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

Δ^4-9-Methyloctalin-3,8-dione

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The synthesis of Δ^4-9-methyloctalin-3,8-dione is described. The nature of the cleavage acids arising from the preparation of this substance and its precursor has been elucidated.

A recent article by Wieland and Miescher[1] describes *inter alia* the preparation of Δ^4-9-methyloctalin-3,8-dione (V). Prior to the appearance of this article we had had occasion to prepare this substance,[2] and since our experiences with its synthesis are substantially different, we wish to report them at this time.

We found that the course of the condensation between 1-methylcyclohexane-2,6-dione (I) and methyl vinyl ketone is intimately associated with the conditions employed for effecting reaction. Attempts to prepare this octalindone under the usual conditions of the conventional annulation procedure[3,4] with diethylaminobutanone methiodide in the presence of sodium alkoxides were singularly unsuccessful. Similar efforts to synthesize this individual by effecting direct Michael addition between (I) and methyl vinyl ketone with strong alkaline catalysts were equally unavailing. Aside from a certain amount of ill-defined neutral material, both approaches invariably resulted to a major extent in the formation of an acidic reaction product. Purification of the latter afforded, in good yield, a crystalline α,β-unsaturated ketonic acid, m.p. 46–48°, $\lambda_{\max.}^{C_2H_5OH}$ 2430 Å., $E_{1\,\text{cm.}}^{1\%}$ 617 which gave a semicarbazone, m.p. 204–205° (dec.). In as much as cyclic β-diketones, which are completely substituted at the common α-position, are extremely prone to ring cleavage by alkaline reagents,[5] the above acid was considered to be either (IV) or (VI). Thus, cleavage of the initial Michael adduct (II) would give rise to the intermediate formation of the diketo acid (III). The latter could then recyclize by one or both of two possible routes to yield the respective acids (IV) and/or (VI). Reported cases of 1:5 diketone ring closures[6] indicate that the predominant course of cyclization proceeds with involvement of the carbonyl center which is flanked to the least extent by adjacent substitution. This fact, therefore, gave strong support to structure (IV) for the acid under discussion. It is to be noted, however, that acid (VI) could also arise by a completely independent path involving fission of the octalindione (V), formed as a secondary intermediate by ring closure of the Michael adduct (II). The position of maximum absorption at 2430 Å. appeared to favor the latter possibility; however, a Kuhn–Roth oxidation revealed the presence of two C-methyl groups thereby securing structure (IV) for this compound. This acid proved subsequently to be isomeric with the acid (VI) obtained later from authentic octalindione (V) by alkaline cleavage (see below). The alternative formulation of acid (IV) with a semi-cyclic double bond as represented by (VII) appears to be ruled out in virtue of its stability to temperatures in excess to 200°. Since structure (VII) is that of an extended β-keto acid it would be expected to decarboxylate under these conditions. Dehydrogenation of (IV) with palladium-on-charcoal produced the crystalline aromatic lactone (VIII), m.p. 121.5–122°, exhibiting a carbonyl band in the *infrared* spectrum at 5.88 μ, identical with the carbonyl band position of coumarin.

The successful synthesis of Δ^4-9-methyloctalin-3,8-dione (V) was accomplished by allowing Michael addition to occur between (I) and methyl vinyl ketone in the presence of a catalytic amount of triethylamine, either in aqueous methanol or under anhydrous conditions, to produce the adduct (II). Even under these mild conditions, however, an appreciable amount of the acid (IV) was formed. It was found very difficult, moreover, to obtain a homogeneous derivative of (II), and treatment with 5% aqueous alkali converted it almost instantaneously to the acid (IV). The adduct (II) was caused to cyclize to the octalindione (V) by refluxing in benzene solution with aluminum *t*-butylate, a combination found to be effective in a recent synthesis of vitamin A.[7] Δ^4-9-Methyloctalin-3,8-dione crystallized as small, colorless prisms, m.p. 49–50°,[8] with a $\lambda_{\max.}^{C_2H_5OH}$ 2440 Å., $E_{1\,\text{cm.}}^{1\%}$ 673. It formed a bis-semicarbazone, m.p. 246°, a bis-2,4-dinitrophenylhydrazone, m.p. 264°[8] (dec.), and gave one C-methyl in the Kuhn–Roth determination. This substance is an extended cyclic β-diketone which is completely substituted at the effectively common α-position (see above). As such, it was found to be very sensitive to alkali as anticipated, and was rapidly cleaved by this reagent to give the acid (VI), m.p. 78–79°, $\lambda_{\max.}^{C_2H_5OH}$ 2380, $E_{1\,\text{cm.}}^{1\%}$ 690. The **semicarbazone** of this acid melted at 197–197.5°. It is interesting that the melting point of this semicarbazone is essentially the same as that reported by Wieland and Miescher for the structurally isomeric semicarbazone derived from their Michael adduct. This parallelism would appear to be a coincidence, however, since the acid (IV) rather than (VI) is to be anticipated from cleavage of this intermediate (see above). The isolation of the octalindione (V) in small amounts by Wieland and Miescher under conditions whereby we found the cleavage acid (IV) to be the major product, indicates that this substance is apparently capable, to some extent, of surviving the cleavages to which it and its precursor have been found to be particularly susceptible.

