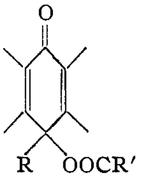
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OREGON]

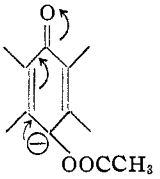
10-Methyl-10-acetoxyanthrone[1]

BY HANS HEYMANN* AND LUCILLE TROWBRIDGE

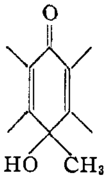
The reaction of a 10-acyloxyanthrone (Ia) with an alkyl Grignard has been shown to result in part in displacement of the acyloxy group by the alkyl group.[1a] In explanation of the fact that a certain fraction of the starting material fails to suffer displacement, the suggestion was voiced that a part of the acyloxyanthrone is converted by the Grignard reagent into the unreactive anion of anthrahydroquinone monoester (II). 10-Methyl-10-acetoxyanthrone (I) does not possess an ionizable hydrogen atom, and we prepared this substance in the hope that it would allow us to study the displacement reaction without the interference of side-reactions.



I, R = CH_3
Ia, R = H



II



III

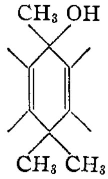
Methylphenylphthalide[2] was obtained in 78% yield by the action of excess methylmagnesium halide on free benzoylbenzoic acid. The α-methylbenzylbenzoic acid resulting on reduction[2] underwent smooth cyclization to 10-methylanthrone, identical with the material Barnett and Mathews had prepared in a different fashion.[3] Introduction of the oxygen substituent at position 10 *via* the 10-bromide was impossible because of intractable bromination products; direct acetoxylation by means of lead tetraacetate likewise failed to yield identifiable substances. Oxidation with chromic anhydride produced 10-methyloxanthrone (III) but the yields were unsatisfactory; however, when oxidized with excess hydrogen peroxide at 70°, the dark solution of the anthrone in alcoholic alkali was rapidly decolorized, and III could be isolated without difficulty in good yield. A small amount of anthraquinone was identified as a by-product, but there was no indication of the presence of the bimolecular oxidation products generally encountered in oxidations of anthrones with one-electron oxidizing agents; the observed change may well be an ionic reaction of the type

$$A^- + HO{:}OH \longrightarrow AOH + OH^-$$

and we hope to test this suggestion experimentally.

The structure of III was confirmed by conversion to and comparison with an authentic sample of 10-methyleneanthrone. The necessary dehydration was accomplished by means of oxalic acid in acetic acid; all other agents tried were either ineffective or led to intractable polymeric products.

Acetylation of III yielded the desired 10-methyl-10-acetoxyanthrone (I) without difficulty. Unfortunately the Grignard reaction with I did not proceed in a clearcut way, as we had hoped; under the conditions employed rather complex mixtures resulted, in which we identified the product resulting from displacement of the acetoxyl group, *viz.*, 9,10,10-trimethyl-9,10-dihydroanthranol (IV), in a yield of 10%, and III, which would be expected from the normal interaction of an ester with a Grignard reagent. The structure of IV was confirmed by an independent synthesis from 10,10-dimethylanthrone (V).[4] This compound is not readily available because its preparation by methylation of anthrone or 10-methylanthrone seems to depend on not clearly defined variables. Apparently, on treatment of anthrone with base and methyl iodide the common anion of the anthrone–anthranol system (VI) undergoes preponderantly C-alkylation; however, neither Meyer[4a] nor the present authors could substantiate Hallgarten's claim[4b] that the resulting methylated synion VII is again primarily C-alkylated (path a), since methylanthranyl methyl ether (VIII) is formed as the main product in a complex mixture which also contained small amounts of V and of III.[5] Whereas Meyer has shown that the direction of alkylation of VI depends to some extent on the nature of the alkylating agent[4a] (halide *vs.* sulfate), no information is available as to the factors that control reaction of VII according to path a or path b. We are planning an investigation of this problem; at the same time an alternate synthesis of V is being studied



IV

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* Harvard University Ph.D. 1941; Faculty 1942–1946.

