hydrous magnesium sulfate. After removal of the ether, the residue was evaporatively distilled at 0.5 mm. There was obtained 0.99 g. of nearly colorless, viscous oil.

Fractional crystallization of this material from ether–petroleum ether (35–60°) (Dry Ice) yielded 350 mg. of material melting at 79–82°. Further recrystallization gave a total of 205 mg. of product, melting at 84–86° to an opaque liquid, clearing at 86–88°. Additional purification was effected by sublimation at 115–125° (0.8 mm.); m. p. 86–89° with slow clearing.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.69; H, 7.75.

The maroon **2,4-dinitrophenylhydrazone**, prepared from a sample of crystalline ketone (m. p. 84–86°), was recrystallized from ethanol–benzene; m. p. 237–238°.

Anal. Calcd. for $C_{22}H_{24}O_6N_4$: C, 59.99; H, 5.49. Found: C, 60.09; H, 5.40.

The cyclization product may have consisted chiefly of a single isomer, although separation of crystalline material in good yield was difficult. A 2,4-dinitrophenylhydrazone sample prepared from a small portion of oil, as obtained directly from the cyclization reaction, melted only a few degrees below the derivative obtained from crystalline material.

Summary

Syntheses of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone and 3,4-dimethoxy-10-keto-5,6,7,8,9,10,-13,14-octahydrophenanthrene are described.

PHILADELPHIA, PENNSYLVANIA RECEIVED MAY 10, 1947

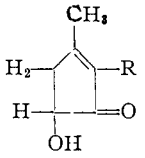
[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH ADMINISTRATION, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE]

Constituents of Pyrethrum Flowers. XXI. Revision of the Structure of Dihydrocinerolone

BY F. B. LAFORGE AND S. B. SOLOWAY

The insecticidal constituents of pyrethrum flowers consist mainly of a mixture of the pyrethrins and cinerins, the pyrethrolone and cinerolone esters of chrysanthemum monocarboxylic acid, and chrysanthemum dicarboxylic acid monomethyl ester. The cinerins have been prepared by partial synthesis by esterification of cinerolone with the chrysanthemum acids. They have been shown to approach the pyrethrins closely in their insecticidal action[1] and to possess the important advantage of decidedly greater stability.

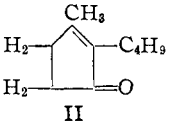
The structure heretofore assigned to pyrethrolone is represented by formula Ia and that of cinerolone by Ib.[2]



Ia, R = $-CH_2-CH=CH-CH=CH_2$
Ib, R = $-CH_2-CH=CH-CH_3$
Ic, R = $-CH_2-CH_2-CH_2-CH_3$

I

These compounds are converted to their respective tetrahydro and dihydro derivatives by hydrogenation of their side chains. Dihydrocinerolone, to which formula Ic had been assigned, is converted to the corresponding desoxy compound, dihydrocinerone, by replacement of the hydroxyl group with hydrogen. The structure of dihydrocinerone, as represented by formula II, has been established by degradation and by synthesis.[3,4]



II

(1) LaForge and Barthel, *J. Org. Chem.*, **12**, 199 (1947); Gersdorff, *J. Econ. Ent.*, in press.
(2) LaForge and Barthel, *J. Org. Chem.*, **10**, 114 (1945).
(3) LaForge and Barthel, *ibid.*, **10**, 222 (1945).
(4) Hunsdiecker, *Ber.*, **75B**, 447, 455, 460 (1942).

It was with a view to the synthesis of cinerolone, and hence, of cinerin itself, that our efforts were first directed to the synthesis of the compound of structure Ic. After attempts to substitute chlorine or bromine directly into position 5 of dihydrocinerone (II), to be followed by replacement with hydroxyl, were unsuccessful, the synthesis of 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic) was accomplished by two routes, each involving four steps.

