Anal. Calcd. for $C_{20}H_{21}O_2N$: C, 78.15; H, 6.89; N, 4.58. Found: C, 78.21; H, 6.85; N, 4.32.

Butyl 2-Methyl-5-phenyl-3-indoleacetate (VII).—*p*-Xenylhydrazine hydrochloride (11.0 g., 0.05 mole), butyl levulinate (8.6 g., 0.050 mole), butyl alcohol (120 ml.) and sulfuric acid (10 ml.) were refluxed for 10 hours. The product was purified by the procedure used for VI. The yield of purified product was 2.7 g. (17%), m.p. 76–76.5°.

Anal. Calcd. for $C_{21}H_{23}O_2N$: C, 78.47; H, 7.21; N, 4.37. Found: C, 78.38; H, 7.04; N, 4.27.

2-Methyl-5-phenyl-3-indoleacetic Acid (VIII).—A solution of isopropyl ester VI (13.5 g., 0.044 mole) and potassium hydroxide (12.0 g., 0.044 mole) in methanol (100 ml.) was refluxed for three hours. The volume was reduced to 50 ml. and diluted with 150 ml. of water. The solution was decolorized, cooled, and acidified by adding 6 *N* hydrochloric acid until the *p*H was 4. The white crystalline precipitate was collected (11.3 g.) and recrystallized from ethanol-water with decolorization, yield 7.5 g. (64%), m.p. 155–156°. A similar yield was obtained from the butyl ester VII.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 4.97. Found: C, 77.12; H, 5.66; N, 4.93.

2-Methyl-5-phenyl-3-indoleacetamide (IX).—The isopropyl ester VI (3.0 g., 98 mmoles) was transesterified with methanol (60 ml.) and sulfuric acid (0.5 ml.) by refluxing for five hours. The solution was poured into ice, and extracted with ether. The ether solution (150 ml.) was dried, evaporated, and the crude methyl ester, without further purification, was dissolved in methanol (100 ml.) that had been saturated at 0° with ammonia. The solution was heated for 120 hours at 100° in a stainless steel pressure vessel. Decolorization and concentration of the solution yielded 1.85 g. of tan crystals, m.p. 178.5–180°. Recrystallization from ethanol gave 1.35 g. (53%) of product, m.p. 180–181°.

Anal. Calcd. for $C_{17}H_{16}ON_2$: N, 10.6. Found: N, 11.0.

Ethyl 2-Methyl-4,5-benzindole-3-acetate (X).—Levulinic acid (16.0 g., 0.138 mole) and α-naphthylhydrazine hydrochloride[6] (27.0 g., 0.138 mole) were converted under nitrogen to the ester by the Fox–Bullock procedure.[4] The crude ester which was a solid was recrystallized from ethanol-water, yield 5.0 g. (13%), m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.36. Found: N, 5.09.

2-Methyl-4,5-benzindoleacetic Acid (XI).—A solution of the ethyl ester X (2.5 g., 9.4 mmoles) and potassium hydroxide (1.8 g.) in methanol was refluxed for 3.5 hours. Water (100 ml.) was added and the methanol removed by distillation. The solution was decolorized and acidified with 6 *N* hydrochloric acid to *p*H 4. The precipitated acid (2.0 g.) was recrystallized from acetone–chloroform; yield 1.8 g. (80%), m.p. 189–191° dec. No m.p. for the free acid was reported by Fischer.[6]

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.61.

Ethyl 2,5-Dimethyl-3-indoleacetate (XII).—Ethyl levulinate (22.2 g., 0.140 mole) and *p*-tolylhydrazine hydrochloride[10] (21.8 g., 0.145 mole) were converted under nitrogen to the ester by the Fox–Bullock procedure.[4] The crude ester, an oil, was distilled, and the fraction with b.p. 201–206° (0.5 mm.) was collected. The distillate solidified upon standing, m.p. 37–38°, yield 21.0 g. (67%).

Anal. Calcd. for $C_{14}H_{17}O_2N$: N, 6.06. Found: N, 5.87.

2,5-Dimethyl-3-indoleacetic Acid (XIII).[7]—Five grams (21.6 mmoles) of the ethyl ester XII was saponified and the free acid obtained in the usual manner; yield 3.6 g. (82%), m.p. 174–177° dec. After several recrystallizations from methanol the m.p. was 177–178° dec. The reported m.p. is 172–173°.[7]

Anal. Calcd. for $C_{12}H_{13}O_2N$: N, 6.89. Found: N, 6.78.

