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Antifertility agents—synthesis and activity

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Abstract. Basic ethers, 2-phenyl-3-(*p*-*β*-dialkylaminoalkoxy)-phenyl 7(H) oxo furanocoumarin(VIa) and 9-methyl analog 2-phenyl-3-(*p*-*β*-dialkylaminoalkoxy)-phenyl-9-methyl 7(H) oxo furanocoumarin (VIb) have been synthesised by condensing 2-phenyl-3-*p*-hydroxyphenyl 7(H) oxo furanocoumarin (Va) and its 9-methyl analog (Vb) with appropriate *β*-tertiary aminoalkyl halide in acetone-potassium carbonate. Va and Vb were obtained by demethylating the methyl ethers IVa and IVb respectively with pyridine hydrochloride. IVa and IVb themselves were formed from the alkali-induced cyclisation of the ketones IIIa and IIIb. Among the compounds tested for antifertility activity, the basic ethers 12*, 14*, and 18* were found to have marked anti-implantation properties.

Keywords. Furano benzopyrans synthesis; antifertility activity.

1. Introduction

The development of non-steroidal antifertility agents for human usage is gaining importance as no such agents are available now except the diethyl stilbestrol. An attempt has therefore been made to synthesise basic ethers of diphenyl furanocoumarins.

A number of organic compounds containing a triarylethylene structure have been shown to possess a marked effect on reproductive system (Lerner *et al* 1958; Miquel 1960; Fox *et al* 1964; Lednicer *et al* 1961).

2,3-Diphenyl benzofurans incorporate in their structure a triaryl ethylene group, though in rigid form endowed with antifertility activity; benzofurans (Bicoff *et al* 1958; Longman *et al* 1963; Singh and Kapil 1959, 1960) show estrogenic activity, derivatives of 2,3-diphenyl benzofurans exhibit marked antifertility activity. Grover *et al* (1965) synthesised 2-phenyl-3-*p*-(*β*-diethylamino ethoxy)-phenyl-6-methoxy benzofuran which showed antifertility activity.

Another group of compounds possessing a cyclic triaryl ethylene group are 2,3-diphenyl indenes (Lednicer *et al* 1965) which exhibit antifertility activity in

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rats. Based on the steric structural relationship with 2,3-diphenyl indenes, 3,4-diphenyl coumarins (Lednicer *et al* 1965) were reported to have exhibited antifertility activity as some of them were active at a dose of 0·1 mg/kg/rat/day. Further supporting evidence for the furanocoumarins activity was drawn from the observation of Pomashehenko (1967) that psoralen and isopsoralen prevent pregnancy in rats at a dose of 100 mg/kg.

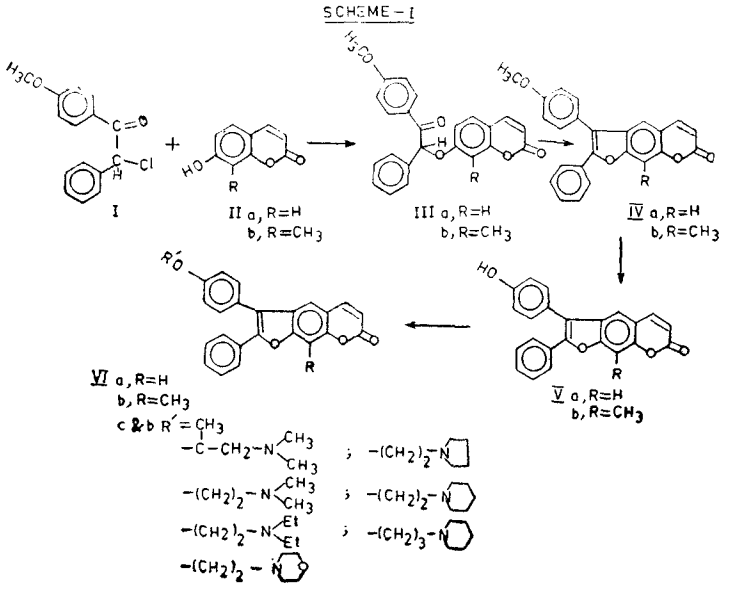
On the basis of the above data it seemed worth while to synthesise basic ethers of diphenyl furanocoumarins and investigate their antifertility activity with a view to study their structure and activity relationship.

It was hoped that these basic ethers of diphenyl furanocoumarin derivatives which contain both benzofuran and coumarin moieties in their structures, may show a pronounced and wider range of antifertility activity than the simple diphenyl benzofuran and coumarin units.

