

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

^aSee ref 11. ^bSee ref 12. ^cEstimate 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 point⁵ that 6,6-difluoro steroids are quite stable toward a variety of reagents. The preparation of the 17 α -propadienyl derivatives of steroids from the 17 α -[2-(2,2-dihalocyclopropyl)carbinyl],¹³ 17 α -(3-halopropynyl),¹⁴ and quaternary ammonium 17 α -propynyl^{15,16} derivatives of steroids is described in the patent literature.

Experimental Section[#]

17 β -Hydroxy-6,6-difluoro-17 α -propadienyl-4-estren-3-one (1c). A soln of propargyl tetrahydropyranyl ether¹⁷ (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 ketal¹⁵ (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 x 75 ml of C₆H₆. 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 Na₂SO₄ 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 H₂O (100 ml) and extd with 3 x 50 ml of CHCl₃. The ext was washed with 5% NaHCO₃ and H₂O, dried, and evapd to leave 2.23 g of crude 1c. This was purified by prep tlc using 10% Me₂CO-CHCl₃ 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, $\nu_{\max}^{\text{CHCl}_3}$ 3610, 1960, and 1690 cm⁻¹, *Anal.* (C₂₁H₂₆F₂O₂) high-resolution mass spectrum. The major by-products¹⁵ were 17 β -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%).

17 β -Hydroxy-6,6-difluoro-17 α -(1-propynyl)-4-estren-3-one (1d). The propynyl deriv 3b was prepd similarly from 2 (1.0 g) and LiC \equiv CCH₃, an excess of propyne in the reactn mixt^{††} being retained by a Dry Ice condenser. Crude 3b (0.97 g) had $\nu_{\max}^{\text{CHCl}_3}$ 3600, 3400 cm⁻¹. Hydrolysis with 90% HOAc gave crude 1d as a syrup which was purified by prep tlc using 5% Me₂CO-CHCl₃ as eluant. Purified 1d was obtd as a colorless syrup (0.3683 g, 37%), $\nu_{\max}^{\text{CHCl}_3}$ 3500 and 1690 cm⁻¹, $[\alpha]^{25D} -72^\circ$ (c 1.00 CHCl₃). *Anal.* (C₂₁H₂₆F₂O₂) high-resolution mass spectrum.

17 β -Hydroxy-6,6-difluoro-17 α -(3,3,3-trifluoropropynyl)-4-estren-3-one (1e). The Li deriv of 3,3,3-trifluoropropyne,¹⁸ prepared in Et₂O 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), $\nu_{\max}^{\text{CHCl}_3}$ 3650, 3450, and 2280 cm⁻¹. Treatment with 90% HOAc gave crude 1e as a tan

[#]In the analysis of 1e indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within $\pm 0.4\%$ 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 \equiv CCH₃ was less satisfactory than material prepd freshly in THF from propyne and *n*-BuLi.

residue (0.89 g) which was purified by prep tlc using 2:1 EtOAc-C₆H₁₂ as eluant. The major band, R_f 0.74-0.87 was product 1e (0.5458 g, 48%), $\nu_{\max}^{\text{CHCl}_3}$ 3590, 3380, 2260, and 1690 cm⁻¹, $[\alpha]^{25D} -73^\circ$ (c 1.04 CHCl₃). *Anal.* (C₂₁H₂₃F₃O₂) C, H, high-resolution mass spectrum.

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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-5H-dibenzo[*a,d*]cyclohepten-5-ylidene)pyrrolidines,¹ we conveniently prepared a key intermediate, 5-(3-hydroxypropyl)-10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-ol (IV, X = CH₂CH₂). In the present paper, we describe a new method for synthesizing disubstituted 1,4-butanediols (IV) and some dehydration products.

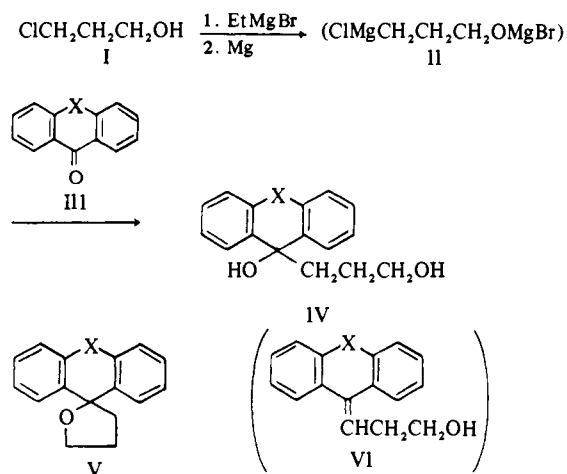
The synthesis of IV (X = CH₂CH₂) from 10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-one (III) (X = CH₂CH₂) via two steps, consisting of condensation with propargyl alcohol and subsequent catalytic reduction, has already been reported,² but we obtained IV (X = CH₂CH₂) in a single run using III (X = CH₂CH₂) 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 = CH₂CH₂) and afforded the desired diol IV (X = CH₂CH₂) quantitatively. This reaction indicated

