vents were without success. The compd is quite unstable, and readily forms a black polymer. It was further characterized as the ethyl acetal (XIX).

α^5-Thiopyridoxal Ethyl Acetal (XIX).—α^5-Thiopyridoxal (XVIII, 50 mg) was suspended in EtOH (5 ml, dry), and 5 drops of Et_2O satd with HCl gas were added. The mixt was allowed to stand at room temp. The reaction was followed by tlc (EtOAc, R_f 0.25 starting material, 0.45 ethyl acetal). After standing for 7 days, only traces of starting material were left. The mixt was evapd to 1 ml *in vacuo*, and the product was sepd by preparative tlc. The material was eluted with EtOAc and evapd to a small vol, and petr ether was added. Crystn yielded 6.8 mg of the ethyl acetal, hygroscopic crystals: mp 120–122° dec, nmr ($CDCl_3$) (CH_3CH_2) −77 (tr), (2-CH_3) −151, (CH_3CH_2) −218 (m), (5-CH_2) −257 (broad), (α^4-H, hemiacetal) −405 (split singlet), (C_6-H) −487. *Anal.* ($C_{10}H_{13}NSO_2$) C, H, S.

Cannizzaro Reaction of Pyridoxal.—Pyridoxal·HCl (50 mmoles, 102 mg), dissolved in 10 ml of satd $Ba(OH)_2$ soln, was refluxed for 24 hr. Tlc of the reaction mixt indicated only spots due to pyridoxol and pyridoxic acid. (The identities of the products were confirmed by retardation by boric acid and a positive Gibbs test, as described earlier.[27]) The mixt was then evapd to dryness, and was thoroughly dried *in vacuo*. The dry white powder was acetylated for gas chromatog (2.5 ml of pyridine and 2.5 ml of Ac_2O for 4 hr). Samples of this mixt were injected into a gas chromatograph operating under standard conditions.[33] Two peaks were observed, with retention times of 9.1 min (pyridoxol acetate) and 2.25 min (4-pyridoxic acid lactone acetate). Comparison of the areas under the curves with each other and with standards run separately showed that the total amts of the acetates were 24.9 mmoles for pyridoxol and 15.4 mmoles for 4-pyridoxic acid. The apparent loss of 4-pyridoxic acid during the reaction may be due to decarboxylation and degradation.

A similar mixt was obtained when pyridoxal·HCl (51 mg, 25 mmoles) was dissolved in strong NaOH soln (1 g of NaOH in 2.5 ml of water) and was heated to 110° for 24 hr.

Hydrazine-d_4 Experiments. (a) 4-Deoxypyridoxol-α^2-d_3,α^4-d_3,α^6-d from Pyridoxol.—Pyridoxol·HCl (251 mg) and hydrazine-d_4 (2 ml, anhyd, supplied by Volk Radiochemical Co.) were refluxed for 16 hr, moisture being excluded. After evapn of excess hydrazine [80° (0.1 mm)], the residue was extd with boiling EtOH (5 ml) for 10 min and cooled, and the hydrazine·2HCl that crystd was removed by filtration. To the filtrate, 1.5 ml of methanolic HCl (11.2% HCl) was added. On chilling, cryst 4-deoxypyridoxol·HCl pptd. The yield was 178 mg (73%), mp 254° dec. On addn of Et_2O to the mother liquors, a further 40 mg of 4-deoxypyridoxol could be obtd; but it was contaminated. Recrystn of the main crop from boiling EtOH gave the pure product, mp 271° (lit.[14] mp 273°), migrating as one spot on tlc (50:50 $CHCl_3$–MeOH; R_f 0.75, not retarded by boric acid). The nmr spectrum in 1 *N* D_2SO_4 shows only an α^4-H_2 peak at −321 cps; α^2-H_3, α^4-H_3, and C_6-H appear as small bumps, indicating virtually complete deuteration.

(b) 4-Deoxypyridoxol-α^2-d_3,α^4-d_3,α^6-d from 4-Deoxypyridoxol.—4-Deoxypyridoxol·HCl (251 mg) and hydrazine-d_4 (2.5 ml) were refluxed for 110 hr. The reaction mixt was worked up as in the preceding expt, yielding 139 mg (60%) of deuterated 4-deoxypyridoxol·HCl. By using an internal standard and integration, it could be established that α^5 protons were not exchanged, but that α^2-H_3, α^4-H_3, and α^6-H protons were exchanged to the extent of 94–95%.

(c).—Collidine (0.40 ml, pure by nmr spectroscopy) was heated with hydrazine-d_4 (2.0 ml) at 120° for 120 hr. On cooling, the reaction mixt sepd into 2 layers, the upper one containing mostly γ-collidine. The nmr spectrum of this layer was exactly the same as that of the starting γ-collidine, indicating no D exchange.

Acknowledgments.—This study was supported in part by research grants (CA-08793 and CA-11047) from the National Cancer Institutes, U. S. Public Health Service. We wish to express our thanks to Drs. Harry B. Wood and Robert E. Engle of the Cancer Chemotherapy National Service Center for making available to us a quantity of α^5-pyridoxylmethanol·HCl. Dr. B. Paul prepd compd XII and Mr. N. Angelino compd XIII. We are also indebted to Drs. A. Bloch, M. Hakala, E. Mihich, and F. Rosen of our department for the biological evaluation of some of the compds reported, and to Mr. N. Angelino for the pyridoxal phosphokinase inhibition studies.

