Tetrahedron. Vol. 25. pp. 1219 to 1239. Pergamon Press 1969. Printed in Great Britain

THE METHYLENATION OF UNSATURATED KETONES—PART VII[1]

ADDITION OF DIFLUOROMETHYLENE TO MONO AND POLYUNSATURATED KETOSTEROIDS[2]

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(*Received in USA* 23 *September* 1968; *Received in the UK for publication* 14 *October* 1968)

Abstract—Reaction of $\Delta^{4,6}$- and $\Delta^{1,4,6}$-3-keto-steroids (with or without a 6-chloro substituent) with difluoromethylene generated by thermal decarboxylation of sodium chlorodifluoroacetate in boiling diglyme yields the 6α,7α-difluoromethylene-Δ^4- and $\Delta^{1,4}$-3-ketones respectively as principal products. Under the same conditions Δ^1-3-ketones and Δ^{16}-20-ketones give the corresponding α-difluoromethylene ketones in moderate yield. Similar addition to 19-nor-$\Delta^{4,6}$-3-ketones produced both 6α,7α and 6β,7β-difluoromethylene adducts. The presence of a 9α-fluoro substituent severely impedes CF_2 addition to the 6,7-double bond of a $\Delta^{4,6}$-3-ketosteroid. Difluoromethylenation of this system was effected in boiling triglyme, the isomeric 6α,7α and 6β,7β-adducts being obtained in roughly equal amounts. A number of by-products arising from attack of CF_2 on the carbonyl oxygen of the unsaturated ketone were isolated from these reactions. The stereochemistry of the various adducts was elucidated by chemical and spectroscopic methods. A route to 7α-difluoromethyl-Δ^4-3-ketosteroids is also described.

INTEREST in the chemistry of carbene and carbenoid species has continued at a high level in the years since Doering's classical investigations on dichlorocarbene were reported in 1954.[4] This can be attributed largely to the unusual reactivity of these electron-deficient species which attack a diverse variety of functional groups and centres of unsaturation in organic compounds.[5] In the area of organic synthesis, carbenes have been utilized very effectively from the construction of cyclopropane ring systems.[5] Despite the wealth of experimental data which has accumulated on the latter topic during the last decade, it is pertinent to note that only a very limited number of examples of carbene additions to the double bond of unsaturated carbonyl systems have been observed. While the present investigation was in progress, Becher and Loewenthal[6] reported a novel α-cyclopropyl ketone synthesis by the thermal fragmentation of a diazoketone with intramolecular addition of the resultant α-keto-carbene to a cyclohexenone system. Shortly thereafter, Seyferth *et al.* described an efficient route to α-dichlorocyclopropyl carbonyl compounds by reaction of a series of aliphatic α,β-unsaturated ketones, esters, etc, with phenyl(trichloromethyl) mercury.[7] The first examples of the synthesis of α-difluorocyclopropyl ketones by the addition of difluorocarbene to a series of steroidal enones and dienones were announced two years ago.[8] The present contribution provides a detailed account of the latter investigations and, in addition, describes further developments in this area relating to the steric requirements for difluoromethylenation and the stereochemistry of the products.

Difluorocyclopropanes are conveniently prepared by the reaction of olefins with

TABLE 1.

Steroid	ClF_2CCO_2Na equiv.	Time (hr)	Yield (%)	m.p. °C
17α-Acetoxy-6β-chloro-6α,7α-difluoromethylene-pregna-1,4-diene-3,20-dione (**2a**)	20	1[a]	55[b]	221–223[c]
17α-Acetoxy-6β-chloro-6α,7α-difluoromethylene-pregn-4-ene-3,20-dione (**2b**)	10	1·5[a]	74[b]	200–203[c]
17α-Acetoxy-6α,7α-difluoromethylenepregn-4-ene-3,20-dione (**2c**)	25	1[a]	40[b]	228–231[c]
17α-Acetoxy-6α,7α-difluoromethylenepregna-1,4-diene-3,20-dione (**2d**)[e]	16	0·5[a]	65[f]	190–191[c]
17β-Hydroxy-6α,7α-difluoromethylenandrost-4-en-3-one (**34**)	15	0·5[a]	25[g,b]	229–232[h]
17α,20:20,21-Bismethylenedioxy-9α-fluoro-11β-hydroxy-16α-methyl-6α,7α-difluoromethylenepregn-4-en-3-one (**4**)	120	1·5[d]	16[g,f]	300–303[c]
17α,20:20,21-Bismethylenedioxy-9α-fluoro-11β-hydroxy-16α-methyl-6β,7β-difluoromethylenepregn-4-en-3-one (**5**)	120	1·5[d]	19[g,f]	amorphous
6α,7α-Difluoromethylenestr-4-ene-3,17-dione (**10**)	95	1[a]	20[f,f]	143–144[i]
6β,7β-Difluoromethylenestr-4-ene-3,17-dione (**11**)	95	1[a]	7[f,f]	168–169[i]
17β-Acetoxy-1α,2α-difluoromethylen-5α-androstan-3-one (**20a**)	10	1[a]	44[b]	147–149[k]
17α,20:20,21-Bismethylenedioxy-1α,2α-difluoromethylene-5α-pregnan-3-one (**20b**)	51	9[a]	42[b]	159–160[m]
3β-Acetoxy-16α,17α-difluoromethylene-5β-pregnan-20-one (**22**)	62	2·5[a]	24[n,f]	193–194°

[a] Reaction carried out in boiling diglyme.
[b] Product purified by alumina chromatography.
[c] Crystallized from acetone–hexane.
[d] Spectrum determined in methanol.
[e] Experiment performed by Dr. A. Van Horn.
[f] Product purified by TLC.
[g] Crude product saponified by dilute sodium methoxide in methanol.
[h] Crystallized from methanol.

"difluorocarbene", in turn generated by the thermal decarboxylation of sodium chlorodifluoroacetate in aprotic solvents such as diglyme.[9] The method has been used with success to synthesize steroidal difluorocyclopropanes from monoene and diene precursors, the methylenation reaction being conducted by the portionwise addition of an excess of dry salt to a diglyme solution of the substrate at temperatures between 120 and 150°.[10]

The present investigation was initiated to explore the possibility of utilizing the sodium chlorodifluoroacetate thermolysis procedure for the synthesis of difluorocyclopropylketones from steroidal enone and dienones. Conjugated carbonyl systems appeared *a priori* to be relatively poor substrates for attack by electrophilic difluorocarbene species since the nucleophilic character of the enone double bond is considerably reduced by electron delocalization with the carbonyl group.[11] Nevertheless, certain electrophilies such as peracids are known to react with the electron deficient double bonds of enone and dienone systems[11,12] and in the light of these findings, a systematic investigation was undertaken to determine the fate of various α,β- and polyunsaturated ketosteroids after exposure to a large excess of "difluorocarbene"

DIFLUOROMETHYLENE ADDUCTS

$[\alpha]_D$ deg	λ_{max}(log ε) mμ	NMR 18-H 19-H ppm	Formula	Required C	Required H	Required F	Found C	Found H	Found F
−116	245 (4·24)[d]	0·73 1·38	$C_{24}H_{27}O_4ClF_2$	63·63	6·01	8·40	63·74	6·02	8·84
−27	247 (4·02)	0·71 1·27	$C_{24}H_{29}O_4ClF_2$	63·34	6·39	8·36	63·45	6·51	8·06
+61	246 (4·18)	0·70 1·16	$C_{24}H_{30}O_4F_2$	68·49	7·19	9·05	68·68	7·19	9·00
−34	243 (4·20)	0·73 1·27	$C_{24}H_{28}O_4F_2$	68·88	6·74	9·08	68·69	6·77	8·89
+118	246 (4·14)	0·82 1·14	$C_{20}H_{26}O_2F_2$	71·40	7·79	11·30	71·68	7·75	11·80
+10[k]	243 (4·09)[d]	0·90 1·50	$C_{25}H_{31}O_6F_3$	61·96	6·45	—	61·83	6·13	—
−153[k]	251 (4·06)[d]	0·90 1·44 (d, J_{HF}2·5 cps)	$C_{25}H_{31}O_6F_3$	61·96	6·45	—	62·10	6·52	—
+149	247 (4·21)	0·94 —	$C_{19}H_{22}O_2F_2$	71·22	6·92	11·86	71·29	7·13	12·03
−101	248 (4·25)	0·93 —	$C_{19}H_{22}O_2F_2$	71·22	6·92	11·86	71·41	7·12	12·19
+67	—	0·82 1·07	$C_{22}H_{30}O_3F_2$	69·45	7·95	9·99	69·09	7·91	10·04
−21	—	0·85 1·07	$C_{24}H_{32}O_5F_2$	65·73	7·36	8·67	65·86	7·64	8·70
+73	—	0·82 0·98	$C_{24}H_{34}O_3F_2$	70·60	8·33	9·31	70·83	8·36	9·04

[i] Reaction carried out in boiling triglyme.
[j] Product purified by silica gel chromatography.
[k] Rotation determined in dioxane.
[l] Crystallized from acetone–heptane.
[m] Crystallized from hexane.
[n] Unreacted starting material removed by treating crude product with Girard's reagent P.
[o] Crystallized from ether–hexane.

under a variety of experimental conditions. Additionally, the synthesis of steroidal difluorocyclopropylketones appeared to be an attractive goal in view of the clinical importance of many fluorinated steroids.[13]

When 17α-acetoxy-6-chloropregna-1,4,6-triene-3,20-dione (**1a**)[14] was allowed to react with an excess of sodium chlorodifluoroacetate according to the above procedure,[10] only starting material was recovered in high yield. Various modifications of this method, conducted in diglyme at 120–150°, also failed to promote difluoromethylenation of **1a** as judged by careful scrutiny of the reaction products by spectroscopic and thin-layer chromatographic techniques. However, portionwise, addition of the dry salt to a boiling solution of **1a** in diglyme produced a gradual reduction in the characteristic UV maxima at 228, 269, and 295 mμ of the starting **1a** with formation of a new broad maximum at 245 mμ, indicating that CF_2 addition had taken place on the 6,7-double bond. Purification of the reaction mixture by chromatography afforded in 40% yield 17α-acetoxy-6β-chloro-6α,7α-difluoromethylenepregna-1,4-diene-3,20-dione (**2a**) whose elemental analysis and spectroscopic properties (Table 1) were in accord with the assigned structure.

The methylenation procedure was improved further by the simple expedient of adding a solution of the salt dissolved in hot or cold diglyme to a diglyme solution of the steroid held at reflux. This modification allowed better control of the reaction and gave a higher yield of the adduct. All difluoromethylenation reactions described in the sequel were conducted in this manner.

