by slow acidification with dilute HCl. The yield of product was 93.8 g (57.4%), mp >300 °C. A mixture of 79.5 g (0.29 mol) of dibenzothiophenedicarboxylic acids, 1000 ml of $SOCl_2$, and 1 ml of pyridine was stirred and refluxed for 16 h. Excess $SOCl_2$ was removed by distillation, the last traces being removed by azeotropic distillation with dry toluene. The crude material was recrystallized from dry toluene to yield 62.3 g (69.7%), mp 194–207 °C.

2,8-Dihydroxybenzothiophene (69). The compound was prepared by the method of Richter and Fuller: mp 274–277 °C (lit.[13] 278–279 °C).

2,6- (and 2,8-) Bis(chloroacetyl)dibenzothiophene (70). A solution of 50.0 g (0.27 mol) of dibenzothiophene and 77.0 g (0.68 mol) of chloroacetyl chloride in 400 ml of CH_2Cl_2 was chilled to −20 °C and 76.5 g (0.572 mol) of $AlCl_3$ was added with rapid stirring. Stirring at room temperature was continued for 16 h and then the reaction was poured onto ice–concentrated HCl. Solvent was removed by boiling. Crude product was filtered and recrystallized from DMF–MeOH. The yield was 72.3 g (37.6%); mp 209–213 °C. Anal. ($C_{16}H_{10}O_2SCl_2$) C, H, Cl.

2,8-Bis(4-chlorobutyryl)dibenzothiophene (71). The procedure used for the preparation of this compound was analogous to that described for the preparation of **70**. Recrystallization of crude product from $CHCl_3$–Me_2CO gave the 2,8 isomer: 57.1 g (53.5%); mp 131–133 °C. Anal. ($C_{20}H_{18}O_2SCl_2$) C, H, Cl.

2,6-Bis(4-chlorobutyryl)dibenzothiophene (72). Repeating the reaction on the same scale and recrystallizing from $CHCl_3$ yielded the 2,6 isomer: 12.1 g (11.4%); mp 147–148.5 °C. Anal. ($C_{20}H_{18}O_2SCl_2$) C, H, Cl.

2,6-Bis(bromoacetyl)dibenzothiophene (73). A solution of 5.0 g (0.019 mol) of 2,8-diacetyldibenzothiophene[14] in 200 ml of $CHCl_3$ was stirred and refluxed while a solution of 6.1 g (0.038 mol) of bromine in 25 ml of $CHCl_3$ was added dropwise. After complete addition, the mixture was stirred and refluxed an additional hour. Upon cooling to room temperature, product was filtered and recrystallized from acetic acid. The yield was 3.2 g (39.5%); mp 187–189 °C dec. Anal. ($C_{16}H_{10}O_2SBr_2$) C, H, Br.

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Antagonists of Slow Reacting Substance of Anaphylaxis. Synthesis of a Series of Chromone-2-carboxylic Acids

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A series of substituted chromone-2-carboxylic acids was synthesized and tested as antagonists of SRS-A induced contractions of isolated guinea pig ileum. This work led to the discovery of sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate (FPL 55712) which is the first reported specific antagonist of SRS-A. Some structural requirements for biological activity within this series are discussed.

It is well established that anaphylaxis in the lung of the guinea pig involves the release of the mediators histamine and slow reacting substance of anaphylaxis (SRS-A).[1] In this species the inhibitory action of antihistamines[2] demonstrates that histamine plays the major role. In man, while both histamine and SRS-A have been shown to be

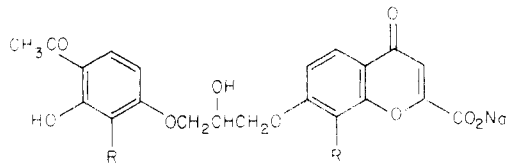
released from isolated sensitized human lung tissue after antigen challenge,[3] antihistamines are of little importance in the clinical treatment of asthma,[4] indicating that histamine does not play a major role.

Furthermore, there is much indirect evidence to indicate that SRS-A does play a role in inducing the bronchospasm of human allergic asthma.[5] The discovery of a specific antagonist of SRS-A would be of considerable value in extending the understanding of the pathophysiological role of this mediator and might well prove to be of therapeutic value.[6]

In an earlier publication we described in detail the selective inhibitory effect of FPL 55712 (**40**) against SRS-A on the guinea pig ileum.[7] This was the first report of a specific antagonist of SRS-A. Subsequently, a series of hydratropic acids was reported as antagonists of SRS-A on guinea pig tracheal chain.[8] These compounds appear, however, to be less specific, particularly with respect to their action against $PGF_{2\alpha}$, and to a lesser degree bradykinin. In this present paper the chemistry and structure–activity studies which led to the synthesis of compound **40** are described.

Discussion

For a number of years, as part of an antiallergy screening program, compounds synthesized in our laboratories were evaluated as potential antagonists of SRS-A induced contractions of isolated guinea pig ileum. By this means compound **38** was discovered. This compound was of considerable interest because when evaluated using a range of agonists (SRS-A, histamine, bradykinin, 5-hydroxytryptamine, $PGF_{2\alpha}$, and PGE_1), it was found to be selective against SRS-A. This observation led to the synthesis of a series of related compounds to investigate the structure–activity requirements for this type of activity.



38, R = allyl
40, R = propyl

Initially we investigated a structurally related, but simplified series of phenoxypolymethyleneoxychromone-2-carboxylic acids in order to delineate the major structural features of compound **38** which were important for activity. Compounds were synthesized to allow the study of (1) the position of the substituent group on the chromone ring, (2) the length of the polyalkylenedioxy chain, (3) the presence of the terminal oxygen atoms in the chain, and (4) the substituents in the phenyl ring.

A comparison of the activities of compounds **2**, **6**, **12**, and **19** and also **3**, **7**, **13**, and **20** (Table I) led to the conclusion that substitution on the 7 position of the chromone ring was to be preferred. However, no definite conclusion could be made relating to the optimum length for the polyalkylenedioxy chain as this appeared to be dependent on the position of substitution. For example, in the 5-substituted series highest activity was seen with a heptamethylenedioxy chain (**4**), while in the 7-substituted series maximum activity was achieved with a pentamethylenedioxy chain (**13**). Terminal oxygen atoms in the chain appeared to have only a marginal effect on activity. This is illustrated by compounds in which the oxygen is omitted or replaced by sulfur, for example, in the series where substitution on the chromone is in the 7 position (**13** and **16–18**). Similarly, in the 6-substituted series, neither replacement of oxygen by a methylene group (**6** and **10**) nor variation of the polymethylene chain length (**8–10**) had any significant effect. As an extension of these studies the effect on activity of the acetyl, hydroxyl, and allyl substituents in the phenoxy ring was evaluated using compound **13** as the parent of the series (Table II). This table also includes some compounds carrying other, closely related substituents. With the exception of **33**, which was prepared at a later time, only one compound (**27**) was appreciably more active than the parent compound (**13**), and therefore it was difficult to draw any general conclusions. However, it was surprising that compound **29** possessing a pentamethylenedioxy chain was less active than compound **38** (Table II), since a comparison of compounds **13** and **34** (Table III) suggests that replacement of a 2-hydroxypropylenedioxy chain by a pentamethylenedioxy chain should result in an enhancement in activity.

