Antiviral Activity of Some β-Diketones. 2. Aryloxy Alkyl Diketones. In Vitro Activity against Both RNA and DNA Viruses[1]

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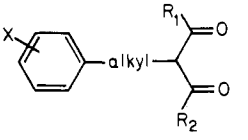
A series of aryloxy alkyl diketones II was synthesized and screened in vitro for antiviral activity. The effect of various substituents on the phenyl ring, as well as the length of the alkyl bridge, was examined to establish the requirements for optimum activity. One of the most active members of the series, 4-[6-(2-chloro-4-methoxy)phenoxy]hexyl-3,5-heptanedione (**56**), exhibited a high level of activity against both DNA and RNA viruses in both the tissue culture and organ culture screens and was particularly effective against herpesvirus types 1 and 2.

In our previous paper,[2] we reported that a series of aryl alkyl diketones I had exhibited a wide range of antiviral activity in vitro against both RNA and DNA viruses. As

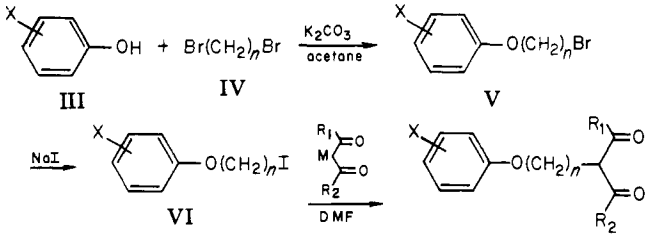


I

an extension of this work, a related series of compounds, II, was synthesized and evaluated for antiviral activity.

Chemistry. Two synthetic routes, which are described below, were employed to prepare the diketones. Procedure A was used to prepare those compounds with modified alkyl bridges between the diketone and the aryl groups. Homologous compounds containing the hexamethylene bridge were prepared by procedure B since this procedure provided more flexibility with regard to varying substituents on the phenyl ring.

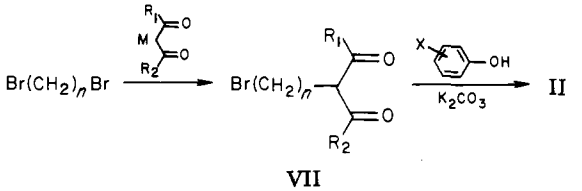
procedure A



III IV V VI II

Initially, the lithium salt of the appropriate diketone in DMF was used in the preparation of II, since it was anticipated that predominantly C-alkylation would result under these conditions.[3-8] However, it was subsequently found that potassium carbonate–acetone served as an equally effective base–solvent system.

procedure B



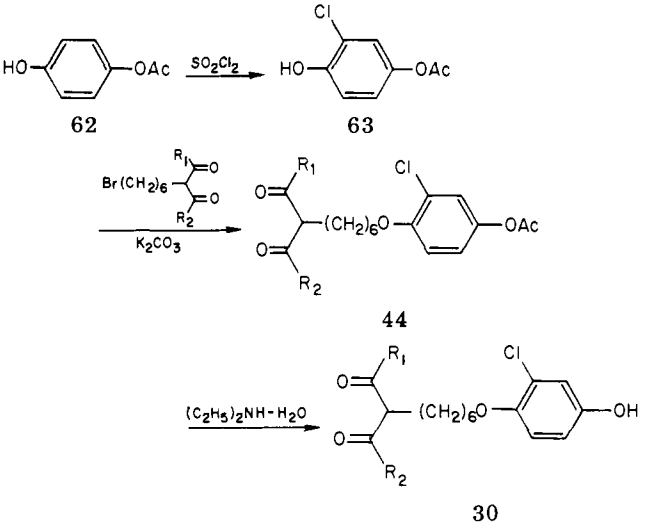
VII

Compound **51** was prepared by alkylation of **23** with diethylaminoethyl chloride, using K_2CO_3 in DMF.

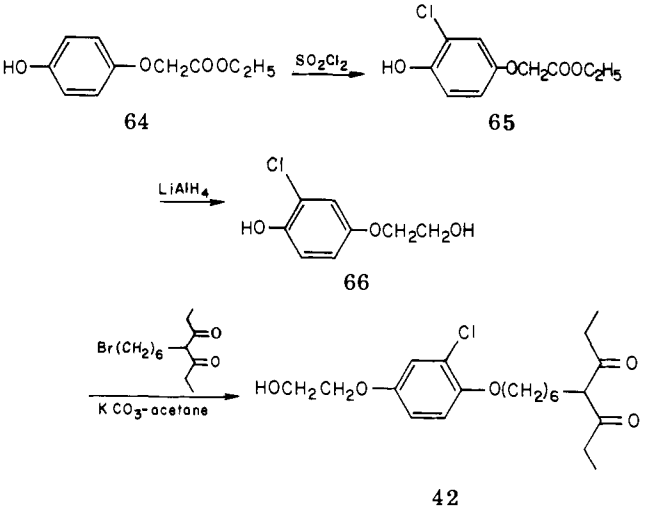
Initially, **30** was synthesized in 13% yield by debenzylation of **25** with boron tribromide.[9] Alternately, procedure C was used.