17α-Acetoxy-6-chloropregna-4,6-diene-3,20-dione (**1b**),[14] 17α-acetoxypregna-4.6-diene-3,20-dione (**1c**),[15] and 17α-acetoxypregna-1,4,6-triene-3,20-dione (**1d**)[16] were then converted into their corresponding 6α,7α-difluoromethylene adducts (**2b**; 74%; **2c**; 40% and **2d**; 65%) by treatment with an excess of sodium chlorodifluoroacetate in boiling diglyme. These experiments show that the 1,2-double bond and the chlorine substituent are not required for difluoromethylenation of the $\Delta^{4,6}$-3-ketone system. Also noteworthy is the fact that CF_2 addition occurs preferentially on the double bond most distant from the carbonyl group. In this respect difluoromethylenation parallels the reactions of $\Delta^{4,6}$-3-ketosteroids with peracids which occur exclusively at the 6,7-double bond.[12b,c] Additional examples of difluoromethylenation of various unsaturated ketosteroids are described in the sequel and illustrate the scope and limitations of this reaction (Table 1 and Experimental).

Examination of the chemical and spectral evidence available at this stage allows only a tentative prediction to be made of the sterochemistry of the CF_2 addition products. The formation of 6α,7α-adducts is clearly favored on steric grounds, since perpendicular approach of CF_2 or related species to the plane of the 6,7-double bond from the β face is markedly restricted by the axial C_8–βH and the C-10 Me group, whereas only the more remote C_9–αH is encountered in α-face attack. Experimental support for this hypothesis is provided by the previously cited epoxidation reaction which takes place predominantly from the α-side of the molecule, thereby yielding the 6α,7α-epoxides.[12b,c] On the other hand, it should be noted that CF_2 attacks the double bond of steroidal 5-enes from the β-face exclusively.[10]

Inspection of the NMR spectra of the 6,7-difluoromethylene adducts reveals in all cases sharp 3-H singlets for the C-19 angular Me proton resonances (Table 1) which is taken to indicate the 6α,7α-stereochemistry. Since long range H_{19}–F coupling is observed in 2β,3β- and 5β,6β-difluoromethylenesteroids,[10] a 6β,7β–CF_2 adduct would be expected to show splitting of the 19-H signal by long-range coupling with fluorine. Indeed, inspection of the Dreiding model of a 6β,7β-difluoromethylene steroid reveals that the 19-protons and the oppositely disposed β-fluorine atom are ideally positioned so as to fulfill the geometrical requirements for maximal long-range H–F coupling as defined by the converging vector rule.[17]

In order to provide rigorous experimental support for the above interpretations, 17α,20:20,21-bismethylenedioxy-9α-fluoro-11β-hydroxy-16α-methylpregna-4,6-dien-3-one (**3**) and 17β-acetoxyestra-4,6-dien-3-one (**6**)[18] were allowed to react with difluorocarbene with the expectation that these substrates would be more susceptible to β-face attack than the previous examples. Indeed, the presence of the 9α-fluorine in **3** should restrict the approach of CF_2 or related species from the α face, whereas in the case of the latter 19-nordienone (**6**) β-face attack should be facilitated since hydrogen has replaced the C_{10} β-Me group. These predictions were substantiated by the following experiments. Treatment of the 9α-fluoro-dienone (**3**) with 60 equivalents of salt as before gave back the starting material in high yield with no evidence of difluoromethylenation. The desired addition was effected, however, by conducting

the reaction in the higher boiling triglyme (b.p. 216°), a total of 120 equivalents of salt being required to give a crude product devoid of UV absorption at 280 mμ. Brief treatment of the resulting mixture with sodium methoxide followed by extensive chromatographic purification afforded pure samples of the 6α,7α- and 6β,7β-adducts (**4** and **5**) in 16% and 19% yields, respectively, in addition to a mixed fraction (ca. 20%) containing roughly equal amounts of the two isomers. The NMR spectra of these key compounds show the 19-H resonance of the 6β,7β adduct as a doublet centred at 1·44 ppm, J_{HF} = 2·5 c/s, which arises from long-range coupling of the angular Me protons with fluorine on the β-oriented cyclopropane ring.[17] As in the previous examples, (Tables 1 and 3) the 19-H resonance of the α-adduct appears as a sharp singlet centered in the case of (4) at 1·50 ppm. Thus, the presence of the 9α-fluoro substituent dramatically alters both the rate and direction of CF_2 addition to the $\Delta^{4,6}$-3-ketone system. Several other C-10 methylated 6β,7β-difluoromethylene adducts (9α-H series) were obtained during the course of this investigation, and these compounds exhibit the same splitting pattern (J_{HF} = 1·5–3·5 c/s) for the 19-protons (Tables 1, 3 and Experimental). Thus, in the C-10 methylated series NMR spectroscopy provides an effective and unambiguous method for the sterochemical differentiation of isomeric pairs of 6,7-difluoromethylene-Δ^4-3-ketones and for the determination of the stereochemistry of a single adduct.

The addition of CF_2 to the 19-norsteroid 17β-acetoxyestra-4,6-dien-3-one (**6**) (diglyme) afforded a TLC homogeneous product which could not be induced to crystallize. Alkaline hydrolysis followed by benzoylation of the TLC homogeneous non-crystalline alcohol fraction and purification on preparative plates furnished 17β-benzoyloxy-6α,7α-difluoromethylenestr-4-en-3-one (**7**) and the isomeric 6β,7β-adduct (**8**) in 17% and 14% yields respectively (based on the starting dienone). Difluoromethylenation of estra-4,6-diene-3,17-dione (**9**)[19] also resulted in the formation of significant quantities of the 6β,7β-adduct, (**11**; 7%) although in contrast to the preceding experiment the product ratio was roughly 3:1 in favor of the 6α,7α-adduct, (**10**; 20%).

The stereochemistry of the 19-noradducts was established as follows. The isomeric 6,7-difluoromethylenestr-4-ene-3,17-diones (**10** and **11**) were reduced by lithium tri-t-butoxyaluminum hydride, and the resulting 3,17-diols oxidized without prior purification by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[20] in dioxane to the respective 6,7-difluoromethylene-19-nortestosterones (**12** and **13**). The rotatory dispersion curves of these products showed notable differences, and of greater significance the curve of the 17-hydroxy-6,7-difluoromethylene-Δ^4-3-ketone derived from the predominant adduct was virtually identical with the spectrum of 17β-hydroxy-6α,7α-difluoromethylenandrost-4-en-3-one (Fig. 1), a substance of established sterochemistry (NMR data Tables 1 and 3). It follows that the difluorocyclopropane ring of the predominant 19-norandrostenedione adduct (**10**) and its derived 17-alcohol (**12**) has the 6α,7α-stereochemistry whereas the adduct (**11**) produced in lesser quantity and its 17β-alcohol (**13**) belong to the 6β,7β-difluoromethylene series. Treatment of the 17β-hydroxy-6α,7α-difluoromethylene-Δ^4-3-ketone (**12**) and the 6β,7β-isomer (**13**) with benzoyl chloride in pyridine produced the respective 17-benzoates (**7** and **8**), thus permitting the identification of the isomeric pairs of benzoates obtained from difluoromethylenation of 17β-acetoxyestra-4,6-diene-3-one (**6**).

A second stereochemical correlation was achieved in the 19-nor series by difluoro-

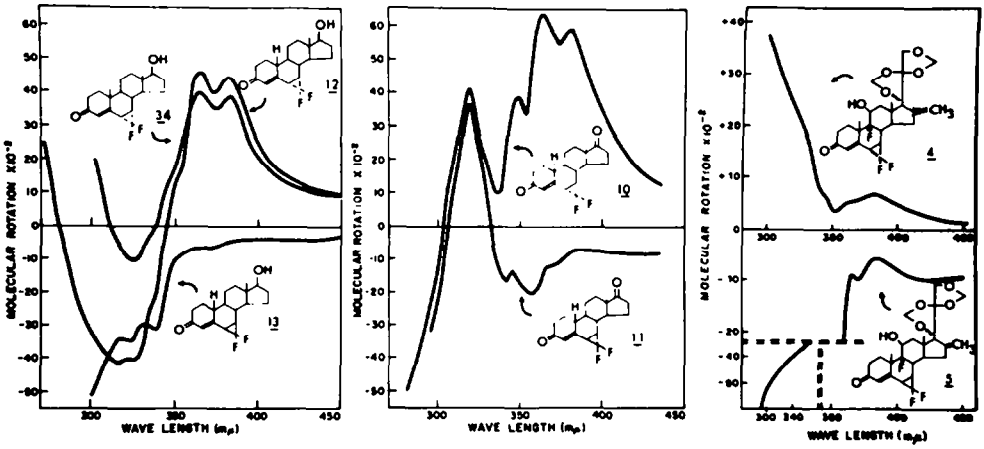


FIG. 1 Rotatory dispersion curves (dioxane solution).

methylenation of 19-acetoxyandrosta-4,6-diene-3,17-dione (**14**) which was expected to provide an excess of the 6α,7α-CF_2 adduct. Indeed, chromatographic purification of the crude reaction product afforded 19-acetoxy-6α,7α-difluoromethylenandrost-4-ene-3,17-dione (**15**; 40%) and 19-hydroxy-6α,7α-difluoromethylenandrost-4-ene-3,17-dione (**16**; 14·5%; convertible into **15** by acetylation) in addition to an oily fraction (90% purity estimated by TLC) presumed to be the 6β,7β-adduct (**17**; 5%).† Oxidation of the 19-hydroxy adduct (**16**) with chromium trioxide gave the 19-carboxylic acid which on acid catalysed decarboxylation afforded 6α,7α-difluoromethylenestr-4-ene-3,17-dione (**10**) identical with the 6α,7α-adduct obtained from the difluoromethylenation of estra-4,6-diene-3,17-dione.

The foregoing experiments show that difluoromethylene adds to $\Delta^{4,6}$-3-keto-androstanes and pregnanes (9α-H) predominantly from the α- face giving the 6α,7α-adducts. Although 6β,7β-isomers are undoubtedly formed in small amounts in these reactions, the presence of such adducts was actually confirmed in only one experiment. Preference for α-addition within this series appears to be governed principally by steric factors, since CF_2 additions to $\Delta^{4,6}$-3-ketones bearing a 9α-fluorine or lacking the C-19 angular Me group led to significant increases in the yield of 6β,7β adducts.

The difluoromethylenation reactions described thus far were carried out on substrates with linear dienone systems, with addition of CF_2 taking place on the more electron-rich γ,δ-double bond. However, addition can also be achieved with simple α,β-unsaturated keto steroids. Thus 17β-acetoxy-5α-androst-1-en-3-one (**19a**)[21] and 17α,20:20, 21-bismethylenedioxy-5α-pregn-1-en-3-one (**19b**)‡ were converted into the corresponding 1α,2α-difluoromethylene compounds (**20a**; 44%) and

† The NMR spectrum of this product revealed the 19-protons as a broadened AB pattern.

‡ We wish to thank Mr. I. Jamieson for preparing this substance.

(**20b**; 42%) when treated with sodium chlorodifluoroacetate by the standard procedure. Similarly, 3β-acetoxy-5β-pregn-16-en-20-one (**21**) gave the 16α,17α-difluoromethylene-20-ketopregnane (**22**) in 24% yield. The evidence supporting the 1α,2α-stereochemistry allocated to the adducts (**20a** and **20b**) is based on the absence of observable splitting of the 19-H resonances in their respective NMR spectra.[17] Molecular rotation differences calculated for **20a** and several 1,2-epoxy and 1,2-methylene dihydrotestosterones also are qualitatively in agreement with this conclusion, the 1α,2α-substituted compounds showing somewhat more positive $\Delta[M]_D$ values than the 1β,2β-oxide derivative (Table 2).

