TABLE II

$(C_6H_5)C(R_1)COOCH_2C{\equiv}CCH_2R_2 \cdot HCl$

No.	R_1	R_2	Method	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
21	SCH_3	$N(C_2H_5)_2$	B[a]	30	146–148[a]	$C_{23}H_{27}NO_2S \cdot HCl$	66.07	66.45	6.75	6.72	3.35	3.30
22	SCH_3	C_4H_8N[c]	B[a]	37	154–156[d]	$C_{25}H_{29}NO_2S \cdot HCl$[e]	66.40	66.37	6.31	6.51	3.37	3.42
23	SCH_3	$C_5H_{10}N$[f]	B[a]	35	171.5–173[g]	$C_{24}H_{27}NO_2S \cdot HCl$	67.03	66.89	6.56	6.53	3.25	2.79
24	SCH_3	C_4H_8NO[h]	B[i]	15	171–173.5[b]	$C_{23}H_{25}NO_3S \cdot HCl$	63.93	63.99	6.07	6.02	3.24	3.03
25	OCH_3	$C_5H_{10}N$[f]	B[i]	58	170.5–172[b]	$C_{24}H_{27}NO_3 \cdot HCl$	69.61	69.71	6.81	6.90	3.39	3.22
26	OCH_2CH_3	$N(CH_3)_2$	C(b)	24	166.5–168.5[b]	$C_{22}H_{25}NO_3 \cdot HCl$	68.12	68.09	6.75	7.04	3.61	3.73
27	OCH_2CH_3	$C_5H_{10}N$[f]	C(b)	32	173.5–175[b]	$C_{25}H_{29}NO_3 \cdot HCl$	70.15	69.60	7.07	6.82	3.27	3.41

[a] Used sodium methoxide catalyst. [b] Recrystallized from ethyl acetate–ethanol. [c] C_4H_8N = pyrrolidino. [d] Recrystallized from isopropyl alcohol. [e] *Anal.* Calcd.: Cl, 8.52. Found: Cl, 8.43. [f] $C_5H_{10}N$ = piperidino. [g] Recrystallized from ethyl acetate–petroleum ether. [h] C_4H_8NO = morpholino. [i] Used sodium metal catalyst.

4-Diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride (**19**) was found to possess about 10% of the activity of atropine on several types of extravascular smooth muscle plus strong papaverine-like action. A comprehensive study of the pharmacological properties of this compound by Lish, *et al.*,[6] will be published shortly.

Experimental[7]

4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols were prepared from 4-chloro-2-butynol and the corresponding secondary amines as previously described for 4-morpholino-2-butynol.[8] The following known 2-butynols were prepared: 4-dimethylamino-,[9,10] 4-diethylamino-,[11] 4-pyrrolidino-,[2] 4-piperidino-,[2] and 4-morpholino-.[8]

General Procedures for the Preparation of Esters of 4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols. A. Mannich Reaction.—This procedure is analogous to that described by Jones, *et al.*[4] Various aromatic esters of propargyl alcohol were employed and the products were isolated as the hydrochloride salts. The solvents used for the recrystallization of the hydrochlorides obtained by this and the subsequent methods are available from Tables I and II.

B. Ester–Alcohol Interchange.—Equivalent amounts of the methyl ester (0.035 mole) and the appropriate 4-amino-2-butynol were dissolved in 50 ml. of heptane and about 0.2 g. of sodium methoxide (or 0.2 g. of sodium metal) catalyst was added. The reaction mixture was stirred and allowed to reflux, and the heptane–methanol azeotrope was collected and measured in a Dean–Stark trap to determine the extent of reaction. The reaction mixture was cooled in an ice bath and washed with water. The heptane solution was washed with 2 *N* HCl and the acidic extract was neutralized with 2 *N* NaOH. The oily free base was dissolved in ether, and the resultant solution was dried ($MgSO_4$) and treated with HCl to precipitate the hydrochloride salt.

