washed again with water and taken to dryness. The residue was dissolved (CH_2Cl_2) and washed with 20% HI, and the former solution was taken to dryness. The residual solid was recrystallized from methylene chloride–ethyl acetate to afford 1.17 g of **42**, mp 220–222°. An extensively purified sample melted at 222–223°, λ_{max} 283 mμ (ε 17,800).

Acknowledgment.—We wish to express our indebtedness to Mr. Brooke D. Aspergren of these laboratories for generous supplies of 2-phenyl-6-methoxy-1-tetralone, and to Mr. Richard D. Eliasen for help in the preparation of some of these compounds.

Substituted Aminoalkoxytriarylhaloethylenes[1]

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A series of triarylhaloethylene compounds were synthesized and screened for their effects on pituitary gonadotrophins in animals. One, 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate (1, clomiphene citrate) was selected for further testing in animals and in humans.

Robson and Schönberg[3] reported that triphenylethylene and triphenylchloroethylene were estrogens of low potency but of unusual duration of action. Shelton, *et al.*,[4] and others[5,6] have shown that substitution with alkoxy groups increased the potency of these derivatives. This report concerns a series of substituted aminoalkoxytriarylhaloethylenes having gonadotrophin inhibitory properties when tested in rats (see Table I).

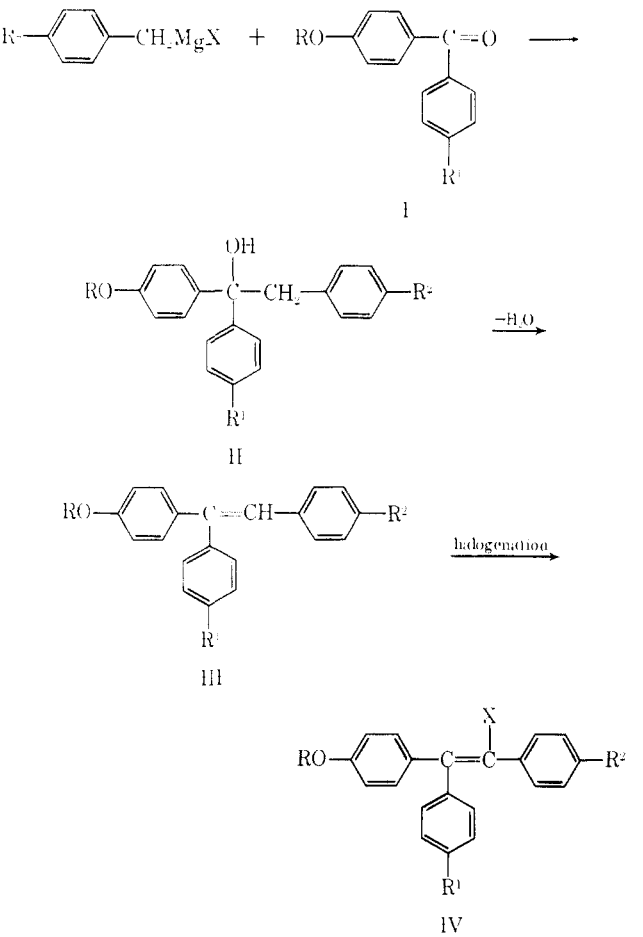
The compounds were prepared by the reaction of appropriate benzylmagnesium halides with substituted diaryl ketones (I), followed by dehydration of the resulting ethanols (II) to the triarylethylenes (III), which upon halogenation yielded the haloethylenes (IV) (Scheme I).

The basic substituted ketones I were generally prepared by the reaction of a substituted aminoalkyl halide with the sodium salt of the hydroxybenzophenone in ethanol.

Halogenation was attempted by a variety of methods,[7] the most successful being direct chlorination in chloroform. The use of N-chlorosuccinimide or N-bromosuccinimide was found to be less satisfactory, as the products obtained with these agents required considerable purification. In one case, direct bromination of 1-[*p*-(β-dimethylaminoethoxy)phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol gave a low yield of the desired haloethylene.

Noncrystalline hydrochloride salts of the compounds were converted to the bases with 10% sodium hydroxide solution and then to dihydrogen citrate salts with an equivalent amount of citric acid in butanone. The dihydrogen citrate salts are subsequently recrystallized from butanone or 2-propanol.