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Antiestrogenic and Antifertility Compounds. 4. 1,1,2-Triarylalkan-1-ols and 1,1,2-Triarylalk-1-enes Containing Basic Ether Groups[1]

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In an attempt to relate structure to antiestrogenic and antifertility activity, several 1,1,2-triarylalkan-1-ols and 1,1,2-trialkylalk-1-enes containing a basic ether group have been synthesized, and their biological activities examined. Assignments of geometric isomerism in the triarylalkenes are made on the basis of nmr data.

The discoveries that the compds **3a**,[2,3] **1**,[4,5] and **2**[6] are orally active antifertility agents, and that by sc administration they inhibit simultaneously applied estradiol,[2,7–9] prompted us to undertake the synthesis of **3b** and **3c**, which are previously unknown positional isomers of **3a**, and of compds **4**, which are open chain analogs of **1** and **2**. After we began this work, patents[10,11] appeared describing some compds of the general type **4**, but these included only 2 of those described in this paper.

Chemistry.—Most of the compds were prepared by standard procedures described in the Experimental Section. Attempts to prepare 1-{*p*-[2-(*N*,*N*-diethyl-

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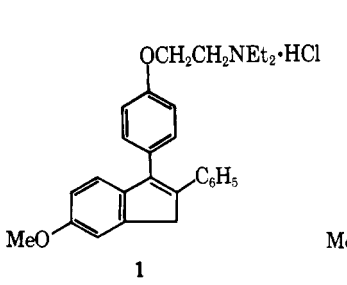

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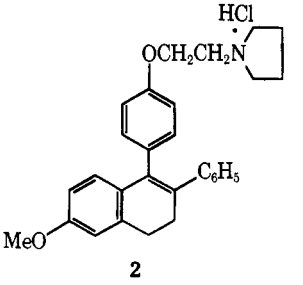

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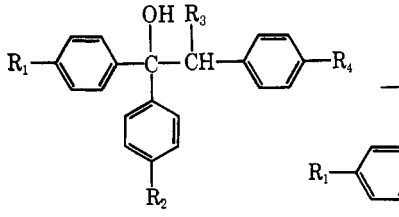

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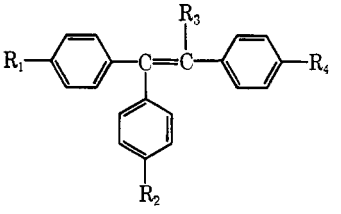
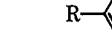
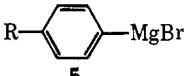


4

	R_1	R_2	R_3	R_4
3a	$OCH_2CH_2NEt_2$	H	H	OMe
3b	$OCH_2CH_2NEt_2$	OMe	H	H
3c	H	OMe	H	$OCH_2CH_2NEt_2$
3d	H	OMe	H	OTpy
3e	H	OMe	Me	H
3f	$OCH_2CH_2NEt_2$	OMe	Me	OMe
3g	$OCH_2CH_2NEt_2$	H	Et	OMe
3h		OMe	Et	OMe
3i	$OCH_2CH_2NMe_2$	OMe	Et	OMe
3j	$OCH_2CH_2NEt_2$	OH	Et	OMe
4a	$OCH_2CH_2NEt_2$	OMe	H	H
4b	H	OMe	Me	H
4c	$OCH_2CH_2NEt_2$	OMe	Me	H
4d	$OCH_2CH_2NEt_2$	OMe	Me	OMe
4e	$OCH_2CH_2NEt_2$	H	Et	OMe
4f		OMe	Et	OMe
4g	$OCH_2CH_2NMe_2$	OMe	Et	OMe
4h	$OCH_2CH_2NEt_2$	OH	Et	OMe
4i	$OCH_2CH_2NEt_2$	OMe	Et	OMe
4j	$OCH_2CH_2NEt_2$	OMe	$CHMe_2$	OMe
4k		OMe	$CHMe_2$	OMe
4l	$OCH_2CH_2NMe_2$	H	Et	H
4m	$OCH_2CH_2NEt_2$	OMe	Et	H
4n	$OCH_2CH_2NEt_2$	H	Et	H
4o		OMe	NO_2	H
4p	OMe	OMe	Et	$OCH_2CH_2NEt_2$
4q	OMe	H	Et	$OCH_2CH_2NEt_2$



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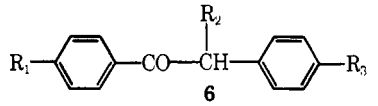


6

	R		R_1	R_2	R_3
5a	$OCH_2CH_2NEt_2$	**6a**	H	H	OMe
5b	$OCH_2CH_2NMe_2$	**6b**	OMe	H	H
5c		**6c**	OMe	Me	H
		6d	H	Et	OMe
		6e	OTpy	Et	OMe
		6f	OMe	Me	OMe
		6g	OMe	Et	OMe
		6h	OMe	$CHMe_2$	OMe
		6i	H	H	OTpy
		6j	H	H	$OCH_2CH_2NEt_2$

amino)ethoxy]phenyl}-1-(*p*-methoxyphenyl)-2-phenylethanol (**3b**) by reaction of the Grignard reagent from *p*-[2-(*N*,*N*-diethylamino)ethoxy]bromobenzene with 2-phenyl-4′-methoxyacetophenone gave only the dehydration product **4a** upon work-up with NH_4Cl. Extreme ease of dehydration of **3b** compared with **3a** and **3c** is probably due to efficient stabilization of the potential carbonium ion from **3b** by the 1,1-di-*p*-alkoxyphenyl system. The carbinol **3c** was readily obtained by reaction of *p*-$MeOC_6H_4MgBr$ with 2-{*p*-[2-(*N*,*N*-diethylamino)ethoxy]phenyl}acetophenone (**6j**).