C. Esterification with an Acid Chloride. (a).—To a stirred solution of acid chloride (0.074 mole), triethylamine (22.0 g., 0.37 mole), and 70 ml. of benzene was added, dropwise, the appropriate 4-amino-2-butynol (0.07 mole) dissolved in 25 ml. of benzene. The reaction mixture was heated on a steam bath for 3 hr. and poured onto crushed ice and water. The organic layer was separated, washed with water, and extracted with several 5-ml. portions of 2 *N* HCl to remove excess triethylamine (the extracts were made basic to determine if insoluble product was being extracted). Additional extractions with 2 *N* HCl were carried out and the extracts were combined, cooled in an ice bath, and neutralized with 2 *N* NaOH. The oil which separated was taken up in ether, and the ether solution was dried ($MgSO_4$). The solution was treated with dry HCl to precipitate the hydrochloride salt.

(b).—Equivalent amounts of 2,2-diphenyl-2-chloroacetyl chloride (0.043 mole) and the appropriate 4-amino-2-butynol were mixed and heated at 100–105° for 25 min., then at 70° for 30 min., and the resultant brown viscous oil was washed thoroughly with anhydrous ether and dissolved in 100 ml. of anhydrous ethanol. The ethanolic solution was allowed to reflux for 25 hr. with 5 g. of Na_2CO_3. The reaction mixture was cooled, filtered, and neutralized with 2 *N* NaOH, and most of the ethanol was removed under reduced pressure. The remaining aqueous mixture was extracted with ether and the extract was dried ($MgSO_4$). Hydrogen chloride was passed into the ether solution to precipitate the hydrochloride salt.

D. Ester–Ester Interchange.—Equivalent amounts (0.25 mole) of 4-diethylamino-2-butynyl acetate and the methyl ester of the appropriate carboxylic acid were dissolved in 400 ml. of heptane and 1.25 g. of sodium methoxide was added. The mixture was stirred and heated, and a solution of heptane and methyl acetate was slowly distilled from the reaction vessel over a period of about 1 hr. The reaction mixture was cooled, washed thoroughly with water, and extracted with 2 *N* NaOH, and the oily base was taken up in ether. The ether solution was dried ($MgSO_4$) and treated with HCl to precipitate an oily hydrochloride salt which solidified on cooling.

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New Antifertility Agents. 2,3-Diphenylbenzofurans[1a]

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A number of organic compounds which possess the triarylethylene structure have been shown to possess marked effect on the reproductive system.[2,3] In a search for new antifertility agents, the 2,3-diphenyl-

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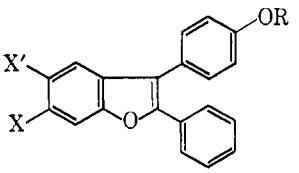
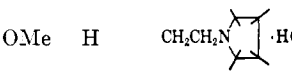
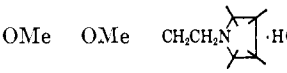
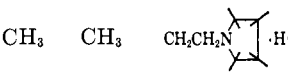
TABLE I



No.	X	X'	R	M.p., °C.	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
1	OMe	H	H	167–168	$C_{21}H_{16}O_3$	79.70	5.00	..	80.12	5.35	..
2	OMe	H	$COCH_3$	134–135	$C_{23}H_{18}O_4$	76.88	5.00	..	76.98	5.32	..
3	OMe	H	$CH_2C_6H_5$	127–128	$C_{28}H_{22}O_3$	82.75	5.41	..	82.42	5.82	..
4	OMe	H	$CH_2CH_2N(C_2H_5)_2\cdot HCl$	185–186	$C_{27}H_{29}NO_3\cdot HCl$	71.68	6.60	3.09	71.23	7.02	3.26
5	OMe	H		209–210	$C_{27}H_{27}NO_3\cdot HCl$	72.20	6.23	3.01	72.49	6.63	2.75
6	OMe	OMe	H	187–188	$C_{22}H_{18}O_4$	76.30	5.21	..	76.59	5.63	..
7	OMe	OMe	$CH_2C_6H_5$	181–182	$C_{29}H_{24}O_4$	79.82	5.50	..	80.26	6.02	..
8	OMe	OMe	$CH_2CH_2N(C_2H_5)_2\cdot HCl$	158–159	$C_{28}H_{31}NO_4\cdot HCl\cdot 0.5H_2O$	68.50	6.73	2.83	68.35	7.19	3.03
9	OMe	OMe		229–230	$C_{28}H_{29}NO_4\cdot HCl$	70.07	6.25	2.92	70.23	6.41	3.08
10	CH_3	CH_3	H	199–200	$C_{22}H_{18}O_2$	84.07	5.76	..	83.94	6.32	..
11	CH_3	CH_3	$COCH_3$	170	$C_{24}H_{20}O_3$	80.89	5.78	..	80.77	6.18	..
12	CH_3	CH_3	$CH_2CH_2N(C_2H_5)_2\cdot HCl$	167–168	$C_{28}H_{29}NO_2\cdot HCl$	74.70	7.10	3.11	74.65	7.42	2.83
13	CH_3	CH_3		225–226	$C_{28}H_{27}NO_2\cdot HCl$	75.08	6.73	3.13	75.02	7.05	3.20

