petroleum ether (bp 30–60°) in Et_2O was used in the development), there was obtained 0.076 g of 2α,3α-methanol-5α-androstan-17β-ol, mp 129–130° after recrystallization from MeOH. Ir and nmr spectra and mixture melting point were indistinguishable from those of the authentic sample.[2]

The compound with lower R_f value was isolated in a yield of 0.093 g and was shown to be a single isomer of **2α,3α-(bromomethano)-5α-androstan-17β-ol.** One recrystallization from EtOH gave colorless crystals: mp 145–146°; nmr 0.72 (C-19 methyl), 0.75 (C-18 methyl), 2.55 (triplet, bromo proton) 3.73 (triplet, 17α-H) ppm.

2α,3α-(ξ-Bromomethano)-5α-androstan-17-one (19).—To a refluxing mixture of 1.50 g (0.0045 mole) of **6** and 2.00 g of red HgO in anhydrous CCl_4 was added 0.72 g (0.0045 mole) of Br_2 in 5 ml of anhydrous CCl_4. The resulting mixture was refluxed gently for 1.5 hr and was filtered after cooling. The clear yellow filtrate was washed (H_2O, 5% NaOH, H_2O), dried (Na_2SO_4), and evaporated *in vacuo*. The oily residue was treated with petroleum ether (bp 30–60°) to give 0.60 g (36%) of crystals. Several recrystallizations from Me_2CO gave the analytical sample: mp 159–160°; nmr 0.77, 0.78 (C-19 CH_3) ppm. *Anal.* ($C_{20}H_{29}BrO$) C, H.

Synthesis of 6,7-Difluoromethylene Corticoids[1]

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The synthesis of 6α,7α- and 6β,7β-difluoromethylene corticoids by addition of "difluorocarbene" to selected $\Delta^{4,6}$-3-keto steroids is described. The observed potentiation of corticoid activity by both α- and β-face difluoromethylene adducts is inconsistent with an antiinflammatory receptor site which requires binding to rings A and B of the steroid molecule.

The enormous effort expended in the synthesis and modification of cortisone has led to the accumulation of a considerable body of empirical knowledge relating structure to antiinflammatory activity. Within the last two decades every position of the cortisone molecule has been subject to scrutiny and chemical modification. These efforts have resulted in the discovery of a number of activity-enhancing and activity-modifying groups which alone or in combination have led to the development of several clinically useful corticoids.

Although the primary locus of corticoid action is unknown, the hypothesis is generally accepted that biological action is the result of an interaction with a complementary receptor site. Considerable speculation as to the nature and geometry of the receptor site has led to the suggestion that corticoids interact with a surface complementary to a portion of the β face of the steroid molecule.[3-6]

Sarett[3,4] has further defined the properties of the receptor by suggesting rigid geometry with provisions for specific binding to the 11β-hydroxyl and to the 3- and 20-keto groups of hydrocortisone.[7] Additional interactions are provided by the summation of London forces over the total of the β face of the steroid molecule.

Alternatively, Bush[6] envisages little if any binding to rings A and B with the major interactions being provided by the 11β-hydroxyl, rings C and D, and the side chain. With this hypothesis, the requirements of the receptor would not be inconsistent with axial β-face B-ring substituents. The inactivity of 6β-halo and 6β-methyl corticoids, an important consideration in the previous proposal,[3,4] was rationalized by the suggestion that a general distortion of the steroid molecule due to intramolecular interaction with the axial 6-substituent interfered with binding.[6,8]

Clearly a critical evaluation of these hypotheses must be based on biologically active compounds.[9] In particular, an active corticoid substituted with bulky β-face B-ring substituents would provide evidence in support of the proposal that rings A and B are not involved in binding to the complementary surface of the receptor.

We have recently reported an efficient method for the preparation of 6,7-difluoromethylene steroids.[10,11] The application of these findings to the corticoid series provided an opportunity to further evaluate the requirements for biological activity.

