the solution warmed to room temperature whereupon it was made alkaline with 20% sodium hydroxide solution. The resulting mixture was washed well with ether and the aqueous layer acidified. The yellow oil which separated was thoroughly extracted with ether, dried, and concentrated under reduced pressure to give 16.7 g. of crude oxime in the form of a dark oil which did not crystallize.

To the crude oxime was added 85 ml. of 37% formaldehyde solution. Then 21 ml. of concentrated hydrochloric acid was added dropwise during 10 minutes causing the temperature to rise to 37°. After standing overnight, the solution was extracted with three 150-ml. portions of ether and the extracts were dried, concentrated, and distilled through a short column. The 0.85 g. of yellow liquid thus obtained, b.p. 53° (15 mm.), possessed essentially the same physical properties as β-ethoxy-α-ketobutyraldehyde prepared according to Rappen's procedure.

The preparation of **β-ethoxy-α-ketobutyraldehyde** through hydrolysis of either of two pure acetals, β-ethoxy-α-ketobutyraldehyde diethylacetal and di-(methoxyethyl)-acetal (see below), also gave material of no better quality than that prepared by Rappen's method.[2]

β-Ethoxy-α-ketobutyraldehyde Diethylacetal.—A solution of 200 g. (actually 160 g., 1.23 moles) of 80% pure β-ethoxy-α-ketobutyraldehyde,[2] 1 l. of anhydrous alcohol and 1 ml. of concentrated sulfuric acid was distilled slowly for 30 hours replacing portions of alcohol from time to time. After 3 days at room temperature the solution was neutralized with calcium carbonate, filtered, and concentrated. The residual liquid was distilled through an efficient column, giving 147 g. (47%) of a yellow oil, b.p. 56–60° (0.3 mm.), $n^{23}D$ 1.4147.

A stirred solution of 87.0 g. of crude β-ethoxy-α-ketobutyraldehyde diethylacetal in 385 ml. of ethanol was made basic with 154 ml. of 0.1 *N* sodium hydroxide solution and then 616 ml. of 3% hydrogen peroxide solution added. During the following 10 minutes 458 ml. of 0.1 *N* sodium hydroxide solution was added. The ethanol was largely removed by distillation under reduced pressure at 35–40° and the colorless residue was saturated with salt and extracted with three 500-ml. portions of benzene. These were washed with 500 ml. of 5% sodium bisulfite solution, then washed with 100 ml. of water, dried and concentrated. The residue was distilled through a short column giving 60.8 g. (70%, based on the crude acetal) of a colorless liquid boiling at 76–77° (3.2 mm.), $n^{20}D$ 1.4156.

Anal. Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.99; H, 10.06.

β-Ethoxy-α-ketobutyraldehyde di-(methoxyethyl)-acetal was prepared from 130 g. (actually 104 g., 0.80 mole) of 80% pure β-ethoxy-α-ethoxy-α-ketobutyraldehyde,[2] 266 g. (3.5 moles) of methoxyethanol, 300 ml. of benzene and 0.5 ml. of concentrated sulfuric acid according to a procedure similar to that described above for β-ethoxy-α-ketobutyraldehyde diethylacetal. The product consisted of 43 g. (16%) of yellow oil, b.p. 122° (1.5 mm.), $n^{20}D$ 1.4334. A sample was redistilled for analysis, b.p. 119–120° (0.5 mm.), $n^{27}D$ 1.4304.

Anal. Calcd. for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.64; H, 9.10.

β-Ethoxy-α-hydroxybutyraldehyde Diethylacetal.—A solution of 40.8 g. (0.20 mole) of β-ethoxy-α-ketobutyraldehyde diethylacetal in 100 ml. of absolute ethanol was hydrogenated in the presence of 0.2 g. of platinum oxide at room temperature and 40 lb. pressure. Hydrogen up-take was complete in 2 hours. The reaction mixture was filtered, concentrated, and distilled through a short column giving 30 g. (73%) of a colorless oil, b.p. 64–64.5° (0.65 mm.), $n^{24}D$ 1.4218.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75. Found: C, 58.25; H, 10.73.

