130.5°, in 1 ml. of glacial acetic acid was oxidized[20] with 0.022 g. of potassium chromate in 0.1 ml. of water. After 22 hr. at room temperature (occasional shaking), the mixture was treated as described above. The crude, partly crystalline residue obtained on evaporation of the extraction solvents, was chromatographed on 2 g. of acid-washed activated alumina. Elution with 1:99 ethyl acetate–benzene gave 0.012 g. of diketone, m.p. 123.5–125.5°, undepressed on admixture with the sample of XXIII obtained from the Raney nickel hydrogenation experiment described above.

MADISON, WISCONSIN

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

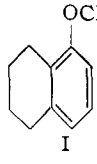
Steroid Total Synthesis—Hydrochrysene Approach. VII.[1] Metal-in-Ammonia Reduction of the Aromatic Nucleus. *dl*-Epiandrosterone and the Lumi Epimer

BY WILLIAM S. JOHNSON, BRIAN BANNISTER[2] AND RAPHAEL PAPPO[3]

RECEIVED MAY 31, 1956

A composite utilization of established metal-in-ammonia reduction procedures has made possible the successful reduction of the aromatic nucleus of the dodecahydrochrysene derivative II. After acid hydrolysis of the resulting enol ether and isomerization of the olefinic bond, both possible α,β-unsaturated ketones III and IV were produced. The latter on catalytic hydrogenation gave *dl*-18-nor-D-homoepiandrosterone (VI) which had been obtained as a minor product from the catalytic hydrogenation study reported in the previous paper of this series. Catalytic reduction of III gave the unstable 13-iso-hydroxy ketone V which is easily isomerized with alkali to VI. To prepare VI, the mixture of III and IV could be hydrogenated in the presence of alkali. The new reduction procedure was applied directly to the tetracyclic ketone XI, to give directly the unsaturated ketones III and IV. The combination of two reduction steps thus has led to a stereoselective synthesis of VI from XI involving the introduction of no less than 6 new asymmetric centers. The angular methylation–ring contraction sequence for converting the α-decalone system to the 17-keto C/D steroid moiety has been improved by use of the furfurylidine blocking group. Application to the hydroxy ketone VI (by the steps indicated in chart 2) led to *dl*-epiandrosterone (XVIII) and the 13-iso epimer XVII. The identity of these substances as well as some of the precursors was established by infrared comparison with naturally derived substances. The preparation of some additional *dl*-18-nor-D-homo steroids (XIX, R = H and R = Ac, and XX) for physiological examination is described.

This paper contains a report of exploratory studies of the metal-in-ammonia reduction[4] of the aromatic nucleus of the dodecahydrochrysene derivative II which, as already described,[5] is easily obtained by a one-step reduction of the readily accessible tetracyclic ketone XI. It was hoped that the reduction would proceed according to established precedents[4] to give, *via* the intermediates expressed in sequence a of Chart 1, the unsaturated ketone III. In the event of success we expected to be able to reduce III further to *dl*-18-nor-D-homoepiandrosterone (VI), which had already been obtained—in amounts sufficient only for characterization, but by a route establishing configuration—as a minor product in the study of the reduction of the aromatic nucleus by catalytic hydrogenation.[1] We hoped, then, to employ the hydroxy ketone in the angular methylation–ring contraction sequence[6] to produce the natural steroid epiandrosterone (XVIII). All of these objectives have been realized and the details are reported below.[7]



I

The sodium–ammonia–alcohol reduction of 1-methoxy-5,6,7,8-tetrahydronaphthalene (I), which serves as a model of the C/D ring system of II, has been examined by Birch[8] who obtained $\Delta^{9,10}$-1-octalone (as the 2,4-dinitrophenylhydrazone) in "trace" yield, formed undoubtedly according to the steps indicated by sequence a in Chart 1. We confirmed the results of Birch. At the time we were making this study, the excellent modification of Wilds and Nelson[9] involving the use of lithium in ammonia followed by alcohol was brought to our attention.[10] Application of this procedure to the methoxytetralin I gave the octalone, isolated as the 2,4-dinitrophenylhydrazone, in 42% yield. The details of this experiment are not described here, because further study[10] has resulted in improved yields of 55–58%, and these results are already recorded.[9] Much to our surprise the new reduction procedure failed completely with the tetracyclic compound II. After numerous unsuccessful attempts this approach was abandoned temporarily, until a modification in the metal–ammonia reduction procedure discovered by Short came to our attention.[11] The modification involves the use of approximately 40% (instead of 10%) of alcohol

(1) Paper VI, W. S. Johnson, E. R. Rogier and J. Ackerman, THIS JOURNAL, **78**, 6322 (1956).

(2) Postdoctoral Project Associate supported by the Wisconsin Alumni Research Foundation, 1952–1953, and the the National Science Foundation, 1953–1954.

(3) Merck and Co., Inc., Postdoctoral Fellow, 1952–1953. On leave of absence from the Weizmann Institute, Israel.

(4) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).

(5) Paper III, W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, THIS JOURNAL, **78**, 6289 (1956).

(6) (a) W. S. Johnson, *ibid.*, **65**, 1317 (1943); **66**, 215 (1944); (b) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(7) A preliminary report of this and some earlier work has appeared: W. S. Johnson, B. Bannister, B. M. Bloom, A. D. Kemp, R. Pappo, E. R. Rogier and J. Szmuszkovicz, *ibid.*, **75**, 2275 (1953).

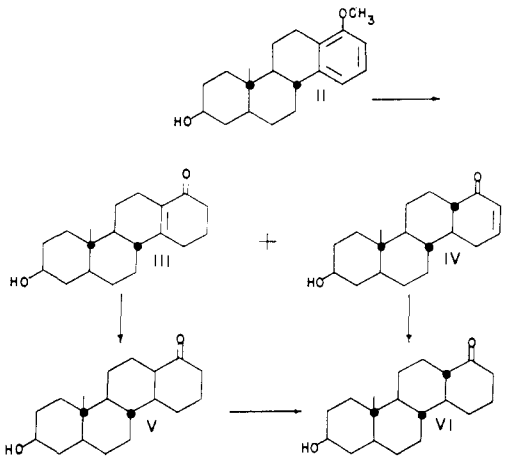
(8) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(9) A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5360 (1953).

(10) We are indebted to Prof. A. L. Wilds for informing us of his discoveries prior to publication (ref. 9) and for urging us to use his procedures in the present study. We also thank him for allowing E. R Rogier of our laboratory to carry out the preliminary examination of the applicaion of the new method to the methoxytetralin I which was one of the substances scheduled for study by Prof. Wilds. It should be emphasized that while the Wilds–Nelson procedure in its original form failed to reduce the tetracyclic compound (see below), the success of the procedure which finally evolved may be attributed in large measure to the discovery of Wilds and Nelson of the special reducing properties of lithium.

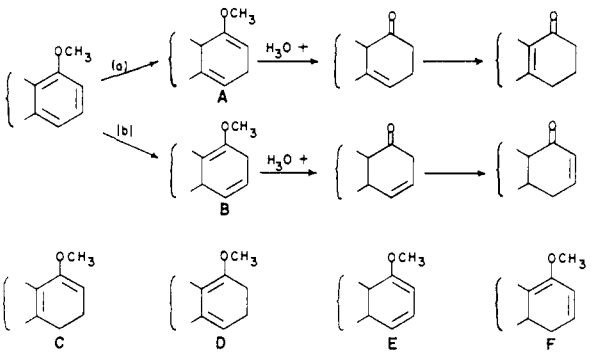
(11) Personal communication of unpublished results to one of us (B.B.) *via* Sir Robert Robinson from Dr. W. F. Short of Messrs. Boots Pure Drug Co., Ltd.

and controlled addition of the metal (sodium) so as to effect and maintain the separation of a bronze-colored phase.[12] The first experiments utilizing this modification were tried with sodium on the *trans-anti-cis* stereoisomer[5] of II. For the first time there was evidence of reduction as detected by a positive but faint test with 2,4-dinitrophenylhydrazine reagent. Almost all of the starting material was recovered. When lithium[9,10] was used in place of sodium, the product, after acid treatment, gave an immediate deep-red coloration with 2,4-dinitrophenylhydrazine reagent and could be separated into 83% starting material and 15% oily material which absorbed strongly at 247 mμ indicating the presence of appreciable amounts of α,β-unsaturated ketone. With this initial success we turned our attention to the *trans-anti-trans* series.



