Anal. Calcd. for $C_{11}H_{16}O_5$: 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.

KALAMAZOO, MICHIGAN

[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

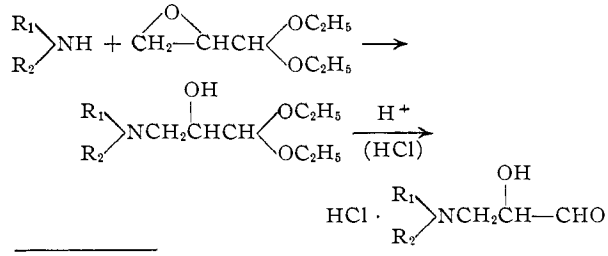
RECEIVED JUNE 12, 1956

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).

followed by cleavage of the resulting aminoacetals with acid. Wöhl and Momber[4] have prepared β-aminolactaldehyde dimethylacetal in a somewhat similar way by the reaction of glycidaldehyde dimethylacetal and ammonia.

The substituted β-aminolactaldehydes that were prepared are listed in Table I and the corresponding acetals are listed in Table II. In addition to these compounds, the dilactaldehydes derived from piperazine and methylamine were prepared.

TABLE I

β-AMINOLACTALDEHYDE HYDROCHLORIDES $R_1R_2NCH_2CH(OH)CHO\cdot HCl$

R_1	R_2	M.p., °C.	Yield, %	Procedure	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CH_3	121.5–123.5[c]	69	C	$C_5H_{12}ClNO_2$	39.09	7.88	[l]	39.10	7.94	[l]
C_2H_5	H	155.5 d.[i,d]	78	..	$C_5H_{12}ClNO_2$	39.09	7.88	9.12	39.25	7.68	8.97
C_2H_5	C_2H_5	130–131[c]	57	..	$C_7H_{16}ClNO_2$	46.28	8.88	7.71	46.40	8.68	7.65
i-C_3H_7	i-C_3H_7	200 d.[d]	29	..	$C_9H_{20}ClNO_2$	51.54	9.61	6.68	51.61	9.87	6.52
n-C_4H_9	H	187 d.[g,d]	87	C[p]	$C_7H_{16}ClNO_2$	46.28	8.88	7.71	46.38	9.06	7.43
n-C_4H_9	n-C_4H_9	179–181 d.[i,d]	40	..	$C_{11}H_{24}ClNO_2$	55.56	10.17	5.89	55.30	9.94	5.69
n-C_6H_{13}	n-C_6H_{13}	148–150 d.[d]	20	..	$C_{15}H_{32}ClNO_2$	61.30	10.98	4.77	61.39	10.83	4.66
Pyridyl	CH_3	151.5–153.5[a,i]	34	..	$C_9H_{13}ClN_2O_2$	49.89	6.05	[b]	50.20	6.28	[b]
Pyrrolidino[k]		138–139[a]	50	C[m,q]	$C_7H_{14}ClNO_2$	46.80[h]	7.85	7.80	47.39[h]	7.93	7.93
Piperidino[k]		156–157[e]	64	C[n,r]	$C_8H_{16}ClNO_2$	49.61	8.33	[i]	49.80	8.28	[i]
1-Benzimidazolyl[k]		154.5 d.[f,i]	51	..	$C_{10}H_{11}ClN_2O_2$	[e]	[e]	12.36	[e]	[e]	12.08

[a] The material began to darken at 149°. [b] Calcd. for Cl: 16.37, found 16.32. [c] Infrared spectrum indicates that this compound exists in the monomeric form. [d] Infrared spectrum indicates that this material probably exists in the dimeric form. [e] Calcd. for Cl: 15.64, found 15.09. [f] The material starts to discolor at about 144°. [g] The material starts to turn brown at about 150°. [h] Calcd. for Cl: 19.74, found 19.49. [i] Calcd. for Cl: 18.31, found 18.37. [j] Corrected for stem exposure. [k] The R_1 and R_2 groups are incorporated into a cyclic ring (*e.g.*, $-N<^{R_1}_{R_2} = -N(CH_2-CH_2)_2$). [l] Calcd. for Cl: 23.08, found 22.97. [m] The residual material was recrystallized from ethanol–ether. [n] The residual gum was dried by distillation with benzene. [p] The residual gum was triturated with acetone. The final product was recrystallized from a large volume of methanol. [q] Recrystallized from ethanol–ether. [r] Recrystallized from ethanol–ethyl acetate (3:2).

