

ppm m (Hb), 2.63 s (NCH<sub>3</sub>), 2.9 m (Hc), 4.5 m (Ha, Hd), 5.45 b exchange (OH). *Anal.* (C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>) C, H, N.

(b) From isoxazolidine 17a. A soln of  $\alpha$ -phenyl-*N*-methylnitron (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<sub>3</sub> 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<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> · 2H<sub>2</sub>O (0.8 g, 2.6 mmoles) in 20% H<sub>2</sub>SO<sub>4</sub> (2.6 ml). Following an addnl 10 min at room temp, the reaction mixt was added to ice cold H<sub>2</sub>O (350 ml) and the resulting soln extd with CHCl<sub>3</sub>. Removal of the solvent gave an oil which solidified on standing. Crystn from Me<sub>2</sub>CO-hexane gave pure 22 (0.9 g, 90%): mp 139–140°; ir 1170 cm<sup>-1</sup> (ketone C=O), 1700 (lactam C=O); nmr  $\delta$  = 2.57 ppm q,  $J_{bc}$  = 19 Hz,  $J_{ac}$  = 3.5 Hz (Hc), 3.00 s (NCH<sub>3</sub>), 3.25 q,  $J_{bc}$  = 19 Hz,  $J_{ab}$  = 8 Hz (Hb), 4.93 q (Ha), 7.5 m (Ar). *Anal.* (C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>) 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<sub>2</sub>O (5 ml) contg anhyd pyridine (1 ml) was maintained at 5° for 18 hr. The reaction mixt in ice H<sub>2</sub>O (200 ml) was made basic (NaHCO<sub>3</sub>) and extd with CHCl<sub>3</sub>. The oil obtd was sublimed at 50° (0.01 mm) to yield pure enol acetate: mp 51–53°; nmr  $\delta$  2.30 ppm s (CCH<sub>3</sub>), 2.83 s (NCH<sub>3</sub>), 5.00 d,  $J$  = 2 Hz (Ha), 6.83 d,  $J$  = 2 Hz (Hb), 7.4 m (Ar). *Anal.* (C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub>) 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<sub>6</sub>H<sub>6</sub>-hexane to yield 0.25 g (1.1 mmoles, 63%) pure 25a: mp 110–111°; ir 1750 cm<sup>-1</sup> (ester C=O), 1700 (lactam C=O); nmr  $\delta$  1.8 ppm m (Hc), 2.6 s (CCH<sub>3</sub>), 3.0 m (Hb), 4.43 t,  $J$  = 8 Hz (Ha), 5.38 t,  $J$  = 8 Hz (Hd), 7.4 m (Ar). *Anal.* (C<sub>13</sub>H<sub>15</sub>NO<sub>2</sub>) 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<sub>2</sub> (99%) over Pd/C (100 mg) for 4 hr. Work-up gave an oil which crystd from C<sub>6</sub>H<sub>6</sub>-hexane to yield pure 26: mp 110–111°; ir 1750 cm<sup>-1</sup> (ester C=O), 1700 (lactam C=O); nmr  $\delta$  1.80 ppm d,  $J$  = 8 Hz (Hc), 2.17 s (CCH<sub>3</sub>), 4.40 d,  $J$  = 8 Hz (Ha), 7.4 m (Ar); mass spectrum (C<sub>13</sub>H<sub>13</sub>D<sub>2</sub>NO<sub>2</sub>) 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<sub>3</sub> extn of the hydrolysis residue showed no CH<sub>3</sub>CO<sub>2</sub> signal although the C-3 D had completely exchanged during the reaction.

Oxidn of this material with Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>-H<sub>2</sub>SO<sub>4</sub> as previously described gave the required dione 29: mp 139–140°; ir, 1770 cm<sup>-1</sup> (ketone C=O), 1700 (lactam C=O); nmr  $\delta$ <sup>100</sup> 2.57 ppm d,  $J$  = 3.5 Hz (Hc), 2.91 s (NCH<sub>3</sub>), 4.95 d,  $J$  = 3.5 Hz (Ha), 7.4 m (Ar).

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## (±)-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.