The preparation of **42** is described below. Purification of these compounds was accomplished by either column chromatography, distillation, or, in some cases, recrystallization. Compound **61** was ultimately purified via its copper chelate (see Table I).

procedure C



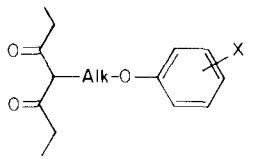
62 63 44 30



64 65 66 42

Structure–Activity Studies. Antiviral effects of the compounds were evaluated according to the procedure outlined in the previous paper.[2] The initial lead compound, which was discovered in the aryl alkyl series described in the previous paper, possessed the 3,4-methylenedioxy group on the phenyl ring. Since this present series was pursued concurrently with the former, a structure–activity study was initially done by maintaining both the 3,4-methylenedioxyphenyl and the 3,5-heptanedione moieties and varying the connecting chain (compounds **1–6**). Peak activity against equine rhinovirus

Table I. Chemical and Antiviral Properties of Aryloxy Alkyl Diketones



Compd	Alk	X	Procedure	Mp or bp (mm), °C	% yield[b]	Formula	MIC,[a] μg/mL: Equine rhino	MIC,[a] μg/mL: HSV[c] type 2
1	$-(CH_2)_3$	3,4-($-OCH_2O-$)	A	179-180 (0.1)	21	$C_{17}H_{22}O_5$	Inact.	Inact.
2	$-(CH_2)_4$	3,4-($-OCH_2O-$)	A	*d*	24	$C_{18}H_{24}O_5$	25-12	Inact.
3	$-(CH_2)_5$	3,4-($-OCH_2O-$)	A	*d*	46	$C_{19}H_{26}O_5$	Inact.	Inact.
4	$-(CH_2)_6$	3,4-($-OCH_2O-$)	A	*d*	43	$C_{20}H_{28}O_5$	6-3	Inact.
5	$-(CH_2)_7$	3,4-($-OCH_2O-$)	A	*e*	35	$C_{21}H_{30}O_5$	12-6	Inact.
6	$-(CH_2)_8$	3,4-($-OCH_2O-$)	A	*f*	43	$C_{22}H_{32}O_5$	Inact.	Inact.
7	$-(CH_2)_6$	4-Cl	A	168-178 (0.01)	23	$C_{19}H_{27}ClO_3$	6-3	Inact.
8	$-(CH_2)_6$	2-Cl	B	180-185 (0.005)	36	$C_{19}H_{27}ClO_3$	12-3	12-6
9	$-(CH_2)_6$	4-Br	B	31-33[g]	41	$C_{19}H_{27}BrO_3$	6-3	12-6
10	$-(CH_2)_6$	4-F	B	160-165 (0.01)	35	$C_{19}H_{27}FO_3$	12-3	6-3
11	$-(CH_2)_6$	2-F	B	160-163 (0.005)	42	$C_{19}H_{27}FO_3$	12-3	25-12
12	$-(CH_2)_6$	2-I	B	195-198 (0.005)	62	$C_{19}H_{27}IO_3$	25-12	Inact.
13	$-(CH_2)_6$	3-I	B	193-198 (0.005)	50	$C_{19}H_{27}IO_3$	12-6	12-6
14	$-(CH_2)_6$	4-I	B	55-56[h]	53	$C_{19}H_{27}IO_3$	6-3	12-6
15	$-(CH_2)_6$	2-Cl, 4-F	B	170-175 (0.005)	54	$C_{19}H_{26}ClFO_3$	6-3	12-6
