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THE REACTIONS OF STEROIDAL ALCOHOLS WITH 2-CHLORO-1,1,2-TRIFLUOROTRIETHYLAMINE[1]

Lawrence H. Knox, E. Velarde, S. Berger, D. Cuadriello and A.D. Cross

Research Laboratories, Syntex, S.A., Apartado 2679, México, D.F.

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Recently, Yarovenko and Raksha found that the passage of chlorotrifluoroethylene into cold diethylamine for 10 hours, then vacuum distillation, led to 2-chloro-1,1,2-trifluorotriethylamine (I) which readily converted aliphatic primary and secondary alcohols into the corresponding fluoro derivatives.[2] Accordingly, we have studied the action of this reagent upon steroid primary, secondary and tertiary alcohols and have found that besides fluorination, numerous elimination reactions also occur, frequently accompanied by rearrangement.[3]

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[1]This communication constitutes Steroids CCXXIX. For Steroids CCXXVIII see A. D. Cross, P. W. Landis and L. H. Knox, J. Am. Chem. Soc., submitted for publication.

[2]N. N. Yarovenko and M. A. Raksha, Zhur. Obschceĭ Khim. 29, 2159 (1959). Cf. Chem. Abs. 54, 9724h (1960).

[3]At the Gordon Conferences, July, 1962, we learned that Dr. D. E. Ayer had independently carried out a similar investigation. By mutual agreement our results are published simultaneously. Some of our results differ considerably from those obtained by Dr. Ayer which we attribute to the marked effect on product composition of the solvent and temperature employed for the reactions. A more detailed discussion of these aspects will appear in our full report.

2-Hydroxymethyl-Δ^2-androstene-17β-ol acetate[4] when treated in ethereal solution with 1 molar equivalent of 2-chloro-1,1,2-trifluorotriethylamine (I) (hereafter referred to simply as the reagent), followed by evaporation, brief warming of the crystalline residue and chromatography over florisil, afforded 35% of 2-fluoromethyl-Δ^2-androstene-17β-ol acetate identical by mixed m.p. and infrared spectrum with an authentic sample prepared by an alternative route.[4] Similarly, Δ^5-pregnene-3β-ol-20-one with the reagent furnished the known 3β-fluoro-Δ^5-pregnene-20-one[5] in 60% yield. The retention of configuration in this substitution reaction is in accord with the stereochemical control exhibited in similar substitution reactions of Δ^5-3β-alcohols.[6]

Testosterone (II, R=OH; R'=H) with the reagent gave three products, separable by chromatography on florisil, which proved to be testosterone chlorofluoracetate (II, R=O_2C:CHClF; R'=H),[7] m.p. 177-179°, $[\alpha]_D$ +81°, λmax. 240-242 mμ (log ε 4.21), 17α-fluoro-Δ^4-androstene-3-one (II; R=H; R'=F),[8] m.p. 146-148°, $[\alpha]_D$ +103°,

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[4] J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibáñez, E. Necoechea, A. de la Roz, E. Segovia, R. Urquiza and A. Bowers, J. Org. Chem. in press.

[5] A. Bowers, P. G. Holton, E. Denot, M. C. Loza and R. Urquiza, J. Am. Chem. Soc. 84, 1050 (1962)

[6] Cf. L. F. Fieser and M. Fieser, Steroids, Reinhold, New York, 1959, pp. 321-4.

[7] Satisfactory analyses have been obtained for all new compounds. Rotations were determined for ca. 0.3% chloroform solutions and ultraviolet spectra were measured for ethanol solutions.

[8] Subsequent to the completion of our work, an alternative synthesis of this compound was described by H. B. Henbest and W. R. Jackson, J. Chem. Soc. 954 (1962). The physical constants of our compound are in good agreement with the published values.

and the 18-nor compound (III, R=Me; R'=H) m.p. 112-113°, $[\alpha]_D$ +69°, resulting from a Wagner Meerwein rearrangement. In the nuclear magnetic resonance (n.m.r.) spectrum[9] of the 17α-fluoro compound (II, R=H; R'=F) long-range coupling of the fluorine with the 18-protons is observed, J, 2.0 c./s.[10] This coupling constant is of similar magnitude to that observed for other known 17α-fluoro steroids.[10] The rearrangement product (III, R=Me; R'=H) was identified by elemental analysis and the n.m.r. spectrum[9] from which was apparent the disappearance of a hydroxyl proton and the 18-angular methyl 3H singlet of the precursor (II, R=OH; R'=H) with concomitant introduction of an allylic methyl 3H doublet (δ, 55.2 and 61.5 c./s., J, 6.3 c./s.). No vinyl protons, other than that at C_4 (338 c./s.), are present after the rearrangement. The spectral data thus exclude the isomeric structures containing Δ^{12} or $\Delta^{13(17)}$ double bonds.[11]

