MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS. XLIX.[1] THE MASS SPECTROMETRIC FRAGMENTATION OF 5α-ANDROSTAN-11-ONE. SYNTHESIS OF 19-d_1-5α-ANDROSTAN-11-ONE.[2]

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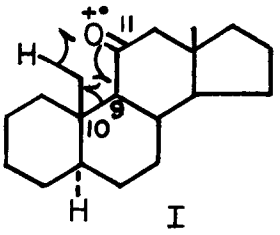
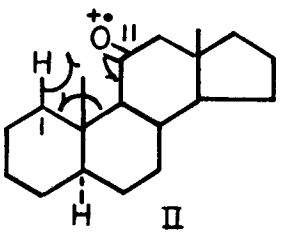
The preparation of 19-d_1-5α-androstan-11-one is reported. The mass spectrum of this compound has given further insight into the complex manner in which 5α-androstan-11-one fragments upon electron impact.

Our recent comprehensive study[3] of the mass spectrometric fragmentation of a typical 11-keto steroid, 5α-androstan-11-one (I), via deuteriated analogs, illustrated that extensive hydrogen transfer reactions accompany the bond-breaking processes. In particular, it was concluded that formation of the base peak (m/e 164, ketonic fragment, cleavage (1)) of the spectrum (Fig. 1) involved migration of one and two hydrogens in each direction (no net hydrogen transfer). However, in order to complete our program of deuterium labeling it was felt for two reasons that the spectrum of a C-19 labeled analog should be determined. First, the hydrogen atoms attached to C-19 were the only ones of those available to be transferred to the m/e 164 ion which had not been replaced by the heavy isotope.

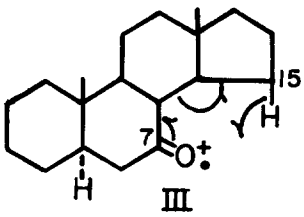
Second, hydrogen (or deuterium) attached to C-19 is available for transfer to the carbonyl group in a six-membered transition state with concomitant fission of the 9-10 bond (I). Similar processes occur in the fragmentation of aliphatic ketones and esters,[4] and it was indeed surprising to find that the postulated analogous hydrogen transfers from C-1 in 11-ketones[5,6] (see II) and from C-7 in 15-ketones[5] (see III) were not in fact operative.[3,7] The preparation of 5α-19-d_1-androstan-11-one was therefore undertaken and is described in the sequel, along with the conclusions of mechanistic significance which were obtained from its mass spectrum.