16	$-(CH_2)_6$	2,4-Cl_2	B	195-200 (0.005)	52	$C_{19}H_{26}Cl_2O_3$	Inact.	6-3
17	$-(CH_2)_6$	2-CF_3	B	165-166 (0.005)	71	$C_{20}H_{27}F_3O_3$	12-6	12-6
18	$-(CH_2)_6$	3-CF_3	B	153-155 (0.005)	33	$C_{20}H_{27}F_3O_3$	Inact.	Inact.
19	$-(CH_2)_6$	4-CH_3S	B	63-64[h]	38	$C_{20}H_{30}O_3S$	6-3	Inact.
20	$-(CH_2)_6$	4-CH_3O	A	161-171 (0.01)	67	$C_{20}H_{30}O_4$	12-6	50-25
21	$-(CH_2)_6$	H	A	165 (0.05)	54	$C_{19}H_{28}O_3$	12-6	12-1.5
22	$-(CH_2)_6$	4-$C_6H_5CH_2O$	A	*i*	41	$C_{26}H_{34}O_4$	3-1.5	3-1.5
23	$-(CH_2)_6$	4-OH		65-66[j]	71[k]	$C_{19}H_{28}O_4$	25-12	6-3
24	$-(CH_2)_6$	3-$(CH_3)_2N$	A	*i*	32.5	$C_{21}H_{33}NO_3$	12-6	Inact.
25	$-(CH_2)_6$	2-Cl, 4-$C_6H_5CH_2O$	A	75-76[j]	60	$C_{26}H_{33}ClO_4$	6-3	12-3
26	$-(CH_2)_6$	4-(p-$CH_3OC_6H_4COO-$)		65-66[l]	21[m]	$C_{27}H_{34}O_5$	25-12	Inact.
27	$-(CH_2)_6$	4-(4-$CH_2CH_2OCH_2CH_2N(CH_2)_3COO-$)		83-85[n]	35[m]	$C_{27}H_{41}NO_6 \cdot HCl$	25-12	25-12
28	$-(CH_2)_6$	3-Cl, 5-CH_3O	A	180-184 (0.006)	54.6	$C_{20}H_{29}ClO_4$	12-6	25-12
29	$-(CH_2)_6$	2-Br, 4-CH_3O	A	54.5-66	55	$C_{20}H_{29}BrO_4$	6-3	12-6
30	$-(CH_2)_6$	2-Cl, 4-OH		51-54	13[o]	$C_{19}H_{27}ClO_4$	Inact.	12-6
31	$-(CH_2)_6$	4-Br, 2-Cl	B	210-215 (0.007)	41	$C_{19}H_{26}BrClO_3$	6-3	6-3
32	$-(CH_2)_6$	4-CN	B	205-210 (0.005)	33	$C_{20}H_{27}NO_3$	Inact.	Inact.
33	$-(CH_2)_6$	4-C_2H_5	B	159-161 (0.005)	40	$C_{21}H_{32}O_3$	12-6	25-12
34	$-(CH_2)_6$	2,3,4,5,6-Cl_5	B	61-62[p]	61	$C_{19}H_{23}Cl_5O_3$	25-12	Inact.
35	$-(CH_2)_6$	2,4,6-I_3	B	70-73[g]	23	$C_{19}H_{25}I_3O_3$	25-12	50-6
36	$-(CH_2)_6$	4-CH_3O, 2-NO_2	B	63-64[q]	32	$C_{20}H_{29}NO_6$	12-3	50-6
37	$-(CH_2)_6$	2,3,4,5,6-F_5	B	135-138 (0.005)	24	$C_{19}H_{23}F_5O_3$	Inact.	50-12
38	$-(CH_2)_6$	3-NO_2	B	46-47[j]	27	$C_{19}H_{27}NO_5$	6-3	Inact.
39	$-(CH_2)_6$	2-NO_2	B	*r*	24	$C_{19}H_{27}NO_5$	12-6	50-6
40	$-(CH_2)_6$	2-Cl, 4-NO_2	B	200-205 (0.01)	25	$C_{19}H_{26}ClNO_5$	6-3	12-3
41	$-(CH_2)_6$	4-NH_2SO_2-	B	86-87[s]	9	$C_{19}H_{29}NO_5S$	Inact.	50-12
42	$-(CH_2)_6$	2-Cl, 4-$HOCH_2CH_2O$	B	*t*	40	$C_{21}H_{33}ClO_5$	6-3	25-1.5
43	$-(CH_2)_6$	4-CH_3CO-, 2-CH_3O	B	59-60[g]	42	$C_{22}H_{32}O_5$	Inact.	50-12
44	$-(CH_2)_6$	2-Cl, 4-CH_3OOC-	B	205-210 (0.03)	67	$C_{21}H_{29}ClO_5$	25-12	Inact.

