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A NEW METHOD FOR THE PREPARATION OF FLUORO STEROIDS[1]

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THE reaction of certain primary and secondary hydroxy-steroids with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine[2] (1) provides a simple, direct route to the corresponding fluoro-compounds.[3] Thus when a solution of 3β-hydroxyandrost-5-en-17-one (2) and excess (1) in dichloromethane was allowed to stand at 25°, there was obtained 96% of 3β-fluoroandrost-5-en-17-one (3) identical by infrared with an authentic sample (m.p. 152°). One recrystallization gave 78% of (3), m.p. 152-154°. The previous preparations of (3) required a three-step sequence via the tosylate of (2) and the iodide[4] or 3:5-cyclo-6β-hydroxy compound[5] derived therefrom. A high yield of 3β-fluoropregn-5-en-20-one, m.p. 166-170°, identical with an authentic sample[4,5] was obtained from 6β-hydroxy-3:5-cyclopregnan-20-one[5] furnishing evidence for participation of the homoallylic cation.

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[1] An oral presentation of this material was given at The Gordon Research Conference on Steroids and Other Natural Products at New Hampton, New Hampshire July 16-20, 1962.

[2] R.L. Pratt, J.T. Barr, K.E. Rapp, C.T. Bahner, J.D. Gibson and R.H. Lafferty, Jr., J. Am. Chem. Soc. 72, 3646 (1950).

[3] N.N. Yarovenko and M.A. Raksha, Zhur. Obshchei Khim. 29, 2159 (1959), report the preparation of the 1-fluorobutane in 66% yield by the reaction of butan-1-ol and (1).

[4] T.N. Jacobsen and E.V. Jensen, Chem. and Ind. 172 (1957).

[5] C.W. Shoppee and G.R. Summers, J. Chem. Soc. 4813 (1957).

The axial alcohol 3α-hydroxy-5α-androstan-17-one gave under similar conditions a mixture of 3β-fluoro-5α-androstan-17-one (4) and 5α-androst-2-en-17-one (5), m.p. 104°.[6] Following purification by ozonization and chromatography there was obtained 16% of (4), m.p. 129-131°, $[\alpha]_D$ + 81° identical with an authentic sample.[7] Similarly the equatorial alcohol 3β-hydroxy-5α-androstan-17-one yielded (5) and 35% of 3α-fluoro-5α-androstan-17-one (6), m.p. 119-120°, $[\alpha]_D$ + 80°. Paper chromatography[8] of the crude samples of (4) and (6) showed no cross-contamination. Thus the replacement of hydroxyl by fluorine proceeds with essentially complete inversion of configuration.[9] In similar fashion testosterone was converted to 17α-fluoro-androst-4-en-3-one (7), m.p. 150-151°.[10] The reaction of (1) with the Ψ-equatorial alcohol 15α-hydroxypregn-4-ene-3,11,20-trione (8)[11] gave 15β-fluoropregn-4-ene-3,11,20-trione (9), m.p. 159-161° in good yield accompanied by smaller amounts of 4,14-pregnadiene-3,11,20-trione (10) identical with an authentic sample[12] and the 15-chlorofluoroacetate of (8), m.p. 182-18

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[6] Reported m.p. 104.5-105.5°, V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, Helv. Chim. Acta 28, 618 (1945) and references cited therein.

[7] Ref. 4 reports m.p. 130-132°, $[\alpha]_D$ + 35°. However a repeat rotation on a sample kindly provided by Dr. Jensen gave $[\alpha]_D$ + 82°.

[8] Ethyleneglycol monophenylether-heptane, R. Neher and A. Wettstein, Helv. Chim. Acta 35, 276 (1952).

[9] The reactions of N,N-diethyl-1,2,2-trichlorovinylamine or (1) with alcohols are similar in some respects. For example, the reaction of the former reagent with d-sec-butyl alcohol to give l-sec-butyl chloride of high optical purity has been described by A.J. Speziale and R.C. Freeman, J. Am. Chem. Soc. 82, 909 (1960).

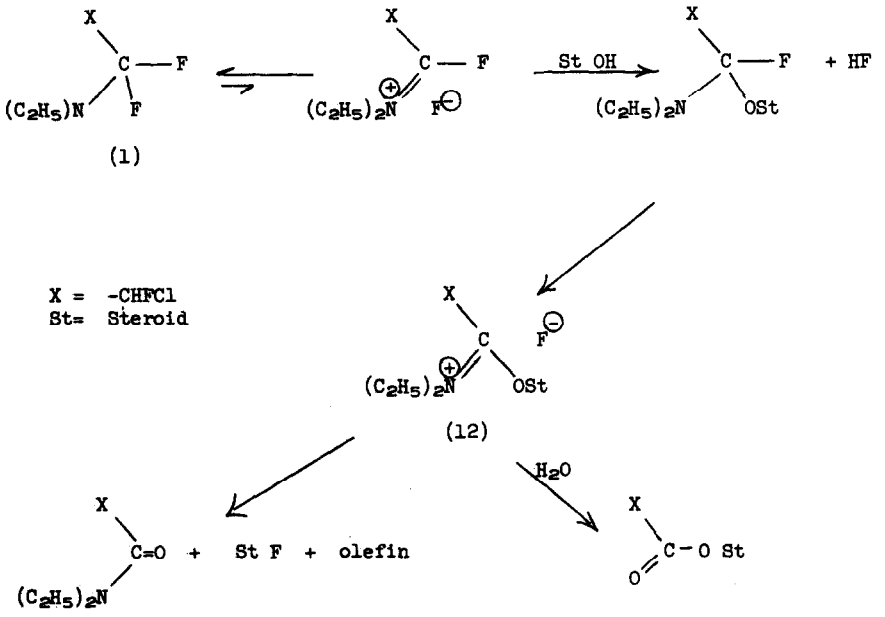
[10] The preparation in high yield of (7), m.p. 149-151°, from the reaction of testosterone tosylate and tetrabutylammonium fluoride was recently reported by H.B. Henbest and W.R. Jackson, J. Chem. Soc. 954 (1962).