(1) $HN(CH_2CH_2)_2NH + 2\ CH_2(O)CH-CH(OC_2H_5)_2 \longrightarrow$

$(C_2H_5O)_2CHCH(OH)CH_2N(CH_2CH_2)_2NCH_2CH(OH)CH(OC_2H_5)_2 \xrightarrow{H^+ (HCl)}$

$OHC-CH(OH)-CH_2N(CH_2CH_2)_2NCH_2CH(OH)CHO\cdot 2HCl$

(2) $CH_3NH_2 + 2\ CH_2(O)CH-CH(OC_2H_5)_2 \longrightarrow$

$(C_2H_5O)_2CHCH(OH)CH_2N(CH_3)CH_2CH(OH)CH(OC_2H_5)_2 \xrightarrow{H^+ (HCl)}$

$OHCCHCH_2N(CH_3)CH_2CH(OH)CHO\cdot HCl$

The reaction between the various amines and glycidaldehyde diethylacetal proceeded readily and gave the β-aminolactaldehyde diethylacetals in very good yield. Cleavage with hydrochloric acid gave the β-aminolactaldehyde hydrochlorides, which were crystalline compounds possessing definite melting points. Infrared spectral studies on these compounds indicated that with some of the compounds carbonyl absorption was present, signifying that the material evidently exists in the monomeric form, while in other cases no carbonyl absorption was present, indicating that the latter compounds may exist in a polymeric state, probably as a cyclic dimer. Cyclic dimers of lactaldehyde and other simple α-hydroxyaldehydes have been reported.[5] Whether the monomeric or dimeric form separated depended on the conditions for the hydrolysis and the work-up of the product of the reaction.

A number of periodic acid titrations were carried out on one of the compounds prepared, namely, β-diethylaminolactaldehyde hydrochloride. These titrations showed this compound to have a purity of 100 ± 1%.

Several of the aminolactaldehydes prepared showed a high order of antiviral activity, two of the more active compounds being β-diethylamino- and β-diisopropylaminolactaldehyde hydrochlorides. The antiviral activities of these compounds are listed in Table III.[6] The diethylacetals of the compounds listed in this table were also tested; however, these were found to be inactive.

Acknowledgments.—We wish to thank Mr. William A. Struck and his staff for the microanalyses reported and Dr. James L. Johnson and his staff for the infrared determinations. We also wish to thank Dr. R. Bruce Moffett for the periodic acid titration data, Mr. Arthur Barton for tech-

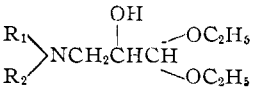
(4) A. Wöhl and F. Momber, *Ber.*, **47**, 3350 (1914).

(5) A. Wöhl, *ibid.*, **41**, 3599 (1908).

(6) A preliminary report on the activity of these compounds was presented by Dr. G. Underwood at the Fifth Medicinal Chemistry Symposium of the American Chemical Society, East Lansing, Mich., June 23, 1956.

