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Investigations on Steroids. XIII.[1] Synthesis of the Compounds related to the Metabolites of Furazabol (17*β*-Hydroxy-17*α*-methyl-5*α*-androstano[2,3-*c*]furazan)

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The compounds required for the study of the metabolites of furazabol (17*β*-hydroxy-17*α*-methyl-5*α*-androstano[2,3-*c*]furazan; Ia) were synthesized; these are the labelled furazabol (Ib) with ^{14}C at 17*α*-methyl position, the 18-hydroxy derivative (II) of furazabol, the 18,17*β*-lactone (III), 18-oic acid (IVa), the 16*β*-hydroxy derivative (Va) and the 17*α*-hydroxymethyl derivative (VIa). Oxidation of the 18,17*β*-dihydroxy-17*α*-methyl compound (II) with chromic acid proved to give the corresponding 18,17*β*-lactone (III) and 18-oic acid (IVa).

In Part XII,[1] the isolation and characterization of metabolites of furazabol (17*β*-hydroxy-17*α*-methyl-5*α*-androstano[2,3-*c*]furazan; Ia) after administration of the compound to rats were reported. This paper describes the synthesis of the furazabol labelled with ^{14}C at the 17*α*-methyl position (Ib) which was used for administration and of the compounds which were required for identification of five of the metabolites, the 18-hydroxy derivative (II), the 18,17*β*-lactone (III), the corresponding hydroxy acid (IVa), the 16*β*-hydroxy compound (Va) and the 17*α*-hydroxymethyl derivative (VIa).

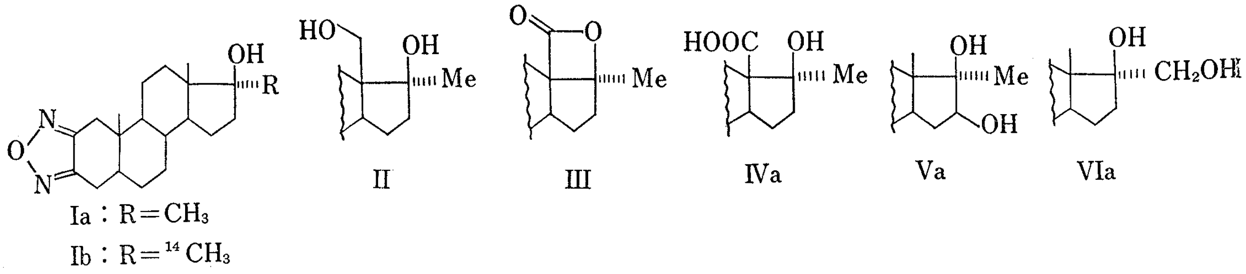

Chart 1

The labelled furazabol (Ib) was prepared from 3-ethylenedioxy-5*α*-androstan-17-one (VII) through the sequence as shown in Chart 2. Reaction of VII with ^{14}C-methyllithium derived from ^{14}C-methyl iodide introduced the radioactive 17*α*-methyl group. Hydrolysis of the ketal (VIII) gave the 3-ketone (IX) which was converted into the androstano furazan (Ib) by the established procedure[3] consisting of hydroxyimination with *t*-butyl nitrite in the presence of hydrogen chloride to the 2-hydroxyimino-3-ketone (X), oximation to the 2,3-dioxime (XI) and ring formation by the use of base at 180—190°. The overall radiochemical yield from ^{14}C-methyl iodide was 21.2%.

In the synthesis of the 18-hydroxyandrostano furazan (II) and its derivatives III and IVa, the key intermediate was the diacetate (XX) of 3*β*,18-dihydroxy-5*α*-androstan-17-one

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[1] Part XII: T. Takegoshi, H. Tachizawa, and G. Ohta, *Chem. Pharm. Bull.* (Tokyo), **20**, 1243 (1972).

[2] Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

[3] G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1450 (1965).

[4] *a*) E. Iseli and D.K. Fukushima, *Steroids, Suppl.*, **1**, 11 (1965); *b*) P.J. Sykes and R.W. Kelly, *J. Chem. Soc.* (*C*), **1968**, 2913; *c*) R. Pappo, U.S. Patent 3017410, 3043836 (1962).

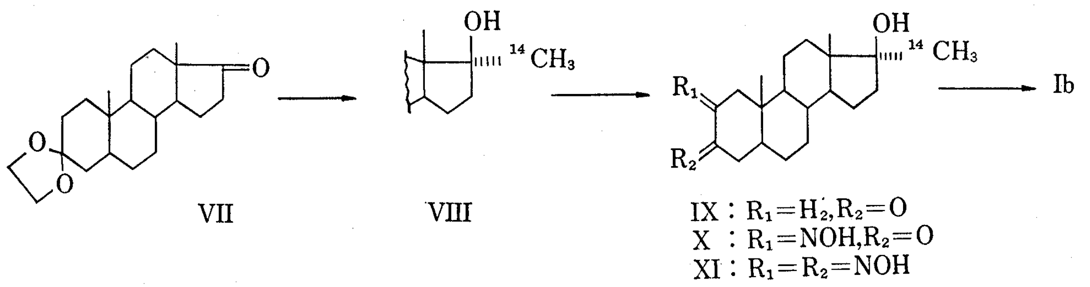

Chart 2

which was prepared according to the method used for the synthesis of the 18-hydroxy-17-ketones of 5β-androstane and Δ^5-androstene series.[4] Introduction of the hydroxy group at C-18 was achieved by application of the well-known intramolecular radical reaction of 20β-hydroxypregnanes[5] as described below (XIII→XIV→XV→XVIa) and the essentially same results have been reported recently.[6]

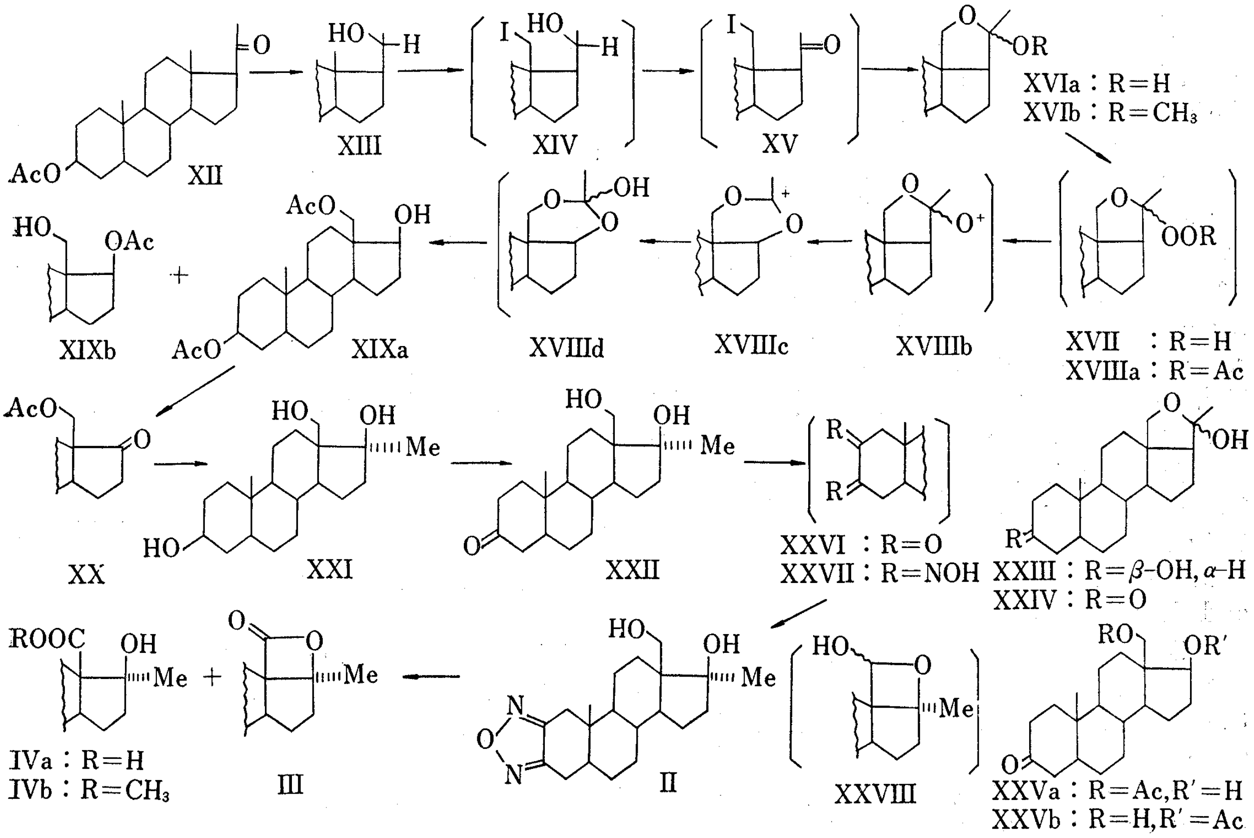

Chart 3

Reduction of 3β-acetoxy-5α-pregnan-20-one (XII) with lithium tri-*t*-butoxyaluminium hydride gave the corresponding 20β-ol (XIII) which was heated with iodine, lead tetraacetate and calcium carbonate in cyclohexane by irradiation of the solution with a tungsten lamp to yield the 18-iodo-20β-ol (XIV). Without isolation, this was oxidized with chromium trioxide in acetone to give a product containing the corresponding 20-ketone (XV) which also without purification was heated in methanol with silver acetate to afford the crude 18,

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5) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 1317 (1962).