Synthesis No. 1

In the preparation of dihydrocinerone by the procedure of Hunsdiecker,[4] we had worked out the conditions for preparing ethyl β-oxocaprylate in good yields by carbethoxylation of methyl *n*-amyl ketone with ethyl carbonate, employing sodium hydride as the condensing agent.[5] By the same condensation procedure, or one employing sodium ethoxide, 5-carbethoxydihydrocinerone (III) was obtained from dihydrocinerone (II). This derivative furnished 5-acetoxy-5-carbethoxydihydrocinerone (IV) on treatment with lead tetraacetate. On treatment with concentrated ammonium hydroxide, compound IV was converted to the crystalline 5-carbamyl-5-hydroxydihydrocinerone (V), which by acid hydrolysis furnished the end-product, 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic).

This synthesis does not constitute a rigorous proof that the acetoxy group entered at the 5-position. The presence of the carbethoxy group at this position was indicated by the purple color obtained with alcoholic ferric chloride, whereas the compound with the carbethoxy group at the 4-position,[6] which is a vinylog of the 5-carbethoxy compound, gives only an orange coloration with this reagent. That the nuclear methyl group is

(5) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947).
(6) Unpublished result.

not involved in the carbethoxylation reaction is shown by the terminal-methyl determination.

Synthesis No. 2

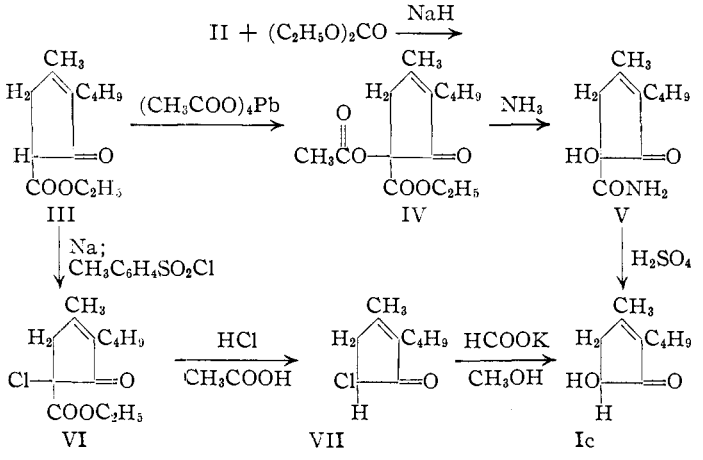
A second synthesis of 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic), which is unambiguous with respect to the positions of the substituents in the intermediate and final products, proceeds from the same 5-carbethoxydihydrocinerone (III) that was employed in the first synthesis.

Chlorine was substituted for the active hydrogen in position 5 by application of a reaction described by Meyer and Findeisen[7] for the chlorination of ethyl acetoacetate by the agency of *p*-toluenesulfonyl chloride. The reaction can be represented by the following generalized equations

$$ROOCC(R')=C(R'')(ONa) + CH_3C_6H_4SO_2Cl \longrightarrow [ROOCC(R')(Cl)C(R'')(ONa)(O_2SC_6H_4CH_3)] \longrightarrow ROOCC(R')ClC{=}O(R'') + CH_3C_6H_4SO_2Na$$

This reaction furnished 5-carbethoxy-5-chlorodihydrocinerone (VI) in good yield, which on decarbethoxylation by boiling with a mixture of acetic and hydrochloric acids yielded 5-chlorodihydrocinerone (VII). Replacement of the chlorine by hydroxyl was accomplished by boiling the chloro compound in absolute methanol with potassium formate, and yielded 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic) identical with that obtained by the reactions of synthesis no. 1.

The two synthetic routes are represented by the following schematic diagram



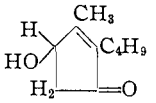
The compounds obtained by both routes exhibit the same properties and furnish the same semicarbazone melting at 169°. The free hydroxyketones reduce Fehling solution vigorously and give a silver mirror with Tollens reagent. They yield with phenylhydrazine an osazone of characteristic properties and are decomposed in sodium ethoxide solution. The chlorine in the corresponding chlorodihydrocinerone (VII) could be removed only by long boiling with aqueous sodium carbonate with resulting resinification of the reaction product. This is contrary to the behavior of the chlorocinerone obtained by replacement of the hydroxyl group in natural cinerolone with chlorine. This chloro derivative is readily converted to cinerolone on boiling with an aqueous suspension of calcium carbonate.

