ppm m (Hb), 2.63 s (NCH_3), 2.9 m (Hc), 4.5 m (Ha, Hd), 5.45 b exchange (OH). *Anal.* ($C_{11}H_{13}NO_2$) C, H, N.

(b) From isoxazolidine 17a. A soln of α-phenyl-*N*-methylnitrone (18, 16 g, 120 mmoles) in methyl acrylate (100 ml) was heated under reflux for 2 hr. After removal of solvent, the nmr showed the presence of 3 isomeric isoxazolidines as previously observed in the prepn of the pyridine compd **11a**. The mixt of isoxazolidines was hydrogenated (2 atm) in abs EtOH (100 ml) over Raney Ni (2.0 g). Al (150 g) chromatography of the residue obtd from the redn gave with 1% MeOH–$CHCl_3$ **16a** (7.0 g, 36.5 mmoles, 30%), identical with the material from **23**.

1-Methyl-5-phenyl-2,3-pyrrolidinedione (22). To a cooled, stirred soln of **16a** (1.0 g, 5.3 mmoles) in 40 ml of glacial HOAc was added dropwise (30 min) an ice cold soln of $Na_2Cr_2O_7 \cdot 2H_2O$ (0.8 g, 2.6 mmoles) in 20% H_2SO_4 (2.6 ml). Following an addnl 10 min at room temp, the reaction mixt was added to ice cold H_2O (350 ml) and the resulting soln extd with $CHCl_3$. Removal of the solvent gave an oil which solidified on standing. Crystn from Me_2CO–hexane gave pure **22** (0.9 g, 90%): mp 139–140°; ir 1170 cm^{-1} (ketone C=O), 1700 (lactam C=O); nmr δ = 2.57 ppm q, J_{bc} = 19 Hz, J_{ac} = 3.5 Hz (Hc), 3.00 s (NCH_3), 3.25 q, J_{bc} = 19 Hz, J_{ab} = 8 Hz (Hb), 4.93 q (Ha), 7.5 m (Ar). *Anal.* ($C_{11}H_{11}NO_2$) C, H, N.

1-Methyl-3-acetoxy-5-phenyl-3-pyrrolin-2-one (24). A soln of the dione **22** (0.44 g, 2.3 mmoles) in Ac_2O (5 ml) contg anhyd pyridine (1 ml) was maintained at 5° for 18 hr. The reaction mixt in ice H_2O (200 ml) was made basic ($NaHCO_3$) and extd with $CHCl_3$. The oil obtd was sublimed at 50° (0.01 mm) to yield pure enol acetate: mp 51–53°; nmr δ 2.30 ppm s (CCH_3), 2.83 s (NCH_3), 5.00 d, J = 2 Hz (Ha), 6.83 d, J = 2 Hz (Hb), 7.4 m (Ar). *Anal.* ($C_{13}H_{13}NO_3$) C, H, N.

***cis*-1-Methyl-3-acetoxy-5-phenyl-2-pyrrolidinone (25a).** The enol acetate **24** (0.40 g, 1.7 mmoles) in abs EtOH (10 ml) was hydrogenated (1 atm) over 10% Pd/C (100 mg) for 7 hr. The solid obtd after filtering and removing solvent was crystd from C_6H_6–hexane to yield 0.25 g (1.1 mmoles, 63%) pure **25a**: mp 110–111°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.8 ppm m (Hc), 2.6 s (CCH_3), 3.0 m (Hb), 4.43 t, J = 8 Hz (Ha), 5.38 t, J = 8 Hz (Hd), 7.4 m (Ar). *Anal.* ($C_{13}H_{15}NO_3$) calcd C, 66.94; H, 6.48; N, 6.00. Found: C, 67.51; H, 6.32; N, 6.42.

1-Methyl-*cis*-(3-acetoxy-5-phenyl)-*cis*-3,4-dideuterio-2-pyrrolidinone (26). The enol acetate **24** (0.35 g, 1.5 mmoles) was hydrogenated (1 atm) in EtOAc (20 ml) with D_2 (99%) over Pd/C (100 mg) for 4 hr. Work-up gave an oil which crystd from C_6H_6–hexane to yield pure **26**: mp 110–111°; ir 1750 cm^{-1} (ester C=O), 1700 (lactam C=O); nmr δ 1.80 ppm d, J = 8 Hz (Hc), 2.17 s (CCH_3), 4.40 d, J = 8 Hz (Ha), 7.4 m (Ar); mass spectrum ($C_{13}H_{13}D_2NO_3$) calcd: 235.11773, found: 235.11807, mass fragments, *m/e* 192, 175, 118, 107.