Because of this anomalous result, further investigation on the effect of substituents was carried out using direct analogues of compound **38**. A study of the effect of allyl substitution showed that both allyl groups contribute to activity in an additive manner. The greater effect was obtained by allyl substitution in the phenyl ring (**35–38**). Replacement of allyl by propyl not only produced a similar structure–activity pattern but also resulted in an increase in activity (**36** and **39**, **38** and **40**).

Additionally, a related series of compounds which lacked both acetyl and phenolic hydroxyl substituents (**41–43**) was compared with compounds **39**, **40**, and **36**, clearly demonstrating that these two groups made a substantial contribution to activity.

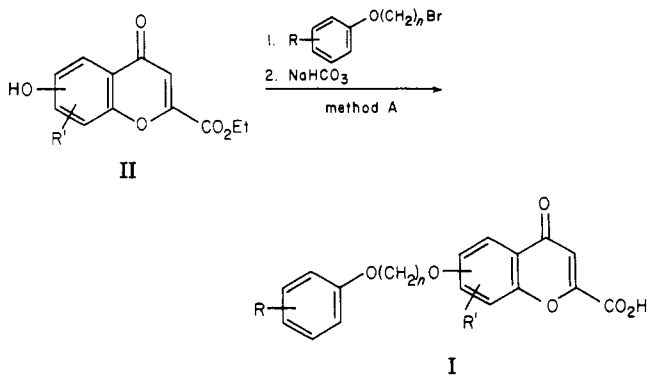
The importance of the substituent groups was also demonstrated by modifying or varying their position of substitution. In all cases this led to a reduction in activity. These changes included propyl substitution in the 6 instead of the 8 position of the chromone ring (**44** and **42**) and replacement of the phenolic hydroxyl group by methoxy or hydrogen (**40**, **45**, and **46**).

These studies gave us a greater understanding of some of the structural features which are important for activity and resulted in the initial activity of compound **38** being increased tenfold by the discovery of compound **40**. One structural modification, mentioned previously, which had given equivocal results involved hydroxylation of the polyalkylenedioxy chain. For this reason compound **33**, the dehydroxy analogue of compound **40**, was synthesized. This analogue (IC_{50} = 0.001 μg/ml) proved to be more active than compound **40**. By this time some in vivo biological studies had been carried out on compound **40**, and a subsequent limited in vivo study on **33** indicated that **33** offered no worthwhile advantage. More extensive biological investigations were therefore continued with compound **40**, and these results have been reported in part.[7]

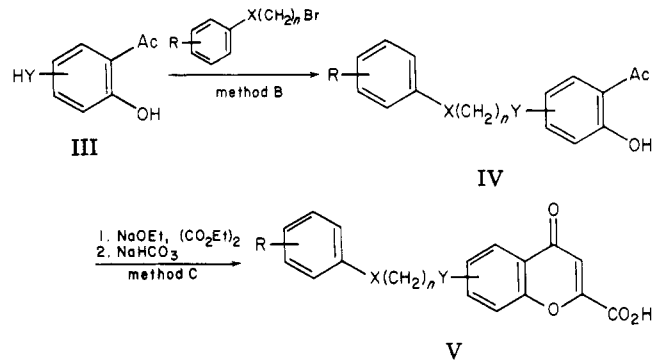
Chemistry. The majority of the chromone-2-carboxylic acids (I) in Tables I and II were prepared by alkylation of a hydroxychromone-2-carboxylate ethyl ester (II) (Table IV) with the appropriate substituted bromoalkane and subsequent hydrolysis (Scheme I, method A).

5-Hydroxychromones are not readily alkylated because of hydrogen bonding of the OH group with the adjacent carbonyl, and so chromones carrying a phenoxyalkoxy substituent in the 5 position (compounds **1–5**) were obtained (Scheme II) by alkylation of the common precursor, 2,6-dihydroxyacetophenone (III, Y = O) (method B), followed by pyrone ring formation (method C). The latter procedure was performed by Claisen condensation of the

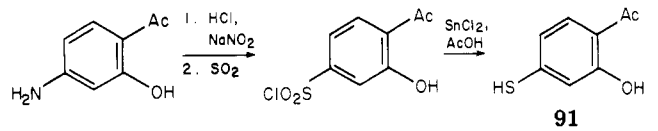
Scheme I



Scheme II



Scheme III



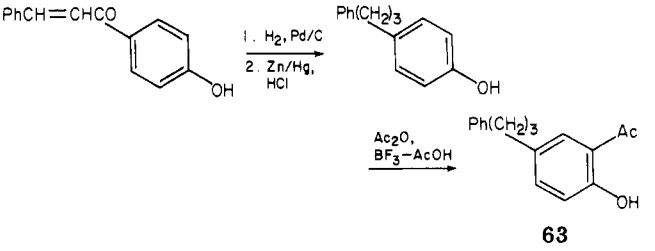
linked acetophenone intermediate (IV, X = Y = O) with diethyl oxalate, cyclization under acid conditions, and finally ester hydrolysis to give the chromonecarboxylic acid (V, X = Y = O).

The sulfur-linked chromones **16** and **17** and the phenylalkylchromones **8** and **9** were obtained similarly from the appropriate 2-hydroxyacetophenones (IV) (Table V) by a Claisen condensation (Scheme II, method C). The 2-hydroxyacetophenone intermediate **61** for compound **16** was prepared by condensation of thiophenol and 4′-(5-bromopentyloxy)-2′-hydroxyacetophenone **75**. The isomeric intermediate **62** for compound **17** was obtained from 5-bromopentyloxybenzene and 2′-hydroxy-4′-mercaptoacetophenone **91**, which was derived (Scheme III) from the diazonium salt of 4-amino-2-hydroxyacetophenone by treatment with SO_2 and reduction of the sulfonyl halide so formed.

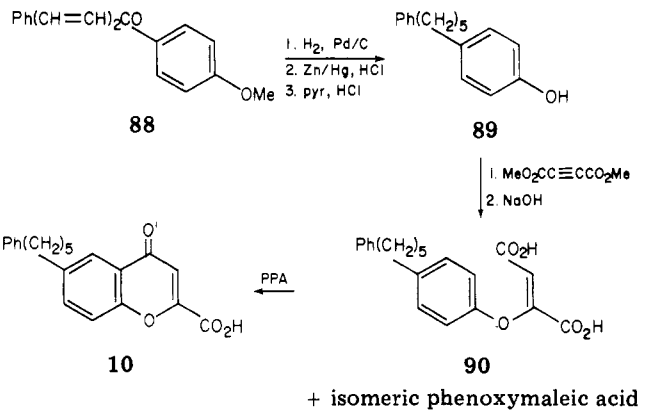
It was found convenient to prepare 4-(3-phenylpropyl)phenol (Scheme IV) by stepwise reduction of (4-hydroxybenzylidene)acetophenone via catalytic hydrogenation and subsequent Clemmensen reduction. Acetylation of this aralkylphenol in the presence of the BF_3–acetic acid complex afforded the 2-hydroxyacetophenone intermediate **63** for compound **9**.