Reduction of the *trans-anti-trans* hydroxy compound II under conditions similar to those used successfully above yielded, after acid treatment, an oily product from which ketonic fractions were isolated by chromatography in about 33% total yield. From these fractions there were isolated two isomeric crystalline substances of the expected composition, one melting at 139° with λ_{max} 226 mμ (log ε 3.89) and the other (preponderant isomer) melting at 165° with λ_{max} 248.5 mμ (log ε 4.12). The spectral data showed clearly that these isomers were structurally the α,β-unsaturated ketones IV (calcd. λ_{max} 227 mμ[13]) and III (calcd. λ_{max} 249 mμ[13]), respectively. To our knowledge this is the first case of the isolation of both possible α,β-unsaturated ketones from metal-in-ammonia reduction of an anisole system, although there is presumptive evidence that both isomers are formed in the case of *o*-cresyl methyl ether.[8] There are various modes by which these ketones could arise. The reduction may take the two courses (a and b) depicted in Chart 1. On the other hand, either of the primary reduction products A or B could give rise to both ketones by isomerization (on acid treatment) to the conjugated diene system prior to or during the hydrolysis of the enol ether. The preferred[4] 1,4-dihydro enol ether A thus could yield the conjugated isomers C, D and E. On hydrolysis, C and D would lead to ketone III while E would yield ketone IV. Similarly the alternative primary reduction product B could isomerize to D, E and F, hydrolysis of which would lead to ketone III (from D) and IV (from E and F). Some light has been shed on this problem from the results of a study of the reduction of related compounds described in subsequent papers of this series.[14]

CHART I



When *trans-anti-cis*-8β,11β-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene was thus reduced, a pure crystalline 1,4-dihydro enol ether was isolated, and acid hydrolysis yielded a single product—the 13,14-dehydro ketone (corresponding to III).[14a] This result indicated that each α,β-unsaturated ketone was derived from a different 1,4-dihydro enol ether, and sequences a and b (Chart 1) provide the most logical rationalization compatible with this conclusion. The crystalline 1,4-dihydro enol ether, accordingly, most probably had the structure corresponding to formula A. The alternative, less likely, possibility that the 1,4-dihydro enol ether (either A or B) was selectively isomerized exclusively to either C or D before hydrolysis, however, has not been excluded.

When the enol ether mixture from a similar reduction in another series[14b] was submitted to mild (oxalic) acid hydrolysis, a mixture of β,γ-unsaturated ketones was produced which on treatment with sodium acetate was isomerized to the α,β-isomers. This behavior precludes the dienes C and F as intermediates in this case and is quite consistent with sequence a and b.

Catalytic hydrogenation of the 16,17-dehydro ketone IV proceeded rapidly over 10% palladium-on-carbon to give *dl*-18-nor-D-homoepiandrosterone (VI).[1] The 13,14-dehydro ketone III was more resistant to hydrogenation, which proceeded satisfactorily, however, in the presence of 30% palladium hydroxide-on-strontium carbonate to give the labile 13-isohydroxy ketone V.[1] Since this substance had been shown to be isomerized readily with alkali to give VI,[1] it was not surprising to find that hydrogenation of III over 10% palladium-on-carbon in the presence of a trace of potassium hydroxide gave the hydroxy ketone VI directly. The

(12) This phase separates at higher concentrations of metal in ammonia and has been shown to consist of a moderately concentrated solution of the metal in ammonia; C. A. Kraus, THIS JOURNAL, **29**, 1557 (1907).

(13) R. B. Woodward, *ibid.*, **63**, 1123(1941); **64**, 76(1942).

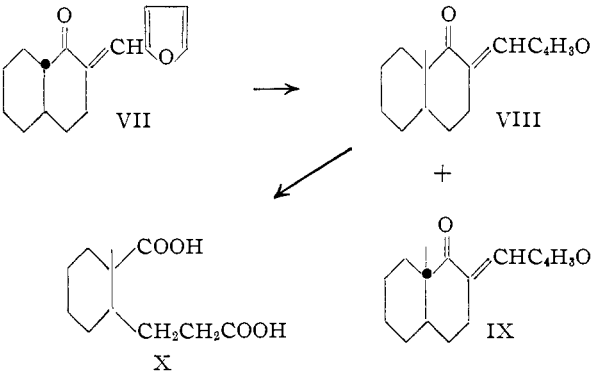
(14) (a) Paper VIII, W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956); (b) paper X, W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).

hydrogenation was rapid, and the reaction may not have proceeded *via* the 13-iso compound V.[15] For preparative purposes it was unnecessary to separate the mixture of III and IV which could thus be hydrogenated directly to VI.

Since the *trans-anti-trans*-hydroxy compound is produced stereoselectively by the Wilds–Nelson[9] lithium-in-ammonia reduction of the tetracyclic ketone XI, it seemed worthwhile to investigate an over-all reduction by the modified procedure with the expectation that the two steps could be combined to give the unsaturated ketones III and IV directly from XI. In such an experiment the tetracyclic ketone XI was reduced as described for II above except that dioxane was employed as a co-solvent to increase solubility and a larger excess of lithium was used. The oily product was essentially transparent in the ultraviolet spectrum except for end absorption due to isolated olefinic bonds. After acid treatment the product exhibited strong absorption in the 240–250 mμ region showing that conjugation of bonds had been effected. This product could not be crystallized and was therefore submitted to chromatography. The early eluates yielded about 24% of oily material which could be crystallized from ether and absorbed strongly at 236 and 244 mμ. This fraction has not been investigated further, but from the absorption in the ultraviolet region and its position on the chromatogram, it appears to be composed mainly of 17a-desoxy heteroannular conjugated dienes produced by hydrogenolysis[4] followed by conjugative isomerization. Further elution gave about 14% of material apparently containing some unreduced aromatic substance as indicated by weak absorption at 272 and 278 mμ. From later fractions the 16,17-dehydroketone was obtained in 6% yield, directly followed by the 13,14-dehydro isomer which was isolated in 23% yield. The reduction conditions were improved somewhat by increasing the proportion of ammonia and adjusting conditions so as to maintain a higher concentration of lithium in the alcohol–ammonia phase.[14] From such a reduction it was possible to crystallize a portion (10%) of the 13,14-dehydro ketone directly from the crude acid-treated product. The total yield of combined unsaturated ketones III and IV after chromatography was 43%. Since both of these substances may be hydrogenated in good yield to *dl*-18-nor-D-homoepiandrosterone (VI) (see above), the two combined reduction steps constitute a stereoselective synthesis of VI from XI, a process involving the introduction of no less than six new asymmetric centers. The hitherto[1] rare intermediate (VI), required for production of a natural steroid, thus became unusually accessible.

It is clear from our studies that the best conditions for reduction of XI or of II have not yet been ascertained. Subsequent to the present study, the reduction method was applied successfully to other cases[14a,16] and some improvements were discovered. In one experiment some of these modifications were tried with II. The proportion of lithium was reduced by one-half, and minor changes were made in the rate of addition of reagents, as well as in the acid hydrolysis and isomerization steps which were carried out separately[16] with oxalic acid and with alkaline alumina, respectively. In this way the combined yield of the α,β-unsaturated ketones was 48%. The best procedure available for reducing these systems[16] has not yet been applied to II or to XI.

