fraction with m.p. 114–116° (reported[7] 114–115°) was eluted with benzene. This substance had a strong adsorption band at 5.75 μ. The semicarbazone melted at 273–274° (reported[7] 274–275°).

1,2,3,4-Tetrahydro-17-equilenyl Methyl Ketone.—Acid XVI (879 mg.) was converted to the acid chloride by refluxing with thionyl chloride (18 ml.) for 90 minutes and then removing the excess reagent *in vacuo*. The acid chloride was purified by sublimation at 133°(0.01 mm.), m.p. 120–131°. This compound (858 mg.) was added to a solution of dimethylcadmium in benzene prepared from cadmium chloride (526 mg.), magnesium (140 mg.) and methyl iodide (1.15 g.).[15] The reaction mixture was refluxed for 2.25 hours and then ice, dilute hydrochloric acid and ether were added. The ether layer was washed with water and sodium bicarbonate solution and then dried and concentrated to yield 926 mg. of crude product. This material was chromatographed on a column of Florisil (30 g.); elution with benzene–petroleum ether (1:2) removed six semi-solid fractions containing the desired ketone (773 mg.). Recrystallization from methanol yielded 424 mg. (53%) of product which melted at 110–115° and 160 mg. of less pure material, m.p. 85–110°. The analytical sample melted at 116.5–118°.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 84.76; H, 9.12.

17-Equilenyl Methyl Ketone (XXII).—Acid XV (950 mg.) was converted to the acid chloride and this crude product allowed to react with dimethylcadmium (from 642 mg. of cadmium chloride) exactly as with the tetrahydro derivative of XXII. The crude product (1.246 g.) was chromatographed on Florisil (40 g.) to yield 490 mg. (52%) of XXII which melted at 160–166°. Recrystallization from methanol afforded a product (345 mg.) of analytical purity, m.p. 162–165°.

(15) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.94; H, 7.99.

***d,l-trans*-3-Desoxyequilenin (XXIV).**—A solution of ketone XXII (345 mg.) in acetic anhydride (32 ml.) containing *p*-toluenesulfonic acid (80 mg.) was slowly distilled during 5.3 hours. The residual solution was concentrated *in vacuo* and then ice and sodium carbonate solution were added. The product was extracted with ether, the extract was dried and concentrated. The dark residue was dissolved in petroleum ether and passed through a column of alumina (4 g.) to yield 270 mg. (68%) of semi-solid enol acetate XXIII. Attempts to recrystallize a portion (29 mg.) of this substance from petroleum ether were not successful.

The enol acetate (240 mg.) was dissolved in ethyl acetate (100 ml.) and methanol (100 ml.) and cooled to −78°. A solution of ozone (1 millimole/min.) was passed through the solution for 1.5 minutes. The cold solution was shaken with hydrogen in the presence of pre-reduced palladium-on-calcium carbonate catalyst (1.1 g.) for 18 minutes. The solution was filtered and concentrated and the residue (245 mg.) was chromatographed on alumina. A crystalline fraction (41 mg., 22%) was eluted with 2% chloroform in benzene. This material melted at 170–177° but recrystallization from methanol–acetone furnished nearly pure XXIV (26 mg., 14%), m.p. 189–191.5° (evacuated capillary). Sublimation and an additional recrystallization from ethanol raised the melting point (190–191.5°) only slightly. The infrared spectrum was identical with that of an authentic sample.[8]

The semicarbazone melted at 256–257.5° (dec., cap.) after recrystallization from ethanol (reported[2b] 256.5–257.5°). The trinitrobenzene adduct, prepared in ethanol, melted at 153–154° (cap.) (reported[16] 153–154°).

(16) W. E. Bachmann and A. S. Dreiding, THIS JOURNAL, **72**, 1323 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, WORCESTER, MASSS., FROM THE POSTGRADUATE MEDICAL SCHOOL OF LONDON, LONDON, ENG., AND FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASS.]

