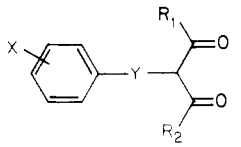
Antiviral Activity of Some β-Diketones. 1. Aryl Alkyl Diketones. In Vitro Activity against Both RNA and DNA Viruses[1]

Guy D. Diana,* U. Joseph Salvador, Ethel S. Zalay, Robert E. Johnson, Joseph C. Collins, David Johnson, William B. Hinshaw, Roman R. Lorenz, William H. Thielking, and Francis Pancic

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received July 30, 1976*

The discovery that 4-[3-ethyl-6-[(3,4-methylenedioxy)phenyl]-3-hexenyl]-3,5-heptanedione (40) exhibited an in vitro inhibitory effect against equine rhinovirus led to a structure–activity study to establish the criteria for optimum activity. Modification of the bridge included removal of the ethyl group and reduction of the double bond. The heptanedione was replaced with hexanedione and pentanedione with a minimal effect. The effect of replacing the heptanedione with β-keto esters and monoketones was also investigated. Maintaining the hexamethylene bridge and heptanedione, the methylenedioxy group was replaced with various substitutents. In general, most substituents did not adversely affect activity particularly against equine rhinovirus although there was some variation in activity against herpesvirus. Strongly hydrophilic groups significantly reduced activity. Finally, the effect of varying the length of the alkyl bridge was examined in the 4-hydroxyphenyl series, where peak activity was attained with $n = 8$.

During the course of routine screening of compounds for antiviral activity, it was discovered in our laboratory that several aryl diketones of the general structure I were active against equine rhinovirus in vitro. In the past, cyclic β-diketones,[2] α-dicarbonyl compounds,[3] and quinones[4,5] as well as some related structures[6] including the nucleosides[7] have been reported to exhibit antiviral activity. However, to our knowledge there have been no



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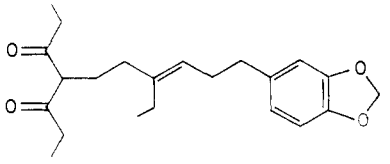
reports of acyclic β-diketones demonstrating this activity. In view of the novelty of this structural class as an antiviral agent, we commenced the synthesis of a substantial number of homologues in an effort to establish a structure–activity relationship. The methylenedioxy diketone **40** was the original lead compound and our chemical approach was to examine five parameters with respect to activity: (1) the size of the diketone moiety, (2) the necessity of the ethyl side chain, (3) the necessity of the



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double bond, (4) the size of the bridge, and (5) effect of various substituents on the ring.

Chemistry. The majority of compounds were prepared from the cyclopropyl ketones II as shown in Scheme I.[8] The cyclopropyl styryl ketones IV (Table I) were either reduced directly to the saturated alcohols VI (Table II) or sequentially to the ketones V with Pd/C and subsequently to the alcohols VI with $NaBH_4$. Treatment of VI with PBr_3 and collidine in ether[9] gave the bromides VII which were immediately treated with $ZnBr_2$ to give the isomeric bromides VIII.[10] The latter were converted to the corresponding iodides XII and finally to XI via alkylation of the lithium salt of the appropriate dicarbonyl in DMF or tetramethylurea, followed by reduction with Pd/C. Alternately, XI was prepared from the saturated iodide X. Due to their instability to heat, the bromides VIII and iodides XII were characterized but not purified further.

Two synthetic routes were used to prepare homologous bridged compounds. The preparation of **83** is described in Scheme II. Treatment of the bromide XIV[11] with HI in acetic acid produced iodide XV in 71% yield. An alternate approach is shown in Scheme III exemplified by the synthesis of **86**. Reduction of acid XVI with diborane in THF produced alcohol XVII in 96% yield. XVII was converted with HI in acetic acid to iodide XVIII which was in turn allowed to react with the lithium salt of 3,5-heptanedione to give **86** in 52% yield.

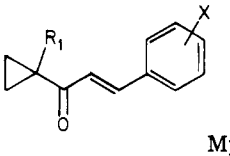
Structure–Activity Studies. Upon the discovery of antiviral activity with the β-diketones, we examined the effects of other related groups (Table III). Although some activity was observed with the β-keto esters **33–35** and the cyclopentanone **38**, the degree of activity was significantly lower. Additional work in this area did not prove fruitful with regard to antiviral activity; consequently, our efforts were directed toward the diketone series.

The evaluation of three of the five parameters discussed previously is shown in Table IV. No significant difference in activity was observed between the corresponding heptanedione (**40**), hexanedione (**41**), and pentanedione (**42**). Reducing the ethyl side chain (**40**) to methyl (**44**) and finally to hydrogen (**45**) caused a slight increase in activity from 6 to 3 μg/mL. Reduction of the double bond of both **40** and **45** to give compounds **46** and **47**, respectively, did not result in any loss of antiviral activity.

We chose at this point to maintain both the heptanedione and the hexamethylene bridge and vary the substituents on the phenyl ring (Tables V and VI). In general, activity was maintained with a few notable exceptions. The introduction of a hydrophilic group (**66** and 78) destroyed activity. Although the 4-chloro-2-hydroxy homologue **70** was very active, the transposition of these two substituents (**71**) destroyed activity. The 2-, 3-, and 4-methyl (**75–77**), 3-methoxy (**72**), and 3,4,5-trimethoxy (**74**) benzoates, respectively, exhibited some activity whereas the 3,5-dimethoxy benzoate ester **73** was inactive. The corresponding 4-morpholinobutyrate ester **78** was also inactive.