The 1,1,2-triarylalkanols listed in Table I were prepared in a similar manner and were dehydrated with either *p*-TsOH or with 20% v/v H_2SO_4 in HOAc to give the 1,1,2-triarylalkenes listed in Table II.

It was considered that some of the basic triarylethylenes might possibly have been contaminated with the by-product of Grignard coupling. Pure 4,4′-bis[2-(*N*,*N*-diethylamino)ethoxy]biphenyl was prepared and its nmr spectrum measured: it was not detected in any of the compds prepared from *p*-[2-(*N*,*N*-diethylamino)ethoxy]phenylmagnesium bromide.

Geometric Isomerism and Nmr Data.—Resolution of geometric isomers was difficult. Pure trans isomers of the olefins **4i** and **4f** were obtained, but in no case could the cis isomer be isolated pure. Assignments of geometric configuration to pure isomers, and to component peaks in the nmr spectra of cis–trans mixtures are tentative, and were made, in part, by analogy with the work of Bedford and Richardson[12] who used nmr chemical shifts to distinguish between *cis*- and *trans*-**4l**, the configurations of which were subsequently established by X-ray crystallography.[13]

The most useful diagnostic resonances in the nmr spectra of **4l** and related triarylethylenes are those of the triplets due to the OCH_2 of the basic ether groups and to the MeO singlets. For direct comparison we have measured the nmr spectrum of samples of *cis*- and *trans*-**4l**. The OCH_2 triplet for *cis*-**4l** shows a downfield shift of $\Delta = 0.17$ ppm with respect to the corresponding triplet of the trans isomer. This is consistent with the expectation that an ArO group "trans conjugated" with an aromatic ring in **4** should be deshielded with respect to the corresponding ArO group which is trans to the alkyl group in the geometric isomer. However, out of plane rotation of the Ar group might invalidate this assumption. Certainly, this empirical correlation holds for the simpler case of 4,4′-dimethoxy-α,α'-dimethylstilbene (**7**), the trans isomer of which shows a downfield shift of 0.11 ppm for the OMe protons relative to the corresponding peak for the cis isomer.

Particularly relevant in this respect is the nmr spectrum of **4p**, a positional isomer of **4i** which cannot exist in geometric isomers. The chemical shift difference ($\Delta = 0.13$ ppm) is the same as that observed between the OMe groups of *cis*- and *trans*-**4q**, and between the peaks at δ 3.66 (*cis*-**4i**), and 3.79 (*trans*-**4i**) for the OMe groups which are, respectively, trans to an Et or an anisyl group; similarly in **4f** and **4g**.

For the triplet due to the OCH_2 of the basic ether group, the cis isomers of **4f**, **g**, **i**, and **l** show a downfield

(12) G. R. Bedford and D. N. Richardson, *Nature (London)*, **212**, 733 (1966).

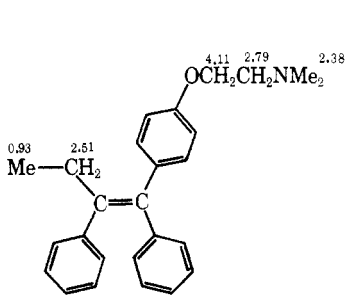
(13) B. T. Kilbourn, R. H. B. Mais, and P. G. Owston, *Chem. Commun.*, 291 (1968).

TABLE I

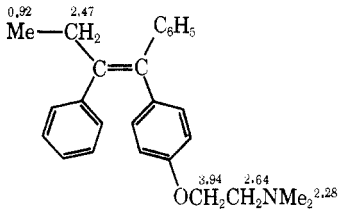
1,1,2-TRIARYLALKAN-1-OLS

No.	Structure R1	R2	R3	R4	Mp, °C	Mol formula	*Anal.*
3c	H	OMe	H	$OCH_2CH_2NEt_2$	97–98	$C_{27}H_{33}NO_3$	C, H, N
3d	H	OMe	H	OTpy	121–122	$C_{26}H_{28}O_4$	C, H
3e	H	OMe	Me	H	101–102	$C_{22}H_{22}O_2$	C, H
3g	$OCH_2CH_2NEt_2$· citrate	H	Et	OMe	Gum	$C_{28}H_{37}NO_3$	C, H, N
		H	Et	OMe	101–104	$C_{35}H_{45}NO_{10}$	C, H, N
3h		OMe	Et	OMe	145–147	$C_{30}H_{37}NO_4$	C, H, N
3i isomer "a"	$OCH_2CH_2NMe_2$	OMe	Et	OMe	73–75	$C_{28}H_{35}NO_4$	C, H, N
3i isomer "b"	$OCH_2CH_2NMe_2$	OMe	Et	OMe	114–115	$C_{28}H_{35}NO_4$	C, H, N
3i	Isomer "b" HCl salt				206–207	$C_{28}H_{36}ClNO_4$	C, H, N, Cl
3j	$OCH_2CH_2NEt_2$· citrate	OH	Et	OMe	99–100	$C_{35}H_{45}NO_{11}$	C, H, N[a]

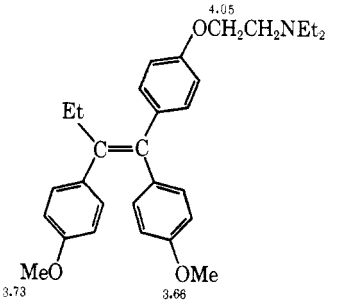
[a] C: calcd, 64.1; found, 63.5.