D-Homosteroids. IV.[1] 17β,17aβ-Dimethyl-17α-17aα-dihydroxy- and 17,17-Dimethyl-17a-keto-D-homosteroids[2]

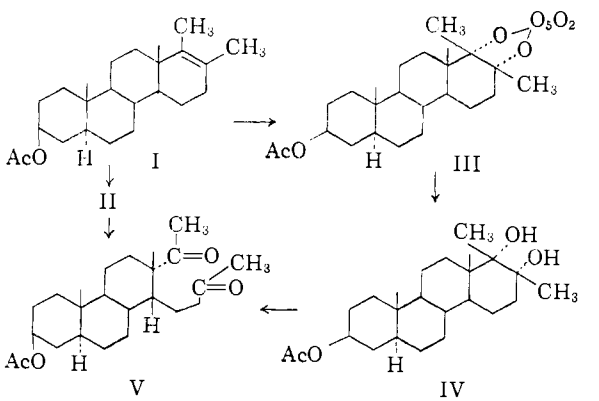
BY MILAN USKOKOVIĆ, MARCEL GUT, EDWARD N. TRACHTENBERG, W. KLYNE AND R. I. DORFMAN

RECEIVED MARCH 1, 1960

Hydroxylation of 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate with osmium tetroxide produced 17β,17aβ-dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-acetate. Chromic acid oxidation of this glycol produced 3β-acetoxy-17,17a-dimethyl-17,17a-secohomoandrostane-17,17a-dione. The glycol also underwent a pinacolic rearrangement to 3β-acetoxy-17,17-dimethyl-D-homoandrostan-17-one which is quite novel in that it required a boat conformation for ring D in the transition state. To explain the course of this rearrangement, mechanistic arguments are presented and supported by optical rotatory dispersion findings which indicate that ring D in the product also does not possess an ideal chair conformation.

It has been shown in a previous paper[1] that 17,-17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate (I) gave an ozonolysis product which was tentatively assigned the structure 3β-acetoxy-16-acetyl-17-methylandrostane-17-hydroperoxide (II). Compound II decomposed on heating to 3β-acetoxy-17,-17a-dimethyl-17,17a-secohomoandrostane-17,17a-dione (V).

It has now been found that treatment of I with osmium tetroxide in dioxane gave the crystalline osmic ester III of the 17α,17aα-glycol, which was



decomposed by hydrogen sulfide to 17β,17aβ-dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-

(1) Paper III, Milan Uskoković, Marcel Gut and R. I. Dorfman, THIS JOURNAL, **82**, 3668 (1960).

(2) Taken in part from a dissertation by Milan Uskoković in partial fulfillment of the requirements for the Ph.D. degree in Organic Chemistry, Clark University. Presented, in part, before the Division of Organic Chemistry, 136th National A.C.S. Meeting, Atlantic City, N. J., Sept., 1959, p. 82P. This investigation was supported, in part, by grants PSH-C-321 and PHS-CY-2193.

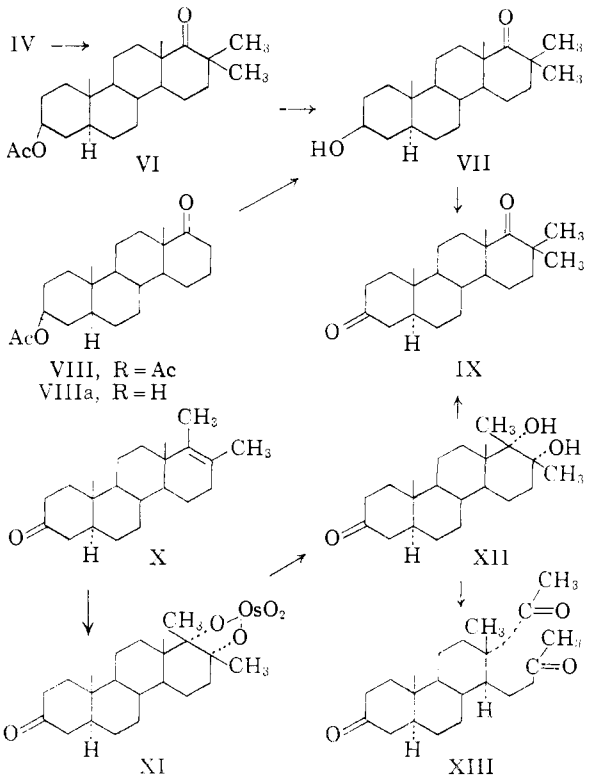
acetate (IV). The oxidation of IV with either sodium bismuthate in acetic acid or chromium trioxide in acetic acid–methylene chloride gave V in quantitative yield. This is believed to be the first reported case of the splitting of a ditertiary 1,2-glycol to a diketone using chromium trioxide. Judging from the observed color change of the solution, this reaction was slow and required approximately 3 days to go to completion. That compound IV has the 17α,17aα-dihydroxy structure follows from analogy to other reactions,[3] for which proof was furnished that the attacking osmium tetroxide approached the steroid molecule from the less hindered α-side, due to steric blocking of the β-side by the angular methyl group at C_{13}. It is also known that osmic esters are cleaved by hydrogen sulfide[4] to give *cis*-glycols without inversion of the two carbon centers involved. This is in line with the fact that the 3-keto-analog XII derived from IV showed neither androgenic nor antiandrogenic activity (which should be expected from a 17aβ-hydroxy-D-homoandrostane derivative).