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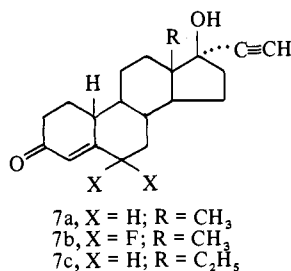
Totally synthetic (±)-6,6-difluoronorgestrel (6) was prepared from (±)-17 $\beta$ -hydroxy-13 $\beta$ -ethyl-4-gonen-3-one (1) using the NOF and SF<sub>4</sub> chemistry outlined in Scheme I. The title compound was prepared to see if the potentiation of progestational activity caused individually by 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<sup>1-8</sup> the use of NOF and SF<sub>4</sub> as synthetic reagents which are useful in multistep syntheses of fluorinated steroids.<sup>9-14</sup> An important extension of this method has now been made in going from 13 $\beta$ -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 pro-

gestational hormones,<sup>15,16</sup> norethindrone (7a),<sup>15,16</sup> 6,6-difluoronorethindrone (7b),<sup>7,8</sup> and norgestrel (7c).<sup>17-19</sup> Since the individual potentiating effects of 18-methyl and 6,6-difluoro substitution in 17 $\beta$ -hydroxy-17 $\alpha$ -ethynyl-19-norsteroids have been established,<sup>15,16,20,21</sup> 6 represents a combination of these effects within a single molecule.

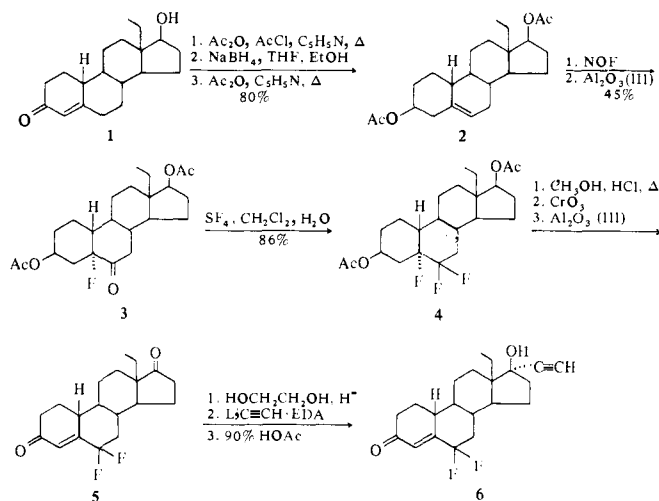
Because 6 and 7c possess an angular ethyl group, it is necessary to prepare them by total synthesis. The necessary intermediate, (±)-17 $\beta$ -hydroxy-13 $\beta$ -ethyl-4-gonen-3-one (1) was obtained by the classical 19-norsteroid total syntheses

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developed by Nazarov and Torgov,<sup>22-25</sup> Smith,<sup>17-19</sup> and Kuo, *et al.*<sup>26</sup> 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,<sup>17-19,22-25</sup> we used 6-methoxy-1,2,3,4-tetrahydronaphthylidene ethyl isothiuronium acetate (8)<sup>26</sup> in the initial condensation with 2-ethylcyclopentane-1,3-dione (9b) (Scheme II). This method was also used

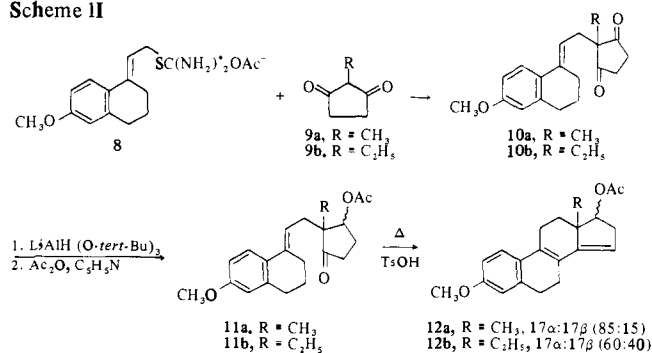
## Scheme I



recently to prepare a 13β-propenyl steroid.<sup>27</sup> 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<sup>17-19</sup> was discarded because the sensitive pentanone 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<sup>26</sup> (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**,<sup>26</sup> 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,<sup>17-19</sup> followed by LiAlH(O-*tert*-Bu)<sub>3</sub> 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.<sup>17-19</sup>

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<sub>4</sub>, 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<sub>4</sub> procedures<sup>1-8</sup> 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<sup>5,7,8</sup> was not found among the products of this NOF reaction. The SF<sub>4</sub> 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,<sup>29-32</sup> and dehydrofluorination of the resulting trifluorodione by alumina chromatography.<sup>1-8</sup> Selective ketalization of the 3-carbonyl of **5** is very clean when oxalic acid is used as the catalyst.<sup>33</sup> 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,<sup>7,8</sup> 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,<sup>18,8,§</sup> 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<sup>15,20,21</sup> 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.*<sup>28</sup> Where 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.<sup>34</sup>

Table 1. 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 17 $\alpha$ -ethynyl-19-norsteroids.<sup>1-8,21</sup>

### 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<sup>23,26</sup> (0.065 mole) with 9b<sup>17-19</sup> (0.071 mole) in the 2-phase H<sub>2</sub>O-C<sub>6</sub>H<sub>6</sub>-Et<sub>2</sub>O system. The crude secosteroid 10b, purified by short-path distn at 135° (0.05 mm), and by recrystn from MeOH<sup>18</sup> was obt'd in 61% yield, colorless needles, mp 60-60.5°. *Anal.* (C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>) C, H.