45	$-(CH_2)_6-$	2,5-Cl_2, 4-CH_3O	B	190–195 (0.03)	75	$C_{20}H_{28}Cl_2O_4$	6–3	25–6
46	$-(CH_2)_6-$	2-Cl, 4-CH_3O	B	185–190 (0.007)	65[u]	$C_{18}H_{25}ClO_4$	Inact.	50–12
47	$-(CH_2)_6-$	2-Cl, 4-CH_3O	A	[v]	62[x]	$C_{19}H_{27}ClO_5$	12–6	Inact.
48	$-(CH_2)_6-$	2-Cl, 4-CH_3O	A	45–46[p]	19[y]	$C_{24}H_{37}ClO_4$	Inact.	50–6
49	$-(CH_2)_6-$	4-$COOC_2H_5$	A	47–48[j]	68.5	$C_{22}H_{32}O_5$	12–6	50–3
50	$-(CH_2)_6-$	4-COOH		99–101[g]	33[w]	$C_{20}H_{28}O_5$	25–6	Inact.
51	$-(CH_2)_6-$	4-$(C_2H_5)_2NCH_2CH_2O$		90–92[j]	14[m]	$C_{25}H_{41}NO_4 \cdot HCl$	50–25	Inact.
52	$-(CH_2)_6-$	4-C_6H_5COO-		76–77[g]	59[m]	$C_{26}H_{32}O_5$	Inact.	Inact.
53	$-(CH_2)_6-$	4-(4-$CH_3OC_6H_4COO-$)		68–70[l]	33[m]	$C_{27}H_{34}O_6$	12–6	Inact.
54	$-(CH_2)_4-$	2-Cl, 4-CH_3O	A	191–193 (0.06)	50	$C_{18}H_{25}ClO_4$	Inact.	Inact.
55	$-(CH_2)_5-$	2-Cl, 4-CH_3O	A	195.7 (0.06)	50	$C_{19}H_{27}ClO_4$	12–6	50–6
56	$-(CH_2)_6-$	2-Cl, 4-CH_3O	A	56–58[e]	71	$C_{20}H_{29}ClO_4$	6–1.5	25–6
57	$-(CH_2)_7-$	2-Cl, 4-CH_3O	A	195–196 (0.005)	49.5	$C_{21}H_{31}ClO_4$	6–3	12–6
58	$-(CH_2)_8-$	2-Cl, 4-CH_3O	A	199–202 (0.02)	60	$C_{22}H_{33}ClO_4$	6–3	25–3
59	$-(CH_2)_9-$	2-Cl, 4-CH_3O	A	206–208 (0.03)	52.5	$C_{23}H_{35}ClO_4$	12–6	25–12
60	$-(CH_2)_{10}-$	2-Cl, 4-CH_3O	A	224–226 (0.07)	60	$C_{24}H_{37}ClO_4$	25–12	12–6
61	$-CH_2CH_2OCH_2CH_2-$	2-Cl, 4-CH_3O	A	168–172 (0.005)	21	$C_{18}H_{25}ClO_5$	50–25	25–12

[a] Minimum inhibitory concentration. [b] Yields refer to analytically pure product. [c] Herpesvirus. [d] Pure sample obtained from column chromatography on Florisil and eluted with C_5H_{12}–C_6H_6 (50:50); [e] $CHCl_3$; [f] C_6H_6–C_5H_{12} (60:40). [g] Recrystallized from ether. [h] Recrystallized from hexane–cyclohexane. [i] Pure sample obtained from column chromatography on Florisil and eluted with $CHCl_3$–C_6H_6 (80:20). [j] Recrystallized from pentane–ether. [k] Prepared by the reduction of the corresponding benzyloxy homologue. [l] Recrystallized from pentane–methanol. [m] Prepared from 23. [n] Recrystallized from 2-propanol. [o] Prepared from 25 (see Experimental Section). [p] Recrystallized from pentane. [q] Recrystallized from methanol. [r] Purified via its copper chelate. [s] Recrystallized from acetone–ether. [t] Pure sample obtained from column chromatography on Florisil and eluted with Et_2O–C_6H_6 (50:50). [u] β-Diketone. [v] Pure sample obtained from column chromatography on Florisil and eluted with C_6H_{14}–$CH_3COOC_2H_5$ (80:20). [w] Prepared from the hydrolysis of ester **49**. [x] [y] .

was reached with the hexamethylene (**4**) and heptamethylene (**5**) bridged homologues. No activity was evident against herpesvirus type 2.

We next retained the C_6 bridge and heptanedione moiety and varied the functional groups on the phenyl ring. In general, substituent effects paralleled those observed in the aryl alkyl series. Although activity against herpesvirus and equine rhinovirus was closely related, there were some exceptions. Compound **16**, which was inactive against equine rhinovirus, exhibited good activity against herpesvirus. The converse was true with compounds **7** and **38**, for example.