6) F.L. Berner-Fenz, H. Berner, W. Graf, and H. Wehrli, *Helv. Chim. Acta*, **53**, 2258 (1970).

20-epoxy-20ξ-ol (XVIa) in a yield of 48% from XIII. Preparative thin-layer chromatography (TLC) separated a pure sample of XVIa and a by-product which was shown by its nuclear magnetic resonance (NMR) spectrum to be the 20ξ-methoxy analog (XVIb). The compound (XVIb) was readily yielded by dissolution of XVIa in hot methanol, as was reported in the case of the corresponding 3β-hydroxy compound.[7] Oxidation of the 20ξ-ol (XVIa) with hydrogen peroxide furnished the hydroperoxide (XVII) which was immediately acetylated to give the acetate (XVIIIa). This material, without purification, was heated with trimethylamine in aqueous dioxane to give a mixture of the 18-acetoxy-17β-ol (XIXa) and the 17β-acetoxy-18-ol (XIXb) which were separated by preparative TLC. Comparison of the NMR spectra of the two compounds provided the evidence for the structures. The spectrum of the main product (XIXa) exhibited the signal of the protons at C-18 adjacent to the acetoxy group (AB doublet, 4.16 and 4.31 ppm, $J=12$ Hz) and the signal of the 17α-proton adjacent to the hydroxy group (triplet, 3.76 ppm, $J=8.5$ Hz), whereas the spectrum of the minor product (XIXb) showed the signals of the methylene protons at the 18-hydroxymethyl group (AB doublet, 3.66 and 3.76 ppm, $J=12$ Hz) and of the 17α-proton adjacent to the acetoxy group (triplet, 4.68 ppm, $J=7.5$ Hz). The formation of the two acetates (XIXa and XIXb) and their NMR spectral properties are comparable with the results reported for the corresponding 5β-androstane derivatives.[4a] The degradation of carbon atoms 20 and 21 as described above is the known procedure[4] involving Baeyer–Villiger oxidation, whose reaction mechanism can explain the retention of configuration at C-17 and formation of the two acetates as illustrated in Chart 3 (XVIIIa→b→c→d→XIXa and XIXb).

The 18-acetoxy-17β-ol (XIXa) was oxidized with chromium trioxide to give the 17-ketone (XX). Reaction of XX with methylmagnesium iodide formed the 17β-hydroxy-17α-methyl grouping, concurrently removing the two acetyl groups, to yield the 17α-methyl-3β,17β,18-triol (XXI). For the selective oxidation of the 3β-hydroxy group of XXI, N-bromoacetamide was used as the oxidizing agent since the hydroxymethyl group at C-10 remains unchanged by this reagent.[8] The oxidation product was proved to be the expected 17β,18-dihydroxy-3-ketone (XXII) by its NMR spectrum containing the peaks of the methylene protons of the 18-hydroxymethyl group.

In preliminary experiments for an alternative route to XXII, 3β-acetoxy-18,20-epoxy-20ξ-ol (XVIa) was converted into the 3-ketone (XXIV) which was further transformed similarly as described above into the 18-acetoxy-17β-hydroxy-3-ketone (XXVa). An attempted ketalization of the 3-oxo group of XXVa without hydrolysis of the 18-acetoxy group failed and the route was abandoned.

Oxidation of the 17β,18-dihydroxy-3-ketone (XXII) with oxygen in the presence of potassium *t*-butoxide afforded the 2,3-diketone (XXVI) which was further converted *via* the dioxime (XXVII) into the desired 17β,18-dihydroxyandrostano furazan (II) similarly as reported earlier.[3]

Oxidation of II with chromium trioxide in acetone furnished the 18,17β-lactone (III) and the 18-oic acid (IVa), confirming the previous observation in the study of the metabolites.[1] The structure of each compound was proved by the spectral properties. The infrared (IR) spectrum of III with a band at 1785 cm^{-1} indicative of the β-lactone and the mass spectrum of III were described previously.[1] Furthermore, the NMR spectrum of III showed a signal at 1.52 ppm attributable to the 17α-methyl protons which are deshielded by the effect of the lactone ring. The properties of the acid (IVa) were also reported in the preceding paper[1] and hence additional observations are presented. Alkaline hydrolysis of the lactone (III) afforded the acid (IVa) which was reconvertible into the lactone by treatment with acetic anhydride in pyridine at room temperature but not with hydrogen chloride

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7) L. Lábler and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 2975 (1959).

8) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, 1963, pp. 118—119.

or acetic acid in refluxing methanol. The formation of β-lactone from β-hydroxy acid is generally difficult and has rarely been effected.[9] The ready lactonization of the acid (IVa) by means of acetic anhydride can be explained in terms of the favorable steric situation of the fixed 13-carboxyl and 17-hydroxyl groups. In connection with these results, the process of oxidation of the 18-ol (II) yielding the lactone (III) appears to involve the formation of the intermediate aldehyde hemiacetal (XXVIII) followed by further oxidation to III, since under the oxidation conditions lactonization of the acid (IVa) is unlikely. It should be noted here that, in contrast to β-propiolactone,[9] the lactone (III) is unreactive with cysteine or benzylamine under the usual conditions.

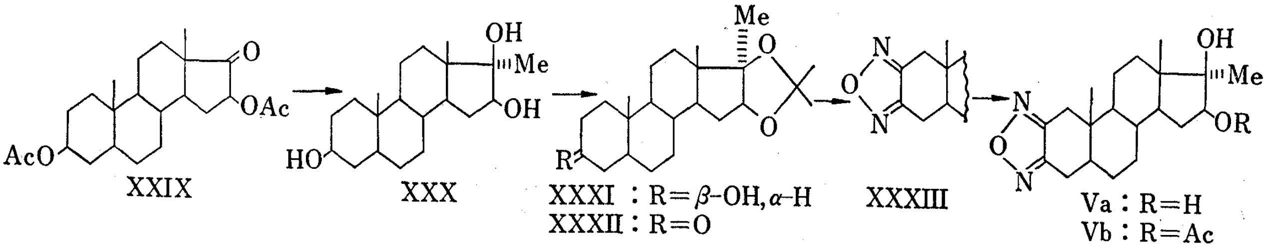

Chart 4

The 16β-hydroxylated furazabol (Va) was prepared from 3β,16β-diacetoxy-5α-androstan-17-one (XXIX). Reaction of XXIX with methylmagnesium iodide followed by complete alkaline hydrolysis of the product afforded the 17α-methyl-3β,16β,17β-triol (XXX), from which its acetonide (XXXI) was obtained and oxidized to give the 3-ketone (XXXII). The NMR spectrum of the triol acetonide (XXXI) showed the signal of the 16α-proton as quartet at 4.18 ppm, confirming the structure of XXXI and hence that of XXX. Thus, the known rearrangement of the 16β-acetoxy-17-ketone into the more stable 17β-acetoxy-16-ketone[10] proved not to take place during the Grignard reaction of XXIX. The 3-ketone (XXXII) was converted into the furazano compound by the standard procedure[3] and removal of the protective group at C–16 and C–17 gave the desired compound (Va).

