Tetrahedron Letters No. 15, pp 1315 - 1318, 1978. Pergamon Press. Printed in Great Britain.

ADDITION OF BROMINE FLUORIDE TO UNSATURATED BONDS IN STEROIDAL COMPOUNDS

R.Míčková *, J.Moural and V.Schwarz

Research Institute for Pharmacy and Biochemistry
194 04 Prague 9, Czechoslovakia

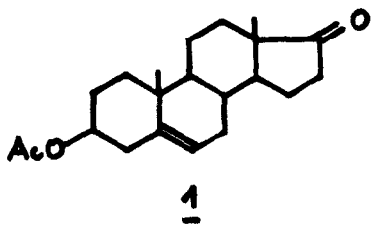
(Received in UK 16 February 1978; accepted for publication 27 February 1978)

In connexion with the preparation of some steroidal compounds possessing pharmacological activities we investigated fluorination of steroidal molecules in the positions 6 or 11. Several procedures lead to fluorinated steroidal compounds [1]; especially expedient is addition to the appropriate double bond of bromine fluoride, liberated in situ by reaction of anhydrous hydrogen fluoride with N-bromoamide or N-bromoimide [2) 3)]. This reaction, however, requires very low temperatures and cannot be performed in glass equipment. We found another suitable source of fluoride anions in connexion with a N-halogenamide in the Yarovenko reagent, that is, N-(1,1,2-trifluoro-2-chloroethyl) diethylamine [4] (in further text, fluoroamine), originally used for replacing hydroxyl group by fluorine [5) 6)]. This reagent in combination with N-bromoacetamide leads to a product of bromine fluoride addition to a double bond. The reaction is not inhibited by the presence of tertiery hydroxyl or of epoxidic ring, proceeds at temperatures from 0°C to room temperature, and can be performed in glass equipment. The reagent acts simultaneously as solvent; the presence of other solvents inhibits the reaction.

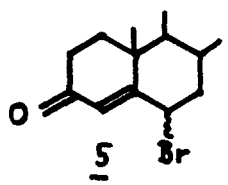
With 9(11)-unsaturated compounds the addition produces 9α-bromo-11β-fluoro derivatives with satisfactory yields. A mixture consisting of 21-acetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (1.15 g), N-bromoacetamide (0.8 g), and fluoroamine (10 ml) was allowed to stand for 40 minutes at room temperature; the product was extracted with dichloromethane, and the volatile fractions were steam-distilled. Routine processing produced 21-acetoxy-9α-bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione (1.01 g), m.p. 203-207°C, $[\alpha]_D$ + 140° [2) 3)].

Addition to a 5,6-double bond is more complicated, in accordance with experiences with the addition of hypobromous acid or a halogen. 3β-Acetoxy-5-androsten-17-one (1) (3.3 g) under analogous conditions yielded a crude reaction product, which was partitioned by column chromatography on silica gel (elution with benzene and benzene - dichloromethane mixtures) to three fractions (crystallized from