A similar two-step reduction procedure (Scheme V) applied to the chalcone **88** with subsequent demethylation provided the aralkylphenol **89**, which, by modification[9] of the process described by Ruhemann[10] for the formation of chromone-2-carboxylic acids from phenols, was converted to the chromone **10**. After hydrolysis of the Michael addition product, the crude mixture of the phenoxyfumaric acid (**90**) and the isomeric phenoxymaleic acid was treated

Scheme IV

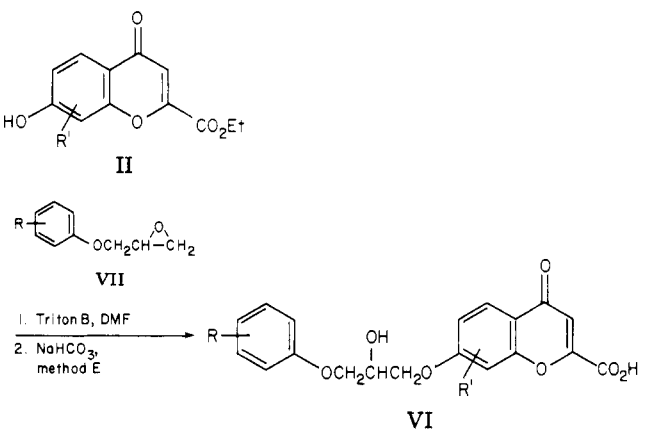


Scheme V



+ isomeric phenoxymaleic acid

Scheme VI



directly with dehydrating agent. Only the fumaric acid cyclized to the chromone acid, which was easily freed from the more water-soluble uncyclized phenoxymaleic acid.

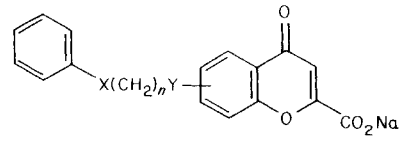
Compound **22** was obtained directly by debenzylation of the ethyl ester of **23** under acid conditions.

The unsubstituted, and substituted, ω-bromoalkoxybenzenes required for the routes in Schemes I and II were either available commercially or prepared conventionally from the appropriate phenol and an α,ω-dibromoalkane (method G, Table VI).

In Scheme VI nucleophilic opening of an epoxide ring by the appropriate hydroxychromone ester II in the presence of benzyltrimethylammonium hydroxide (Triton B) (method E) afforded compounds (VI) (Table III) with a hydroxyl group in the trimethylene linking chain. These conditions failed for compound **45**, so the reaction was effected with potassium *tert*-amyl oxide (method F).

The 2,3-epoxypropyloxy intermediates VII were obtained by condensation of a substituted phenol and epichlorohydrin (method D, Table VII). The required phenols were either commercially available or were prepared by reported procedures. 4-Hydroxy-3-propylacetophenone **92**, the desired precursor of the epoxide **85**, was obtained by catalytic reduction of the allyl analogue.

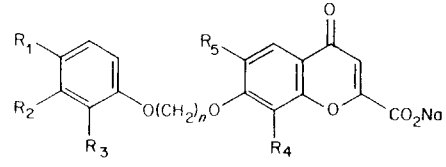
Table I



Compd no.	Substn position in chromone ring	X	n	Y	Anti-SRS-A act., IC_{50}, μg/ml	Method	Mp, °C (ethyl ester[a])	Crystn solvent, ester	Mp, °C (acid)	Formula of acid[a]	Crystn solvent, acid	Yield of acid, %
1	5	O	2	O	100	B, C	137.5-138	EtOH	210-211 dec	$C_{18}H_{14}O_6$	*b*	81[c]
2		O	3	O	35	B, C	108-110	EtOH	172-173	$C_{19}H_{16}O_6$	*b*	77[c]
3		O	5	O	17.5	B, C			120-123	$C_{21}H_{20}O_6$[d]	EtOH-Et_2O	15
4		O	7	O	0.8	B, C			91-93	$C_{23}H_{24}O_6$[e]	EtOH	14
5		O	9	O	6.0	B, C			89-92	$C_{25}H_{28}O_6$	EtOH	33
6	6	O	3	O	3.3	A			186	$C_{19}H_{16}O_6$[d]	EtOH	55
7		O	5	O	3.3	A	120-120.5	EtOH	167-168	$C_{21}H_{20}O_6$	EtOH	46[c]
8			1		6.6	C	124.5-125	EtOAc	219-221.5	$C_{17}H_{12}O_4$	EtOH	79[c]
9			3		3.0	C			157-158	$C_{19}H_{16}O_4$	EtOH	35
10			5		4.5				157-158	$C_{21}H_{20}O_4$	*b*	7
11	7	O	2	O	15	A	119-119.5[f]	EtOH	222.5-223.5	$C_{18}H_{14}O_6$	Dioxane-EtOH	23
12		O	3	O	1.4	A			201-203	$C_{19}H_{16}O_6$	Dioxane-EtOH	75
13		O	5	O	0.4	A	80-81[d]	EtOH	191-192	$C_{21}H_{20}O_6$	EtOH	38[c]
14		O	7	O	1.8	A	64.5-65.5	*g*	167-168	$C_{23}H_{24}O_6$	EtOH	65[c]
15		O	9	O	1.8	A			153-154	$C_{25}H_{28}O_6$	EtOH	42
16		S	5	O	0.4	C			196-197	$C_{21}H_{20}O_5S$[h]	EtOH	47
17		O	5	S	0.3	C			190-191	$C_{21}H_{20}O_5S$[h]	EtOH	40
18		CH_2	4	O	0.6	A			193-194	$C_{21}H_{20}O_5$[e]	$CHCl_3$	28
19	8	O	3	O	50	A			167	$C_{19}H_{16}O_6$	EtOH	16
20		O	5	O	9	A	62	EtOH	145-146	$C_{21}H_{20}O_6$	$CHCl_3$	30[c]

[a] All isolated compounds were analyzed for C and H. [b] Compound was obtained analytically pure from acidification of hydrolysis reaction. [c] Yield of ester. [d] Analysis for $0.5H_2O$. [e] Analysis for $1H_2O$. [f] Obtained by esterification of acid. [g] Purified by chromatography on silica using Et_2O-petroleum ether (3:1) as eluent. [h] Analysis for C, H, and S.

