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Approaches to the Total Synthesis of Adrenal Steroids. VIII. A New Method for the Attachment of Ring D. Part B

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A method is described for attaching to tricyclic intermediates the final two carbon atoms necessary for building the pregnane skeleton. With ethoxyacetylenemagnesium bromide the methyl methallyl diketone I gives the ethoxyethinylcarbinol II. Mild treatment of the latter with sulfuric acid yields as the major product the $\Delta^{1,\alpha}$-ester IVA. Reduction of the corresponding acid IVb first with sodium borohydride and then with potassium in liquid ammonia–2-propanol proceeds stereospecifically in high yield to the dihydro acid having the desired natural configuration. Factors influencing the stereochemical course of this reduction include the nature of the reducing metal and the nature of the substituents at C_1 and C_4.

In part VII[1] of this series the preparation of the polyhydrophenanthrene derivative shown in formula I was described. The transformation of this compound to a pregnane requires the attachment of two carbon atoms at C_1 and eventual closure of the five-membered ring. A means of accomplishing the first of these objectives forms the subject of the present communication.

When the diketone I was treated with ethoxyacetylenemagnesium bromide[2] only the C_1-keto group was attacked and the ethoxyethinylcarbinol II[3] was formed in good yield. A small amount of the isomeric carbinol III also was formed.

Ethoxyethinylcarbinols have been reported to yield β-hydroxy esters and α,β-unsaturated esters on treatment with mineral acids.[4] In the present case it was necessary to perform the acid treatment of the carbinol under the mildest possible conditions in order to retain the ethylenedioxy group in ring A. Suitable conditions for the selective reaction of the ethoxyethinylcarbinol grouping consisted of treatment with dilute acid in tetrahydrofuran at room temperature. When sulfuric acid was employed, the major product obtained from carbinol II was the α,β-unsaturated ester IVa, accompanied by a smaller amount of the β-hydroxy ester Va.[5] An interesting contrast was provided

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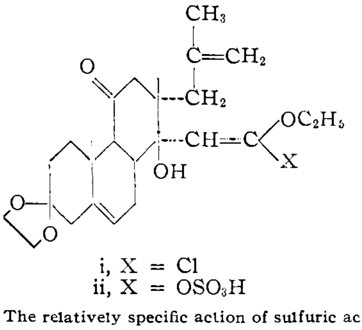
[1] L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, THIS JOURNAL, **75**, 2112 (1953).

[2] J. F. Arens and D. A. van Dorp, *Nature*, **160**, 189 (1947).

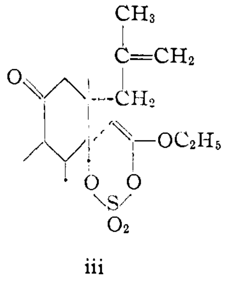
[3] Assignment of the β-configuration to the C_1-hydroxyl group was tentatively made by analogy with the stereochemical results of lithium aluminum hydride reduction of the unsubstituted 1,4-diketone, which was shown to give the 1β-hydroxy derivative (see ref. 8); *cf.* D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).

[4] (a) I. Heilbron, E. R. H. Jones, M. Julia and B. C. L. Weedon, *J. Chem. Soc.*, 1823 (1949); (b) M. N. Shchukina and I. A. Rubtsov, *J. Gen. Chem.*, **18**, 1645 (1948); (c) N. A. Preobrazhenskiĭ and I. A. Rubtsov, *ibid.*, **18**, 1719 (1948); (d) H. Heusser, K. Eichenberger and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1088 (1950); (e) J. Queck, *Abhandl. Braunschweig. Wiss. Ges.*, IV, 37 (1952).

[5] Only sulfuric acid gave appreciable yields of α,β-unsaturated ester under these mild conditions. Dilute hydrochloric acid in tetrahydrofuran at room temperature gave none of the α,β-unsaturated ester. The main product was a mixture of two chloro compounds, undoubtebly the geometric isomers of i; a smaller quantity of β-hydroxy ester Va was also obtained. Trichloroacetic acid in benzene also added to the triple bond of II giving a monoadduct. Saponification of this adduct gave the 7-keto-β-hydroxy acid corresponding to Vb. In tetrahydrofuran, dilute perchloric acid converted II into about 15% of crude non-crystalline α,β-unsaturated ester (identified by saponification to the crystalline acid IVb) and 15% of β-hydroxy ester Va.



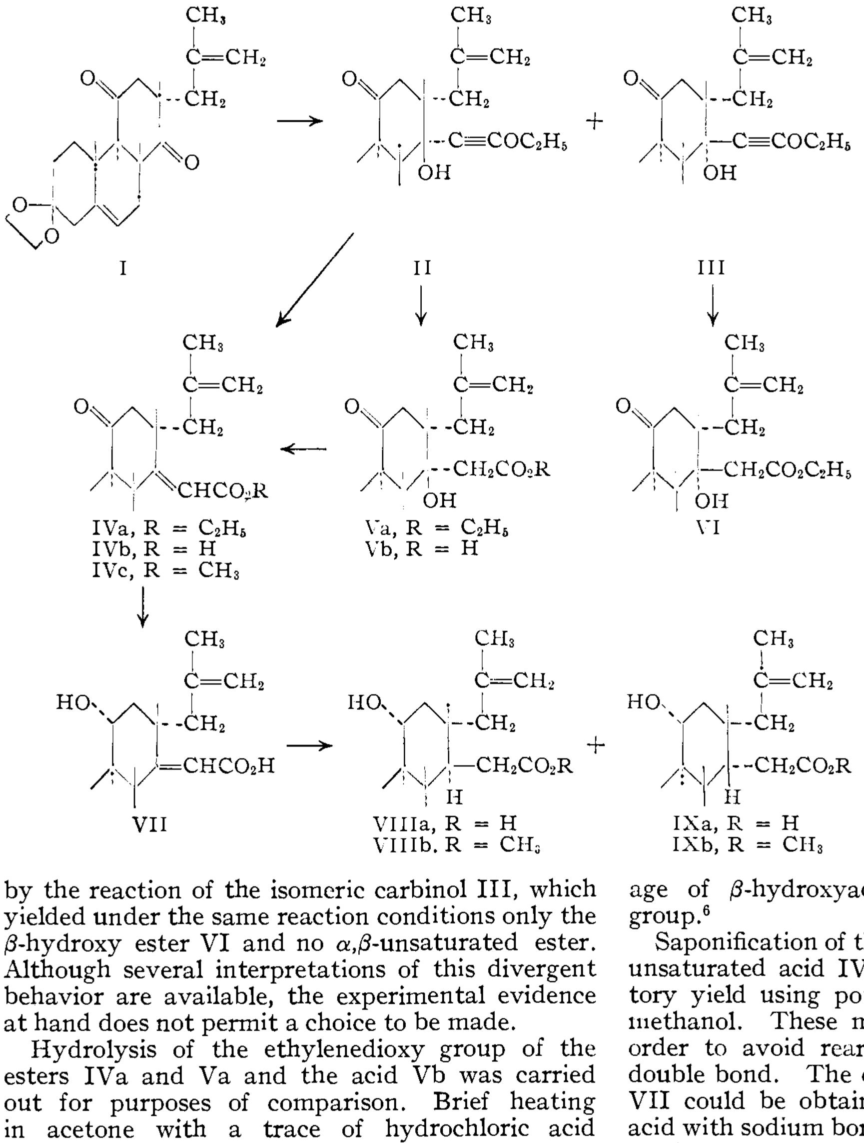
i, X = Cl
ii, X = OSO_3H



iii

The relatively specific action of sulfuric acid in favoring the formation of α,β-unsaturated ester under mild conditions suggets that, at least in part, the mechanism of reaction with this acid may be different from that with monobasic acids. A possible route could involve the cyclic intermediate iii formed by an intramolecular esterification of the geometrically favorable primary addition product ii. Hydrolytic cleavage of the enol sulfate linkage of iii, prototropic shift, and elimination of sulfate ion would give IVa.