(±)-3-Methoxy-13 $\beta$ -ethyl-1,3,5(10),8(9),14(15)-gonapentaen-17 $\beta$ -ol 17 $\beta$ -Acetate (12b). a. A soln of 10b (4.70 g) in the THF (120 ml) was reduced at 25° with LiAlH (O-*tert*-Bu)<sub>3</sub> (5.20 g) for 23 hr. The crude 17 $\xi$ -alcohol product, isolated by decompn with sat'd Na<sub>2</sub>SO<sub>4</sub> and Et<sub>2</sub>O extn, was left at 25° for 48 hr in C<sub>5</sub>H<sub>5</sub>N (8 ml) and Ac<sub>2</sub>O (2 ml). The crude 17 $\xi$ -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<sub>6</sub>H<sub>6</sub> (100 ml) and TsOH (2.72 g). By nmr,†† the brown oil (5.03 g) consisted of a 60:40 mixture of the 17 $\alpha$ -OAc: 17 $\beta$ -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<sub>3</sub> mixtures enabled the pure 17 $\beta$ -acetate to be sep'd by recrystn (Me<sub>2</sub>CO-MeOH) of material (1.1364 g) from fractions 13, 14. Pure (±)-3-methoxy-13 $\beta$ -ethyl-1,3,5(10),8(9),14(15)-gonapentaen-17 $\beta$ -ol 17 $\beta$ -acetate, colorless crystals, mp 91-92°. <sup>1</sup>H nmr,  $\delta$  305 Hz (apparent triplet, 8 Hz sep'n.†† *Anal.* (C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>) C, H.

b. A soln of 10b (10.0 g) in C<sub>6</sub>H<sub>6</sub> (200 ml) was heated to reflux and treated at once with TsOH (6.1 g). After 5-min reflux,‡‡ the soln was ext'd with 5% NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evap'd to leave crude (±)-3-methoxy-13 $\beta$ -ethyl-1,3,5(10),9(11),14(15)-gonapentaen-17-one<sup>17-19</sup> as an oil. This was reduced in THF (150 ml) with LiAlH(O-*tert*-Bu)<sub>3</sub> (10.0 g) at 25° over 3 hr, and the resulting (±)-3-methoxy-13 $\beta$ -ethyl-1,3,5(10),9(11),14(15)-gonapentaen-17 $\beta$ -ol was isolated (sat'd Na<sub>2</sub>SO<sub>4</sub>, evapn) as a colorless syrup which was acetylated in a mixture of C<sub>5</sub>H<sub>5</sub>N (80 ml) and Ac<sub>2</sub>O (20 ml) at 25° overnight. Isoln and chromatog as in a gave 10.39 g (96% from 10b) of the 17 $\beta$ -OAc epimer of 12b, which after recrystn was identical with that obt'd in a.

(±)-3 $\beta$ -17 $\beta$ -Dihydroxy-13 $\beta$ -ethyl-5-gonene 3,17-Diacetate (3). a. A mixt of (±)-17 $\beta$ -hydroxy-13 $\beta$ -ethyl-4-gonen-3-one (1)§§ (13.80 g), Ac<sub>2</sub>O (120 ml), AcCl (60 ml), and C<sub>5</sub>H<sub>5</sub>N (6 ml) was heated under reflux for 2 hr. The mixt was conc'd by vac distn and poured into MeOH (100 ml), yield 17.82 g (100%) of cryst (±)-3,17 $\beta$ -dihydroxy-13 $\beta$ -ethyl-3,5-gonadiene 3,17 $\beta$ -diacetate, mp 147-150°. The ana-

\*\*Where analyses are indicated only by symbols of the elements or functions, analytical results for those elements or functions were within  $\pm 0.4\%$  of the theoretical values. Tlc analyses and preps 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.*,<sup>26</sup> we used the appearance of the C<sub>17</sub> proton signal to indicate whether its orientation was  $\alpha$  (apparent triplet or  $\beta$  (apparent doublet)). In fact, this signal is the X part of an ABX pattern, but the weakness of the outer members and the J/ $\delta$  values combine to give the observed patterns.

