g 58%): MS, m/e 324 (M^+). Anal. ($C_{17}H_{24}O_6 \cdot 0.5H_2O$) C, H.

2-[2-(2-Hydroxyethoxy)phenoxy]pentan-1-ol (18). A solution of the ester **16** (3.0 g, 9.6 mmol) in THF (15 mL) was added under N_2 to a stirred suspension of $LiAlH_4$ (0.41 g, 10.8 mmol) in THF (20 mL), which was cooled by ice–H_2O. H_2O (15 mL) and 2 N HCl (15 mL) were added dropwise, and the mixture was extracted with EtOAc. The EtOAc was dried ($MgSO_4$) and evaporated to an oil. The oil was purified by column chromatography on silica gel ($CHCl_3$), and elution with 1:1 $CHCl_3$–EtOAc gave **18** as an oil (1.8 g, 82%): MS, m/e 240 (M^+). Anal. ($C_{13}H_{20}O_4$) C, H.

5-*n*-Propyl-2,3-benzo-15-crown-5 (4). NaH, (50%, 0.44 g, 9.2 mmol) was added under N_2 to a stirred solution of **18** (1.1 g, 4.6 mmol) in THF (50 mL), and the mixture was heated to reflux. Ditosyldiethylene glycol (1.89 g, 5.1 mmol) in THF (50 mL) was added during 3.5 h to the boiling mixture, and heating was continued for a further 18 h. The mixture was cooled by ice–H_2O, and H_2O (10 drops) was added before filtration. The filtrate was evaporated to remove the THF, and the residue was purified by column chromatography on silica gel ($CHCl_3$). Elution with 1:1 $CHCl_3$/EtOAc gave **4** as an oil (0.45 g, 32%) MS, m/e 310 (M^+). Anal. ($C_{17}H_{26}O_5$) C, H.

Ethyl 2-[2-[(Ethoxycarbonyl)methoxy]phenoxy]acetate (17). Catechol (11.0 g, 100 mmol) was added to a stirred solution of Na (4.6 g, 200 mmol) in EtOH (200 mL) under N_2. Ethyl bromoacetate (33.4 g, 200 mmol) was added during 10 min, and the mixture was heated under reflux for 16 h. The EtOH was evaporated, and the residue was shaken with EtOAc and H_2O. The EtOAc was washed with 5% NaOH solution and H_2O, dried ($MgSO_4$), and evaporated to an oil (13.7 g 49%), bp 138–139 °C (0.2 mm). Anal. ($C_{14}H_{18}O_6$) C, H.

2-[(2-Hydroxyethoxy)phenoxy]ethanol (19). The ester **17** (6.9 g, 24 mmol) in THF (25 mL) was added under N_2 during 45 min to stirred $LiAlH_4$ (1.1 g, 29 mmol) in THF (90 mL). The mixture was heated under reflux for 30 min and cooled in ice–H_2O. H_2O (20 mL) and 2 N HCl (20 mL) were added cautiously, and the mixture was extracted with EtOAc. The EtOAc was dried (MgSO4) and evaporated. The residue was crystallized from toluene to give **19** (4.7 g, 100%), mp 81–82 °C. Anal. ($C_{10}H_{14}O_4$) C, H.

2,3,8,9,14,15,20,21-Tetrabenzo-24-crown-8 (8). *p*-Toluenesulfonyl chloride (5.7 g, 30 mmol) was added during 15 min to a solution of the diol **19** (2.95 g, 15 mmol) in pyridine (10 mL) cooled to 5 °C by ice H_2O. The mixture was stirred for 4 h at 10 °C and poured on to ice–H_2O. The solid product was collected and crystallized from toluene to give **20** (6.1 g, 80%), mp 91–93 °C. A solution of catechol (1.1 g, 10 mmol) in dimethylacetamide (DMAc) (25 mL) was added during 10 min to a suspension of 50% NaH (1.0 g, 21 mmol) in DMAc (25 mL) under N_2. The mixture was warmed to 60 °C, and **20** (5.1 g, 10 mmol) in DMAc (10 mL) was added during 10 min. The mixture was heated and stirred at 160 °C for 16 h and cooled before evaporation of the DMAc. The residue was purified by filtration through alumina in $CHCl_3$. The $CHCl_3$ was evaporated to give a solid, which crystallized from EtOAc to give **8** (0.9 g, 67%): mp 150–151 °C (lit.[4] mp 150–152 °C); MS, m/e 544 (M^+). Anal. ($C_{32}H_{32}O_8$) C, H.