Under more vigorous conditions, hydrochloric and perchloric acids gave fair yields of α,β-unsaturated ester accompanied by β-hydroxy ester (with hydrolysis of the ethylenedioxy function). The reaction path for the formation of α,β-unsaturated ester by the use of *mono-*



by the reaction of the isomeric carbinol III, which yielded under the same reaction conditions only the β-hydroxy ester VI and no α,β-unsaturated ester. Although several interpretations of this divergent behavior are available, the experimental evidence at hand does not permit a choice to be made.

Hydrolysis of the ethylenedioxy group of the esters IVa and Va and the acid Vb was carried out for purposes of comparison. Brief heating in acetone with a trace of hydrochloric acid provided the corresponding α,β-unsaturated 7-ketones in excellent yield.

The dehydration of hydroxy ester Va with thionyl chloride in pyridine afforded the α,β-unsaturated ester IVa in good yield thus increasing the over-all conversion from the carbinol II. From a similar dehydration of the hydroxy ester VI, none of the crystalline IVa could be isolated.

A point of further interest arose in connection with attempts to dehydrate the β-hydroxy esters with alkoxides. A very mild treatment of the hydroxy esters Va and VI with potassium *t*-butoxide regenerated the parent diketone I in good yield. In the 2β-methallyl series (see below) the acetic acid residue was removed with both sodium ethoxide and potassium *t*-butoxide. The ease of this retrograde aldol reaction seems noteworthy in the light of the strong aqueous alkaline conditions that have been employed for the cleavage of β-hydroxyacetic acids having a γ-aryl group.[6]

Saponification of the unsaturated ester IVa to the unsaturated acid IVb was carried out in satisfactory yield using potassium carbonate in aqueous methanol. These mild conditions were chosen in order to avoid rearrangement of the conjugated double bond. The corresponding 4α-hydroxy acid VII could be obtained by reduction of the keto acid with sodium borohydride.[7]

The reduction of the $\Delta^{1,\alpha}$-bond in the unsaturated acids establishes the last fixed asymmetric center in the steroid nucleus. Although the reduction of the carbon–carbon double bond of an α,β-unsaturated acid has been carried out by a variety of methods, our attention was turned to a reduction by alkali metals since this method seemed to offer the greatest opportunity for controlling the introduction of asymmetry at C_1. Thus the action of an alkali metal upon the conjugated double bond giving a carbanion or radical at C_1 followed by the irreversible addition of a proton to this center[8] might be expected to give predominantly the thermodynamically more stable epimer. The classical

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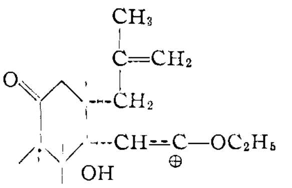
basic acids would most logically involve the facile addition of a proton to the triple bond of II giving resonance forms of cation iv [analogous to the mechanism for acetylenic ether hydration of T. L. Jacobs and S. Searles, THIS JOURNAL, **66**, 686 (1944)]. A 1,3-shift of the hydroxyl



iv

followed by elimination of a proton would lead to α,β-unsaturated ester. Obviously reaction of iv with water followed by proton elimination would give β-hydroxy ester. The possibility that β-hydroxy ester was an intermediate in the formation of α,β-unsaturated ester was excluded; the 7-keto-β-hydroxy ester corresponding to Va was recovered unchanged after being heated under comparable conditions with both dilute hydrochloric and sulfuric acids.

The isolation of hydroxy derivatives, particularly compounds i and Va from the reaction of hydrochloric acid with II, leaves little doubt that reaction proceeds initially by addition to the triple bond. Thus the mechanism proposed by Shchukina and Rubtsov (ref. 4b and 4e) involving the formation of a propargylcarbonium ion and rearrangement to an allenic carbonium ion seems inapplicable to the reaction of II with acids under mild conditions.

(6) See, for example, W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940); D. Ivanov, *Bull. soc. chim.*, **7**, 569 (1940).

(7) The α-configuration has been obtained with other 4-ketopolyhydrophenanthrenes; *cf.* part V of this series: G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953). As in previous instances the α-configuration of the C_4-hydroxyl group was shown by the ease of acetylation under standard conditions.

(8) For a fundamental treatment of the mechanism of reducing metals, see A. J. Birch, *J. Chem. Soc.*, 1551 (1950), and a review by the same author, *Quart. Rev.*, **4**, 69 (1950).

sodium–alcohol reduction of Δ^4-cholesten-3-one to cholestanol[9] provides support for this view[10]; the more stable *trans*-ring junction is favored in the reduction of a double bond terminating at a junction of two six-membered rings.[11]

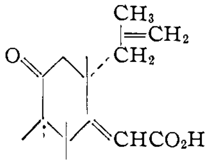
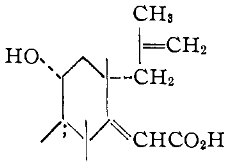
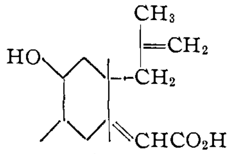
On the basis of this analysis the product resulting from treatment of VII with dissolving metals would consist of a mixture of the two dihydro acids (VIIIa and IXa) in which the more stable isomer preponderates. It seemed possible in this instance to assess which dihydro acid should be the more stable since several steric factors operate in the same direction. Thus in the β-configuration, the carboxymethyl side chain of VIII has a *trans* relationship to the bulky methallyl group. It is also *trans* to the α-oriented C_4-hydroxyl group (probably alkoxide ion during the reduction). In addition the β-side chain at C_1 is equatorial and the non-bonded repulsions characteristic of the fused cyclohexane ring[12] may also contribute to the greater stability of VIII over IX.

Although in a general way this analysis was borne out in the alkali metal reductions of IVb and its 4-hydroxy analogs, it was found that other factors also played an important part in the determination of the stereochemical course of the reaction. It was possible to obtain either or both of the reduced acids epimeric at C_1 by suitably varying the group at C_4 or the reducing conditions.[13] Pertinent data are given in Table I.

