[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

Dimerized Cyclopentadienones from Esters of Allethrolone

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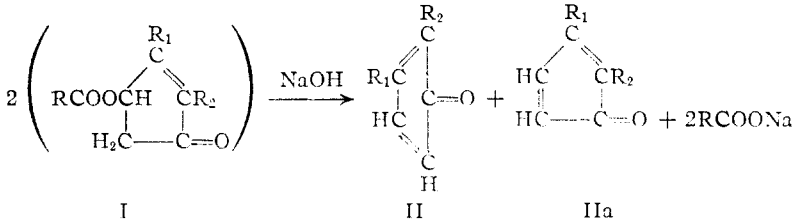
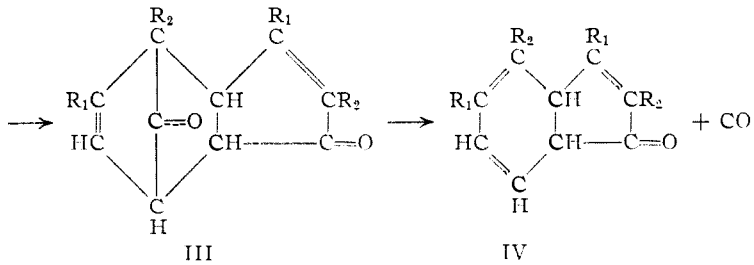
Esters of allethrolone are saponified to the combined acid and to 2-allyl-3-methyl-2,4-cyclopentadienone which undergoes the Diels–Alder reaction yielding the dimeric compound (III) as the main product. The dimer exhibits the reactions characteristic of carbonyl bridge compounds. It furnished both a mono- and a disemicarbazone and upon heating sheds carbon monoxide with formation of a tetrasubstituted indanone. These reactions of allethrolone esters on saponification probably would occur with all esters of 4-hydroxycyclopentenones including the pyrethrins. The structures presented, although extremely likely, are based on analogy rather than on direct experimental evidence.

Saponification of allethrin (formula I, where R = $(CH_3)_2C{-}CH{-}CH{=}C(CH_3)_2$ with HC⁻ bridging) which takes place rapidly at ordinary temperatures, does not proceed normally to chrysanthemum monocarboxylic acid and the expected cyclopentenolone component, allethrolone (2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one),[1] but instead mainly to complex dimers (III) of 2-allyl-3-methyl-2,4-cyclopentadien-1-one (II).

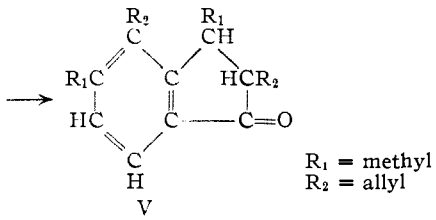
This course of the saponification reaction is not limited to allethrin, but is probably common to all esters of 4-hydroxy-2,3-cyclopentenones, including the pyrethrins, where it leads to analogous products. In the case of allethrolone acid phthalate the saponification seems to proceed nearly exclusively in this manner. In the other two examples some of the reaction products are unaccounted for or have not been identified. The main reactions occur, however, as indicated below.



I II IIa



III IV

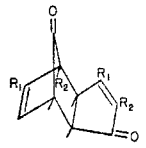


V

R_1 = methyl
R_2 = allyl

The reactions occurring after saponification were first observed by Japp and co-workers[2] for analogous aromatic substituted cyclopentadienones. The structures of the compounds involved were determined by Allen and Spanagel.[3]

It should be emphasized at this point that no degradation experiments have been made on any of the compounds of structures II to V which have been deduced from analogy with the compounds and reactions referred to in the literature. The spatial configuration of the adduct would be *cis* and most likely *exo*, as represented by formula IIIa.