***trans*-1-Methyl-4-deuterio-5-phenyl-2,3-pyrrolidinedione (29).** A soln of **26** (200 mg, 0.84 mmole) in MeOH (5 ml) contg NaOH (100 mg) was heated under reflux for 1 hr. The nmr spectrum of the crude product **28** obtained by $CHCl_3$ extn of the hydrolysis residue showed no CH_3CO_2 signal although the C-3 D had completely exchanged during the reaction.

Oxidn of this material with $Na_2Cr_2O_7$–H_2SO_4 as previously described gave the required dione **29**: mp 139–140°; ir, 1770 cm^{-1} (ketone C=O), 1700 (lactam C=O); nmr δ^{100} 2.57 ppm d, J = 3.5 Hz (Hc), 2.91 s (NCH_3), 4.95 d, J = 3.5 Hz (Ha), 7.4 m (Ar).

References

(1) H. McKennis, Jr., S. L. Schwartz, and E. R. Bowman, *J. Biol. Chem.*, **239**, 3990 (1964).
(2) M. S. G. Clark, M. J. Rand, and S. Vanov, *Arch. Int. Pharmacodyn.*, **156**, 363 (1965).
(3) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman, and E. Tamaki, *J. Org. Chem.*, **28**, 383 (1963).
(4) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman, and E. Wada, *J. Amer. Chem. Soc.*, **81**, 3951 (1959).
(5) H. McKennis, Jr., L. B. Turnbull, S. L. Schwartz, E. Tamaki, and E. R. Bowman, *J. Biol. Chem.*, **237**, 541 (1962).
(6) E. R. Bowman and H. McKennis, Jr., *J. Pharmacol. Exp. Ther.*, **135**, 306 (1962).
(7) T. Stalhandske, *Acta Physiol. Scand.*, 78, 236 (1970); E. Hansson and C. G. Schmiterlow in "Tobacco Alkaloids and Related Compounds," U. S. von Euler, Ed., Pergamon Press, Long Island City, N. Y., 1965, p 83.
(8) F. C. Whitmore and D. P. Langlois, *J. Amer. Chem. Soc.*, **54**, 3441 (1932); A. Streitwieser and W. D. Schaeffer, *ibid.*, 79, 2888 (1957).
(9) W. Sadee, W. Garland, and N. Castagnoli, Jr., *J. Med. Chem.*, **14**, 643 (1971).
(10) E. R. Bowman and H. McKennis, *Biochem. Prep.*, **10**, 36 (1963).
(11) H. H. Wasserman and R. C. Koch, *J. Org. Chem.*, **27**, 35 (1962).
(12) P. L. Southwick, E. P. Previc, J. Casanova, Jr., E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).
(13) J. R. Merchant, V. Srinivasan, and R. M. Brandakar, *Indian J. Chem.*, **1**, 165 (1963).
(14) R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).
(15) M. S. Cushman and N. Castagnoli, Jr., *J. Org. Chem.*, **36**, 3404 (1971).
(16) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 747.
(17) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).
(18) N. Castagnoli, Jr., *J. Org. Chem.*, **34**, 3187 (1969).

(±)-6,6-Difluoronorgestrel, a New Synthetic Hormonal Steroid†

Alexander L. Johnson

Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.

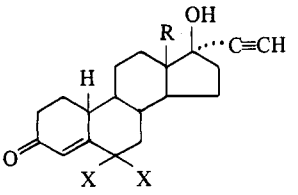
Received August 9, 1971

Totally synthetic (±)-6,6-difluoronorgestrel (**6**) was prepared from (±)-17β-hydroxy-13β-ethyl-4-gonen-3-one (**1**) using the NOF and SF_4 chemistry outlined in Scheme I. The title compound was prepared to see if the potentiation of progestational activity caused individually by 6,6-difluoro and 18-methyl substitution of norethindrone could be combined into a single compound. The progestational activity of **6** was approximately the same as that of (±)-norgestrel.