SCHEME I



Repeated recrystallization of certain of the hydrochloride salts of these compounds allowed the separation of the compounds into their *cis*[8] and *trans*[8] isomers (*i.e.*, **1a** and **1b**) which were subsequently characterized.

Tests for gonadotrophin inhibition were performed on intact immature male rats. The test compounds were administered subcutaneously in an oil vehicle at an initial dose of 50 mg/kg/day for 10 days. Lower doses were utilized in subsequent studies. Autopsies were

(1) Presented in part at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, Abstracts, p 20N.

(2) To whom correspondence should be addressed.

(3) J. M. Robson and A. Schönberg, *Nature*, **140**, 196 (1937).

(4) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen, and K. K. Wycoff, *J. Am. Chem. Soc.*, **75**, 5491 (1953).

(5) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

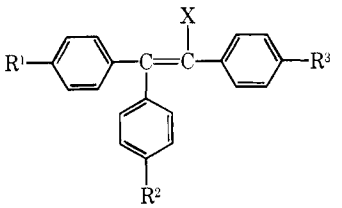
(6) C. R. Thompson and H. W. Werner, *Proc. Soc. Exptl. Biol. Med.*, **77**, 491 (1951).

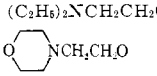
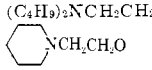
(7) R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. Van Campen, Jr., U. S. Patent 2,914,563 (1959); *Chem. Abstr.*, **54**, 5581e (1960).

(8) *cis* and *trans* are defined here in terms of the geometric relationship of the two unsubstituted phenyl rings.

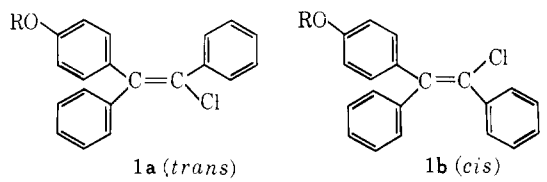
TABLE I

AMINOALKOXYTRIARYLHALOETHYLENES



No.	R^1	R^2	R^3	X	Mp, °C[a]	Method	Yield, %	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found
1	$(C_2H_5)_2NCH_2CH_2O$	H	H	Cl	116–118	A	91	$C_{26}H_{26}ClNO$[c]	64.26	64.38	6.07	6.36	5.93	5.50
1a	$(C_2H_5)_2NCH_2CH_2O$	H	H	Cl	156.5–158.0	E	...	$C_{26}H_{28}ClNO$[b]	70.58	70.45	6.61	6.64	16.03	15.87
1b	$(C_2H_5)_2NCH_2CH_2O$	H	H	Cl	149.0–150.5[e]	E	...	$C_{26}H_{28}ClNO$[b]	70.58	70.84	6.61	6.54	16.03	15.92
2	$(C_2H_5)_2NCH_2CH_2O$	H	H	Br	125–127	C	37	$C_{26}H_{28}BrNO$[c]	59.81	60.31	5.65	5.72	12.45	12.06
3		H	H	Cl	203	B	42	$C_{26}H_{26}ClNO_2$[b]	68.40	68.16	5.96	5.86	3.07[d]	3.18
4	$(C_2H_5)_2NCH_2CH_2CH_2O$	H	H	Cl	110–112	B	62	$C_{27}H_{30}ClNO$[c]	64.74	64.39	6.26	6.32	5.79	5.40
5	$(CH_3)_2NCH_2CH_2O$	H	OCH_3	Cl	100–102	B	51	$C_{26}H_{26}ClNO_2$[c]	62.04	62.31	5.71	6.09	5.91	5.92
6	$(CH_3)_2NCH_2CH_2O$	H	OCH_3	Br	114–116	D	9.3	$C_{26}H_{26}BrNO_2$[c]	57.76	57.54	5.32	5.55	12.40	12.94
7	$(C_2H_5)_2NCH_2CH_2O$	H	OCH_3	Cl	127	B	71	$C_{27}H_{30}ClNO_2$[c]	63.10	63.32	6.10	6.36	5.64	5.33
8	$(C_2H_5)_2NCH_2CH_2O$	H	OCH_3	Br	128–130	C	6.2	$C_{27}H_{30}BrNO_2$[c]	58.93	58.54	5.69	5.58	11.88	11.47
9	$(C_4H_9)_2NCH_2CH_2O$	H	OCH_3	Cl	149–153	B	33	$C_{31}H_{38}ClNO_2$[b]	70.43	70.38	7.44	7.40	13.42	13.44
10		H	OCH_3	Cl	186–187	B	38	$C_{26}H_{30}ClNO_2$[b]	69.42	69.56	6.45	6.84	14.64	14.14
11	$(C_2H_5)_2NCH_2CH_2O$	H	Cl	Cl	111–112	A	52	$C_{26}H_{27}Cl_2NO$[c]	60.76	60.14	5.58	5.70	2.22[d]	2.26
12	$(C_2H_5)_2NCH_2CH_2O$	Cl	OCH_3	Cl	180–185	B	63	$C_{27}H_{29}Cl_2NO_2$[b]	63.97	63.88	5.97	6.10	20.99	21.18
13	$(C_2H_5)_2NCH_2CH_2O$	OCH_3	H	Cl	103–107	A	68	$C_{27}H_{30}ClNO_2$[c]	63.10	63.12	6.10	6.10	5.64	5.62
14	$(C_2H_5)_2NCH_2CH_2O$	H	F	Cl	199–201	A	8	$C_{26}H_{27}ClFNO$[b]	67.82	67.43	6.13	6.44	3.04[d]	2.95