[11] A. Schubert, R. Siebert and G. Langbein, German Pat. 1,067,020.

[12] Compounds (10) and (11) were prepared by P.F. Beal and R.W. Jackson of these Laboratories in another investigation (U.S. Patent 3,021,327).

ν_{max}^{Nujol} 1765, 1750, 1705, 1665, 1615 cm.$^{-1}$ The 15β-configuration assigned to the fluoro substituent is supported by NMR data[13] wherein the 13-methyl group appears as a doublet (49, 50 cps.). Such long-range couplings with fluorine are not uncommon.[14] However the Ψ-axial alcohol 15β-hydroxypregn-4-ene-3,11,20-trione (11)[12] gave principally the olefin (10). A number of 15β-fluoro corticoids have been prepared starting from the intermediate (9).[15]

Preliminary experiments indicate the presence of a rapidly-formed intermediate such as (12) which reacts further to give the observed mixture of products.



[13] NMR spectra (60 Mc.) were measured in deuterochloroform with tetramethylsilane as an internal standard.

[14] See G. Slomp, Mellon Letters 31, 8 (1961) and A.D. Cross and P.W. Landis, J. Am. Chem. Soc. 84, 1736 (1962).

[15] D.E. Ayer, submitted for publication.

A considerable difference in reactivity was displayed by 11β- and 11α-hydroxy compounds. Thus even at 5°, 11α-hydroxypregn-4-ene-3,20-dione[16] reacted rapidly with (1) to give 4,9(11)-pregnadiene-3,20-dione (13), m.p. 122-124°,[17] in high yield accompanied by a small amount of 11β-fluoropregn-4-ene-3,20-dione (14), m.p. 156-158° contaminated with 9α-fluoropregn-4-ene-3,20-dione (15).[18]

At 40° 11β-hydroxypregn-4-ene-3,20-dione (16)[19] gave principally (13) and a small amount of (15), m.p. 174-194°, λ_{max} 238 mμ (ε 16,950).[20] The diol 6β,11α-dihydroxypregn-4-ene-3,20-dione[16] gave 6α-fluoropregna-4,9(11)-diene-3,20-dione[21] in low yield. A 46% yield of 16β-fluoromethyl-17α-pregn-4-ene-3,20-dione (18) identical with an authentic sample[22] was obtained from the corresponding 16-hydroxymethyl compound (17).

The reactions of N-(2-chloro-1,1,2-trifluoroethyl)diethylamine with other steroidal alcohls and with other classes of biologically-active compound will be described in a future publication.

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[16] D.H. Peterson, H.C. Murray, S.H. Eppstein, L.M. Reineke, A. Weintraub, P.D. Meister, and H.M. Leigh, J. Am. Chem. Soc. 74, 5933 (1952).

[17] Reported m.p. 120-122°, C.W. Shoppee and T. Reichstein, Helv. Chim. Acta 24, 351 (1941); P. Hegner and T. Reichstein, ibid 26, 715 (1943).

[18] The C_{18} and C_{19} protons of (14) appear as doublets (47,50 and 80,83 cps. respectively) in the NMR spectrum (60 Mc.). Compound (15) showed the corresponding angular methyl resonances at 41 and 79 cps. The assistance of G. Slomp and F. MacKellar in the interpretation of this data is gratefully acknowledged.

[19] T. Reichstein and H.G. Fuchs, Helv. Chim. Acta 23, 684 (1940).

[20] C.G. Bergstrom and R.M. Dodson, German Patent 1,081,888, report the preparation of 9α-fluoropregn-4-ene-3,20-dione, m.p. 196-200°, λ_{max} 237.5 mμ (ε 17,400) from the reaction of (16) and a pyridine-hydrogen fluoride complex. See also J. Am. Chem. Soc. 82, 3479 (1960).

[21] J.A. Campbell, J.C. Babcock and J.A. Hogg, U.S. Patent 2,880,205.

[22] Compound (18) was first prepared in these Laboratories by J.E. Pike by another route. The ORD curves of (17) and (18) have been reported: W.A. Struck and R.L. Houtman, J. Org. Chem. 26, 3883 (1961).

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