amine, according to the procedure of Phillips,[29] and used in the preparation of N,N′-hexamethylene bis-{2-[1,N-dimethyl-3-(2,2,6-trimethylcyclohexyl)propylamino]acetamide}bis(methyl chloride) (Table IV, **24**). For the preparation of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]}ammonium chloride (Table IV, **20**), 1,2-bis-(2-iodoethoxy)ethane was used as the starting material. The latter was prepared from the commercially available 1,2-bis(2-chloroethoxy)ethane ("triglycol dichloride") by treatment with sodium iodide in acetone.[30]

N,N′-Bis[1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]-N,N′-dimethyl-1,3-propanediamine Bis(methobromide) Dihydrate. Method E.—Compound **2** (Table III) is described as a representative example. [1-Methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]dimethylamine (13.4 g., 0.06 mole) (Table I, **2**) and 6.1 g. (0.03 mole) of 1,3-dibromopropane was dissolved in 150 ml. of ethanol and refluxed for 72 hr. The colorless solution was concentrated to a sirup at steam temperature and water vacuum. The sirup was triturated with ether and crystallized from acetone–ether, to give 9.3 g. (45%) of product, m.p. 195–196°.

N,N′-Bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexanediamine Bis(methochloride). Method F.—Compound **7** (Table IV) may serve as a representative example. To 5 g. of N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexanediamine (Table II, **5**), dissolved in 100 ml. of methanol, was added, at 4°, 10 g. of methyl chloride dissolved in 100 ml. of methanol. The solution was heated in a closed vessel at 60° for 15 hr. The colorless solution was concentrated and the resulting white solid crystallized from ethanol–acetonitrile–ether, to give 4.5 g. (74%) of material, m.p. 255–257°.

The synthesis of **[ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-dimethylcyclohexyl)propyl]}ammonium chloride** (Table IV, **20**) is an example of Method G.—To 18.5 g. (0.05 mole) of 1,2-bis(2-iodoethoxy)ethane,[30] dissolved in 150 ml. of acetonitrile, was added 24.8 g. (0.11 mole) of [1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]dimethylamine (Table I, **5**). After refluxing for 22 hr., the yellow solution was concentrated to a sirup, at steam temperature and water vacuum. The sirup was triturated with ether and crystallized from acetonitrile–ether, to give 16.5 g. (40%) of the diiodide, m.p. 206–207° dec.

Anal. Calcd. for $C_{36}H_{74}I_2N_2O_2$: C, 52.69; H, 9.09. Found: C, 52.99; H, 8.89.

To 9.85 g. (0.012 mole) of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]}ammonium iodide suspended in 3 l. of water was added freshly precipitated silver chloride obtained from 25 g. (0.15 mole) of silver nitrate. The mixture was stirred vigorously for 4 hr. then filtered. The filtrate was concentrated and the resulting yellow gum crystallized from acetonitrile–acetone–ether, to give 6 g. (79%) of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-dimethylcyclohexyl)propyl]}ammonium chloride, m.p. 190–192°.

N,N′-Bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-diethyl-1,6-hexanediamine Bis(ethobromide), Monohydrate. Method H.—Compound **9** (Table IV) is described as an example. To 19 g. (0.04 mole) of N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine (Table II, **4**) and 65.5 (0.6 mole) of ethyl bromide, dissolved in 300 ml. of ethanol, was added 8.2 g. (0.08 mole) of anhydrous sodium carbonate. The mixture was heated, with shaking, in a closed vessel at 100° for 15 hr. The solids were filtered and the yellow colored filtrate concentrated to a sirup, at steam temperature and water vacuum. The sirup was extracted with chloroform and the extract taken to dryness. The residue was crystallized from chloroform–acetone–ether, to give 5.5 g. (18%) of product, m.p. 195–196°.

Acknowledgments.—We are indebted to Dr. A. Steyermark and his staff for the microanalyses, and to Miss G. Orth, Mr. E. Stafford, and Mrs. B. O'Brien for assistance in the synthesis of some of the compounds.

(29) A. P. Phillips, *J. Am. Chem. Soc.*, **77**, 2401 (1955).

(30) Procedure provided by Dr. L. M. Jampolsky; b.p. 92–97° (0.05 mm.), $n^{28}D$ 1.5383.