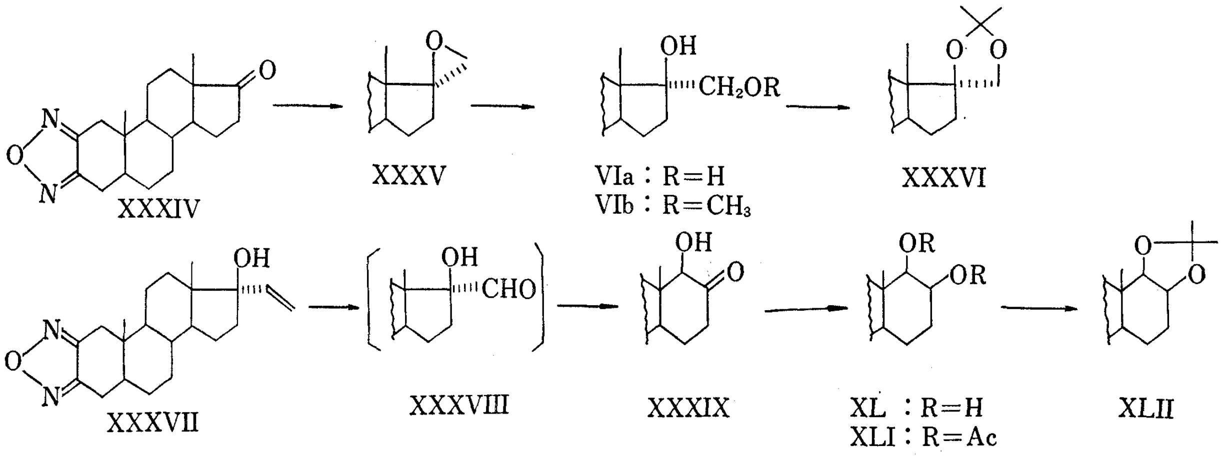

Chart 5

The 17α-hydroxymethyl derivative (VIa) was synthesized from the 17-ketone (XXXIV) *via* the spiro-17-oxirane (XXXV). Reaction of the 17-ketone (XXXIV) with dimethylsulfonium methylide afforded the (17*S*)-spiro-17,2′-oxirane (XXXV). The β-oxide structure

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9) Y. Etienne and N. Fischer, "The Chemistry of Heterocyclic Compounds," Vol. 19 (2), ed. by A. Weissberger, Interscience Publishers, Inc., New York, N.Y., p. 729.

10) N.S. Leed, D.K. Fukushima, and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).

of XXXV was assigned by analogy with the similar reactions of the 17-ketones of androstene[11a)] and estrane series,[11b)] and the C–18 methyl signal at 0.92 ppm of the NMR spectrum of XXXV was consistent with that of the corresponding reported compounds. Cleavage of the oxide ring with sodium hydroxide in *t*-butanol gave the 17α-hydroxymethyl compound (VIa), from which its acetonide (XXXVI) was prepared. The optimal reaction conditions of the oxide ring opening were not examined in detail, but in methanolic solution the desired product (VIa) was obtained in a poor yield and the main product was the 17α-methoxymethyl derivative (VIb), whose structure was determined by its NMR spectrum showing the methyl signal of the methoxy group at 3.41 ppm.[11a)]

An attempt was also made to prepare VIa from the 17α-vinyl derivative (XXXVII) *via* the 17α-aldehyde (XXXVIII). However, ozonization of XXXVII followed by reduction of the ozonide with zinc and acetic acid gave, instead of the desired aldehyde (XXXVIII), the D-homo-17aβ-hydroxy-17-ketone (XXXIX). Its structure was assigned on the basis of the known D-homo annulation reaction of a 17α-aldehyde.[12)] In order to confirm the structure, the ketone was reduced with sodium borohydride and the reduction product (XL) was immediately converted into the diacetate (XLI) and also characterized as the acetonide (XLII). The NMR spectrum of XXXIX showed a proton adjacent to a hydroxyl group as a singlet at 3.81 ppm, indicating the location of the hydroxy group at C–17a. In the spectrum of XLI the signal of the 17-proton at 5.29 ppm, multiplet with a half-height-width of 8 Hz indicated the 17-hydrogen to be equatorial (α) and the signal of the 17a-proton at 4.53 ppm, doublet with a coupling constant of 3 Hz showed it to be axial (α). Reduction of XXXIX with sodium borohydride giving the β-hydroxy function and the formation of the acetonide (XLII) are compatible with the assigned structure.

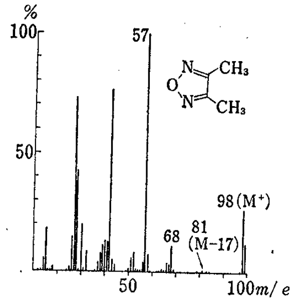

Fig. 1. Mass Spectrum of Dimethylfurazan

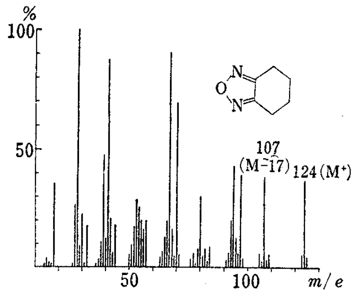

Fig. 2. Mass Spectrum of Cyclohexano[*c*]furazan

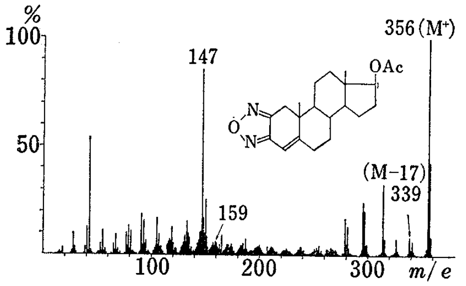

Fig. 3. Mass Spectrum of 17β-Acetoxyandrost-4-eno[2,3-*c*] furazan

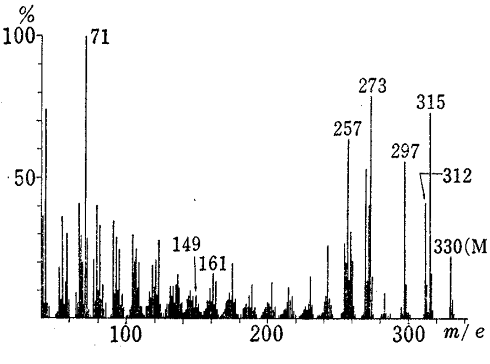

Fig. 4. Mass Spectrum of Furazabol (Ia)

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11) *a*) D. Bertin and L. Nedelec, *Bull. Soc. Chim. France*, **1964**, 2140; *b*) C.E. Cook, R.C. Corley, and M.E. Wall, *J. Org. Chem.*, **33**, 2789 (1968).

12) T.C. Miller, *J. Org. Chem.*, **34**, 3829 (1969).

Since the mass spectra of the metabolites were utilized as an important clue for the structure determination, some features of the spectra of furazano compounds are noted here. 17β-Acetoxyandrost-4-eno furazan (XLV) possessing no hydroxy function showed an M-17 fragment; the same fragment was observable in the spectrum of cyclohexano[*c*]furazan and, although very weak, in that of dimethylfurazan. The M-17 fragment is probably associated with the furazan ring but the fragmentation process and the nature of the 17 mass units remain to be solved. As discussed previously,[1] fragments due to fission of the steroidal ring B occur at *m/e* 159 and *m/e* 147 in the case of 4,5-unsaturated steroid furazan and at *m/e* 161 and *m/e* 149 in that of saturated compounds, *e.g.* furazabol (Ia). In accordance to the fragnemtation of the known C-17 substituted steroids a number of peaks are assignable to the ring D degraded fragments. The spectra of the above compounds are shown in Fig. 1—4. The fragments of other compounds and assignments are given in Experimental.

Experimental[13]

3,3-Ethylenedioxy-17α-methyl[-^{14}C]-5α-androstan-17β-ol (VIII)——A mixture of lithium (21.5 mg; 3.10 mmole) and ether (5 ml) was cooled in a liquid N_2-bath and evacuated. To this was introduced methyl-[-^{14}C] iodide (specific activity: 13.6 mCi/mmole; 1.49 mmole; radioactivity: 20.2 mCi) and the container was sealed. The mixture was stirred at room temperature for 1.5 hr to give a solution of methyl[-^{14}C] lithium. The solution was cooled in a liquid N_2-bath, and N_2 was introduced. A solution of 3,3-ethylenedioxy-5α-androstan-17-one (VII) (500 mg; 1.50 mmole) in ether (15 ml) was added and after solidification of the mixture, the container was evacuated and sealed. The mixture was kept at room temperature, then gradually heated to 50°, and stirred at this temperature for 2 hr and at room temperature for 12 hr. The container was opened, and benzene (20 ml) and H_2O were added. The organic layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated. The residue redissolved in benzene–hexane (2:1) was adsorbed on a column of Al_2O_3 (20 g) and eluted with benzene–hexane (2:1) (100 ml), benzene (130 ml) and benzene–ether (9:1) (130 ml). The radioactive materials obtained from the benzene and benzene–ether fractions were collected to give crystals (333.5 mg) of VIII which on TLC (benzene–MeOH (9:1)) showed the spots of VIII (main), VII (about 10%) and others. The total radioactivity was 11.9 mCi; the radiochemical yield was 58.9%.