The properties of synthetic 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic) are distinctly different from those of dihydrocinerolone, obtained from natural cinerolone, which yields a semicarbazone melting at 185°,[3] does not form a phenylosazone, and reduces Fehling and Tollens solution only to a slight extent.

Synthetic 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic), therefore is not identical with dihydrocinerolone, to which a structure other than Ic must now be assigned.

The location by Staudinger and Ruzicka,[8] of the hydroxyl group in pyrethrolone in position 5 was based solely on the formation of a compound of very high melting point, which they assumed to be a *p*-nitrophenylosazone. Although this compound analyzed as such, it was probably of some other nature. The authors were unaware of the presence of the double bond in the nucleus of pyrethrolone, which would lend to it the properties of a compound with activated hydrogen atoms in positions allylic to this double bond.

With consideration of other known facts, only the position 4, allylic to the ring double bond, remains for the hydroxyl group in a revised structure for dihydrocinerolone, and in all probability for pyrethrolone. With this revision dihydrocinerolone would be represented by formula VIII.



VIII

It is apparent that a compound of this structure would possess properties in agreement with those of dihydrocinerolone and different from those exhibited by the compound Ic, the synthesis of which has been described. It would not be expected to reduce Fehling solution or to yield a phenylosazone. The ethers and esters, in agreement with observation, should readily undergo hydrogenolysis.[9] The corresponding 4-chlorocine-

(7) Meyer and Findeisen, *J. prakt. Chem.*, **65**, [2] 528 (1902).

(8) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 212 (1924).

(9) This behavior is characteristic of the esters and ethers of pyrethrolone. On the contrary, Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 377 (1924), state that the acetate of 2-hydroxy-4-methylcyclopentanone is stable to catalytic hydrogenation. They were unable to explain this unexpected discrepancy. Recently, Kindler and Blaas, *Ber.*, **77B**, 585 (1944), reported that, when compounds of the type $ArCOCH_2OAc$ are subjected to catalytic hydrogenation, reduction of the carbonyl group to either carbinol or hydrocarbon, depending upon the solvent, is the preferred course of the reaction, hydrogenolysis of the ester group occurring only to a subordinate degree.

rone would be very reactive, which is in harmony with the facts.

Structure VIII involves no discrepancies with respect to observed spectrographic data.[10]

Experimental

5-Carbethoxydihydrocinerone (III) (a) **By Sodium Ethoxide-catalyzed Condensation.**—This method employs the forced condensation procedure of Wallingford, Homeyer and Jones[11] for the preparation of β-keto esters. In one experiment the reaction was carried out with 20 g. (0.13 mole) of dihydrocinerone, 78 g. (0.66 mole) of ethyl carbonate and sodium ethoxide, prepared from 3.0 g. (0.13 mole) of sodium 25 ml. of ethanol and 60 ml. of benzene. The reaction mixture yielded, on distillation through a modified Claisen flask, 6.6 g. of starting material and 16.5 g. of product b. p. 113–119° (0.5 mm.) 83.5% on the basis of reacted material. A fraction boiling at 116–120° (0.5 mm.), $n^{25}D$ 1.4740, was collected for analysis.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; C_2H_5O, 20.1; $3CH_3$, 20.1. Found: C, 69.45; H, 8.96; C_2H_5O, 19.9; CH_3, 20.1.

(b) **By Sodium Hydride-catalyzed Condensation.**—Commercial sodium hydride, 19.2 g. (0.8 mole), was weighed under nitrogen and transferred to a nitrogen-swept 2-liter three-necked flask equipped with reflux condenser, mercury-sealed stirrer and dropping funnel. The sodium hydride was covered with 200 ml. of dry ether, and 94.4 g. (0.8 mole) of ethyl carbonate was added. The mixture was brought to reflux and 60.7 g. (0.4 mole) of dihydrocinerone dissolved in 50 ml. of dry ether was added dropwise, with stirring, over a period of five hours. The reflux and stirring were continued for one-half hour after the addition, and the mixture was allowed to stand overnight. It was then poured onto a slurry of ice containing 60 ml. of glacial acetic acid, and the oil which separated was taken up in ether and washed free of acid with dilute sodium bicarbonate. The ether solution was dried and, after removal of the solvent and excess ethyl carbonate by distillation, a fraction, b. p. 108–114° (0.3 mm.), $n^{26}D$ 1.4735, was obtained, amounting to 75.3 g. (84%).