Table II

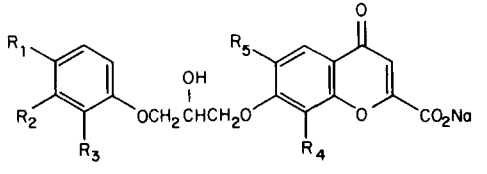


Compd no.	R_1	R_2	R_3	R_4	R_5	n	Anti-SRS-A act., IC_{50}, μg/ml	Method; precursors	Mp, °C (ethyl ester[a])	Crystn solvent, ester	Mp, °C (acid)	Formula of acid[a]	Crystn solvent, acid	Yield of acid, %

13	H	H	H	H	H	5	0.43							
21	Allyl	HO	Ac	H	H	5	0.9	A; 50, 68			159-160	$C_{26}H_{26}O_8$	EtOH	50
22	H	HO	H	H	H	5	1.5	*b*			186-188	$C_{21}H_{20}O_7$	*c*	40
23	H	$PhCH_2O$	H	H	H	5	1.0	A; 50, 69	69-70[d]	*e*	152-153	$C_{28}H_{26}O_7$	*c*	72[f]
24	H	MeO	H	H	H	5	1.5	A; 50, 70	86-88	EtOH	155-157	$C_{22}H_{22}O_7$	Dioxane	49[f]
25	Ac	H	H	H	H	5	3.5	A; 50, 71	141-142	EtOH	219-221	$C_{23}H_{22}O_7$	Dioxane	32[f]
26	AcNH	H	H	Allyl	H	5	3.9	A; 52, 72			126-128	$C_{26}H_{27}NO_7$[g]	EtOH	64
27	H	HO	Ac	Allyl	H	5	0.05	A; 52, 73			171-174	$C_{26}H_{26}O_8$	*c*	56
28	Ac	H	H	Allyl	H	5	2.4	A; 52, 71			201-203	$C_{26}H_{26}O_7$	*c*	85
29	Ac	HO	Allyl	Allyl	H	5	1.23	A; 52, 74	104-105	EtOH	196-197	$C_{29}H_{30}O_8$	Dioxane-EtOH	60[f]
30	Ac	HO	H	H	H	5	6.8	A; 50, 75	136-137	EtOH	226-228	$C_{23}H_{22}O_8$	Dioxane-EtOH	75[f]
31	H	H	*n*-Pr	*n*-Pr	H	3	0.18	A; 53, 76			162-163	$C_{25}H_{28}O_6$	Benzene	20
32	H	H	*n*-Pr	H	*n*-Pr	3	18.0	A; 54, 76			138-139	$C_{25}H_{28}O_6$	EtOAc-petr ether	22
33	Ac	HO	*n*-Pr	*n*-Pr	H	3	0.001	A; 53, 77	113-114	EtOH	173-174	$C_{27}H_{30}O_8$	EtOAc	65[f]

[a] See footnote *a*, Table I. [b] From ester of **23**. [c] See footnote *b*, Table I. [d] Obtained by esterification of acid. [e] See footnote *g*, Table I. [f] Yield of ester. [g] Analysis for $0.5H_2O$ (C, H, N).

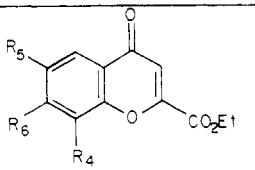
Table III



Compd no.	R_1	R_2	R_3	R_4	R_5	Anti-SRS-A act., IC_{50}, μg/ml	Method; precursors	Mp, °C (ethyl ester[a])	Crystn solvent, ester	Mp, °C (acid)	Formula of acid[a]	Crystn solvent, acid	Yield of acid, %
34	H	H	H	H	H	7.0	E; 50, 78			237-238[b]	$C_{19}H_{16}O_7$	EtOH	15
35	Ac	OH	H	H	H	28	E; 50, 79			251-252	$C_{21}H_{18}O_9$[c]	Dioxane-EtOH	36
36	Ac	OH	Allyl	H	H	0.1	E; 50, 80	175-176	EtOH	120-125 dec	$C_{24}H_{22}O_9$[d]	EtOH	25[e]
37	Ac	OH	H	Allyl	H	3.3	E; 52, 79			205[f]	$C_{24}H_{22}O_9$[c]	EtOH-H_2O	18
38	Ac	OH	Allyl	Allyl	H	0.05	E; 52, 80			235 dec	$C_{27}H_{26}O_9$[c,g]	Benzene	18
39	Ac	OH	*n*-Pr	H	H	0.08	E; 50, 81	177-178	EtOH	194-195	$C_{24}H_{24}O_9$[c]	EtOH	27[e]
40	Ac	OH	*n*-Pr	*n*-Pr	H	0.005	E; 53, 81	121-123[h]	Benzene-petr ether	204	$C_{27}H_{30}O_9$[i]	*j*	24
41	H	H	*n*-Pr	H	H	2.0	E; 50, 82	122-123	EtOH	174-175	$C_{22}H_{22}O_7$	EtOH	36[e]
42	H	H	*n*-Pr	*n*-Pr	H	0.044	E; 53, 82			129-130	$C_{25}H_{28}O_7$	Et_2O	20
43	H	H	Allyl	H	H	1.8	E; 50, 83			181-183	$C_{22}H_{20}O_7$	EtOH	25
44	H	H	*n*-Pr	H	*n*-Pr	1.6	E; 54, 82			215-216	$C_{25}H_{28}O_7$	EtOH-H_2O	34
45	Ac	MeO	*n*-Pr	*n*-Pr	H	45	F; 53, 84				$C_{28}H_{32}O_9$[k]		3[l]
46	Ac	H	*n*-Pr	*n*-Pr	H	0.15	E; 53, 85			78	$C_{27}H_{30}O_8$[c]	CCl_4-MeOH	20
47	H	$PhCH_2O$	*n*-Pr	*n*-Pr	H	1	E; 53, 86			92-93	$C_{32}H_{34}O_8$[d]	*j*	14
48	H	OH	Ac	*n*-Pr	H	0.3	E; 53, 87			200-201	$C_{24}H_{24}O_9$[c]	EtOH	15

[a] See footnote *a*, Table I. [b] Lit. mp 222-223 °C: Belgian Patent 793 969 (1973). [c] Analysis for $0.5H_2O$. [d] Analysis for $1.5H_2O$. [e] Yield of ester. [f] Indefinite. [g] C: calcd, 64.3; found, 63.7. [h] Obtained by esterification of acid (EtOH-HCl). [i] Analysis for H_2O. [j] See footnote *b*, Table I. [k] Analysis on Na salt for $3H_2O$. [l] Yield of Na salt.

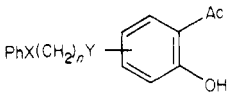
Table IV. Intermediate Hydroxychromone Esters



Compd no.	R_4	R_6	R_5	Mp, °C	Formula	Rxn solvent	Yield, %	Analyses
49	H	H	HO	209-211[a]	$C_{12}H_{10}O_5$	EtOH	59	
50	H	HO	H	224-225[b]	$C_{12}H_{10}O_5$	EtOH	53	
51	HO	H	H	200-201	$C_{12}H_{10}O_5$	EtOH	23	C, H
52	Allyl	HO	H	165-166	$C_{15}H_{14}O_5$	EtOH	44	H; C[c]
53	Pr	HO	H	166-167	$C_{15}H_{16}O_5$	EtOAc-petr ether	48	C, H
54	H	HO	Pr	185-186	$C_{15}H_{16}O_5$	EtOH	60	C, H

[a] Lit.[11] mp 208-209 °C. [b] Lit.[12] mp 219-221 °C. [c] C: calcd, 65.7; found, 65.15.