TABLE II

β-AMINOLACTALDEHYDE DIETHYLACETALS



R_1	R_2	B.p. °C.	Mm.	n_D	Yield, %	Procedure	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3[c]	H[c]	110[k]	13[k]	.....	64[l]	B	$C_9H_{19}NO_3$	54.21	10.80	7.90	54.01	10.47	7.82
CH_3	CH_3	100–101	12	1.4292[d]	73	A	$C_9H_{21}NO_3$	56.51	11.07	7.52	56.43	11.24	7.89
C_2H_5	H	117–119[a]	13[a]	.....	79	B[k]	$C_9H_{21}NO_3$	56.51	11.07	7.52	56.82	10.97	7.58
C_2H_5	C_2H_5	73–74	0.45	1.4336[g]	92	A	$C_{11}H_{25}NO_3$	60.24	11.49	6.39	59.96	11.44	6.55
i-C_3H_7	i-C_3H_7	129.5–130.5	12	1.4357[d]	73	A	$C_{13}H_{29}NO_3$	63.12	11.82	5.66	63.89	11.71	5.63
n-C_4H_9	H	138	12	1.4413[g]	81	B[l]	$C_{11}H_{25}NO_3$	60.24	11.49	6.39	59.86	11.22	6.30
n-C_4H_9	n-C_4H_9	158–158.5	14	1.4376[e]	84	A[m]	$C_{15}H_{33}NO_3$	65.41	12.08	5.09	66.03	12.00	5.68
C_6H_{13}	C_6H_{13}	138.5–142.5	0.5	1.4428[e]	89	A[n]	$C_{19}H_{41}NO_3$	68.83	12.47	4.22	69.11	11.96	4.14
Pyridyl[b]	CH[b]	149–151	2.1	.....	33	..	$C_{14}H_{22}N_2O_3$	61.39	8.72	...	61.57	8.46	...
Pyrrolidino[j]		88–90	0.5	1.4522[h]	71	A[p]	$C_{14}H_{28}NO_3$	60.80	10.67	6.45	61.17	10.58	6.38
Piperidino[j]		143–145	13.5	1.4550[d]	89	A[p]	$C_{15}H_{30}NO_3$	62.30	10.89	6.06	62.20	10.99	6.06
1-Benzimidazolyl[j]		[f]	[f]	.....	53	..	$C_{14}H_{29}NO_3$	63.61	7.63	10.60	63.72	7.42	10.57

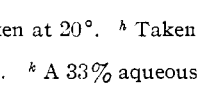
[a] The distillate solidified to a colorless solid which upon recrystallization from petroleum ether (Skellysolve B) gave colorless asbestos-like needles melting at 54.5–55.5°. [b] This compound was prepared by the reaction between 2-bromopyridine and β-methylamino-lactaldehyde diethylacetal (*cf.* Experimental part). [c] This compound was not converted to the corresponding β-methylaminolactaldehyde hydrochloride. It was prepared as an intermediate in the preparation of β-[(2-pyrrolidyl)-methylamino]-lactaldehyde diethylacetal (*i.e.*, R_1 = pyridyl; R_2 = CH_3). [d] Taken at 25°. [e] Taken at 24°. [f] M.p. 92.5–94°. [g] Taken at 20°. [h] Taken at 26.5°. [i] The R_1 and R_2 groups are incorporated into a cyclic ring (*e.g.* ). [k] A 33% aqueous $C_2H_5NH_2$ solution was used. [l] Anhydrous butylamine was used and 3 ml. of methanol. The reaction mixture was heated under reflux for 2 hours. [m] An exothermic reaction took place. After the initial heat of the reaction had subsided the reaction mixture was heated at 120–130° for 2.5 hours. [n] The reaction mixture was heated on the steam-bath for 2 hours instead of heating under reflux for 1 hour. [p] Upon mixing the amine, glycidaldehyde diethylacetal and methanol together a vigorous exothermic reaction took place. Cooling of the reaction mixture in an ice-bath was necessary to keep it under control.

