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SYNTHETIC INVESTIGATIONS ON TESTOSTERONE AND ITS ANALOGUES—I

THE TOTAL SYNTHESIS OF 8-ISOTESTOSTERONE AND ITS ANTHRACENE ANALOGUE*

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Abstract—The total synthesis of 8-isotestosterone (II) and the corresponding anthracene analogue (III) following the benzohydrindane route is reported. Catalytic hydrogenation of *trans*-1β-acetoxy-8-methyl-4,5-(3′-methyl-4′-hydroxybenzo)-hydrindane (V) followed by oxidation has furnished two isomeric tricyclic keto acetates, *viz.* 1β,2α-(3′-acetoxycyclopentano)-2,5-dimethyl-6-keto-1α,2,3,4,4aα,-5α,6,7,8,8aα-decahydronaphthalene (VII) and 1β,2α-(3′-acetoxycyclopentano)-2,5-dimethyl-6-keto-1α,2,3,4,4aβ,5,6,7,8,8aβ-decahydronaphthalene (IX) which are *cis*-non-steroid and *cis*-steroid configurations of the same cyclopentano-*cis*-decalins. A difference in the direction of enolization of the keto acetate (VII) in alkylation reaction and enol acetylation towards the methine and the methylene carbon atoms respectively has been observed.

As a part of a broad programme for the synthesis of steroids through the benzohydrindane route, we reported[1] the sterospecific syntheses of the benzohydrindane (Ia and Ib) with the expressed intention of converting them to the steroids *via* the obvious sequence involving the Birch reduction of the aromatic ring and the elaboration of ring A. During the course of this work, Velluz *et al.* published[2] a series of papers describing the conversion of Ia and one of its optical antipodes to 19-nortestosterone, cortisone and oestradiol, the starting material having been prepared by our method. Later, utilizing the same tricyclic intermediate (Ia), Chinn and Dryden reported[3] the synthesis of 19-nortestosterone. This communication describes improved yields in the preparation of the intermediate (Ib) which is used in a total synthesis of 8-isotestosterone (II) and the corresponding anthracene analogue (III).

During our investigation on the Birch reduction of the aromatic nucleus of Ib, Djerassi *et al.* reported[4] the multi-stage conversion of diosgenin to 8-isotestosterone which besides retaining nearly one half the biological activity of testosterone, presents an interesting conformational feature in that the B ring exists in the boat form.[5]

* A preliminary communication describing this work has appeared in *Tetrahedron Letters*, No. 12, 23 (1960).

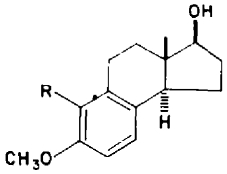
[1] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Amer. Chem. Soc.* **78**, 3769 (1956); D. K. Banerjee and S. K. Balasubramanian, *J. Org. Chem.* **23**, 105 (1958).

[2] L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier and A. Pierdet, *C.R. Acad. Sci. Paris* **250**, 1084 (1960); L. Velluz, G. Nomine, J. Mathieu, E. Toromanoff, D. Bertin, R. Bucourt and J. Tessier, *C.R. Acad. Sci. Paris* **250**, 1293 (1960); L. Velluz, G. Nomine, J.Mathieu, E. Toromanoff, D. Bertin, M. Vignan and J. Tessier, *C.R. Acad. Sci. Paris* **250**, 1510 (1960); L. Velluz, G. Nomine and J. Mathieu, *Angew. Chem.* **72**, 725 (1960).

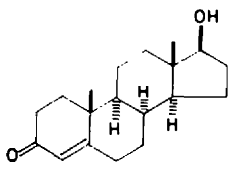
[3] L. J. Chinn and H. L. Dryden Jr., *J. Org. Chem.* **26**, 3904 (1961).

[4] C. Djerassi, A. J. Manson and H. Bendas, *Tetrahedron* **1**, 22 (1957).

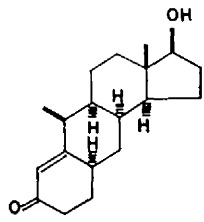
[5] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362, 6377 (1956).



Ia, R=H
b, R=CH3



II



III

The latter factor makes the total synthesis of this molecule particularly attractive.

In the preparation of Ib from β-naphthol by the procedure reported earlier,[1] a significant improvement in yield may be effected at two stages. 2-Methoxynaphthaldehyde, previously hydrogenated to 5-methyl-6-methoxytetralin in 42%[1] and 46%[6] yields, may be produced in a 89% yield by using an excess of acetic acid in the hydrogenation. In the crucial step involving the Johnson–Stobbe condensation[1] of 1-keto-2-methyl-2-cyano-5-methyl-6-methoxytetralin to give methyl 1-keto-8-methyl-4,5-(3'-methyl-4'-methoxybenzo)- $\Delta^{3(9)}$-hydrindene-3-carboxylate, the yield was raised from 53% to 81%.

In the demethylation of Ib to the hydroxy phenol (IV), if pyridinium chloride is used instead of methyl magnesium iodide,[7] the operation is greatly simplified while the yield is only reduced from 79% to 75%. In the preferential acetylation of the secondary alcoholic group in IV, the ester exchange with ethyl acetate and *p*-toluenesulphonic acid[7b] as well as selective saponification of the diacetate with aqueous potassium carbonate solution[8] affords the monoacetate (V) in moderate yields. The best yield of 70% was achieved by refluxing IV in acetic acid in the presence of *p*-toluenesulphonic acid following the procedure of Chen.[9] Catalytic hydrogenation of V was expected to take place from the less hindered α-side of the molecule since the bulky methyl group would, following Linstead's concept,[10] offer serious hindrance to the approach of the molecule on the catalyst surface from the same side. Accordingly, by using 5% ruthenium on carbon catalyst[11] at 300 atmospheres pressure and 100°, an oily mixture was obtained which on chromatography afforded mainly VIa besides small quantities of the hydrogenolysed material (VIb) and a gummy material. The last fraction eluted from the column immediately after the product VIa showed in its IR spectrum bands for both hydroxy and acetoxy groups. Oxidation of VIa using Jones' reagent[12] gave the keto acetate (VII; 95%) existing in two polymorphic modifications. Similar oxidation of the gummy fraction (which took place at a slower rate) afforded more of the keto acetate (VII) and in addition, an isomeric

[6] J. W. Cornforth, O. Kauder, J. E. Pike and R. Robinson, *J. Chem. Soc.* 3353 (1955).