When 17β,17aβ-dimethyl-D-homoandrostane-3β,-17α,17aα-triol 3β-acetate (IV) was refluxed in acetic acid containing a few crystals of iodine, a pinacolic rearrangement took place to give an 85% yield of 3β-acetoxy-17,17-dimethyl-D-homoandrostan-17a-one (VI).

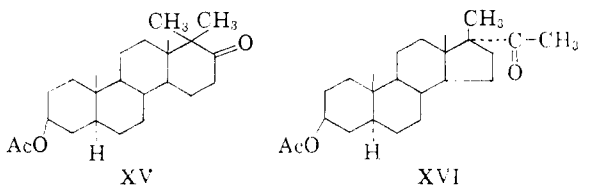
The structure assignment of VI is based on elemental analysis; infrared absorption spectrum ν_{max} 1710 (17a-ketone), 1725 and 1245 (3β-acetoxy), 1154 cm.$^{-1}$ (*gem*-dimethyl group); ultraviolet absorption λ_{max} 297 mμ ϵ60, being characteristic for highly hindered six ring ketones[5]; negative Zimmermann reaction; by its failure to undergo bromination and finally from the following transformations. Alkaline hydrolysis of VI yielded 3β-hydroxy-17,17-dimethyl-D-homoandrostan-17a-one (VII), which was also obtained by the direct methylation of 3β-acetoxy-D-homoandrostan-17a-one (VIII).[6-9]

The oxidation of VII with chromium trioxide gave 17,17-dimethyl-D-homoandrostane-3,17a-dione (IX), which was also obtained from 17,17a-dimethyl-D-homoandrost-17(17a)-en-3-one (X)[1] by the following transformations. Treatment of X with osmium tetroxide in dioxane was followed by decomposition of the osmic ester (XI) with hydrogen sulfide to yield 17α,17aα-dihydroxy-17β,17aβ-dimethyl-D-homoandrostan-3-one (XII). Pinacolic rearrangement of XII furnished the diketone IX. The oxidation of the glycol XII, either with sodium bismuthate or chromium trioxide, gave 17,17a-dimethyl-17,17a-secohomoandrostane-3,-17,17a-trione (XIII). Neither the diketone IX nor the glycol XII showed any androgenic or antiandrogenic activity.

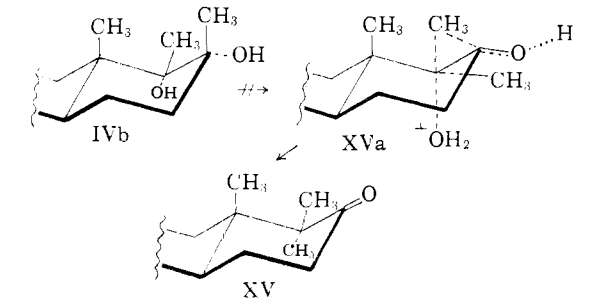
In this interesting rearrangement, ring D almost certainly must have assumed a boat conformation



because the chair form would have led to either 3β-acetoxy-17a,17a-dimethyl-D-homoandrostan-17-one (XV)[10] or 3β-acetoxy-17β-methyl-5α,17α-pregnan-20-one (XVI) depending on whether the 17a- or the 17-hydroxyl had been protonated, respectively. However, the *trans*-diaxial conformation of 17α-hydroxyl and 17$\alpha\beta$-methyl required for the observed transformation of IV to VI is only possible with ring D in the boat form. Conformational analysis suggests that the boat IVa and chair IVb forms are energetically fairly close.