1,3-Bis(2-hydroxyphenoxy)propane (21). 1,3-Dibromopropane (5.0 g, 25 mmol), anhydrous K_2CO_3 (2.8 g, 20 mmol) and 2-(tetrahydropyran-2-yloxy)phenol (9.8 g, 50 mmol) were heated in acetone (40 mL) under reflux under N_2 for 22 h. The mixture was poured into H_2O (1 L) and extracted with EtOAc. The EtOAc was dried ($MgSO_4$), and concentrated HCl (5 drops) was added. The EtOAc was evaporated to give a solid, which crystallized fro $CHCl_3$ to give **21** (1.0 g, 15%), mp 117–118 °C. Anal. ($C_{15}H_{16}O_4$) C, H.

Registry No. **1**, 70844-47-2; **2**, 14098-44-3; **3**, 15196-73-3; **4**, 84433-54-5; **5**, 14174-06-2; **6**, 14187-32-7; **7**, 14174-09-5; **8**, 14098-25-0; **9**, 17455-25-3; **10**, 33100-27-5; **11**, 17454-48-7; **12**, 17455-13-9; **13**, 16069-36-6; **15**, 84433-55-6; **16**, 84433-56-7; **17**, 52376-09-7; **18**, 84433-57-8; **19**, 10234-40-9; **20**, 54535-06-7; **21**, 42397-72-8; catechol, 120-80-9; ethyl 2-bromovalerate, 615-83-8; ethyl bromoacetate, 105-36-2; 1,3-dibromopropane, 109-64-8; 2-(tetrahydropyran-2-yloxy)phenol, 21645-25-0.

Antifertility Agents. 38. Effect of the Side Chain and Its Position on the Activity of 3,4-Diarylchromans[1]

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In a study of the effect of the substituent on the receptor binding affinity (RBA), estrogenicity, and antiimplantation (AI) activity in *trans*-3,4-diarylchromans, it has been found that demethylation of *trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (centchroman, 1)[2,3] to the corresponding 7-hydroxy compound (**7**) results in a 20-fold increase in RBA (112%) without any appreciable change in AI activity. On the other hand, absence of the pyrrolidinoethyl group from the 4-phenyl residue (**6**) leads to a drop in both RBA and AI activity. A chain length of two to three carbon atoms and a pyrrolidino ring appear to be necessary for activity in these compounds. It has been found that while the trans isomers with the tertiary aminoalkoxy side chain in the para position of the 4-phenyl radical were the most active, in the corresponding *cis*-chromans and chromenes, analogues with this chain in the meta position were most active; the ortho substituted compounds of all these series were inactive. In 3-phenyl-substituted compounds, the trans isomer carrying the *p*-hydroxy substituent (**33**) was found to be the most active; the corresponding pyrrolidinoethyl ether (**13**) showed a lower order of activity. The implication of these observations on the mapping of the different subsites on the receptor has been discussed.

In a study on antifertility activity, it has been found that the activity is confined mainly to the trans diastereomer for the 2,2-dimethyl-3,4-diphenylchromans[2] and to the levo enantiomer for the two optical antipodes. As a result of the detailed biological evaluation of these compounds, *trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)-phenyl]-7-methoxychroman (centchroman, **1**, Chart I)[2,3] has emerged as a candidate drug for postcoital contraception and is in phase III clinical studies. In a substructure analysis, the effect of the tertiary aminoalkoxy side chain and of 7-methoxy group toward cytosol receptor binding affinity (RBA), estrogenicity, and antiimplantation (AI) activity has now been studied, and the results are reported in this paper.