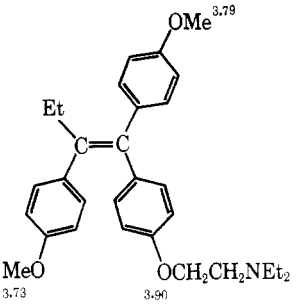
cis-4



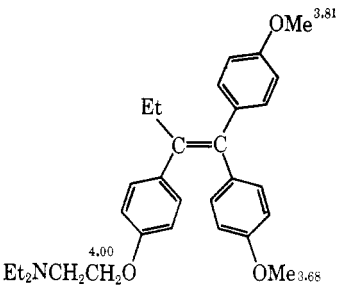
trans-4



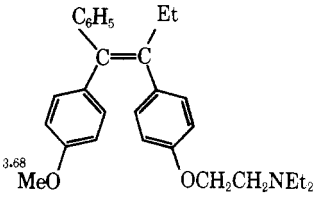
cis-4i



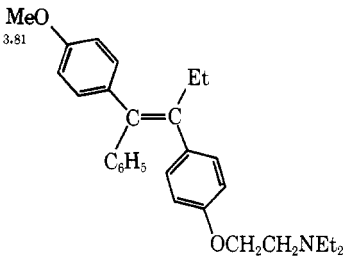
trans-4i



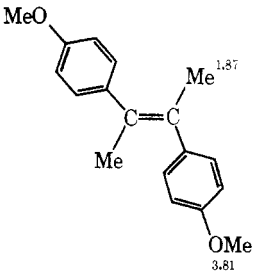
4p



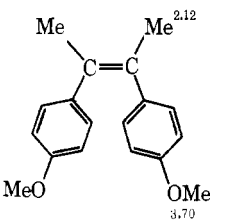
cis-4q



trans-4q



trans-7



cis-7

shift of 0.13–0.17 ppm relative to that for the respective trans isomers; in the case of the *i*-Pr-substituted olefins **4j** and **k**, this downfield shift was appreciably smaller (0.08 ppm), apparently reflecting a steric effect.

Ratios of cis and trans isomers were estimated from peak heights due to appropriate MeO resonances.

Results of Biological Assays.—Randomly bred mice of the QS strain, or randomly bred albino rats remotely derived from the Wistar strain were used in all tests. Vaginal smear tests of estrogenic activity were as described by Emmens.[14] Tests of antiestrogenic activity were all against estradiol-3,17β, simultaneously administered with the test compd but in a separate injection.

(14) C. W. Emmens, *Methods Horm. Res.*, **2A**, 62 (1969).

TABLE II

1,1,2-TRIARYLALK-1-ENES

No.	Structure R1	R2	R3	R4	Salt	Mp, °C	Mol formula	Anal.
4a	$OCH_2CH_2NEt_2$	OMe	H	H	Citrate	106–109	$C_{33}H_{39}NO_9 \cdot H_2O$	C, H, N[a]
4b	OMe	H	Me	H		108	$C_{22}H_{20}O$	C, H
4c[b]	$OCH_2CH_2NEt_2$	OMe	Me	H	Citrate	106–109	$C_{34}H_{41}NO_9$	
4d[c] (cis:trans, 55:45)	$OCH_2CH_2NEt_2$	OMe	Me	OMe	Citrate	113–114	$C_{35}H_{43}NO_{10} \cdot H_2O$	C, H, N
4e	$OCH_2CH_2NEt_2$	H	Et	OMe		90–91	$C_{29}H_{35}NO_2$	C, H, N
trans-4f	OCH_2CH_2-*N*-pyrrolidyl	OMe	Et	OMe	HCl	216–218 dec	$C_{30}H_{36}ClNO_3$	C, H, N, Cl
4f (cis:trans, 63:37)	OCH_2CH_2-*N*-pyrrolidyl	OMe	Et	OMe	HCl	186–191	$C_{30}H_{36}ClNO_3$	C, H, N, Cl
4g (cis:trans, 50:50)	$OCH_2CH_2NMe_2$	OMe	Et	OMe	HCl	158–160	$C_{28}H_{34}ClNO_3$	C, H, N, Cl
4h	$OCH_2CH_2NEt_2$	OH	Et	OMe		159–160	$C_{29}H_{35}NO_3$	C, H, N
trans-4i	$OCH_2CH_2NEt_2$	OMe	Et	OMe	HCl	192–193	$C_{30}H_{38}ClNO_3$	C, H, N, Cl
4i (cis:trans, 62:38)	$OCH_2CH_2NEt_2$	OMe	Et	OMe		Oil	$C_{30}H_{37}NO_3$	C, H, N
4i (cis:trans, 62:38)	$OCH_2CH_2NEt_2$	OMe	Et	OMe	Citrate	109–111	$C_{36}H_{45}NO_{10}$	
4j (cis:trans, 39:61)	$OCH_2CH_2NEt_2$	OMe	$CHMe_2$	OMe	HCl	182–183	$C_{31}H_{40}ClNO_3$	C, H, N, Cl
4k (cis:trans, 18:82)	OCH_2CH_2N-pyrrolidyl	OMe	$CHMe_2$	OMe	HCl	235–236	$C_{31}H_{38}ClNO_3$	C, H, N, Cl

[a] Calcd C, 64.8; H, 6.8; N, 2.3. Found: C, 64.0; H, 6.8; N, 2.4. [b] Lit.[10] mp 102–104°. [c] Lit.[10] mp 106–108°.