A purple color was produced with alcoholic ferric chloride. The reaction product, in agreement with the statement of Hunsdiecker,[4] did not yield a semicarbazone. Upon standing overnight under concentrated ammonium hydroxide in a stoppered flask at room temperature, it yielded an amide. It crystallized from water in prismatic needles (m. p. 98–99°).

Anal. Calcd. for $C_{11}H_{17}O_2N$: N, 7.2. Found: N, 7.0.

5-Acetoxy-5-carbethoxydihydrocinerone (IV).—Fifteen and seven-tenths grams (0.07 mole) of III was dissolved in 50 ml. of glacial acetic acid contained in a 100-ml. three-necked flask equipped with stirrer and thermometer. One molecular equivalent of lead tetraacetate was added in successive small portions, permitting the yellow color which formed with each addition to disappear. The reaction being exothermic, the temperature of the solution rose to 40°, where it was maintained by the constant addition of reagent. The process required about ninety minutes and, when the solution gave a negative starch–iodide test, a small excess of reagent was added. When the test persisted after fifteen minutes additional stirring, the excess reagent was decomposed with glycerol. The resulting solution was then poured into cold water and extracted twice with petroleum ether. The organic layer was freed of acid with dilute sodium bicarbonate and dried, and the solvent was removed. The product was fractionally distilled, yielding 11.1 g. (56%) of a fraction, b. p. 130–132° (0.4 mm.), $n^{29}D$ 1.4709. There was no forerun.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; C_2H_5O, 16.0. Found: C, 63.58; H, 8.04; C_2H_5O, 15.8.

In later experiments red lead was employed directly in glacial acetic acid at 60°, and yields of 70% were realized by more complete extraction with ethyl ether.

Several attempts to hydrolyze the compound IV directly to 5-hydroxydihydrocinerone (Ic) were generally unsuccessful. It was not altered on refluxing with 1 *N* sulfuric acid. Refluxing with aqueous-ethanolic barium hydroxide produced a small amount of oil which yielded a semicarbazone, m. p. 247°, identical with a semicarbazone obtained as a by-product of the acid hydrolysis of 5-carbamyl-5-hydroxydihydrocinerone (V) (see below). Treatment with 5% aqueous potassium hydroxide gave a low yield of the hydroxyketone (Ic) (semicarbazone, m. p 169°).

Hydrolysis of IV with a mixture of acetic and hydrochloric acids, a procedure which succeeded with 5-carbethoxy-5-chlorodihydrocinerone (VI) was not tried.

5-Carbamyl-5-hydroxydihydrocinerone (V).—This derivative was obtained in practically quantitative yield by allowing IV to stand under four times its weight of concentrated ammonium hydroxide in a stoppered flask at room temperature. After eight days the liquid material had been transformed into a mass of needle-like crystals which were collected and recrystallized from water, m. p. 91°.

Anal. Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.73; H, 8.35; N, 6.51.

2-Butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic). **Synthesis No. 1.**—Two and one-half grams of the amide V was boiled under reflux in 15 ml. of 10% sulfuric acid. The amide first dissolved in the hot solution from which an oil soon began to separate. Refluxing was continued for about one hour, after which the reaction mixture was cooled and extracted with ether. The ethereal solution was washed with dilute sodium bicarbonate and dried, and the residue fractionally distilled, yielding 1.2 g. (60%) of product, b. p. 92° (0.3 mm.), $n^{27}D$ 1.4930.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.82, 70.89; H, 9.69, 9.56.

The semicarbazone was prepared and recrystallized from ethyl acetate, m. p. 169°.

Anal. Calcd. for $C_{11}H_{19}O_2N_3$: C, 58.64; H, 8.50. Found: C, 58.34, 58.41; H, 8.66, 8.57.