I



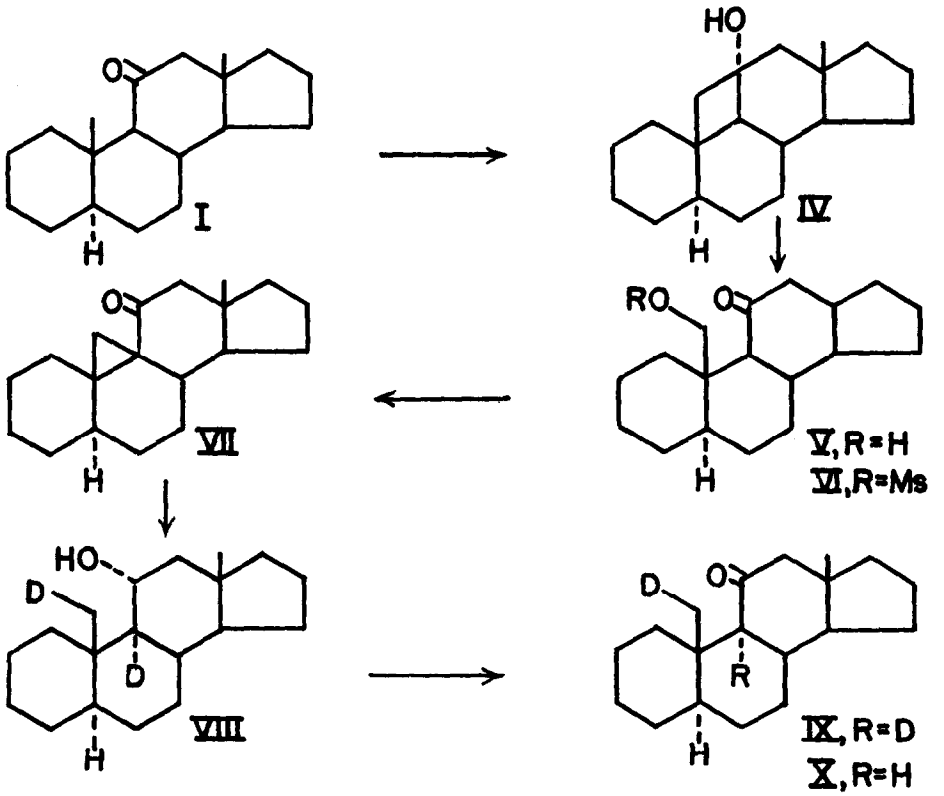
II



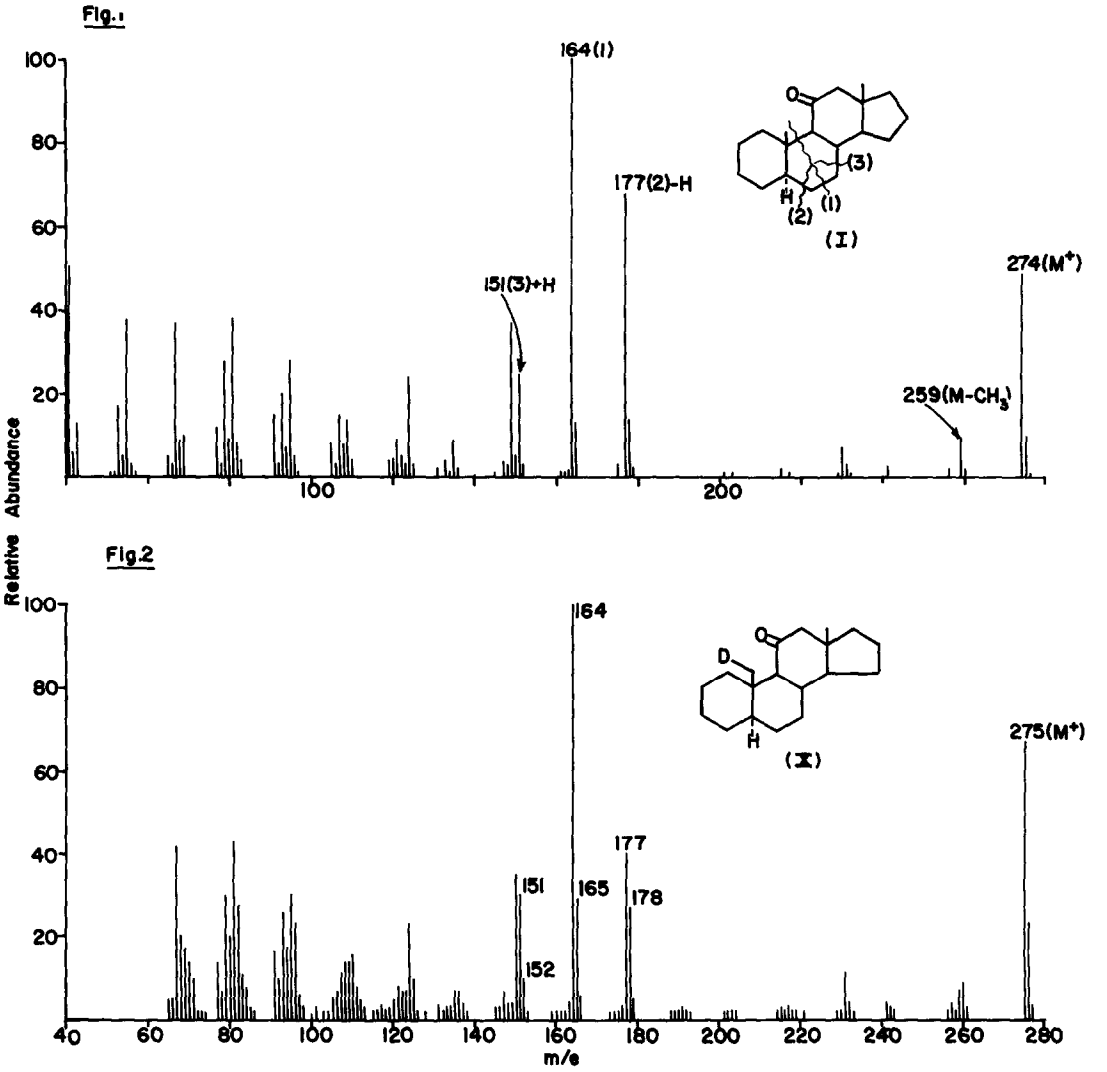
III

The functionalization of the C-19 methyl group by the irradiation of 11-keto steroids with ultraviolet light has been previously described[8] and proved eminently suitable for our present purposes. Irradiation of 5α-androstan-11-one (I) with ultraviolet light in dilute ethanol solution gave the cyclobutanol IV, which on treatment with lead tetraacetate furnished the ketol V. Esterification of this ketol with mesyl chloride in pyridine yielded the mesylate VI, which could be quantitatively converted to the cyclopropyl ketone VII by the action of sodium methoxide in methanol. The unusual n.m.r. spectrum of VII, exhibiting a C-18 methyl

resonance broadened by spin-spin coupling to one of the methylene protons at C-12 has been described elsewhere.[9] The reported reduction of the cyclopropane ring with sodium in propanol[8] was attempted using deuterioisopropanol (prepared by hydrolysis of aluminium isopropoxide with deuterium oxide) as the alcohol, and, although slow, could be forced to completion by using large quantities of sodium. Oxidation of the 9,19-d_2-11α-ol (VIII) so obtained, followed by back-exchange of deuterium from C-9 in the ketone (IX), gave 19-d_1-5α-androstan-11-one (X, d_0, 19%; d_1, 71%; d_2, 10%).