TABLE III

ANTIVIRAL ACTIVITY

	Compound[a]	Antiviral activity[b] Newcastle (N.J.-K.D.) virus	Influenza (PR-8) virus
1	β-Dimethylaminolactaldehyde	++	+
2	β-Ethylaminolactaldehyde	++	[c]
3	β-Diethylaminolactaldehyde	++	+
4	β-Diisopropylaminolactaldehyde	++	++
5	β-Butylaminolactaldehyde	+	[c]
6	β-Dibutylaminolactaldehyde	++	[c]
7	β-Dihexylaminolactaldehyde	−	[c]
8	β-(2-Pyridylmethylamine)-lactaldehyde	−	−
9	β-Pyrrolidinolactaldehyde	+	+
10	β-Piperidinolactaldehyde	+	+
11	β-(1-Benzimidazoyl)-lactaldehyde	+	+
12	1,4-Piperazinedilactaldehyde	++	+
13	N-Methyl-3,3′-iminodilactaldehyde	++	[c]

[a] All of the compounds were tested as their hydrochloride salts. [b] ++ = 50–100% survivors, + = 10–50% survivors, and − = <10% survivors when tested in eleven day old embryonated eggs. Each compound was administered at approximately 85% of its maximum tolerated dose. [c] Not tested as yet.

nical assistance and Dr. W. F. McLimans[7] and his staff for the antiviral data reported.

Experimental[8]

β-Diethylaminolactaldehyde Diethylacetal. Procedure A.—A solution of 1781 g. (12.2 moles) of glycidaldehyde diethylacetal,[3] 980 g. (10% excess) of freshly distilled diethylamine and 10 ml. of methanol was heated under reflux for 1.5 hours and then all low-boiling material was removed by heating on a steam-bath. The residue was distilled under reduced pressure through a short column.

(7) Wistar Institute, Philadelphia, Penna.

(8) All melting points reported in this paper are uncorrected for stem exposures unless otherwise stated.

β-Dimethylaminolactaldehyde Diethylacetal.—The above procedure (procedure A) was modified in that the amount of methanol was increased. To a cold solution of 22.59 g. (0.50 mole) of dimethylamine in 200 ml. of methanol was added 73 g. (0.50 mole) of glycidaldehyde diethylacetal. The reaction mixture was kept in a refrigerator for 1 hour, at room temperature for 3 hours, and then heated under reflux for 1 hour. The reaction mixture was worked up as described in procedure A.

β-Methylaminolactaldehyde Diethylacetal. Procedure B.—To a solution of 195 g. (approx. 1.50 moles) of an aqueous 25% methylamine solution in 50 ml. of methanol was added dropwise over the course of about 3 hours 76.0 g. (0.52 mole) of glycidaldehyde diethylacetal. The reaction mixture was held below 55° by occasional cooling. The solution was then heated under reflux for 1 hour and concentrated under reduced pressure. The solid residue was distilled *in vacuo* through a short column giving 58.9 g. (64%) of colorless solid, m.p. 56°. Recrystallization from petroleum ether (Skellysolve B) gave asbestos-like needles of the same melting point.

Besides the main fraction there was also obtained a small amount of the corresponding bis compound. The yield of the latter compound could be increased by decreasing the amount of methylamine in the reaction. For example, from 50 ml. (0.404 mole) of 25% aqueous methylamine solution and 76.0 g. of glycidaldehyde diethylacetal there was obtained 13.2 g. (14.4%) of β-methylaminolactaldehyde diethylacetal and 66.2 g. (79%) of N-methyl-3,3′-iminodilactaldehyde tetraethylacetal, a colorless liquid, b.p. 155° (0.6 mm.), $n^{20}D$ 1.4460.

Anal. Calcd. for $C_9H_{21}NO_3$: C, 56.51; H, 11.07; N, 7.52. Found: C, 56.82; H, 10.97; N, 7.58.

β-(2-Pyridylmethylamino)-lactaldehyde Diethylacetal.—A mixture of 15.8 g. (0.1 mole) of 2-bromopyridine and 35.4 g. (0.2 mole) of β-methylaminolactaldehyde diethylacetal in a flask fitted with air condenser was heated on the steam-bath overnight and then in an oil-bath at 125° for an additional 24 hours. The dark brown reaction mixture was diluted with 200 ml. of water and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and the ether removed. The residue was distilled under reduced pressure. After a small amount of forerun (unreacted 2-bromopyridine) there was obtained 8.35 g. of a colorless liquid boiling at 149–151° (2.1 mm.).

