Notes

Synthetic Antigonadotropins. III

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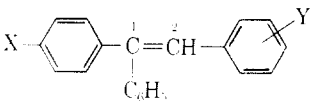


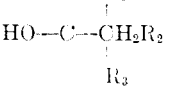
X = H, CH_3O, OH
Y = H, F, CF_3

In a previous report[1b] we described the synthesis of some new triarylethylenes which possess marked antigonadotropin activity. The same study showed that the substitution of a 2- or 4-pyridyl group for one of the phenyl groups on C-1 resulted in the loss of activity. Subsequently, in an extension of this work it was shown that any of the following changes also resulted in the loss of activity: (1) substitution of a cycloalkyl group such as cyclobutyl or cyclopentyl groups for one of the phenyl groups on C-1; (2) bridging the two phenyl groups attached to C-1 so as to produce a fluorene group or a dibenzocycloheptadiene or a dibenzocycloheptatriene structure; (3) substitution of a cyclopropyl group for the ethylene link to which the three phenyl groups are attached; or (4) substitution of a nitrogen atom for C-2.

There was one notable exception to the general loss of activity associated with the structural changes de-

Table I

Triphenylethanol Derivatives



Compd.	R_1	R_2	R_3	M.p., °C.	Calcd. % C	Calcd. % H	Found[a] % C	Found[a] % H
I	*p*-$CH_3OC_6H_4$	*m*-$CF_3C_6H_4$	C_6H_5	73.5–74.5	71.0	5.1	71.3	5.6
II	C_6H_5	*m*-FC_6H_4	C_6H_5	73–74	82.2	5.9	82.4	5.8
III	*p*-$CH_3OC_6H_4$	2-Cl-5-$CF_3C_6H_3$	C_6H_5	109–110	65.0	4.4	65.5	4.9
IV	*p*-$C_6H_5CH_2OC_6H_4$	*p*-FC_6H_4	C_6H_5	104–105	81.4	5.8	81.5	5.7
V	*p*-$C_6H_5CH_2OC_6H_4$	*o*-FC_6H_4	C_6H_5	128.5–129.5	81.4	5.8	81.5	5.9
VI	*p*-$C_6H_5CH_2OC_6H_4$	*m*-FC_6H_4	C_6H_5	111–112	81.4	5.9	81.7	5.9
VII	*p*-$CH_3OC_6H_4$	*m*-FC_6H_4	C_6H_5	70.5–72	78.2	5.9	78.3	6.0

[a] Microanalyses were performed by Dr. A. Steyermark and staff of these laboratories.

Table II

Triphenylethylene Derivatives

$R_1R_3C{=}CHR_2$

Compd.	R_1	R_2	R_3	B.p. (mm.) or m.p., °C.	Calcd. % C	Calcd. % H	Found % C	Found % H
VIII	C_6H_5	*m*-$CF_3C_6H_4$	C_6H_5	138 (0.15)	77.8	4.6	78.2	4.9
IX	*p*-$CH_3OC_6H_4$	*m*-$CF_3C_6H_4$	C_6H_5	154–159 (0.16)	74.6	4.8	75.1	5.1
X	C_6H_5	*m*-FC_6H_4	C_6H_5	58–59.5	87.6	5.5	87.4	5.7
XI	*p*-HOC_6H_5	*o*-FC_6H_4	C_6H_5	180–185 (0.18)	82.6	5.2	82.4	5.3
XII	*p*-$CH_3OC_6H_4$	3-CF_3-4-ClC_6H_3	C_6H_5	197–198 (0.23)	68.0	4.1	67.8	4.3
XIII	*p*-$CH_3OC_6H_4$	2-Cl-5-$CF_3C_6H_3$	C_6H_5	160–164 (0.18)	68.0	4.1	68.2	4.4
XIV	*p*-$CH_3OC_6H_4$	*m*-FC_6H_4	C_6H_5	178–179 (0.18)	82.9	5.6	82.9	5.5
XV	*p*-HOC_6H_4	*p*-FC_6H_4	C_6H_5	200–210 (0.2)	82.6	5.2	82.2	5.2
XVI	*p*-HOC_6H_4	*m*-FC_6H_4	C_6H_5	192–195 (0.2)	82.6	5.2	82.4	5.7

