JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

(Registered in U. S. Patent Office) (Copyright, 1952, by the American Chemical Society)

VOLUME 74 SEPTEMBER 6, 1952 NUMBER 17

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Total Synthesis of Steroids[1]

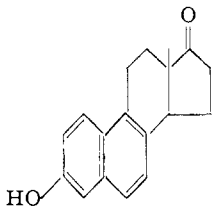
BY R. B. WOODWARD, FRANZ SONDHEIMER, DAVID TAUB, KARL HEUSLER AND W. M. MCLAMORE

RECEIVED APRIL 4, 1952

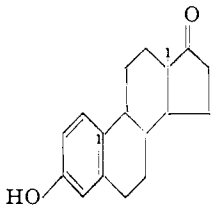
4-Methoxytoluquinone (VI) is transformed in twenty stages into *dl*-$\Delta^{9(11),16}$-bisdehydro-20-norprogesterone (LXIV) (*ca.* 1 g./100 g. VI). This substance, the first totally synthetic non-aromatic steroid, is converted to methyl *dl*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI), and resolved. The identity of the synthetic dextrorotatory ester with a substance of the same structure derived from natural sources is shown. In view of the large body of known interconversions within the steroid group, and of the presence in (LXVI) of reactive functions in opposite positions in rings A, C and D, the transformation of the ester into many other steroids may be brought about directly by substantially routine methods. Thus, the triply unsaturated ester is converted by full hydrogenation and oxidation to methyl 3-ketoetio allocholanate (LXX, R = Me) and thence to cholestanol (LXXVII, R = H). On the other hand, by partial hydrogenation, followed by reduction of the 3-keto group and acetylation, methyl 3α-acetoxy-$\Delta^{9(11)}$-etiocholenate (LXXX, R = Ac, R′ = Me) is obtained. From these intermediates, the paths to progesterone, desoxycorticosterone, testosterone, androsterone, cholesterol and cortisone have been described previously by other investigators.

The extensive and brilliant researches of Windaus and Wieland on the earliest known steroids, the members of the cholesterol and cholic acid groups, led to the proposal of the correct structures for those substances in 1932.[2] Interest in the total synthesis of steroids has been widespread since that time, and has received added impetus as the recognition of the great importance of steroids in medicine and in animal physiology has grown. The attack on the problem has been marked by certain signal successes. The first bastion fell with the synthesis of equilenin (I) by Bachmann, Cole and Wilds in 1939.[3] Almost a decade later, the more difficult problem presented by the synthesis of oestrone (II) was first surmounted by Anner and Miescher.[4] These advances were consolidated by the achievement of independent syntheses of both aromatic steroidal hormones by Johnson and his associates.[5]

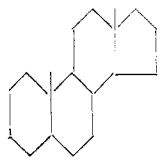
There remained the task of the synthesis of naturally occurring steroids, such as the sterols proper and the androgenic and progestational hormones, which contain the complete hydroaromatic tetracyclic nucleus (III), whose presence is characteristic of the vast majority of steroidal substances. A particularly challenging objective was provided by the emergence of the rare 11-oxygenated cortical steroids as powerful agents in the treatment of disease. In this communication we describe the achievement of each of these goals,[6] by methods of particular applicability to the cortical group.



I



II



III

(1) The investigations which form the subject of this paper were first described at a Centenary Lecture before the Chemical Society (London) at Burlington House on April 26, 1951, and in a series of preliminary communications [THIS JOURNAL, **73**, 2403, 3547, 3548, 4057 (1951)].

(2) Wieland and Dane, *Z. physiol. Chem.*, **210**, 268 (1932) [*cf.* Rosenheim and King, *Chemistry and Industry*, **51**, 954 (1932)]. An excellent general account of the final stages of the structural work is given by Heilbron, Simpson and Spring, *J. Chem. Soc.*, 626 (1933).

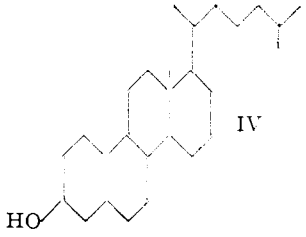
(3) Bachmann, Cole and Wilds, THIS JOURNAL, **61**, 974 (1939); **62**, 824 (1940).

(4) Anner and Miescher, *Experientia*, **4**, 25 (1948); *Helv. Chim. Acta*, **31**, 2173 (1948); Miescher, *Experientia*, **5**, 1 (1949).

(5) Johnson, Petersen and Gutsche, THIS JOURNAL, **67**, 2274 (1945); **69**, 2942 (1947); Johnson, Banerjee, Schneider and Gutsche, *ibid.*, **72**, 1426 (1950); Johnson and Christiansen, *ibid.*, **73**, 5511 (1951).

(6) For preliminary notice of an alternative, independent synthesis of the androgenic hormones, *cf.* Cardwell, Cornforth, Duff, Holtermann and Robinson, *Chemistry and Industry*, 389 (May 19, 1951). See also footnote 66.

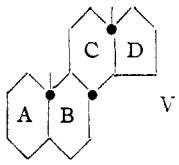
Every approach to the synthesis of steroids has been complicated by the presence in these substances of a number of asymmetric carbon atoms. Inevitably the resulting stereochemical problem has become ever more serious as the more remote objectives have been brought under attack. Thus, the presence in cholestanol (IV) of nine such centers makes possible the existence of five hundred and



IV

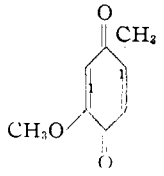
twelve stereoisomers of that structure. Some comfort might be taken in the fact that the steric course of interconversions *within the steroid group* often is subject to control, or in any event is well understood. None the less the stereochemical aspect of the synthetic problem is still formidable, and in these circumstances we considered it advisable, in so far as it was possible, to introduce successive asymmetric carbon atoms in a stereochemically controlled fashion.

Fortunately the arrangement about the asymmetric centers in the nucleus (V)[7] of the synthetic objective was known completely.[8] We focused

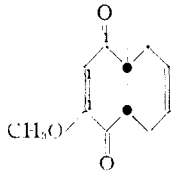


V

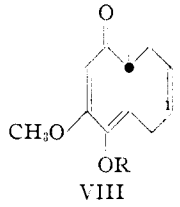
our attention first upon the *trans* fused bicyclic system represented by rings C and D. Since the stable configuration of hydrindanes of this type is known to be *cis*,[9] we chose to establish the desired *trans* fused array by equilibration in a decalin system, in which the *trans* isomer might be expected to be relatively highly favored.[10] 4-Methoxy-2,5-toluquinone (VI)[11] combined smoothly with butadiene in benzene solution to give the *cis* adduct (VII),[12] m.p. 94.5–95.5°. Since in this adduct a carbonyl group is adjacent to a bridgehead position which bears a hydrogen atom, conversion to an enolate (VIII, R = ⊖), and thence to a stereoisomeric *trans* product (IX) seemed possible.



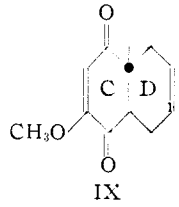
VI



VII



VIII



IX

In point of fact, when the *cis* adduct, in benzene solution, was stirred for long periods with sodium hydride, the desired enolate was formed, with evolution of a mole of hydrogen. Acidification of the salt gave a mixture of products from which in 40% yield a new substance, m.p. 130–131°, was isolable, which proved to be the *trans* isomer (IX), and large amounts of *cis* material were recovered. While it cannot be assumed with certainty that experiments of this sort lead to products in the equilibrium ratio, our experience suggests strongly that in this system, the *trans* isomer does not predominate at equilibrium to the extent which obtains with simple saturated decalins, *e.g.*, the pair *cis*-α-decalone/*trans*-α-decalone.[13] Further progress toward the development of a practical method for effecting the isomerization (VII) → (IX) was facilitated by the discovery that the *cis* adduct was sufficiently acidic to permit its dissolution in aqueous basic media. Acidification of such solutions again ordinarily gave isomer mixtures similar in composition to those described above.[14] Occasionally, however, in such experiments complete isomerization to the *trans* isomer was observed. This variability of result was traced to the adventitious initial crystallization of small amounts of the *trans* isomer in the more successful inversions. Thus, *when seeds of the latter were added deliberately before acidification, complete isomerization took place in all experiments.* These circumstances provided a simple, practical solution to our first stereochemical problem, *viz.*, the establishment of the *trans* relationship which obtains for rings C and D of the steroids.

We turned our attention next to modification of

(7) The convention used in this and subsequent formulas is that of Linstead [THIS JOURNAL, **56**, 510 (1937)], the dot indicating that the attached hydrogen atom or methyl group lies above the plane of the paper. In the sequel an open circle is used to indicate that the configuration at the atom so marked is not known, or not specified.

(8) *Cf.* Turner, Chapter X in "Natural Products Related to Phenanthrene," by Fieser and Fieser (Reinhold Publishing Corp., New York, N. Y., 1949). See also Heusner, *Angew. Chem.*, **63**, 59 (1951).

(9) Hückel, Sachs, Yantschulewitsch and Nerdel, *Ann.*, **518**, 155 (1935); Linstead, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, **32**, 310 (1935); Dimroth and Jonsson, *Ber.*, **74**, 520 (1941).

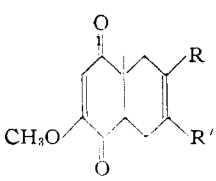
(10) Hückel and Brinkmann, *Ann.*, **441**, 21 (1925); Hückel, Danneel, Gross and Naab, *ibid.*, **502**, 99 (1933).

(11) This quinone was prepared in quantity from toluquinone through 2,4,5-triacetoxytoluene, 2,4,5-trihydroxytoluene and 4-hydroxytoluquinone [*cf.* Thiele and Winter, *ibid.*, **311**, 341 (1900)].

(12) This adduct had been prepared previously [Orchin and Butz, *J. Org. Chem.*, **8**, 509 (1943)], and assigned the *trans* configuration on the basis of a dubious theoretical argument.

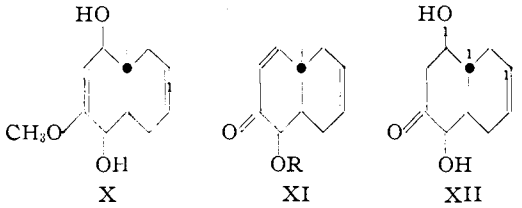
(13) For references, see footnote 10. It is recognized that the energy difference between *cis*- and *trans*-decalins is small in the completely saturated cases, and that the introduction of double bonds and trigonal atoms into the ring system may well effect significant changes in the equilibrium position.

(14) On the other hand, when solutions in base were *poured into excess acid*, a third isomeric substance, the unstable crystalline enol (VIII: R = H), m. p. 140–150° (characterized as the tosylate (VIII: R = $SO_2C_7H_7$-*p*), m.p. 121–122°) was precipitated. Parallel phenomena were observed and more extensively studied in the cases of the related adducts (i: R = H, R′ = Me) and (i: R = Me, R′ = H). These studies, which were carried out in collaboration with Dr. Frank L. Weisenborn and Mr. Theodore W. Brilet, will be described in detail in a separate communication.



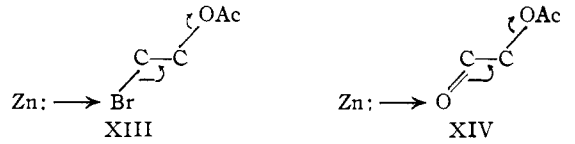
i

the functions attached to ring C of the *trans* adduct (IX) in such wise as to set the stage for the construction of ring B of the projected steroid nucleus in the proper sense. Reduction of the *trans* adduct by lithium aluminum hydride gave the glycol



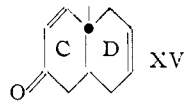
X XI XII

(X), m.p. 139–140°.[15] The latter was smoothly converted by mineral acids in aqueous media directly to the *trans* bicyclic ketol (XI, R = H), m.p. 71.5–73°. It is clear that this transformation involves the initial hydrolysis of the acid-labile enol ether function of (X), with formation of the β-hydroxyketone (XII); like many such substances, this compound suffers spontaneous elimination of water under the reaction conditions. We now desired to remove the remaining hydroxyl function from the ketol (XI, R = H). The most frequently used method for effecting such a change, involving the use of metal–acid combinations,[16] was inapplicable in our case, since it was, for reasons which will be clear in the sequel, imperative to retain the conjugated ethylenic linkage. Nor were we able to convert the ketol to the tosylate, or to the corresponding α-bromoketone, either of which might have been useful for the purpose at hand. In these circumstances, a new method was developed, based upon the well-known fact that metallic zinc alone converts 1,2-dibromides readily to olefins. Since this reaction is applicable also to 1,2-bromoacetoxy compounds (XIII, *arrows*), it seemed likely that the changes symbolized in (XIV, *arrows*) could be realized in the case of α-ketol acetates. In the event, the ketol acetate (XI, R = Ac), m.p. 55°, prepared from (XI, R = H) in the normal manner, was readily attacked by



XIII XIV

metallic zinc in boiling xylene, or preferably in hot acetic anhydride,[17] with the formation of the desired *trans* bicyclic ketone (XV), m.p. 34.5–

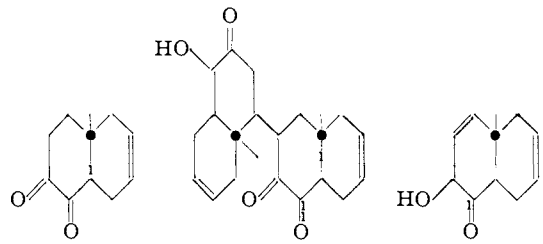


XV

35.5°.[18] The over-all yield in the sequence (IX) → (XV) was *ca.* 45%. At this point, our bicyclic objective had been reached.

We now digress to describe ancillary experiments in the bicyclic series which are not without intrinsic interest.

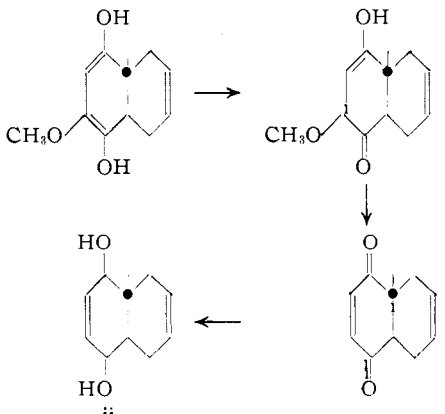
a.—Treatment of the ketol acetate (XI, R = Ac) with cold methanolic potash resulted in changes more deep-seated than simple hydrolysis, and gave a *substance*, m.p. 96.5–98°, which is clearly one of the enols corresponding to the α-diketone (XVI), as well as a small amount of an isomeric (and probably dimeric) compound, m.p. 237–238° (dec.), which may possess the structure (XVII). It is evident that in the formation of (XVI), the initially formed ketol is equilibrated with the isomeric ketol (XVIII), the double bond of which shifts into conjugation with the carbonyl group.



XVI XVII XVIII

b.—The *trans* adduct (IX) was hydrogenated smoothly over palladium–calcium carbonate to the dihydro adduct (XIX), m.p. 84.5–85°. On the other hand, hydrogenation over reduced platinum oxide led to a mixture of the tetrahydro adduct (XX), m.p. 147–148°,[19] and a hexahydro compound, m.p. 122–122.5°, presumably of the structure (XXI). When larger amounts of platinum were used, the fully hydrogenated octahydro adduct (XXII), m.p. 145–146°, was produced. The struc-

(15) A *by-product*, $C_{11}H_{16}O_2$, m.p. 167–168°, was isolated which contained (a) hydroxyl group(s), no carbonyl groups, and no $-C=C-OR$ system (infrared spectrum). This substance is very probably the glycol (ii), formed by initial 1,4-reduction, ketonization, elimination and reduction

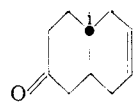


ii

(16) *Cf.*, *inter al.*, Prelog, Frenkiel, Kobelt and Barman, *Helv. Chim. Acta*, **30**, 1741 (1947); Stoll, *ibid.*, **30**, 1837 (1947). See also footnote 18.

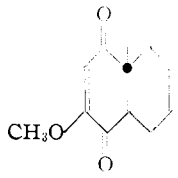
(17) In this case, the zinc enolate initially formed was converted to the corresponding enol acetate, which could be isolated, but was normally hydrolyzed during the isolation procedure.

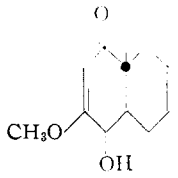
(18) That the conjugated ethylenic bond in these bicyclic substances is perhaps even more sensitive to reduction by metal-acid combinations than might have been anticipated, is demonstrated by the fact that when the ketol (XI, R = H) itself was subjected to the zinc-acetic anhydride procedure, the unsaturated ketone (XV) formed was seriously contaminated by the reduced ketone (iii).

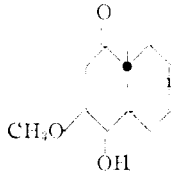


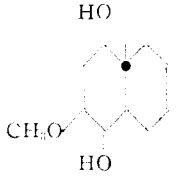
iii

(19) It is worthy of note that of the two carbonyl groups in the adduct (IX), one is much less susceptible to reduction than the other; this behavior is undoubtedly associated with the interaction of the unreactive group with the methoxyl function through the double bond (*cf.* $-C-\overset{O}{\overset{\|}{C}}-C=C-OCH_3$).


XIX

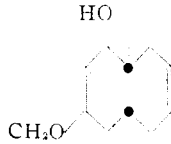

XX

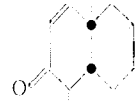

XXI

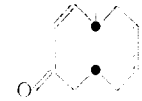

XXII

tures of these compounds were deduced from infrared data; thus, the dihydro adduct (XIX) possesses a typical adduct spectrum in the double bond region (5.82, 5.98, 6.18 μ), while the spectrum of the tetrahydro compound (XX) in that region is similar (6.02, 6.13 μ) to that of the ethyl ether of dihydroresorcinol.[20]

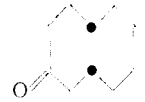
c.—The *cis* adduct (VII) was converted, by the methods outlined above for the *trans* isomer, through the glycol (XXIII), m.p. 119–121°, and the ketol (XXIV) to the *cis* doubly unsaturated ketone (XXV). The *semicarbazone*, m.p. 182.5–

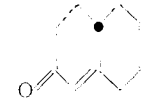

XXIII


XXIV

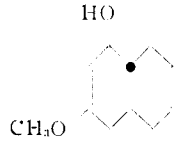

XXV

184.5°, of the latter was hydrogenated to the *semicarbazone*, m.p. 201–202°, of the saturated *cis* ketone (XXVI), identical with a sample prepared from the crystalline ketone (XXVI), m.p. 46–48°, which was found to be the major product of the hydrogenation of the known octalone (XXVII).[21]

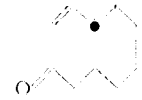

XXVI


XXVII

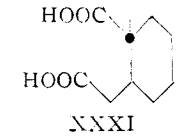
d.—The dihydro *trans* adduct (XIX) was transformed *via* the glycol (XXVIII), m.p. 129–130°, and ketol (XXIX), m.p. 86.5°, to the ketone (XXX).[22] When the latter was oxidized with

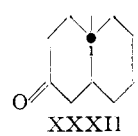

XXVIII


XXIX


XXX

potassium permanganate, the known *trans* dicarboxylic acid (XXXI)[23] was obtained. The unsaturated ketone (XXX) was hydrogenated to the saturated *trans*-2-keto-10-methyldecalin (XXXII), which was also obtained by reduction of the doubly unsaturated ketone (XV), and as a minor product in the above mentioned hydrogenation of the octalone (XXVII). These facts are of some relevance to the main synthetic series, in that


XXXI


XXXII

they provide an unequivocal direct demonstration of the structure and stereochemistry of the key bicyclic ketone (XV).

The application of our methods thus has permitted the preparation, *with complete stereochemical*

TABLE I

	Semicarbazone m.p., °C.	2,4-Dinitrophenylhydrazone, m.p., °C.
cis	201–202[a]	175–176[b]
trans	202–203	178–179[c]
cis	203–204[d]	.....
trans	186	161–162
cis	.....	.....
trans	203–204	170.5–172
	206.5–208[e]	173–174[e]
cis	182.5–184	149–151
trans	178–179	159–160
	.....	127–129[f]
	.....	148–150[g]

[a] Burnop and Linstead, *J. Chem. Soc.*, 720 (1940), give m.p. 200–201°. [b] du Feu, McQuillin and Robinson, *ibid.*, 53 (1937), found m.p. 152–152.5°; Woodward, THIS JOURNAL, **62**, 1208 (1940), found m.p. 151–152°, and Woodward and T. Singh, *ibid.*, **72**, 494 (1950), 125.5–127°. This derivative is remarkable in its capacity to exhibit sharp melting points over a wide range of values (*cf.* Experimental part). The above value was attained only after repeated crystallization. [c] In soft glass tubes; occasionally, *in Pyrex*, m.p. 160–161.5°. [d] Burnop and Linstead, ref. *a*. [e] du Feu, McQuillin and Robinson, ref. *b*, give 203.5–204° for the semicarbazone and 169° for the dinitrophenylhydrazone. [f] Woodward and T. Singh, ref. *b*. [g] Sandoval, Miramontes, Rosenkranz and Djerassi, THIS JOURNAL, **73**, 990 (1951).

(20) Unpublished observations made in this Laboratory by Mr. R. J. Wineman [Dissertation, Harvard, 1949].

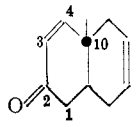
(21) The saturated ketone had been prepared in the same way by du Feu, McQuillin and Robinson, [*J. Chem. Soc.*, 53 (1937)], who did not report the formation of any *trans* ketone (*vide infra*).

(22) This direct zinc reduction of the ketol was carried out before the superior method involving prior acetylation was discovered in the main synthetic series. *Cf.* footnote 18.

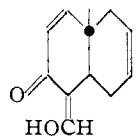
(23) (a) Linstead, *et al.*, *J. Chem. Soc.*, 470, 476, 478 (1936), (*cf. ibid.*, 1140 (1937), for reassignment of configuration); (b) Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943). We are much indebted to the late Professor W. E. Bachmann, and to Professor W. S. Johnson, for kindly providing us with authentic specimens of the *trans* diacid.

control, of the *cis*- and *trans*-2-keto-10-methyldecalins, and a number of unsaturated congeners. These substances, taken with a number of previously known compounds, now form a relatively complete class, the characterization of whose members is summarized in Table I.

We return now to the main synthetic path. In the bicyclic ketone (XXXIII ≡ XV), the presence of the $\Delta^{3,4}$-double bond, with the attached quaternary center (C.10), makes possible the unambiguous introduction of substituents at C.1.[24] Condensation of (XXXIII) with ethyl formate readily led to the hydroxymethylene ketone (XXXIV). The

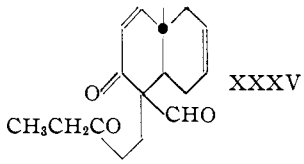


XXXIII



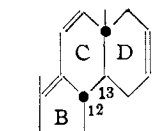
XXXIV

smooth addition of the latter to ethyl vinyl ketone, with formation of the adduct (XXXV), m.p. 98.5–99°, was brought about by catalytic amounts of potassium *t*-butoxide in *t*-butanol. When the adduct was treated with potassium hydroxide in

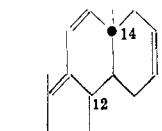


XXXV

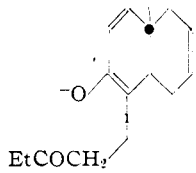
aqueous dioxane, ring closure took place, the formyl group was eliminated, and a single tricyclic ketone (XXXVI), m.p. 72–73°, was produced substantially quantitatively.[25] The over-all yield in the sequence (XXXIII) → (XXXVI) was *ca.* 55–60%.[26] No step in this sequence has involved the possibility of inversion at C.13, and the presence in (XXXVI) of the *trans* fused C/D system is assured. On the other hand, with the fusion of ring B, a new asymmetric center has been introduced, at C.12. *A priori*, this center might be oriented as in (XXXVI), as desired, or alternatively as in (XXXVII). However, it may be noted that whether cyclization precedes deformylation, or *vice versa*, the product will possess the *more stable* of the two possible configurations, since in either case addition of a proton to an enolate (XXXVIII *or* XXXIX) in which C.12 is not asymmetric is involved. Now, (XXXVI) may be expected to be more stable than the 12-epimer (XXXVII) for these reasons: (i) considerable steric repulsion may be expected between the *polar*[27] alkyl groups



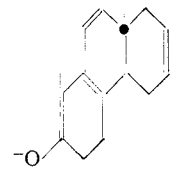
XXXVI



XXXVII



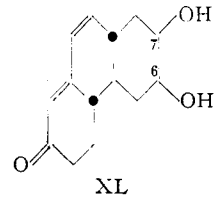
XXXVIII



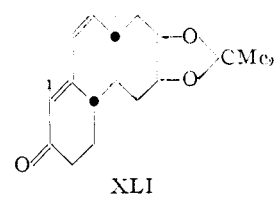
XXXIX

attached at C.12 and C.14 in (XXXVII), while in (XXXVI), only a weak hydrogen–methyl interaction is operative; (ii) coplanarity of the doubly unsaturated carbonyl system and the attached atoms is necessary for maximal resonance stabilization, and readily possible only in the relatively flat matrix of (XXXVI). Consequently, we were confident that our ketone possessed the *anti trans* structure (XXXVI) and that entrance into the tricyclic stage of our synthesis had been achieved with complete stereochemical control.

In order to carry out the reactions contemplated for the construction of ring A, protection of the isolated double bond of the tricyclic ketone (XXXVI) was necessary. This object was realized and at the same time the first step was taken in the necessary modification of ring D, when the ketone was hydroxylated by osmium tetroxide. The two possible *cis* glycols of the structure (XL),[28] m.p. 157.5–158.5°, and m.p. 181–182°, were formed; the former predominated, and was used for the

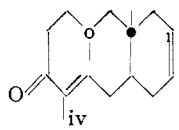


XL



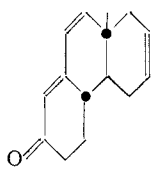
XLI

(24) Without the double bond, in hydronaphthalene ketones of this type condensation reactions might *a priori* occur either at the 1- or the 3-position. Further, there is abundant evidence that in fact, *when the ring fusion is trans*, as above, attack at the 3-position is preferred [*cf.*, the case of *trans*-β-decalone (du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937)); it may be noted further that condensation, substitution and cleavage reactions of cholestanone invariably involve initial attack at C.2 (≡C.3, above formula)]. For these reasons we believe that a tricyclic ketone, m.p. 81–82°, obtained from the 3,4-dihydro derivative of (XXXIII) (*cf.* footnote 18) by the reactions described in the sequel possesses the hydroanthracene structure (iv).



iv

(25) A similar series of reactions involving *methyl* vinyl ketone led through a Michael adduct, m.p. 99-104°, to the corresponding norketone (v), m.p. 76-80° (λ_{max} 281 mμ, ε 29,400).