TABLE 2. MOLECULAR ROTATION DATA FOR 1α,2α-METHYLENE-,1α,2α-DIFLUOROMETHYLENE-,1α,2α- AND 1β,2β-EPOXYDIHYDROTESTOSTERONE DERIVATIVES

Steroid	$[\alpha]_D^{CHCl_3}$	$[M]_D$	$\Delta[M]_D$
17β-Acetoxy-5α-androstan-3-one (i)[a]	+26°	+86°	—
17β-Acetoxy-1α,2α-oxido-5α-androstan-3-one (ii)[b]	+91°	+315°	(ii)–(i) +229°
17β-Acetoxy-1β,2β-oxido-5α-androstan-3-one (iii)[c]	+38·5°	+133°	(iii)–(i) +47°
17β-Acetoxy-1α,2α-methylene-5α-androstan-3-one (iv)[d]	+54°	+186°	(iv)–(i) +100°
17β-Acetoxy-1α,2α-difluoromethylene-5α-androstan-3-one (**20a**)	+70°	+254°	(20a)–(i) +169°

[a] C. Djerassi, *J. Org. Chem.* **12**, 824 (1947).
[b] C. Djerassi, D. H. Williams and B. Berkoz, *Ibid.* **27**, 2205 (1962).
[c] R. E. Counsell and P. D. Klimstra, *J. Med. Pharm. Chem.* **5**, 477 (1962).
[d] R. Wiechert and E. Kaspar, *Chem. Ber.* **93**, 1710 (1960).

The NMR spectrum of the 16α,17α-difluoromethylene pregnane adduct (**22**) appears to be consistent with the assigned structure, although the 18-H resonance signal is visibly broadened.† A 16β,17β-adduct would be expected to show 18-H,F coupling comparable to the $J_{H_{18},F}$ = 1·5–3·0 c/s exhibited by 6β,7β-difluoromethylene adducts.

Two important side reactions were frequently encountered in CF_2 additions to unsaturated ketosteroids. Unprotected OH groups were transformed in high yield into the corresponding chlorodifluoroacetates presumably by the action of chlorodifluoroacetyl chloride or chlorodifluoroacetic anhydride generated *in situ* during the course of the reaction.‡ For example, difluoromethylenation of 11β,21-dihydroxy-16α-methylpregn-4-ene-3,20-dione 21-acetate (**23**) afforded the isomeric 6,7-difluoromethylene-11-chlorodifluoroacetates (**24a**; 27% and **25a**; 6%) as the initial products. Since these diacylated derivatives were converted into the parent diols (**24b** and **25b**) in high yield by mild alkaline hydrolysis, the chlorodifluoroacetylation reaction had a negligible effect on the overall yield of the required adducts.

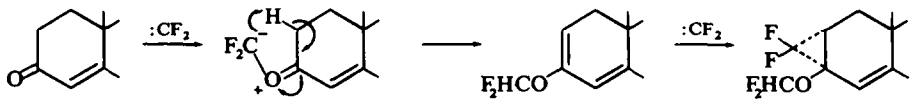
Attack of difluoromethylene on the carbonyl oxygen of the unsaturated ketone constituted a more serious preparative problem. This reaction gave rise to varying

† The half-band width of this signal calculated from a 100 c/s sweep width scan was 2 c/s. The same measurement revealed $W_{\frac{1}{2}}$ = 1 c/s for the 19-H signal.

‡ Trichloroacetic anhydride has been identified as a product of the thermal decarboxylation of sodium trichloroacetate.[22]

amounts of the novel 2α,3α-difluoromethylene-3-difluoromethylethers presumably by the following process:†

SCHEME 1



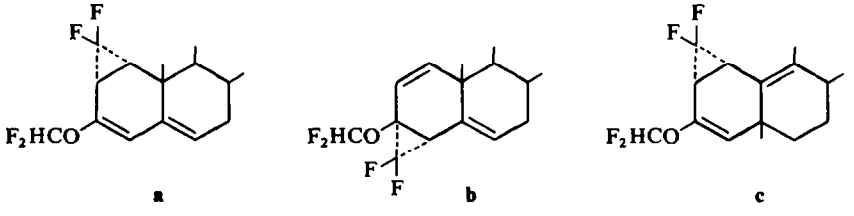
Thus, CF_2 addition to the $\Delta^{4,6}$-3-ketones (**14** and **23**) gave as the side products the 2α,3α-difluoromethylene-3β-difluoromethylethers (**18**) and (**26a**; characterized as the diol **26b**) in 21% and 2·7% yields respectively.‡ The constitutions of these adducts follow from their elemental analyses and NMR spectra. The latter determination revealed in each case the low field proton of the difluoromethylether function as a pair of doublets due to geminal HF coupling and a singlet for the 19-protons. Difluoromethylether formation was not observed in the CF_2 additions to the $\Delta^{1,4,6}$-3-ketone system.

In contrast to the difluoromethylenation of 17α-acetoxypregna-1,4,6-triene-3,20-dione (**1d**) which yields a single adduct (**2d**) the addition of CF_2 (20 equiv. salt/triglyme) to the cross-conjugated dienone 17β-acetoxyandrosta-1,4-dien-3-one (**27**)[25] afforded a complex mixture of products which was partially resolved by alumina chromatography into an unidentified difluoromethylether fraction (30%),§ recovered starting material (20%) and the aromatic compound **28a** or **28b** (ca. 2·5%). The constitution of the aromatic product was deduced by mass spectral analysis and by its NMR spectrum which shows a 3-H singlet at 2·17 ppm (aromatic Me group) and a partially resolved unsymmetrical 2-H multiplet consisting of two pairs of overlapping quartets centered at 6·83 ppm attributable to the resonance of the C-2 and C-3 aromatic protons.‖ The genesis of this compound by a classical dienone-phenol type rearrange-

† A similar mechanism has been preposed to account for the products resulting from attack of ethoxycarbonylcarbene on the carbonyl group of cyclohexanone.[23]

‡ For additional examples of difluoromethylether formation during the difluoromethylenation of other unsaturated ketosteroids, see ref. 24.

§ The elemental analysis and mass spectrum of a purified sample (homog. by TLC and GLC) of this fraction indicated four F atoms and the NMR spectrum confirmed the presence of an $OCHF_2$ group (1-H triplet centered at 6·28 ppm, J_{HF} = 74 c/s). However, the presence of only one olefinic proton (singlet at 4·82 ppm) excludes simple adducts of type *a* and *b* and suggests a rearranged structure such as *c*.



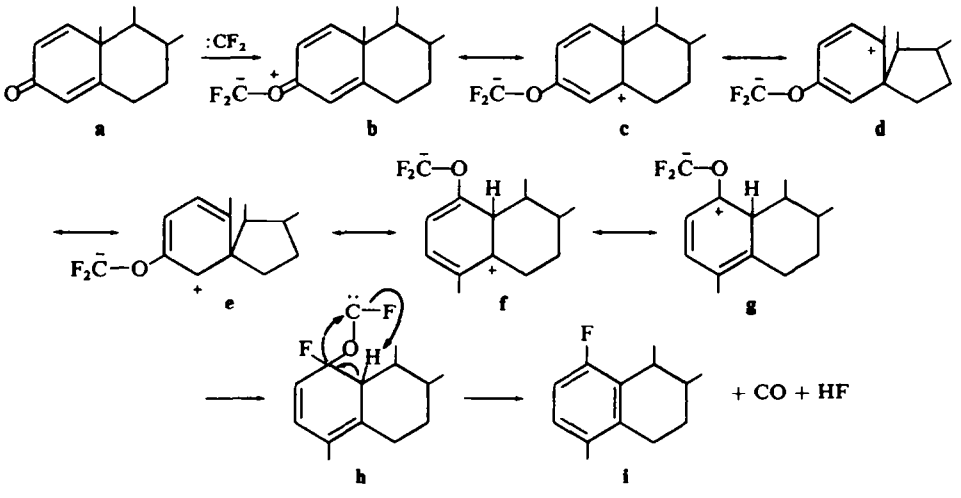
This aspect of the problem was not pursued further since a crystalline sample of the difluoromethylether (m.p. 80–95°) was shown to be a two component mixture by ^{19}F NMR.

‖ The shape of this multiplet is very similar to the resonance pattern exhibited by the aromatic protons of 1-fluoro-4,17α-dimethylestra-1,3,5(10)-trien-17β-ol acetate.

This sample was kindly provided by Dr. D. F. Morrow of Parke Davis and Co.[26]

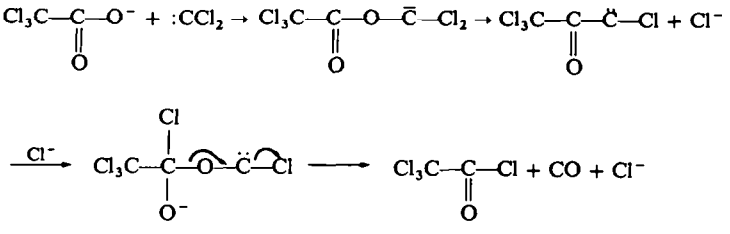
ment[27] would be expected to produce the 1-fluoro-4-methylestra-1,3,5(10)-triene (**28a**), although the alternate structure **28b** cannot be excluded on the basis of the spectral evidence. A plausible mechanism which accounts for the formation of **28a** is shown in Scheme 2 below:

SCHEME 2



The rearrangement of the zwitterion *g* to the carbene *h* is analogous to the transformation of the anion of dichloromethyl trichloroacetate to the corresponding acid chloride (Scheme 3), which presumably takes place by attack of chloride ion on the carbonyl group of the intermediate carbene followed by loss of carbon monoxide and the second Cl atom.[23]

SCHEME 3



The effect of blocking the 3-carbonyl group of steroidal dienones with a view to reducing by-product formation and/or facilitating CF_2 addition to the resulting olefins was briefly investigated with the cycloethylenedioxy and methoxime protecting groups. However, a large excess of difluoromethylene generated from the salt in triglyme at 145° failed to attack either double bond of 3-cycloethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxypregna-4,6-dien-20-one 16,17-acetonide 21-acetate (**29**). The only product isolated from this reaction after workup (dilute methanolic

sodium methoxide hydrolysis followed by acetylation and chromatography) proved to be the 3-(β-acetoxyethoxy)-2α,3α-difluoromethylene-$\Delta^{4,6}$-compound (**30**; 15%) as deduced from analytical and spectral data. Use of higher temperatures for this reaction led to intractable mixtures. The resulting product arises by attack of difluoromethylene on the electron rich 2,3-double bond of the intermediate 3-(β-hydroxyethoxy) pregna-2,4,6-triene in turn formed by pyrolytic cleavage of the ketal C—O bond. The methoxime approach was equally unsuccessful; reaction of 17β-acetoxyandrosta-1,4-dien-3-one methoxime (**31**) with 3 equiv of the salt in boiling diglyme afforded only aromatic products. Chromatographic purification gave in low yield the known 4-methylestra-1,3,5(10)-trien-17β-ol acetate (**32**)[28] and a second product for which the chlorodifluoroacetylamino-estr-1,3,5(10)-triene structure (**33a** or **b**) is suggested from spectral and analytical data.