We next chose to examine the effect of altering the bridge between the diketone and aryl portions of the molecule and selected **61** as the candidate. The results are summarized in Table VII, which includes antiviral data against herpesvirus type 2, an example of a DNA virus. The tetramethylene homologue **82** exhibited moderate activity against both viruses, which increased with in-

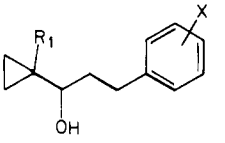
Table I. Cyclopropyl Styryl Ketones



Compd	R_1	X	Mp, °C	% yield	Formula
1	C_2H_5	3,4-(-OCH_2O-)	62-64[a]	53	$C_{15}H_{16}O_3$
2	CH_3	3,4-(-OCH_2O-)	88-90[a,b]	39	$C_{14}H_{14}O_3$
3	H	3,4-(-OCH_2O-)	85-87[a]	85	$C_{13}H_{12}O_3$
4	C_2H_5	4-COOH	183.5-184.5[c]	62	$C_{15}H_{16}O_3$
5	H	H	60-61[a]	66	$C_{12}H_{12}O$
6	H	2,4-Cl_2	85-87[a]	90.2	$C_{12}H_{10}Cl_2O$
7	H	4-CH_3O-	70-72[a]	86	$C_{13}H_{14}O_2$
8	H	4-$(CH_3)_2N$-	137-139[a]	56	$C_{14}H_{17}NO$
9	H	4-Cl	63-65[a]	66	$C_{12}H_{11}ClO$
10	H	4-$C_6H_5CH_2O$-	111-113[a]	77.7	$C_{19}H_{18}O_2$
11	H	4-CH_3	78-80[a]	85	$C_{13}H_{14}O$
12	H	4-CH_3CONH-	191-192[a]	78.5	$C_{14}H_{15}NO_2$
13	H	3,4-$(C_6H_5CH_2O)_2$	100-102[a]	68.4	$C_{26}H_{24}O_3$
14	H	4-$(C_6H_5CH_2O)$-3,5-$(CH_3O)_2$	98-99[a]	91	$C_{21}H_{22}O_4$
15	H	2-CH_3O-	117-118 (0.03)[d]	61	$C_{13}H_{14}O_2$
16	H	4-NH_2SO_2-	173[a]	58.5	$C_{12}H_{13}NO_3S$

[a] Recrystallized from EtOH. [b] C: calcd, 73.04; found, 72.00. [c] Recrystallized from 2-PrOH. [d] Boiling point (mm).

Table II. 3-Aryl-1-cyclopropylpropanols



Compd	R_1	X	Mp or bp (mm), °C	% yield	Formula
17	C_2H_5	3,4-(-OCH_2O-)	128-130 (0.02)	96	$C_{15}H_{20}O_3$
18	CH_3	3,4-(-OCH_2O-)	130-131 (0.001)	80	$C_{14}H_{18}O_3$
19	H	3,4-(-OCH_2O-)	64-65[a]	62.5	$C_{13}H_{16}O_3$
20	C_2H_5	4-COOH	116-117[b]	92	$C_{15}H_{20}O_3$
21	H	4-CH_3O-	116-117 (0.05)	81.4	$C_{13}H_{18}O_2$
22	H	H	89-90 (0.02)	78.4	$C_{12}H_{16}O$
23	H	4-CH_3	91-92 (0.03)	80	$C_{13}H_{18}O$
24	H	4-Cl	114-115 (0.15)	75	$C_{12}H_{15}ClO$
25	H	4-$(CH_3)_2N$-	126-128 (0.2)	87.5	$C_{14}H_{21}NO$
26	H	4-$C_6H_5CH_2O$-	76-77[a]	77	$C_{19}H_{22}O_2$
27	H	4-CH_3CONH-	142-143[c]	72	$C_{14}H_{19}NO_2$
28	H	3,4-$(C_6H_5CH_2O)_2$	62-64[d]	67.7	$C_{26}H_{28}O_3$
29	H	4-$(C_2H_5)_2N(CH_2)_2O$-	170-171 (0.02)	93.5	$C_{18}H_{29}NO_2$
30	H	2-CH_3O-	87-88 (0.03)	61	$C_{13}H_{18}O_2$
31	H	4-NH_2SO_2-	90-91[e]	36	$C_{12}H_{17}NO_3S$
32	H	4-F_3CO-	80-85 (0.05)	58.5	$C_{13}H_{15}F_3O_2$

[a] Recrystallized from Et_2O; [b] EtOH; [c] $CH_3COOC_2H_5$; [d] Et_2O-pentane; [e] MeOH-pentane.

creasing length of the bridge. Peak activity was attained against equine rhinovirus with $n = 6$ and was maintained through $n = 8$. In the case of herpesvirus type 2, maximum activity was exhibited with $n = 8$.

Compound **61**, as a representative of this class of compounds, was tested against a wide range of viruses (Table VIII). The most striking result was the broad spectrum of activity against both RNA and DNA viruses. Significant activity was also observed against influenza A_2 Jap 170 and equine rhinovirus in the organ culture test.