Table I. 1,1-Disubstituted 1,4-Butanediols (IV) and 2,2-Disubstituted Furans (V)

Type	X	R ₁	R ₂	Yield, %	Mp, °C ^a	Formula	Analyses ^b
A		H		q ^c	107-108 ^d	C ₁₆ H ₁₈ O ₂	
A		Cl		q	122-123	C ₁₆ H ₁₆ Cl ₂ O ₂	C, H, Cl
B	CH ₂ CH ₂		H	q	80-88 ^e	C ₁₈ H ₂₀ O ₂	
B	CH ₂ CH ₂		CH ₃	q	51-55	C ₁₉ H ₂₂ O ₂	C, H
B	CH ₂ CH ₂		Cl	q	Oil ^f	C ₁₈ H ₁₉ ClO ₂	
B	C(CH ₃) ₂		H	95	138	C ₁₉ H ₂₂ O ₂	C, H
B	S		Cl	95	Oil ^g	C ₁₆ H ₁₅ ClO ₂ S	
C	OH ^h		H	q	83-84	C ₁₆ H ₁₄ O ₂	C, H
C	O		Cl	q	104-105	C ₁₆ H ₁₃ ClO ₂	C, H, Cl

^aMelting points are uncorrected. ^bAnalytical values represented by symbols of the elements are within ±0.4% of the theoretical values. ^cq means that the reaction proceeded almost quantitatively. ^dReported mp 108° (ref 5). ^eReported mp 82-86.5° (ref 2). ^fThis compd was determined by the comparison of its ir and nmr spectra with those of X = CH₂CH₂ and by appropriate procedures after transformation into related 1-pyrroline (cf. ref 1). ^gThis compd was characterized by the ir absorption at 3300 cm⁻¹, showing the presence of OH, and uv absorption; λ_{max} (95% EtOH) 270 mμ (log ε 4.23) (cf. ref 4). ^hSpectral data are expressed in Experimental Section.

Scheme 1



the presence of a new Grignard reagent (II) as an intermediate. When this method was applied to several ketones, related diols were obtained, mostly in high yield, and they are listed in Table I. In the xanthene series, however, related diols (IV, X = O) were not stable enough to permit their recognition by techniques other than ir spectra and accordingly changed readily into the corresponding dehydration products. Their spectral data demonstrated that the dehydration products are not olefinic alcohols (VI) but the corresponding tetrahydrofurans (V). Their spectra showed no absorption characteristic of hydroxyl groups (ir) or olefinic protons (nmr). It is of interest that diols IV (X = O) exclusively afforded the corresponding furans⁴ in good yield under mild conditions, in contrast to cases of IV (X = CH₂CH₂)² and 4,4-diphenyl-1,4-butanediol,⁵ where mixtures of olefinic alcohols and furans were produced under elaborate conditions.

Experimental Section

General Procedure for Reaction of II and III. To an EtMgBr soln (prepd from 0.22 mole of EtBr, 0.20 g-atom of Mg, and 98 ml of THF) cooled in an ice bath, 0.2 mole of I was added dropwise with stirring. After the addn was complete, this mixt was stirred for 0.5 hr, and 0.20 g-atom of Mg was further added. The stirring was continued at 60° until the Mg disappeared nearly completely. To this mixt a soln contg 0.10 mole of ketone III in 73 ml of THF was

added dropwise and refluxed for 3 hr with stirring. Then the reaction mixt was cooled in an ice bath and hydrolyzed with satd NH₄Cl. THF was evaporated under reduced pressure and the residue was extd with Et₂O. The Et₂O ext was dried and concd to give a crude diol IV and/or furan V.

Spectra† of spiro(tetrahydrofuran-2,9'-xanthene) (IV, X = O) showed nmr (CDCl₃, TMS) δ 1.8-2.4 (m, 4, CCH₂CH₂CO), 4.36 (t, 2, J = 7 Hz, OCH₂C), 7.0-7.7 (m, 8, aromatic protons; λ_{max}^{95% EtOH} 238.5 mμ (log ε 4.23), 282.5 (3.49), and 320 (3.20).

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†Nmr spectra were determined at 60 MHz on a Varian Model A-60 spectrometer.

Synthesis and Anthelmintic Activity of Some Sulfonylbenzimidazoles

R. D. Haugwitz,* B. V. Maurer, and V. L. Narayanan

The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903. Received January 17, 1972

Three different types of substituted sulfonylbenzimidazoles were synthesized for evaluation of their anthelmintic activity. Whereas the 1- and 2-substituted sulfonylbenzimidazoles were derived from peracid oxidation of the corresponding sulfides, the symmetric sulfones were obtained from acid-catalyzed cyclization of *o*-phenylenediamines with sulfonyldiacetic acid. Of these, only the 2-substituted sulfonylbenzimidazoles showed marginal anthelmintic activity.

The well-documented anthelmintic activity of several