The 6α,7α-difluoromethylene-Δ^4-3-ketones were useful starting materials for the synthesis of hitherto unknown 7α-difluoromethyl steroids. Thus, treatment of 6α,7α-difluoromethylene-17β-hydroxyandrost-4-en-3-one (**34**; Table 1) with zinc dust in boiling acetic acid furnished in low yield the 7α-difluoromethyl-Δ^4-3-ketone as the only identifiable product.† This compound shows an UV max. at 242 mμ (log ε 4·16) and the proton of the difluoromethyl group appears in the NMR spectrum as a triplet, centered at 5·85 ppm, $J_{7'H,F} = 56$ c/s, broadened by coupling with the 7-H.

Reductive cleavage of 6,7-difluoromethylene-Δ^4-3-ketones may also occur at the C_6—C_7 bond. This was observed in the reaction of 19-hydroxy-6α,7α-difluoromethylenandrost-4-ene-3,17-dione (**16**) with zinc–copper couple in boiling ethanol/n-propanol mixture. Purification of the resulting product by preparative TLC afforded 7α-difluoromethyl-19-hydroxyandrost-4-ene-3,17-dione (**35**; 24%) and 7α-fluoro-7β,19-oxido-B-homoandrost-4-ene-3,17-dione (**36**; 13%) which were identified by spectroscopic methods. The NMR spectrum of the latter product reveals the 19-protons as an A/B pattern centered at 3·98 ppm, $J_{AB} = 11$ c/s, and the 6-protons as a broad 2-H singlet centered at 2·97 ppm. The low field arm of the 19-H quartet shows additional splitting, $J = 2$ c/s, due to long-range coupling, presumably with the 9α-H or the 7-fluorine atom. A Dreiding model of the most stable conformation of the ring B bicyclo-[3.2.2]-system present in **36** (non-bonded interactions minimized) shows that the atom chain commencing with the 19-H projecting towards ring A, and terminating the the 9α-H, i.e. H_{19}—C_{19}—C_{10}—C_9—H_9 is held in the coplanar W arrangement, the most suitable disposition of these atoms for maximal 1,5-coupling.[30]

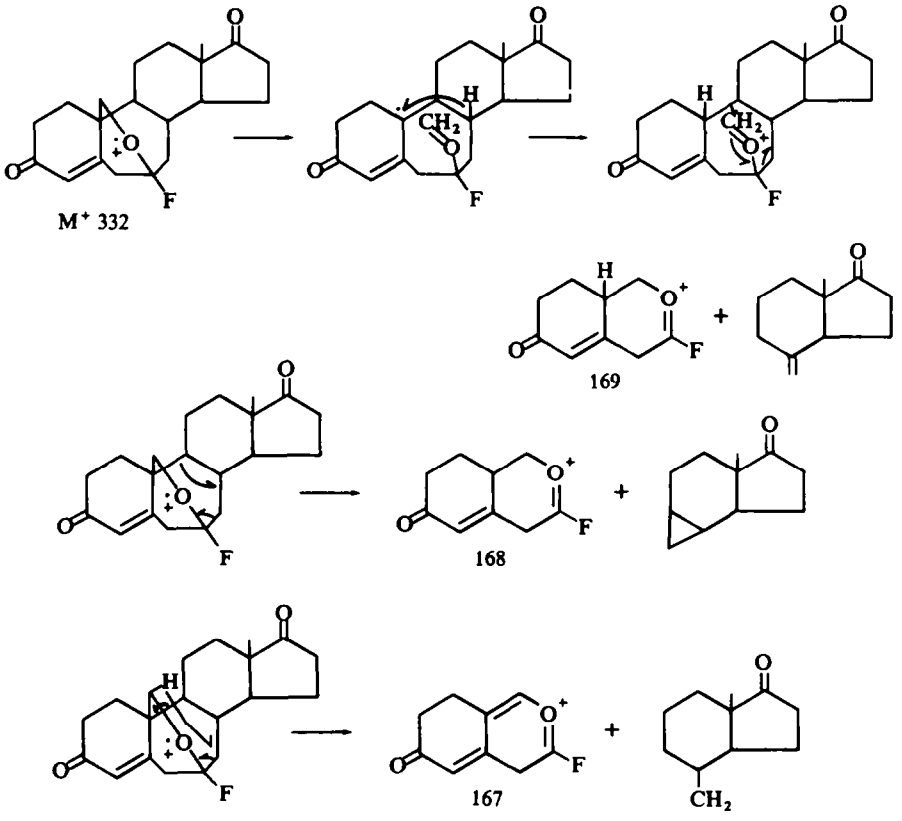
The bridged ring B system can adopt a second conformation which brings a new chain of atoms commencing with the same 19-H and terminating with fluorine, i.e. H_{19}—C_{19}—O—C_7—F into the W arrangement.‡ However, this conformation is energetically less favorable since a strong non-bonded interaction exists between the second 19-H and the 8β-H.

The molecular ion of **36** appears at *m/e* 332 in the mass spectrum; ions are also observed at *m/e* 167, *m/e* 168 and *m/e* 169 which correspond to the loss of the C, D rings by cleavage at C_7—C_{7a} and C_9—C_{10} as shown in Scheme 4.

† The reductive opening of 17β-acetoxy-6α, 7α-methylenandrost-4-en-3-one to the corresponding 7α-methylenone with zinc dust in acetic acid has been described.[29]

‡ Long range proton–proton coupling across the oxygen atoms of 1,3-dioxanes has been reported.[31]

SCHEME 4



Formation of the fluoro-oxide (**36**) is depicted as proceeding *via* the enolate (*b*: see Scheme 5) protonation and conjugation to the 7-fluoro dienone (*c*), acetate exchange (*d*), and intramolecular 1,6-addition of the 19-OH group (*e*). (Scheme 5).

SCHEME 5

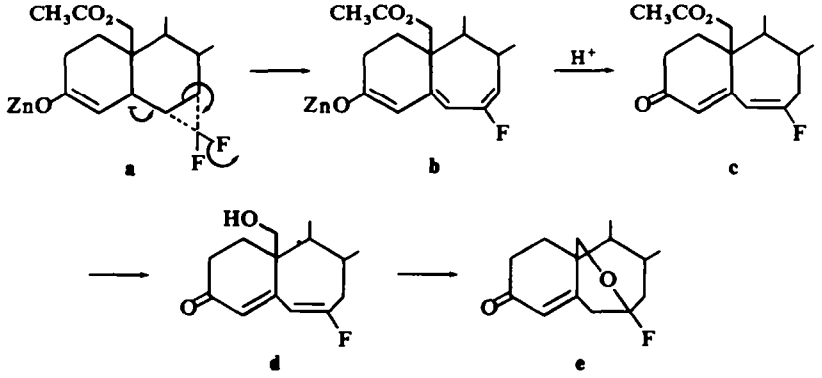


TABLE 3. EFFECT OF 6,7-DIFLUOROMETHYLENE GROUP ON 19-H AND 4-H RESONANCES

Steroid	δ ppm		δ ppm Parent enone		Chemical shift effect of 6,7 difluorocyclopropyl substituent (ppm)	
	19-H	4-H	19-H	4-H	19-H	4-H
6α,7α-*difluoromethylene*-17β-hydroxyandrost-4-en-3-one (**34**)	1·14	5·98	1·19	5·73	−0·05	+0·25
17α,20:20,21-bismethylenedioxy-6α,7α-*difluoromethylene*-11β-hydroxypregn-4-en-3-one (**38**)[a]	1·42	5·90	1·43	5·68	−0·01	+0·22
17α-acetoxy-6α,7α-*difluoromethylene*-pregn-4-en-3,20-dione (**2c**)	1·15	5·98	1·20	5·75	−0·05	+0·23
17α-acetoxy-6β,7β-*difluoromethylene*-pregn-4-en-3,20-dione (**35**)[b] (d, J_{HF} = 1·5 c/s)	1·12	5·97	1·20	5·75	−0·08	+0·22
17α-acetoxy-6α,7α-*difluoromethylene*-pregna-1,4-diene-3,20-dione (**2d**)	1·28	6·33	1·23	6·10	+0·05	+0·23
17α,20:20,21-bismethylenedioxy-6α,7α-*difluoromethylene*-11β-hydroxy-16α-methylpregn-4-en-3-one (**39**)[a]	1·41	5·91	1·44	5·70	−0·03	+0·21
21-acetoxy-6α,7α-*difluoromethylene*-11β-hydroxy-16α-methylpregn-4-ene-3,20-dione (**24c**)	1·41	5·93	1·37	5·60	+0·04	+0·33
21-acetoxy-6β,7β-*difluoromethylene*-11β-hydroxy-16α-methylpregn-4-ene-3,20-dione (**25c**) (d, J_{HF} = 3·0 c/s)	1·36	5·93	1·37	5·60	−0·01	+0·33
17α-acetoxy-6β-chloro-6α,7α-*difluoromethylene*-pregna-1,4-diene-3,20-dione (**2a**)	1·38	6·58	1·52	6·30	−0·14	+0·28
17α-acetoxy-6β-chloro-6α,7α-*difluoromethylene*-pregn-4-ene-3,20-dione (**2b**)	1·27	6·44	1·46	5·88	−0·19	+0·56
6α,7α-*difluoromethylen*-estr-4-ene-3,17-dione (**10**)	—	6·05	—	5·87	—	+0·18
6β,7β-*difluoromethylen*-estr-4-ene-3,17-dione (**11**)	—	6·05	—	5·87	—	+0·18
17β-hydroxy-6α,7α-*difluoromethylen*-estr-4-en-3-one (**12**)	—	6·05	—	5·85	—	+0·20
17β-hydroxy-6β,7β-*difluoromethylen*-estr-4-en-3-one (**13**)	—	6·12	—	5·85	—	+0·27

[a] For the preparation of this compound see Ref. 1.

[b] This compound was prepared by reacting 17α-acetoxypregna-4,6-diene-3,20-dione (1c) with trimethyl-trifluoromethyltin in the presence of sodium iodide.[33] A detailed account of this work will be presented in a forthcoming publication.

