The pooled urine from nine rats was acidified to pH 2–3 and extracted with two 100-ml portions of ether. The Et_2O solution was dried (Na_2SO_4), then concentrated with a rotoevaporator. Over 90% of the activity was extracted from the urine. The Et_2O concentrate was taken directly into the mass spectrometer (see below).

Isolation and Identification of Urinary Metabolites. A. Phenyltrimethylsilane (I). Hexamethyldisiloxane.—To the crude urine from three rats was added 100 ml of ether containing 1.0 g of nonlabeled hexamethyldisiloxane. After acidification, the urine was extracted once. The ethereal solution was concentrated to 25 ml, and a portion was subjected to glpc separation. The peak corresponding to the hexamethyldisiloxane was collected and counted. Of the total urinary activity, 3% could be accounted for as hexamethyldisiloxane.

Extracted Metabolites.—An aliquot (0.256 μCi) from the EtOAc concentrate was spotted on a tlc plate (silica gel) and developed with ether–petroleum ether (30–60°) (1:1). Active spots were found at R_f 0.68 (0.044 μCi, 17%), 0.56 (0.079 μCi, 31%), and the origin (0.090 μCi, 35%). The first two compounds were separated on preparative tlc plates and were removed from the silica gel with Et_2O. The compounds at the origin on these plates were removed from the silica gel with MeOH and were rechromatographed with EtOAc–PrOH (1:1). One active spot (R_f 0.09) was observed and this compound also was isolated by preparative tlc. Numerous other spots were observed in these tlc runs. Since they did not show activity, they were ignored.

This isolation procedure did not yield analytically pure material. However, the metabolites were sufficiently pure that their structures could be identified by spectral methods; for the radioactive metabolite R_f 0.68 (IV): ir (CCl_4), 3.0 (vs), 3.4 (w), 5.8 (w), 6.2 (s), 6.6 (s), 7.0 (s,) 7.3 (w), 7.9 (vs), 8.5 (w), 9.0 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 6.6 (triplet) (combined area 7), 3.5 (singlet) (area 1), 0 (singlet) (area 14.5); mass spectrum ($\Sigma^{\%}_{100}$), m/e 105 (2), 107 (4), 135 (4), 151 (52), 152 (8), 153 (3), 166 (6), 167 (1), 180 (3); for synthetic *p*-trimethylsilylphenol: ir (CCl_4), 3.0 (vs), 3.4 (w), 6.3 (s), 6.7 (s), 7.1 (s), 7.4 (w), 8.0 (vs), 8.5 (w), 9.0 (vs) μ; nmr (CCl_4), δ 7.15, 7.04 (doublet), 6.34, 6.46, 6.56 (triplet) (combined area 1.0), 0 (area 2.3); mass spectrum ($\Sigma^{\%}_{100}$), 105 (2), 107 (3), 135 (2), 151 (64), 152 (10), 153 (3), 166 (7), 167 (1), 168 (0.8).

Authentic samples of *o*- and *m*-trimethylsilylphenol were also available.[11] Comparison of the ir and nmr spectra of these two compounds with those of the metabolite R_f 0.68 showed that the metabolite was neither of these compounds. The differences between the three were particularly evident in the fine structure and symmetry of the aromatic region (δ 7–7.5) of the nmr spectra; spectral data for radioactive metabolite R_f 0.56 (III): ir (CCl_4), 2.9 (vs), 3.5 (w), 3.85 (s), 7.0 (s), 7.95 (s), 8.95 (s), 9.9 (s) μ; nmr (CCl_4), δ 6.96 (broad multiplet) (area 4.8), 3.15 (singlet) (area 2), 0 (singlet) (area 6); mass spectrum ($\Sigma^{\%}_{135}$), m/e 151 (5), 135 (52), 136 (8), 137 (3); spectral data for synthetic (hydroxymethyl)dimethylphenylsilane: ir (neat), 3.0 (s), 3.4 (w), 7.0 (s), 8.0 (vs), 9.0 (s), 10.0 (s) μ; nmr (CCl_4), δ 7.0 (broad multiplet) (area 5), 3.15 (singlet) (area 2), 0 (singlet) (area 6); mass spectrum ($\Sigma^{\%}_{135}$), m/e 151 (7), 135 (68), 136 (11), 137 (4); spectral data for radioactive material R_f 0.09: ir, no data, soluble only in H_2O; nmr (D_2O), δ 6.96 (singlet) (area 5.6), 3.2 (singlet) (area 2), 0 (singlet) (area 5.8); mass spectrum (direct probe) ($\Sigma^{\%}_{100}$), m/e 105 (8.5), 107 (4.5), 135 (53), 136 (8.5), 137 (5.5), 147 (13), 148 (2), 149 (2), 151 (7.5), 152 (2.3), 153 (1.2).