Chemistry. *trans*-2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman (**6**) was prepared by dimsyl cation isomerization, followed by debenzylation of

(1) CDRI communication no. 3152.
(2) Suprabhat Ray, P. K. Grover, V. P. Kamboj, B. S. Setty, A. B. Kar, and N. Anand, *J. Med. Chem.*, **19**, 276 (1976).
(3) N. Anand and S. Ray, *Indian J. Exp. Biol.*, **15**, 1142–1143 (1977).
(4) Md. Salman, Suprabhat Ray, V. P. Kamboj, and N. Anand, U.K. Patent Application GB 2055836A (1980).

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the corresponding *cis*-(benzyloxy)chroman 4. For the synthesis of *trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)phenyl]-7-hydroxychroman (7), after some preliminary exploration, it was found that demethylation of centchroman was the most convenient route. Demethylation of centchroman under alkaline conditions gave 7 in 25% yield, along with 6 and unreacted compound, which were separated by column chromatography with basic alumina.

For the variation in the basic side chain, the common intermediate 6 was alkylated with appropriate tertiary aminoalkyl chlorides by refluxing them in dry acetone in the presence of K_2CO_3.

The synthesis of *trans*-2,2-dimethyl-3-phenyl-4-[*m*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (11) was started from *m*-hydroxybenzoic acid (14). Friedel–Craft reaction of 14 with *m*-methoxyphenol (15) gave 2,3′-dihydroxy-4-methoxybenzophenone (16), which on condensation with phenylacetic acid (17) in the presence of Ac_2O and $N(C_2H_5)_3$ gave 3-phenyl-4-(*m*-acetoxyphenyl)-7-methoxycoumarin (18). Grignard reaction of 18 with excess of MeMgI furnished 2,2-dimethyl-3-phenyl-4-(*m*-hydroxyphenyl)-7-methoxychromene (19), which on alkylation with *N*-(2-chloroethyl)pyrrolidine hydrochloride led to 2,2-dimethyl-3-phenyl-4-[*m*-(β-pyrrolidinoethoxy)-phenyl]-7-methoxychromene (20). Catalytic hydrogenation of 19 with 10% Pd/C gave *cis*-2,2-dimethyl-3-phenyl-4-(*m*-hydroxyphenyl)-7-methoxychroman (21). Alkylation of 21 with *N*-(2-chloroethyl)pyrrolidine hydrochloride furnished 22, which was isomerized with dimsyl cation to the *trans*-chroman 11.

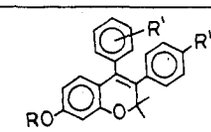
The synthesis of *trans*-2,2-dimethyl-3-phenyl-4-[*o*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (12) was achieved from 2,2-dimethyl-3-phenyl-4-(*o*-hydroxyphenyl)-7-methoxychromene (23)[5] following the same sequence of reactions as described for 11 through the *cis*-chromans 24 and 25. Alkylation of 23 with *N*-(2-chloroethyl)pyrrolidine hydrochloride gave 34.

The synthesis of *trans*-2,2-dimethyl-3-[*p*-(β-pyrrolidinoethoxy)phenyl]-4-phenyl-7-methoxychroman (13) was carried out from 2-hydroxy-4-methoxybenzophenone (26).[6] Its condensation with *p*-hydroxyphenylacetic acid (27) gave 3-(*p*-acetoxyphenyl)-4-phenyl-7-methoxycoumarin (28), which was converted to the desired chroman 13 through the hydroxychromene (29) and the *cis*-chromans (31 and 32) following the sequence of reactions described for 11. Alkylation of 29 with *N*-(2-chloroethyl)pyrrolidine hydrochloride gave the chromene 30. The *trans*-hydroxychroman 33 was synthesized by *n*-BuLi isomerization of 31.