Antiviral Activity of Glyoxals and Derivatives

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A series of aromatic, polyaromatic, and heterocyclic glyoxals have been prepared. These were treated with *p*-aminobenzoic acid to give a variety of products depending upon the reaction conditions. The chemical and antiviral properties of these compounds are discussed. Many of these compounds possess considerable *in ovo* activity against the herpes simplex virus and the influenza (PR-8) virus.

The antiviral activity of a series of glyoxals and derivatives was first disclosed by Underwood and co-workers.[2] This report, as well as subsequent papers[3-5] on the extension of this work, indicated that certain compounds of this type were effective against Newcastle disease virus (NJKD strain) and influenza virus (PR-8 strain) when administered to embryonated eggs. It was reported later[6] that the compounds did not possess antiviral activity in animals. Shortly thereafter, de Bock and co-workers[7] observed that a series of α,β-dicarbonyl derivatives possessed growth-inhibiting activity toward influenza virus A-USA-47 (A′-strain former designation FM_1). Cavallini and co-workers[8] more recently extended this study to biphenylyl glyoxals and derivatives. Many of these compounds exhibited *in vitro* activity and several were reported to have *in vivo* activity against influenza virus A-PR-8 and hepatitic virus MHV_3. Some of these compounds

(1) Deceased.

(2) G. E. Underwood, Fifth National Medicinal Chemistry Symposium, East Lansing, Michigan, June, 1956.

(3) B. D. Tiffany, J. B. Wright, R. B. Moffett, R. V. Heinzelman, R. E. Strube, B. D. Aspergren, E. H. Lincoln, and J. L. White, *J. Am. Chem. Soc.*, **79**, 1682 (1957).

(4) R. B. Moffett, B. D. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *ibid.*, **79**, 1687 (1957).

(5) J. B. Wright, E. H. Lincoln, and R. V. Heinzelman, *ibid.*, **79**, 1690 (1957).

(6) G. E. Underwood, R. A. Siem, S. A. Gerpheide, and J. H. Hunter, *Proc. Soc. Exp. Biol. Med.*, **100**, 312 (1959).

(7) C. A. de Bock, J. Brug, and J. N. Walop, *Nature*, **179**, 706 (1957).

(8) (a) G. Cavallini and E. Massarani, *J. Med. Pharm. Chem.*, **1**, 365 (1959); (b) G. Cavallini, E. Massarani, D. Nardi, F. Magrassi, P. Altucci, G. Lorenzutti, and V. Sapio, *ibid.*, **1**, 601 (1959); (c) G. Cavallini, E. Massarani, and D. Nardi, *ibid.*, **2**, 99 (1960).

TABLE I
R—$COCH_3$

R	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
1-Trifluoromethylphenyl[a]	*b*	17	$C_9H_7F_3O$	57.45	57.29	3.75	3.92
5-(4-Acetylphenyl)thiophene-2	174–175	23	$C_{12}H_{10}O_2S$	68.88	68.64	4.95	4.67
2,3-Dimethylnaphthalene-1,4	75–77	62	$C_{14}H_{14}O$	84.81	85.13	7.12	7.24
2,3-Dimethylnaphthalene-1,4	116–117	53	$C_{16}H_{16}O_2$	79.97	79.87	6.71	6.65
2-Chlorothiaxanthene-7	149–151	73	$C_{13}H_9ClOS$	65.57	65.59	4.04	4.09
Thiaxanthene-2	114–116	50	$C_{13}H_{10}OS$	74.97	74.88	5.03	4.96

[a] Prepared by an adaptation of the method of M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948). [b] B.p. 52–57° (0.25 mm.).

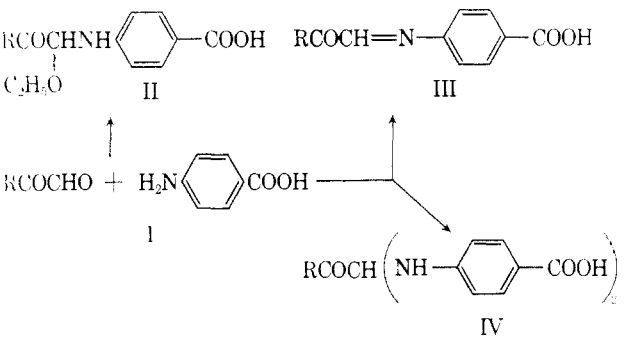
have undergone clinical investigation for use in cases of influenza and other respiratory infections.

We are reporting the synthesis and preliminary antiviral activity of a series of glyoxals and derivatives which we have prepared in our Laboratories and tested for antiviral activity.