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[1] Wieland and Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).

[2] Wendler and Slates, U. S. Patent 2,542,223.

[3] du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

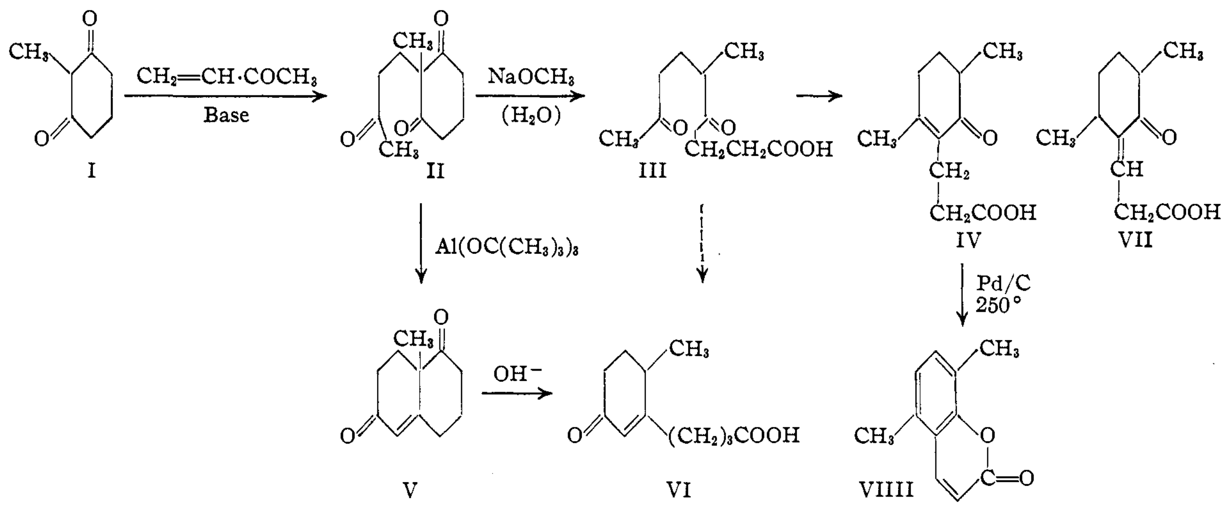
[4] Shunk and Wilds, THIS JOURNAL, **71**, 3946 (1949).

[5] See, for example, Desai, *J. Chem. Soc.*, 1097 (1932).

[6] See, for example, Henecka, "Chemie der Beta-Dicarbonyl Verbindungen" Springer Verlag, Berlin, 1950, p. 259.

[7] Wendler, Slates and Tishler, THIS JOURNAL, **73**, 719 (1950).

[8] Wieland and Miescher reported a melting point of 41.5–42.5° for their octalindione and 247–248° for its bis-2,4-dinitrophenylhydrazone derivative.