17β-Hydroxy-17α-methyl[-^{14}C]-5α-androstan-3-one (IX)——A solution of the above crude ketal (VIII) and *p*-TsOH·H_2O (34 mg) in acetone (10 ml) was refluxed for 1 hr, concentrated *in vacuo* and treated with H_2O. The mixture was extracted with benzene, and the benzene solution was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated to give the crude 3-ketone (IX) which was used without further purification.

17β-Hydroxy-17α-methyl[-^{14}C]-5α-androstano[2,3-*c*]furazan (Ib)——To a solution of the above ketone (IX) in benzene–MeOH (60:1) (12.2 ml) was added a mixture of 35% HCl, MeOH and H_2O (8:4:1) (0.32 ml) and then at 18—20° a solution of *t*-butyl nitrite (120 mg) in benzene (0.9 ml) dropwise with stirring. The mixture was stirred for 1 hr and the separated product was collected, and washed with 5% $NaHCO_3$ (5 ml) and H_2O. The crude hydroxyimino ketone (X) thus obtained was dissolved in MeOH (15 ml), hydroxylamine hydrochloride (80 mg) and pyridine (3 ml) were added, and the mixture was refluxed for 40 min. Concentration of the mixture and addition of H_2O separated the crude dioxime (XI), which was collected by filtration. A mixture of the above dioxime (XI), KOH (100 mg) and ethyleneglycol (3 ml) was heated at 180—190° for 20 min, cooled and poured into H_2O (20 ml). After acidification with 10% HCl, the mixture was extracted with benzene, and the benzene solution was washed with H_2O, dried and concentrated. The residue was dissolved in benzene (10 ml), hexane (3 ml) was added and the solution was percholated through a column of Al_2O_3 (12 g). The column was eluted with hexane–benzene (9:1, 70 ml; 1:9, 50 ml), benzene (100 ml) and benzene–ether (9:1, 110 ml); each 10 ml fraction was checked by TLC. The fractions which were eluted with benzene and benzene–ether and which gave the single spot of Ib on TLC were collected to afford the crude product of Ib (141.2 mg; 4.28 mCi). The radiochemical yield was 36.0% from the ketal (VII), and 21.2% from methyl[-^{14}C] iodide. The crude material (70.6 mg) was mixed with Ia (50 mg) and crystallized from aqueous MeOH to give Ib as needles (86.1 mg), mp and mixed mp 152—153°, specific activity: 6.75 mCi/mmole, 20.4 μCi/mg. To the mother liquor was added Ia (1.0 g) and the mixture was crystallized to give the second crop (871.1 mg), mp 151—153°; total activity, 266 μCi; specific activity: 101 μCi/mmole.

3β-Acetoxy-5α-pregnan-20β-ol (XIII)——To an ice-cooled suspension of LiAl(*t*-BuO)$_3$H (33 g) in tetrahydrofuran (600 ml) was added dropwise with stirring under N_2 a solution of 3β-acetoxy-5α-pregnan-20-one (XII) (20.2 g) in tetrahydrofuran (200 ml). The mixture was stirred for 6 hr and kept at room tem-

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13) For general procedure, see Part XII.[1]

14) W. Klyne and D.H.R. Barton, *J. Am. Chem. Soc.*, 71, 1500 (1949).

perature overnight. The excess reagent was decomposed by addition of an aqueous solution of $(NH_4)_2SO_4$ (saturated) under ice-cooling. After the mixture was acidified with 10% HCl, H_2O was added and the product was extracted with $CHCl_3$. The evaporated residue of the $CHCl_3$ solution was chromatographed over silica gel (250 g). Elution with benzene gave XII (2.7 g) and subsequent elution with benzene–AcOEt (9:1) gave XIII (16.3 g) melting at 171—172°. Recrystallization from hexane afforded a pure sample of XIII, mp 172.5—173°, $[\alpha]_D$ $-11.9°$ ($c=0.46$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3500, 1720. *Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 75.98; H, 10.62. (Reported[14] mp 168—169°, $[\alpha]_D$ $-6°$.)

3β-Acetoxy-18,20-epoxy-5α-pregnan-20ξ-ol (XVIa)——A mixture of $CaCO_3$ (13.0 g) and $Pb(AcO)_4$ (60.0 g) in anhydrous cyclohexane (800 ml) was refluxed with stirring for 1 hr, and cooled. To this were added the 20ξ-ol (XIII) (13.0 g) and, after dissolution of XIII, iodine (4.7 g). The stirred mixture was refluxed by irradiation with a 300W tungsten lamp for 30 min, when the iodine color disappeared. The cooled mixture was filtered and the filtrate was washed with a 1% aqueous $Na_2S_2O_3$ solution and H_2O, dried and evaporated. The residue was dissolved in acetone (400 ml), Jones reagent[15] (15.4 ml) was added dropwise at 0—5° and after being stirred for 30 min at this temperature the mixture was poured into an aqueous solution of CH_3COONa (50%, 400 ml). Extraction with benzene and evaporation of the washed and dried organic solution gave an oily residue consisting mainly of the 18-iodo-20-ketone (XV). A mixture of the residue, CH_3COOAg (24.5 g) and MeOH (400 ml) was refluxed with stirring for 2.5 hr, cooled and filtered. The filtrate was evaporated and the residue redissolved in benzene was chromatographed over silica gel (H_2O content, 10%; 400 g). The column was eluted with benzene (1000 ml) and benzene–AcOEt (9:1) (1000 ml), and the fraction eluted with the latter solvent was crystallized from aqueous acetone to yield the crude crystalline material of XVIa (6.46 g), mp 160.5—162.5°.

A portion of the material (100 mg) was subjected to preparative TLC and developed with cyclohexane–ether (8:2). Two bands appeared at *Rf* 0.10 (main) and at *Rf* 0.39 (minor), and the compound obtained from the band at *Rf* 0.10 was recrystallized from aqueous acetone to give a pure sample of XVIa (70 mg), mp 166—167°, after being dried at 70° *in vacuo* it melted at 156—157°, $[\alpha]_D$ $+31.1°$ ($c=0.81$, $CHCl_3$). (Reported[5]: mp 169°, $[\alpha]_D$ $+33°$). IR ν_{max}^{KBr} cm^{-1}: 3410, 1703, 1276, 1047, 890. NMR ($CDCl_3$) δ_{ppm}: 0.76 (19-Me), 1.48 (21-Me), 2.02 (3-AcO), 3.69 (2H, singlet, 18-methylene), 4.67 (multiplet, 3α-H). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.46; H, 9.61.

The material from the band at *Rf* 0.39 was crystallized similarly to give plates of 3β-acetoxy-20ξ-methoxy-5α-pregnan-18,20-epoxide (XVIb) (12 mg), mp 164—164.5°, identical with the authentic sample described below.

A solution of XVIa in MeOH was refluxed for 10 min and cooled to separate crystals of XVIb, mp 164—164.5°, which after being dried at 70° *in vacuo* for 5 hr, melted at 157—161°. IR ν_{max}^{KBr} cm^{-1}: 1725, 1250, 1038, 869. NMR ($CDCl_3$) δ_{ppm}: 0.76 (19-Me), 1.32 (21-Me), 2.01 (3-AcO), 3.17 (20ξ-OMe), 3.42 and 3.66 (doublet, $J=9$ Hz, 18-methylene), 4.66 (multiplet, 3α-H). *Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.57; H, 9.76. (Reported[7] mp 172.5—173°).

Another portion of the crude hemiketal (XVIa) (6.36 g) was dissolved in 90% aqueous acetone and acetic acid (1 ml) was added. After being refluxed for 30 min, the solution was concentrated and cooled to separate crystals (6.15 g) which melted at 165—166° and showed on TLC only the spot corresponding to XVIa. A pure sample obtained by recrystallization from aqueous acetone was identical with the authentic sample of XVIa.

