base was collected and washed with H_2O: yield 46.5 g (87%); mp 59 °C. Anal. ($C_{18}H_{21}NO$) C, H, N. The hydrochloride was prepared by conventional procedure and was crystallized from *i*-PrOH, mp 187 °C. Anal. ($C_{18}H_{21}NO$·HCl) C, H, Cl, N.

4′-(β-Phenylethyl)-3-(dimethylamino)propiophenone was prepared according to the above procedure from 4′-(β-phenylethyl)acetophenone. The hydrochloride was prepared by conventional procedure and crystallized from *i*-PrOH: yield 70%; mp 144–145 °C. Anal. ($C_{19}H_{23}NO$·HCl) C, H, Cl, N.

***N*-[β-(4-Phenylbenzoyl)ethyl]imidazole (16). Method E.** A stirred mixture of 4′-phenyl-3-(dimethylamino)propiophenone hydrochloride (2.9 g, 0.01 mol), imidazole (0.68 g, 0.01 mol), and 15 mL of 50% EtOH was refluxed for 3 h. After the mixture cooled, the separated crystals were collected and recrystallized (see Table I).

General Procedure for the Preparation of *N*-(ω-Phenyl-ω-hydroxyalkyl)imidazoles. Method F. A mixture of the appropriate *N*-(benzoylalkyl)imidazole (0.01 mol), $NaBH_4$ (0.38 g, 0.01 mol), and 20 mL of MeOH was refluxed for 2 h. After solvent evaporation, 20 mL of H_2O was added to the residue. The mixture was neutralized with dilute HCl and than refluxed for 30 min. After the mixture cooled, the solution was alkalinized with NaOH, and the precipitate was collected and crystallized. Yields, melting points, solvents of crystallization, and analytical data are reported in Table III.

***N*-[β-(4-Aminophenyl)-β-hydroxyethyl]imidazole (26). Method G.** A solution of *N*-[β-(4-nitrophenyl)-β-hydroxyethyl]imidazole hydrochloride (25; 2.69 g, 0.01 mol) in 40 mL of 50% MeOH was reduced with H_2 in the presence of 5% Pd/C catalyst (0.2 g) in a Parr apparatus with an initial pressure of 60 psi. After the solution was filtered, the solvent was evaporated and the residue was crystallized (see Table III).

Determination of Partition Coefficients. Partition coefficients of *N*-phenacylimidazole (42) and *N*-(β-phenyl-β-hydroxyethyl)imidazole (47) were experimentally measured by a modified Hansch procedure, employing a 1-octanol/phosphate buffer (0.2 M, pH 7.4, ionic strength adjusted to 0.5 with KCl) system. Partitioning was carried out at room temperature (20 ± 5 °C) with gentle shaking for 6 h. After centrifugation (15 min at 2000 rpm), the octanol phase was analyzed by gas chromatography (Hewlett Packard 5830A instrument). The amount of solute found was then subtracted from the total sample to obtain the amount in the second phase. Three repetitions were made to ensure an unforeseen loss.

The observed log P_{app} values were corrected by ionization according to the formula[10] $\log P = \log P_{app} - \log (1/1 + 10^{pK_a'-pH})$, obtaining log *P* values of 1.03 for 42 and 0.99 for 47. The calculated log *P* values reported in the text were obtained by adding the π values taken from the compilation of Hansch et al.[11] to the above experimentally obtained values.

Determination of Ionization Constants. The ionization constants of *N*-phenacylimidazole (42; $pK_a' = 6.32$ at 22 °C) and *N*-(β-phenyl-β-hydroxyethyl)imidazole (47; $pK_a' = 6.68$ at 22 °C) were determined by potentiometric titration according to Albert and Serjeant.[12] Methanolic–aqueous solutions (10^{-3} M) of the hydrochlorides were titrated with 0.02 M KOH using a glass–calomel electrode system on an expanded pH scale. pK_a' values obtained from different methanolic–aqueous mixtures were plotted vs. the corresponding methanol concentration, and extrapolation was made to calculate the pK_a' corresponding to a purely aqueous solution.