IIIa

Hence there should be two (racemic) *exo* dimers[4] according to whether dienone IIa reacts as shown or in the inverted position. Saponification of allethrin, the acid phthalate and acetate of allethrolone furnished as the predominant neutral product the same dimer of probable structure III. This compound was obtained in crystalline form first by regeneration from its semicarbazone and later, when material for seeding was available, by direct crystallization from the neutral reaction mixture. It possesses all the properties characteristic of compounds of analogous structure described by Allen.[3] It forms both a mono- and a disemicarbazone. On heating it sheds carbon monoxide, and is converted primarily to a tetra-substituted indenone probably of formula IV which rearranges to the more stable isomeric form of formula V. This structure is substantiated by failure to react with maleic anhydride. The disemicarbazone is a high-melting compound practically insoluble in all the usual solvents. It is hence easily separated from the soluble monosemicarbazone. Its properties are so nearly like those of the semicarbazone of "altered

(1) Milton S. Schechter, Nathan Green and F. B. LaForge, THIS JOURNAL, 71, 3165 (1949).

(2) (a) F. R. Japp and F. Klingemann, *J. Chem. Soc.*, **57**, 662 (1890); (b) F. R. Japp and G. D. Langer, *ibid.*, **71**, 123 (1897); (c) F. R. Japp and A. N. Meldrum, *ibid.*, **79**, 1024 (1901).

(3) C. F. H. Allen and E. W. Spanagel, THIS JOURNAL, **55**, 3773 (1933). For a review of the literature of carbonyl bridge compounds see C. F. H. Allen, *Chem. Revs.*, **37**, 209 (1945).

(4) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

pyrethrolone" first observed by Staudinger and Ruzicka,[5] that it may be concluded that they are of the same nature, although the latter must be a much more complex mixture.

The monosemicarbazone of another isomeric dimer has also been isolated in small quantity from the non-crystalline neutral saponification products. The corresponding disemicarbazone melts a few degrees lower than the derivative obtained from the crystalline dimer.

Experimental

Allethrolone Acid Phthalate.—Phthalic anhydride, 25 g. (0.169 mole), and allethrolone, 25 g. (0.164 mole), were heated together in an oven at 110° for seven hours. After being cooled, the glassy mass was stirred with dilute aqueous ammonia, and the milky solution was extracted with ether to remove unreacted material. On acidification the half-ester was precipitated from the clear solution as an oil, which slowly crystallized on rubbing with petroleum ether. It was dried in a desiccator and recrystallized by dissolving in warm benzene and carefully adding petroleum ether (b.p. 60–70°), yield 38 g., m.p. 93.5–94°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37; mol. wt., 300. Found: C, 68.00, 68.08; H, 5.31, 5.37; mol. wt. (titration), 301.

From another experiment 89 g. of this acid phthalate was obtained from 46 g. of allethrolone that had been regenerated from the semicarbazone and 46 g. of phthalic anhydride.

Saponification of Allethrolone Acid Phthalate—2,4-Diallyl-3,5-dimethyl-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione (III).—Allethrolone acid phthalate, 30 g. (0.1 mole), was added to a solution of 9.0 g. (0.22 mole) of sodium hydroxide in 200 ml. of water at room temperature. Even before all had dissolved, separation of an oil began and was complete in about 20 minutes. The separated material was extracted with petroleum ether, the solution was washed and dried, and the solvent was removed in vacuum; yield 11.9 g. The product was subjected to molecular distillation at 2–3 microns with a bath temperature of 75–80°; three equal fractions were collected having $n^{25}D$ 1.5340, 1.5342, and 1.5349 for fractions 1, 2 and 3, respectively. Fraction 2 was analyzed.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51; mol. wt., 268. Found: C, 80.37; H, 7.70; mol. wt. (cryoscopic), 271.

In small quantity the compound could be distilled at 0.1–0.2 mm., b.p. about 145°. At higher temperatures it began to decompose with evolution of carbon monoxide.