Experimental

3-(2,5-Dimethyl-6-keto-1-cyclohexen-1-yl)-propionic Acid (IV). A.—To a solution of sodium methoxide prepared from 650 mg. (0.028 mole) of sodium and 20 cc. of anhydrous methanol was added 15 cc. of benzene and 3.5 g. of 1-methylcyclohexane-2,6-dione. Solution was effected by gentle warming followed by cooling and addition of 8 g. of diethylaminobutanone methiodide[3] with swirling. The system was flushed with nitrogen, refluxed one hour and allowed to stand at room temperature overnight. At the end of this period the solvents were removed *in vacuo* and the residue shaken with 100 cc. of water. The aqueous emulsion was saturated with sodium chloride and a neutral fraction, amounting to 2.2 g. of a dark oil, was removed by ether extraction. This neutral oil decomposed in part on distillation in high vacuum. All attempts to prepare a homogeneous semicarbazone derivative of this material were unsuccessful.

The aqueous layer from the above preparation was acidified to congo red with 10% hydrochloric acid, saturated with sodium chloride and thoroughly extracted with ether. The ether solution was washed several times with small portions of saturated salt solution and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded 2.5 g. of a pale orange oil. Evaporative distillation of this oil at 105–110° and 0.03 mm. yielded (IV) as colorless material which crystallized on standing at room temperature as soft colorless needles, m.p. 46–48°, $\lambda^{\mathrm{C_2H_5OH}}_{\mathrm{max.}}$ 2430 Å., $E^{1\%}_{1\,\mathrm{cm.}}$ 617.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.11; C-methyl, 2.00. Found: C, 67.19; H, 8.27; C-methyl, 1.75.

Semicarbazone obtained as colorless rectangular plates m.p. 204–205° (dec.).

Anal. Calcd. for $C_{12}H_{19}O_3N_3$: C, 56.90; H, 7.56; N, 16.59. Found: C, 56.91; H, 7.41; N, 16.71.

The 2,4-dinitrophenylhydrazone of the ethyl ester of (IV) was obtained as bright red needles from ethanol, m.p. 101–102°.

Anal. Calcd. for $C_{17}H_{15}O_6N_4$: C, 56.52; H, 5.94; N, 13.85. Found: C, 56.57; H, 5.54; N, 13.97.

B.—2-Methylcyclohexan-1,3-dione, 6.3 g., was dissolved in 95 ml. of methanol and 8.4 g. of methyl vinyl ketone (as the 85% MVK–water azeotrope) was added. This mixture was treated with 10 drops of triethylamine and allowed to stand at room temperature for 24 hours. The solvent was removed *in vacuo* and the resultant oil evaporatively distilled at 0.02 mm. to yield two fractions—a neutral oil distilling at 90–100° (bath temperature) amounting to 6.3 g., and an acidic fraction distilling at 150–160° (bath temperature) amounting to 4.0 g. The acidic product was identified as its semicarbazone, m.p. 205° (dec.). The melting point was not depressed on admixture with the semicarbazone of (IV) from method A above.

C.—The Michael adduct (II) (neutral oil from method B above), 700 mg., was treated with 20 ml. of 2% aqueous sodium hydroxide solution, flushed with nitrogen, and allowed to stand at room temperature for 15 hours. After an ether extraction the reaction mixture was acidified to congo red with 2.5 *N* hydrochloric acid, salted with sodium chloride and thoroughly extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the solvents were removed *in vacuo* to yield 620 mg. of an acidic oil. The latter was converted to a crystalline semicarbazone, m.p. 207° (dec.). The melting point was not depressed on admixture with the semicarbazone of (IV) from method A above. Alternatively, treatment of II with 5% aqueous sodium hydroxide with swirling produced almost immediate solution. Ether extraction and acidification of the aqueous layer afforded the same acid.

Preparation of the Michael Adduct (II).—A solution of 10.0 g. (0.079 mole) of 2-methylcyclohexan-1,3-dione in 155 ml. of methanol was treated with 13.8 ml. (0.159 mole) of methyl vinyl ketone (as the 85% MVK–water azeotrope) and 1.5 ml. of triethylamine. The reaction mixture was shaken periodically and allowed to stand at room temperature for 16–20 hours. The solution was filtered from traces of polymeric materials and concentrated *in vacuo* to a light colored oil. The latter was dissolved in ether and extracted with 5% aqueous sodium bicarbonate solution, washed neutral with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue evaporatively distilled at 95–100° (0.01 mm.) to yield 6.0 g. (42%) of crude (II), $\lambda^{\mathrm{C_2H_5OH}}_{\mathrm{max.}}$ 2820 Å., $E^{1\%}_{1\,\mathrm{cm.}}$ 4.3 (carbonyl absorption).