Pharmacological Methods. NMRI albino mice of either sex, weighing 20–30 g, were employed for pharmacological studies. The compounds were tested ip and po as aqueous solutions or suspensions in 10% aqueous acacia gum. LD_{50} values were determined in mice both intraperitoneally and orally (10 animals per dose). The mortality rate was recorded over a 7-day period. The animals were also observed for their behaviorial symptoms according to the Irwin scheme.[13] The anticonvulsant activity was evaluated by the maximal electroshock seizure test (MES), using a modification of the method described by E. A. Swinyard.[14] Groups of 10 animals were employed. Maximal seizures were elicited, by a 60-Hz alternating current of 25 mA delivered for 0.2 s via corneal electrodes, 30–60 min after administration. The failure to show tonic–extensor seizures indicated protecting activity. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[15]

Acknowledgment. We thank B. Olgiati for microanalytical data.

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Synthesis and Antiherpetic Activity of Some 4-[(Aryloxy)alkyl]pyrazoles[1]

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A series of 4-[(aryloxy)alkyl]pyrazoles has been prepared and evaluated in vitro against Herpes simplex virus type 2. Several compounds exhibited minimum inhibitory concentrations in the range of 0.7–6 μg/mL. Some of the more active homologues were evaluated in vivo in the mouse genital model against Herpes simplex virus (HSV) types 1 and 2. At a concentration of 5%, an aqueous solution of compound **3** exhibited a 60% survival rate against HSV-1 and 90% against HSV-2.

We have recently reported on the antiviral evaluation of several series of β-diketones[2-4] and have tested the more promising compounds against Herpes simplex viruses (HSV) in vivo.[5] As an extension of this work, we have

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(2) G. D. Diana, U. J. Salvador, E. S. Zalay, R. E. Johnson, J. C. Collins, D. Johnson, W. B. Hinshaw, R. R. Lorenz, W. H. Thielking, and F. Pancic, *J. Med. Chem.*, **20**, 750 (1977).
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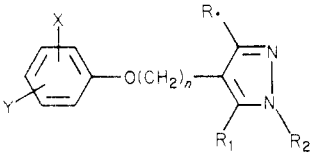
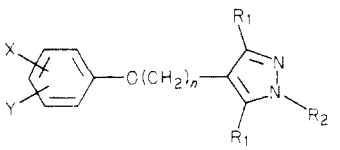
Table I



