Synthetic Antigonadotropins. II

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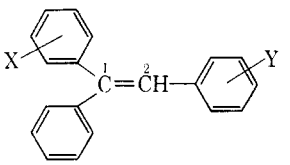
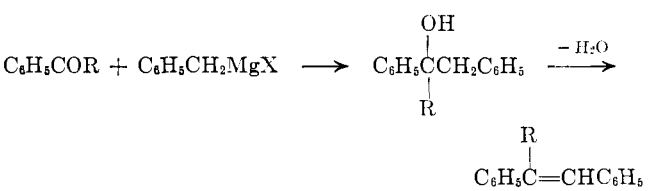
In an attempt to relate structure and antigonadotropin activity, a series of changes were effected on the active triphenylethylene structures. These changes include: (1) substitution of a cycloalkyl group for one of the benzene rings; (2) bridging two of the benzene rings to give fluorene, dibenzocycloheptadiene, and dibenzocycloheptatriene groups; (3) replacement of the ethylenic link with a cyclopropyl group; (4) replacement of one of the aliphatic carbon atoms with a nitrogen atom. With the exception of 1-cyclohexyl-1-phenyl-2-(*o*-fluorophenyl)ethylene (IX), all of the compounds so prepared were inactive.

In a previous report,[2] it was shown that compounds of the general type



X = H, CH_3O
Y = H, Cl, F

had pronounced antigonadotropin activity and that this activity disappeared if one of the benzene rings on C-1 was replaced by a 2- or 4-pyridyl grouping. To explore further the relationship between structure and activity, a series of compounds was prepared in which one of the benzene rings on C-1 was replaced by a cyclohexyl, a cyclopentyl, or a cyclobutyl group. The compounds of this series were all prepared by substantially the same procedure. Reaction of the appropriate ketone and Grignard reagent gave the corresponding trisubstituted ethanol which was then dehydrated to give the desired ethylene derivative. In the case of the cyclopentyl and cyclohexyl derivatives, the trisubstituted ethanols were not isolated in pure form because simple distillation sufficed to convert them to the ethylene derivative. The ethylenic character of these compounds is supported by the fact that all of them gave the high ultraviolet absorptions characteristic of the extended conjugation of stilbene derivatives. This sequence of reactions is illustrated in the following equation.



R = cyclobutyl, cyclopentyl, or cyclohexyl

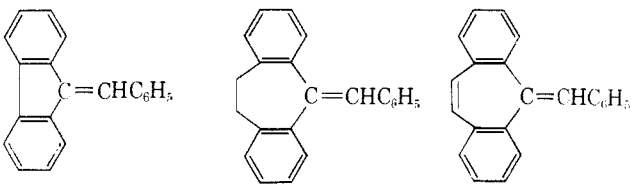
Several attempts were made to introduce the cyclopropyl group in the same fashion. Though 1-cyclopropyl-1-phenyl-2-(*p*-fluorophenyl)ethanol (I) could be obtained, all attempts to dehydrate it to the ethylene derivative resulted in mixtures which were not resolved.

The cycloalkane ethanol and ethylene derivatives prepared in this series are listed in Tables I and II, respectively.

(1) Cyclo Chemical Corp., Los Angeles, Calif.

(2) H. H. Fox, J. T. Gibas, H. L. Lee, and A. Boris, *J. Med. Chem.*, **7**, 606 (1964).

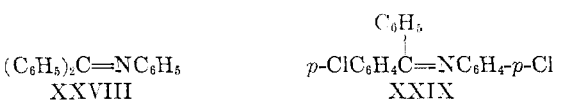
Another structural change which was explored to determine its effect on activity was the bridging of the two benzene rings at C-1 to give fluorene and dibenzocycloheptene structures.



These compounds were prepared by Grignard reactions on the corresponding ketones to give the tertiary alcohols which, in some instances, rapidly dehydrated on simple distillation to give the desired unsaturated structures. The tertiary alcohols so prepared are listed in Table III and the corresponding unsaturated structures in Table IV.

Although the presence of the double bond linking the two aliphatic carbon atoms seemed to be a prime requisite to antigonadotropin activity, several compounds were prepared in which a methylene or substituted methylene group replaced one of the ethylene bonds linking the two aliphatic carbon atoms. The resulting triaryl cyclopropanes are listed in Table V.