We recently described[1-8] the use of NOF and SF_4 as synthetic reagents which are useful in multistep syntheses of fluorinated steroids.[9-14] An important extension of this method has now been made in going from 13β-methyl steroids formally derived from natural materials to totally synthetic (±)-6,6-difluoronorgestrel (**6**), a compound of interest because of its relationship to the potent synthetic progestational hormones,[15,16] norethindrone (**7a**),[15,16] 6,6-difluoronorethindrone (**7b**),[7,8] and norgestrel (**7c**).[17-19] Since the individual potentiating effects of 18-methyl and 6,6-difluoro substitution in 17β-hydroxy-17α-ethynyl-19-norsteroids have been established,[15,16,20,21] **6** represents a combination of these effects within a single molecule.

Because **6** and **7c** possess an angular ethyl group, it is necessary to prepare them by total synthesis. The necessary intermediate, (±)-17β-hydroxy-13β-ethyl-4-gonen-3-one (**1**) was obtained by the classical 19-norsteroid total syntheses

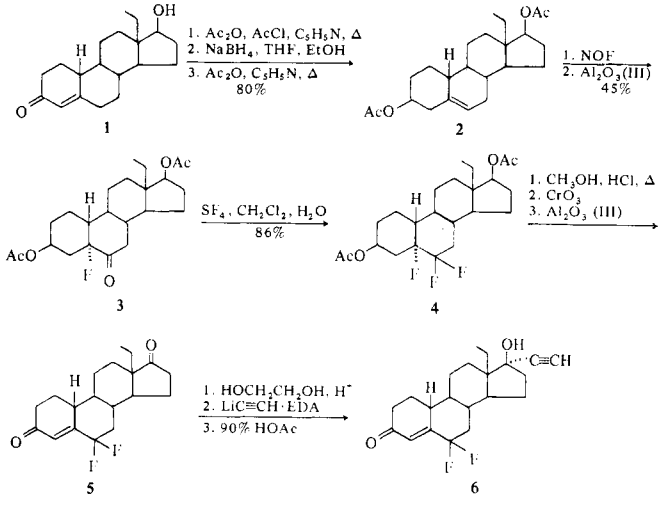
†This is Contribution No. 1789 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Del. 19898.



7a, X = H; R = CH_3
7b, X = F; R = CH_3
7c, X = H; R = C_2H_5

developed by Nazarov and Torgov,[22-25] Smith,[17-19] and Kuo, *et al.*[26] Several changes were incorporated into our procedure, and these are now briefly described. In place of the rather unstable 1-hydroxy-1-vinyl-6-methoxytetralin employed by earlier workers,[17-19,22-25] we used 6-methoxy-1,2,3,4-tetrahydronaphthylidene ethyl isothiuronium acetate (**8**)[26] in the initial condensation with 2-ethylcyclopentane-1,3-dione (**9b**) (Scheme II). This method was also used

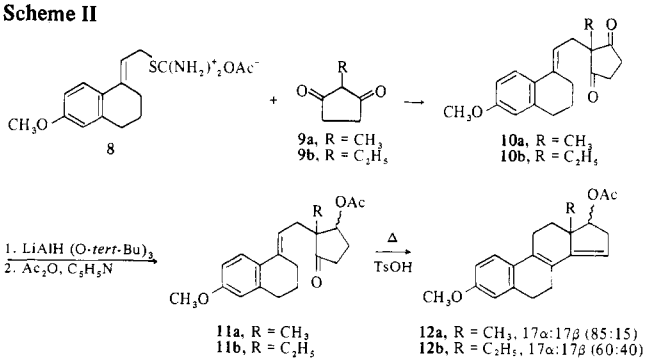
Scheme I



recently to prepare a 13β-propenyl steroid.[27] Several possibilities exist for the further conversion of the bicyclic intermediate **10b** to **1**. Immediate closure of the C ring followed by catalytic reduction of the newly formed 14(15) double bond[17-19] was discarded because the sensitive pentaenone resulting from the cyclization was difficult to purify and did not hydrogenate cleanly in our hands. Likewise, preliminary hydride reduction of the potential 17-carbonyl group in **10b** to a secondary hydroxyl, followed by acetylation to **11b** and cyclization to **12b** was abandoned because there was less steric control over the product than was observed in the 13β-methyl series[26] (**9a** → **10a** → **11a** → **12a**). Thus, while the 17α-acetoxy derivative constitutes up to 85% of the epimer mixture in **12a**, its proportion drops to 60% in **12b**, and the separation of the epimers of **12b** requires an extremely tedious chromatography. While the presence of the 17α epimer in **12b** may not be an important factor because of eventual conversion back to a carbonyl group, it was felt to detract from the stereospecificity of the catalytic reduction of the 14(15) double bond in **12b**. The lower yield in the preparation of **10b** and the loss in specificity in its reduction, compared to **10a**,[26] are attributable to the larger ethyl group.