β-Ethoxy-α-hydroxy-α-methylbutyraldehyde Diethylacetal.—To a solution of methylmagnesium iodide, prepared from 21.9 g. (0.9 g.-atom) of magnesium, 127.7 g. (0.9 mole) of methyl iodide and 600 ml. of anhydrous ether, was slowly added with stirring 51.0 g. (0.25 mole) of β-ethoxy-α-ketobutyraldehyde diethylacetal at 0–5°. The white precipitate which began to form almost immediately soon made stirring difficult. After 20 hours at room temperature the mixture was decomposed with ice and 300 ml. of cold 20% ammonium chloride solution. An ether extract was dried, concentrated, and distilled through a short column affording 48.2 g. (88%) of a colorless liquid, b.p. 74° (2.5 mm.), $n^{25}D$ 1.4212. Infrared analysis indicated the absence of carbonyl.

Anal. Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 60.57; H, 10.92.

β-Ethoxy-α-hydroxy-α-methylbutyraldehyde.—A solution of 27.4 g. (0.125 mole) of β-ethoxy-α-hydroxy-α-methylbutyraldehyde diethylacetal and 200 ml. of 0.1 *N* sulfuric acid in about 150 ml. of dioxane was kept at room temperature for 4 days. It was neutralized exactly with 0.35 *N* barium hydroxide solution and concentrated under reduced pressure at 40–60° to 25 ml. The mixture was diluted with 100 ml. of water, filtered, and concentrated as above. The residue was dissolved in ether, filtered, dried and concentrated. When dried in a vacuum desiccator over concentrated sulfuric acid, the colorless oily residue amounted to 5.5 g. (30%).

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.76; H, 9.48.

β-Ethoxybutyraldehyde.—A mixture of 75 ml. of 5% hydrochloric acid and 75 ml. (0.34 mole) of β-ethoxybutyraldehyde diethylacetal[14] was shaken for 30 minutes, becoming homogeneous. An ether extract of this was washed, dried and distilled to give 16.0 g. (41%) of oil, b.p. 135–138°, $n^{20}D$ 1.4077.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.03; H, 10.42. Found: C, 62.16; H, 10.25.

α-Hydroxyadipaldehyde disodium bisulfite addition compound was prepared from 5.9 g. (0.045 mole) of α-hydroxyadipaldehyde and 12.5 g. (0.12 mole) of freshly prepared sodium bisulfite[13] in aqueous solution, adding ethanol to precipitate the product. Recrystallization from 20% dimethylformamide and from dilute methanol gave 4.12 g. of white crystals.

Anal. Calcd. for $C_6H_{12}Na_2O_9S_2$: Na, 13.60. Found: Na, 13.30.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Antiviral Compounds. II. Aromatic Glyoxals

BY ROBERT BRUCE MOFFETT, BURRIS D. TIFFANY, BROOKE D. ASPERGREN AND RICHARD V. HEINZELMAN

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A number of aromatic glyoxals have been found to be highly active against Newcastle disease virus and influenza virus in embryonated eggs. Several new aromatic glyoxals, sodium bisulfite addition products and related compounds are reported and some previously known glyoxal hydrates have been more completely characterized.

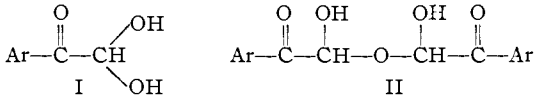
The high antiviral activity of certain glyoxals[1,2] in protecting embryonated eggs against Newcastle disease and influenza has prompted us to prepare a number of aromatic glyoxals for screening against these viruses. These glyoxals (and a few other related compounds) are listed in Table I with an in-

(1) 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, THIS JOURNAL, **79**, 1682 (1957).

