tive Cotton effect associated with the lowest frequency *cisoid* diene absorption band (~260–280 mμ in polycyclic compounds) means the presence of *cisoid* diene chromophore twisted in the sense of a righthanded helix (VIIIA). A strong negative Cotton effect is indicative of the lefthanded twist (VIIIB).

As further test of the theory, the four stereoisomers: ergosterol (III), lumisterol[3] (I), pyrocalciferol (IV), and isopyrocalciferol (V) were investigated. The Cotton effects found (see Fig. 2) are in agreement with the predictions from the above rule, provided that the Dreiding models for (IV) and (V) are adjusted to relieve the interatomic hydrogen repulsions at C11 and C1. On the other hand, attempted analysis of the contributions by the three asymmetric carbon atoms (C9, C10, C14) adjacent to the chromophore on a "classical" basis runs into an irreconcilable contradiction: the inverse sign of the Cotton effect of (I) and (III), antipodal at both C9 and C10 but equal at C14, suggests that the former pair is in control, C14 contributing little; however, the similar Cotton effects of (IV) and (V), likewise antipodal to each other at both C9 and C10 but equal at C14, would lead to the precisely opposite conclusion of a negligible influence of C9 and C10 and a very strong one of C14. This discrepancy (also noted by Deen and Jacobs[3]) shows clearly that it is the skew sense of the diene that controls the sign of the rotatory dispersion in this spectral region. The rule we have stated thus provides a method for the conformational analysis of these compounds in a case where "classical" considerations fail.

The powerful influence of the skewed diene is further demonstrated in the case of thebainone methyl enolate (VI) where a positive Cotton effect is observed corresponding to the righthanded skew sense predicted from the models. This, to our knowledge, is the only compound in the (−)-codeine series that exhibits a long-wave-length positive rotatory dispersion curve.[7] In thebaine (VII) the skew sense of the diene is such as to predict a strong negative Cotton effect, as observed.

(7) J. M. Bobbitt, U. Weiss and D. D. Hanessian, *J. Org. Chem.*, **24**, 1582 (1959).

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RECEIVED SEPTEMBER 23, 1961

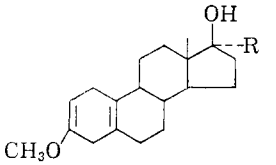
NOVEL GONADOTROPHIN INHIBITORS IN THE 19-NORSTEROID SERIES

Sir:

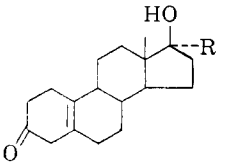
The inhibition of pituitary gonadotrophin secretion has been one of the most promising approaches in the search for an effective antifertility agent. The anovulatory response[1] to 17α-ethynyl-19-nor-4-androstene-17β-ol-3-one[2] (I), and 17α-ethynyl-19-nor-5(10)-androstene-17β-ol-3-one[3] (II), has been shown to be mediated *via* suppression of pituitary gonadotrophin secretion.

We wish to report a number of compounds exhibiting greatly increased gonadotrophin inhibition over previously known hormonal agents.

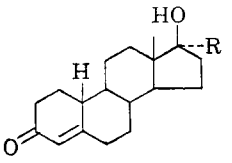
Reaction of 1,4-dihydroestrone-3-methyl ether III,[4] with trifluoropropynylmagnesium bromide (prepared from ethylmagnesium bromide and excess



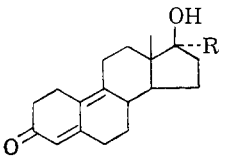
IV, R = —C≡CCF3
VIII, R = —C≡CCl



II, R = —C≡CH
V, R = —C≡CCF3
IX, R = —C≡CCl



I, R = —C≡CH
VI, R = —C≡CCF3
VII, R = —CH=CH—CF3
X, R = —C≡CCl
XII, R = —C≡CBr
XVII, R = —CF=CF2



XV, R = —C≡CCl
XVIII, R = —C≡CH

trifluoropropyne[5] in tetrahydrofuran solution) affords 17α-trifluoropropynyl-3-methoxy-19-nor-2,5-(10)-androstadiene-17β-ol (IV). Hydrolysis of the enol ether function in IV with a mixture consisting of aqueous acetic acid, dioxane and ethanol affords 17α-trifluoropropynyl-19-nor-5(10)-androstene-17β-ol-3-one (V), m.p. 137–140°; $\alpha^{24}D$ +100 (dioxane). (*Anal.* Found: C, 68.77; H, 7.00; F, 17.3), while hydrolysis with *p*-toluenesulfonic acid in acetone yields 17α-trifluoropropynyl-19-nor-4-androstene-17β-ol-3-one (VI), m.p. 128–132°; $\alpha^{26}D$ −21 (chloroform), ultraviolet λ_{max}^{MeOH} 238 mμ, ε 15,000 (*Anal.* Found: C, 68.30; H, 7.00.)