A comparative evaluation of the in vitro antiherpetic activity of compound **61** with other active antiviral agents is shown in Table IX. *ara*-C exhibited a lower MIC, with compound **61**, idoxuridine, and *ara*-A demonstrating comparable activity against both herpes simplex types 1 and 2.

Discussion

The basic structural requirements for optimum activity for this class of compounds have been narrowed down to a β-diketone, separated from a substituted benzene ring by an alkyl chain of from six to eight carbon atoms. It would appear that the necessity of the substituents on the phenyl ring is mainly to contribute to the lipophilicity of the molecule. It is difficult to explain the inactivity of the *p*-fluoro homologue **64** or the inactivity of the 2-chloro-4-hydroxy compound **71** since the positional isomer **70** was highly active.

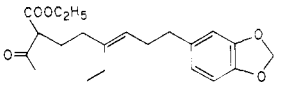
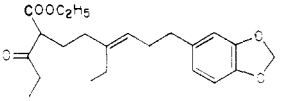
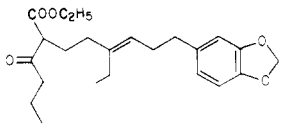
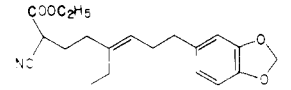
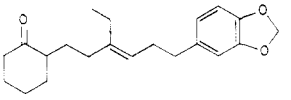
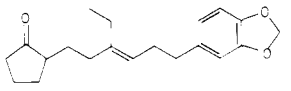
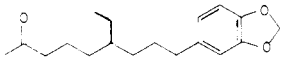
In general, the antiviral profile of **61** is representative of this class of compounds. However, the level of activity against the viruses in Table VIII has not necessarily been consistent for all of the compounds tested. For example, the catechol **65** which exhibited activity at 1.5 μg/mL against equine rhinovirus was inactive against herpes virus types 1 and 2.

Several of the more highly active compounds are being evaluated in animal models, the results of which will be reported in the near future.

Experimental Section

Melting points were run according to the USP procedure and are uncorrected. Where analyses are indicated only by symbols

Table III. Physical Properties and in Vitro Antiviral Activity

Compd	Structure	Formula	% yield[a]	MIC (μg/mL), equine rhinovirus
33		$C_{21}H_{28}O_5$	51	12-6
34		$C_{22}H_{30}O_5$	55[b]	Inact.
35		$C_{23}H_{32}O_5$	39	25-12
36		$C_{20}H_{25}NO_4$	39	Inact.
37		$C_{21}H_{28}O_3$	12	Inact.
38		$C_{20}H_{26}O_3$	37	12-6
39		$C_{18}H_{24}O_3$	32	Inact.

[a] Purified by column chromatography on silica gel and eluted with $CHCl_3$-C_6H_6 (80:20). [b] C: calcd, 70.56; found, 71.60.

of the elements, analytical results are within ±0.4% of the theoretical values. Analyses were perfomed by Instranal Laboratories, Rensselaer, N.Y. NMR spectra were determined on a Varian A-60 spectrophotometer and the mass spectra on a Jeolco double-focusing high-resolution mass spectrometer by R. K. Kullnig and S. Clemans.

Antiviral Evaluation Method. Primary screening of the compounds against all viruses was carried out in stationary tissue culture tubes. All tissue culture monolayers were propagated in Eagles medium with Hanks balanced solution and 10% fetal calf serum. After the addition of virus and drug to the cultures, a maintenance medium of M-199 + 5% inactivated fetal calf serum was used routinely.

Susceptible cells for each virus were infected with 100 tissue culture infective dose units contained in 0.2 mL of M-199. The virus was allowed to adsorb for 1 h, after which appropriate concentrations of compound in 0.8 mL of maintenance medium were added to the tubes. Concentrations of 50–0.3 μg/mL in twofold dilutions were tested using four tubes per dilution. Virus control and tissue culture control tubes were included in each test. Cytotoxicity for each level of compound on test was monitored in a parallel noninfected set of tissue culture tubes.

Cultures inoculated with rhinoviruses were incubated at 33 °C, all other viruses at 37 °C. After 48 and 72 h of incubation, cultures were examined for the presence or absence of cytopathic effect. The degree of cytopathic effect produced by virus was scored as 0 for 100% inhibition of viral CPE; 1+ for minimal CPE, not more than two lesions; 2+ for 25% of monolayer involvement or less; 3+ for 50% monolayer involvement; and 4+ for total involvement of monolayers.

Tests were judged completed when the control virus tubes read 4+. Only those concentrations of compound which showed no toxic effect to the cells in the toxicity controls were valid for interpretation of viral inhibition.

The minimal inhibitory concentration was reported as the lowest nontoxic level of compound which completely inhibited viral CPE. The higher of the two reported values in Tables III–VII represents the level at which drug-related cellular toxicity was observed. A compound was judged inactive if no virus inhibition was observed at 50 μg/mL.

The effect of **61** on the growth of influenza virus A_2 Jap 170 was demonstrated in ferret trachea organ cultures and on the growth of equine rhinovirus in rhesus monkey trachea. This system of organized tissue permitted measurement of the titer of the viruses in the nutrient fluid, as well as observance of the effect of the compound on the ciliary cells of the trachea as a measure of toxicity.

