and 200 mg/kg ip. These results indicate relatively weak peripheral anticholinergic activity and this was confirmed *in vitro* on the guinea pig isolated ileum when a pA_2[6] of 6.7 for acetylcholine was obtained. Central anticholinergic activity was assessed by measuring the ability of **4** to antagonize the tremors induced by oxotremorine.[7] Compd **4** was given orally at 50, 100, and 200 mg/kg to groups of 8 mice (CFW) 1 hr before the iv injection of 150 μg/kg of oxotremorine, and symptoms were observed for 20 min. A control group treated with oxotremorine alone was tested concurrently; 50 mg/kg of **4** caused a 40% reduction in tremor compared with the controls, but the effect was not increased at the higher doses. Almost complete inhibition of the salivation and lachrymation caused by the oxotremorine occurred at all doses used, reflecting the peripheral anticholinergic effect of **4**. A selective central anticholinergic effect of **4** was not demonstrated therefore.

Experimental Section‡

2-Ethoxycarbonyl-1-adamant-1-yl-1-phenylethanol (2). A soln of phenyl adamant-1-yl ketone[8] (24.03 g, 0.1 mole) and ethyl bromoacetate (11.15 ml, 0.1 mole) in 150 ml of a 2:1 mixture of C_6H_6 and toluene was added over 45 min to 6.9 g of Zn–Cu couple and was allowed to come to reflux. Two further equivalents of Zn–Cu couple and ester were added at 30-min intervals and reflux was continued for 1 hr. The solid, after extn and removal of solvent, was recrystd from MeOH to give 24.6 g of **2** (75%); mp 110.5–111°. *Anal.* ($C_{21}H_{28}O_3$) C, H, O.

***N*-(2-Adamant-1-yl-2-hydroxy-2-phenylpropionyl)pyrrolidine (5).** Compd **2** (7.0 g, 21 mmoles) and approx 50 mg of *tert*-BuOK were refluxed with 70 ml of pyrrolidine for 72 hr. The cream-colored solid left after evapn was recrystd from C_6H_6–hexane to give 4.9 g of **5** (65%); mp 168–169°. *Anal.* ($C_{23}H_{31}NO_2$) C, H, N, O.

1-Adamant-1-yl-1-phenyl-3-*N*-pyrrolidino-1-propanol Hydrochloride (4). Compd **5** (2.0 g, 5.7 mmoles) reduced with LAH (THF) for 20 hr after extn gave the amine which was sepd as the HCl salt and recrystd from EtOH, to give 1.1 g of **4** (52%); mp 278°. *Anal.* ($C_{23}H_{34}ClNO$) C, H, Cl, N, O.

3-Adamant-1-yl-3-hydroxy-3-phenylpropionic Acid (3). Compd **2** (1.64 g, 5 mmoles), sapond with KOH (1.65 g) in 90% aqueous EtOH (35 ml), after recrystn from MeOH–H_2O, gave 1.35 g (90%); mp 210°. *Anal.* ($C_{19}H_{24}O_3$) C, H, O.

4-Adamant-1-yl-4-phenyl-2-oxetanone (6). Compd **3** (1.0 g, 3 mmoles), warmed with 5 ml of $SOCl_2$ and 2 drops of pyridine for 30 min, after extn, gave a residue which was unchanged after reflux with pyrrolidine in ether for 15 min. The residue was recrystd from *n*-hexane to give 0.9 g of **6** (95%); mp 112–112.5°, ir C=O (β-lactone), 1830 cm^{-1}; mass spectrum M^+ 282. No amide **5** was detected by tlc. *Anal.* ($C_{19}H_{22}O_2$) C, H, O.

Acknowledgments. We thank Dr. R. W. Brimblecombe (C.D.E.E., Porton Down, Wiltshire, England) for the supply of oxotremorine, Mrs. S. Sutton and K. G. Cranstone for valuable technical assistance, and Dr. D. M. Rackham and associates for spectroscopic data.