B. Phenyldimethylsilane (II).—A portion of ether concentrate was taken directly to the mass spectrometer. The remainder of the material was purified using preparative tlc and the "purified" material was analyzed using spectral methods. Since the composition of the metabolite changed upon "purification" both sets of spectral data are given and discussed in the text; mass spectrum of radioactive metabolite prior to the purification (VII): m/e ($\Sigma^{\%}_{100}$) 105 (4), 107 (7.5), 122 (3), 128 (3), 137 (36.5), 138 (5.8), 139 (3.5), 152 (10.8), 153 (3), 154 (2.5), 193 (10.5), 194 (3), 195 (2.5), 271 (7.5), 272 (3), 273 (1); mass spectrum of synthetic dimethylphenylsilanol: m/e ($\Sigma^{\%}_{100}$) 137 (95), 138 (10), 139 (4).

Isolation of the Metabolite.—An aliquot (0.255 μCi) of the ether concentrate was subjected to tlc (silica gel, ether). Two active components were observed: one at R_f 0.80 (0.23 μCi, 90% of the activity) and another near the origin. Preparative tlc was used to isolate the compounds. Attempts to identify the compound(s) giving rise to the spot near the origin were unsuccessful; spectra data for radioactive R_f 0.80 metabolite: ir (CCl_4), 3.45 (w), 7.0 (s), 8.0 (s), 9.0 (s), 9.5 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 0 (singlet); mass spectrum ($\Sigma^{\%}_{89}$), m/e 89 (13), 105 (7), 107 (4), 121 (5), 122 (4), 123 (4), 128 (9), 135 (7), 163 (4), 165 (4), 179 (3), 193 (24), 194 (6), 125 (4), 271 (11), 272 (4), 273 (1); spectral data for synthetic diphenyltetramethyldisiloxane: ir (neat), 3.4 (w), 7.0 (s), 8.0 (vs), 8.95 (vs), 9.5 (vs) μ; nmr (CCl_4), δ 7.0 (multiplet), 0 (singlet); mass spectrum ($\Sigma^{\%}_{89}$), m/e 89 (15), 128 (70), 135 (7), 193 (30), 194 (7), 195 (4), 271 (15), 272 (4), 271 (1).

Antifertility Agents. IV. 2,3-Diphenylbenzo- and 5,6-Polymethylenebenzofurans, 1,2-Diphenylnaphthofurans, and Some Related Compounds[1a]

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Among 2-phenyl-3-(*p*-β-*t*-aminoalkoxy- and thioalkoxyphenyl)-5,6-substituted benzofurans, naphtho[2,1-*b*]-furans, and some related compounds synthesized and tested, 1-(*p*-β-pyrrolidinoethoxyphenyl)-2-phenylnaphtho-[2,1-*b*]furan (**26**) and 2-phenyl-3-(*p*-β-pyrrolidinoethoxyphenyl)-5,6-tetramethylenebenzofuran (**50**) were found to possess marked antiimplantation activity in rats. Extended biological studies have been carried out with **26** for its antifertility activity. 2,3-Bis(*p*-methoxyphenyl)-5,6-dimethylbenzofuran showed significant antiinflammatory activity.

The synthesis of some substituted 2,3-diphenylbenzofurans and the antifertility activity of 2-phenyl-3-(*p*-β-pyrrolidinoethoxyphenyl)-6-methoxybenzofuran[1b] were reported earlier. This led to a further exploration of this group of compounds for antifertility activity and a study of their structure–activity relationship. The results are reported in this communication.

2-Phenyl-3-(*p*-hydroxyphenyl)benzofurans (I)[2] were prepared by a modification of the method of Brown,

(1) (a) Communication No. 1381 from the Central Drug Research Institute, Lucknow. (b) P. K. Grover, H. P. S. Chawla, N. Anand, V. P. Kamboj, and A. B. Kar, *J. Med. Chem.*, **8**, 720 (1965); (c) A. B. Kar, V. P. Kamboj, and B. S. Setty, *Indian J. Exp. Biol.*, **5**, 80 (1967).

(2) Roman numerals refer to the type of compounds, while Arabic numerals refer to the specific compounds as they appear in Table I.

et al.,[3] by the condensation of *p*-benzylozybenzoin with various phenols. As this method gave extremely poor yields with phenols carrying no activating group at the *meta* position, alternative methods were investigated for the synthesis of 2-phenyl-3-(*p*-hydroxyphenyl)-benzofuran (**20**). 2-Phenyl-3-(*p*-methoxyphenyl)-6-tosyloxybenzofuran (**17**), prepared from **16**, was recovered unchanged after treatment with H_2 and Raney Ni. This difficulty in hydrogenolysis of **17** is inexplicable particularly since 2,3-bis(*p*-methoxyphenyl)-6-tosyloxybenzofuran (**14**) could be smoothly hydrogenolyzed under the same conditions to give the corresponding 2,3-bis(*p*-methoxyphenyl)benzofuran (**15**). Compound **19** could, however, be prepared by the hydrogenolysis of 2-phenyl-3-(*p*-methoxyphenyl)-6-(1-phenyl-5-tetrazolyl)benzofuran (**18**) by the method of Musliner and Gates.[4] It was also obtained in reasonable yield by the condensation of phenol and 4-methoxybenzoin using boric acid[5] as the condensing agent in place of HCl used earlier.