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

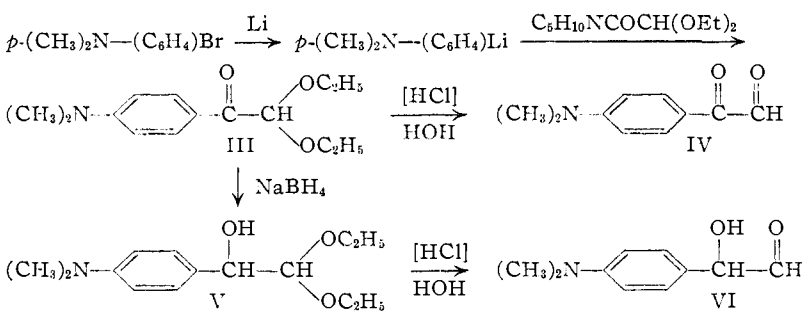
dication of their activities. In general the glyoxals were highly active, most of the exceptions being compounds that were quite insoluble in water or were too toxic to allow an adequate dose. In general the sodium bisulfite addition compounds were more active than the parent glyoxal hydrates. This may be due partly to the significant antiviral activity of sodium bisulfite itself but is probably mostly due to increased solubility. The glyoxal acetals were inactive. Since methyl vinyl ketone and certain other α,β-unsaturated ketones have been reported[3] to show some virucidal activity, we tested a few substituted benzal acetones (*i.e.*, *p*-methoxy-, 2-methoxy-5-bromo- and 3-methoxy-4-hydroxybenzalacetones) but they were all inactive. Likewise simple aromatic aldehydes, α-diketones and α-ketoacids were inactive.

Many aromatic glyoxal hydrates have been previously reported but frequently without analysis or other indication of the degree of hydration. Some aromatic glyoxal hydrates appear to contain one molecule of water and presumably have the structure I, while others contain only one-half molecule of water and presumably have the structure II. The new compounds and some old compounds which we have more adequately characterized are listed with the chemical data in Table II.



Most of the glyoxals were prepared from the corresponding methyl ketones by oxidation with selenium dioxide.[4] This method is illustrated by one example in the Experimental part. The sodium bisulfite addition compounds were made by the treatment of an alcoholic (or tetrahydrofuran) solution of the glyoxal hydrate with sodium bisulfite solution. An example is given in the Experimental part. Even "analytical reagent" sodium bisulfite contains considerable sodium sulfate which would be difficult to separate from the product. Therefore, the sodium bisulfite solution was prepared from sodium carbonate and sulfur dioxide in the absence of air.[1]

p-Dimethylaminophenylglyoxal (IV) was prepared by the hydrolysis of its diethylacetal (III) which was in turn prepared by the action of dimethylaminophenyllithium[5] on diethoxyacetylpiperidine. The glyoxal was isolated in the form of a complex with methanol (probably a hemiacetal). The acetal III also was reduced with sodium borohydride to the hydroxy acetal V which was hydrolyzed to the free *p*-dimethylaminomandelaldehyde (VI). This hydroxyaldehyde VI and also its hydrochloride salt seem to exist as dimers (or polymers).



Several derivatives of *p*-acetylbenzoic acid were made as intermediates in connection with this work. Although they were not carried on to glyoxals their preparation is included in the Experimental part.

TABLE I

ANTIVIRAL ACTIVITY

No.	Compound	Antiviral activity[a] Newcastle Disease (NJKD strain)	Influenza (PR-8 strain)
1	Phenylglyoxal·H_2O[b]	++	++
2	Phenylglyoxal diethylacetal[c]	−	
3	Mesitylglyoxal·H_2O[d]	−	
4	Mesitylglyoxal·$NaHSO_3$·H_2O	−	
5	*p*-Chlorophenylglyoxal·$^1/_2H_2O$	−	
6	*p*-Chlorophenylglyoxal·$NaHSO_3$	++	+
7	*p*-Bromophenylglyoxal·$^1/_2H_2O$	+	−
8	*p*-Bromophenylglyoxal·$NaHSO_3$	++	++
9	*p*-Hydroxyphenylglyoxal·H_2O[e]	++	++
10	*p*-Hydroxyphenylglyoxal·$NaHSO_3$	++	+
11	*p*-Methoxyphenylglyoxal·H_2O[f]	−	
12	*p*-Methoxyphenylglyoxal·$NaHSO_3$·H_2O	++	
13	*m*-Methoxyphenylglyoxal·$^1/_2H_2O$	−	
14	*m*-Methoxyphenylglyoxal·$NaHSO_3$·$^1/_2H_2O$	++	
15	*p*-Hydroxy-*m*-methoxyphenylglyoxal·H_2O	++	++
16	*p*-Nitrophenylglyoxal·H_2O[g]	+	+
17	*p*-Acetamidophenylglyoxal·H_2O[g]	++	
18	*p*-Carbomethoxyphenylglyoxal·H_2O	+	++
19	*p*-Carbomethoxyphenylglyoxal·$NaHSO_3$	++	++
20	*p*-Carboxyphenylglyoxal·H_4O[h]	++	
21	*p*-Carboxyphenylglyoxal·$NaHSO_3$	++	
22	*p*-Dimethylaminophenylglyoxal·MeOH	−	
23	*p*-Dimethylaminophenylglyoxal diethylacetal	−	
24	*p*-Dimethylaminomandelaldehyde·HCl	−	
25	*p*-Dimethylaminomandelaldehyde diethylacetal	−	
26	Furanglyoxal·H_2O	++	++
27	Thiopheneglyoxal·$^1/_2H_2O$[i]	+	+

