Chemistry of Difluorocarbene Adducts of Sterically-hindered Acetylenes[1]

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Summary Novel findings associated with the addition of difluorocarbene to acetylenic bonds are mentioned: the first example of acyl migration occurring during a difluorocarbene addition reaction is reported.

THE difluorocarbene addition to the 17α-ethynyl side chain of ethynyloestradiol 3-methyl ether 17β-acetate (**1**A) and on some novel transformations of the resulting products were reported in a previous paper.[2] During further studies of the addition of difluorocarbene to acetylenic bonds,[1] we reinvestigated this reaction since some of the products exhibited unusual chemical and spectral characteristics. The study was extended to the 3β-acetoxy-5α-androstane series (**1**B; R = Ac) and on the basis of new evidence we now report the isolation of additional reaction compounds and revised structures for the previously reported bisadduct† and its hydrogen fluoride elimination product.†

By analogy with our results in the oestrane series[2] the major product (76%) from the reaction of 17α-ethynyl-5α-androstane-3β,17β-diol diacetate (**1**B; R = Ac) with difluorocarbene (generated *in situ* by decomposition of the sodium salt of chlorodifluoroacetic acid[3] in boiling diglyme) is the difluorocyclopropene monoadduct (**2**B; R = Ac), m.p. 138—139°, $[\alpha]_D - 57°$.

The second major product (obtained in 10% yield) is a bisadduct {m.p. 141—142°; $[\alpha]_D - 1°$; ν_{max} 1740, 1695 cm^{-1} (weak); H n.m.r. 0·87 (18-H), 0·83 (19-H), 2·01 (3β-acetate), 2·11 p.p.m. (20-acetate)},‡ which is analogous to

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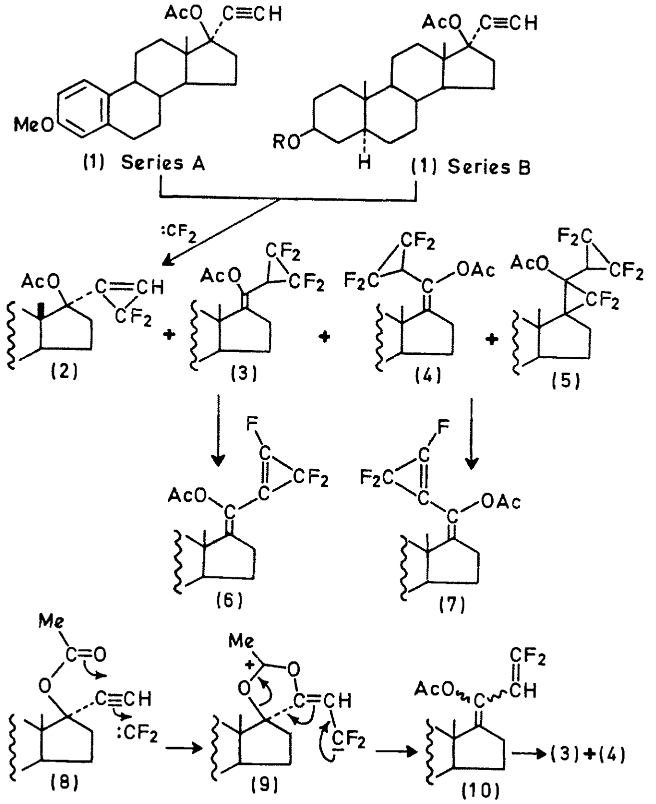
† See structures 3 and 10 in reference 2.

‡ The ^1H n.m.r. and ^{19}F n.m.r. spectra were measured and reported herein as described in reference 2; d = doublet, dd = double doublet, t = triplet, m = multiplet, bm = broad multiplet. The mass spectra were measured on an Atlas CH-4 mass spectrometer, equipped with an EFO-4B ion source, the ionizing energy was maintained at 70 ev. Satisfactory analyses have been obtained for all compounds mentioned in this Communication.

the reported[2] tetrafluorobicyclo[1,1,0]butane derivative in the oestrane series. In both the oestrane and the androstane series, we have now isolated a second isomeric bisadduct in 2 and 0·25% yield, respectively. The structure of the latter products could not be explained satisfactorily in terms of a tetrafluorobicyclo[1,1,0]butane moiety unless a highly unusual isomerization at C-17 is postulated during the course of carbene addition. This observation together with unsuccessful attempts to convert the monoadduct into a bisadduct under a variety of conditions led us to examine the main bisadduct in the androstane series of *X*-ray crystallographic analysis. Examination of the 3β-(*p*-bromobenzoate) derivative ($C_{32}H_{37}O_4F_4Br$; orthorhombic crystals, a = 24·94, b = 11·17, c = 10·80 Å; space group $P2_12_12_1$ fron systematic absences[4]) showed that the structure of this compound is (3B; R = *p*-bromobenzoate) {m.p. 234—235°; $[\alpha]_D$ + 4°; ^{1}H n.m.r. 0·87 (18 and 19-H), 2·10 (20-acetate), 4·95 (bm, 3α-H); ^{19}F n.m.r. 140, 154 (difluoromethylene, J^{FF} (*gem*) 180 Hz) and 141·5, 153 p.p.m. (difluoromethylene, J_{FF} (*gem*) 180 Hz); m.s. *m/e* 640 and 642 $(M^+)^+$. The isomeric minor bisadduct is therefore (4B; R = Ac) {m.p. 167—168°; $[\alpha]_D$ + 25°; ν_{max} 1760, 1740, 1710 cm^{-1} (weak); ^{1}H n.m.r. 0·83 (19-H), 0·93 (18-H), 2·01 (3β-acetate), 2·10 p.p.m. (20-acetate)}.