Chemistry.—The ketones required for conversion to glyoxals were prepared by acylation of the requisite ring system with acetyl chloride under standard Friedel–Crafts reaction conditions, using aluminum chloride as the catalyst.[9] By using an excess of reagents, the diacetylated compounds could be obtained. If the ring system contained sulfur, it was advantageous to use stannic chloride as the catalyst. For example, acylation of 2-phenylthiophene[10] using stannic chloride as a catalyst gave excellent yields of the monoketone but was not effective for the introduction of the second acetyl group. This could be done only by using aluminum chloride in carbon disulfide at room temperature for 48 hr. In the case of bithiophene, the use of stannic chloride gave good yields of 5-acetyl-2,2′-bithiophene, but a suitable catalyst could not be found for the preparation of the bisacetyl compound without the occurrence of extensive decomposition. Those ketones which have not previously been prepared are listed in Table I.

The ketones were oxidized with selenium dioxide in dioxane to give the glyoxals.[11] In most cases, the products were isolated as the solid hydrates by recrystallization from aqueous solvent systems, most frequently dilute acetic acid. In a few instances, the products were purified by distillation and frequently by conversion to the sodium bisulfite addition compounds to increase solubility and stability. The glyoxals prepared are listed in Table II.

The data presented by previous workers[5] indicated that a high degree of antiviral activity was associated with the condensation products of biphenylyl glyoxals with *p*-aminobenzoic acid. As a means of better correlating structure–activity relationships, we have treated a variety of aromatic, polyaromatic, and heterocyclic glyoxals with *p*-aminobenzoic acid and studied the antiviral activities of the products. The reaction of a glyoxal with *p*-aminobenzoic acid (PABA) may follow three reaction paths, depending upon the reaction conditions employed. The procedure employed for the preparation of compounds of type II was essentially that described by Cavallini,[9b] namely, refluxing



a mixture of the glyoxal and *p*-aminobenzoic acid in ethanol. The compounds thus prepared are shown in Table III. The yields were variable, due to the difficulty in purification. Most of the compounds were quite insoluble and in many instances, merely warming in a solvent was sufficient to cause loss of ethanol, giving rise to compounds of type III.

Compounds of type III were most readily prepared from II by heating at about 100° *in vacuo* for several hours. Frequently, however, traces of material which had not been de-ethoxylated would remain which could be detected readily by an examination of the infrared spectra. A more convenient procedure was to heat the glyoxal and *p*-aminobenzoic acid in an anhydrous solvent such as benzene and distil the ethanol from the reaction mixture. The compounds of this type are shown in Table IV.

Compounds of type IV, as shown in Table V, sometimes were formed under either of the reaction conditions described earlier. The reasons for the reactions following this course are not immediately apparent. Compounds of this general type have been reported to occur as the reaction products of aldehydes and various aniline derivatives.[12] However, only one reaction between a glyoxal and an amine has been described. Tiffany and co-workers[3] treated two moles of *p*-aminobenzoic acid with one mole of β-ethoxy-α-ketobutyraldehyde monohydrate in tetrahydrofuran and described their product only as an anil in which one mole of *p*-aminobenzoic acid had reacted with the α-keto group and the other with the aldehyde. We have repeated the preparation of this compound and have duplicated their melting point and elemental analyses. However, on the basis of the infrared spectrum (double peak at 2.98 and 3.05 μ for NH, two peaks at 3.80 and 3.95 μ for the two acids, and strong ketone absorption at 5.80 μ), followed by a strong broad peak at 6.0 μ

(9) C. C. Price, *Org. Reactions*, **3**, 1 (1946).

(10) We were unable to prepare 2-phenylthiophene as described by W. Steinkopf and H. J. v. Petersdorff, *Ann.*, **543**, 139 (1940). The procedure of A. I. Kosak, R. J. F. Palchak, W. A. Steele, and C. M. Selwitz, *J. Am. Chem. Soc.*, **76**, 1150 (1954), was quite satisfactory.

(11) N. Rabjohn, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 331.

(12) (a) R. Brossi, D. Vargazon, and V. Halos, *Arkiv. Kemi.*, **27**, 33 (1955); (b) R. W. Drisko and H. McKennis, *J. Am. Chem. Soc.*, **74**, 2626 (1952); (c) M. M. Sprung, *Chem. Rev.*, **26**, 318 (1940); (d) A. S. Wheeler, *J. Am. Chem. Soc.*, **31**, 937 (1909).