CHART 2



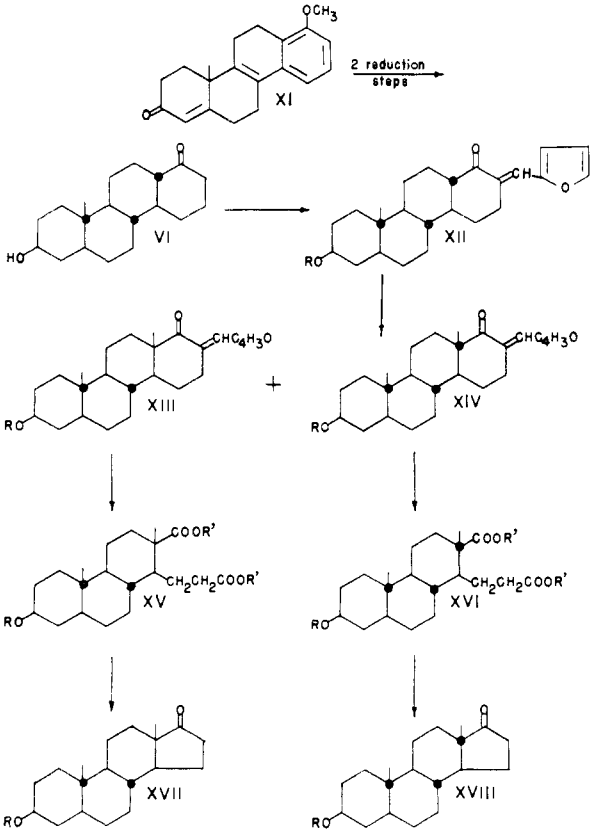
With a good method of preparing the hydroxy ketone VI at hand, attention was turned to its use in the angular methylation-ring contraction sequence for conversion of the α-decalone ring system into the 17-keto C/D ring steroid moiety.[6] In the present work some improvements in the scheme were developed in the model series, where it was discovered that the furfurylidene blocking group has advantages over the previously employed benzylidene residue.[6] Condensation of α-decalone with furfuraldehyde gave the furfurylidene derivative VII, m.p. 116°, in 90% yield after a reaction period of 2 hr. at room temperature. This is to be compared with the benzylidene derivative obtained in 75% yield after 2 days.[6a] Treatment of VII with potassium *t*-butoxide and methyl iodide afforded the expected[6] mixture of angularly methylated epimers. In contrast with the comparable mixture in the benzylidene series from which it was particularly difficult to isolate the *trans* isomer because it was not only less preponderant but also more soluble than the *cis* form, a single crystallization of the furfurylidene mixture effected essentially complete separation of the *trans* isomer IX, m.p. 110°, in 26% yield. The more soluble, preponderant *cis* form obtained from the mother liquors melted at 44°. The configurations were proved by ozonization of the crude *cis* isomer which gave authentic *cis*-diacid X of good purity in 75% yield. The configurations of the two methylated isomers were further confirmed by comparison with authentic specimens produced by condensation of the pure 9-methyl-1-decalones[6a] with furfuraldehyde.

It was noted that the position of the principal maximum in the ultraviolet spectrum appeared at 325 mμ for the *cis* (VIII) and 321 mμ for the *trans* (IX) methylated isomer. Although small, this difference proved to be significant, for examination of a number of *cis-trans* pairs of angularly methylated arylmethylene decalone derivatives has revealed that in general the *trans* forms exhibit a 3–5

(15) See A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, THIS JOURNAL, **72**, 5524 (1950).

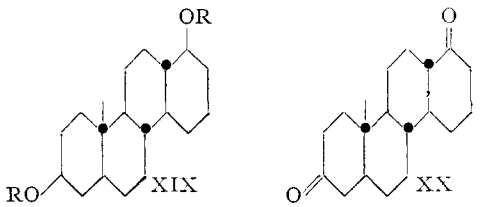
(16) Paper X, W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).

mμ hypsochromic shift relative to the *cis* isomers.[17] The unmethylated arylmethylene derivatives usually, but not always, absorb at some intermediate point: VII, for example, exhibited λ_{max} 323.5 mμ. This rule has proved helpful as a guide in selecting the natural from the unnatural (13-iso) stereochemical series, as illustrated here (see below) as well as in subsequent total syntheses.[14,16]



The modified approach was applied to the hydroxy ketone VI, which on condensation with furfuraldehyde afforded the furfurylidene ketone XII (R = H), m.p. 207°, λ_{max} 324.5 mμ, in 98% yield. As in the 14-iso series,[1] the 3-hydroxyl group was protected by conversion to the tetrahydropyranyl ether,[18] which was methylated as usual, then submitted to mild acid hydrolysis to remove the tetrahydropyranyl blocking group. As in the α-decalone series, the C/D *trans*-furfurylidene derivative, m.p. 225°, was less soluble than the preponderant *cis* isomer, m.p. 90°, from which it was therefore easily separated. These epimers, respectively, were obtained in about 24 and 52% yield and exhibited λ_{max} 323 and 326.5 mμ, providing suggestive evidence for assignment of configurations (see above). That the 225° isomer was in fact *dl*-17-furfurylidene-D-homoepiandrosterone (XIV, R = H) was established in the course of the completion of the synthesis. Acetylation yielded the *dl*-acetate XIV (R = Ac), m.p. 192°, the infrared spectrum of which was identical with that of authentic (naturally derived) *d*-XIV (R = Ac).[19] Ozonolysis of the *dl*-acetate afforded the diacid XVI (R = Ac, R′ = H), m.p. 239°, which on treatment with diazomethane was converted to *dl*-dimethyl 3β-acetoxyetioallohomobilianate (XVI, R = Ac, R′ = CH_3), m.p. 137°, with an infrared spectrum indistinguishable from that of authentic (naturally derived) *d*-XVI (R = Ac, R′ = CH_3).[19] The Dieckmann cyclization was first studied with the naturally derived *d*-diester. To our surprise preliminary experiments on cyclization by the sodium methoxide method that had been so successful in the equilenin and estrone series[20] did not look promising. A single attempt to effect cyclization with sodium hydride[21] also failed. It was then discovered that alcohol-free potassium *t*-butoxide in benzene—a combination which, to our knowledge, has not been used hitherto for Dieckmann cyclizations—effected ring closure in excellent yield. This method was applied to the *dl*-diester and the resulting β-keto ester hydrolyzed and decarboxylated to give *dl*-epiandrosterone (XVIII, R = H), m.p. 162°. The infrared spectrum of this substance was identical with that of naturally derived *d*-epiandrosterone.

The angular methylation–ring contraction sequence was applied also to the 13-isofurfurylidene derivative XIII (R = H). Ozonization of the acetate XIII (R = Ac) yielded the diacid XV (R = Ac, R′ = H), m.p. 247°. The dimethyl ester XV (R = Ac, R′ = CH_3), m.p. 117°, was cyclized as described above to give *dl*-13-isoepiandrosterone (XVII, R = H), m.p. 158°, having an infrared spectrum identical with that of authentic lumiepiandrosterone prepared by irradiation of *d*-epiandrosterone.[22]



As part of a program designed to produce 18-nor-D-homosteroids for physiological examination, *dl*-18-nor-D-homoepiandrosterone (VI) was reduced with lithium and alcohol in ammonia to give *dl*-3β,17aβ-dihydroxy-18-nor-D-homoandrostane, isolated as the diacetate XIX (R = Ac), m.p. 170°. The pure diol XIX (R = H), m.p. 211°, was obtained by saponification of the diacetate. The easiest route to these compounds was by lithium–ammonia–alcohol reduction of the 13,14-dehydro ketone III. The diacetate XIX (R = Ac) was thus produced directly from III in 82% yield.

Oxidation of *dl*-18-nor-D-homoepiandrosterone

(17) For a summary, see R. J. Highet, Ph.D. Thesis, University of Wisconsin, 1953.

(18) G. F. Woods and D. N. Kramer, THIS JOURNAL, **69**, 2246 (1947); W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948); C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951); A. C. Ott, M. F. Murray and R. L. Pederson, THIS JOURNAL, **74**, 1239 (1952).

(19) Paper IX, R. Pappo, B. M. Bloom and W. S. Johnson, *ibid.*, **78**, 6347 (1956).

(20) W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940); W. E. Bachmann, S. Kushner and A. C. Stevenson, *ibid.*, **64**, 974 (1942).

(21) D. K. Banerjee and P. R. Shafer, *ibid.*, **72**, 1931 (1950).