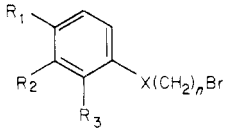
Table V. 2-Hydroxyacetophenones



Compd no.	X	n	Y	Position of substn	Mp, °C	Formula	Analyses
55	O	2	O	6	79-80[a]	$C_{16}H_{16}O_4$	C, H
56	O	3	O	6	*b*	$C_{17}H_{18}O_4$	
57	O	5	O	6	*b*	$C_{19}H_{22}O_4$	
58	O	7	O	6	*b*	$C_{21}H_{26}O_4$	
59	O	9	O	6	*b*	$C_{23}H_{30}O_4$	
60		1		5	55-56[c,d]	$C_{15}H_{14}O_2$	C, H
61	S	5	O	4	44-45	$C_{19}H_{22}O_3S$	C, H, S
62	O	5	S	4	75-76	$C_{19}H_{22}O_3S$	C, H, S
63		3		5	*b*	$C_{17}H_{18}O_2$	

[a] Crystallized from Et_2O. [b] Obtained as an oil; not purified further. [c] Crystallized from EtOH. [d] Lit.[17] mp 56 °C.

Table VI. ω-Bromoalkoxybenzenes



Compd no.	R_1	R_2	R_3	X	n	Mp or bp (mm), °C	Formula	Analyses
64	H	H	H	O	5	100-110 (0.1)[a]	$C_{11}H_{15}BrO$	
65	H	H	H	O	7	130-135 (0.3)[b]	$C_{13}H_{19}BrO$	
66	H	H	H	O	9	137-140 (0.5)	$C_{15}H_{23}BrO$	
67	H	H	H	CH_2	4	142-148 (16)[c]	$C_{11}H_{15}Br$	
68	Allyl	HO	Ac	O	5	180-200 (0.1)[d]	$C_{16}H_{21}BrO_3$	
69	H	$PhCH_2O$	H	O	5	*e*	$C_{18}H_{21}BrO_2$	
70	H	MeO	H	O	5	140-150 (0.1)	$C_{12}H_{17}BrO_2$	C, H
71	Ac	H	H	O	5	165-180 (0.4)	$C_{13}H_{17}BrO_2$	C, H
72	AcNH	H	H	O	5	113-115[f]	$C_{13}H_{18}BrNO_2$	
73	H	HO	Ac	O	5	35-36	$C_{13}H_{17}BrO_3$	C, H
74	Ac	HO	Allyl	O	5	*e, g*	$C_{16}H_{21}BrO_3$	
75	Ac	HO	H	O	5	64-66	$C_{13}H_{17}BrO_3$	C, H
76	H	H	*n*-Pr	O	3	118-120 (1.8)[h]	$C_{12}H_{17}BrO$	
77	Ac	HO	*n*-Pr	O	3	172-180 (0.02)[g]	$C_{16}H_{23}BrO_3$	

[a] Belgian Patent 830 519; *Chem. Abstr.*, **54**, 18567*h* (1960). [b] L. Peyron and J. Peyron, *Bull. Soc. Chim. Fr.*, 1062 (1950). [c] E. R. Lynch and E. B. McCall, *J. Chem. Soc.*, 1254 (1960). [d] Phenol precursor: French Patent 1 533 506 (1968); *Chem. Abstr.*, 71, 101 709 (1969). [e] Obtained as an oil; not purified further. [f] Crystallized from EtOH. [g] Phenol precursor; see ref 12. [h] Phenol precursor: L. H. Farinholdt, W. C. Harden, and D. Twiss, *J. Am. Chem. Soc.*, **55**, 3386 (1933).

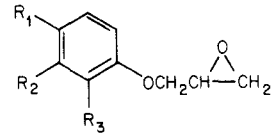
Monobenzylation of 2-propylresorcinol gave 3-benzyloxy-2-propylphenol (**93**), which was required for the epoxide **86**. The epoxide **84** was obtained directly by methylation of the epoxide **81**.

The necessary hydroxychromone esters II (Table IV) were synthesized conventionally by the Claisen condensation of the appropriate dihydroxyacetophenone and diethyl oxalate (method H). Ethyl 6-hydroxychromone-2-carboxylate (**49**) and the 7-hydroxy isomer **50** have been described previously.[11,12]

Experimental Section

Chemistry. Melting points are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical

Table VII. 2,3-Epoxypropyloxybenzenes



Compd no.	R_1	R_2	R_3	Mp or bp (mm), °C	Formula	Analyses
78	H	H	H	80-83 (1.5)	$C_9H_{10}O_2$	
79	Ac	HO	H	72-73[a,b]	$C_{11}H_{12}O_4$	
80	Ac	HO	Allyl	67.5-68.5[c]	$C_{14}H_{16}O_4$	C, H
81	Ac	HO	*n*-Pr	54-55[c]	$C_{14}H_{18}O_4$	C, H
82	H	H	*n*-Pr	146-148 (15)	$C_{12}H_{16}O_2$	C, H
83	H	H	Allyl	155-157 (15)[d]	$C_{12}H_{14}O_2$	
84	Ac	MeO	*n*-Pr	148-156 (0.15)	$C_{15}H_{20}O_4$	C, H
85	Ac	H	*n*-Pr	155-165 (0.03)	$C_{14}H_{18}O_3$	
86	H	$PhCH_2O$	*n*-Pr	*e*	$C_{19}H_{22}O_3$	
87	H	HO	Ac	61-63[f]	$C_{11}H_{12}O_4$	C, H

[a] Crystallized from Et_2O. [b] Lit. mp 78 °C: D. R. Nadkarni and T. S. Wheeler, *J. Chem. Soc.*, 589 (1936). [c] Crystallized from petroleum ether (bp 40-60 °C). [d] Lit. bp 99-100 °C (0.6 mm): V. Petrow, O. Stephenson, A. J. Thomas, and A. M. Wild, *J. Pharm. Pharmacol.*, **10**, 86 (1958). [e] Isolated as an oil after chromatography on silica gel ($CHCl_3$-petroleum ether, 1:1). [f] Crystallized from EtOH.

results obtained for those elements were within ±0.4% of the theoretical values. ^1H NMR spectra were recorded in either Me_2SO-d_6 or $CDCl_3$ with Me_4Si as internal reference on a Perkin-Elmer R12 spectrometer. IR spectra (KBr disks) were obtained on a Perkin-Elmer 457 grating spectrophotometer, and a Perkin-Elmer 402 spectrophotometer was used for UV spectra (in EtOH). Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6 spectrometer. All spectra were consistent with the assigned structures.

The chromone acids were tested (see Biological Test Procedure) as their sodium salts. These were prepared by dissolving the acid and an equivalent of $NaHCO_3$ in distilled water and freeze-drying the resultant solution.

