Mammalian Antifertility Agents. II. Basic Ethers of 3,4-Diphenylcoumarins[1]

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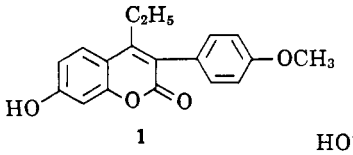
In the previous work it was shown that the basic ether derivatives of a series of 2,3-diphenylindenes exhibit potent antifertility activity in the rat. The evidence presently available seems to indicate that this activity is related to the estrogen-antagonistic



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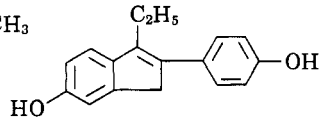

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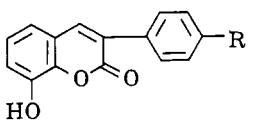

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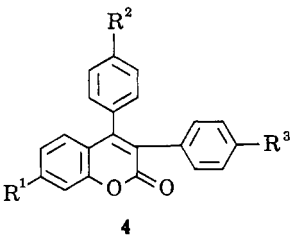

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properties of these compounds.[2] In order to further explore the structural scope of this activity it was decided to investigate the sterically related 3,4-diphenylcoumarins. The observation that both the coumarin 1[3] and the closely related indene 2[4] exhibit estrogenic properties suggested that the argument of steric analogy as an explanation for the activities of these compounds possessed some validity. More recently, Buu-Hoi, *et al.*,[5] prepared an extensive series of both mono- and bisarylcoumarins. The former (4, R = H, CH_3, Cl) were inactive as estrogens. The results of bioassays on the latter series (4, one or more of the R groups is a hydroxyl group) were not stated.

In that work, the arylcoumarins were prepared by the elegant demethylation–cyclization of *o*-methoxyarylcinnamonitriles. That approach was precluded in the present work as we wished to prepare compounds which possessed methoxyl groups as well as the free phenolic hydroxyl. Thus, the older and relatively low-yielding Perkin-type condensation[6] was employed. The acetates thus obtained were saponified to the free phenols. Alkylation of these last compounds with β-chlorodiethylamine led to the desired basic ethers. The physical and analytical constants of the various products are summarized in Tables I–III.

Biological Activity.—The coumarins thus prepared were tested for antifertility activity in the rat in the manner previously described.[1] The maximum dose employed was 10 mg./rat/day (approximately 50 mg./kg.). Compounds inactive at this dose were not followed further. The results of the antifertility screening of the coumarins are summarized in Table IV.

The two most potent members of the series were assayed for uterotropic activity in the immature ovariectomized rat. Compounds were administered daily for 10 days, subcutaneously in sterile water containing 0.25% methylcellulose. Fresh uterine weights were

TABLE I

Compd.	M.p., °C.	Yield, %[a]	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
11	197–199	28	$C_{24}H_{18}O_5$	74.60	74.37	4.70	4.87
12	231–234	10[b]	$C_{23}H_{16}O_4$	77.51	77.40	4.53	4.75
13	175.5–177.5	20.5	$C_{24}H_{18}O_5$	74.60	74.05	4.70	4.53
14	222–225	22					

[a] Based on benzophenone. [b] There was recovered 60% of the benzophenone as its diacetate, m.p. 84–87°.

TABLE II

HYDROXY-3,4-DIARYLCOUMARINS

Compd.	M.p., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
15	235–237	86	$C_{22}H_{16}O_4$	76.73	76.99	4.68	4.67
16	291.5–295[a]	96					
17	254–256	89	$C_{22}H_{16}O_4$	76.73	76.73	4.68	4.69
18	287–289[b]	94					

[a] Lit.[5] m.p. 295°. [b] B. H. Ghosh, [*J. Chem. Soc.*, **109**, 117 (1916)] reported m.p. 285–286°.