[7a] A. L. Wilds and W. B. McCormack, *J. Amer. Chem. Soc.* **70**, 4127 (1948);

[b] W. S. Johnson, E. R. Rogier and J. Ackerman, *J. Amer. Chem. Soc.* **78**, 6322 (1956).

[8] E. Walton, A. N. Wilson, A. C. Haven Jr., C. H. Hoffman, E. L. Johnston, W. F. Newhall, F. M. Robinson and F. W. Holly, *J. Amer. Chem. Soc.* **78**, 4760 (1956).

[9] C. Chen, private communication; cf. *Tetrahedron* **3**, 43 (1958).

[10] R. P. Lindstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942).

[11] We are indebted to Baker & Co., London, for a gift of this catalyst.

[12] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

material which has been assigned the configuration (IX). IR spectra (Fig. 1) of the two keto acetates (VII and IX) show a difference in the finger print region and the mixture melting point of the two is depressed.

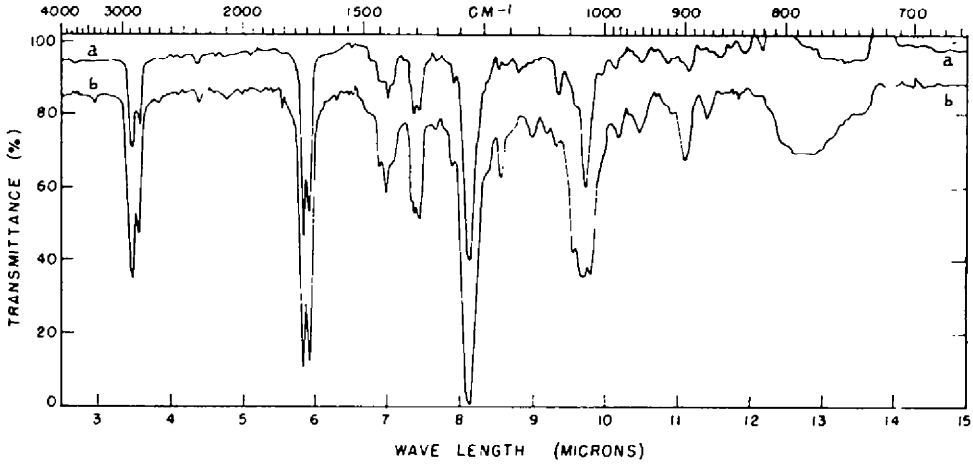


FIG. 1. IR spectra of VIIa and IXb.

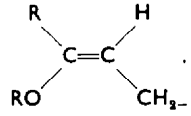
These results can be explained by assuming that, in the catalytic hydrogenation of V, the adsorption of V on the catalyst surface from the same side as the angular methyl group results in the formation of small quantities of an isomeric material (VIII) together with the preponderant isomer VIa. Such a conclusion is not without an analogy.[9] The conformational formulae (X and Xa) of VIa and the minor isomer reveals that they have axial and equatorial hydroxy groups respectively. In addition, their behaviour during chromatography as well as in chromic acid oxidation indicates marked structural differences. If it is assumed that part of the axial hydroxyl of VIa has epimerized during chromatography, then the resulting new isomer (XIII) together with VIII may be expected to elute at about the same rate to give a mixture. Recovery of the keto acetate (VII), unaffected after treatment with potassium t-butoxide in t-butanol, indicates an equatorial conformation of the methyl group adjacent to the carbonyl. Similar treatment of the isomeric keto acetate (IX) could not be carried out for want of sufficient material, and considering the possibility of epimerization of the methyl group during chromic acid oxidation, conformation of the methyl group in IX has been left undetermined. Examination of a model of the keto acetate (VII) indicates that the *cis*-2-decalone moiety in the molecule is frozen in the non-steroid conformation (XI), and therefore the steroid conformation (XIa) has been assigned to the corresponding part of the isomeric keto acetate (IX). This is probably the first instance where both isomers of the same *cis*-decalin system have been isolated.

It appears that caution is needed in predicting the course of alkylation in the *cis*-(NS)-decalone system of the keto acetate (VII). Instances are available in the literature where bromination as well as alkylation of *cis*-decalones has shown a preference for enolization towards C-3 rather than C-1. Dreiding[13] rationalized these observations by suggesting that the chances of enolization towards either C_1 or C_3 are even in the case of *cis*-2-decalone reacting in the non-steroid conformation. In

[13] A. S. Dreiding, *Chem. & Ind.* 1419 (1954).

the case of the keto acetate (VII), even if the steric factors directing enolization towards either the methylene or the methine carbon are even, the balance will be tilted in favour of the latter since the developing double bond of the enolate in this position will be stabilized to a greater extent by hyperconjugation.[14,15] Axial alkylation at the methine carbon in VII should take place from the convex face of the *cis*-2-decalone cage and the resulting product could cyclize only by forcing the B-ring into a boat conformation. Addition of methyl vinyl ketone to VII in presence of Triton B furnished a crystalline α,β-unsaturated ketone in 21% yield together with some resin. The identity of our material with authentic 8-isotestosterone prepared by Djerassi *et al.*[4] could not be proved as a sample of the latter was not available. However, an IR spectrum (Baird Spectrophotometer, Fig. 2) of the authentic material, kindly furnished by Professor Djerassi, compared favourably with the IR spectrum (Perkin–Elmer Infracord, Model 137, Fig. 2) of the totally synthetic material. In order to provide definite proof of the structural assignment to the molecule (II), the methylene group in the keto acetate (VII) was blocked as the methylanilinomethylene derivative so as to direct the alkylation exclusively to the methine carbon. Condensation with methyl vinyl ketone followed by removal of the blocking group afforded a material identical with the one obtained by direct alkylation. Additional evidence in favour of the structure (II) was obtained by the formation of a different unsaturated keto alcohol through condensation of the hydroxymethylene derivative of the keto acetate (VII) with methyl vinyl ketone, non-identity with the previous product being proved by comparison of the IR spectra (Fig. 2) and mixture melting point determination. A linear structure (III) has been assigned to the new tetracyclic compound which may be considered as an anthracene analogue of 8-isotestosterone.