Results and Discussion

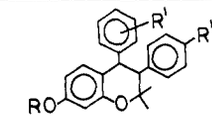
In centchroman (1), similar to other antiestrogens,[10-12] absence of the pyrrolidinoethyl side chain, as in 6, resulted in a drop in RBA and AI activity. On the other hand, demethylated centchroman (7) showed a 20-fold increase in RBA over the parent compound (1), without any appreciable change in AI activity. These results would indicate that the 7-position of 1 corresponds to the 3-position of estradiol and that the tertiary amino alkyl chain pro-

Table I



compd	mp, °C	yield, %	mol formula	anal.
4	113–114	80	$C_{31}H_{30}O_3$	C, H
5	148.5–149	95	$C_{31}H_{30}O_3$	C, H
6	263–264	93	$C_{24}H_{24}O_3$	C, H
7	294–296	25	$C_{29}H_{33}NO_3$	C, H, N
8	161–163	69	$C_{30}H_{37}NO_3 \cdot HCl$	C, H, N
9	217–218	95	$C_{28}H_{33}NO_3 \cdot HCl$	C, H, N
10	213–215	93	$C_{31}H_{40}NO_3 \cdot HCl$	C, H, N
11	179.5–181	85	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N
12	170–171	90	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N
13	134.5–135	85	$C_{30}H_{35}NO_3$	C, H, N
16	113–114	26	$C_{14}H_{12}O_4$	C, H
18	148–149	81	$C_{24}H_{18}O_5$	C, H
19	183–184	51	$C_{24}H_{22}O_3$	C, H
20	178–179	65	$C_{30}H_{33}NO_3 \cdot HCl$	C, H, N
21	177.5–178	90	$C_{24}H_{24}O_3$	C, H
22	151–153	74.5	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N
24	198.5–199	70	$C_{24}H_{24}O_3$	C, H
25	240–241	86	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N
28	197.5–198	71	$C_{24}H_{18}O_5$	C, H
29	152–153	56	$C_{24}H_{22}O_3$	C, H
30	201–203	82	$C_{30}H_{33}NO_3 \cdot HCl$	C, H, N
31	195–196	76	$C_{24}H_{24}O_3$	C, H
32	146–148	81	$C_{30}H_{35}NO_3 \cdot HCl$	C, H, N
33	212.5–213	84	$C_{24}H_{24}O_3$	C, H
34	217–218	81	$C_{30}H_{33}NO_3 \cdot HCl$	C, H, N

Table II



compd	RBA	estrogenicity	AI act.[a] (rat): ED_{100}, (mg/kg)/day
estradiol	100	100	
1	5.24 ± 1.45	0.56	0.25
2	0.0008	nil	50
6	0.58 ± 0.05	0.20	nil
7	112 ± 18	11.80	0.25
8	3.22 ± 0.77		0.3
9	1.89 ± 0.82		2.0
10	4.50 ± 1.77		0.3
11	0.78 ± 0.14		−ve at 2.0
12	nil		−ve at 2.0
13	0.14 ± 0.03	2.2	2.0
20	8.28 ± 0.38		1
22	0.10 ± 0.01		−ve at 2.0
25	nil		
29	0.47 ± 0.141		+ve at 10.0, −ve at 2.0
30	nil		−ve at 2.0
31	0.06 ± 0.01		−ve at 10.0
32	nil		−ve at 2.0
33	0.29 ± 0.061		1.0
34	nil		−ve at 10.0
35	0.86 ± 0.10		5.0

[a] −ve and +ve denote the inactivity and activity, respectively, of the compounds at the mentioned dose.