[a] Melting points are those of the salts indicated in the formula. [b] Hydrochloride salt. [c] Dihydrogen citrate salt. [d] Indicates N analysis. [e] A polymorphic form of this isomer melts at 159–161°.



1a (*trans*) 1b (*cis*)

R = HCl·$(C_2H_5)_2NCH_2CH_2$

performed on the day after the last injection, and the organs were removed and weighed.

In comparison with the untreated controls, immature male rats treated with high doses of the haloethylenes showed significantly lower weights of the sex and sex accessory organs. Confirmatory tests in parabiotic rats also showed the potent gonadotrophin inhibitory qualities of the haloethylenes.

One representative compound, 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate (**1**, clomiphene citrate),[9] gave 50% inhibition of ovarian hypertrophy in parabiotic rats at a dose of 0.1 mg/kg/day.[10] Animal studies further suggested that in addition to gonadotrophin-inhibiting properties, **1** had estrogenic and antiestrogenic actions.[10,11] Tests[10,12] performed with low doses (0.1–0.5 mg/kg/day) of **1** in intact, immature rats resulted in increased ventral prostate weight of the test animals above that of the controls. These results suggest gonadotrophin stimulation by low doses of **1**. Reports[13,14] on subsequent clinical studies showed that **1** induced ovulatory-type menses in anovulatory, amenorrheic women.

(9) Clomid® is the Wm. S. Merrell Co. trademark name. The accepted generic name is clomiphene citrate. In early literature reports, it was also referred to as chloramiphene citrate.

(10) D. E. Holtkamp, J. G. Greslin, C. A. Root, and L. J. Lerner, *Proc. Soc. Exptl. Biol. Med.*, **105**, 197 (1960).

(11) D. E. Holtkamp, R. E. Staples, J. G. Greslin, and R. H. Davis, *Excerpta Med.*, in press.

(12) S. Roy, V. B. Mahesh, and R. B. Greenblatt, *Acta Endocrinol.*, **47**, 345 (1964).

(13) R. B. Greenblatt, W. E. Barfield, E. C. Jungck, and A. W. Roy, *J. Am. Med. Assoc.*, **178**, 101 (1961).

(14) R. W. Kistner, *Am. J. Obstet. Gynecol.*, **92**, 380 (1965).

Experimental Section

The ethylene starting materials for **1–4** and **7** are described in ref 7 while those for the remaining haloethylenes (except **13**) are described in ref 15. The starting material for **13** was prepared from 4-(β-diethylaminoethoxy)-4′-methoxybenzophenone[16] according to ref 15.