The important factors which influence the stereochemical course of the reduction may be summarized as follows[14]: 1. Nature of the substituent at C_4. Prereduction of the 4-ketone in IVb with sodium borohydride gave increased proportions of 1β-dihydro acid VIIIa and improved the combined yield. Direct reduction of IVb led to products with a C_4-α-hydroxyl group; it is likely that the rate of reduction of the C_4-ketone was faster than that of the conjugated double bond so that the reduction of IVb proceeded mainly by way of the anion of the 4α-hydroxy unsaturated acid VII. From the 4β-hydroxy unsaturated acid (XIb, see below), only the 1α-dihydro acid could be isolated. From this remarkable reversal it is apparent that the configuration of the C_4-hydroxyl group has a dominant influence on the stereochemical course of reduction at C_1.

TABLE I

ALKALI METAL REDUCTIONS OF α,β-UNSATURATED ACIDS

Compound reduced	Metal	Solvent	Yield,[a] % C_1 β-side-chain	C_1 α-side-chain
 IVb	Li	Ammonia	15	25
	Na	Ethanol	33	17
	Na	1-Butanol	40	30
	K	1-Butanol	40	15
	K	2-Propanol	55	15
	K	Ammonia–2-propanol	62	10
 VII	Li	Ammonia	30	40
	Li	Ammonia–2-propanol	30	40
	Li	1-Butanol	27	18
	Na	1-Butanol	48	30
	K	Ammonia	45	[b]
	K	Ammonia–2-propanol	80	[b]
 XIb	Li	Ammonia	[b]	40
	Na	Ammonia–2-propanol	[b]	46
	K	Ammonia–2-propanol	[b]	68

[a] Yields of the 4α-hydroxy products are estimated to be within ±5% for the 1β-isomer and ±10% for the 1α-isomer. [b] None was isolated.

2. Nature of the reducing metal. Under comparable conditions in both ammonia and ammonia–2-propanol, the 4α-hydroxy acid VII was reduced to about an equal mixture of C_1-epimers with lithium, while potassium reduction gave only the 1β-product. A difference in the stereochemical course of an alkali metal reduction due only to different metals does not appear to have been noted previously.

3. Nature of the substituent at C_1: A sodium–butanol reduction was carried out on the 4-keto-α,β-unsaturated *ester* IVa. From the crude product a fraction was obtained consisting of saturated primary carbinols resulting from Bouveault–Blanc reduction of the carbethoxy group. This fraction was found to contain more than 55% of the 1α-hydroxyethyl derivative (XIV). The α-configurations at C_1 and C_4 in XIV were proved by its preparation from the C_1,C_4-α-ester IXb by reduction with lithium aluminum anhydride. Thus the carbethoxy group in place of the carboxylate ion as the terminal function of the C_1 side-chain profoundly affected the course of the reduction.

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(9) O. Diels and E. Abderhalden, *Ber.*, **39**, 884 (1906).

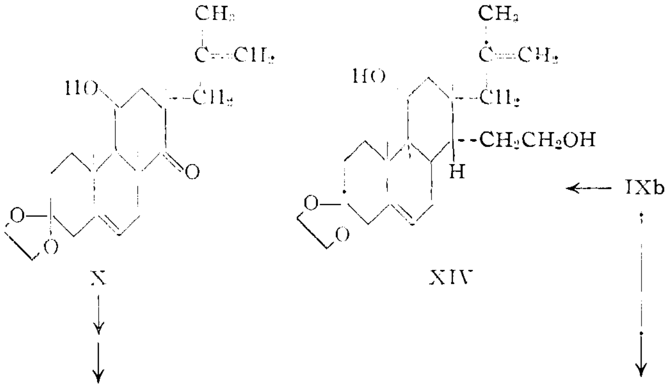
(10) Since the inception of the work described in this paper, a number of additional examples of the rate-controlled alkali metal reductions of conjugated double bonds to give the more stable reduction product have been reported: *e.g.*, the reduction of steroid $\Delta^{8,9}$-11-ketones (E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Rheinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, THIS JOURNAL, **74**, 2696 (1952); F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953); K. Heusler, H. Heusser and R. Anliker, *Helv. Chim. Acta*, **36**, 652 (1953)); the reduction of a steroid $\Delta^{8,14}$-15-ketone (C. S. Barnes, D. H. R. Barton and G. F. Laws, *Chem. and Ind.*, **25**, 616 (1953)); the reduction of a triterpenoid $\Delta^{8,9}$-7-ketone (D. H. R. Barton and B. R. Thomas, *J. Chem. Soc.*, 1842 (1953)) and reductions of unsaturated hydrochrysenes (A. J. Birch and J. A. K. Quartey, *Chem. and Ind.*, **25**, 489 (1953); W. S. Johnson, B. Bannister, B. M. Bloom, A. D. Kemp, R. Pappo, E. R. Rogier and J. Szmuszkovicz, THIS JOURNAL, **75**, 2276 (1953)).

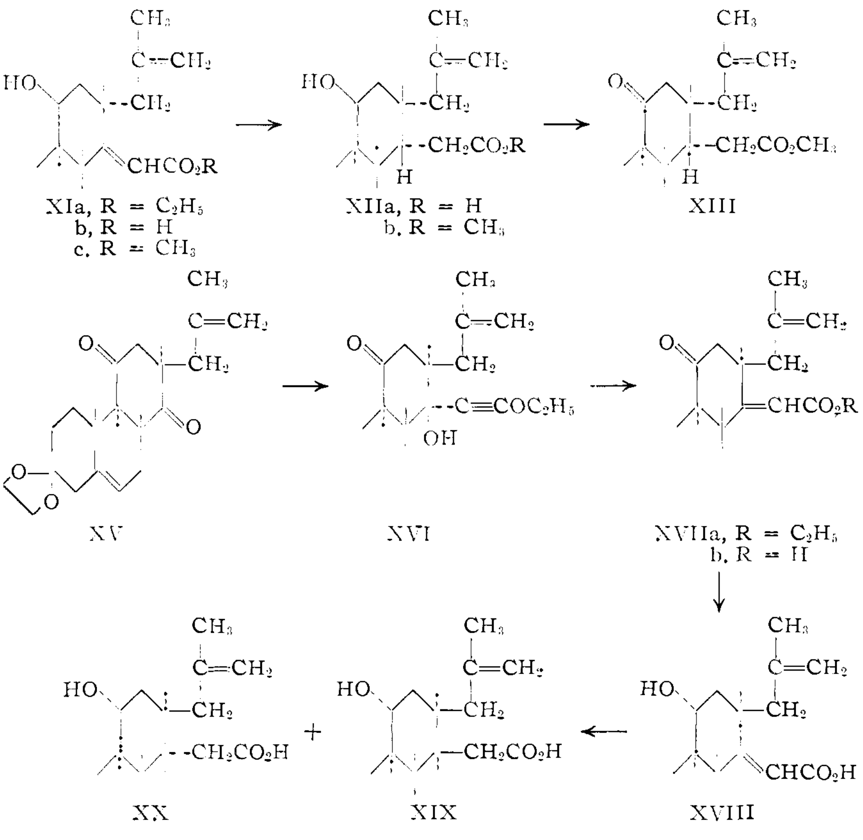
(11) A. J. Birch, *Ann. Reports* XLVIII, 193 (1951).

(12) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(13) The inferential assignment of configuration at C_1 was later borne out by comparison with natural materials; L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, THIS JOURNAL, **74**, 4974 (1952).