References

(1) J. K. Chakrabarti and A. Todd, *J. Chem. Soc. D*, 556 (1971) (paper 4).
(2) R. B. Moffett, *J. Med. Chem.*, **12**, 715 (1969).
(3) R. S. Schwab, A. C. England, D. C. Poskanzer, and R. R. Young, *J. Amer. Med. Ass.*, **208**, 1168 (1969).
(4) D. W. Eoplin, "The Pharmacological Basis of Therapeutics," 3rd ed, L. S. Goodman and A. Gilman, Ed., Macmillan, New York, N.Y., 1965, p. 242.
(5) N. K. Drake, C. H. Eaker, and W. Shenk, *J. Amer. Chem. Soc.*, 70, 677 (1948).
(6) H. O. Schild, *Brit. J. Pharmacol.*, **2**, 189 (1947).
(7) A. K. Cho, W. L. Haslett, and D. J. Jendon, *J. Pharmacol. Exp. Ther.*, **138**, 249 (1962).
(8) H. Stetter and E. Rauscher, *Chem. Ber.*, **93**, 1161 (1960).

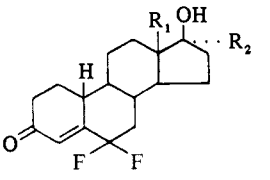
‡All new compounds give satisfactory nmr and ir spectra. Melting points were taken on a Kofler hot-stage microscope and are uncorrected.

17α-Propadienyl, 17α-Propynyl, and 17α-Trifluoropropynyl Analogs of 6,6-Difluoronorethindrone†

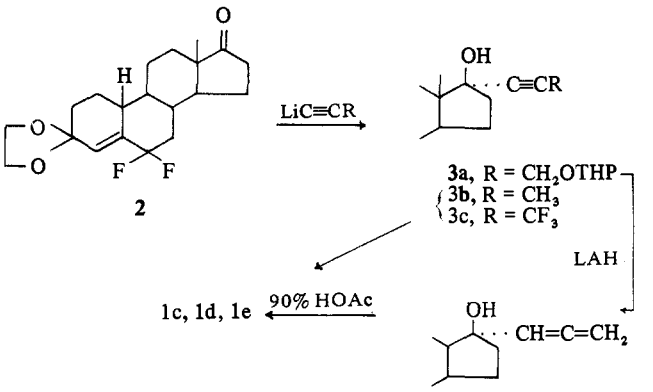
Alexander L. Johnson

Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898.
Received January 12, 1972

The synthesis of 6,6-difluoronorethindrone (**1a**), a progestational agent with enhanced activity, was recently reported.[1-5] As an extension of this discovery, the syntheses of (±)-6,6-difluoronorgestrel (**1b**),[6,7] 17β-hydroxy-6,6-difluoro-17α-propadienyl-4-estren-3-one (**1c**), 17β-hydroxy-6,6-difluoro-17α-(1-propynyl)-4-estren-3-one (**1d**), and 17β-hydroxy-6,6-difluoro-17α-(3,3,3-trifluoropropynyl)-4-estren-3-one (**1e**) have been completed. Each of these compounds is a potent oral progestational agent (Table I). Comparison of this data with that for related compounds[1-7,‡] clearly shows the extent of enhancement in both 17α-ethynyl- and 17α-propadienyl-17β-ols of the Δ^4-estren-3-one series. The 6,6-*gem*-difluoro group is an important means of enhancing the progestational activity of the parent compounds.



1a, $R_1 = CH_3$; $R_2 = C{\equiv}CH$
1b, $R_1 = C_2H_5$; $R_2 = C{\equiv}CH$
1c, $R_1 = CH_3$; $R_2 = CH{=}C{=}CH_2$
1d, $R_1 = CH_3$; $R_2 = C{\equiv}CCH_3$
1e, $R_1 = CH_3$; $R_2 = C{\equiv}CCF_3$



Compounds **1c**, **1d**, and **1e** were prepared from a common precursor, 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (**2**), first used in the synthesis[1-5] of **1a**. When the 17-keto group of **2** reacts with the lithium derivative of the appropriate acetylene, the intermediate ethynylated ketals **3a**, **3b**, and **3c** are produced. LAH reduction of **3a** converts the 17α-(3-tetrahydropyranyloxypropynyl) derivative to the 17α-propadienyl 3-ethylene ketal derivative‡,9,§ **4**. Mild acid cleavage of the ethylene ketal function in the inter-

†Contribution No. 1835.

‡Biollaz, *et al.*,[8] describe the reaction of acetylenic Grignard reagents with steroidal 17-ketones.

§Cowie, *et al.*,[10] report a similar reaction in an unrelated series of compounds.