The phenylosazone was obtained by warming the hydroxyketone for one hour in a dilute aqueous solution containing a slight excess of phenylhydrazine acetate and about 10% ethanol. The osazone separated from the solution in the form of orange-yellow needles, which were recrystallized from 1:1 ethanol–water, m. p. 147°.

Anal. Calcd. for $C_{22}H_{26}N_4$: N, 16.2. Found: N, 15.2, 15.3 (Kjeldahl–Friedrich).

The 3,5-dinitrobenzoate was prepared from the acid chloride and the hydroxyketone in benzene containing pyridine, forming plates from ethanol, m. p. 125–126°.

Anal. Calcd. for $C_{17}H_{18}O_7N_2$: C, 56.35; H, 5.01. Found: C, 56.76; H, 5.24.

The free hydroxyketone reduced Fehling solution and gave a strongly positive test with Tollens reagent. On warming with sodium methoxide in methanol, the solution rapidly turned black with decomposition.

When the hydrolysis of the amide was carried out with 25% sulfuric acid, an oil was obtained which yielded, together with the semicarbazone of m. p. 169°, a compound, which, according to the analysis, is a di-semicarbazone, probably of the diketone resulting from oxidation of the hydroxyketone. The di-semicarbazone was readily isolated because of its lesser solubility and was recrystallized from a large volume of ethyl acetate, m. p. 244°, and it did not depress the melting point of the semicarbazone obtained from the barium hydroxide–hydrolytic product of 5-acetoxy-5-carbethoxydihydrocinerone (IV).

Anal. Calcd. for $C_{13}H_{20}O_2N_6$: C, 51.41; H, 7.19. Found: C, 51.48; H, 7.92.

5-Carbethoxy-5-chlorodihydrocinerone (VI).—Metallic sodium, 1.72 g. (0.075 mole), was powdered by stirring

(10) LaForge and Barthel, *J. Org. Chem.*, **10**, 106 (1945).

(11) Wallingford, Homeyer and Jones, This Journal, **63**, 2252 (1941).

under boiling xylene in a 300-ml. three-necked flask equipped with reflux condenser, mercury-sealed stirrer and dropping funnel. The xylene was decanted and the sodium covered with 35 ml. of dry ether. A solution of 16.8 g. (0.075 mole) of 5-carbethoxydihydrocinerone (III) in 35 ml. of dry ether was slowly added through the dropping funnel, causing vigorous evolution of hydrogen. When all the sodium had dissolved with the formation of the ether-soluble enolate, 14.3 g. (0.075 mole) of *p*-toluenesulfonyl chloride in 50 ml. of ether was added at room temperature over about ten seconds to the stirred solution, causing immediate separation of a white solid material. The suspension was refluxed for one hour, when a test showed it to be neutral in reaction. Upon addition of water the solid material dissolved and the separated organic layer was washed with water and dried. The solvent was removed and the residue fractionally distilled, yielding 17.4 g. (90%) of product, b. p. 115–124° (0.4 mm.), $n^{25}D$ 1.4829.

Anal. Calcd. for $C_{13}H_{19}O_3Cl$: C, 60.34; H, 7.40; Cl, 13.70. Found: C, 60.41; H, 7.51; Cl, 13.79.

Addition of an excess of mineral acid to the combined aqueous phases caused the separation of *p*-toluenesulfinic acid in quantity equivalent to that of the chloro-compound which had formed.

5-Chlorodihydrocinerone (VII).—From a number of attempts to accomplish the decarbethoxylation of 5-carbethoxy-5-chlorodihydrocinerone (VI), refluxing with a mixture of glacial acetic and hydrochloric acids has been the only one which proved successful. Four grams of VI in 10 ml. of glacial acetic acid and 3 ml. of concentrated hydrochloric acid were refluxed for one-half hour. The reaction proceeded with vigorous evolution of carbon dioxide, and the solution took on a reddish color. The mixture was cooled, and poured into cold water, and the reaction products were extracted twice with petroleum ether. The organic layer was washed free of acid with dilute sodium bicarbonate and dried, and the solvent removed. Distillation yielded 2.4 g. (83%) of a product boiling 73–93° (0.4 mm.); a chlorine analysis indicated that it was 82% pure. An analytical sample was prepared by redistillation, b. p. 84° (0.4 mm.), $n^{23}D$ 1.5000.