Epitestosterone (II, R=H; R'=OH) on treatment with the reagent in ether furnished the chlorofluoroacetate ester

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[9] N.m.r. spectra are for deuterochloroform solutions containing tetramethylsilane (TMS) as a reference standard (0.0 c./s.). Chemical shifts, δ, are reported as c./s. downfield from the TMS reference and have an accuracy better than ± 1 c./s. Coupling constants, J, are reported as c./s. and are accurate to ± 0.3 c./s. Measurements were taken on the Varian A-60 spectrometer at the Universidad Nacional Autónoma de México through the courtesy of Prof. A. Sandoval.

[10] For other examples of long-range coupling of fluorine with angular methyl protons see A. D. Cross and P. W. Landis, J. Am. Chem. Soc. 84, 1736 (1962); A. D. Cross and P. W. Landis, ibid., in press; and footnote 1.

[11] For n.m.r. spectral analysis of similar rearrangement products see Varian Tech. Info. Bull. 3, No. 2 (1961); A.D. Cross, H. Carpio and H. J. Ringold, J. Org. Chem. in press.

(II, R=H; R'=$O_2C.CHClF$), m.p. 148-150°, $[\alpha]_D$ +63°, the rearrangement product (III, R=Me, R'=H), and a trace of a product considered to be 17β-fluoro-Δ^4-androstene-3-one (II, R=F; R'=H), m.p. 112-114°. 17α-Methyltestosterone (II, R=OH; R'=Me) in refluxing acetonitrile with the reagent (I) gave 17,17-dimethyl-$\Delta^{4,13}$-18-norandrostadiene-3-one (III, R=R'=Me), m.p. 74-75°, $[\alpha]_D$ +58°, as the sole reaction product and, under similar reaction conditions, 17α-methyldihydrotestosterone led to 17,17-dimethyl-Δ^{13}-18-norandrostene-3-one (III, R=R'=Me; 4,5-dihydro), m.p. 142-143°, $[\alpha]_D$ ±0°. On treatment with the reagent in hot tetrahydrofuran 3β-methyl-androstane-3α,17β-diol-17β-acetate (IV yielded the elimination product 3-methyl-Δ^2-androstene-17β-ol acetate (V, R=H), m.p. 99-100°, $[\alpha]_D$ +47°, in 62% yield. Androstane-3β-ol-17-one and the epimeric 3α-alcohol both furnished Δ^2-androstene-17-one[12] when subjected to the reagent. 2,2-Dimethyl-androstane-3β,17β-diol 17-acetate[13] and the reagent yielded a rearrangement product, m.p. 141-143°, $[\alpha]_D$ +36°, which was shown to be 2,3-dimethyl-Δ^2-androstene-17β-ol acetate (V, R=Me) by n.m.r. spectroscopy. Proton absorptions due to the gem dimethyl, hydroxyl and 3α-H in the precursor had disappeared and new 3H absorption singlets for two vinyl methyls (coalesced at 100 c./s.), but no vinyl protons, were present.[9]

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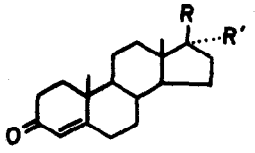
[12] See A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, J. Org. Chem. in press, and footnote 22 included therein.