[a] We are indebted to Drs. W. F. McLimans (Wistar Institute, Philadelphia, Pa.), G. E. Underwood and E. A. Slater and Messrs. E. V. Davis and S. D. Weed of our Department of Infectious Diseases for the data from which these indications of activities were derived. The compounds were tested in embryonated eggs at a dose slightly below the maximum tolerated dose. The eggs were inoculated with many times the lethal dose of virus and the number of survivors noted. ++ indicates high activity, 50–100% survivors, + indicates moderate activity, 10–50% survivors, − indicates little if any activity, 10% survivors. [b] H. A. Riley and A. R. Gray, "Organic Syntheses," Coll. Vol. II, 1943, p. 509. [c] W. L. Evans and C. R. Parkinson, THIS JOURNAL, **35**, 1770 (1913). [d] A. R. Gray and R. C. Fuson, *ibid.*, **56**, 739 (1934). [e] G. Fodor and O. Kovacs, *ibid.*, **71**, 1045 (1949). [f] K. Sisido and H. Nozaki, *ibid.*, **70**, 3326 (1948). [g] C. Musante and V. Parrini, *Gazz. chim. ital.*, **81**, 451 (1951). [h] This compound could not be obtained pure. The material tested titrated 92% as the monohydrate. [i] S. Fujise, *Biochem. Z.*, **236**, 241 (1931); F. Kipnis and J. Ornfelt, THIS JOURNAL, **68**, 2734 (1946).

(3) B. E. Sanders, A. R. Kelly, S. L. Piepes, A. M. Wallbank and G. H. Mangum, Div. of Biol. Chem., Am. Chem. Soc., 119th Meeting, Boston, Mass., April, 1951, Abstracts, p. 22-C.

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

(5) L. Hellerman, C. C. Porter, H. J. Lowe and H. F. Doster, THIS JOURNAL, **68**, 1890 (1946).