Attempts to form a derivative of this material were very unsatisfactory. The major product obtained under a variety of conditions was a mixture as adjudged from analyses.

Δ^4-9-Methyloctalin-3,8-dione (V).—The crude Michael adduct (II), 4.0 g., was dissolved in 50 ml. of dry benzene and the solution was treated with 4.0 g. of aluminum *t*-butoxide and refluxed in a nitrogen atmosphere for 16–20 hours. After cooling, the reaction mixture was shaken with water and ice, acidified to congo red with 2.5 *N* hydrochloric acid, and extracted thoroughly with ether. The ether solution was washed with small volumes of saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield a viscous oil, wt. 3.75 g., $\lambda^{\mathrm{C_2H_5OH}}_{\mathrm{max.}}$ 2450 Å., $E^{1\%}_{1\,\mathrm{cm.}}$ 279; yield 40% based on an $E^{1\%}_{1\,\mathrm{cm.}}$ of 673 for pure material. This product was chromatographed on 200 g. of acid washed alumina, elution being effected with mixtures of benzene and ether. The crystalline fractions (*ca.* 1 g.) were recrystallized from 50% ether–petroleum ether to afford Δ^4-9-methyloctalin-3,8-dione as small, colorless prisms, m.p. 49–50°, $\lambda^{\mathrm{C_2H_5OH}}_{\mathrm{max.}}$ 2440 Å., $E^{1\%}_{1\,\mathrm{cm.}}$ 673.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86; C-methyl, 1.00. Found: C, 74.35; H, 7.73; C-methyl, 0.97.

Bis-2,4-dinitrophenylhydrazone, recrystallized from pyridine–methanol, as brick-red, microcrystalline needles, m.p. 264° (dec.).

Anal. Calcd. for $C_{23}H_{22}O_8N_8$: C, 51.50; N, 4.09; N, 20.82. Found: C, 51.79; H, 4.22; N, 20.66.

Bis-semicarbazone, recrystallized from a large volume of methanol, as colorless, microcrystalline rhombs, m.p. 246°.

Anal. Calcd. for $C_{12}H_{20}O_2N_6$: C, 53.42; H, 6.85; N, 28.77. Found: C, 53.36; H. 6.66; N, 28.77.

γ-(6-Methyl-3-keto-cyclohexen-1-yl)-butyric Acid (VI).—Δ^4-9-Methyloctalin-3,8-dione, 500 mg., was shaken with 20 ml. of 2% aqueous sodium hydroxide solution whereupon it dissolved rapidly. The solution was allowed to stand at room temperature for 2 hours in an atmosphere of nitrogen. After an ether extraction the reaction mixture was acidified to congo red with 2.5 *N* hydrochloric acid, salted with sodium chloride and the product was isolated through ether extraction. The ether solution was washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to yield 300 mg. of a pale yellow oil. This product was purified by chromatography on 15 g. of acid washed alumina, elution being effected with mixtures of ether and acetic acid. The crystalline fractions, were sublimed at 100° (0.05 mm.) and recrystallized from ether–petroleum ether to afford (VI) as lustrous needles, m.p. 78–79°, $\lambda_{\max.}^{C_2H_5OH}$ 2380 Å., $E_{1\,\mathrm{cm.}}^{1\%}$ 690.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.11; C-methyl, 1.0. Found: C, 67.38; H, 8.25; C-methyl, 0.78.

The semicarbazone, recrystallized from methanol, was obtained as colorless needles, m.p. 197–197.5° (dec.).

Anal. Calcd. for $C_{12}H_{19}O_3N_3$: C, 57.14; H, 7.41; N, 16.67. Found: C, 57.10; H, 7.37; N, 16.63.

Dehydrogenation of Acid (IV) to 5,8-Dimethylcoumarin (VIII).—A mixture of 1.78 g. of acid (IV), m.p. 46–48°, and 830 mg. of 10% palladium-on-charcoal were heated at 250° for 1 hour in an open tube. After cooling, the product was dissolved in ether and filtered from the catalyst. The ether solution was given a Norite treatment, filtered and the ether evaporated to a tan colored solid. Two recrystallizations of this material from ether–petroleum ether afforded colorless needles, m.p. 121.5–122°, $\lambda_{\max.}^{CH_3OH}$ 2900 Å., $E_{1\,\mathrm{cm.}}^{1\%}$ 744.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.80; H, 5.75. Found: C, 75.75; H, 5.65.