Freshly removed tracheas were washed in Hanks balanced solution, excess connective tissue was removed, and the trachea was cut into explants of 3–4 mm^2 or rings of 1–2 cartilage segments. Three to four pieces of tracheal explant were placed in scored 60-mm Falcon petri dishes and oriented with the mucosa upward. Leibowitz L-15 medium (1 mL) was added to each dish as maintenance medium. Cultures were incubated in a CO_2 atmosphere at 37 °C. Organ cultures were inoculated with virus 24 h after they were initiated. Culture fluid was removed and 0.1 mL of virus inoculum was placed directly on the epithelial surface of each explant (total virus inoculum was usually between 3000 and 10000 $TCID_{50}$'s). The virus was allowed to adsorb for 1 h at 37 °C and then washed off.

Fresh maintenance medium containing various concentrations of **61** was added to the cultures at the end of virus adsorption. Virus controls, drug controls, and cell controls were included in each test. Fresh medium containing the compound was replaced after 3 days of incubation.

Twenty-four hours before fluids were removed for virus titrations, drug-containing fluids were removed and maintenance medium without **61** was inoculated to prevent carryover of the compound into the assay systems. Harvested fluids were titered immediately.

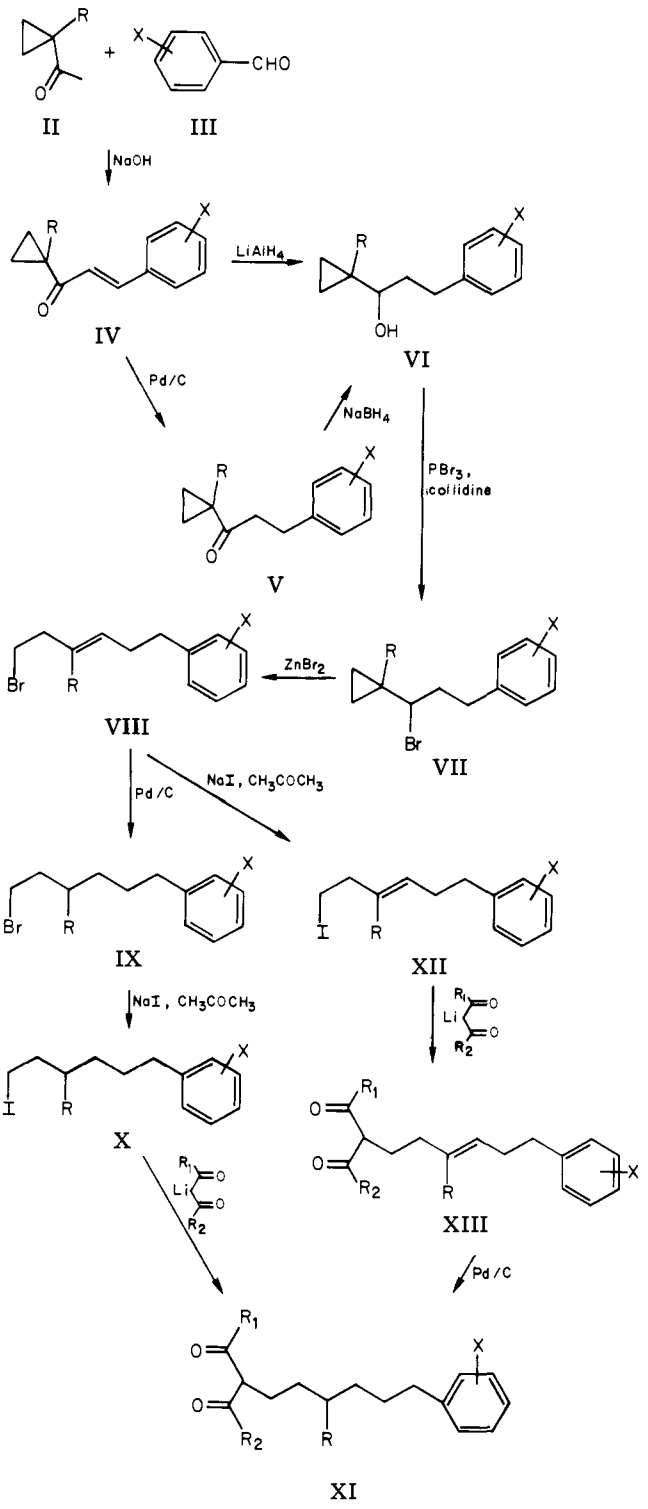
Trachael explants were examined for ciliary movements by reflected light under a dissecting microscope and by transmitted light under a light microscope.

Tissue viability was also checked by vital staining with tetrazolium salt and trypan blue.

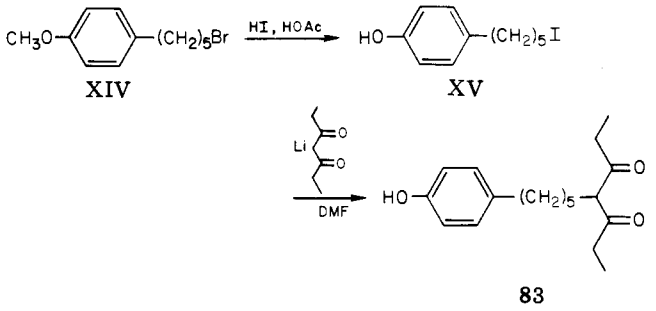
Virus assay of organ culture samples for influenza virus was carried out in 9-day-old chick embryos by end-point hemagglutination titration and equine rhinovirus in cell cultures of CATR (human amnion) by cytopathic effect end-point tube titration, the 50% end-point being calculated by the method of Reed and Muench.[12]