Addition of "difluorocarbene" to the dienones **1a, b** gave a mixture of products from which the 6α,-7α-difluoromethylene adducts **2a, b** were isolated after

(1) Publication 340 from the Syntex Institute of Steroid Chemistry. For publication 339 see P. H. Nelson, J. W. Murphy, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, in press. This publication is also part VI of the series, Methylenation of Unsaturated Ketones. Part V: G. Tarzia, N. H. Dyson, I. T. Harrison, J. A. Edwards, and J. H. Fried, *Steroids*, **9**, 387 (1967). A portion of this material was presented at the symposium on Antiinflammatory Agents sponsored by the Medicinal Chemistry Section at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) Institute of Hormone Biology, Syntex Research.

(3) L. H. Sarett, *Ann. N.Y. Acad. Sci.*, **82**, 802 (1959).

(4) L. H. Sarett, A. A. Patchett, and S. L. Steelman, *Progr. Drug Res.*, **5**, 13 (1963).

(5) J. Fried, "Mechanism of Action of Steroid Hormones," The MacMillan Co., New York, N. Y., 1961, p 232.

(6) I. E. Bush, *Pharmacol. Rev.*, **14**, 447 (1963).

(7) The 3-ketone can be replaced by a 2,3-fused heterocyclic ring with a considerable enhancement of biological activity; *cf.* R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963); J. H. Fried, P. Buchschacher, and H. Mrozik, *Steroids*, **2**, 399 (1963); H. Mrozik, P. Buchschacher, J. Hannah, and J. H. Fried, *J. Med. Chem.*, **7**, 584 (1964); P. DeRuggieri, C. Candolfi, H. Guzzi, D. Chiaiamonte, and C. Ferrari, *Farmaco*, **20**, 280 (1965).

(8) The contrasting antiinflammatory activities of 6β- and 6α-fluoro corticoids can also be attributed to a more rapid metabolic reduction of the C-3 ketone in the 6β-fluoro series; *cf.* H. J. Ringold, S. Rainachandran, and E. Forchielli, *Biochim. Biophys. Acta*, **82**, 143 (1964).

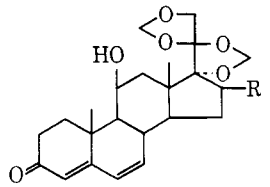
(9) Since the biological action of hormones depends upon numerous biochemical and physicochemical equilibria involved in the process of absorption, distribution, and metabolism, absence of biological activity cannot be safely ascribed to the lack of binding and, therfore, inferences as to the geometry of the receptor site based on inactive compounds are open to question.

(10) C. Beard, N. H. Dyson, and J. H. Fried, *Tetrahedron Letters*, 3281 (1966); C. Beard, I. T. Harrison, L. Kirkham, and J. H. Fried, *ibid.*, 3287 (1966).

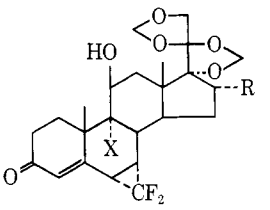
(11) G. Tarzia, N. H. Dyson, I. T. Harrison, J. A. Edwards, and J. H. Fried, *Steroids*, **9**, 387 (1967); C. Beard, B. Berkoz, N. H. Dyson, I. T. Harrison, P. Hodge, L. Kirkham, G. Lewis, D. Giannini, J. A. Edwards, and J. H. Fried, to be published.

hydrolysis of the 11-chlorodifluoro acetate ester formed during the course of the reaction.

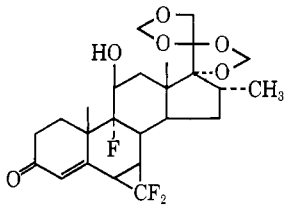
Introduction of the 1,2 double bond into **2b**, **2c**, and **3** was carried out by dehydrogenation with dichlorodicyanoquinone[12] to give **6b**, **6c**, and **7**.