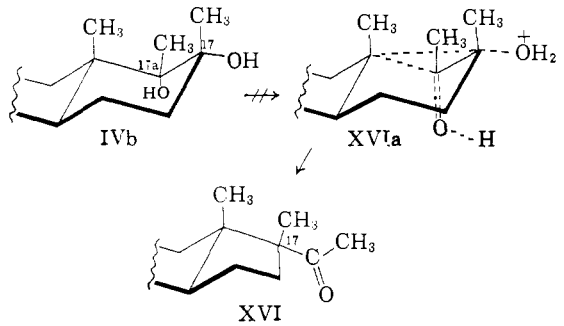
That compounds XV and XVI were not obtained is probably due to the high energies of their respective transition states resulting from severe



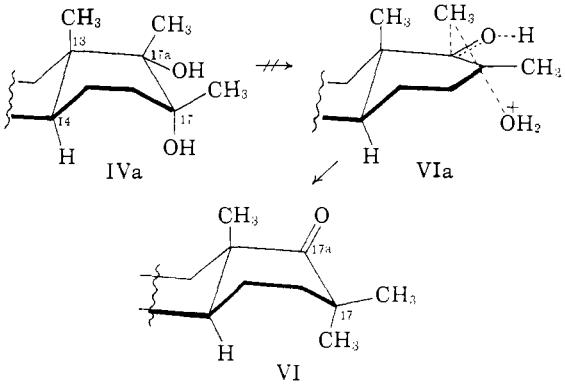
(3) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).
(4) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).
(5) O. H. Wheeler and J. L. Mateos, *Anal. Chem.*, **29**, 538 (1957).
(6) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940).
(7) M. W. Goldberg and R. Monnier, *ibid.*, **23**, 840 (1940).
(8) M. W. Goldberg and E. Wydler, *ibid.*, **26**, 1142 (1943).
(9) H. Heusser, P. Th. Herzig, A. Fürst, Pl. A. Plattner, *ibid.*, **33**, 1093 (1950).
(10) M. Uskoković, M. Gut and R. I. Dorfman, THIS JOURNAL, **81**, 4561 (1959).

steric crowding. Thus, in the transition state XVa leading to XV, the 17-methyl is brought closer to the 13-methyl in what presumably is an even more severe non-bonded interaction than the typical 1,3-diaxial one.

The transition state XVIa leading to XVI results in an incipient cyclopropane structure with three *cis*-methyl groups (17,17a,13) badly eclipsed.



These steric situations appear less favorable than in the transition VIa in which the D ring is in the boat conformation. It should be noted that there is steric relief of the eclipsing of the 17aβ- and 13β-methyl groups in going to VIa and that the interaction between the 17α-hydroxyl and 14α-hydrogen, normally a very serious destabilizing influence in a boat conformation, may be less here since the C_{17} C-O bond is stretched and is inclined at a greater angle away from C_{14}.



The boat conformation for the D-ring in VI is preferred, since the chair form will be highly destabilized by 1,3-diaxial interaction of the 13β- and the 17β-methyl groups; in contradistinction, the eclipsed interactions in the alternative boat forms are relieved by the 17a-keto group. The rotatory dispersion curve of VI is clearly incompatible with the presence of an ideal chair conformation for ring D.

Rotatory Dispersion Curves.—The study of these curves raises some interesting points. The unmethylated 17a-ketone (as VIIIa) is an important anomaly studied in earlier work by Djerassi.[11,12] It gives a rotary dispersion curve which shows no true Cotton effect: a qualitative explanation of this fact in terms of the Octant Rule[13] has been given elsewhere.[14]

(11) The rotatory dispersion curve of VIIIa has also been recorded by C. Djerassi *et al.*, ref. 12.

(12) C. Djerassi, W. Closson and A. E. Lippman, THIS JOURNAL, **78**, 3163 (1956).

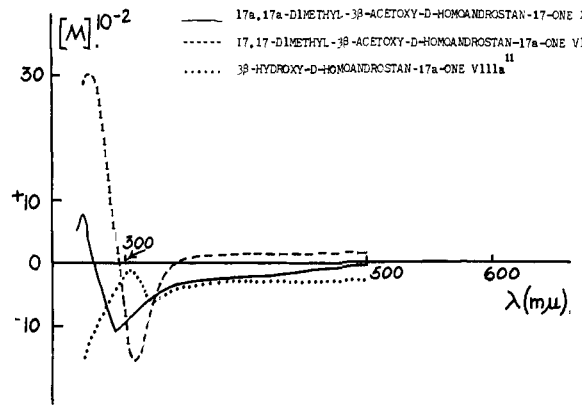
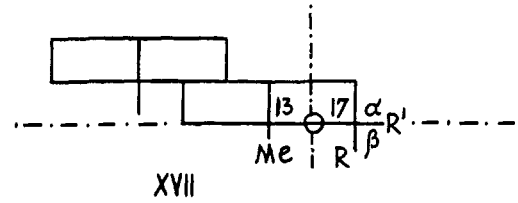


Fig. 1.