[1] A partial report of this investigation was presented at the Northwest Regional Meeting of the Am. Chem. Soc. in May, 1949, at Pullman, Washington and Moscow, Idaho.

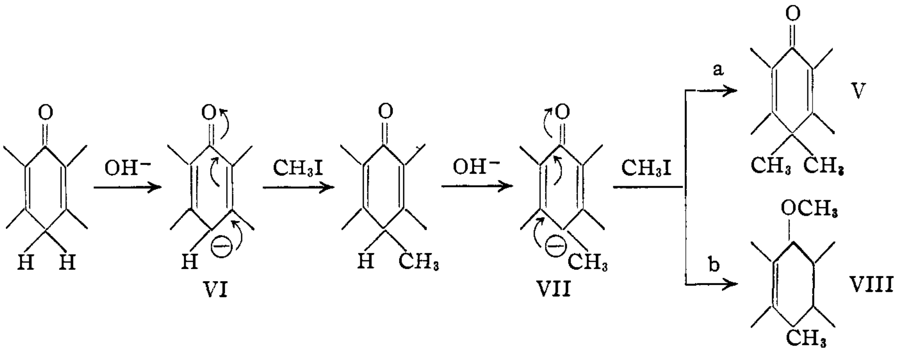
[1a] Fieser and Heymann, THIS JOURNAL, **64**, 376–382 (1942).

[2] Ernst Bergmann, *J. Org. Chem.*, **4**, 1 (1939).

[3] Barnett and Mathews, *Ber.*, **59**, 767 (1926).

[4] (a) Meyer and Sander, *Ann.*, **420**, 126 (1920); (b) Hallgarten, *Ber.*, **21**, 2508 (1888).

[5] It is of interest that III and V form mixed crystals which are well shaped and melt sharply; *e. g.*, a 1:5 mixture of III and V forms colorless, elongated plates melting 111–112°, having a composition closely corresponding to the formula $C_{16}H_{14}O$.



to make available larger amounts of the alcohol IV, whose acetate we hope to examine as to its behavior toward Grignard reagents.

Experimental Part[6]

Methylphenylphthalide[2] was obtained in 78% yield when 90 g. of *o*-benzoylbenzoic acid was allowed to react with methylmagnesium iodide prepared from 23 g. of the metal. Reduction with zinc and alcoholic ammonia[2] yielded 92.5% of *o*-(α-methylbenzyl)-benzoic acid.[3]

10-Methylanthrone.—A solution of 5 g. of the forementioned acid in 50 cc. of concentrated sulfuric acid stood for one-half hour at room temperature. The mixture was poured on ice, the solid was collected and recrystallized from methanol–water, which deposited 3.1 g. (58%) of the anthrone, m. p. 64.5–65.5°. The acetate, prepared with pyridine and acetic anhydride, melts at 164–165.5°. The literature values[3] are 65 and 167°, respectively. In subsequent runs yields of 87% were realized.

10-Methyl-10-hydroxyanthrone (III).—To a solution of 16.65 g. of crude 10-methylanthrone in 200 cc. of hot ethanol was added 41 cc. (5 equivalents) of 30% hydrogen peroxide solution and 90 cc. of 10% sodium hydroxide solution. Within three minutes the deep red-brown color of the solution had faded to a pale orange. Dilution with water to a volume of 1000 cc. precipitated 12.1 g. (67%) of III, m. p. 148–152°. On recrystallization from alcohol a small amount of anthraquinone was removed, identified by vat test and reductive acetate; further crystallization from ligroin yielded pure III in the form of colorless needles which have the double melting point 146–148°, 153.2–155°.

A solution of 2 g. of oxalic acid and of 1 g. of III in 10 cc. of glacial acid was boiled for thirty seconds and immediately poured into cold water. The ligroin-soluble fraction of the resulting yellow solid was recrystallized four times from that solvent and then from methanol, which deposited pale yellow platelets of **10-methyleneanthrone**, m. p. 145–147.5°, identical with an authentic sample.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.51, 80.38; H, 5.48, 5.65.