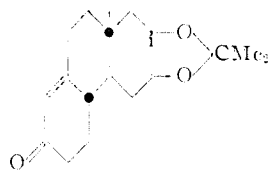
v

(26) The reactions used in the construction of ring B represent an extension (to an unsaturated ketone) and modification of the elegant Wilds version [Shunk and Wilds, THIS JOURNAL, **71**, 3946 (1949)] of the Robinson Mannich base methiodide method for the preparation of polycyclic *cyclo*hexenones from saturated ketones or β-keto esters. The use of Mannich base methiodides in condensations involving (XXXIII) and (XXXIV) was uniformly unsatisfactory. For example, when the Shunk-Wilds procedure was followed exactly, the tricyclic ketone was obtained from (XXXIV) in only 10-15% yield. The substitution of the vinyl ketone for the corresponding methiodide, and the use of the system potassium *t*-butoxide-*t*-butanol were crucial in the development of a satisfactory method, which was found only after extensive experimentation.

(27) Barton, *Experientia*, **6**, 316 (1950); Barton and Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

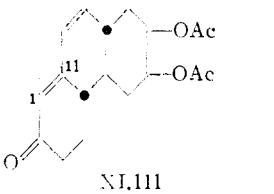
(28) The configurations at C.6 and C.7 of the glycols are not known and are ignored in (XL) and subsequent formulas. It is likely that in the major product the hydroxyl groups are below the plane of the ring system.

experiments described in the sequel.[29] Reaction of (XL) with acetone in the presence of anhydrous copper sulfate[30] gave the acetonide (XLI), m.p. 98–99° (labile) and 116–118.5° (stable). In dry benzene solution the latter absorbed only one mole of hydrogen in the presence of palladium–strontium carbonate, and was converted in excellent yield to the desired dihydro derivative (XLII), m.p. 157.5–158.5°.



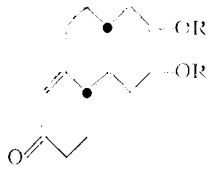
XLII

The smooth procedure for the partial saturation of the doubly unsaturated carbonyl system of (XLI) was discovered in the course of extensive experiments, no longer germane to the main synthetic scheme, with the glycol (XL), and the corresponding diacetate (XLIII), m.p. 184.5–185.5°. The hydrogenation of either compound

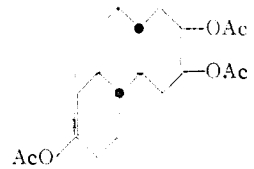


XLIII

in alcohol or ethyl acetate did not cease with the absorption of one mole of hydrogen, but when the reduction was arbitrarily stopped at that point, mixtures were obtained whose ultraviolet spectra indicated the presence of 55–65% of the dihydro derivative (XLIV, R = H or Ac), and from which, after treatment under vigorous acetylating conditions, the enol triacetate (XLV), m.p. 146–147.5°,



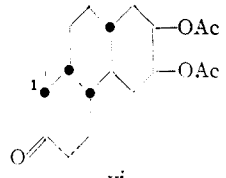
XLIV



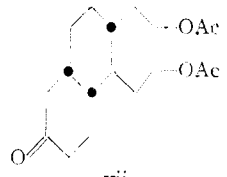
XLV

could be isolated in 50–60% over-all yield. The presence of a distributed diene system in (XLV) was deduced from the ultraviolet spectrum (λ_{max} 234 mμ, ε 16,600). On the other hand, the desired isopropylidene compound (XLII) could not be obtained from such mixtures in more than *ca.* 30% yield. When the hydrogenation of (XLIII) in polar solvents over supported palladium was permitted to proceed to completion, two moles of gas were smoothly absorbed and a complicated mixture of stereoisomeric saturated keto-diacetates was obtained, from which three individuals, A (m.p. 182–184°), B (m.p. 134.5–135.5° (labile) and m.p. 145–146° (stable)) and C (m.p. 150–151°) were isolated.[31] The isolation, directly from hydrogenation mixtures, of *three* stereoisomeric ketones indicates strongly that the saturation of the $\Delta^{1(11)}$-bond does not proceed by simple *cis* addition of hydrogen to the ethylenic function.[32] The very fact that the reduction of the *tetra-substituted* double bond occurs with such facility further implicates the adjacent carbonyl function. It is possible that 1,4 (or 1,6) reduction to an enol is involved, or that it is an enol which is reduced; in either case polar (O–H) bonds would be involved, and we felt that such processes might be suppressed through the use of a non-polar solvent.[33] In the event, hydrogenation of the doubly unsaturated diacetate (XLIII) or of the isopropylidene compound (XLI) in benzene over palladium stopped completely after the absorption of one mole of gas, and excellent yields of the semi-reduced ketones were obtained.

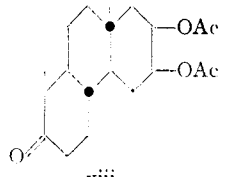
Our attention was next directed to the construction of ring A. In the ketone (XLVI ≡



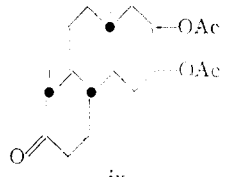
vi



vii

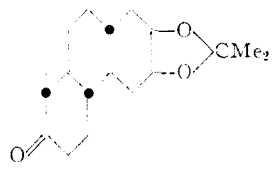


viii

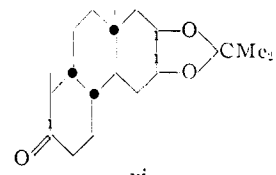


ix

the remaining expressions, which may be assigned to the compounds A, B and C, the B/C *trans* structures (viii) and (ix) are related through a common enol, and should therefore be interconvertible. In fact, it was found that isomer A was transformed, by treatment with base and reacetylation, into isomer C, whereas B was recovered unchanged from such experiments. It follows that isomer B possesses the B/C *cis* structure (vii), and that the unstable isomer A is (viii), in which the methyl group at C.1 is polar (*cf.* footnote 27), while (ix), with an equatorial methyl group, represents C. Support for these assignments is available in the observation that isomer C, as would be expected of an almost completely planar structure such as (ix), was more strongly adsorbed on alumina than was B. In view of the relationships described above, it is not surprising that isomers A and C, after hydrolysis gave the same acetonide (x), m.p. 104°, while B gave an isomer (xi), m.p. 111.5–112.5°.



x



xi

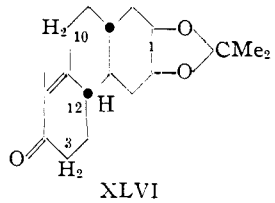
(29) Since at a subsequent stage asymmetry at C.6 and C.7 is destroyed, there is no reason why the higher melting glycol should not also be utilizable in the reaction sequence which follows. *Cf.* also footnote 45.

(30) *Cf.* Salomon and Reichstein, *Helv. Chim. Acta*, **30**, 1929 (1947).

(31) Since two new asymmetric centers were introduced in the saturation of the $\Delta^{1(11)}$-bond of (XLIII), four isomers might have been expected, but in repeated reductions no evidence of the presence of a fourth substance in the hydrogenation mixtures could be found. Inspection of models reveals that of the four possible structures, one (vii) represents a molecule in which steric repulsions are so extreme that the existence of a compound of that structure may be doubted, particularly in view of the juxtaposition of C.1 to a carbonyl function. Of

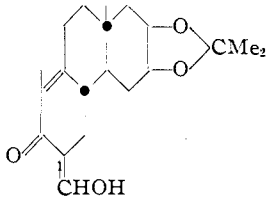
(32) *Cf.* Linstead, *et al.*, THIS JOURNAL, **64**, 1985 (1942).

(33) It is noteworthy that Weygand [*Ber.*, **76**, 498 (1943)] found that when relatively simple unsaturated ketones were hydrogenated in benzene solution, bimolecular product formation and reduction of the carbonyl function were suppressed.

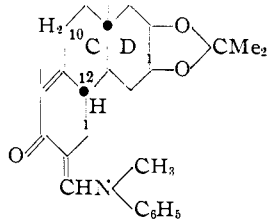


XLVI

XLII), five hydrogen atoms, distributed over three sites (C.3, C.10, and C.12), are activated by the carbonyl function. It was anticipated that in any *rate controlled* base condensation reaction, attack would occur mainly at the directly attached center C.3. In fact, condensation of (XLVI) with ethyl formate led to the hydroxymethylene ketone (XLVII), m.p. 128–130°, whose constitution was apparent from the close similarity of the ultraviolet spectrum of the substance to that of the analogous bicyclic derivative (XXXIV). By condensation with methylaniline in methanol solution, (XLVII) was converted to the methylanilinomethylene ketone (XLVIII), m.p. 222–224°; these smooth changes sufficed to block undesired condensation reactions at C.3, through the interpolation of a pro-

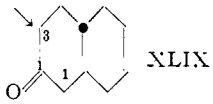


XLVII



XLVIII

tecting group which could be removed easily at a later stage.[34,35] In (XLVIII), three activated hydrogen atoms remained. Of these, it seemed likely that one of those at C.10 would be removed preferentially by basic reagents, for two reasons. (i) Access of a basic reagent to within bonding distance of the atom to be removed is more difficult in the case of the relatively highly hindered C.12 hydrogen atom. (ii) In *trans*-β-decalone systems (XLIX), the preferential removal of a proton from C.3 has been firmly established.[24] It will be noted

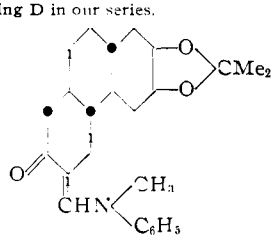


XLIX

that position 10 in the C/D *trans* decalin system of (XLVIII) is analogous to position 3 of the models

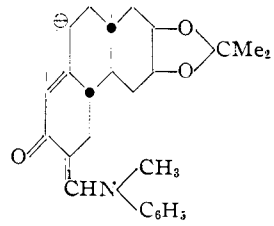
(34) The use of the methylanilinomethylene grouping as a blocking system was introduced by Birch and Robinson [*J. Chem. Soc.*, 501 (1944); *cf.* also Birch, Jaeger and Robinson, *ibid.*, 582 (1945)]. These authors removed the grouping by treatment first with acid and then with base. We found that the removal could be effected by base alone. This fact was of importance in view of the desirability of maintaining intact the ketal function attached to ring D in our series.

(35) The saturated acetonide (x, footnote 31) was similarly converted through a hydroxymethylene derivative, m.p. 126-129°, to the corresponding methylanilinomethylene compound (xii), m.p. 159.5-161°.

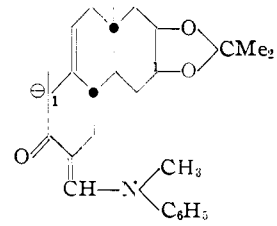


xii

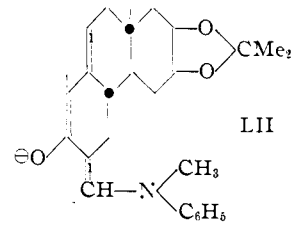
containing the comparable system (XLIX). It may further be mentioned that presumptive evidence for preferred attack at C.10 in a closely related case was available in the formation of the enol triacetate (XLV) from (XLIV, R = H *or* Ac). In the anion formed from (XLVIII) by removal of a proton from C.10, electrons are available at three sites (*cf.* (L) ↔ (LI) ↔ (LII)) for formation of a new bond by combination with a positive center in a suitable molecule. Excellent evidence was available[36] that reaction at the de-



L



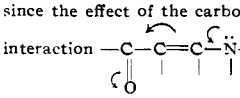
LI

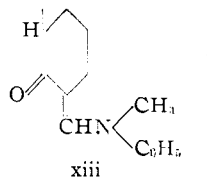


LII

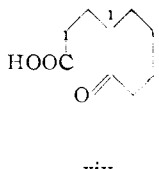
sired position, C.1 (*cf.* (LI)), would predominate in our case. In the event, when the methylanilinomethylene ketone (XLVIII) was condensed with acrylonitrile in *t*-butanol–benzene–water[37] solution in the presence of Triton B, cyanoethylation took place exclusively at C.1. Thus, the crude reaction product (LIII) was converted by vigorous base

(36) Bruson and Riener, THIS JOURNAL, **65**, 18 (1943); *cf.* also Birch, *J. Chem. Soc.*, 1551 (1950).

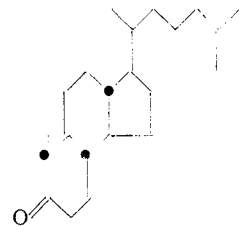
(37) The hydrogen atoms at C.10 are relatively weakly activated, since the effect of the carbonyl group, already weakened through the interaction  , must operate through the $\Delta^{1(11)}$-double bond. Consequently, strongly basic conditions are required for the generation of the corresponding anion. On the other hand, acrylonitrile is often readily polymerized by strongly basic reagents. Thus acrylonitrile in dry *t*-butanol is very rapidly converted to a yellow insoluble polymer after addition of Triton B. In our system, polymerization was suppressed by the addition to the reaction medium of small quantities of water. These conditions were developed through study of the model compound (xiii), m.p. 51-52.5°, which was converted through the corresponding cyanoethylated derivative into the keto-acid (xiv), m.p. 49-50° [Frank and Pierle, THIS JOURNAL, **73**, 724 (1951)], in over 80% yield. After completion of our work, Pinder and Robinson [*Nature*, **167**, 484 (1951)] reported a similar reaction sequence starting from the saturated Inhoffen ketone (xv), derived from natural sources.



xiii

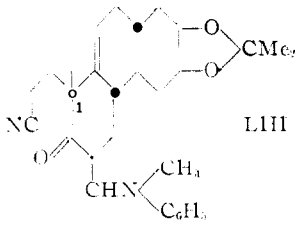


xiv



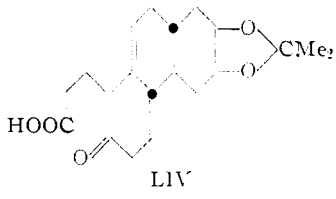
xv

We have not as yet been able to define conditions under which addition of the very readily polymerizable methyl vinyl ketone to either (XLVIII) or (xiii) could be effected.

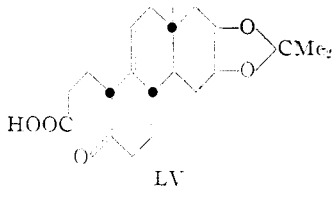


LIII

hydrolysis to a mixture of keto-acids, whose infrared spectrum demonstrated conclusively the absence of any α,β-unsaturated ketonic material. However, while substitution occurred at the desired position, the new asymmetric center at C.1 was introduced in a way in which little stereospecificity could be expected, nor was observed. From the acidic reaction product, one pure substance, m.p. 171–173° (stable) *or* m.p. 148–150° (labile), arbitrarily designated the α isomer, was easily separable. This acid has been assigned the structure (LIV), for reasons which will be clear from the sequel, while the companion β acid,[38] which remained in the mother liquors, has been shown to possess the structure (LV). At this stage, only

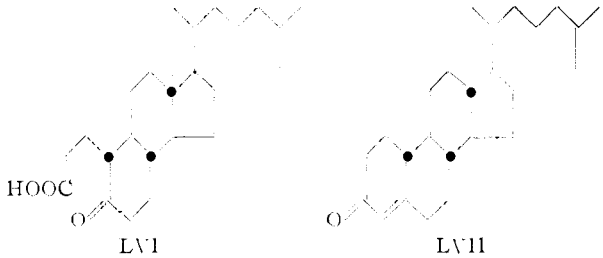


LIV



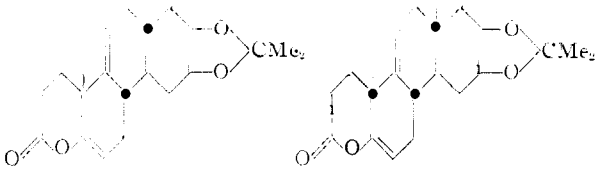
LV

one carbon atom of a potential ring A was lacking; the remaining problem was similar to that surmounted by Turner[39] and Fujimoto[40] in converting the keto-acid (LVI) derived from natural



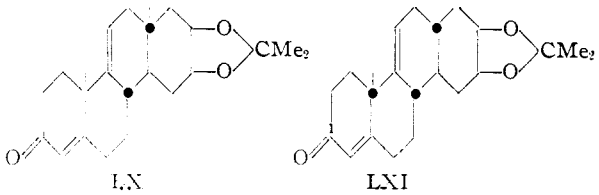
LVI LVII

cholesterol, into cholestenone (LVII). In these methods the first step consisted in conversion of the keto-acid to the corresponding enol lactone. In our case, the α acid was transformed by boiling acetic anhydride containing a trace of sodium acetate into the α enol lactone (LVIII), m.p. 177–178°,[41] while under similar conditions, the crude β acid gave the isomeric β enol lactone



LVIII LIX

(LIX), m.p. 223–225°. These isomeric lactones differed remarkably in their behavior toward the Grignard reagent. When the α isomer (LVIII) was treated with slightly more than a mole of methylmagnesium bromide, a reaction mixture was produced from which, by base-catalyzed cyclization, the tetracyclic ketone (LX), m.p. 168–169°, of the α series was obtained only in *ca.* 10% yield. At the same time much material was formed which appeared to result from the combination of more than one mole of the organometallic reagent with (LVIII), and considerable quantities of the α keto-acid could be recovered. Variation of reaction conditions over a wide range led to no sensible improvement in result.[42] On the



LX LXI

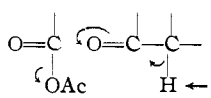
other hand, when the β enol lactone was treated with methylmagnesium halide, followed by base, the β tetracyclic ketone (LXI), m.p. 200–202°, was produced smoothly in good yield. Indeed, *the phenomena observed in this case paralleled closely those noted by Fujimoto in the cholesterol series,*[40]

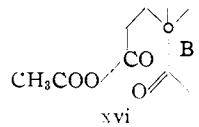
(38) The β acid was not obtained crystalline in this investigation; indeed, no attempt to bring about the crystallization of the acid was made, since it was felt that the presence of seeds of the latter might interfere with the very facile separation of the α isomer. Subsequently Drs. William S. Knowles and Emil White in this Laboratory have obtained the β acid (LV) in the crystalline state (m.p. 144-145°).

(39) Turner, THIS JOURNAL, **72**, 579 (1950).

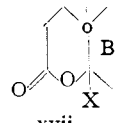
(40) Fujimoto, *ibid.*, **73**, 1856 (1951). We are much indebted to our former collaborator Dr. George Fujimoto (Utah) for disclosing the details of his method to us considerably in advance of publication.

(41) It is worthy of note that in pure acetic anhydride, enol lactone formation occurred only very slowly; the product from such reactions was largely the mixed anhydride (xvi), and not the lactol acetate (xvii, X = OAc) which might have been expected [*cf.* the formation of the chloro lactone (xvii, X = Cl) from the keto-acid (LVI) (Turner, footnote 39)]. It is clear that sodium acetate catalyzes the transformation (xvi) → (LVIII) through the process



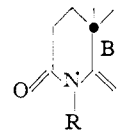


xvi

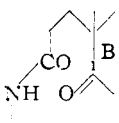


xvii

(42) An alternative method, which was applied with success in the cholesterol series, was likewise unsatisfactory in detail in the α synthetic series. Thus the keto-acid (LVI) was transformed in excellent yield by hot benzylamine to the cyclic benzylamide (xviii, R = $CH_2C_6H_5$), m.p. 124-127°. When the lactam was treated with (excess) methylmagnesium iodide, followed by base, cholestenone (LVII) was produced in *ca.* 50% yield. On the other hand, the α acid (LIV) in the benzylamine reaction gave a mixture of the corresponding lactam, m.p. 145-146.5°, and the open chain keto-amide (xix), m.p. 172-175°. These substances were not interconvertible, and the Grignard reagent–base treatment of the lactam gave the α tetracyclic ketone (LX) in very low yield.



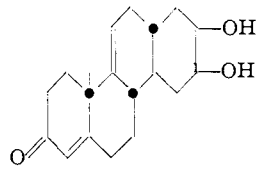
xviii



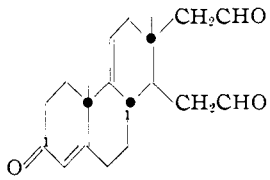
xix

and it was this fact which first suggested strongly that our β synthetic series corresponded in configuration to the natural steroids.[43] Consequently further attention was devoted exclusively to the β series, in which there was good reason to believe that the complete stereochemical problem posed by the steroid nucleus had been solved.

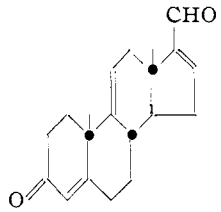
We turned next to the contraction of ring D of the synthetic D-homosteroid. When the tetracyclic ketone (LXI) was treated with periodic acid in aqueous dioxane, and the resulting product was heated directly in benzene solution in the presence of a catalytic amount of piperidine acetate, *dl*-$\Delta^{9(11),16}$-bisdehydro-20-norprogesterone (LXIV),[44] m.p. 178–178.5°, was produced in 65% yield. Although this transformation is best carried out directly in practice, we have characterized the separate steps involved. Thus, dilute mineral acids hydrolyzed the acetonide (LXI) rapidly to the corresponding glycol (LXII), m.p. 248–253° (dec.). This substance was cleaved by periodic acid to the dialdehyde (LXIII), m.p. 129–132°, and this in



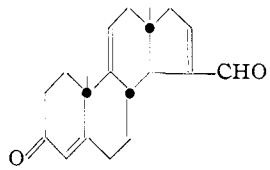
LXII



LXIII



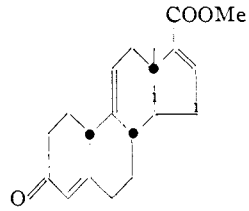
LXIV



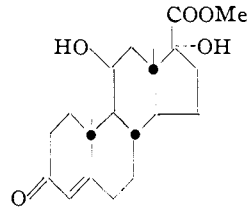
LXV

turn was cyclized to the unsaturated aldehyde (LXIV) by the method described above. It is of considerable interest that very little of the isomeric aldehyde (LXV) was produced by this procedure.[45] On the other hand, in earlier, less satisfactory experiments, in which cyclization was brought about by heating the dialdehyde (LXIII) in aqueous dioxane, the desired aldehyde (LXIV) was accompanied by lesser amounts of the isomer (LXV), m.p. 154.5–156°. It is not unreasonable to suppose that the predominance of (LXIV) is attributable to the relatively uncrowded environment of the upper activated methylene group in (LXIII) as compared with the lower. This relationship, which is apparent from inspection of models, permits the more ready access of catalyst to the upper center, with consequent more facile initiation of the changes which lead to (LXIV).

We now know that at this stage, our primary synthetic objective had been reached, and the first total synthesis of a non-aromatic steroid was complete. But the task of establishing identity of a synthetic product with a natural steroid remained. The first step in this direction was taken when the aldehyde (LXIV) was oxidized by sodium dichromate in acetic acid to the corresponding acid, m.p. 226–229° (dec.), which was converted by diazomethane to methyl *dl*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI), m.p. 160–162°. We next prepared the dextrorotatory isomer, m.p. 188–190° ($[\alpha]^{22}D$ + 180 ± 5°), of the same structure



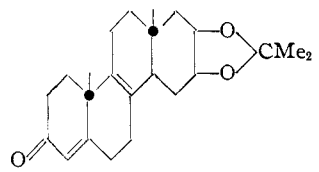
LXVI



LXVII

from the known methyl 3-keto-11β,17α-dihydroxy-Δ^4-etiocholenate (LXVII)[46] by dehydration with phosphorus oxychloride in hot pyridine. *The very characteristic infrared spectra (Fig. 1) of the natural and totally synthetic esters were identical in every respect.* Further, X-ray powder photographs of the

(43) Unequivocal proof of this identification of the β series is forthcoming in the sequel. The formulas assigned above to the members of the α series followed first by exclusion. Latterly, the possibility that the α compounds possess $\Delta^{8,9}$-unsaturation [as in (xx)] has been rigorously excluded through careful infrared studies by Dr. Emil White, who found that the spectrum of the methyl ester of the α acid, like that of the pure β ester, possesses a band at 3.38 μ, characteristic of H—C=C, and a weak vibrational band at 6.0μ, which is not found for tetrasubstituted double bonds. This conclusion has been confirmed through the kindness of Dr. H. B. Henbest (Manchester) whose far ultraviolet studies indicated that both acids possess trisubstituted double bonds.



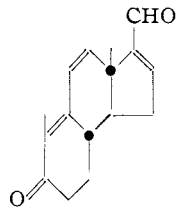
XX

It is worthy of note that model considerations clearly permit the conclusion that the more reactive of the enol-lactones (LVIII) and (LIX) will he (LVIII). Consequently, it is possible on the basis of our synthetic work to deduce independently the accepted configuration of the steroid nucleus at C.10, as well as at C.8, C.13 and C.14.

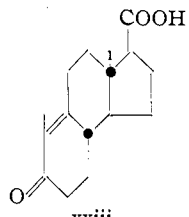
(44) For clarity this structure, rather than the alternative (LXV), is assigned to this product at this point in the text, although of course during our investigation we could not be certain of the correctness of this expression until a later stage.

(45) We should like to express our appreciation to Dr. Richard B. Turner of this Laboratory for his development of this cyclization procedure. Dr. Turner based his experiments upon studies carried out in this Laboratory by Dr. Ajay K. Bose, who had used a similar method for the contraction of ring D of the isomeric tricyclic *cis*-glycol (XL), m.p. 181-182° (*cf.* footnotes 28 and 29). These studies led to the unsaturated aldehyde (xxii), m.p. 132–133°, and a series of related substances, among them the reduced keto-acid (xxiii), m.p. 229.5-231°.

These experiments will be reported in a separate communication in due course.



xxii



xxiii

(46) Prepared from Kendall's compound F as described by von Euw and Reichstein (*Helv. Chim. Acta*, **25**, 1019 (1942)). We are much indebted to Dr. Max Tishler and his associates of Merck and Company, Inc. (Rahway) for their kindness in supplying us with compound F acetate.

