The Synthesis and Configuration of C-Nor-D-homotestosterone Acetate[1,2]

By S. Morris Kupchan and Seymour D. Levine[3]

The synthesis is described of the C-nor-D-homotestosterone derivatives XXIV and XXVII, which possess the testosterone configuration at each of the ring junctions. Jervine was degraded to II and II was hydrolyzed to III. Oppenauer oxidation of III yielded IV, which was converted to the 3-ethylene ketal V. Osmium tetroxide hydroxylation followed by periodic acid oxidation gave VII, and reduction of VII gave IX. Sodium borohydride reduction of IX afforded the epimeric alcohols XIX and XX. Upon Wolff–Kishner reduction, ethylene ketal hydrolysis, and acetylation, alcohols XIX and XX were converted to the respective epimeric hormone analogs. Evidence for the configuration at each of the asymmetric centers of XXIV and XXVII is presented.

The past decade has witnessed considerable interest in the modification of the basic steroid skeleton of hormones to seek analogs with enhanced or more specific pharmacological properties. In view of the natural occurrence of the C-nor-D-homosteroid ring system (e.g., in jervine (I)[4,5] and veratramine[6]), the synthesis of related hormone analogs seemed a particularly attractive target. We describe herewith the synthesis of the C-nor-D-homotestosterone derivatives XXIV and XXVII, which possess the testosterone configuration at each of the ring junctions. The latter compounds appear to be the first reported C-nor-D-homosteroid hormone analogs.

The readily available veratrum alkaloid jervine (I) was the starting material for our investigation. Degradation of jervine was effected by the fragmentation reaction developed in the course of the structure elucidation of the alkaloid.[4] Attempts to improve the reaction by the use of other Lewis acids as catalysts had proved unsuccessful.[7] However, a modification of the work-up procedure, when using boron fluoride etherate as the catalyst, resulted in a 10% increase in yield of $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-3β-ol-11-one acetate (II) and eliminated the need for chromatography in isolating the product.[7] During the course of our work an improved degradation procedure developed by Japanese workers became available to us.[8] When N-methyljervine[9] was used in the reaction, the degradation product $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-3β-ol-11-one (III) could be obtained in 70% yield. The trienolone III could also be obtained in almost quantitative yield upon alkaline hydrolysis of the 3-acetate (a marked improvement in yield[4] over earlier work).

Oppenauer oxidation with aluminum isopropoxide in toluene and cyclohexanone of the trienolone III afforded $\Delta^{4,12,17(20)}$-17-ethyletiojervatriene-3,11-dione[10] (IV) in 77% yield. The 11-ketone in the trienedione IV is subject to considerable steric hindrance, and treatment with ethylene glycol in the presence of p-toluenesulfonic acid effected monoketalization at C-3 in

67% yield and afforded $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-3,11,-dione 3-ethylene ketal (V).[10] Lithium aluminum hydride treatment of the ketaltrienone V in ether effected reduction of the 11-ketone, and yielded $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-11β-ol-3-one 3-ethylene ketal (VI) in 58% yield. The reduction of the 11-keto group by metal hydrides has been shown to give rise to the 11β-alcohol.[11] In agreement with the assigned structure, the infrared spectrum showed peaks at 2.75 and 2.85 μ (–OH), but failed to exhibit any carbonyl absorption. The ultraviolet spectrum exhibited three peaks at 243 mμ (15,500), 250 mμ (18,000), and 258 mμ (10,400) which is in agreement with the spectrum obtained with similar diene systems.[12]
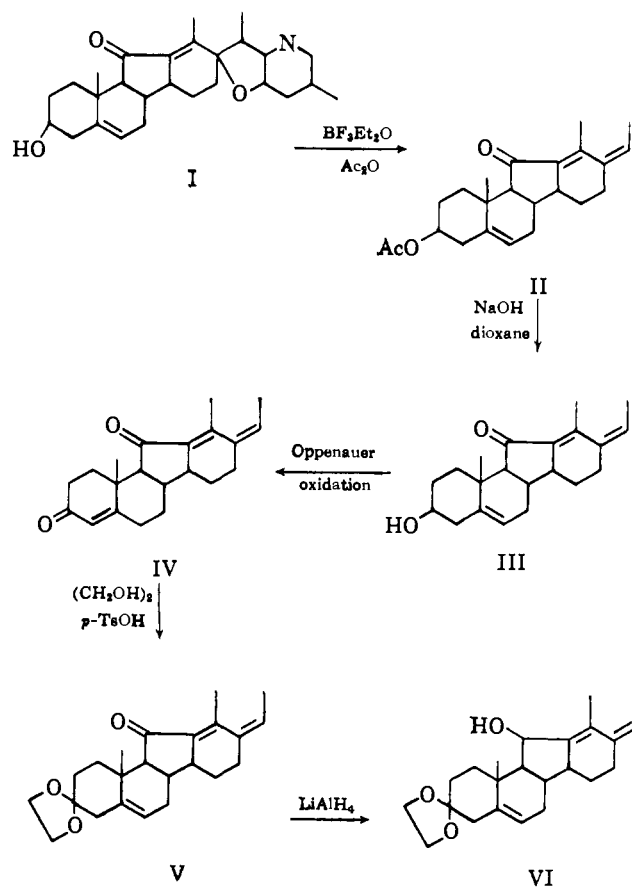
The next step in the synthesis required the oxidative cleavage of the 17(20) double bond in the ketaltrienone V. Several approaches were tried in an attempt to find the most efficient procedure for effecting this change. Chromic acid in acetic acid treatment of V afforded $\Delta^{5,12}$-etiojervadiene-3,11,17-trione 3-ethylene ketal (VII) in 11% yield. A higher yield (14%) of VII was

(1) This investigation was supported in part by a generous research grant from the Squibb Institute for Medical Research.

(2) The work was presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1–4, 1963, Abstracts, p. 4L.

(3) Wisconsin Alumni Research Foundation Fellow (1959–1961); National Science Foundation Cooperative Graduate Fellow (1961–1962); National Institutes of Health Predoctoral Fellow (1962–1963); recipient of 1963 Lunsford Richardson Pharmacy Award for a paper including part of this work.

(4) J. Fried and A. Klingsberg, J. Am. Chem. Soc., 75, 4929 (1953).

(5) The numbering system follows that used for the jerveratrum alkaloids; cf. L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959, p. 871.

(6) O. Wintersteiner, M. Moore, and N. Hosansky, J. Am. Chem. Soc., 75, 2781 (1953).

(7) J. E. Herz and J. Fried, ibid., 76, 5621 (1954).

(8) T. Masamune and A. Murai, private communications.

(9) K. Saito, H. Suginome, and M. Takaoka, Bull. Chem. Soc. Japan, 11, 172 (1936).

(10) S. M. Kupchan, T. Masamune, and G. W. A. Milne, J. Org. Chem., in press.

(11) O. Wintersteiner, J. Am. Chem. Soc., 78, 403 (1956).

(12) L. Dorfman, Chem. Rev., 53, 47 (1953).

obtained when sodium dichromate was used as the oxidant.[13] The ketaltrienone V was recovered unchanged when treated with the periodate–permanganate reagent of Wall and Serota,[14] and with the osmium tetroxide–sodium periodate combination of Johnson and Lemieux.[15] However, treatment of V in a benzene–pyridine solution with 1 mole of osmium tetroxide effected hydroxylation of the more reactive 17(20) double bond. After decomposition of the initially formed osmate ester with an alkaline mannitol solution, the known crystalline diol, $\Delta^{5,12}$-17-ethyletiojervadiene-3,11-dione-17ξ,20ξ-diol 3-ethylene ketal was isolated.[10] Periodic acid treatment of the diol led to the oxidized product VII in an over-all yield of 40% (2 steps). Use of the crude diol for the periodic acid treatment elevated the yield of ketone to 50%, but made it necessary to chromatograph the reaction product on acid-washed alumina. It should be noted that the ethylene ketal grouping at C-3 is sufficiently stable to allow the compounds containing this moiety to be chromatographed on acid-washed alumina without undergoing hydrolysis to the ketone. The ultraviolet spectrum of the yellow enedione VII showed a peak at 267 mμ (14,000), while the infrared spectrum showed major peaks at 5.81 (5-membered α,β-unsaturated ring ketone) 5.96 (6-membered α,β-unsaturated ring ketone), 6.14 (conjugated double bond), and 9.0, 9.2 μ (ethylene ketal).

The enedione grouping of VII was readily reduced by treatment with zinc in acetic acid to the dihydro product in 50–70% yields. In accord with the assigned structure (Δ^5-etiojervene-3,11,17-trione 3-ethylene ketal, IX), the reduction product showed no peak at 267 mμ (assignable to the enedione chromophore) and its infrared spectrum now showed the five- and six-membered ring ketones at 5.75 and 5.85 μ, respectively. Catalytic hydrogenation (10% Pd–C) of VII in an ethanolic solution containing potassium hydroxide also afforded the dihydro product IX in 39% yield. The stereochemistry of this reduction product will be discussed later.