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(9) A. B. Kar, V. P. Kamboj, and B. S. Setty, *Indian J. Exp. Biol.*, **5**, 80 (1967).
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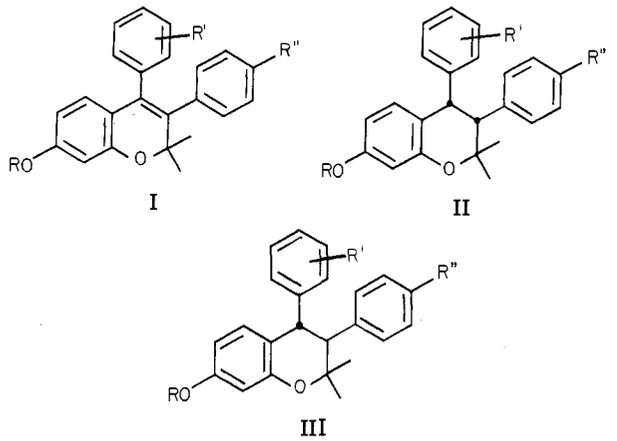
(12) D. W. Robertson, J. A. Katzenellenbogen, J. R. Hayes, and B. S. Katzenellenbogen, *J. Med. Chem.*, **25**, 167 (1982).

Chart I



I II III

no.	type	R	R'	R''
1[a]	III	Me	p-OCH_2CH_2A[b]	H
2[a]	II	Me	p-OCH_2CH_2A	H
3[a]	II	Me	p-OH	H
4	II	Me	p-OCH_2Ph	H
5	III	Me	p-OCH_2Ph	H
6	III	Me	p-OH	H
7	III	H	p-OCH_2CH_2A	H
8	III	Me	p-OCH_2CH_2B[c]	H
9	III	Me	p-OCH_2CH_2C[d]	H
10	III	Me	p-$OCH_2CH_2CH_2A$	H
11	III	Me	m-OCH_2CH_2A	H
12	III	Me	o-OCH_2CH_2A	H
13	III	Me	H	p-OCH_2CH_2A
19	I	Me	m-OH	H
20	I	Me	m-OCH_2CH_2A	H
21	II	Me	m-OH	H
22	II	Me	m-OCH_2CH_2A	H
23[e]	I	Me	o-OH	H
24	II	Me	o-OH	H
25	II	Me	o-OCH_2CH_2A	H
29	I	Me	H	p-OH
30	I	Me	H	p-OCH_2CH_2A
31	II	Me	H	p-OH
32	II	Me	H	p-OCH_2CH_2A
33	III	Me	H	p-OH
34	I	Me	o-OCH_2CH_2A	H
35[a]	I	Me	p-OCH_2CH_2A	H

[a] Reference 2. [b] A = c-NC_4H_8. [c] B = NEt_2. [d] C = NMe_2. [e] Reference 5.

vided enhanced binding.[12] The increase in biological activity of *trans*-2,2-dimethyl-3-(*p*-hydroxyphenyl)-4-phenyl-7-methoxychroman (**33**) over the corresponding 3-[*p*-(β-pyrrolidinoethoxy)phenyl]chroman (**13**) suggests that this 3-*p*-hydroxy position corresponds to the 17β-OH of estradiol, a subsite proposed for estrogen binding.[13]

The results of RBA and AI activity of *trans*-chromans **1** and **8–10** (Table II) suggest a preference for the basic side chain in the order p-$O(CH_2)_2$-c-NC_4H_8 > p-$O(CH_2)_3NEt_2$ > p-$O(CH_2)_2NEt_2$ > p-$O(CH_2)_2NMe_2$ (cf. Lednicer et al.[10] for AI activity).

As regards the effect of the position of the side chain in the 4-phenyl ring of *trans*-chromans, the biological activity of the para-substituted compound was found to be more than the corresponding meta isomer. However, in chromenes, the meta-substituted compound **20** was more active as compared to the para-substituted compound **35**. This is very likely due to a change in the alignment of the 4-phenyl ring to the plane of the molecule, requiring the cationic substituent at the meta position to provide optimum binding possibility. A similar effect was observed with *cis*-chromans (**22** and **2**). The ortho-substituted compounds were found to be inactive. From a study of the Dreiding models, it can be seen that in ortho-substituted compounds, steric factors cause aplanarity in the molecule, which may result in a loss in receptor binding and consequent drop in biological activity.

A comparison of the results of compounds **20**, **34**, and **35** and **20**, **1**, and **33** would show that whereas RBA and AI activities are directly related within a particular series, there is no correlation between the two of two different series.