The stability of the geminal fluoro-oxide system of **36** compares favorably with the properties of the analogous fluoroglucoside derivatives.[32]

Table 3 lists the 19-H and 4-H chemical shifts of a representative number of 6,7-difluoromethylene steroids as well as the chemical shift effects of the α and β oriented difluoromethylene groups on the 19-H and 4-H resonances. It is apparent that the general variability of the latter values precludes the assignment of adduct stereochemistry on the basis of chemical shift effects. Indeed comparison of the 19-H resonances of the 6α,7α-adducts (**2a–d**; **24c**, **34**, **38** and **39** to the 19-H resonances of the parent steroids reveals chemical shift effects for the difluorocyclopropane ring extending from −0·08 to +0·05 ppm. For the 6β,7β-adducts (**25c** and **35**), the chemical shift effect of the difluorocyclopropane ring on the 19-protons amounts to −0·1 and −0·08 ppm respectively. The presence of the 6,7-difluoromethylene substituent led to a marked downfield shift (≥0·18 ppm) of the 4-H resonance which was without stereochemical implication. In fact, the 4-H resonances of three of four isomeric pairs of adducts listed in the table experienced the same chemical shift effect from the 6α,7α and 6β,7β-difluorocyclopropane rings.†

To establish unambiguously the stereochemistry of the isomeric 6,7-difluoromethylene-19-nor-Δ^4-3-ketones recourse was made to optical rotation and rotatory dispersion measurements. Fig. 1 shows the rotatory dispersion curves of 17β-hydroxy-6α,7α-difluoromethylenandrost-4-en-3-one (**34**) and the 6α,7α-difluoromethylene-19-nor-Δ^4-3-ketones (**10** and **12**). These spectra are characterized by relatively complex positive Cotton effect curves with the peaks in the 365 mμ region attributable to the n–π* transition of the enone chromophore.

The RD curves of the 6β, 7β-difluoromethylene-19-nor-Δ^4-3-ketones (**11** and **13**) are characterized by a series of weak intensity inflections over the 300–400 mμ

TABLE 4. SPECIFIC ROTATIONS FOR ISOMERIC 6,7-DIFLUOROMETHYLENE-Δ^4-3-KETONES

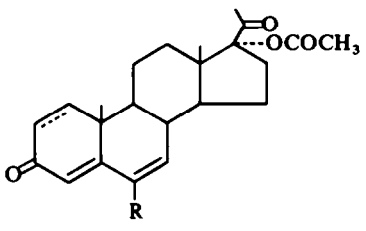
Steroid	$[\alpha]_D$ 6α,7α-CF_2	$[\alpha]_D$ 6β,7β-CF_2
17α,20:20,21-Bismethylenedioxy-9α-fluoro-11β-hydroxy-16α-methyl-6,7-difluoromethylenepregn-4-en-3-one.	+10°(dioxane)	−153°(dioxane)
21-Acetoxy-11β-chlorodifluoroacetoxy-16α-methyl-6,7-difluoro-methylenepregn-4-ene-3,20-dione.	+159°	±0°
11β,21-Dihydroxy-16α-methyl-6,7-difluoromethylenepregn-4-ene-3,20-dione.	+175°	−71°
17β-Benzoyloxy-6,7-difluqromethylenestr-4-en-3-one.	+135°	−65°
6,7-Difluoromethylenestr-4-ene-3,17-dione.	+149°	−101°

spectral region in striking distinction to the well-resolved positive curves of the 6α,7α-difluoromethylene adducts. The prominent maximum at 310 mμ in the curves of the diketones (**10** and **11**) is due to the Cotton effect of the 17-ketone. The 9α-fluoro-6α,7α-difluoromethylene-Δ^4-3-ketone (**4**) and its 6β,7β-isomer (**5**) also have dissimilar RD curves essentially devoid of fine structure. In addition, the intensity of

† These NMR spectral results are in striking contrast to the chemical shift effects of a 6,7-methylene substituent on the 4-H and 19-H resonance. An unsubstituted 6β,7β-methylene group shields the 19-H and deshields the 4-H by roughly 0·11 and 0·27 ppm respectively whereas the corresponding 6α,7α-methylene groups causes shielding of the 19-H by about 0·06 ppm and deshielding of the 4-H by 0·22 ppm.[8c]

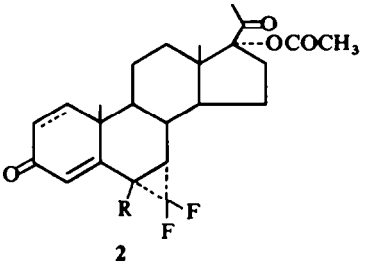
the long-wave length maximum in the curve of the 6α,7α-adduct is strongly diminished relative to the corresponding Cotton effects of other 6α,7α-difluoromethylene-Δ^4-3-ketones.

Isomeric pairs of 6,7-difluoromethylene-Δ^4-3-ketones also exhibit consistent differences in their specific rotations. The results, summarized in Table 4, show that the rotations of the 6α,7α-adducts are strongly dextrorotatory with respect to the 6β,7β-adducts and thus provide additional support for the stereochemical assignments based on rotatory dispersion and NMR data.



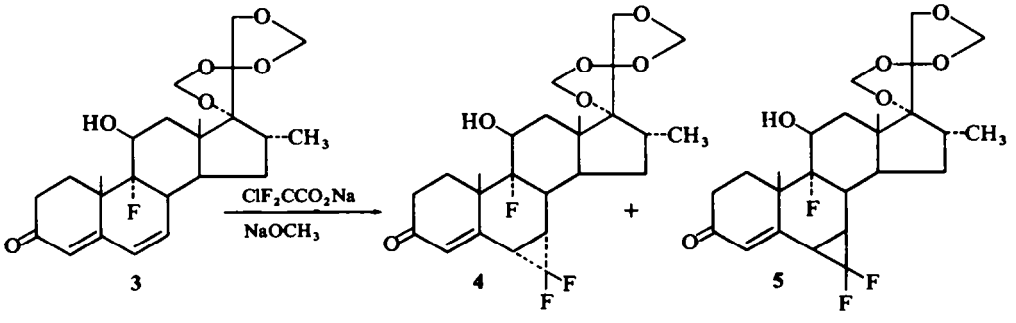
1

a: R = Cl; 1,2-double bond
b: R = Cl; 1,2-dihydro
c: R = H; 1,2-dihydro
d: R = H; 1,2-double bond

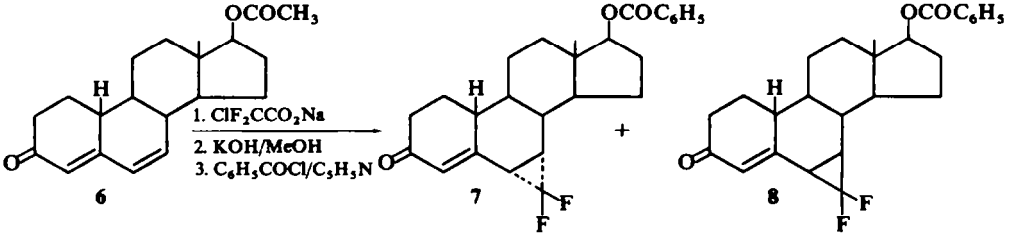


2

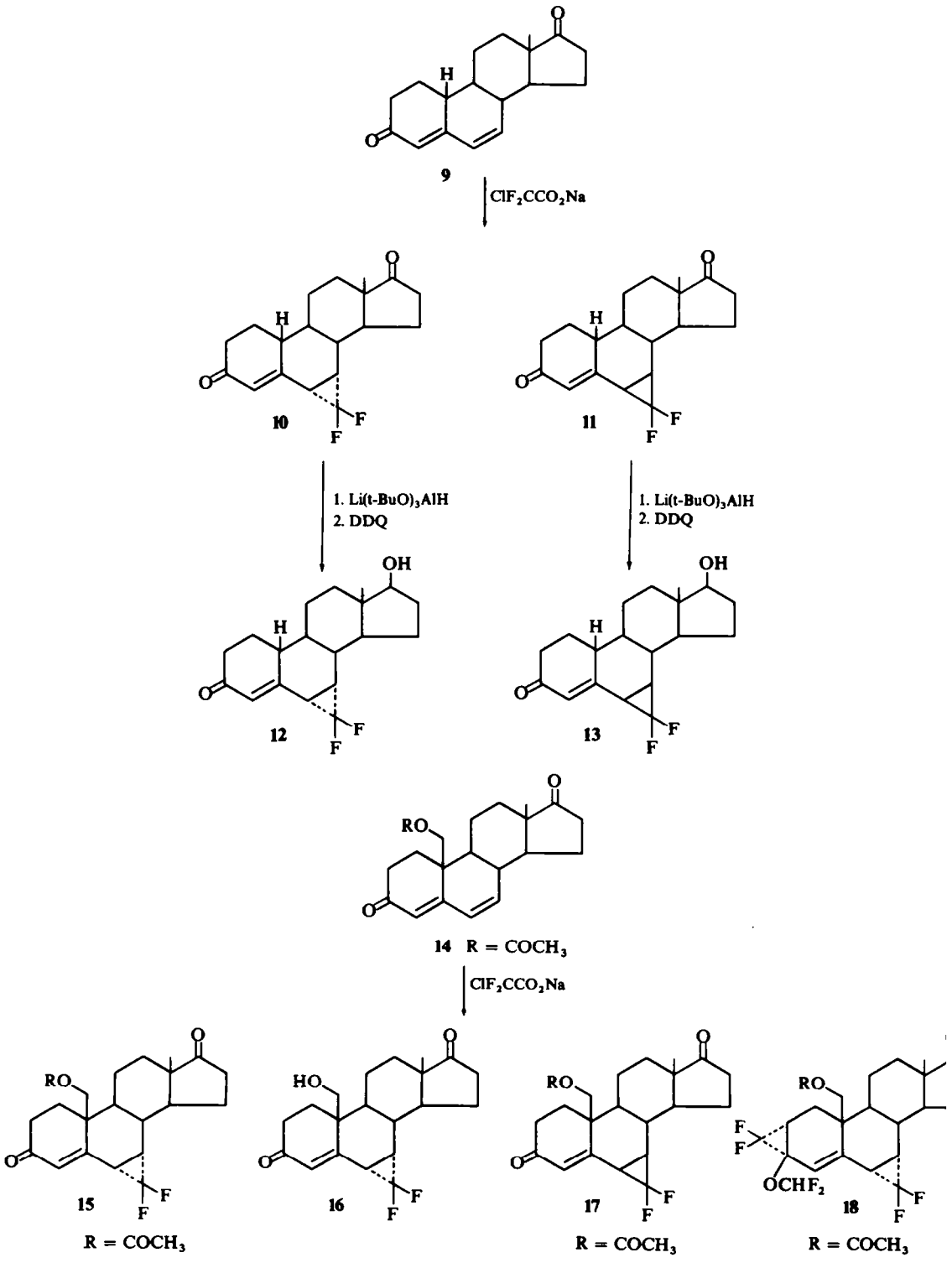
a: R = Cl; 1,2-double bond
b R = Cl; 1,2-dihydro
c: R = H; 1,2-dihydro
d: R = H; 1,2-double bond

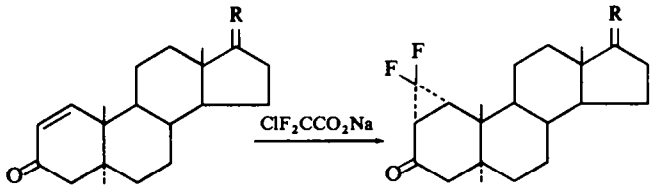


3 4 5



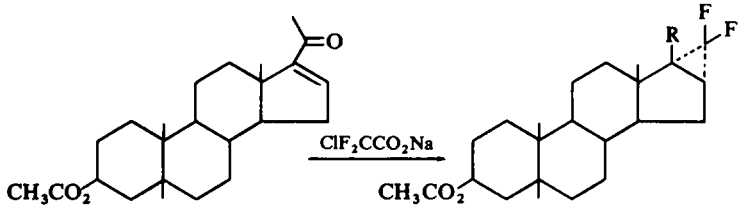
6 7 8


9
ClF2CCO2Na
10
11
1. Li(t-BuO)3AlH
2. DDQ
1. Li(t-BuO)3AlH
2. DDQ
12
13
14 R = COCH3
ClF2CCO2Na
15
R = COCH3
16
17
R = COCH3
18
R = COCH3