Method A. 7-[5-(4-Acetyl-3-hydroxyphenoxy)pentyloxy]-4-oxo-4*H*-1-benzopyran-2-carboxylic Acid (30). A mixture of the bromopentyloxyacetophenone **75** (3.01 g, 0.01 mol), ethyl 7-hydroxychromone ester **50** (2.34 g, 0.01 mol), anhydrous K_2CO_3 (1.38 g, 0.01 mol), KI (0.5 g), and Me_2CO (200 ml) was stirred and refluxed for 24 h and then filtered while hot. Evaporation of the filtrate gave an oil, which was taken into EtOAc and washed with 2% NaOH and water, dried, and evaporated to an oil. Trituration with Et_2O gave a solid which crystallized from EtOH to afford the ethyl ester of **30** (3.3 g). The ester (2.0 g), $NaHCO_3$ (2 g), and H_2O (10 ml) in EtOH (100 ml) were heated for 1 h. The solution was diluted with H_2O and acidified to give a solid, which crystallized from EtOH–dioxane to yield **30** (1.6 g, 85% yield).

The ethyl esters of compounds **6**, **12**, **15**, **18**, **19**, **21**, **26–28**, **31**, and **32** were not obtained as solids and were hydrolyzed directly to the acids.

Method B. 2′-Hydroxy-6′-(2-phenoxyethoxy)acetophenone (55). A mixture of 2′,6′-dihydroxyacetophenone (11.6 g, 0.082 mol), 2-bromoethoxybenzene (15.5 g, 0.077 mol), and anhydrous K_2CO_3 (5.3 g, 0.038 mol) in dry Me_2CO (150 ml) was refluxed for 72 h. The solution was cooled and filtered, and the filtrate was evaporated. The residue was dissolved in EtOAc and washed with 5% NaOH solution and water, dried, and evaporated to leave a residue. The residue was extracted with boiling Et_2O, from which compound **55** (7.2 g, 34% yield) crystallized on cooling.

Method C. 4-Oxo-5-(2-phenoxyethoxy)-4*H*-1-benzopyran-2-carboxylic Acid (1). A solution of the acetophenone **55** (5.0 g, 0.018 mol) in diethyl oxalate (15 ml, 0.11 mol) and Et_2O (50 ml) was added to a solution of NaOEt [prepared from Na (1.5 g, 0.065 g-atom) and 20 ml of EtOH]. The mixture was refluxed for 4 h, cooled, and diluted with Et_2O. The sodium salt of the β-diketone intermediate was filtered off, dissolved in water, and acidified to give an orange solid which was refluxed with ethanol (30 ml) containing concentrated HCl (1 ml) for 20 min. On cooling needles were obtained, which were crystallized from EtOH to yield the ethyl ester of compound **1** (5.2 g). The crude β-diketone intermediates of the remainder of the compounds prepared by this method were isolated by pouring the cooled reaction mixture into a mixture of chloroform and dilute HCl. Evaporation of the chloroform gave the crude β-diketone, which was then cyclized to the chromone ester as described.

The ethyl ester of compound **1** was hydrolyzed as described in method A. Acidification of the aqueous alkaline solution gave the acid **1** (95%).

Method D. 4′-(2,3-Epoxy)propoxy-2′-hydroxy-3′-propylacetophenone (81). A solution of KOH (33.6 g, 0.6 mol) dissolved in EtOH (150 ml) containing H_2O (3 ml) was added dropwise over 15 min to a stirred refluxing mixture of 2′,4′-dihydroxy-3′-propylacetophenone[13] (108 g, 0.56 mol) and epichlorohydrin (131 ml, 1.68 mol) in EtOH (90 ml). The mixture was refluxed for 1.5 h, cooled, diluted with H_2O, and extracted with Et_2O. Evaporation of the Et_2O gave an oil which was distilled at 170–175 °C (0.5 mm). The distillate solidified and was crystallized from petroleum ether (bp 40–60 °C) to afford **81** (81 g, 64% yield).

The remaining epoxides of Table VII were mostly obtained as oils and distilled before use. Purity was checked by NMR and TLC or GC.

Method E. 7-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic Acid (40). A mixture of the epoxide **81** (27.5 g, 0.11 mol), the ethyl chromone-2-carboxylate **53** (27.6 g, 0.10 mol), and DMF (150 ml) containing Triton B (5 drops) was refluxed for 4 h and then evaporated to an oil, which was taken into EtOAc and washed with 2% NaOH and water. The organic phase was dried and evaporated to afford the ester product as an oil. The oil was hydrolyzed with $NaHCO_3$ in aqueous EtOH as in method A. The acid product was obtained as an oil, which was purified by dissolving in an excess of a hot saturated solution of $NaHCO_3$. On cooling the sodium salt was deposited as an oil, which was isolated by decantation and then triturated with ice-cold H_2O to afford a solid. This was dissolved in hot water and acidified to give the acid **40** (13.0 g).

Only the ethyl esters of **36**, **39**, and **41** could be obtained directly from the condensation reaction as solids and subsequently characterized. The crude oily esters of the remainder of the compounds of Table III were hydrolyzed directly to the corresponding acids.

Method F. 7-[3-(4-Acetyl-3-methoxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic Acid (45). The chromone ester **53** (3.31 g, 0.012 mol) was added to a stirred, refluxing solution of K (0.476 g, 0.012 g-atom) in $EtMe_2COH$ (90 ml) to give a yellow suspension. The epoxide **84** (3.24 g, 0.012 mol) in $EtMe_2COH$ (90 ml) was added, and the mixture was stirred and refluxed for 5 days. The mixture was poured into water, acidified, and extracted with Et_2O, which gave a gum on evaporation. Chromatography on silica gel with Et_2O furnished the ethyl ester of **45** as a gum, which was hydrolyzed as described in method A to give the acid **45** also as a

gum. Both products were homogeneous on TLC and displayed NMR and mass spectra consistent with their assigned structures. The acid was neutralized with aqueous $NaHCO_3$ and freeze-dried to give the hygroscopic Na salt of **45** (0.20 g).

Method G. 4′-(5-Bromopentyloxy)-2′-hydroxyacetophenone (75). To a refluxing mixture of 1,5-dibromopentane (34 g, 0.14 mol), K_2CO_3 (19.2 g, 0.14 mol), and KI (0.5 g) in Me_2CO (250 ml) was added dropwise a solution of resacetophenone (20 g, 0.13 mol) in 100 ml of Me_2CO. The reaction was heated at reflux for 14 h. The mixture was filtered while hot and the solvent was removed to leave an oil, which was dissolved in Et_2O and washed with dilute NaOH. The Et_2O was removed to leave a solid which was chromatographed on silica gel with Et_2O as eluent to yield **75** (13.6 g, 34% yield).

Many of the ω-bromoalkoxyaryl intermediates were obtained as oils which were mostly distilled before use. Purity was checked by NMR and TLC or GC.