2,4-Diallyl-3,5-dimethylindan-1-one (V).—Six grams of III was heated in a small flask to 200–210° until no more carbon monoxide was given off. The gas could be ignited at the exit tube; it could also be detected by bubbling through a palladium chloride solution. The residue was distilled from a small Claisen flask to give 1.7 g. of product, b.p. 123–125° (0.15 mm.), $n^{25}D$ 1.5510.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 85.10, 84.03; H, 8.86, 8.40.

The semicarbazone was prepared in ethanol–water–pyridine solution. It was obtained by precipitation with water and dried. After recrystallization from ethyl acetate it melted at 164–169°.

Anal. Calcd. for $C_{18}H_{23}ON_3$: N, 14.14. Found: N, 14.23.

Semicarbazones of Dimer III.—The crude dimer from 20 g. of allethrolone acid phthalate was dissolved in a solution containing 9.5 g. of semicarbazide hydrochloride, 8.0 ml. of pyridine and 50 ml. of 90% ethanol. After about 18 hours the separated material was removed by filtration, washed with water, and dried. It was then refluxed with 200 ml. of methanol and 2.6 g. of the insoluble semicarbazone filtered off. It was practically insoluble in all the usual solvents and melted at 246–247° with decomposition. It was the disemicarbazone of III, but might be a mixture of isomers.

Anal. Calcd. for $C_{20}H_{26}O_2N_6$: C, 62.80; H, 6.85; N, 21.98. Found: C, 63.02; H, 7.23; N, 20.58.

The methanol solution on concentration deposited 3.75 g. of the monosemicarbazone of dimer III, m.p. 209–210°, identical with the monosemicarbazone obtained from the saponification of allethrin.

Regeneration of Dimer III from Its Monosemicarbazone.—This monosemicarbazone, 6.4 g., was refluxed for 45 minutes with 20 ml. of glacial acetic acid containing 2.5 ml. of concentrated hydrochloric acid. The solution was then poured into several volumes of water, and the separated oil was extracted with petroleum ether. The colorless solution was washed free of acid and the solvent was evaporated. The residue crystallized completely and was recrystallized from ligroin to yield 4.55 g., m.p. 66–68°. The compound separated from the solution in large nearly perfect crystals.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 79.94; H, 7.72.

In agreement with its postulated structure, it was found to possess 1.1 equivalent of active hydrogen and showed 1.16 addition equivalents. It absorbed four equivalents of hydrogen; two very rapidly (the allyl groups), and two at a slower rate.[6] The ultraviolet spectrum of the compound gave a curve that was typical of an α,β-unsaturated ketone.[7] The K band was at 239 mμ (ϵ 9110), and the R band at about 320 mμ (ϵ 110) in ethanol.

One-half gram of the crystalline dimer yielded 0.1 g. of insoluble disemicarbazone, m.p. 245°, and 0.4 g. of the soluble monosemicarbazone, m.p. 210°, identical with the original semicarbazone.

The crude dimer prepared from 15 g. of allethrolone acid phthalate crystallized in part on seeding with the crystalline compound, yielding 3.0 g. of product, m.p. 66–67°, identical with that regenerated from the semicarbazone and 2.5 g. of sirupy material, $n^{25}D$ 1.5329, which deposited more of the crystalline product on longer standing until only very little of the liquid form remained. When the semicarbazone was prepared from 1.5 g. of the non-crystalline part some of the monosemicarbazone, m.p. 209–210°, was obtained. On dilution of the mother liquor a sirup was precipitated which soon crystallized. It was recrystallized from about four parts of ethyl acetate and melted then at 183–185°. It was identical with the semicarbazone of m.p. 185° from allethrin described below (mixed m.p. 182–184°).

Decarbonylation of Crystalline Dimer III to Compound V (*via* Compound IV).—The crystalline compound III, 2.5 g., was heated in a small flask at 200° until no more carbon monoxide was shed (10 minutes). On distillation of the residue the decarbonylated compound was obtained in about 50% yield, b.p. 135–140° at 0.4 mm., $n^{25}D$ 1.5480.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.54; H, 8.59.