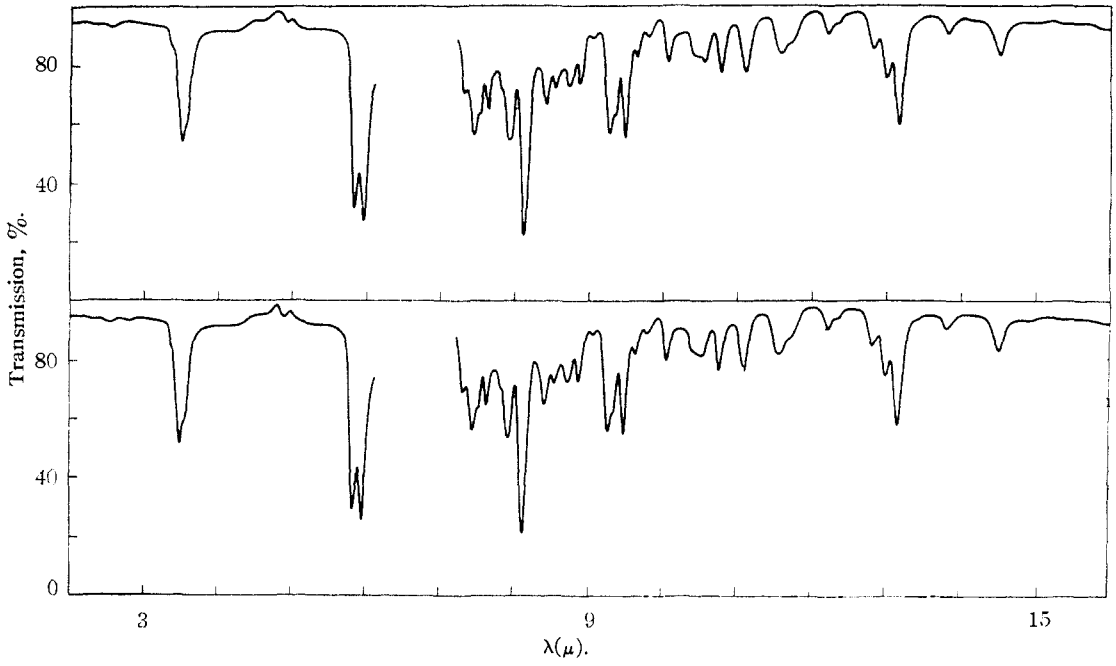
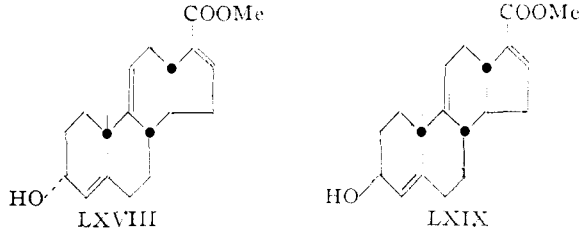


Fig. 1.—Infrared spectra of methyl 3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate in carbon bisulfide: above, synthetic *dl*-ester; below, natural *d*-ester.

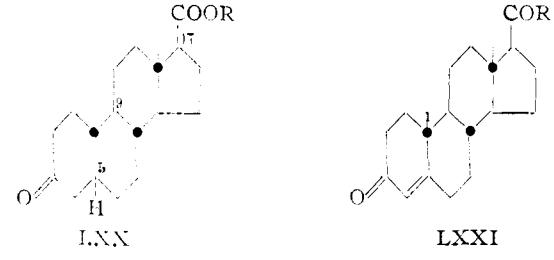
two esters gave identical diffraction patterns.[47] Finally, the synthetic racemic ester was resolved, in the following manner. Reduction of the ester with sodium borohydride in ethanol gave a mixture of racemic 3α-hydroxy (LXVIII) and 3β-hydroxy (LXIX) esters.[48] From this mixture, the dextro-



LXVIII LXIX

rotatory form of the β alcohol (LXIX) was precipitated preferentially by digitonin. Consequently, repeated digitonin precipitation gave material, heavily enriched in *d*-3β-hydroxy ester, from which on Oppenauer oxidation and crystallization, pure synthetic methyl *d*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI), m.p. 188–191° ($[\alpha]_D$ + 182 ± 7°), was isolated. The melting point of either ester was not depressed on admixture with the other.

There remained the task of completing the total synthesis of the more important naturally occurring members of the steroid group. This objective was reached through transformation of our synthetic steroids into well-known key intermediates, from which the paths to the natural substances had been laid down in the course of the phenomenal development of steroid chemistry during the past two decades. Thus, hydrogenation of the dextrorotatory keto-ester (LXVI) over reduced platinum oxide in acetic acid, followed by oxidation of the resulting saturated product with chromic acid in acetic acid, gave a mixture[49] from which methyl 3-ketoetioallocholanate (LXX, R = Me), m.p. 177–180°, identical with an authentic sample, was



LXX LXXI

isolated. This key ester had previously been converted[50] to the Δ^4-unsaturated ketone (LXXI, R = OMe), which we hydrolyzed to the known parent acid (LXXI, R = OH), m.p. 250–254°. The latter had been converted to the acid chloride (LXXI, R = Cl),[51] and thence on the one hand, by reaction with cadmium methyl, to *progesterone* (LXXI, R = CH_3),[52] and on the other, through the diazoketone (LXXI, R = CHN_2) to *desoxycorticosterone* (LXXI, R = CH_2OH).[51]

The degradation of the acid (LXX, R = H), m.p. 257–261°, which we obtained by hydrolysis of the ester (LXX, R = Me), to the simpler substances of the androstane series had also been described previously. Hydrogenation in acetic acid followed by acetylation and esterification

(47) We wish to thank Professor C. Frondel of the Department of Mineralogy (Harvard) for this determination.

(48) *Cf.* McKennis and Gaffney, *J. Biol. Chem.*, **175**, 217 (1948), and Plattner, Heusser and Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949), for similar reductions of cholestenone.

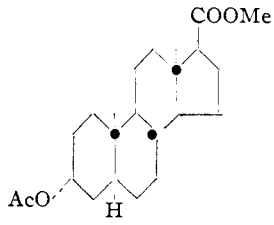
(49) In this hydrogenation three new asymmetric centers (C.5, C.9 and C.17) are introduced. It is known that the hydrogenation of $\Delta^{9(11)}$ and Δ^{16}-double bonds proceeds in a stereospecific manner, to give the natural steroid configurations; on the other hand, saturation of the Δ^4-linkage often gives a mixture of C.5 epimers.

(50) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

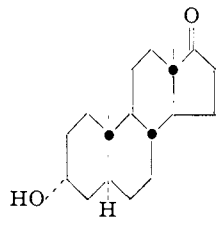
(51) Wilds and Shunk, *ibid.*, **70**, 2427 (1948).

(52) Riegel and Prout, *J. Org. Chem.*, **13**, 933 (1948).

had given[53] methyl 3α-acetoxyetioallocholanate (LXXII), which was transformed by the Barbier–Wieland degradation to *androsterone* (LXXIII).[54]

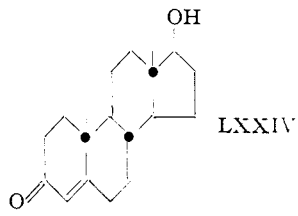


LXXII



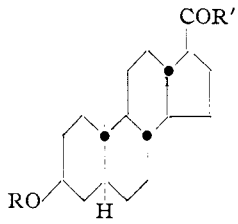
LXXIII

The paths from this hormone to *testosterone* (LXXIV) *via* androstanedione-3,17 and Δ^4-androstenedione-3,17 were well-known.[55]

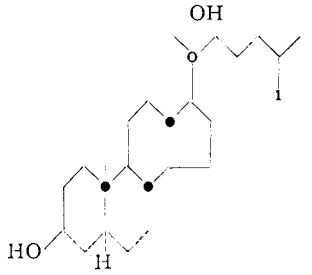


LXXIV

We turn now to the remaining stages in the total synthesis of cholesterol. Reduction of the saturated keto-ester (LXX, R = Me) with sodium borohydride gave mainly methyl 3β-hydroxyetioallocholanate (LXXV, R = H, R′ = OMe), m.p. 168–170°, which was hydrolyzed to the corresponding hydroxy-acid (LXXV, R = H, R′ = OH), m.p. 249–251°, and transformed to the acetyl derivative (LXXV, R = Ac, R′ = OH), m.p. 246–250°. The latter was converted by thionyl chloride to the acid chloride (LXXV, R = Ac, R′ = Cl), m.p. 134–136°, which with methylcadmium yielded crude 3β-acetoxyallopregnanone-20 (LXXV, R = Ac, R′ = CH_3), m.p. 139–144°. This ketone was treated with excess isohexylmagnesium bromide, and the product, a mixture containing the C.20 epimeric cholestane-3β,20-diols (LXXVI), was heated first with acetic acid, and then with acetic acid–acetic anhydride, to effect dehydration at C.20 and acetylation at C.3.[56] Direct hydrogenation of the resulting reaction-



LXXV



LXXVI

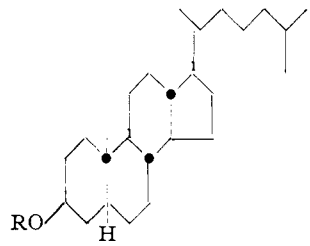
(53) Plattner and Fürst, *Helv. Chim. Acta*, **26**, 2266 (1943).

(54) Dalmer, v. Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935).

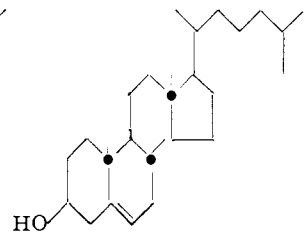
(55) *Inter al.*, Butenandt and Tscherning, *Z. physiol. Chem.*, **229**, 185 (1934); Djerassi and Scholz, *J. Org. Chem.*, **13**, 697 (1948); Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950); Miescher and Fischer, *Helv. Chim. Acta*, **22**, 158 (1939).

(56) *Cf.* Butenandt and Cobler, *Z. physiol. Chem.*, **234**, 218 (1935); Butenandt and Müller, *Ber.*, **71**, 191 (1938); Koechlin and Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

mixture over reduced platinum oxide gave a saturated product, from which cholestanol acetate (LXXVII, R = Ac), m.p. 109–110°, identical with



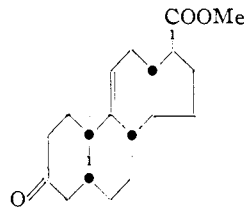
LXXVII



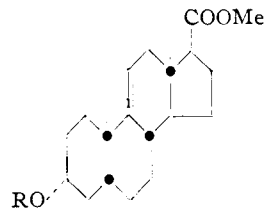
LXXVIII

material from natural sources, was readily isolated. Further, hydrolysis of the synthetic acetate furnished *cholestanol* (LXXVII, R = H, ≡ IV), m.p. 142–142.5°, whose identity with natural material was also established. The route from cholestanol, *via* cholestanone[57] and Δ^4-cholestenone,[58] to *cholesterol* (LXXVIII)[59] has already been described.

A prime objective of our synthetic work was the establishment of routes to the important cortical hormones containing oxygen in ring C. This object was rendered the easier of achievement through the presence of $\Delta^{9(11)}$-unsaturation in our original synthetic steroids. When the dextrorotatory triply unsaturated ester (LXVI) was *partially* reduced, by hydrogen over palladium–strontium carbonate in neutral media, a mixture of methyl 3-keto-$\Delta^{9(11)}$-etiocholenate (LXXIX) and the corresponding allo isomer was obtained. This mixture was then reduced with sodium borohydride in ethanol, and the resulting methyl 3α-hydroxy-$\Delta^{9(11)}$-etiocholenate (LXXX, R = H) and 3β-hydroxy-$\Delta^{9(11)}$-etioallocholenate were readily separated through precipitation of the latter by digitonin.



LXXIX



LXXX

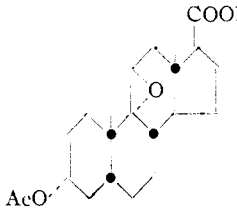
Acetylation of the α isomer gave methyl 3α-acetoxy-$\Delta^{9(11)}$-etiocholenate (LXXX, R = Ac), double m.p. 126–128° *and* 134–136°, identical with an authentic sample. At this point our synthetic work intersects the lines laid down in the extensive prior investigations by many groups on the partial synthesis, from natural sources, of cortisone (XCI) and other cortical steroids. Thus, (LXXX, R = Ac) had been transformed into the oxide (LXXXI), and thence by hydrolysis and chromic acid oxidation into methyl 3β-hydroxy-3α,9α-oxido-11-keto-

(57) *Inter al.*, Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 139.

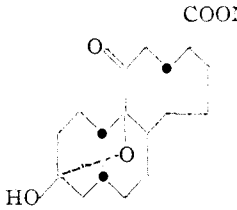
(58) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935); Ruzicka, Plattner and Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938).

(59) Reich and Lardon, *ibid.*, **29**, 671 (1946); Dauben and Eastham, THIS JOURNAL, **72**, 2305 (1950); **73**, 3260, 4463 (1951); Birch, *J. Chem. Soc.*, 2325 (1950); Schwenk, Gut and Belisle, *Arch. Biochem. Biophys.*, **31**, 456 (1951); Belleau and Gallagher, THIS JOURNAL, **73**, 4458 (1951).

etiocholanate (LXXXII).[60] The latter was converted[60] by hydrogen bromide to the bromoketone

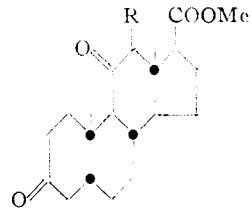


LXXXI

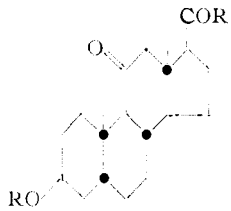


LXXXII

(LXXXIII, R = Br) and reduced[61] to methyl 3,11-diketoetiocholanate (LXXXIII, R = H). Methyl 3α-acetoxy-11-ketoetiocholanate (LXXXIV, R = Ac, R′ = OMe) had been obtained from (LXXXIII, R = H) by catalytic hydrogenation[62] and acetyla-

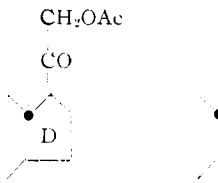


LXXXIII



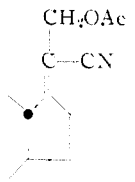
LXXXIV

tion, and transformed[63] to (LXXXIV, R = H, R′ = CH_2OAc) by the diazoketone method. The latter had been converted, by the cyanohydrin synthesis [(LXXXV) through (LXXXIX)], with oxidation at C.3 at an intermediate stage, to

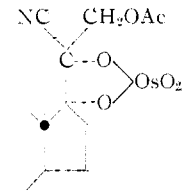


LXXXV

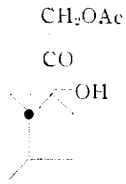
LXXXVI



LXXXVII

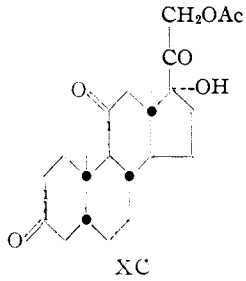


LXXXVIII

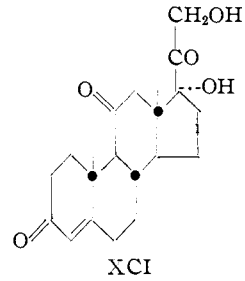


LXXXIX

(XC).[64] Introduction of the Δ^4-double bond,[65] and hydrolysis at C.21 complete the total synthesis of cortisone (XCI).[66]



XC



XCI

Experimental

Melting points, unless otherwise stated, were determined in soft-glass capillary tubes, and are corrected. Those marked "(Kof.)" were taken on a Kofler micro hot-stage. Boiling points are uncorrected. The term *ligroin* refers to the fraction b.p. 60–90°. All solvents unless otherwise specified are of reagent grade. Ultraviolet spectra were measured in ethanol solution with a Beckman quartz spectrophotometer, model DU. Microanalyses were carried out by Dr. S. M. Nagy and his associates of the microanalytical laboratory, M.I.T.

Infrared measurements were used for control purposes throughout this investigation, and spectra of all pure substances prepared were determined. However, in the sequel, spectra are recorded ordinarily only for the substances in the main line of the synthesis. In each case, the abscissa is plotted in *wave lengths* (2 to 12 μ), and the ordinate in *percentage transmission* (0 to 100%). For other substances, pertinent features of the spectra are described textually where desirable. The measurements were made with a Baird double beam infrared recording spectrophotometer, model B, in chloroform solution, unless otherwise stated.

4-Hydroxy-2,5-toluquinone.—The method used for converting toluquinone to 4-hydroxy-2,5-toluquinone was based on that described by Thiele and Winter.[11]

Toluquinone (250 g.) dissolved in acetic anhydride (370 cc.) was added slowly to a solution of concentrated sulfuric acid (20.3 cc.) in acetic anhydride (370 cc.) with stirring; the temperature was kept at 50–55° by occasional ice-cooling. The solution was allowed to stand overnight at room temperature and poured into cold water (*ca.* 3 l.), and the mixture was stirred until the precipitated oil solidified. The solid was filtered off, washed well with water, and crystallized from ethanol (charcoal). The 2,4,5-triacetoxytoluene weighed 233 g. (43%) and had m.p. 110–113°.

The triacetate (163 g.), concentrated sulfuric acid (7.3 cc.) and methanol (220 cc.) were refluxed for 45 minutes. Most of the solvent was removed under reduced pressure and the residual crude 2,4,5-trihydroxytoluene, dissolved in water (550 cc.), was added to a rapidly stirred solution of ferric chloride hexahydrate (440 g.) in water (*ca.* 120 cc.) at room temperature. The reaction mixture was cooled in ice for a short time, and the yellow quinone was filtered off. The solid was suspended in saturated salt solution, again collected by filtration, and finally washed with a small volume of ice water. After being pressed as dry as possible, the 4-hydroxytoluquinone was pressed on clay plates, and then dried to constant weight in a vacuum desiccator; yield 70 g. (83%). The compound decomposes when dried at elevated temperatures.

4-Methoxy-2,5-toluquinone (VI) (*Cf.* Orchin and Butz[67]). —*The carefully dried* 4-hydroxytoluquinone (117 g.), dry methanol (1170 cc.) and sulfuric acid (23.5 cc.) were heated under reflux for ten minutes. The methoxyquinone pre-

(60) Heymann and Fieser, THIS JOURNAL, **73**, 4054 (1951). *Cf.* also Fieser, Heymann and Rajagopalan, *ibid.*, **72**, 2306 (1950), and Heymann and Fieser, *ibid.*, **73**, 5252 (1951).

(61) Lardon and Reichstein, *Helv. Chim. Acta*, **26**, 705 (1943).

(62) Lardon and Reichstein, footnote 61. The catalytic hydrogenation was carried out in glacial acetic acid by the Swiss workers, and the 3α-hydroxy compound, as expected under these conditions, was the minor product. We have found that the reduction of (LXXXIII, R = H) by sodium borohydride in ethanol, followed by acetylation and reoxidation, proceeds smoothly to the required (LXXXIV, R = Ac, R′ = OMe).

(63) v. Euw, Lardon and Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944).

(64) Sarett, THIS JOURNAL, **70**, 1454 (1948); **71**, 2443 (1949).

(65) Mattox and Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(66) After the conclusion of our investigations, Rosenkranz, Pataki and Djerassi [THIS JOURNAL, **73**, 4055 (1951); *cf.* also Chemerda, Chamberlain, Wilson and Tishler, *ibid.*, **73**, 4052 (1951)] described the last stages in their conversion of the well-known steroid intermediate pregnenolone to cortisone. As these authors pointed out, their work completes a total synthesis of cortisone, in view of the fact that the path from our *saturated* synthetic steroid ester (LXX, R = Me) to pregnenolone was known. Further, since *epi*androsterone is obtainable by an alternative total synthesis (Cardwell, Cornforth, Duff, Holtermann and Robinson, footnote 6), and can be converted to our ester (LXX, R = Me), two paths exist for the synthesis of cortisone through saturated steroid intermediates lacking functional groups in ring C.

It is clear that both of these total syntheses are of a higher order of complexity than the direct synthesis from our triply unsaturated ester (LXVI).

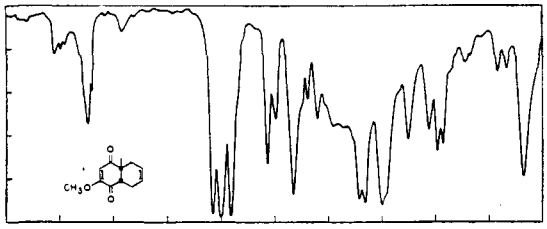
(67) Luff, Perkin and Robinson, [*J. Chem. Soc.*, **97**, 1131 (1910)] give m.p. 170–172°; Ashley [*ibid.*, 1471 (1937)] gives m.p. 172–173°. Orchin and Butz [*J. Org. Chem.*, **8**, 509 (1943)] give m.p. 176.2–178.4°.

cipitated during the reaction as yellow plates, and crystallization was completed by cooling the mixture in ice. The product was filtered off and washed with a little cold methanol. It weighed 90 g. and had m.p. 170–172°. A small second crop (2.5 g., total yield 72%) was obtained by concentration of the mother liquors. Pure quinone was obtained by adding a little alumina to a chloroform solution of the combined crops, concentrating the filtered solution to small volume, and adding methanol. It formed sparkling bright yellow plates, m.p. 174–175.5°.[67]

The method of Ashley[67] was also investigated; the quinone, m.p. 170–173° (undepressed on admixture with the specimen prepared above), was obtained only in *ca.* 12% yield. Moreover the material prepared by this method contained zinc salts, which were difficult to remove by crystallization, and which lowered the yield in the subsequent step.

cis-1,4-Diketo-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (*cis* Adduct) (VII) (*Cf.* Orchin and Butz[12]).—4-Methoxy-2,5-toluquinone (250 g., m.p. 174–175.5°), freshly distilled butadiene (450 cc.), benzene (600 cc.) and a trace of hydroquinone were shaken in a glass-lined autoclave at 100° for 96 hours. The light-yellow reaction mixture was filtered through a plug of glass wool to remove a little solid matter, and concentrated to *ca.* 600 cc. Ligroin (500 cc.) was added, and the product was allowed to crystallize at room temperature with stirring. The first crop (260 g.) had m.p. 93–95°, and a second crop (32 g., total yield 86%), m.p. 86–92°, was obtained from the mother liquors. Crystallization from petroleum ether gave a specimen of the pure *cis* adduct, m.p. 94.5–95.5° (Orchin and Butz[12] give m.p. 94.5–95.5°).

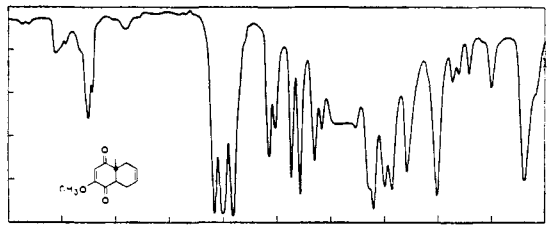
Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.91; H, 6.88.



Lower yields were obtained when ethanol was used as solvent for the reaction, or when no glass liner was employed.

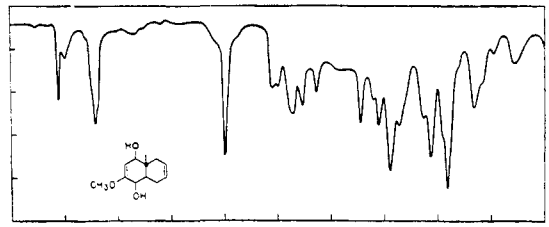
trans-1,4-Diketo-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (*trans* Adduct) (IX).—The pure *cis* adduct (60 g., m.p. 93–95°) was dissolved in dioxane (80 cc.) at 40–50°. The source of heat was removed, and aqueous sodium hydroxide (312 cc., 0.975 *N*, 5% excess) was added dropwise during ten minutes with stirring, under nitrogen. The brownish-orange solution was diluted with water (600 cc.) and was then seeded with finely powdered *trans* adduct (3 g., m.p. 126–129°). Aqueous hydrochloric acid (1 *N*) was added dropwise to the vigorously stirred mixture; a solid precipitate started to separate immediately. Addition of acid was stopped when the mixture changed color to lemon yellow, as this change indicated complete neutralization of the base. More water (200 cc.) was added, and the *trans* adduct was filtered off, washed well with water, and dried. It was obtained as a granular cream-colored solid, m.p. 126–129°, and weighed 57 g. (90% yield).[68] Crystallization from methanol gave the analytical sample as prisms, m.p. 130–131°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.90; H, 6.90.



trans-1,4-Dihydroxy-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (*trans* Bicyclic Glycol) (X).—The *trans* adduct (IX) (260 g.) in dry redistilled tetrahydrofuran (2 l.) was added gradually to a stirred solution of lithium aluminum hydride (50 g.) in dry ether (1.4 l.) under nitrogen at such a rate as to keep the solvent refluxing gently (addition time *ca.* one hour). During the addition, a viscous sticky precipitate separated, which changed into a white powder toward the end. Stirring was continued for a further five minutes, and the excess reagent was decomposed by the careful addition of ethyl acetate, with ice cooling, until no more reaction was observed. Saturated aqueous sodium sulfate was added gradually, with vigorous stirring, until the precipitate became slightly wet and adhered to the sides of the flask. The reaction mixture was then stirred with anhydrous magnesium sulfate (200 g.) for ten minutes, the precipitated salts were filtered off and washed well with ether. Evaporation of solvents left a viscous gum which was diluted with a small volume of ether and left overnight at 0°, whereupon the glycol crystallized. It was obtained as a white powder, m.p. 120–138°, and weighed 158 g. It was combined with a second crop (11 g.), m.p. 110–138°, obtained from the mother liquors, and this material (64% yield) was suitable for use in the next steps. Crystallization from benzene gave the analytical sample, m.p. 139–140°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.78; H, 8.77.



The mother liquors on evaporation gave a yellow viscous oil (92 g.) which could also be used for the following transformations (see below). A by-product could be isolated from it, which, after several crystallizations from benzene, formed colorless prisms, m.p. 167–168°, and is probably *trans*-1,4-dihydroxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (ii).

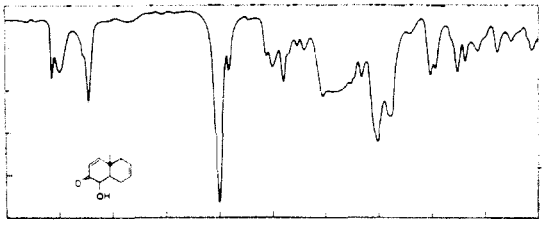
Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 72.81, 73.49; H, 8.82, 9.11.

Infrared spectrum: bands at 2.78 and 2.91 μ (hydroxyl); no appreciable bands from 5.0 to 6.6 μ.

trans-1-Hydroxy-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (*trans* Bicyclic Ketol) (XI, R = H).—The crude solid *trans*-glycol (X) (169 g.) was dissolved in dioxane (930 cc.), and 2 *N* sulfuric acid (745 cc.) was added. The clear solution was allowed to stand for 24 hours at room temperature, and was then poured into ether and water. The aqueous layer was washed twice more with ether, the combined organic extracts were washed with sodium bicarbonate solution and water, and were then dried and evaporated. The crude ketol (142 g., 99%) remained as a crystalline residue and was used for the next step. The analytical sample was obtained by crystallization from aqueous methanol or ligroin, and had m.p. 71.5–73°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.03; H, 8.06.

(68) Early runs of the Diels-Alder reaction, not performed under optimum conditions, yielded the *cis* adduct (VII) contaminated with unchanged methoxytoluquinone. When the above isomerization procedure was applied to this material, low yields of the *trans* isomer were obtained. The following method was however found satisfactory: The crude *cis* adduct (80 g.) was dissolved in dioxane (150 cc.) at 60-70°. Solid sodium hydrosulfite (5 g.) was added, and the mixture was warmed for another five minutes with vigorous stirring. The source of heat was removed, a solution of sodium hydrosulfite (15 g.) in 1 *N* sodium hydroxide (100 cc.) was added dropwise during ten minutes *in a nitrogen atmosphere*, and then another 375 cc. of 1 *N* sodium hydroxide during the next ten minutes. Finely powdered *trans* adduct (5 g.) was added to the brown solution, which was then diluted with water (1 l.). Hydrochloric acid (1 *N*) was added with stirring until the color of the mixture changed to yellow, and another 1 l. of water was added. Filtration, washing with water and drying gave the *trans* adduct (63 g., 73%), m.p. 127.5–130°.