The catalytic hydrogenation of VII with Pd–C as the catalyst in dioxane was allowed to proceed until 1 mole equivalent of hydrogen was consumed. Subsequent chromatography of the crude reaction product on acid-washed alumina yielded first a mixture of starting material and reduced enedione as evidenced by its infrared spectrum. Rechromatography of this mixture on acid-washed alumina afforded starting material and a small amount of an impure enedione whose infrared spectrum was identical with that of IX, but lacked sharp detail. Continued elution of the original column yielded $\Delta^{5,12}$-etiojervadiene-3,11-dione-17ξ-ol 3-ethylene ketal (VIII) in 20% yield. In accord with the assigned structure, a peak at 250 mμ (14,250) was observed in the ultraviolet, and the infrared spectrum showed major peaks at 2.75, 2.85 (–OH), 5.83 (5-membered α,β-unsaturated ring ketone), and 6.05 μ (conjugated double bond). Further elution yielded another crystalline alcohol in 10% yield. This alcohol had a peak at 243 mμ (10,000) in the ultraviolet, and major peaks at 2.75, 2.85 (–OH), 5.88 μ (5-membered α,β-unsaturated ring ketone), and 6.09 μ (conjugated double bond) in the infrared. These physical constants are consistent with an alcohol whose structure is $\Delta^{5,12(14)}$-etiojervadiene-3,11-dione-17ξ-ol 3-ethylene ketal (X). A double bond isomerization of this nature has been observed in the treatment of $\Delta^{5,12}$-etiojervadiene-3β-ol-11,17-dione acetate (XII) under similar hydrogenation

VII
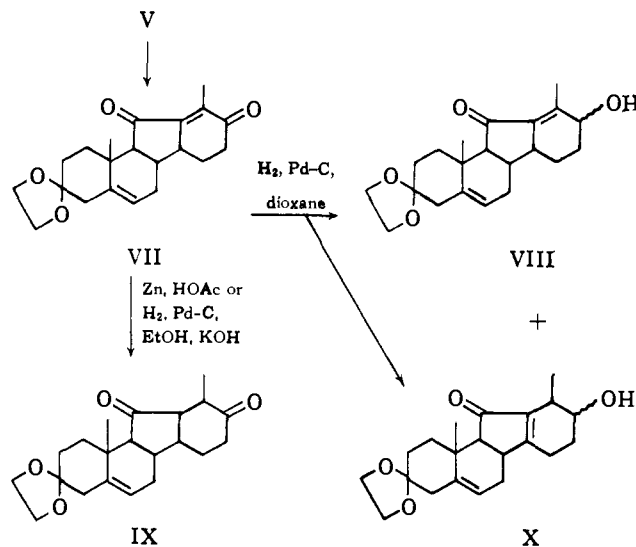
conditions, and in the catalytic reduction of jervine in 10% aqueous acetic acid solution with palladium black as the catalyst.[4,16]

It was deemed desirable for stereochemical assignments to link our newly synthesized compounds with those prepared earlier by the Squibb group.[4] With this goal in mind, the jervine degradation product II was oxidized with chromic acid in glacial acetic acid to the known enedione, $\Delta^{5,12}$-etiojervadiene-3β-ol-11,17-dione acetate (XII)[4] in 40% yield. The enedione could also be prepared by hydroxylation of II with osmium tetroxide in benzene and pyridine solution to give the diol $\Delta^{5,12}$-17-ethyletiojervadiene-11-one-3β,17ξ,20ξ-triol 3-acetate (XI) in 62% yield, followed by oxidative cleavage of the side chain at C-17 in 62% yield with periodic acid.

The 3-acetate in XII was hydrolyzed in almost quantitative yield by hydrochloric acid in aqueous dioxane to afford the previously prepared $\Delta^{5,12}$-etiojervadiene-3β-ol-11,17-dione (XIII).[4] Oppenauer oxidation of XIII using aluminum isopropoxide in refluxing toluene with cyclohexanone as the hydrogen acceptor gave the known $\Delta^{4,12}$-etiojervadiene-3,11,17-trione (XIV) in 60% yield.[4] Hydrolysis of the 3-ethylene ketal of VII
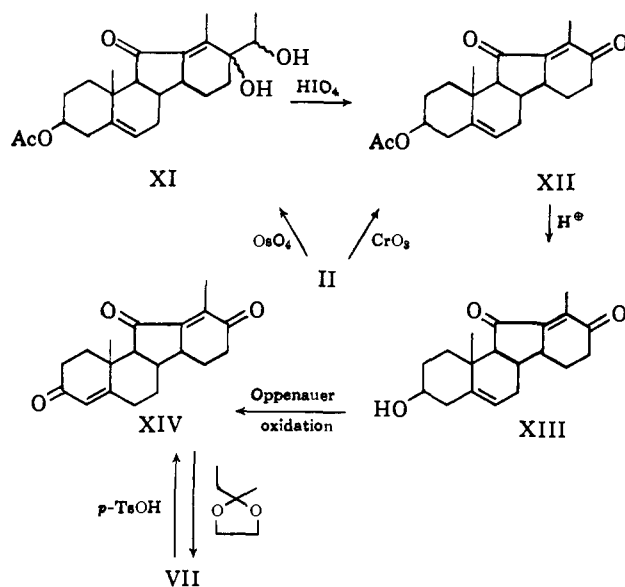
with p-toluenesulfonic acid in aqueous acetone afforded the trione XIV in 77% yield.

(13) L. F. Fieser, J. Am. Chem. Soc., 75, 4386 (1953).

(14) S. Serota and M. E. Wall, J. Org. Chem., 24, 742 (1959).

(15) W. S. Johnson and R. Lemieux, ibid., 21, 478 (1956).

(16) O. Wintersteiner and B. M. Iselin, J. Am. Chem. Soc., 77, 5318 (1955).

Steroidal ketones are known to undergo acid-catalyzed exchange with the cyclic ethylene ketal of butanone to form ethylene ketal derivatives.[17] Exchange dioxolanation appears to be more subject to steric and electronic effects than direct dioxolanation. The 17-keto group in normal steroids is inert to the reagent, and the selective conversion of Δ^4-androstene-3,17-dione and its 3-ethylene ketal is possible in high yield. This seemed to be a promising means for converting X1V selectively into its 3-ethylene ketal derivative VII. Treatment of trione XIV with 2-methyl-2-ethyl-1,3-dioxolane[17] led to a low yield (13%) of VII.

The Squibb group also reduced the dienedione XII with zinc and 52% acetic acid to produce Δ^5-etiojervene-3β-ol-11,17-dione acetate (XV) in 38% yield.[4] The stereochemical implications of this reduction led us to interrelate XV with the dihydro product IX, which we obtained following a similar reduction. By using zinc in *glacial* acetic acid, we were able to obtain a 67% yield of XV. Hydrochloric acid treatment of XV in dioxane afforded an 88% yield of the hydrolyzed product Δ^5-etiojervene-3β-ol-11,17-dione (XVI). The infrared spectrum showed major peaks at 2.75, 2.85 (–OH), 5.75, 5.85 μ (5- and 6-membered saturated ring ketones, respectively). Oppenauer oxidation (aluminum isopropoxide, cyclohexanone, toluene) of XVI yielded the oxidation product Δ^4-etiojervene-3,11,17-trione (XVII) in 47% yield. The infrared spectrum showed no alcohol peaks, but showed a new carbonyl absorption at 6.01 (Δ^4-3-one) and a peak at 6.18 μ (conjugated double bond). A peak at 240 mμ (15,700) was observed in the ultraviolet. The change in molecular rotation accompanying this oxidation (Δ[M]D +724°) agrees very

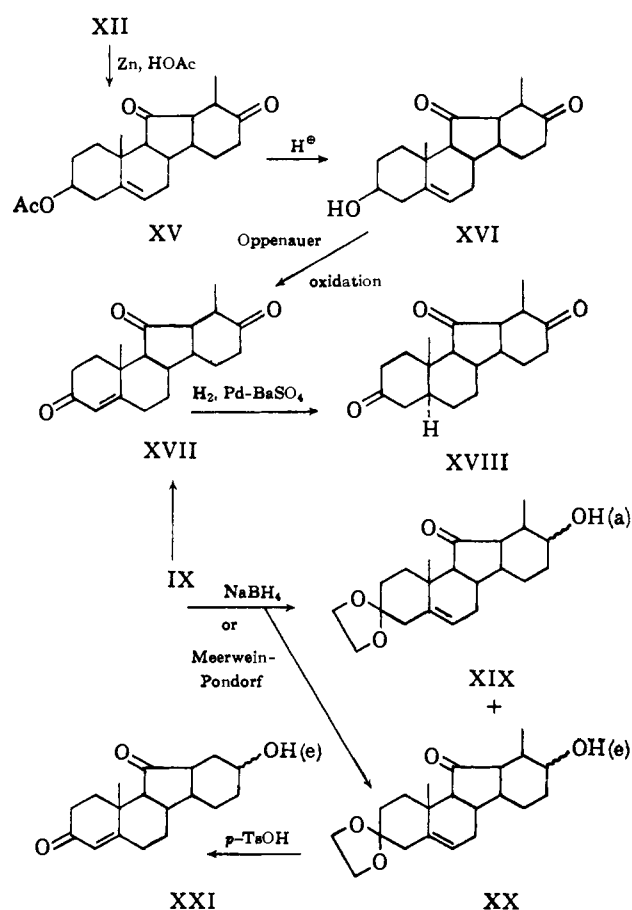well with that observed in the analogous oxidation of jervine to Δ^4-jervone (Δ[M]D +742°).