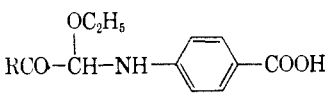
TABLE II

RCO–CHO

Compd. no.	R	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
1	6,7-Dimethyl-1,2,3,4-tetrahydronaphthalene-5	105–108	19	$C_{14}H_{16}O_2 \cdot H_2O$	71.77	71.70	7.74	7.43
2	4-Trifluoromethylphenyl	90–105	34	$C_9H_5F_3O_3 \cdot H_2O$	49.10	49.40	3.21	3.49
3	2,3-Dimethylnaphthalene-1	120–123	17	$C_{14}H_{12}O_2 \cdot 0.5H_2O$	76.00	76.19	5.92	5.99
4	4-Benzamidophenyl	181–183	69	$C_{15}H_{11}NO_3 \cdot 0.75H_2O$	67.53[a]	67.67	4.72	4.98
5	2,3-Dimethylnaphthalene-1,4	300	16	$C_{16}H_{14}O_{10}S_2Na_2 \cdot 4H_2O$[b]	35.03	35.77	4.04	4.08
6	2,3,5,6-Tetramethylphenyl-1,4	212–214	45	$C_{14}H_{14}O_4 \cdot 2H_2O$	59.56	59.41	6.43	6.20
7	4′-Sulfonic acid-biphenyl-4	295 dec.	14	$C_{14}H_{10}O_5S \cdot 1.5H_2O$	52.99[c]	52.82	4.13	4.22
8	5-Phenylthiophene-2	136–138	51	$C_{12}H_8O_2S \cdot H_2O$	61.52	61.67	4.30	4.39
9	5-Phenylthiophene-2,4	146–150	24	$C_{14}H_8O_4S \cdot H_2O$	57.92	57.63	3.47	4.28
10	2,2-Bithiophene-5	126–130	37	$C_{10}H_6O_2S_2 \cdot H_2O$	49.98	49.68	3.36	3.32
11	Fluorene-2	127–129	46	$C_{15}H_{10}O_2 \cdot H_2O$	74.99	74.69	5.03	4.97
12	Fluorene-2,7	217–218	64	$C_{17}H_{10}O_4 \cdot 2H_2O$	64.97	64.75	4.49	4.44
13	Dibenzofuran-2	135–137	30	$C_{14}H_8O_3 \cdot H_2O$	69.42	69.44	4.16	4.13
14	Dibenzofuran-2,8	120–123	36	$C_{16}H_8O_5 \cdot H_2O$	64.43	64.82	3.35	3.69
15	Dibenzothiophene-2	135–141	27	$C_{14}H_8O_2S \cdot 0.5H_2O$	67.45	67.32	3.64	3.60
16	Phenoxathiin-3	206 dec.	63	$C_{14}H_9O_6S_2Na$[d]	46.66	46.64	2.52	2.47
17	Phenoxathiin-3,7	138–144	20	$C_{16}H_8O_5S \cdot 2.25H_2O$	54.47	54.48	3.57	3.69
18	Xanthene-2,7	144–145	45	$C_{17}H_{10}O_5 \cdot 2H_2O$	61.82	60.80	4.27	4.18
19	Thiaxanthene-2	123–133	18	$C_{15}H_{10}O_2S \cdot H_2O$	66.16	65.75	4.44	4.45
20	2-Chlorothiaxanthene-7	144–146	36	$C_{15}H_9ClO_2S \cdot 0.75H_2O$	59.63	59.46	3.50	3.54
21	Anthracene-9	115–118	32	$C_{16}H_{10}O_2 \cdot H_2O$	76.18	76.46	4.79	5.04
22	Anthracene-2	157	30	$C_{16}H_{10}O_2 \cdot H_2O$	76.18	75.80	4.80	4.94
23	Phenanthrene-3	125–130	12	$C_{16}H_{10}O_2 \cdot H_2O$	76.18	76.00	4.80	4.73
24	Phenanthrene-2	136–138	79	$C_{16}H_{10}O_2 \cdot H_2O$	76.18	75.90	4.80	4.66
25	Phenanthrene-9	106–109	45	$C_{16}H_{10}O_2 \cdot H_2O$	76.18	76.40	4.80	5.00

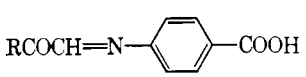
[a] Nitrogen: Calcd.: 5.25. Found: 5.37. [b] Isolated as the sodium bisulfite addition product. Drying for 68 hr. at 115° *in vacuo* gave the monohydrate. *Anal.* Calcd. for $C_{16}H_{14}NaO_{10}S \cdot H_2O$: C, 38.90; H, 3.27. Found: C, 38.76; H, 3.46. [c] Sulfur: Calcd.: 5.25. Found: 5.37. [d] Isolated as the sodium bisulfite addition product.