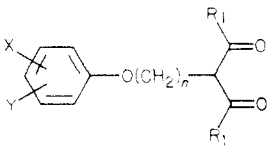
no.	X	Y	n	R_1	R_2	mp or bp (mm), °C	% yield[b]	formula[c]	MIC,[a] μg/mL, of HSV-2[d]
1	2-Cl	4-CH_3O	4	C_2H_5	H	117-119[e]	60.6	$C_{18}H_{25}ClN_2O_2 \cdot HCl$	6
2	2-Cl	4-CH_3O	5	C_2H_5	H	80-83[e]	70.9	$C_{19}H_{27}ClN_2O_2 \cdot HCl$	6
3	2-Cl	4-CH_3O	6	C_2H_5	H	*f*	68.7	$C_{20}H_{29}ClN_2O_2$	6
4	2-Cl	4-CH_3O	7	C_2H_5	H	109-110[e]	43.2	$C_{21}H_{31}ClN_2O_2 \cdot HCl$	6
5	2-Cl	4-CH_3O	6	CH_3	H	150-151[g]	60.2	$C_{18}H_{25}ClN_2O_2 \cdot HCl$	3
6	2-Cl	4-CH_3O	6	CH_3	CH_3	200-205 (0.03)	33.7	$C_{19}H_{27}ClN_2O_2$	0.7
7	2-Cl	4-CH_3O	6	CH_3	C_2H_5	*h*	35.3[i]	$C_{20}H_{29}ClN_2O_2$	0.7
8	2-Cl	4-CH_3O	6	CH_3	$(CH_2)_2CH_3$	195-200 (0.025)	23.7[i]	$C_{21}H_{31}ClN_2O_2$	1.5
9	2-Cl	4-CH_3O	6	CH_3	$(CH_2)_3CH_3$	210 (0.05)	36.9[i]	$C_{22}H_{33}ClN_2O_2$	6
10	2-Cl	4-CH_3O	5	C_2H_5	CH_3	190-200 (0.1)	47.9	$C_{20}H_{29}ClN_2O_2$	3
11	2-Cl	4-CH_3O	6	C_2H_5	CH_3	190-195 (0.01)	44.5	$C_{21}H_{31}ClN_2O_2$	6
12	2-Cl	4-CH_3O	6	C_2H_5	C_6H_5	215-220 (0.05)	22.7	$C_{26}H_{33}ClN_2O_2$	3
13	2-Cl	4-CH_3O	7	CH_3	CH_3	175-185 (0.1)	44.5	$C_{20}H_{29}ClN_2O_2$	0.7
14	2-Cl	4-CH_3O	6	C_2H_5	CH_2CH_2OH	*j*	53.4	$C_{22}H_{33}ClN_2O_3$	12
15	2-Cl	4-CH_3O	6	C_2H_5	CH_2CF_3	*k*	72.5	$C_{22}H_{30}ClF_3N_2O_2$	inact
16	2-Cl	4-CH_3O	6	C_2H_5	$CH_2COOC_2H_5$	205-210 (0.05)	78.5	$C_{24}H_{35}ClN_2O_4$	6
17	2-Cl	4-CH_3O	6	C_2H_5	CH_2COOH	121-123[l]	82.3[m]	$C_{22}H_{31}ClN_2O_4$	inact
18	2-Cl	4-CH_3O	6	C_2H_5	4-morpholinobutyryl	93-95	37.8[n]	$C_{28}H_{42}ClN_3O_4 \cdot HCl$	3
19	2-Cl	4-CH_3O	6	C_2H_5	$OCCH_3$	182-186 (0.05)	84.5[n]	$C_{22}H_{31}ClN_2O_3$	inact
20	2-Cl	4-CH_3O	6	C_2H_5	$(CH_2)_2N(CH_3)_2$	210-215 (0.03)	78	$C_{24}H_{38}ClN_3O_2$	6
21	2-Cl	4-CH_3O	6	C_2H_5	2-pyridyl	215-222 (0.025)	81.8	$C_{25}H_{32}ClN_3O_2$	6
22	2-Cl	4-CH_3O	6	C_2H_5	H	147-150[g]	51.1	$C_{28}H_{29}ClN_2O_2 \cdot HCl$	3
23	2-Cl	4-NO_2	6	C_2H_5	H	130-132[g]	78.6	$C_{19}H_{26}ClN_3O_3 \cdot HCl$	inact
24	H	4-Br	6	C_2H_5	H	78-80[g]	87.9	$C_{19}H_{27}BrN_2O$	inact
25	2,5-Cl_2	4-CH_3O	6	C_2H_5	H	148-150[g]	57.2	$C_{20}H_{28}Cl_2N_2O_2 \cdot HCl$	inact
26	2-Cl	4-OH	6	C_2H_5	H	109-111[g]	31.7[o]	$C_{19}H_{27}ClN_2O_2$	12
27	H	H	6	C_2H_5	H	119-121[e]	41.9	$C_{19}H_{28}N_2O \cdot HCl$	inact
28	H	4-Cl	6	C_2H_5	H	130-132[g]	8	$C_{19}H_{27}ClN_2O \cdot HCl$	6
29	H	4-CH_3O	6	C_2H_5	H	103-105[g]	22	$C_{20}H_{30}N_2O_2 \cdot HCl$	inact
30	2-Cl	4-CH_3S	6	C_2H_5	H	150-152[p]	70.5	$C_{20}H_{29}ClN_2OS \cdot HCl$	inact
31	2-Cl	4-CH_3SO	6	C_2H_5	H	107-108[e]	51.6	$C_{20}H_{29}ClN_2O_2S \cdot HCl$	3

[a] Minimum inhibitory concentration. [b] Yields refer to analytically pure product. [c] Analyzed for C, H, and N or Cl where applicable. [d] Herpes simplex virus type 2. [e] Recrystallized from isopropyl acetate. [f] See experimental preparation for purification. [g] Recrystallized from acetonitrile. [h] Pure sample obtained by column chromatography on silica and eluted with hexane-ethyl acetate-acetonitrile (4:2:1). [i] Prepared by the alkylation of 5 (see Experimental Section). [j] Pure sample obtained by column chromatography on silica and eluting with ethyl acetate. [k] Pure sample obtained by column chromatography on silica and eluting with ether. [l] Recrystallized from methanol. [m] Prepared by the hydrolysis of 16. [n] Prepared from 3. [o] Recrystallized from ethanol. [p] See Experimental Section for preparation.

prepared a series of pyrazoles (I) derived from the β-diketones II and evaluated them against HSV types 1 and 2.