In order to study the bromination of the keto acetate (VII), a crystalline enol acetate (XII) was prepared by treating VII with acetic anhydride in the presence of perchloric acid. The enolization involves the methylene carbon and not the methine carbon. This was unambiguously proved by the NMR spectrum[16] (Fig. 3) which exhibits a triplet at 5·48 τ (J = 7 c/s) assignable to an olefinic proton of the system



8-Isotestosterone having been synthesized, the possibility of converting it into testosterone was explored. This could presumably be done by introducing a double bond in the 6,7 position of II, which under enolization conditions, might bring about the inversion of the asymmetric centre at C_8 to the more stable configuration of natural steroids. In recent years highly reactive quinones have been used for the introduction of a Δ^6 double bond in a Δ^4-3-keto steroid.[17] The interaction of II with chloranil, however, failed to yield any of the desired dienone. The reaction is known to proceed as the enol[17,18] followed by the loss of the axial hydrogen at C_7

[14] B. Berkoz, E. P. Chavez and C. Djerassi, *J. Chem. Soc.* 1323 (1962).
[15] M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*1312 (1962).
[16] We are grateful to Dr. Sukh Dev of the National Chemical Laboratory, Poona, India, for the NMR spectrum and its interpretation.
[17] E. J. Agnello and G. D. Laubach, *J. Amer. Chem. Soc.* **82**, 4293 (1960).
[18] H. J. Ringold and A. Turner, *Chem. & Ind.*, 211 (1962).

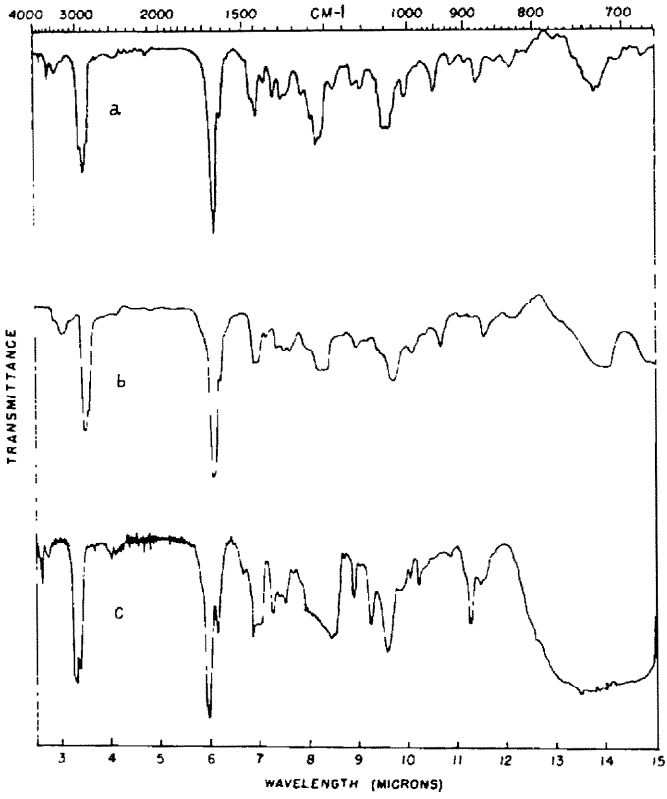


FIG. 2. IR spectra of (a) DL-8-isotestosterone prepared by us, (b) DL-8-isotestosterone furnished by Professor Djerassi, and (c) the anthracene analogue.

as the hydride ion[19] probably in a linear transition state between the substrate and the quinone.[20] Examination of a model of the enolate from 8-isotestosterone reveals that the approach of the bulky chloranil to the 7β axial hydrogen is sterically hindered, this hydrogen being shielded by the 13-methyl group within the concave face of the molecule.

EXPERIMENTAL[21]

5-Methyl-6-methoxytetralin

A mixture of 2-methoxy-1-naphthaldehyde (50 g), freshly prepared (T_1) Raney Ni catalyst (ca. 5 g), glacial acetic acid (30 ml) and ethanol (60 ml) was hydrogenated at 200 atm and 100° for 9 hr. After removal of the catalyst and the solvent, the residue was taken up in a minimum quantity of methanol to form a clear solution and chilled. The crystalline plates of 5-methyl-6-methoxytetralin, m.p. 46–48°, amounted to 42·2 g (89%).

Methyl-1-oxo-8-methyl-4,5-(3'-methyl-4'-methoxybenzo)-$\Delta^{3(9)}$-hydrindene-3-carboxylate

A flame-dried flask was charged with 1-keto-2-methyl-2-cyano-5-methyl-6-methoxy-tetralin (50 g). Under N_2 atm, a mixture of dimethyl succinate (200 ml) and potassium t-butoxide (from 50 g K and

[19] J. A. Campbell and J. C. Babcock, *J. Amer. Chem. Soc.* **81**, 4069 (1959).

[20] E. A. Braude, L. M. Jackman and R. P. Linstead, *J. Chem. Soc.* 3548, 3564 (1954).

[21] M.ps reported herein are uncorrected. UV spectra were determined in 95% ethanol using a Beckmann DU Model Spectrophotometer. IR spectra were taken with a Perkin–Elmer Infracord, Model 137. Pet. ether, b.p. 40–60°, only has been used. Microanalyses were carried out by Messrs. B. R. Seetharamia and D. P. Bose of this department.