The mass spectrum of the C-19 labeled analog is reproduced in Fig. 2. It has been established previous-



ly[3] that the prominent ions occurring at m/e 151, 164 and 177 in the spectrum (Fig. 1) of the parent ketone are due to cleavages (3), (1) and (2) with respectively net gain of one hydrogen, no net transfer, and net loss of one hydrogen by the ketonic, charge-retaining fragment. Calculations show that in the formation of all three of these fragment ions, hydrogen is trans-

ferred from C-19 to the charged fragment. The extent of transfer is summarized in Table 1 and implies that mechanisms in addition to those already put forward must be operative in the genesis of all three ions.

Table 1

Deuterium transferred from C-19 in spectrum of hypothetical 19-d_3-derivative*

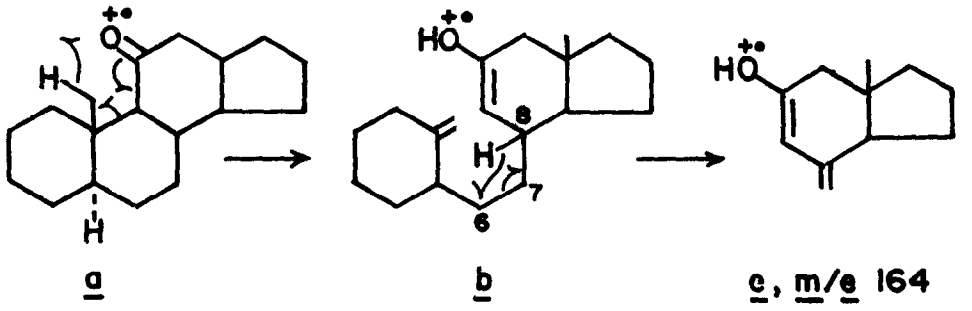
	m/e 151	m/e 164	m/e 177
Atoms Transferred to Ketonic Fragment	0.27	0.18	0.30†

* The calculations are based on the assumption that no isotope effect is operating. In any event, the isotope effect would not be anticipated to be large (ca. 0.9).[10]

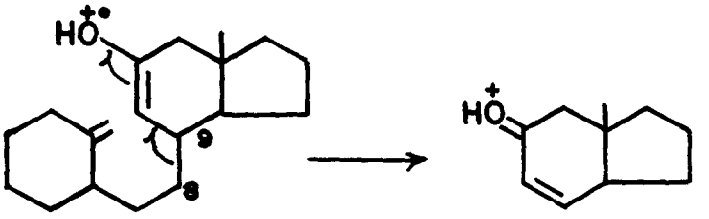
† Value obtained after correcting for the composite nature of m/e 177.[3]

Mechanistic proposals which accommodate these findings are outlined in the sequel, but it must be borne in mind that these only complement the previous suggestions[3] and operate only in a minority of the molecules undergoing fragmentation.