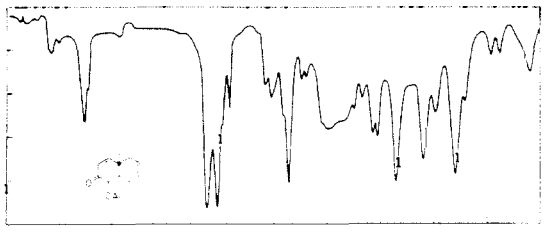
Ultraviolet spectrum: λ_{max} 227 mμ (ϵ 11,700).

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate–ethanol as orange laths, m.p. 223–225°.

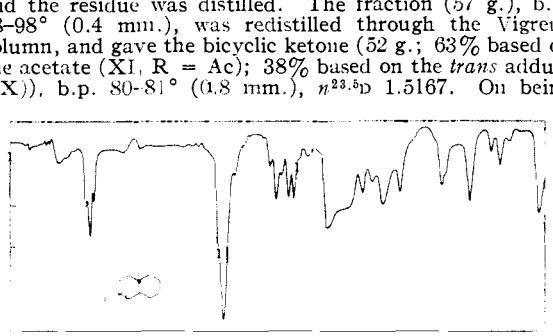
Anal. Calcd. for $C_{17}H_{18}O_5N_4$: C, 56.98; H, 5.06. Found: C, 57.02; H, 5.19.

trans-1-**Acetoxy-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (XI, R = Ac)**.—The crude ketol (XI, R = H) (142 g.) was dissolved in dry pyridine (730 cc.) and acetic anhydride (145 cc.) was added. The solution was heated on the steam-bath for a few minutes with exclusion of moisture, and was then left at room temperature for 12 hours. It was concentrated to small volume at the water-pump, ether was added, and the solution was washed successively with water, dilute sulfuric acid, sodium bicarbonate and water. The dried extract was evaporated, and the acetate remained as an orange oil (169 g., 96%) which solidified when scratched. It was employed without further purification for the following step. The analytical sample was obtained by crystallization from ligroin; it formed colorless plates, m.p. 55°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.66; H, 7.45.



trans-2-**Keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene** (*trans* **Bicyclic Ketone**) **(XV)**. **Method A**.—The crude acetate (XI, R = Ac) (60 g.) and redistilled acetic anhydride (550 cc.) were heated to boiling by immersion in an oil-bath kept at 145–150°. Commercial zinc dust (550 g.) was added all at once to the vigorously stirred solution, from which moisture was excluded, and the refluxing mixture was stirred for a further eight minutes at this temperature. It was cooled in ice, the zinc was filtered off and washed well with ether.[69] The experiment was repeated under identical conditions with a second batch of crude acetate (52 g.), acetic anhydride (500 cc.) and zinc dust (500 g.). The filtrates and ether washings from both experiments were combined, the ether was evaporated, and the acetic anhydride was removed through a short Vigreux column at the water-pump. The light yellow residue (*ca.* 110 g.) was diluted with ether, and the organic layer was washed successively with dilute sulfuric acid, sodium carbonate solution and water. The dried ($MgSO_4$) extract was evaporated, and the residue was distilled. The fraction (57 g.), b.p. 68–98° (0.4 mm.), was redistilled through the Vigreux column, and gave the bicyclic ketone (52 g.; 63% based on the acetate (XI, R = Ac); 38% based on the *trans* adduct (IX)), b.p. 80–81° (0.8 mm.), $n^{23.5}D$ 1.5167. On being seeded at room temperature, it solidified, and had m.p. 26–29°. The analytical sample was obtained by low temperature crystallization from petroleum ether (b.p. 20–40°); it formed colorless needles, m.p. 34.5–35.5°.



(69) The filtered zinc becomes pyrophoric when dry and it should be covered with water to prevent ignition.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.43; H, 8.70. Found: C, 81.02; H, 8.98.

Ultraviolet spectrum: λ_{max} 225 mμ (ϵ 10,300).

The 2,4-dinitrophenylhydrazone crystallized from ethanol as red plates, m.p. 159–160°.

Anal. Calcd. for $C_{17}H_{18}O_4N_4$: C, 59.64; H, 5.30. Found: C, 59.31; H, 5.33.

The semicarbazone crystallized from aqueous methanol or benzene–petroleum ether, and had m.p. 178–179°.

Anal. Calcd. for $C_{12}H_{17}ON_3$: C, 65.72; H, 7.82; N, 19.16. Found: C, 65.10; H, 7.79; N, 18.76.

The pure ketone could be regenerated from this derivative with dilute sulfuric acid and ligroin in the usual way.

The over-all yield of the bicyclic ketone (XV) could be increased by utilizing the non-crystalline material after removal of the solid glycol (X) (see above). The oil (435 g., derived from *ca.* 1230 g. of *trans* adduct) was hydrolyzed with 2 *N* sulfuric acid (1.8 l.) and dioxane (2.3 l.) as before, and the crude ketol was distilled. The fraction (207 g.), b.p. 75–130° (0.05 mm.), was acetylated with acetic anhydride (215 cc.) in pyridine (1 l.), and the product (253 g.) was treated with zinc and acetic anhydride in 50-g. portions as described before. A rough distillation, followed by careful fractionation through a Vigreux column, then yielded the additional bicyclic ketone (68 g., 7% based on *trans* adduct (IX); total yield from (IX) = 45%), b.p. 77–78° (0.5 mm.); it crystallized when seeded at 15°, and had m.p. *ca.* 20–25°. It was used for subsequent steps, and gave yields comparable to those obtained with the purer ketone.

Method B.—The ketol acetate (XI, R = Ac) (18.7 g.) dissolved in xylene (160 cc.) was refluxed with activated[70] granular zinc (140 g., 30 mesh) with vigorous stirring for 41 hours. The liquid was decanted, the metal was washed well with ether and water, and the organic layers were washed successively with dilute sulfuric acid, sodium bicarbonate and water. The dried extract was evaporated, and the residue was distilled through a Vigreux column. The bicyclic ketone (6.1 g., 44%) had b.p. 67–70° (0.05 mm.), and m.p. 27–30° after being seeded. Centrifugation gave a completely pure sample, m.p. 33.5–35.5°, undepressed on admixture with the analytical sample prepared by method A.

trans-2-**Keto-10-methyl-Δ^{6}-octahydronaphthalene** (iii).—Before the best conditions for the preparation of the bicyclic ketone (XV) had been worked out, it was prepared by treating the ketol (XI, R = H) directly with zinc in acetic anhydride. Under these conditions the ketone (XV) was contaminated with the dihydro bicyclic ketone (iii). The latter was characterized by crystalline derivatives. The 2,4-dinitrophenylhydrazone crystallized from benzene–petroleum ether in small yellow clusters, m.p. 170.5–172°.

Anal. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.27; H, 5.85; N, 16.28. Found: C, 58.91; H, 5.89; N, 16.29.

The semicarbazone, crystallized from methanol, had m.p. 203–204°.

Anal. Calcd. for $C_{12}H_{19}ON_3$: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.23; H, 8.63; N, 18.71.

The ketone was regenerated from the semicarbazone (100 mg.) with 2 *N* sulfuric acid and ligroin in the usual way. Its infrared spectrum showed a band at 5.83 μ in the carbonyl region (saturated carbonyl grouping).

Action of Potassium Hydroxide on the Ketol Acetate (XI, R = Ac).—The pure ketol acetate (XI, R = Ac) (5.0 g.) in methanol (25 cc.) was added to a solution of potassium hydroxide (7.5 g.) in methanol (50 cc.), and the reaction mixture was allowed to stand at room temperature under nitrogen for 40 hours. The orange solution was then acidified with dilute hydrochloric acid (the color changed to light yellow) and thoroughly extracted with ether. The combined organic extracts were washed with salt solution, and were dried and evaporated. A little ether was added

(70) The zinc was activated by being immersed in concentrated sulfuric acid. A few drops of concentrated nitric acid were added, and the mixture was heated on the steam-bath for five minutes. The liquid was decanted, the metal was washed well with water, then with acetone and ether, and finally dried in air.

to the crystalline residue, and the insoluble solid (234 mg.), m.p. 237–238° (dec.) was filtered off. On recrystallization from benzene, glistening colorless plates having the same melting point were obtained. This material is believed to possess the dimeric structure (XVII).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.90.

Infrared spectrum: bands at 2.92 μ (hydroxyl), 5.86 μ (saturated carbonyl), 6.01 and 6.17 μ (enolized α-diketone).

The ethereal filtrate was evaporated, and the residue was crystallized from ether–ligroin. The α-diketone (XVI) (2.49 g., 62%) separated as light yellow plates, m.p. 92–93°, raised to 96.5–98° on recrystallization from aqueous methanol.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.72; H, 8.07.

Infrared spectrum: bands at 2.92 μ (hydroxyl). 6.01 and 6.17 μ (enolized α-diketone).

The compound gave a purple ferric chloride color. It was rather unstable and soon turned gummy when kept at room temperature.

trans-**1,4-Diketo-2-methoxy-10-methyl-Δ^2-octahydronaphthalene (Dihydro *trans* Adduct) (XIX).**—The *trans* adduct (14.3 g.) in ethyl acetate (250 cc.) was shaken in hydrogen in the presence of a prereduced palladium–calcium carbonate catalyst[71] (4 g., 5% Pd) at 23° and 762 mm. In seven hours 1750 cc. of gas had been absorbed (equivalent to 1.04 double bonds) and uptake had practically stopped. The catalyst was filtered off, the solvent was removed, and the residue was crystallized from benzene–ligroin. The dihydro adduct (12.2 g., 85%) was obtained as needles, m.p. 83–84°, raised to 84.5–85° by further crystallization from aqueous methanol.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.05; H, 7.70.

Infrared spectrum: bands at 5.82, 5.98 and 6.18 μ (characteristic adduct spectrum).

trans-**1-Hydroxy-2-methoxy-4-keto-10-methyl-Δ^2-octahydronaphthalene (Tetrahydro *trans* Adduct) (XX) and *trans*-1-Hydroxy-2-methoxy-4-keto-10-methyldecahydronaphthalene (Hexahydro *trans* Adduct) (XXI).**—The *trans* adduct (1.04 g.) in ethyl acetate (30 cc.) and a prereduced platinum oxide catalyst (50 mg.) were shaken in hydrogen at 22° and 770 mm. Three hundred and twenty-four cc. of gas (equivalent to 2.69 double bonds) was absorbed in six hours, when the uptake stopped. The product was isolated in the usual way, and the solid residue was crystallized from benzene–petroleum ether to give a powder (0.71 g.), m.p. 95–100°. Crystallization of the latter from nitromethane gave the crude tetrahydro compound (XX) (0.31 g.) as long needles, m.p. 125–135°, raised to 147–148° by two more crystallizations from the same solvent.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.63. Found: C, 68.11; H, 8.50.

Infrared spectrum: bands at 2.80 and 2.95 μ (hydroxyl), 6.02 and 6.13 μ (enolized β-diketone ether[20]).

The mother liquors from the first nitromethane crystallization were evaporated, and the solid residue was crystallized from benzene. The crude hexahydro adduct (XXI) (0.27 g.) formed needles, m.p. 118–120°, raised to 122–122.5° by further crystallization from the same solvent.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.90; H, 9.50. Found: C, 68.21; H, 9.67.

Infrared spectrum: bands at 2.80 and 2.96 μ (hydroxyl), and 5.80 μ (saturated carbonyl).

trans-**1,4-Dihydroxy-2-methoxy-10-methyldecahydronaphthalene (Octahydro *trans* Adduct) (XXII). (A) By Hydrogenation of the *trans* Adduct (IX).**—The *trans* adduct (IX) (0.50 g.) in ethyl acetate (15 cc.) and a prereduced platinum oxide catalyst (0.15 g.) were shaken in hydrogen until absorption stopped (202 cc. of gas taken up at 23° and 765 mm., equivalent to 3.45 double bonds). Removal of catalyst and solvent left a semi-solid residue, which after two crystallizations from nitromethane furnished the octahydro adduct (0.22 g.) as long regular needles, m.p. 144–145°, raised to 145–146° by further crystallization from the same solvent.

(71) This catalyst was prepared by a method analogous to that used for the preparation of the palladium-strontium carbonate catalyst (footnote 72).

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.30; H, 10.33.

Infrared spectrum: bands at 2.81 μ and 2.92 μ (hydroxyl); no bands in region 5–6.6 μ.

On admixture with the tetrahydro adduct (XX) (m.p. 147–148°), the m.p. was depressed to 118–125°.

(B) **By Hydrogenation of the Glycol (XXVIII).**—The glycol (XXVIII) (150 mg.), described below, in ethyl acetate (15 cc.) was shaken in hydrogen in the presence of a prereduced platinum oxide catalyst until absorption was complete. The catalyst and solvent were removed, and the solid residue on crystallization from nitromethane yielded the octahydro compound (118 mg.), m.p. 142–144°, raised to 145–146° on further crystallization. The infrared spectrum was identical with that of the compound prepared as in (A), and no depression in melting point was observed on admixture. On admixture with the tetrahydro adduct (XX) (m.p. 147–148°), the melting point was depressed to 115–122°.

cis-**1,4-Dihydroxy-2-methoxy-10-methyl-$\Delta^{2,6}$-hexahydronaphthalene (*cis* Bicyclic Glycol) (XXIII).**—The *cis* adduct (VII) (10.0 g.) dissolved in ether (250 cc.) was added dropwise to a stirred solution of lithium aluminum hydride (2.2 g.) in ether (200 cc.) at such a rate as to maintain gentle reflux. The mixture was stirred for a further 30 minutes at room temperature. The excess reagent was destroyed by the careful addition of ethyl acetate, and a solution of acetic acid (15 cc.) in water (185 cc.) was then gradually added with cooling. The aqueous layer was washed with ether, the combined organic extracts were shaken with sodium bicarbonate solution and water, and were dried. Evaporation of the solvent left the crude glycol (9.83 g.) as a semi-solid mass, which was used in the subsequent stages. On crystallization from ether it gave pure (XXIII) as needles, m.p. 119–121°.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 69.03; H, 8.79.

cis-**2-Keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (*cis* Bicyclic Ketone (XXV).**—The crude *cis* bicyclic glycol (XXIII) (8.6 g.) was dissolved in dioxane (90 cc.) and 2 *N* sulfuric acid (90 cc.) and allowed to stand at room temperature for 40 hours. The product was isolated with ether in the usual way, and distilled. The crude *cis* bicyclic ketol (XXIV) (5.5 g.) had b.p. 120–130° (3 mm.). A higher boiling fraction was also obtained, but this was not investigated further.

The crude ketol (XXIV) (5.5 g.) in dry pyridine (27 cc.) and acetic anhydride (6.0 cc.) was heated on the steam-bath for a few minutes, with exclusion of moisture. The solution was allowed to stand overnight, and was then concentrated *in vacuo*. Isolation with ether gave the crude acetate (6.70 g.) as a yellow oil. The acetate, dissolved in xylene (100 cc.), and activated[70] granular zinc (70 g., 30 mesh) were heated to boiling under reflux with vigorous stirring for 18 hours. The liquid was decanted from the metal, which was washed with ether and water. Dilute hydrochloric acid was added to the combined liquids, and the organic layer was washed with sodium bicarbonate solution and water. The dried extract was evaporated through a short Vigreux column, and the residue was distilled. The crude *cis* bicyclic ketone (XXV) (1.1 g., 16% based on *cis* adduct) had b.p. 75–85° (0.4 mm.) [infrared bands at 5.98 μ (strong) and 6.15 μ (weak)].

The semicarbazone was prepared from the ketone in the usual way. It weighed 1.33 g., and after crystallization from aqueous ethanol had m.p. 182.5–184.5°.

Anal. Calcd. for $C_{12}H_{17}ON_3$: C, 65.72; H, 7.82; N, 19.16. Found: C, 65.31; H, 7.83; N, 18.74.

On admixture with the derivative of the *trans* ketone (XV) (m.p. 178–179°) the m.p. was depressed to 170–176°. The hydrogenation of this compound is described below.

The 2,4-dinitrophenylhydrazone crystallized from benzene–petroleum ether, and had m.p. 149–151°.

Anal. Calcd. for $C_{17}H_{18}O_4N_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.23; H, 5.71; N, 15.91.

trans-**1,4-Dihydroxy-2-methoxy-10-methyl-Δ^2-octahydronaphthalene (XXVIII).**—A solution of the dihydro *trans* adduct (XIX) (11.0 g.) in dry ether (180 cc.) was added dropwise to a stirred solution of lithium aluminum hydride (7.0 g.) in ether (200 cc.) in a nitrogen atmosphere at such a rate as to keep the solvent boiling gently (*ca.* 30 minutes).

The mixture was stirred a further 45 minutes, and the excess reagent was then destroyed by the careful addition of ethyl acetate. The resulting suspension was poured into iced dilute acetic acid. The aqueous layer was shaken twice with ether, the combined ether extracts were shaken with sodium bicarbonate solution and water and then dried ($MgSO_4$). Evaporation of the solvent left a semi-solid residue, which on crystallization from benzene gave the glycol (XXVIII) (5.2 g., 46%) as pearly prisms, m.p. 129–130°, not raised by further crystallization from the same solvent.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.90; H, 9.50. Found: C, 68.34; H, 9.65.

Infrared spectrum: bands at 2.82 and 2.97 μ (hydroxyl), and 5.98 μ (enol ether).

On admixture with the isomeric hexahydro adduct (XXI) (m.p. 122–122.5°), the melting point was depressed to 95–110°.

trans-1-**Hydroxy-2-keto-10-methyl-Δ^3-octahydronaphthalene** (**XXIX**).—The glycol (XXVIII), m.p. 129–130°, (1.50 g.) was dissolved in pure dioxane (60 cc.) and 2 *N* sulfuric acid (30 cc.) was added. The clear solution was allowed to stand at 22° for 11 hours. The product was isolated with ether and crystallized from ligroin. The ketol (XXIX) (1.06 g., 83%) separated as shining plates, m.p. 82–84°, raised to 86.5° by further crystallization.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 72.79; H, 8.96.

Infrared spectrum: bands at 2.90 and 3.02 μ (hydroxyl), 6.00 μ (conjugated carbonyl) and 6.20 μ (weak; conjugated double bond).

The 2,4-dinitrophenylhydrazone crystallized from ethanol as orange plates, m.p. 181°.

Anal. Calcd. for $C_{17}H_{20}O_5N_4$: N, 15.55. Found: N, 15.80.

trans-1-**Acetoxy-2-keto-10-methyl-Δ^3-octahydronaphthalene**.—The ketol (XXIX) (0.80 g.) was dissolved in dry pyridine (4 cc.) and acetic anhydride (0.8 cc.) was added. The solution, from which moisture was excluded, was warmed on the steam-bath for a few minutes and was then set aside at 23° for 12 hours. Isolation with ether in the usual way, followed by crystallization from petroleum ether gave the dihydro ketol acetate (0.65 g.) as hexagonal plates, m.p. 64–66°, raised to 66–66.5° by recrystallization.

Infrared spectrum: bands at 5.78 μ (ester), 6.00 μ (conjugated carbonyl) and 6.21 μ (weak; conjugated double bond).

trans-**2-Keto-10-methyl-Δ^3-octahydronaphthalene** (**XXX**).—The dihydro ketol (XXIX)[22] (8.5 g.) and freshly distilled acetic anhydride (70 cc.) were heated to boiling in an oil-bath kept at 140–145° with exclusion of moisture. Commercial zinc dust (16 g.) was added all at once to the vigorously stirred solution, which was then stirred and boiled for ten minutes. More zinc (16 g.) was added, and the reaction was allowed to proceed for another 20 minutes. The mixture was cooled, and the metal was filtered off and washed well with ether. The solvent was evaporated through a short Vigreux column at the water-pump, and the residue was distilled. A mobile liquid (4.7 g.), b.p. 130–135° (0.5 mm.), was obtained, which probably contained the enol acetate of (XXX). It was heated at 60° with a solution of semicarbazide acetate in 80% aqueous methanol for ten minutes, left overnight at room temperature and diluted with water. Crystallization of the precipitated semi-solid mass from aqueous methanol gave the semicarbazone of (XXX) (2.1 g., 20%) as plates, m.p. 186°.

Anal. Calcd. for $C_{12}H_{19}ON_3$: C, 65.13; H, 8.65; N, 18.99. Found: C, 65.38; H, 8.62; N, 18.94.

A stirred suspension of the semicarbazone (1.8 g.) in ligroin (30 cc.) and 2 *N* sulfuric acid (30 cc.) was heated under reflux in a nitrogen atmosphere for 30 minutes. The two clear layers were separated, the aqueous layer was washed with ether, and the combined organic extracts were washed with water, dried and evaporated. Distillation of the residue gave the ketone (XXX) (1.2 g., 90% recovery), b.p. 69° (0.1 mm.), $n^{26}D$ 1.5006.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.60; H, 10.05.

The infrared spectrum (strong band at 6.0 μ, inflection at 5.88 μ) indicated that this material was contaminated by a small amount of the saturated ketone (XXXII) (*cf.* footnote 18).

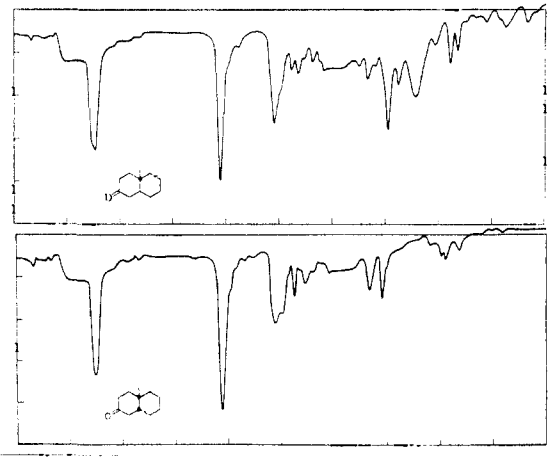
The 2,4-dinitrophenylhydrazone crystallized from ethanol as red plates, m.p. 161–162°.

Anal. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.27; H, 5.85; N, 16.28. Found: C, 59.11; H, 5.59; N, 16.24.

trans-**2-Methyl-2-carboxycyclohexane-1-acetic Acid** (**XXXI**).—To a stirred suspension of the ketone (XXX) (250 mg.) in distilled water (25 cc.) maintained at 70°, finely powdered potassium permanganate (803 mg., equivalent to 5 atoms of oxygen) was added in small portions. The mixture was stirred until it had become colorless, the manganese dioxide was filtered off and washed with water. The aqueous solution was acidified with dilute hydrochloric acid, saturated with salt, and repeatedly extracted with ether. The combined organic extracts were dried and evaporated, and the semi-solid residue was triturated with benzene–ligroin. The solid was filtered off and recrystallized from water. The *trans* dicarboxylic acid (XXXI) (68 mg., 22%) formed prisms, m.p. 177° [Linstead, *et al.*,[23a] give m.p. 175° (highest value); Bachmann and Kushner[23b] give m.p. 175–177.8°]. There was no depression on admixture with an authentic sample, kindly provided by the late Professor Bachmann.

cis-**2-Keto-10-methyldecalin** (**XXVI**).—The *cis* bicyclic ketone (XXV) semicarbazone (240 mg.), described above, dissolved in ethanol (50 cc.) was shaken in hydrogen in the presence of a palladium–strontium carbonate catalyst (700 mg., 2%)[72] at 25° and 765 mm. In 15 minutes 56.4 cc. of gas (equivalent to 2.1 double bonds) had been absorbed, and uptake stopped. Removal of catalyst and solvent and crystallization of the residue from ethanol gave the semicarbazone of *cis*-2-keto-10-methyldecalin, m.p. 201–202°. The 2,4-dinitrophenylhydrazone, prepared by treating the pure semicarbazone with the hot reagent (in methanol and sulfuric acid), had m.p. 127–129° after one crystallization from ethanol. Two more crystallizations from benzene–ligroin raised the melting point to 150–151°, and after further crystallization the constant m.p. 172–174° was attained. This melting point behavior may explain the m.p. 125.5–127° reported for the derivative of this *cis* ketone by Woodward and Singh[73] and m.p. 151–152° and 152–152.2° reported by Woodward,[74] and by Du Feu, McQuillin and Robinson,[75] respectively.

trans-**2-Keto-10-methyldecalin** (**XXXII**). (**A**) **From** (**XV**).—The *trans* bicyclic ketone (XV) (6.135 g.) in methanol (50 cc.) was hydrogenated in the presence of a palladium–strontium carbonate catalyst[72] (3.0 g., 2%) at 24° and 765 mm. In two hours 1798 cc. of gas (equivalent to 1.96 double bonds) had been absorbed. Removal of catalyst



(72) This catalyst was prepared in the following manner. Palladium chloride (4 g.) was dissolved in concentrated hydrochloric acid (*ca.* 8 cc.), and the solution was diluted with water (800 cc.). Strontium carbonate was added in small amounts with shaking until carbon dioxide evolution had stopped. Excess strontium carbonate (120 g.) was then added, and the mixture was shaken mechanically overnight. The solid was filtered off, washed thoroughly with distilled water, then with methanol and ether, and was finally dried at 50°. The catalyst was freshly reduced in hydrogen before use.

(73) Woodward and Singh, THIS JOURNAL, **72**, 494 (1950).

(74) Woodward, *ibid.*, **62**, 1208 (1940).

(75) Du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

and solvent and distillation of the residue gave the saturated *trans* ketone, b.p. 130° (20 mm.), $n^{24}D$ 1.4862.

For comparison, the infrared spectra of this ketone and the corresponding *cis* isomer (XXVI), m.p. 46–48° (see below), are reproduced here.

The 2,4-dinitrophenylhydrazone crystallized from ethanol as yellow plates, m.p. 177–178° (soft glass capillary).

Anal. Calcd. for $C_{17}H_{22}O_4N_4$: C, 58.92; H, 6.40; N, 16.17. Found: C, 58.90; H, 6.54; N, 16.22.

On admixture with the derivative (m.p. 172–174°) of the *cis* ketone described above, the melting point was depressed to 150–162°.

The semicarbazone crystallized from methanol as plates, m.p. 202–203°.

Anal. Calcd. for $C_{12}H_{21}ON_3$: C, 64.55; H, 9.48; N, 18.82. Found: C, 64.74; H, 9.27; N, 18.52.

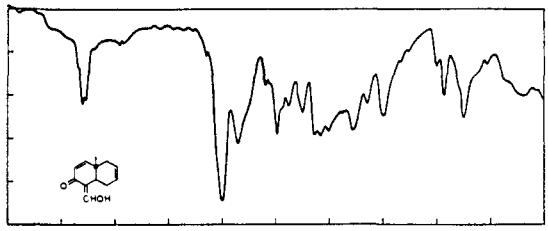
On admixture with the derivative (m.p. 201–202°) of the *cis* ketone described above, the melting point was depressed to 191–193°.