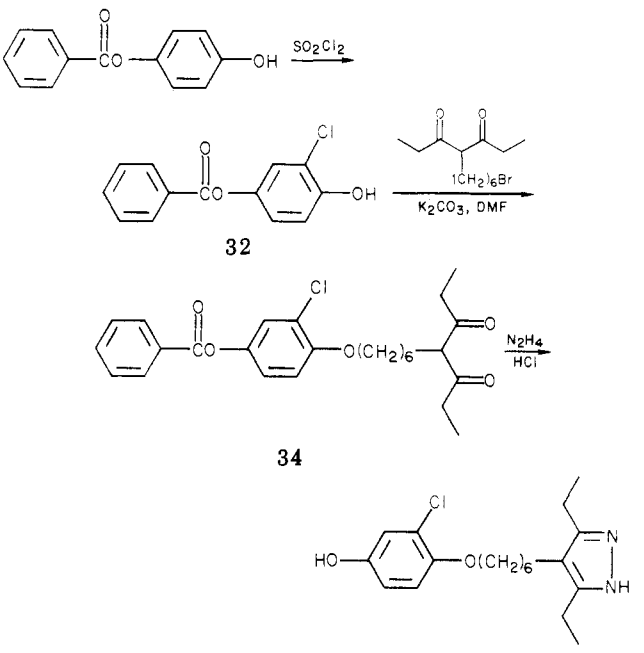
I



II

Chemistry. With few exceptions, the compounds were prepared from the diketones II and the appropriate hydrazines. Compounds **7**–**9** were prepared by the alkylation of **5**, using sodium hydride in DMF, and compounds **18** and **19** were obtained by the acylation of **3** (Table I). The synthesis of compound **26** is outlined in Scheme I. Treatment of (benzoyloxy)phenol with sulfuryl chloride gave the chlorophenol **32** in 59% yield. **34** was obtained from **32** as an oil and was treated, without purification,

Scheme I



(5) B. A. Steinberg and F. Pancic, paper presented at the 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, Oct 27–29, 1976.

Table II. Comparative Effect of Compounds 3, 7, and 13 on the Survival Rate of Mice Infected Intravaginally with Herpes Simplex Virus Type 2

compd	daily dose (b.i.d.),[a,b] %	% survival	av survival time, days
3	5	60	>11
	2.5	40	>11
	1.25	30	>10
7	10	30	>9
	5	30	>10
13	10	30	>10
	5	10	>7
placebo		10	>6

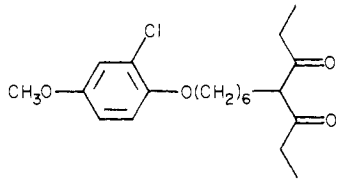
[a] Administered intravaginally in gum tragacanth. [b] Treatment initiated 4 h postinfection and continued for 7 days.

with hydrazine hydrate, followed by 6 N HCl, to give **26** in 57.2% yield.

Biological Results

The compounds in Table I were evaluated in vitro against HSV-2 according to the procedure which was described in a previous publication.[2] Drawing from the results we obtained from our related work with regard to the effect of substituents on antiviral activity, we initially chose to utilize the 2-chloro-4-methoxyphenyl group and to examine the effects of varying the length of the alkyl bridge. In addition, we examined, to a limited degree, the effect of different groups in the 1, 3, and 5 positions of the pyrazole ring. Varying the bridge from butyl to heptyl (compounds 1–4) had no effect on the minimum inhibitory concentration (MIC). When R_1 was changed from ethyl to methyl, where $n = 6$, an increase in activity was apparent (compound **5**). An even more dramatic change was observed when a methyl group was introduced in the 1 position (**6**), where the MIC was 0.7 μg/mL. The analogous compound where $R_1 = C_2H_5$ (**11**), although exhibiting activity equal to the demethyl homologue **4**, was considerably less active than **6**. This high level of activity was maintained when an ethyl group was introduced in the 1 position (**7**) and, to a lesser degree, with the introduction of a propyl group (**8**). Compound **13**, where $n = 7$ and R_1 and R^2 = methyl, also exhibited an MIC of 0.7 μg/mL. The morpholinobutyramide (**18**) was prepared in an effort to solubilize the molecule. This compound did exhibit appreciable activity. Although the ester **16** demonstrated activity, the corresponding acid **17** was inactive.