The 17,17-dimethyl ketone VI shows a negative Cotton effect curve of moderate amplitude ($10^{-2}a = -46$); *i.e.*, the *gem*-dimethyl group at C-17 has made a contribution of −46 units. On the basis of the Octant Rule, one would expect for VI a positive Cotton effect. If one considers the projection formula XVII, the introduction into the molecule of an axial methyl group at C-17 (R = Me) should produce a positive contribution (the equatorial methyl group (R′ = Me) should make little contribution in either direction).



XVII

The experimental fact that the dimethyl ketone VI shows a *negative* Cotton effect supports the suggestion, made above on mechanistic grounds, that these "crowded" polymethylcyclohexane derivatives exist in modified chair or modified boat conformations; *cf.* the discussions of skew conformations by Reeves[15] and Dreiding,[16] and the consideration of polymethylcyclohexanones by Ourisson.[17] The understanding of rotary dispersion curves is not as yet sufficient to allow one to apply the experimental findings to indicate *which* of the many possible modified conformations must be present in VI to give the observed negative curve.

Experimental[18]

17β,17aβ-Dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-Acetate (IV) from I.—A solution of 1 g. of I and 1 g.

(13) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(14) W. Klyne in "Advances in Organic Chemistry," Ed. R. A. Raphael, Vol. 1, Interscience Publ., Inc., New York, N. Y., 1950, p. 239.

(15) R. E. Reeves, *Ann. Rev. Biochem.*, **27**, 15 (1958).

(16) A. S. Dreiding, *Bull. soc. chim. France*, Colloquium in Stereochemistry (in press).

(17) C. Sandris and G. Ourisson, *ibid.*, 1524 (1958).

(18) All melting points were taken on a Kofler block. Rotations were taken in a 1-dm. tube in chloroform. Ultraviolet absorption spectra were determined in methanol by means of a Cary model 11 MS spectrophotometer. The infrared spectra were obtained from a pressed potassium bromide pellet taken on a Perkin-Elmer model 12C spectrometer. All chromatographic separations were made on Davison silica gel mesh 60–200. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

of osmium tetroxide in 100 ml. of dioxane was allowed to stand for 10 days in the dark at room temperature, whereby crystalline osmic ester III was formed. The reaction mixture was then saturated with hydrogen sulfide. The precipitated osmium metal was filtered off and the dioxane solution was evaporated to dryness *in vacuo*. The dark-green colored crystalline residue was recrystallized from ether to give 970 mg. of IV, m.p. 181–183°, $[\alpha]^{20}D$ +13° (*c* 1.49); infrared absorption maxima ν_{max} 3650 and 3550 (hydroxyl groups), 1725 and 1270 (3β-acetoxy group), 1390 and 1370 cm.$^{-1}$ (methyl groups).

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.71; H, 10.47.

3β-Acetoxy-17,17a-dimethyl-17,17a-secohomoandrostane-17,17a-dione (V) from IV. a. To a solution of 300 mg. of IV in 100 ml. of 75% acetic acid was added 2.5 g. of sodium bismuthate, and the suspension was shaken for 18 hours at room temperature. The excess sodium bismuthate was reduced with saturated aqueous sodium bisulfite solution, and after addition of a large excess of water, the resulting suspension was extracted with chloroform. The extract was washed to neutrality with saturated aqueous sodium bicarbonate solution and then with water, dried over sodium sulfate and evaporated to dyness *in vacuo*. The crystalline residue was recrystallized from methanol and then from ether-petroleum ether to give 260 mg. of V, which was identical in melting point, optical rotation, elemental and infrared analysis with an authentic sample of the compound obtained previously.

b.—To a solution of 100 mg. of IV in 50 ml. of methylene chloride was added 1 ml. of a 2% solution of chromium trioxide in 80% aqueous acetic acid, and the two-phase system was shaken for 72 hours at room temperature until the acetic acid layer had a violet color. Then the methylene chloride solution was washed with water, dried over sodium sulfate and evaporated to dryness. The white crystalline residue was refluxed with petroleum ether to give 45 mg. of V, identical with a previously obtained specimen.