Finally, we selected the 2-chloro-4-methoxyphenyl moiety (**56**) and examined the effect of varying the size of the bridge. Optimum activity was attained with C_6 (**56**) in the case of equine rhinovirus where a plateau was reached through C_8 (**58**) at which point activity decreased through C_{10} (**60**). Peak activity against herpesvirus was exhibited with the C_8 bridge.

Compound **56** (WIN 38 020) was screened broadly in vitro and exhibited activity against both DNA and RNA viruses (Table II). The MIC's against three strains of human rhinovirus were consistently low and of the same order of magnitude as those against equine rhinoviruses. In addition, WIN 38 020 was equally active against parainfluenza, respiratory syncytial, and herpes simplex viruses. In the organ culture test, good activity was observed at 200 μg/mL against influenza A_2 Jap 170 and against equine rhinovirus at 100 μg/mL.

In Table III, a comparison is made between the antiherpetic activity of WIN 38 020, idoxuridine, *ara*-A, and *ara*-C against both herpes simplex types 1 and 2.

Discussion

It appears from our structure–activity study that the substituents on the phenyl ring influence the *antiviral activity* through their effect on the lipophilicity of the molecule. In general, most of the compounds were equally effective against equine rhinovirus and herpesvirus type 2. It is difficult to rationalize the inactivity of the 3-trifluoromethyl homologue (**18**) in view of the activity of its isomeric counterpart (**17**) or the inactivity of **16** against equine rhinovirus considering its high activity against herpesvirus.

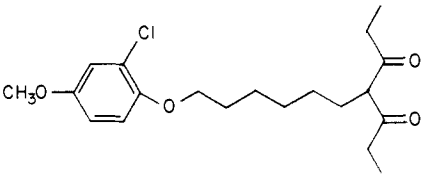
The activity of the aryloxy alkyl diketones against herpesvirus was of particular interest. Clinically, herpesvirus infections manifest themselves, for example, as cold sores (herpes labialis), genital infections (herpes genitalis), shingles (varicella zoster), and eye infections (herpes keratitis), varying in severity from unsightly but self-limiting infections to life-threatening situations. There is a need for an antiherpetic agent since, at the present time, the only herpesvirus infection which is treated chemotherapeutically in the U.S. is herpes keratitis. As a result, WIN 38 020 has been examined topically in the rabbit eye and guinea pig skin against herpesvirus types 1 and 2 and found to be highly effective. The results of this work will be reported elsewhere.

Experimental Section

Melting points were taken on a Fisher-Jones melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Analyses were performed by Instranal Laboratories, Rensselaer, N.Y.

Preparation of Aryloxy Alkyl Diketones. Method A. 1-(2-Chloro-4-methoxyphenoxy)-6-bromohexane (V, X = 2-Cl, 4-CH_3O; n = 6). A mixture of 32 g (0.2 mol) of 2-chloro-4-methoxyphenol,[10] 53.8 g (0.39 mol) of K_2CO_3, 94 g (0.39 mol) of 1,6-dibromohexane, and 350 mL of acetone was refluxed for 48

Table II. In Vitro Antiviral Activity of WIN 38 020



Tissue culture			Organ culture			
Virus	Type	MIC, μg/mL	Virus	Tissue	Concn, μg/mL	% redn in virus yield
Human rhino type 2	RNA	0.7	Influenza	Ferret	200	90
Human rhino type 14	RNA	1.5	A_2 Jap 170	trachea	400	99.9
Human rhino type 17	RNA	3.0				
Equine rhino	RNA	1.5	Equine	Monkey	100	70
Parainfluenza	RNA	1.5	rhino	trachea	200	98
Resp. syncytial	RNA	3.0			400	99.5
Herpes simplex type 1	DNA	6.0				
Herpes simplex type 2	DNA	6.0				

Table III. In Vitro Comparison of WIN 38 020 with Other Active Antiviral Agents

	Minimal viral inhibitory concn, μg/mL	
Agent tested	Herpes simplex type 1, Sheely strain, μg/mL	Herpes simplex type 2, Curtis strain, μg/mL
WIN 38 020	6	6
Idoxuridine	6	6
ara-A	12	12
ara-C	<3	<3

h. The mixture was concentrated to dryness and then partitioned between water (200 mL) and $CHCl_3$ (300 mL). The aqueous phase was extracted twice with 200 mL of $CHCl_3$ and the combined organic layers were washed with H_2O and dried. Removal of the solvent gave 127 g of yellow oil which was fractionally distilled: 51 g (78%); bp 145 °C (0.1 mm). Anal. ($C_{13}H_{18}BrClO_2$) C, H, Cl.