The Δ^4-double bond in XVII was readily reduced by catalytic hydrogenation in ethyl acetate using 10% Pb–BaSO$_4$ as the catalyst. The reduction product 5α-etiojervane-3,11,17-trione (XVIII) was obtained in 77% yield. Δ^4-3-Ketosteroids which possess an 11β-hydroxyl or 11-ketone function (e.g., 11-ketoprogesterone, corticosterone acetate, 17α-hydroxycorticosterone) are reduced by catalytic hydrogenation with a palladium catalyst predominantly to the 5α-isomer.[18] The reduced trione was therefore assigned the 5α-configuration by analogy with these examples. The infrared spectrum showed carbonyl absorption at 5.75 and 5.85 μ for the 5- and 6-membered saturated ring ketones, respectively. Ketal hydrolysis of IX in refluxing aqueous acetone containing p-toluenesulfonic acid afforded XVII in 91% yield. Thus, the reduction of the Δ^{12}-double bond by zinc in acetic acid proceeded in the same fashion in both cases.

An attempt to form selectively the 3-ethylene ketal of XVII using the exchange dioxolanation procedure with 2-methyl-2-ethyl-1,3-dioxolane failed. The infrared spectrum of the crude reaction product showed that both the 3-ketone and 17-ketone had reacted. The absence of selectivity may be attributed to the relatively unhindered nature of the 17-ketone in compound XVII. In the case of Δ^4-androstene-3,17-dione, where selective ketalization is possible, the 17-position is strongly hindered by the adjacent angular C-18 methyl group and is inert to the reagent. In XVII, the adjacent methyl group does not occupy an angular position and the 17-keto group can react with the reagent.

The next step in the synthesis was the reduction of IX with sodium borohydride in methanol at 0°. The crystalline alcohol Δ^5-etiojervene-3,11-dione-17ξ-ol 3-ethylene ketal (XX) could be obtained in 50–67% yield by direct crystallization of the reaction product from ether and chromatography of the mother liquor. In accord with the assigned structure, peaks at 2.75, 2.85 (–OH), and 5.75 μ (5-membered saturated ring ketone) were prominent in the infrared spectrum. The mother liquor was chromatographed on acid-washed alumina and yielded first a 4% yield of the isomeric alcohol Δ^5-etiojervene-3,11-dione-17ξ-ol 3-ethylene ketal (XIX). Further elution of the alumina column afforded additional amounts of XX which was formulated as the equatorial epimer on the following bases: (a) XIX is oxidized by chromic acid in acetic acid more than twice as fast as XX[19]; (b) XX is the major product of sodium borohydride reduction of the unhindered 17-ketone[20]; (c) XX is more strongly adsorbed on acid-washed alumina than XIX.[21] Reduction of IX with aluminum isopropoxide in isopropyl alcohol afforded a higher percentage of the axial epimer XIX (see below).[22]

The equatorial alcohol XX was treated with p-toluenesulfonic acid in aqueous acetone to effect hydrolysis of the 3-ethylene ketal. A 74% yield of Δ^4-etiojervene-3,11-dione-17ξ-ol (XXI) was obtained. The infrared spectrum showed major peaks at 2.75, 2.87 (–OH), 5.75 (5-membered saturated ring ketone), 6.00 (Δ^4-3-one),

XII

Zn, HOAc

XV   Oppenauer   XVI

oxidation

H$_2$, Pd–BaSO$_4$

XVII   XVIII

IX   NaBH$_4$
or
Meerwein-
Pondorf

XIX
+

OH(a)

XXI   XX

OH(e)   OH(e)

p-TsOH

(17) H. J. Dauben, B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(18) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Biol. Chem.*, **195**, 751 (1952).

(19) *Cf.* F. Westheimer, *J. Am. Chem. Soc.*, **71**, 25 (1949); J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1959).

(20) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(21) *Cf.* D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(22) *Cf.* W. G. Dauben, G. F. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).
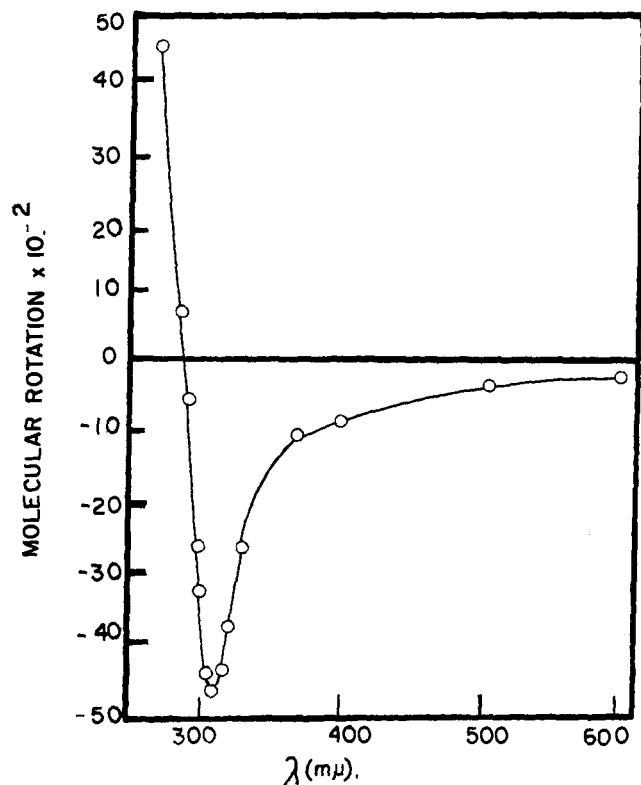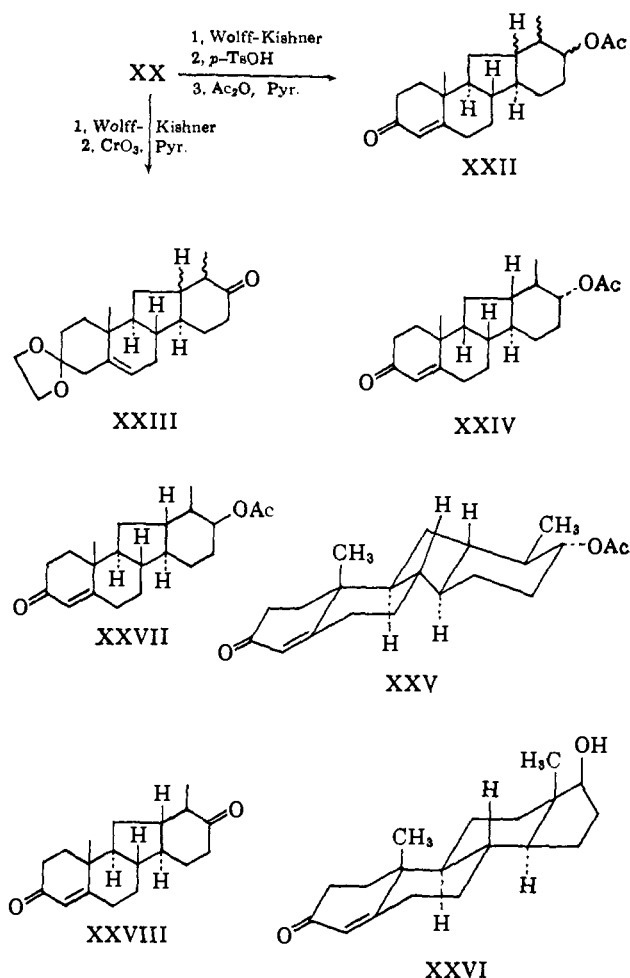
Figure 1.

and 6.18 μ (conjugated double bond) and a single peak in the ultraviolet at 240 mμ (15,500).