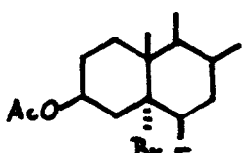
acetone - hexane): a) 3β-acetoxy-5-bromo-6β-fluoro-5α-androstan-17-one (2) (1.05 g), m.p. 185-190°C (decomp.), $/\alpha/_D$ - 4° 7) 8), p.m.r.: 5.36 m (CHOAc), 4.51, 5.14 m (CHF), 2.02 s (OAc), 1.25 s, 1.30 s (19-H), 0.88 s (18-H) ; b) 1:1 mixture of isomeric 3β-acetoxy-5-fluoro-6-bromo-5α-androstan-17-ones (3) (0.45 g), m.p. 233-236°C (decomp.), $/\alpha/_D$ - 6°, i.r. : 1735 cm^{-1}, p.m.r.: 5.00m(CHOAc), 4.14 m (CHBr), 2.02 s (OAc), 1.35 s, 0.90 s (angular methyls); c) 3β,5-diacetoxy-6--bromo-5α-androstan-17-one (4) (0.8 g), m.p. 210-214°C, $/\alpha/_D$ - 34°, i.r.: 1739 cm^{-1}, p.m.r.: 5.34 m (CHOAc), 2.70 s, 2.02 s (OAc), 1.33 s, 0.90 s (angular methyls). Analogously there were obtained 3β-acetoxy-5-bromo-6β-fluoro-5α-pregnan--20-one, m.p. 171-177°C (decomp.) 5) and 3β-acetoxy-5-bromo-6β-fluoro-5α-cholestane, m.p. 136-141°C (decomp.), $/\alpha/_D$ - 19° 9). The physical constants and the p.m.r. spectrum of compound 2 agree with data published in the literature. The structure of the 5α-fluoro-6-bromo derivative 3 was deduced on the basis of its p.m.r. spectrum and its conversion to 6-bromo-4-androsten-3,17-dione (5) . We never succeeded in separating the components of the equilibrium mixture of epimers, but the location and the character of the p.m.r. signal for the angular C_{10}-methyl group indicate preserved trans-annelation of the A/B rings, that is, 5α-fluoro substitution; consequently, the isomerism pertains solely the 6-bromine. The same reasoning applies to the 5α-acetoxy-6-bromo derivative 4. If after completion of the reaction the volatile fractions are removed by distillation in vacuum, the yield of the desired derivative 2 increases by about one third, and the portion of the 5α-acetoxy-6-bromo derivative 4 markedly diminishes.