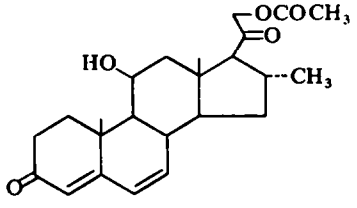
19a: R = β-$OCOCH_3$, αH
b: R = bismethylenedioxy

20a: R = β-$OCOCH_3$, αH
b: R = bismethylenedioxy

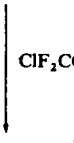


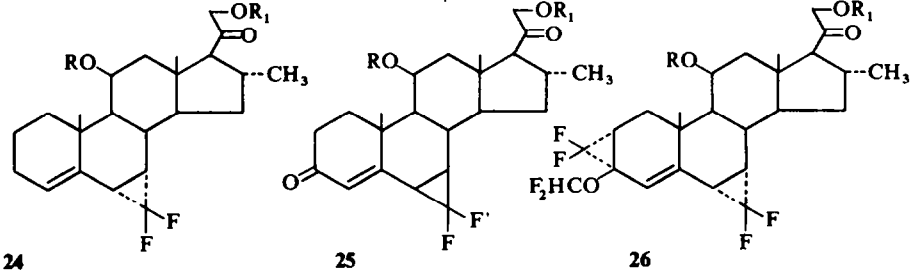
21

22 R = CH_3CO



23





24

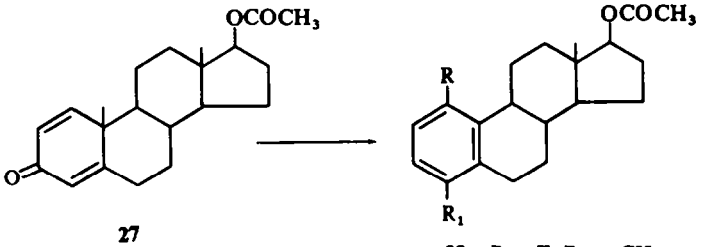
a: R = ClF_2CCO; R_1 = CH_3CO
b: R = R_1 = H
c: R = H; R_1 = CH_3CO

25

a: R = ClF_2CCO; R_1 = CH_3CO
b: R = R_1 = H
c: R = H; R_1 = CH_3CO

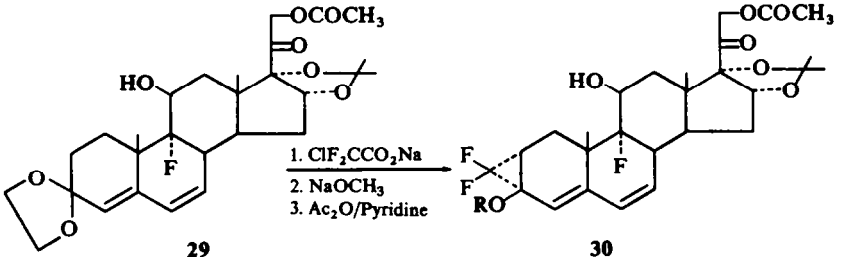
26

a: R = ClF_2CCO; R_1 = CH_3CO
b: R = R_1 = H



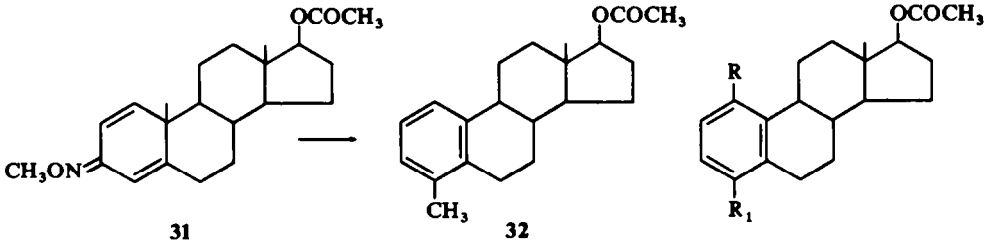
27

28a: R = F; R_1 = CH_3
b: R = CH_3; R_1 = F



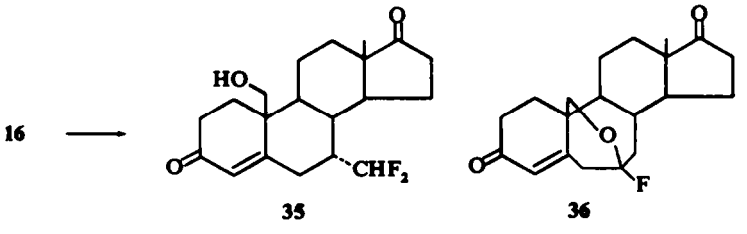
29 30

R = $CH_2CH_2OCOCH_3$



31 32

33a: R = $NHCOCClF_2$; R_1 = CH_3
b: R = CH_3; R_1 = $NHCOCClF_2$



16

35 36

EXPERIMENTAL†

17α,20:20,21-*Bismethylenedioxy*-9α-*fluoro*-11β-*hydroxy*-16α-*methylpregna*-4,6-*dien*-3-*one* (**3**). This substance was prepared by treating 17α,20:20,21-bismethylenedioxy-9α-fluoro-11β-hydroxy-16α-methylpregn-4-en-3-one with chloranil in boiling t-butanol. It showed m.p. 290–292°; $[\alpha]_D$ −28°, λ_{max} 279 mμ (log ε 4·26). (Found: C, 65·95; H, 7·27; F, 4·02. $C_{24}H_{31}O_6F$ requires: C, 66·30; H, 7·14; F, 4·37%).

19-*Acetoxyandrosta*-4,6-*diene*-3,17-*dione* (**14**). Treatment of 19-hydroxyandrosta-4,6-diene-3,17-dione[19] with Ac_2O–pyridine furnished **14** as a gum, $[\alpha]_D$ +136°; λ_{max} 277 mμ (log ε 4·27). MS 342 (M^+). $C_{21}H_{26}O_4$ requires: mol wt 342·4.

21-*Acetoxy*-11β-*hydroxy*-16α-*methylpregna*-4,6-*diene*-3,20-*dione* (**23**). This substance, prepared by chloranil dehydrogenation of 21-acetoxy-11β-hydroxy-16α-methylpregn-4-en-3,20-dione[34] in boiling t-butanol, showed m.p. 192–193° (from acetone–heptane); $[\alpha]_D$ +204°; λ_{max} 284 mμ (log ε 4·40). (Found: C, 72·18; H, 8·10; O, 19·91. $C_{24}H_{32}O_5$ requires: C, 71·97; H, 8·05; O, 19·98%).

21-*Acetoxy*-3-*cycloethylenedioxy*-9α-*fluoro*-11β,16α-17α-*trihydroxypregna*-4,6-*dien*-20-*one* 16,17-*acetonide* (**29**). A mixture of 1 ml ethylene glycol and 80 mg sulfosalicyclic acid in 200 ml benzene was heated under reflux with removal of water by a Dean–Stark separator until homogeneous. To this soln was added 0·5 g 21-acetoxy-9α-fluoro-11β,16α,17α-trihydroxypregna-4,6-diene-3,20-dione 16,17-acetonide,[35] and the separator dried and filled with molecular sieves. After heating for a further 20 hr the acid was neutralized by the addition of 0·5 ml pyridine and the cooled soln was washed with $NaHCO_3$aq. Evaporation gave crystalline **29**: λ_{max} 230 (infl.), 238, 245 (infl.) mμ. The ketal reverted to the starting dienone on attempted purification.

17β-*Acetoxyandrosta*-1,4-*dien*-3-*one methoxime* (**31**). This substance was prepared by treating 17β-acetoxyandrosta-1,4-dien-3-one with methoxylamine hydrochloride in pyridine. It showed m.p. 118–119°; $[\alpha]_D$ +83°; λ_{max} 245 (sh), 269 mμ (log ε 4·03, 4·18). (Found: C, 74·36; H, 8·97; N, 4·08. $C_{22}H_{31}O_3N$ requires: C, 73·91; H, 8·74; N, 3·92%).

General procedure for difluoromethylenation of unsaturated ketosteroids. A soln of the steroid in diglyme or triglyme was heated to reflux and treated dropwise with a soln of anhyd sodium chlorodifluoroacetate dissolved in the same solvent. Aliquots were withdrawn periodically for UV spectral determination to monitor the progress of the reaction. When all starting material was consumed, the resulting dark soln was cooled, filtered and the solvent evaporated under reduced press to yield a brown syrup. A cleaner crude product was usually obtained from reactions carried out in the higher boiling triglyme. Purification was achieved by column chromatography (silica gel or alumina), or preparative TLC† or by a combination of these techniques.

Difluoromethylenation of 17β-*acetoxyestra*-4,6-*dien*-3-*one* (**6**). The following procedure was developed from a number of trial experiments. Sodium chlorodifluoroacetate (30·5 g, 200 mmol) in 75 ml diglyme was added dropwise during 20 min to a boiling soln of 1·3 g (4·1 mmol) of **6** in 25 ml diglyme and after the usual processing, the resulting product was adsorbed from $CHCl_3$ onto a column of silica gel (200 g). Elution with $CHCl_3$ and $CHCl_3$–EtOAc (1:1) afforded 1·9 g of a yellow oil, which was hydrolyzed with 1·3 g KOH in 50 ml boiling MeOH–water (9:1). Treatment of the resulting crude alcohols with benzoyl chloride (9 ml) in pyridine (60 ml) afforded a two component mixture readily separable by preparative TLC (EtOAc–hexane, 1:3) into **7** (300 mg) m.p. 163–164° (from acetone–heptane); $[\alpha]_D$ +135°; λ_{max} 234 mμ (log ε 4·34); NMR 1·02 (s, 18-H), 6·07 ppm (s, 4-H). (Found: C, 73·42; H, 6·71. $C_{26}H_{28}O_3F_2$ requires: C, 73·21; H, 6·61%),

† M.ps are corrected. Optical rotations were measured in $CHCl_3$ soln at 27° and UV spectra in 95% EtOH unless specified otherwise. NMR spectra were recorded for 5–10% solns (w/v) in $CDCl_3$ containing TMS as internal reference on Varian A-60 and HA-100 spectrometers. Chemical shifts are reported as ppm on the δ scale. We wish to thank Mr. J. Murphy and Miss J. Tremble for these determinations. In most cases the reporting of NMR data is restricted to 18-H, 19-H and other significant resonance signals. In the presentation of data s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 KV. We wish to thank Mr. J. Smith for assistance with these measurements. ORD curves were measured in dioxan soln on a Jasco ORD/UV-5 spectrometer. Microanalyses were performed by Midwest Micro Labs, Indianapolis, Ind., and by A. Bernhardt, Mulheim (Ruhr), West Germany.