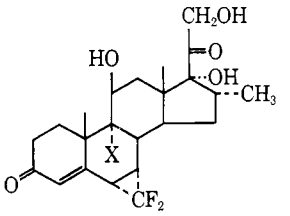
1a-b



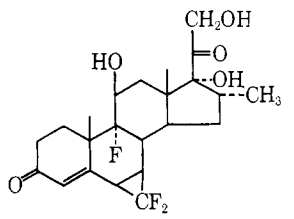
2a-c



3



4a-c



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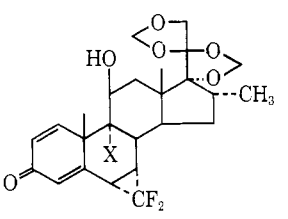
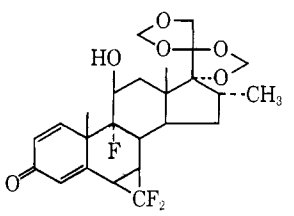


6b-c



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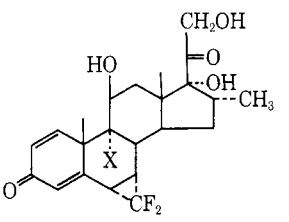
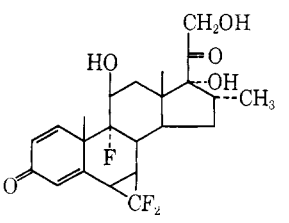


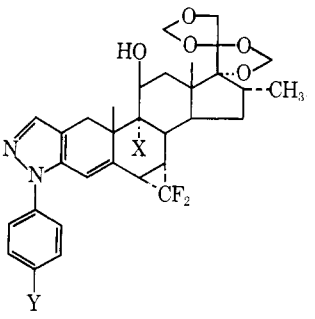
8b-c



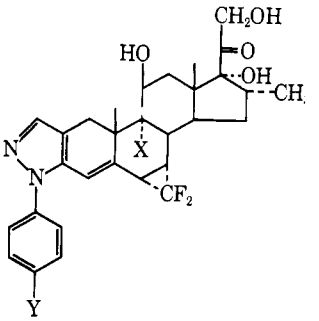
9

The A-ring-fused phenylpyrazole derivatives **10a-c** and **12** were synthesized by standard procedures.[13] It is noteworthy, however, that treatment of the 2-formyl 3-ketone with phenylhydrazines in aqueous methanol or ethanol gave mainly the [3,2-*c*]-2′-phenylpyrazoles while in other experiments anhydrous alcohol or acetic acid led to mixtures containing substantial quantities of the isomeric [2,3-*d*]-2′-phenylpyrazoles in addition to the required [3,2-*c*]-2′-phenylpyrazoles.

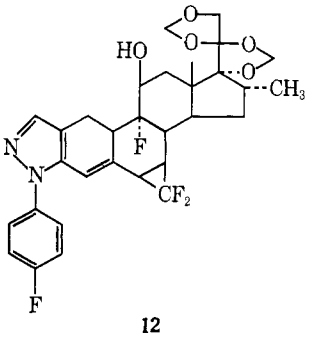
Cleavage of the bismethylenedioxy protecting group in the various difluoromethylene steroids was accomplished with 40% aqueous hydrofluoric acid[14] to give the corresponding side-chain ketols in high yield.