TABLE II

CHEMICAL DATA

No. from Table I	Yield, %	M.p.,[a] °C.	Crystallization solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]	Other element Calcd.	Other element Found[b]	Titration[c] (equiv. wt.) Calcd.	Titration[c] (equiv. wt.) Found
4	94	.....	H_2O	$C_{11}H_{11}NaO_5S \cdot H_2O$	44.30	44.40	5.06	5.09	.....	.....	99.4	96.8
5	[d,e]	130	H_2O + acetone then $CHCl_3$ + hexane	$C_8H_5ClO_2 \cdot {}^1/_2 \cdot H_2O$	54.10	53.92 54.27	3.41	3.64 3.67	Cl, 19.96	Cl, 19.91	88.8	91.2
6	84	.....	H_2O + EtOH	$C_8H_4ClNaO_5S$	35.25	35.64	2.22	2.51	Na, 8.44	Na, 8.48	90.9	90.0
7	54[d,e]	127–130.5	PhH + H_2O	$C_8H_5BrO_2 \cdot {}^1/_2H_2O$	43.27	43.37	2.72	2.82	.....	.....	111.0	110.0
8	87	.....	H_2O + THF[f]	$C_8H_4BrNaO_5S$	30.30	30.05	1.91	2.18	S, 10.11	S, 10.37	105.7	105.0
10	96	.....	H_2O + EtOH	$C_8H_7NaO_6S$	37.79	37.99	2.78	3.14	.....	.....	...	...
12	70	.....	H_2O + EtOH	$C_9H_9NaO_6S \cdot H_2O$	37.77	37.56	3.88	3.58	.....	.....	...	...
13	..	98–101	H_2O + pentane	$C_9H_8O_3 \cdot {}^1/_2H_2O$	62.42	62.30	5.24	5.51	.....	.....	86.6	86.1
14	91	.....	H_2O + EtOH	$C_9H_9NaO_6S \cdot {}^1/_2H_2O$	39.00	39.05	3.95	3.76	.....	.....	92.4	91.6
15	[d,g]	98–100	H_2O	$C_8H_8O_4 \cdot H_2O$	54 54	54.50	5.09	5.06	.....	.....	...	...
18	72	127–129	THF + H_2O + PhH	$C_{10}H_8O_4 \cdot H_2O$	57.14	57.29	4.80	4.79	.....	.....	105.1	106.0
19	97	.....	H_2O + EtOH	$C_{10}H_9NaO_7S$	40.54	39.53	3.06	3.01	Na, 7.76	Na, 7.81	98.7	97.0
21	37	.....	H_2O	$C_9H_7NaO_7S$	38.30	37.85	2.50	2.97	Na, 8.15	Na, 7.72	70.5	70.3
22	46	118–122	MeOH	$C_{10}H_{11}NO_2 \cdot CH_3OH$[h]	63.14	63.54	7.23	7.15	N, 6.70	N, 6.95	104.6	101.0
23	91	37–38	Pentane	$C_{14}H_{21}NO_4$	66.90	66.75	8.42	8.81	N, 5.57	N, 5.53	...	...
24	34	175–180	H_2O + MeOH + acetone	$C_{10}H_{14}ClNO_2$	55.69	55.63	6.54	6.46	N, 6.50 Cl, 16.45	N, 6.60 Cl, 16.00	...	...
25	95	.....	.....	$C_{14}H_{23}NO_3$	66.37	66.20	9.15	8.96	N, 5.53	N, 5.60	...	...
26	30[d,i]	78–81	PhH	$C_8H_4O_4 \cdot H_2O$	50.71	50.71	4.25	4.40	.....	.....	71.1	72.0

[a] Melting points were taken in capillary tubes and are uncorrected. These materials (except 23) melted with decomposition and often considerable variation in values was observed under different conditions. The sodium bisulfite addition compounds had no recognizable melting points. [b] Elemental analyses are by Mr. William A. Struck and staff of our Analytical Chemistry Laboratory. [c] This titration, which has proved extremely useful for glyoxals and their sodium bisulfite addition compounds, has been described previously (T. E. Friedemann, *J. Biol. Chem.*, **73**, 331 (1927)). It involves hydrogen peroxide oxidation of the substance and titration of the acids produced.[1] equiv. wt. = wt. of sample × 1000/ml. of NaOH × *N*. The equivalent weight is one-half the molecular weight of glyoxals and one-third the molecular weight of their sodium bisulfite addition compounds. [d] This hydrate has been reported previously but no analysis or other indication of the structure was given. [e] A. T. Arnold and R. C. Fuson, THIS JOURNAL, **58**, 1295 (1936). [f] THF = tetrahydrofuran. [g] L. Ach and E. Schick, German Patent 496,646; *Chem. Zentr.*, 101, II, 2442 (1930). [h] Methoxyl determination: calcd. 14.83, found 13.84. [i] F. Kipnis and J. Ornfelt, THIS JOURNAL, **70**, 3948 (1948).