The product of decarbonylation of Compound III is more likely of structure V than of IV. It gives a deep red color with azoxybenzene and aluminum chloride in chloroform indicating an aromatic nucleus.[8] The same test applied to compound III was negative. Further evidence of the presence of an aromatic nucleus was obtained from the ultraviolet absorption spectrum of the decarbonylated compound which gives a marked absorption in the 260–310 mμ region with evidence of a maximum about 285 mμ. Compound IV has two chromophores: the α,β-unsaturated ketone, and the conjugated double bonds. These structures would not account for the absorption obtained in the 260–310 mμ region as would the aromatic nucleus, as is shown in Formula V.[9]

When the crystalline dimer was converted to the semicarbazone at room temperature, a mixture of the mono- and disemicarbazones was formed regardless of the amount of reagent employed. However, when the reaction was carried out in a large volume of the hot solvent, the disemicarbazone was the exclusive product.

When 2 g. of crystalline dimer III was warmed for three hours in 150 ml. of ethanol, with 1.8 g. of semicarbazide hydrochloride and 1.8 ml. of pyridine, 2.7 g. of the disemicarbazone of III, m.p. 256–258°, was obtained.

(5) H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, **7**, 189, 234 (1924).

(6) Private communication from C. F. H. Allen.

(7) L. N. Ferguson, *Chem. Revs.*, **48**, 402 (1948).

(8) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 88.

(9) Ultraviolet absorption data by M. Beroza of this Division.

Saponification of Allethrin.—Allethrin, 30 g. (0.1 mole), that had been prepared from pure materials was dissolved in 180 ml. of 75% ethanol containing 4.8 g. (0.12 mole) of sodium hydroxide. After three and a half hours most of the ethanol was removed in vacuum and the residue, after dilution with water, was extracted with petroleum ether. The yield of crude product from which the solvent had been removed in vacuum was 12.7 g., $n^{25}D$ 1.5310. It was dissolved in 80 ml. of 75% ethanol containing 14 g. of semicarbazide hydrochloride and 11 ml. of pyridine. The crystalline material which had separated overnight was filtered off and refluxed with methanol. Three grams of insoluble disemicarbazone was removed by filtration and dried, m.p. 248–250°. The soluble semicarbazone obtained on concentrating the methanol solution melted at 207–210°, and was identical with the monosemicarbazone from allethrolone acid phthalate; yield 3.0 g.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.62; H, 7.91; N, 12.45.

Water was added to the concentrated mother liquor, and the suspended material was extracted with a large volume of ether. On concentration of the washed and dried ether solution, a small amount of monosemicarbazone melting at 185° was obtained.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.25; H, 7.41; N, 13.46.

From another experiment under identical conditions, 12.6 g. of the crude dimer mixture was obtained from 31 g. of pure allethrin. Upon seeding with the dimer (III), 4.35 g. of the crystalline product was obtained on standing, m.p. 66–67° after recrystallization from ligroin. The yield of insoluble disemicarbazone was 3.3 g.

Allethrolone Acetate.—Allethrolone, 12 g., in about 15 ml. of acetic anhydride with a little anhydrous sodium acetate was allowed to stand overnight and then warmed for half an hour on the steam-bath. The excess of anhydride and the acetic acid were removed in vacuum, water was added to the residue, and the ester extracted with about 150 ml. of petroleum ether. The solution was extracted with sodium carbonate solution and dried. The solvent was removed, leaving 12.9 g. of the ester. It was distilled at 0.5 mm., b.p. 96–97°, $n^{25}D$ 1.4902.

Anal. Calcd. for $C_{11}H_{14}O_3$: CH_3CO, 22.2. Found: CH_3CO, 21.2.

