bicarbonate solution and water and was then dried and evaporated. Crystallization of the residue from methanol yielded 213 mg. (69%) of the dienyne VII with m.p. 124–126°. The analytical sample showed m.p. 128–130°, $\lambda_{max}^{isooctane}$ 265 and 279 mμ (ε 17,400 and 13,000, respectively), no hydroxyl band in the infrared.

Anal. Calcd. for $C_{28}H_{42}$: C, 88.82; H, 11.18. Found: C, 88.70; H, 11.01.

Dehydration of the higher melting glycol (m.p. 209–210°) with potassium hydrogen sulfate under the above described conditions yielded a non-crystalline residue, $\lambda_{max}^{isooctane}$ 240 mμ (ε 7,100). Chromatography of this material on alumina showed it to be a complex mixture and no pure substance could be isolated.

***sym*-Di-5β-(1,1,10β-trimethyl-*trans*-decalin)-ethane (Racemic Dinoronocerane) (VIII).**—A solution of 226 mg. of the dienyne VII in 20 cc. of dioxane and 25 cc. of glacial acetic acid was shaken in hydrogen over 300 mg. of a pre-reduced platinum catalyst at room temperature and atmospheric pressure overnight. The catalyst was then removed and the solvents were evaporated. The crystalline residue, which gave a negative unsaturation test with tetranitromethane, was dissolved in hexane and passed through a column containing 15 g. of alumina. The solvent was again evaporated and the resulting material on crystallization from chloroform–methanol yielded the saturated racemic hydrocarbon VIII with m.p. 184–185°.

Anal. Calcd. for $C_{28}H_{50}$: C, 86.97; H, 13.03. Found: C, 86.84; H, 12.83.

The synthetic compound in chloroform solution showed infrared bands at 3.42, 6.86, 6.94, 7.24, 7.35, 7.46, 7.63, 7.86, 10.28 and 10.53 μ. A sample of the natural optically active dinoronocerane (m.p. 118–119°, $[\alpha]_D$ +62°)[2] showed a completely superimposable spectrum in this solvent. Similarly identical spectra were obtained in carbon disulfide solution.

REHOVOTH, ISRAEL

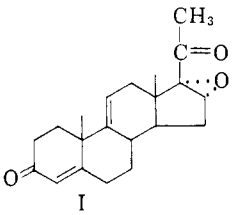
COMMUNICATIONS TO THE EDITOR

17α-ACETOXY-9-HALO-11-OXYGENATED-PROGESTERONES. A NEW CLASS OF ORALLY ACTIVE PROGESTINS

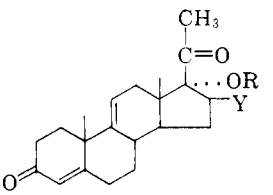
Sir:

The demonstrated clinical utility of 17α-ethynyl-17β-hydroxy-4-estren-3-one (Norlutin)[1] and 17-α-ethynyl-17β-hydroxy-5(10)-estren-3-one (Enovid)[1] has intensified the search for more potent, orally active progestins. Our recent discovery of the high oral progestational activity of 21-fluoro-17α-acyloxyprogesterones[2] has prompted us to prepare other fluorinated 17α-acyloxyprogesterones.

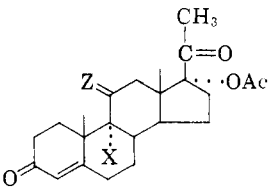
Treatment of 16,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (I),[3] m.p. 181–182°; $[\alpha]_D$ +190° ($CHCl_3$); $\lambda_{max.}^{methanol}$ 239 mμ, ε = 16,900; (found: C, 77.31; H, 7.77); with hydriodic acid[4] in acetic acid gave in excellent yield 16β-iodo-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (II); m.p. 161–163° dec.; $[\alpha]_D$ +78.2 ($CHCl_3$); $\lambda_{max.}^{methanol}$ 238.5 mμ, ε = 17,800; (found: C, 55.78; H, 5.97; I, 27.78). The 16-iodine was removed readily with Raney nickel,[4] and the resulting 17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (III),[5] was acetylated with acetic anhydride and *p*-toluenesulfonic acid to give 17α-acetoxy-4,9(11)-pregnadiene-3,20-dione (IV); m.p. 243–246°; $[\alpha]_D$ +53.1 °($CHCl_3$); $\lambda_{max.}^{methanol}$ 239 mμ, ε = 18,150; (found: C, 74.42; H, 8.24). This $\Delta^{9,11}$-steroid was converted in the conventional manner[5] to 9α-bromo-11β-hydroxy-17α-acetoxyprogesterone (V); m.p. 133–138° dec.; $\lambda_{max.}^{methanol}$ 242.5 mμ, ε = 15,900; $[\alpha]_D$ +100° ($CHCl_3$); (found: C, 58.77; H, 6.59). In order to prepare the 9α-fluoro-derivatives, 9,11β-epoxy-17α-acetoxyprogesterone (VI); m.p. 229–232.5°; $\lambda_{max.}^{methanol}$ 243.5 mμ; ε = 15,100; $[\alpha]_D$ −49.5° ($CHCl_3$); (found: C, 71.28; H, 7.58); was obtained from V by treatment with sodium carbonate