(14) Changes in solvent did not significantly change the *stereochemical* course of reduction. However, the combined yield of reduced acids was dependent upon the solvent system. Liquid ammonia–2-propanol proved to be the most efficient solvent medium. The organic acid separated as an insoluble salt in all of the reductions involving liquid ammonia. No attempt was made in these cases to vary solvents and obtain homogeneous conditions, a factor which has been found to influence the course of metal reductions (E. F. Schoenewaldt, L. B. Turnbull, L. Mandell, T. Utne, E. M. Chamberlin, J. M. Chemerda and M. Tishler, THIS JOURNAL, forthcoming publication). Other factors known to affect the results of metal reductions such as varying the time before addition of the proton source (reference above) or changing the order of addition of reagents (A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953)) were not examined.





For the preparation of the 4β-hydroxy unsaturated acid XIb, the 4β-hydroxy ketone X[1] was carried through the same sequence of reactions as I. The single ethoxyethinylcarbinol from X gave mainly the α,β-unsaturated ester XIa with dilute sulfuric acid in tetrahydrofuran. Mild saponification of XIa proceeded normally to give XIb, and the dihydro-acid XIIa was obtained by reduction as described above. The 4α-hydroxy and 4β-hydroxy dihydro acids were correlated through the 4-ketone. Thus chromium trioxide–pyridine oxidation of the methyl ester XIIb gave the same compound XIII obtained by a similar oxidation of IXb. This also served to prove that the diketone I had been attacked at C_1 by ethoxyacetylenemagnesium bromide.

A series of compounds differing only in the configuration at C_2 was available from the 2β-methallyl diketone XV.[1] With ethoxyacetylenemagnesium bromide XV gave the single ethoxyethinylcarbinol XVI. The β-configuration was assigned to the C_1-hydroxyl group of this product from the same considerations that led to assignment of configuration in carbinol II.[3] The reaction of XVI with sulfuric acid in tetrahydrofuran led principally to the α,β-unsaturated ester XVIIa (a behavior noted with the 1β-hydroxy compound II but not the 1α-hydroxy compound III). The β-hydroxy ester accompanying XVIIa was dehydrated with thionyl chloride–pyridine to XVIIa.

Reduction of XVIIb with sodium borohydride gave the 4α-hydroxy acid XVIII. Potassium in liquid ammonia–2-propanol converted XVIII to the single dihydro acid XIX in 81% yield. The reduction of XVIII with lithium in liquid ammonia gave the same major product XIX along with a smaller quantity of the C_1-isomer XX. The ability of the C_4-hydroxyl group to control the configuration of the side chain at C_1 in the 2α-methallyl series has been described above. If the effect of the C_4-hydroxyl group outweighs that of the C_2-methallyl group, then the more abundant dihydro acid derived from XVIII has the 1β side-chain, *i.e.*, structure XIX. The less abundant isomer must then be assigned formula XX.

Acknowledgment.—The authors are indebted to Mr. L. H. Peterson for technical assistance.

Experimental[15]

2β,4b-Dimethyl-1-ethoxyethinyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β-ol-4-one (II).—Ethylmagnesium bromide was prepared from 680 mg. (0.0280 mole) of magnesium in 40 ml. of ether in the usual fashion and treated with an excess of ethoxyacetylene[16] in ether. When the evolution of ethane had ceased, the oily Grignard reagent was dissolved by the addition of 20 ml. of benzene. To the resulting homogeneous brown solution was added in one portion a solution of 5.00 g. (0.0140 mole) of 2β,4b-dimethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (I) in 50 ml. of benzene. After four hours at room temperature, the homogeneous reaction mixture was poured into ice-water. Ether was added and then saturated ammonium chloride solution in a quantity just sufficient to break the emulsion that had formed. The aqueous layer was separated and extracted twice with ether. The combined organic extract was washed with water, dried and concentrated *in vacuo*. A benzene solution of the crude crystalline product was adsorbed on alkaline alumina. With 1:1 ether–petroleum ether there was eluted 4.57 g.

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(15) Melting points were determined on the Kofler micro hotstage. Ultraviolet spectra were measured in methanol solution and infrared spectra are of the crystalline solids in Nujol unless otherwise noted.

(16) A. E. Favorskii and M. N. Shchukina, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 394 (1945); T. L. Jacobs, R. Cramer and J. E. Jansen, THIS JOURNAL, **64**, 223 (1942).

(76%) of II, m.p. 125-131°. The analytical sample melted at 131–132° after recrystallization from ether; λ_{max} 2.76, 4.48, 5.90, 6.08 μ.

Anal. Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.88; H, 8.36.

A less-stable crystalline form of this compound melting at 114–115.5° was obtained from the initial experiments.

Further elution with ether yielded 590 mg. (9.8%) of the isomeric 2β,4b-dimethyl-1-ethoxyethinyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1α-ol-4-one (III) melting at 150–161°. Recrystallization from ether gave a sample with m.p. 159–161°; λ_{max} 2.85, 4.50, 5.90, 6.08 μ.

Anal. Found: C, 72.81; H, 8.24.

2β,4b-Dimethyl-1-carbethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1α-ol-4-one (VI).—One-quarter milliliter of 10% sulfuric acid was added to a solution of 140 mg. of III in 4 ml. of tetrahydrofuran. After seven hours at room temperature, the reaction mixture was poured into excess sodium bicarbonate solution and the tetrahydrofuran was removed *in vacuo*. The product was extracted with ether and chromatographed over 4.5 g. of alkaline alumina. With 3:7 ether–petroleum ether there was eluted 109 mg. (75%) of VI melting at 114–118°. The analytical sample had a melting point of 118-119° after recrystallization from petroleum ether; λ_{max} 2.83, 5.83, 6.03 μ.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.26; H, 8.50.

2β,4b-Dimethyl-1-carbethoxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (IVa).—A solution of 8.50 g. of II in 65 ml. of tetrahydrofuran was cooled to 20° and with stirring treated with 3.9 ml. of 10% sulfuric acid. After 3 hours at room temperature, 30 ml. of 0.5 *N* sodium bicarbonate was added to the reaction mixture, the tetrahydrofuran was distilled under vacuum and the organic product was extracted with ether. Concentration of the ether gave 8.56 g. of a non-crystalline residue which was dissolved in petroleum ether and adsorbed on 120 g. of alkaline alumina. Elution with 3:7 ether–petroleum ether gave 3.86 g. (45%) of IVa, m.p. 89–96°. A sample crystallized twice from ether–petroleum ether melted at 94–96°; λ_{max} 224 mμ, E_{mol} 12,650; λ_{max} 5.86, 6.13 μ.

Anal. Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.65; H, 8.25.

Further elution with ether gave 2.48 g. (28%) of 2β,4b-dimethyl-1-carbethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β-ol-4-one (Va) melting at 143–146°. Recrystallization from ether raised the melting point to 146–147°; λ_{max} 2.84, 5.81, 5.87, 6.05 μ.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.34; H, 8.64.