The synthesis of basic ethers of diphenyl furanocoumarins (VIa, VIb) was achieved, starting from 7-hydroxycoumarin (IIa) (Dey *et al* 1934), 7-hydroxy-8-methylcoumarin (IIb) (Seshadri and Venkateshwarlu 1941) condensing them separately with *α*-chlorobenzyl-*p*-methoxyphenyl ketone (I) in acetone/potassium carbonate and cyclising the resulting ether (IIIa and b) with potassium hydroxide (0·1 N). The aqueous potassium hydroxide (0·1 N) is an effective cyclising agent (Kanakalingeswar Rao *et al* 1976) to synthesize linear furanocoumarins. The resulting 2-phenyl-3-*p*-methoxyphenyl7(H)oxofuro(3,2-g)(1)benzopyran (IVa and b) were demethylated using pyridine hydrochloride. The resulting 2-phenyl 3-(*p*-hydroxy)-phenyl7(H)oxofuro(3,2-g)(1)benzopyran (Va and Vb) were refluxed with appropriate *β*-tertiary aminoalkyl halide to yield respective basic ethers (VIa and b) (Scheme I).

The physical characteristics of the compounds synthesised are shown in table 1.

SCHEME – I



2. Biological activity

Compounds were assayed for antiimplantation activity by the standard method (Lednicer *et al* 1965). In the basic ether series three of the compounds 12* 14* and 18* are effective antiimplantation agents at a dose of 10 mg/kg/day/rat post coitally.

It was observed that relatively small structural changes have profound effect on the antiimplantation potency of compounds within the basic ether series.

In all the basic ether series (table 1) from compound 3 to 9, it is observed that displacement of 4'-H of compound (1) by dimethylamino ethyloxy, diethylamino ethyloxy, morpholino ethyloxy, peiperidino ethyloxy, piperidino propyloxy respectively improves the antiimplantation activity by 25 to 50%. Further, the comparison of compounds (table 1) 3, 5 and 9 with 12*, 14* and 18* reveals that the introduction of $-CH_3$ group at position 9 of the compounds 3, 5 and 9 has markedly improved the antiimplantation activity (50 to 100%). The compound 3 which is devoid of any antiimplantation activity at 10 mg dose has showed improved antiimplantation potency by 100% by the introduction of $-CH_3$ group at position 9. Further detailed investigations of these active compounds are under progress.

3. Experimental

3.1. 7-(1-*phenyl*-2-*p*-*methoxyphenyl*-2-*oxo*)-*ethyloxy benzopyran* : (IIIa)

An intimate mixture of 7-hydroxycoumarin (Dey *et al* 1934) (1·78 g) and *α*-chlorobenzyl-*p*-methoxyphenyl ketone (2·6 g) in acetone (150 ml) was treated with anhydrous potassium carbonate (8 g). The mixture was refluxed for 20 hr Then the potassium salts were filtered off and the excess solvent was removed. 7-(1-phenyl-2-*p*-methoxyphenyl-2-oxo)-ethyloxy benzopyran crystals remained in the flask. The solid obtained was recrystallised from alcohol as shining needles. Yield: 3·4 g. m.p. 143° C. I.R. ν max (KBr) 1680 cm^{-1} (acyl carbonyl), 1710 cm^{-1} (lactone carbonyl).

Similarly (IIIb) was prepared using 7-hydroxy-8-methylcoumarin (Seshadri and Venkateshwarlu 1941).

3.2. 2-*Phenyl*-3-(*p*-*methoxy*)-*phenyl* 7 (*H*) *oxo furo* (3,2-*g*) (1) *benzopyran* : (IVa)

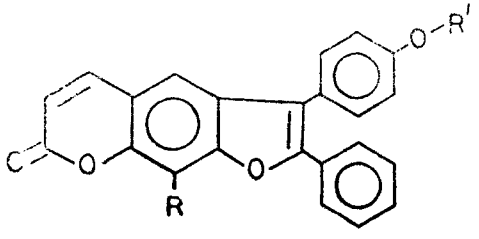
IIIa (3·5 g) and 300 ml 0·1 N aqueous potassium hydroxide solution were refluxed together for about 8 hr. Then the alkaline solution was cooled, filtered and the filtrate was acidified with dilute hydrochloric acid. The solid (IVa) obtained was washed well with water and crystallised from dioxan as shining needles. Yield: 3·15 g. m.p. 175° C.

Similarly (IVb) was obtained using (IIIb).