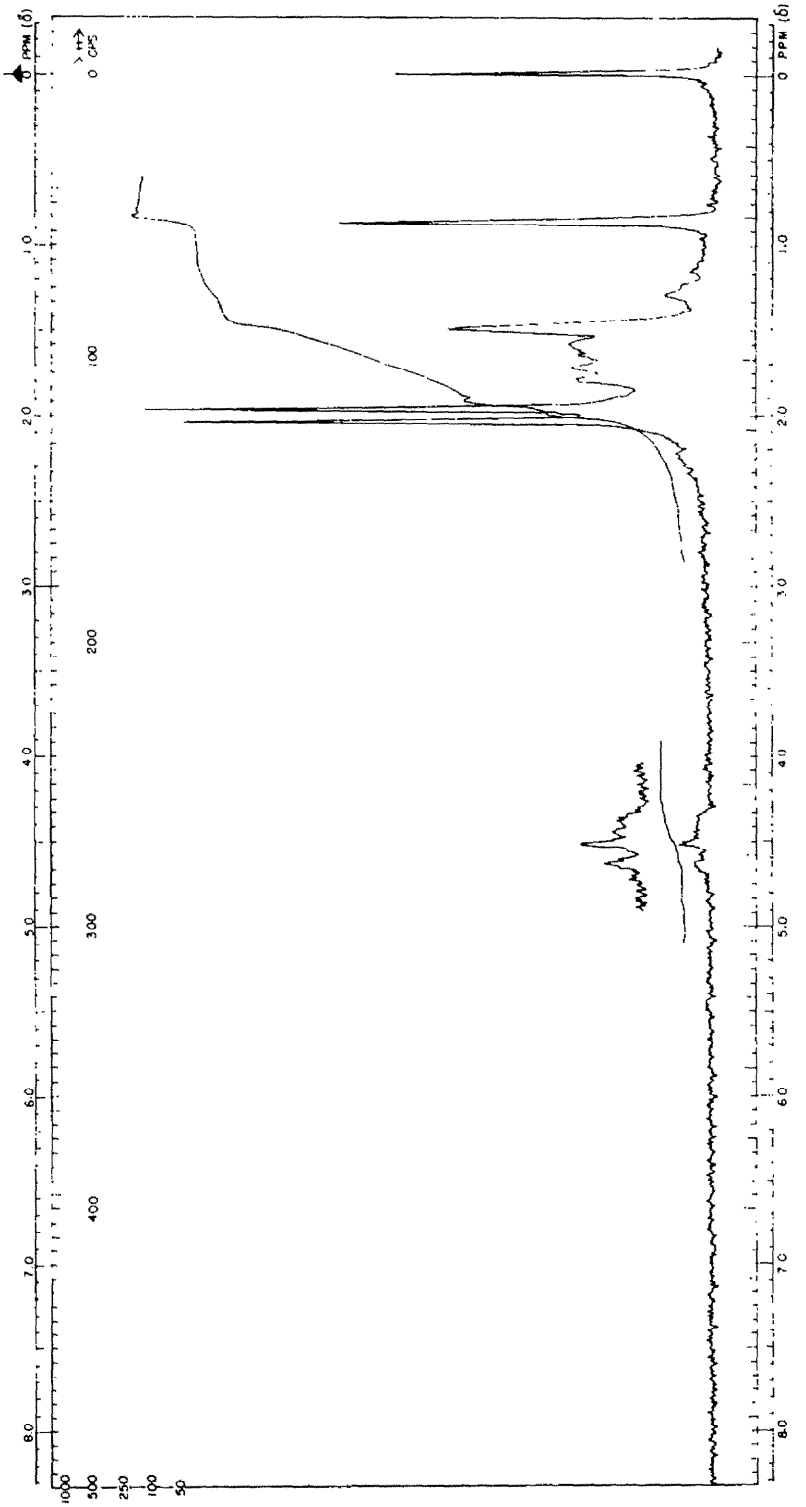
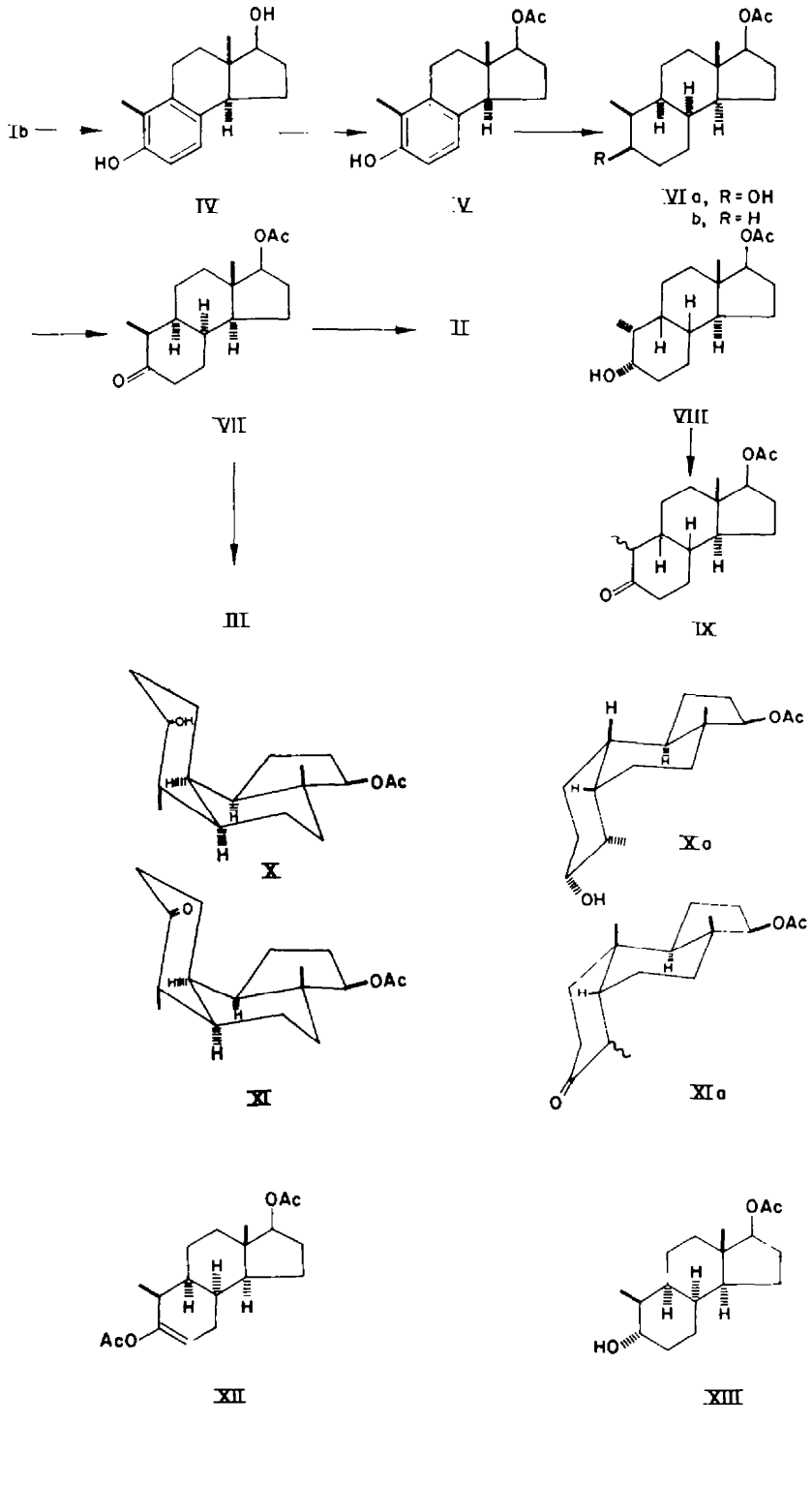


