## CONSTITUENTS OF PYRETHRUM FLOWERS. XIV.\* THE STRUCTURES OF THE ENOLS OF PYRETHROLONE

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When pyrethrolone is boiled in a dilute methanol solution of sodium methoxide, it is converted into a mixture of two isomeric compounds which are soluble in aqueous alkali and which exhibit the properties of enols.<sup>1</sup> The two compounds can be separated by fractional distillation, and both correspond to the empirical formula  $C_{11}H_{14}O_2$ . Since this formula contains two hydrogen atoms less than that originally proposed by Staudinger and Ruzicka for pyrethrolone, the enols were regarded by them as oxidation products. They were only superficially studied by these authors, with the following results.

The isomer that boiled at  $82^{\circ}$  (0.05 mm.), yielded a semicarbazone melting at 255° with decomposition. On hydrogenation it furnished the same cyclic ketone of formula I, 2-amyl-3-methyl-cyclopentanone-1, that had already been obtained by hydrogenation of pyrethrolone.



The hydrogenated compound exists in two stereoisomeric forms, the semicarbazones of which melt at 196° and 160°, respectively,<sup>2,3,4</sup> the lower-

\* For article XIII of this series see Schechter and Haller, Soap, 14, (11), 101 (1938).

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<sup>1</sup> STAUDINGER AND RUZICKA, Helv. Chim. Acta, 7, 220 (1924).

<sup>2</sup> STAUDINGER AND RUZICKA, *ibid.*, 7, 237 (1924).

\* TREFF AND WERNER, Ber., 66, 1521 (1933).

<sup>4</sup> HALLER AND LAFORGE, J. ORG. CHEM., 2, 49 (1937).

melting form being the more stable. On the basis of these results formula II was assigned to the lower-boiling isomer.



In a previous paper<sup>5</sup> the formula for pyrethrolone was revised from one derived from cyclopentanolone to one with a cyclopentenolone nucleus, III.



On the basis of this revised formula, the enol of formula II is not an oxidation product but is formed by rearrangement of pyrethrolone.

The second isomeric enolic compound, which is the major product of the action of alkali on pyrethrolone, boiled at 145° (0.05 mm.), and was regarded by Staudinger and Ruzicka as a polymer of the compound of formula II. It yielded no semicarbazone. The results described in the present article now permit an explanation of the nature of this compound.

In our first experiments tetrahydropyrethrolone in which the side-chain is saturated was treated with alcoholic alkali in the presence of zinc dust to avoid oxidation. The reaction product consisted of an enolic compound boiling at 150° (0.25 mm.), together with some optically inactive tetrahydropyrethrolone. The enol was found to correspond to the empirical formula  $C_{11}H_{18}O_2$ . Under the conditions employed no lower-boiling isomer was isolated. That the compound is not a polymer was shown by

<sup>&</sup>lt;sup>5</sup> LAFORGE AND HALLER, J. Am. Chem. Soc., 58, 1777 (1936).

a molecular-weight determination. It yielded a monoacetyl derivative. The higher-boiling enol prepared by the directions of Staudinger and Ruzicka<sup>1</sup> from pyrethrolone furnished a tetrahydro derivative on hydrogenation. This was identical with the enol obtained by alkali treatment of tetrahydropyrethrolone. The monoacetyl derivative was also identical with the corresponding derivative obtained from the hydrogenated pyrethrolone enol. It is hence immaterial whether the pyrethrolone is first subjected to alkali treatment and then hydrogenated or these reactions are carried out in the reverse order.

The nuclear double bond in the higher-boiling enols, unlike that of formula II, is comparatively resistant to hydrogenation. This is not the case with the corresponding acetyl derivatives. On hydrogenation of the acetyl tetrahydropyrethrolone enol 2 moles of hydrogen was absorbed, with saturation of the nuclear double bond and elimination of the acetyl group. As products of the reaction two compounds were formed which were isolated as semicarbazones. One was difficultly soluble in ethanol and melted at 206°, the other very soluble and melted at 143°. Both have the same empirical formula,  $C_{12}H_{23}N_3O$ , and are different but isomeric with the semicarbazones of the compounds of formula I, which with reference to the revised conception of pyrethrone are designated as hexahydropyrethrones.