[13] This compound was prepared by lithium aluminum hydride reduction of 2,2-dimethylandrostane-17β-ol-3-one acetate, which has been described by H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, J. Am. Chem. Soc. 81, 427 (1959)



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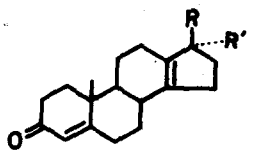

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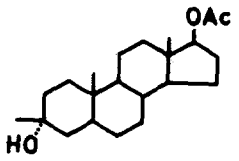

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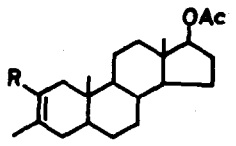

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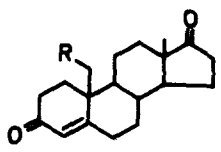

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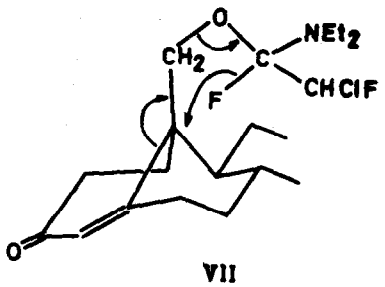
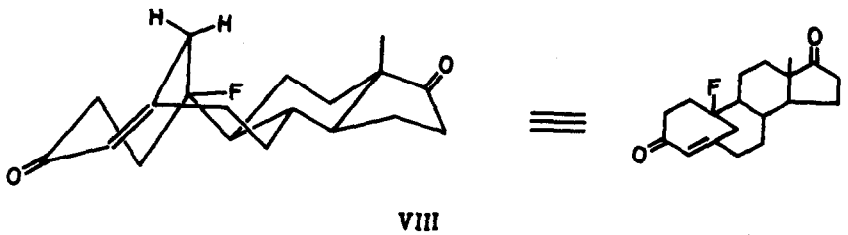


VII



VIII

6β-Hydroxytestosterone[14] underwent an elimination reaction on treatment with the reagent to give the known 6-dehydrotestosterone acetate.[15]

An extremely interesting rearrangement took place when a solution of 19-hydroxy-Δ^4-androstene-3,17-dione (VI, R=OH)[16] in hot acetonitrile was treated with the reagent (I). A single crystalline product was isolated, m.p. 179-181°, $[\alpha]_D$ - 52°, λmax. 240 mμ (log ε 4.09) which, though having elemental analysis compatible with the expected 19-fluoro analog (VI, R=F), is considered to be the rearranged fluoro compound (VIII) from the n.m.r. spectral data. No absorption for a CH_2F group was visible but a doublet, J 5.0 c./s., equivalent to ONE HALF OF ONE PROTON ABSORPTION was observed at 19.8 and 24.8 c./s.[9] This is interpreted as due to a proton in the environment $C-\overset{\overset{C}{|}}{\underset{\underset{F}{|}}{C}}-CH_2-\overset{\overset{C}{|}}{\underset{\underset{C}{|}}{C}}-C$, where each methylene proton couples with the other proton, J_{HH} 5.0 c./s., and also with fluorine, J_{HF} 7 - 25 c./s.,[17] to give a pair of doublets. One of the protons lies in a shielding environment such that one doublet of the pair for this proton is visible at high field. The remaining doublet of this pair, and both doublets of the other proton, are buried beneath the broad absorption 'hump' due to aliphatic CH_3, CH_2, and CH protons.

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[14] C. Amendolla, G. Rosenkranz and F. Sondheimer, J. Chem. Soc., 1226 (1956); J. Romo, G. Rosenkranz, C. Djerassi, St. Kaufmann and J. Pataki, J. Org. Chem. 19, 1509 (1954).

[15] C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, J. Am. Chem. Soc. 72, 4534 (1950).

[16] A. S. Meyer, Experientia, 11, 99 (1955); A. Bowers, R. Villotti, J. A. Edwards, E. Denot and O. Halpern, J. Am. Chem. Soc., in press.

This interpretation supports the logical reaction mechanism (VII, see arrows) whereby the intermediate ether leads to a 4,4,1-bicyclo-undecane ring system in the product (VIII). Molecular models reveal that the Δ^4-3-ketone system in VIII is almost coplanar so that little change in the ultraviolet absorption maximum is to be expected.

11α-Hydroxyprogesterone with the reagent in ether gave none of the expected 11β-fluoro derivative for which splitting of both the 18- and 19-proton absorption frequencies by the fluorine atom has been predicted,[10] but only the $\Delta^{9(11)}$-elimination product.[15]

A detailed discussion of the mechanisms of these rearrangement displacement and elimination reactions is deferred for the full paper.

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[17] Cf. C. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry', Pergamon, London, 1959, p. 86; A. D. Cross unpublished observations.

[18] C. W. Shoppee and T. Reichstein, Helv. Chim. Acta, 24, 351 (1941).