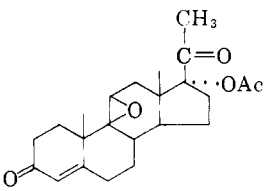


I



II, R = H; Y = I
III, R = H; Y = H
IV, R = Ac; Y = H





V, X = Br, Z = α-H, β-OH
VII, X = F, Z = α-H, β-OH
VIII, X = F, Z = α-H, β-OAC
IX, X = F, Z = O =

VI

in aqueous tetrahydrofuran. The opening of the oxide ring in VI with hydrogen fluoride in tetrahydrofuran[6] yielded the desired 9α-fluoro-11β-hydroxy-17α-acetoxyprogesterone (VII); m.p. 266–269°; $[\alpha]_D$ +77.6° ($CHCl_3$); $\lambda_{max.}^{methanol}$ 238 mμ, ε = 17,500; (found: C, 67.74; H, 7.60). Compound VII was acetylated with acetic anhydride, *p*-toluenesulfonic acid[7] to 9α-fluoro-11β,17α-diacetoxyprogesterone (VIII); m.p. 277–282°; $[\alpha]_D$ +94.8° ($CHCl_3$); $\lambda_{max.}^{methanol}$ 236.5 mμ, ε = 17,400;

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(3) R. M. Dodson and C. G. Bergstrom, U. S. Patent 2,705,711, April 5, 1955.

(4) S. P. Barton, B. Ellis and V. Petrow, *J. Chem. Soc.*, 478 (1959).

(5) J. Fried, J. F. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, THIS JOURNAL, **77**, 1068 (1955).

(6) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(7) R. B. Turner, *ibid.*, **75**, 3489 (1953). Note the low progestational activity of similar compounds devoid of the 9α-fluorine. E. P. Oliveto, R. Rausser, C. Gerold, E. B. Hershberg, M. Eisler, R. Neri and P. L. Perlman, *J. Org. Chem.*, **23**, 121 (1958).

(found: C, 67.08; H, 7.44); and also was oxidized with chromium trioxide in pyridine to 9α-fluoro-17α-acetoxy-4-pregnene-3,11,20-trione (IX); m.p. 256–258°; $[\alpha]_D$ +112° ($CHCl_3$); $\lambda_{max.}^{methanol}$ 235 mμ, ϵ = 16,990; (found: C, 68.62; H, 7.07).

When tested orally in the Clauberg assay[8] at a level producing a +2 degree of glandular arborization the compounds had these relative potencies (subcutaneous progesterone = 1); V = 5; VII = 25; VIII = 10; IX = 10. In our hands compound VII is 2500 times as potent as progesterone is orally, 25 times as potent as Norlutin,[1] and 5 times as potent as 6α-methyl-17α-acetoxyprogesterone.[9]

(8) C. W. Emmens, "Hormone Assay," Academic Press, Inc., New York, N. Y., 1950, p. 422.

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A NOVEL RESOLUTION OF 1-PHENYL-2-PROPYLHYDRAZINE

Sir:

In view of the recent paper by Biel and coworkers[1] on the chemistry and structure-activity relationships of aralkyl hydrazines as central stimulants and the current interest in several of these compounds as possible therapeutic agents,[2] we wish to report at this time a unique resolution of 1-phenyl-2-propylhydrazine by means of its L-pyroglutamoyl derivative. L-Pyroglutamic hydrazide,[3] $[\alpha]^{25}_D$ − 10.1 (*c*,1.0 in water) was condensed with 1-phenyl-2-propanone to yield N-L-pyroglutamoyl-N'-(1-phenyl-2-propylidene)-hydrazine, m.p. 152–154°, $[\alpha]^{27}_D$ +17° (*c*, 1.0 in ethanol). *Anal.* Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.84; H, 6.61. Found: C, 65.07; H, 6.39. Reduction of this hydrazide with sodium borohydride in aqueous methanol yielded a mixture of isomers which were separated by fractional crystallization from water or acetonitrile. The higher-melting insoluble isomer (A) melted at 163–164°, $[\alpha]^{25}_D$ +24.4 (*c*, 1.0 in water). *Anal.* Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.32; N, 16.08. Found: C, 64.39; H, 7.20; N, 16.01. The lower-melting soluble isomer (B) melted at 83–86°, $[\alpha]^{24}_D$ −14.6° (*c*, 1.0 in water). *Anal.* Found: C, 64.31; H, 7.34; N, 15.96. Hydrolysis of (A) in aqueous hydrochloric acid gave D-1-phenyl-2-propylhydrazine hydrochloride, m.p. 148–149°, $[\alpha]^{25}_D$ +13.8° (*c*, 1.0 in water). *Anal.* Calcd. for $C_9H_{15}ClN_2$: Cl, 18.99; N, 15.00. Found: Cl, 18.70; N, 14.81. Hydrolysis of (B) under similar conditions gave L-1-phenyl-2-propylhydrazine hydrochloride, m.p. 148–149°, $[\alpha]^{25}_D$ −14.0° (*c*, 1.0 in water).

To establish the configuration of the isomers relative to D-amphetamine, the D-isomer was reduced with palladium-on-charcoal as the catalyst. The amine thus obtained was benzoylated to yield D-N-(1-phenyl-2-propyl)-benzamide, m.p. 155–156°, $[\alpha]^{25}_D$ +71.6° (*c*, 1.1 in methanol). *Anal.* Calcd. for $C_{16}H_{17}NO$. N, 5.85. Found: N, 6.05. A sample of D-amphetamine also was benzoylated to yield an authentic sample of D-N-(1-phenyl-2-propyl)-benazmide, m.p. 155–156°, $[\alpha]^{25}_D$ +72° (*c*, 1.0 in methanol).[4] A mixture m.p. showed no depression. A similar reduction of the L-isomer with subsequent benzoylation yielded L-N-(1-phenyl-2-propyl)-benzamide, m.p. 155–156°, $[\alpha]^{25}_D$ −71.3° (*c*, 0.97 in methanol). A mixture m.p. with D-N-(1-phenyl-2-propyl)-benzamide was 130–131°.

Preliminary pharmacological tests indicate that D-1-phenyl-2-propylhydrazine hydrochloride is approximately twice as active as the racemate and four times as active as the L-isomer when screened *in vitro* as an inhibitor of monoamine oxidase of mouse brain. In an antireserpine test in mice,[5] the racemate appeared to be of the same order of activity as the D-isomer, which was approximately four times as active as the L-isomer. In normal mice, not reserpine treated, the racemate appeared to resemble closely the D-isomer in that both produced hyperactivity and hyperirritability during the first hour after treatment, a period of relative quiescency during the next hour, and then a second period of hyperactivity which lasted for several hours. The L-isomer, however, in normal mice manifested much less early hyperactivity although the delayed hyperactivity was observed.

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(2) "Amine Oxidase Inhibitors," *Ann. N. Y. Acad. Sci.*, in press.

(3) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, THIS JOURNAL, **75**, 1933 (1953).

(4) W. Leithe, *Ber.*, **65B**, 660 (1932), reported a m.p. of 159–160°, $[\alpha]^{11}_D$ +72° (*c*, 1.14 in methanol).

(5) Drug administered to mice intraperitoneally four hours prior to the intraperitoneal administration of 10 mg./kg. of reserpine.

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THE STRUCTURE OF ULEINE

Sir:

The alkaloid uleine, $C_{18}H_{22}N_2$, from *Aspidosperma ulei* Mgf., is remarkable for its C_{17} skeleton which contains two carbons less than most other indole alkaloids.[1] A previous investigation[1] led to the tentative proposal of structure I which we now wish to replace by II. The infrared spectrum of the alkaloid exhibited bands at 877, 1635 and 3030 cm.$^{-1}$ whilet he n.m.r. spectrum (all values for 60 mc. in $CDCl_3$) possessed peaks at 68, 86 (2 vinyl H); −134 (NH of indole); −73 to −38 c.p.s. (4 arom. H) relative to the benzene proton at 0 c.p.s. These findings, coupled with earlier ultraviolet evidence,[1] demand part structure III. In agreement with III the bands associated with the terminal methylene group were missing in the spectra of dihydrouleine. The optically inactive IV, available by two Hofmann degradations,[1] is a vinylcarbazole. Thus, osmylation of IV gave a diol which on cleavage with periodate was converted to formaldehyde and the yellow aldehyde

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