory analytical results. It was only when the samples for the combustions were weighed out immediately after distillation that values close to the theoretical for carbon and hydrogen were obtained. Subsequent analyses always showed a decreasing carbon content. When samples were redistilled after standing for a few days, a vigorous evolution of vapor preceded the distillation. This property, not referred to in the literature, may have contributed to the faulty analyses reported. It does not, however, appear to be shared by the enolic forms of pyrethrolone and tetrahydropyrethrolone or by the acetates and ethers.

### Experimental

**Pyrethrolone.**—Staudinger and Ruzicka prepared pyrethrolone by shaking its semicarbazone for a long time in the cold with a concentrated solution of potassium bisulfate in the presence of benzene. The method has been changed slightly, because at a temperature near 0° the salt crystallized out and the benzene solidified. Instead of benzene, peroxide-free ether has been employed as the solvent and the operation carried out during the cool season in a room with open window. Many experiments were performed with quantities of semicarbazone ranging from 5 to 15 g., about 75 g. of potassium bisulfate dissolved in 150 cc. of water, and about 150 cc. of ether. The air in the container was displaced by carbon dioxide. The time required for practically complete decomposition ranged from one to three weeks, depending on the quantity of semicarbazone used. The ether solution was separated, washed, and dried, and the solvent evaporated. The yields of crude product were always somewhat less than quantitative, and a small amount of insoluble solid material always remained. It was necessary to avoid contact of the ether with rubber, as otherwise sulfur was dissolved which was impossible to remove.

The colorless crude product was distilled at about 0.25 mm. and passed over between 130 and 135°. The distillate should be protected as much as possible from contact with air, if satisfactory analytical results are to be obtained. The samples for combustion were therefore weighed out immediately after distillation. Even when all possible care was taken, the figures obtained are not all that could be desired. Results obtained on samples weighed even an hour after distillation showed a decrease in carbon and an increase in hydrogen content, and weighed portions were observed to gain in weight visibly on the balance. When preparations that had been in contact with air a few days were redistilled, a vigorous evolution of vapor preceded the distillation, and the distilled product when again immediately analyzed gave results very close to the calculated. There is also a slight loss in distillation, due perhaps to oxidation or polymerization.

*Anal.* (freshly distilled material) Calcd. for  $C_{11}H_{14}O_2$ :

C, 74.15; H, 7.87; for  $C_{11}H_{16}O_2$ : C, 73.33; H, 8.89. Found: C, 73.94, 73.77, 73.36, 73.33; H, 8.34, 8.35, 8.31, 8.13.

**Tetrahydropyrethrolone.**—The free ketone alcohol was always prepared from the corresponding semicarbazone<sup>4</sup> by hydrolysis with potassium bisulfate under exactly the same conditions as described above. The time required for complete reaction was shorter than for pyrethrolone.

Tetrahydropyrethrolone closely resembles the unhydrogenated compound in its physical properties. The two compounds are both hygroscopic and require the same precautions in handling. It boils at about 120–125° and 0.25 mm.

The following results were obtained with material analyzed immediately after distillation:

*Anal.* Calcd. for  $C_{11}H_{18}O_2$ : C, 72.53; H, 9.98; for  $C_{11}H_{20}O_2$ : C, 71.74; H, 10.88. Found: C, 72.19, 71.90, 72.00, 71.75; H, 10.05, 10.15, 10.05, 10.05.

The compound gives a pale yellow coloration with tetranitromethane. In ethyl alcohol  $[\alpha]^{20}_D +11.9^\circ$ ,  $c = 7$ ;  $l = 1$  dm. Staudinger and Ruzicka<sup>8</sup> report a levo rotation ( $-11.3^\circ$ ).

**Racemic Tetrahydropyrethrolone and its Semicarbazone.**—When the semicarbazone is prepared from distilled tetrahydropyrethrolone, two compounds are obtained. For the most part the mixture consists of the original semicarbazone melting at 196°. The remainder is the semicarbazone of the racemic compound melting at 170°. One gram of distilled tetrahydropyrethrolone was dissolved in 10 cc. of 95% alcohol and 3 cc. of pyridine, and 0.6 g. of semicarbazide hydrochloride in a few drops of water was added to the solution. After standing for two days the 0.6 g. of separated crystalline material was removed by filtration. It melted at 196°. Water was added to the filtrate, and the precipitated material was separated. It melted at 180–185°. It was recrystallized from ethyl acetate and yielded 0.3 g. of the material melting at 196°. The residue obtained on complete evaporation of the solvent was recrystallized from ethyl acetate with addition of benzene. It melted at 170°. The yield was 0.2 g. The total yield of the main product was thus about 66% of the theoretical.

When the semicarbazone of tetrahydropyrethrolone (m. p. 196°) is hydrolyzed with bisulfate solution at 100°, all the resulting tetrahydropyrethrolone is converted into the inactive form, the semicarbazone of which melts at 170°. Two and a half grams of tetrahydropyrethrolone semicarbazone (m. p. 196°) was shaken at 100° with a solution of 15 g. of potassium bisulfate in 30 cc. of water and 15 cc. of toluene. After three hours the toluene solution was diluted with ether, separated from the aqueous solution, washed, dried, and the solvents removed. The residue distilled at about 120° and 0.2 mm. The yield of pure substance was 1.4 g. The compound is optically inactive. A 6.8% solution in ethyl alcohol showed no detectable rotation in a 1-dm. tube. The semicarbazone was prepared and found to melt at 170°.