† Preparative TLC was conducted using silica gels GF and HF (from Brinkmann Instruments, Inc., N.Y.) at thicknesses of 1·3 mm and steroid loadings of 2 mg/cm.

and **8** (240 mg) m.p. 194–196° (from acetone–heptane); $[\alpha]_D$ −65°; λ_{max} 237 mμ (log ε 4·36); NMR 1·02 (s, 18-H), 6·08 ppm (s, 4-H). (Found: C, 73·41; H, 6·72; F, 8·88. $C_{26}H_{28}O_3F_2$ requires: C, 73·21; H, 6·61; F, 8·91%).

17β-*Hydroxy*-6α,7α-*difluoromethylenestr*-4-*en*-3-*one* (**12**). Compound **10** (100 mg) was reduced during 1 hr by lithium tri-t-butoxyaluminum hydride (760 mg) in boiling THF (5 ml) to the 3β,17β-diol. Oxidation of the latter product (100 mg) with 2,3-dichloro-5,6-dicyanobenzoquinone (100 mg) in dioxan soln (3 ml) for 18 hr followed by dilution with $CHCl_3$ and filtration through a short column of alumina furnished (**12**; 30 mg) m.p. 167–168° (from acetone–heptane); $[\alpha]_D$ +90°; λ_{max} 245 mμ (log ε 4·21); NMR 0·83 (s, 18-H), 6·05 ppm (broad s, 4-H). (Found: C, 70·78; H, 7·50; F, 11·70. $C_{19}H_{24}O_2F_2$ requires: C, 70·60; H, 7·40; F, 11·56%). The corresponding 17-benzoate, m.p. 163–164°, was identical in all respects with **7** m.p. 163–164°, described in the preceding experiment.

17β-*Hydroxy*-6β,7β-*difluoromethylenestr*-4-*en*-3-*one* (**13**). Compound **11** (200 mg) was treated exactly as described in the preceding experiment to furnish **13** (100 mg) as an oil; NMR 0·82 (s, 18-H), 6·10 ppm (broad s, 4-H). Its 17-benzoate derivative, m.p. 194–196°, was identical by mixed m.p. and IR spectral comparison with **8** obtained from difluoromethylenation of **6**.

Difluoromethylenation of 19-*acetoxyandrosta*-4,6-*diene*-3,17-*dione* (**14**). Sodium chlorodifluoroacetate (750 g, 4·9 mol) in 1·3 l diglyme was added dropwise during 6 hr to a boiling soln of **14** (67·5 g, 0·2 mol). A benzene soln of the resulting brown syrup obtained after the usual workup procedure was chromatographed on 2 kg of neutral alumina to yield the following compounds: (a) **18** (20 g, eluted with benzene) m.p. 174–175° (from MeOH); $[\alpha]_D$ +76°; NMR 0·92 (s, 18-H), 6·03 (s, 4-H), 5·20, 6·44, 6·47, 7·71 ppm (pair of d, J_{HF} = 74 c/s, $OCHF_2$). (Found: C, 58·51; H, 5·39; F, 23·05. $C_{24}H_{26}O_4F_6$ requires: C, 58·53; H, 5·32; F, 23·14%); (b) **15** (25 g, eluted with $CHCl_3$) m.p. 112–113° (from EtOH); $[\alpha]_D$ +174°; λ_{max} 243 mμ (log ε 4·13); NMR 0·93 (s, 18-H), 4·38 (AB pattern, J_{AB} = 12 c/s, 19-H), 6·15 ppm (s, 4-H). (Found: C, 67·52; H, 6·84; F, 9·43. $C_{22}H_{26}O_4F_2$ requires: C, 67·32; H, 6·67; F, 9·68%); (c) **17**; (2·5 g of oil eluted with EtOAc–$CHCl_3$, 4:1); λ_{max} 250 mμ; NMR 0·94 (s, 18-H), 4·25 (broadened AB pattern, J_{AB} 12 c/s, 19-H), 3·69 ppm (s, 4-H); (d) **16** (10 g eluted with EtOAc–$CHCl_3$; 1:1) m.p. 226–228° (from acetone–toluene); $[\alpha]_D$ +165°; λ_{max} 248 mμ (log ε 4·11); NMR 0·95 (s, 18-H), 3·94 (d, $J_{H,OH}$ = 5 c/s, 19-H), 6·12 ppm (s, 4-H). (Found: C, 68·46; H, 6·93; F, 10·61. $C_{20}H_{24}O_3F_2$ requires: C, 68·55; H, 6·90; F, 10·84%).

Difluoromethylenation of 21-*acetoxy*-11β-*hydroxy*-16α-*methylpregna*-4,6-*diene*-3,20-*dione* (**23**). A soln of 185 g (1·2 mol) sodium chlorodifluoroacetate in 350 ml diglyme was added in 3·5 ml portions during 2 hr to a soln of 5·1 g (12·7 mmol) of **23** in diglyme held at reflux. After the usual workup procedure, the resulting $CHCl_3$ concentrate (50 ml) was adsorbed on 300 g silica gel. Elution with $CHCl_3$–EtOAc (1:1) afforded 8·0 g of an oil which was purified by preparative TLC (EtOAc–hexane, 1:1). The following compounds were isolated in order of increasing polarity: (a) **26a** (190 mg) hydrolyzed by dil NaOMe in MeOH (24 hr/20°) to **26b** m.p. 171–173° (from CH_2Cl_2–hexane); $[\alpha]_D$ +79°; NMR 0·95 (s, 18-H), 1·35 (s, 19-H), 5·55, 6·27, 6·31, 7·04 ppm (pair of d, J_{HF} = 43 c/s, $OCHF_2$). (Found: C, 59·14; H, 6·08; F, 22·10. $C_{25}H_{30}O_4F_6$ requires: C, 59·04; H, 5·94; F, 22·41%); (b) **24a** (1·9 g) m.p. 161–163° (from acetone–heptane); $[\alpha]_D$ +159°; λ_{max} 244 mμ (log ε 4·14); NMR 0·85 (s, 18-H), 1·31 (s, 19-H), 5·98 ppm (s, 4-H). (Found: C, 57·86; H, 5·73; Cl, 6·13; F, 13·35. $C_{27}H_{31}O_6ClF_4$ requires: C, 57·60; H, 5·51; Cl, 6·31; F, 13·51%); (c) **25a** (410 mg) m.p. 201–203° (from acetone–heptane); $[\alpha]_D$ ±0°; λ_{max} 252 mμ (log ε 4·19); NMR 0·91 (s, 18-H), 1·27 (d, J_{HF} = 3·5 c/s, 19-H), 5·94 ppm (s, 4-H). (Found: C, 57·86; H, 5·77; Cl, 6·18; F, 13·39. $C_{27}H_{31}O_6ClF_4$ requires: C, 57·60; H, 5·51; Cl, 6·31; F, 13·51%).

11β,21-*Dihydroxy*-16α-*methyl*-6α,7α-difluoromethylenepregn-4-ene-3,20-dione (**24b**). A soln of 1·9 g of **24a** in 50 ml MeOH containing 20 mg NaOMe was kept in a N_2 atm for 16 hr. Addition of water containing AcOH precipitated **24b** (1·3 g) m.p. 201–203° (from MeOH); $[\alpha]_D$ +175°; λ_{max} 248 mμ (log ε 4·17); NMR 0·99 (s, 18-H), 1·41 (s, 19-H), 5·95 ppm (s, 4-H). (Found: C, 67·86; H, 17·74. $C_{23}H_{30}O_4F_2$ requires: C, 67·65; H, 7·35%). Treatment of **24b** with Ac_2O–pyridine afforded **24c** m.p. 223–224° (from acetone–heptane); $[\alpha]_D$ +360°; λ_{max} 246 mμ (log ε 4·15); NMR 0·99 (s, 18-H), 1·41 (s, 19-H), 5·93 ppm (s, 4-H). (Found: C, 66·64; H, 6·96; F, 8·37. $C_{25}H_{32}O_5F_2$ requires: C, 66·66; H, 7·11; F, 8·44%).

11β,21-*Dihydroxy*-16α-*methyl*-6β,7β-*difluoromethylenepregn*-4-*ene*-3,20-*dione* (**25b**). Compound **25a** (480 mg) was hydrolyzed with NaOMe in MeOH as described in the preceding experiment to yield the corresponding **25b** (336 mg) m.p. 230–233° (from acetone–heptane); $[\alpha]_D$ −71°; λ_{max} 257 mμ (log ε 4·21); NMR 0·89 (s, 18-H), 1·31 (d, J_{HF} = 3·0 c/s, 19-H), 5·89 ppm (s, 4-H); (Found: C, 67·69; H, 7·45. $C_{23}H_{30}O_4F_2$ requires: C, 67·65; H, 7·35%). Treatment of **25b** with Ac_2O–pyridine afforded **25c** m.p. 203–205° (from acetone–heptane); $[\alpha]_D$ +31°; λ_{max} 255 mμ (log ε 4·22); NMR 0·98 (s, 18-H), 1·36 (d, J_{HF} = 3·0 c/s, 19-H), 5·93 ppm (s, 4-H). (Found: C, 66·60; H, 7·20. $C_{25}H_{32}O_5F_2$ requires: C, 66·66; H, 7·11%).

Difluoromethylenation of 17β-*acetoxyandrosta*-1,4-*dien*-3-*one* (**27**). The diene **27** (1·5 g, 4·5 mmol) in boiling triglyme was treated with sodium chlorodifluoroacetate (14 g, 91 mmol) during 2 hr after which time the reaction mixture was processed as described previously. The resulting oil (2·1 g), consisting of ca. 20%) of starting material and 8 products (GLC analysis), was dissolved in hexane–CH_2Cl_2 (9:1) and adsorbed on 100 g of neutral alumina. Elution with hexane–CH_2Cl_2 (1:1) furnished the aromatic compound (**28a** or **b**, 40 mg) m.p. 168–170° (from hexane–ether); λ_{max} 266, 275 mμ (log ε 2·90, 2·91): NMR 0·85 (s, 18-H), 2·17 (s, aromatic Me), 6·83 ppm (unsymmetrical m, 2 pairs of overlapping quartets, aromatic-H). (MS 330 (M^+) $C_{21}H_{27}O_2F$ requires: mol. wt. 330). Continued elution with hexane–CH_2Cl_2 (1:2 and 1:4) afforded 450 mg of oil, no significant UV absorption; NMR 0·82 (s, 18-H), 1·20 (s, tert Me) 2·04 (s, 17β-acetoxy-H), 6·37 ppm (t, J_{HF} = 74 c/s, $OCHF_2$). (Found: F, 17·64; $C_{23}H_{28}O_3F_4$ (mol. wt. 428) requires: F, 17·77%; MS 428 (M^+) Trituration of this oil with hexane afforded a TLC homogeneous compound m.p. 80–95°, the ^{19}F NMR spectrum of which showed signals due to three pairs of geminal fluorines.