(22) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **34**, 2053 (1951); see also A. Butenandt and L. Poschmann, *Ber.*, **77**, 394 (1944).

with chromium trioxide in acetic acid[23] afforded the *dl*-18-nor-D-homoandrostane-3,17a-done (XX) which was conveniently isolated and purified through its insoluble sodium bisulfite adduct.

A preliminary brief account of the interesting physiological behavior of these substances has been published.[24] A more detailed report will be forthcoming.[25]

Acknowledgment.—We wish to express our gratitude to the agencies named in references 2 and 3 for supporting this work, and to the Sterling-Winthrop Research Institute for providing generous supplies of intermediates.

Experimental[26]

Reduction of *trans-anti-trans*-1-Methoxy-8β-hydroxy-10a-methyl - 4b,5,6,6a,7,8,9,10,10a,10b,11,12 - dodecahydrochrysene (II). (a) With a High Proportion of Lithium.—A solution of 1.00 g. of the hydroxy compound II,[5] m.p. 124–125°, in 130 ml. of absolute ethanol was added cautiously to 150 ml. of liquid ammonia. Lithium metal (10 g.) was added in portions with vigorous stirring together with additional ethanol (100 ml.) and ammonia (150 ml.) to maintain the bronze phase. When the addition was complete (about 30 minutes), the mixture was stirred until all of the lithium reacted, then the ammonia was allowed to evaporate. Water was added, the aqueous layer extracted with chloroform and the combined organic layers washed with water and concentrated. The oily residue was dissolved in 100 ml. of ethyl acetate, 40 ml. of 0.5 *N* hydrochloric acid was added and the mixture heated at reflux for 15 minutes. Isolation of the organic material by chloroform extraction as above yielded an oily product which gave an immediate deep-red coloration with ethanolic 2,4-dinitrophenylhydrazine sulfate.

The crude yellow oily product (0.980 g.) was chromatographed on 40 g. of Florisil. After elution of 0.195 g. of oily forerun with 3:1 benzene–petroleum ether (60–68°), 0.261 g. of crystalline starting material, m.p. 123–125°, was eluted with benzene. Recrystallization of this fraction from petroleum ether (90–100°) raised the m.p. to 124–125°, undepressed on admixture with authentic starting material II. Elution with benzene–ether up to a 1:1 ratio afforded a forerun of 0.024 g. of non-ketonic oil. Elution with ether gave in order 0.076 g. of oil, λ_{max} 225 mμ (orange 2,4-dinitrophenylhydrazone); 0.032 g. of oil, λ_{max} 230 mμ (orange 2,4-dinitrophenylhydrazone); and 0.212 g. of oil which crystallized on adding ether, λ_{max} 247 mμ (deep-red 2,4-dinitrophenylhydrazone). The last fraction was recrystallized twice from diisopropyl ether, then sublimed at 130° (at high vacuum) and finally recrystallized again from the same solvent to give ***dl*-13,14-dehydro-18-nor-D-homoepiandrosterone** (III) as colorless elongated hexagonal prisms, m.p. 163.5–165°, λ_{max} 248.5 mμ (log ε 4.12); λ_{max}^{mull} 2.82 μ (OH), 6.05 (C=C—C=O), 6.17 (C=C).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.8; H, 9.76.

Crystallization of the other two fractions from diisopropyl ether yielded a further quantity (about 0.01 g.) of the 13,14-dehydroketone. The residues from the mother liquors were combined and evaporatively distilled at 125° (at high vacuum). Crystallization of the distillate from diisopropyl ether gave a specimen of ***dl*-16,17-dehydro-18-nor-D-homoepiandrosterone** (IV), as colorless rods, m.p. 138–139°, λ_{max} 226 mμ (log ε 3.89); λ_{max}^{mull} 3.05 μ (bonded OH), 6.05 (C=C—C=O).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.3; H, 9.8.

(b) With a Reduced Proportion of Lithium.—A solution of 2.38 g. of the hydroxy compound, m.p. 124–125°, in 250 ml. of absolute ethanol was added cautiously to 580 ml. of liquid ammonia. A total of 12 g. of lithium wire was added in small portions with vigorous stirring, together with additional ammonia (300 ml.) and ethanol (350 ml.). The rate of addition of reagents was carried out so as to maintain a slight blue coloration as well as the bronze phase. After the addition was complete and all of the lithium had reacted (about 45 minutes), the ammonia was evaporated, water and ether added and the aqueous layer extracted with ether. The combined ether layers were washed thoroughly with water (until neutral), then dried over anhydrous sodium sulfate.

The colorless oily residue was dissolved in 130 ml. of methanol, and a solution of 2 g. of oxalic acid in 25 ml. of water was added. After 2 hr. at room temperature, most of the solvent was removed at 25° (10 mm.) and the concentrate was made alkaline by the addition of excess aqueous potassium carbonate. The mixture was extracted with ether, the ether layers washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave a yellow oily mixture exhibiting strong absorption at 5.88 μ (saturated C=O) and weak absorption at 6.05 μ due to isolated olefinic bonds. In the ultraviolet region this substance absorbed strongly only at short wave lengths.

The oily product was dissolved in 50 ml. each of benzene and of petroleum ether (60–68°), and 50 g. of Alcoa alkaline alumina was added. After 12 hr. at room temperature the solvent was separated and the alumina washed thoroughly with ethyl acetate to effect complete desorption. The colorless oily residue obtained on evaporation of the combined organic solutions crystallized on standing with a small volume of ether. In another similar experiment with the reduced proportion of lithium, but with the usual one-step (mineral acid) hydrolysis, isolation of the crystalline fraction at this stage afforded the 13,14-dehydro ketone, m.p. 161–164°, in 24% yield.

The product from the alumina treatment exhibited strong absorption at 6.07 μ and 248 mμ and very weak absorption at 5.88 μ, indicating that most of the ketonic material was conjugated. This product was chromatographed on 100 g. of Florisil. A total of 1.10 g. of α,β-unsaturated ketone fraction (composed of the 16,17- and 13,14-dehydro isomers as described in detail above) was obtained from the ether–benzene 1:10 and 1:1 eluates. Material of this quality has been catalytically hydrogenated as described below.

From the fraction eluted with 1:20 ether–benzene (just preceding that containing the 16,17-dehydro ketone) there was obtained 0.61 g. of an oil which partially crystallized on standing. This material exhibited λ_{max} 241 mμ with shoulders at 235 and 250 mμ. With 2,4-dinitrophenylhydrazine reagent it gave a yellow precipitate turning orange on standing or warming. This fraction has not been examined further but undoubtedly contains some of the unconjugated ketones, possibly together with some saturated ketones[4] (perhaps some of VI).

***dl*-18-Nor-D-homoepiandrosterone** (VI). **(a) From the 13,14-Dehydro Ketone III.**—A solution of 1.00 g. of the 13,14-dehydro ketone, m.p. 163–165°, in 50 ml. of 95% ethanol (distilled from Raney nickel) was hydrogenated over 0.30 g. of 30% palladium hydroxide-on-strontium carbonate[27] at 36 p.s.i. initial pressure and room temperature. After about 15 minutes shaking the gas absorption, which was approximately one mole-equivalent, had ceased. The mixture was filtered and the filtrate evaporated to give a colorless oil, showing no absorption in the 245 mμ region, which partially crystallized on standing with a little ether. A specimen was recrystallized from petroleum ether (60–68°) to give colorless prisms, m.p. 148–150°, undepressed on admixture with the 13-iso (unstable) ketone V.[1]

All of the residues from the reduction were heated at reflux for 1 hr. in 50 ml. of 4 *N* ethanolic potassium hydroxide. The mixture was neutralized with acetic acid, concentrated under reduced pressure, then diluted with

(23) Note: The excellent method of G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953), was not available at the time this work was done.

(24) W. S. Johnson, H. Lemaire and R. Pappo, *ibid.*, **75**, 4866 (1953).

(25) R. K. Meyer and Elva G. Shipley.

(26) The new substances described in this section are racemic compounds, but the prefix "*dl*" has generally been omitted. Unless otherwise indicated, melting points of analytical specimens are corrected for stem exposure; those followed by "(vac.)" were determined in a capillary evacuated to <0.2 mm. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer (model 11 MS), 95% alcohol being employed as the solvent. Infrared spectra were determined on a Baird double beam infrared recording spectrophotometer, model B. Unless otherwise specified, carbon disulfide was used as the solvent. Nujol was employed for mulls.