1,2-Diphenylnaphtho[2,1-*b*]furans (II) were prepared by the condensation of the appropriate 2-naphthols with 4-benzyloxybenzoin using the condition of Brown, *et al.*[3] 1-Naphthol when condensed with 4-benzyloxybenzoin in presence of boric acid gave III. Condensation of resorcinol and 2,6-dihydroxynaphthalene with 4-benzyloxybenzoin gave the corresponding difurans V and VI, respectively.

In the condensation of 3,4-polymethylenephenols with alkoxybenzoins, 5,6-polymethylenebenzofurans ("linear") and the sterically less favored 4,5-polymethylenebenzofurans ("angular") could be formed. With 3,4-tetramethylenephenol and 4-benzyloxybenzoin the "linear" benzofuran **48** was exclusively formed, since dehydrogenation with DDQ of 2-phenyl-3-(*p*-β-pyrrolidinoethoxyphenyl)tetramethylenebenzofuran (**50**) obtained from **48** gave a naphthofuran which was found to be different from the angular 1-(*p*-β-pyrrolidinoethoxyphenyl)-2-phenylnaphtho[2,1-*b*]-furan (**26**) prepared from 2-naphthol. 2,3-Bis(*p*-methoxyphenyl)-5,6-tetramethylenebenzofuran, on DDQ dehydrogenation, however, gave a mixture of the linear and the angular naphthofurans. The chemical shift of the two MeO groups in the two naphthofurans was different. In the nmr spectrum of the angular naphthofuran, obtained directly from 2-naphthol, the signals for the two OCH_3 appeared at τ 6.10 and 6.30, whereas in the linear form the signals for the two OCH_3 were at τ 6.15 and 6.25. The ratio of the angular form in the mixture, as deduced from the nmr spectrum, appeared to be *ca.* 20%.

The thiophenol **39** was prepared from the corresponding phenol **22** by condensation with dimethylthiocarbamoyl chloride followed by thermal rearrangement and hydrolysis according to the method of Newman.[6]

The various hydroxyl and mercapto compounds were converted into the corresponding β-*t*-aminoalkoxy derivatives by condensation with β-*t*-aminoalkyl halides in acetone in presence of potassium carbonate.

(3) B. R. Brown, G. A. Somerfield, and P. D. J. Weitzman, *J. Chem. Soc.*, 4305 (1958).

(4) W. J. Musliner and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **88**, 4271 (1966).

(5) B. Arventiev, H. Wexler, and M. Strul, *Acad. Rep. Populare Romine, Filiala Iasi, Studii Cerectari Stiint., Chim.*, **11**, 63 (1960); *Chem. Abstr.*, **55**, 15433 (1961).

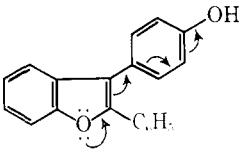
(6) M. S. Newman, *J. Org. Chem.*, **31**, 3980 (1966).

Experimental Section

The compounds were routinely checked by ir spectroscopy; tlc was carried out on silica gel G plates and the compounds were detected under a uv lamp or by exposure to iodine vapors; the melting points were determined in an H_2SO_4 bath by the capillary tube method.

Hydroxydiphenylbenzo-, naphtho-, and polymethylenebenzofurans were synthesized by the general method of Brown, *et al.*[3] The preparations described below illustrate a few of the experimental modifications of the general reaction conditions to suit individual cases. The intermediate hydroxy compounds were purified either by chromatography on silica gel or by conversion to acetates followed by saponification. The compounds thus synthesized are reported in Table I.

1-(*p*-Hydroxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (22). (a) 2-Naphthol (4.38 g, 0.03 mole) and *p*-benzyloxybenzoin (9.54 g, 0.03 mole) in peroxide-free dioxane (140 ml) were heated under reflux with concentrated HCl (43 ml) for 24 hr. An additional amount of HCl (43 ml) was added and refluxing continued for 48 hr. The reaction mixture was diluted (H_2O) and extracted (Et_2O). The Et_2O was washed (2 *N* NaOH,[7] H_2O), then dried



(Na_2SO_4) and concentrated to give an oily product. It was purified by passing through a column of silica gel using benzene–hexane (1:1) as eluent; yield 4.6 g (42%).

(b) Compound **23** (4.80 g) was refluxed in 2 *N* aqueous–methanolic NaOH (100 ml) for 2 hr. After the removal of solvent, the residue was acidified and extracted (Et_2O). The Et_2O extract was washed (H_2O) to neutral and dried and the solvent was removed; yield 4.5 g (87%).

1-(*p*-Acetoxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (23).—The oily residue obtained in a above (7.5 g) was dissolved in dry pyridine (30 ml), Ac_2O (12 ml) was added, and the solution was allowed to stand for 16 hr. The reaction mixture was poured over ice and HCl. The oil which separated was taken up in Et_2O, washed (5% Na_2CO_3 solution, H_2O), dried (Na_2SO_4), and concentrated, and the residue was crystallized from MeOH; yield 4.8 g (87%).