Two compounds, XXVIII and XXIX, were prepared in which one of the aliphatic carbon atoms was replaced by a nitrogen atom to produce the analogous ketimine structure. The first of these compounds, XXVIII, was previously reported by Reddelien.[3] The synthesis of the second XXIX is given in Experimental under the heading Miscellaneous.



XXVIII XXIX

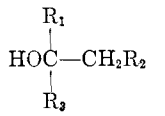
The details of preparation of those compounds not previously reported in the literature are given in Experimental.

Pharmacology.—The antigonadotropic activity was determined according to the method previously described.[2] In the initial screening only those compounds were considered active which when given to 50–60 g. immature male rats at a dose level of 50 mg./kg./day for 10 working days depressed both testes and prostate growth by more than 25% as compared to the controls. All of the compounds with the exception of 1-cyclohexyl-1-phenyl-2-(*o*-fluorophenyl)ethylene (IX) were inactive. This is a rather noteworthy exception since

(3) C. Reddelien, *Ber.*, **48**, 1462 (1915).

TABLE I

CYCLOALKYLATED ETHANOL DERIVATIVES

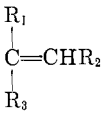


Compd.	R_1	R_2	R_3	B.p. (mm.) or m.p., °C.	Calcd., %[a] C	Calcd., %[a] H	Found, %[a] C	Found, %[a] H
I	C_6H_5	p-FC_6H_4	C_3H_5[b]	58–59	79.7	6.6	80.1	6.7
II	C_6H_5	o-FC_6H_4	C_4H_7[c]	125–126 (0.13)	80.0	7.0	80.1	7.0
III	C_6H_5	p-FC_6H_4	C_4H_7[c]	129–130 (0.13)	80.0	7.0	79.7	7.4

[a] The microanalyses were performed by Dr. A. Steyermark and his staff of these laboratories. [b] C_3H_5 = cyclopropyl. [c] C_4H_7 = cyclobutyl.

TABLE II

CYCLOALKYLATED ETHYLENE DERIVATIVES

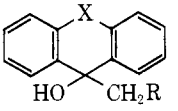


Compd.	R_1	R_2	R_3	B.p., °C. (mm.)	Calcd., %[a] C	Calcd., %[a] H	Found, %[a] C	Found, %[a] H
IV	C_6H_5	p-FC_6H_4	C_4H_7[b]	120–122 (0.15)	85.7	6.7	85.7	6.8
V	C_6H_5	o-FC_6H_4	C_4H_7[b]	123–125 (0.15)	85.7	6.7	85.5	7.0
VI	C_6H_5	p-FC_6H_4	C_5H_9[c]	131 (0.15)	85.7	7.2	85.5	7.4
VII	C_6H_5	o-FC_6H_4	C_5H_9[c]	133–134 (0.15)	85.7	7.2	85.8	6.9
VIII	C_6H_5	p-FC_6H_4	C_6H_{11}[d]	138 (0.15)	85.7	7.5	86.1	7.7
IX	C_6H_5	o-FC_6H_4	C_6H_{11}[d]	136 (0.15)	85.7	7.5	86.0	7.8

[a] The microanalyses were performed by Dr. A. Steyermark and his staff of these laboratories. [b] C_4H_7 = cyclobutyl. [c] C_5H_9 = cyclopentyl. [d] C_6H_{11} = cyclohexyl.

TABLE III

FLUORENOL AND DIBENZOCYCLOHEPTENOL DERIVATIVES

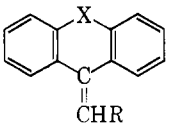


Compd.	X	R	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
X[a]	...	p-FC_6H_4	109.5–110						
XI[b]	...	p-ClC_6H_4	137–138	78.4	4.9		78.2	5.1	
XII	...	o-FC_6H_4	139–140	82.8	5.2		82.8	5.5	
XIII	—CH_2CH_2—	p-ClC_6H_4	106.5–107	79.0	5.7		78.8	5.9	
XIV	—CH_2CH_2—	p-FC_6H_4	103.5–104	83.0	6.0		82.9	5.8	
XV	—CH=CH—	p-FC_6H_4	140–141	83.6	5.4	6.0	83.6	5.6	5.9

[a] E. D. Bergmann, Y. Hirshberg, D. Lavie, Y. Sprinzak, and J. Szmuszkovicz, *Bull. soc. chim. France*, 703 (1952). [b] E. D. Bergmann, G. Berthier, D. Ginsburg, Y. Hirshberg, D. Lavie, S. Pinchas, B. Pullman, and A. Pullman, *ibid.*, 661 (1959).