Tests of antifertility activity were postcoital, as described in detail by Martin, *et al.*[15] Females were allowed to mate, then dosed on days 1–3 after mating or days 4–6 after mating inclusive, day 1 being the day of finding sperm in the vagina or a vaginal plug. Groups of 10 animals were normally used in these tests. Approximate values for the ED_{50} derived from such tests are presented, the ED_{50} being defined as the dose which reduces the number of litters produced to 50% of the control values. For injection, peanut oil was used; for oral administration, 25–50% of propylene glycol in H_2O.

No precise limits of error are presented because only the order of activity of a compd was required, but the error ($P = 0.05$) would not usually exceed 50–200% in antifertility tests. However, in vaginal smear tests in the mouse, most of the compds discussed have remarkably low dose–response slopes (see Table IV) whether given orally or sc, so that estimates of estrogenic activity are very imprecise and would be dependent on technique and perhaps strain of animals to a considerable degree. Thus, a compd with an ED_{50} of, for example, 1 mg, may still elicit some positive responses at 0.025 mg.

The trans isomer of **4l** had no detectable change in effect over a range of 0.2–5.0 mg in the spayed rat, whereas *cis*-**4l** showed a steeper slope and could be assigned an ED_{50} of 0.20 mg by injection and 0.25 mg orally.

Before the pure trans isomer of **4i** was obtained, a cis–trans mixture (about 62% cis) was examined quite extensively, and bioassay results are given for this, as well as for the pure trans isomer. Detailed examination shows that **4i** is very brief in estrogenic action, and that conventional tests must tend to provide negative smears if more than one, at the peak of reaction, is taken. However, even under such attempted conditions, 100% of positive responses was not obtainable. Emmens[16] has shown that **4i** and other similar compds produce a refractoriness to estrogenic stimulation, even to their own action, which develops some days after injection and may be related to the point under discussion. Strangely, tests of antiestrogenicity conducted as described above are negative.

Dose–response lines for these compds as antifertility agents are quite normal. Thus, **4i** administered sc to the mouse in daily doses of 4, 8, and 16 μg on days 1–3 after mating resulted in 80, 22, and 10% of pregnancies, and on days 4–6 after mating in 70, 60, and 22% of pregnancies.

By sc administration, the pure trans isomer of **4i** was less estrogenic and more antifertility in action than the cis-enriched material (**4i**), however, given orally they showed about the same potency as estrogens (Table III).

These compds were not antiestrogenic when given sc in mice, except for **4a** and **4b** both of which showed weak activity. However, most were highly active as postcoital antifertility agents in the mouse, and where tested, in the rat. Only **4a** failed to show such activity when tested at doses up to 1 mg/day by injection, the rest showed ED_{50} values of from <0.002 to 0.060 mg/day (days 1–3) or 0.005 to 0.25 mg/day (days 4–6).

There is thus no correlation between antiestrogenic activity (as currently tested) and antifertility activity. With a typical estrogen[17] the daily dose required postcoitally on days 1–3 or 4–6 approximates to the vaginal smear ED_{50} in the mouse. Clearly, these compds do not follow that rule. In the isomeric pair, *trans*-**4l** and *cis*-**4l**, the trans compd is less estrogenic than the cis compd, but more potent as an antifertility agent. Pure *cis*-**4i** was not obtained, but comparison of the cis-enriched material with pure *trans*-**4i** shows similar divergence of activity. Thus, by the assay methods used, there appears to be a dissociation of estrogenic and antifertility activities.

Harper and Walpole[18] reported that *cis*-**4l** is estrogenic in rats and mice and has antifertility activities reasonably explicable on that basis, and that *trans*-**4l** is a more potent estrogen in the mouse than its isomer, and also more potent as an antifertility agent. In the rat, however, they found *trans*-**4l** to be strongly antiestrogenic and yet highly potent as an antifertility agent. We do not find this compd to be more potent as an estrogen than its cis isomer in either species, although it is more potent as an antifertility agent in both species.

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TABLE III

BIOLOGICAL ACTIVITIES OF 1,1,2-TRIARYLALK-1-ENES AND 1,1,2-TRIARYLALKAN-1-OLS

	Biological activities[a]											
	Estrogenic[b]				Antiest[b]	Antifertility (daily dose over 3 days)						
						Mouse				Rat			
	Mouse		Rat		mouse	Days 1-3		Days 4-6		Days 1-3		Days 4-6	
Compd	sc	oral	sc	oral	sc	sc	oral	sc	oral	sc	oral	sc	oral
4a	>1.00	0.90			0.5	>1.000		1.000					
trans-4l[d]	>0.25	0.25	0.2-5.0	0.2-5.0	Na[c]	0.002	0.001	0.005	0.010	0.015	0.015	0.015	0.015
cis-4l[d]	0.20	0.75	0.20	0.25	Na	0.060	0.020	0.100	0.100	0.150	0.150	0.150	0.150
4c	1.00	0.20			Na	0.020		0.250					
4m[d]	<0.10				Na	>0.018		0.018					
4n[d]	0.60				Na	>0.018		0.018					
4i (cis:trans, 62:38)	2.00	0.20	>2.70	>2.70	Na	0.006	<0.005	0.050	0.015	0.030	0.010	0.100	0.030
trans-4i	>2.70	0.30			Na	0.003		0.006					
trans-4f	0.10	0.10			Na	0.003		0.006					
4j (cis:trans, 39:61)	0.10	*Ca.* 1.00			Na	<0.002		0.006					
4d (cis:trans, 55:45)	1.00	0.30			1.0	0.020		0.100		0.010	0.010	0.050	<0.050
4o[d]	1.00				Na	0.050		0.100					
3a	>1.00		40.0		1.0	1.000		1.000					
3c	>2.70	>2.70			Na	>0.400		>0.400					
3h	0.20	<0.10			Na	0.050		0.200					
3i	1.00	1.00			Na	0.008		0.050					

[a] Tested in rodents; ED_{50} in mg. [b] Vaginal smear assay. [c] Na = not active at doses up to 1 mg. [d] Tested and included for direct comparison, see Acknowledgments.