(27) Footnote 39, ref. 5.

water and extracted with benzene. The organic layer was washed with water, saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The oil obtained on evaporation of the solvent was crystallized from petroleum ether (90–100°) and recrystallized from dilute ethanol to give a total of 0.70 g. of material, m.p. 158–161°. Sublimation at 142° (high vacuum) gave material with the same m.p. which was undepressed on admixture with the analytical specimen of *dl*-18-nor-D-homoepiandrosterone (VI).[1] The infrared spectra of the two samples were identical.

A solution of 0.901 g. of the 13,14-dehydro ketone, m.p. 161–164°, in 150 ml. of 95% ethanol (distilled from Raney nickel) containing 0.06 g. of potassium hydroxide was hydrogenated over 0.30 g. of 10% palladium-on-carbon (American Platinum Works) at 38 p.s.i. initial pressure and room temperature. Within 10 minutes the rapid absorption of gas ceased. The mixture was neutralized with acetic acid, filtered and the filtrate evaporated. The colorless oily residue was crystallized from petroleum ether (90–100°) to give 0.844 g. (93% yield) of the hydroxy ketone VI, m.p. 157–159°, undepressed on admixture with authentic material.

(b) **From the 16,17-Dehydro Ketone IV.**—A solution of 0.470 g. of the 16,17-dehydro ketone, m.p. 135–137°, in 20 ml. of 95% ethanol (distilled from Raney nickel) was hydrogenated over 0.10 g. of 10% palladium-on-carbon (American Platinum Works) at atmospheric pressure and room temperature. Within 9 minutes the rapid absorption of gas, which amounted to one mole-equivalent, had ceased. The product was isolated as described above to give after crystallization 0.458 g. (97% yield) of ketone VI, m.p. 158–160°, undepressed on admixture with authentic material.

(c) **From the Crude Mixture of 13,14-Dehydro and 16,17-Dehydro Ketones.**—A solution of the 1.10-g. residue of mixture of ketones, obtained from the experiment on the reduction of the tetracyclic ketone XI described below, in 75 ml. of 95% ethanol (distilled from Raney nickel) containing 0.15 g. of potassium hydroxide was hydrogenated over 0.30 g. of 10% palladium-on-carbon (American Platinum Works) at 38 p.s.i. initial pressure and room temperature. The initial uptake of hydrogen was rapid and then became constant at a slower rate. A sample of the mixture removed after the initial rapid absorption of hydrogen exhibited λ_{max} 248 mμ showing that, as expected, the 16,17-dehydro compound had been reduced first. After the hydrogenation was complete the product was isolated as described above to give a total of 0.748 g. of the hydroxy ketone VI, m.p. 158–160°.

Reduction of 1-Methoxy-8-keto-10a-methyl-5,6,8,9,10,-10a,11,12-octahydrochrysene (XI).—This experiment is described in considerable detail, because of our own experience of difficulty in repeating results from less complete directions.

A solution of 20.0 g. of the tetracyclic ketone, m.p. 172–175°, in 300 ml. of purified dioxane and 1 l. of absolute ethanol was added cautiously to 3 l. of liquid ammonia in a 12-l. flask. While the mixture was agitated vigorously with a large Hershberg stirrer driven by an air motor, 159 g. (4900 cm.) of lithium wire was added in approximately 1-in. portions. At first the solution, which was cloudy due to the partial suspension of the ketone, was blue only in streaks around the undissolved metal. During the first 25 minutes 4 meters of wire were added; after the addition of more ethanol (100 ml.), the appearance of bronze-red globules was noticed on the surface of the still blue-flecked mixture as the addition of lithium was continued. The additions of further reagents were made as follows, total (cumulative) amount of lithium added being indicated in parentheses after the period of time: after a total of 45 minutes from the beginning of the reaction (10 meters), 100 ml. of ethanol; 60 minutes (14 meters), 200 ml. of ethanol; 80 minutes (23 meters), 100 ml. of ethanol; 110 minutes (28 meters), 1 l. of ammonia; 130 minutes (32 meters), 1 l. of ammonia and 200 ml. of ethanol; 150 minutes (49 meters), 100 ml. of ethanol. Under these conditions the mixture continually retained a dull, bronze color.

The mixture was then allowed to stir until most of the lithium disappeared (total reaction time, about 3 hr.), an additional 1 l. of ammonia being added to prevent the mixture from becoming too viscous. Finally 500 ml. of ethanol was added to react with any remaining lithium, and the ammonia was allowed to evaporate. Water and chloroform were added, the aqueous layer extracted with chloroform and the combined extracts washed with water until neutral to litmus. Evaporation of the solvent left a viscous red oil, which absorbed strongly only at short wave lengths in the ultraviolet region.

The crude oily product was dissolved in 200 ml. of ethanol, 30 ml. of 8% hydrochloric acid added and the mixture heated at reflux in an atmosphere of nitrogen for 1 hr. Most of the ethanol was removed at reduced pressure (20°), water and chloroform were added and the aqueous layer extracted with chloroform. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a dark-red glassy residue exhibiting λ_{max} 222 mμ, with a minor peak at 238 mμ and a shoulder at 254 mμ.

Chromatography on 600 g. of Florisil gave the following major fractions: (1) eluted with 3:1 benzene–petroleum ether (60–68°) through pure benzene, 4.79 g. of oil which partially crystallized from ether, λ_{max} 244 mμ with shoulders at 236 and 254 mμ; (2) eluted with 9:1 benzene–ether, 2.77 g. of oil which partially crystallized from ether, λ_{max} 224, 244, 272 and 278 mμ; (3) eluted further with 9:1 benzene–ether, 2.05 g. of intermediate oily fraction showing only end absorption in the ultraviolet region; (4) eluted with 5:1 benzene–ether, 1.25 g. of oil which crystallized, λ_{max} 225–228 mμ; (5) eluted further with 5:1 benzene–ether through pure ether, 4.43 g. of crystalline material, λ_{max} 248 mμ.

Crystallization of fraction 4 from diisopropyl ether yielded 0.644 g. of the 16,17-dehydro ketone, m.p. 134–139°, λ_{max} 225 mμ. A specimen after sublimation at 110° (high vacuum) was obtained as colorless prisms, m.p. 138–139°, undepressed on admixture with the authentic material described above. The infrared spectra of the two specimens were indistinguishable.

Crystallization of fraction 5 from diisopropyl ether yielded 3.66 g. of the 13,14-dehydro ketone, m.p. 161–163°, λ_{max} 248 mμ. The m.p. was undepressed on admixture with authentic material.

The mother liquors from the crystallization of fractions 4 and 5 were combined, evaporated and the residue evaporatively distilled at 140° (high vacuum). The pale yellow, semi-crystalline distillate amounted to 1.10 g., λ_{max} 242 mμ. This material was employed in the hydrogenation experiment described above.

Another reduction experiment with 20.0 g. of ketone was carried out as described above except that the concentration of ammonia was increased 1.5-fold and conditions were maintained during the reaction so that, although the bronze phase was present, the color of the mixture always verged upon blue. This state was achieved by the judicious addition of ethanol at frequent intervals in order to prevent the blue color from becoming pronounced.

The isolation and acid hydrolysis were carried out as described above. The crude product was a lighter-red than in the previous case. On dissolution in 50 ml. of ether and leaving at 0° for 12 hr., 1.63 g. (first crop) and after concentration 0.328 g. (second crop) of the 13,14-dehydro ketone, λ_{max} 248 mμ, were obtained. The combined crops were sublimed at 138° (high vacuum) to give 1.92 g. of colorless rods, m.p. 162–164°.

Chromatography of the residues as above gave a total 6.57 g. of a mixture of the two α,β-unsaturated ketones, 1.39 g. of which was mainly the 16,17-dehydro isomer and 4.27 g. of which was the 13,14-dehydro isomer. The total yield of material suitable for the next reduction step (see above) was thus 8.49 g. The examination of the remaining fractions of the chromatogram has not been completed.