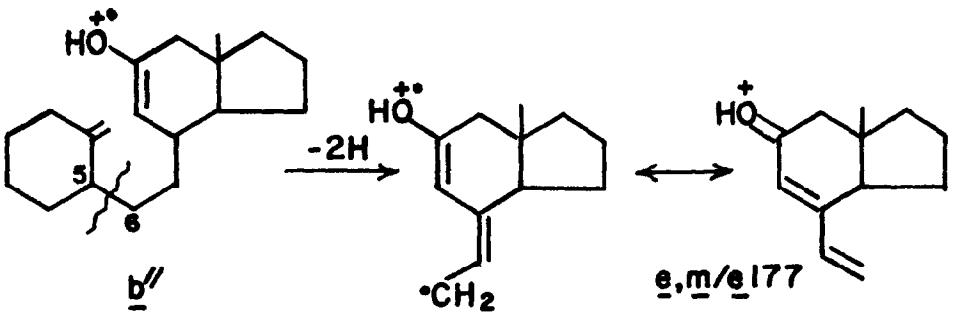
It would appear from the above results (Table 1) that some ionization is occurring specifically at the carbonyl function to furnish a. Transfer of a hydrogen from C-19 in a homolytic process with concomitant cleavage of the 9-10 bond leads to b, which can then decompose in various manners to yield the required ions.



a b c, m/e 164



b' d, m/e 151



b'' e, m/e 177

Thus, b may undergo fission of the 6-7 bond, with associated transfer of hydrogen from C-8 to the potential neutral fragment, to give c (m/e 164). The almost complete hydrogen loss from C-8 in the formation of m/e 164 has, in fact, been previously demonstrated.[3] Alternatively, simple homolysis of the allylic 8-9 bond in b' can yield the conjugated species d (m/e 151). Finally, rupture of the allylic 5-6 linkage (b"), with

associated loss of hydrogen from C-7 and C-8 (loss from the latter position also established by isotopic labeling[3]) furnishes the resonance-stabilized ion e (m/e 177). It must, however, be stressed again that these modes represent only a small portion of what is an extremely complicated fragmentation pattern.[3]

It is worthy of note that the mass spectrum of the cyclopropyl ketone (VII), in which the labile 9-10 bond is bridged by the C-19 methylene group, exhibits very little fragmentation and an extremely intense molecular ion.

EXPERIMENTAL

All melting points are corrected and were determined in capillaries. Thin-layer chromatography (TLC) was performed on silica gel G (E. Merck, A.G., Darmstadt), the spots being developed by spraying with a 2% solution of ceric sulfate in 2N sulfuric acid and subsequent heating. All mass spectra were determined by Dr. H. Budzikiewicz and Mr. John Smith with a Consolidated Electrodynamics Corp. mass spectrometer No. 21-103C using an all glass inlet system heated to 200°, while the isatron temperature was maintained at 270°. The ionizing energy was kept at 70 eV and the ionizing current at 50 μa. The microanalyses are due to Messrs. E. Meier and J. Consul.

11,19-Cyclo-5α-androstan-11α-ol (IV). - A solution of 5α-androstan-11-one (I, 1.4 g.) in 95% ethanol (1 l.) was irradiated in a water-cooled quartz probe with

ultraviolet light (Hanovia 250 watt mercury vapor lamp) for 23 hours. Thin layer chromatography (plate developed by benzene) demonstrated the presence of starting material plus a more polar product. Evaporation of the solvent gave an oil which was absorbed onto a column of alumina (Merck, grade II, neutral, 80 g.) in hexane. Development with hexane containing 20% benzene (250 cc.) gave an oil (1.12 g.) which on crystallization from aqueous methanol gave 5α-androstan-11-one (502 mg.), m.p. 47-48.5°. Further development with benzene containing 20% ether (100 cc.) gave a crystalline product (277 mg.) which, on recrystallization from aqueous methanol furnished 11,19-cyclo-5α-androstan-11α-ol (IV, 220 mg.), m.p. 134-135°, unchanged on further recrystallization. Molecular weight 274 (mass spec.).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.14; H, 10.87.