Method A. Direct Chlorination. 2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine Dihydrogen Citrate (1).—To a solution of 250 g (0.615 mole) of 2-[*p*-(1,2-diphenylvinyl)phenoxy]-triethylamine hydrochloride in 900 ml of dry chloroform was added, over a period of 2 hr, 1190 ml of a CCl_4 solution containing 38.6 g (0.646 mole) of Cl_2/l. After the addition was completed, the solution was stirred at room temperature for 30 min and then refluxed for 1 hr. The solution was cooled and made basic by addition of a Na_2CO_3 or NaOH solution. The organic layer was removed and dried ($MgSO_4$). The chloroform was removed under reduced pressure and the residue that remained was converted to the dihydrogen citrate salt using 115 g (0.615 mole) of citric acid in 1000 ml of butanone and 300 ml of hot methanol. On cooling 334 g (91%) of product, melting at 116–118°, was obtained.

In a number of trials, the yields varied from 41–93%, with most of them being near 90%.

Method B. Halogenation with N-Chlorosuccinimide. N-[2-{*p*-Chloro-2-*p*-methoxyphenyl-1-phenyl)vinyl]phenoxy}ethyl]dibutylamine Hydrochloride (9).—To a solution of 14.5 g (0.029 mole) of N-[2-{*p*-(2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy}-ethyl]dibutylamine hydrochloride in 150 ml of dry chloroform was added a solution of 4.4 g (0.033 mole) of N-chlorosuccinimide in 100 ml of dry $CHCl_3$. The reaction mixture was refluxed for 14 hr, cooled, and washed with water. After drying the chloroform solution ($MgSO_4$), the chloroform was removed by distillation and ethyl acetate was added. The white crystalline product obtained was recrystallized twice from ethyl acetate to give 5.0 g (33%) of product, which melted at 118°, then resolidified and

(15) R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. Van Campen, Jr., U. S. Patent 2,914,561 (Nov 24, 1959); *Chem. Abstr.*, **54**, 5581e (1960).

(16) British Patent 929,254 (June 19, 1963); *Chem. Abstr.*, **60**, 2827g (1964).

melted at 150°. After the product was dried at 100° *in vacuo*, it melted at 140–153°.

Method C. Halogenation with N-Bromosuccinimide. 2-[*p*-(2-Bromo-2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy]triethylamine Dihydrogen Citrate (8).—To a solution of 46.1 g (0.095 mole) of 2-[*p*-(2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy]triethylamine hydrochloride in 200 ml of dry $CHCl_3$ at 0° was added a suspension of 19.6 g (0.11 mole) of N-bromosuccinimide in 300 ml of dry chloroform. The mixture was stirred at 0° for 8 hr then was allowed to stand for 24 hr at 0°. The reaction mixture was kept at 0° while an excess of 10% NaOH was added. The organic layer was removed and dried ($MgSO_4$). The residue that remained upon removal of the chloroform was converted to the dihydrogen citrate salt, using 18.3 g (0.095 mole) of citric acid in butanone. The crystalline product obtained was recrystallized seven times from butanone and once from 2-propanol to give 4.0 g (6.2%) of product, melting at 128–130°.

Method D. Bromine in Glacial Acetic Acid. N-[2-[*p*-(2-Bromo-2-*p*-methoxyphenyl-1-phenylvinyl)phenoxy]ethyl]dimethylamine Dihydrogen Citrate (6).—To a solution of 10.0 g (0.025 mole) of 1-[*p*-(β-dimethylaminoethoxy)phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol in 50 ml of glacial acetic acid was added a solution of 8.0 g (0.05 mole) of bromine in 50 ml of glacial acetic acid at 15°. The reaction mixture was stirred for 1 hr after the addition was completed at 15°, then cooled to 0° and made basic with an excess of NaOH. The free amine was extracted with ether and dried ($MgSO_4$). The residue that remained after removal of the ether was converted to the dihydrogen citrate salt, using 4.8 g (0.025 mole) of citric acid in butanone. The product was recrystallized six times from butanone to give 1.5 g (9.3%) of product melting at 114–116°.

Method E. Fractional Recrystallization. Isomers of 2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine Hydrochloride.

The dihydrogen citrate salt of **1** was converted to the base with aqueous NaOH solution. The base was extracted with ether, dried ($MgSO_4$), filtered, and treated with alcoholic HCl. The oil which separated was taken up in hot butanone, and upon cooling, a solid fraction was obtained. Further fractions were obtained by condensing the mother liquor of the previous fraction and cooling. Repetition of this process yielded isomer **a** hydrochloride (**1a**) which melted at 156.5–158.0° [$\lambda_{max}^{CH_3OH}$ 230 mμ (ε 20,500), 291 mμ (ε 12,700)], and isomer **b** hydrochloride (**1b**) which melted at 149.0–150.5° [$\lambda_{max}^{CH_3OH}$ 239 mμ (ε 22,100), 207 mμ (ε 11,600)].