TABLE III



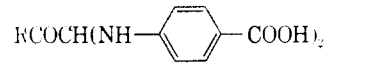
Compd. no.	R	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
26	1-Trifluoromethylphenyl-4	159–160	46	$C_{18}H_{16}F_3NO_4$	58.86	58.85	4.39	4.46	3.81	4.02
27	2,3,5,6-Tetramethylphenyl-1,4	331–333	55	$C_{32}H_{36}N_2O_8$	66.65	66.52	6.29	6.21	4.86	4.98
28	Thiophene-2	177–179	65	$C_{15}H_{15}NO_4S$	59.00	59.12	4.95	5.09	4.59	4.67
29	Naphthalene-1	185–187	26	$C_{21}H_{19}NO_4$	72.19	72.09	5.48	5.71	4.01	4.09
30	6,7-Dimethyltetralin-5	211–213	38	$C_{23}H_{27}NO_4$	72.42	72.06	7.13	7.08	3.67	3.61
31	2,2′-Bithiophene-5	267–269	86	$C_{19}H_{17}NO_4S_2$	58.89	58.65	4.42	4.60	3.62	3.67
32	Fluorene-2	203–205	44	$C_{24}H_{21}NO_4$	74.40	74.39	5.46	5.44	3.62	3.57
33	Dibenzofuran-2,8	>360	76	$C_{34}H_{30}N_2O_9 \cdot 0.5H_2O$	65.91	66.10	5.04	5.09	4.52	4.20
34	Phenoxathiin-3	200–203	43	$C_{23}H_{19}NO_5S$	65.54	65.46	4.54	4.75	3.32	3.25
35	2-Chlorothiaxanthene-7	249–250	43	$C_{24}H_{20}ClNO_4S$	63.50	63.57	4.44	4.64	3.09	2.85
36	Phenanthrene-9	197–198	21	$C_{25}H_{21}NO_4$	75.17	74.80	5.30	5.23	3.51	3.47

TABLE IV



Compd. no.	R	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
37	2,3,5,6-Tetramethylphenyl-1,4	>315	56	$C_{28}H_{24}N_2O_6 \cdot 0.5H_2O$	68.14	68.35	5.11	5.19	5.68	5.54
38	Naphthalene-1	184–185	57	$C_{19}H_{13}NO_3$	75.24	75.13	4.32	4.67	4.62	4.63
39	Thianaphthene-3	171–173	78	$C_{17}H_{11}NO_3S$	66.01	65.53	3.58	4.31	4.53	5.14
40	Fluorene-2	203–205	91	$C_{22}H_{15}NO_3$	77.41	77.24	4.43	4.80	4.10	4.12
41	Dibenzofuran-2	225–227	67	$C_{21}H_{13}NO_4 \cdot 0.5H_2O$	71.56	71.13	4.00	4.09	3.97	3.78
42	2-Chlorothiaxanthene-7	236–238	100	$C_{22}H_{14}ClNO_3S$	64.78	64.60	3.46	3.78	3.43	3.51
43	Phenoxathiin-2	208–210	59	$C_{21}H_{13}NO_4S$	67.19	67.11	3.49	3.74	3.73	3.54
44	Phenanthrene-2	212–213	62	$C_{23}H_{15}NO_3$	78.17	77.70	4.28	4.27	3.96	4.06
45	Phenanthrene-9	199–200	90	$C_{23}H_{15}NO_3$	78.17	77.40	4.28	4.19	3.96	4.13