Experimental Section

Biochemical and Biological Methods. Receptor Affinity. Relative binding affinities (RBA) for uterine cytosol 17β-estradiol receptors obtained from immature Charles Foster rats, 21–25 days old, were determined by a competition assay, employing dextran-coated charcoal (DCC) for separation of unbound steroids according to the method of Korenman,[7] as modified by Katzenellenbogen,[8] and are listed in Table II.

Antifertility Activity. Pregnancy-inhibiting activity of the compounds shown in Table II was studied in female albino rats mated to coeval males of proven fertility as described earlier.[9] The compounds were suspended in gum acacia and administered orally to colony-bred adult-mated female rats (150–170 g) on days 1–7 *postcoitum*. The results were scored as positive only if implants were totally absent in both the uterine horns.

Estrogenic Activity. The estrogenic activity of the compounds, reported in Table II, was evaluated in immature rats (25–30 g) as assessed by uterine weight gain.[9] The compounds were administered subcutaneously once daily over a 3-day period in 0.2 mL of saline/propylene glycol (1:1, v/v).

Synthetic Method. All melting points were determined in a sulfuric acid bath and are uncorrected. IR spectra were run on a Model 137, 157, or 177 Perkin-Elmer spectrophotometer and are expressed in reciprocal centimeters. ^1H NMR spectra were taken in $CDCl_3$, unless otherwise mentioned, on a Varian A-60D or Perkin-Elmer R-32 (90 MHz) spectrophotometer, with Me_4Si as internal standard. Mass spectra were recorded on a Hitachi RMU-6E fitted with a direct-inlet system and JMS-JEOL D300 instruments. The purity of compounds was routinely checked by silica gel G or basic/neutral alumina TLC plates.

The following experiments represent typical experimental procedures employed in the preparation of the compounds given in Table I.

***cis*-2,2-Dimethyl-3-phenyl-4-[*p*-(benzyloxy)phenyl]-7-methoxychroman (4).** *cis*-2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman[2] (**3**; 21.6 g, 0.06 mol) benzyl chloride (7.59 g, 0.06 mol), and anhydrous potassium carbonate (50 g) were taken in dry acetone (300 mL). The reaction mixture was refluxed for 35 h, cooled, and filtered. Acetone was distilled off, and the residual oil was taken in ethyl acetate (200 mL) and washed with water until neutral. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Compound **4** thus obtained was crystallized from benzene–hexane: IR (KBr) 2950 and 1610 cm^{-1}; ^1H NMR (CCl_4) δ 1.1 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 2.72 (d, 1 H, PhC*H*, J = 6 Hz), 3.63 (s, 3 H, OCH_3), 4.42 (d, 1 H, PhC*H*Ph, J = 6 Hz), 4.76 (s, 2 H, OCH_2Ph), ca. 6.1–7.1 (m, 17 H, Ar*H*).

***trans*-2,2-Dimethyl-3-phenyl-4-[*p*-(benzyloxy)phenyl]-7-methoxychroman (5).** A solution of *n*-BuLi in hexane (50 mL, 20%) was gradually added to a stirred solution of **4** (15 g) in dry Me_2SO (200 mL) under dry nitrogen atmosphere. The reaction mixture that turned pink was left at room temperature for 16 h and decomposed with water. The solid obtained was collected by filtration and crystallized from benzene–hexane: IR (KBr) 2900 and 1610 cm^{-1}; ^1H NMR (CCl_4) δ 1.13 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 3.02 (d, 1 H, PhC*H*, J = 12 Hz), 3.6 (s, 3 H, OCH_3), 4.16 (d, 1 H, PhC*H*Ph, J = 12 Hz), 4.7 (s, 2 H, OCH_2Ph), 6.1–7.1 (m, 17 H, Ar*H*).