The method of choice was to prepare the 17β-acetoxy epimer of **12b** by closure to the ketone,[17-19] followed by LiAlH(O-*tert*-Bu)$_3$ reduction to the 17β-alcohol and acetylation. In this way, the β face of **12b** in the neighborhood of the D ring is almost inaccessible to the catalyst, and a high

Scheme II



yield of the 14α,17β isomer of dihydro-**12b** was obtained on reduction. The remainder of the synthesis of **1** followed Smith's procedure.[17-19]

The rest of the synthesis is devoted to the fluorination and ethynylation procedures necessary to prepare the final product. The isomerization of the double bond from the 4 to the 5 position with concomitant protection of the 3 and 17 positions was done by preparing the 3,5-dien-3-ol acetate from **1**, selectively hydrolyzing the 3-acetate and reducing the 3,4 double bond with $NaBH_4$, and reacetylating the resulting 3β alcohol.‡ The 3β,17β-diacetate **2** was the only isomer isolated under the recrystallization conditions used, although this does not exclude the possibility that some 3α, 17β isomer remained in the mother liquors.‡ The NOF and SF_4 procedures[1-8] worked very satisfactorily in this series of compounds, the intermediate 5α-fluoro-6-nitrimine from the NOF reaction being readily hydrolyzed to the 5α-fluoro 6-ketone **3** by alumina chromatography. A fluoronitroso dimer[5,7,8] was not found among the products of this NOF reaction. The SF_4 fluorination of **3** to **4** proceeded smoothly in high yield, and at this point all the necessary functionalization has occurred for the final modifications of the molecule.

The important intermediate, (±)-6,6-difluoro-13β-ethyl-4-gonene-3,17-dione (**5**) was obtained from **4** by hydrolysis of the acetate groups, oxidation of the intermediate diol with Jones' reagent,[29-32] and dehydrofluorination of the resulting trifluorodione by alumina chromatography.[1-8] Selective ketalization of the 3-carbonyl of **5** is very clean when oxalic acid is used as the catalyst.[33] Only a trace of the 3,-17-bisethylene ketal of **5** was detected in the mass spectrum of the 3-monoethylene ketal of **5**. This is in contrast with the 6,6-difluoroestrane series,[7,8] where the corresponding 3-monoketal is accompanied by 14% of the bisketal. The 17 position of the 3-monoketal of **5** was ethynylated with lithium acetylide,[18,§,#] and the final product, (±)-6,6-difluoronorgestrel (**6**) was obtained by hydrolysis of the intermediate ethynylated ketal with 90% HOAc. Because **6** was prepared from optically inactive starting materials without any intermediate optical resolutions, this final product is the racemic form.

Biological Activity. The relative oral progestational activities of **6**, **7a-c**, obtained by Clauberg rabbit assay[15,20,21] using **7a** as the reference compound, are compared in Table I. The individual effects of the 6,6-difluoro and 18-methyl substitution upon **7a** are to enhance this activity two and

‡ *Cf.* the procedure used in the estrane by Villotti, *et al.*[28] Whereas these authors did not report any 3α,17β isomer, in separate experiments we have found about 10% of this isomer to be produced under our reducing conditions in the estrane series, identifiable in the recrystn mother liquors.

§ Obtained from Foote Mineral Company, Exton, Pa.

Cf. procedure of Huffman and Arapakos.[34]

Table I. Oral Progestational Activities of 6,6-Difluoro-19-norsteroids

Compound	Relative activity
(±)-6	7.0
7a	1.0
7b	2.0
(±)-7c	7.0

seven times, respectively (**7b, 7c**), but in combination, product **6** shows about the same activity as (±)-norgestrel, **7c**. This indicates, at least, that 6,6-difluoro substitution is not detrimental to the progestational activity of 17α-ethynyl-19-norsteroids.[1-8,21]

Experimental Section **

(±)-3-Methoxy-13-ethyl-8(14)-seco-1,3,5(10),9(11)-gonatetraene-14,17-dione (10b). The procedure of ref 26 was used to condense **8**[22,26] (0.065 mole) with **9b**[17-19] (0.071 mole) in the 2-phase H_2O-C_6H_6-Et_2O system. The crude secosteroid **10b**, purified by short-path distn at 135° (0.05 mm), and by recrystn from MeOH[18] was obtd in 61% yield, colorless needles, mp 60–60.5°. *Anal.* ($C_{20}H_{24}O_3$) C, H.