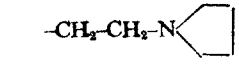
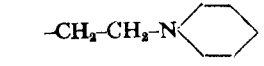
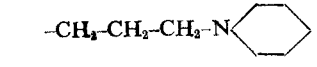
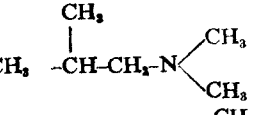
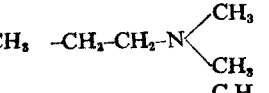
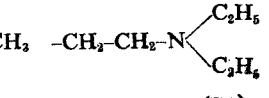
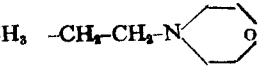
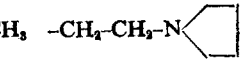
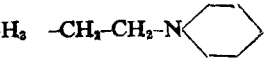
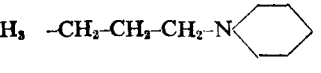
3.3. 2-*Phenyl*-3-(*p*-*hydroxy*)-*phenyl*7(*H*)*oxofuro*(3,2-*g*)(1)*benzopyran*: (Va)

IVa (3·42 g) and pyridine hydrochloride (11·5 g) were refluxed for half an hour at 220° C, cooled and then mixture poured in water, washed and filtered.

Table 1. Physical characteristics and antiimplantation activity.



Sl. No.	R	R'	M.P. °C	Formula	Required			Found			% inhibition at 10 mg/kg/rat
					C	H	N	C	H	N	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1.	H	H	228	$C_{23}H_{14}O_4$	77·96	3·95	..	77·89	3·98	..	0·0
2.	H	CH_3	175	$C_{24}H_{16}O_4$	78·26	4·34	..	78·28	4·33	..	0·0
3.	H	$-CH(CH_3)-CH_2-N(CH_3)_2$	122	$C_{25}H_{24}NO_4$	76·71	5·47	3·19	76·75	5·49	3·14	0·0
4.	H	$-CH_2-CH_2-N(CH_3)_2$	115	$C_{27}H_{23}NO_4$	76·23	5·41	3·29	76·20	5·43	3·27	25·0
5.	H	$-CH_2-CH_2-N(C_2H_5)_2$	225	$C_{29}H_{27}NO_4$	76·82	5·96	3·09	76·85	5·99	3·12	33·0
6.	H	$-CH_2-CH_2-N$(morpholino)	165	$C_{29}H_{25}NO_5$	77·85	5·59	3·13	77·87	5·56	3·11	33·33

7.	H		240	$C_{29}H_{25}NO_4$	77·16	5·54	3·10	77·20	5·51	3·12	0·0
8.	H		139	$C_{30}H_{27}NO_4$	77·41	5·85	3·01	77·38	5·89	3·04	40·0
9.	H		130	$C_{31}H_{29}NO_4$	77·66	6·05	2·9	77·69	6·1	3·01	50·00
10.	CH_3	CH_3	181	$C_{25}H_{18}O_4$	80·64	4·83	..	80·67	4·87	..	33·33
11.	H	CH_3	278	$C_{24}H_{16}O_4$	78·76	4·34	..	78·30	4·31	..	0·0
*12.	CH_3		115	$C_{29}H_{26}NO_4$	76·99	5·75	3·09	77·01	5·73	3·12	100·0
13.	CH_3		110	$C_{28}H_{25}NO_4$	76·30	5·06	3·01	76·33	5·09	3·12	66·00
*14.	CH_3		109	$C_{30}H_{29}NO_4$	77·08	6·20	2·99	77·10	6·23	3·01	100·0
15.	CH_3		103	$C_{30}H_{27}NO_5$	74·85	5·61	2·91	74·87	5·63	2·93	0·0
16.	CH_3		280	$C_{30}H_{27}NO_4$	77·41	5·80	3·01	77·44	5·79	2·99	0·0
17.	CH_3		258	$C_{31}H_{29}NO_4$	77·61	6·05	2·92	77·62	6·08	2·89	50·0
*18.	CH_3		153	$C_{32}H_{31}NO_4$	77·89	6·28	2·83	77·91	6·26	2·87	100·0

2-Phenyl-3-(*p*-hydroxy)-phenyl 7(H) oxo furo (3,2-g) (1) benzopyran dried and crystallised from dioxan. Yield: 3·1 g. m.p. 228° C. I.R. 3300 cm^{-1} (4'-hydroxyl); 1710 cm^{-1} (lactone carbonyl).

Similarly (Vb) was obtained from (IVb) as above.

3.4. *2-Phenyl-3-(p-β-tertiaryaminoalkoxy)-phenyl 7(H) oxo furo (3,2-g) (1) benzopyran*: (VIa and VIb)

A mixture of appropriate β-tertiary aminoalkyl halide hydrochloride (0·001 mol), 2-phenyl-3-(*p*-hydroxy)-phenyl 7(H) oxo furo (3,2-g) (1) benzopyran and its 9-methyl analogue (0·001 mol) freshly ignited potassium carbonate (5 g) and dry acetone (150 ml) was refluxed for 24 hr. After the removal of the excess acetone, the mixture was treated with cold water and the solid separated out was filtered, washed with 3% aqueous sodium hydroxide and water successively. It was crystallized from dioxan-water.

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