1-(*p*-Benzyloxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (24).—2-Naphthol (4.38 g, 0.03 mole) and *p*-benzyloxybenzoin (9.54 g, 0.03 mole) were refluxed in peroxide-free dioxane (140 ml) and concentrated HCl (43 ml) for 24 hr. The reaction mixture was worked up in the usual manner and the residue was crystallized from EtOH; yield 2.6 g (20%). The mother liquor when concentrated and crystallized from benzene–hexane gave **22**; yield 2.1 g (42%).

The mixture of **22** and **24** obtained above could also be separated by chromatography over a column of silica gel (80 mesh). Elution with benzene–hexane (1:3) gave **24**. Further elution with benzene–hexane (1:1) furnished **22**.

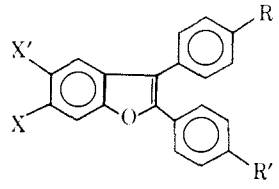
1-[*p*-(β-Diethylaminoethoxy)phenyl]-2-phenylnaphtho[2,1-*b*]-furan (25).—The method described below for the preparation of **25** is representative of the general method followed for the alkylation of hydroxydiphenylbenzo-, naphtho-, and polymethylenebenzofurans with ω-*t*-aminoalkyl halides.

1-(*p*-Hydroxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (**22**) (0.336 g, 0.001 mole) was heated under reflux in anhydrous AcMe (75 ml) with anhydrous K_2CO_3 (1.5 g) and $Et_2N(CH_2)_2Cl\cdot HCl$ (0.264 g, 0.0012 mole) for 12 hr. K_2CO_3 was removed by filtration, the filtrate was concentrated under reduced pressure, and H_2O was added. The oil which separated was taken up in Et_2O, and the ether layer was washed with water to neutral, dried (Na_2SO_4) and concentrated. The residue was converted to its hydrochloride in Et_2O. Crystallization from Et_2OH–Et_2O gave **25**; yield 0.43 g (88%).

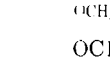
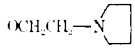
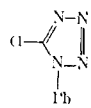
2,3-Bis(*p*-methoxyphenyl)-6-tosyloxybenzofuran (14).—*p*-Toluenesulfonyl chloride (0.382 g, 0.02 mole) was added to 2,3-bis(*p*-methoxyphenyl)-6-hydroxybenzofuran (obtained by the condensation of resorcinol with anisoin) (0.69 g, 0.02 mole) dis-

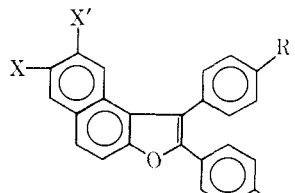
(7) These compounds were insoluble in aqueous alkali presumably because the 3-*p*-OH group, being in conjugation with the furan ring oxygen atom, is rendered less acidic as shown.

TABLE I



I

No.	X or x	X′	R	R′	Yield, %	Solvent, of crystn[a]	Mp or bp (mm), °C	Formula	Analyses	MED_{50} mg/kg
1	OCH_3	H	$OCH_2CH_2N(C_2H_5)_2$	H	97	C	185–186[b]	$C_{27}H_{29}NO_3 \cdot HCl$	C, H, N	8
2	OCH_3	H		H	95	C	209–210[b]	$C_{27}H_{27}NO_3 \cdot HCl$	C, H, N	4
3	OCH_3	H	$O(CH_2)_3N(C_2H_5)_2$	H	90	C	164	$C_{28}H_{31}NO_3 \cdot HCl$	C, H, N	20
4	OCH_3	H		H	92	C	204	$C_{28}H_{29}NO_3 \cdot HCl$	C, H, N	20
5	OCH_3	H	OCH_3	OCH_3	75	A	90–91[c]	$C_{23}H_{20}O_4$	C, H	>50
6	OCH_3	OCH_3		H	92	C	229–230[b]	$C_{28}H_{29}NO_4 \cdot HCl$	C, H, N	80
7	CH_3	CH_3		H	93	C	225–226[b]	$C_{28}H_{29}NO_2 \cdot HCl$	C, H, N	>30
8	CH_3	CH_3	OCH_3	OCH_3	89	A	152	$C_{24}H_{22}O_3$	C, H	>20
9	CH_3	CH_3	OH	OH	76	B	180	$C_{22}H_{18}O_3$	C, H	
10	CH_3	CH_3	$OCH_2CH_2N(C_2H_5)_2$	$OCH_2CH_2N(C_2H_5)_2$	85	C	206	$C_{30}H_{34}N_2O_3 \cdot 2HCl$	C, H, N	>20
11	OH	H	OCH_3	OCH_3	65	A	137[d]	$C_{22}H_{18}O_4$	C, H	
12	$OCOCH_3$	H	OCH_3	OCH_3	90	A	124	$C_{24}H_{20}O_5$	C, H	
13		H	OCH_3	OCH_3	81	C	201	$C_{28}H_{29}NO_4 \cdot HCl$	C, H, N	>20
14	OTS	H	OCH_3	OCH_3	95	A	85	$C_{29}H_{24}O_6S$	C, H	
15	H	H	OCH_3	OCH_3	75	B	147[c]	$C_{22}H_{18}O_2$	C, H	
16	OH	H	OCH_3	H	68	B	137–138	$C_{21}H_{16}O_3$	C, H	
17	OTS	H	OCH_3	H	72	A	149	$C_{28}H_{22}O_5S$	C, H	
18		H	OCH_3	H	70	A	121	$C_{28}H_{20}N_4O_3$	C, H, N	
19	H	H	OCH_3	H	42	B	85	$C_{21}H_{16}O_2$	C, H	
20	H	H	OH	H	87	B	149	$C_{20}H_{14}O_2$	C, H	
21	H	H		H	89	C	205	$C_{26}H_{25}NO_2 \cdot HCl$	C, H, N	20