10-Methyl-10-acetoxyanthrone (I).—A solution of 0.5 g. of III and 1.5 cc. of acetic anhydride in 3 cc. of pyridine was heated at 100° for one hour. After decomposition with water 0.54 g. (91%) of I was isolated, m. p. 93–100°. Recrystallization from ethanol yielded long flat needles, m. p. 104–104.9°.

When 0.95 g. of *o*-(α-methylbenzyl-)-benzoic acid was converted to I as described without, however, purification of the intermediates, 0.58 g. (52%) of I was obtained in satisfactory purity; m. p. 96–102°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.60, 76.60; H, 5.47; 5.54.

Methylation of Anthrone.—A mixture of 12 g. of anthrone, 12 g. of potassium hydroxide, 40 g. of methyl iodide and 60 cc. of water was stirred at room temperature in a nitrogen atmosphere for six hours. Recrystallization of the deposited solid from alcohol yielded methyl anthranyl methyl ether (VIII). The alcoholic mother liquor was diluted with water and the precipitated solids were fractionally crystallized from ligroin. From the least soluble fractions a small amount (90 mg.) of III was eventually iosolated in pure form and identified by mixed melting point determination. The most soluble fractions yielded 400 mg. of crude **10,10-dimethylanthrone** (V), m. p. 97–100°, from which the pure compound was obtained by further recrystallization and vacuum sublimation. Compound V crystallizes from ligroin or aqueous alcohol as colorless needles which melt at 99.5–100.5°. Meyer[4a] reported a melting point of 93–94°. Compound V is resistant to acids and bases, and is non-fluorescent; these properties in conjunction with the composition confirm the structure of V.

The fractions of intermediate solubility crystallized in nicely shaped elongated plates from aqueous alcohol, melting over a narrow range near 110°, and having a composition closely agreeing with the formula $C_{14}H_{12}O$. Prolonged recrystallizations as well as the preparation of such crystals by crystallization from aqueous alcohol of a 1:5 mixture of III and V demonstrated the conglomerate nature of this substance. Pure V is easily isolated from the mixture after destruction of the III by treatment with hydrogen chloride in acetic acid.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.24; H, 6.40. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Calcd. for a 1:5 mixture of III and V: C, 85.42; H, 6.18. Found: C, 85.66, 85.59; H, 6.33, 6.31.

Grignard Reaction with I.—To the methylmagnesium iodide solution resulting from 1.51 g. (*ca.* 5 equivalents) of the metal was added an ethereal solution of 3.57 g. of V. The reaction mixture was well cooled in ice during the addition. A red gum was deposited; the mixture was agitated for forty-five minutes and hydrolyzed with saturated ammonium chloride solution. The yellow fluorescent ether layer was dried, evaporated to dryness, and upon digestion of the residual reddish oil with alcohol 330 mg. (10%) of 9,10,10-trimethyl-9,10-dihydroanthranol (IV) was deposited. Recrystallization from ligroin and then from 75% ethanol yielded pure IV in the form of flat, hexagonal plates, m. p. 173–175° with sintering at 160°. The alcoholic mother liquor was evaporated to dryness and the residue was fractionated, in benzene solution, by the liquid-chromatogram technique on alumina. The only identifiable products were small amounts of III and IV.

When the Grignard reaction was conducted at room temperature an even more intractable mixture resulted, in which 9,10-dimethylanthracene was identified, formed presumably as a result of addition to III followed by reduction.

For the purpose of identification a sample of IV was synthesized by permitting the methylmagnesium iodide solution from 24 mg. of the metal to react with 197 mg. of V. A yield of 125 mg. of IV was obtained, identical with the product of the displacement reaction.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.58, 85.41; H, 7.52, 7.69.

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[6] All melting points are corrected.

Acknowledgment.—The authors thank the Graduate Council of the University of Oregon for a grant which helped to further the investigation reported.