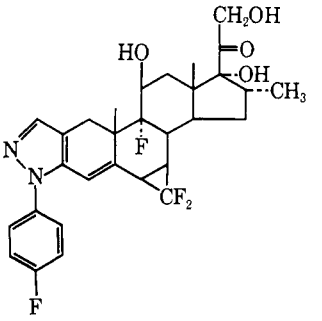
10a-c



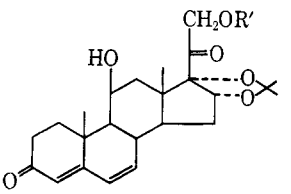
11a-c



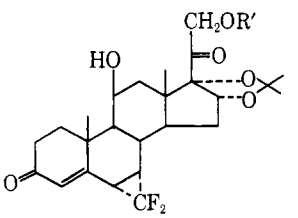
12



13



14a-c



15a-c

Introduction of the 6α,7α-difluoromethylene group potentiates the thymolytic activity of hydrocortisone by a factor of four. Additivity of activity-enhancing groups (Table I) is observed in combination with the 16α-methyl group, 1,2-dehydrogenation, and the A-ring-fused [3,2-*c*]-2′-*p*-fluorophenylpyrazole. However, the additional effect of introducing the 9α-fluoro substituent is severalfold smaller than observed in less highly substituted compounds.[15] The 9α-fluoro group[16] is believed[6] to potentiate activity by increasing the ratio of the active 11β-carbinol to inactive 11-ketone in circulation within the organism as well as by an increase in the strength of the 11β-hydroxyl hydrogen bond to the receptor site.[17] It is possible that, with the highly substituted corticoids examined, metabolic stabilization of the 11-carbinol is already an inherent feature of the molecule and that the 9α-fluoro adds uniquely only to binding to the receptor.

The most noteworthy observation in this series is the potent thymolytic activity of the 6β,7β-difluoromethylene adducts. The potentiation of thymolytic activity for the β-face difluoromethylene adducts is equal to or greater than that observed with the corresponding α-face adducts. Examination of models indicates that the carbon of the cyclopropane ring is

(12) *Cf.* D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(13) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Am. Chem. Soc.*, **86**, 1520 (1964).

(14) F. Alvarez, J. B. Siddall, and A. Ruiz, U. S. Patent 3,338,930 (1967).

(15) A similar conclusion may be drawn from the observation reported in the 6-methyl-6-dehydro series; *cf.* J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 236 (1963).

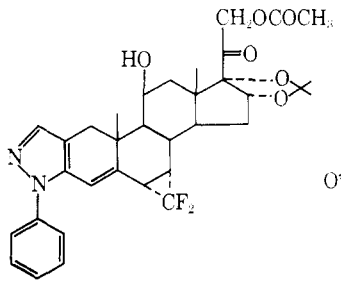
(16) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(17) J. Fried and A. Borman, *Vitamins Hormones*, **16**, 303 (1958).

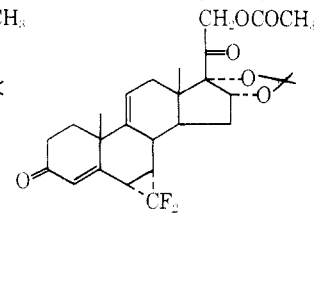
tilted upward from the plane defined by the steroid skeleton by an angle of 65°, and that the *syn*-fluorine atom is actually tilted toward the angular methyl group and thus may be termed a "super axial" substituent. The 6β,7β-difluoromethylene group clearly prevents the juxtaposition of the β face of the B ring and the lower edge of the A ring to any part of a complementary binding surface. The observation of high biological activity in the presence of this group is therefore strong evidence in support of the views of Bush[6] and is inconsistent with the alternate definition of geometry of the receptor site expressed by Sarett.[3,4]

The clinically important topical antiinflammatory action elicited by several corticoids incorporating a 16α,17α-isopropylidenedioxy group led to an examination of the effect of 6,7-difluoromethylenation in the acetonide series.

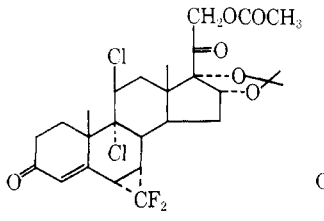
Addition of difluoromethylene to the 6-fluorodienone **19** afforded the 6α,7α adduct which, after hydrolysis to