Acid Hydrolysis of IVa.—Two hundred milligrams of unsaturated ester, m.p. 90–95°, in 5 ml. of acetone was treated with 5 drops of 10% hydrochloric acid and heated under reflux for 20 minutes. Water was added, the acetone was distilled and the product was extracted with ether. Crystallization from ether–petroleum ether gave 147 mg. (82%) of 2β,4b-dimethyl-1-carbethoxymethylene-2-methallyl-1,2,3,4,4aα,4b,5,6,7,9,10,10aβ-dodecahydrophenanthrene-4,7-dione, m.p. 107–111°. A sample recrystallized from ether for analysis had m.p. 111–112°; λ_{max} 234 mμ, E_{mol} 25,600.

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.34. Found: C, 74.68; H, 8.27.

Dehydration of the β-Hydroxy Ester Va.—A solution of 16 g. of the β-hydroxy ester Va in 160 ml. of dry pyridine was cooled to 10°, and to it, with stirring, was added a solution of 8 ml. of freshly distilled thionyl chloride in 25 ml. of dry pyridine. The solution was allowed to stand for 10 minutes, whereupon it was poured into a liter of ice-water containing 100 g. of sodium bicarbonate. The mixture was extracted three times with petroleum ether and the solvent was evaporated from the combined extracts *in vacuo*. The amorphous residue was dissolved in petroleum ether and chromatographed over 600 g. of alkaline alumina. Elution with 1:3 ether–petroleum ether gave 12.1 g. of crystals. Recrystallization from petroleum ether afforded 11.4 g. (75%) of the unsaturated ester IVa, m.p. 88–92°.

Acid Hydrolysis of Va.—A solution of 200 mg. of the β-hydroxy ester Va in acetone was hydrolyzed with a few drops of 10% hydrochloric acid as described above. The product, 2β,4b-dimethyl-1-carbethoxymethyl-2-methallyl-1,2,3,4,4aα,4b,5,6,7,9,10,10aβ-dodecahydrophenanthrene-1β-ol-4,7-dione, amounted to 143 mg. (80%) melting at 122–124° after crystallization from ether; λ_{max} 2.88, 5.82, 5.93, 6.05, 6.13 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.64.

A solution of 313 mg. of this β-hydroxy ester in 4 ml. of tetrahydrofuran and 2 ml. of 10% sulfuric acid was heated under reflux for one hour. Evaporation of the solvent, extraction with ether, concentration and crystallization returned 287 mg. (92%) of starting material in two crops.

A similar experiment with 302 mg. of the same β-hydroxy ester in 5 ml. of tetrahydrofuran and 2 ml. of 10% hydrochloric acid returned 270 mg. (89%) of unchanged hydroxy ester.

Saponification and Acid Hydrolysis of Va.—Saponification of the hydroxy ester was carried out by heating 300 mg. of Va in 10 ml. of 2 *N* potassium carbonate in 50% aqueous methanol under reflux for seven hours. The methanol was removed and the alkaline solution was extracted with ether. Evaporation of the ether gave 85 mg. of neutral crystalline residue, largely starting material. Acidification of the aqueous part with excess sodium dihydrogen phosphate followed by extraction with chloroform, drying and concentration left 178 mg. (63%) of crystalline 2β,4b-dimethyl-1-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β-ol-4-one (Vb) melting at 213–215° after recrystallization from ethyl acetate.

Forty-five milligrams of Vb was heated briefly in acetone with a trace of hydrochloric acid. Dilution with water gave 36 mg. (90%) of 2β,4b-dimethyl-1-carboxymethyl-2-methallyl-1,2,3,4,4aα,4b,5,6,7,9,10,10aβ-dodecahydrophenanthrene-1β-ol-4,7-dione melting at 205–210° dec. Recrystallization from benzene and ethyl acetate did not raise the melting point.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.40; H, 7.93.

Dehydration of the β-Hydroxy Ester VI.—Three grams of the β-hydroxy ester VI was dissolved in 30 ml. of dry pyridine, and to this solution was added 1.5 ml. of redistilled thionyl chloride in 5 ml. of pyridine. After 10 minutes the mixture was worked up and chromatographed as described above for Va yielding 2.0 g. of amorphous material. This material was boiled for 3.5 hours in 60 ml. of 50% aqueous methanol containing 4.3 g. of potassium carbonate. The methanol was evaporated *in vacuo*, the aqueous mixture was acidified with excess sodium dihydrogen phosphate, and extracted three times with ether. Evaporation of the combined extracts left 1.6 g. of a gum, λ_{max} 230 mμ, E_{mol} 5,320. Successive reductions of this product with sodium borohydride and with potassium–ammonia–2-propanol in the manner described below for the acid IVb gave as the only crystalline product 150 mg. (*ca.* 10%) of the acid VIIIa.

Reaction of β-Hydroxy Esters with Potassium *t*-Butoxide.—A solution of 165 mg. of the hydroxy ester Va in 7 ml. of dry benzene was treated with 0.6 ml. of 1 *M* potassium *t*-butoxide in *t*-butyl alcohol. After five minutes the reaction was quenched with 5 ml. of water, the benzene layer was separated, and the aqueous layer was extracted twice with ether. The three combined extracts were evaporated *in vacuo*, leaving a crystalline residue. Recrystallization from ether–petroleum ether gave 100 mg. (75%) of the diketone I, m.p. and mixed m.p. 132–136°. When 165 mg. of the hydroxy ester VI was treated with potassium *t*-butoxide in the same manner as was the hydroxy ester Va, 95 mg. (70%) of the expected diketone I, m.p. and mixed m.p. 130–135°, was obtained.

Reaction of II with Acids. A. With Hydrochloric Acid.—One milliliter of 10% hydrochloric acid was added to a solution of 500 mg. of ethoxyethinylcarbinol II in 8 ml. of tetrahydrofuran. After three hours at room temperature, 5 ml. of saturated sodium bicarbonate solution was added to the reaction mixture and the tetrahydrofuran was distilled *in vacuo*. Extraction with ether, drying and concentration of the extract gave 548 mg. of non-crystalline product which was adsorbed on 16 g. of alkaline alumina. Elution with 1:3 ether–petroleum ether gave 72 mg. (13%) of chloro compound ia, m.p. 145–153°. Recrystallization from petroleum ether afforded a sample melting at 155–157°; λ_{max} 2.82, 5.90, 6.05 μ. This compound precipitated silver chloride after brief warming in alcoholic silver nitrate solution.

Anal. Calcd. for $C_{26}H_{37}O_5Cl$: Cl, 7.63. Found: Cl, 7.62.

Further elution with 3:7 ether–petroleum ether gave 180 mg. (33%) of an isomeric chloro compound ib melting at 115–125°. A sample was recrystallized from ether–petroleum ether for analysis; m.p. 127.5–129°; λ_{max} 2.83, 5.90, 6.08 μ.

Anal. Found: Cl, 7.21.

Further elution with 2:3 ether–petroleum ether yielded 116 mg. (22%) of Va, m.p. and mixed m.p. 143–146° after crystallization from ether.

A solution of 404 mg. of II in 10 ml. of ethanol and 5 ml. of 10% hydrochloric acid was heated under reflux for one hour. Water was added to the reaction mixture, the ethanol was removed *in vacuo* and the product extracted with ether. The ether extract was washed with bicarbonate solution, dried and evaporated leaving 348 mg. of non-crystalline product which was chromatographed over 11 g. of alkaline alumina. The 1:1 ether–petroleum ether eluates yielded 170 mg. (47%) of 7-keto-α,β-unsaturated ester, m.p. and mixed m.p. 108–112° after recrystallization from ether. Further elution gave mixtures of esters.