***trans*-2-Furfurylidene-1-decalone (VII).**—As in the preparation of the benzylidene derivative,[6a] 15.20 g. of α-decalone in 100 ml. of 95% ethanol was treated with 40 ml. of 15% sodium hydroxide solution, followed by 10.5 ml. of freshly distilled furfuraldehyde. The homogeneous mixture became warm and within about 3 minutes the furfurylidene derivative began to crystallize. After 2 hr. the precipitate was separated by filtration and washed thoroughly with 50% ethanol, dilute acetic acid and finally water. The dried product amounted to 20.75 g. (90% yield), m.p. 108–111°. A specimen after two recrystallizations from methanol was obtained as cream colored prisms, m.p. 115.5–116.5°, λ_{max} 323.5 mμ (log ε 4.34).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.3; H, 7.93.

Methylation of VII.—As in the benzylidene series,[6a] 16.3 g. of *trans*-2-furfurylidene-1-decalone, m.p. 108–111°, was added to a stirred solution of 11.0 g. of potassium in 270 ml. of dry *t*-butyl alcohol under nitrogen. The solution was cooled in an ice-bath and 33 ml. of methyl iodide was introduced. After 4 hr. at room temperature (stirring) the mixture was neutral to litmus, and most of the *t*-butyl alcohol was evaporated under reduced pressure. Water was added and the mixture stirred for 1 hr. to effect crystallization of the oily product. The precipitate was separated, triturated with 40 ml. of methanol, separated by filtration and washed with about 10 ml. of methanol. Crystallization of this material from methanol gave 4.4 g. (26% yield) of ***trans*-2-furfurylidene-9-methyl-1-decalone (IX)**, m.p. 108–110°. A specimen recrystallized twice from methanol was obtained as cream-colored elongated prisms, m.p. 108–110°, λ_{max} 321 mμ (log ε 4.39).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.9; H, 8.47.

Condensation of furfuraldehyde with authentic *trans*-9-methyl-1-decalone as described[6a] for the benzylidene derivative gave, in 95% yield, material, m.p. after recrystallization, 110–111°, alone or on admixture with the specimen produced in the methylation experiment described above.

The mother liquors from the separation of the *trans* isomer IX were cooled to −5° for 15 hr. The crystalline precipitate was separated and washed with cold (−10°) methanol. The dried product amounted to 7.00 g. of ***cis*-2-furfurylidene-9-methyl-1-decalone (VIII)**, m.p. 38–42°. Repeated recrystallization from dilute methanol, followed by evaporative distillation at 80° (0.1 mm.), gave a pale yellow micro-crystalline powder, m.p. 43–44°, λ_{max} 325 mμ (log ε 4.34).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.5; H, 8.21.

An authentic sample of VIII prepared from furfuraldehyde and *cis*-9-methyl-1-decalone[6a] melted at 43–44° alone or on admixture with the specimen described above.

Ozonolysis of *cis*-2-furfurylidene-9-methyl-1-decalone (1.00 g. of crude material, m.p. 38–42°) in 15 ml. of ethyl acetate was carried out at −70°. Ozone was introduced until the solution became blue, then the solvent was evaporated at 75° under reduced pressure. The residue was dissolved in 40 ml. of acetic acid, and 5 ml. of 30% hydrogen peroxide was added, followed by 1 ml. of 33% hydrochloric acid. After 15 hr. at room temperature, most of the solvent was evaporated at reduced pressure and the residue treated with excess aqueous potassium bicarbonate and ether. The aqueous layer was separated, acidified, extracted thoroughly with ether, and the ether layers were dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the ether crystallized on trituration with water and seeding. The solid was separated, washed with a little water and dried over phosphorus pentoxide. The yield was 0.66 g. (75%), m.p. 97–102°, undepressed on admixture with an authentic specimen of *cis*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid, m.p. 99.5–103°.[6a]

***dl*-17-Furfurylidene-18-nor-D-homoepiandrosterone (XII, R = H).**—A 0.100-g. sample of the hydroxy ketone VI, m.p. 157–159°, was dissolved in 3.5 ml. of methanol; 0.5 ml. of freshly distilled furfuraldehyde was added followed by 1.8 ml. of 33% sodium hydroxide solution and the mixture left in the dark at room temperature for 4 hr. in an atmosphere of nitrogen. The crystalline precipitate was separated by filtration and washed with dilute methanol. The dried material amounted to 0.107 g. (84% yield), m.p. 201–203°. Two recrystallizations from ethyl acetate gave very pale yellow plates, m.p. 207.4–207.9°, λ_{max} 324.5 mμ (log ε 4.41).

Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.0; H, 8.80.

When carried out on a larger (2.16-g.) scale the condensation yielded 2.70 g. (98%) of crude furfurylidene derivative, m.p. 202–204°, suitable for use in the next step.

Angular Methylation.—The tetrahydropyranyl ether XII (R = $-\underline{CHCH_2CH_2CH_2CH_2O}$) was prepared by a slight modification of described procedures.[18] A 2.70-g. sample of the hydroxy furfurylidene ketone XII (R = H), m.p. 202–204°, was dissolved in a mixture of 35 ml. of dry benzene and 10 ml. of dihydropyran (freshly distilled from sodium), 0.09 g. of *p*-toluenesulfonic acid monohydrate added, the flask stoppered and the mixture stirred magnetically at room temperature. After 3 hr. the mixture was made alkaline with dilute methanolic sodium hydroxide, then the benzene layer was separated, washed thoroughly with water and dried over anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure yielded 3.12 g. (97%) of pale yellow crystalline residue, m.p. 155–158° with slow decomposition. This material was used directly in the methylation step.

A suspension of the 3.12-g. residue in 30 ml. of dry *t*-butyl alcohol was added with stirring to a cooled (10°) solution of 1.95 g. of potassium in 60 ml. of dry *t*-butyl alcohol under an atmosphere of nitrogen. Methyl iodide (10 ml.) was then added with stirring, and after 2 hr. at room temperature the mixture was found to be neutral to litmus. The solution was cooled again to 10° and a solution of 1.95 g. of potassium in 60 ml. of *t*-butyl alcohol added, followed by 10 ml. of methyl iodide.[28] After 16 hr. at room temperature, the solvent was evaporated at 80° (10 mm.), water added and the mixture extracted with chloroform. The combined organic layers were washed well with water and dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was dissolved in 45 ml. of absolute ethanol, 0.10 g. of *p*-toluenesulfonic acid monohydrate was added and the solution heated at reflux under nitrogen with magnetic stirring. After 1 hr. 1.0 g. of potassium bicarbonate in 10 ml. of water was added and the mixture distilled to dryness at 20° (10 mm.). Ether and water were added, the ether layer washed with water and dried over anhydrous sodium sulfate. The yellow-brown, semi-solid residue obtained on evaporation of the ether crystallized on adding a small volume of ether. The crystals were separated by filtration and washed well with ether to give 0.344 g. of ***dl*-17-furfurylidene-D-homoepiandrosterone (XIV, R = H)**, m.p. 223–225°. A sample (m.p. 224–226° from the chromatogram described below) was purified by repeated recrystallization from ethanol. It was thus obtained as colorless plates, m.p. 223.5–225°, λ_{max} 323 mμ (log ε 4.34).

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.48; H, 9.14.

The residues from the separation of XIV (R = H) were chromatographed on 80 g. of Florisil. Elution with 9:1 benzene–ether gave 1.43 g. of semi-solid material, λ_{max} 325 mμ, consisting mainly of the 13-iso compound (see below). Further elution with 9:1 benzene–ether afforded an additional 0.297 g. of XIV (R = H) in fractions melting between 218–220° and 224–226°, λ_{max} 322 mμ.

The center fractions (0.780 g.) from the 9:1 benzene–ether eluate (1.43 g. total) described above represented ***dl*-17-furfurylidene-13-iso-D-homoepiandrosterone (XIII, R = H)** of suitable purity for use in subsequent steps in the synthesis (see below). It was not easily obtained in a high state of purity. Three recrystallizations from ether gave a darkened product which was dissolved in benzene and filtered through 1.5 g. of Florex. After evaporation of the eluate, the residue was recrystallized again from ether to give thick yellowish prisms. After drying for 6 hr. at 65° (0.05 mm.), it melted at 88–90° to a glass rather than a free-flowing liquid, λ_{max} 326.5 mμ (log ε 4.33).