Attempted difluoromethylenation of 21-*acetoxy*-3-*cycloethylenedioxy*-9α-*fluoro*-11β,16α,17α-*trihydroxypregna*-4,6-*dien*-20-*one*-16,17-*acetonide* (**29**). A soln of 70 g sodium chlorodifluoroacetate in 275 ml triglyme was added during 25 min to a soln of 3 g of **29** in 75 ml triglyme at 145°. After heating for a further 25 min the soln was cooled, filtered to remove inorganic salts and the triglyme removed *in vacuo*. The product was dissolved in 50 ml methanolic N/2 NaOMe and allowed to stand at 20° for 20 min. Excess AcOH was added and the solvent removed *in vacuo*. Trituration of the residue with CH_2Cl_2, filtration and evaporation of the solvent, gave a brown gum which was acetylated by heating with 10 ml pyridine and 5 ml Ac_2O for 1 hr at 65°. The reagents were removed *in vacuo* and the product chromatographed on silica gel yielding 525 mg of **30** m.p. 175–176° (from MeOH); $[\alpha]_D$ ±0°; λ_{max} 245 mμ (log ε 4·30); NMR 0·93 (s, 18-H), 1·22 (s, 19-H), 3·80 (m, $OC\underline{H}_2CH_2OCOCH_3$), 4·25 (m, $OCH_2C\underline{H}_2OCOCH_3$), 5·57 (s, 4-H), 5·57, 6·16 ppm (pair of d, J = 11 c/s, 6-H and 7-H), (Found: C, 60·97; H, 6·63; F, 9·10. $C_{31}H_{39}O_9F_3$ requires: C, 60·79; H, 6·42; F, 9·30%).

Difluoromethylenation of 17β-*acetoxyandrosta*-1,4-*dien*-3-*one methoxime* (**31**). A soln of sodium chlorodifluoroacetate (14 g, 9 mmol) in diglyme (7 ml) was added during 2 hr to a boiling solution of **31**; (1·1 g, 3 mmol) in diglyme (8 ml). After the usual workup the resulting brown oil was chromatographed on neutral alumina (120 g) to yield **32** (30 mg, eluted with CH_2Cl_2), m.p. 179–182° (from MeOH); λ_{max} 263 mμ (log ε 2·58) [lit[29] reports m.p. 172–173°; λ_{max} 262 mμ (log ε 2·25)]; NMR 0·82 (s, 18-H), 2·20 (s, aromatic Me), 7·07 ppm (m, aromatic H). (Mass spectrum 312 (M^+); $C_{21}H_{28}O_2$ requires: mol. 312), and impure **33a** or **b** (116 mg, eluted with CH_2Cl_2).

Preparative TLC afforded a pure sample of the latter product, m.p. 276–277° (from benzene); λ_{max} 240 mμ (log ε 3·72); NMR 0·86 (s, 18-H), 2·22 (s, aromatic Me), 7·02 and 7·30 (pair of d, J = 9 c/s, aromatic H), 7·95 ppm (m, N—H). (Found: C, 66·24; H, 6·54; N, 3·37. $C_{23}H_{28}O_3ClF_2N$ [mol. wt. 439, 441 (^{37}Cl)] requires: C, 62·79; H, 6·42; N, 3·18%). [MS 439 (^{35}Cl, M^+), 441 (^{37}Cl, M^+)].

17β-*Hydroxy*-7α-*difluoromethylandrost*-4-*en*-3-*one*. A soln of 700 mg of **34** in 25 ml AcOH was stirred with 7 g Zn dust for 1 hr and then partitioned between water and EtOAc. The organic phase was washed with dil $NaHCO_3$aq and water, dried (Na_2SO_4) and evaporated. Purification of the resulting gum by chromatography over alumina afforded the 7α-difluoromethyl-Δ^4-3-ketone (45 mg) m.p. 213–218°; $[\alpha]_D$ +80°; λ_{max} 242 mμ (log ε 4·16); NMR 0·80 (s, 18-H), 1·24 (s, 19-H), 5·78 (broadened s, 4-H), 5·85 ppm (broad, t, J_{HF} = 56 c/s, CHF_2). (Found: 71·15: H, 8·29. $C_{20}H_{28}O_2F_2$ requires: C, 70·98; H, 8·34%) and recovered **34** (320 mg).

Reductive cleavage of 19-*hydroxy*-6α,7α-*difluoromethylenandrost*-4-*ene*-3.17-*dione* (**16**) *with zinc dust*. A soln of 740 mg of **16** in 90 ml EtOH–n-propanol (1:2) was heated under reflux with stirring for 96 hr with 20 g of Zn–Cu couple (prepared by treating 20 g Zn dust with 500 ml 2% $CuSO_4$aq). Separation of the Zn dust by filtration followed by evaporation of the solvents gave an oil which was purified by preparative TLC (EtOAc–hexane, 1:1). This afforded **35** (180 mg) m.p. 181–183°; $[\alpha]_D$ +146°; λ_{max} 244 mμ (log ε 4·08); NMR 0·93 (s, 18-H), 4·01 (s, 19-H), 5·43, 6·37 (2 pairs of overlapping doublets, $J_{7H,7'H}$ = 4 c/s, $J_{7'H,F}$ = 55 c/s, CHF_2), 5·93 ppm (s, 4-H). (Found: C, 68·07; H, 7·25; F, 11·05. $C_{20}H_{26}O_3F_2$ requires: C, 68·16; H, 7·43; F, 10·78%) and **36** (90 mg) m.p. 210–212° (from hexane); λ_{max} 240 mμ (log ε 4·04) NMR 0·97 (s, 18-H), 2·97 (broad s, 6-H), 3·72, 3·90 (d of AB pattern J_{AB} = 11 c/s, 19-H_a), 4·05, 4·23 (d of AB pattern J_{AB} = 11 c/s. $J_{19Hb,9\alpha H}$ or $J_{19Hb,7\alpha F}$ = 2 c/s, 19-H_b), 5·85 ppm (s, 4-H). (Found: C, 72·07; H, 7·78; F, 5·95. $C_{20}H_{25}O_3F$ (mol. wt. 332) requires: C, 72·26; H, 7·58; F, 5·71%; MS 332 (M^+), 169, 168, 167.

REFERENCES

[1] For part 6 see I. T. Harrison, C. Beard, L. Kirkham, B. Lewis, I. M. Jamieson, W. Rooks and J. H. Fried, *J. Med. Chem.* **11**, 868 (1968).

[2] Publication #349 from the Syntex Institute of Steroid Chemistry. For publication #348 see R. Zurfluh, E. N. Wall, J. B. Siddall, J. A. Edwards, *J. Am. Chem. Soc.* **90**, 6224 (1968).

[3] Syntex Postdoctoral Fellow: **a** 1964–1965; **b** 1965–1966.

[4] W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.* **76**, 6162 (1954).

[5] For comprehensive surveys of these topics see **a** J. Hine in *Divalent Carbon*. Ronald Press, New York, N.Y. (1964); **b** W. Kirmse, *Carbene Chemistry*. Academic Press, New York, N.Y. (1964).

[6] D. Becker and H. J. E. Loewenthal, *Chem. Commun.* 149 (1965).

[7] D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y-P. Mui, H. D. Simmons, Jr., A. J. H. Trieber and S. R. Dowd, *J. Am. Chem. Soc.* **87**, 4259 (1965).

[8] [a] C. Beard, N. H. Dyson and J. H. Fried, *Tetrahedron Letters* 3281 (1966);
[b] C. Beard, I. T. Harrison, L. H. Kirkham and J. H. Fried, *Ibid.* 3287 (1966);
[c] G. Tarzia, N. H. Dyson, I. T. Harrison, J. A. Edwards and J. H. Fried, *Steroids* **9**, 387 (1967).

[9] J. M. Birchall, G. W. Cross and R. N. Haszeldine, *Proc. Chem. Soc.* 229 (1959).

[10] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis and A. D. Cross, *J. Am. Chem. Soc.* **85**, 1851 (1963).

[11] [a] H. B. Henbest, W. R. Jackson and I. Malunowicz, *J. Chem. Soc.* (C), 2469 (1967);
[b] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958).

[12] For typical examples in the steroid field see [a] P. L. Julian, E. W. Meyer and I. Ryden, *J. Am. Chem. Soc.* **72**, 367 (1950);
[b] A. L. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, *Ibid.* **80**, 2722 (1958);
[c] L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi and H. J. Ringold, *Ibid.* **82**, 1230 (1960).

[13] See L. H. Sarett, A. A. Patchett and S. Steelman, *Progress in Drug Research* (Edited by E. Jucker) Vol. 5. p. 11–154. Birkhauser Verlag, Basel (1963).

[14] H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, *J. Am. Chem. Soc.* **81**, 3485 (1959).

[15] R. Sciaky, *Gazz. Chim. Ital.* **91**, 545 (1961).

[16] K. Bruckner, B. Hampel and U. Johnsen, *Chem. Ber.* **94**, 1225 (1961).

[17] A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.* **86**, 4005 (1964). See also M. Takahashi, D. R. Davis and J. D. Roberts, *Ibid.* **84**, 2935 (1962).

[18] J. Hartman, *Ibid.* **77**, 5151 (1955).

[19] K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner and A. Wettstein, *Experientia* **18**, 464 (1962).

[20] D. Burn, V. Petrow and G. O. Weston, *Tetrahedron Letters* No. 9, 14, (1960).

[21] A. Butenandt and H. Dannenberg, *Chem. Ber.* **73**, 206 (1940).

[22] W. M. Wagner, H. Kloosterziel and A. F. Bickel, *Rec. Trav. Chim.*, **81**, 925 (1962).

[23] M. S. Kharasch, T. Rudy, W. Nudenberg and G. Büchi, *J. Org. Chem.* **18**, 1030 (1953).

[24] T. L. Popper, F. E. Carlon, H. M. Marigliano and M. D. Yudes, *Chem. Commun.* 277 (1968).

[25] R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *J. Am. Chem. Soc.* **77**, 661 (1955).

[26] For synthetic details see G. W. Moersch, T. P. Culbertson, D. F. Morrow, E. L. Wittle, R. R. Humphrey, W. A. Neuklis, M. E. Butler and M. M. Creger, *J. Med. Chem.* **7**, 741 (1964).

[27] R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Menzel, *Chem. Ber.* **86**, 594 (1953).

[28] H. Dutler, C. Ganter, H. Ryf, E. C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2346 (1962).

[29] J. Pfister, H. Wehrli and K. Schaffner, *Helv. Chim. Acta* **50**, 166 (1967).

[30] K. B. Wiberg, B. K. Lowry and B. J. Nist, *J. Am. Chem. Soc.* **84**, 1594 (1962).

[31] J. Delman and J. Duplan, *Tetrahedron Letters* 559 (1966); K. C. Ramey and J. Messick, *Ibid.* 4423 (1965).

[32] For examples see F. Michael and A. Klimer, *Advances in Carbohydrate Chemistry* Vol. 16; p. 85. Academic Press, New York, N.Y. (1961).

[33] D. Seyferth, J. Y-P. Mui, M. E. Gordon and J. M. Burlitch, *J. Am. Chem. Soc.* **87**, 681 (1965).

[34] G. Raspé, K. Kieslich and U. Kerb, *Arzneimittel-Forsch.* **14**, 450 (1964).

[35] S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.* **82**, 3680 (1960).