B. With Perchloric Acid.—One-half gram of II in 8 ml. of tetrahydrofuran was treated with 0.5 ml. of 2 *N* perchloric acid. After three hours excess bicarbonate solution was added, the tetrahydrofuran was distilled *in vacuo* and the residual mixture was extracted with ether. The dried ether extract was evaporated and the resulting gummy product was chromatographed over 15 g. of acid-washed alumina. The first ether–petroleum ether (1:9) eluate gave 78 mg. (15%) of IVa as a gum that could not be induced to crystallize. Saponification of this fraction in aqueous methanolic potassium carbonate afforded 49 mg. of crystalline unsaturated acid IVb (see below), m.p. and mixed m.p. 195–198° after recrystallization from ethyl acetate. Elution with 3:17 and 2:8 ether–petroleum ether yielded 85 mg. (16%) of β-hydroxy ester Va, m.p. 143–146° from methanol. Further elution gave non-crystalline materials.

A solution of 204 mg. of II in 4 ml. of tetrahydrofuran was treated with 2 ml. of 2 *N* perchloric acid and allowed to stand at room temperature for 42 hours. The reaction mixture was worked up as described above and the product was chromatographed over 5 g. of alkaline alumina. Ether–petroleum ether elution yielded 52 mg. (30%) of 7-keto-α,β-unsaturated ester, m.p. and mixed m.p. 107–110°. With ether–chloroform there was eluted 76 mg. (40%) of the 7-keto-β-hydroxy ester, m.p. and mixed m.p. 118–122°.

C. With Trichloroacetic Acid.—The ethoxyethinylcarbinol II (170 mg.) was dissolved in 5 ml. of benzene containing 400 mg. of trichloroacetic acid. After one hour at room temperature the solution was washed with sodium bicarbonate solution, dried and evaporated. Crystallization from ether–petroleum ether gave 214 mg. (98%) of 7-keto monoadduct, m.p. *ca.* 180° dec.; λ_{max} 2.77, 5.59, 5.83, 5.90, 5.97, 6.13, 8.3, 14.9 μ.

Anal. Calcd. for $C_{27}H_{32}O_6Cl_3$: C, 58.02; H, 5.77. Found: C, 58.10; H, 5.79.

A solution of 45 mg. of trichloroacetic acid adduct above in 6 ml. of 0.5 *N* potassium carbonate in 50% aqueous methanol was heated for two hours. Methanol was distilled, the neutral material was extracted with ether and the aqueous layer was acidified with excess sodium dihydrogen phosphate. The liberated acid amounted to 24 mg. (77%), m.p. 204–208° dec. from ether. The melting point was not lowered on admixture with the 7-keto-β-hydroxy acid from Vb.

2β.4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (IVb).—Thirty-five grams of potassium carbonate in 250 ml. of water was added to a solution of 16.2 g. of IVa in 250 ml. of methanol. The mixture was heated under reflux for three hours after which the methanol was distilled under vacuum. Water was added to dissolve the oily potassium salt and the resulting solution was acidified with excess sodium dihydrogen phosphate. The precipitated acid was extracted with chloroform and after concentration and crystallization from ethyl acetate–petroleum ether amounted to 12.6 g. (83.5%), m.p. 191–196°. A sample recrystallized from ethanol for analysis melted at 203–205°; λ_{max} 220 mμ, E_{mol} 10,300; λ_{max} 5.86, 6.15 μ.

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.75; H, 7.78.

Esterification with diazomethane in ether gave the methyl ester IVc, m.p. 152–154°; λ_{max} 5.83, 6.13 μ.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.67; H, 8.26.

2β,4b-Dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4β,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (VIIIa).—A suspension of 17.3 g. of the unsaturated acid IVb in 300 ml. of water was treated with 12 ml. of 4 *N* sodium hydroxide solution, and in the resulting homogeneous solution 17 g. of sodium borohydride was dissolved. The solution was kept at room temperature overnight, and then heated for 1 hour at 100°. After acidification with excess solid sodium dihydrogen phosphate the reaction mixture was extracted thrice with chloroform. Evaporation of the chloroform from the combined extracts left 18 g. of VII as an amorphous residue which could not be induced to crystallize. This non-crystalline 4α-hydroxy acid VII was suspended in 800 ml. of liquid ammonia at −80° and 20 g. of potassium metal was added with rapid stirring. The stirring was continued for 10 minutes after the final addition of potassium, and then 300 ml. of dry 2-propanol was added over a five-minute period. The cooling bath was removed and the stirring was continued until the blue color was discharged. The ammonia was evaporated *in vacuo*, the residual solution being warmed to 40° to expel the remaining ammonia. The reaction mixture was diluted with 200 ml. of water, cooled in ice, and neutralized with a solution of 200 g. of sodium dihydrogen phosphate in 400 ml. of 1.25 *N* hydrochloric acid. A copious white precipitate of 2β,4b-dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy - 1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4α-ol (VIIIa) formed. This was collected on a filter, slurried in water, collected again, washed with ethanol and then with ether. The yield was 13.5 g. (78%), m.p. 247–250°. A portion recrystallized from ethanol had m.p. 255-257°, λ_{max} 3.07–4.3, 5.82, 5.98 μ.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.36; H, 8.73.

This procedure was used for the reduction of IVb and XIb in ammonia–2-propanol. The results are given in Table I (see Discussion).

Treatment of a portion of the saturated acid VIIIa with diazomethane in ether afforded the methyl ester VIIIb, m.p. 157–158° after recrystallization from ether; λ_{max} 2.85, 5.79, 6.05 μ.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.71; H, 9.15. Found: C, 71.85; H, 8.84.

Acetylation of VIIIb in acetic anhydride–pyridine gave the 4-acetate, m.p. 140–141° from ether–petroleum ether.

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.65; H, 8.57.

2β,4b-Dimethyl-1α-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (IXa).—A solution of 6.5 g. of the unsaturated acid IVb in 700 ml. of 1-butanol was heated to 105° under reflux, and with rapid stirring 20 g. of sodium metal was added as rapidly as possible. After 15 minutes all the sodium was in solution and the vigorous boiling subsided. The solution was cooled and acidified with saturated aqueous sodium dihydrogen phosphate solution. The mixture was extracted four time with chloroform, and the combined extracts were evaporated to dryness *in vacuo*. The crystalline residue was triturated with acetone, and the insoluble material was collected on a filter. (This consisted mostly of the 1β-carboxymethyl compound VIIIa.) The filtrate was evaporated to dryness and the crystalline residue was recrystallized from ethyl acetate, giving 2.0 g. (31%) of 2β,4b-dimethyl-1α-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ - dodecahydrophenanthrene-4α-ol (IXa), m.p. 218–220°; λ_{max} 3.9–4.0, 5.82 (shoulder), 5.89 μ.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.09; H, 9.00.

All of the alkali metal–alcohol reductions of IVb and of VII were carried out by the procedure described above and the results are presented in Table I (see Discussion).