TABLE V



Compd. no.	R	M.p., °C.	Yield, %	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
46	Naphthalene-1	192–194	69	$C_{28}H_{20}N_2O_5$	70.90	70.62	4.58	4.63	6.36	6.15
47	Naphthalene-2	196–198	80	$C_{28}H_{20}N_2O_5$	70.90	70.60	4.58	4.52	6.36	6.57
48	2,4,6-Trimethylphenyl	232–233	66	$C_{25}H_{24}N_2O_5$	69.43	69.03	5.59	5.82	6.48	6.73
49	Dibenzothiophene-2	225–228	84	$C_{28}H_{20}N_2O_5S \cdot 0.5H_2O$	66.52	66.42	4.26	4.23	6.34	6.38
50	α-Ethoxyethyl	181–182	71	$C_{20}H_{22}N_2O_6$	62.17	62.11	5.74	5.97	7.25	7.34

for the acids), we would suggest structure $CH_3CH(OC_2H_5)COCH(p\text{-}NHC_6H_4COOH)_2$ for this product. The compounds listed in Table V exhibited similar infrared absorption characteristics. The formation of derivatives of this type could be readily circumvented by briefly refluxing the glyoxal in alcohol containing a few drops of concentrated sulfuric acid. The hemiacetal thus formed *in situ* reacted normally with the *p*-aminobenzoic acid to give the desired product.

Testing Methods

Influenza Virus (PR-8).—Compounds were tested for activity against influenza virus in 10-day-old chick embryos. Four twofold dilutions of the compound, starting with the maximum tolerated dose, were inoculated *via* the allantoic cavity into each of five chick embryos. This was followed immediately with inoculation of approximately 100 EID_{50}'s of influenza virus, strain PR-8. The eggs were sealed and incubated for 24 hr., when virus control eggs showed a hemagglutination titer of 1000 or more. The allantoic fluid was then harvested, pooled for each compound level, and then titrated for "hemagglutination reduction factor," that is, the HA titer of the virus controls divided by the HA titer of the treated groups. An HA reduction factor of 10 or greater was considered significant. The minimum effective dose, therefore, is the dose per egg which will produce an HA factor of 10 or greater.

Herpes Simplex Virus.—This test was run in 10-day-old embryonated eggs in essentially the same manner as the influenza group, with the exception that eight eggs per group were used and the eggs were observed for survival for 10 days rather than for HA determinations. A survival rate of 50% or greater in the treated group was considered significant. The effective dose, therefore, is that dose level at which a survival rate of 50% or greater is observed.

Structure–Activity Relationships.—All of the compounds listed in Tables II, III, IV, and V were tested in both virus systems, but to reduce the amount of data reported, the therapeutic index obtained for the influenza (PR-8) virus has been arbitrarily selected as a criterion of activity. The compounds shown in Table VI are arranged in order of decreasing therapeutic index with respect to the influenza (PR-8) virus. Only those compounds with a therapeutic index of two or more are listed in the table. The exceptions are compounds **5** and **6** which had unusually high activity in the herpes simplex system.

In general, it was found that the bisglyoxals in the heterocyclic series were quite active, in most cases more so than the biphenyl analog. These compounds were more active as the free glyoxal rather than the *p*-aminobenzoic acid reaction products. The most notable exception is the durene bisglyoxal reaction product with *p*-aminobenzoic acid in ethanol, no. **27**. This compound was quite active in both test systems.

In the case of the monoglyoxals, greater activity was usually obtained when combined with *p*-aminobenzoic acid in the presence of alcohol. The de-ethoxylated products were usually less active. Compounds **46**, **47**, **48**, and **49**, which contain two moles of *p*-aminobenzoic acid, had a moderate degree of antiviral activity. Compounds derived from the polyaromatic ring systems (**21-25**, **36**, **44**, **45**) were relatively inactive, probably due to the very low solubility.

As a means of comparing steric effects upon antiviral activity with the bulk afforded by the heterocyclic systems, a number of substituted benzene, naphthalene, and tetralin derivatives were prepared (**3**, **5**, **6**, **30**, **37**). Although some of these possessed slightly more activity than the parent ring systems, the increase was not great and was much less than that afforded by the bulkier ring systems.

Many of these compounds have been found to be effective antiviral agents in *in vivo* test systems, and the results of these tests will be reported in a later communication.

Experimental[13]

Ketones.—The following procedure is typical of that used for the preparation of the ketones described in Table I.

2-Acetyl-5-(4-acetylphenyl)thiophene.—To a mixture of 62.5 g. (0.468 mole) of anhydrous aluminum chloride in 150 ml. of carbon disulfide at 0° was added a solution of 25 g. (0.156 mole) of 2-phenylthiophene and 37.2 g. (0.468 mole) of acetyl chloride in 125 ml. of carbon disulfide. The addition was effected during 1.5 hr. while maintaining the temperature between 0 and 5°. The reaction mixture was then left at room temperature for 48 hr. when it was poured into a mixture of 260 ml. of concentrated hydrochloric acid and 430 g. of crushed ice. When the ice had melted, the solid was collected by filtration and washed with cold water. Recrystallization from 600 ml. of ethanol gave 21 g. (23%) of ketone.