Since compound **3** is the pyrazole analogue of Arildone (III), it was evaluated along with compounds **7** and **13** in



III

the mouse genital screen against herpes simplex virus type 2 according to the procedure described under Experimental Section. The results obtained are summarized in Table II.

The relative activities demonstrated by the compounds in Table II were interesting when relating them to the in vitro results. Compound **3** consistently produced a higher percentage of survivors.

Since a water-soluble compound would be much more desirable, we prepared several salts of **3**. In order to prepare stable salts, it was necessary to use strong acids, since in many cases dissociation in water was sufficient to precipitate the free base. We finally were successful in preparing the methanesulfonate salt **3a**, which was sufficiently stable in aqueous solution. This salt was tested intravaginally in the mouse[6] with 1% gum tragacanth in water and compared with phosphonoacetic acid (PAA), adenine arabinoside (*ara*-A), and iododeoxyuridine (IdUrd). The results are shown in Table III. Treatment was started 4 h postinfection and carried out for 7 days. The test was terminated at 14 days. Any surviving mice were arbitrarily assigned a survival time of >14. The survival rate of mice treated with 5% **3a** was 80 and 60% for the 2% concentrate as compared to 0% in the control group. The average survival time for the animals treated with 5% of **3a** was >13 and >11 days for the group treated with 2% of the drug. Mice treated with 5% PAA had a 90% survival rate with an average survival time of >13 days, while those treated with 2% PAA also had a 90% survival rate with an average survival time of >13 days. Mice treated with 5% *ara*-A had a 60% survival rate, and those treated with 2% *ara*-A had a survival rate of 10%, which was the same as the control. The average survival time of the two groups was >13 and >9 days, respectively. Although animals treated with 2% IdUrd had a very low survival rate, the average survival time for the medicated group was >11.0 days vs. >6 days for the placebo-treated controls.

Table III. Comparative Effect on the Survival Rate with 3a, Phosphonoacetic Acid, *ara*-A, and IdUrd Administered Intravaginally in Mouse Herpes Genitalis (HSV-2)

drug prepared in water + 1% gum tragacanth	daily dose (b.i.d.),[a] %	% survival	av survival time, days
placebo		0	6
3a	2	60	>11
	5	80	>13
PAA	2	90	>13
	5	90	>13
ara-A	2	10	>9
	5	60	>13
IdUrd	2	40	>11
	5	10	>9

[a] Treatment started 4 h postinfection.

Table IV. Effect of Intravaginally Administered 3a on the Survival of Mice Infected with Herpes Simplex Virus Types 2 and 1

treatment[a]	daily dose (b.i.d.), %	% survival	av survival time, days
	HSV-2		
3a in water	10	90	>13
	5	90	>13
	2.5	70	>12
	1.25	40	>10
placebo control		20	>8
	HSV-1		
3a in water	10	70	>13
	5	60	>12
	2.5	40	>11
	1.25	30	>10
placebo control		30	>9

[a] Treatment started 4 h postinfection.

(6) J. C. Overall, Jr., E. R. Kern, R. I. Schlitzer, S. B. Friedman, and I. A. Glasgow, *Infect. Immun.*, 11, 476 (1975).

Table V. Effect of Compound 3a on the Growth of Virus in the Vagina of Mice Infected with Herpes Simplex Type 2, Curtis Strain[a]

medication	day of sampling					
	1	2	3	4	6	7
placebo	1/10[b]	2/10	4/10	5/10	3/6[c]	all dead
10% 3a	0/10	0/10	0/10	0/10	0/10	0/10
5% 3a	1/10	0/10	0/10	0/10	0/8	0/8
2.5% 3a	0/10	1/10	0/10	0/10	0/10	0/8
1.25% 3a	0/10	1/10	0/10	0/10	ND[d]	0/7

[a] Medication administered topically with drug-impregnated tapons 4 h postinfection. [b] Numerator = number of mice with recoverable virus; denominator = number of mice sampled. [c] Denominator less than 10 indicates death of mice; a denominator of 6 indicates that 4 mice died. [d] ND = not determined.

Compound **3a** was tested against HSV-1 and -2 in an aqueous solution. The results are shown in Table IV. In this test a 5% solution of **3a** produced a 90% survival rate against HSV-2 as opposed to 20% for the placebo control with an average survival time of >13 and >8 days, respectively. Under the same conditions, a 10% solution of **3a** gave a 70% survival and an average survival time of >13 days.