TABLE IV

DOSE-RESPONSE LINES FOR VAGINAL SMEAR TESTS OF **4i** (CIS:TRANS, 62:38) IN MICE (10 TO 20 ANIMALS PER GROUP)

Test	Dose of **4i** (cis:trans, 62:38), mg	Responses, % +ve, to Injection	Gavage	Dose of estradiol-3,17β, μg	Response to injection, % +ve
1	0.5	40	60	0.015	15
	1.0	53	33	0.030	48
	2.0	48	45	0.060	90
	4.0	53	63		
2	0.05	13	40	0.015	18
	0.10	30	35	0.030	38
	0.20	48	50	0.060	93
	0.40	45	58		

Structure–activity correlations, other than the cis and trans examples cited above, are difficult to see. Substitution of OCH_3 for H at R_4 appears to make no difference, **4d** *vs.* **4c**. Comparison of **4c** with **4a** shows that substitution of CH_3 for H at R_3 increases both estrogenic and antifertility potencies; antifertility potency appears to rise throughout the series H, CH_3, C_2H_5, $CH(CH_3)_2$ at R_3.

Experimental Section[19]

Starting Materials.—The *p*-[2-(*N*,*N*-dialkylamino)ethoxy]-bromobenzenes (**5a,b,c**) were prepd as described by Lednicer, *et al.*[4]

The following deoxybenzoin derivatives were prepd by the std procedures: 2-(*p*-methoxyphenyl)acetophenone (**6a**), mp 95–96° (lit.[20] 96°); demethylation of this with HBr gave 2-(*p*-hydroxyphenyl)acetophenone, mp 137–139° (lit.[21] 129°, prepd from the corresponding *p*-amino compd); 2-phenyl-4′-methoxyacetophenone (**6b**), mp 74–75° (lit.[22] 74–75°); 2-phenyl-4′-methoxypropiophenone (**6c**), bp 224–226° (25 mm), mp 53–56° (lit.[23] 53.5–55°); 2-(*p*-methoxyphenyl)butyrophenone (**6d**), an oil purified by column chromatog, and shown to be >99% pure by glc (lit.[20] mp 38–39°) was prepd by alkylation of the corresponding acetophenone with EtI in liq NH_3 contg $NaNH_2$; 2-(*p*-methoxyphenyl)-4′-tetrahydropyranyloxybutyrophenone (**6e**), mp 90–91°, was prepd as previously described.[24] α-Methyldeoxyanisoin (**6f**), mp 43–45° (lit. 53–57°,[25] 43°[26]); α-ethyldeoxyanisoin (**6g**), mp 51–52° (lit.[26,27] 47–48°); and α-isopropyldeoxyanisoin (**6h**), mp 56–58° [lit.[25] bp 210–214° (0.8 mm)] were obtd by the method of Dodds, *et al.*[25]

2-(*p*-Tetrahydropyranyloxyphenyl)acetophenone (6i).—Treatment of 2-(*p*-hydroxyphenyl)acetophenone with dihydropyran in the usual way gave **2-(*p*-tetrahydropyranyloxyphenyl)acetophenone,** mp 112–113°. *Anal.* ($C_{19}H_{20}O_3$) C, H.

2-{*p*-[2-(*N*,*N*-Diethylamino)ethoxy]phenyl} acetophenone (6j).—Alkylation of 2-(*p*-hydroxyphenyl)acetophenone with *N*-(2-chloroethyl)diethylamine in EtOH contg NaOEt afforded **2-{*p*-[2-(*N*,*N*-diethylamino)ethoxy]phenyl}acetophenone,** mp 69–70°. *Anal.* ($C_{20}H_{25}NO_2$) C, H, N.

4,4′-Bis[2-(*N*,*N*-diethylamino)ethoxy]biphenyl.—The Grignard reagent was prepd from *p*-[2-(*N*,*N*-diethylamino)ethoxy]-bromobenzene (5.4 g) and Mg turnings (0.48 g) in dry THF under N_2. The cooled reagent was added dropwise to a soln of EtBr (2.2 g) in dry Et_2O (10 ml) contg a suspension of anhyd $CoCl_2$ (0.15 g) at such a rate as to maintain gentle reflux. The mixt was heated under reflux for 1 hr, then satd NH_4Cl (10 ml) was added. Isolation in the usual way afforded an oil (3.6 g) from which a fraction (0.86 g), bp 230–240° (0.8 mm), was isolated and treated with dry HCl in Et_2O to yield, after several crystns from acetone, the **dihydrochloride:** mp 243–245° dec; nmr spectrum, δ 6.87–7.04 (8 H, AA′BB′ aromatic), 4.08 (t, 4 H, J = 6.5 Hz, 2 × $OCH_2CH_2N<$), 2.87 (t, 4 H, J = 6.5 Hz, 2 × $OCH_2CH_2N<$), 2.63 (q, 8 H, J = 6.5 Hz, 2 × $N(CH_2CH_3)_2$), 1.07 (t, 12 H, J = 6.5 Hz, 2 × $N(CH_2CH_3)_2$. *Anal.* ($C_{24}H_{38}Cl_2N_2O_2$) C, H, N, Cl.