3β-Acetoxy-17,17-dimethyl-D-homoandrostan-17a-one (VI) from IV.—A solution of 300 mg. of IV and 6 mg. of iodine in 100 ml. of glacial acetic acid was refluxed for half an hour under nitrogen. The iodine was reduced with a few drops of saturated aqueous sodium bisulfite solution, and after a large excess of water was added, the resulting suspension was extracted with methylene chloride. The extract was washed with 1 *N* sodium hydroxide solution and water to neutrality, dried over sodium sulfate and evaporated to dryness *in vacuo*. The sirupy residue was chromatographed whereby the first five fractions with 2% ethyl acetate in benzene gave a crystalline residue, which on recrystallization from methanol gave 160 mg. of VI, m.p. 110–111°, $[\alpha]^{20}D$ −29° (*c* 1.17); infrared absorption maxima ν_{max} 1710 (17-ketone), 1725 and 1245 (3β-acetoxy), 1154 cm.$^{-1}$ (*gem*-dimethyl group); ultraviolet absorption λ_{max} 297 mμ, ε 59.5. The substance does not give a positive Zimmermann reaction, nor does it take up bromine in an ether-acetic acid solution; rotatory dispersion curve in methanol, 0.2 mg./ml., at 20°: negative Cotton effect curve; peak, 315 mμ, $[\phi]$ −1570°; trough, 280 mμ, $[\phi]$ + 3020°. amplitude $10^{-2}a$ −46.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.22; H, 10.14.

The remainder of the fractions with 2% ethyl acetate in benzene did not give a crystalline residue, and was rechromatographed on a column of Woelm aluminum oxide, activity grade 1. This time, two fractions were obtained with 2.5% ethyl acetate in benzene, which, on crystallization from methanol, gave an additional 25 mg. of VI. From the fractions with 5% ethyl acetate in benzene, crystallization from acetone gave trace amounts of 3β-acetoxy-17a,17a-dimethyl-D-homoandrostan-17-one (XV), m.p. 172–174°, identified by comparison of its infrared spectrum with that of an authentic sample.

3β-Hydroxy-17,17-dimethyl-D-homoandrostan-17a-one (VII) from VI.—To a solution of 100 mg. of VI in 10 ml. of methanol was added 1 ml. of 1 *N* sodium hydroxide, and the reaction mixture was allowed to stand overnight at room temperature. A large excess of water was added and the resulting suspension was extracted with methylene chloride. The extract was washed with water to neutrality, dried over sodium sulfate and evaporated *in vacuo*. The crystalline residue was recrystallized from ether, giving 75 mg. of VII, m.p. 150–152°, $[\alpha]^{20}D$ −24° (*c* 0.36); infrared absorption maxima ν_{max} 3550 and 1043 (3β-hydroxy), 1710 (17a-ketone), 1163 cm.$^{-1}$ (*gem*-dimethyl group).

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.67; H, 10.84.

3β-Hydroxy-17,17-dimethyl-D-homoandrostan-17a-one (VII) from VIII.—A solution of 500 mg. of VIII in 30 ml. of benzene was dried by azeotropic distillation of a small volume of solvent. Then a solution of potassium *t*-butoxide, prepared from 500 mg. of potassium and 20 ml. of anhydrous *t*-butyl alcohol was added. To the refluxing reaction mixture was added slowly 5 ml. of methyl iodide in 20 ml. benzene, and the resultant mixture was refluxed for 1 hour. After cooling, the hydrolysis of the excess potassium *t*-butoxide was accomplished by adding ice, and the mixture was extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The crystalline residue was recrystallized several times from ether to yield 160 mg. of pure VII, m.p. 152–155°, which was in all respects identical with an authentic sample obtained previously.

17,17-Dimethyl-D-homoandrostan-3,17a-dione (IX) from VII.—To a solution of 100 mg. of VII in 50 ml. of methylene chloride was added 1.5 ml. of 2% chromium trioxide solution in 80% aqueous acetic acid, and the reaction mixture was shaken for 24 hours at room temperature. The methylene chloride layer was washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed whereby the eluates with 5% ether in benzene gave, after recrystallization from methanol, 93 mg. of IX, m.p. 129–131.5°, $[\alpha]^{20}D$ +12° (*c* 1.05); infrared absorption maxima ν_{max} 1728 and 1712 cm.$^{-1}$ (ketone groups).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.97; H, 10.37. Found: C, 80.20; H, 10.36.