(±)-3-Methoxy-13β-ethyl-1,3,5(10),8(9),14(15)-gonapentaen-17β-ol 17β-Acetate (12b). a. A soln of **10b** (4.70 g) in the THF (120 ml) was reduced at 25° with LiAlH (O-*tert*-Bu)$_3$ (5.20 g) for 23 hr. The crude 17ξ-alcohol product, isolated by decompn with satd Na_2SO_4 and Et_2O extn, was left at 25° for 48 hr in C_5H_5N (8 ml) and Ac_2O (2 ml). The crude 17ξ-acetate (**11b**) isolated by evapn at 25° (0.1 mm), was converted to the epimer mixture **12b** by 3-hr reflux (Dean–Stark) in C_6H_6 (100 ml) and TsOH (2.72 g). By nmr,†† the brown oil (5.03 g) consisted of a 60:40 mixture of the 17α-OAc: 17β-OAc epimers of **12b**. Chromatography of the crude mixt on SilicAR CC-7 (100–200 mesh) taking 200-ml fractions of cyclohexane and cyclohexane–$CHCl_3$ mixtures enabled the pure 17β-acetate to be sepd by recrystn (Me_2CO–MeOH) of material (1.1364 g) from fractions 13, 14. Pure (±)-3-methoxy-13β-ethyl-1,3,5(10),8(9),14(15)-gonapentaen-17β-ol 17β-acetate, colorless crystals, mp 91–92°, ^{1}H nmr, δ 305 Hz (apparent triplet, 8 Hz sepn.†† *Anal.* ($C_{22}H_{26}O_3$) C, H.

b. A soln of **10b** (10.0 g) in C_6H_6 (200 ml) was heated to reflux and treated at once with TsOH (6.1 g). After 5-min reflux,‡‡ the soln was extd with 5% $NaHCO_3$, brine, dried (Na_2SO_4), and evapd to leave crude (±)-3-methoxy-13β-ethyl-1,3,5(10),9(11),14(15)-gonapentaen-17-one[17-19] as an oil. This was reduced in THF (150 ml) with LiAlH(O-*tert*-Bu)$_3$ (10.0 g) at 25° over 3 hr, and the resulting (±)-3-methoxy-13β-ethyl-1,3,5(10),9(11),14(15)-gonapentaen-17β-ol was isolated (satd Na_2SO_4, evapn) as a colorless syrup which was acetylated in a mixture of C_5H_5N (80 ml) and Ac_2O (20 ml) at 25° overnight. Isoln and chromatog as in a gave 10.39 g (96% from **10b**) of the 17β-OAc epimer of **12b**, which after recrystn was identical with that obtd in a.

(±)-3β-17β-Dihydroxy-13β-ethyl-5-gonene 3,17-Diacetate (3). a. A mixt of (±)-17β-hydroxy-13β-ethyl-4-gonen-3-one (**1**)§§ (13.80 g), Ac_2O (120 ml), AcCl (60 ml), and C_5H_5N (6 ml) was heated under reflux for 2 hr. The mixt was concd by vac distn and poured into MeOH (100 ml), yield 17.82 g (100%) of cryst (±)-3,17β-dihydroxy-13β-ethyl-3,5-gonadiene 3,17β-diacetate, mp 147–150°. The analytical sample (from MeOH and $CHCl_3$) had mp 147-149°. *Anal.* ($C_{23}H_{32}O_4$) C, H.

b. The dienol acetate (a) (10.0 g) was reduced in THF (100 ml) with $NaBH_4$ (4.17 g) in EtOH (150 ml) at 25° overnight. The crude (±)-3β,17β-dihydroxy-13β-ethyl-5-gonene 17β-acetate (8.4 g, 95%), isolated by pouring the mixt into ice H_2O (500 ml), was recrystd once (MeOH and H_2O), mp 138–160° dec. *Anal.* ($C_{21}H_{32}O_3$) C, H.

c. The 17β-acetate-3β-ol (b) was heated under reflux for 2 hr with Ac_2O (35 ml) and C_5H_5N (35 ml). The crude product, isolated by pouring the mixt onto ice, was recrystd from 300 ml of MeOH, yield 85% of **2**, mp 142–144°. Analytical sample, mp 144.5–145.5°. *Anal.* ($C_{23}H_{34}O_4$) C, H.