FIG. 3 NMR SPECTRUM OF XII


Ib
OH
HO
OAc
R
IV
V
VI a, R = OH
b, R = H
VII
II
VIII
III
IX
X
XI
X a
XI a
XII
XIII
AcO

1300 ml of t-butanol[22]) was added with stirring in about 2·5 hr. Stirring was continued for additional 3 hr and the reaction mixture left overnight. The thick yellow pasty mass was cooled and acidified with ice-cold conc. HCl. Most of the t-butanol was removed under suction at as low a temp as possible and the residual mass was diluted with water and extracted repeatedly with ether. The combined extract was washed successively with water, 5% KOH aq and water. After removal of the solvent, the last traces of dimethyl succinate were removed at 1 mm pressure. The product, m.p. 134–141° (53 g; 81%), could be used for the subsequent experiment.

trans-1*β*-*Hydroxy*-8-*methyl*-4,5-(3′-*methyl*-4′-*hydroxybenzo*)-*hydrindane* (IV)

(a) A suspension of Ib (5 g) in dry ether was added dropwise under N_2 atm to the Grignard reagent, prepared from Mg (5 g), CH_3I (35 g) and dry ether (30 ml). A total of 400 ml ether was used for transferring the compound. The complex formed remained as a clear solution. The ether was removed under suction and the residue heated under red. press. (2 mm) at 100° for ½ hr. The system was flushed with dry N_2 and the heating continued at 175° for ¾ hr, when brisk evolution of gas was observed. The content was cooled in an ice-bath and treated with pet. ether and ethyl acetate, the latter interacting with the excess Grignard reagent. The product was treated with cold dil. H_2SO_4 (75 ml) and then, after dilution with water, thoroughly extracted with ether. After washing the ether extract with water, the demethylated product was extracted by repeated washing with cold 5% NaOH aq. The combined alkaline solution was acidified with conc. HCl and the separated solid filtered, washed well with water and dried, m.p. 199° (vac), (3·72 g; 79%). One crystallization from ether-pet. ether afforded the pure sample, m.p. 202–204°. (Found: C, 77·62; H, 8·62. $C_{15}H_{20}O_2$ requires: C, 77·59; H, 8·62%).

(b) This method is based on the procedure of Sheehan *et al.*[23] A mixture of Ib (5 g) and anhydrous pyridine hydrochloride (100 g) was heated at 200° for 40 min under N_2 atm. The mixture was cooled and, after addition of dil. HCl (250 ml), was thoroughly extracted with ether. The combined extract was worked up as in the case of the foregoing experiment to give 3·55 g (75·3%) of the demethylated product (IV), m.p. 200–203° (vac).

trans-1*β*-*Acetoxy*-8-*methyl*-4,5-(3′-*methyl*-4′-*hydroxybenzo*)-*hydrindane* (V)

(a) A solution of 0·4 g phenolic alcohol (IV) in ethyl acetate (85 ml) containing *p*-toluenesulphonic acid (0·5 g) was refluxed on a steam-bath. After 3 hr, an additional 0·5 g *p*-toluenesulphonic acid was added and the refluxing continued for 2 hr more. After cooling, the orange solution was washed successively with water, $NaHCO_3$ aq and water and dried (Na_2SO_4). The solvent was removed under red. press. and the oily residue boiled with pet. ether. On cooling, 0·24 g (50%) pale yellow crystals of the phenol acetate (V), m.p. 140–143°, separated out. Short-path distillation of this product at 125° (5×10^{-4} mm) afforded a colourless material which on recrystallization from pet. ether furnished the pure sample, m.p. 146–147·5°. (Found: C, 74·04; H, 8·13. $C_{17}H_{22}O_3$ requires: C, 74·4; H, 8·08%). UV λ_{max} 280 mμ (ϵ 1400) IR ($CHCl_3$) peaks at 3676 cm^{-1} (O—H), 1740 cm^{-1} (ester C=O); 1269 cm^{-1} (acetate C—O).