1-(2-Chloro-4-methoxyphenoxy)-6-iodohexane (VI, X = 2-Cl, 4-CH_3O; n = 6). A solution of 51 g (0.142 mol) of 1-(2-chloro-4-methoxyphenoxy)-6-bromohexane and 20.86 g (0.142 mol) of NaI in 400 mL of CH_3COCH_3 was refluxed for 2 h. The solid was removed by filtration and the filtrate concentrated to dryness leaving 50.8 g (87%) of a yellow oil which was of sufficient purity to be used in the next step.

4-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-3,5-heptanedione (56). A solution of 50.8 g (0.138 mol) of iodide VI (n = 2; X = 2-Cl, 4-CH_3O) and 26.8 g (0.2 mol) of lithio-3,5-heptanedione (prepared from n-butyllithium and 3,5-heptanedione in ether) in 350 mL of DMF was heated to 60 °C and left for 48 h. The solution was poured into 1200 mL of cold water containing 20 mL of concentrated HCl and the oil which separated was extracted with ether. The dried organic layer was concentrated to dryness and the residual oil distilled: 16 g (32%); bp 162–180 °C (0.05 mm).

Alkylation Using K_2CO_3–Acetone. A suspension of 170 g (0.5 mol) of 1-(2-chloro-4-methoxyphenoxy)-6-bromohexane, 41.5 g (0.125 mol) of KI, 147 g (1.15 mol) of 3,5-heptanedione, and 145 g (1.05 mol) of powdered anhydrous K_2CO_3 in 2 L of acetone was stirred at reflux for 24 h. Solvent (1 L) was distilled off and the remainder poured into a solution of 4 L of ice–water containing 160 mL of concentrated HCl. The separated yellowish oil was extracted with 3 × 1.5 L of ether. The combined ether fractions were washed with a saturated NaCl solution and dried. Removal of the solvent produced a yellow oil which crystallized from cyclohexane: 130 g (71%); mp 56–58 °C. Anal. ($C_{20}H_{29}ClO_4$) C, H, Cl.

Method B. 4-(6-Bromohexyl)-3,5-heptanedione (VII, n = 6). To a suspension of 3.65 g (0.46 mol) of LiH in 400 mL of DMF was added over a 45-min period 64.1 g (0.5 mol) of 3,5-heptanedione in 200 mL of DMF. The temperature was maintained at 10 °C. After the addition was complete, 488 g (2.0 mol) of 1,6-dibromohexane was added and the solution heated to 60–70 °C for 24 h. The DMF was removed in vacuo and water was added to the residue. The mixture was extracted twice with CH_2Cl_2 and the organic layer dried. The solvent was removed and the residual oil distilled: 73 g (54.5%); bp 130–135 °C (0.03 mm). Anal. ($C_{13}H_{23}BrO_2$) C, H, Br.

4-[6-(2,4-Dichlorophenoxy)hexyl]-3,5-heptanedione (16). A 50% sodium hydride dispersion, 2.5 g (0.052 mol), was washed free of mineral oil with n-hexane and suspended in 75 mL of dry DMF. 2,4-Dichlorophenol, 8.5 g (0.052 mol), was slowly added. After the evolution of H_2 ceased, 11.7 g (0.104 mol) of the bromo diketone (VII, n = 6) was added and the mixture stirred on a steam bath for 8 h. The mixture was poured into 200 mL of ice–water and 2 mL of concentrated HCl and extracted twice with 200-mL portions of CH_2Cl_2 and the combined organic layers were washed and dried. Removal of the solvent gave a yellow oil which was distilled: 9.7 g (51.9%); bp 195–200 °C (0.005 mm). Anal. ($C_{19}H_{26}Cl_2O_3$) C, H, Cl.

4-[6-(4-Hydroxyphenoxy)hexyl]-3,5-heptanedione (23). A suspension of 800 mg of palladium on charcoal in 200 mL of ethanol containing 9 g (0.0219 mol) of **22** was hydrogenated at 50 psi at room temperature. After the theoretical amount of hydrogen was consumed, the catalyst was removed and the ethanolic solution concentrated to dryness. The residual solid was recrystallized from ether–pentane: 5 g (71%); mp 65–66 °C. Anal. ($C_{19}H_{28}O_4$) C, H.