1-Ethylcyclopropyl 3,4-Methylenedioxystyryl Ketone (1).[13] To a solution of 11.2 g (0.1 mol) of 1-ethylcyclopropyl methyl ketone and 15 g (0.1 mol) of piperonal in 7 mL of EtOH was added

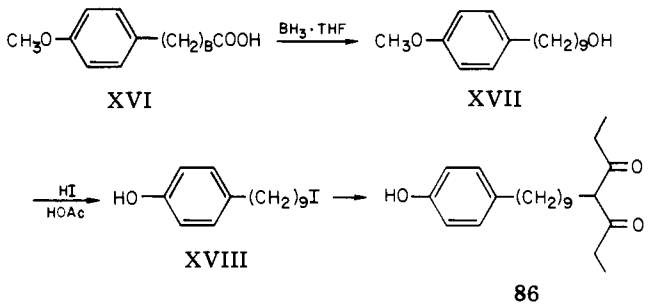
Scheme I



Scheme II



Scheme III



dropwise at room temperature with stirring 7 mL of 20% aqueous NaOH. After the addition was complete (30 min) the mixture was stirred for an additional 3 h at 40 °C and then left overnight at room temperature. During this time, a solid had separated which was removed by filtration, washed with 50% aqueous EtOH, and dried. Solid (21.5 g) was obtained which was recrystallized from EtOH: 13 g (53%); mp 62–64 °C. Anal. ($C_{15}H_{16}O_3$) C, H.

1-(1-Ethylcyclopropyl)-3-[3,4-(methylenedioxy)phenyl]-1-propanol (17). To a suspension of 4.4 g (0.116 mol) of $LiAlH_4$ in 250 mL of THF was added dropwise at reflux and under an atmosphere of N_2, 28 g (0.105 mol) of 1 in 200 mL of THF. After the addition was complete (30 min) the mixture was stirred at reflux for 45 min and then 90 mL of 50% aqueous THF was added dropwise to the cooled mixture. After stirring for an additional 30 min, the salts were removed by filtration and washed with THF. The filtrate was concentrated to dryness and the residual oil distilled: 271 g (96%); bp 128–130 °C (0.02 mm). Anal. ($C_{15}H_{20}O_3$) C, H.

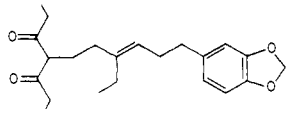
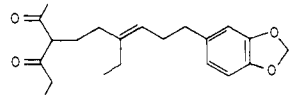
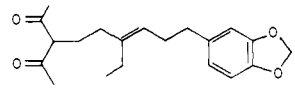
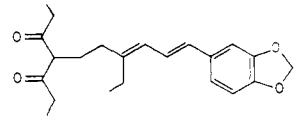
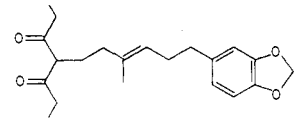
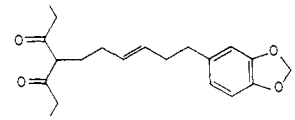
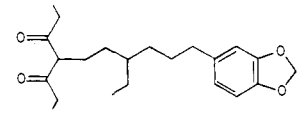
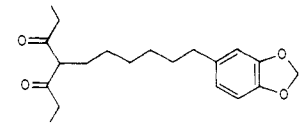
1-Bromo-3-ethyl-6-(3,4-methylenedioxyphenyl)-hex-3-ene [VIII, R = C_2H_5; X = 3,4-(-OCH_2O-)]. To a mixture of 27.1 g (0.115 mol) of 17, 26.7 g (0.115 mol) of LiBr, and 7 mL of collidine in 275 mL of Et_2O was added dropwise, at −60°C, 25.7 g (0.0955 mol) of PBr_3. After the addition was complete, the mixture was allowed to warm to 0 °C and then left for 2 h at this temperature. Collidine (38 mL) was then added and the mixture poured into 400 mL of ice–water. The Et_2O layer was separated and the aqueous layer extracted with Et_2O. The combined Et_2O extracts were then washed with H_2O and dilute H_2SO_4 and finally dried. The solution was concentrated to 400 mL and 27 g of $ZnBr_2$ was added. After stirring overnight at room temperature the solution was extracted five times with H_2O and dried. Removal of the solvent gave 29.9 g of oil: mass spectrum *m/e* 136; NMR ($CDCl_3$) δ 5.18 (t, >C=CH–) and 3.35 (M, $-CH_2Br$). This material was not purified further.

3-Ethyl-1-iodo-6-(3,4-methylenedioxyphenyl)hex-3-ene [XII, R = C_2H_5; X = 3,4-(OCH_2O)]. A solution of 29.9 g (0.0965 mol) of VIII [R = C_2H_5; X = 3,4-(-OCH_2O-)] and 15 g (0.1 mol) of NaI in 150 mL of CH_3COCH_3 was refluxed for 3 h. The solid was removed by filtration and the filtrate concentrated to dryness. The residual oil was partitioned between Et_2O and H_2O and the Et_2O layer dried and the solvent removed. Oil (29 g) was obtained: mass spectrum *m/e* 358; NMR ($CDCL_3$) δ 5.21 (t, >C=CH–) and 3.19 (M, $-CH_2I$). This material was used directly to prepare **40**.