As further indication of the activity of **3a**, the titer of virus recovered from the vaginal tract was determined after treatment with various concentrations of drug. The results shown in Table V indicate that virus was not detected in washings from animals treated with 10% of **3a** on days 1 through 7. This group showed 100% survival at the end of 14 days postinfection. At the end of same period, in the group of mice treated with 5, 2.5, and 1.25% of **3a**, virus was detected in only one animal in each group. In the placebo-treated animals, virus was detected in 5 out of 10 animals on day 4 postinfection, and by day 7 postinfection all ten animals had died.

Discussion

Among the compounds in Table I which exhibited high levels of antiherpetic activity, compound **3** emerged as a candidate for further in vivo evaluation. The activity of the compounds tested in vivo did not reflect the relative levels of in vitro activity, since compound **3** exhibited the highest MIC (lowest level of activity) of the compounds tested. The effects of the methanesulfonate salt, **3a**, were very encouraging, since this allowed us to administer the drug as an aqueous solution. The results obtained with **3a** were more impressive than those obtained using the free base **3**. At the end of the 14-day postinfection period, the survival rate of HSV-2 and HSV-1 infected animals treated with a 10% aqueous solution of **3a** ranged from 90 to 70%.

At the present time, the mode of action of these compounds is unknown; however, they are not virucidal but, rather, appear to interfere with viral replication.

Experimental Section

Melting points were run according to the USP procedure 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, NY, and Galbraith Laboratories, Knoxville, TN. NMR spectra were determined on a Varian HA-100 spectrophotometer and the mass spectra on a Jeolco double-focusing high-resolution mass spectrophotometer by S. Clemans. Diketones whose syntheses are not described in this paper were previously reported.[3]

Mouse Genital Infection with Herpes Simplex Virus Types 1 and 2. Swiss, albino, Blue Spruce female mice weighing 11–13 g were divided into groups of 10 and were infected intravaginally with approximately 100 000 $TCID_{50}$'s of herpes virus per mouse. Virus suspensions were delivered into the vagina in cotton tampons (no. 4 dental pellets) saturated with a virus suspension. Animals were treated intravaginally, starting 4 h postinfection, with a cotton tampon saturated with the appropriate concentration of drug in gum tragacanth. The tampons were left inserted for 24 h but were moistened 6 h after insertion with a second treatment consisting of 0.02 mL of drug suspension. Tampons were removed daily and replaced with fresh, saturated tampons, followed by the addition of 0.02 mL of compound 6 h later. The treatment was carried out for 4 days. Mice were kept for 14 days postinfection, and deaths were recorded daily. Placebo-treated animals developed severe vaginitis, followed by fatal ascending paralysis, usually developing 4–5 days postinfection.

The quantity of virus recovered from the vaginal tract was determined after treatment with various concentrations of compound **3** or placebo, by daily sampling. In these experiments, groups of mice were infected with HSV-2, Curtis strain, and treated with solutions containing 10, 5, 2.5, and 1.25% of **3** administered intravaginally in saturated cotton tampons, starting 4 h postinfection. Samples were obtained by daily vaginal washings from day 1 through 7 postinfection. Washings were done each morning, prior to the insertion of fresh tampons, by gently introducing 1.5 mL of tissue culture medium M-199 into the vagina with a syringe and recovering the washings in sterile vials. The washings were frozen at −70 °C and assayed in BSC-1 cells.

Preparation of Pyrazoles. 4-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-3,5-diethyl-1*H*-pyrazole (3). A solution of 7.4 g (0.02 mol) of 4-[6-(2-chloro-4-methoxyphenoxyl)hexyl]-3,5-heptanedione,[3] 2.0 mL (0.041 mol) of 100% hydrazine hydrate, and 40 mL of C_2H_5OH was heated to reflux and left for 5 h. The resulting solution was concentrated to dryness in vacuo leaving a viscous oil which was dissolved in 150 mL of CH_2Cl_2 and stirred for 2 h with 100 g of silica gel. The mixture was filtered and the filtrate concentrated to an oil. This material, 5 g, appeared to be one component when examined by thin-layer chromatography and was submitted for analysis without further purification. Anal. ($C_{20}H_{29}ClN_2O_2$) C, H, N. The methanesulfonate salt, **3a**, was prepared by adding 1.32 g (0.0137 mol) of methanesulfonic acid to 5 g (0.0137 mol) of **3** in 25 mL of ethanol. The resulting solution was concentrated to dryness and the resulting oil triturated with ether to give a white solid. The material was recrystallized from CH_3CN-Et_2O to give 3.8 g (64%), mp 93–95 °C. Anal. ($C_{20}H_{29}ClN_2O_2 \cdot CH_3SO_3H$) C, H, Cl.