(b) A mixture of IV (0·5 g), acetic anhydride (0·8 ml) and acetic acid (3·5 ml) was heated for 4 hr on a steam-bath. The reaction mixture was poured into water (200 ml) and thoroughly extracted with ether. The extract was worked up as before and the brown residue, obtained after removal of the solvent, was dissolved in ethanol (5 ml) and treated with K_2CO_3 (0·17 g dissolved in 3 ml H_2O) under reflux for ½ hr. The reaction mixture was cooled and acidified with dil. HCl. The precipitated solid was filtered, and washed well with water and dried. The crude material, m.p. 131–135°, weighed 0·57 g. Two crystallizations from pet. ether afforded 0·3 g (51%) of V, m.p. 141–143°.

(c) Solution of IV (2 g) in acetic acid (10 ml) and *p*-toluenesulphonic acid (0·2 g) were refluxed for 1 hr. The cooled reaction mixture was diluted with water and thoroughly extracted with ether. On working up in the usual way, 2·2 g of the crude product, m.p. 133–138°, was obtained. One crystallization from aqueous acetic acid followed by short-path distillation at 130° (4×10^{-3} mm) afforded 1·65 g (70%) white crystalline acetoxy phenol (V), m.p. 140–143°.

[22] t-Butanol was dried by distilling over aluminium t-butoxide.

[23] J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, *J. Amer. Chem. Soc.* **75**, 6231 (1953).

Catalytic hydrogenation of trans-1*β*-*acetoxy*-8-*methyl*-4,5-(3′-*methyl*-4′-*hydroxybenzo*)-*hydrindane* (V)

After numerous trial experiments, using Raney Ni, 5% Rh–Al and 5% Ru–C catalysts at press., temp and period ranging from 100–300 atm, 50–120° and 6–26 hr respectively, the following optimum conditions for the reduction were established.

A solution of 2 g of the phenol acetate (V) in ethanol (50 ml) was hydrogenated over 5% Ru–C catalyst (1 g) at 100° under 300 atm for 6 hr. After cooling the mixture was filtered and the catalyst was washed thoroughly with acetone. The filtrate and the washings were combined and the solvents removed under red. press. to leave an oily residue (2·1 g) exhibiting a weak absorption in the 250–280 mμ region. By chromatography on 50 g neutral alumina,[24] the oil was separated into the following fractions:

Fractions	Eluent	Wt eluted g	Spectral characteristics
A	Pet. ether (40–60°)	0·024	Transparent in the 250–280 mμ region
B	1:1 Benzene–pet. ether (40–60°)	1·400	Transparent in the 250–280 mμ region
C	Benzene	0·230	Transparent in the 250–280 mμ region
D	Ether	0·280	Absorbs in the 250–280 mμ region

Fraction A. This consisted of a highly crystalline material, m.p. 71–74°. Two recrystallizations from pet. ether furnished the pure hydrogenolysis product, 1*β*,2*α*-(3′-*acetoxycyclopentano*)-2,5-*dimethyl*-1*α*,2,3,4,4a*α*,5*α*,6,7,8,8a*α*-*decahydronaphthalene* (VIb), m.p. 75–76°. (Found: C, 77·57 H, 10·32. $C_{17}H_{28}O_2$ requires: C, 77·27; H, 10·61%). IR (CCl_4) peaks at 1721 cm^{-1} (acetate C=O); 1238 cm^{-1} (acetate C—O); O—H peak was absent.

Fraction B. This fraction, m.p. 92–95°, which was also highly crystalline, after one crystallization from pet. ether afforded the pure 1*β*,2*α*-(3′-acetoxycyclopentano)-2,5-dimethyl-6*β*-hydroxy-1*α*,2,3,-4,4a*α*,5*α*,6*α*,7,8,8a*α*-decahydronaphthalene (VIa), existing in two polymorphic modifications, m.p. 88° and 95°. (Found: C, 72·64; H, 10·1. $C_{17}H_{28}O_3$ requires: C, 72·85; H, 10·0%). IR (CCl_4) peaks at 3650 cm^{-1} (O—H); 1721 cm^{-1} (acetate C=O); 1239 cm^{-1} (acetate C—O).

Fractions C and D could not be crystallized. Oxidation experiment with the former has been reported in the sequel. UV spectra of the latter indicated that it contained considerable phenolic material, and this fraction was not further investigated.

1*β*,2*α*-(3′-*Acetoxycyclopentano*)-2,5-*dimethyl*-6-*keto*-1*α*,2,3,4,4a*α*,5*α*,6,7,8,8a*α*-*decahydronaphthalene* (VII)

A cooled and briskly stirred solution of 5 g VIa in 400 ml pure acetone (distilled over $KMnO_4$) was titrated against chromic acid reagent. A solid separated on dilution with water, which was filtered, washed thoroughly with water and dried. The crude product, m.p. 157–157·5°, weighed 4·72 g (94%). One crystallization from pet. ether afforded the pure VII, m.p. 159–160°. Occasionally a polymorph, m.p. 144–145°, was also obtained. (Found: C, 72·95; H, 9·29. $C_{17}H_{26}O_3$ requires: C, 73·35; H, 9·41%). IR (CCl_4) peaks at 1701 cm^{-1} (6-membered ring C=O); 1721 cm^{-1} (acetate C=O); 1235 cm^{-1} (acetate C—O).

1*β*,2*α*-(3′-*Acetoxycyclopentano*)-2,5-*dimethyl*-6-*keto*-1*α*,2,3,4,4a*β*,5,6,7,8,8a*β*-*decahydronaphthalene* (IX)

The gummy fraction C (0·23 g), obtained after chromatography of the crude hydrogenated product, was dissolved in pure acetone (10 ml) and oxidized with Jones' reagent as described in the foregoing experiment. The change in colour of the reagent provided a qualitative idea of the rate of oxidation and, in the present case, the rate was considerably slower than that observed in the previous experiment. The oxidation mixture was worked up as in the previous case to give 0·18 g of an orange semi-solid mass which was crystallized from pet. ether after treatment with norit. After collecting two crops of crystals of VII (0·08 g), evaporation of the mother liquors left a solid residue, m.p.