(±)-3β,17β-Dihydroxy-5α-fluoro-13β-ethylgonan-6-one 3β,17β-Diacetate (3). A soln of **2** (7.21 g) in CH_2Cl_2 (80 ml) at 0° was treated with a slow stream of NOF## (6.37 g). After standing at 0° overnight, (±-3β,17β-dihydroxy-5α-fluoro-6-nitrimino-13β-ethylgonane 3β,17β-diacetate was isolated as a yellow-green gum by washing the CH_2Cl_2 soln with brine and 5% $NaHCO_3$, drying (Na_2SO_4), and evapn. This material was taken up in 30 ml of C_6H_6 and filtered through 100 g of Woelm neut act III Al_2O_3 (C_6H_6 eluant). The crude fluoro ketone 3 was rechromatographed, then recrystd from Me_2CO (10 ml) and hexane (50 ml), yield 3.58 g (45%), mp 144.5–148°. Pure 3 had mp 150–154°. *Anal.* ($C_{23}H_{33}FO_5$) C, H.

(±)-3β,17β-Dihydroxy-5α,6,6-trifluoro-13β-ethylgonane (4). A mixt of fluoro ketone 3 (6.13 g), CH_2Cl_2 (80 ml), H_2O (2 ml), and SF_4 (160 g) was shaken in a bomb at 25° for 10 hr. The crude trifluoro compd **4**, isolated by rinsing the CH_2Cl_2 soln with H_2O, 5% $NaHCO_3$, and brine, drying (Na_2SO_4), and evapn was chromatographed on 200 g of Florisil using 100-ml fractions of hexane and Me_2CO–hexane. The purified compd from the 5% Me_2CO–hexane fractions, was recrystd from Me_2CO (20 ml) and hexane (50 ml), recovery 5.56 g (86%), mp 170–171°. *Anal.* ($C_{23}H_{33}F_3O_4$) C, H.

(±)-6,6-Difluoro-13β-ethyl-4-gonene-3,17-dione (5). a. Diacetate **4** (5.56 g) was hydrolyzed to (±)-3β,17β-dihydroxy-5α,6,6-trifluoro-13β-ethylgonane by heating at reflux for 1 hr in MeOH (50 ml) and concd HCl (6.0 ml). The crude product (4.37 g, 98%), isolated by diln with H_2O, can be recrystd from Me_2CO–H_2O as a colorless solid, mp 95° dec. *Anal.* ($C_{19}H_{29}F_3O_2$) C, H.

b. Diol (a) (4.3 g) was stirred at 15–25° for 30 min with Me_2CO (100 ml) and 8 *N* CrO_3[29-32] (12.0 ml). Diln to 550 ml with H_2O pptd colorless cryst (±)-5α,6,6-trifluoro-13β-ethylgona-3,17-dione (3.92 g, 92%). Recrystn (1:1 Me_2CO–hexane) gave pure dione, mp 189–190° dec. *Anal.* ($C_{19}H_{25}F_3O_2$) C, H.

c. Trifluorodione (b) (3.82 g) was dissolved in C_6H_6 and allowed to stand 30 min on 150 g of Woelm neut act III Al_2O_3. Elution with C_6H_6 (1000 ml) gave crude **5**, which was recrystd from Me_2CO–hexane, yield 3.21 g (90%). A further recrystn gave colorless crystals mp 171–172°. *Anal.**** Calcd for $C_{19}H_{24}F_2O_2$: C, 70.78; H, 7.50; Found: C, 72.16; H, 8.14.

(±)-6,6-Difluoronorgestrel (6). a. A mixture of dione **5** (2.50 g), ethylene glycol (7.5 ml), oxalic acid · $2H_2O$ (2.50 g), and C_6H_6 (100 ml) was heated under reflux (Dean–Stark) for 7 hr. Essentially pure 3-ethylene ketal of **5** was obtained by evapg the dried (Na_2SO_4) C_6H_6 soln after 5% $NaHCO_3$ extn. This ketal, colorless solid, had mp 186–193°. *Anal.* ($C_{21}H_{28}F_2O_3$) C, H, contained <1% of the 3,17-bisethylene ketal ($C_{23}H_{32}F_2O_3$) by mass spectroscopy.

