buffer of pH 3.9 (80 ml), prepared by mixing 0.1 *N* AcOH (90 ml) and 0.1 *N* NaOAc (10 ml), was added. The reaction mixt was refluxed for 1 hr, cooled at room temp, and allowed to crystallize overnight. The pptd crystals were collected, washed (H_2O), and dried *in vacuo* to give III (7.8 g); mp 224–227°. Trituration with Me_2CO–Et_2O of the material recovered after concn of the mother liquor gave a second crop (3 g) of comparable product. Crystn of the combined yields from Me_2CO–Et_2O gave pure III (8.9 g); mp 225–228°; tlc, R_f 0.3; [α]D +63.5°. *Anal.* ($C_{29}H_{33}O_6F$) C, H.

Betamethasone 21-Benzoate (IV). To a solution of III (0.5 g) in MeOH (10 ml), kept stirring under an atmosphere of N_2, MeOH–0.1 *N* KOH (0.5 ml) was added. After 25 min, crystals began to sep. After 1 hr a 10% aq soln of AcOH (1 ml) was added, and the ppt (250 mg), mp 252–256°, was recovered by filtration. Crystallization (EtOH) gave IV; mp 252–256°; tlc, R_f 0.47; [α]D +170°. *Anal.* ($C_{29}H_{33}O_6F$) C, H. Identity with authentic IV, prepared from I by a conventional procedure, was established.

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References

(1) R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Lett.*, 448 (1961).
(2) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 431 (1963).
(3) R. Gardi, R. Vitali, G. Falconi, and A. Ercoli, *J. Med. Chem.*, **15**, 556 (1972), and ref therein.
(4) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 413 (1963).
(5) A. Ercoli, R. Gardi, and R. Vitali, German Patent Application 2,031,205 (June 26, 1969).
(6) L. Salce, G. G. Hazen, and E. F. Shoenewaldt, *J. Org. Chem.*, **35**, 1681 (1970).
(7) R. Vitali, R. Gardi, and A. Ercoli, *Gazz. Chim. Ital.*, **96**, 1115 (1966).
(8) A. W. McKenzie and R. M. Atkinson, *Arch. Dermatol.*, **89**, 741 (1964).
(9) (a) G. DiPasquale, C. L. Rassaert, and E. McDougall, *Steroids*, **16**, 663 (1970); (b) *ibid.*, **16**, 679 (1970); (c) G. DiPasquale and L. Tripp, *ibid.*, **16**, 693 (1970).
(10) A. Cresseri and A. Meli, *Arch. Sci. Biol. (Bologna)*, **37**, 551 (1953).
(11) H. Selye, *Proc. Soc. Exp. Biol. Med.*, **82**, 328 (1953).
(12) G. Tonelli, L. Thibault, and I. Ringler, *Endocrinology*, 77, 625 (1965).
(13) A. W. McKenzie and R. B. Stoughton, *Arch. Dermatol.*, **86**, 608 (1962).

6,6-Difluoro-19-norprogesterone†

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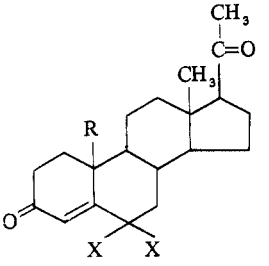
We recently described[1-8] the synthesis of several 6,6-difluoro-19-norsteroid progestational agents related to norethindrone and norgestrel. The oral progestational activities of 17α-ethynyl- and 17α-propadienyl-19-nortestosterones are enhanced by the *gem*-6,6-difluoro substitution,[1-4,7-9] so it was of interest to prepare some pregnanes with this γ,γ-difluoro-α,β-enone structural unit to see if a similar enhancement could be produced with subcutaneous progestational activities. The conversion of progesterone (**1**) to 6,6-difluoroprogesterone (**2**) has already been described,[1,10,11] and the present notice describes a parallel conversion of 19-norprogesterone (**3**)[12] to its 6,6-difluoro derivative (**4**). Unlike the estrane series, 6,6-difluoro substitution in the pregnane and 19-norpregnane series did not enhance their progestational activity, as illustrated in Table I. It is clear that the biological profiles of 17α-ethynyl-19-nortestosterones and pregnanes are distinct,[13] and modificiations to one series do not necessarily translate to the other series.

†Contribution No. 1905.