(B) From (**XXX**).—The ketone (XXX) (220 mg.) in methanol (20 cc.) was shaken in hydrogen with a palladium–calcium carbonate catalyst[71] (50 mg., 5%) until uptake of gas was complete. In 15 minutes 35.1 cc. of hydrogen had been absorbed at 22° and 761 mm. (equivalent to 1.1 double bonds). The catalyst was filtered off, the solvent was evaporated, and the residue was converted to derivatives. The 2,4-dinitrophenylhydrazone crystallized from ethanol as golden-yellow plates, m.p. 178–179° (soft glass capillary), 157–158.5° (Pyrex capillary), undepressed on admixture with the derivative prepared as in (A). The semicarbazone crystallized from methanol as plates, m.p. 201–202°, also undepressed on admixture with the derivative prepared as in (A).

Hydrogenation of 2-Keto-10-methyl-$\Delta^{1(9)}$-octahydronaphthalene (XXVII). *cis*- and *trans*-2-Keto-10-methyldecalin (XXVI) and (XXXII).—The unsaturated ketone (XXVII)[75] (0.62 g.) in ethanol (10 cc.) was shaken in hydrogen over a palladium–strontium carbonate catalyst[72] (0.1 g., 2%) until gas absorption was complete. In 30 minutes 87.8 cc. had been taken up at 25° and 762 mm. (equivalent to 0.95 double bond). The catalyst and solvent were removed, and the residue was purified by low-temperature crystallization from petroleum ether. The *cis* ketone (XXVI) was obtained as a crystalline solid, m.p. 46–48° (Robinson, *et al.*,[75] give m.p. 47°; Woodward[74] gives m.p. 46°) (for the infrared spectrum of this ketone, see above). The semicarbazone of this material on crystallization from ethanol had m.p. 199.5–200°. No depression was observed on admixture with the derivative (m.p. 201–202°) of the *cis* ketone described above, but on admixture with the *trans* derivative (m.p. 202–203°), the melting point was depressed to 190–193°. The 2,4-dinitrophenylhydrazone after crystallization from ethanol and then from benzene–ligroin formed light-orange needles, m.p. 158–159°. Recrystallization only raised the melting point by *ca.* 1°, but on further crystallization the melting point was suddenly raised to 174.5–175.5°. No depression was observed on admixture with the derivative (m.p. 172–174°) of the *cis* ketone described above, but on admixture with the *trans* derivative (m.p. 178–179°), the melting point was depressed to 148–160°.

In another experiment, the hydrogenation of the unsaturated ketone (XXVII) was repeated under the conditions described, and the total product, without crystallization, was converted to the 2,4-dinitrophenylhydrazone. Crystallization from benzene–ligroin gave separate clusters of light-orange and golden-yellow crystals, which were separated mechanically. The former on recrystallization gave the pure *cis* derivative, m.p. 175–176°, undepressed on admixture with the compound (m.p. 174.5–175.5°) prepared in the preceding paragraph. The latter on crystallization gave the pure *trans* derivative, m.p. 176–178° (soft glass capillary), 160–161.5° (Pyrex capillary), undepressed on admixture with the *trans* compound (m.p. 178–179° and 157–158.5°, respectively) obtained by the hydrogenation of XXX).

***trans*-1-Hydroxymethylene-2-keto-10-methyl-$\Delta^{5,6}$-hexahydronaphthalene (XXXIV).**—Sodium methoxide,[76] prepared from sodium (38.5 g.) and dry methanol (500 cc.), was freed of excess solvent, finally by heating at 160° *in vacuo* (1 mm.). It was cooled in nitrogen, the solid was broken up and suspended in dry benzene (460 cc.). Ethyl formate (230 cc., dried over K_2CO_3 and freshly distilled) was added in a thin stream at room temperature to the vigorously stirred suspension which throughout the experiment was kept under an atmosphere of nitrogen. The mixture was stirred for a further one-half hour, and was then cooled in ice. The bicyclic ketone (XV) (100 g.), dissolved in benzene (460 cc.), was added dropwise during one hour with stirring and ice-cooling. More benzene (460 cc.) was added, the ice-bath was removed, and stirring at room temperature was continued overnight. The yellow gelatinous mixture was diluted with benzene and iced dilute sulfuric acid, and the aqueous layer was washed with ether and benzene. The combined organic extracts were shaken with excess ice-cold 2% potassium hydroxide solution.[77] The alkaline layer was washed with ether, acidified with dilute hydrochloric acid, and well extracted with a benzene–ether mixture.[78] The organic extract was washed with water, dried and evaporated at the water-pump. The light-orange residue (111 g., 94%; 89–95% yields were obtained in other experiments) was suitable for use in the next stage. A sample of the pure hydroxymethylene compound was obtained by distillation. It was a light yellow mobile liquid, b.p. 88–90° (0.015 mm.), $n^{28}D$ 1.5552.



Ultraviolet spectrum: λ_{max} 238 mμ (ε 8,300) and 315 mμ (ε 4,400). In 0.1 *N* alcoholic NaOEt solution: λ_{max} 229 mμ (ε 10,000) and 361 mμ (ε 7,600).

The combined neutral fractions from a number of such experiments were distilled, and crystalline bicyclic ketone was recovered. This brought the average yield in this step up to *ca.* 98%.

Ethyl Vinyl Ketone.—1-Chloropentanone-3 was prepared from propionyl chloride and ethylene essentially by the method of McMahon, *et al.*[79] Chloroform was used as solvent, the ethylene was bubbled into the reaction mixture as rapidly as its absorption would allow (uptake complete in *ca.* 2.5 hours for the experiment indicated below), and no diethylaniline was added during distillation. In this way propionyl chloride (600 g.) and aluminum chloride (907 g.) in chloroform (2 l.) gave the pure chloroketone (567 g., 73%; 71–76% yields were obtained in other experiments), b.p. 63° (25 mm.), $n^{25}D$ 1.4330 (McMahon, *et al.*,[79] report a 45% yield, b.p. 32.3–33.3° (2.5 mm.), $n^{20}D$ 1.4361).

The chloroketone (39 g.) and commercial diethylaniline (160 cc.) were heated in a 1-l. flask connected through a condenser to a receiver cooled in Dry Ice and acetone, as described by McMahon, *et al.*[79] When the oil-bath reached 180° a very vigorous reaction took place and *ca.* 25 cc. of distillate was driven over all at once. The temperature of the bath was taken to 200°, and the distillate, to which a little hydroquinone had been added, was dried over $CaCl_2$ at 0°. Distillation through a small Vigreux column gave ethyl vinyl ketone (15.0 g., 55%) as a middle fraction, b.p. 45–47° (100 mm.), $n^{23}D$ 1.4181. Material of this quality was used for the next step; on redistillation through the same column into several fractions, it had constant b.p. 44° (90 mm.), $n^{25}D$ 1.4162. The yield was considerably reduced when the scale of the experiment was increased. When larger quantities of ketone are required, it is advantageous to run a number of consecutive experi-

(76) Use of commercial sodium methoxide gave variable yields of (XXXIV).

(77) If sodium hydroxide is used at this stage, the insoluble sodium salt of (XXXIV) separates, and this promotes the formation of emulsions.

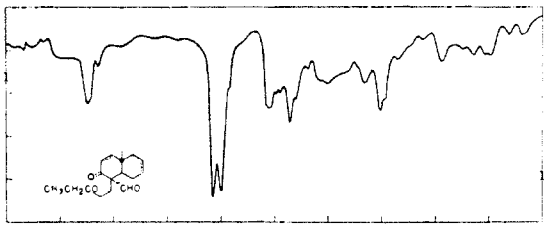
(78) Some benzene should be used at this stage, as on subsequent evaporation it removes the small amount of formic acid present by co-distillation.

(79) McMahon, Roper, Utermohlen, Hasek, Harris and Brant, THIS JOURNAL, **70**, 2971 (1948).

ments on the scale described, and combine the distillates for working up.

trans-1-Formyl-1-γ-ketopentyl-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (XXXV).—A solution of freshly distilled ethyl vinyl ketone (62 g.) and the hydroxymethylene ketone (XXXIV) (111 g.) in dry redistilled *t*-butanol (440 cc.) was cooled in ice. The air was displaced by nitrogen, and a potassium *t*-butoxide solution, prepared by dissolving potassium (2.45 g.) in *t*-butanol (60 cc.), was added. Ice-cooling was continued until the butanol started to crystallize; the ice-bath was then removed and the solution was allowed to stand under nitrogen for ten hours at room temperature. On scratching, a heavy precipitate of sparkling plates separated. The mixture was cooled in ice, the adduct (XXXV) was filtered off and washed with cold *t*-butanol. It weighed 77.8 g. and had m.p. 93–97°. When the mother liquors were diluted with petroleum ether, a second crop (6.5 g., total yield 53%), m.p. 92–97°, was obtained. In other experiments carried out under these conditions, the yields varied between 45 and 57%. The analytical sample was crystallized from ligroin; it formed large sparkling plates, m.p. 98.5–99°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.43; H, 8.15.

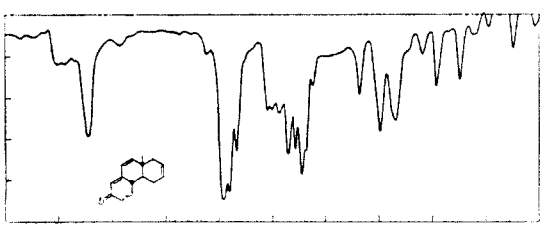


Ultraviolet spectrum: λ_{max} 227 mμ (ε 8,900) and 300 mμ (ε 94).

The mother liquors were diluted with ether, extracted with aqueous potassium hydroxide solution (only a negligible amount of unchanged (XXXIV) was obtained from the basic extracts after acidification), dried and evaporated. The cyclization of the residue is described below.

1,14-Dimethyl-2-keto-$\Delta^{1(11),6,9}$-octahydrophenanthrene (Tricyclic Ketone) (XXXVI).—The crystalline ethyl vinyl ketone adduct (XXXV) (84.3 g.) dissolved in dioxane (3 l.) was cooled in ice. An ice-cold solution of potassium hydroxide (84 g.) in water (3 l.) was added, the air was displaced by nitrogen, and the solution was allowed to attain room temperature. It was then allowed to stand for three hours with occasional shaking.[80] The initially clear solution became turbid after a few minutes and a small upper layer separated. Ether and saturated salt solution were added, and the product was isolated in the usual way. Evaporation of the solvent at the water pump left a residue which solidified completely. Crystallization from methanol gave the tricyclic ketone (XXXVI) (61.7 g., 88%; 86–89% yields were obtained in other experiments run under identical conditions), as cream-colored prisms, m.p. 70.5–72.5°. The mother liquors were converted to the semicarbazone (see below) in the usual way, and 3.4 g. (additional 4%) of the derivative, m.p. 242–245°, could be isolated.

Alternately the cyclization may be carried out in an inhomogeneous medium. The ethyl vinyl ketone adduct (50 g.) in dioxane (400 cc.) was stirred at room temperature with a solution of potassium hydroxide (40 g.) in water (1600 cc.) for 3 hours under nitrogen, and the product was isolated in the usual manner. Although a saving of solvents may be effected by this method, the yield of crystalline tricyclic ketone is reduced to 78–80%.



(80) The ultraviolet spectrum at this stage indicated the cyclization to be 97% complete.

The analytical sample was obtained by crystallization from methanol or petroleum ether. It formed prisms, m.p. 72–73°.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.19; H, 8.83. Found: C, 84.05; H, 8.72.

Ultraviolet spectrum: λ_{max} 289 mμ (ε 26,100).

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate as dark purple laths, m.p. 251–253°.

Anal. Calcd. for $C_{22}H_{24}O_4N_4$: C, 64.69; H, 5.92. Found: C, 64.73; H, 6.13.

The semicarbazone crystallized from chloroform–ethanol as sparkling plates, m.p. 247–248°.

Anal. Calcd. for $C_{17}H_{25}ON_3$: C, 71.54; H, 8.12. Found: C, 71.15; H, 8.09.

When the cyclization was carried out with potassium hydroxide in aqueous methanol (*cf.* Shunk and Wilds[81]) under nitrogen, the best yield was obtained after 2.5 hours, and amounted to 73% as indicated by the ultraviolet spectrum. Cyclization could also be effected under acidic conditions (AcOH–HCl) at room temperature, but the maximum yield (by ultraviolet spectrum) was only 52%.

The over-all yield of tricyclic ketone (XXXVI) could be increased by carrying out the base cyclization with the residues obtained from the mother liquors after removal of the crystalline ethyl vinyl ketone adduct (XXXV) (see above). One thousand four hundred and eighty grams of these residues (derived from *ca.* 2500 g. of bicyclic ketone (XV)) was dissolved in dioxane (5.5 l.) and the solution was stirred vigorously with 10% aqueous potassium hydroxide (5 l.) under nitrogen for three hours. The product was isolated with ether and distilled at 10^{-3} mm., when a mobile low-boiling fraction (*ca.* 400 g.) and a viscous yellow high-boiling fraction (*ca.* 200 g.) were obtained. Redistillation of the former gave recovered bicyclic ketone (XV) (297 g., 12% over-all recovery), b.p. 73–75° (0.2 mm.), which solidified completely, m.p. 25–29°. The high-boiling portion was converted to the semicarbazone of (XXXVI) in the usual way. The derivative after one crystallization weighed 108 g. (2.5% additional yield based on (XV)), and had m.p. 245–247°. It was stirred and refluxed for 24 hours with ligroin (2400 cc.), ethanol (700 cc.) and 2 *N* sulfuric acid (1800 cc.). The tricyclic ketone after one crystallization weighed 81 g. (94% recovery) and had m.p. 70–72°. The total yield of tricyclic ketone (XXXVI) from (XV) corrected for recovered bicyclic ketone is thus *ca.* 57%.

1,14-Dimethyl-2-keto-$\Delta^{1(12),6}$-decahydroanthracene (iv).—The ketone (iii), obtained as by-product in the earlier preparations of the bicyclic ketone (XV), was also converted through the stages of formylation, ethyl vinyl ketone addition and cyclization to a tricyclic ketone by the procedure described above. The product, which is best represented by the formula (iv), crystallized from aqueous methanol as colorless prisms, m.p. 81–82°.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.42; H, 9.63. Found: C, 83.32; H, 9.82.

Infrared spectrum: bands at 5.99 μ (conjugated carbonyl) and 6.12 μ (weak; conjugated double bond).

Ultraviolet spectrum: λ_{max} 249 mμ (ε 15,100).

The 2,4-dinitrophenylhydrazone crystallized from ethanol–ethyl acetate as red shiny plates, m.p. 201–203°.

Anal. Calcd. for $C_{22}H_{26}O_4N_4$: C, 64.37; H, 6.39; N, 13.65. Found: C, 64.42; H, 6.55; N, 13.60.

The semicarbazone, after crystallization from chloroform–methanol, had m.p. 251–253°.

2-Keto-14-methyl-$\Delta^{1(11),6,9}$-octahydrophenanthrene (v).—Methyl vinyl ketone was treated with the hydroxymethylene compound (XXXIV) in the presence of potassium *t*-butoxide in *t*-butanol as described above for the higher homolog. The adduct, m.p. 99–104°, was cyclized with potassium hydroxide in aqueous dioxane as before. The resulting tricyclic ketone (v) after crystallization from ether–petroleum ether had m.p. 76–80°.

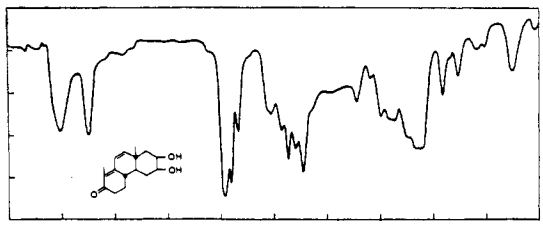
Ultraviolet spectrum: λ_{max} 281 mμ (ε 29,400).

1,14-Dimethyl-2-keto-6,7-dihydroxy-$\Delta^{1(11),9}$-decahydrophenanthrene (Isomers A and B) (XL).—Osmium tetroxide (68.48 g.) dissolved in sodium-dried ether (750 cc.) was cooled in ice. The solution was added to the tricyclic

(81) Shunk and Wilds, THIS JOURNAL, **71**, 3946 (1949).

ketone (XXXVI) (61.56 g.) dissolved in ice-cold ether (1.5 l.), with swirling. The mixture was set aside in the dark at room temperature for five to eight days, and the brown complex was then filtered off and washed with ether. It was dissolved in methylene dichloride (1 l.) and shaken mechanically with a solution of mannitol (350 g.) and potassium hydroxide (100 g.) in water (2.6 l.) until the organic layer became pale-yellow (*ca.* one hour). The methylene chloride layer was separated, the aqueous layer was saturated with salt and extracted four times with chloroform. The combined organic solutions were washed with salt solution, dried and evaporated at the water-pump. The residue (yield *ca.* 90%) crystallized when scratched. It was triturated with warm benzene (*ca.* 250 cc.), the mixture was cooled, and the solid was filtered off. It weighed 49 g., and had m.p. 138–152°. Recrystallization from chloroform–benzene gave the isomer A (34.55 g., 49%), m.p. 152–156.5° (47–52% yields were obtained in other experiments). The analytical sample, obtained by crystallization from a large volume of benzene, formed silky needles, m.p. 157.5–158.5°. This isomer was used for the subsequent experiments.

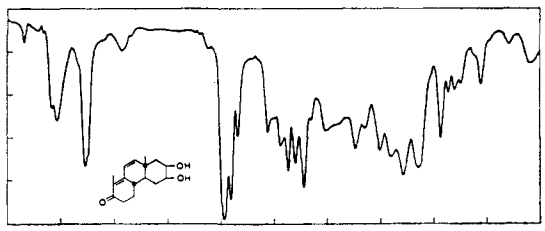
Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.24; H, 8.45. Found: C, 72.87; H, 8.61.



Ultraviolet spectrum: λ_{max} 289 mμ (ϵ 26,300).

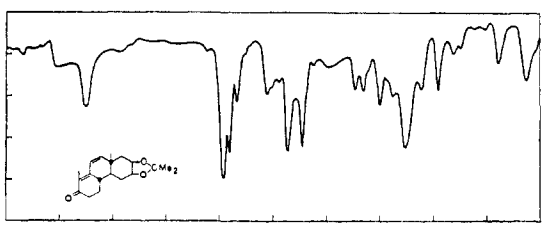
The combined mother liquors on evaporation left a semi-solid residue, from which by fractional crystallization from chloroform–benzene a further quantity (*ca.* 8%, total yield *ca.* 57%) of the glycol A was obtained. In addition the isomer B could be isolated as bold prisms, m.p. 181–182°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.24; H, 8.45. Found: C, 73.22; H, 8.44.



When the osmium tetroxide hydroxylation was carried out in the presence of pyridine, the reaction time was considerably reduced. However, the product was much darker in color, and no improvement in yield was achieved.

1,14-Dimethyl-2-keto-6,7-dihydroxy-$\Delta^{1(11),9}$-decahydrophenanthrene Acetonide (XLI).—The glycol (XL) (20 g., m.p. 152–156.6°) dissolved in acetone (2 l., dried over K_2CO_3) was shaken vigorously with anhydrous copper sulfate (100 g.) for 36 hours. The salt was filtered off, and the filtrate was shaken with anhydrous potassium carbonate (*ca.* 50 g.) for 20 minutes. The filtered solution was evaporated at the water-pump, and the residue, after being heated at *ca.* 50° (0.2 mm.) (to remove the mesityl oxide formed during the reaction), solidified. Crystallization from benzene–petroleum ether gave the acetonide (19.1 g.; 83%) as transparent prisms, m.p. 95–98°, raised to 98–99° by further crystallization.



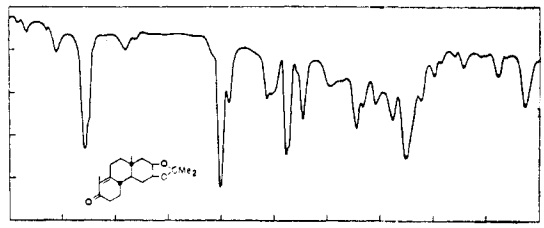
Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.32; H, 8.73.

The mother liquors consist of a mixture of the acetonide (XLI) and the unchanged glycol (XL). By recycling the combined mother liquors from a number of experiments, the yield of the acetonide was increased to over 90%.

After a large number of experiments had been carried out, a product of m.p. 116–118.5° was obtained; this proved to be a polymorphic modification of the lower melting form.

1,14-Dimethyl-2-keto-6,7-dihydroxy-$\Delta^{1(11)}$-dodecahydrophenanthrene Acetonide (XLII). (A) By **Partial Hydrogenation** of (**XLI**).—The doubly unsaturated acetonide (14.73 g.) dissolved in dry benzene (100 cc.), was shaken in hydrogen in the presence of a palladium–strontium carbonate catalyst[72] (7.3 g., 2%) at 28° and 765 mm. In 3.5 hours 1224 cc. of gas (equivalent to 1.02 double bonds) had been absorbed, and uptake had stopped. Removal of catalyst and solvent left a solid residue which on crystallization from benzene–petroleum ether gave the mono-unsaturated acetonide (XLII) (12.65 g., 85%), m.p. 153–156°. The yields in other experiments varied between 82 and 87%. The analytical sample, obtained by further crystallization from the same solvent mixture or from aqueous acetone, had m.p. 157.5–158.5°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.37.



Ultraviolet spectrum: λ_{max} 250 mμ (ϵ 15,200).

The ultraviolet spectrum of the mother liquors from this experiment showed that they still contained a considerable proportion of the required mono-unsaturated acetonide (XLII); this material could be separated most conveniently in the form of the very insoluble methylanilinomethylene compound (XLVIII) (see below).

(B) By **Partial Hydrogenation** of (**XL**).[82]—The crude mono-unsaturated glycol (XLIV, R = H) (520 mg., λ_{max} 249 mμ, ϵ 9,200), prepared from (XL) by hydrogenation over palladium–strontium carbonate in ethyl acetate solution as described below in connection with the preparation of the triacetate (XLV) by method (A), was converted to the acetonide with anhydrous copper sulfate (3.0 g.) in dry acetone (100 cc.) as described before. The product after two crystallizations from ligroin had m.p. 122–136°, and only after repeated crystallization from this solvent or aqueous acetone could the acetonide (XLII) (195 mg., 30% based on (XL)), m.p. 153.5–154.5°, be obtained. There was no depression on admixture with a sample prepared by method A.

1,14-Dimethyl-2-keto-6,7-diacetoxy-$\Delta^{1(11),9}$-decahydrophenanthrene (XLIII).—The tricyclic glycol (XL) (isomer A, m.p. 152–156.5°) (1.0 g.) dissolved in dry pyridine (3.0 cc.) was cooled in ice, and acetic anhydride (3.00 cc.) was added. The solution was allowed to stand at room temperature for three days, and the product was then isolated with ether in the usual way. The diacetate (1.21 g., 92%) crystallized from ether–petroleum ether as large colorless prisms, m.p. 184.5–185.5°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.23; H, 7.68.

Infrared spectrum: bands at 5.79 μ (ester) and 6.05, 6.18 and 6.31 μ (doubly unsaturated ketone).

1,14-Dimethyl-2,6,7-triacetoxy-$\Delta^{1,10}$-decahydrophenanthrene (XLV). (A) By **Semi-hydrogenation of the Glycol (XL).**—The glycol (XL) (2.724 g., m.p. 155–157°) in absolute ethanol (125 cc.) was shaken in hydrogen in the presence of a palladium–strontium carbonate catalyst[72] (1.2 g., 2%) at 28° and 761 mm. When 256 cc. (1 mole) of gas had been

(82) This experiment was carried out before the best hydrogenation conditions had been discovered.

absorbed, the reaction was stopped, although there was no change in the rate of uptake at this point. The catalyst was filtered off and the solvent was evaporated. The crude mono-unsaturated glycol (XLIV, R = H) remained as a light yellow glass, which resisted attempts at crystallization. The ultraviolet spectrum showed λ_{max} 249 mμ (ε 9,300) and 289 mμ (ε 3,400). Assuming λ_{max} 249 mμ (ε 15,200) for the pure glycol (XLIV, R = H) (*cf.* the corresponding acetonide (XLII) described above), this would correspond to a 61% content of (XLIV, R = H), and a 13% content of unchanged (XL). The infrared spectrum showed a weak band at 5.82 mμ, indicative of some over-reduced material (saturated ketone). In other experiments, in which either ethanol or ethyl acetate was used as solvent, the ultraviolet maximum at 249 mμ varied between ε 9,200 and 9,800.

The crude glycol was heated to boiling with acetyl chloride (72 cc.) and acetic anhydride (48 cc.) under reflux in an oil-bath with the exclusion of moisture; a slow stream of nitrogen was passed over the surface of the boiling solution. The oil-bath was heated to 100° at first, and the temperature was slowly raised, as the acetyl chloride was driven off, so as to keep the solution refluxing gently. After two hours the bath temperature had reached 130°, and after a further two hours had reached 150°. It was kept there for another half-hour, the solution was cooled, and the solvents were removed at the water-pump. The residue solidified when scratched, and on crystallization from methanol gave the enol triacetate (XLV) (2.22 g., 55% based on the glycol (XL)) as transparent prisms, m.p. 142.5–145.5°. The analytical sample, obtained by further crystallization from the same solvent, had m.p. 146–147.5°.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.66; H, 7.75. Found: C, 68.26; H, 7.98.

Infrared spectrum: bands at 5.78 μ (broad; enol ester carbonyl and ester carbonyl superimposed) and 5.98 μ (double bond of enol ester).

Ultraviolet spectrum: λ_{max} 234 mμ (ε 16,600).

Unlike the acetonide (XLII) which was also prepared from the crude glycol (see above), this triacetate had excellent crystallizing properties, and could easily be separated from the accompanying impurities.

(B) **By Semi-hydrogenation of the Diacetate (XLIII).**—The diacetate (XLIII) (500 mg.) in reagent grade benzene (40 cc.) was shaken in hydrogen in the presence of a palladium–strontium carbonate catalyst[72] (250 mg., 2%) at 28° and 767 mm. After 40 minutes 37.8 cc. of gas (1.07 moles) had been taken up, and absorption stopped completely. Removal of catalyst and solvent left a viscous non-crystalline residue (501 mg.). The ultraviolet spectrum showed λ_{max} 249 mμ (ε 11,700) (no max. at 289 mμ). This corresponds to a *ca.* 77% content of (XLIV, R = Ac) if ε 15,200 (*cf.* the acetonide described above) is assumed for the pure compound.

When the above reaction was carried out in dry benzene as solvent, even more favorable results were obtained. When ethanol or ethyl acetate were substituted for benzene, the products showed ultraviolet maxima at 249 mμ varying between ε 8000 and 8700.