Glyoxals.—The glyoxals were all prepared by previously reported procedures.[9] The preparations described are typical of the compounds listed in Table II.

5-Phenylthiophene-2-glyoxal Hydrate (8).—A mixture of 39 g. (0.194 mole) of 2-acetyl-5-phenylthiophene,[9] 21.4 g. (0.194 mole) of selenium dioxide, 175 ml. of dioxane, and 5.5 ml. of water was stirred at the reflux temperature for 2 hr. The hot reaction mixture was filtered to remove selenium, and the filtrate was cooled and diluted with 200 ml. of water. The solid was separated by filtration and dried to give 35 g. (72.5%) of solid, m.p. 135–138° dec. Recrystallization from a mixture of acetic acid and water gave 23.3 g. (51%) of pure material.

5-Phenylthiophene-2,4-bisglyoxal Hydrate (9).—A mixture of 31 g. (0.127 mole) of 2-acetyl-5-(4-acetylphenyl)thiophene, 28.2 g. (0.254 mole) of selenium dioxide, 175 ml. of dioxane, and 5 ml. of water was stirred at the reflux temperature for 2 hr. The hot solution was filtered, and the filtrate was diluted with 800 ml. of water. Attempted purification by recrystallization from aqueous acetic acid was unsuccessful. The solid was dissolved in alcohol

(13) All melting points were taken on a Hoover-Thomas melting point apparatus and are corrected.

TABLE VI: ANTIVIRAL ACTIVITIES *In Ovo*

Compd. no.	Table no.	Influenza (PR-8) virus: Toxic level, (mg./egg)	Influenza (PR-8) virus: Effective level, (mg./egg)	Influenza (PR-8) virus: Therapeutic index	Herpes simplex virus: Toxic level, (mg./egg)	Herpes simplex virus: Effective level, (mg./egg)	Herpes simplex virus: Therapeutic index
14	II	8	0.064	128	8	0.064	128
12	II	64	1	64	64	4	16
9	II	64	1	64	64	4	16
18	II	64	1	64	64	4	16
45	II	16	1	16	16	0	0
(a)	III	128	16	8	128	16	8
17	II	8	1	8	8	0.125	64
27	III	32	4	8	32	1	32
43	III	16	2	8	16	0	0
49	V	8	1	8	8	2	4
4	II	64	16	4	64	0	0
(b)	II	8	2	4	8	4	0
33	II	64	16	4	64	16	4
(c)	II	8	2	4	8	4	2
(d)	II	64	16	4	64	64	1
11	II	64	16	4	64	0	0
16	II	2	0.5	4	2	0	0
(e)	II	4	1	4	4	0	0
(f)	IV	6	1.5	4	6	0	0
28	III	32	8	4	32	0	0
40	IV	8	2	4	8	0	0
38	IV	8	2	4	8	0	0
46	V	32	8	4	32	0	0
47	V	8	2	4	8	0	0
48	V	8	4	2	8	0	0
37	III	8	4	2	8	1	8
(g)	II	4	2	2	4	0	0
(h)	II	4	2	2	4	0	0
13	II	4	2	2	4	0	0
5	II	8	0	0	8	0.125	64
6	II	8	0	0	8	0.5	16

[a] R = biphenyl-4, ref. 8c. [b] R = thiophene-2, F. Kipnis and J. Ornfelt, *J. Am. Chem. Soc.*, **68**, 2734 (1946). [c] R = thianaphthene-3, C. Hansh and H. C. Lindwall, *J. Org. Chem.*, **10,** 381 (1945). [d] R = biphenyl-4,4′, ref. 8b. [e] R = naphthalene-1, L. N. Goldyrev and I. YaPostovskii, *J. Gen. Chem.*, **10,** 39 (1940); *Chem. Abstr.*, **34,** 4732 (1940). [f] R = biphenyl-4,4′, ref. 8c. [g] R = naphthalene-2, W. Madelung and M. E. Oberwegner, *Chem. Ber.*, **65,** 939 (1932). [h] R = biphenyl-4, ref. 8c.

and treated with excess sodium bisulfite solution. The precipitated bisulfite addition product was recrystallized from aqueous alcohol and the glyoxal liberated by heating with dilute hydrochloric acid. After washing with water and drying, there were obtained 8.8 g. (24%) of pure glyoxal.