Table I. Subcutaneous Progestational Activities of Progesterone Derivatives

Compound	Activity[a]
1	1.0
2	~0.2
3	4–8[b]
4	<2

[a] Clauberg assay *vs.* progesterone standard using estrogen-primed rabbits, *cf.* ref 13. [b] See ref 14.



1, R = CH_3; X = H
2, R = CH_3; X = F
3, R = H; X = H
4, R = H; X = F

Experimental Section‡

6,6-Difluoro-19-norprogesterone (4). 19-Norprogesterone[12] (**3**) (5.0 g) was reduced (LiAlH(*O-tert*-Bu)$_3$–THF) to the corresponding 3β,20β-diol which was reoxidized (DDQ–dioxan) to 20β-hydroxy-19-nor-4-pregnen-3-one, mp 178–182°, in overall yield of 49% after recrystn (hexane–Me_2CO). This was converted[15] (Ac_2O–AcCl–C_5H_5N) in 73% yield to 3,20β-dihydroxy-19-nor-3,5-pregnadiene 3,20-diacetate, mp 148–154° dec, redn of which ($NaBH_4$–THF–EtOH), followed by reacetylation (Ac_2O–C_5H_5N), gave 3β,20β-dihydroxy-19-nor-5-pregnene 3,20-diacetate, mp 198–200°, in 52% yield. Treatment of the latter with NOF and Al_2O_3 chromatography gave a 53% yield of colorless crystalline 3β,20β-dihydroxy-5α-fluoro-19-norpregnan-6-one 3,20-diacetate, mp 144–150° dec. The 6-oxo function was converted to 6,6-*gem*-difluoro (SF_4) in 65% yield. 3β,20β-Dihydroxy-5α,6,6-trifluoro-19-norpregnane 3,20-diacetate, mp 115–117°, was hydrolyzed (MeOH–HCl) to the parent diol and oxidized (8 *N* CrO_3–Me_2CO) to 5α,6,6-trifluoro-19-norpregnane-3,20-dione, which was dehydrofluorinated (Al_2O_3 chromatography) to crude **4** (0.3040 g, 5.5% overall yield).

Two recrystallizations of **4** (Me_2CO–hexane) gave 0.1276 g of colorless crystalline 6,6-difluoro-19-norprogesterone: mp 101–102°; ν_{max}^{KBr} 1725 and 1690 cm^{-1}; λ_{max}^{EtOH} 330 (ε 40), 285 (53), and 226 nm (13,700); [α]^{25}D +16° (*c* 0.25, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{26}O_2F_2$: C, 71.40; H, 7.79; *m/e* 336.1900. Found: C, 71.84; H, 8.32; *m/e* 336.1902.

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References

(1) G. A. Boswell, Jr., U. S. Patents 3,219,673 (1965), 3,511,861 (1970), and 3,621,010 (1971).

‡Because the synthesis was a direct parallel to that used for **2**[1,10,11] only the final product is described in detail. The structural assignments of intermediate products were in agreement with their ir, uv, and nmr spectra.

(2) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *Angew. Chem.*, **83**, 116 (1971).
(3) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *Angew. Chem., Int. Ed. Engl.*, **10**, 140 (1971).
(4) G. A. Boswell, Jr., A. L. Johnson, and J. P. McDevitt, *J. Org. Chem.*, **36**, 575 (1971).
(5) A. L. Johnson, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, Abstract FLUO-28.
(6) A. L. Johnson, *J. Med. Chem.*, **15**, 360 (1972).
(7) A. L. Johnson, German Patent 2,053,608 (1971).
(8) A. L. Johnson, unpublished work.
(9) J. A. Edwards, German Patent 2,018,055 (1970).
(10) G. A. Boswell, Jr., *J. Org. Chem.*, **31**, 991 (1966).
(11) G. A. Boswell Jr., *ibid.*, **33**, 3699 (1968).
(12) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, **80**, 6118 (1958).
(13) D. Lednicer, "Contraception–The Chemical Control of Fertility," Marcel Dekker, New York, N. Y., 1969, pp 29–31, 253.
(14) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 589.
(15) R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959).