Summary

1. 10-Methyl-10-hydroxyanthrone has been prepared by hydrogen peroxide oxidation of 10-methylanthrone. The alcohol has been converted to 10-methyl-10-acetoxyanthrone.

2. Methylmagnesium iodide displaces the acetoxyl group in 10-methyl-10-acetoxyanthrone to give a 10% yield of 9,10,10-trimethyl-9,10-dihydroanthranol, which was synthesized independently from 10,10-dimethylanthrone.

3. The course of the methylation of anthrone to 10,10-dimethylanthrone or to 9-methylanthranyl methyl ether is discussed.

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Studies in Steroid Metabolism. VIII. The Detection and Location of Ethylenic Double Bonds in Steroids by Infrared Spectrometry

BY R. NORMAN JONES,* P. HUMPHRIES, E. PACKARD AND KONRAD DOBRINER

In preceding papers of this series, the application of infrared spectrometry to the elucidation of steroid structure[2,3] and to the study of steroid metabolism[4] has been discussed. The correlations of molecular structure and spectra have aided in establishing the structure of several metabolites of steroid hormones isolated from urine.[5,6,7]

The work so far described has been concerned mainly with the characterization of the carbonyl group from the position of the maximum of the C=O stretching vibration which occurs between 1660 and 1770 cm.$^{-1}$.

The detection of ethylenic unsaturation and the location of the ethylenic bonds in steroids are also problems of considerable importance. Difficulties arise in this connection if, as frequently occurs, the quantities of the steroid available are insufficient to allow chemical characterization by hydrogenation and by oxidative degradation to compounds of known structure. Conjugated dienes, α,β-unsaturated ketones and the aromatic ring systems of the estrogens can be identified from the intense and characteristic absorption in the medium ultraviolet region of the spectrum,[8,9] but, as yet, no suitable methods have been developed for the location of the non-conjugated ethylenic double bond.

Detection of Ethylenic Double Bonds by Infrared Spectrometry.—Absorption bands characteristic of carbon–carbon unsaturation occur in three regions of the infrared spectrum. Fox and Martin[10] have noted that the *stretching vibration of carbon–hydrogen bond* in the system —C=C—H occurs between 3000 and 3100 cm.$^{-1}$, while in a saturated alkyl system the corresponding bands lie between 2800 and 3000 cm.$^{-1}$. The use of this region of the spectrum in the investigation of unsaturated hydrocarbons has been discussed recently by Saier and Coggeshall.[11]

Absorption associated with the stretching motion of the C=C bond occurs between 1580 and 1680 cm.$^{-1}$, and a third type of double bond absorption involving the *angular deformation of the carbon–hydrogen bond* in —C=C—H is found in the region between 800 and 970 cm.$^{-1}$. The absorption in all three of these regions has been utilized by Sheppard and Sutherland[12] in an investigation of the double bond structure of terpenoid compounds, while the 800–970 and the 1580–1680 cm.$^{-1}$ regions have been employed recently by Gunthard and Ruzicka[13] and by Thompson and Whiffen[14] in similar investigations. Blout, Fields and Karplus have studied the C=C stretching bands in conjugated polyenes.[15]

This paper is concerned with a study of the spectra of various types of unsaturated steroids, principally in the region of the C=C stretching vibrations.

The C=C Stretching Vibrations in Steroids (1580–1680 Cm.$^{-1}$).—Whereas the C=O stretching vibration gives rise to one of the most intense absorption bands in the whole infrared spectrum, the C=C stretching band is weak in compounds containing non-conjugated ethylenic groups, and its observation is complicated by its superposition on water vapor bands which occur in this region of the spectrum. In spite of these experimental difficulties, measure-

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* Harvard University Research Fellow 1937–1942.

[1] Published as Contribution No. 2027 from The Laboratories of The National Research Council of Canada.

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[4] Dobriner, Lieberman, Rhoads, Jones, Williams and Barnes, *J. Biol. Chem.*, **172**, 297 (1948).

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[14] Thompson and Whiffen, *J. Chem. Soc.*, 1412 (1948).

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