4-[3-Ethyl-6-[3,4-(methylenedioxy)phenyl]-3-hexenyl]-3,5-heptanedione (40). A solution of 59 g (0.159 mol) of iodide XII [R = C_2H_5; X = 3,4-(-OCH_2O-)] and 40 g (0.298 mol) of lithium heptanedione in 300 mL of tetramethylurea (TMU) was heated to 40 °C for 24 h. The TMU was removed in vacuo and the residue extracted with Et_2O and H_2O. The Et_2O layer was dried and after removal of the solvent, the residual oil was passed through a chromatographic column containing Florisil. The desired material was removed from the column with a mixture of 70% $CHCl_3$ and 30% C_6H_6: 21.6 g (18%); IR 5.82 and 5.92 μ (β-diketone). Anal. ($C_{22}H_{30}O_4$) C, H.

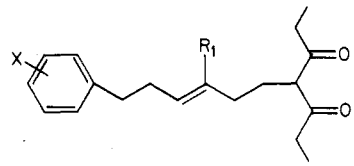
4-[(3-Cyclopropyl-3-oxo)propyl]benzenesulfonamide (V, R = H; X = SO_2NH_2). A solution of 24.3 g (0.0968 mol) of ketone 12 in 1200 mL of EtOH was hydrogenated with 2.5 g of Pd/C at 46 psi. After the theoretical amount of hydrogen was absorbed (10 min), the mixture was filtered and the filtrate concentrated to dryness. The solid residue was recrystallized from EtOH: 14.1 g (58%); mp 141–143 °C. Anal. ($C_{12}H_{15}NO_3S$) C, H, N.

Table IV. Physical Properties and in Vitro Antiviral Activity

Compd	Structure	Formula	Bp (mm), °C	% yield	MIC (μg/mL), equine rhinovirus
40		$C_{22}H_{30}O_4$	*a*	18	12-6
41		$C_{21}H_{28}O_4$	*a*	57	25-12
42		$C_{20}H_{26}O_4$	*b*	24	25-6
43		$C_{22}H_{28}O_4$	*c*	27	12-6
44		$C_{21}H_{28}O_4$	*d*	35	12-3
45		$C_{20}H_{26}O_4$	*c*	56	6-3
46		$C_{22}H_{32}O_4$	*e*	81	6-3
47		$C_{20}H_{28}O_4$	178-185 (0.002)	59.5	12-6

[a] Purified by column chromatography on silica gel and eluted with C_6H_6-Et_2O (97:3); [b] C_6H_6-Et_2O (80:20); [c] C_6H_6-$CHCl_3$ (40:60); [d] C_6H_6-Et_2O (50:50); [e] C_6H_6-Et_2O (99:1).

Table V. Physical Properties and in Vitro Antiviral Activity



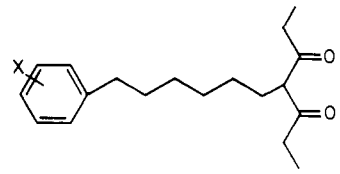
Compd	R_1	X	Mp or bp (mm), °C	% yield	Formula	MIC (μg/mL), equine rhinovirus
48	C_2H_5	3,4-$(CH_3O)_2$	*a*	45	$C_{23}H_{34}O_4$	Inact.
49	C_2H_5	4-CH_3OOC-	*b*	18.5	$C_{23}H_{32}O_4$	50-25
50	H	4-CH_3	147-149 (0.02)	67	$C_{20}H_{28}O_2$	Inact.
51	H	4-F_3CO-	138-140 (0.05)	38	$C_{20}H_{25}F_3O_3$	12-6
52	H	4-$C_6H_5CH_2O$-	36-37[c]	59	$C_{26}H_{32}O_3$	6-3
53	H	4-$CH_3C(=O)NH$-	215-220 (0.02)	37.5	$C_{21}H_{29}NO_3$	25-12
54	H	4-$C_6H_5CH_2O$-3,5-$(CH_3O)_2$	*d*	33	$C_{28}H_{36}O_5$	12-6
55	H	4-NH_2SO_2-	*e*	10.5	$C_{19}H_{27}NO_4S$	Inact.

[a] Purified by column chromatography on silica gel and eluted with $CHCl_3$-Et_2O (95:5); [b] C_6H_6-Et_2O (98:2). [c] Recrystallized from Et_2O. [d] Purified by column chromatography on Florisil and eluted with $CHCl_3$-C_6H_6 (70:30); [e] C_6H_6-$CH_3COOC_2H_5$) (80:20).

4-[(3-Cyclopropyl-3-hydroxy)propyl]benzenesulfonamide (31). To 7.7 g (0.21 mol) of $NaBH_4$ in 700 mL of MeOH was added, at 0°C, 18.5 g (0.073 mol) of V (R = H; X = $-SO_2NH_2$) during a 40-min period. The solution was then refluxed for 10 min, evaporated in vacuo, and extracted with H_2O and Et_2O. The Et_2O layer was collected and the aqueous layer extracted twice with 200 mL of Et_2O. The combined organic layer was washed in the usual manner. Removal of the solvent gave a solid which was recrystallized from MeOH–pentane: 13.4 g (72%); mp 90–91 °C. Anal. ($C_{12}H_{17}NO_3S$) C, H, S.