16



17



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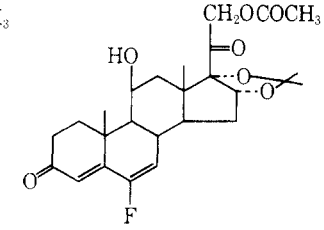
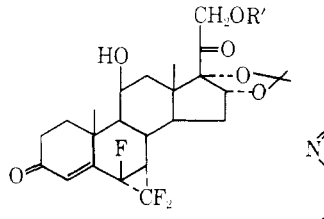
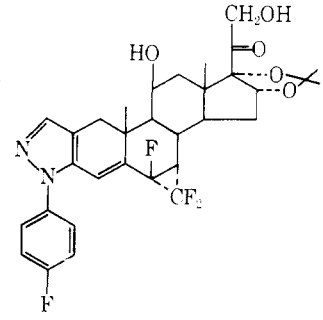


19



20a–c



21

a, R = H; X = H; Y = H; R′ = H

b, R = CH_3; X = H; Y = F; R′ = $COCH_3$

c, R = CH_3; X = F; Y = F; R′ = 

give **20a** and protection of the 21-hydroxyl as the tetrahydropyranyl ether **20c**, was formylated[18] and then condensed with *p*-fluorophenylhydrazine to give the A-ring-fused [3,2-*c*]-2′-*p*-fluorophenylpyrazole[13] **21**.

In contrast, the dienone **14b** lacking the 6-fluoro substituent did not give a difluoromethylene adduct under the usual reaction conditions but afforded only the 11-chlorodifluoro acetate ester. However, the 21-tetrahydropyranyl ether **14c** reacted normally to give the adduct **15a** after hydrolysis. The latter compound was converted to the phenylpyrazole **16** after protection of the 21-hydroxyl as the tetrahydropyranyl ether.[13,18]

Dehydration of **15b** gave the 9(11)-dehydro compound **17** which added chlorine rapidly to give the dichloride **18**. However, reactions with N-bromosuccinimide were found to be sluggish. Apparently the size of the α-face difluoromethylene group is sufficiently large to hinder approach of the solvated bromonium ion but not approach of chlorine.

In contrast to the potentiation of antiinflammatory activity observed by introduction of a 16α-methyl substituent into 6α,7α-difluoromethylene corticoids, a substantial decrease in activity (Table I) was observed by introduction of the 16α,17α-isopropylidenedioxy group. Possibly conformational distortion of rings C and D due to the configuration of two large α-face substituents impairs interaction with the receptor site. This supposition is being examined and the results will be reported in a subsequent publication.

TABLE I

Compd	Systemic antiinflam[a,d] (thymolytic assay)	Topical antiinflam[b,d] (suppression of ear edema)
4a	4	. . .
4b	13	. . .
4c	25	. . .
5	26	. . .
8b	100	38
8c	100	. . .
9	85	. . .
11a	860	90
11b	750	153[c]
11c	1400	70
13	1920	110
15a	1	≤1
16	16	. . .
20b	1	. . .
21	130	<25

[a] Thymolytic assay. Modification of the method of R. I. Dorfman, F. A. Kincl, and H. J. Ringold, *Endocrinology*, **68**, 616 (1961). [b] Suppression of ear edema. Modification of the method of G. Tonelli, L. Thibault, and I. Ringler, *ibid.*, **77**, 625 (1965). [c] One to two times as potent as fluocinolone acetonide in the vasoconstrictor assay of A. N. McKenzie and R. B. Stoughton, *Arch. Dermatol.*, **86**, 608 (1962). We are grateful to Dr. J. Giner for this determination. [d] Unless otherwise noted activities are relative to hydrocortisone.

Experimental Section[19]

17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-11β-hydroxy-16α-methylpregn-4-en-3-one (2b).—A solution of 100 g of sodium chlorodifluoroacetate in 300 ml of diglyme was added during 1.5 hr to a stirred solution of 35 g of the dienone **1b** in 100 ml of diglyme heated in an oil bath at 190°. The cooled solution was filtered to remove the precipitated salts and concentrated *in vacuo*. The residue was then hydrolyzed by addition of 1 *N* methanolic NaOMe. After 15 min dilute AcOH and H_2O were added and the product was extracted (CH_2Cl_2). Chromatography and crystallization from acetone–hexane gave 5 g of **2b**, mp 275–283° dec, $[\alpha]D$ −34°, λ_{max} 248 mμ (ε 13,500). *Anal.* ($C_{25}H_{32}F_2O_6$) C, H.