Hydrogenation of V at 40 psi. with Lindlar catalyst followed by treatment with *p*-toluenesulfonic acid in acetone affords 17α-trifluoropropenyl-19-nor-4-androstene-17β-ol-3-one (VII), m.p. 138–142°; $\alpha^{24}D$ +44 (chloroform), λ_{max}^{MeOH} 239 mμ, ε 15,800 (*Anal.* Found: C, 68.47; H, 7.60).

Addition of chloroethynyllithium (prepared *in situ* from *cis*-dichloroethylene and methyllithium)[6] to III affords 17α-chloroethynyl-3-methoxy-19-nor-2,5(10)-androstadiene-17β-ol (VIII), m.p. 112–115°; $\alpha^{26}D$ +69 (dioxane). (*Anal.* Found: C, 72.85; H, 8.15.) Hydrolysis as above produces 17α-chloroethynyl-19-nor-5(10)-androstene-17β-ol-3-one (IX), m.p. indef. *ca.* 160°; $\alpha^{25}D$ +86 (dioxane). (*Anal.* Found: C, 71.63; H, 7.65) and 17α-chloroethynyl-19-nor-4-androstene-17β-ol-3-one (X), m.p. 198–201°; $\alpha^{25}D$ −49 (chloroform), ultraviolet λ_{max}^{MeOH} 240 mμ, ε 15,000 (*Anal.* Found: C, 72.27; H, 7.57; Cl, 9.90.)

(1) G. Pincus, *Vitamins and Hormones*, **17**, 307 (1959), Academic Press, New York, N. Y., and references cited.

(2) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954).

(3) F. B. Colton, U. S. Patent 2,725,389.

(4) F. B. Colton, L. N. Nysted, B. Riegel and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(5) W. R. Hasek, W. C. Smith and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(6) H. G. Viehe, *Chem. Ber.*, **92**, 1950 (1959).

TABLE I

GONADOTROPHIN INHIBITION AND PROGESTATIONAL ASSAYS

Entry	Compound	Oral gonadotrophin inhibition[13] (parabiotic rats)	Oral progestational activity[14]
I	17α-Ethynyl-19-nor-4-androstene-17β-ol-3-one	1	1
II	17α-Ethynyl-19-nor-5(10)-androstene-17β-ol-3-one	2–3	0.1
V	17α-Trifluoropropynyl-19-nor-5(10)-andostene-17β-ol-3-one	5–6	0
VI	17α-Trifluoropropynyl-19-nor-4-androstene-17β-ol-3-one	2–3	0.5
VII	17α-Trifluoropropenyl-19-nor-4-androstene-17β-ol-3-one	1–1.5	0.2
IX	17α-Chloroethynyl-19-nor-5(10)-androstene-17β-ol-3-one	3–4	0.1
X	17α-Chloroethynyl-19-nor-4-androstene-17β-ol-3-one	3	2–3
XII	17α-Bromoethynyl-19-nor-4-androstene-17β-ol-3-one	1–2	1.0–1.5 (s.c.)
XIII	17α-Chloroethynyl-19-nor-4-androstene-17β-ol-3-one acetate	2	1–2
XIV	3-Cyclopentyloxy-17α-chloroethynyl-19-nor-3,5-androstadiene-17β-ol acetate	3–4	1–2
XV	17α-Chloroethynyl-19-nor-4,10(9)-androstadiene-17β-ol-3-one	6–8	5–6
XVI	17α-Chloroethynyl-19-nor-4,10(9)-androstadiene-17β-ol-3-one acetate	6–8	2
XVII	17α-Trifluorovinyl-19-nor-4-androstene-17β-ol-3-one	<1	2
XVIII	17α-Ethynyl-19-nor-4,10(9)-androstene-17β-ol-3-one[10]	1.5	1.0–1.5

Alternatively, X can be obtained by protecting I sequentially at the C-3 ketone and 17β-ol by formation of the dioxolane and tetrahydropyranyl ether to yield XI, and then chlorination at C-21 with potassium *t*-butoxide and *t*-butyl hypochlorite,[7] and hydrolysis of the protecting groups. Similarly successive bromination of XI at C-21 with N-bromosuccinimide and potassium *t*-butoxide,[7] and then hydrolysis, yields 17α-bromoethynyl-19-nor-4-androstene-17β-ol-3-one (XII), m.p. 180–182°; $\alpha^{25}D$ −52 (chloroform), ultraviolet λ_{max}^{MeOH} 239 mμ, ε 16,300 (*Anal.* Found: C, 64.11; H, 7.05).