The enol of boiling point 155–160° (0.7 mm.), from pyrethrolone furnished a monoacetyl derivative, which on hydrogenation consumed 4 moles of hydrogen and yielded two isohexahydropyrethrones, which were isolated as semicarbazones identical with those obtained from tetrahydropyrethrolone enol acetate. A partial hydrogenation of acetyl pyrethrolone enol, involving only the double bonds in the side-chain, was possible with the use of a platinum oxide catalyst in denatured ethyl acetate, with the formation of the same tetrahydropyrethrolone enol acetate as that derived from tetrahydropyrethrolone enol. From the results described there can be no doubt that the higher-boiling enol obtained from pyrethrolone, which will be designated as isopyrethrolone enol, should be represented by formula IV, and the isohexahydropyrethrones by formula V (3-amyl-4-methylcyclopentanone-1).



This conclusion is substantiated by several analogies to be found in the reports of Staudinger and Ruzicka in connection with the synthetic preparation of cyclopentanolones related to pyrethrolone. In several instances where the reactions were expected to lead to compounds analogous to formula II, compounds analogous to formula IV or mixtures of the two were obtained.<sup>6</sup>

## EXPERIMENTAL

Conversion of pyrethrolone to the enol forms.—Seven and two-tenths grams of pyrethrolone was treated with sodium methoxide solution according to the directions of Staudinger and Ruzicka<sup>1</sup> except that the solution was refluxed for 20 hours instead of 7 hours. The enolic fraction was distilled at 0.7 mm., and two fractions were collected. The first fraction (1.1 g.) passed over from 90–155°, the second fraction (2.35 g.) from 155–160°.

On redistillation of the first fraction 0.5 g. of distillate boiling at  $93^{\circ}$  (0.7 mm.) was obtained. This part was used for the preparation of the semicarbazone, the proportions of reagents being ethanol 5 cc., pyridine 1 cc., and semicarbazide hydrochloride 0.75 g. in 1 cc. of water. The semicarbazone separated almost instantly. After standing for several hours it was removed by filtration. The yield was 0.52 g. It melted with decomposition at about 255° after it had sintered at 220°. It was recrystallized from glacial acetic acid and then melted with decomposition at about 255°. The analysis indicates that the compound has the same empirical formula as pyrethrolone semicarbazone.‡

Anal. Calc'd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 61.27; H, 7.23.

Found: C, 61.49, 61.14; H, 7.11, 6.99.

The enolic fraction boiling from  $155-160^{\circ}$  contained a little of the lower-boiling material. When 0.55 g. was treated with semicarbazide hydrochloride in pyridineethanol solution under the above conditions, about 0.025 g. of semicarbazone separated at once. After it has been recrystallized from acetic acid, it melted with decomposition at 255° and was found by a mixture-melting point determination to be identical with the semicarbazone from the lower-boiling fraction.

The enolic fraction boiling from  $155-160^{\circ}$  (0.7 mm.) (isopyrethrolone enol) has been analyzed by Staudinger and Ruzicka and found to correspond to the formula  $C_{11}H_{14}O_2$ .

Contrary to the results of Staudinger and Ruzicka,<sup>1</sup> the total enolic product is soluble in alkali carbonate as well as in alkali hydroxide.

Isopyrethrolone enol acetate.—The acetate of isopyrethrolone enol was easily obtained in almost quantitative yield by allowing 1 part of the enol in 4 to 5 parts of acetic anhydride to stand overnight and completing the reaction by warming for 4 hours on the steam bath. After removal of the excess reagent by distillation with

<sup>&</sup>lt;sup>6</sup> STAUDINGER AND RUZICKA, Helv. Chim. Acta, 7, 409, 421 (1924).

<sup>&</sup>lt;sup>‡</sup> STAUDINGER AND RUZICKA [(*Helv. Chim. Acta*, 7, 234 (1924)] report analyses on a semicarbazone melting at about 230-260°, which is always obtained in small amount as a by-product in the preparation of pyrethrolone semicarbazone. The analytical results obtained on this compound indicate that it corresponds to the formula  $C_{12}H_{17}N_{s}O$ , *i.e.*, an anhydropyrethrolone semicarbazone. It is evident that the semicarbazone derived from the lower-boiling pyrethrolone enol is different from this product.

the aid of the water pump, the reaction product was distilled. It boiled at 118–120° (0.4 mm.);  $n_{\rm D}^{\rm m} = 1.5047$ ;  $n_{\rm F}^{\rm m} - n_{\rm C}^{\rm m} = 0.0146$ .