β-(1-Benzimidazolyl)-lactaldehyde Diethylacetal.—A mixture of 35.5 g. (0.3 mole) of benzimidazole, 43.8 g. (0.3

mole) of glycidaldehyde diethylacetal and 100 ml. of ethanol was heated on a steam-bath with stirring for 3.5 hours. The mixture was concentrated under reduced pressure and to the thick red-brown residue was added 50 ml. of acetone and then petroleum ether (Skellysolve B) was added at the boiling point to turbidity. After cooling in the refrigerator, the solid was collected and boiled with 500 ml. of anhydrous ether giving 41.7 g. of solid, m.p. 90.5°. It was purified further by recrystallization from ether–acetone (500:1).

β-Dimethylaminolactaldehyde Hydrochloride. Procedure C.—A solution of 57.3 g. (0.50 mole) of β-dimethylaminolactaldehyde diethylacetal in 150 ml. of 10% (w./v.) hydrochloric acid was heated on a steam-bath for 2 hours and then concentrated under reduced pressure. The residual gum was crystallized from ethanol–ethyl acetate (1:1) giving 32 g. (69%) of crystals, m.p. 117–118.5°. Recrystallization from the same solvent mixture after treatment with decolorizing carbon, gave material m.p. 121.5–123.5°.

β-Diethylaminolactaldehyde Hydrochloride.—To 438 g. (2.0 moles) of β-diethylaminolactaldehyde diethylacetal was added 1214 ml. of 4 *N* hydrochloric acid. The solution warmed spontaneously to 55–60° and became pink in color. After standing at room temperature for 2 days the solution was concentrated under reduced pressure (finally at 1 mm.) using a water-bath at 60–70°. After triturating with acetone the gum usually solidified. The acetone was filtered or decanted and the solid dissolved in 1200 ml. of hot absolute ethanol. After filtering, the alcoholic solution was diluted with a mixture of 1600 ml. of ethyl acetate and 1000 ml. of ether. The white crystalline material was filtered immediately, washed with ethyl acetate and dried in a vacuum desiccator; wt. 202 g., m.p. 126–132°. Dilution of filtrates with ether gave additional material (52 g.). Recrystallization from ethanol–ethyl acetate (2:3) gave 205 g. (57%) of material melting at 130–131°.

β-Diethylaminolactaldehyde Hydrochloride (Dimer ?).—A solution of 30 g. (0.14 mole) of β-diethylaminolactaldehyde diethylacetal in 30 ml. of 6 *N* hydrochloric acid was kept overnight at room temperature, then concentrated under reduced pressure, and the residual gum was dried by azeotropic distillation with toluene. The gum was dissolved in ethanol and a mixture of ethyl acetate–ether (1:1) added to turbidity. Cooling in the refrigerator gave colorless crystals which were collected on a filter; wt. 4.0 g., m.p. 162–164° dec. Additional material (8.5 g., m.p. 164–166° dec.) was obtained by dilution of the mother liquors with ether. Recrystallization from methanol–ether gave 8.0 g. of material melting at 165° dec. after starting to darken at about 130°.

Anal. Calcd. for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; Cl, 19.52. Found: C, 46.43; H, 9.02; Cl, 19.38.

β-Diisopropylaminolactaldehyde Hydrochloride.—To 74 g. (0.3 mole) of β-isopropylaminolactaldehyde diethylacetal was added dropwise 75 ml. of 6 *N* hydrochloric acid which caused the temperature to rise to 50–60°. After standing overnight the solution was concentrated under reduced pressure from a water-bath at 65° and the last traces of water were removed by azeotropic distillation with benzene. Acetone (200 ml.) was added and the mixture stirred. The crystalline solid was collected, boiled with 400 ml. of ethanol, and the hot suspension filtered. The colorless crystalline residue weighed 159 g., m.p. 200–202° dec. From the filtrate an additional 10 g. of material was isolated. The two crops were combined and recrystallized from methanol–ether (1:3).