Reaction of X with acetic anhydride and pyridine affords 17α-chloroethynyl-19-nor-4-androstene-17β-ol-3-one acetate[8] XIII as an oil, infrared: λ_{max} 4.50, 5.78, 6.02, 6.22 μ; ultraviolet λ_{max}^{MeOH} 239 mμ, ε 14,900. Enol ether formation[9] with cyclopentyl orthoformate, cyclopentanol and *p*-toluenesulfonic acid yields 3-cyclopentyloxy-17α-chloroethynyl-19-nor-3,5-androstadiene-17β-ol acetate XIV, m.p. 142–145° (evacuated sealed capillary); $\alpha^{24}D$ −278 (benzene), ultraviolet $\lambda_{max}^{cyclohexane}$ 245 mμ, ε 19,800 (*Anal.* Found: C, 73.28; H, 7.66; Cl, 8.32).

Reaction of IX with pyridinium bromide hydrobromide in pyridine solution[10] affords 17α-chloroethynyl-19-nor-4,10(9)-androstadiene-17β-ol-3-one (XV), m.p. 151–152°; $\alpha^{24}D$ −276 (chloroform), ultraviolet λ_{max}^{MeOH} 303 mμ, ε 19,500, infl. 235 mμ, ε 5,600 (*Anal.* Found: C, 72.57; H, 7.10). Acetylation of XV affords 17α-chloroethynyl-19-nor-4,10(9)-androstadiene-17β-ol-3-one acetate XVI, m.p. 144–145°; $\alpha^{25}D$ −282 (chloroform), ultraviolet λ_{max}^{MeOH} 304 mμ, ε 20,200, infl. 237 mμ, ε 5,600 (*Anal.* Found: C, 71.35; H, 6.77).

Addition of trifluorovinylmagnesium bromide[11] to the 3-dioxolane of 19-nor-4-androstene-3,17-dione,[12] and hydrolysis of the ketal protecting group with *p*-toluenesulfonic acid in acetone, yields 17α-trifluorovinyl-19-nor-4-androstene-17β-ol-3-one XVII, m.p. 175–178°; $\alpha^{24}D$ +31 (chloroform) ultraviolet λ_{max}^{MeOH} 240 mμ, ε 16,500 (*Anal.* Found: C, 67.50; H, 7.17; F, 16.30).

Table I shows an increase in both gonadotrophin inhibition and progestational activity as a consequence of substitution at C-21 with chlorine or bromine. The 10,9-unsaturated analog XV of 17α-chloroethynyl-19-nor-4-androstene-17β-ol-3-one and the corresponding acetate XVI are the most potent gonadotrophin inhibitors retaining high progestational activity for which data sufficient for comparison has been published.

(7) *Cf.* F. Strauss, L. Kollek and W. Heyn, *Ber.*, **63**, 1868 (1930).

(8) *Cf.* O. Engelfried, E. Kaspar, A. Popper and M. Schenk, German Patent 1,017,166 (1957).

(9) *Cf.* A. Ercoli and R. Gardi, *J. Am. Chem. Soc.*, **82**, 746 (1960).

(10) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay and R. T. Rapala, *ibid.*, **82**, 2402 (1960).

(11) I. L. Knunyants, R. N. Sterlin, R. D. Yatsenko and L. N. Pinkina, *Izvest. Akad. Nauk S.S.S.R., Otdel khim. Nauk*, 1345 (1958); *C. A.*, **53**, 6987g (1959).

(12) Prepared from 19-nortestosterone 3-ethylene ketal [J. A. Zderic, D. H. Limon, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3120 (1959)] by Oppenauer oxidation[4] at C-17 (*Anal.* Found: C, 75.87; H, 8.83).

(13) J. A. Epstein, H. S. Kupperman and A. Cutler, *Annals N. Y. Acad. Sci.*, **71**, 560 (1958).

(14) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).

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ON THE ASSIGNMENT OF n → π* TRANSITIONS IN POLYNUCLEOTIDES

Sir:

A recent communication[1] reports the identification of certain bands in the ultraviolet spectra of polynucleotides as n → π* transitions. Among these, a shoulder at 280 mμ in the spectrum of the helical complex polyadenylic + polyuridylic acid (poly(A + U)) is postulated to be a n → π* transition on the ground that it shows increased absorption (hyperchromism) relative to the parent polymers, in contrast to the hypochromism of the main peak at 259 mμ. The authors point out that hyperchromism is predicted, by an extension of Tinoco's theory[2] of polynucleotide spectra, for a band whose transition moment lies along the helix axis, and

(1) A. Rich and M. Kasha, *J. Am. Chem. Soc.*, **82**, 6197 (1960).

(2) I. Tinoco, *ibid.*, **82**, 4785 (1960).