In order to prepare a testosterone analog, it was necessary to reduce the 11-keto function in XX to methylene. A modification of the Huang-Minlon procedure for Wolff–Kishner reduction met with success[23] (in contrast to normal steroids, where the C-11 ketone is not attacked). Alcohol XX was treated with hydrazine hydrate (99–100%) and potassium hydroxide in diethylene glycol. The crude reduction product was treated with p-toluenesulfonic acid in aqueous acetone to yield a solid material whose infrared spectrum showed peaks at 2.75 2.87 (–OH), 6.00 (Δ⁴-3-one), and 6.18 μ (conjugated double bond). Treatment of the solid material with acetic anhydride and pyridine afforded Δ⁴-etiojervene-3-one-17ξ-ol acetate (XXII) in an over-all yield of 22% (3 steps). This C-nor-D-homotestosterone acetate had prominent peaks at 5.78 (ester carbonyl), 6.00 (Δ⁴-3-one), and 6.18 μ (conjugated double bond) in the infrared, and a peak in the ultraviolet at 240 mμ (15,700).

The C-nor-D-homotestosterone derivative XXII possesses seven asymmetric carbon atoms. The configurations at four centers (C-8, C-9, C-10, and C-14) may be assigned those of normal steroids as a result of the recent elegant interrelation of hecogenin with a jervine degradation product by Mitsuhashi and Shimizu.[24] Evidence is advanced for assignment of configuration at each of the three remaining centers, namely, C-12, C-13, and C-17. Alcohol XX was reduced by the Wolff–Kishner conditions described above. An infrared spectrum of the product showed no carbonyl peak and was consistent with Δ⁵-etiojervene-3-one-17ξ-ol 3-ethylene ketal. Treatment of this material with chromic acid in pyridine oxidized the alcoholic function at C-17 and afforded Δ⁵-etiojervene-3,17-dione 3-ethylene ketal (XXIII) in an over-all yield of 22% (2 steps).

Examination of the molecular model of ketone XXIII indicated that if the C/D ring fusion were *trans*, its O.R.D. curve should be enantiomeric with that of B-norcholestane-3-one, whereas if the C/D ring fusion were *cis*, the curve should be enantiomeric with that of B-norcoprostane-3-one.[25] The O.R.D. curve[26] of XXIII exhibited a negative Cotton curve (Fig. 1) enantiomeric with that of B-norcholestane-3-one. The amplitudes[27] of the curves of the respective ketones (XXIII, a = −92° !; B-norcholestane-3-one, a = 97°) were in good agreement, indicating that the methyl group at C-13 possessed the equatorial (β) configuration.[25] In accord with the latter view, XXIII was recovered unchanged after attempts to effect epimerization by heating under reflux in 5% alcoholic potassium hydroxide solution. The equatorial hydroxyl group at C-17 could now be assigned the α-configuration, leading to the C-nor-D-homo-17-epitestosterone acetate (XXIV) representation; XXIV possesses the testosterone configuration at each of the ring junctions and the planarity of the molecule (*cf.* XXV) resembles the planarity of testosterone (XXVI).

The synthesis of C-nor-D-homotestosterone acetate (XXVII) necessitated the preparation of additional amounts of the axial alcohol XIX. Since the sodium borohydride reduction of IX afforded only small amounts (4%) of XIX, a more efficient preparation of the epimer was sought. Meerwein–Ponndorf reduction (aluminum isopropoxide–isopropyl alcohol) of IX afforded a 25% yield of XIX.[22] Modified Huang-

(23) Huang-Minlon. *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(24) H. Mitsuhashi and Y. Shimizu. *Tetrahedron Letters*, **21**, 777 (1961); *Tetrahedron*, **19**, 1027 (1963).

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

(26) Appreciation is expressed to Professor W. Klyne (University of London) for determination and valuable discussion of the O.R.D. curve.

(27) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

Minlon reduction of XIX followed by hydrolysis of the 3-ethylene ketal with *p*-toluenesulfonic acid in aqueous acetone yielded a product whose infrared spectrum was consistent with a C-nor-D-homotestosterone structure. Acetylation with acetic anhydride in pyridine yielded C-nor-D-homotestosterone, acetate (XXVII) in an over-all yield of 30% (3 steps); XXVII showed prominent peaks at 5.78 (ester carbonyl), 6.00 (Δ^4-3-one), and 6.18 μ (conjugated double bond) in the infrared, and a peak at 240 mμ (15,500) in the ultraviolet.

Hydrolysis of the 3-ethylene ketal grouping of XXIII with *p*-toluenesulfonic acid in aqueous acetone afforded Δ^4-etiojervene-3,17-dione (XXVIII) in 68% yield. This C-nor-D-homoandrostenedione exhibited absorption peaks at 240 mμ (15,400) and at 5.85 (6-membered ring ketone), 6.00 (Δ^4-3-one), and 6.18 μ (conjugated double bond).

It appears likely that the configuration in all the products formed by zinc and acetic acid reduction of the Δ^{12}-double bond is the same as in the C-nor-D-homotestosterone derivatives XXIV and XXVII. Zinc and acetic acid reduction of 1,4-diones may yield either *cis* or *trans* reduction products,[28] and it is likely that the reduction proceeds by attack on oxygen yielding the dienediol, which then undergoes a kinetically controlled protonation. Sodium borohydride treatment of the zinc–acetic acid reduction product IX afforded alcohol XX, which was not epimerized upon treatment with either sodium hydride (15 hr.) or 5% ethanolic potassium hydroxide solution (20 hr.). The failure of ketone XXIII to epimerize has been previously mentioned. The latter experiments indicate the stability of the configurations at C-12 and C-13 and favor assignment of the 12-β-H and 13-α-H configurations as in XXIV and XXVII.

Experimental

Melting points were taken on a Fisher–Johns melting point apparatus. Values of [α]D have been approximated to the nearest degree. Ultraviolet absorption spectra were determined on a Model 11 MS Cary recording spectrophotometer. Infrared spectra were determined on a Model 5 Beckman double beam infrared recording spectrophotometer. Microanalyses were carried out by Mr. J. Alicino, Metuchen, N. J., and Dr. S. M. Nagy, Cambridge, Mass. Petroleum ether refers to the fraction of boiling point 60–80°. Alumina refers to Merck acid-washed alumina. Pyridine was dried over potassium hydroxide. Boron fluoride etherate was freshly distilled before use. Benzene was distilled and dried over sodium. Dioxane was purified as described in Vogel.[29] Aluminum isopropoxide refers to Eastman practical grade aluminum isopropoxide. Zinc refers to Fisher technical dust zinc.

$\Delta^{5,12,17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (II).—A solution of jervine[30] (I, 74.3 g., m.p. 248–250° dec.) in acetic anhydride (600 ml.) and boron fluoride etherate (7.5 ml.) was refluxed for 5 hr. The reaction mixture was concentrated by vacuum distillation until crystalline material began to appear in the flask. After cooling in a refrigerator, the solid material was filtered and washed with water. Crystallization from acetone yielded II[4] (16.4 g., m.p. 187–189°. 26%). The infrared spectrum was identical with that of an authentic sample.

$\Delta^{5,12,17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one (III).—(A) N-Methyljervine[9] (Ia, 10 g., m.p. 208–211°) in ethylene glycol (75 ml.) and boron fluoride etherate (1 ml.) was refluxed for 5 hr. After cooling, the precipitate was filtered. The crude crystalline material was washed with petroleum ether and recrystallized from acetone. The original filtrate was poured into chloroform and washed with water, 1 N hydrochloric acid, and water once again. The solution was dried over sodium sulfate and evaporated to a residue which crystallized from acetone to afford III[4] (5.1 g., m.p. 148–150°, 72%).

(B) $\Delta^{5,12,17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one acetate (II, 12.7 g., m.p. 187–189°) in dioxane (300 ml.) and 1 N sodium hydroxide (300 ml.) was refluxed for 95 min. After cooling at room temperature overnight, the crystals were filtered, collected, and dried over phosphorus pentoxide to afford III[4] (10.9 g., m.p. 148–150°, 97%).

$\Delta^{4,12,17(20)}$-17-Ethyletiojervatriene-3,11-dione (IV) was prepared from $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-3β-ol-11-one (III) by the procedure of Kupchan, Masamune, and Milne.[10]

$\Delta^{5,12,17(20)}$-17-Ethyletiojervatriene-3,11-dione 3-Ethylene Ketal (V) was prepared from $\Delta^{4,12,17(20)}$-17-ethyletiojervatriene-3,11-dione (IV) by the procedure of Kupchan, Masamune, and Milne.[10]

$\Delta^{5,12,17(20)}$-17-Ethyletiojervatriene-11β-ol-3-one 3-Ethylene Ketal (VI).—$\Delta^{5,12,17(20)}$-Ethyletiojervatriene-3,11-dione 3-ethylene ketal (V, 1 g., m.p. 156–158°) in ether (75 ml.) was added from a dropping funnel to lithium aluminum hydride (225 mg.) in ether (50 ml.) and stirred at room temperature for 30 min., and then stirred under reflux for 5 hr. Excess hydride was destroyed by the cautious addition of water, and the complex destroyed with 1 N sulfuric acid. The ether layer was separated and the water layer extracted with additional ether. The combined ether extracts were washed with a saturated sodium bicarbonate solution and water and dried over sodium sulfate. Crystallization from ether afforded VI (577 mg., m.p. 130–132°, 58%). A sample was recrystallized for analysis from ether; m.p. 134–136°, [α]^{27}D +25° (*c* 0.77, EtOH); λ_{max}^{EtOH} 250 mμ (18,000), 243 mμ (15,500), 258 mμ (10,400); $\lambda_{max}^{CHCl_3}$ 2.75, 2.85 μ.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.14. Found: C, 77.65; H, 9.05.