3β,18-Diacetoxy-5α-androstan-17β-ol (XIXa) and 3β,17β-Diacetoxy-5α-androstan-18-ol (XIXb)——To a solution of the 20ξ-ol (XVIa) (2.00 g) and *p*-TsOH·H_2O (40 mg) in dioxane (20 ml) was added 30% H_2O_2 (4 ml) dropwise with stirring at 0—5°. The mixture was stirred for 1 hr, AcOEt was added and the organic layer was separated, washed with 5% $NaHCO_3$ and H_2O, dried and evaporated at room temperature. The oily residue (XVII) was acetylated with Ac_2O (8 ml) and pyridine (20 ml) at 5° overnight. The reaction mixture was poured into ice-water and extraction of the product with benzene afforded the crude crystalline acetate (XVIIIa). This was dissolved in dioxane (40 ml) and an aqueous solution of trimethylamine (30%, 4 ml) and H_2O (1.2 ml) were added. The mixture was refluxed for 1 hr. The cooled solution was extracted with AcOEt, and the organic solution was washed with 5% HCl, 5% $NaHCO_3$ and H_2O, dried and evaporated. The oily residue was mixed with hexane and the solid obtained was crystallized from acetone–hexane to afford a mixture of XIXa and XIXb (1.06 g), mp 128—133°; from the mother liquor, after chromatography on silica gel, the second crop (164 mg) was obtained. Total yield of the mixture of XIXa and XIXb was 50%. The mixture showed in TLC developed with benzene–AcOEt (4:1) two spots; *Rf* 0.19 (main) and 0.36 (minor). After preparative TLC, the materials of *Rf* 0.19 were collected and crystallized from acetone–hexane to separate XIXa (995 mg), mp 135—136°, $[\alpha]_D$ $+6.3°$ ($c=0.43$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3460, 1733, 1702, 1262, 1239, 1060, 1053, 1027. NMR ($CDCl_3$) δ_{ppm}: 0.85 (19-Me), 2.01 (3-AcO), 2.08 (18-AcO), 3.76 (triplet, $J=8.5$ Hz, 17α-H), 4.16 and 4.31 (AB doublet, $J=12$ Hz, 18-methylene). *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.49; H, 9.35.

The materials of *Rf* 0.36 were collected and crystallized from MeOH to give XIXb (173 mg), mp 173—175°. IR ν_{max}^{KBr} cm^{-1}: 3570, 3450, 1748, 1722, 1268, 1254, 1240, 1063, 1045, 1020. NMR ($CDCl_3$) δ_{ppm}: 0.83

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[15] K. Bowden, I.M. Heilbron, E.R.H. Jones, and B.C.L. Weeden, *J. Chem. Soc.*, **1946**, 39.

(19-Me), 2.00 (3-AcO), 2.05 (17-AcO), 3.66 and 3.76 (AB doublet, $J=12$ Hz, 18-methylene), 4.60 (multiplet, 3α-H), 4.68 (triplet, $J=7.5$ Hz, 17α-H). *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.48; H, 9.08.

3β, 18-Diacetoxy-5α-androstan-17-one (XX)——To an ice-cooled solution of the 17β-ol (XIXa) (120 mg) in acetone (4 ml) was added Jones reagent (0.4 ml). The mixture was stirred for 15 min, H_2O was added, and the product was extracted with benzene. The benzene solution was washed with 5% $NaHCO_3$ and H_2O, dried and concentrated. Crystallization of the residue from acetone–hexane separated XX (105 mg), mp 71—72°, $[\alpha]_D$ +47.2° ($c=0.34$, $CHCl_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1740, 1230, 1040. *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.79. Found: C, 70.78; H, 8.57.

17α-Methyl-5α-androstan-3β,17β,18-triol (XXI)——A solution of the 17-ketone (XX) (105 mg) in benzene (10 ml) was added to a solution of MeMgI (prepared from Mg (98 mg) and MeI (580 mg)) in ether under N_2 and the mixture was stirred at room temperature for 30 min and then at reflux temperature for 10 hr. To the cooled solution were added H_2O and 5% HCl, and the product was extracted with AcOEt. The washed and dried AcOEt solution was evaporated and the residue was crystallized from MeOH–acetone to give XXI (58 mg), mp 235—236°. Repeated recrystallizations from the same solvent gave a pure sample, mp 236—237°, $[\alpha]_D$ −17.6° ($c=0.38$, pyridine). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3340. NMR (Me_2SO-d_6) δ_{ppm}: 0.77 (19-Me), 1.10 (17α-Me), 3.34 (multiplet, 3α-H), 3.59 (AB part of ABX system, $J_{AB}=11.5$ Hz, $J_{AX}=8.5$ Hz, $J_{BX}=3.0$ Hz; after treatment with D_2O, AB doublet, $J_{AB}=11.5$ Hz, 18-methylene), 4.08 (X part of ABX system, $J=8.5$ and 3.0 Hz; disappeared after addition of D_2O, 18-OH), 4.36 (doublet, $J=4$ Hz, disappeared after addition of D_2O, 3β-OH), 5.14 (singlet, disappeared after addition of D_2O, 17β-OH). *Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.27; H, 10.36.

17β,18-Dihydroxy-17α-methyl-5α-androstan-3-one (XXII)——To a mixture of N-bromoacetamide (100 mg), pyridine (0.16 ml), H_2O (0.54 ml) and MeOH (10 ml) was added the triol (XXI) (100 mg) and the mixture was stirred at room temperature in the dark overnight. N-Bromoacetamide (50 mg) was added and stirring was continued for further 7 hr. Extraction of the product with AcOEt, and the evaporation of the neutral dried AcOEt solution gave a crude product which was subjected to preparative TLC (solvent, $CHCl_3$–MeOH (9:1)). The band at *Rf* 0.49 (impurities were at *Rf* 0.30) was collected and the material was crystallized from hexane to give XXII (53 mg), mp 187—189°. Recrystallization from acetone–hexane gave a pure sample, mp 188—190°, $[\alpha]_D$ +11.1° ($c=0.40$, $CHCl_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3420, 1715. NMR ($CDCl_3$) δ_{ppm}: 1.02 (19-Me), 1.25 (17α-Me), 3.79 (AB doublet, $J=12$ Hz, 18-methylene). *Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.70; H, 9.87.

18,20-Epoxy-5α-pregnane-3β,20ξ-diol (XXIII)——A mixture of the 3β-acetate (XVIa) (0.72 g) and 1% KOH in MeOH–H_2O (9:1) (30 ml) was refluxed for 1 hr. Water was added and the precipitates were collected (0.64 g). Crystallization from aqueous acetone afforded a pure sample of XXIII, mp 159.5—161°; after being dried *in vacuo* at 70° for 4 hr, it showed double mp 150/195°, $[\alpha]_D$ +43.8° ($c=0.53$, $CHCl_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3400, 1022, 892. *Anal.* Calcd. for $C_{21}H_{34}O_3 \cdot 1/2\ H_2O$: C, 79.43; H, 10.27. Found: C, 73.68; H, 10.13. (Lit.: monohydrate, mp 158—159°,[16] 158.8—159°,[7] $[\alpha]_D$ +46°[7,16])

18,20-Epoxy-20ξ-hydroxy-5α-pregnan-3-one (XXIV)——The diol (XXIII) (0.45 g) in pyridine (5 ml) was added to a stirred suspension of CrO_3–pyridine complex prepared from CrO_3 (0.40 g) and pyridine (5 ml) and after being stirred for 1 hr, the mixture was kept overnight. Benzene (30 ml) was added, and the filtered solution was washed with H_2O, dried and evaporated. The residue in benzene was chromatographed over silica gel (15 g) and the fraction eluted with benzene–AcOEt (9:1) was crystallized from aqueous acetone to give XXIV (0.33 g), mp 143—145°. Recrystallization afforded a pure sample melting at 147—149°, $[\alpha]_D$ +64.9° ($c=0.55$, $CHCl_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3510, 1715, 898. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.95; H, 9.70. (Lit.: mp 128—130°, 159—160°, $[\alpha]_D$ +98°[17]; mp 155—160°; $[\alpha]_D$ +60°[18])

18-Acetoxy-17β-hydroxy-5α-androstan-3-one (XXVa) and 17β-Acetoxy-18-hydroxy-5α-androstan-3-one (XXVb)——The 20ξ-ol-3-one (XXIV) (328 mg) was treated with 30% H_2O_2 (0.3 ml) and *p*-TsOH·H_2O (13 mg) in dioxane–ether (2:1) (10 ml) in a similar manner as described for XIXa and XIXb. Acetylation of the crude 20ξ-hydroperoxide with Ac_2O (4 ml) and pyridine (4 ml), followed by treatment of the acetate with trimethylamine (30% aqueous solution, 2 ml) in dioxane (20 ml) containing H_2O (0.6 ml) at reflux temperature, furnished an oily mixture of XXVa and XXVb. The oil in benzene was chromatographed over silica gel (10 g) and eluted with benzene, benzene–AcOEt (9:1), (8:2) and (7:3). The fractions eluted with benzene–AcOEt (8:2) and (7:3) were collected and crystallized from acetone–hexane to give needles (105 mg), mp 107—118°, which showed in TLC (benzene–AcOEt (4:1)) two spots; *Rf* 0.18 (minor), 0.13 (main). A portion (70 mg) of the mixture was separated by preparative TLC developed with the same solvent system as above. The materials of *Rf* 0.13 were collected and crystallized from acetone–hexane to give needles of XXVa (54 mg), mp 116—120°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.52; H, 9.09. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3450, 1713, 1250, 1056. NMR ($CDCl_3$) δ_{ppm}: 1.03 (19-Me), 2.08 (18-AcO),

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17) L. Lábler and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 4010 (1959).