4-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-1-ethyl-3,5-dimethyl-1*H*-pyrazole (7). To a solution of 6.8 g (0.02 mol) of 4-[6-(2-chloro-4-methoxyphenoxy)hexyl]-3,5-dimethyl-1*H*-pyrazole (**6**) in 100 mL of DMF was added 1.13 g of 50% NaH (0.024 mol) which was washed twice with hexane. The mixture was stirred at room temperature for 1 h, and then 3.8 g (0.0243 mol) of C_2H_5I was added and the mixture was stirred at room temperature for 16 h. The mixture was concentrated in vacuo, and the residue was extracted with dilute HCl and CH_2Cl_2. The organic layer was washed with H_2O and dried. Removal of the solvent gave a brown oil which was passed through 400 g of silica gel using a mixture of hexane/ethyl acetate/acetonitrile in the ratio of 4:2:1, respectively. The product was obtained as a yellow oil: yield 2.6 g (35.3%). Anal. ($C_{20}H_{29}ClN_2O_2$) C, H, N.

4-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-3,5-diethyl-1*H*-pyrazole-1-acetic Acid (17). A mixture of 21 g (0.049 mol) of **16** and 150 mL of 10% NaOH solution was heated on a steam bath for 5 min, after which time a clear solution was obtained. H_2O, 100 mL, was added, and the solution was heated for an additional 10 min. The solution was then chilled and acidified with concentrated HCl. A white solid separated and was collected after chilling. The material was recrystallized from CH_3OH to give 17.4 g (82.3%), mp 121–123 °C. Anal. ($C_{22}H_{31}ClN_2O_4$) C, H, N.

4-[6-(2-Chloro-4-methoxyphenoxy)hexyl]-3,5-diethyl-1-[4-(4-morpholinyl)-1-oxobutyl]-1*H*-pyrazole Hydrochloride (18). A mixture of 27 g (0.074 mol) of **3**, 15.95 g (0.074 mol) of 4-morpholinobutyric acid hydrochloride, 16.83 g (0.074 mol) of dicyclohexylcarbodiimide, and 180 mL of CH_2Cl_2 was stirred at room temperature for 5 days. The solid was removed by filtration and the filtrate was concentrated to dryness, leaving a thick gum which solidified on trituration with $(C_2H_5)_2O$. The solid was collected, washed with $(C_2H_5)_2O$, and dried: yield 15.5 g (37.8%); mp 93–95 °C. Anal. ($C_{28}H_{42}ClN_3O_4 \cdot HCl$) C, H, N.

2-Chloro-4-(benzoyloxy)phenol (32). To a suspension of 107.1 g (0.5 mol) of 4-(benzoyloxy)phenol[7] in 1500 mL of $CHCl_3$ was added dropwise 67.5 g (0.5 mol) of SO_2Cl_2 in 100 mL of $CHCl_3$ over a 30-min period. The suspension was then stirred overnight at room temperature. A small amount of undissolved material was separated by filtration and the filtrate was concentrated in vacuo to a white solid. The material was recrystallized from EtOAc: yield 73.5 g (59.2%); mp 123–124 °C. Anal. ($C_{13}H_9ClO_3$) C, H, Cl.

4-[6-(2-Chloro-4-hydroxyphenoxy)hexyl]-3,5-diethyl-1*H*-pyrazole (26). A mixture of 24.9 g (0.1 mol) of 2-chloro-4-(benzoyloxy)phenol (**32**), 29.1 g (0.1 mol) of 4-(6-bromohexyl)-3,5-heptanedione,[3] 27.6 g (0.2 mol) of anhydrous K_2CO_3, 6 g of KI, and 400 mL of CH_3COCH_3 was refluxed with stirring for 24 h. The insoluble material was removed by filtration. The filtrate was concentrated to ~100 mL and diluted with 500 mL of $(C_2H_5)_2O$, and then the organic layer was washed with H_2O and dried. Removal of the solvent gave an oil, 45.9 g, which would not solidify. To a solution of 14.2 g (0.1 mol) of the oil obtained above in 50 mL of absolute C_2H_5OH was added 10 mL (0.2 mol) of hydrazine hydrate. The solution was refluxed with stirring for 2 h and then the solvent was removed in vacuo. To the residual oil was added 20 mL of 6 N HCl and the mixture was stirred until a solid formed. The material was collected and recrystallized from CH_3CN: yield 12.2 g (31.79%); mp 109–111 °C. Anal. ($C_{19}H_{27}ClN_2O_2$) C, H, N.