II

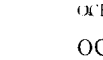
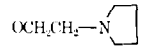
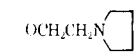
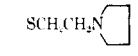
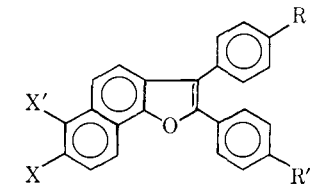
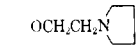
22	H	H	OH	H	42	B	175	$C_{24}H_{16}O_2$	C, H	>20
23	H	H	$OCOCH_3$	H	87	A	147	$C_{26}H_{18}O_3$	C, H	20
24	H	H	OCH_2Ph	H	20	A	160	$C_{31}H_{22}O_2$	C, H	
25	H	H	$OCH_2CH_2N(C_2H_5)_2$	H	88	E	166–168	$C_{30}H_{29}NO_2 \cdot HCl$	C, H, N	4
26	H	H		H	91	A	81	$C_{30}H_{27}NO_2$		
						C	211	$C_{30}H_{27}NO_2 \cdot HCl$	C, H, N	2
27	H	H	OCH_3	OCH_3	85	A	117–118[f]	$C_{26}H_{20}O_3$	C, H	
28	OCH_3	H	OH	H	10	B	199	$C_{25}H_{18}O_3$	C, H	
29	OCH_3	H		H	80	C	226	$C_{31}H_{29}NO_3 \cdot HCl$	C, H, N	2
30	H	OCH_3	OH	H	9	B	176–178	$C_{25}H_{18}O_3$	C, H	
31	H	OCH_3		H	85	C	216–218	$C_{31}H_{29}NO_3 \cdot HCl$	C, H, N	>4
32	H	OH	OCH_3	H	8	B	181–182	$C_{25}H_{18}O_3$	C, H	
33	H		OCH_3	H	83	C	196–197	$C_{31}H_{29}NO_4 \cdot HCl$	C, H, N	4
34	H	OH	OH	H	24	B	264	$C_{24}H_{16}O_3$	C, H	
35	H	$OCOCH_3$	$OCOCH_3$	H	91	A	132–133	$C_{28}H_{20}O_5$	C, H	

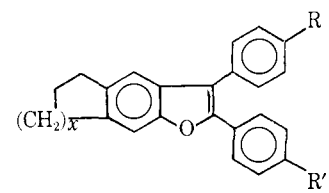
TABLE I (*Continued*)

No.	X or *x*	X′	R	R′	Yield, %	Solvent, of crystn[a]	Mp or bp (mm), °C	Formula	Analyses	MED_{10} mg/kg
36	H			H	79		Viscous oil	$C_{36}H_{38}N_2O_3$	C, H, N	
37	H	H	$OCSN(CH_3)_2$	H	80	D	182	$C_{27}H_{21}NO_2S$	C, H, N	
38	H	H	$SCON(CH_3)_2$	H	90	D	135	$C_{27}H_{21}NO_2S$	C, H, N	
39	H	H	SH	H	95	B	215	$C_{24}H_{16}OS$	C, H	
40	H	H		H	65	C	239	$C_{30}H_{27}NOS \cdot HCl$	C, H, N	>10

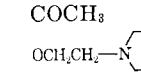
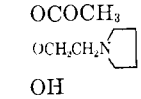
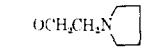


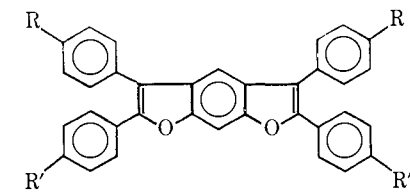
III

41	H	H	OCH_3	H	15	A	154	$C_{25}H_{18}O_2$	C, H	
42	H	H	OH	H	85	B	165	$C_{24}H_{16}O_2$	C, H	
43	H	H		H	70	C	208	$C_{30}H_{27}NO_2 \cdot HCl$	C, H, N	20