18) M.M. Janot, X. Lusinchi, L. Lábler, and R. Goutarel, *Bull. Soc. Chim. France*, **1966**, 3276.

3.77 (quartet, $J=10$ and 7.5 Hz, 17α-H), 4.18 and 4.33 (AB doublet, $J=12$ Hz, 18-methylene). Mass Spectrum *m/e*: 348 (M^+).

The materials of *Rf* 0.18 were collected and crystallized from acetone–hexane to give needles of XXVb (8 mg), mp 166—168°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.31; H, 9.33. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3600, 3500, 1744, 1708, 1250, 1052. NMR ($CDCl_3$) δ_{ppm}: 1.02 (19-Me), 2.06 (17β-AcO), 3.70 and 3.80 (AB doublet, $J=12$ Hz, 18-methylene), 4.70 (quartet, $J=9$ and 7 Hz, 17α-H). Mass Spectrum *m/e*: 348 (M^+).

17β,18-Dihydroxy-17α-methyl-5α-androstano[2,3-*c*]furazan (II)——To a solution of the 17β,18-dihydroxy-3-ketone (XXII) (850 mg) in *t*-BuOH (10 ml) was added *t*-BuOK prepared from K (453 mg) and *t*-BuOH (16 ml), and the mixture was stirred under O_2 for 30 min. A mixture of AcOH (770 mg) and MeOH (15 ml) and then $NH_2OH \cdot HCl$ (460 mg) were added. The mixture was refluxed for 1 hr and about two thirds of the solvent were removed *in vacuo*. Addition of H_2O and filtration of the precipitate gave the crude dioxime (XXVII). This was heated with KOH (150 mg) in ethyleneglycol (5 ml) at 170—180° for 15 min. The cooled mixture was diluted with H_2O, acidified with 10% HCl and extracted with AcOEt. The AcOEt solution was washed with H_2O, dried and concentrated. The residue redissolved in benzene was chromatographed over Al_2O_3 (grade II—III) and the fraction eluted with benzene–AcOEt (1:1) was crystallized from AcOEt to give II (302 mg), mp 215—218°. Purification of the mother liquor by preparative TLC (solvent: benzene–AcOEt (4:1)) afforded a further crop (30 mg), mp 216—218.5°. Repeated crystallizations from acetone–hexane separated a pure sample, mp 221—223°, $[\alpha]_D$ +39.1° ($c=0.36$, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3310, 1488, 1005, 873, 765, 739. UV $\lambda_{\max}^{\text{EtOH}}$: 217 m$\mu$ (ε 4300). NMR ($CDCl_3$) δ_{ppm}: 0.78 (19-Me), 1.28 (17α-Me), 2.67 (2H, disappeared after addition of D_2O, 17β-OH and 18-OH), 3.73 and 3.89 (AB doublet, $J=12$ Hz, 18-methylene), 2.27 (doublet, $J_{1\alpha,1\beta}=16$ Hz, 1α-H), 3.11 (doublet, $J_{1\alpha,1\beta}=16$ Hz, 1β-H), 2.91 (quartet, $J_{4\alpha,4\beta}=17.5$ Hz, $J_{4\alpha,4\beta}=5$ Hz, 4α-H), 2.40 (quartet, $J_{4\alpha,4\beta}=17.5$ Hz, $J_{4\alpha,5\beta}=12$ Hz, 4β-H). Mass Spectrum *m/e* (relative abundance; assignment): 328 (6.2; M-H_2O), 310 (22.6; M-2×H_2O), 298 (8.6; M-H_2O-CH_2OH), 295 (6.6; 310-H_2O), 283 (3.9; 298-CH_3), 270 (100; M-H_2O-CH_3COCH_3), 255 (6.6; 270-CH_3). *Anal.* Calcd. for $C_{20}H_{30}O_3N_2$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.49; H, 8.63; N, 8.13.

17α-Methyl-5α-adrostano[2,3-*c*]furazan-18,17β-lactone (III)——To an ice-cooled solution of the 17β,18-diol (II) (100 mg) in acetone (3 ml) was added dropwise with stirring Jones reagent (0.20 ml). After the mixture was stirred for 30 min, H_2O was added and the product was extracted with AcOEt. The AcOEt solution was extracted with 2% aqueous NaOH to romove acidic materials, washed with H_2O, dried and concentrated. The product in benzene solution was purified by percholation through silica gel and crystallized from acetone–MeOH to separate the lactone (III) (50 mg), mp 152—154° (decomp.). An analytical sample melted at 156.5—157° (decomp.), $[\alpha]_D$ +61.3° ($c=0.40$, $CHCl_3$). UV $\lambda_{\max}^{\text{EtOH}}$: 217 m$\mu$ (ε 5000). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1785, 1492, 1208, 1003, 860, 840, 805, 770, 750. NMR ($CDCl_3$) δ_{ppm}: 0.82 (19-Me), 1.52 (17α-Me), 2.29 (doublet, 1α-H), 2.45 (quartet, 4β-H), 2.95 (quartet, 4α-H), 3.14 (doublet, 1β-H); $J_{1\alpha,1\beta}=18$ Hz, $J_{4\alpha,4\beta}=18$ Hz, $J_{4\alpha,5\alpha}=5$ Hz, $J_{4\beta,5\alpha}=11$ Hz. Mass Spectrum *m/e* (relative abundance; assignment): 314 (3.1; M-CO), 298 (100; M-CO_2), 283 (60.5; M-CO_2-CH_3). *Anal.* Calcd. for $C_{20}H_{26}O_3N_2$: C, 70.15; H, 7.65; N, 8.18. Found: C, 69.92; H, 7.47; N, 8.13.

Acidification of the above alkaline solution with 5% HCl, extraction of the acidic materials with AcOEt and crystallization of the product from aqueous MeOH gave the acid (IVa) (15 mg), mp 204—208° (decomp.), identical (in TLC and IR) with the sample described below.

A mixture of the lactone (1.0 mg) and L-cysteine (1.0 mg) in MeOH (1.0 ml) was kept under N_2 at room temperature overnight and then heated at reflux temperature for 2 hr. Examination of the treated mixture by TLC (solvent: benzene–AcOEt (4:1)) detected only the unchanged lactone.

Similar treatment of the lactone with benzylamine gave no reaction product.

17β-Hydroxy-17α-methyl-5α-androstano[2,3-*c*]furazan-18-oic Acid (IVa)——A 5% aqueous NaOH solution (0.3 ml) was added to a solution of the lactone (III) (30 mg) in MeOH (3 ml) and the mixture was refluxed for 1 hr. A 5% aqueous NaOH solution and AcOEt were added, and the aqueous layer was separated. The aqueous solution was acidified with 5% HCl and the product was separated by means of AcOEt. Crystallization from aqueous MeOH gave IVa (23 mg), mp 210—213° (decomp.). Further recrystallization from acetone–hexane afforded a pure sample, mp 215—217° (decomp.). UV $\lambda_{\max}^{\text{EtOH}}$: 217 m$\mu$ (ε 5300). $[\alpha]_D$ +32.5° ($c=0.15$, MeOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3430, 2600 (broad), 1708, 1492, 1005, 872, 768, 742. NMR ($CDCl_3$) δ_{ppm}: 0.68 (19-Me), 1.32 (17α-Me), 2.26 (doublet, 1α-H), 2.36 (quartet, 4β-H), 2.90 (quartet, 4α-H), 3.05 (doublet, 1β-H), 4.83 (broad, 2×OH); $J_{1\alpha,1\beta}=16$ Hz, $J_{4\alpha,4\beta}=16$ Hz, $J_{4\alpha,5\alpha}=4$ Hz, $J_{4\beta,5\alpha}=10$ Hz. Mass Spectrum *m/e* (relative abundance; assignment): 342 (1.3; M-H_2O), 314 (100; M-COOH-H), 298 (15.1; M-CO_2-H_2O), 289 (14.8; M-CH_2CH_2-$COCH_3$), 284 (23.4; 298-CH_3+H), 283 (0.8; 298-CH_3). *Anal.* Calcd. for $C_{20}H_{28}O_4N_2$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.34; H, 7.79; N, 7.79.

