

TABLE I  
 GONADOTROPHIN INHIBITION AND PROGESTATIONAL ASSAYS

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

Alternatively, X can be obtained by protecting I sequentially at the C-3 ketone and 17 $\beta$ -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,<sup>7</sup> and hydrolysis of the protecting groups. Similarly successive bromination of XI at C-21 with N-bromosuccinimide and potassium *t*-butoxide,<sup>7</sup> and then hydrolysis, yields 17 $\alpha$ -bromoethynyl-19-nor-4-androstene-17 $\beta$ -ol-3-one (XII), m.p. 180-182°;  $\alpha^{25}D$  -52 (chloroform), ultraviolet  $\lambda_{max}^{MeOH}$  239  $\mu$ ,  $\epsilon$  16,300 (*Anal.* Found: C, 64.11; H, 7.05).

Reaction of X with acetic anhydride and pyridine affords 17 $\alpha$ -chloroethynyl-19-nor-4-androstene-17 $\beta$ -ol-3-one acetate<sup>8</sup> XIII as an oil, infrared:  $\lambda_{max}$  4.50, 5.78, 6.02, 6.22  $\mu$ ; ultraviolet  $\lambda_{max}^{MeOH}$  239  $\mu$ ,  $\epsilon$  14,900. Enol ether formation<sup>9</sup> with cyclopentyl orthoformate, cyclopentanol and *p*-toluenesulfonic acid yields 3-cyclopentyloxy-17 $\alpha$ -chloroethynyl-19-nor-3,5-androstadiene-17 $\beta$ -ol acetate XIV, m.p. 142-145° (evacuated sealed capillary);  $\alpha^{25}D$  -278 (benzene), ultraviolet  $\lambda_{max}^{cyclohexane}$  245  $\mu$ ,  $\epsilon$  19,800 (*Anal.* Found: C, 73.28; H, 7.66; Cl, 8.32).

Reaction of IX with pyridinium bromide hydrobromide in pyridine solution<sup>10</sup> affords 17 $\alpha$ -chloroethynyl-19-nor-4,10(9)-androstadiene-17 $\beta$ -ol-3-one (XV), m.p. 151-152°;  $\alpha^{25}D$  -276 (chloroform), ultraviolet  $\lambda_{max}^{MeOH}$  303  $\mu$ ,  $\epsilon$  19,500, inf. 235  $\mu$ ,  $\epsilon$  5,600 (*Anal.* Found: C, 72.57; H, 7.10). Acetylation of XV affords 17 $\alpha$ -chloroethynyl-19-nor-4,10(9)-androstadiene-17 $\beta$ -ol-3-one acetate XVI, m.p. 144-145°;  $\alpha^{25}D$  -282 (chloroform), ultraviolet  $\lambda_{max}^{MeOH}$  304  $\mu$ ,  $\epsilon$  20,200, inf. 237  $\mu$ ,  $\epsilon$  5,600 (*Anal.* Found: C, 71.35; H, 6.77).

Addition of trifluorovinylmagnesium bromide<sup>11</sup> to the 3-dioxolane of 19-nor-4-androstene-3,17-dione,<sup>12</sup> and hydrolysis of the ketal protecting

group with *p*-toluenesulfonic acid in acetone, yields 17 $\alpha$ -trifluorovinyl-19-nor-4-androstene-17 $\beta$ -ol-3-one XVII, m.p. 175-178°;  $\alpha^{25}D$  +31 (chloroform) ultraviolet  $\lambda_{max}^{MeOH}$  240  $\mu$ ,  $\epsilon$  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 17 $\alpha$ -chloroethynyl-19-nor-4-androstene-17 $\beta$ -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.

81, 3120 (1959)] by Oppenauer oxidation<sup>1</sup> 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 $n \rightarrow \pi^*$ TRANSITIONS IN POLYNUCLEOTIDES

Sir:

A recent communication<sup>1</sup> reports the identification of certain bands in the ultraviolet spectra of polynucleotides as  $n \rightarrow \pi^*$  transitions. Among these, a shoulder at 280  $\mu$  in the spectrum of the helical complex polyadenylic + polyuridylic acid (poly-(A + U)) is postulated to be a  $n \rightarrow \pi^*$  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  $\mu$ . The authors point out that hyperchromism is predicted, by an extension of Tinoco's theory<sup>2</sup> 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).

(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. Førnefeld, 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.*,

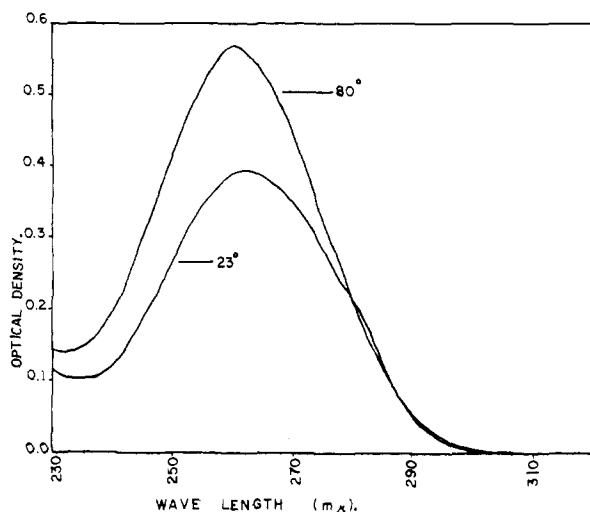


Fig. 1.—Ultraviolet absorption spectra of poly-(dAT), native and denatured by heating. The spectra were taken at the given temperatures. The solution is in 0.002 *M* LiCl, pH 7.

hence is out-of-plane with respect to the nucleotide bases. The assignment as a  $n \rightarrow \pi^*$  transition is deduced from the out-of-plane moment.<sup>3</sup> The authors also mention polarized spectra of poly-(A + U), but do not draw conclusions sufficient to aid in assigning the transition.