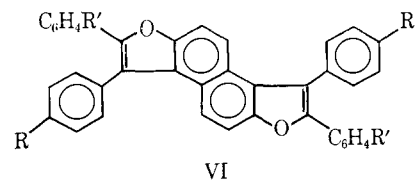
IV

44	1		OH	H	33	B	184	$C_{23}H_{18}O_2$	C, H	
45	1		$COCH_3$	H	79	A	155	$C_{25}H_{20}O_3$	C, H	
46	1			H	81	C	207	$C_{29}H_{29}NO_2 \cdot HCl$	C, H, N	20
47	1		OCH_3	OCH_3	72	A	134	$C_{25}H_{22}O_3$	C, H	
48	2		OH	H	31	B	146	$C_{24}H_{20}O_2$	C, H	
49	2		$OCOCH_3$	H	82	A	109	$C_{26}H_2O_3$	C, H	
50	2			H	89	C	228–229	$C_{30}H_{31}NO_2 \cdot HCl$	C, H, N	2
51	3		OH	H	33	B	158	$C_{25}H_{22}O_2$	C, H	
52	3			H	87	C	251	$C_{31}H_{33}NO_2 \cdot HCl$	C, H, N	10

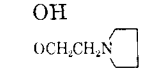


V

53			OH	H	91	B	249	$C_{34}H_{22}O_4$	C, H	
54			$OCOCH_3$	H	10	A	230	$C_{38}H_{26}O_6$	C, H	
55			$OCH_2CH_2N(C_2H_5)_2$	H	90	C	266	$C_{46}H_{48}N_2O_4$ $2HCl \cdot 0.5H_2O$	C, H	>10



VI

56			OH	H	29	E	280	$C_{38}H_{24}O_4$	C, H	
57				H	93	F	223	$C_{50}H_{48}N_2O_4$	C, H, N	>10

[a] A, EtOH; B, C_6H_6–C_6H_{14}; C, EtOH–Et_2O; D, C_6H_6–EtOH; E, MeAc; F, CH_2Cl_2–MeOH. [b] Reported[1a] in an earlier communication. [c] Lit.[3] mp 91–92°. [d] Lit.[3] mp 136–137. [e] Lit.[11] mp 148–149, yield 2.4%. [f] Lit.[3] mp 116–117°.

solved in 2 *N* NaOH (1 ml) and the mixture was heated on a steam bath for 0.5 hr. The reaction mixture was cooled and diluted (H_2O) and the colorless crystalline product obtained was removed by filtration and recrystallized (EtOH); yield 0.95 g (95%).

2,3-Bis(*p*-methoxyphenyl)benzofuran (15).—H_2 was bubbled through a vigorously stirred solution of **14** (0.5 g, 0.001 mole) in EtOH (75 ml) containing Raney Ni (5 g) for 6 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed over a column of basic alumina using benzene–hexane (1:1) as eluent, yield 0.25 g (75%).

1-Phenyl-5-chloro-1H-tetrazole.—Phenyl isocyanide dichloride prepared according to the method of Bly, *et al.*,[8] was condensed with NaN_3 to give 1-phenyl-5-chloro-1H-tetrazole, mp 79° (lit.[9] 78–80°).

2-Phenyl-3-(*p*-methoxyphenyl)-6-(1-phenyl-5-tetrazolyl)benzofuran (18).—2-Phenyl-3-(*p*-methoxyphenyl)-6-hydroxybenzofuran (**16**) (3.16 g, 0.01 mole) was heated under reflux in anhydrous MeAc (50 ml) with anhydrous K_2CO_3 (3.0 g) and 1-phenyl-5-chloro-1H-tetrazole (1.81 g, 0.01 mole) for 8 hr. K_2CO_3 was filtered and the residue was taken up in C_6H_6, washed (2 *N* NaOH, H_2O), and dried (Na_2SO_4), solvent was removed under vacuum, and the residue was crystallized (EtOH): yield 3.25 g (70%).

2-Phenyl-3-(*p*-methoxyphenyl)benzofuran (19). (a) A solution of **18** (3.25 g, 0.007 mole) in AcOH (75 ml) was hydrogenated in presence of 10% Pd–C (3.00 g) at 2.5 kg/cm² and 55° for 12 hr. The catalyst was removed by filtration and AcOH distillation under reduced pressure. The residue was taken up in Et_2O the extract was washed (1 *N* NaOH, H_2O) and dried (Na_2SO_4), and solvent was removed. The residue was chromatographed over alumina with benzene–hexane (1:1) as eluent. Removal of eluent gave **19**, yield 0.88 g (42%).

(b) A mixture of phenol (3.10 g, 0.003 mole), 4-methoxybenzoin (7.23 g, 0.03 mole), and $B(OH)_3$ (6 g) was heated at 200° for 3 hr. The contents were cooled, diluted (H_2O and Et_2O), washed (5% Na_2CO_3–H_2O), and dried (Na_2SO_4), the solvent was removed, and the residue was chromatographed as above; yield 2.25 g (45%).

2-Phenyl-3-(*p*-hydroxyphenyl)benzofuran (20).—A solution of **19** (0.6 g, 0.002 mole) in AcOH (10 ml) containing 48% HBr (3 ml) was refluxed for 6 hr. The reaction mixture was concentrated under vacuum and the residue was added onto H_2O. The precipitate which separated was crystallized from benzene–hexane; yield 0.51 g (87%).