**Tetrahydropyrethrolone Methyl Ether.**—Two grams of tetrahydropyrethrolone semicarbazone in 20 cc. of methanol containing 1 cc. of concentrated sulfuric acid was boiled under reflux for two and one-half hours. The solution was poured into 200 cc. of water, and the separated oil was

extracted with petroleum ether. Some solid material insoluble in petroleum ether was removed by filtration. Although not further examined, it was probably the semicarbazone of tetrahydropyretrolone methyl ether. The petroleum ether solution was washed with water and dried. After removal of the solvent the residual oil was distilled and boiled at 82° and 0.35 mm. The yield of distilled product was 0.6 g.

*Anal.* Calcd. for  $C_{12}H_{20}O_2$ : C, 73.47; H, 10.20;  $CH_3O$ , 15.82. For  $C_{12}H_{22}O_2$ : C, 72.72; H, 11.11. Found: C, 73.00, 73.16, 73.25; H, 10.01, 10.27, 10.06;  $CH_3O$ , 16.1.

**3,5-Dinitrobenzoyl Ester of Pyretrolone.**—Four-tenths of a gram of pyretrolone was dissolved in 8 cc. of benzene and 2 cc. of quinoline, and 0.7 g. of 3,5-dinitrobenzoyl chloride was added in small portions. The solution was heated under reflux on the steam-bath for one hour, and then poured into ice water and extracted with ether. The ether solution was washed with water and carbonate solution, and the residue left on evaporation of the solvent was combined with the small quantity of solid material that had separated during extraction and was recrystallized from methanol. The yield was about 0.5 g. It melted at 145°.

*Anal.* Calcd. for  $C_{18}H_{16}O_7N_2$ : C, 58.06; H, 4.28; for  $C_{18}H_{18}O_7N_2$ : C, 57.76; H, 4.81. Found: C, 57.86, 57.85; H, 4.24, 4.48.

**5-Chlorotetrahydropyretrolone (Formula IV) from Active Tetrahydropyretrolone.**—One gram of tetrahydropyretrolone was cooled to 0°, and 1 cc. of thionyl chloride was added in small portions. Reaction took place readily with gas evolution. After the main reaction had subsided, an additional 0.5 cc. of thionyl chloride was added and the reaction allowed to proceed about fifteen minutes at room temperature. The excess of thionyl chloride was removed by distillation at about 15 mm., and the chloro derivative was then distilled at 0.6 mm. Practically all passed over at 97–100°. The yield was 0.9 g.

*Anal.* Calcd. for  $C_{11}H_{17}OCl$ : C, 65.84; H, 8.47. Found: C, 65.19, 65.16; H, 8.52, 8.59.

**Tetrahydropyretrolone (Dihydrojasmonone), Formula V.**—Two grams of zinc dust was added in small portions to a solution of 0.8 g. of 5-chlorotetrahydropyretrolone in 5 cc. of acetic acid. The solution warmed up spontaneously, and the reaction was completed by heating for one hour on the steam-bath. Water was then added and the aqueous suspension decanted. The separated oil was extracted with ether and the ethereal solution freed from acetic acid by washing with water and sodium carbonate solution. The solvent was then removed and the remaining liquid distilled at 15 mm. The temperature was not recorded owing to the small quantity of material handled. The yield of tetrahydropyretrolone was 0.7 g. It has a pleasant odor and  $n_D^{25}$  1.476. It is optically inactive. A 7% solution in alcohol showed no rotation in a 1-dm. tube.

*Anal.* Calcd. for  $C_{11}H_{18}O$ : C, 79.46; H, 10.84. Found: C, 78.92, 78.92; H, 11.16, 10.80.

The semicarbazone was obtained in quantitative yield from 0.1 g. of material and 0.15 g. of semicarbazide hydrochloride in pyridine–alcohol solution. It melted at 176°. The melting point was unchanged after recrystallization from benzene.

**5-Chlorotetrahydropyretrolone and Tetrahydropyretrolone (Dihydrojasmonone) from Inactive Tetrahydropyretrolone.**—The preparation of the chloro compound and its reduction to dihydrojasmonone were repeated to show that no migration of the double bond had occurred in the inactivation of tetrahydropyretrolone. One and six-tenths grams of the inactive tetrahydropyretrolone was converted into the chloro derivative by the procedure described above and yielded 1.4 g. of distilled product.

*Anal.* Calcd. for  $C_{11}H_{17}OCl$ : Cl, 17.70. Found: Cl, 17.90, 17.93.

One and three-tenths grams of the chloro compound yielded, on reduction with zinc and acetic acid, 1.1 g. of tetrahydropyretrolone,  $n_D^{25}$  1.476. The semicarbazone melted at 176°, and when mixed with an equal quantity of the same compound obtained from active tetrahydropyretrolone or with authentic dihydrojasmonone semicarbazone the melting point was also 176°. The *p*-nitrophenylhydrazone was prepared by dissolving equal quantities of the ketone and *p*-nitrophenylhydrazine hydrochloride in methanolic solution. After recrystallization it melted at 106–107°. Ruzicka and Pfeiffer record the melting point of the *p*-nitrophenylhydrazone of dihydrojasmonone as 111.6 The *p*-nitrophenylhydrazone of the compound of formula VII is reported to melt at 88°.13

### Summary

The formula I for pyretrolone proposed by Staudinger and Ruzicka has been revised by placing an additional double bond within the cyclopentane nucleus in the 2,3-position and by changing the cumulated double-bond system in the side chain to a system of conjugated double bonds. The same revision of the nucleus is also made in the formula for tetrahydropyretrolone. These changes are in agreement with the analytical results found for pyretrolone and its derivatives.

The new formulas II and III for pyretrolone and tetrahydropyretrolone are substantiated by the conversion of the latter compound into a chloro derivative, which on reduction yields dihydrojasmonone of the established structure V.

WASHINGTON, D. C.

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(13) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 259 (1924).