Preparation of Carbinols (3).—To a cooled soln of the Grignard reagent from Mg turnings (0.72 g, 0.03 g-atom) and *N*-pyrrolidinoethoxybromobenzene (8.1 g, 0.03 mole) in THF (50 ml) was added a soln of α-ethyldeoxyanisoin (7.1 g, 0.025 mole) in THF (50 ml). The mixt was heated under reflux under N_2 for 10–18 hr. The cooled reaction mixt was treated with satd NH_4Cl soln (30 ml), and the product extd with Et_2O–PhH. The org ext was washed, dried, and evapd to yield an oil which, in some cases, crystd on addn of Et_2O. However, with most prepns the Et_2O–PhH layer was sepd into basic and neutral fractions by extn with HCl (2 *N*). The acid soln was either extd with CH_2Cl_2 to afford the triarylethanol and/or triarylethylene as its hydrochloride, or made alk and reextd with Et_2O–PhH, washed, dried,

(19) Melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 137 infracord spectrophotometer. Proton resonance spectra were taken in deuteriochloroform (Me_4Si) on a Varian A60 spectrometer; we are indebted to the Department of Chemistry for these measurements. A 0.25-mm layer of silica gel G (Merck) was used for thin-layer chromatography. Light petroleum refers to the fraction of bp 40–60°. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne, Australia.

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and evapd. The resultant product was crystd as the free base or purified whenever possible, as the citrate salt.

Dehydration of the Carbinols (3).—Dehydration to the triarylethylene was effected by heating for 5 hr under reflux with *p*-TsOH in PhMe, or by treatment with H_2SO_4–AcOH mixt (20% v/v H_2SO_4) for 5 min at room temp. The hydrochloride was prepared by extn from 2 *N* HCl into CH_2Cl_2. If this HCl salt was noncryst, the base was regenerated, chromatogd on basic alumina (Merck, Grade III), then either converted to the citrate, or to the hydrochloride by std procedures.

Nmr Data.—Nmr data are given in the following manner: chem shifts (δ) are in ppm from Me_4Si; multiplicity, s, singlet; d, doublet; t, triplet; q, quartet, with intensities approx 1:3:3:1; m, multiplet. Relative intensities are given in the number of protons, *e.g.*, 3 H denotes a relative intensity of three protons. Coupling consts (J) are in hertz. All data are considered significant to ±1 of the last significant figure.

In no case was the pure cis form of the triarylethylene obtained. When the pure trans form was available, the nmr spectrum of the cis isomer was derived by difference from the spectrum of a mixt of the isomers. If the nmr spectrum of only a cis–trans mist was obtained, peaks were tentatively assigned to each isomer by analogy with chem shifts for other related pairs. Only the peaks which clearly differed from those in the nmr spectrum for the trans form are noted for the *cis* isomer.

The cis:trans ratio was estd by measurement of the peak height of the upfield OMe singlet for the cis isomer against that for the OMe singlet common to both isomers. The downfield OMe peak for the trans isomer in some instances overlapped the upper band of the triplet due to OCH_2 of the trans isomer.

1-{*p*-[2-(*N*,*N*-Dimethylamino)ethoxy]phenyl}-1,2-diphenylbut-1-ene (4l).—For *trans*-**4l** the nmr data were δ 3.94 (t, 2 H, J = 6 Hz, OCH_2CH_2N), 2.64 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 2.47 (q, 2 H, J = 7 Hz, $=CCH_2CH_3$), 2.28 (s, 6 H, $N(CH_3)_2$), 0.92 (t, 3 H, J = 7 Hz, $=CCH_2CH_3$). For *cis*-**4l** the nmr data were δ 4.11 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 2.79 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 2.51 (q, 2 H, J = 7 Hz, $=CCH_2CH_3$), 2.38 (s, 6 H, $N(CH_3)_2$), 0.93 (t, 3 H, J = 7 Hz, $=CCH_2CH_3$).

1,2-Bis-(*p*-methoxyphenyl)-1-{*p*-[2-(*N*,*N*-diethylamino)ethoxy]phenyl}but-1-ene (4i).—For *trans*-**4i** the nmr data were δ 3.90 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2N<$, upfield wing obscured by OCH_3 signal), 3.79 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 2.25–2.87 (m, 8 H, overlapping quartets for $=CCH_2CH_3$, $N(CH_2CH_3)_2$, and the triplet for $OCH_2CH_2N<$), 0.79–1.17 (m, 9 H, overlapping triplets for $=CCH_2CH_3$ and $N(CH_2CH_3)_2$). For *cis*-**4i** the nmr data were δ 4.05 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2N<$), 3.73 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 2.27–2,97 (m, 8 H overlapping quartets for $=CCH_2CH_3$ plus $N(CH_2CH_3)_2$ and the triplets for $OCH_2CH_2N<$), 0.79–1.19 (m, 9 H, overlapping triplets for $=CCH_2CH_3$ and $N(CH_2CH_3)_2$).

A prepn designated **4i** was shown to have a cis:trans ratio of approximately 62:38.

1-{*p*-[2-(*N*,*N*-Diethylamino)ethoxy]phenyl}-1,2-bis(*p*-methoxyphenyl)prop-1-ene (4d).—For *trans*-**4d** the nmr data were δ 3.91 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.79, 3.72 (s, 6 H, 2 × OCH_3), 2.38–2.98 (m, 6 H, overlapping triplet and quartets due to $OCH_2CH_2N(CH_2CH_3)_2$), 2.09 (s, 3 H, $=CCH_3$), 1.07, 1.02 (t, 6 H, J = 6 Hz, $N(CH_2CH_3)_2$, signal from cis:trans mixture). For *cis*-**4d** the nmr data were δ, 4.04 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.72, 3.67 (s, 6 H, 2 × OCH_3).