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4-[6-[2-Chloro-4-(methylthio)phenoxy]hexyl]-3,5-heptanedione (33). A mixture of 25.7 g (0.147 mol) of 2-chloro-4-(methylthio)phenol,[8] 48.6 g (0.15 mol) of 4-(6-bromohexyl)-3,5-heptanedione, 25 g (0.18 mol) of K_2CO_3, 2 g of KI, and 250 mL of $CH_3CH_2COCH_3$ was refluxed with stirring for 20 h. The solid was removed by filtration and the filtrate was concentrated to dryness. The residue was triturated with CH_2Cl_2 and the resulting suspension was filtered. The filtrate was again concentrated to an oil, which was distilled: bp 170 °C (0.4 mm); yield 46.9 g (82.3%). Anal. ($C_{20}H_{29}ClO_3S$) C, H, Cl.

4-[6-[2-Chloro-4-(methylsulfinyl)phenoxy]hexyl]-3,5-heptanedione (35). To a solution of 14 g (0.066 mol) of $NaIO_4$ in 250 mL of H_2O was added, with stirring, a solution of 23.5 g (0.0611 mol) of **33** in 250 mL of CH_3OH. The solution was stirred at room temperature for 18 h, during which time $NaIO_3$ precipitated. The mixture was concentrated in vacuo to a solid and then stirred with CH_2Cl_2 and filtered. The filtrate was concentrated to an oil, which was passed through a chromatographic column packed with 200 g of silica and eluted with ether to remove less polar impurities and then with MeOH. The material obtained by elution with MeOH was then passed through a high-pressure liquid chromatography column and eluted with a solution of 5% CH_3COCH_3–95% ether, and the product was obtained as an orange viscous oil: yield 11.5 g (81%). Anal. Calcd for $C_{20}H_{29}ClO_4S$: C, 59.91; H, 7.29; Cl, 8.84. Found: C, 58.93; H, 7.28; Cl, 8.50.

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Pyrazolo[5,1-*b*]quinazolin-9-ones: A New Series of Antiallergic Agents

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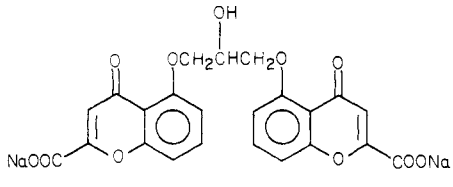
A new series of antiallergic agents, pyrazolo[5,1-*b*]quinazolin-9-ones, was synthesized and evaluated for inhibitory effects in the rat reaginic passive cutaneous anaphylaxis (PCA) screen. Several analogues were found to be more potent than cromolyn sodium intravenously. Structure–activity relationships are discussed. One of the compounds, 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (**36**), was found to be approximately 250 times more potent than cromolyn sodium intravenously.

Cromolyn sodium (DSCG, 1) is a well-established drug



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for the treatment of asthma. Since its discovery, there have been intensive efforts in numerous laboratories to find additional DSCG-like antiallergic agents.[1] The dose (20 mg) of 1 is too large to be delivered by a metered-dose inhaler, so it has to be insufflated as a powder. This method of powder administration poses problems for young patients lacking coordination, and in some individuals the powder can cause irritation and bronchospasm. Moreover, recent studies[2] using ^{99m}Tc-labeled particles suggest that it is likely that there is considerable variation in the quantity and distribution of inhaled drug in patients with airway obstruction. This demonstrates the difficulty in delivering the right amount of drugs to the target organ via the inhalation route. The difficulty is further compounded when the drug must be delivered in high doses, as in the case of 1 (20 mg/dose). Hence, a compound which is at least 100–300 times more potent than 1 will reduce the dose (0.2–0.07 mg/dose) to a more acceptable range, thereby reducing the variability in the amount of drugs delivered to the target organ, and will probably increase the efficacy of the drug.

A desirable compound should share with cromolyn sodium[3] the capacity to inhibit allergen-induced mast-cell

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