Consequently, the structure of the major bisadduct in the oestrane series[2] is (3A), m.p. 131—132°, and the newly isolated minor (2%) isomeric bisadduct is (4A) {m.p. 174—175°; $[\alpha]_D$ + 53°; ν_{max} 1760, 1695 cm^{-1}; ^{1}H n.m.r. 0·97 (18-H), 2·11 (20-acetate); ^{19}F n.m.r. 139·5, 148 (difluoromethylene, J_{FF} (*gem*) 178 Hz) and 139·5, 150 p.p.m. (difluoromethylene, J_{FF} (*gem*) 178 Hz); m.s. *m/e* 452 (M^+)}.

The geometrical isomeric relationship of the enolacetates (3) and (4) is supported by the observation that upon hydrolysis with 2% sodium hydroxide in methanol both (3A) and (4A) give the same ketone. The structure of this compound and additional transformations in this series will be the subject of a subsequent report.

A mechanism which accounts for the migration of the acyl group during the reaction is depicted by the sequence (**8**) → (**10**). To our knowledge this is the first example of such acyl migration during the course of difluorocarbene reactions even though related alkyl migrations have been reported in the literature.[5] Addition of a second molecule of difluorocarbene to the terminal double bond in the intermediate (**10**) yields the bisadducts (**3**) and (**4**).

When the hydrolysis of (3A) and (4A) is carried out with 2% aqueous sodium hydroxide in acetone, hydrogen fluoride elimination takes place yielding (**6**A) {m.p. 111°; $[\alpha]_D$ + 31°; ν_{max} 1775, 1855 cm^{-1}; λ_{max} 232, 278, and 287 nm (log ε 4·46, 3·33, and 3·29); ^{1}H n.m.r. 0·95 (18-H), 2·20 p.p.m. (20-acetate); ^{19}F n.m.r. (ABX pattern) 92·5 (dd, J_{FF} (*gem*) 117, J_{FF} (*vic*) 43 Hz), 94 (dd, J_{FF} (*gem*) 117, J_{FF} (*vic*) 43 Hz), and 140 p.p.m. (t, J_{FF} (*vic*) 43 Hz); m.s. *m/e* 432 (M^+)}, and (**7**A) {m.p. 112°; $[\alpha]_D$ + 36°; ν_{max} 1860, 1775, 1240 cm^{-1}; λ_{max} 230, 278, and 287 nm (log ε 4·36, 3·33, and 3·27); ^{1}H n.m.r. 0·99 (18-H), 2·17 p.p.m. (20-acetate); ^{19}F n.m.r. (A_2X pattern) 91.5 (d, J_{FF} (*vic*) 43 Hz) and 137·5 (t, J_{FF} (*vic*) 43 Hz); m.s. *m/e* 432 (M^+)}, in 83% and 77% yield respectively. Similar treatment of (3B; R = Ac) and (4B; R = Ac) gives compounds (**6**B; R = Ac) and (7B; R = Ac) in 73% and 50% yield, respectively, and minor amounts of the 3β-hydroxy-analogues. Both compounds (**6**A) and (**6**B) (R = Ac) are also obtained in very low yield from the difluorocarbene treatment of (**1**A) and (**1**B) (R = Ac) presumably due to dehydrofluorination of (3A) and (3B) (R = Ac) by traces of sodium hydroxide in the reaction medium.

An additional difluorocarbene adduct which has been isolated in trace amounts in series A is a tris-adduct which on the basis of the limited spectral evidence available is apparently (5A) {m.p. 133—135°; $[\alpha]_D$ − 22°; ν_{max} 1780 cm^{-1}; ^{1}H n.m.r. 1·06 (18-H), 2·10 (20-acetate); m.s. *m/e* 502 (M^+)}.

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[1] For previous parts in the series see P. Crabbé, R. Grezemkovsky, and L. H. Knox, *Bull. Soc. chim. France*, 1968, 789; P. Crabbé, P. Anderson, and E. Velarde, *J. Amer. Chem. Soc.*, 1968, **90**, 2998, and reference 2.

[2] P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, J. Murphy, and E. Velarde, *J. Amer. Chem. Soc.*, 1968, **90**, 3888.

[3] W. M. Wagner, *Proc. Chem. Soc.*, 1959, 229; J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *ibid.*, 1960, 81.

[4] Intensities were measured on a Picker four-circle automatic diffractometer. A total of 2960 unique reflections were scanned by the use of the 2θ—θ technique. The structure was solved by the heavy-atom method and the positional and anisotropic temperature parameters were refined by block-diagonal least-squares to a final reliability factor of 6·7%. Full details of the *X*-ray work will be published in *Acta Cryst.*