The crude partially hydrogenated diacetate (XLIV, R = Ac) (446 mg.) described above was converted to the enol acetate with acetyl chloride (14 cc.) and acetic anhydride (9 cc.) as described previously for the corresponding glycol (XLIV, R = H). Crystallization of the solid reaction product from methanol yielded the enol triacetate (XLV) (360 mg., 72% based on (XL)), m.p. 145–147.5°, undepressed on admixture with a sample prepared as in (A).

1,14-Dimethyl-2-keto-6,7-diacetoxyperhydrophenanthrene (Isomers A, B, and C) (viii), (vii) and (ix).—The doubly unsaturated diacetate (XLIII) (5.85 g.) in methanol (350 cc.) was shaken in hydrogen in the presence of a palladium–strontium carbonate catalyst[72] (2.5 g., 2%). In about two hours 853 cc. of gas had been absorbed at 24° and 761 mm. (equivalent to 2.07 double bonds) and uptake stopped. The catalyst and the solvent were removed; addition of ethyl acetate to the residue caused the precipitation of a small amount of flocculent precipitate which was removed by filtration. The filtrate was evaporated, the residue was diluted with a little ethyl acetate and petroleum ether, and kept overnight at 0°. The crystalline precipitate, m.p. 157–175°, was combined with a second crop, m.p. 140–160°, and on recrystallization from the same mixture of solvents gave isomer A (752 mg.) as colorless pyramids, m.p. 176–181°. The analytical sample had m.p. 182–184°.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.28; H, 8.75.

Infrared spectrum: bands at 5.79 μ (ester) and 5.82 μ (saturated carbonyl).

The mother liquors, after the removal of the first two crystalline crops, were evaporated, and the oily residue (4.91 g.) was chromatographed on neutral alumina (180 g.). Five hundred-cc. fractions were collected:

Fraction	Solvent	Weight, mg.	M.p., °C.
1–2	Benzene–pet. ether (1:3)	13	Oil
3–5	Benzene–pet. ether (1:1)	272	133–135
6–9	Benzene–pet. ether (1:1)	574	130–134
10	Benzene–pet. ether (1:1)	84	129–133
11	Benzene–pet. ether (1:1)	88	124–132
12	Benzene–pet. ether (1:1)	100	118–134
13–16	Benzene–pet. ether (1:1)	266	107–129
17–18	Benzene–pet. ether (2:1)	191	118–135
19	Benzene–pet. ether (2:1)	120	147–149
20–25	Benzene	902	147–148.5
26	Benzene	64	147–149
27	Benzene–ethyl acetate (20:1)	306	118–184
28–29	Benzene–ethyl acetate (20:1)	293	Indefinite
30–33	Benzene–ethyl acetate (10:1)	252	Indefinite
34–35	Benzene–ethyl acetate (3:1)	241	Gum
36–39	Ethyl acetate	485	Gum
40–43	Methanol	596	Gum
	Total	4.847 g.	

Fractions 3–11 (1.018 g.) were combined and recrystallized from ethyl acetate–petroleum ether. Isomer B was obtained as wedges, m.p. 134.5–135.5°. After a number of experiments, in which this form was consistently obtained, another polymorphic form, m.p. 145–146° (finely ground) was observed. The two forms were identical, as evidenced by mixture melting point and infrared spectra.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.24; H, 8.74.

Infrared spectrum: bands at 5.78 μ (ester) and 5.82 μ (saturated carbonyl).

Fractions 19–26 (1.086 g.) were combined and crystallized from ethyl acetate–petroleum ether. Isomer C was obtained as heavy prismatic clusters, m.p. 147–150°, raised to 150–151° on further crystallization.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.51; H, 8.74.

Infrared spectrum: bands at 5.78 μ (ester) and 5.83 μ (saturated carbonyl).

The three isomers crystallized in characteristic different forms, by which they could be recognized. Any two of the isomers on admixture mutually depressed each other in melting point. There was no indication of the presence of any other pure substance, although occasionally crystallization of some chromatogram fractions yielded beautiful silky needles, melting unsharply at any point between *ca.* 100 and 150°. These were found to be a mixture of isomers A and C; when these substances were mixed and recrystallized, the same phenomenon occurred. No other pair of isomers showed this behavior.

Direct Inversion of Isomer A (viii) to Isomer C (ix).—A solution of isomer A (100 mg., m.p. 178–181°) in methanol (1 cc.) was refluxed with a solution of sodium (18.2 mg., 2.78 equivalents) in methanol (0.7 g.) for 1.75 hours. Acetic acid (52 mg.) in ether (5 cc.) was added, and the solvent was removed *in vacuo*. Pyridine (0.5 cc.) and acetic anhydride (0.5 cc.) were added to the residue, and the mixture was warmed at 70° for one hour. The product was isolated with ether in the usual manner, and after two crystallizations from ethyl acetate–petroleum ether had m.p. 149.5–151°. On admixture with a sample of isomer C (m.p. 148.5–151°) no depression in melting point was observed. The melting point of isomer B was depressed to 108–127° on admixture.

Under the same conditions isomer B (m.p. 134–135°) was recovered unchanged, as evidenced by mixture melting point.

B/C-*cis*-1,14-Dimethyl-2-keto-6,7-dihydroxyperhydrophenanthrene Acetonide (xi).—Isomer B (190 mg., m.p. 134–135°) was refluxed with potassium hydroxide (200 mg.) in methanol (5 cc.) for four hours. Water was added, and the product was removed by repeated chloroform extraction. Evaporation of the solvent left the crude glycol (133 mg., 92%) as a colorless glass which resisted attempts at crystallization.

A portion of the glycol (27 mg.) was reacetylated with pyridine (0.5 cc.) and acetic anhydride (0.5 cc.) in the usual way. Crystallization of the product from ethyl acetate–petroleum ether gave back isomer B, m.p. 134.5–135°, undepressed with the starting material.

The remaining glycol (106 mg.) dissolved in dry acetone (25 cc.) was shaken with anhydrous copper sulfate (500 mg.) for 48 hours. The solid was filtered off, the filtrate was shaken with potassium carbonate (*ca.* 500 mg.) for a few minutes, and was then again filtered and evaporated. The residue was heated at 0.1 mm. to remove mesityl oxide, and solidified when cooled. Crystallization from petroleum ether gave the *cis* saturated acetonide (xi) (105 mg., 87%) as colorless prisms, m.p. 111.5–112.5°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.48; H, 9.89.

B/C-*trans*-1,14-Dimethyl-2-keto-6,7-dihydroxyperhydrophenanthrene Acetonide (x). Method I (from Isomer A).—Isomer A (921 mg., m.p. 178–181°) was hydrolyzed with potassium hydroxide (1.2 g.) in methanol (20 cc.) as described in the preceding experiment for isomer B. The crude B/C-*trans* glycol (678 mg., 97%) formed a glass which resisted all attempts at crystallization.

A portion of the glycol (28 mg.) was acetylated with acetic anhydride (0.5 cc.) in pyridine (0.5 cc.) as before. Crystallization from ethyl acetate–petroleum ether yielded isomer C (22 mg.); m.p. 147–149°, undepressed on admixture with an authentic specimen.

The remaining glycol (650 mg.) in dry acetone (300 cc.) was shaken with anhydrous copper sulfate (6 g.) for 36 hours. The product, isolated in the same way as the B/C-*cis* isomer, crystallized on standing. The B/C-*trans* saturated acetonide (x) (566 mg., 76%) crystallized from petroleum ether as colorless prisms, m.p. 99–101°, raised to 104° on further crystallization.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.92; H, 9.96.

Method II (From Isomer C).—Isomer C (379 mg., m.p. 147–150°) was hydrolyzed with potassium hydroxide (410 mg.) in methanol (10 cc.) as described previously for isomers B and A. The glycol remained as a glass and weighed 280 mg. (97%).

The glycol in dry acetone (70 cc.) was shaken with anhydrous copper sulfate (2 g.) for 42 hours. Isolation in the usual way and recrystallization from petroleum ether gave the B/C-*trans* saturated acetonide (x) (256 mg., 79%), m.p. 101–103°, undepressed on admixture with the material prepared by method I.

2-Methylanilinomethylene-6-methylcyclohexanone (xiii).—2-Hydroxymethylene-6-methylcyclohexanone was prepared from 2-methylcyclohexanone, sodium methoxide and ethyl formate,[83] the molar proportion of reagents being 1:3:5.[81] It was obtained in *ca.* 85% yield as a pale yellow liquid, b.p. 78–79° (18 mm.) (v. Auwers and Krollpfeiffer[84] give b.p. 79.2–79.4° (10 mm.); Johnson and Posvic[83] give b.p. 76–77° (8 mm.)).

Freshly distilled methylaniline (58.9 g.) was added to a solution of the hydroxymethylene ketone (57.6 g.) in benzene (150 cc.). An exothermic reaction occurred and water started to separate. After 13 hours at room temperature, the aqueous layer was separated, and the organic layer was evaporated on the steam-bath during the course of 1.5 hours. Distillation of the residue gave first a low-boiling fore-run, and then the methylanilinomethylene ketone (xiii) (80.5 g., 86%) as a yellow oil, b.p. *ca.* 150° (0.2 mm.). The fore-run on heating with benzene, followed by evaporation and distillation, yielded another 5.0 g. of (xiii) (total yield 91%). The product solidified when scratched and after one crystallization from petroleum ether formed pale yellow needles of constant m.p. 51–52.5°.

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35. Found: C, 78.23; H, 8.22.

Infrared spectrum: bands at 6.10, 6.23, 6.46 + 6.56 (broad doublet) and 6.72 μ.

The crystalline material, kept at room temperature, soon turned to an oil.

2-(β-Carboxyethyl)-2-methylcyclohexanone (xiv).—A 3.5% solution of Triton B in *t*-butanol (20 cc., prepared from the commercial reagent in methanol by evaporating the solvent at room temperature *in vacuo*, diluting with *t*-butanol, and repeating the process) was diluted with water (1.5 cc.) and this reagent was added to a solution of the methylanilinomethylene ketone (xiii) (6.84 g.) in *t*-butanol (250 cc.). Freshly distilled acrylonitrile (2.4 g.) and a trace of hydroquinone were added, and the homogeneous solution was allowed to stand at room temperature under nitrogen for 22 hours. Ether and dilute hydrochloric acid were added, the aqueous layer was well extracted with ether, and the combined organic fractions were washed with salt solution, dried and evaporated. The residue was heated to boiling with a solution of potassium hydroxide (20 g.) in water (100 cc.) for seven hours under nitrogen. The acidic material, isolated in the usual way, was distilled and yielded the keto-acid (xiv) (4.45 g., 81%) as a colorless liquid, b.p. 134–136° (0.2 mm.), which solidified, m.p. 46–49°. Crystallization from ether–petroleum ether gave the analytical sample as prisms, m.p. 49–50°.[85]

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.55; H, 8.93.

Infrared spectrum: broad ascending band, *ca.* 2.90–3.30 μ (typical carboxyl absorption); 5.84 μ (broad; superimposed acid carbonyl and saturated ketone).

The semicarbazone crystallized from ethanol as fine prisms, m.p. 199–200°.

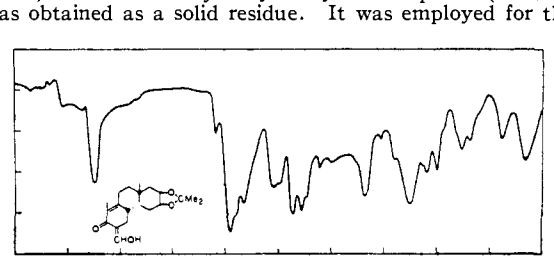
Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.93. Found: C, 54.43; H, 8.08.

2-Keto-10-methyl-Δ⁸-1-oxaoctahydronaphthalene.—A solution of the keto-acid (xiv) (27.05 g.) in acetic anhydride (100 cc.) containing a trace of sodium acetate was refluxed for 21 hours. The acetic anhydride was evaporated at the water-pump, and the residue was distilled. The enol lactone (22.86 g., 94%) was obtained as a water-white liquid, b.p. 82° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.91; H, 8.65.

Infrared spectrum: bands at 5.76 μ (enol ester carbonyl) and 5.95 μ (enol ester double bond).

1,14-Dimethyl-2-keto-3-hydroxymethylene-6,7-dihydroxy-Δ¹⁽¹¹⁾-dodecahydrophenanthrene Acetonide (XLVII).—Freshly prepared sodium methoxide (from 7.8 g. of sodium) was covered with dry benzene (230 cc.) in a nitrogen atmosphere, and ethyl formate (44 cc., dried over K_2CO_3 and freshly distilled) was added to the stirred mixture in a thin stream. After 30 minutes at room temperature, a solution of the mono-unsaturated acetonide (XLII) (32.1 g., m.p. 153–156°) in benzene (210 cc.) was added gradually. The mixture was stirred in nitrogen until a thick gelatinous precipitate separated (one to two hours) and was then allowed to stand overnight. A phosphate buffer solution (prepared by adding 205 cc. of 0.7 molar KH_2PO_4 to 1645 cc. of 0.7 molar $Na_2HPO_4 \cdot 7H_2O$) was added with ice-cooling, and the aqueous layer (*ca.* *p*H 8) was well extracted with ether. The dried organic layers were evaporated, and the crude hydroxymethylene compound (XLVII) was obtained as a solid residue. It was employed for the



(83) Johnson and Posvic, THIS JOURNAL, **69**, 1361 (1947).

(84) v. Auwers and Krollpfeiffer, *Ber.*, **48**, 1226 (1915).

(85) This compound has since been described [Frank and Pierle, THIS JOURNAL, **73**, 724 (1951)] as a solid, m.p. 48°.

subsequent step without further purification, but could be crystallized from ether–petroleum ether to give clusters of light-yellow prisms, m.p. 128–130°.

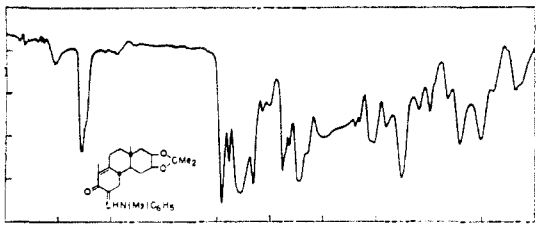
Anal. Calcd. for $C_{29}H_{38}O_4$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.58.

Ultraviolet spectrum: λ_{max} 258 mμ (ε 9,300) and 310 mμ (ε 5,300). In 0.1 *N* alcoholic NaOEt solution: λ_{max} 246 mμ (ε 12,000) and 361 mμ (ε 9,800).

The compound gave a strong green ferric chloride color.

1,14-Dimethyl-2-keto-3-methylanilinomethylene-6,7-dihydroxy - $\Delta^{(11)}$ - dodecahydrophenanthrene Acetonide (XLVIII).—The above crude hydroxymethylene compound (XLVII) (prepared from 32.1 g. of (XLII)) was dissolved in methanol (370 cc.), and methylaniline (76 cc.) was added. The yellow solution was allowed to stand at room temperature for 24 hours, and the precipitated methylanilinomethylene ketone (XLVIII) was filtered off and washed with petroleum ether until the odor of methylaniline could no longer be detected. It formed beautiful bright-yellow sparkling plates, m.p. 219–222°, and weighed 39.2 g. (88% based on (XLII)). Only very small additional crops could be obtained from the filtrate. The analytical sample was obtained by crystallization from chloroform–methanol, and had m.p. 222–224°.

Anal. Calcd. for $C_{37}H_{35}O_3N$: C, 76.93; H, 8.37; N, 3.32. Found: C, 76.59; H, 8.30; N, 3.51.



When the reaction was carried out under the conditions used by Birch and Robinson[34] in other cases (boiling in benzene solution in a constant water separator and removing water azeotropically), or by heating in toluene solution at 100°,[34] poorer yields of (XLVIII) were obtained (*cf.* the preparation of (xii) described below).

The mother liquors from the preparation of the crystalline mono-unsaturated acetonide (XLII) were also converted to (XLVIII). Twenty grams of the oily residue (derived from *ca.* 140 g. of the doubly unsaturated acetonide (XLI)) was converted to the crude hydroxymethylene ketone with the same proportions of sodium methoxide and ethyl formate as had been used for the crystalline compound. Treatment with methylaniline in methanol then gave a precipitate of the crude methylanilinomethylene ketone (XLVIII), m.p. 214–221°; after one crystallization from methanol–chloroform, it weighed 9.4 g. (additional 5% yield based on (XLI)), and had m.p. 218–221°. The over-all yield from (XLI) is thus *ca.* 80%.

B/C-*trans*-1,14-Dimethyl-2-keto-3-methylanilinomethylene-6,7-dihydroxyperhydrophenanthrene Acetonide (xii).—Dry freshly distilled ethyl formate (0.4 cc.) was added to a suspension of freshly prepared sodium methoxide (130 mg.) in dry benzene (1.6 cc.). The mixture was allowed to stand under nitrogen for ten minutes with occasional swirling and a solution of the *trans* saturated acetonide (x) (245 mg., m.p. 101–103°) in benzene (2 cc.) was then added. After *ca.* ten minutes a gelatinous precipitate separated, and the mixture was allowed to stand under nitrogen at room temperature overnight. Ice and water were added, and the solution was extracted well with ether. The organic layer, after being washed with water, dried and evaporated left a crystalline residue (208 mg.), m.p. 126–129° (large depression with starting material), which gave an intense violet ferric chloride color, and proved to be the hydroxymethylene compound. Apparently in this case the α-hydroxymethylene ketone was extractable by ether from an alkaline solution. The alkaline aqueous layer was adjusted to *ca.* *p*H 7.4 by the addition of 20 cc. of an aqueous buffer solution (prepared by the addition of 2.5 cc. of a 0.7 molar KH_2PO_4 solution to 17.5 cc. of a 0.7 molar $Na_2HPO_4 \cdot 7H_2O$ solution). An organic oil separated, and this was isolated with ether in the usual way. The crystalline residue (52 mg.) had m.p. 122–128° and was shown to be additional hydroxymethylene ketone by mixture melting point. Total yield of crude product was 97%.

The crude hydroxymethylene compound (260 mg.) and methylaniline (120 mg.) were dissolved in dry benzene (20 cc.). The solution was heated to boiling in nitrogen under a constant water separator and fresh benzene was added to keep the volume constant as the solvent distilled off. After one hour another 50 mg. of methylaniline was added, and distillation was continued for another hour. The solvent was then evaporated, and the residue, after being heated at 0.005 mm., partially solidified. Crystallization from ligroin gave the methylanilinomethylene ketone (xii) (152 mg., 46%) as faintly cream-colored prisms, m.p. 154–158°. The analytical sample was obtained by further crystallization from the same solvent, and had m.p. 159.5–161°.

Anal. Calcd. for $C_{23}H_{37}O_3N$: C, 76.56; H, 8.81; N, 3.31. Found: C, 76.66; H, 8.95; N, 3.22.

Infrared spectrum: bands at 6.09, 6.24, 6.46 + 6.5 (broad doublet) and 6.72 μ.

The compound gave a ferric chloride color only after several minutes.

No additional product could be obtained by treating the mother liquors again with methylaniline in benzene. It was subsequently found that this type of reaction proceeds more satisfactorily when carried out in methanol solution at room temperature (see above).

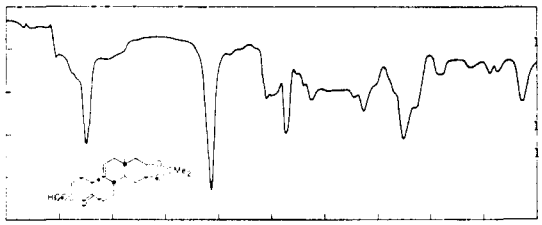
1-(β-Carboxyethyl)-1,14-dimethyl-2-keto-6,7-dihydroxy-Δ^{10}-dodecahydrophenanthrene Acetonide [α Isomer (LIV) and β Isomer (LV)].—The methylanilinomethylene compound (XLVIII) (84.0 g.) was dissolved in a hot mixture of benzene (1400 cc.) and *t*-butanol (2800 cc.). The bright-yellow solution was cooled to 50°, freshly distilled acrylonitrile (37 g.) was added, and then a mixture of a 3.5% solution of Triton B in *t*-butanol (140 cc.)[86] and water (9.8 cc.). The homogeneous reaction mixture was kept at 50° under a nitrogen atmosphere for 45 hours, when it had become light-red in color. The solvent was removed at the water pump, and ether (*ca.* 1 l.) was added to the dark residue. The ether solution was decanted from the dark insoluble tar, which was washed again several times with ether. Evaporation of the combined organic extracts left the crude acrylonitrile addition product (LIII) (109.2 g.) as a viscous golden-yellow gum.

The above product was divided into two equal portions, and each was heated to boiling with a solution of potassium hydroxide (56 g.) in water (350 cc.) in a nitrogen atmosphere until evolution of ammonia had ceased (usually about seven hours). The original dark-yellow rather viscous upper layer decreased in size and changed to a very light yellow mobile liquid (methylaniline). Each reaction mixture was cooled to room temperature and thoroughly extracted with ether. A small amount of yellow solid stayed suspended at the interface, and this on filtration proved to be recovered methylanilinomethylene compound (XLVIII) (2.5 g. total), m.p. 216–220°. The combined ether extracts from both runs were shaken with dilute hydrochloric acid and water, and were then dried ($MgSO_4$) and evaporated. The total neutral product (4.3 g.) was a viscous yellow oil and was not further investigated. The combined alkaline extracts were cooled to 0° in ice, a little crushed ice and ether were added, and the stirred mixture was carefully acidified with 2 *N* hydrochloric acid. The aqueous layer was washed again rapidly with ether, and the combined organic layers were extracted several times with small quantities of water. The dried ($MgSO_4$) ether extract was evaporated, and the residue was heated at 80° (1 mm.) for one hour to remove some volatile material. The acidic product formed a very viscous yellow sirup, and weighed 59.3 g. [79% from (XLVIII)]. It was stirred with ether (*ca.* 150 cc.) with slight warming; a crystalline precipitate soon separated, but stirring had to be continued for about half an hour to ensure complete dissolution of the remaining gum. The mixture was set aside at 0° overnight, and the crystalline α acid was filtered off and washed with a little cold ether. It formed small sparkling plates, m.p. 168–172°. Small second and third crops, melting a few degrees lower, were

(86) This solution was prepared by evaporating a solution of Triton B in methanol (14 cc., 35%) at room temperature at *ca.* 1 mm. *t*-Butanol was added to the residue, and the solvent was again removed at room temperature. This process was repeated several times, and the solution was finally diluted to 140 cc. with *t*-butanol.

obtained by leaving a solution of the concentrated mother liquors in a little ether–petroleum ether at 0° for several days. The total crystalline α acid (LIV) weighed 24.7 g. [33% from (XLVIII)] and after crystallization from ether–petroleum ether the melting point was raised to 171–173°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.78; H, 8.55.



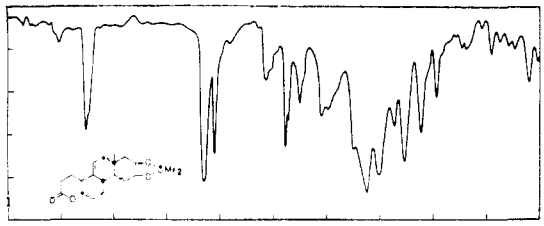
The remaining gummy acidic product, containing the β isomer (LV), weighed 34.6 g. (46%) and resisted attempts at further crystallization (but see footnote 38).

The infrared spectrum of this material was similar in general outline to that of the α acid, and contained no trace of absorption at 6.0 μ.

In earlier experiments, similar yields of the α acid (LIV) were obtained by the procedure described above, but all the crops had m.p. *ca.* 146–149°; crystallization from ether–petroleum ether gave soft pearly plates of constant m.p. 148–150°. This material had the same infrared spectrum as the higher-melting form, into which it could be converted by seeding.

***dl*-3-Keto-16,17-dihydroxy-$\Delta^{5,9(11)}$-10-epi-4-oxa-D-homoandrostadiene Acetonide (α Enol Lactone) (LVIII).**—The α keto-acid (LIV) (7.54 g.) and redistilled acetic anhydride (65 cc.) were heated to boiling in an atmosphere of nitrogen by immersion in an oil-bath kept at *ca.* 150°. After two hours, anhydrous sodium acetate (*ca.* 30 mg.) was added, and boiling was continued for a further two hours. The acetic anhydride was removed at the water-pump, and the solid residue was dissolved in a mixture of benzene and ether. The solution was washed twice with dilute sodium carbonate, and then with water. The extract was dried ($MgSO_4$) and evaporated, and the residue was crystallized from benzene–ligroin. The α enol lactone (LVIII) (5.11 g., 71%) separated as plates, m.p. 177–178°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.69; H, 8.44. Found: C, 73.53; H, 8.40.



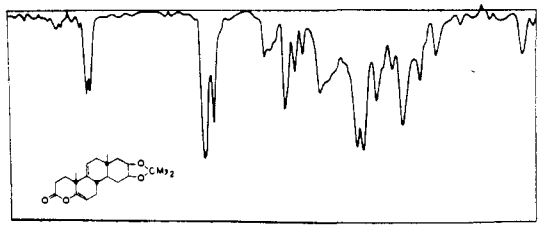
The total gummy residue, after the crystalline lactone had been removed, was heated with aqueous sodium hydroxide (50 cc., 10%) on the steam-bath in nitrogen for 20 minutes. The clear yellow solution was cooled in ice, washed with ether, carefully acidified with dilute hydrochloric acid, and again shaken with ether. The latter extract was washed with water, dried and evaporated. The residue on crystallization from a little ether yielded recovered α keto acid (0.92 g., 12%), m.p. 168–170°.

When the addition of sodium acetate was omitted in the preparation of the enol lactone, variable yields (15, 30, 38%) of the crystalline product were obtained, although the refluxing time was 18 hours (even smaller yields were obtained when this time was reduced). In these cases, the infrared spectra of the mother liquors showed bands at 5.51 and 5.72 μ, typical of an acid anhydride and a band at 5.84 μ (saturated ketone). This was due to the presence of the mixed anhydride (xvi), and the mother liquors, when boiled with acetic anhydride and a trace of sodium acetate, were largely converted to the crystalline α enol lactone (LVIII).

When the pure α enol lactone was heated on the steam-bath with 5% aqueous sodium hydroxide solution for five minutes, it dissolved completely. The α keto-acid, obtained in quantitative yield by acidification and ether extraction of the solution, had m.p. 170–173° after one crystallization, and there was no depression on admixture with an authentic sample.

***dl*-3-Keto-16,17-dihydroxy-$\Delta^{5,9(11)}$-4-oxa-D-homoandrostadiene Acetonide (β Enol Lactone) (LIX).**—The crude β keto-acid (LV) [34.6 g. from the experiment described above; obtained from 84 g. of the methylanilinomethylene compound (XLVIII)], acetic anhydride (265 cc.) and anhydrous sodium acetate (150 mg.) were heated to boiling in an atmosphere of nitrogen for four hours. The acetic anhydride was removed at the water-pump, and the product was isolated in the same way as has been described above for the α isomer. The residue was dissolved in a small volume of ether, and the solution was left overnight at 0°, whereupon the crude β enol lactone (LIX) crystallized. It weighed 6.13 g. and had m.p. 202–218°. The mother liquors gave a second crop, m.p. 170–205°; recrystallization of this from benzene–ligroin gave a further 3.24 g., m.p. 204–216°, which was combined with the first crop (total yield 9.37 g., 13% based on the methylanilinomethylene compound (XLVIII)). The infrared spectrum of this material was not substantially different from that of the analytical sample. Additional crops of lower melting point were obtained from the combined mother liquors. On admixture of the high-melting β lactone with the α isomer (m.p. 177–178°), the melting point was depressed to 155–164°. On recrystallization from ether or carbon tetrachloride, the analytical sample, m.p. 223–225°, was obtained.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.69; H, 8.44. Found: C, 73.63; H, 8.35.