Method H. Ethyl 7-Hydroxy-8-propyl-4-oxo-4*H*-1-benzopyran-2-carboxylate (53). To a stirred solution of NaOEt (1.6 mol), prepared from Na (36.8 g) and ethanol (500 ml), was added slowly a solution of diethyl oxalate (122 ml), 2′,4′-dihydroxy-3′-propylacetophenone (78.0 g, 0.40 mol), EtOH (100 ml), and dry Et_2O (100 ml). The mixture was refluxed for 3 h, cooled, poured into an excess of dilute HCl, and extracted with ether. Evaporation furnished an oil, which was heated in EtOH (300 ml) containing concentrated HCl (5 ml) for 45 min, evaporated to small volume, and partitioned between EtOAc and H_2O. The organic layer was washed with $NaHCO_3$ solution and H_2O, dried, and evaporated to a solid which crystallized from EtOAc–petroleum ether (bp 60–80 °C) to give **53** (51 g).

4-Oxo-6-(5-phenylpentyl)-4*H*-1-benzopyran-2-carboxylic Acid (10). A mixture of **89** (14.9 g, 0.062 mol), dimethyl acetylenedicarboxylate (8.7 g, 0.062 mol), and 5 drops of a solution of benzyltrimethylammonium hydroxide (40% w/w in H_2O) in dioxane (50 ml) was heated at 100 °C for 30 min. To this solution of the Michael addition products was added 20% NaOH (40 ml). The mixture was refluxed for 30 min, diluted with H_2O, and acidified to give a pale green solid (16.5 g). The crude mixture containing the phenoxyfumaric acid (**90**) was heated at 115 °C with PPA (180 g) for 3 h and poured into H_2O to give a solid, which was treated with hot water. The remaining solid was esterified (EtOH–0.5 ml of concentrated H_2SO_4) and chromatographed on silica gel with ether–petroleum ether (bp 40–60 °C) (1:1), and the pure oily ester was hydrolyzed as in method A to give **10** (1.5 g).

7-[5-(3-Hydroxyphenoxy)pentyloxy]-4-oxo-4*H*-1-benzopyran-2-carboxylic Acid (22). Ethyl 7-[5-(3-benzyloxyphenoxy)pentyloxy]-4-oxo-4*H*-1-benzopyran-2-carboxylate, the ethyl ester of compound **23** (2.0 g, 0.004 mol), was heated at 100 °C for 30 min in 30 ml of a solution of 30% HCl in AcOH. The solution was flooded with water to give a mixture of product ester and carboxylic acid as an oily solid. The mixture was esterified with EtOH and a trace of concentrated H_2SO_4. Chromatography ($CHCl_3$ on silica gel) gave an oil which was heated with $NaHCO_3$ in aqueous EtOH. Acidification gave the acid **22** (0.7 g).

2′-Hydroxy-4′-mercaptoacetophenone (91). 2-Acetyl-5-aminophenol[14] (46 g, 0.4 mol) was suspended in concentrated HCl (160 ml) and stirred at 0 °C. A solution of $NaNO_2$ (23.6 g, 0.34 mol) in water (40 ml) was added at a rate sufficient to maintain the temperature below 3 °C to give a pale brown solution of the diazonium salt. The diazonium salt solution was added during 5 min to a stirred solution of glacial acetic acid (200 ml), liquid SO_2 (90 ml), and a saturated aqueous solution containing $CaCl_2$ (12.4 g).[15] The mixture was stirred until nitrogen ceased to be evolved and water (1 l.) was added. The product was extracted with $CHCl_3$ (3 × 100 ml), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated giving crude 2-acetyl-5-chlorosulfonylphenol as an orange solid. This was dissolved in glacial acetic acid (100 ml) and added with stirring to a suspension of $SnCl_2$ (320 g, 1.69 mol) in glacial acetic acid (1.2 l.), previously saturated with HCl gas, to give a white precipitate. After 30 min the mixture was added to concentrated HCl (1.2 l.) and crushed ice (2 l.). The solid was filtered off, washed with H_2O, and dried in vacuo to yield **91** (32.4 g, 63% yield), mp 60–62 °C. Anal. ($C_8H_8O_2S$) C, H, S.

2′-Hydroxy-4′-(5-phenoxypentylthio)acetophenone (62). A mixture of **91** (9.0 g, 0.054 mol), 5-bromopentyloxybenzene (**64**) (13.3 g, 0.055 mol), anhydrous K_2CO_3 (17.6 g, 0.055 mol), and KI (0.5 g) in dry acetone (300 ml) was refluxed for 4 h. The mixture was filtered and the filtrate was evaporated. The residue was crystallized from EtOH to give **62** (14.3 g, 87% yield). Similarly, **75** and thiophenol gave **61** (58% yield).

2′-Hydroxy-5′-(3-phenylpropyl)acetophenone (63). 1-(4-Hydroxyphenyl)-3-phenylprop-2-enone was reduced with H_2 at 3.25 kg/cm^2 in the presence of 5% Pd/C[16] and then with zinc amalgam and concentrated HCl[17] to give 4-(3-phenylpropyl)-phenol, bp 206–210 °C (**15**).

A mixture of the phenol (15.9 g, 0.075 mol), acetic anhydride (7.7 g, 0.075 mol), and BF_3–AcOH complex (40%, 60 ml) was heated at 100 °C for 2 h, poured onto ice and dilute HCl, and extracted with $CHCl_3$. The organic phase was washed with 5% NaOH solution, dried, and evaporated. The residue was chromatographed on silica gel with $CHCl_3$–petroleum ether (bp 40–60 °C) (1:1) as eluent to yield **63** as an oil, which was homogeneous on TLC and gave satisfactory NMR and MS spectral data.

4′-(2,3-Epoxypropyloxy)-2′-methoxy-3′-propylacetophenone (84). The epoxide **81** (5.0 g, 0.02 mol) in HMPT (70 ml) was added slowly to a stirred suspension of NaH (0.48 g, 0.02 mol) in HMPT (30 ml) at 0 °C under N_2. After 10 min, MeI (3.9 g, 0.027 mol) was added dropwise, and the mixture was stirred at 0 °C for 2 h. The mixture was poured onto ice–dilute HCl and extracted with Et_2O, which was washed with water, dried, and evaporated to an oil. Distillation gave **84** as a clear oil (3.2 g, 62% yield).

4-(5-Phenylpentyl)phenol (89). A solution of 1-(4-methoxyphenyl)-5-phenylpenta-2,4-dienone[18] (**88**) (10.6 g, 0.04 mol) in EtOAc (250 ml) was reduced in a H_2 atmosphere at 3.25 kg/cm^2 in the presence of 5% Pd/C (0.2 g). When no further uptake occurred, the solution was filtered and evaporated to an oil. The oil was distilled at 220–222 °C (1.0 mm) to afford 1-(4-methoxyphenyl)-5-phenylpentanone (10 g), which later solidified: mp 52–54 °C. This ketone (32.2 g, 0.12 mol) was heated under reflux for 12 h with amalgamated zinc (150 g, 2.4 mol), concentrated HCl (200 ml), and EtOH (200 ml). The mixture was poured into water and extracted with Et_2O which was dried and evaporated to an oil. Distillation at 155–160 °C (0.25 mm) gave 4-(5-phenylpentyl)anisole (19 g) [lit.[19] bp 138–140 °C (0.03 mm)].