4-[8-Oxo-7-(1-oxopropyl)decyl]phenyl 4-(4-Morpholenyl)butanoate Hydrochloride (78).[14] To a solution of 5 g (0.0164

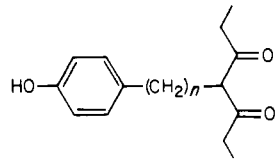
Table VI. Physical Properties and in Vitro Antiviral Activity



Compd	X	Mp or bp (mm), °C	% yield[a]	Formula	MIC (μg/mL), equine rhinovirus
56	4-CH_3O-	162-163 (0.03)	65	$C_{20}H_{30}O_3$	6-3
57	2-CH_3O-	158 (0.04)	83	$C_{20}H_{30}O_3$	25-12
58	4-Cl	159-160 (0.03)	64	$C_{19}H_{27}ClO_2$	6-1.5
59	4-CH_3	145-146 (0.01)	80	$C_{20}H_{30}O_2$	12-6
60	4-F_3CO-	124-127 (0.001)	68	$C_{20}H_{27}F_3O_3$	12-6
61	4-OH	76-77[b]	70	$C_{19}H_{28}O_3$	6-3
62	2-OH	*c*	93	$C_{19}H_{28}O_3$	12-6
63	3-OH	*d*	77.5	$C_{19}H_{28}O_3$	12-6
64	4-F	138-144 (0.2)	67	$C_{19}H_{27}FO_2$	Inact.
65	3,4-$(OH)_2$	*e*	49	$C_{19}H_{28}O_4$	3-1.5
66	4-$(C_2H_5)_2NCH_2CH_2O$-	205-206 (0.003)	60	$C_{25}H_{41}NO_3$	Inact.
67	4-OH-3,5-$(CH_3O)_2$	*f*	21	$C_{21}H_{32}O_5$	Inact.
68	H	135-136 (0.03)	60	$C_{19}H_{28}O_2$	12-6
69	4-Cl-2-CH_3O-	*c*	100	$C_{20}H_{29}ClO_3$	6-3
70	4-Cl-2-OH	58-59[k]	47[l]	$C_{19}H_{27}ClO_3$	3-0.7
71	2-Cl-4-OH	55-56[k]	41	$C_{19}H_{27}ClO_3$	Inact.
72	4-(3-$CH_3OC_6H_4COO$-)	*g*	73[m]	$C_{27}H_{34}O_5$	12-3
73	4-[3,5-$(CH_3O)_2C_6H_3COO$-	*h*	52[m]	$C_{28}H_{36}O_6$	Inact.
74	4-[3,4,5-$(CH_3O)_3C_6H_2COO$-]	*h*	61[m]	$C_{29}H_{38}O_7$	12-6
75	4-(2-$CH_3C_6H_4COO$-)	*i*	86.5[m]	$C_{27}H_{34}O_4$	12-6
76	4-(3-$CH_3C_6H_4COO$-)	*i*	96[m]	$C_{27}H_{34}O_4$	6-3
77	4-(4-$CH_3C_6H_4COO$-)	72-74[n]	58[m]	$C_{27}H_{34}O_4$	25-12
78	4-c-$O(CH_2CH_2)_2N(CH_2)_3COO$-	57-59[o]	91[m]	$C_{27}H_{41}NO_5 \cdot HCl$	Inact.
79	4-CH_3COO-	*j*	35	$C_{21}H_{30}O_4$	12-6
80	2,4-Cl_2	179-181 (0.3)	61	$C_{19}H_{26}Cl_2O_2$	6-3

[a] Based on immediate precursor. [b] Recrystallized from 2-PrOH. [c] Purified by column chromatography on silica gel and eluted with hexane-$CH_3COOC_2H_5$ (80:20); [d] $CHCl_3$-$CH_3COOC_2H_5$ (90:10); [e] $CHCl_3$-Et_2O (90:10). [f] Purified by column chromatography on Florisil and eluted with C_6H_6-Et_2O (60:40); [g] C_6H_6-Et_2O (80:20); [h] C_6H_6; [i] C_6H_6-Et_2O (80:20); [j] C_6H_6-$CH_3COOCH(CH_3)_2$ (95:5). [k] Recrystallized from Et_2O-hexane. [l] Prepared from 69, see Experimental Section. [m] Prepared from 61. [n] Recrystallized from pentane. [o] Recrystallized from Et_2O.

Table VII. Physical Properties and in Vitro Antiviral Activity



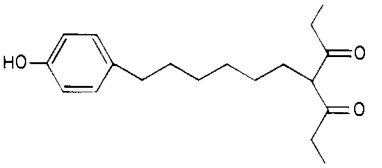
Compd	*n*	Mp, °C	% yield	Formula	MIC, μg/mL: Equine rhinovirus	MIC, μg/mL: Herpes II
81	3	150-152 (0.5)[d]	60.5	$C_{16}H_{22}O_3$	Inact.	Inact.
82	4	67-69[a]	58	$C_{17}H_{24}O_3$	25-6	25-12
83	5	52-54[a]	35	$C_{18}H_{26}O_3$	25-12	25-12
61	6	76-77[b]	70	$C_{19}H_{28}O_3$	6-3	25-12
84	7	57-58[b]	75	$C_{20}H_{30}O_3$	12-6	12-6
85	8	64-65[a]	63	$C_{21}H_{32}O_3$	6-3	6-3
86	9	47-48[c]	52	$C_{22}H_{34}O_3$	Inact.	12-6
87	10	70-72[b]	72	$C_{23}H_{36}O_3$	25-12	25-12

[a] Recrystallized from Et_2O-pentane; [b] 2-PrOH; [c] Et_2O. [d] Boiling point (mm).

mol) of **61** and 3.74 g (0.01845 mol) of DCC in 50 mL of CH_2Cl_2 was added 3.45 g (0.0165 mol) of 4-morpholinobutyric acid hydrochloride. The mixture was stirred at room temperature for 2 days. The cyclohexylurea was removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated to dryness and the gummy residue triturated with Et_2O. The resulting solid was collected and dried: 7.45 g (91%); mp 57–59 °C. Anal. ($C_{27}H_{41}NO_5 \cdot HCl$) C, H, N, Cl.