TABLE IV

BENZYLIDENE DERIVATIVES OF FLUORENE AND DIBENZOCYCLOHEPTENES



Compd.	X	R	B.p. (mm.) or m.p., °C.	Calcd., % C	Calcd., % H	Calcd., % F	Found, % C	Found, % H	Found, % F
XVI[a]	...	p-FC_6H_4	120–121						
XVII	...	o-FC_6H_4	192–195 (0.2)	88.3	4.8		88.1	5.0	
XVIII[b]	...	p-ClC_6H_4	150–151						
XIX[c]	—CH_2CH_2	p-ClC_6H_4	206–209 (0.3)						
XX	—CH_2CH_2	p-FC_6H_4	63–65	88.0	5.7		87.8	5.5	6.2
XXI	—CH_2CH_2	o-FC_6H_4	138–138.5	88.0	5.7	6.3	87.8	5.5	6.2
XXII[c]	—CH_2CH_2	C_6H_5	179–181 (0.15)						
XXIII	—CH=CH—	p-FC_6H_4	127–128	88.6	5.0		88.7	5.3	
XXIV	—CH=CH—	o-FC_6H_4	141–142	88.6	5.0		88.7	4.9	

[a] E. D. Bergmann, Y. Hirshberg, D. Lavie, Y. Sprinzak, and J. Szmuszkovicz, *Bull. soc. chim. France*, 703 (1952). [b] E. D. Bergmann, G. Berthier, D. Ginsburg, Y. Hirshberg, D. Lavie, S. Pinchas, B. Pullman, and A. Pullman, *ibid.*, 661 (1959). [c] E. D. Bergmann, E. Fischer, D. Ginsberg, Y. Hirshberg, D. Lavie, M. Mayot, A. Pullman, and B. Pullman, *ibid.*, 684 (1951).

TABLE V

TRIARYLCYCLOPROPANE DERIVATIVES

$(C_6H_5)_2C$——CHC_6H_5
\ /
CHR

Compd.	R	B.p. (mm.) or m.p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
XXV[a]	—COOEt	94–95				
XXVI[a]	—COOH	202–203				
XXVII	H	166–168 (0.2)	93.4	6.6	93.6	6.8

[a] H. Staudinger, E. Anthes, and F. Pfenninger, *Ber.*, **49**, 1928 (1916).

even its *p*-fluorophenyl isomer VIII was inactive. We have no explanation for this exceptional behavior.

Experimental[4]

General Method.—Many of the compounds reported in this study were prepared by means of a Grignard reaction according to the following procedure. To a Grignard reagent made by the interaction of slightly more than 1 g.-atom of Mg with slightly more than 1 equiv. of the appropriate benzyl halide in ether was added an ether solution of 1 equiv. of the appropriate ketone. The mixture was refluxed for 1–2 hr. and was finally cooled and treated with a slight excess of water or methanol. The reaction mixture was then extracted with ether, the ether solution was dried, and the ether was removed to give the desired alcohol. Some of the alcohols so prepared could be purified by distillation. Others lost a molecule of water when distilled either alone or with a few drops of sulfuric acid and gave the corresponding unsaturated derivatives. Some of the pertinent details are given in Table VI.

Triarylcyclopropane Derivatives (Table V). 1,1,2-Triphenylcyclopropane (XXVII).—Six grams of 2,2,3-triphenylcyclopropanecarboxylic acid prepared according to the method of Staudinger[5] was heated above 290° until the evolution of CO_2 ceased. The reaction mixture was then distilled and the fraction boiling at 160–180° (0.2 mm.) was collected. Upon redistillation, the product was obtained in the form of a soft yellow glass boiling at 166–168° (0.2 mm.).

(4) All melting points are corrected; the boiling points are uncorrected.

(5) See Table V, footnote *a*.