1-(*p*-Dimethylthiocarbamoyloxyphenyl)-2-phenylnaphtho[2,1-*b*]furan (37).—To a cooled solution of **22** (3.36 g, 0.01 mole) in dry DMF (25 ml), NaH (0.24 g, 0.01 mole) was added in small portions. After the evolution of H_2 the solution was cooled to 10°, dimethylthiocarbamoyl chloride (1.63 g, 0.013 mole) was added all at once, and the mixture was heated at 90° for 1 hr. It was cooled and poured onto water. The precipitate so obtained was filtered and crystallized from C_6H_6–EtOH; yield 3.49 g, (80%), ir (KBr) ν 1520 and 1210 cm^{-1}.

1-(*p*-Dimethylcarbamoylmercaptophenyl)-2-phenylnaphtho[2,1-*b*]furan (38).—Compound **37** (2.12 g, 0.005 mole) was heated to 260° for 1 hr and cooled. Crystallization from PhH–EtOH yielded **38**: yield 1.90 g (90%), ir (KBr) ν 1667 cm^{-1}, no peaks at ν 1520 and 1210 cm^{-1} characteristic of O-arylthiocarbamates.

1-(*p*-Mercaptophenyl)-2-phenylnaphtho[2,1-*b*]furan (39).—Compound **38** (0.85 g, 0.002 mole) was dissolved in MeOH (100 ml) containing aqueous NaOH (5 ml) and refluxed under N_2 for 3 hr. The contents were concentrated under vacuum, diluted (H_2O), acidified with dilute HCl, and extracted (EtOAc). Removal of the solvent and crystallization of the residue from C_6H_6–C_6H_{14} furnished **39**, yield 0.6 g (95%).

Dehydrogenation of 2-Phenyl-3-(*p*-(β-pyrrolidinoethoxy)-phenyl)-5,6-tetramethylenebenzofuran (50).—A solution of **50** (0.87 g, 0.002 mole) and DDQ (0.90 g, 0.004 mole) in dioxane (10 ml) was refluxed for 6 hr. The contents were diluted (H_2O), extracted (EtOAc), washed (1 *N* NaOH, H_2O), and dried (Na_2SO_4), and solvent was removed. The residue was converted to its hydrochloride and crystallized (EtOH–Et_2O) to give 2-phenyl-3-[*p*-(β-pyrrolidinoethoxy)phenyl]naphtho[2,3-*b*]furan hydrochloride (**58**), mp 238°, yield 0.56 g (89%).

(8) R. S. Bly, G. A. Perkins, and W. L. Lewis, *J. Amer. Chem. Soc.*, **44**, 2896 (1922).

(9) C. A. Maggiulli and R. A. Paine, Belgian Patent 671,492 (1966); *Chem. Abstr.*, **65**, 8926 (1966).

Biological Activity

Antifertility Activity.—The antiimplantation activity was tested in female rats by the method described earlier.[10] The results were scored as positive only if implantations were totally absent in both uterine horns (MED_{100}).

The antiimplantation potency of different compounds tested is presented in Table I. It is seen from the results (Table I) that compounds **26** and **50** were the most active in the present series. Accordingly, these compounds were also evaluated in a single oral dose regime on any of the days 1–5 *post coitus*. The results are presented in Table II. It is evident that both the compounds completely prevented implantation at a dose of 5–10 mg/kg given orally on any one of the days 1–4 *post coitus*. Since compound **26** showed a better therapeutic index, it was subjected to detailed biological investigation.

TABLE II
EFFECT OF A SINGLE ORAL DOSE OF **26** AND **50** ON PREGNANCY IN RATS

Treatment,[a] mg/kg	Days of pregnancy[b] 1	2	3	4	5
26					
10	0.0	0.0	0.0	0.0	6.0[b]
5	1.0	2.3	1.2	1.7	4.3
50					
10	0.0	0.0	0.0	0.0	5.3
7	0.0	0.0	0.0	0.0	6.0
5	0.0	0.0	0.0	0.0	4.6
2	5.2	3.8	5.0	2.8	6.2

[a] Four to six rats were used in each case. [b] The values given are an average of the total number of implants observed; control group gave an average of 6.6.

Hormonal Properties of 26.—Estrogenic and antiestrogenic activities of **26** were determined in immature rats by the uterine weight and vaginal cornification methods. At the antifertility dose (10 mg/kg oral), it showed mild uteratrophic activity (130% increase as compared to 600% with estrone), but did not cause vaginal cornification. In "delayed implantation" assay no estrogenic activity was seen. The compound was devoid of androgenic, antiandrogenic, and antigonadotrophine properties.

Effect on Ova.—Effect on ova development and transport was investigated in rats; the compound was administered orally (10 mg/kg) on day 1 and the ova were collected from the fallopian tube and the uterus on days 2–6 *post coitus*. No effect won fertilization, development, and transport of ova was observed. A substantial number of morphologically normal blastocysts were collected from the uterus of treated animals on day 6 of pregnancy, whereas hardly any blastocyst could be recovered from the controls. Apparently, in the latter the ova had implanted by this time.

Effect on decidua formation was investigated by the method of Dorfman[10] and the dose used was 10 mg/kg given orally on day 1 of pregnancy. It was found that the deciduoma formation was inhibited in contrast to control animals in which massive decidualization was noticed.