To the acid (IVa) (5.0 mg) in pyridine (0.3 ml) was added Ac_2O (0.3 ml) and the mixture was kept at room temperature overnight. The product isolated by means of benzene was redissolved in benzene, purified by chromatography over silica gel and crystallized from MeOH to give the lactone (III) (3.0 mg), mp and mixed mp 155—156°; the IR spectrum was identical with that described above.

Methyl Ester of IVa: A mixture of the acid (IVa) (15 mg) and a large excess of diazomethane in ether (5 ml) was kept at room temperature overnight, and concentrated *in vacuo*. The crystalline residue was recrystallized from aqueous MeOH to give the methyl ester (IVb) (11 mg), mp 164—165°. UV $\lambda_{\max}^{\text{EtOH}}$: 217 mμ (ε 4600). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3495 (sh.), 3460, 3400, 1724, 1490, 1006, 877, 766, 747. Mass Spectrum *m/e* (relative abundance; assignment): 374 (3.0; M^+), 359 (0.4; M-CH_3), 356 (0.6; M-H_2O), 342 (1.6; M-CH_3OH), 327 (0.8; 342-CH_3), 324 (1.0; 342-H_2O), 314 (100; M-$COOCH_3$-H), 303 (29.9; M-$CH_2CH_2COCH_3$), 298 (5.1; M-$COOCH_3$-OH), 297 (8.7; M-$COOCH_3$-H_2O), 284 (19.9; 298-CH_3+H), 283 (2.5; 298-CH_3). *Anal.* Calcd. for $C_{21}H_{30}O_4N_2$: C, 67.35; H, 8.08; N, 7.48. Found: C, 67.41; H, 8.01; N, 7.33.

17α-Methyl-5α-androstane-3β,16β,17β-triol (XXX)——To a solution of MeMgI in ether (10 ml) prepared from Mg (310 mg) and MeI (1.80 g) was added under N_2 at room temperature dropwise a solution of 3β,16β-diacetoxy-5α-androstan-17-one (XXIX)[19] (500 mg) in benzene (30 ml) and after being stirred for 30 min, the mixture was refluxed for 17 hr. To the cooled solution were added successively AcOEt (20 ml), ice-water (20 ml) and 10% HCl (10 ml). The precipitated product was filtered, the organic phase of the filtrate was separated, and the dried neutral organic solution was concentrated. The residue and the above precipitate were combined and dissolved in MeOH (3 ml), a 3% NaOH solution (0.5 ml) was added and the solution was refluxed for 1 hr. The reaction mixture was concentrated to its half volume and diluted with H_2O to separate a precipitate which was collected. Crystallization from MeOH gave XXX (319 mg), mp 274—283. Recrystallization from pyridine–MeOH afforded a pure sample, mp 285—289°, $[\alpha]_D$ −5.0° (c=0.40, pyridine). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3370, 3300. *Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.76; H, 10.54.

17α-Methyl-5α-androstane-3β,16β,17β-triol 16,17-Acetonide (XXXI)——To a suspension of the triol (XXX) (230 mg) in acetone (10 ml) was added 2 drops of 70% $HClO_4$ and the mixture was allowed to stand, with occasional shaking, overnight. The obtained clear solution was concentrated at room temperature to one third of its volume. Benzene (20 ml) was added and the solution was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated. The residue redissolved in benzene was chromatographed on Al_2O_3 (5 g) and the fraction eluted with benzene–ether (9:1) was crystallized from hexane to give the acetonide (XXXI) (206 mg), mp 172—178°. Recrystallization from acetone–hexane separated an analytical sample, mp 180—184°, $[\alpha]_D$ −2.8° (c=0.64, $CHCl_3$). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3470, 1208, 1129, 1071. NMR ($CDCl_3$) δ_{ppm}: 0.82 (19-Me), 0.90 (18-Me), 1.31 (17α-Me), 1.38 and 1.48 (Me in acetonide), 1.75 (OH), 3.57 (multiplet, 3α-H), 4.18 (quartet, $J_{15\alpha,16\alpha}=4$ Hz, $J_{15\beta,16\alpha}=7.5$ Hz, 16α-H). *Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.40; H, 10.42.

16β,17β-Dihydroxy-17α-methyl-5α-androstan-3-one 16,17-Acetonide (XXXII)——To a suspension of CrO_3–pyridine complex prepared from CrO_3 (770 mg) and pyridine (15 ml) was added at 15—20° a solution of XXXI (930 mg) in pyridine (15 ml). After being stirred for 1 hr, the mixture was kept overnight. Benzene (50 ml) was added and the filtered solution was washed with H_2O, dried and evaporated. The residue redissolved in benzene was purified by chromatography through Al_2O_3 (20 g) and the product was crystallized from aqueous acetone to separate XXXII (764 mg), mp 168—173°. An analytical sample melted at 173.5—176.5°, $[\alpha]_D$ +15.3° (c=0.72, $CHCl_3$). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1706, 1204, 1067. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.02. Found: C, 76.38; H, 10.01.

16β,17β-Dihydroxy-17α-methyl-5α-androstano[2,3-*c*]furazan 16,17-Acetonide (XXXIII)——To a solution of the ketone (XXXII) (622 mg) in *t*-BuOH (4 ml) was added a *t*-butanolic solution of *t*-BuOK (K, 288 mg and *t*-BuOH, 11 ml) and the mixture was stirred under O_2 for 30 min. Acetic acid (435 mg) and then MeOH (3 ml) and $NH_2OH \cdot HCl$ (288 mg) were added. After being refluxed for 1 hr, the mixture was concentrated and diluted with H_2O to precipitate the crude dioxime. A mixture of the above dioxime and KOH (200 mg) in ethyleneglycol (5 ml) was heated at 180° for 20 min, cooled, diluted with H_2O and acidified with 10% HCl. The product was separated by means of benzene, purified in benzene solution by chromatography over Al_2O_3 (15 g) and crystallized from MeOH to give XXXIII (341 mg), 231—236°. An analytical sample melted at 240—243°, $[\alpha]_D$ +44.3° (c=0.70, $CHCl_3$). UV $\lambda_{\max}^{\text{EtOH}}$: 217 mμ (ε 4400). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1620, 1578, 1493, 1200, 1061, 1001, 872, 765, 738. Mass Spectrum *m/e* (relative abundance; assignment): 386 (100; M^+), 371 (15.3; M-CH_3), 343 (2.5; M-CH_3CO), 329 (2.3; M-CH_3COCH_2), 328 (1.8; 343-CH_3), 325 (2.8; 343-H_2O), 311 (30.9; 329-H_2O), 301 (7.0), 299 (1.8), 298 (1.4), 295 (1.3), 285 (1.5), 283 (1.4), 270 (5.1), 258 (7.7), 257 (9.2), 255 (4.8), 243 (33.8), 149 (2.2), 71 (15.5), 43 (50.5). *Anal.* Calcd. for $C_{23}H_{34}O_3N_2$: C, 71.47; H, 8.87; N, 7.25. Found: C, 7.39; H, 8.64; N, 7.16.

16β,17β-Dihydroxy-17α-methyl-5α-androstano[2,3-*c*]furazan (Va)——A mixture of the above acetonide (XXXIII) (328 mg), *p*-TsOH·H_2O (50 mg) and EtOH (15 ml) was stirred at 60—70° for 1 hr, cooled, concentrated *in vacuo* and diluted with H_2O to separate a precipitate which was dissolved in a minute amount of $CHCl_3$ and adsorbed on a column of Al_2O_3 (10 g) in benzene. The column was eluted with benzene, benzene–ether (9:1) and (6:4). The fraction eluted with benzene afforded the starting material (30 mg). The crystals from benzene–ether (6:4) fraction were recrystallized from aqueous MeOH to give Va (248 mg), mp 217—220°. A pure sample melted at 222—223°, $[\alpha]_D$ +38.3° (c=0.47, $CHCl_3$). UV $\lambda_{\max}^{\text{EtOH}}$: 217 mμ (ε 6000). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3430, 3350, 1485, 1000, 873, 768, 732. *Anal.* Calcd. for $C_{20}H_{30}O_3N_2$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.60; H, 8.66; N, 8.06.

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19) W.S. Johnson, B. Gastambide, and P. Pappo, *J. Am. Chem. Soc.*, 79, 1991 (1957).