[24] C. Djerassi and W. Rittel, *J. Amer. Chem. Soc.* **79**, 3528 (1957).

90–130°, which on crystallization from a large volume of pet. ether, furnished two distinct crystalline modifications, long needles and rectangular slabs. These were easily separated by hand-picking and the needles, m.p. 144–149°, were identified with the keto acetate (VII). The rectangular slabs (0·025 g), m.p. 96–104°, after two recrystallizations from the same solvent afforded the pure IX, m.p. 104–105°. Later it was found that repeated fractional crystallization of the mixture also furnished this product. (Found: C, 72·96; H, 9·29. $C_{17}H_{26}O_3$ requires: C, 73·35; H, 9·41%). IR (CCl_4) peaks at 1695 cm^{-1}; 1718 cm^{-1}; 1235 cm^{-1}. The mixed m.p. of this material with VII was 95–101°.

Equilibration experiment with the keto acetate (VII)

A mixture of 0·15 g of the keto acetate (VII) dissolved in benzene (4 ml) and potassium t-butoxide solution, prepared from 0·045 g K and 1·5 ml t-butanol, was stirred for 7 hr at room temp. Glacial acetic acid (4 ml) was added and the volatile matter was removed under red. press. Ice-water was added to the residue and the mixture extracted with ethyl acetate. On complete removal of the solvent, the residue indicated the presence of hydroxyl group along with acetate in the IR spectrum, so that it was treated with acetic anhydride (3·2 ml) and dry pyridine (3 ml), and the mixture allowed to stand overnight. It was then poured into crushed ice and extracted with ether–benzene mixture. The extract was washed successively with water, cold HCl and water. The gummy residue, obtained after removal of the solvent, on crystallization from pet. ether afforded 0·075 g VII, m.p. 147–147·5°, as the first crop and a further quantity of 0·06 g of the impure product, m.p. 134–148°.

DL-8-*Isotestosterone* (II)

(a) To a suspension of 0·1 g VII in ethanol (2 ml) was added 0·4 ml "Triton B" (35% of benzyltrimethylammonium hydroxide in methanol). A solution of freshly distilled methyl vinyl ketone (0·08 g) in ethanol (4 ml) was added to the mixture under N_2 atm. After refluxing for 2 hr, the reaction mixture was cooled and acidified with 3N HCl (1 ml) and again heated on a steam-bath for 10 min. The cooled reaction mixture was poured into crushed ice and thoroughly extracted with ether. The extract was washed successively with dil. HCl, water, $NaHCO_3$ aq and water. After removal of the solvent, the residue (0·16 g) was chromatographed over 15 g neutral alumina, and the following fractions collected:

Fraction	Eluent	Wt eluted g	Characteristics
A	Benzene	0·015	Colourless oil
B	1:1 Benzene–ether	0·076	Pale yellow viscous oil
C	Acetone	0·050	Yellow resinous material

Fraction B was suspended in boiling hexane and then dissolved by dropwise addition of acetone. On standing overnight at 0°, 0·024 g of yellow crystalline mass, m.p. 162–165°, was deposited. One crystallization from acetone–hexane afforded 0·022 g (21·2%) 8-isotestosterone, m.p. 168–171°. Two more crystallizations from the same solvent furnished the product with the constant m.p. 172·5–173·5°. (Found: C, 78·72; H, 9·90. $C_{19}H_{28}O_2$ requires: C, 79·17; H, 9·72%). UV λ_{max} 242 mμ (ϵ 15,800); IR ($CHCl_3$) peaks at 3676 cm^{-1} (O—H); 1672 cm^{-1} (conjugated C=O); 1631 cm^{-1} (C=C).

(b) To a stirred cooled (ice) suspension of sodium methoxide, prepared from 0·5 g Na and 1·2 g methanol, in dry benzene (10 ml) under N_2 was added 2 g ethyl formate in 5 ml benzene. This was followed by the addition of 2 g VII in benzene (50 ml) during the course of 20 min. The reaction mixture was left overnight when a pale yellow solid separated out. It was treated with iced water and the aqueous layer was separated. The benzene layer was repeatedly extracted with cold 2% KOH aq, and the alkaline extract was combined with the aqueous layer and poured on to crushed ice containing 30 ml HCl. The milky solution was thoroughly extracted with ether and the extract washed with cold water and dried (Na_2SO_4). Removal of the solvent left behind 1·85 g of an oily residue which showed positive $FeCl_3$ test.

A solution of the aforementioned hydroxymethylene derivative and freshly distilled N-methylaniline (1·5 g) in benzene was slowly distilled until a test portion did not give any violet colour with alcoholic $FeCl_3$; this required distillation of 600 ml benzene in 16 hr. Removal of the benzene and last traces of N-methylaniline *in vacuo* afforded 2·42 g of a red gummy material.

To a stirred mixture of a solution of the above crude methylanilinomethylene derivative in ethanol (40 ml) and "Triton B" (12 ml) under N_2 was added a solution of 2·5 g methyl vinyl ketone in 10 ml ethanol. The mixture was refluxed for 2 hr on steam-bath, cooled, treated with 3N HCl (30 ml) and again refluxed for ½ hr. After removal of the volatile matter under suction, an ethereal solution of the residue was washed with water and the ether removed. The residue was then refluxed under N_2 with 20% KOH (100 ml) for 1 hr. After cooling the mixture was thoroughly extracted with ether–$CHCl_3$ mixture and the extract washed successively with water, dil. HCl, water, $NaHCO_3$ aq and water. Removal of the solvent furnished 2·96 g of a dark resinous material which was chromatographed over neutral alumina (100 g). Elution with 50% ether in benzene gave a thick oil (0·75 g) which showed absorption in the 240 mμ region. This was rechromatographed over neutral alumina (30 g). The crystalline material, m.p. 163–170°, eluted out with 25% ether in benzene amounted to 0·175 g, one recrystallization of which from acetone–hexane afforded the pure sample of II, m.p. 174°; the mixed m.p. with the sample prepared by direct condensation remained undepressed.