Table I. Clauberg Oral Progestational Activities[a,b] of 6,6-Difluoronorethindrone Analogs

Compound	Relative act.
Norethindrone	1
1a	4
1b	7
1c	20
1d	~2[c]
1e	~4[c]

[a]See ref 11. [b]See ref 12. [c]Estimate based on limited data from 3 rabbits (1d) and 4 rabbits (1e).

mediates **3b**, 3c, and 4 then regenerates the 6,6-difluoro-Δ^4-3-keto function of the desired products 1c, **1d**, and 1e. These reactions further illustrate the point[5] that 6,6-difluoro steroids are quite stable toward a variety of reagents. The preparation of the 17α-propadienyl derivatives of steroids from the 17α-[2-(2,2-dihalocyclopropyl)carbinyl],[13] 17α-(3-halopropynyl),[14] and quaternary ammonium 17α-propynyl[15,16] derivatives of steroids is described in the patent literature.

Experimental Section#

17β-Hydroxy-6,6-difluoro-17α-propadienyl-4-estren-3-one (1c). A soln of propargyl tetrahydropyranyl ether[17] (1.12 g, 8.0 mmoles) in THF** (20 ml) was cooled to −20° and treated under Ar with *n*-BuLi (6.25 mmoles). A soln of 6,6-difluoro-4-estren-3,17-dione 3-ethylene ketal[1-5] (**2**) (2.30 g, 6.50 mmoles) in THF (40 ml) was added to the Li deriv, and the mixt was stirred (25°, 20 hr under Ar). The reaction was terminated by pouring the mixt into brine (250 ml) and extg the THP deriv 3a with 4 × 75 ml of C_6H_6. Evapn of the dried exts gave crude 3a as a syrup, ν_{max}^{film} 3450 cm^{-1}. Crude 3a was reduced at 25° in THF (50 ml) with LAH (0.48 g, 2.6 mmoles), the progress of the reactn being followed by the appearance of the 1960-cm^{-1} propadienyl ir band. After 2-hr redn, satd Na_2SO_4 isoln gave crude 4 as a syrup (~3 g). Crude 4 was stirred at 25° for 2 hr with 90% HOAc (20 ml); the mixt was poured into H_2O (100 ml) and extd with 3 × 50 ml of $CHCl_3$. The ext was washed with 5% $NaHCO_3$ and H_2O, dried, and evapd to leave 2.23 g of crude 1c. This was purified by prep tlc using 10% Me_2CO–$CHCl_3$ as eluant. Purified 1c was extd from the R_f 0.40–0.53 band (0.9763 g, 63% conversion, 68% yield) as a colorless syrup, $\nu_{max}^{CHCl_3}$ 3610, 1960, and 1690 cm^{-1}, *Anal.* ($C_{21}H_{26}F_2O_2$) high-resolution mass spectrum. The major by-products[1-5] were 17ξ-hydroxy-6,6-difluoro-4-estren-3-one (R_f 0.19–0.30, 0.4647 g) and its 3-ethylene ketal (R_f 0.57–0.64, 0.3191 g) which arose from unreacted **2** (37%).

17β-Hydroxy-6,6-difluoro-17α-(1-propynyl)-4-estren-3-one (1d). The propynyl deriv **3b** was prepd similarly from **2** (1.0 g) and LiC≡CCH_3, an excess of propyne in the reactn mixt†† being retained by a Dry Ice condenser. Crude **3b** (0.97 g) had $\nu_{max}^{CHCl_3}$ 3600, 3400 cm^{-1}. Hydrolysis with 90% HOAc gave crude 1d as a syrup which was purified by prep tlc using 5% Me_2CO–$CHCl_3$ as eluant. Purified 1d was obtd as a colorless syrup (0.3683 g, 37%), $\nu_{max}^{CHCl_3}$ 3500 and 1690 cm^{-1}, $[\alpha]^{25}D$ −72° (*c* 1.00 $CHCl_3$). *Anal.* ($C_{21}H_{26}F_2O_2$) high-resolution mass spectrum.