Experimental[6]

p-**Carbomethoxyphenylglyoxal Monohydrate** (18).—A mixture of 55.5 g. (0.500 mole) of selenium dioxide, 89.09 g. (0.5 mole) of methyl *p*-acetylbenzoate, 40 ml.of water and 300 ml. of dioxane was refluxed with stirring for 5 hours and kept at room temperature overnight. The crystallized mixture was dissolved by adding 50 ml. more dioxane and warming. It was filtered with pressure from the selenium which was washed with 50 ml. of hot dioxane. The nearly white crystals which separated upon cooling were collected and recrystallized from 1 l. of 30% aqueous tetrahydrofuran to give 52.7 g. of nearly white silky crystals, m.p. 125–128° dec. Filtrates yielded additional crude product which crystallized from hot aqueous tetrahydrofuran solution upon adding benzene to afford 23.4 g. of nicely crystalline product, m.p. 127–129°, for a total yield of 76.1 g. (72%). A sample recrystallized from water retained the same m.p. The properties are given in Table II.

Sodium Bisulfite Addition Compound (19).—To a filtered solution of 42.8 g. (0.2 mole) of *p*-carbomethoxyphenylglyoxal hydrate in 400 ml. of methanol was added 60 ml. (0.2 mole) of 3.32 *M* sodium bisulfite solution. A crystalline precipitate soon separated. After 3 days at 5° it was collected, washed with methanol and dried; yield 57.6 g. (97%).

p-**Carboxyphenylglyoxal Hydrate and Sodium Bisulfite Addition Compound** (21).—This was prepared from 24.69 g. (0.15 mole) of *p*-acetylbenzoic acid as described above for the methyl ester. After removal of the precipitated selenium the solvent was removed under reduced pressure giving a gelatinous residue which could be dissolved in boiling water or hot acetic acid and obtained on cooling as a white amorphous solid. This appeared to be more or less associated or polymerized in the solid state. The best sample titrated as 92% monohydrate (20).

Anal. Calcd. for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 56.28, 56.04; H, 4.40, 4.12.

A suspension of 6.0 g. of this crude hydrate in 35 ml. of water was treated with 7.5 ml. (0.025 mole) of sodium bisulfite solution, warmed slightly, and shaken at intervals for 3 hours, diluted with 15 ml. of water, filtered hot under pressure and cooled. The solid which separated was collected, shaken with methanol, filtered, and recrystallized from 75 ml. of water, affording 3.13 g. (37%) of a solid with properties given in Table II.

β-**Diethylaminoethyl** *p*-**Acetylbenzoate Hydrochloride.**—A solution of 16.4 g. (0.1 mole) of *p*-acetylbenzoic acid and 13.6 g. (0.1 mole) of β-diethylaminoethyl chloride, in 100 ml. of isopropyl alcohol was heated under reflux for 12 hours. After long cooling the crystalline product was collected and dried, giving 28 g. of material, m.p. 142–159°, which contained some unchanged acid. This was shaken with ice-water, filtered, thoroughly extracted with ether, and distilled to dryness below 20° under reduced pressure. The residue crystallized from 100 ml. of absolute ethanol giving 21 g. (70%) of white crystals, m.p. 156–158°.

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 60.09; H, 7.40; Cl, 11.83. Found: C, 59.80; H, 7.28; Cl, 12.05.

p-(α-**Bromoacetyl**)-**benzoic Acid.**—To a suspension of 49.3 g. (0.3 mole) of *p*-acetylbenzoic acid in 250 ml. of acetic acid was added dropwise with stirring 48 g. (0.3 mole) of bromine in 50 ml. of acetic acid during 1.5 hours. A temperature of 30–40° was necessary to maintain bromination. An additional 50 ml. of acetic acid was added and the mixture was warmed to 70°, cooled, and filtered. The product was washed well with acetic acid and then with absolute ether and dried; yield 65.2 g. (89.5%), m.p. 218–220°. A sample was recrystallized from methanol, m.p. 224–225°.