Table III

Active Compounds

Compd.	Structure	Antigonad. activity[a] % change testes	Antigonad. activity[a] % change prostate	Estrogenic activity[b] % change in uterus
X	$(C_6H_5)_2C{=}CHC_6H_4F$-*m*	−45	−39	+108
XI	*p*-$HOC_6H_4(C_6H_5)C{=}CHC_6H_4F$-*o*	−70	−66	+54
XIV	*p*-$CH_3OC_6H_4(C_6H_5)C{=}CHC_6H_4F$-*m*	−46	−61	+74
XV	*p*-$HOC_6H_4(C_6H_5)C{=}CHC_6H_4F$-*p*	−67	−69	+139
XVI	*p*-$HOC_6H_4(C_6H_5)C{=}CHC_6H_4F$-*m*	−49	−49	...

[a] Dose of 50 mg./kg./day. [b] Dose 5 mg./rat/day.

(1) (a) Cyclo Chemical Corp., Los Angeles, Calif. (b) H. H. Fox, J. T. Gibas, H. L. Lee, and A. Boris, *J. Med. Chem.*, **7**, 606 (1964).

scribed. When a cyclohexyl group was substituted for one of the phenyl groups on C-1, and the phenyl group on C-2 had a fluorine atom in the *ortho* position, activity was retained. Shifting the fluorine atom to the *para* position caused a loss of activity.

In the light of these findings it seemed likely that in the compounds of this series, antigonadotropin activity was associated with the triphenylethylene structure. To maximize this effect and minimize the estrogenic activity which was also a frequent accompaniment, the study was extended in the direction which retained the basic triphenylethylene structure and changed only the substituent groupings on the benzene rings.

The compounds reported in this study fall into two general categories; namely, the triphenylethanol and the triphenylethylene derivatives. They are all new compounds and were all prepared by the general methods previously described.[1,2] The triphenylethanol derivatives are listed in Table I and the triphenylethylene derivatives in Table II.

Pharmacology.—The antigonadotropin and estrogenic activity of the compounds was determined by the methods previously described.[1,2] The triphenylethanol derivatives were all inactive as antigonadotropins though some of them had weak estrogenic activity. Five of the triphenylethylene derivatives were active as antigonadotropins and as estrogens. The latter compounds are listed in Table III.

Synthesis of 6- and 7-Bis(2-chloroethyl)amino-DL-tryptophan[1a]

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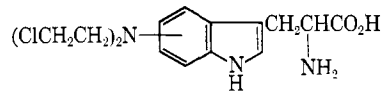
The interesting antitumor activity[2] of 5-bis(2-chloroethyl)amino-DL-tryptophan[1c,3] (IIIa) stimulated us to prepare two other substitution isomers (IIIb and IIIc) of IIIa with the hope of synthesizing a better antitumor drug. In the case of another aromatic nitrogen mustard system, that derived from phenylalanine, the *meta* and *para* isomers have significantly different antitumor activity.[4] The route used to prepare IIIb and IIIc was the same as that used in preparing IIIa. Thus the appropriate substituted gramine I was converted to the acetamidomalonate II that was reduced catalytically to the amine IV. Reaction of IV with ethylene oxide yielded the bis(2-hydroxyethyl)amine V which with methanesulfonyl chloride in pyridine afforded the bis(2-chloroethyl)amine VI. The hydrolysis of both VIb and VIc to IIIb and IIIc, respectively, required a careful control of conditions to obtain the pure nitrogen mustards.

In the course of the work 6-nitro-L-tryptophan[5] was reduced catalytically to the hitherto unreported 6-amino-L-tryptophan (VII).

The antitumor activity[6] of the three tryptophan mustards against the Walker 256 (subcutaneous) tumor in rats is presented in Table I. The increase in therapeutic index of IIIc as compared to IIIa is evident. The 7-mustard IIIc also shows activity against the Sarcoma 180 tumor in contrast with IIIa which does not respond to that tumor. All three tryptophan mustards givea good response in the leukemia L1210 system.