1-Hydroxy-9-(4-methoxyphenyl)nonane (XVII). To a solution of 81.5 g (0.308 mol) of 9-(4-methoxyphenyl)nonanoic acid[15] in 460 mL of anhydrous THF was added, at 0 °C, 460 mL (0.460 mol) of 1 M BH_3·THF dropwise. After the addition was complete, the solution was stirred at room temperature for 1.5 h, cooled, and treated dropwise with 280 mL of 2 N HCl. The mixture was stirred for an additional 2 h and then concentrated in vacuo. When most of the THF was removed, the remaining solution was heated to 100 °C and stirred for 3 h. After cooling, the mixture was extracted four times with 200-mL portions of Et_2O. The combined Et_2O layers were washed and dried and the solvent was removed. The residual solid was recrystallized from

Table VIII. 4-[6-(4-Hydroxyphenyl)hexyl]-3,5-heptanedione (61)



Tissue culture, in vitro			Organ culture, in vitro			
Virus	Type	MIC, μg/mL	Virus	Tissue	Concn, μg/mL	% redn in virus yield
Human rhino type 2	RNA	3	Influenza A_2 Jap 170	Ferret trachea	100	94
Human rhino type 14	RNA	6			200	99.9
Human rhino type 17	RNA	6				
Equine rhino	RNA	3	Equine rhino	Monkey trachea	100	95
Parainfluenza	RNA	3				
Resp. syncytial	RNA	6				
Herpes simplex type 1	DNA	12				
Herpes simplex type 2	DNA	12				

Table IX. In Vitro Comparison of Compound 61 with Other Active Antiviral Agents

	Minimal viral inhibitory concn, μg/mL	
Agent tested	Herpes simplex type 1, Sheely strain, μL/mL	Herpes simplex type 2, Curtis strain, μL/mL
61	12	12
Idoxuridine	6	6
ara-A	12	12
ara-C	<3	<3

Et_2O: 74 g (96%); mp 45–46.5 °C. Anal. ($C_{16}H_{26}O_2$) C, H.

1-(4-Hydroxyphenyl)-9-iodononane (XVIII). A solution of 61.5 g (0.246 mol) of XVII in 500 mL of HOAc and 196 mL of 47% HI was refluxed for 24 h. After the initial 6 h an additional 98 mL of 47% HI was added. The solution was concentrated in vacuo and the residual oil extracted with H_2O–Et_2O. The organic layer was collected and the aqueous layer extracted twice with 500-mL portions of Et_2O. The combined organic layers were washed with H_2O and then with 200 mL of a 5% $Na_2S_2O_5$ and finally with an additional 200 mL of H_2O. After drying, the solvent was removed and the residual solid recrystallized from MeOH–pentane: 69.5 g (81.5%); mp 63–65 °C. Anal. ($C_{15}H_{23}IO$) C, H, I.

4-[8-Oxo-7-(1-oxopropyl)decyl]phenyl 4-Methylbenzoate (77). To 6.8 g (0.04 mol) of **61** in 30 mL of pyridine was added dropwise 6.93 g (0.045 mol) of *p*-toluoyl chloride over a period of 10 min. The temperature was maintained at 5–10 °C for 2 h and the mixture was then left overnight in the refrigerator. The mixture was poured into H_2O and extracted three times with 100-ml portions of Et_2O. The combined Et_2O extracts were washed with 2 N HCl, H_2O, and 5% $NaHCO_3$ and finally dried. Removal of the solvent gave 11.5 g of yellow solid which was purified by column chromatography. The material obtained was crystallized from pentane: 5.0 g (58%); mp 72–74 °C. Anal. ($C_{27}H_{34}O_4$) C, H.

4-[6-(4-Chloro-2-hydroxyphenyl)hexyl]-3,5-heptanedione (70). To a solution of 53 g (0.15 mol) of **69** in 300 mL of CH_2Cl_2 cooled to −70 °C was added dropwise 57 g (0.227 mol) of BBr_3 in 300 mL of CH_2Cl_2 over a 45-min period. The solution was stirred at this temperature for an additional 2 h and then left at room temperature overnight. The solution was poured into 2 L of H_2O and 500 mL of Et_2O added. The ethereal layer was separated after stirring for 45 min and washed with $NaHCO_3$ and dried. Removal of the solvent gave 52 g of oil which was put on a chromatographic column containing 1.5 kg of SiO_2 and eluted with a solution of 1 part $CH_3COOC_2H_5$ and 1 part hexane. Oil (42 g) was obtained which was crystallized from Et_2O–hexane giving 24 g of solid: mp 58–59 °C. Anal. ($C_{19}H_{27}ClO_3$) C, H, Cl.

References and Notes

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