Anal. Calcd. for $C_{10}H_{15}OCl$: C, 64.34; H, 8.10; Cl, 19.0. Found: C, 64.03; H, 8.49; Cl, 19.1.

In a much larger experiment the decarbethoxylation was carried out on 31 g. of crude VI, resulting in a 64% overall yield of VII.

2-Butyl-5-hydroxy-3-methyl-2-cyclopentene-1-one (Ic). Synthesis no. 2.—Two and one-half grams (0.064 mole) of potassium metal was dissolved in 15 ml. of absolute methanol in a 125-ml. Erlenmeyer flask and converted to the hydroxide by the addition of 1.15 ml. (0.064 mole) of water. After several minutes, 7.1 g. (0.096 mole) of dry ethyl formate was added, causing a vigorous reaction and the separation of potassium formate. The flask was attached to a condenser protected from moisture, the mixture was refluxed for one-half hour and then cooled, and 6.0 g. (0.032 mole) of VII was added. The reaction was then allowed to proceed under reflux for sixteen hours. Ether was added to the reaction products and the separation of the salts completed by cooling in the refrigerator. The separated salt was filtered off and washed with ether. The solvents were then removed on the steam-bath and the residue distilled. The product, b. p. 84–86° (0.15 mm.), amounting to 3.0 g. (56%), was found to contain 2% of methoxyl and, hence, a calculated content of 12% of 5-methoxydihydrocinerone. The pure compound was obtained by regeneration from its recrystallized semicarbazone, b. p. 89–91° (0.3 mm.), $n^{27}D$ 1.4930.

The semicarbazone prepared from the first distillation, when recrystallized from ethyl acetate, melted at 169–170°, and did not depress the melting point of the semicarbazone of the hydroxyketone obtained by synthesis no. 1.

The hydroxyketone also showed properties identical with the one prepared by the first synthetic route with respect to its behavior with Fehling and Tollens reagents and sodium methoxide in methanol and, also, in the formation of the same phenylosazone.

Hydrolysis of Chlorocinerone Derived from Natural Cinerolone.—Three and one-half grams of chlorocinerone[2] was boiled in 50 ml. of water with 12 g. of calcium carbonate, freshly precipitated and washed free of chloride, which was added in two portions two hours apart. After boiling for a total period of five hours, the reaction mixture was cooled and the suspended oil extracted with ether. The organic phase was dried, the solvent removed, and the residue distilled, yielding 2.6 g. of product, b. p. 122–125° (0.5 mm.), $n^{24}D$ 1.5210, $[\alpha]^{25}D$ +2.2 ± 0.3 (*c*, 6.4 in methanol). It yielded a semicarbazone, m. p. 200°, and was further characterized by conversion to the acetyl compound, b. p. 112–115° (0.5 mm.), $n^{20}D$ 1.5006, from which semicarbazones of the active and racemic forms were obtained.[2] The cinerolone was therefore partly racemized during hydrolysis.

Summary

The synthesis of 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic), the structure heretofore assigned to dihydrocinerolone, is described.

That the synthetic compound is not identical with dihydrocinerolone prepared by hydrogenation of natural cinerolone has been established by a comparison of their respective properties.

The formula of dihydrocinerolone has therefore been revised by reallocation of the hydroxyl group from position 5 to position 4 in the cyclopentene nucleus. A compound of the revised structure having the hydroxyl group in position 4, allylic to the nuclear double bond, would be expected to exhibit properties in all respects in agreement with those observed for dihydrocinerolone. A similar revision would in all probability apply to pyrethrolone.[12]

BELTSVILLE, MD. RECEIVED JUNE 23, 1947

(12) Since this article was submitted, the synthesis of 2-butyl-4-hydroxy-3-methyl-2-cyclopentene-1-one, VIII, dihydrocinerolone, (Soloway and LaForge, THIS JOURNAL, **69**, 979 (1947)) and of 2-amyl-4-hydroxy-3-methylcyclopenten-1-one, tetrahydropyrethrolone (Dauben and Wenkert, *ibid.*, **69**, 2074 (1947)) have been described.