***trans*-2,2-Dimethyl-3-phenyl-4-(*p*-hydroxyphenyl)-7-methoxychroman (6).** Compound **5** (4 g) was debenzylated by hydrogenation over Raney Ni (2 g) at 60 psi of hydrogen pressure

(13) S. Durani, A. K. Agarwal, R. Saxena, B. S. Setty, R. C. Gupta, P. L. Kole, S. Ray, and N. Anand, *J. Steroid Biochem.*, 11, 67 (1979).

in methanol (100 mL) for 8 h. Catalyst was removed by filtration through hyflo supercel, concentrated, and crystallized from THF–benzene.

***trans*-2,2-Dimethyl-3-phenyl-4-[*p*-(β-pyrrolidinoethoxy)phenyl]-7-hydroxychroman (7).** A mixture of 1 (4.57 g, 0.01 mol), finely powdered KOH (12.8 g, 0.22 mol), diethylene glycol (120 mL), and hydrazine hydrate (1.0 mL) was heated at 240 °C for 30 min under a dry N_2 atmosphere, cooled, poured over sodium dithionate solution (1.4 g in 1600 mL of H_2O), and acidified with the minimum amount of concentrated HCl. The solid that separated was collected by filtration, dried, and purified by column chromatography (basic alumina, 1% MeOH/$CHCl_3$).

***trans*-2,2-Dimethyl-3-phenyl-4-[*p*-[β-(diethylamino)ethoxy]phenyl]-7-methoxychroman Hydrochloride (8).** A mixture of 6 (0.9 g, 2.5 mmol), 2-(diethylamino)ethyl chloride hydrochloride (0.43 g, 2.5 mmol), anhydrous K_2CO_3 (8 g), and dry acetone (60 mL) was refluxed for 14 h, cooled, and filtered. Acetone was distilled off, and the residual oil was taken into ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated. The oily residue was purified by filtration through basic alumina (benzene) to give 8 free base (0.8 g), which was converted to its hydrochloride salt.

2,3′-Dihydroxy-4-methoxybenzophenone (16). A mixture of *m*-methoxyphenol (12.4 g, 0.1 mol), *m*-hydroxybenzoic acid (13.8 g, 0.1 mol), and $SnCl_4$ (100 mL) was refluxed for 8 h, cooled, poured over crushed ice (500 g), and extracted with ethyl acetate; the organic extract washed with $NaHCO_3$ solution and then with water until neutral, dried (Na_2SO_4), and concentrated. The residual oil was chromatographed over silica gel (5% EtOAc/benzene) to give 16, recrystallized from benzene–hexane: IR (KBr) 3400, 1620, 1580 cm^{-1}.

3-Phenyl-4-(*m*-acetoxyphenyl)-7-methoxycoumarin (18). A solution of 16 (10.7 g, 0.043 mol) and phenylacetic acid (5.84 g, 0.043 mol) in Ac_2O (20 mL) and NEt_3 (9 mL) was refluxed under anhydrous conditions for 10 h. The reaction mixture was diluted with ethanol, and the solid thus obtained was collected by filtration, washed thoroughly with ethanol, dried, and crystallized from benzene–hexane: IR (KBr) 1770, 1710, 1600 cm^{-1}.

Similarly, 28 was obtained from 26 and *p*-hydroxyphenylacetic acid.

2,2-Dimethyl-3-phenyl-4-(*m*-hydroxyphenyl)-7-methoxychromene (19). To a stirred solution of MeMgI, prepared from 27.97 g of CH_3I (0.197 mol) and 4.74 g of Mg (0.197 g-atom) in dry ether (200 mL), was added dropwise a solution of 18 (13.0 g, 0.033 mol) in dry THF (250 mL). The reaction mixture was refluxed for 4 h, cooled, and decomposed with the minimum amount of concentrated HCl. THF was distilled off, and the residual oil was taken in ethyl acetate, washed with water until neutral, dried (Na_2SO_4) and concentrated. Residual oil was chromatographed over silica gel (1% EtOAc/C_6H_6) to give 19: IR (KBr) 3350, 2950, 1605 cm^{-1}; ^1H NMR δ 1.38 (s, 6 H, $2CH_3$), 3.21 (nh, 1 H, O*H*), 3.61 (s, 3 H, OCH_3), 6.1–7.1 (m, 12 H, Ar*H*).