*1β,2α-(3′-Hydroxycyclopentano)-2,5-dimethyl-7-keto-*1α,2,3,4,4aα,5α,7,8,9,9aα,10,10aα-*dodecahydroanthracene* (III)

A stirred cooled (ice) mixture of a solution of the hydroxymethylene derivative (0·8 g), prepared as described before from sodium methoxide (0·157 g of Na) in dry benzene (3 ml), ethyl formate (1·2 ml) and 1 g VII in dry benzene (10 ml), in methanol (3 ml) and sodium methoxide, from 0·065 g Na and 3 ml methanol, was brought under N_2 and treated with a solution of freshly distilled methyl vinyl ketone (0·65 g) in methanol (3 ml). After standing overnight at room temp, ice-cold 2% NaOH aq (30 ml) was added to the reaction mixture and that was extracted with ether–benzene. The extract was successively washed with water, ice-cold 3N HCl and water. Removal of the solvent gave a gummy residue (0·59 g).

A mixture of a solution of the aforementioned adduct (0·92 g), collected in two experiments, methanol (80 ml) and KOH (2·75 g) dissolved in water (5·5 ml) was stirred for 2 hr at room temp under N_2. It was then poured into brine (220 ml) and thoroughly extracted with ether. The extract was repeatedly washed with brine and the solvent removed. The gummy residue (0·57 g) was chromatographed over neutral alumina (44 g). The gummy product obtained by elution with benzene–ether (1:1) could be induced to crystallize from acetone–hexane. Two more crystallizations from the same solvent mixture gave pure tetracyclic unsaturated keto alcohol (III), m.p. 195–196°. Admixture of this product with DL-8-isotestosterone (II), m.p. 172–173·5°, depressed the m.p. to 158°. (Found: C, 79·36; H, 9·81. $C_{19}H_{28}O_2$ requires: C, 79·17; H, 9·72%). UV λ_{max} 240–241 mμ (ε 14,830); IR ($CHCl_3$) peaks at 3650 cm^{-1} (O—H); 1672 cm^{-1} (conjugated C=O); 1623 cm^{-1} (C=C).

*1β,2α-(3′-Acetoxycyclopentano)-2,5-dimethyl-6-acetoxy-*1α,2,3,4,4aα,5α,8,8aα-*octahydronaphthalene* (XII)

To an ice-cold solution of 1 g of the keto acetate (VII) in a mixture of dry benzene (40 ml) and CCl_4 (16 ml) was added dropwise a cooled mixture of acetic anhydride (7 ml) and 60% perchloric acid (12 drops) with swirling during the course of 3 min. After standing the mixture at room temp for 4·5 hr, ice-cold water (30 ml) and CCl_4 (30 ml) were added to it. The aqueous layer was separated and extracted with CCl_4, and the extract was combined with the organic layer and washed successively with $NaHCO_3$ aq and cold water. Removal of the solvent gave a light brown solid (1·18 g), m.p. 103–109°. One crystallization from methanol furnished 1 g (87%) of nearly white crystals, m.p. 110°. By repeated crystallization m.p. could be raised to 110·5°. (Found C, 71·82; H, 9·00. $C_{19}H_{28}O_4$ requires: C, 71·24; H, 8·81%). IR peaks at 1757 cm^{-1} and 1748 cm^{-1} (acetate C=O); 1621 cm^{-1} (C=C); 1250 cm^{-1} (acetate C—O) NMR[25] (CCl_4) triplet at 5·48 T.

Studies in the conversion of 8-isotestosterone to testosterone

17-*Acetoxy-8-isotestosterone*. To a solution of 8-isotestosterone (0·05 g) in dry pyridine (1 ml) was added acetic anhydride (1 ml) and the mixture was allowed to stand overnight. The reaction mixture was poured into crushed ice and worked up in the usual way to afford a semi-solid, which was dissolved in benzene and filtered through a column of neutral alumina to give, after removal of

[5] Varian Associates A-60 Spectrometer with tetramethylsilane as the internal standard.

the solvent, a crystalline material (0·055 g), m.p. 134–136°. One crystallization from hexane furnished 0·046 g (80%) 8-isotestosterone acetate, m.p. 137–139°. Repeated crystallization raised the m.p. to 143–146°. (Found: C, 76·15; H, 8·82. $C_{21}H_{30}O_3$ requires: C, 76·36; H, 9·09%). UV λ_{max} (ϵ 14,470) IR ($CHCl_3$) peaks at 1718 cm^{-1} (acetate C=O); 1661 cm^{-1} (conjugated C=O); 1613 cm^{-1} (C=C); 1252 cm^{-1} (acetate C—O).

Dehydrogenation experiments with chloranil. (a) A solution of 8-isotestosterone acetate (0·05 g) in dry t-butanol (4 ml) was stirred and refluxed with powdered chloranil (0·2 g) for 4 hr. The reaction mixture was filtered and the residue was washed with small portions of t-butanol. The filtrate and washings were combined and residue obtained after removal of the t-butanol was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, repeatedly with 5% NaOH aq (till no more colour was extracted from the $CHCl_3$ layer) and water. The oily residue (0·1 g) left behind after removal of $CHCl_3$ was chromatographed over neutral alumina (10 g). None of the 4 fractions collected showed the presence of the expected dienone in the UV spectrum.

(b) A stirred mixture of a solution of 8-isotestosterone acetate (0·06 g) in dry t-butanol (4 ml), chloranil (0·2 g) and *p*-toluenesulphonic acid (0·01 g) was refluxed for 20 hr. The deep red solution was worked up as in the case of the foregoing experiment, and the dark product exhibited a shoulder at 285 mμ (ϵ 2,300). A careful chromatography of the material over 10 g alumina failed to furnish the desired dienone.