β-Dibutylaminolactaldehyde Hydrochloride.—A solution of 27.5 g. (0.1 mole) of β-dibutylaminolactaldehyde diethylacetal in 82.5 ml. of 4 *N* hydrochloric acid was allowed to stand overnight and concentrated under reduced pressure from a water-bath at 60–70°. The residual gum was dissolved in hot acetone, diluted one-third with ether, and cooled in the refrigerator. The precipitated material was recrystallized from ethanol–ethyl acetate (1:2).

β-(2-Pyridylmethylamino)-lactaldehyde Hydrochloride.—To 7.0 g. of β-(2-pyridylmethylamino)-lactaldehyde diethylacetal was added a solution of 47.6 ml. of 1 *N* hydrochloric acid in 200 ml. of water. After 3 days at room temperature, the light green solution was treated with decolorizing carbon and concentrated under reduced pressure from a water-bath below 40°. The viscous amber residue was dried by azeotropic distillation with benzene and stored in a vacuum desiccator over calcium chloride and potassium hydroxide until crystallization occurred. The crystals were triturated with 15 ml. of anhydrous ethanol and recrystallized from anhydrous isopropyl alcohol–acetone (1:1).

β-(1-Benzimidazolyl)-lactaldehyde Hydrochloride.—To a solution of 7.13 g. of concentrated hydrochloric acid in 19.2 ml. of water was added 17.3 g. (0.066 mole) of β-(benzimidazolyl)-lactaldehyde diethylacetal. The solution was heated on the steam-bath for 0.5 hour. After standing under nitrogen for two weeks the product was collected and washed with a little ethanol.

β-Dihexylaminolactaldehyde Hydrochloride.—A solution of 16.5 g. (0.05 mole) of β-dihexylaminolactaldehyde diethylacetal and 500 ml. of 0.1 *N* hydrochloric acid was kept at room temperature for 1 week and then warmed on the steam-bath for 2 hours. The solution was concentrated under reduced pressure from a water-bath at 50°, the gummy residue dissolved in 150 ml. of ethanol and diluted with 450 ml. of ethyl acetate and 750 ml. of ether. After chilling in a Dry Ice chest, there separated 5 g. of crystalline material which was recrystallized from ethanol–ether.

β-Ethylaminolactaldehyde Hydrochloride.—A solution of 48.8 g. (0.256 mole) of β-ethylaminolactaldehyde diethylacetal in 42.4 ml. (0.512 mole) of concentrated hydrochloric acid and 53 ml. of water was kept at room temperature for 3 days and then concentrated under reduced pressure using a water-bath at 40°. The solid residue was dried finally in a vacuum desiccator over concentrated sulfuric acid and then over potassium hydroxide. The material was triturated with 100 ml. of anhydrous ethanol and recrystallized from a large volume of methanol.

β-Diethylamino-α-acetoxypropionaldehyde Diethylacetal.—To 43.8 g. (0.2 mole) of β-diethylaminolactaldehyde diethylacetal in a flask fitted with an air condenser protected by a calcium chloride tube was added, with stirring, 20.4 g. (0.2 mole) of acetic anhydride. An exothermic reaction caused the temperature to rise to 90°. After cooling to room temperature, the mixture was poured into 200 ml. of ice-water. To the aqueous solution was added solid sodium bicarbonate and the mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the ether was removed, and the product distilled under reduced pressure giving 46.7 g. (80%) of a colorless liquid, b.p. 99–101° (2.5 mm.), $n^{22}D$ 1.4281.