The methyl ester IXb was prepared by treating IXa with an excess of diazomethane in ether; m.p. 120–121° from methanol; λ_{max} 2.85, 5.75, 6.06 μ.

Anal. Found: C, 71.86; H, 9.25.

Acetylation in acetic anhydride–pyridine gave the 4-acetate of IXb, m.p. 125–126° from ether.

Anal. Found: C, 70.43; H, 8.61.

2β,4b-Dimethyl-1α-carbomethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XIII).—To the complex prepared from 3.5 g. of chromium trioxide and 35 ml. of pyridine was added a solution of 3.5 g. of IXb in 35 ml. of pyridine. After standing at room temperature overnight, the reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed, dried and concentrated and the residue crystallized from methanol; yield 3.1 g. (89%), m.p. 138–141°; λ_{max} 5.79, 5.92, 6.08 μ.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.46; H, 8.66.

2β,4b-Dimethyl-1α-(2-hydroxyethyl)-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XIV).—To a rapidly stirred solution of 2.00 g. of α,β-unsaturated ester IVa in 200 ml. of 1-butanol at 100° was added 7 g. of sodium metal. When the sodium had reacted (*ca.* five minutes), the solution was concentrated under vacuum to one-third the original volume, treated with 100 ml. of 50% aqueous methanol and heated under reflux for 30 minutes. Alcohol was distilled *in vacuo* and the residue was diluted with water and extracted with ether and chloroform. Acidification of the aqueous portion with sodium dihydrogen phosphate followed by chloroform extraction, drying and concentration gave 640 mg. of a mixture of crystalline acids which was not investigated further. The combined ether and chloroform extracts of the alkaline solution were dried and concentrated to dryness leaving 1.28 g. (70%) of crude crystalline diol, m.p. 167–177°. By recrystallization from ethyl acetate–petroleum ether there was obtained pure XIV, m.p. 182–183°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.91; H, 9.71.

For assignment of configurations at C_1 and C_4 in this diol, 150 mg. of IXb was reduced with excess lithium aluminum hydride in tetrahydrofuran. Excess reagent was decomposed with water, the inorganic salts were separated by filtration and the solvent was evaporated. Crystallization of the residue from ether gave 90 mg. of XIV, m.p. 179–180°, which gave no depression in melting point on admixture with the product from the preceding experiment.

2β,4b-Dimethyl-1-ethoxyethinyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β,4β-diol.—Five grams of the hydroxyketone X was allowed to react with excess ethoxyacetylenemagnesium bromide and was worked up as described above. The product amounted to 4.80 g. (83%) melting at 108–111°. Only one isomer could be isolated. The analytical sample was recrystallized from ether–petroleum ether, m.p. 111–113°; λ_{max} 2.92, 4.47, 6.06 μ.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.51; H, 8.90. Found: C, 72.06, 72.94; H, 8.60, 8.41.

2β,4b-Dimethyl-1-carbethoxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol (XIa).—A tetrahydrofuran solution of 5.00 g. of 2β,4b-dimethyl-1-ethoxyethinyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β,4β-diol was allowed to react with 10% sulfuric acid and worked up as described above. There was obtained 3.50 g. (70%) of XIa, m.p. 105–120°; λ_{max}^{EtOH} 236 mμ, E_{mol} 7,040; λ_{max} 2.82, 5.82, 6.08, 6.13 μ.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.51; H, 8.90. Found: C, 72.43; H, 8.47.

2β,4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol (XIb).—Saponification of 1.30 g. of XIa in 50 ml. of 0.5 *N* potassium hydroxide in 50% methanol by heating under reflux for 1.5 hours followed by crystallization of the acid portion from benzene–petroleum ether gave 990 mg. (81%) of XIb, m.p. 172–181°. A recrystallization from ethyl acetate–petroleum ether yielded a sample melting at 174–180°; λ_{max}^{EtOH} 231 μ, E_{mol} 9,900; λ_{max} 3–4, 5.78, 5.90, 6.15 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.63; H, 8.52; neut. equiv., 402. Found: C, 72.01; H, 8.67; neut. equiv., 396.

It was not possible to obtain a sharply melting sample of this compound; most melting points were in the range 170–180° with a transition point at 130–140°. The unusual 5.78 μ infrared band was not present in all samples and may have indicated a variable degree of hydrogen bonding.

A sample of XIb reacted readily with diazomethane in ether giving the methyl ester XIc, m.p. 134–135°.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.10; H, 8.71. Found: C, 71.73; H, 8.68.

Oxidation of the methyl ester with chromic anhydride–pyridine according to the procedure described above afforded the 4-ketoester IVc, m.p. and mixed m.p. 150–153°.

2β,4b-Dimethyl-1α-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol (XIIa).—To a suspension of 1 g. of XIb in 50 ml. of liquid ammonia 190 mg. of lithium was added in portions. The blue solution was stirred at −40° for two hours after which the ammonia was allowed to evaporate. Excess lithium was decomposed with ethyl acetate. The residue was dissolved in cold water, partially neutralized with 10% hydrochloric acid, and then excess sodium dihydrogen phosphate was added. The acid was extracted with benzene and chloroform. Evaporation of the extract *in vacuo* left 910 mg. of amorphous residue which was crystallized from benzene, giving 405 mg. (40%) of product, m.p. 169–191°. Recrystallization from benzene and prolonged drying yielded a sample melting at 195–197°; λ_{max} 3.01, 5.94 μ.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.26; H, 9.03. Found: C, 71.75; H, 8.98.

The unsaturated acids IVb and VII were reduced in liquid ammonia with alkali metals by this procedure; *cf.* Table I for results.

The acid XIIa (90 mg.) reacted rapidly with ethereal diazomethane to give the methyl ester XIIb, m.p. 142–144°, which crystallized from cold ether. This ester was oxidized with 105 mg. of chromic anhydride in 4 ml. of pyridine according to the procedure described previously. The crude crystalline product was recrystallized five times from ether yielding 50 mg. of the 4-keto ester XIII, m.p. and mixed m.p. 138–141°.

2α,4b-Dimethyl-1-ethoxyethinyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β-ol-4-one (XVI).—Reaction of 600 mg. of the 2α-methyl-2-methallyl diketone XV with excess ethoxyacetylenemagnesium bromide in the manner previously described gave 540 mg. (75%) of XVI as the sole product, m.p. 133–134° from ether; λ_{max} 2.89, 4.49, 5.87, 6.08 μ.

Anal. Found: C, 72.95; H, 8.30.

2α,4b-Dimethyl-1-carbethoxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XVIIa).—A solution of 2.4 g. of XVI in 8 ml. of tetrahydrofuran was treated with 0.5 ml. of 10% sulfuric acid and maintained at room temperature for 3.5 hours. The reaction mixture was worked up as above and the product was chromatographed over 90 g. of acid-washed alumina. Early ether–petroleum ether fractions yielded 1.0 g. (41%) of unsaturated ester XVIIa, m.p. 133–135° and 154–155° from ether–petroleum ether; λ_{max} 5.84, 6.15 μ.

Anal. Found: C, 72.97; H, 8.63.