17α,17aα-Dihydroxy-17β,17aβ-dimethyl-D-homoandrostan-3-one (XII) from X.—To a solution of 1 g. of X in 200 ml. of dioxane was added 1 g. of osmium tetroxide, and the solution was allowed to stand in the dark for 10 days at room temperature. By that time, the black osmic ester XI had crystallized out. Saturation of the reaction mixture with hydrogen sulfide reduced the osmic ester to metallic osmium, which precipitated from the solution. It was filtered with Celite, the dioxane solution was then evaporated to dryness and the dark colored crystalline residue was chromatographed. The fractions with 25% ethyl acetate in benzene gave, after concentration to dryness and recrystallization from ether, 840 mg. of XII, m.p. 183–184°, $[\alpha]^{20}D$ +28° (*c* 1.064); infrared absorption maxima ν_{max} 3500 (hydroxyl), 1700 (3-ketone), 1390 and 1370 cm.$^{-1}$ (methyl groups).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.71; H, 10.41. Found: C, 75.62; H, 10.06.

17,17-Dimethyl-D-homoandrostan-3,17a-dione (IX) from XII.—A solution of 300 mg. of XII and 6 mg. of iodine in 100 ml. glacial acetic acid was refluxed for 0.5 hour under nitrogen. After cooling, the iodine was reduced with a few drops of saturated aqueous sodium bisulfite solution, and after adding a large excess of water the resulting suspension was extracted with chloroform. The extract was washed with diluted aqueous sodium hydroxide solution and water to neutrality, dried over sodium sulfate and evaporated *in vacuo*. The sirupy residue was chromatographed whereby the eluates with 2 and 5% ether in benzene gave, after evaporation to dryness and recrystallization from methanol, 120 mg. of IX, m.p. 128–130°; this sample had an infrared spectrum identical with the authentic material and did not depress the melting point on admixture with it.

17,17a-Dimethyl-17,17a-secohomoandrostane-3,17,17a-trione (XIII) from XII. a.—To a solution of 300 mg. of XII in 100 ml. of 50% aqueous acetic acid was added 5 g. of sodium bismuthate, and the suspension shaken for 18 hours at room temperature. The excess of sodium bismuthate was reduced with saturated aqueous sodium bisulfite solution and, after addition of a large excess of water, the resulting suspension was extracted with chloroform, the extract washed to neutrality with saturated sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from methanol to give 280 mg. of XIII, m.p. 171–172°, $[\alpha]^{20}D$ +31° (*c* 0.604); infrared absorption maxima ν_{max} 1718 (3-ketone), 1695 cm.$^{-1}$ (17- and 17a-ketone).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.40; H, 9.64.

b.—To a solution of 100 mg. of XII in 50 ml. of methylene chloride was added 1 ml. of a 2% solution of chromium trioxide in 80% aqueous acetic acid, and the two-phase system was shaken for 70 hours at room temperature. The methylene chloride layer was washed with water, dried over sodium sulfate and evaporated to dryness. The crystalline residue was recrystallized from ether to give 80 mg. of XIII in long prisms, m.p. 170–172°. The product showed the same infrared spectrum as the product obtained by bismuthate oxidation, and the mixed melting point was not depressed.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA, COLUMBIA, S. C.]

Intramolecular Free Radical Arylation and Related Reactions[1]

BY DELOS F. DETAR AND CHIN-CHIUN CHU[2,3]

RECEIVED JANUARY 18, 1960

A study has been made of the reactions of the 2-*o*-terphenyl free radical as obtained both from the peroxide of *o*-terphenyl-2-carboxylic acid and from the diazonium salt derived from 2-amino-*o*-terphenyl. Cyclization to triphenylene (IX) occurs to the exclusion of the intermolecular reaction with benzene or with carbon tetrachloride. However, bromine abstraction from bromotrichloromethane does compete with cyclization. This behavior is in contrast to that of the *o*-benzoylphenyl radical, which was found in previous work to give a higher yield of 2-phenylbenzophenone by intermolecular reaction with benzene than of the intramolecular cyclic product, fluorenone. The peroxide of *o*-(1-naphthyl)-benzoic acid (VI) was also investigated, but the acyloxy radical failed to decarboxylate. The main product found was the lactone VIII of *o*-(2-hydroxy-1-naphthyl)-benzoic acid.