Anal. Calcd. for $C_{13}H_{27}NO_4$: C, 59.74; H, 10.41; N, 5.36. Found: C, 60.07; H, 10.05; N, 5.60.

1,4-Piperazinedilactaldehyde Tetraethylacetal.—A mixture of 87.6 g. (0.60 mole) of glycidaldehyde diethylacetal, 10 ml. of methanol and 38.85 g. (0.20 mole) of piperazine hexahydrate was heated on a steam-bath with stirring for 1 hour, during which time a yellow homogeneous solution was formed. After standing overnight, the solution was concentrated through a short column. After a forerun of methanol and water there was obtained 7.0 g. of a fraction[9] boiling at 82–90° (1.0 mm.). The distillation was stopped. On standing in the refrigerator, the dark oily residue partially solidified and was recrystallized from 200 ml. of petroleum ether (Skellysolve B). The light brown solid (wt. 39.8 g. m.p. 66–75°) was recrystallized 3 times from the same solvent after treatment with decolorizing charcoal. There was obtained 17.0 g. (22.5%) of a colorless solid, m.p. 87–88° (cor.).

Anal. Calcd. for $C_{18}H_{38}N_2O_6$: C, 57.11; H, 10.12; N, 7.40. Found: C, 57.41; H, 10.20; N, 7.56.

1,4-Piperazinedilactaldehyde Dihydrochloride.—A solution of 16.9 g. of 1,4-piperazinedilactaldehyde tetraethylacetal in 35 ml. of 3 *N* hydrochloric acid was stirred at 55° for 1 hour and was then allowed to stand for two weeks. The product was removed by filtration, washed with 5 ml. of cold water and dried in a vacuum desiccator. There was obtained 4.85 g. (36%) of material melting at 131.5–132.5° (cor.) (with decomposition after starting to darken at 113°). Infrared spectral analysis indicated the material to exist in the dimeric form.

N-Methyl-3,3′-iminodilactaldehyde Hydrochloride.—To 5.2 g. of N-methyl-3,3′-iminodilactaldehyde tetraethyl acetal was added 50 ml. of 1.1 *N* hydrochloric acid solution and the mixture was allowed to stand for 3 days. The solution was concentrated under reduced pressure using a water-bath below 40° and the colorless residue stored in a vacuum

(9) This fraction was undoubtedly β-(piperidino)-lactaldehyde diethylacetal.

desiccator over sulfuric acid. The material was triturated with acetone, filtered, and placed in a vacuum desiccator over potassium hydroxide pellets. There was obtained 1.0 g. of a colorless solid, m.p. 105° dec.

Anal. Calcd. for $C_7H_{13}NO_4 \cdot HCl$: C, 39.72; H, 6.67; N, 6.62. Found: C, 39.81; H, 6.96; N, 6.82.