benzofurans seemed a worthy choice for exploration in view of the incorporation of the triarylethylene pattern in their structure though in a more rigid form, the association of estrogenic activity with many benzofurans,[4] and their close structural similarity to 1,2-diphenylindenes[3,5] which have been shown to possess antiimplantation properties. The synthesis of certain 2-phenyl-3-(*p*-substituted phenyl)benzofurans and biological evaluation of one of these is described in this note.

Experimental

These compounds were synthesized by a modification of the method of Brown, *et al.*[6] In a typical run resorcinol monomethyl ether (0.01 mole) and *p*-benzyloxybenzoin (0.01 mole) in peroxide-free dioxane (30 ml.) were heated under reflux with concentrated HCl (10 ml.) for 24 hr., when a mixture of 2-phenyl-3-*p*-benzyloxyphenyl-6-methoxybenzofuran and the corresponding 2-phenyl-3-*p*-hydroxyphenyl compound was obtained. Addition of a further quantity of concentrated HCl (10 ml.) and work-up of the reaction mixture after 72 hr. yielded exclusively the 2-phenyl-3-*p*-hydroxyphenylbenzofuran which was purified through its acetate. Saponification of the acetate gave 2-phenyl-3-*p*-hydroxyphenyl-6-methoxybenzofuran which on treatment with β-diethylaminoethyl chloride hydrochloride in the presence of anhydrous K_2CO_3 in refluxing acetone for 24 hr. gave 2-phenyl-3-*p*-(β-diethylaminoethoxy)phenyl-6-methoxybenzofuran, isolated as the hydrochloride. The different compounds thus prepared are listed in Table I.

Biological Activity.—Colony bred female albino rats of the Institute (130–150 g.) were mated to coeval males of proven fertility. The day on which the vaginal smears showed the presence of spermatozoa was considered day 1 of pregnancy. The compound was macerated with an equal amount of gum acacia and suspended in 1 ml. of distilled water. The suspension was introduced into the lower part of the esophagus by a feeding needle. The control animals received a mixture of gum acacia and distilled water. The results were scored as positive only if implantations were absent in both uterine horns examined on day 10 of pregnancy.

It will be seen from the results presented in Table II that compound **4** administered daily at doses of 1, 2, and 4 mg. on days 1 to 5 of pregnancy was 100% effective in preventing implantation. A single dose of 20 mg. given on days 1 to 3 of pregnancy was equally effective in preventing implantation. The failure of the compound to prevent implantation on days 4 and 5 suggested that its primary site of action was the Fallopian tubes rather than the uterus. Detailed studies of this group of compounds are in progress.

TABLE II

EFFECT OF COMPOUND 4 ON IMPLANTATION IN RATS

Dose, mg./rat	Days	No. of rats	Total mean of implantations (range)
Control		12	7.3 (4.0–9.0)
0.5	1–5	12	7.5 (5.0–9.0)
0.75	1–5	6	1.8 (0.0–4.0)
1	1–5	12	0.0 (0.0–0.0)
2	1–5	8	0.0 (0.0–0.0)
4	1–5	12	0.0 (0.0–0.0)
20	1, 2, or 3	5	0.0 (0.0–0.0)
20	4	4	0.75 (0.0–3.0)
20	5	4	5.8 (5.0–7.0)

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