$\Delta^{5,12}$-Etiojervadiene-3,11,17-trione 3-Ethylene Ketal (VII).—(A) To a solution of $\Delta^{5,12,17,(20)}$-17-ethyletiojervatriene-3,11-dione 3-ethylene ketal (V, 7.25 g., m.p. 156–158°) in benzene (125 ml.) and pyridine (5 ml.) was added osmium tetroxide (5 g.). The reaction mixture solidified in about 10 min. and additional benzene was added to allow stirring at room temperature for 10 hr. The benzene was removed *in vacuo*, and the residue dissolved in chloroform (300 ml.) and stirred vigorously for 11 hr. with 1% potassium hydroxide solution (600 ml.) containing mannitol (60 g.). The layers were separated and the aqueous layer extracted with additional chloroform (100 ml.). The combined chloroform solutions were stirred once again with 1% potassium hydroxide solution (300 ml.) containing mannitol (30 g.) for 25 hr. The layers were separated and the chloroform layer was dried over sodium sulfate and evaporated to dryness.

The residue (8 g.) was dissolved in a mixture of methanol (200 ml.), dioxane (40 ml.), and pyridine (30 ml.); periodic acid (6.4 g.) in water (50 ml.) was added, and the solution was stirred at room temperature for 4 hr. Saturated sodium bicarbonate solution (200 ml.) and water (50 ml.) were added and the solution concentrated to a small volume *in vacuo*. The product was extracted into ether and washed with 0.1 N phosphoric acid (ice-cold), 10% sodium bicarbonate solution, and water and dried over sodium sulfate. Evaporation of the ether left a residue (5.5 g.) which was dissolved in benzene and chromatographed on alumina (120 g.). Elution with petroleum ether, petroleum ether –benzene mixtures, and benzene–ether mixtures (up to 7% ether) afforded the crude enedione which was crystallized from acetone-isopropyl ether to yield VII (3.48 g., m.p. 176–178°, 50%). A sample was recrystallized for analysis from isopropyl ether; m.p. 176–178°, [α]^{27}D −226° (*c* 0.71, CHCl₃), λ_{max}^{EtOH} 267 mμ (14,000); $\lambda_{max}^{CHCl_3}$ 5.81, 5.96, 6.14, 9.0, 9.2 μ.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.33; H, 7.38.

(B) $\Delta^{4,12}$-Etiojervadiene-3,11,17-trione (XIV, 400 mg., m.p. 194–196°) was dissolved in 2-methyl-2-ethyl-1,3-dioxolane[17] (10 ml.) and *p*-toluenesulfonic acid (7.5 mg.) was added. The reaction mixture was slowly distilled through a glass helices-packed column (22 × 1 cm.) fitted with a partial takeoff head for 5.5 hr. The reaction mixture was diluted with benzene and washed with 5% sodium bicarbonate solution and water and dried over sodium sulfate. Evaporation left a residue (500 mg.) which was dissolved in benzene and chromatographed on alumina (10 g.). Elution with benzene–petroleum ether (2:1 and 3:1) yielded a residue (249 mg.) whose infrared spectrum was consistent with a 3-ethylene ketal derivative. Rechromatography of the residue on alumina (10 g.) yielded to benzene–petroleum ether mixtures (1:1, 2:1, 3:1) a crude solid material (174 mg.) whose infrared spectrum was identical with VII. The residue was dissolved in ether, and petroleum ether added dropwise to precipitate colored impurity. After filtration, the solution was evaporated to dryness. The residue was triturated with isopropyl ether and the isopropyl ether-soluble portion was decanted and evaporated to dryness. Crystallization from absolute ethanol yielded VII (61 mg., m.p. 176–178°, 13%). A mixture m.p. with a sample of VII prepared as described in part A showed no depression.

Δ^5-Etiojervene-3,11,17-trione 3-Ethylene Ketal (IX).—(A) $\Delta^{5,12}$-Etiojervadiene-3,11,17-trione 3-ethylene ketal (VII, 2 g., m.p. 176–178°) was dissolved in glacial acetic acid (160 ml.), and zinc (6.2 g.) was added in small portions while warming the flask by swirling over a steam bath. After the yellow color was discharged, the zinc was filtered and washed with chloroform. The filtrate was concentrated to near dryness *in vacuo* and water

(28) J. F. McGhie, M. K. Pradhan, and J. F. Cavalla, *J. Chem. Soc.*, 3176 (1952); D. H. R. Barton, *ibid.*, 3751 (1962); C. S. Barnes and D. H. R. Barton, *ibid.*, 1419 (1953).

(29) A. Vogel, "Practical Organic Chemistry," Third Edition, Longmans, London, 1961, p. 177.

(30) We wish to thank Riker Laboratories for their generous gift of an alkaloidal extract rich in jervine.

(75 ml.) was added. The product was extracted into chloroform (4 × 50 ml.) and washed with 10% sodium bicarbonate solution and water and dried over sodium sulfate. The residue after evaporation was crystallized from isopropyl ether to afford IX (1.04 g., m.p. 164–167°, 0.37 g., m.p. 158–160°, 70%). A sample was recrystallized for analysis from isopropyl ether; m.p. 165–167°, [α]^{30}D −95° (c 0.46, EtOH); λ$^{CHCl_3}_{max}$ 5.75, 5.85 μ.

Anal. Calcd. for C$_{21}$H$_{28}$O$_4$: C, 73.22; H, 8.19. Found: C, 73.24; H, 8.15.

(B) Δ^{5,12}-Etiojervadiene-3,11,17-trione 3-ethylene ketal (VII, 700 mg., m.p. 176–178°) in ethanolic potassium hydroxide solution (0.135 N) was hydrogenated in the presence of prereduced 10% palladium-on-carbon (300 mg.). The hydrogenation was stopped after 5 hr., at which time 1 mole equivalent had been taken up. The catalyst was filtered and the filtrate neutralized with acetic acid. The solution was concentrated *in vacuo*, diluted with water, and extracted with chloroform and dried over sodium sulfate. Evaporation of the chloroform gave a residue (594 mg.) which was dissolved in benzene and chromatographed on alumina (15 g.). Elution with petroleum ether and petroleum ether–benzene (3:1) yielded crude reduction product (428 mg.), which was recrystallized from ether–petroleum ether–chloroform to afforded IX (193 mg., m.p. 159–161°, 80 mg., m.p. 156–158°, 39%). Thin layer chromatography on Silica Gel G with an authentic sample of IX (eluent, chloroform–5% MeOH; spray, 2,4-dinitrophenylhydrazine) showed the presence of trace amounts of two impurities along with IX. Four recrystallizations from methanol raised the m.p. to 165–167° and a mixture m.p. with an authentic sample of IX showed no depression.

Δ^{5,12}-Etiojervadiene-3,11-dione-17ξ-ol 3-Ethylene Ketal (VIII); Δ$^{5,12(14)}$-Etiojervadiene-3,11-dione-17ξ-ol 3-Ethylene Ketal (X).—Δ^{5,12}-Etiojervadiene-3,11,17-trione 3-ethylene ketal (VII, 700 mg., m.p. 176–178°) in dioxane (25 ml.) was hydrogenated in the presence of prereduced 10% palladium-on-carbon (300 mg.). The hydrogenation was stopped after 1 mole equivalent of hydrogen had been taken up (10 hr.). The catalyst was filtered and washed with water. The filtrate was concentrated *in vacuo*, diluted with water (60 ml.), and extracted with chloroform (4 × 25 ml.). The chloroform solution was dried over sodium sulfate and evaporated to a residue (680 mg.) which was chromatographed on alumina (13 g.). Elution with benzene–petroleum ether (1:1) afforded a crude mixture of products (188 mg.). Rechromatography on alumina (9.5 g.) afforded starting material and impure reduction product (56 mg., m.p. 152–154°). The infrared spectrum of this impure product was identical with IX, but further purification was not carried out. Further elution of the original column with benzene and benzene–5% ether yielded VIII (141 mg., m.p. 225–230°, 20%). A sample was recrystallized for analysis from isopropyl ether; m.p. 231.5–232.5°, [α]^{24}D −140° (c 0.30, CHCl$_3$); λ$^{CHCl_3}_{max}$ 250 mμ (14,250); 2.75, 2.85, 5.83, 6.05 μ.