4-[[8-Oxo-7-(1-oxypropyl)decyl]oxy]benzoic Acid (50). HCl gas was bubbled slowly through a refluxing solution of 13.2 g (0.0351 mol) of ester **49** in 190 mL of dioxane and 37.8 mL of concentrated HCl for 18 h and the solution was heated to reflux for an additional 24 h and then concentrated in vacuo. The residual oil was taken up in ether and the ethereal solution extracted with 10% K_2CO_3. The aqueous extracts were acidified with concentrated HCl and the precipitated material was extracted four times with 200 mL of ether. The combined ethereal extracts were dried and the solvent was removed. The residual solid was warmed with 200 mL of ether and the undissolved material removed by filtration. The filtrate was chilled. A white solid was obtained, which was recrystallized from ether: 4 g (33%); mp 99–101 °C. Anal. ($C_{20}H_{28}O_5$) C, H.

4-[6-[4-[2-(Diethylamino)ethoxy]phenoxy]hexyl]-3,5-heptanedione Hydrochloride (51). A mixture of 9.66 g (0.07 mol) of K_2CO_3 in 200 mL of DMF containing 11 g (0.03 mol) of **23** and 4.97 g (0.039 mol) of diethylaminoethyl chloride was stirred at room temperature for 3 h and then at 30 °C for 72 h. The mixture was concentrated in vacuo and the residue partitioned between ether–water. Ethereal layer was washed with water and dried. After removal of the solvent, 13 g of yellow oil remained. The material was purified by column chromatography on Florisil and was eluted with 1% methanol and 99% benzene. Oil (4.5 g) was obtained which was converted to its hydrochloride salt:

2 g (13%); mp 90–92 °C. Anal. ($C_{25}H_{41}NO_4$·HCl) C, H, N.

4-[6-(4-Hydroxyphenoxy)hexyl]-3,5-heptanedione 4-Morpholinebutyrate (27). A suspension of 1 g (3.1 mmol) of **23**, 680 mg (3.27 mmol) of 4-morpholinebutyric acid hydrochloride, and 876 mg (4.28 mmol) of dicyclohexylcarbodiimide in 10 mL of CH_2Cl_2 was stirred overnight at room temperature. The solid was removed by filtration and washed with CH_2Cl_2 and the filtrate concentrated in vacuo. The syrupy residue was dissolved in water and extracted three times with CH_2Cl_2 and the combined organic layers were washed and dried. Removal of the solvent gave a white solid which was recrystallized from 2-propanol: 560 mg (35%); mp 83–85 °C. Anal. ($C_{27}H_{41}NO_6$·HCl) C, H, N, Cl.

4-[6-(2-Chloro-4-hydroxyphenoxy)hexyl]-3,5-heptanedione (30). A solution of 20 g (0.045 mol) of **25** in 150 mL of CH_2Cl_2 was cooled to −65 °C and 6.7 mL of boron tribromide in 150 mL of CH_2Cl_2 was slowly added. After the addition, complete solution was obtained and the temperature was allowed to rise to 25 °C in 2 h. H_2O, 500 mL, was added, followed by 1 L of ether. The mixture was stirred for 30 min and the organic layer separated and washed with a saturated $NaHCO_3$ solution. The solution was then extracted with two portions of 50 mL of 2 N NaOH. The aqueous extracts were immediately neutralized with 2 N HCl and extracted with ether. After drying, the ethereal layer was concentrated in vacuo and the residual oil was passed through a chromatographic column containing silica gel and eluted with a mixture of 20% ethyl acetate and 80% hexane. The material obtained was crystallized from hexane: 2.7 g (13%); mp 51–54 °C. Anal. ($C_{19}H_{27}ClO_4$) C, H, Cl.

Alternate Procedure to 30. (3-Chloro-4-hydroxy)-phenylacetate (63). To a solution of 17.9 g (0.118 mol) of 4-hydroxyphenylacetate in 50 mL of $CHCl_3$ was added dropwise over 1 h, at 25 °C, 10.2 mL (17 g, 0.125 mol) of SO_2Cl_2 in 5 mL of $CHCl_3$. After the addition was complete, the mixture was stirred for 72 h at room temperature. The resulting solid was removed by filtration and the filtrate concentrated to dryness. The resulting solid residue was recrystallized from cyclohexane giving 15 g of material. Further recrystallization from $(C_2H_5)_2O$ gave 8 g (37.6%): mp 87–89 °C; mass spectra M^+ 186. Anal. ($C_8H_7ClO_3$) C: calcd, 51.51; found, 51.98. Repeated recrystallization of the material did not remove the starting material which represented a major impurity.

4-[6-(4-Acetoxy-2-chlorophenoxy)hexyl]-3,5-heptanedione (44) was prepared according to procedure B in 67% yield: bp 205–210 °C (0.03 mm). Anal. ($C_{21}H_{29}ClO_5$) C, H, Cl.