TABLE III

BASIC ETHERS OF 3,4-DIARYLCOUMARINS

Compd.	M.p., °C.	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
19	131.5–133	74	$C_{28}H_{29}NO_4$	75.82	75.55	6.59	6.46	..	..
20	82.5–86	51	$C_{27}H_{27}NO_3$	78.42	78.45	6.58	6.50	3.39	3.37
21	95–97	68	$C_{28}H_{29}NO_4$	75.82	76.20	6.59	6.66	3.16	3.06
22	95–97	67	$C_{27}H_{27}NO_3$	78.42	78.03	6.58	6.64	3.39	3.82

(1) Previous paper: D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 52 (1965).

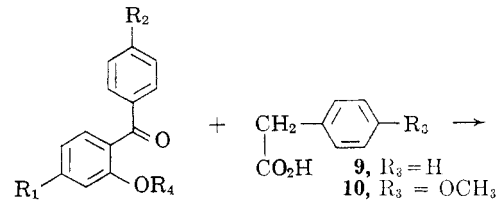
(2) G. W. Duncan, J. C. Stucki, S. C. Lyster, and D. Lednicer, *Proc. Soc. Exptl. Biol. Med.*, **109**, 163 (1962).

(3) P. Gley and C. Mentzer, *Compt. rend. soc. biol.*, **139**, 1055 (1945).

(4) U. V. Solmssen, *J. Am. Chem. Soc.*, **65**, 2370 (1943).

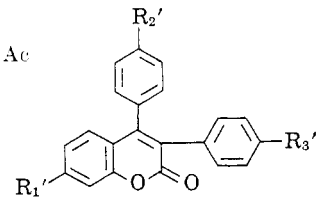
(5) Ng. Ph. Buu-Hoi, B. Ekert, and R. Royer, *J. Org. Chem.*, **19**, 1584 (1954).

(6) G. Bargellini, *Gazz. chim. ital.*, **57**, 457 (1927).

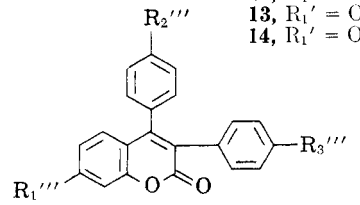


6, $R_1 = R_4 = H$; $R_2 = OH$
7, $R_1 = OH$; $R_2 = R_4 = H$
8, $R_1 = H$; $R_2 = OAc$; $R_4 = Ac$

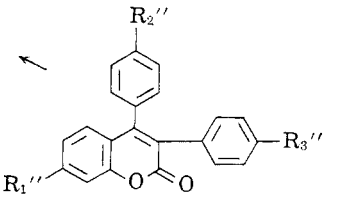
9, $R_3 = H$
10, $R_3 = OCH_3$



11, $R_1' = H$; $R_2' = OAc$; $R_3' = OCH_3$
12, $R_1' = H$; $R_2' = OAc$; $R_3' = H$
13, $R_1' = OAc$; $R_2' = H$; $R_3' = OCH_3$
14, $R_1' = OAc$; $R_2' = H$; $R_3' = H$



19, $R_1''' = H$; $R_2''' = OCH_2CH_2N(C_2H_5)_2$; $R_3''' = OCH_3$
20, $R_1''' = H$; $R_2''' = OCH_2CH_2N(C_2N_5)_2$; $R_3''' = H$
21, $R_1''' = OCH_2CH_2N(C_2H_5)_2$; $R_2''' = H$; $R_3''' = OCH_3$
22, $R_1''' = OCH_2CH_2N(C_2H_5)_2$; $R_2''' = H$; $R_3''' = H$



15, $R_1'' = H$; $R_2'' = OH$; $R_3'' = OCH_3$
16, $R_1'' = H$; $R_2'' = OH$; $R_3'' = H$
17, $R_1'' = OH$; $R_2'' = H$; $R_3'' = OCH_3$
18, $R_1'' = OH$; $R_2'' = H$; $R_3'' = H$

obtained 24 hr. after the last dose. Both **13** and **14** induced marked uterine weight responses and were equivalent in potency to 0.04 and 0.03% of estradiol, respectively. Compound **22** which was 1/1000 as potent in the antifertility assay was also considerably less potent in the uterotropic assay.