Anal. Calcd. for C$_{21}$H$_{28}$O$_4$: C, 73.22; H, 8.19. Found: C, 73.22; H, 8.31.

Continued elution with ether–1% methanol afforded X (71 mg., 183–185°, 10%). A sample was recrystallized for analysis from ether–petroleum ether; m.p. 187–189°, [α]^{24}D −76° (c 0.25, CHCl$_3$), λ$^{CHCl_3}_{max}$ 243 mμ (10,000); 2.75, 2.85, 5.88, 6.09 μ.

Anal. Calcd. for C$_{21}$H$_{28}$O$_4$: C, 73.22; H, 8.19 μ. Found: C, 73.29; H, 8.27.

Δ^{5,12}-17-Ethyletiojervadiene-11-one-3β,17ξ,20ξ-triol 3-Acetate (XI).—Δ$^{5,12,17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one acetate (II, 1.28 g., m.p. 186–188°) was dissolved in benzene (15 ml.), and pyridine (1.1 ml.) and osmium tetroxide (1 g.) were added. The solution was stirred at room temperature for 18 hr. before removal of the benzene *in vacuo*. The residue was dissolved in chloroform (100 ml.) and stirred vigorously with a 1% potassium hydroxide solution (200 ml.) containing mannitol (20 g.) until the chloroform layer was almost colorless. The layers were separated and the aqueous layer washed with additional chloroform (2 × 50 ml.). The combined chloroform solutions were dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was crystallized from acetone to yield XI (969 mg., m.p. 205–210°, 69%). A sample was recrystallized for analysis from ether, then acetone–petroleum ether, and finally 95% ethanol; m.p. 221–223°, [α]^{25}D −221° (c 0.30, EtOH), λ$^{EtOH}_{max}$ 252 mμ (14,500); λ$^{CHCl_3}_{max}$ 2.80, 5.78 (sh), 5.83, 6.10, 8.0, 8.2 μ.

Anal. Calcd. for C$_{23}$H$_{32}$O$_5$: C, 71.10; H, 8.30. Found: C, 71.27; H, 8.45.

Δ^{5,12}-Etiojervadiene-3β-ol-11,17-dione Acetate (XII).—(A) Δ$^{5,12,17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one acetate (II, 21.5 g., m.p. 186–188°) was dissolved in glacial acetic acid (1.5 l.) and a solution of chromium trioxide (9 g.) in 95% acetic acid (225 ml.) was added dropwise with stirring over a 45-min. period. The reaction mixture was stirred at room temperature for another 30 min., and then concentrated *in vacuo*. The residue was distributed between water (500 ml.) and chloroform (500 ml.) and extracted with additional chloroform (1.1 l.). The chloroform layer was washed with 5% sodium bicarbonate solution (1 l.),

10% sodium bicarbonate solution (1 l.), and water (500 ml.), dried over sodium sulfate, and evaporated to dryness. The residue (24 g.) was chromatographed on alumina (450 g.). Elution with benzene–petroleum ether (2:1) afforded starting material (1.9 g.). Further elution with benzene–petroleum ether mixtures (3:1, 4:1, 5:1), benzene, and benzene–chloroform (5:1) gave 9.53 g. of crystalline material. Recrystallization from acetone yielded XII[4] (7.53 g., m.p. 182–183°, 40%).

(B) Δ^{5,12}-17-Ethyletiojervadiene-11-one-3β,17ξ,20ξ-triol 3-acetate (XI, 50 mg., m.p. 218–219°) was dissolved in methanol (10 ml.) and pyridine (0.1 ml.). Periodic acid (45 mg.) in water (1.5 ml.) was added and the reaction mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated to ca. 2 ml., diluted with water, and extracted with ether. The ether extracts were dried over sodium sulfate and evaporated to dryness. The residue was crystallized from acetone–isopropyl ether and yielded XII[4] (28 mg., m.p. 180–182°, 62%). A single recrystallization from acetone–isopropyl ether raised the m.p. to 182–183°.

Δ^{5,12}-Etiojervadiene-3β-ol-11,17-dione (XIII).—Δ^{5,12}-Etiojervadiene-3β-ol-11,17-dione acetate (XII, 400 g., m.p. 182–183°) was dissolved in a mixture of dioxane (38 ml.) and water (12 ml.). Concentrated hydrochloric acid (3.6 ml.) was added and the solution stirred at room temperature for 24 hr. The solution was concentrated *in vacuo* until crystals began to appear, diluted with water, and allowed to stand overnight at room temperature. The crystalline material was collected and air-dried to yield XIII[4] (338 mg., m.p. 171.6–172.6°, 97%).

Δ^{4,12}-Etiojervadiene-3,11,17-trione (XIV).—(A) Δ^{5,12}-Etiojervadiene-3β-ol-11,17-dione (XIII, 250 mg., m.p. 171.6–172.6°) was dissolved in a mixture of toluene (30 ml.) and cyclohexanone (1.6 ml.), and toluene was distilled to remove water from the system. A solution of aluminum isopropoxide (510 mg.) in toluene (55 ml., distilled) was added dropwise over a 30-min. period to the hot reaction mixture while toluene was being slowly distilled off. After the addition was complete, the reaction mixture was refluxed for 15 min., cooled, and steam distilled for 30 min. The aqueous layer was extracted with chloroform (3 × 50 ml.), and the chloroform layer dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from acetone afforded XIV[4] (102 mg., m.p. 196–198°, 46 mg., m.p. 188–192°, 60%).

(B) Δ^{5,12}-Etiojervadiene-3,11,17-trione 3-ethylene ketal (VII, 360 mg., m.p. 176–178°) was refluxed in acetone (20 ml.) and water (2 ml.) containing p-toluenesulfonic acid (20 mg.) for 22 hr. The acetone was evaporated and the reaction mixture diluted with water, and extracted with ether. The ether extracts were washed with 10% sodium bicarbonate solution, water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from acetone to yield XIV[4] (215 mg., m.p. 196–198°, 16 mg., m.p. 195–197°, 74%).

Δ^5-Etiojervene-3β-ol-11,17-dione Acetate (XV).—Δ^{5,12}-Etiojervadiene-3β-ol-11,17-dione acetate (XII, 2.79 g., m.p. 178–180°) was dissolved in glacial acetic acid (225 ml.), and zinc (3.2 g.) was added in small portions while warming the flask by swirling over a steam bath. After the yellow color was discharged, the zinc was filtered and washed with chloroform. The filtrate was concentrated to near dryness *in vacuo* and diluted with a saturated sodium bicarbonate solution. After extracting several times with chloroform, the combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from isopropyl ether to yield a slightly yellow product (1.73 g., m.p. 141–143°) which was chromatographed on alumina (90 g.). Elution with benzene–petroleum ether (3:1), benzene, and benzene–ether mixtures (up to 33% ether) and crystallization from isopropyl ether yielded XV, (1.47 g., m.p. 171–172°). The mother liquor from the reaction (1.12 g.) was also chromatographed on alumina (60 g.). Elution with the solvents as described above and crystallization from isopropyl ether afforded additional XV[4] (410 mg., m.p. 166–168°, total yield 67%).

Δ^5-Etiojervene-3β-ol-11,17-dione (XVI).—Δ^5-Etiojervene-3β-ol-11,17-dione acetate (XV, 300 mg., 170–171°) was dissolved in a mixture of dioxane (29 ml.) and water (9 ml.). Concentrated hydrochloric acid (2.7 ml.) was added and the solution stirred at room temperature for 24 hr. The solution was concentrated *in vacuo* until crystals began to appear and then diluted with water. The crystals were filtered to yield XVI (231 mg., m.p. 147–150°, 88%). A sample was recrystallized for analysis from ether; m.p. 152.5–153.5°, [α]^{25}D −196° (c 0.94, EtOH); λ$^{CHCl_3}_{max}$ 2.75, 2.85, 5.75, 5.85 μ.

Anal. Calcd. for C$_{19}$H$_{26}$O$_3$: C, 75.46; H, 8.67. Found: C, 75.30; H, 8.76.