Compound 30. To a solution of 8.8 g of **44** in 10 mL of CH_3OH was added 80 mL of 44% aqueous $(CH_3)_2NH$. CH_3OH was added until all of the suspended oil was solubilized. The solution was stirred for 2 h at 25 °C and then concentrated to about 50 mL and H_2O added. The suspension was extracted with 200 mL of $(C_2H_5)_2O$. The ethereal layer was washed and dried. Removal of the solvent gave 8 g of oil which was crystallized from $(C_2H_5)_2O$–pentane giving 7 g (79%) of **30**.

Ethyl (3-Chloro-4-hydroxyphenoxy)acetate (65). To a solution of 29 g (0.148 mol) of ethyl (4-hydroxyphenoxy)acetate[11] (**64**) in 50 mL of $CHCl_3$ was added, at 0 °C, 20.2 g (0.15 mol) of SO_2Cl_2 in 20 mL of $CHCl_3$ over a period of 1 h. After the addition was complete, the solution was kept at 0 °C for an additional 1 h and then allowed to come to room temperature and stirred for 20 h. The solution was then concentrated to dryness leaving a solid which was recrystallized from hexane: 31.5 g (87%); mp 80–82 °C. Anal. ($C_{10}H_{11}ClO_4$) C, H, Cl.

2-Chloro-4-(2-hydroxyethoxy)phenol (66). To a suspension of 3 g (0.08 mol) of $LiAlH_4$ in 500 mL of $(C_2H_5)_2O$ was added dropwise 12 g (0.052 mol) of ethyl (3-chloro-4-hydroxyphenoxy)acetate (**65**) in 300 mL of $(C_2H_5)_2O$ over a period of 1.5 h. After the addition was complete, the mixture was refluxed for 5 h, cooled, and treated dropwise with 300 mL of 5% H_2SO_4. The organic layer was separated and extracted with two 150-mL portions of water and dried. Removal of the solvent gave 13.2 g of a white solid which, after recrystallization from 2-propanol–pentane, gave 7.7 g (78%): mp 89–90 °C. Anal. ($C_8H_9ClO_3$) C, H, Cl.

4-[2-[2-(2-Chloro-4-methoxyphenoxy)ethoxy]ethyl]-3,5-heptanedione (61). a. 2-Chloroethyl-2′-[(2-chloro-4-methoxyphenoxy)ethyl] Ether (67). To a suspension of 9.6 g (0.2 mol) of 50% NaH in 250 mL of dry DMF was added, at 25 °C, 31.6 g (0.2 mol) of 2-chloro-4-methoxyphenol in small portions. After the evolution of hydrogen ceased, 143 g (1.0 mol) of bis-(2-chloroethyl) ether was added in one portion. The mixture was refluxed for 8 h and then left overnight at room temperature. The mixture was concentrated in vacuo to an oil. H_2O, 500 mL, was added and the mixture was extracted with CH_2Cl_2 and the organic layer was washed with H_2O and dried. Removal of the solvent gave a dark oil which was distilled in vacuo. The fraction boiling at 130–143 °C (0.02 mm) was collected. Redistillation gave 32.2 g (60.8%): bp 139–140 °C (0.05 mm). Anal. ($C_{11}H_{14}Cl_2O_3$) C, H, Cl.

b. 2-[(2-Chloro-4-methoxyphenoxy)ethyl]-2′-iodoethyl ether was prepared from 24.7 g (0.0769 mol) of chloride (**67**) and 13.5 g (0.9 mol) of NaI in 200 mL of butanone in quantitative yield. The material was not purified but used directly to prepare the diketone.

c. Diketone (61) was prepared by procedure A from 31.7 g (0.077 mol) of iodide, 21.8 g (0.17 mol) of 3,5-heptanedione, and 1.27 g (0.16 mol) of LiH in 125 mL of DMF. The crude mixture was distilled to give 7.6 g of oil: bp 155–205 °C (0.03 mm). This material proved to be impure and was further purified as follows. To a solution of 7.6 g (0.0213 mol) of crude product in 100 mL of CH_3OH was added 2.49 g (0.0125 mol) of cupric acetate monohydrate in 20 mL of H_2O and 5 mL of concentrated NH_4OH. The solution was heated to reflux and stirred for 15 min. A gray solid precipitated, was collected, and recrystallized from 2-butanone. The solid was suspended in 200 mL of dilute HCl and 200 mL of CH_2Cl_2 and stirred for 10 min. The organic layer was collected and dried and the solvent removed. The oil was distilled: 4.1 g (21%); bp 168–172 °C (0.005 mm). Anal. ($C_{18}H_{25}ClO_5$) C, H, Cl.

References and Notes

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