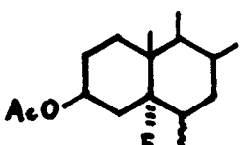
1



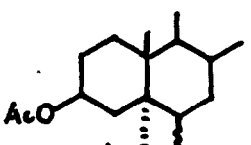
5



2



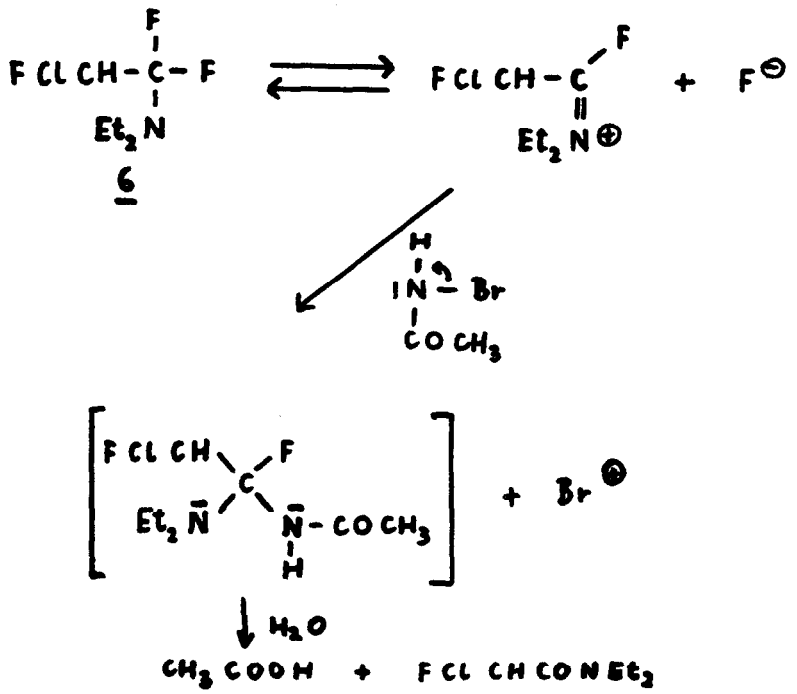
3

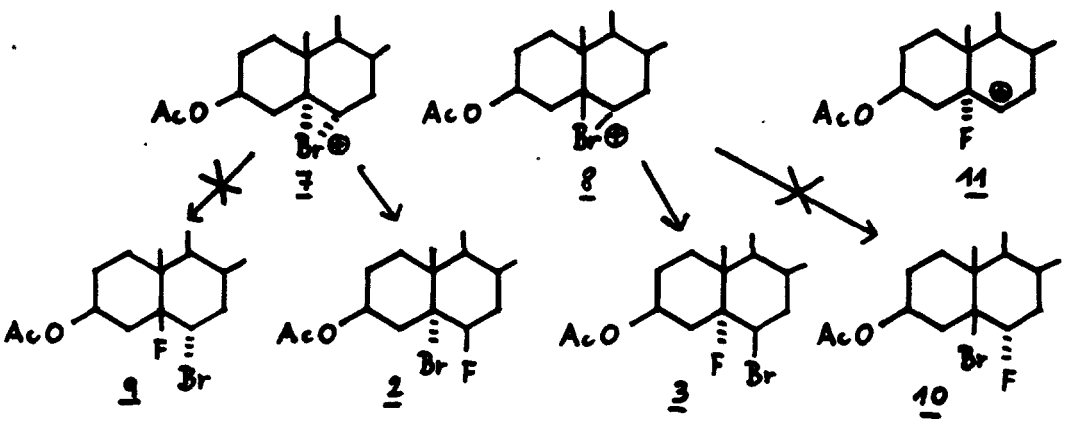


4

In our opinion, the formation of side products and the reaction mechanism can be explained on the basis of the assumption that fluoroamine 6 releases fluoride anion as it does in the substitution of hydroxyl group, and that after its interaction with N-bromoacetamide, or with the latter's rest after separation of

the bromonium cation, an unstable product forms with two nitrogens attached to one carbon atom, which decomposes further in dependence on the mode of processing In the presence of water, acetic acid forms; its presence was proved in a blank test, and so was that of bromine fluoride and of fluorochloroacetic acid diethylamide; moreover, presence of bromide anions was proved as well. Consequently, not only the cyclic bromonium cation 7, but also the isomeric cation 8 must be assumed to form; the latter has not been observed as yet in additions of bromine fluoride, but did form in additions of iodine fluoride.





We did not succeed in proving the presence of the theoretically possible fluoro derivatives 9 and 10. The cleavage of the β-bromonium cation 8 by action of the fluoride ion apparently proceeds slowly, because on decomposition by water of the reaction mixture the forming acetate anion reacts with preference as a stronger nucleophile. This assumption is corroborated by the fact that the starting substance was not isolated any more. Besides, the axial 6β-bromine is simultaneously subjected to epimerization by splitting off and readdition to the transitory carbonium ion 11. We assume that this interpretation is supported by the proof of presence of bromide anions in the reaction mixture.

References and footnotes

1) J.Fried and N.A.Abraham, in: J.Fried and J.A.Edwards : Organic reactions in steroid chemistry, Vol.I, Van Nostrand Reinhold Company, New York 1972, p.423-493.

2) A.Bowers, J.Amer.Chem.Soc. 81, 4107 (1959).

3) Optical rotations were measured in chloroform; p.m.r. spectra at 80 MHz in deuterochloroform.

4) N.N.Yarovenko and M.A.Raksha, Zh.obshtch.khim. 29, 2159 (1959).

5) A.Bowers, L.C.Ibáñez, E.Denot and R.Becerra, J.Amer.Chem.Soc. 82, 4001 (1960).

6) D.E.Ayer, Tetrahedron Letters 1962, 1065.

7) L.H.Knox, E.Velarde, S.Berger, D.Cuadriello and A.D.Cross, J.Org.Chem. 29, 2187 (1964).

8) A.D.Cross, J.Amer.Chem.Soc. 86, 4011 (1964).

9) Elementar analysis and p.m.r. spectrum were compatible with the given structure.