Effect of Progesterone on Antifertility Action.—Progesterone was injected (6 mg/rat) on days 1–10 *post coitus* to animals fed with the compound at a dose

(10) R. I. Dorfman, *Methods Hormone Res.*, **2**, 191 (1962).

TABLE III
ANTIINFLAMMATORY ACTIVITY OF 8

Drug	Dose, mg/kg	Carrageenin-induced hygroma in rats: Mean wt of hygroma, g	Carrageenin-induced hygroma in rats: % reduction from control	Carrageenin-induced rat paw edema: Mean paw vol, ml	Carrageenin-induced rat paw edema: % reduction from control
Water		1.410(5)[a]		0.82(5)	
8	100	0.979(5)	30.6	0.28(5)	65.9
	158	0.878(5)	37.6	0.26(5)	68.3
	275	0.842(5)	40.3		
Prednisolone	12	0.935(10)	47.9		
Indomethacine	3			0.50(5)	39.1

[a] Number of rats used is in parentheses.

of 10 mg/kg. This regime did induce implantations even though the number was less than that in the controls.

These results suggest that the antifertility activity of this compound may in part be due to inhibition of deciduoma formation by virtue of its antiprogestational activity; tubal transport, fertilization, and development and viability of ova were unaffected.

Subacute Toxicity Studies.—In subacute toxicity studies **26** when administered to rats at 50 and 25 mg/kg caused death in most of the animals after 15 and 21 days, respectively, of administration. No apparent cause of death could be found.

Structure–Activity Relationship.—Quite early in this work, it was found that 2-phenyl-3-[*p*-(β-pyrrolidinoethoxy)phenyl]-6-methoxybenzofuran (**2**) had antiimplantation activity and prevented pregnancy in rats at a dose of 4 mg/kg. Further efforts in molecular modification were, therefore, directed toward finding out the contribution of each part of the molecule in determining its biological activity. The two main modifications carried out were in the 3-phenyl ring and the benzene part of the heterocyclic residue.

Removal of the 6-MeO (**21**) decreased the activity to one-fifth and the introduction of an additional MeO at position 5 (**6**) resulted in a fall of activity to one-twentieth. The 5,6-dimethyl analog (**7**) was completely devoid of activity. Surprisingly, when these two Me in **7** were made a part of a homocyclic ring system, the resulting 5,6-polymethylene compounds possessed significant activity. Among the polymethylenebenzofurans, the tetramethylene compound **50** was active at 2 mg/kg. The corresponding tri- and pentamethylene compounds (**46** and **52**, respectively) were much less active, being 80 and 100% effective at 10 mg/kg and were much more toxic, their LD_{100} being between 15 and 20 mg/kg.

The significant difference in the antifertility activity of naphtho[2,1-*b*]furans (**26**, MED_{100} 2 mg) and naphtho[1,2-*b*]furans (**43**, MED_{100} 20 mg) would point to the fact that increase in planar area of the heterocyclic residue *per se* does not increase the activity and a specific orientation of the molecules seems to be of importance. Compound **33** carrying the basic side chain in the naphthalene residue at position 8 was active at 4 mg/kg. When the same change was made in benzofurans the resulting **13**, surprisingly, did not show any activity. In the naphthofuran series, 3-*p*-hydroxyphenyl and 3-*p*-acetoxyphenyl compounds (**22**, **23**) did not have any antifertility activity, thus showing the presence of a *t*-aminoalkyl residue to be necessary for antifertility activity. In general, compounds carrying a β-pyrrolidinoethoxy chain (**2** and **26**) were more active than the corresponding β-dimethylaminoethoxy compounds (**1** and **25**). Compounds **3** and **4**, however, had the same magnitude of activity. Lengthening of β-*t*-aminoethoxy chain to γ-*t*-aminopropoxy residue (**3**, **4**) or the replacement of β-pyrrolidinoethoxyl residue (**22**) by β-pyrrolidinoethylmercapto residue (**40**) appreciable decreased the activity. The compounds carrying side chains at both 2- and 3-phenyl rings of the benzofurans (**10**) did not show any activity.

Benzodifuran (**55**) and naphthodifuran (**57**) also did not have any activity.

Antiinflammatory Activity.—In view of the recently reported antiinflammatory activity of some 2,3-diphenylindole and 2,3-diphenylbenzofurans[11] some of the benzofurans now synthesized (**5**, **8**, **11**, **27**, and **47**) were also tested for their antiinflammatory activity. Only 2,3-bis(*p*-methoxyphenyl)-5,6-dimethylbenzofuran (**8**) showed significant antiinflammatory activity. It proved to be a relatively potent antiinflammatory agent against carrageenin-induced hygroma and carrageenin-induced rat paw edema, when administered intragastrically. Its efficacy in comparison to predisolone and indomethacine is recorded in Table III.

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(11) J. Szumuskovicz, E. M. Glenn, R. V. Heizalman, J. B. Hester, Jr., and G. A. Youngdale, *J. Med. Chem.*, **9**, 527 (1966).