Anal. Calcd. for $C_9H_7BrO_3$: C, 44.47; H, 2.90; Br, 32.88. Found: C, 44.89; H, 3.20; Br, 32.16.

p-(α-**Acetoxyacetyl**)-**benzoic Acid.**—A mixture of 64.0 g. (0.263 mole) of *p*-(α-bromoacetyl)-benzoic acid, 51.6 g. (0.526 mole) of potassium acetate and 500 ml. of methanol was shaken for 5.5 hours at room temperature, and heated under reflux for 30 minutes. The solid was never all in solution. The mixture was concentrated under reduced pressure below 50° nearly to dryness. About 700 ml. of water and a little acetic acid was added and after thorough shaking the precipitate was collected, washed with water, and dried in a vacuum desiccator; weight 54 g. This was reprecipitated from glacial acetic acid and then from isopropyl alcohol to give 24.3 g. of non-crystalline white solid, m.p. 200–207° dec. Infrared analysis was in agreement with the proposed structure.

(6) Infrared spectra were obtained on most of these compounds by Dr. James L. Johnson and associates in our Department of Physics. In all cases these spectra supported the structures given.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54; neut. equiv., 222.19. Found: C, 59.65; H, 4.34; neut. equiv., 222.20.

***p*-Dimethylaminophenylglyoxal Diethylacetal (23).**—In a 2-liter, round-bottomed, 3-necked flask, fitted with stirrer, reflux condenser (protected by a $CaCl_2$ tube), dropping funnel and nitrogen inlet, was placed 9.72 g. (1.4 moles) of finely cut lithium wire and 400 ml. of absolute ether. In the dropping funnel was placed a solution of 140.6 g. (0.7 mole) of twice redistilled *p*-bromodimethylaniline in 300 ml. of absolute ether. A little of this solution was run into the flask and the reaction was started by adding a little methyllithium and heating under reflux. The rest of the solution was added at such a rate that the ether refluxed smoothly. When all the lithium had reacted, 107.5 g. (0.5 mole) of diethoxyacetylpiperidine[7] was added at such a rate that the ether refluxed gently. Then the mixture was heated under reflux for 2 hours more. After standing overnight in the refrigerator the reaction mixture was added to ice-water containing 40 ml. of acetic acid. The aqueous layer was separated and extracted twice with ether. The combined ether solution was washed twice with water then with saturated salt solution and dried over sodium sulfate. The ether was removed and the product was distilled through a short column, b.p. 135° (0.05 mm.), giving 114 g. (90.7%) of a viscous yellow liquid, $n^{25}D$ 1.5763. On standing in the refrigerator it crystallized, m.p. 33–37°. A sample was recrystallized from pentane, m.p. 37–38°.

***p*-Dimethylaminophenylglyoxal Methyl Alcoholate (22).**—The above acetal (17 g.) was shaken under nitrogen with a solution of 17.5 ml. of concentrated hydrochloric acid diluted to 175 ml. until all of the acetal dissolved giving a dark green solution. After standing at room temperature for 41 hours a few ml. more concentrated hydrochloric acid was added and the solution was cooled with ice and extracted with ether. The aqueous solution was neutralized to *p*H 6 by slowly adding dilute sodium hydroxide solution while keeping the mixture cold by the addition of ice. The precipitate was collected, washed with water and dried in a vacuum desiccator giving 12.6 g. of brown solid. Recrystallization from 50 ml. of methanol gave 6.53 g. (46%) of yellow crystals, m.p. 103–108° dec. (on Fisher–Johns block). The purest fraction after several recrystallizations from methanol had a m.p. of about 105–109° dec. on block or about 118–122° dec. in capillary tube, after starting to turn orange in color at about 100°. This was shown to contain methanol (probably as the hemiacetal) by the titration and analyses given in Table II.

(7) A. Wöhl and M. Lange, *Ber.*, **41**, 3612 (1908).

***p*-Dimethylaminomandelaldehyde Diethylacetal (25).**—To a solution of 37.7 g. (0.15 mole) of the above *p*-dimethylaminophenylglyoxal diethylacetal in 200 ml. of 95% ethanol was slowly added with stirring a solution of 5.2 g. of sodium borohydride in 25 ml. of 0.1 *N* aqueous sodium hydroxide. The solution became warm and was stirred without further heating for 5 hours. After standing for 3 days most of the alcohol was removed by distillation under reduced pressure below 40° during which water was added from time-to-time to keep the volume constant. The mixture was then extracted three times with ether and the ether solution washed twice with water, then with saturated salt solution, and dried over anhydrous sodium sulfate. The solvent was removed and the product was distilled from a claisen flask, b.p. 106° (0.01 mm.), giving 36.1 g. (95%) of a nearly colorless oil, $n^{25}D$ 1.5244.