KALAMAZOO, MICHIGAN

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

Some Reactions of Glycidaldehyde Diethylacetal

BY JOHN B. WRIGHT

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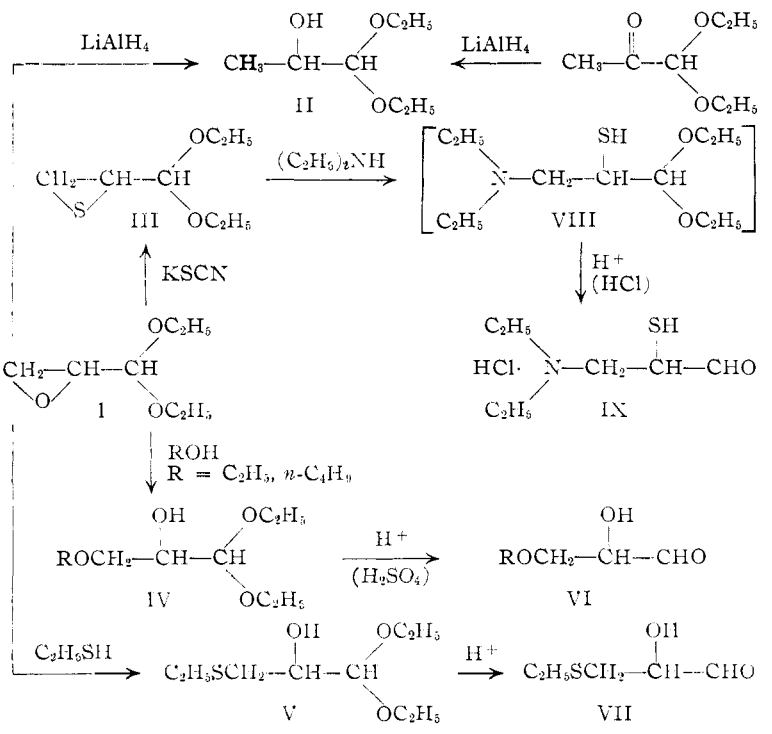
Glycidaldehyde diethylacetal (I) was found to react readily with lithium aluminum hydride, alcohols and mercaptans (ethyl mercaptan) with opening of the oxirane ring. Treatment with potassium thiocyanate gave thioglycidaldehyde diethyl acetal (III). The latter substance with diethylamine gave β-diethylamino-α-mercaptopropionaldehyde diethylacetal. The acetals obtained in this reaction were cleaved with acid to the corresponding aldehydes.

Glycidaldehyde diethylacetal (I) is a highly versatile intermediate that may be prepared readily in good yield from acrolein diethylacetal.[1] In the previous paper[2] are reported the reactions of various amines with this compound. In this paper we wish to report some additional studies on the chemistry of this substance.

Reduction of glycidaldehyde diethylacetal with lithium aluminum hydride gave lactaldehyde diethylacetal (II) in excellent yield.



The infrared spectrum of this substance was identical with that of the product from the reduction of pyruvaldehyde diethylacetal, indicating that the opening of the oxirane ring with lithium aluminum hydride proceeded in a manner to give a secondary hydroxyl group.

Treatment of glycidaldehyde diethylacetal with potassium thiocyanate[3] gave thioglycidaldehyde diethyl acetal (III) in good yield. Reaction with alcohols and with mercaptans (ethyl mercaptan) gave the corresponding β-alkoxylactaldehyde diethylacetals (IV) and β-ethylmercaptolactaldehyde diethylacetal (V), respectively. The latter reactions were carried out using methods identical to those that have been used with propylene oxide and in which the oxirane ring is known to open in such a manner as to give a secondary hydroxyl group. The structure of these compounds is assigned on the basis of this analogy with propylene oxide. The acetals IV and V were cleaved with acid to give the corresponding β-alkoxylacetaldehydes VI and β-ethylmercaptolactaldehyde (VII), respectively.

Thioglycidaldehyde diethyl acetal (III) reacted with diethylamine to give a compound thought to be the aminomercaptan VIII. However, when this compound was subjected to distillation under reduced pressure only thioglycidaldehyde diethyl acetal was isolated, indicating that diethylamine is probably split out readily from this compound. Treatment of crude undistilled VIII with dilute hydrochloric acid gave β-diethylamino-α-mercaptopropionaldehyde hydrochloride (IX).

Infrared spectra of the aldehydes VI, VII and IX indicated that these compounds contain no carbonyl group and hence probably exist in a dimeric (or polymeric) form. Lactaldehyde is reported[4] to exist in a similar dimeric form.

The aldehydes VI, VII and IX were tested for their antiviral activity. The results[5] of these tests are indicated in Table I.

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

(3) (a) J. M. Stewart and H. P. Cordts, *ibid.*, **74**, 5880 (1952); (b) H. R. Snyder, J. M. Stewart and J. B. Ziegler, *ibid.*, **69**, 2672 (1947).

(4) A. Wohl, *Ber.*, **41**, 3599 (1908).

(5) For these results we are indebted to the Staff of our Department of Infectious Diseases.