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.3; H, 9.16.

The melting point of this compound was variable (between 88 and 115°) depending on the solvent employed for crystallization and on the rate of heating.

***dl*-17-Furfurylidene-D-homoepiandrosterone Acetate (XIV, R = Ac).**—A mixture of 0.344 g. of the *trans*-methylation product, m.p. 223–225°, described above, 40 ml. of dry benzene, 15 ml. of isopropenyl acetate and 0.10 g. of *p*-toluenesulfonic acid monohydrate was heated at reflux in an atmosphere of nitrogen. After 3.5 hr., most of the solvent was removed at reduced pressure, 10 ml. of saturated sodium bicarbonate added and the product extracted with benzene. The organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded a viscous brown oil which crystallized on cooling. A solution of this material in benzene was filtered through a column of 3.0 g. of acid-washed

(28) This repeated treatment was probably unnecessary (*cf.* previous cases, ref. 6) but was done to ensure complete methylation.

activated alumina to remove the color. The eluates yielded a pale yellow oil which on crystallization from petroleum ether afforded 0.365 g. (96% yield) of long pale yellow rods, m.p. 192–192.5°, λ_{max} 322.5 mμ (log ε 4.34).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.2; H, 8.53.

The infrared spectrum of this *dl*-compound was identical with that of naturally derived *d*-XIV (R = Ac).[19]

***dl*-3β-Acetoxyetioallohomobilianic Acid (XVI, R = Ac, R′ = H).**—Ozone was passed into a solution of 0.365 g. of the acetate XIV (R = Ac), m.p. 191–192°, in 50 ml. of ethyl acetate at −70°. After 14 minutes the solution turned blue-violet (indicating an excess of ozone), and the treatment was continued for an additional 5 minutes. The solvent was removed at 20° (10 mm.), and the residue dissolved in 40 ml. of glacial acetic acid; then 2 ml. of water was added followed by 1 drop of concentrated hydrochloric acid and 5 ml. of 30% hydrogen peroxide. The mixture with suspended solid was allowed to stir at room temperature overnight.

The solvent was removed at 50° (10 mm.), the semi-solid residue dissolved in ether and extracted thoroughly with 10% potassium bicarbonate solution. The combined bicarbonate extracts were washed well with ether, acidified with concentrated hydrochloric acid and the solid that separated was taken up in ether. The ether solution was washed thoroughly with water and dried over anhydrous sodium sulfate. The oily residue obtained on evaporation of the solvent crystallized on standing with a little ether; yield 0.295 g., m.p. 185–188°. Recrystallization from methyl ethyl ketone gave colorless crystals, m.p. 190–192°, which was not altered by further recrystallization. After standing for several months this material had undergone a polymorphic change to a form melting at 237–239°. In later preparations this latter form was obtained directly by recrystallization of crude (186–188°) material.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.95; H, 8.56.

The dimethyl ester XVI (R = Ac, R′ = CH_3) was prepared from 0.145 g. of crude acid, m.p. 185–188°, by treatment with an excess of diazomethane in ether. The crude neutral product amounted to 0.150 g., m.p. 129–132°. Two recrystallizations from methanol yielded *dl*-dimethyl 3β-acetoxyetioallohomobilianate as colorless feathery needles, m.p. 136–137°.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.1; H, 9.29.

The infrared spectrum of this racemic material was identical with that of naturally derived *d*-XVI (R = Ac, R′ = CH_3).[19]

***dl*-Epiandrosterone (XVIII, R = H).**—A solution of 0.310 g. of potassium in 50 ml. of dry (freshly distilled from calcium hydride) *t*-butyl alcohol was concentrated to dryness at reduced pressure. Dry benzene (about 50 ml.) was added, then removed by distillation at atmospheric pressure, and this process was repeated to ensure removal of *t*-butyl alcohol. Fifty milliliters of dry benzene was added to the dry residue followed by 0.075 g. of once-recrystallized (87% recovery, see above) dimethyl ester XVI (R = Ac, R′ = CH_3), m.p. 134–136°. The mixture was heated at reflux with stirring under nitrogen for 4 hr. After an additional 8 hr. at room temperature, the mixture was acidified with dilute sulfuric acid and the aqueous layer extracted with benzene. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained on removal of the solvent at reduced pressure gave an intense blue color with ferric chloride. It was dissolved in 10 ml. of acetic acid, 5 ml. of concentrated hydrochloric acid and 1 ml. of water added and the solution heated at reflux under nitrogen. After 1 hr., the solvent was evaporated at 40° under reduced pressure, 20 ml. of methanol and 15 ml. of 5% sodium hydroxide solution were added and the mixture heated at reflux under nitrogen for an additional hour. Most of the alcohol was evaporated under reduced pressure, ether and water were added and the aqueous layer extracted thoroughly with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. The yellow oily residue obtained on evaporation of the ether crystallized on standing; yield 0.049 g. (94%), m.p. 154–157°. No acidic material was obtained on acidification of the aqueous alkaline layer.

The crude epiandrosterone was sublimed at 130° (high vacuum) and then recrystallized twice from methylcyclohexane to give 0.028 g. of colorless chunky prisms, m.p. 161–162°, undergoing a change in crystalline form at 140–150° and giving off a characteristic musk-like odor when hot.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.4; H, 10.49.

The infrared spectrum of this *dl*-compound was identical with that of authentic *d*-epiandrosterone, m.p. 173–174°.[29]

***dl*-3β-Acetoxy-13-iso-etioallohomobilianic Acid (XV, R = Ac, R′ = H).**—A 0.490-g. sample of the crude 13-isohydroxy furfurylidene ketone XIII (R = H) obtained directly by chromatography as described above was acetylated in 20 ml. of dry benzene with 10 ml. of isopropenyl acetate and 0.10 g. of *p*-toluenesulfonic acid monohydrate. The mixture was heated at reflux for 2 hr. and the product isolated and purified by chromatography as described above for the C_{13}-epimer. The acetate XIII (R = Ac) thus obtained amounted to 0.399 g. of oily product which did not crystallize. This product was ozonized in 40 ml. of ethyl acetate at −70° as described above for the C_{13}-epimer. After treatment of the ozonide in 25 ml. of acetic acid with 1 ml. of 30% hydrogen peroxide and 2 ml. of water for 12 hr. at room temperature, the product was isolated as described above to give 0.340 g. of crude (bicarbonate-soluble) acid which crystallized on trituration with ethyl acetate. After trituration with three portions of ether, 0.300 g. remained, m.p. 248–249°. A specimen recrystallized three times from methyl ethyl ketone, twice from ethyl acetate and dried at 100° (0.1 mm.) for 17 hr. was obtained as small thick colorless prisms, m.p. 246–247°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.3; H, 8.75.

The dimethyl ester XV (R = Ac, R′ = CH_3) was prepared from 0.227 g. of the acid, m.p. 248–249°, by treatment of a solution in 3 ml. of methanol with excess ethereal diazomethane. The crude neutral product amounted to 0.233 g., m.p. 114–116°. A specimen twice recrystallized from methanol and sublimed at 105° (0.05 mm.) was obtained as colorless elongated prisms, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.4; H, 9.29.