b. Ketal (a) (1.0 g) was stirred under N_2 with DMAC (20 ml) and satd with C_2H_2. Lithium acetylide EDA complex# (1.0 g) was added, and the mixture stirred for 2 hr under C_2H_2. The crude ethynylated ketal, isolated by decompg the mixt with brine and C_6H_6 extn, was immediately hydrolyzed by stirring for 3 hr at 25° in 90% HOAc (25 ml). Crude (±)-6,6-difluoronorgestrel (**6**), isolated by pouring the mixt into H_2O, extg with CH_2Cl_2, washing the extracts with 5% $NaHCO_3$, drying (Na_2SO_4), and evaporating was purified by prep tlc in 1:3 cyclohexane–EtOAc and two recrystn from 2:1 cyclohexane–EtOAc. Pure **6**, colorless needles, has mp 163–164°, λ_{max}^{EtOH} 328 (ε 44) and 228 nm (ε 13,500), ν_{max}^{KBr} 1685 cm^{-1}. *Anal.* ($C_{21}H_{26}F_2O_2$), C, H, high-resolution mass spectroscopy.

Acknowledgments. The author wishes to thank Dr. G. A. Boswell, Jr., of this department for his encouragement and valuable discussions during this work, Dr. Frank Weigert for discussions of nmr spectra, and Mr. W. H. Rooks II and Dr. R. I. Dorfman, Syntex Corporation, Palo Alto, Calif., for

**Where analyses are indicated only by symbols of the elements or functions, analytical results for those elements or functions were within ±0.4% of the theoretical values. Tlc analyses and prepns were done on silica gel plates, mps (uncorrected) were determined in capillary tubes in a Mel-Temp apparatus. Routine spectral measurements are not reported, but were made for all compounds prepared on Perkin-Elmer 621 (ir), Cary 14 (uv), Varian Associates A-60 (nmr), and CEC-103 (mass spectrum) instruments. In a few cases, exact molecular masses were checked by ion-impact or field-ionization spectroscopy on a CEC-110 high-resolution mass spectrometer.

††Like Kuo, *et al.*,[26] we used the appearance of the C_{17} proton signal to indicate whether its orientation was α (apparent triplet or β (apparent doublet). In fact, this signal is the X part of an ABX pattern, but the weakness of the outer members and the J/δ values combine to give the observed patterns.

‡‡The sensitive pentaenone formed in this reaction is degraded by more prolonged heating.

§§Prepared from the 17β-OAc epimer of **12b** by catalytic redn of the 14(15) double bond, Li-NH_3 redn of the 8(9) double bond, Birch redn of the A ring, and acid hydrolysis of the 3-enol ether. The details do not differ significantly from those given by Smith, *et al.*,[17-19] for these reactions.

##Obtained from Ozark-Mahoning Company, Tulsa, Okla.

***No explanation is apparent for these poor analytical results. The spectral data and subsequent trnasformations of **5** are in accord with the structural assignment.

the biological evaluation of the compounds described herein.

References

(1) G. A. Boswell, Jr., U. S. Patent 3,219,673 (1965).
(2) G. A. Boswell, Jr., *Chem. Ind. (London)*, 1929 (1965).
(3) G. A. Boswell, Jr., *J. Org. Chem.*, 31, 991 (1966).
(4) S. Andreades and G. A. Boswell, Jr., U.S. Patent 3,320,291 (1967).
(5) G. A. Boswell, Jr., *J. Org. Chem.*, 33, 3699 (1968).
(6) G. A. Boswell, Jr., U. S. Patent 3,511,861 (1970).
(7) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *Angew. Chem.*, 83, 116 (1971); *Angew. Chem. Int. Ed., Engl.*, 10, 140 (1971).
(8) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *J. Org. Chem.*, 36, 575 (1971).
(9) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, 76, 1455 (1954).
(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, pp 593 and 682–686.
(11) C. Djerassi, "Steroid Reactions," Holden-Day Inc., San Francisco, Calif., 1963, pp 155–177.
(12) A. A. Akhrem, I. G. Reshetova, and Yu. A. Titov, *Russ. Chem. Rev.*, 34, 926 (1965).
(13) V. M. Khutoretskii, L. V. Okhlobystina, and A. A. Fainzilberg, *ibid.*, 36, 145 (1967).
(14) G. Schiemann and B. Cornils, "Chemie and Technologie cyclischer Fluorverbindungen," F. Enke, Stuttgart, 1969, pp 114–128.
(15) D. Lednicer, "Contraception, The Chemical Control of Fertility," Marcel Dekker, New York, N. Y., 1969.
(16) P. D. Klimstra, "The Chemistry and Biochemistry of Steroids," Intra-Science Research Foundation, Santa Monica, Calif., 1969, Chapter VII.
(17) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLaughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).
(18) H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, B. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics, and D. H. P. Watson, *ibid.*, 4472 (1964).
(19) D. Hartley and H. Smith, *ibid.*, 4492 (1964).
(20) R. A. Edgren, H. Smith, D. L. Peterson, and D. L. Carter, *Steroids*, 2, 319 (1963).
(21) W. H. Rooks II, and R. I. Dorfman, *Contraception*, 1, 403 (1970).
(22) I. N. Nazarov, I. V. Torgov, and G. P. Verkholetova, *Dokl. Akad. Nauk SSSR*, 112, 1067 (1957).
(23) A. A. Akhrem and Yu. A. Titov, "Total Steroid Synthesis," English translation by B. J. Hazzard, Plenum Press, New York, N. Y., 1970, pp 111–175.
(24) Ref 15, pp 86, 88, 104, 105.
(25) Ref 16, p 65.
(26) C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 33, 3126 (1968).
(27) K. Yoshioka, G. Goto, T. Asako, K. Hiraga, and T. Miki, *Chem. Commun.*, 336 (1971).
(28) R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, 81, 4566 (1959).
(29) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(30) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951).
(31) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 21, 1547 (1956).
(32) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).
(33) J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, 18, 309 (1962).
(34) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, 30, 1604 (1965).