Saponification of Allethrolone Acetate.—Allethrolone acetate, 15 g., was allowed to stand overnight in 180 ml. of 75% ethanol containing a small excess of sodium hydroxide. Most of the solvent was removed in vacuum, and the separated oil was extracted with low-boiling petroleum ether in the usual manner to yield 7.0 g. of colorless oil, which, combined with 1.8 g. of the same material from a previous experiment, was dissolved in 40 ml. of methanol. A solution of 3.7 g. of semicarbazide hydrochloride in 14 ml. of 60% methanol and 4 ml. of pyridine was added at intervals of one-half hour. Crystallization began shortly after the first addition. The 3.4 g. of total product, obtained directly and on partial evaporation of the solvents, was still a mixture containing 1.65 g. of the monosemicarbazone of the dimer (III) soluble in hot methanol, m.p. 207–208°, and 0.9 g. of the insoluble disemicarbazone, m.p. 250–252°.

The unreacted liquid product that separated on dilution of the mother liquor was extracted with petroleum ether. The 1.7 g. of residue crystallized for the most part to the dimer III, which after recrystallization melted at 65–66°.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

Steroid 17(α)-Acetates*

BY HUANG-MINLON, EVELYN WILSON, N. L. WENDLER AND M. TISHLER

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In contrast to statements in the literature, it has been found possible to acetylate a variety of 17(α)-hydroxy-20-ketosteroids under mild as well as vigorous conditions without invoking structural change.

The 17(α)-hydroxyl group of 20-ketosteroids has been generally acknowledged to be strongly hindered and not acetylatable.[1] In contrast thereto, the direct acetylation of steroid tertiary hydroxyl functions situated 17(β)[2] and 5(α)[3] has been successfully accomplished employing acetic anhydride in pyridine at 100° and refluxing acetic anhydride, respectively. The recently reported isolation of a 17(α)-lactone from the oxidation of sitosterol[4] as well as an earlier described diacetate derived from 3(β), 17(α)-dihydroxy-11-keto-etioallocholanic acid[5] indicated the possibility of esterification of steroid 17(α)-hydroxyl groups in general. It had been of interest to us, for some time, to investigate the reactivity of this functional group and attempt to define the conditions necessary for its participation in direct acetylation. It was anticipated that as the conditions of forced reaction were made more extreme, dehydration and/or rearrangement might intervene. In this latter regard, numerous 17-hydroxy steroids, including 17(α)-hydroxyprogesterone,[6] have been observed to be exceptionally prone to D-ring homoannulation under a variety of conditions.[7] Of particular significance with regard to the compounds of the type reported in the present work is the recent discovery by Mattox[8] that the 20-keto-17(α),21-dihydroxy cortical side chain is smoothly converted to a substituted glyoxal derivative in the presence of methanolic hydrogen chloride. In this connection, however, it is noteworthy that this rearrangement does not occur to any measurable extent with hydrogen chloride in acetic acid.[9]

Conditions found to be sufficient to acetylate steroid 17(β)-hydroxyl groups[2] (acetylation employing acetic anhydride in pyridine at 100°) were found in the present work to be essentially without

* We regret that through inadvertence on our part a Communication (THIS JOURNAL, **74**, 4220 (1952)) on the same subject was received and accepted after the definitive paper published here.—THE EDITORS.

(1) *See for example:* (a) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **30**, 205 (1947); (b) L. F. Fieser, *Experientia*, **6**, 312 (1950); (c) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 411; (d) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952).

(2) C. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 185 (1943).

(3) Pl. Plattner, Th. Petrzilka and W. Lang, *ibid.*, **27**, 513 (1944).

(4) A. J. Ryer and W. H. Gebert, THIS JOURNAL, **74**, 41 (1952).

(5) H. L. Mason, W. M. Hoehn and E. C. Kendall, *J. Biol. Chem.*, **124**, 459 (1938).

(6) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

(7) Reference 1c, p. 377.

(8) V. R. Mattox, Abstracts of the Gordon Conferences on Steroids, New Hampton, N. H., Aug. 13–15 (1951).

(9) Observation by Dr. R. P. Graber of these laboratories.