In this note, evidence is presented contradictory to this assignment, for a closely related system. An alternant copolymer of deoxyadenylic and deoxythymidylic acids (poly-(dAT)) has been synthesized and described.<sup>4</sup> The spectrum (Fig. 1) of this material in solution also shows a shoulder at 280  $m\mu$ , which is hyperchromic with respect to the heated (denatured) polymer. The close similarity of this spectrum to that of poly-(A + U) is not surprising since poly-(A + U) and poly-(dAT) have very similar spatial structures, both close to that of DNA,<sup>5,6</sup> and since thymine differs from uracil only by a methyl group.

By the analysis used by Rich and Kasha, this hyperchromic shoulder in the poly-(dAT) spectrum would also be assigned as out-of-plane and therefore a  $n \rightarrow \pi^*$  transition.

In order to test this assignment, polarized spectra of oriented streaks of poly-(dAT) have been measured. Poly-(dAT) has higher molecular weight, and hence can be better oriented, than available samples of poly-(A + U). Streaks were made by placing a drop of concentrated poly-(dAT) solution (lithium form), containing about 1% glycerol, on a quartz slide, and stroking it while viewing between crossed polarizers, until good (negative) birefringence was seen. Spectra were taken in a Cary model 14 spectrometer, with a Glan prism polarizer set parallel or perpendicular to the direction of stroking. Appropriate blank spectra, with the polarizer and an empty quartz plate, were also taken. Correction was made for the scattering of

(3) M. Kasha, in "Symposium on Light and Life," Johns Hopkins University Press, Baltimore, Md., 1960.

(4) H. K. Schachman, J. Adler, C. M. Radding, I. R. Lehman and A. Kornberg, *J. Biol. Chem.*, **235**, 3242 (1960).

(5) A. Rich and D. R. Davies, *J. Am. Chem. Soc.*, **78**, 3548 (1956).

(6) R. L. Baldwin and D. R. Davies, to be published.

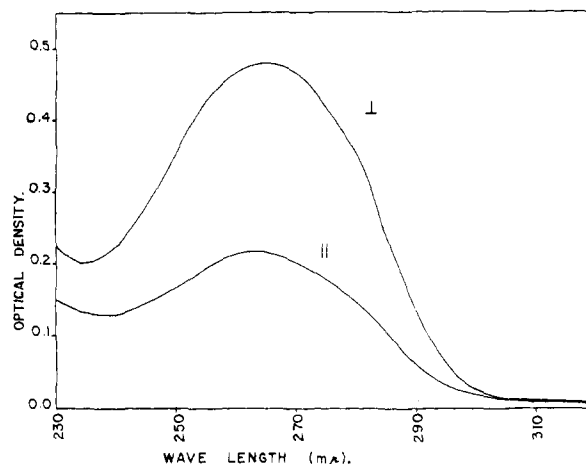


Fig. 2.—Polarized ultraviolet absorption spectra of an oriented streak of poly-(dAT). The polarizations are indicated relative to the direction of streaking. Spectra taken at 23°, 60% relative humidity.

the poly-(dAT) streak by taking the optical density at 320  $m\mu$  as equal to zero, and subtracting this constant amount at all wave lengths. The sample was at room temperature (23°) and about 60% relative humidity. Under these conditions, fibers of poly-(dAT) show an X-ray diffraction pattern very like the B form of DNA.<sup>6</sup>

The spectra thus obtained (Fig. 2) give a dichroism ( $\epsilon_{\perp}/\epsilon_{\parallel}$ ) of 2.3 at the peak, and closely similar values over the whole band. More precisely, the dichroism is 2.2 at 290  $m\mu$ , 2.5 at 280  $m\mu$ , 2.4 at 270  $m\mu$ , 2.3 at 260  $m\mu$  and 2.2 at 250  $m\mu$ . If the shoulder at 280  $m\mu$  had the inverse dichroism to the main peak, the measured dichroism at that wave length would necessarily drop well below 2.0. One is forced to conclude that the 280  $m\mu$  shoulder has closely the same perpendicular polarization as the main peak, and most probably also represents a transition in the plane of the bases. It is thus highly unlikely to be an  $n \rightarrow \pi^*$  transition. The nature of the transition is being investigated.

Since poly-(dAT) and poly-(A + U) have similar structures and spectra, this result also casts some doubt on the assignment of the 280  $m\mu$  band in poly-(A + U). Apparently the presence of a hyperchromic band is not of itself a sufficient criterion for the assignment of a  $n \rightarrow \pi^*$  transition.

I am greatly indebted to Prof. R. L. Baldwin for a gift of poly-(dAT), and for valuable discussions on its properties.

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#### DENSITY OF LIQUID URANIUM<sup>1</sup>

Sir:

The density of pure liquid uranium was determined by using the Archimedean method, from its melting point (1406°K.) to about 1900°K.

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