(18) H. M. Kissman, A. S. Hoffman, J. F. Poletto, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 950 (1962).

(19) Except where stated otherwise, optical rotations were measured in $CHCl_3$, uv spectra in MeOH, and nmr spectra in $CDCl_3$. We wish to thank Dr. L. Throop and his associates for the determination of physical properties of the products reported. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

6α,7α-Difluoromethylene-16α-methyl-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (4b).—A solution of 1 g of the enone **2b** in 3 ml of THF was added to 25 ml of 48% HF at 0° and the mixture was stirred for 1 hr.[14] The resulting solution was poured into excess $NaHCO_3$ solution and the product was extracted (EtOAc). Evaporation of the solvent and crystallization from EtOAc gave 750 mg of **4b**, mp 228–232°, $[\alpha]D$ +82°, λ_{max} 246 mμ (ε 15,050). *Anal.* ($C_{23}H_{30}F_2O_5$) C, H.

17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-11β-hydroxypregn-4-en-3-one (2a) was similarly prepared by addition of CF_2 to the enone **1a**. Crystals were obtained from ether; mp 226–230°, $[\alpha]D$ +37°, λ_{max} 246 mμ (ε 15,200). *Anal.* ($C_{24}H_{30}F_2O_6$) C, H, F.

6α,7α-Difluoromethylene-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (4a) was prepared by cleavage[14] of the bismethylenedioxy protecting group of the enone **2a**. Crystallization from EtOAc gave a product, mp 243–246°, $[\alpha]D$ + 155° (ethanol), λ_{max} 246 mμ (ε 15,200). *Anal.* ($C_{22}H_{28}F_2O_5$) C, H.

17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-11β-hydroxy-16α-methylpregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (10b).—A mixture of 1 g of the enone **2b** and 1 g of NaH (50% dispersion in mineral oil) in 6 ml of ethyl formate and 15 ml of dry C_6H_6 was stirred for 1 hr at 0°. Excess NaH was decomposed with EtOH, and the mixture was acidified with dilute HCl and extracted (C_6H_6). Evaporation gave the 2-formyl derivative. To this was added 20 ml of MeOH, 200 mg of *p*-fluorophenylhydrazine hydrochloride, and 500 mg of NaOAc in 2 ml of H_2O, and the mixture was stirred at 0° for 6 hr. The mixture was acidified with excess dilute HCl and allowed to stand for 1 hr at 20°. Dilution with H_2O, extraction with C_6H_6, and chromatography on silica gel gave 490 mg of amorphous solid, $[\alpha]D$ +38°, λ_{max} 271 mμ (ε 16,000). A satisfactory elemental analysis was not obtained.[20]

17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-11β-hydroxy-16α-methylpregn-4-ene[3,2-c]-2′-phenylpyrazole (10a) was similarly prepared; mp 285–286° dec, $[\alpha]D$ −41°, λ_{max} 267 mμ (ε 16,000). *Anal.* ($C_{32}H_{36}F_2N_2O_5$) C, H, F, N.

6α,7α-Difluoromethylene-16α-methyl-11β,21-trihydroxypregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (11b).—Cleavage of the side-chain protecting group of the pyrazole with HF[14] gave, after crystallization from MeOH, a product, mp 233–236°, λ_{max} 270 mμ (ε 16,620). *Anal.* ($C_{30}H_{33}F_3N_2O_4$) C, H, N.

6α,7α-Difluoromethylene-16α-methyl-11β,17α,21-trihydroxypregn-4-ene[3,2-c]-2′-phenylpyrazole (11a) was similarly prepared; mp 250–251°, $[\alpha]D$ +26°, λ_{max} 267 mμ (ε 15,200). *Anal.* ($C_{30}H_{34}F_2N_2O_4 \cdot H_2O$) C, H, N.