A number of mechanisms have been proposed for the free radical arylation reactions which take place on decomposing a diacyl peroxide in an aromatic solvent, in the Gomberg–Bachmann reaction of diazonium salts, and in other related reactions.[4–6] In these reactions a carbon–carbon bond is formed and a carbon–hydrogen bond is broken. If carbon–carbon bond formation is the key step, then mechanisms of type I (eq. 1 or 2) result. If the carbon–hydrogen bond is broken first, then the mechanisms are of type II (eq. 3a and 3b). The

$$\mathrm{Ar\cdot + Ar'H \longrightarrow ArAr' + (H\cdot)} \quad (1)$$

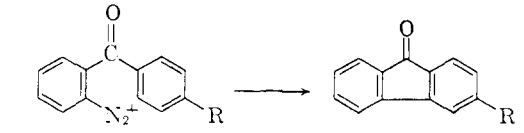
$$\mathrm{Ar\cdot + Ar'H \longrightarrow ArAr'H\cdot} \quad (2)$$

$$\mathrm{X\cdot + Ar'H \longrightarrow XH + Ar'\cdot} \quad (3a)$$

$$\mathrm{Ar'\cdot + P \longrightarrow Ar'Ar + X\cdot} \quad (3b)$$

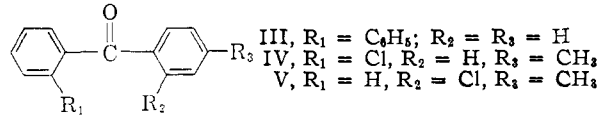
complete over-all mechanisms must also specify the source of the radicals Ar. and the detailed fate of radicals formed in eq. 2 and 3a, etc.

Some years ago we sought to distinguish between type I and type II mechanisms by a study of diazonium ring closure reactions (eq. 4).[7,8] Thus the diazonium salt (I) was allowed to react under alkaline conditions so that a free *o*-benzoylphenyl radical would be formed. A type I mechanism would then give fluorenone if the reaction were intramolecular or, in the presence of benzene, 2-benzoylbiphenyl (III) if the reaction were intermolecular. A type II mechanism (eq. 3a and b) would give mainly the intermolecular product III, for there is no reason to expect that a radical X· (X· = ·OH, *e.g.*) will perferentially attack the 2′-position of a diazo-species.[9] This approach is based on one of the important empirical generalizations of organic chemistry; namely, that the reaction of two functional groups to form a five- or a six-membered ring wins out over intermolecular reactions of these same groups.



(4)

I, R = H
II, R = CH_3



III, R_1 = C_6H_5; R_2 = R_3 = H
IV, R_1 = Cl, R_2 = H, R_3 = CH_3
V, R_1 = H, R_2 = Cl, R_3 = CH_3

The Gomberg–Bachmann reaction of 2-benzoylbenzenediazonium salts (I) in the presence of benzene and of alkali gave the usual complex mixture (*i.e.*, tars are formed). Some fluorenone was present, but the principal isolable product was 2-phenylbenzophenone (15%) (III).[7] This experiment was repeated during the present investigation and the products (analyzed by gas chromatography) were benzophenone (6%), fluorenone (6%) and 2-phenylbenzophenone (13%); the remaining products were less volatile and were not identified. On decomposition in alkaline media in the absence of an added organic solvent the fluorenone yield ranges from 5–25%.[10,11] On the other hand, under acidic conditions the fluorenone yield is 65–75%, the other product being 2-hydroxybenzophenone.[10–12] The diazonium salt derived from 2-

(1) Intramolecular Reactions VI. Previous paper: D. F. DeTar and T. E. Whiteley, THIS JOURNAL, **79**, 2498 (1957).

(2) From the Ph.D. dissertation of Chin-Chiun Chu.

(3) We gratefully acknowledge the support of this work by the Air Force Office of Scientific Research under contract AF 49(638)-88.

(4) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 474, 518.

(5) (a) O. C. Dermer and M. T. Edmison, *Chem. Revs.*, **57**, 77 (1957); (b) D. R. Augood and G. H. Williams, *ibid.*, **57**, 123 (1957).

(6) E. L. Eliel, S. Meyerson Z. Welvart and S. H. Wilen, THIS JOURNAL, **82**, 2936 (1960).

(7) D. F. DeTar and S. V. Sagmanli, *ibid.*, **72**, 965 (1950).

(8) D. F. DeTar, *Org. Reactions*, **9**, 409 (1957).

(9) In these equations P represents some such species as a diazohydroxide and X· would then be a hydroxyl radical. The species actually involved in the Gomberg–Bachmann reactions have not been identified. If a peroxide source were used then P would represent a peroxide molecule and X· would refer to an acyloxy radical.

(10) D. F. DeTar and D. I. Relyea, THIS JOURNAL, **76**, 1680 (1954).

(11) D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 2276 (1952).

(12) D. F. DeTar and T. E. Whiteley, THIS JOURNAL, **79**, 2498 (1957).