4-Benzyl-Δ^5-4-azacholestenone-3 (*Cf.* xviii, R = $CH_2C_6H_5$).—The keto-acid (LVI)[39] (1.55 g.), derived from cholestenone, and freshly distilled benzylamine (6 cc.) were heated in nitrogen at 180° for one hour. The cooled solution was diluted with ether, and was washed successively with dilute hydrochloric acid, sodium carbonate solution and water. The dried extract was evaporated, and the residue (1.81 g., 99%) completely solidified. One crystallization from ligroin gave a sample of the cyclic benzylamide as needles, m.p. 124–127°.

Infrared spectrum: band at 6.09 μ (lactam carbonyl) and slight inflection at *ca.* 6.0 μ.

4-Phenyl-Δ^5-4-azacholestenone-3 (*Cf.* xviii, R = C_6H_5).—The keto-acid (LVI)[39] (1.00 g.) and redistilled aniline (6.5 cc.) were heated in nitrogen at 180° for 11 hours. The cyclic anilide, isolated in the usual way, after crystallization from ligroin weighed 0.955 g. (84% yield) and showed m.p. 154–155.5°.

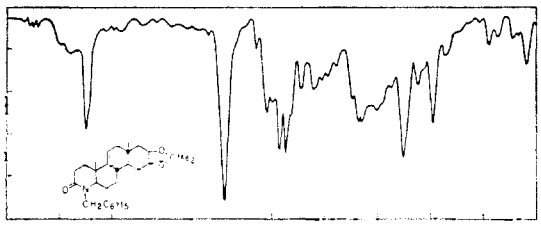
Anal. Calcd. for $C_{32}H_{47}ON$: C, 83.22; H, 10.26. Found: C, 83.34; H, 10.18.

Infrared spectrum: band at 6.09 μ (lactam carbonyl) and slight inflection at *ca.* 6.0 μ.

When the heating time was one hour, the yield of the lactam was 33%, while a four-hour heating period gave a 72% yield.

***dl*-3-Keto-4-benzyl-16,17-dihydroxy-$\Delta^{5,9(11)}$-10-epi-4-aza-D-homoandrostadiene Acetonide (α Cyclic Benzylamide)** (*Cf.* xviii, R = $CH_2C_6H_5$). A.—The crystalline α keto-acid (LIV) (1.500 g.) and freshly distilled benzylamine (6 cc.) were heated in nitrogen at 180° for one hour. The cooled solution was diluted with ether, and was washed successively with dilute ice-cold hydrochloric acid, sodium carbonate solution and water. The dried extract was evaporated, and the residue (0.951 g., 53%) solidified after standing for several days. It was used for the subsequent reaction. Crystallization from ether–ligroin gave the pure cyclic benzylamide (0.716 g., 40%) as shining plates, m.p. 145–146.5°.

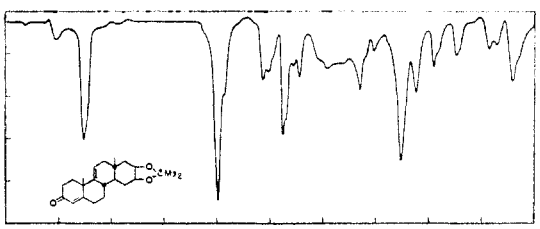
Anal. Calcd. for $C_{29}H_{37}NO_3$: C, 77.82; H, 8.33. Found: C, 77.53; H, 8.32.



B.—The reaction was carried out as in A with the α keto-acid (LIV) (400 mg.) and benzylamine (1.6 cc.) for one hour at 180°. The excess reagent was evaporated *in vacuo*, the residue was dissolved in ether, and was washed successively with dilute acetic acid, sodium carbonate solution and water. The dried extract on evaporation left a residue (440 mg.), the infrared spectrum of which showed it to consist of a mixture of the cyclic benzylamide obtained in A, and the keto amide described below. The product was dissolved in a little ether, and left at 0° overnight. A crystalline product (90 mg.), m.p. 172–175°, separated; the keto amide structure (*cf.* xix) was assigned to this material on the basis of the infrared spectrum [bands at 5.83 μ (saturated carbonyl), 5.98 μ (amide carbonyl) and 6.63 μ (monosubstituted amide)].

***dl*-3-Keto-16,17-dihydroxy-$\Delta^{4,9(11)}$-10-epi-D-homoandrostadiene Acetonide (α Tetracyclic Ketone) (LX).** **Method A.**—A solution of methylmagnesium iodide in ether (5 cc.) was prepared from magnesium (130 mg.) in the usual way. The crude α cyclic benzylamide (910 mg.) dissolved in benzene (2 cc.) and ether (15 cc.) was added all at once, and the stirred reaction mixture was heated under reflux under nitrogen for 40 hours. The solvent was evaporated, and a solution of potassium hydroxide (1 g.) in water (2 cc.) and methanol (20 cc.) was added to the residual complex. The mixture was boiled under nitrogen for two hours, and was then diluted with ether and water. The organic layer was washed with dilute ice-cold hydrochloric acid and water. The dried extract was evaporated, and the residue (310 mg.) was purified by chromatography. The fractions eluted with benzene were recrystallized from ligroin. The α tetracyclic ketone (LX) (25 mg., 1.8% based on the α keto-acid) separated as small needles, m.p. 166–168.5°, raised to 168–169° by further crystallization.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.50; H, 9.05. Found: C, 77.11; H, 9.18.



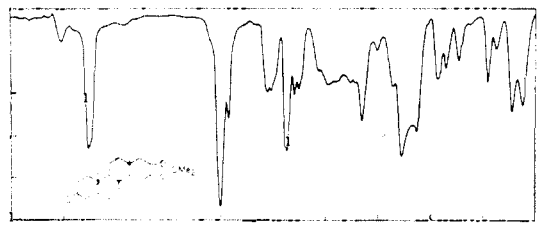
Ultraviolet spectrum: λ_{max} 237 mμ (ε 14,100).

Method B.—The α enol lactone (LVIII) (358 mg.) was dissolved in benzene (3 cc.) and ether (3 cc.), and the solution was stirred at 0° in a nitrogen atmosphere. An ethereal methylmagnesium bromide solution (5.1 cc., 0.237 molar, 20% excess) was added dropwise during the course of 40 minutes, and the mixture was allowed to stand at 0° for a further 12 hours. It was decomposed with cold dilute hydrochloric acid, the organic layer was washed with sodium carbonate solution and water, and was then dried and evaporated. The residue (360 mg.) was heated with sodium hydroxide (0.23 g.) in water (1 cc.) and methanol (25 cc.) under nitrogen for two hours, and the product was isolated with ether in the usual way. It weighed 147 mg., and on addition of ether, over-reacted material (46 mg.), m.p. 232–236°, precipitated (infrared spectrum: no bands in 5.0–6.5 μ region). The mother liquors were dissolved in benzene and filtered through an alumina column (2.5 g.) which was then well washed with benzene. Evaporation of the solvent and crystallization from ether at −70° gave the α tetracyclic ketone (LX) (41 mg., 11.5%), m.p. 162–168°, raised to 167–168° on recrystallization, and undepressed on admixture with the sample prepared by method A. Crystalline α keto-acid could be recovered from the acid fraction.

Lithium methyl could be substituted for the Grignard reagent in this reaction, but the yield of (LX) was thereby decreased.

***dl*-3-Keto-16,17-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene Acetonide (β Tetracyclic Ketone) (LXI).**—A solution of methylmagnesium bromide in ether was prepared from methyl bromide and magnesium in the usual manner. The clear solution was blown into a dry buret (fitted with ground glass joints at both ends) by means of a nitrogen stream, and the Grignard reagent was kept under nitrogen throughout. It was standardized just before use and was found to be 0.336 molar. Thirty-three and two-tenths cc. (1 equivalent) of this solution was added dropwise during the course of three hours to a stirred solution of the crude β enol lactone (LIX) (4.00 g., m.p. *ca.* 202–218°) in dry benzene (65 cc.) and dry ether (65 cc.), which was kept at *ca.* −18° during the addition by means of an ice–salt cooling bath. The reaction was conducted in nitrogen, and every effort was made to add the Grignard reagent as small drops at a steady rate throughout (this was facilitated by having a small tip fused on to the bottom of the buret). The clear light-yellow solution was stirred at −18° for another five minutes, and was then decomposed by the addition of excess ice-cold dilute hydrochloric acid. The aqueous layer was washed with ether, the combined organic extracts were shaken several times with small amounts of water, and were then dried and evaporated. The product remained as a crystalline residue, but was not further investigated at this stage. It was dissolved in methanol (300 cc.), sodium hydroxide (3.0 g.) in water (30 cc.) was added, and the solution was heated under reflux in nitrogen for two hours. It was cooled, water and ether were added, and the aqueous layer was washed well with ether. The combined organic extracts were washed with salt solution, and were then dried and evaporated. The solid residue was dissolved in benzene, filtered through a small alumina column (*ca.* 4 g.) which was then washed with benzene until no more crystalline material was eluted. Crystallization of the product from ethanol gave the β tetracyclic ketone (LXI) [2.30 g., 58% based on the crude β enol lactone (LIX); 7.6% over-all from the methylanilinomethylene compound (XLVIII)] as stout laths, m.p. 197–202°, raised to 200–202° by further crystallization from the same solvent or from benzene–ligroin.

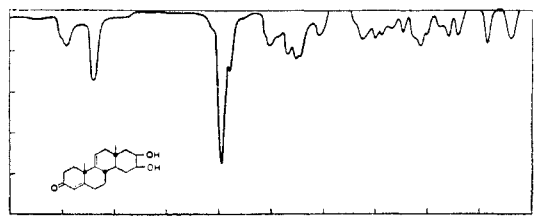
Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.50; H, 9.05. Found: C, 77.31; H, 9.27.



Ultraviolet spectrum: λ_{max} 239 mμ (ε 14,100).

The over-all yield of (LXI) (from XLVIII) was raised to *ca.* 10% by carrying out the Grignard reaction and cyclization with the lower melting additional crops of the β enol lactone (LIX). In this way, 2.17 g. of lactone, m.p. 150–185°, yielded another 0.70 g. (32%) of (LXI), m.p. 196–202°.

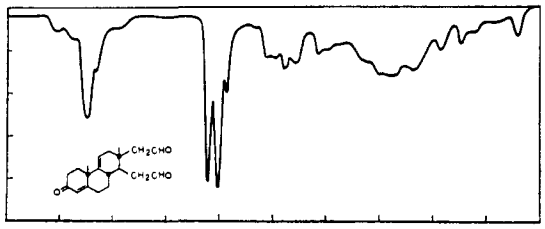
***dl*-3-Keto-16,17-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene (LXII).**—The β tetracyclic acetonide (LXI) was dissolved in warm dioxane, a little dilute hydrochloric acid was added, and the solution was allowed to cool, finally in an ice-bath. The glycol was precipitated in nearly quantita-



tive yield as regular prisms, m.p. 248–253° (*dec.*) after one crystallization from a large volume of ethanol.

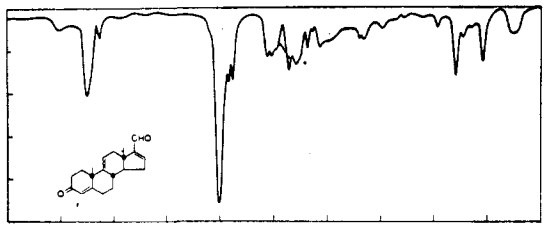
Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.56; H, 9.10.

***dl*-$\Delta^{9(11),16}$-Bisdehydro-20-norprogesterone (LXIV). A.**—The β tetracyclic acetonide (LXI) (500 mg.) was dissolved in dioxane (25 cc., freshly distilled from sodium) and a solution of periodic acid dihydrate (450 mg.) in distilled water (8 cc.) was added at room temperature. The solution was allowed to stand for 14 hours at 0° under nitrogen, and the bulk of the solvent was then distilled off at room temperature at the water-pump. Water and ether were added to the residue, the aqueous layer was washed with ether, and the combined organic extracts were washed with dilute sodium carbonate solution and water. The dried ($MgSO_4$) solution was evaporated, finally at 50° (20 mm.), and the crude dialdehyde (LXIII) crystallized on scratching. It was found in other experiments that this compound, after one crystallization from ether, formed prisms, m.p. 129–132°.



It was however rather unstable, and there was no advantage in isolating it. The total crude dialdehyde was dissolved in dry benzene (30 cc.), and acetic acid (3 drops) and piperidine (2 drops) were added. The solution was heated at 60° in a slow stream of nitrogen under a constant water separator for one hour. It was then cooled, diluted with ether, and the organic layer was washed successively with dilute hydrochloric acid, sodium carbonate solution and water. The dried extract was evaporated, and the residue was crystallized from benzene–petroleum ether. The unsaturated aldehyde (LXIV) (275 mg., 66%) separated as needles, m.p. 178–178.5°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.45; H, 8.40.



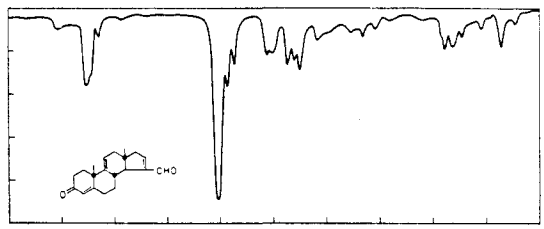
The mother liquors yielded further crops of solid, m.p. *ca.* 130–135°; the infrared spectra indicated these to be mixtures of the two isomeric aldehydes (LXIV) and (LXV).

B.—A solution of periodic acid dihydrate (1.8 g.) in water (32 cc.) was added to a mixture of the β tetracyclic glycol (LXII) (1.62 g.) and redistilled dioxane (120 cc.) at room temperature. The reaction mixture was shaken occasionally, and two further lots of the acid (0.5 g.) in water (5 cc.) were added at two-hour intervals. After six hours the solution had become homogeneous, and was allowed to stand for a further 12 hours at 0°. The dialdehyde was isolated in the same way as previously, and solidified when scratched. It was cyclized in benzene (120 cc.) with acetic acid (9 drops) and piperidine (6 drops). The unsaturated aldehyde (LXIV) (775 mg., 51%), had m.p. 172.5–176°, raised to 177.5–178.5° by crystallization from aqueous methanol.

***dl*-3-Keto-15-formyl-$\Delta^{4,9(11),15}$-androstatriene (LXV).**—The dialdehyde (LXIII) was prepared by the periodic acid cleavage of the β tetracyclic acetonide (LXI) (1.590 g.) as described above. It was divided into three portions, and each was heated with distilled water (16 cc., freshly boiled before use to expel dissolved oxygen), pure dioxane (25 cc.) and a trace of hydroquinone under nitrogen in sealed glass tubes at 145° for 7.5 hours. The cooled solutions were combined, ether was added, and the organic layer was washed with sodium carbonate solution and water. The dried extract was evaporated, and the residue was crystallized from methanol. The mother liquors were sublimed at 140–160° (10^{-3} mm.), and another crop of solid was obtained from the sublimate. The total cyclic aldehyde (LXIV) (0.355 g., 27%) had m.p. 168–173°, raised to 177–178° by further crystallization.

The mother liquors from several such experiments were combined, and chromatographed on alumina. The fractions that were eluted with benzene–ether (90:10) and (80:20) were crystallized from benzene–petroleum ether. The isomeric cyclic aldehyde (LXV) formed short rods, m.p. 154.5–156°. On admixture with the aldehyde (LXIV), the melting point was depressed to 130–136°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.38; H, 8.37.



Methyl *dl*-3-Keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI).—Sodium dichromate dihydrate (3.30 g.), dissolved in water (*ca.* 3 cc.) was diluted to 100 cc. with acetic acid. Eleven and six-tenths cc. of this solution was added to the cyclic aldehyde (LXIV) (1.160 g.) dissolved in acetic acid (8 cc.), and the solution was allowed to stand at room temperature for ten hours. Water and ether were added, and the organic layer was washed with dilute potassium carbonate solution. The acidic fraction, obtained by acidification and ether extraction of the alkaline layer, weighed 405 mg. (33%). The neutral fraction (778 mg.) on crystallization from aqueous methanol gave unchanged aldehyde (541 mg., 47%), m.p. 168–176°. The latter in acetic acid (4 cc.) was again oxidized with the above dichromate solution (5.4 cc.) as before. The acidic fraction was combined with the previous one, and the neutral fraction after recrystallization was reoxidized. This process was then repeated once more. The combined acidic product (704 mg., 58%) crystallized in part when scratched, but was not further purified at this stage.

The crude acid was dissolved in a little benzene, excess ethereal diazomethane was added, and the solution was allowed to stand at room temperature for 20 minutes. Excess reagent and solvent were removed at the water-pump, and the crystalline residue, the infrared spectrum of which showed it to be contaminated with material in which the ester grouping is no longer α,β-unsaturated (inflection at 5.78 μ), was purified by chromatography on alumina. The fractions eluted with benzene and benzene–ether (2:1) after one crystallization from acetone gave the pure keto-ester (LXVI) (377 mg., 30%), m.p. 160–162° (Kof.).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.16; H, 8.13.

The infrared spectrum is shown in Fig. 1.

Oxidation of the aldehyde (LXIV) with neutral silver oxide, alkaline silver oxide, Tollens reagent, Fehling solution or chromium trioxide in aqueous acetone gave inferior results.

Methyl *d*-3-Keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI) from Kendall's Compound F.—Compound F acetate (5.0 g. in methanol (500 cc.)) was hydrolyzed with potassium bicarbonate (5.0 g.) in water (100 cc.) at room temperature, as described by Reichstein and v. Euw.[87] The crude compound F (*ca.* 4.4 g.), obtained as the neutral fraction,[88] dissolved in freshly distilled dioxane (500 cc.) was cleaved with periodic acid dihydrate (5.0 g.) in water (175 cc.), and the α-hydroxy acid produced, was treated, in methanol solution, with excess ethereal diazomethane, as described by v. Euw and Reichstein.[46] The resulting methyl 3-keto-11β,17α-

(87) Reichstein and v. Euw, *Helv. Chim. Acta*, **21**, 1183 (1938).

(88) A non-crystalline acidic fraction (0.43 g.) was also obtained, but this was not further investigated.

Δ^4-etiocholenate (LXVII)[89] (3.9 g.) was obtained as a crystalline residue. A pure sample was obtained by crystallization from acetone–ether, and had m.p. 202–203° (Kof.) (v. Euw and Reichstein[46] give m.p. 207–208°).

The crude ester (LXVII) (1.0 g.) was heated under reflux with dry pyridine (40 cc.) and freshly distilled phosphorus oxychloride (4 cc.) for 1.5 hours under nitrogen by means of an oil-bath kept at *ca.* 140°. The cooled red-black solution was poured into iced dilute hydrochloric acid, and the mixture was extracted with ether (most of the color remained in the aqueous layer). The organic layer was shaken with water, sodium carbonate solution and again water. The experiment was repeated with a second batch of crude (LXVII) (1.5 g.), pyridine (60 cc.) and phosphorus oxychloride (6 cc.), and the combined ethereal extracts were dried and evaporated. The yellow residue (548 mg.), dissolved in a little benzene, was filtered through a short column of alumina (*ca.* 4 g.) which was then washed well with benzene. The product (405 mg.) partly solidified when scratched, and on trituration with cold ether, followed by filtration and crystallization of the solid from methanol gave pure methyl *d*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI) (85 mg.) as prisms, m.p. 188–190° (Kof.); $[\alpha]^{23}_D$ +180 ± 5° (0.92%, chloroform).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 77.27; H, 8.03. Found: C, 76.73; H, 8.11.

The infrared spectrum is shown in Fig. 1.

Further small quantities of the trienic ester (LXVI) could be obtained by chromatography of the mother liquors after removal of the crystalline crops, and crystallization of the fractions eluted with benzene–ether (2:1). The over-all yield of (LXVI) from compound F acetate was thus raised to *ca.* 4%.

Attempted dehydration of (LXVII) with pyridine–phosphorus oxychloride at room temperature or on the steam-bath gave less satisfactory results.

Hydrolysis and Re-esterification of (LXVI).—Potassium hydroxide (100 mg.) in distilled water (1.5 cc.) was added to the *d*-trienic ester (LXVI) (12.5 mg.) dissolved in freshly distilled dioxane (1.5 cc.), and the homogeneous solution was heated on the steam-bath under reflux in nitrogen for two hours. Ether and water were added, and the acidic fraction was obtained by acidification and ether extraction of the alkaline layer. It was obtained as a crystalline residue (12.0 mg.); $[\alpha]^{24}_D$ +168 ± 8° (0.52%, chloroform). One crystallization from benzene–petroleum ether gave a specimen, m.p. 226–230° (Kof.) (dec.). There was no appreciable amount of material in the neutral fraction.

The total acidic fraction was dissolved in a little benzene, excess ethereal diazomethane was added, and the solution was allowed to stand at room temperature for 20 minutes. Evaporation of solvent left a crystalline residue, the infrared spectrum of which (in CS_2) was practically identical with that of the pure trienic ester (LXVI) (no indication of attack on the 16,17-double bond could be detected). After one crystallization from acetone–ether, it had m.p. 185–189° (Kof.) undepressed on admixture with an authentic sample.

The *dl*-keto ester (LXVI) was similarly hydrolyzed to the corresponding acid, m.p. 226–229° (Kof.) (dec.).

Resolution of Methyl *dl*-3-Keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI).—Preliminary experiments were carried out with the natural *d*-enantiomorph. This compound (17 mg.) in ethanol (2 cc.) was added to sodium borohydride (20 mg.) dissolved in ethanol (4 cc.), and the solution was allowed to stand at room temperature for 1.5 hours. Water was added, and the organic material was extracted with chloroform. The product (17 mg.) consisted essentially of a mixture of the 3α- and 3β-hydroxy-esters (LXVIII) and (LXIX). The infrared spectrum had bands at 2.82 μ (hydroxyl), 5.82 μ (α,β-unsaturated ester grouping still present), no band at 6.0 μ (reduction of α,β-unsaturated ketone). There was a slight inflection at 5.78 μ, perhaps indicating some reduction of the 16,17-double bond.[90]

The crude reduction product was dissolved in 90% aqueous ethanol (2 cc.) and digitonin (80 mg.) in 90% ethanol (3 cc.) was added. A precipitate was formed in a few seconds, and it was filtered off after one hour. It weighed 35 mg., and the steroid was regenerated by dissolving it in a few drops of pyridine and adding ether. Filtration and evaporation of the solvent left the crude 3β-hydroxy-ester (LXIX) (7.4 mg.) as a solid residue. Crystallization from aqueous methanol gave feathery needles (2.63 mg.), m.p. 106–110° (Kof.); $[\alpha]^{21}_D$ +115 ± 7° (0.33%, chloroform). This material probably contained water of crystallization; on further crystallization from methanol it melted partly at 110° and partly at *ca.* 135° (Kof.), whereas on crystallization from ligroin, it formed stout prisms, m.p. 141–142° (Kof.).

The *dl*-trienic ester (LXVI) (52 mg.) in ethanol (4 cc.) was reduced with sodium borohydride (65 mg.) in ethanol (6 cc.) in the same way as described above for the *d*-compound. The infrared spectrum of the reduction product (52 mg.) was identical with that of the corresponding product derived from the *d*-ester. It was dissolved in 90% aqueous ethanol (5 cc.) and a solution of digitonin (150 mg.) in 90% ethanol (5 cc.) was added. A precipitate appeared after a few seconds, and was filtered off after 30 minutes.[91] Treatment of this material (104 mg.) with pyridine and ether in the usual way gave the partially resolved 3β-hydroxy-ester (LXIX) (21 mg.), which on scratching crystallized; $[\alpha]^{24}_D$ +35 ± 2° (2.6%, chloroform). The digitonin precipitation, followed by fission with pyridine and ether, was repeated twice more, and the product (6.0 mg.) then showed $[\alpha]^{24}_D$ *ca.* +83° (chloroform).

This material was dissolved in dry benzene (3.5 cc.) and dry acetone (1.5 cc.), aluminum *t*-butoxide (100 mg.) was added, and the solution was refluxed in nitrogen for 30 hours. Ether and dilute hydrochloric acid were added, the organic layer was washed with water, dried and evaporated, finally at 0.1 mm. to remove mesityl oxide. The product was freed of impurities by chromatography on alumina, and the fractions eluted with benzene–ether (2:1) were combined. They weighed 2.7 mg. and showed $[\alpha]^{24}_D$ *ca.* +130° (chloroform). Three crystallizations from acetone–ether gave the pure methyl *d*-3-ketoetiocholatrienate (LXVI) (1.10 mg.) as shining prisms, m.p. 188–191° (Kof.); $[\alpha]^{24}_D$ +182 ± 7° (0.14%, chloroform). The appearance of this material under the microscope was indistinguishable from that of the natural compound, and there was no depression in melting point on admixture.

Repetition of the resolution, in essentially the above manner, with 241 mg. of the *dl*-ester, gave 11.7 mg. of very pure synthetic *d*-trienic ester, m.p. 189–191° (Kof.), $[\alpha]^{24}_D$ +184° ± 7°, identical in all respects with material from natural sources.

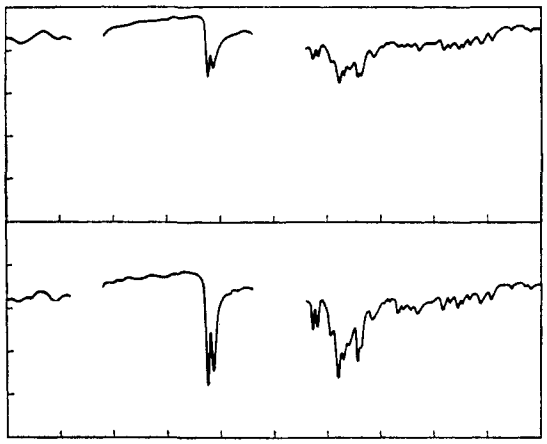
Methyl 3-Ketoetioallocholanate (LXX, R = Me) by Hydrogenation and Oxidation of Methyl *d*-3-Keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI).—The *d*-3-ketoetiocholatrienic ester (LXVI) (50 mg.) in acetic acid (4 cc.) was shaken in hydrogen in the presence of a prereduced platinum oxide catalyst (50 mg.) until no more gas was absorbed. The catalyst was filtered off, the solvent was evaporated and the residue was oxidized with chromium trioxide (50 mg.) in acetic acid (5 cc.) at room temperature overnight. Isolation of the neutral material with ether in the usual way gave an oily product (45 mg.). This material was carefully chromatographed on alumina. A fraction (4.4 mg.) eluted with petroleum ether–benzene (1:1) after two crystallizations from ligroin gave pure methyl 3-ketoetioallocholanate (1.2 mg.) as stout needles, m.p. 177–180° (Kof.) (allotropic transformation to transparent plates at *ca.* 150°). An authentic sample crystallized similarly from ligroin, and had m.p. 178–180° (Kof.) (identical transformation at *ca.* 150°).[92] There was no depression on admixture with the synthetic specimen. Comparative infrared spectra follow:

(89) Owing to a misprint, this compound was designated as the 17β-hydroxy compound in a preliminary communication [Woodward, Sondheimer, Taub, Heusler and McLamore, THIS JOURNAL, **73**, 2403 (1951)].