6α,7α-Difluoromethylene-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-Acetonide (15a).—The dienone **14a** was converted to the 21-tetrahydropyranyl ether **14c** by treatment with dihydropyran in C_6H_6 containing *p*-toluenesulfonic acid and with sodium difluorochloroacetate as in procedures described above. The tetrahydropyranyl ether was cleaved at this stage. The product obtained in 10% yield had mp 249–251° dec, $[\alpha]D$ +164°, λ_{max} 245 mμ (ε 15,300). *Anal.* ($C_{25}H_{32}F_2O_6$) C, H, F.

6α,7α-Difluoromethylene-11β,16α,17α,21-tetrahydroxypregn-4-en-20-one[3,2-c]-2′-phenylpyrazole 16,17-Acetonide 21-Acetate (16).—A solution of 107 mg of the enone (**15a**) in 15 ml of C_6H_6 and 0.1 ml of dihydropyran was dried by distilling part of the solvent. A solution of 1 mg of *p*-toluenesulfonic acid in 1 ml of C_6H_6 was added and the solution was kept at 20° for 45 min. The solution was washed with $NaHCO_3$ and evaporated giving the tetrahydropyranyl ether (**15c**) in quantitative yield. Subsequent formylation, pyrazole formation, and acetylation by procedures given above gave a 35% over-all yield of **16**: mp 264–267°, $[\alpha]D$ +79°, λ_{max} 266 mμ (ε 16,900). The nmr spectrum indicated that the product was a methanol solvate. *Anal.* ($C_{34}H_{38}F_2N_2O_6 \cdot 0.33MeOH$) C, H, F, N.

6α,7α-Difluoromethylene-6β-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16,17-acetonide 21-acetate (20b) was prepared from the enone **19**. The product had mp 245–247° dec, $[\alpha]D$ −622°, λ_{max} 40 mμ (ε 12,000). *Anal.* ($C_{27}H_{33}F_3O_7$) C, H.

6α,7α-Difluoromethylene-6β-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-en-20-one[3,2-c]-2′-p-fluorophenylpyrazole (21) was prepared from the enone **20c**. Crystallization from Me_2CO gave a solvate: mp 159–162°; λ_{max} 268 mμ (ε 16,600); nmr 6.45 (4-H), 7.0–7.7 ppm (aromatic and pyrazole H). A satisfactory elemental analysis was not obtained.[20]

6α,7α-Difluoromethylene-16α,17α,21-trihydroxypregna-4,9(11)-diene-3,20-dione 16,17-Acetonide 21-Acetate (17).—A solution of 1 ml of methanesulfonyl chloride in 20 ml of DMF and 5 ml of collidine containing 200 mg of SO_2[21] was added to 1.35 g of the enone **15b**. After 1.5 hr the solution was diluted with H_2O and the products were extracted with EtOAc which was washed (dilute HCl, H_2O). Evaporation and crystallization from MeOH gave solvated crystals, mp *ca.* 155°. This material was used without further purification in the next reaction.

9α,11β-Dichloro-6α,7α-difluoromethylene-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16,17-Acetonide 21-Acetate (18).—Chlorine was passed for 2 min through a solution of 600 mg of the dienone **17** in 26 ml of $CHCl_3$ and 3 ml of pyridine. The solution was purged with N_2 for 1 hr, washed (dilute H_2SO_4, H_2O), and evaporated. Preparative tlc gave 72 mg of amorphous product, $[\alpha]D$ +124°, λ_{max} 242 mμ (ε 13,500). *Anal.* ($C_{27}H_{32}Cl_2F_2O_6$) Cl.

17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-9α-fluoro-11β-hydroxy-16α-methylpregna-1,4-dien-3-one (6c).—A solution of 90 mg of the enone (**2c**)[11] and 110 mg of dichlorodicyanoquinone in 4 ml of dioxane was refluxed for 8 hr. The solution was then diluted with CH_2Cl_2 and filtered through a short column of silica gel. Evaporation of solvents gave 90 mg of an amorphous product, λ_{max} 249 mμ (ε 10,030), which was not purified further.