5α-Androstan-19-ol-11-one (V). - A mixture of lead tetraacetate (310 mg.) and calcium carbonate (200 mg.) in anhydrous benzene (4 cc.) was quickly boiled and cooled. The cyclo-alcohol (IV, 92 mg.) in benzene (3 cc.) was added and the mixture heated under reflux for 1.5 hours. Ether and water were added to the cooled mixture and solids then removed by filtration. The organic phase of the filtrate was washed twice with water, dried, and evaporated giving a pale yellow oil (100 mg.). This product was chromatographed on a column of alumina (Merck, grade II, neutral, 20 g.). After first eluting

a mixture of unknown substances (53 mg.) with benzene (50 cc.), a crystalline product (43 mg.) was eluted by benzene containing 15% ether (40 cc.); recrystallization from aqueous methanol gave 5α-androstan-19-ol-11-one (V, 20 mg.), m.p. 107-108°. A pure sample showed m.p. 108-109° and molecular weight 290 (mass spec.).

5α-Androstan-19-ol-11-one mesylate (VI). - The above keto-alcohol (V, 11 mg.) in pyridine (100 mg.) was treated with mesyl chloride (0.01 cc.) and the mixture left at room temperature for 6 hours. The usual work up gave a colorless gum (15 mg.), homogeneous by thin layer chromatography.

9β,19-Cyclo-5α-androstan-11-one (VII). - A solution of the above mesylate (15 mg.) in methanol (2 cc.) containing dissolved sodium (14 mg.) was heated under reflux for 1 hour. After this time, thin layer chromatography indicated that the reaction was complete and had yielded a less polar, homogeneous product. On isolation of this product, there was obtained 9β,19-cyclo-5α-androstan-11-one (VII, 11 mg.) as a white crystalline residue; molecular weight 272 (mass spec.). The n.m.r. spectrum of this compound exhibited a single methyl resonance (δ = 0.77 p.p.m.) and an AB pattern (a pair of doublets centered at δ = 2.04 and 2.58 p.p.m.) for the protons at C-12.

Deuterioisopropanol. - Deuterium oxide (7.5 cc.) was added dropwise to aluminium isopropoxide (25 g.).

The mixture was shaken for 5 minutes and then warmed to 70° for 10 minutes. Deuterioisopropanol (13 g.) was distilled from the mixture at room temperature and 1 mm. pressure into a trap cooled by liquid nitrogen. The product was further purified by distillation at atmospheric pressure; 9.5 g. (b.p. 82-83°).

19-d_1-5α-androstan-11-one (X). - A solution of the 9,19-cyclo-11-one (VII, 5.0 mg.) in deuterioisopropanol (1 cc.) was treated with small pieces of sodium during one hour until the solution was saturated with sodium isopropoxide. The process was repeated by adding more deuterioisopropanol and sodium until the total volume of the solution was 4 cc. after 4 hours. The isolated crude reduction product (4 mg.) in acetone (0.4 cc.) was treated with chromium trioxide (5 mg.) in 20% aqueous sulfuric acid (0.02 cc.). The usual work up after 4 minutes gave a colorless oil (4 mg.) which was taken up in 25% aqueous methanol (3 cc.) containing sodium hydroxide (100 mg.) and heated under reflux for 4 hours. The isolated oil (3 mg.) was shown by thin layer chromatography to consist of predominantly a 5α-androstan-11-one plus a small amount of a less polar contaminant. The oil in hexane (0.3 cc.) was therefore absorbed onto a column of alumina (Merck, neutral, grade III, 1.0 g.). The less polar impurity (0.3 mg.) was eluted by hexane (5 cc.); further development with the same solvent (8

cc.) gave 19-d_1-5α-androstan-11-one (X, 1 mg.), which was homogeneous (thin layer chromatogram) and crystallized on standing. The mass spectrum of this material is reproduced in Fig. 2.

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2. In publications from this laboratory, a fishhook ( ) represents a one-electron shift, while a full arrow ( ) indicates a two-electron movement.

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