A mixture of the anisole (13 g, 0.051 mol) and pyridine hydrochloride was heated at 230 °C for 24 h, cooled, poured into H_2O, and extracted with Et_2O, which was evaporated. Chromatography of the residue on silica gel with Et_2O–petroleum ether (bp 40–60 °C) (1:1) gave 4-(5-phenylpentyl)phenol (**89**, 12 g) as an oil, which was a single product on TLC. MS and NMR spectra were as expected for the compound.

4′-Hydroxy-3′-propylacetophenone (92). 3′-Allyl-4′-hydroxyacetophenone[13] (23.0 g, 0.13 mol) in EtOH (250 ml) was hydrogenated at 3.25 kg/cm^2 in the presence of 5% Pd/C (0.5 g) for 3 h. The mixture was filtered and evaporated. The residue was crystallized from aqueous ethanol to give **92** (21 g, 90%), mp 90–91°. Anal. ($C_{11}H_{14}O_2$) C, H.

3-Benzyloxy-2-propylphenol (93). 2-Propylresorcinol[14] (3.04 g, 0.02 mol), benzyl chloride (2.5 g, 0.02 mol), K_2CO_3 (2.8 g, 0.02 mol), and KI (0.01 g) in Me_2CO (100 ml) were refluxed for 72 h. The mixture was evaporated, treated with H_2O, and extracted with Et_2O, which was washed with 10% Na_2CO_3 solution and H_2O, dried, and evaporated to an oil. The oil was distilled at 145–150 °C (air bath) (0.1 mm) to give **93** (0.5 g, 12% yield) as a solid, mp 50–52 °C. Anal. ($C_{16}H_{18}O_2$) C, H.

Biological Test Procedure. An isolated section of the terminal portion of a guinea pig ileum was suspended in a 2-ml organ bath in Tyrode solution which contained atropine sulfate (10^{-6} M) and mepyramine maleate (10^{-6} M). Atropine sulfate was included to reduce the spontaneous activity of the ileum preparation. Mepyramine maleate was included to eliminate the contractile effects of histamine which was known to be present in the lung supernatant used as the source of unpurified SRS-A in these experiments.

The composition of the Tyrode solution in grams per liter of distilled water was NaCl 8.0, KCl 0.2, $CaCl_2$ 0.2, $MgCl_2$ 0.1, $NaHCO_3$ 1.0, $NaH_2PO_4 \cdot 2H_2O$ 0.05, and dextrose 1.0. The tension on the ileum was approximately 600 mg and the bathing temperature 37 °C.

Unpurified guinea pig SRS-A was prepared as previously described[7] and a dose was selected which produced similar repetitive submaximal contractions of the ileum. Each contraction was recorded for 90 s; then the tissue was washed several times to allow complete relaxation. Five minutes was allowed between successive doses of SRS-A. The compound under test was added to the organ bath 30 s before a dose of SRS-A and was present during the induced contraction. Three concentrations of the test compound were chosen which gave inhibitory effects ranging between 10 and 90%. The concentration of compound which would inhibit the ileum contraction due to SRS-A by 50% (IC_{50}) was calculated from the log dose–response graphs. One operator was responsible for all the experimental results reported in this paper. The reproducibility of IC_{50} values in this test system can be assessed by reference to a standard compound FPL 55712[7] which gave an IC_{50} of 0.005 ± 0.001 (mean standard error) μg/ml in six experiments.

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Synthesis and Central Nervous System Activity of Quinazolones Related to 2-Methyl-3-(*o*-tolyl)-4(3*H*)-quinazolone (Methaqualone)

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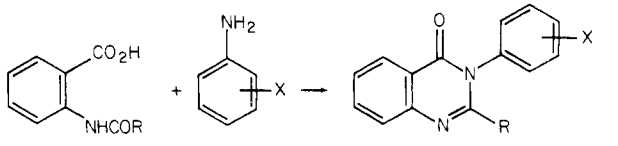
A number of derivatives of 2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolone bearing new substituents on the 2-methyl group have been synthesized. It was established that most substitutions at this position reduce or remove the CNS depressant activity of methaqualone. From the series prepared only the 2-fluoromethyl derivative or certain isothiouronium salts, which could be hydrolyzed in vivo to the 2-mercaptomethyl derivative, showed activity of the same magnitude as methaqualone.

Considerable interest in the pharmacological activity of quinazolones was generated by the observation that febrifugine, the antimalarial principal in an ancient Chinese herbal remedy, was a derivative of 4-quinazolone.[1] Subsequently, the quinazolones have been shown to possess, inter alia, CNS depressant,[2] diuretic,[3] antihypertensive,[4] antiinflammatory,[5] and bronchodilator activity.[6,7] While investigating simple derivatives of febrifugine, Gujral and his co-workers[2] discovered the potent CNS depressant properties of 2-methyl-3-(*o*-tolyl)-4-(3*H*)-quinazolone (methaqualone, Ia), a product which has achieved significant clinical use as a hypnotic agent.[8-10] Our interest in methaqualone (Ia) led us to synthesize some novel derivatives in an attempt to prepare improved hypnotics and the results are reported here. At the commencement of this work such derivatives were unknown, although Japanese[11] and Russian[12] workers have subsequently prepared some of the compounds described.

Chemistry. The 2-alkyl-3-arylquinazolones I were prepared as shown in Scheme I via the $POCl_3$ catalyzed condensation of acetyl anthranilates IIa with the appropriate arylamine.[13]

Bromination of Ia gives a variety of products, the precise nature of which depends on the experimental conditions (Scheme II). The reaction with bromine in glacial acetic acid gives a mixture of products from which the major

Scheme I



IIa, R = CH_3
b, R = CH_2Cl

Ia, R = CH_3; X = *o*-CH_3
e, R = CH_2Cl; X = *o*-CH_3

product, 2-bromomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolone (Ib), can be isolated by crystallization. Alternatively, reaction of Ia with bromine in dimethyl sulfoxide solution results in an exothermic reaction and the 2-dibromomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolone (Ic) can be readily isolated. It has recently been reported[14] that bromination of Ia using *N*-bromosuccinimide in CCl_4 results in reaction at the methyl group of the *o*-tolyl ring to give 3-(*o*-bromomethylphenyl)-2-methyl-3(4*H*)-quinazolone (Id). The product Ib was the key compound for further synthetic work and formed the basis of our preferred approach in contrast to that of the Russian workers[12] who used the chloro analogue Ie, synthesized from chloroacetyl anthranilate IIb. The bromine atom of Ib could be readily displaced by nitrogen, oxygen, and sulfur nucleophiles (Scheme III). The compounds prepared by these reactions are listed in Tables I–VI. Amines, alkoxides, and thiols