Steroid Side-Chain Oxazolidines†,‡

Eugene J. Agnello* and Peter R. Farina

Chemistry Department, Hofstra University, Hempstead, New York 11550.

Received June 24, 1971

Steroid 20,21-glyoxals reacted selectively at C-21 with N-monosubstituted ethanolamines giving moderate yields of oxazolidines which appear to be mixtures of C_{21} epimers. *N*-Methyloxazolidines were obtained simply by heating the glyoxal in a solvent with 2 to 5 molar equivalents of substituted ethanolamine at 50 to 100° for 1–2 hr. The *N*-methyloxazolidine obtained from prednisolone 21-aldehyde was more active than hydrocortisone in the thymolytic assay; the corresponding compound "S" derivative was inactive. The product obtained from prednisolone 21-aldehyde and (−)-epinephrine was inactive in the thymolytic assay but exhibited significant adrenal-suppression activity.

Steroids modified by conversion of a functional group to a heterocyclic moiety may have their biological activities affected profoundly. Well-known examples include antiinflammatory[1] and anabolic[2] agents. The selectivity[3] with which the C-21 aldehyde group of polyfunctional steroids reacts with diazomethane prompted us to investigate other reactions which might provide access to steroid heterocycles *via* routes involving relatively mild reaction conditions. This paper describes our investigation of the reaction of some steroid 21-aldehydes with ethanolamines designed to provide side-chain oxazolidines for testing the group's effectiveness in changing the spectrum of activities of well-known corticoids.

The reaction of unsubstituted ethanolamine with aliphatic carbonyl compounds was reported some time ago by Knorr[4] and later by Cope and Hancock.[5] The results of those studies and of the extensive investigations of the Bergmann group[6] have shown that α,β-unsaturated carbonyl compounds form Schiff bases (I) and that saturated aldehydes and ketones form oxazolidines (II). Hindered ketones, however, such as methyl isobutyl ketone, give equilibrium mixtures of I and II.

The results obtained by Irmscher and his coworkers[7] with ethanolamine and a variety of steroid ketones are generally consistent with the pattern described by the earlier investigators for nonsteroidal compounds. Thus, various α,β-unsaturated 3-keto steroids afforded Schiff bases and saturated 3- and 6- keto steroids produced oxazolidines. However, saturated 17- and 20-ketones gave Schiff bases.

Our early experiments utilizing ethanolamine and 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-al (prednisolone-21-aldehyde) (IIIa) gave intractable products consisting of several components (tlc evidence), indicating perhaps that the reactivity of the 21-aldehyde group toward this reagent was not sufficiently greater than the 3- and 20-keto groups

†A preliminary report of this work was presented before the Division of Medicinal Chemistry, 156th National Meeting of the American Chemical Society, Sept 1968, Atlantic City, N. J.

‡This investigation was supported in part by Public Health Service Research Grant No. 5-R01-AM-10853.