Δ^4-Etiojervene-3,11,17-trione (XVII).—(A) Δ^5-Etiojervene-3β-ol-11,17-dione (XVI, 650 mg., m.p. 152–153°) was dissolved in a mixture of toluene (150 ml.) and cyclohexanone (5 ml.), and toluene was distilled to remove water from the system. A filtered solution of aluminum isopropoxide (700 mg.) in toluene (50 ml., distilled) was added to the hot reaction mixture all at once. The

reaction mixture was refluxed for 90 min. and cooled. A saturated Rochelle salt solution (30 ml.) was added and the reaction mixture steam distilled for 2 hr. After cooling, the reaction mixture was extracted with chloroform, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from ether–petroleum ether to yield XVII (388 mg., m.p. 208–211°, 60%). A sample was recrystallized for analysis from ether–chloroform; m.p. 214.5–215.5°, $[\alpha]^{27}$D +44° (c 0.27, EtOH), $\lambda_{m:x}^{EtOH}$ 240 mμ (15,700); $\lambda_{max}^{CHCl_3}$ 5.75, 5.85, 6.00, 6.18 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.99; H, 8.38.

(B) Δ^5-Etiojervene-3,11,17-trione 3-ethylene ketal (IX, 1.3 g., m.p. 155–158°) was refluxed in acetone (35 ml.) and water (4 ml.) containing p-toluenesulfonic acid (50 mg.) for 20 hr. The acetone was evaporated until crystalline material began to separate and then diluted with water. The crystals were collected and dried to yield XVII (1.04 g., m.p. 214–215°, 91%).

5α-Etiojervane-3,11,17-trione (XVIII).—Δ^4-Etiojervene-3,11,-17-trione (XVII, 495 mg. m.p. 214–215°) in ethyl acetate was hydrogenated in the presence of prereduced 10% palladium-on-barium sulfate (225 mg.). The hydrogenation was brisk, coming to an abrupt halt after 1 mole equivalent had been taken up (65 min.). The catalyst was filtered and washed with chloroform. The solution was concentrated to a small volume on a steam bath and ether added to effect crystallization. The crystals were collected and dried to yield XVIII (380 mg., m.p. 173–175°, 77%). A sample was recrystallized for analysis from chloroform–petroleum ether; m.p. 173–175°, $[\alpha]^{27}$D −72° (c 0.36, CHCl$_3$); $\lambda_{max}^{CHCl_3}$ 5.75, 5.85 μ.

Δ^5-Etiojervene-3,11-dione-17β-ol 3-Ethylene Ketal (XIX); Δ^5-Etiojervene-3,11-dione-17α-ol 3-Ethylene Ketal (XX).—(A) Δ^5-Etiojervene-3,11,17-trione 3-ethylene ketal (IX, 2 g., m.p. 163–165°) in methanol (250 ml.) was stirred at 0–4° with sodium borohydride (328 mg.) for 1 hr. Acetic acid (0.5 ml.) was added and the solution concentrated to dryness *in vacuo*. The residue was distributed between water (15 ml.) and chloroform (25 ml.). The layers were separated and the aqueous layer extracted with additional chloroform (3 × 25 ml.). The combined chloroform extracts were dried over magnesium sulfate and concentrated to a small volume, and ether was added to effect crystallization. The crystals were filtered to yield XX (1.3 g., m.p. 203–205°). A sample was recrystallized for analysis from chloroform–ether–petroleum ether; m.p. 203.5–205.5°, $[\alpha]^{27}$D −113° (c 0.67, CHCl$_3$); $\lambda_{max}^{CHCl_3}$ 2.75, 2.85, 5.75 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.76; H, 8.81.

The mother liquor was chromatographed on alumina (20 g.). Elution with benzene–10% ether afforded an epimeric alcohol, XIX (88 mg., m.p. 175–176°, 4%). A sample was recrystallized for analysis from isopropyl ether; m.p. 178–179°, $[\alpha]^{27}$D −146° (c 0.80, CHCl$_3$); $\lambda_{max}^{CHCl_3}$ 2.75, 2.85, 5.75 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.56; H, 8.57.

Continued elution with benzene–10% ether followed by crystallization from chloroform–ether afforded additional XX (45 mg., m.p. 203–205°, total yield 67%).

The chromic acid oxidation of the isomeric alcohols was carried out by a modification of earlier procedures.[19] The alcohol (2 mg.) was weighed in a colorimeter tube and dissolved in 1.5 ml. of 90% acetic acid (reagent grade distilled from 1% by weight of chromic acid and then fractionated). A freshly prepared solution (0.5 ml.) containing 2 equivalents of chromic acid (analytical reagent) was added and the disappearance of Cr(VI) followed spectrophotometrically at 380 mμ using a Bausch and Lomb Spectronic 20. The sample tube was left in the colorimeter during the experiment and optical density readings taken until they leveled off. Alcohol XIX leveled off in 34 min. and alcohol XX in 75 min.

(B) Δ^5-Etiojervene-3,11,17-trione 3-ethylene ketal (IX, 2 g., m.p. 165–167°) and aluminum isopropoxide (10 g., distilled) in isopropyl alcohol (150 ml., dried over calcium hydride) was refluxed for 3 hr. The isopropyl alcohol was slowly distilled (Vigreux column) for 4 hr. The remaining alcohol was removed by rapid distillation and the residue taken up in benzene (75 ml.) and decomposed with a saturated Rochelle salt solution. The organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue (2 g.) was chromatographed on alumina (25 g.). Elution with benzene and benzene–5% ether followed by crystallization from isopropyl ether afforded XIX (523 mg., m.p. 176–178°, 26%). Further elution with benzene–15% ether, ether, and ether–1% methanol and crystallization from ether afforded XX (580 mg., m.p. 202–204°, 29%).

Δ^4-Etiojervene-3,11-dione-17α-ol (XXI).—Δ^5-Etiojervene-3,11-dione-17α-ol 3-ethylene ketal (XX, 70 mg., m.p. 203–205°) was refluxed in acetone (20 ml.) and water (3 ml.) containing p-

toluenesulfonic acid (15 mg.) for 6 hr. The acetone was evaporated and the residue diluted with water and extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from ether–petroleum ether to yield XXI (45 mg., m.p. 182–185°, 74%). A sample was recrystallized for analysis from ether–petroleum ether; m.p. 192.5–193.5°, $[\alpha]^{29}$D +32° (c 0.61, CHCl$_3$), λ_{max}^{EtOH} 240 mμ (15,500); $\lambda_{max}^{CHCl_3}$ 2.75, 2.87, 5.75, 6.00, 6.18 μ.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.60; H, 8.54.

Δ^4-Etiojervene-3-one-17α-ol Acetate (C-Nor-D-homo-17-epitestosterone Acetate) (XXIV).—Δ^5-Etiojervene-3,11-dione-17α-ol 3-ethylene ketal (XX, 474 mg., m.p. 203–205°) was heated at 140° for 6 hr. in diethylene glycol (45 ml.) containing potassium hydroxide (4.5 g.). The condenser was removed periodically and wiped free from moisture. After cooling to *ca.* 100°, hydrazine hydrate (3.5 ml., 99–100%) was added and the reaction mixture refluxed for 48 hr. The condenser was removed and the solution heated for 1 hr. The condenser was replaced and the solution heated for 3 hr. at 195° before cooling to room temperature. The reaction mixture was poured onto crushed ice and extracted with ether. The ether extracts were washed with 5% hydrochloric acid and water, dried over sodium sulfate, and evaporated to dryness. The residue (420 mg.) showed no ketone absorption in the infrared.

The residue was refluxed in acetone (30 ml.) and water (3 ml.) containing p-toluenesulfonic acid (35 mg.) for 15 hr. The acetone was evaporated and the residue diluted with water and extracted with ether. The ether extracts were washed with a saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. The residue (373 mg.) was chromatographed on alumina (15 mg.). Elution with benzene–ether mixtures (3:1, 2:1, 1:1) yielded a solid material (125 mg.) whose infrared spectrum showed peaks at 2.75, 2.85, 6.00, 6.18 μ. The solid material was warmed for 4 hr. on a steam bath with acetic anhydride (0.5 ml.) and pyridine (0.1 ml.). The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with a saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from isopropyl ether to yield XXIV (71 mg., m.p. 187–189°, 30 mg., m.p. 186–188°, 22%). A sample was recrystallized for analysis from isopropyl ether; m.p. 186.5–188.5°, $[\alpha]^{27}$D +90° (c 0.29, CHCl$_3$), λ_{max}^{EtOH} 240 mμ (15,700); $\lambda_{max}^{CHCl_3}$ 5.78, 6.00, 6.18 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.14; H, 8.95.

Δ^5-Etiojervene-3,17-dione 3-Ethylene Ketal (XXIII).—Δ^5-Etiojervene-3,11-dione-17α-ol 3-ethylene ketal (XX, 530 mg., m.p. 202–204°) was treated under the Wolff–Kishner conditions described for the preparation of XXIV and gave a residue (503 mg.) which was chromatographed on alumina (15 g.). Elution with benzene–5% ether, benzene–10% ether, and benzene–15% ether yielded a solid material (300 mg.) whose infrared spectrum was consistent with the Δ^5-etiojervene-3-one-17α-ol 3-ethylene ketal structure. The solid material was dissolved in pyridine (2 ml.) and treated with a slurry of chromium trioxide (150 mg.) in pyridine (2 ml.) for 16 hr. at room temperature with stirring. The reaction mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with additional ethyl acetate. The combined ethyl acetate layers were washed with a saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from ether–petroleum ether to afford XXIII (149 mg., m.p. 162–164°, 29%). A sample was recrystallized for analysis from ether–petroleum ether; m.p. 168.5–170.5°, $[\alpha]^{18-20}$D −42° (c 0.10, MeOH, from O.R.D. curve), $\lambda_{max}^{CHCl_3}$ 5.85 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.19; H, 9.23.