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

§§Prepared from the 17 $\beta$ -OAc epimer of 12b by catalytic reduct of the 14(15) double bond, Li-NH<sub>2</sub> reduct of the 8(9) double bond, Birch reduct 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.*,<sup>17-19</sup> for these reactions.

lytical sample (from MeOH and CHCl<sub>3</sub>) had mp 147-149°. *Anal.* (C<sub>23</sub>H<sub>32</sub>O<sub>4</sub>) C, H.

b. The dienol acetate (a) (10.0 g) was reduced in THF (100 ml) with NaBH<sub>4</sub> (4.17 g) in EtOH (150 ml) at 25° overnight. The crude (±)-3 $\beta$ ,17 $\beta$ -dihydroxy-13 $\beta$ -ethyl-5-gonene 17 $\beta$ -acetate (8.4 g, 95%), isolated by pouring the mixt into ice H<sub>2</sub>O (500 ml), was recryst'd once (MeOH and H<sub>2</sub>O), mp 138-160° dec. *Anal.* (C<sub>21</sub>H<sub>32</sub>O<sub>3</sub>) C, H.

c. The 17 $\beta$ -acetate-3 $\beta$ -ol (b) was heated under reflux for 2 hr with Ac<sub>2</sub>O (35 ml) and C<sub>5</sub>H<sub>5</sub>N (35 ml). The crude product, isolated by pouring the mixt onto ice, was recryst'd from 300 ml of MeOH, yield 85% of 2, mp 142-144°. Analytical sample, mp 144.5-145.5°. *Anal.* (C<sub>23</sub>H<sub>34</sub>O<sub>4</sub>) C, H.

(±)-3 $\beta$ ,17 $\beta$ -Dihydroxy-5 $\alpha$ -fluoro-13 $\beta$ -ethylgonan-6-one 3 $\beta$ ,17 $\beta$ -Diacetate (3). A soln of 2 (7.21 g) in CH<sub>2</sub>Cl<sub>2</sub> (80 ml) at 0° was treated with a slow stream of NOF## (6.37 g). After standing at 0° overnight, (±)-3 $\beta$ ,17 $\beta$ -dihydroxy-5 $\alpha$ -fluoro-6-nitrimino-13 $\beta$ -ethylgonane 3 $\beta$ ,17 $\beta$ -diacetate was isolated as a yellow-green gum by washing the CH<sub>2</sub>Cl<sub>2</sub> soln with brine and 5% NaHCO<sub>3</sub>, drying (Na<sub>2</sub>SO<sub>4</sub>), and evapn. This material was taken up in 30 ml of C<sub>6</sub>H<sub>6</sub> and filtered through 100 g of Woelm neut act III Al<sub>2</sub>O<sub>3</sub> (C<sub>6</sub>H<sub>6</sub> eluant). The crude fluoro ketone 3 was rechromatographed, then recryst'd from Me<sub>2</sub>CO (10 ml) and hexane (50 ml), yield 3.58 g (45%), mp 144.5-148°. Pure 3 had mp 150-154°. *Anal.* (C<sub>23</sub>H<sub>33</sub>F<sub>2</sub>O<sub>4</sub>) C, H.

(±)-3 $\beta$ ,17 $\beta$ -Dihydroxy-5 $\alpha$ ,6,6-trifluoro-13 $\beta$ -ethylgonane (4). A mixt of fluoro ketone 3 (6.13 g), CH<sub>2</sub>Cl<sub>2</sub> (80 ml), H<sub>2</sub>O (2 ml), and SF<sub>4</sub> (160 g) was shaken in a bomb at 25° for 10 hr. The crude trifluoro comp'd 4, isolated by rinsing the CH<sub>2</sub>Cl<sub>2</sub> soln with H<sub>2</sub>O, 5% NaHCO<sub>3</sub>, and brine, drying (Na<sub>2</sub>SO<sub>4</sub>), and evapn was chromatographed on 200 g of Florisil using 100-ml fractions of hexane and Me<sub>2</sub>CO-hexane. The purified comp'd from the 5% Me<sub>2</sub>CO-hexane fractions, was recryst'd from Me<sub>2</sub>CO (20 ml) and hexane (50 ml), recovery 5.56 g (86%), mp 170-171°. *Anal.* (C<sub>23</sub>H<sub>33</sub>F<sub>3</sub>O<sub>4</sub>) C, H.