TABLE I

ANTITUMOR ACTIVITY OF DL-TRYPTOPHAN NITROGEN MUSTARDS



Isomer	LD_{10}, mg./kg./day[a]	MED, mg./kg./day[b]	T.I.[c]
5-Mustard	1.2	0.31	4
6-Mustard	1.3	0.15	9
7-Mustard	4.8	0.35	14

[a] The LD_{10} is the dose that kills more than 10% of the animals and is the maximum tolerated dose. [b] The minimum effective dose (MED) is that dose which gives a ratio of 0.10 of tumor weight in treated animals to tumor weight in control animals. [c] The therapeutic index (T.I.) is defined as LD_{10}/MED.

Experimental[7]

Ethyl α-acetamido-α-carbethoxy-β-(6-nitro-3-indolyl)propionate (IIb) was prepared in 70% yield from 6-nitrogramine[8] using the procedure of Cavallini and Ravenna[9] described for preparation of IIa. The analytical sample, recrystallized from chloroform or acetonitrile, had m.p. 225–226°; λ_{max}^{Nujol} 3.00 and 6.61 (NH), 5.71 and 5.82 (ester C=O), 6.12 (amide C=O), 7.46 μ (NO_2). A lower melting polymorph (with a correct analysis), m.p. 196–197°, was also noted in some runs and could be converted to the higher melting form by recrystallization and seeding.

Anal. Calcd. for $C_{18}H_{21}N_3O_7$: C, 55.2; H, 5.37; N, 10.8. Found: C, 55.0; H, 5.46; N, 10.6.

Ethyl α-acetamido-α-carbethoxy-β-(7-nitro-3-indolyl)propionate (IIc) was prepared by the procedure described by DaSettimo.[10]

Ethyl α-acetamido-α-carbethoxy-β-(6-amino-3-indolyl)propionate (IVb) was prepared by the procedure described for IVa,[3] to give a 97% yield of product. The analytical sample, recrystallized from acetonitrile, had m.p. 176–177°; λ_{max}^{Nujol} 2.98, 3.02, and 6.55 (NH,NH_2), 5.73 (ester C=O), 6.00 μ (amide C=O).

Anal. Calcd. for $C_{18}H_{23}N_3O_5$: C, 59.8; H, 6.38; N, 11.6. Found: C, 59.9; H, 6.53; N, 11.5.

Ethyl α-acetamido-α-carbethoxy-β-(7-amino-3-indolyl)propionate (IVc) is described by Casini and Goodman.[11]

Ethyl α-Acetamido-α-carbethoxy-β-[6-bis(2-hydroxyethyl)-amino-3-indolyl]propionate (Vb) Hydrochloride.—Ethylene ox-

(1) (a) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. (b) Holder of a NATO fellowship during 1962. (c) In the numbering in the text, the a series represent the 5-substituted compounds, the b series the 6-substituted, and the c series the 7-substituted.

(2) J. DeGraw and L. Goodman, *J. Med. Chem.*, **7**, 213 (1964).

(3) J. DeGraw and L. Goodman, *J. Org. Chem.*, **27**, 1395 (1962).

(4) (a) M. O. Greene, B. R. Baker, and J. Greenberg, *Cancer Res.*, **20**, 1160 (1960); (b) V. I. Trusheikina, *Vopr. Onkol.*, **6**, 63 (1960).

(5) R. DeFazi, G. Berti, and A. DaSettimo, *Gazz. chim. ital.*, **89**, 2238 (1959).

(6) Antitumor testing was carried out under the auspices of the Cancer Chemotherapy National Service Center according to the protocols described in *Cancer Chemotherapy Rept.*, **25**, 11 (1962).

(7) Melting points, uncorrected, were obtained with the Fisher-Johns apparatus. Magnesium sulfate was used to dry organic extracts.

(8) G. Berti and A. DaSettimo, *Gazz. chim. ital.*, **90**, 525 (1960).

(9) G. Cavallini and F. Ravenna, *Farmaco* (Pavia), *Ed. Sci.*, **13**, 105 (1958).

(10) A. DaSettimo, *Ann. Chim.* (Rome), **52**, 17 (1962).

(11) G. Casini and L. Goodman, *Can. J. Chem.*, **42**, 1235 (1964).