17β-Hydroxy-6,6-difluoro-17α-(3,3,3-trifluoropropynyl)-4-estren-3-one (1e). The Li deriv of 3,3,3-trifluoropropyne,[18] prepared in Et_2O under Ar at −78°, was treated with a soln of **2** (1.0 g) in THF (10 ml). After several hours at 25°, the intermediate **3c** was isold similarly to **3a**, **3b** as a brown syrup (1.18 g), $\nu_{max}^{CHCl_3}$ 3650, 3450, and 2280 cm^{-1}. Treatment with 90% HOAc gave crude 1e as a tan residue (0.89 g) which was purified by prep tlc using 2:1 EtOAc–C_6H_{12} as eluant. The major band, R_f 0.74–0.87 was product 1e (0.5458 g, 48%), $\nu_{max}^{CHCl_3}$ 3590, 3380, 2260, and 1690 cm^{-1}, $[\alpha]^{25}D$ −73° (*c* 1.04 $CHCl_3$). *Anal.* ($C_{21}H_{23}F_5O_2$) C, H, high-resolution mass spectrum.

Acknowledgments. The author is indebted to Dr. G. A. Boswell, Jr., of this department for helpful advice, and to Dr. R. I. Dorfman and Mr. W. H. Rooks, II, Syntex Corporation, Palo Alto, Calif., for having the biological data on the compounds described evaluated under the direction of Dr. Elva Shipley, Endocrine Laboratories, Madison, Wis.

References

(1) G. A. Boswell, Jr., U. S. Patent 3,219,673 (1965).
(2) G. A. Boswell, Jr., U. S. Patent 3,511,861 (1970).
(3) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *Angew. Chem.*, 83, 116 (1971).
(4) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *Angew. Chem. Int. Ed.*, 10, 140 (1971).
(5) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *J. Org. Chem.*, 36, 575 (1971).
(6) A. L. Johnson, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 13–17, 1971, FLUO-28.
(7) A. L. Johnson, *J. Med. Chem.*, 15, 360 (1972).
(8) M. Biollaz, R. M. Landeros, L. Cuellar, P. Crabbé, W. Rooks, J. A. Edwards, and J. H. Fried, *ibid.*, 14, 1190 (1971).
(9) J. A. Edwards, German Patent 2,018,055 (1970).
(10) J. S. Cowie, P. D. Landor, and S. R. Landor, *Chem. Commun.*, 541 (1969).
(11) D. Lednicer, "Contraception–The Chemical Control of Fertility," Marcel Dekker, New York, N. Y., 1969, pp 29–31, 253.
(12) W. H. Rooks, II and R. I. Dorfman, *Contraception*, 1, 403 (1970).
(13) J. A. Edwards and L. H. Knox, U. S. Patents 3,392,165 and 3,392,166 (1968).
(14) P. Crabbé and J. H. Fried, German Patent 2,018,087 (1970).
(15) E. E. Galantay and D. A. Habeck, Belgian Patent 742,137 (1969).
(16) E. E. Galantay, German Patent 1,917,087 (1969).
(17) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950).
(18) F. G. Drakesmith, O. J. Stewart, and P. Tarrant, *J. Org. Chem.*, 33, 280 (1968).

#In the analysis of 1e indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Molecular formulas of the final products 1c, 1d, and 1e were determined by high-resolution mass spectrometer, and structural assignments were in agreement with measured ir, uv, and nmr spectra. (*Cf.* ref 1–5.) Preparative tlc separations were done on 2-mm silica gel F-254 plates.

**It is essential to use highly purified THF which has been stored over Na. Less pure THF gives a slow and incomplete reaction and more side products.

††The use of commercial LiC≡CCH_3 was less satisfactory than material prepd freshly in THF from propyne and *n*-BuLi.

Convenient Synthesis of 1,1-Disubstituted 1,4-Butanediols and Derivatives

Suminori Umio,* Ikuo Ueda, and Hiroshi Nojima

The Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. *Received January 21, 1972*

In the course of synthesizing 3-(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)pyrrolidines,[1] we conveniently prepared a key intermediate, 5-(3-hydroxypropyl)-10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (IV, X = CH_2CH_2). In the present paper, we describe a new method for synthesizing disubstituted 1,4-butanediols (IV) and some dehydration products.

The synthesis of IV (X = CH_2CH_2) from 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-one (III) (X = CH_2CH_2) *via* two steps, consisting of condensation with propargyl alcohol and subsequent catalytic reduction, has already been reported,[2] but we obtained IV (X = CH_2CH_2) in a single run using III (X = CH_2CH_2) and trimethylenechlorohydrin (I) as shown in Scheme I. After protecting the hydroxyl group with EtMgBr,[3] I was allowed to react with metallic Mg and then with III (X = CH_2CH_2) and afforded the desired diol IV (X = CH_2CH_2) quantitatively. This reaction indicated