Δ^4-Etiojervene-3-one-17β-ol Acetate (C-Nor-D-homotestosterone Acetate) (XXVII).—Δ^5-Etiojervene-3,11-dione-17β-ol 3-ethylene ketal (XIX, 485 mg., m.p. 176–178°) was treated as described for the preparation of XXIV. Crystallization from ether–petroleum ether afforded XXVII (145 mg., m.p. 131.5–133.5°, 31%). A sample was recrystallized for analysis from ether; m.p. 135.5–136.5°, $[\alpha]^{27}$D +191° (c 0.39, CHCl$_3$), λ_{max}^{EtOH} 240 mμ (15,500); $\lambda_{m:x}^{CHC:}$ 5.78, 6.00, 6.18 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.26; H, 9.09.

Δ^4-Etiojervene-3,17-dione (XXVIII).—Δ^5-Etiojervene-3,17-dione 3-ethylene ketal (XXIII, 149 mg., m.p. 162–164°) in acetone (25 ml.) and water (3 ml.) containing p-toluenesulfonic acid (15 mg.) was refluxed for 7 hr. The acetone was evaporated and the residue diluted with water and extracted with ether.

The ether layer was washed with a saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. Crystallization from ether yielded XXVIII (88 mg., m.p. 180–182°, 68%). A sample was recrystallized for analysis from ether; m.p. 183–185°, $[\alpha]^{27}$D $+119°$ (c 0.21, CHCl₃), λ_{max}^{EtOH} 240 mμ (15,400); $\lambda_{max}^{CHCl_3}$ 5.85, 6.00, 6.18 μ.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 9.42.

Protonation and Substitution Studies on Cyclopenta[c]thiapyran and 2-Phenyl-2-pyrindine[1]

BY ARTHUR G. ANDERSON, JR., AND WILLIAM F. HARRISON[4]

RECEIVED AUGUST 31, 1963

The behavior of the compounds in the title, which are iso-π-electronic hetero-analogs of azulene, with certain acids and bases is reported. The ultraviolet and n.m.r. spectra and comparisons with azulene indicate the probable positions of protonation. The successful electrophilic substitution of cyclopenta[c]thiapyran by a number of reagents, the positions of substitution as indicated by the n.m.r. spectra of the products, the effects of different substituents on the visible spectrum, and some reactions involving nucleophilic reagents are described and discussed.

The syntheses of the first simple π-excessive heterocyclic analogs of azulene, cyclopenta[c]thiapyran (1), and 2-phenyl-2-pyrindine (2), and a comparison of some of their physical properties with those of azulene were described in the previous paper.[5] The similarities observed in the comparison led to the investigation of some of the chemical properties of the heterocycles and the present paper deals with results of these studies.

Behavior with Acids and Bases.—At the time we began these experiments, the basicity of azulene was well known and theoretical calculations, considerations of the spectral and proton magnetic resonance changes that occurred upon reaction with strong acids, and the analogy of electrophilic substitution provided strong evidence that protonation occurred in the 1-position.[6] In the early n.m.r. work by Frey,[7] however, the absorptions attributed to the 2- and 3-protons were not separately resolved and the assignment of the highest field absorption to water impurity appeared to be incorrect. Also the infrared spectral data of Bauder and Gunthard[8] on dideuterioazulene did not seem to be really definitive with regard to this question. Therefore the proton magnetic resonance spectra of azulene in both 98% sulfuric acid and 70% deuterated 98% sulfuric acid were examined. The results (Fig. 1) obtained were clearly consistent only with complete, reversible protonation at the 1- (3-) position. Except that no coupling between the 1,1- and the 2- or 3-hydrogens was detectable, the spectrum in sulfuric acid was very similar to that in trifluoroacetic acid subsequently reported by Danyluk and Schneider.[9] The proton exchange rate in the former solvent is thus appreciably faster and the mean life-time of the ion is only a fraction of a second. The spectrum in deuterated acid did not change after 15 min. and showed deuteration at both the 1- and 3-positions.

These results plus the earlier analysis of the n.m.r. spectrum of cyclopenta[c]thiapyran[5] provided a basis for the interpretation of the spectrum of this compound in acid (Fig. 2). The lack of symmetry in the molecule served to separate the absorptions for most of the different hydrogens, but it also meant that, depending on the relative stabilities of the ions formed by protonation at the 5- (3) or the 7-positions (4), there might be an appreciable concentration of one or two organic cationic species present. The spectrum obtained appeared to represent a single ion and therefore either predominantly one ion was formed or the electronic shielding of the corresponding hydrogens in the 5- and 7-protonated ions was essentially the same. The analysis of the spectrum was therefore as shown (Fig. 2).
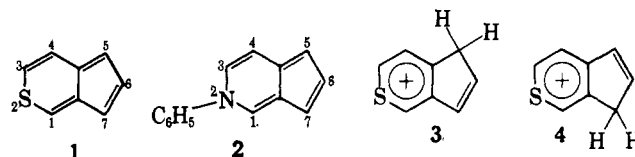
The singlet of twice unit intensity at 5.99 τ was attributed to the 5,5-hydrogens in 3 (or the 7,7-hydrogens in 4). The doublets of unit intensity at 1.99 and 2.48 τ were assigned to the vinylic 6- and 7-hydrogens in 3 (or the 5- and 6-hydrogens in 4). These latter absorptions lie within 0.1 p.p.m. of those found for the corresponding 2- and 3-hydrogens of the azulenium ion. The rather poorly defined doublet at 1.19 τ was interpreted to arise from the 4-hydrogen, which would be coupled with the 3-hydrogen. The absorption in the region near 0.47 τ was explained as representing the superposition of a singlet from the 1-hydrogen and a doublet from the 3-hydrogen. It might be expected that the positions adjacent to the sulfur atom of a thiapyrylium system would be the least shielded. Two further aspects of the assignments should be noted. The relative positions of the peaks attributed to the 3- and 4-hydrogens is the reverse of that deduced for the spectrum of the unprotonated compound[5] (wherein the absorption for the 3-hydrogen was well upfield from that of the 4-hydrogen). The present conclusion was based on the following series of experiments. First, conditions (7 M potassium t-butoxide in O-deuterated absolute t-butyl alcohol at 120–130° for *ca.* 18 hr.) were found which gave deuterium exchange in the 1-, 2-, 3-, 5-, and 7-positions of azulene[10] (determined by

(1) Supported in part by a grant from the National Science Foundation.
(2) A portion of this work was reported in a preliminary communication: A. G. Anderson, Jr., and W. F. Harrison, *Tetrahedron Letters*, **No. 2**, 11 (1960).
(3) From the Ph.D. thesis of William F. Harrison.
(4) Standard Oil of California Fellow, summer, 1958; National Science Foundation Predoctoral Fellow, 1959-1960
(5) A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson. *J. Am. Chem. Soc.*, **85**, 3448 (1963).
(6) For a discussion and references see E. Heilbronner, "Non-Benzenoid Aromatic Compounds," ed. by D. Ginsburg, Interscience Publishers, Inc., New York, N. Y., 1959, Chapter V.
(7) H. M. Frey, *J. Chem. Phys.*, **25**, 600 (1956).
(8) A. Bauder and H. H. Gunthard, *Helv. Chim. Acta*, **41**, 889 (1958).
(9) S. S. Danyluk and W. G. Schneider, *Can. J. Chem.*, **40**, 1777 (1962).

(10) These are precisely the positions of exchange predicted if the mechanism involves attack by the alkoxide ion at the 4- (8-) position as is observed for nucleophilic reaction with alkyl- and aryllithium reagents (K. Hafner, C. Bernhard, and R. Müller, *Ann.*, **650**, 35 (1961)). The deuterium exchange values for the different positions (68% maximum exchange possible) were 1- and 3- (*ca.* 68%); 2- (53%); 5- and 7- (64%); 4-, 6-, and 8- (*ca.* 0%). The absorptions for the 1-, 3-, and 6-positions were not completely resolved and the percentages for these are based on the fact that the total exchange for this region corresponded to complete equilibration for two hydrogens. It is possible that the value for the 1- and 3-positions is some less than 68% and the value for the 6-position is some larger than zero. No exchange was observed when azulene was heated under reflux with 2 M sodium methox-