Anal. Calc'd for C13H16O3: C, 70.90; H, 7.27.

Found: C, 70.37; H, 7.77.

Hydrogenation of isopyrethrolone enol.—On hydrogenation of 0.9 g. of isopyrethrolone enol in ethyl acetate solution, with 0.1 g. of reduced platinum oxide as catalyst, 190 cc. of hydrogen was absorbed in 30 minutes. (The theory requires 224 cc. for 2 mols of hydrogen.)

The solvent was removed under reduced pressure, the residue was dissolved in ether, and the ethereal solution was extracted with 5% sodium carbonate solution. On acidification the carbonate solution yielded an oil, which was extracted with ether. The residue from the dried ether solution was distilled, yielding 0.6 g. of viscous oil boiling at 157-160° (0.3 mm.);  $n_{\rm p}^{\rm 22} = 1.5054$ .  $n_{\rm F}^{\rm 22} - n_{\rm C}^{\rm 22} = 0.0147$ . These constants are the same as those obtained for tetrahydroisopyrethrolone enol prepared from tetrahydropyrethrolone.

Anal. Calc'd for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>: C, 72.52; H, 9.89.

Found: C, 72.28, 72.31; H, 9.80, 9.64.

Tetrahydroisopyrethrolone enol.—Fifteen cubic centimeters of a 10% aqueous solution of potassium hydroxide was dropped over a period of 30 minutes into a boiling solution of 2 g. of tetrahydropyrethrolone in 500 cc. of 95% ethanol containing 3 g. of zinc dust. The reaction was carried out with mechanical stirring, and the boiling was continued for 3 hours. The solution was filtered from zinc, which was then washed with ether. After removal of the alcohol the aqueous solution was extracted with ether and the ethereal solutions were combined. About 0.6 g. of oily residue was obtained from these on evaporation. It was distilled under reduced pressure (b.p. 120°C, p = 0.2 mm.). The product when treated with semicarbazide yielded the semicarbazone of inactive tetrahydropyrethrolone melting at 170°. The identity of the two semicarbazones was confirmed by the mixture melting point.

The aqueous alkaline solution yielded, on acidification and extraction with ether, a thick, slightly yellow oil, which distilled almost completely at 150° (0.25 mm.). The yield of pure material was 1.4 g.;  $n_{\rm p}^{\rm 2s} = 1.5050$ . The compound is a very viscous liquid with a yellow-green fluorescence. It gives a bright yellow color with tetra-nitromethane.

Anal. Calc'd for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>: C, 72.53; H, 9.89; Mol. wt., 182.

Found: C, 72.25, 72.02; H, 10.07, 10.06; Mol. wt. (Rast), 199.

Acetate of tetrahydroisopyrethrolone enol.—The acetate was readily obtained by heating 1 g. of the tetrahydroisopyrethrolone enol with 4 g. of acetic anhydride for several hours on the steam bath. After removal of the excess acetic anhydride by distillation with the aid of the water pump, the remaining liquid product was distilled. It boiled at 115-120° (0.35 mm.), giving 0.9 g. of a colorless mobile liquid;  $n_{\rm p}^{\rm m} = 1.4724$ ;  $n_{\rm r}^{\rm m} - n_{\rm c}^{\rm m} = 0.0102$ .

Anal. Calc'd for C13H20O3: C, 69.64; H, 8.93.

Found: C, 69.41, 69.03; H, 9.10, 8.92.

Hydrogenation of tetrahydroisopyrethrolone enol acetate.—One and six-tenths grams of the acetate was hydrogenated in ethyl acetate solution, with reduced platinum oxide as catalyst. The absorption of hydrogen was very rapid, and 355 cc. was taken up in 15 minutes. (The theoretical requirement for 2 moles is 320 cc.) The solvent was removed under reduced pressure, and the residue was dissolved in ether. After the ethereal solution had been washed with dilute sodium carbonate and water, it was dried with sodium sulfate. The ether was then removed, and the residue was distilled. It boiled at 67-70° (2 nam.). The yield was 1 g.;  $n_{\rm D}^{25} = 1.446$ ;  $n_{\rm F}^{25} - n_{\rm C}^{25} = 0.0066$ .

Anal. Calc'd for C<sub>11</sub>H<sub>20</sub>O: C, 78.57; H, 11.90.

Found: C, 78.12, 78.74; H, 11.72, 11.99.