(±)-6,6-Difluoro-13 $\beta$ -ethyl-4-gonene-3,17-dione (5). a. Diacetate 4 (5.56 g) was hydrolyzed to (±)-3 $\beta$ ,17 $\beta$ -dihydroxy-5 $\alpha$ ,6,6-trifluoro-13 $\beta$ -ethylgonane by heating at reflux for 1 hr in MeOH (50 ml) and conc'd HCl (6.0 ml). The crude product (4.37 g, 98%), isolated by diln with H<sub>2</sub>O, can be recryst'd from Me<sub>2</sub>CO-H<sub>2</sub>O as a colorless solid, mp 95° dec. *Anal.* (C<sub>19</sub>H<sub>25</sub>F<sub>3</sub>O<sub>2</sub>) C, H.

b. Diol (a) (4.3 g) was stirred at 15-25° for 30 min with Me<sub>2</sub>CO (100 ml) and 8 N CrO<sub>3</sub><sup>29-32</sup> (12.0 ml). Diln to 550 ml with H<sub>2</sub>O ppt'd colorless cryst (±)-5 $\alpha$ ,6,6-trifluoro-13 $\beta$ -ethylgonan-3,17-dione (3.92 g, 92%). Recrystn (1:1 Me<sub>2</sub>CO-hexane) gave pure dione, mp 189-190° dec. *Anal.* (C<sub>19</sub>H<sub>25</sub>F<sub>3</sub>O<sub>2</sub>) C, H.

c. Trifluorodione (b) (3.82 g) was dissolved in C<sub>6</sub>H<sub>6</sub> and allowed to stand 30 min on 150 g of Woelm neut act III Al<sub>2</sub>O<sub>3</sub>. Elution with C<sub>6</sub>H<sub>6</sub> (1000 ml) gave crude 5, which was recryst'd from Me<sub>2</sub>CO-hexane, yield 3.21 g (90%). A further recrystn gave colorless crystals mp 171-172°. *Anal.* \*\*\* Calcd for C<sub>19</sub>H<sub>24</sub>F<sub>2</sub>O<sub>2</sub>: 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<sub>2</sub>O (2.50 g), and C<sub>6</sub>H<sub>6</sub> (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<sub>2</sub>SO<sub>4</sub>) C<sub>6</sub>H<sub>6</sub> soln after 5% NaHCO<sub>3</sub> extn. This ketal, colorless solid, had mp 186-193°. *Anal.* (C<sub>21</sub>H<sub>28</sub>F<sub>2</sub>O<sub>2</sub>) C, H, contained <1% of the 3,17-bisethylene ketal (C<sub>23</sub>H<sub>32</sub>F<sub>2</sub>O<sub>3</sub>) by mass spectroscopy.

b. Ketal (a) (1.0 g) was stirred under N<sub>2</sub> with DMAC (20 ml) and sat'd with C<sub>2</sub>H<sub>2</sub>. Lithium acetylide EDA complex# (1.0 g) was added, and the mixture stirred for 2 hr under C<sub>2</sub>H<sub>2</sub>. The crude ethynylated ketal, isolated by decomp'g the mixt with brine and C<sub>6</sub>H<sub>6</sub> 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<sub>2</sub>O, extg with CH<sub>2</sub>Cl<sub>2</sub>, washing the extracts with 5% NaHCO<sub>3</sub>, drying (Na<sub>2</sub>SO<sub>4</sub>), 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°,  $\lambda_{\text{max}}^{\text{EtOH}}$  328 ( $\epsilon$  44) and 228 nm ( $\epsilon$  13,500),  $\nu_{\text{max}}^{\text{KBr}}$  1685 cm<sup>-1</sup>. *Anal.* (C<sub>21</sub>H<sub>26</sub>F<sub>2</sub>O<sub>2</sub>) C, H, high-resolution mass spectroscopy.

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

the biological evaluation of the compounds described herein.

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## 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<sub>21</sub> 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<sup>1</sup> and anabolic<sup>2</sup> agents. The selectivity<sup>3</sup> 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<sup>4</sup>

and later by Cope and Hancock.<sup>5</sup> The results of those studies and of the extensive investigations of the Bergmann group<sup>6</sup> have shown that  $\alpha,\beta$ -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<sup>7</sup> with ethanolamine and a variety of steroid ketones are generally consistent with the pattern described by the earlier investigators for nonsteroidal compounds. Thus, various  $\alpha,\beta$ -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 11 $\beta$ ,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

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