Book Reviews

Arzneimittel: Entwicklung, Wirkung, Darstellung. Edited by Gustav Ehrhart and Heinrich Ruschig. 2nd edition. Vol. 1. Therapeutics Acting on the CNS. xii + 382 pp. Vol. 2. Therapeutics Acting on the Peripheral Nervous System. xii + 471 pp. Vol. 4. Chemotherapeutics, Part 1. xii + 443 pp. 24.5 × 17.5 cm. In preparation: Vol. 3. Drugs Acting on the Respiratory and Digestive Tracts. Vol. 5. Chemotherapeutics, Part 2. Verlag Chemie, Weinheim/Bergstr. 1972. Each volume DM 330, all 5 volumes DM 1450.

When the last two volumes of this treatise will have been published this year, the medicinal chemist will have available one of the most thorough and extensive systematic surveys of drugs and their syntheses ever compiled by a homogeneous group of authors. The late Professor Ehrhart, together with Professor Ruschig, has assembled over 60 chemists, pharmacologists, and microbiologists within the laboratories of Farbwerke Hoechst A.G. to present the discovery, development, mode of action, and synthesis of all major classes of drugs. Arranged according to the diseases they are used to combat, and subdivided according to structural types, all drugs are arranged in a standardized way. A description of physiological conditions or parasitic life processes whose aberrations lead to disease introduces each chapter. Chemists whose training in neuroanatomy, neurophysiology, or microbiology is usually below par, will appreciate the concise, clearly written, and richly illustrated orienting articles in these fields. The discovery and development of drugs varies slightly in quality from one class of drugs to another. Older types, many of which made their first appearance in Europe, are described superbly. Many obscure yet significant historic vignettes will be found here, lovingly documented by contributors whose teachers told them the authentic tales of those events. For many of the drugs introduced in the last 30 years, mostly in the United States and the United Kingdom, the authors had to rely on published and patented information, and the fascinating accounts of their development become thinner.

The mode of action of all drugs is treated on a modern biochemical basis. Finally, without interrupting this narrative, a concluding section deals with the actual mode of synthesis and manufacture of each type of drug.

Each chapter also contains ample information on clinical uses of the drugs under discussion, and critically enumerates advantages, drawbacks, and side effects that limit the respective therapy. The amount of these clinical surveys is just broad enough to satisfy the nonclinical medicinal scientist, and not so detailed as to confuse him.

The American reader will have to overcome the difficulties of reading close to 2000 pages in German. He will be bewildered by the thousands of European Trade Names used in all chapters, although generic names will be found everywhere. He will wonder about the stories of priorities of drug discovery which give credit to foreign scientists while in some domestic texts some such credit has been given to American investigators. Where these stories are adequately documented, however, we may have to conclude that not all our domestic information has been unbiased.

A treatise of such magnitude and scope should have been prefaced by general chapters on the theory of drug design and drug action, and by both chemical and physical methods which point the way to the scientific treatment of medicinal chemistry. There is no such chapter in these volumes; a few pertinent explanations of drug action based on physical-chemical data are interspersed in the text at appropriate junctures. This lack of generalization may be an admission of our present ignorance which, when the chips are down for a clinically useful agent, often condemns us to empiricism as of old.

The second drawback of these books is that molecular modification in each field is illustrated only by the progress from one clinically useful drug to another. Perhaps lack of space dictated this restriction, but the many fascinating and suggestive data divulged by molecular modification of clinically unsuccessful agents has been short-changed. This does not, however, detract from the enormity of this treatise, from the unified style and format in these books, and from the authenticity and care with which they have been prepared.

Few would-be readers will be able to afford these volumes. At the present rate of our monetary devaluation, they cost at least $470.

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Tremors and Tremorogenic Agents. Roger W. Brimblecombe and Roger M. Pinder. Bristol Scientechnica, Bristol, England. 1972. ix + 196 pp. 29.9 × 15 cm. £5.00.

Since Pelnar's clinically oriented book, *Das Zittern* (1913), no other book has covered the phenomenon of tremors. The present authors have pooled their experiences in pharmacology and medicinal chemistry to depict the present status of our knowledge (through 1970) of tremors, their possible causation, experimental production, and their treatment. Behind this compilation looms Parkinson's disease, and much of this book deals with this syndrome. A description of the physiology and pathology of tremor, its classification, and its measurement in animal models introduces the reader to this field. The chemical production of tremor, with emphasis on oxotremorin, is presented well and takes into account the many molecular modifications of tremorogenic agents. This section is followed by a good discussion of tremorogenic mechanisms (amine and cholinergic types) and a short summary of antiparkinsonism drugs. The last few pages float off into speculations about biochemical and neurophys-