***p*-Dimethylaminomandelaldehyde.**—A solution of 25.3 g. (0.1 mole) of *p*-dimethylaminomandelaldehyde diethylacetal in 180 ml. of water and 20 ml. of concentrated hydrochloric acid was kept at room temperature for 24 hours. The resulting light orange colored solution was diluted with ice and made slightly basic with cold dilute sodium hydroxide. A pink gum separated which soon solidified. This was collected and dried giving 16.5 g. of solid, m.p. 133–140°. It was insoluble in water and in most organic solvents but was slightly soluble in hot dioxane, hot pyridine and hot dimethylformamide. It was very soluble in dilute hydrochloric acid. The solid was boiled with acetone which dissolved most of the color. It was filtered leaving 10.7 g. of a nearly white solid, m.p. 145–153° dec., after starting to turn orange-red at about 130° and sintering at about 134–136°. A sample was dissolved in warm pyridine and on the addition of methanol and cooling the material separated as a white precipitate, m.p. 147–147.5° dec. and darkening below the m.p. The infrared spectrum shows the expected bands except for the absence of C=O. This indicates that the material is a hemiacetal dimer or polymer.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.58; H, 7.39; N, 7.79.

Hydrochloride (24).—To a suspension of 7.12 g. of *p*-dimethylaminomandelaldehyde in 25 ml. of methanol was added 3.3 ml. of concentrated hydrochloric acid and 5 ml. of water. The solid dissolved on slight warming and after filtering it was diluted with acetone. Crystals separated on standing; weight 2.97 g., m.p. 170–175° dec. A sample was recrystallized from 90% methanol on the addition of acetone, m.p. 175–180° (dec. and darkening from about 165°). The infrared spectrum shows the absence of C=O which indicates the material is dimeric or polymeric.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Antiviral Compounds. III. Derivatives of β-Aminolactaldehyde

BY JOHN B. WRIGHT, EDWARD H. LINCOLN AND R. V. HEINZELMAN

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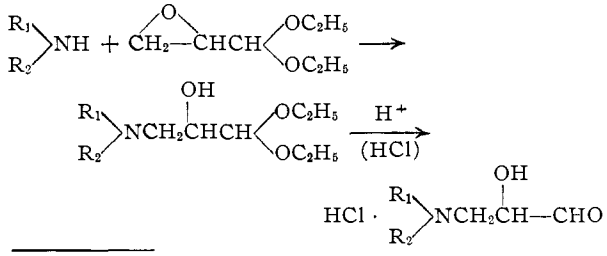
A number of β-aminolactaldehyde derivatives, containing a secondary or tertiary amine group in the amino portion, have been found to possess high antiviral activity against Newcastle disease virus and influenza (PR-8) virus in embryonated eggs. These compounds were prepared by reaction of amines with glycidaldehyde diethylacetal followed by cleavage of the resulting aminoacetals with acid.

It has been observed recently[1,2] in these Laboratories that a number of glyoxals possess exceedingly high antiviral activity in the embryonated egg against several viruses, including influenza (PR-8) and Newcastle disease (N.J.K.D.) viruses. Accordingly, it was of interest to investigate a number of α-hydroxyaldehydes, particularly since the glyoxals presented problems of synthesis and of stability. In this paper we wish to report the synthesis of a number of substituted β-amino-α-hydroxypropionaldehydes.

(1) B. D. Tiffany, *et al.*, THIS JOURNAL, **79**, 1682 (1957).
(2) R. B. Moffett, *et al.*, *ibid.*, **79**, 1687 (1957).

The compounds were prepared by reaction of glycidaldehyde diethylacetal[3] with various amines



(3) D. I. Weisblat, *et al.*, *ibid.*, **75**, 5895 (1953).