The *infrared* spectrum of this substance demonstrated its aromatic character and showed further a band in the carbonyl region at 5.88 μ identical in position with the carbonyl band found in coumarin. This substance was found, moreover, to be insoluble in cold 10% aqueous alkali but dissolved on warming and was reprecipitated on back acidification.

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

Synthesis of 11-Hydroxylated Cortical Steroids. The Preferential Reduction of Carbonyl Systems in the Presence of Carbon–Nitrogen Multiple Bonds

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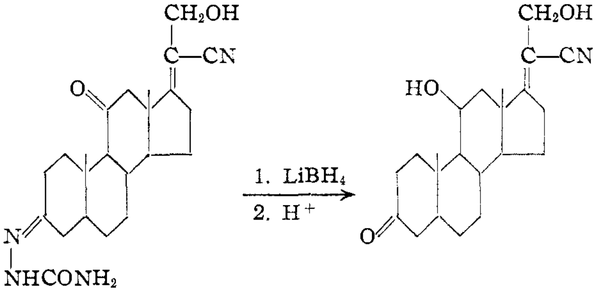
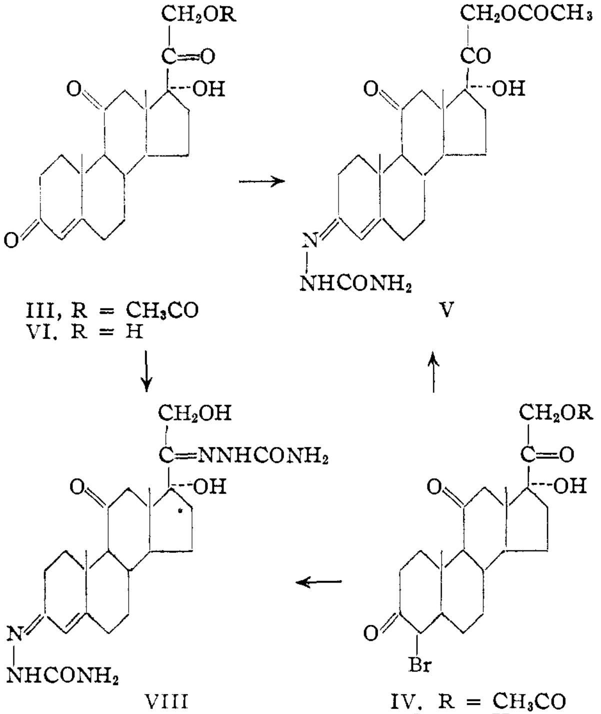
By employing the 3-mono- and 3,20-disemicarbazone derivatives of substituted pregnane-3,11,20-triones, it has been found possible to effect selective reduction of the carbonyl functions at positions 11 and 20 by means of lithium borohydride. This approach has enabled a partial synthesis of Reichstein's Substances E and U as well as the transformation of Cortisone to Compound F and 11-dehydrocorticosterone to corticosterone.

The synthesis of 17(α)-hydroxycorticosterone (Kendall's Compound F) in this Laboratory was reported recently.[1] In connection with that work it had been discovered that 20-cyano-17-pregnene-21-ol-3,11-dione 3-monosemicarbazone (I) on reduction with lithium borohydride and subsequent hydrolysis produced 20-cyano-17-pregnene-11(β), 21-diol-3-one (II).[2] The preferential reduction of the 11-carbonyl function in the presence of both cyano and semicarbazone groupings was thereby established. This ability to effect preferential reduction of carbonyl groups in the presence of carbon–nitrogen multiple bonds, and specifically in the presence of semicarbazone linkages has not only afforded a new route to otherwise difficultly accessible cortical steroids but has also provided a means for their direct interconversions. It should be added,



I II



III, R = CH₃CO
VI. R = H

V

VIII

IV. R = CH₃CO
VII, R = H

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[1] Wendler, Graber, Jones and Tishler, THIS JOURNAL, **72**, 5793 (1950).

[2] To appear in a forthcoming publication.