Acetylation of Va (130 mg) with Ac_2O (0.5 ml) in pyridine (3 ml) at room temperature overnight gave the 16β-acetate (Vb). Recrystallization from MeOH gave a pure sample, mp 221.5—222°, $[\alpha]_D$ +36.9° (c=0.51, $CHCl_3$). UV λ_{max}^{EtOH}: 217 mμ (ε 5400). IR ν_{max}^{KBr} cm^{-1}: 3440, 1710, 1494, 1268, 1008, 879, 769, 738. Mass Spectrum m/e (relative abundance; assignment): 388 (2; M^+), 373 (1; M-CH_3), 370 (1; M-H_2O), 346 (74; M-CH_2=C=O), 328 (31; M-AcOH), 313 (27; M-AcOH-CH_3), 310 (18; M-AcOH-H_2O), 295 (9; M-AcOH-H_2O-CH_3), 285 (19; 303-H_2O), 273 (13), 270 (50), 258 (30), 243 (52), 71 (24), 43 (100). *Anal.* Calcd. for $C_{22}H_{32}O_4N_2$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.75; H, 8.00; N, 7.25.

(17*S*)-Spiro-5α-androstano[2,3-*c*]furazan-17,2′-oxirane (XXXV)——Sodium hydride in parafine (57.7%; 640 mg) was washed three times by trituration with benzene followed by decantation of the supernatant to remove parafine and Me_2SO (10 ml) was added. The mixture was heated under N_2 at 70—75° for 45 min. Tetrahydrofuran (10 ml) was added to the cooled solution, and at −5° a solution of trimethylsulfonium iodide (2.60 g) in Me_2SO (20 ml) was dropped rapidly. To this were added tetrahydrofuran (12 ml) and then dropwise at −5—0° the 17-ketone (XXXIV) (1.0 g) in tetrahydrofuran (20 ml). After being stirred at this temperature for 2 hr, the mixture was diluted with H_2O (200 ml) and extracted with benzene. The benzene solution was washed with H_2O, dried and evaporated to give a residue which on addition of light petroleum crystallized. Recrystallization from MeOH afforded XXXV (893 mg), mp 149—150.5°. A pure sample melted at 152—153°, $[\alpha]_D$ +52.6° (c=0.53, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3060, 1575, 1482, 1222, 1002, 959, 910, 875, 858, 813, 784, 763, 735. NMR ($CDCl_3$) δ_{ppm}: 0.78 (19-Me), 0.92 (18-Me), 2.60 and 2.90 (AB doublet, J=5.0 Hz, 3′-CH_2). *Anal.* Calcd. for $C_{20}H_{28}O_2N_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.97; H, 8.42; N, 8.49.

17β-Hydroxy-17α-hydroxymethyl-5α-andostano[2,3-*c*]furazan (VIa)——To a solution of the oxide (XXXV) (595 mg) in *t*-BuOH (12 ml) was added a 10% aqueous NaOH solution (3 ml). The stirred solution was refluxed for 50 hr and cooled. Water was added to the reaction mixture and the product isolated by means of AcOEt was chromatographed over Al_2O_3 (15 g). The fraction eluted with benzene gave the starting material (350 mg) and from the fraction eluted with ether was obtained, after crystallization from aqueous MeOH, the hydroxymethyl compound (VIa) (141 mg), mp 222—226°. An analytical sample melted at 227—228°, $[\alpha]_D$ +36.3° (c=0.69, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3480, 3410, 1582, 1494, 1142, 1090, 1078, 1036, 1010, 978, 881, 769, 739. NMR ($CDCl_3$) δ_{ppm}: 0.79 (19-Me), 0.94 (18-Me), 2.05 (2×OH), 3.45 and 3.79 (AB doublet, J=11 Hz, 17α-methylene). *Anal.* Calcd. for $C_{20}H_{30}O_3N_2 \cdot 1/4H_2O$: C, 68.44; H, 8.76; N, 7.98. Found: C, 68.57; H, 8.55; N, 7.98.

When the reaction was carried out in MeOH for 4 hr, VIa was obtained in a yield of 8.4%, along with the 17α-methoxymethyl derivative (VIb) (yield, 73%), mp 130.5—131.5°. IR ν_{max}^{KBr} cm^{-1}: 3510, 1582, 1490, 1087, 1003, 947, 875, 767, 718. NMR ($CDCl_3$) δ_{ppm}: 0.79 (19-Me), 0.92 (18-Me), 3.41 (OMe), 3.15 and 3.50 (AB doublet, J=9.0 Hz, 17α-methylene). *Anal.* Calcd. for $C_{21}H_{32}O_3N_2$: C, 69.97; H, 8.95; N, 7.77. Found: C, 70.18; H, 9.07; N, 7.70.

17β-Hydroxy-17α-hydroxymethyl-5α-androstano[2,3-*c*]furazan Acetonide (XXXVI)——A solution of VIa (50 mg) and 70% $HClO_4$ (one drop) in acetone (3 ml) was kept at room temperature for 20 hr. The product was isolated by means of benzene, purified by chromatography on Al_2O_3 (1 g) in benzene and crystallized from MeOH to afford the acetonide (XXXVI) (38 mg), mp 191—193°. A pure sample melted at 193.5—195°. IR ν_{max}^{KBr} cm^{-1}: 1581, 1491, 1223, 1060, 1051, 1008, 872, 767, 739. Mass Spectrum m/e (relative abundance; assignment): 386 (50.2; M^+), 371 (24.8; M-CH_3), 329 (6.0; M-CH_2COCH_3), 311 (55.6; 329-H_2O), 298 (3.8), 295 (5.7), 287 (6.7), 273 (4.3), 270 (11.9), 257 (4.3), 255 (9.5), 243 (4.3), 149 (100), 71 (27.1), 43 (58.6). *Anal.* Calcd. for $C_{23}H_{34}O_3N_2$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.21; H, 8.82; N, 7.49.

17aβ-Hydroxy-17-oxo-5α-D-homoandrostano[2,3-*c*]furazan (XXXIX)——A solution of 17β-hydroxy-17α-vinyl-5α-andorostano-[2,3-*c*]furazan (XXXVII)[3] (500 mg) in $CHCl_3$ (20 ml) was saturated at −50° with O_3. Acetic acid (4 ml) was added. The cold bath was removed and Zn dust (2 g) was added portionwise during 3 hr. The mixture was stirred for 2 hr at room temperature and kept overnight. The filtered solution was washed with 5% $NaHCO_3$ and H_2O, dried and evaporated. Crystallization of the residue from MeOH gave XXXIX (258 mg), mp 194—203°. A pure sample melted at 214—215°, $[\alpha]_D$ −0.1° (c=0.46, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3480, 1708, 1493, 1005, 870, 770, 740. NMR ($CDCl_3$) δ_{ppm}: 0.69 (18-Me), 0.75 (19-Me), 3.81 (17aα-H). *Anal.* Calcd. for $C_{20}H_{28}O_3N_2$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.82; H, 8.22; N, 8.22.

17β,17aβ-Dihydroxy-5α-D-homoandrostano[2,3-*c*]furazan Diacetate (XLI) and Acetonide (XLII)——To a solution of the ketone (XXXIX) (100 mg) in tetrahydrofuran–MeOH (2:1) (7.5 ml) was added an aqueous solution of $NaBH_4$ (70 mg in 0.5 ml). After being stirred for 2 hr, the mixture was kept overnight. Acetic acid (0.3 ml) was added, the solvent was removed *in vacuo* below 40°, and the mixture was diluted with H_2O. Isolation of the product by means of AcOEt and crystallization from MeOH afforded the 17β,17aβ-diol (70 mg), mp 245.5—246.5°, IR ν_{max}^{KBr} cm^{-1}: 3410, 1492, 1000, 877, 766, 738. This was acetylated with Ac_2O (0.5 ml) and pyridine (2.0 ml) at room temperature overnight. Crystallization of the product from MeOH gave the diacetate (XLI) (56 mg), mp 178—180°, $[\alpha]_D$ +43.0° (c=0.40, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1740, 1490, 1004, 875, 766, 738. NMR ($CDCl_3$) δ_{ppm}: 0.75 (19-Me), 1.05 (18-Me), 2.02 (AcO), 2.06 (AcO), 4.53 (doublet, J=3 Hz, 17aα-H), 5.29 (multiplet, $W_{1/2}$=8 Hz, 17α-H). *Anal.* Calcd. for $C_{24}H_{34}O_5N_2$: C, 66.95; H, 7.96; N, 6.51. Found: C, 66.60; H, 8.08; N, 6.78.

The acetonide (XLII) (14 mg) was obtained from the above 17β,17aβ-diol (20 mg) in the same manner described for XXXVI, mp 169—172°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1490, 1000, 872, 767, 731. *Anal.* Calcd. for $C_{27}H_{38}O_5N_2$: C, 68.91; H, 8.14; N, 5.95. Found: C, 68.99; H, 8.08; N, 5.86.

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