Continued elution with ether gave 1.0 g. (41%) of 2α,4b-dimethyl-1-carbethoxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β-ol-4-one, m.p. 99–101° from ether; λ_{max} 2.9, 5.83, 5.86. 6.05 μ.

Anal. Found: C, 69.77; H, 8.26.

Dehydration of this β-hydroxy ester in pyridine with thionyl chloride by the procedure used for the dehydration of Va produced 52% of XVIIa.

A solution of 500 mg. of the β-hydroxy ester, m.p. 99–101°, in 1.5 ml. of 1 *N* sodium ethoxide was allowed to stand at room temperature overnight. The reaction mixture was poured into water and extracted with ether. Evaporation of the organic portion and crystallization from petroleum ether–ether yielded 200 mg. (49%) of XV, m.p. and mixed m.p. 107–109°.

A similar experiment using 1 *M* potassium *t*-butoxide at room temperature for one hour gave 59% of the methyl-methallyl diketone XV.

2α,4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XVIIb).—The unsaturated ester XVIIa (4.10 g.) was saponified in 100 ml. of 50% methanol containing 10 g. of potassium carbonate and 1 g. of potassium hydroxide by boiling for 2.5 hours. The methanol was evaporated, 50 ml. of water was added to dissolve the potassium salt and the aqueous solution was extracted with ether and then acidified with sodium dihydrogen phosphate and extracted with chloroform. Evaporation of the extract and crystallization of the residue from ethyl acetate provided 3.3 g. (86%) of XVIIb, m.p. 223–225°; $\lambda_{\text{shoulder}}$ 220–230 mμ, E_{mol} 5,490; λ_{max} 5.83, 5.91, 6.18 μ.

Anal. Found: C, 71.80; H, 8.06.

2α,4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XVIII).—To a solution of 100 mg. of XVIIb in 2 ml. of methanol and 1 ml. of tetrahydrofuran was added 100 mg. of sodium borohydride. After the gas evolution had subsided, the mixture was heated under reflux for one hour. The solvents were removed *in vacuo* and the residue was dissolved in water and acidified with excess sodium dihydrogen phosphate. The acidified mixture was thrice extracted with chloroform and the chloroform extract was washed with water and dried. Evaporation of the solvent *in vacuo* left a crystalline residue weighing 90 mg., m.p. 214–222°. The product, 2α,4b-dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XVIII), had m.p. 220–222° after two crystallizations from ethyl acetate; λ_{max} 2.8–4.2, 5.90, 6.08, 6.17 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.36.

Acetylation in acetic anhydride-pyridine gave the 4-acetate of XVIII melting at 204–205° after recrystallization from ethyl acetate–petroleum ether; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.81, 5.92, 6.17 μ.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.61; H, 7.88.

2α,4b-Dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XIX).—A solution of 550 mg. of XVIII in 50 ml. of liquid ammonia was treated with 300 mg. of potassium and 10 ml. of 2-propanol by the procedure described above. The crystalline product amounted to 443 mg. (81%) melting at 225–228°. A sample twice recrystallized from ethyl acetate had m.p. 226–228°; λ_{max} 2.93, 5.82, 6.05 μ.

Anal. Found: C, 70.97; H, 8.84.

2α,4b-Dimethyl-1α-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XX).—Five grams of XVIII was reduced with 550 mg. of lithium in 20 ml. of tetrahydrofuran and 180 ml. of liquid ammonia by the previously described procedure. The crude crystalline product was warmed with 50 ml. of ether and the insoluble part separated by filtration. The ether insoluble portion amounted to 3.00 g. (60%) and consisted mostly of the 1β-carboxymethyl isomer XIX. Upon evaporation of the ethereal filtrate to 5 ml., 750 mg. of crystalline material precipitated. Repeated recrystallization of this mixture from ethyl acetate gave the 1α-carboxymethyl isomer XX, m.p. 234–235°; λ_{max} 2.82, 5.82, 6.08 μ.

Anal. Found: C, 71.07; H, 8.74.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

α-Iodoketones (Part 3).[1] Synthesis of 21-Iodo-Δ^{16}-20-keto Steroids by the N-Iodosuccinimide–Enol Acetate Reaction[2]

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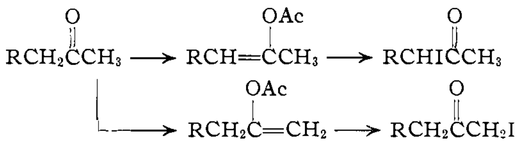
Unsaturated enol acetates such as 20-acetoxy-$\Delta^{16,20}$-dienes, readily obtainable by the reaction of Δ^{16}-20-keto steroids with isopropenyl acetate, are convertible in excellent yield to the hitherto inaccessible 21-iodo-Δ^{16}-20-ketosteroids by treatment with N-iodosuccinimide in dioxane solution. Replacement of the halogen atom by acetate proceeds in nearly quantitative yield, thus opening a route to the Δ^{16}-20-keto-21-acetates and thence by appropriate manipulations to the cortical hormone side chains characteristic of desoxycorticosterone and cortisone. Nuclear double bonds or aromatic rings do not interfere in this reaction.

We have recently described a new synthesis[1] of α-iodo ketones by the reaction of enol acetates with N-iodosuccinimide, a readily available and stable iodine carrier. The utility of this method was illustrated with certain methyl ketones and it was demonstrated that the iodine could be introduced at either the methyl or methylene carbon depending upon the direction of enolization.



$$RCH_2\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow RCH{=}\overset{OAc}{\overset{|}{C}}CH_3 \longrightarrow RCHI\overset{O}{\overset{\|}{C}}CH_3$$
$$\longrightarrow RCH_2\overset{OAc}{\overset{|}{C}}{=}CH_2 \longrightarrow RCH_2\overset{O}{\overset{\|}{C}}CH_2I$$

In an attempt to delineate the scope of this reaction we have turned to certain unsaturated enol acetates and the present paper is concerned with the utilization of this procedure for a novel approach to the cortical hormone side chain characteristic of desoxycorticosterone and cortisone.

In a study of the reaction of 20-keto steroids with isopropenyl acetate, Moffett and Weisblat[4] also investigated two Δ^{16}-20-keto steroids and on the basis of analytical and spectral data concluded that the resulting enol acetates should be formulated as 20-acetoxy-$\Delta^{16,20}$-dienes (*e.g.*, I → II); no reactions of these unsaturated enol acetates were reported. Since the starting material, the Δ^{16}-20-ketone (*e.g.*, IA), is the immediate degradation product of the steroidal sapogenin diosgenin[5] and can thus be considered to be one of the most accessible steroids, it appeared of interest to examine the course of the reaction of its enol acetate IIA with N-iodosuccinimide (NIS). The enol acetate IIA was obtained in 77% yield by a slight modification of the published procedure[4] and upon treatment with NIS in the standard manner[1]

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(1) Part 2, C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).

(2) From part of the Ph.D. dissertation of Carl T. Lenk.

(3) Research Corporation Fellow, 1952-1953.

(4) R. B. Moffett and D. I. Weisblat, THIS JOURNAL, **74**, 2183 (1952).

(5) *Inter al.*, R. E. Marker, *ibid.*, **62**, 3350 (1940).