(90) When the sodium borohydride reduction was carried out at −10°, the infrared spectrum showed a moderate band at 6.0μ (incomplete reduction of the ketone). When lithium aluminum hydride was used for the reduction, the product had a pronounced band at 5.78μ (reduction of the 16,17-double bond without reduction of ester group).

(91) The filtrate slowly deposited a second crop, and this was filtered off after two days. It weighed 28 mg., and regeneration with pyridine and ether in the usual way gave a crystalline residue (5.4 mg.); $(\alpha)^{24}_D$ −74 ± 4° (0.67%, chloroform). It has not been determined whether this material is enriched in the "unnatural" *l*-3β-hydroxy-ester (LXIX) or in the "unnatural" 3α-hydroxy-ester (LXVIII).

(92) *Inter al.*, Steiger and Reichstein [*Helv. Chim. Acta*, **20**, 1040 (1937)] give m.p. 176-179°; Djerassi and Scholz [footnote 50] give m.p. 181-182°.



Micro spectrum in Nujol mull: above, synthetic; below, natural.

Although the A/B *trans* keto-ester was the only product isolated *directly* from reductions carried out in the above manner, we have found that the A/B *cis* isomer, methyl 3-ketoetiocholanate, predominates in the reaction mixtures (*cf.* footnote 49). Thus from 175 mg. of keto-ester mixture (prepared as described above), by sodium borohydride reduction and digitonin separation, 24 mg. of crude methyl 3β-hydroxyetioallocholanate was obtained, which after chromatography and crystallization afforded 5.5 mg. of nearly pure, and thence 1.8 mg. of very pure *trans* ester, m.p. 175–177° (Kof.) (undepressed on admixture with an authentic sample, m.p. 176–178°). From the fraction not precipitated by digitonin, *50 mg. of 3-desoxy material*, and 70 mg. of crude methyl 3α-hydroxyetiocholanate were separated by chromatography. From the latter, by rigorous purification, 15 mg. of the very pure *cis* ester, m.p. 142–144° (Kof.) (undepressed on admixture with an authentic sample) was obtained.[93]

Hydrolysis of Methyl 3-Keto-Δ^4-etiocholenate (LXXI, R = OMe) to 3-Keto-Δ^4-etiocholenic Acid (LXXI, R = OH).—The ester (LXXI, R = OMe) (190 mg., m.p. 132.5–133.5°)[94] dissolved in methanol (8 cc.) was refluxed with potassium hydroxide (0.4 g.) in water (0.5 cc.) under nitrogen for 14 hours. Most of the solvent was evaporated, dilute hydrochloric acid was added, and the precipitate (175 mg.) after crystallization from acetone gave the pure keto-acid (LXXI, R = OH), m.p. 250–254° (dec.) (Kof.).[95] The infrared spectrum had bands at 5.82 μ (saturated acid), 6.00 μ (conjugated carbonyl) and 6.16 μ (weak; conjugated double bond).

Hydrolysis of Methyl 3-Ketoetioallocholanate (LXX, R = Me) to 3-Ketoetioallocholanic Acid (LXX, R = H).—The saturated ester (LXX, R = Me) (65 mg.) in methanol (3 cc.) was refluxed with potassium hydroxide (200 mg.) in water (0.4 cc.) under nitrogen for 12 hours. Most of the solvent was evaporated, water was added to dissolve the precipitated potassium salt, and the solution was then acidified with dilute hydrochloric acid. The precipitated acid (LXX, R = H) (60 mg.) after crystallization from acetone formed plates, m.p. 257–261° (Kof.).[96]

Methyl 3β-Hydroxyetioallocholanate (LXXV, R = H, R′ = OMe).—The saturated keto-ester (LXX, R = Me) (162 mg.) in ethanol (5 cc.) was reduced with sodium borohydride (150 mg.) in ethanol (5 cc.) for four hours at room temperature. Most of the solvent was evaporated, and water was added. The crude solid, consisting presumably mainly of the 3β-hydroxy-ester (LXXV, R = H, R′ = OMe) together with a small amount of the 3α-isomer,[97] had m.p. 156–167° (Kof.), and this value could not be raised by crystallization from acetone–ligroin or methanol. It was therefore dissolved in 90% aqueous ethanol and digitonin (640 mg.) in 90% ethanol was added. A gelatinous precipitate was formed immediately, which after 30 minutes was filtered off; it was dissolved in the minimum volume of pyridine, excess ether was added, the precipitated digitonin was filtered off, and the filtrate was evaporated. Crystallization of the residue from methanol gave the 3β-hydroxy-ester (LXXV, R = H, R′ = OMe) (105 mg.) as stout needles, m.p. 168–170°. An authentic sample, prepared by catalytic hydrogenation of methyl 3β-hydroxy-Δ^5-etiocholenate, had m.p. 169–172°[98] and there was no depression on admixture.

3β-Acetoxyetioallocholanic Acid (LXXV, R = Ac, R′ = OH).—The saturated hydroxy-ester (LXXV, R = H, R′ = OMe) (100 mg.) in methanol (5 cc.) was refluxed with potassium hydroxide (0.2 g.) in water (0.4 cc.) for 12 hours. Water was added, and the acidic fraction, after acidification, was isolated with ether in the usual way. One crystallization from acetone gave the pure 3β-hydroxy acid (LXXV, R = H, R′ = OH), m.p. 249–251° (Kof.).[99] Pyridine (1 cc.) and acetic anhydride (0.6 cc.) were added to 140 mg. of (LXXV, R = H, R′ = OH), and the solution was heated at 60° for three hours. Water (0.6 cc.) was added, and the mixture was heated at *ca.* 95° (steam-bath) for two hours. More water was added, and the crude 3β-acetoxy acid (LXXV, R = Ac, R′ = OH) was filtered off. It weighed 146 mg., and after one crystallization from methanol formed pearly plates, m.p. 246–250° (Kof.). An authentic sample, prepared by the hydrogenation of 3β-acetoxy-Δ^5-etiocholenic acid [kindly furnished by Dr. E. B. Hershberg (Schering)], had m.p. 247–250° (Kof.),[100] and there was no depression on admixture. On admixture with the starting hydroxy-acid (LXXV, R = H, R′ = OH), the melting point was depressed to 208–237°.

3β-Acetoxyallopregnanone-20 (LXXV, R = Ac, R′ = CH_3).—3β-Acetoxyetioallocholanic acid (LXXV, R = Ac, R′ = OH) (1.60 g.) was dissolved in thionyl chloride (5 cc.) at 0° with exclusion of moisture. The solution was kept at this temperature for 14 hours and then at 25° for 1.5 hours. Evaporation at 30° at the water-pump left a residue which solidified when scratched. Crystallization from petroleum ether gave the acid chloride (LXXV, R = Ac, R′ = Cl) (1.51 g., 90%) as long needles, m.p. 134–136° (Kof.).[101] A small sample of this on being heated with water regenerated the acetoxy-acid (mixture melting point).

A solution of methylmagnesium bromide in ether (20 cc.) was prepared from magnesium (0.5 g.) and methyl bromide (2 cc.) in the usual way in a nitrogen atmosphere. Dry anhydrous cadmium chloride (3.5 g.) was added,[102] and the mixture was refluxed with stirring for one hour. Most of the ether was evaporated, dry benzene (*ca.* 20 cc.) was added, and the acid chloride (1.30 g.) in benzene (5 cc.) was then introduced dropwise. The stirred mixture was refluxed for 1.5 hours, ether and ice-cold dilute hydrochloric acid were added, and the organic layer was freed of acidic material by being shaken with potassium carbonate solution. Drying and evaporation gave a solid residue, which on crystallization from aqueous methanol yielded crude 3β-acetoxy-allopregnanone-20 (LXXV, R = Ac, R′ = CH_3) (1.13 g., 92%), m.p. 139–144° (Kof.).[103] This material was of sufficient purity to be employed in the subsequent steps.

(93) This observation provides an alternate route to the androgenic and progestational hormones.

(94) *Inter al.*, Steiger and Reichstein (footnote 93) give m.p. 130-131°; v. Euw and Reichstein [*Helv. Chim. Acta*, **27**, 1851 (1944)] give m.p. 131-132°.

(95) *Inter al.*, Miescher, Hunziker and Wettstein [*ibid.*, **23**, 400 (1940)], give m.p. 256–260°; Julian, Meyer and Printy [THIS JOURNAL, **70**, 887 (1948)] give m.p. 250-255°.

(96) *Inter al.*, Steiger and Reichstein [*Helv. Chim. Acta*, **21**, 161 (1938)] give m.p. 258-261°; Ruzicka, Prelog and Wieland [*ibid.*, **26**, 2050 (1943)] give m.p. 253-254°.

(97) Shoppee and Summers [*J. Chem. Soc.*, 687 (1950)] showed that lithium aluminum hydride reduction of ring A-saturated 3-keto-steroids proceeds with high stereospecificity.

(98) *Inter al.*, Steiger and Reichstein (footnote 93) give m.p. 166-170°; Djerassi and Scholz (footnote 50) give m.p. 174-175°. Very pure material in our hands, had m. p. 176-178° (Kof.) (see above).

(99) *Inter al.*, Marker and Wittle [THIS JOURNAL, **61**, 1329 (1939)] give m.p. 250-252°; Ruzicka, Plattner and Balla [*Helv. Chim. Acta*, **25**, 65 (1942)] give m.p. 247-249°; Sorkin and Reichstein [*ibid.*, **29**, 1209 (1946)] give m.p. 252-253°.

(100) Steiger and Reichstein, (footnote 93) and Marker and Wittle, (footnote 99) both give m.p. 247–249°.

(101) This compound was prepared, but not characterized, by Billeter and Miescher [*Helv. Chim. Acta*, **32**, 564 (1949)].

(102) *Cf.* Cason, *Chem. Revs.*, **40**, 15 (1947).

(103) *Inter al.*, Butenandt and co-workers, [*Ber.*, **67**, 1440, 1897 (1934); *Z. physiol. Chem.*, **227**, 84 (1934)] give m.p. 144.5°; Barton and Cox [*J. Chem. Soc.*, 783 (1948)] give m.p. 143.5-144.5°.

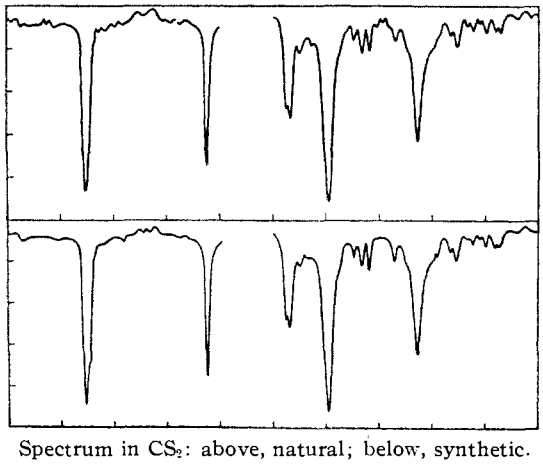
Isohexyl Bromide.—Isohexyl alcohol was prepared from isobutylmagnesium bromide and ethylene oxide. It had b.p. 149–152° (764 mm.), $n^{26}D$ 1.4132.[104] It was converted to the bromide by boiling 48% hydrobromic acid and concentrated sulfuric acid. The isohexyl bromide had b.p. 142–143.5° (763 mm.), $n^{27}D$ 1.4450.[105]

Cholestanol-3 (LXXVII, R = H).—Isohexylmagnesium bromide in dry ether (*ca.* 15 cc.) was prepared from isohexyl bromide (3 g.), magnesium (600 mg.), and a trace of iodine, in the usual way under nitrogen. The crude 3β-acetoxy-allopregnanone-20 (LXXV, R = Ac, R′ = CH_3) (800 mg.), dissolved in dry benzene (10 cc.), was added dropwise, whereupon a precipitate was formed. The mixture was stirred for one hour, and the solvent was then distilled off, while the volume was kept constant by the dropwise addition of benzene, until the temperature of the escaping vapors reached *ca.* 72°. The stirred mixture was heated under reflux for three hours, and was then decomposed with ice-cold dilute hydrochloric acid. The organic material was extracted with ether, and was finally heated at 140° (10^{-2} mm.). The oily residue (1.20 g.) contained 20-hydroxy-cholestanol-3 (LXXVI) and probably the C.20 epimer as well as triisohexylmethylcarbinol (formed by reaction of the C.3 acetate grouping with the Grignard reagent), which could not be removed by evaporation. The infrared spectrum showed no bands in the region of 5.0–6.5 μ; this indicated that the reaction at C.3 and at C.20 had gone to completion.

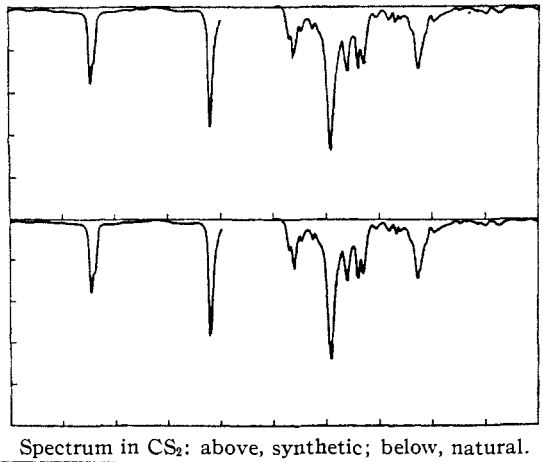
The crude reaction product (1.20 g.) was refluxed with acetic acid (15 cc.) for two hours, acetic anhydride (15 cc.) was added, and refluxing was continued for a further 30 minutes. The cooled solution was shaken in hydrogen with a prereduced platinum oxide catalyst (220 mg.) at 25° and 765 mm. Uptake of gas was rapid initially and after 15 minutes, 57 cc. had been absorbed. Gas absorption then slowed down, and after 30 minutes a steady slow uptake (*ca.* 0.6 cc./minute) was observed. A blank experiment was run with the same amounts of solvents and catalyst, and the same steady slow hydrogen uptake (*ca.* 0.6 cc./minute) was observed. This is probably due to the slow hydrogenolysis of acetic anhydride. The actual hydrogen uptake, after correction for this solvent effect, was 47.5 cc. (0.88 double bond; the dehydrated triisohexylmethylcarbinol is probably responsible for part of the hydrogen absorption). The catalyst was filtered off, the solvents were removed at the water-pump, and the residue, dissolved in petroleum ether, was chromatographed on alumina. Fractions 8–14 (eluted with petroleum ether) and 15–18 [eluted with petroleum ether–benzene (9:1)] all partially crystallized on scratching,[106] and were combined (387 mg.). Crystallization from ethanol readily gave cholestanol-3 acetate (LXXVII, R = Ac) (128 mg., 13.5% based on (LXXV, R = Ac, R′ = CH_3)), as thick needles, m.p. 109–110°. An authentic sample had m.p. 110°[107] and there was no depression on admixture. Comparative infrared spectra are shown above: The mother liquors were presumably enriched in the C.20 epimer of cholestanol acetate, but were not investigated further

The synthetic acetate (48 mg.) dissolved in hot methanol (10 cc.) was hydrolyzed by refluxing with potassium hydroxide (0.5 g.) in water (0.5 cc.) for two hours. Water was added, and the precipitate was filtered off. Crystallization from ethanol gave cholestanol-3 (LXXVII, R = H) (37 mg.) as pearly plates, which on recrystallization and drying over phosphorus pentoxide had m.p. 142–142.5°. An authentic sample had m.p. 142–143°,[108] and there was no depression on admixture.

Methyl 3α-Acetoxy-$\Delta^{9(11)}$-etiocholenate (LXXX, R = Ac).—Methyl *d*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (LXVI) (52 mg.) dissolved in dry benzene (4 cc.) was stirred in hydrogen in the presence of a palladium–strontium carbonate catalyst[72] (65 mg., 2% Pd). Gas absorption proceeded very slowly, and after two hours the catalyst was filtered off, the solvent was evaporated, and the residue in methanol (4 cc.) was again stirred in hydrogen with the palladium catalyst (65 mg.). Removal of catalyst and solvent, after 11 hours, left an oily residue. The infrared spectrum showed bands at 5.78 μ (saturated ester) and 5.84 μ (saturated carbonyl), but no band at 6.0 μ (absence of α,β-unsaturated carbonyl). This material consisted essentially of a mixture of methyl 3-keto-$\Delta^{9(11)}$-etiocholenate (LXXIX) and the corresponding allo isomer, but no satisfactory separation could be achieved by chromatography on alumina. The crystalline fractions eluted with ligroin–benzene (2:1 and 1:1) were combined (36.1 mg.), dissolved in ethanol (1 cc.) and treated at room temperature with sodium borohydride (40 mg.) in ethanol (1 cc.). Water was added, and the organic material was extracted with methylene chloride. The infrared spectrum showed bands at 2.82 and 2.98 μ (hydroxyl) and 5.78 μ (saturated ester), but no band at 5.84 μ (absence of saturated carbonyl). The product was dissolved in 90% methanol (4 cc.), and digitonin (155 mg.) in 90% methanol (2 cc.) was added. The granular precipitate (81 mg.) was filtered off after one hour, the filtrate was evaporated, and the residue was well extracted with benzene. The crude 3α-hydroxy-$\Delta^{9(11)}$-etiocholenate (LXXX) (17 mg.), obtained by evaporation of the solvent, in pyridine (1 cc.) was acetylated by heating with acetic anhydride (0.6 cc.) for a few minutes, and then allowing to stand at room temperature for ten hours. Crystallization of the product from aqueous methanol gave methyl 3α-acetoxy-$\Delta^{9(11)}$-etiocholenate (LXXX, R = Ac) (7.9 mg.) as fine needles, double m.p. 115–124° and 131–133° (Kof.), raised by further crystallization to double m.p. 126–128° and 134–136° (Kof.). An authentic sample, kindly provided by Dr. H. Heymann, had double m.p. 127–128° and 134–136° (Kof.),[109] and on admixture identical behavior was observed. Comparative infrared spectra follow:



Spectrum in CS_2: above, natural; below, synthetic.



Spectrum in CS_2: above, synthetic; below, natural.

(104) *Inter al.*, Norris and Cortese [THIS JOURNAL, **49**, 2640 (1927)] give b.p. 151.8–152.8°, $n^{21}D$ 1.4134.

(105) *Inter al.*, Buelens [*Rec. trav. chim.*, **28**, 113 (1909)] gives b.p. 146–147° (760 mm.), nD 1.4490.

(106) Representatives of these fractions on crystallization all yielded cholestanol-3. Apparently the C.20 epimer is not separated appreciably by chromatography.

(107) *Inter al.*, Willstätter and Mayer [*Ber.*, **41**, 2199 (1908)] give m.p. 110.5-111°.

(108) *Inter al.*, Bruce and Ralls ["Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 191] give m.p. 142-143°.

(109) Lardon and Reichstein [*Helv. Chim. Acta*, **28**, 1420 (1945)] give double m.p. 127-128° and 135-136°.

Methyl 3α-Acetoxy-11-ketoetiocholanate (LXXXIV, R = Ac, R' = OMe).—Methyl 3,11-diketoetiocholanate (LXXXIII, R = H)[110] (40 mg.) dissolved in ethanol (6 cc.) at 0° was reduced with sodium borohydride (40 mg.) in ethanol (1 cc.) at 0° for 20 hours.[111] Isolation with ether in the usual way gave a product which was dissolved in 90% methanol (5 cc.), digitonin (100 mg.) in 90% methanol (5 cc.) was added, and the cloudy solution was left for one hour. The solvent was evaporated at the water pump, and the residue was well extracted with ether. Evaporation of the solvent gave a product (35 mg.) which when seeded with methyl 3α-hydroxy-11-ketoetiocholanate[61] only partially solidified. It was dissolved in pyridine (1 cc.) and acetylated with acetic anhydride (0.5 cc.) in the usual way. The product was dissolved in benzene–petroleum ether (1:1) and poured onto a short alumina column (*ca.* 1 g.), which was washed with the same solvent mixture (50 cc.) and then with methanol (30 cc.). The non-polar solvents gave a solid material (26 mg.) which on crystallization from ether–petroleum ether yielded methyl 3α-acetoxy-11-ketoetiocholanate (LXXXIV, R = Ac, R' = OMe) (18 mg.) as laths, m.p. 150–154° (Kof.). The methanol fraction yielded a crystalline material (12 mg.), m.p. 176–181° (Kof.), probably methyl 3α-acetoxy-11β-hydroxyetiocholanate[112] formed by reduction of both the keto groups of (LXXXIII, R = H). It was combined with the mother liquors from the crystallization of (LXXXIV, R = Ac, R' = OMe), dissolved in acetic acid (0.5 cc.) and oxidized with 0.4 cc. of a 2% chromium trioxide–acetic acid solution at 18° for 12 hours. Isolation with ether gave a solid residue which on crystallization from ether–petroleum ether gave a further 9.5 mg. of (LXXXIV, R = Ac, R' = OMe), m.p. 148–153° (Kof.) (total yield 27.5 mg., 61%). Further crystallization raised the m.p. to 153–154.5° (Kof.). An authentic sample had m.p. 152.5–154.5° (Kof.),[113] and there was no depression on admixture.

We wish to express our very warm appreciation to our preparative assistants, Mrs. Dorothy Voitle and Mr. Irving Osvar. Their skill, hard work and enthusiasm were decisive factors for the successful outcome of this investigation. We are indebted to Dr. Ajay K. Bose and Dr. Richard B. Turner for valuable improvements in certain stages of the synthesis.

For their very generous coöperation, we should like to thank the Monsanto Chemical Company, who placed at our disposal large quantities of 4-methoxytoluquinone and the *trans* adduct (IX), and Merck and Company, Inc., who provided various crucial materials.

Finally, we are grateful to Merck and Company, Inc., for their confidence in supporting our program at its outset, and to Merck, Research Corporation, Eli Lilly and Company, and the United States Public Health Service for continued liberal financial support.

(110) Lardon and Reichstein, footnote 61. A sample was kindly provided by Dr. H. Heymann.

(111) *Cf.* Heymann and Fieser, THIS JOURNAL, **73**, 5252 (1951).

(112) Lardon and Reichstein, (footnote 109) give m.p. 183-185° for this substance.

(113) *Inter al.*, v. Euw, Lardon and Reichstein (footnote 63) give m.p. 152-153°.

CAMBRIDGE, MASSACHUSETTS

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

Studies on Carcinolytic Compounds. IV. 6-Chloro-9-(1'-glycityl)-isoalloxazines

BY CLIFFORD H. SHUNK, FRANK R. KONIUSZY AND KARL FOLKERS

RECEIVED MARCH 31, 1952

Eleven isoalloxazines in which the substituents in the 6-, 7- and 9-positions were varied have been prepared. Seven 6-chloro-9-glycitylisoalloxazines, two 6-methyl-7-chloro-9-glycitylisoalloxazines and the 6-methyl and the 6-methoxy derivatives of 9-dulcitylisoalloxazine were synthesized by the reaction of alloxan with the diamine obtained by hydrogenation of the appropriately substituted 2-nitro-N-glycitylaniline. The isoalloxazines were tested for their effect in enhancing the rate of regression of lymphosarcoma (6C3H-ED) transplants in C3H mice maintained on a riboflavin deficient diet. 6-Chloro-9-(1'-D-sorbityl)-isoalloxazine appeared to show some activity in several tests. The other compounds showed questionable or negative results in single tests.

6,7-Dichloro-9-(1'-D-sorbityl)-isoalloxazine[1] was found to be effective in enhancing the rate of regression of lymphosarcoma transplants in mice. Addition isoalloxazines in which the substituents in the 6-, 7- and 9-positions are varied have been synthesized. Seven 6-chloro-9-glycitylisoalloxazines, two 6-methyl-7-chloro-9-glycitylisoalloxazines and 6-methyl- and 6-methoxy-9-dulcitylisoalloxazine were prepared.

1-Chloro-4-iodo-3-nitrobenzene[2] was heated in pyridine with D-glucamine,[1] D-galactamine,[1] D-mannamine,[3] L-arabinamine,[1] D-arabinamine,[4] D-ribamine[3] and D-xylamine[4] giving 4-chloro-2-nitro-N-(1'-D-sorbityl)-aniline (I), 4-chloro-2-nitro-N-(1'-D-dulcityl)-aniline (II), 4-chloro-2-nitro-N-(1'-D-mannityl)-aniline (III), 4-chloro-2-nitro-N-(1'-L-arabityl)-aniline (IV), 4-chloro-2-nitro-N-(1'-D-arabityl)-aniline (V), 4-chloro-2-nitro-N-(1'-D-ribityl)-aniline (VI) and 4-chloro-2-nitro-N-(1'-D-xylityl)-aniline (VII), respectively. Reaction of 2-chloro-4-iodo-5-nitrotoluene, prepared by the diazotization of 4-amino-2-chloro-5-nitrotoluene[5] followed by treatment with potassium iodide, with D-glucamine and with D-galactamine yielded 3-chloro-4-methyl-6-nitro-N-(1'-D-sorbityl)-aniline (VIII), and 3-chloro-4-methyl-6-nitro-N-(1'-D-dulcityl)-aniline (IX). 4-Methyl-2-nitro-N-(1'-D-dulcityl)-aniline (X) and 4-methoxy-2-nitro-N-(1'-D-dulcityl)-aniline (XI) were prepared by the reaction of D-galactamine with 4-iodo-3-nitrotoluene[6] and with 4-iodo-3-nitroanisole,[7] respectively.

In the condensation of the substituted iodoben-

(1) F. W. Holly, E. W. Peel, R. Mozingo and K. Folkers, THIS JOURNAL, **72**, 5416 (1950).

(2) Körner, *Gazz. chim. ital.*, **4**, 381 (1874).

(3) F. W. Holly, E. W. Peel, J. J. Cahill, F. R. Koniuzy and K. Folkers, THIS JOURNAL, **74**, 4047 (1952).

(4) F. W. Holly, E. W. Peel, J. J. Cahill and K. Folkers, *ibid.*, **73**, 332 (1951).

(5) J. Blanksma, *Rec. trav. chim.*, **39**, 410 (1910).

(6) C. Willgerodt and M. Simonis, *Ber.*, **39**, 269 (1906).

(7) K. Hata, K. Tatematsu and B. Kubata, *Bull. Chem. Soc. Japan*, **10**, 425 (1935).