The longest wavelength maximum in each of the ultraviolet spectra has been attributed to a stilbene-type chromophore. These data suggest that **1b** is the *cis*[8] isomer and therefore **1a** is the *trans*[8] isomer.

Synthesis and Pharmacological Properties of New 9,10-Dihydro-9,10-ethanoanthracene Derivatives

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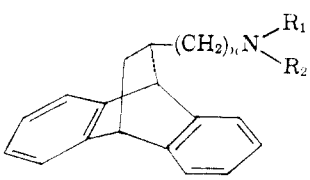
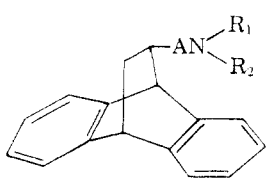
Received July 4, 1966

A number of substituted 9,10-dihydro-9,10-ethanoanthracenes have been synthesized and evaluated for their pharmacological activity. Some of these compounds show marked anticholinergic, hypotensive, antihistaminic, and local anesthetic activities.

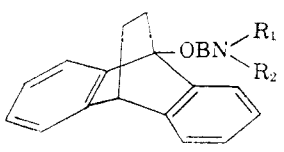
The ability of anthracene to act as a conjugated diene in a Diels–Alder reaction was first reported in 1931.[1] The resulting 9,10-dihydro-9,10-ethanoanthracenes represent a fairly simple polycyclic system which has remained unexplored in the field of medicinal chemistry. Recently, a series of 9-aminoalkyl-9,10-dihydro-9,10-ethanoanthracenes was patented[2] and, while our work was in progress, two patents[3,4] reporting the preparation of 11-aminoalkyl-9,10-dihydro-9,10-ethanoanthracenes were published. Some of these compounds were studied especially for their psychotropic activity.[2,3,5] The present paper describes two series (I and II) of derivatives of 9,10-dihydro-9,10-ethanoanthracene substituted in the 11 position by an aminoalkyl or an aminoalkylamino group (I), or by an aminoalkoxy or an aminoalkoxyalkyl group (II), and one series of 9,10-dihydro-9,10-ethanoanthracene derivatives substituted in the 9 position by an aminoalkoxy group (III). In



I



II



III

each series, NR_1R_2 represents alkylamino or dialkylamino groups or a saturated heterocyclic moiety. In I, NR_1R_2 can represent a 2-dimethylaminoethyl group.

The most convenient route to 11-aminomethyl compounds (I, $n = 1$) was the reductive amination of the readily available 9,10-dihydro-9,10-ethanoanthracene-11-carboxaldehyde[6] by the Leuckart method (method A). Alternatively, the compounds were obtained in two steps from the above aldehyde [or from 9,10-dihydro-9,10-ethanoanthracen-11-one[7] (I, $n = 0$)] and

(1) O. Diels, K. Alder, and S. Beckmann, *Ann. Chem.*, **486**, 191 (1931).

(2) (a) Ciba S. A., French Patent 1,332,530 (1963); (b) Ciba S. A., French Patent 1,744 M (1963); (c) Ciba Ltd., South African Patent 64/4818 (1965); (d) P. Schmidt, M. Wilhem, and K. Eichenberger (to Ciba Ltd.), Swiss Patent 398,570 (1966); (e) Ciba Ltd., South African Patent 65/6631 (1966).

(3) Geigy A. G., Dutch Patent 6,412,205 (1965).

(4) K. Kitahonoki and R. Kido (to Shionogi and Co., Ltd.), French Patent 1,421,996 (1965).

(5) K. A. Flügel, R. Stoerger, and Th. Veil, *Arzneimittel-Forsch.*, **12**, 1392 (1965).

(6) (a) E. A. Arbuzov and E. K. Iskakova, *Uch. Zap. Kazansk. Gos. Univ.*, **116**, 113 (1956); (b) Bataafsche Petroleum Maatschappij, British Patent 749,723 (1956).

(7) S. Wawzonek and J. V. Ballum, *J. Org. Chem.*, **18**, 288 (1953).