17α,20:20,21-Bismethylenedioxy-6β,7β-difluoromethylene-9α-fluoro-11β-hydroxy-16α-methylpregna-1,4-dien-3-one (7) was prepared by reaction of the enone **3**[11] with dichlorodicyanoquinone as in the example above. Crystallization from CH_2Cl_2 gave a product, mp 273–277° dec, $[\alpha]D$ −158°, λ_{max} 245 mμ (ε 12,470).

The following compounds were prepared by processes described above.

(a) **6α,7α-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (4c)**, mp 234–236°, λ_{max} 242 mμ (ε 12,900). *Anal.* ($C_{23}H_{29}F_3O_5$) C, H.

(b) **6β,7β-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregn-4-ene-3,20-dione (5)**, mp 273–278° dec, λ_{max} 252 mμ (ε 16,860). *Anal.* Calcd for $C_{23}H_{29}F_3O_5$: C, 62.40; H, 6.61. Found: C, 61.79; H, 5.95.

(c) **17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-11β-hydroxy-16α-methylpregna-1,4-dien-3-one (6b)**,[22] mp 280–282°, $[\alpha]D$ −52°, λ_{max} 244 mμ (ε 14,800). *Anal.* ($C_{25}H_{30}F_2O_6$) C, H, F.

(d) **6α,7α-Difluoromethylene-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione (8b)**,[22] mp 222–223°, $[\alpha]D$ +35°, λ_{max} 244 mμ (ε 15,500). *Anal.* ($C_{23}H_{28}O_5F_2$) C, H, F.

(e) **17α,20:20,21-Bismethylenedioxy-6β,7β-difluoromethylene-9α-fluoro-11β-hydroxy-16α-methylpregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (12)**, mp 217–219°. *Anal.* ($C_{32}H_{34}F_4N_2O_5$) C, H, N.

(f) **17α,20:20,21-Bismethylenedioxy-6α,7α-difluoromethylene-9α-fluoro-11β-hydroxy-16α-methylpregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (10c)**, amorphous, $[\alpha]D$ −48°. *Anal.* ($C_{32}H_{34}F_4N_2O_5$) C, H.

(g) **6α-7α-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (11c)**, mp 261–263°, $[\alpha]D$ +30°, λ_{max} 269 mμ (ε 15,570), nmr 1.65 ppm (19-H). *Anal.* ($C_{30}H_{32}F_4N_2O_4$) C, H, N.

(h) **6β,7β-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregn-4-ene[3,2-c]-2′-p-fluorophenylpyrazole (13)**, mp 237–240°, λ_{max} 268 mμ (ε 15,590), nmr 1.67 ppm (19-H). *Anal.* ($C_{30}H_{32}F_4N_2O_4$) C, H; N: calcd, 5.75; 6.34.

(i) **6α,7α-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (8c)**: amorphous; λ_{max} 249 mμ (ε 10,030); nmr 1.56 (19-H), 6.28, 6.37 (2-H), 7.11, 7.21 ppm (1-H) in deuteriopyridine. A satisfactory elemental analysis was not obtained;[20] however, the nmr spectrum unequivocally demonstrated the presence of the 1,4-diene system.

(j) **6β,7β-Difluoromethylene-9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (9)**: amorphous; $[\alpha]D$ −23°; λ_{max} 245 mμ (ε 12,200); nmr 1.19, 1.21 (19-H), 6.39, 6.49 (2-H), 7.58, 7.68 ppm (1-H) in deuteriopyridine. A satisfactory elemental analysis was not obtained;[20] the nmr spectrum was, however, consistent with the assigned structure.

(20) Elemental analysis of pyrazole derivatives was often unsatisfactory due to the formation of solvated crystals.

(21) G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, **29**, 1930 (1964).

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