It is of interest that while the majority of the neutral coumarins show some activity as antifertility agents, presumably due to their estrogenic activity, only one of the basic derivatives is potent enough to be picked up by the screen. The results also would seem to indicate that the steric analogy is at least in the case of antifertility activity an oversimplification of operative factors. It should be noted in this connection that the indene corresponding to **19** is active at 0.5 mg./rat/day.[1]

Experimental[7]

The following experiments represent typical procedures for the steps employed in the preparation of the compounds above.

3-(*p*-Methoxyphenyl)-4-(*p*-acetoxyphenyl)coumarin.—A mixture of 2,4′-diacetoxybenzophenone and the alcohol-free salt prepared from 5.56 g. of *p*-methoxyphenylacetic acid and 7.20 g. of 25% methanolic sodium methoxide was heated at reflux with 50 ml. of acetic anhydride for 40 hr. The mixture was allowed to cool, poured into water, and stirred for 2 hr. The aqueous phase was removed by decantation, and the organic gum was dissolved in methylene chloride. The solution was washed in turn with aqueous saturated $NaHCO_3$, water, and brine and taken to dryness *in vacuo*. The residue was recrystallized once from methanol and twice from aqueous acetic acid to give 1.85 g. of the coumarin.

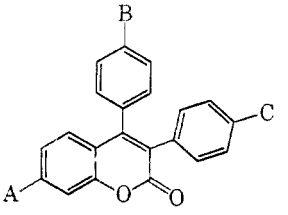
3-(*p*-Methoxyphenyl)-4-(*p*-hydroxyphenyl)coumarin.—A suspension of 15.87 g. of 3-(*p*-methoxyphenyl)-4-(*p*-acetoxyphenyl)coumarin in 200 ml. of 1% aqueous NaOH was shaken mechanically for 16 hr. The small amount of solid which had failed to dissolve was then removed by filtration and the filtrate was acidified. The precipitated phenol was recrystallized from aqueous acetic acid to give 11.6 g. of product.

3,4-Diphenyl-7-(2-diethylaminoethoxy)coumarin.—To a suspension of 3.91 g. of 3,4-diphenyl-7-hydroxycoumarin in 100 ml. of ethanol there was added 2.69 g. of sodium methoxide in methanol (4.64 mequiv./g.). The solid slowly went into solution. At the end of 1 hr. 3.36 g. of a 1:1 solution of β-chlorodiethylamine in toluene was added to the solution. Following 20 hr. of heating under reflux the mixture was allowed to cool, and the solvent was evaporated *in vacuo*. The residue was dissolved in water, ether, and methylene chloride. The organic layer was washed in turn with dilute aqueous NaOH and brine. The crystalline solid which remained when this solution was taken to dryness was recrystallized twice from ligroin to yield 3.46 g. of product.

(7) All melting points were obtained on a Thomas–Hoover melting point apparatus. Elemental analyses were performed by the Department of Physical and Analytical Chemistry of The Upjohn Co.

TABLE IV

ANTIFERTILITY ACTIVITY OF 3,4-DIARYLCOUMARINS



Compd.	A	B	C	MED_{100},[a] mg./rat/day
11	H	OAc	OCH_3	10
12	H	OAc	H	>10
13	OAc	H	OCH_3	0.1
14	OAc	H	H	0.1
15	H	OH	OCH_3	>10
17	OH	H	OCH_3	10[b]
19	H	$OCH_2CH_2N(C_2H_5)_2$	OCH_3	>10
20	H	$OCH_2CH_2N(C_2H_5)_2$	H	>10
21	$OCH_2CH_2N(C_2H_5)_2$	H	OCH_3	>10
22	$OCH_2CH_2N(C_2H_5)_2$	H	H	10

[a] Minimal effective dose for 100% inhibition of pregnancy, subcutaneous administration. [b] Same for oral administration.

TABLE V

UTEROTROPIC RESPONSES OF IMMATURE OVARIECTOMIZED RATS[a]

Compd.	Daily dose, γ	Uterine wt., mg.
Vehicle control		25
13	10	65
	100	101
	500	143
14	10	45
	100	101
	500	146
22	250	31
	500	38
	1000	51
Estradiol	0.01	42
	0.05	125

[a] Ten daily subcutaneous treatments; five rats/dose.