2,2-Dimethyl-3-phenyl-4-[*m*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychromene (20). Alkylation of 19 with *N*-(2-chloroethyl)pyrrolidine hydrochloride as described for 8 and its subsequent conversion to the hydrochloride salt gave the desired compound.

***cis*-2,2-Dimethyl-3-phenyl-4-(*m*-hydroxyphenyl)-7-methoxychroman (21).** Catalytic hydrogenation of 19 (100 mg) over 10% Pd/C (50 mg) in methanol at 60 psi for 8 h on workup gave 21 as a solid, recrystallized from benzene/hexane.

***cis*-2,2-Dimethyl-3-phenyl-4-[*m*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (22).** Alkylation of 21 with *N*-(2-chloroethyl)pyrrolidine hydrochloride and its subsequent conversion to the hydrochloride salt following the procedure described for 8 gave 22.

***trans*-2,2-Dimethyl-3-phenyl-4-[*m*-(β-pyrrolidinoethoxy)phenyl]-7-methoxychroman (11).** Isomerization of 22 with *n*-BuLi in Me_2SO following the procedure described for 5 gave 11.

Registry No. 1, 31477-60-8; 2, 51423-20-2; 3, 51423-18-8; 4, 84394-05-8; 5, 84394-06-9; 6, 57897-46-8; 7, 84394-36-5; 8, 78994-27-1; 8·HCl, 84394-07-0; 9, 78994-28-2; 9·HCl, 84394-08-1; 10, 84394-28-5; 10·HCl, 84394-09-2; 11, 84394-29-6; 11·HCl, 84394-10-5; 12, 84394-30-9; 12·HCl, 84394-11-6; 13, 84394-37-6; 16, 84394-12-7; 18, 84394-13-8; 19, 84394-14-9; 20, 84394-26-3; 20·HCl, 84394-15-0; 21, 84394-16-1; 22, 84394-27-4; 22·HCl, 84394-17-2; 23, 84394-18-3; 24, 84394-19-4; 25, 84394-31-0; 25·HCl, 84394-20-7; 26, 131-57-7; 27, 156-38-7; 28, 84394-21-8; 29, 84394-22-9; 30, 84394-32-1; 30·HCl, 84394-23-0; 31, 84394-24-1; 32, 84394-33-2; 32·HCl, 84394-25-2; 33, 84394-35-4; 34, 84394-34-3; 34·HCl, 84416-61-5; 35, 53996-41-1; 2-(diethylamino)ethyl chloride hydrochloride, 869-24-9; *m*-methoxyphenol, 150-19-6; *m*-hydroxybenzoic acid, 99-06-9; phenylacetic acid, 103-82-2; *N*-(2-chloroethyl)pyrrolidine hydrochloride, 7250-67-1.

Phosphonate Analogues of Pyridoxal Phosphate with Shortened Side Chains

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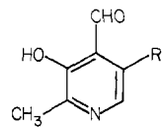
A phosphonate analogue of pyridoxal 5′-phosphate containing a 5-phosphonomethyl group and its monoethyl and diethyl esters have been prepared. Except for the diethyl ester, the compounds appear to bind into the active site of aspartate aminotransferase. However, they lack detectable catalytic activity with this enzyme and with glutamate decarboxylase of *Escherichia coli*. The phosphonomethyl analogue bound to aspartate aminotransferase does react slowly with substrates, as determined by spectrophotometric observations; the monomethyl ester reacts about 20 times less rapidly. Because of the stability of the phosphonate linkage, these compounds may be useful as modifying reagents for various proteins.

The phosphate group of pyridoxal 5′-phosphate (1) is



1, R = $CH_2OPO_3H^-$
5, R = CH_3

necessary for the binding of this coenzyme to the enzymes for which it is essential. Because it is also possible that the phosphate group has a direct function in enzymic catalysis or that it plays an essential structural role in enzymes, the study of analogues of 1 with modified side chains in the 5-position is of interest.[3-8] Additional in-

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