TABLE VI

Ketone	Reactants: Benzyl chloride	Yield of alcohol, %	$n^{25}D$	Yield of unsatd. compd., %	$n^{25}D$
Cyclopropylphenyl[a]	*p*-F	1			
Cyclobutylphenyl[b]	*o*-F	47 II	1.5618	60[c] V	
	p-F	47 III	1.5568	60[c] IV	
Cyclopentylphenyl[d]	*p*-F			48 VI	1.5709[e]
	o-F			59 VII	1.5766
Cyclohexylphenyl[d]	*p*-F			68 VIII	1.5760
	o-F			82 IX	1.5773
Fluorenone	*o*-F	31 XII		69[c] XVII	
10,11-Dihydro-5H-dibenzo[*a,d*]-cyclohepten-5-one[f]	*p*-Cl	XIII			
	p-F	71 XIV		87[c] XX	
	o-F			73 XXI	
5H-Dibenzo[*a,d*]-hepten-5-one[g]	*p*-F	49 XV			
	p-F			93[c] XXIII	
	o-F			XXIV	

[a] M. Kishner, *Chem. Zentr.*, **83**, 1458 (1912). [b] D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.*, **82**, 1965 (1960). [c] Yield obtained from the alcohol. [d] D. H. Hey and O. C. Musgrave, *J. Chem. Soc.*, 3156 (1949). [e] At 28°. [f] A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1676 (1951). [g] W. Treibs and H. J. Klinkhammer, *Ber.*, **84**, 671 (1951).

Miscellaneous. 4-Chloro-N-(4-chlorophenylphenylmethylene)aniline (XXIX).—A mixture of 22 g. of *p*-chlorobenzophenone, 25.6 g. of *p*-chloroaniline, and 5 drops of concentrated HCl was heated to 250° for about 20 min. The melt was cooled, extracted with hot benzene, and the benzene solution was filtered to remove an insoluble crystalline material varying in color from dark brown to dark blue. The benzene was removed and the residue was distilled twice to yield a viscous yellow oil, b.p. 190–192° (0.2 mm.).

Anal. Calcd. for $C_{19}H_{13}Cl_2N$: C, 70.0; H, 4.0; Cl, 21.8. Found: C, 70.2; H, 4.0; Cl, 21.5.

Pyrimidine Derivatives. VI. 2,4,5-Triamino-6-chloro- and -6-mercaptopyrimidine and Related Compounds[1,2]

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The preparation of the title compounds has been accomplished from acyclic starting materials *via* a sequence of steps involving synthesis and reduction of the corresponding 5-phenylazo derivatives. As an alternate approach, nitrosation of two pyrimidine intermediates was attempted. Treatment of 2,4-diamino-6-chloropyrimidine with nitrous acid produced a multicomponent mixture which, by means of exhaustive paper chromatographic analysis, was found to consist of 4-amino-6-chloro-2-hydroxypyrimidine, 2-amino-6-chloro-4-hydroxypyrimidine, 4-amino-2,6-dihydroxypyrimidine, and a trace of unreacted starting material. Attempted nitrosation of 2,4-diamino-6-mercaptopyrimidine, however, resulted only in the oxidation of the sulfur with consequent formation of bis(2,4-diamino-6-pyrimidyl) disulfide. In the course of this work several previously unreported pyrimidines have been prepared. Quantitative ultraviolet absorption spectra are given for all compounds prepared, as well as a summary of growth-inhibitory properties in selected *in vitro* and *in vivo* bioassay systems.

As part of a continuing program of cancer chemotherapy, a number of pyrimidine derivatives have been synthesized in these laboratories for biological evaluation and as precursors of condensed pyrimidine ring systems. We recently reported the synthesis of various substituted pyrimidines using 4-amino-6-chloro-2-methylthiopyrimidine as a versatile starting material.[2] We should like now to describe the preparation of the title compounds, as well as the synthesis and chemistry of some related substituted pyrimidines.

The key intermediate utilized in this investigation was 2,4-diamino-6-chloropyrimidine (IV). This com-

(1) This investigation was supported in part by research grants (CY3335 and C6516) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) For paper V in this series see M. Israel, H. K. Protopapa, H. N. Schlein, and E. J. Modest, *J. Med. Chem.*, **7**, 5 (1964).