Condensation Products of Glyoxals and *p*-Aminobenzoic Acid.—The condensation of glyoxals with *p*-aminobenzoic acid was carried out essentially as described by Cavallini.[8] The procedures described are typical of the methods we employed for the preparation of the compounds listed in Table III.

***p*-[(2-Chloro-7-thiaxanthenylcarbonyl)ethoxymethyleneamino]benzoic Acid (35).**—A mixture of 50 g. (0.176 mole) of 2-chlorothiaxanthene-7-glyoxal hydrate, 500 ml. of ethanol, and 4 drops of concentrated sulfuric acid was heated at the reflux temperature for 15 min. when 23.7 g. (0.176 mole) of *p*-aminobenzoic acid was added. The reaction mixture was heated for an additional 30 min., cooled, and the solid was separated by filtration and washed thoroughly with cold ethanol to give 34 g. (43%) of product. Characteristic infrared bands, λ_{max}^{Nujol} 2.95 (–NH), 6.0 (—C=O), 9.5 (ethoxy), and 10.5 μ (acid).

***p*-[(2-Chloro-7-thiaxanthenylcarbonyl)methyleneamino]benzoic Acid (42).**—*p*-[(2-Chloro-7-thiaxanthenylcarbonyl)ethoxymethylamino]benzoic acid (19 g., 0.032 mole) was heated *in vacuo* at 105° for 4 hr. and then slurried with ether to give 17 g. (100%) of pale yellow solid. Characteristic infrared bands, λ_{max}^{Nujol} 5.95 (—C=O), 6.05 (–C=N—), and 10.6 μ (acid).

***p*-[(2-Fluorenylcarbonyl)methyleneamino]benzoic Acid (40).**—A suspension of 23.8 g. (0.06 mole) of *p*-[(2-fluorenylcarbonyl)-ethoxymethylamino]benzoic acid in 200 ml. of toluene was stirred at the reflux temperature for 3 hr. with slow distillation of solvent. The mixture was cooled and the solid separated by filtration and washed with ether to give 19 g. (92%) of pale yellow solid. Characteristic infrared bands, λ_{max}^{Nujol} 5.98 (—C=O), 6.05 (—C=N—), and 10.7 μ (acid).

4′-Glyoxyloyl-4-biphenylsulfonic Acid (7).—To 87.3 g. (0.75 mole) of chlorosulfonic acid at 5° was added 34.2 g. (0.15 mole) of *p*-biphenylylglyoxal hydrate over 1 hr. The black reaction mixture was heated at 75–80° for 1 hr. and then decomposed with ice water. The gummy solid was separated by filtration and purified by four recrystallizations from dilute acetic acid to give 5.1 g. (14%) of off-white solid.

N,N′-(3-Ethoxy-2-oxobutylidene)bis-*p*-aminobenzoic Acid.—A mixture of 20 g. (0.08 mole) of 58.5% aqueous solution of β-ethoxy-α-ketobutyraldehyde[3] and 22 g. (0.16 mole) of *p*-aminobenzoic acid in 500 ml. of ethanol was stirred at the reflux temperature for 3 hr. and then concentrated to about 100 ml. and diluted with an equal volume of water. The precipitated solid was separated by filtration and purified by recrystallization from aqueous alcohol to give 22 g. (71%) of pale yellow solid. Characteristic infrared bands, λ_{max}^{Nujol} 2.98 and 3.05 (—NH), 3.80 and 3.5 (acids), 5.80 (—C=O) and 6.0 μ, strong and broad (acids).

N,N′-(2,4,6-Trimethylbenzoylmethylene)bis-*p*-aminobenzoic Acid (48).—A mixture of 9.7 g. (0.05 mole) of mesitylglyoxal and 13.7 g. (0.1 mole) of *p*-aminobenzoic acid in 200 ml. of benzene was stirred at the reflux temperature for 2 hr. The mixture was cooled and the solid separated by filtration. Two recrystallizations from aqueous alcohol gave 14.3 g. (66%) of pure product, m.p. 232–233°. Characteristic infrared bands, λ_{max}^{Nujol} 2.95 and 3.1 (—NH), 5.90 (—C=O), 6.05 and 10.5 μ (acids).

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