1,2-Bis(*p*-methoxyphenyl)-1-[*p*-(2-*N*-pyrrolidinoethoxy)phenyl]but-1-ene (4f).—For *trans*-**4f** the nmr data were δ 3,99 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.81 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.24–2.96 (8 H, partially resolved triplets and quartet due to CH_2's bonded to N of $OCH_2CH_2N(CH_2)_4$ and $=CCH_2CH_3$), 1.63–1.92 (m, 4 H, β-CH_2's of pyrrolidinyl), 0.94 (t, 3 H, $=CCH_2CH_3$). For *cis*-**4f** the nmr data were δ 4.13 (t, 2H, J = 6 Hz, $OCH_2CH_2N<$), 3.76 and 3.68 (s, 6 H, 2 × OCH_3), 2.91 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 2.22–2.78 (m, 6 H overlapping bands due to α-CH_2's of pyrrolidinyl and $=CCH_2CH_3$).

1,2-Bis(*p*-methoxyphenyl)-1-{*p*-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}but-1-ene (4g).—For *trans*-**4g** the nmr data were δ 3.95 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.80 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 2.64 (t, 2 H, J = 6 Hz, partially resolved triplet due to $OCH_2CH_2N(CH_3)_2$), 2.33 (s, 6 H, $N(CH_3)_2$), 2.44 (q, 2 H, J = 7 Hz $=CCH_2CH_3$), 0.92 (t, 3 H, J = 7 Hz, $=CCH_2CH_3$). For *cis*-**4g** the nmr data were δ 4.09 (t, 2 H, J = 6 Hz, $OCH_2CH_2N(CH_3)_2$), 3.75 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.74 (t, 2 H, J = 6 Hz, partially resolved triplet due to $OCH_2CH_2N(CH_3)_2$), 2.29 (s, 6 H, $N(CH_3)_2$).

1,2-Bis(*p*-methoxyphenyl)-1-{*p*-[2-(*N*,*N*-diethylamino)ethoxy]phenyl}-3-methylbut-1-ene (4j).—For *trans*-**4j** the nmr data were δ 3.89 (partially resolved triplet, 2 H, J = 6 Hz, $OCH_2CH_2N<$), overlapped by 3.80 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 2.89–3.32 (m, 1 H, $CH(CH_3)_2$), 2.35–2.89 (m, 6 H, $OCH_2CH_2N(CH_2CH_3)_2$), 0.73–1.24 (m, 12 H, incompletely resolved doublets and triplets corresponding to $CH(CH_3)_2$ and $N(CH_2CH_3)_2$ of the cis and trans isomers of **4j**, resp.) For *cis*-**4j** the nmr data were δ 4.05 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.74, 3.62 (s, 6 H, 2 × OCH_3).

1,2-Bis(*p*-methoxyphenyl)-1-[*p*-(2-*N*-pyrrolidinoethoxy)phenyl]-3-methylbut-1-ene (4k).—For *trans*-**4k** the nmr data were δ 3.95 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.81, 3.74 (s, 6 H, 2 × OCH_3), 2.37–3.18 (m, 7 H, $CH(CH_3)_2$ + CH_2's bonded to N of $OCH_2CH_2N(CH_2)_4$), 1.60–1.92 (m, 4 H, β-CH_2's of pyrrolidinyl, 0.93 (d, 6 H, $CH(CH_3)_2$). For *cis*-**4k** the nmr data were δ 4.03 (t, 2 H, $OCH_2CH_2N<$), 3.74, 3.64 (s, 6 H, 2 × OCH_3).

2-{*p*-[2-(*N*,*N*-Diethylamino)ethoxy]phenyl}-1-(*p*-methoxyphenyl)-1-phenylbut-1-ene (4q).—For *trans*-**4q** the nmr data were δ 4.00 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2N<$), 3.81 (s, 3 H, OCH_3), 2.21–1.92 (m, 8 H, $OCH_2CH_2N(CH_2CH_3)_2$ plus $=CCH_2CH_3$, 0.74–1.30 (m, 9 H, $N(CH_2CH_3)_2$, $=CCH_2CH_3$). For *cis*-**4q** the nmr data were δ 3.68 (s, 3 H, OCH_3).

2-{*p*-[2-(*N*,*N*-Diethylamino)ethoxy]phenyl}-1,1-bis(*p*-methoxyphenyl)but-1-ene (4p).—The nmr data for this comp were δ 4.00 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2N<$), 3.81, 3.68 (s, 6 H, 2 × OCH_3), 2.82 (t, 2 H, J = 6.5 Hz, $OCH_2CH_2N<$), 2.63 (q, 4 H, J = 6.5 Hz, $N(CH_2CH_3)_2$), 2.48 (q, 2 H, J = 7 Hz, $=CCH_2CH_3$), 0.76–1.07 (m, 9 H, overlapping triplets for $N(CH_2CH_3)_2$ and $=CCH_2CH_3$).

1,2-Bis(*p*-methoxyphenyl)-1-{*p*-[2-(*N*,*N*-dimethylamino)ethoxy]phenyl}butan-1-ol (3i).—The nmr data for this compd were δ 3.95 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 3.80 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.46 (t, 1 H, J = 7 Hz, benzylic), 2.64 (t, 2 H, J = 6 Hz, $OCH_2CH_2N<$), 2.29 (s, 6 H, $N(CH_3)_2$), 1.76 (quintet, 2 H, $>CHCH_2CH_3$), 0.72 (t, 3 H, J = 7 Hz, CH_2CH_3).

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