***dl*-13-Isoepiandrosterone (XVII, R = H).**—Dry (alcohol-free) potassium *t*-butoxide was prepared from 0.550 g. of potassium as described above under the preparation of epiandrosterone. This reagent was dissolved in 15 ml. of benzene, 0.222 g. of the 13-isodimethyl ester, m.p. 114–116°, in 30 ml. of benzene was added and the mixture (under nitrogen) stirred for 4 hr. at reflux and then overnight at room temperature. The keto ester, isolated as described above, amounted to 0.202 g. of an oil which gave an intense purple color with dilute alcoholic ferric chloride. This oil was heated at reflux in 10 ml. of acetic acid containing 5 ml. of 33% hydrochloric acid and 1 ml. of water. After 1 hr. the solvent was evaporated at reduced pressure and the residue heated at reflux for 1 hr. with 20 ml. of methanol and 15 ml. of 5% sodium hydroxide. The crude (non-saponified) product, isolated as described above, amounted to 0.148 g. of an oil which crystallized on trituration with ether. After sublimation at 135° (0.06 mm.) the m.p. was 145–153°. Two recrystallizations of the sublimate from methylcyclohexane and one from methylcyclohexane–ethyl acetate gave 0.068 g. of small colorless rods, m.p. 157–158°. An additional crop of 0.054 g., m.p. 155–156°, was obtained from the combined mother liquors, making the total yield of good material 80%. The analysis was performed on the 157–158° material.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.3; H, 10.09.

The infrared spectrum of this material was identical with that of *d*-lumiepiandrosterone, m.p. 132–135.5°, prepared by B. Bloom according to the procedure of Billeter and Miescher.[22]

***dl*-3β-17aβ-Diacetoxy-18-nor-D-homoandrostane (XIX, R = Ac).** (a) From ***dl*-18-Nor-D-homoepiandrosterone.**—A solution of 0.534 g. of the hydroxy ketone VI, m.p. 159–

(29) Prepared by catalytic hydrogenation of dehydroepiandrosterone acetate, m.p. 169–170.2°, over 30% palladium-on-strontium carbonate (ref. 27) in 95% ethanol, followed by saponification and recrystallization.

161°, in 60 ml. of absolute ethanol was added cautiously to 600 ml. of ammonia, then 6.0 g. of lithium wire was added as rapidly as possible and the mixture was stirred until the blue color was discharged (about 45 minutes). The ammonia was evaporated, water and ether added, the aqueous layer extracted with ether and the combined organic layers washed thoroughly with water and dried over anhydrous sodium sulfate.

Evaporation of the solvent gave a colorless crystalline residue which was acetylated with 3.0 ml. of acetic anhydride in 6.0 ml. of pyridine. After 16 hr. at room temperature, ice was added and the mixture extracted with ether. The organic layers were washed with water, 2% hydrochloric acid, water, saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave, after trituration with a little ether, 0.639 g. of crude diacetate, m.p. 164–167°. Crystallization from methylcyclohexane, followed by sublimation at 161° (0.06 mm.) and recrystallization from the same solvent yielded 0.363 g. of colorless hexagonal prisms, m.p. 169.5–170°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.5; H, 9.67.

(b) From *dl*-13,14-Dehydro-18-nor-D-homoepiandrosterone.—A 0.140-g. sample of the unsaturated ketone III, m.p. 159–161°, was reduced as described in part (a) above with 30 ml. of ethanol, 270 ml. of ammonia and 3.0 g. of lithium wire. The product was converted to the diacetate as described above. A single crystallization of the crude product from methylcyclohexane gave 0.150 g. (82% yield) of colorless prisms, m.p. 169–170°, undepressed on admixture with the analytical sample described above.

dl-3β-17aβ-Dihydroxy-18-nor-D-homoandrostane (XIX, R = H).—A 0.178-g. sample of the diacetate XIX (R = Ac) was dissolved in 30 ml. of methanol, a solution of 0.15 g. of potassium hydroxide in 2 ml. of water was added and the mixture heated at reflux. After 2 hr., the solution was cooled, neutralized with acetic acid and concentrated at 50° under a stream of nitrogen. Water was added, the product extracted with chloroform and the organic layers washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.152 g. of crude colorless diol, m.p. 206–211°. Two recrystallizations from methyl ethyl ketone afforded fine colorless prisms, m.p. 210–211°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.8; H, 10.9.

dl-18-Nor-D-homoandrostane-3,17a-dione (XX).[30]—The total crude product from the hydrogenation of 0.340 g. of the 13,14-dehydro ketone III, m.p. 158–160°, as described above, was dissolved in 20 ml. of acetic acid, then a solution of 0.185 g. of chromium trioxide in 0.6 ml. of water was added. After 16 hr. at room temperature 1 g. of sodium bisulfite was added, most of the solvent evaporated in a stream of nitrogen at steam-bath temperature, then 30 ml. of water was added, whereupon the insoluble bisulfite adduct of the diketone separated as a finely divided colorless precipitate. The suspension was diluted with an additional 100 ml. of water, extracted thoroughly with ether and the ether layers were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The combined organic layers were washed with 5% sodium hydroxide, then with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.240 g. of crude colorless diketone, m.p. 137.5–145.7°. Trituration with ether, followed by three recrystallizations from methylcyclohexane, gave colorless prisms, m.p. 149–150.5°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.0; H, 9.91.

(30) After a preparation performed by H. Lemaire.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. VIII.[1] *dl*-3β,11β-Dihydroxyandrostane-17-one

BY WILLIAM S. JOHNSON, RAPHAEL PAPPO[2] AND WILLIAM F. JOHNS[3]

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The modified lithium–ammonia–alcohol reduction procedure described in paper VII has been applied to the 11β-hydroxy compound II to give a mixture of 13,14- and 16,17-dehydro ketones III and IV. This mixture, which has been separated into the pure components, could be hydrogenated directly in alkaline solution to give a single dihydroxy ketone V. A procedure has been developed for carrying out the reduction of the 12-oxygenated precursor, as well as of the aromatic nucleus of II in a single step. Condensation of V with furfuraldehyde yielded the furfurylidene ketone VI (R = H), which as its ditetrahydropyranyl ether VI (R = —CHCH$_2$CH$_2$CH$_2$CH$_2$O) was angularly methylated to give, after acid hydrolysis, the C/D *cis* (VII, R = H) and C/D *trans* (VIII, R = H) epimers. The latter (less preponderant) isomer on acetylation, ozonolysis and esterification with diazomethane gave *dl*-dimethyl 3β,11β-diacetoxyetioallohomobilianate (XI, R = Ac, R′ = CH$_3$), the infrared spectrum of which was identical with that of naturally derived *d*-XI (R = Ac, R′ = CH$_3$). Dieckmann cyclization of the *dl*-compound, followed by hydrolysis and decarboxylation in aqueous dioxane at 200–210° afforded, after saponification to cleave the acetate residues, the *dl*-form of the natural product 3β,11β-dihydroxyandrostane-17-one (XIII, R = H). The infrared spectrum of the *dl*-diacetate XIII (R = Ac) was identical with that of authentic (naturally-derived) *d*-XIII (R = Ac). Similarly the 13-isofurfurylidene ketone VII (R = H) was converted to the dimethyl ester X (R = Ac, R′ = CH$_3$) and cyclized to give the 13-isosteroid XII (R = H). When the intermediary diacid X (R = Ac, R′ = H) was saponified to cleave the acetate residues, then acidified, the product was the lactonic acid IX. Since such a lactone was not produced from the epimeric diacid XI (R = R′ = H), these results provide proof for the configuration of these substances and in turn for the C$_{11}$-configuration of the natural 11-hydroxy steroids. A similar reduction study has been carried out with the A/B *cis*-11β-hydroxy compound XV (as well as its precursor). The resulting unsaturated ketones XVI and XVII were converted to XVIII, the configuration of which was proved by relating it to the A/B *trans* series (of established configuration) as follows. Selective Oppenauer oxidation of XVIII gave the hydroxy diketone XIX, which on treatment with one mole-equivalent of bromine followed by dehydrohalogenation gave a mixture of unsaturated ketones XX and XXI. The latter, on reduction with lithium and alcohol in ammonia, followed by acetylation gave a triacetoxy compound identical with that (XXII, R = Ac) produced by similar treatment of the A/B *trans*-compound V.

The previous paper of this series[1] contains a description of the reduction with lithium and alcohol in ammonia of the aromatic nucleus of 1-methoxy-8β-hydroxy-10a-methyldodecahydrochrysene (11-desoxy II) to yield, after acid treatment, a mixture of α,β-unsaturated ketones which on hydrogenation in alkaline solution afforded *dl*-18-nor-D-homo-

(1) Paper VII, W. S. Johnson, B. Bannister and R. Pappo, THIS JOURNAL, **78**, 6331 (1956).

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