One-tenth gram of the distillate was dissolved in 1 cc. of ethanol, and 0.15 cc. of pyridine and 0.15 g. of semicarbazide hydrochloride in a few drops of water were added. After standing overnight the separated crystals were removed by filtration, washed with water and then with cold ethanol, and dried. The yield was 0.05 g. The product melted at 190-192°, and after recrystallization from ethanol at 206°. The melting point was not further raised by recrystallization. The melting point of the semicarbazone of one of the stereoisomeric forms of normal hexahydropyrethrone is 196°. When a sample of this compound was mixed with an equal quantity of the semicarbazone just described, the melting point was depressed to 176-180°.

Anal. Calc'd for  $C_{12}H_{23}N_3O$ : C, 64.00; H, 10.22.

Found: C, 63.68, 63.69; H, 9.94, 10.01.

The ethanolic mother liquor from which the semicarbazone of melting point 206° had separated yielded, on dilution with water, 0.07 g. of another semicarbazone which melted at 140-142°. On recrystallization from benzene it melted at 143°. It is a stereoisomer of the higher-melting compound.

Anal. Calc'd for C<sub>12</sub>H<sub>28</sub>N<sub>8</sub>O: C, 64.00; H, 10.22.

Found: C, 64.22; H, 10.31.

Hydrogenation of isopyrethrolone enol acetate.—One and one-tenth grams of isopyrethrolone enol acetate was hydrogenated in 95% ethanol, with reduced platinum oxide as catalyst. The solution absorbed 465 cc. of hydrogen in 11 minutes. (The theoretical requirement for 4 moles is 448 cc.)

The solution was concentrated under reduced pressure to a volume of about 10 cc., and 1 cc. of pyridine and 1 g. of semicarbazide hydrochloride in 1 cc. of water were added. The solution, on standing overnight, deposited crystals, which were removed by filtration. The yield was 0.26 g. On recrystallization from ethanol the product melted at 206°. It was identical with the semicarbazone of hexahydroisopyrethrone of the same melting point obtained by hydrogenation of tetrahydroisopyrethrolone enol acetate, as was shown by a mixture melting-point determination.

The ethanolic mother liquor from the first crystallization was diluted with water, and the precipitated material was recrystallized from a very small volume of ethanol. It melted at 140°, and after crystallization from benzene at 143°. This compound was found by the mixture melting point to be identical with the corresponding compound obtained from the hydrogenation product of the tetrahydroisopyrethrolone enol acetate.

Partial hydrogenation of isopyrethrolone enol acetate. The acetate of isopyrethrolone enol can be hydrogenated to the tetrahydroisopyrethrolone enol acetate without affecting the double bond in the nucleus or the acetate group if the solvent employed is denatured ethyl acetate.§

One and three-tenths grams of isopyrethrolone enol acetate was reduced in denatured ethyl acetate solution, with reduced platinum oxide as catalyst. The solution absorbed 220 cc. of hydrogen in 40 minutes, when the reaction ceased. (The theory for 2 mols requires 265 cc.) The residue obtained on removal of the solvent was distilled. It boiled at 110-120°, p = 3 mm. The yield was 1.05 g.  $N_F^{25} = 1.4735$ .  $N_F^{25} - N_c^{25} = 0.0102$ . The constants are the same as those of tetrahydroisopyrethrolone enol acetate.

§ The denaturant was probably an oxidized petroleum distillate containing a trace of sulfur-containing product.

## SUMMARY

Pyrethrolone is converted, on treatment with alcoholic alkali, into a mixture of two isomeric enols, having the same empirical formula  $(C_{11}H_{14}O_2)$  as pyrethrolone and therefore also isomeric with it.

The lower-boiling enol yields on hydrogenation 3-methyl-2-amylcyclopentanone-1, which is also obtained on hydrogenation of pyrethrolone. Therefore, the relative positions of the hydroxyl and ketone groups in the enol are the same as in pyrethrolone.

The higher-boiling enol yields an acetyl derivative that is hydrogenated to 3-amyl-4-methylcyclopentanone-1, which compound is also the product of hydrogenation of the acetate of the corresponding enol obtained by the action of alcoholic alkali on tetrahydropyrethrolone.

It follows that the positions occupied by the hydroxyl and ketone groups in the higher-boiling enol, designated isopyrethrolone enol, are reversed with respect to the positions that obtain in pyrethrolone and in the lower-boiling enol.