Butyl 2,5-Dimethyl-3-indoleacetate (XIV).—A solution of the ethyl ester XII (10 g., 0.043 mole) in butanol (35 g.) with sulfuric acid (0.5 ml.) as catalyst was refluxed for several hours and then distilled slowly through a Vigreux column until the b.p. of butanol was reached. Saturated sodium bicarbonate was added to the butanol solution to neutrality. The aqueous layer was discarded. The butanol layer was dried and the alcohol removed by distillation under reduced pressure (25 mm.). The residue was distilled at 0.5 mm., b.p. 151–165°, yield 7.5 g. (67%). Redistillation at 0.5 mm. gave b.p. 163–165°.

Anal. Calcd. for $C_{16}H_{21}O_2N$: N, 5.40. Found: N, 5.21.

(10) G. R. Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, pp. 276–277. The procedure given for phenylhydrazine was used.

AUBURN, ALABAMA

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

Antiviral Compounds. I. Aliphatic Glyoxals, α-Hydroxyaldehydes and Related Compounds

BY BURRIS D. TIFFANY, JOHN B. WRIGHT, ROBERT BRUCE MOFFETT, RICHARD V. HEINZELMAN, RICHARD E. STRUBE, BROOKE D. ASPERGREN, EDWARD H. LINCOLN AND JOHN L. WHITE

RECEIVED JUNE 12, 1956

Preliminary screening data indicate that six types of aliphatic compounds are highly active against Newcastle disease and influenza viruses in the embryonated egg. These compounds include certain: (1) α-ketoaldehydes, (2) α-hydroxyaldehydes, (3) vicinal triketones, (4) cyclic 1,2-diketones, (5) α-keto primary alcohols and (6) enediols. The preparation of some of these compounds and their derivatives is described.

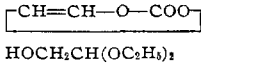
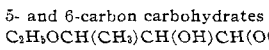
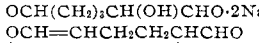
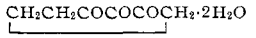
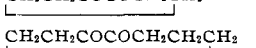
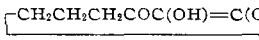
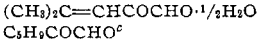
The discovery in these laboratories[1] that β-isopropoxy-α-ketobutyraldehyde was highly active against Newcastle disease virus in the embryonated egg led to an extensive study to determine what structural features are necessary and sufficient for this antiviral activity. Included in Table I are 95 of the compounds studied, along with activity data derived from a preliminary screen against Newcastle disease virus (NJKD strain) and influenza virus (PR-8 strain) when administered to embryonated eggs. In general, six classes of compounds show moderate or marked activity: (1) α-ketoaldehydes, (2) α-hydroxyaldehydes, (3) vicinal triketones, (4) cyclic 1,2-diketones, (5) α-keto primary alcohols and (6) certain enediols.

In all classes, conversion of the active moieties to relatively stable functional derivatives causes loss of activity, whereas at least part of the activity is retained where the derivatives are of the more labile type. For example, acetals and esters are

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

TABLE I

ANTIVIRAL ACTIVITY

No.	Compound	Antiviral activity[a,b] Newcastle disease (NJKD strain)	Antiviral activity[a,b] Influenza (PR-8 strain)
1	OCHCHO	++	++
2	OCHCHO·2NaHSO$_3$	++	+
3	Glyoxal sulfate	++	+
4	$(CH_3CO_2)_2CHCH(OCOCH_3)_2$	+	+
5	CH_3COCHO	++	++
6	$CH_3COCHO·2NaHSO_3·H_2O$	++	+
7	$(CH_3)_3CCOCHO·{}^1/_2H_2O$	++	++
8	n-$C_{12}H_{25}COCHO$[c]	−	
9	$(CH_3)_2C{=}CHCOCHO·{}^1/_2H_2O$	−	+
10	C_5H_9COCHO[c]	++	+
11	$C_6H_{11}COCHO·{}^1/_2H_2O$[c]	++	+
12	$C_6H_{11}COCHO·H_2O·NaHSO_4$[c]	++	++
13	$C_6H_5CH_2COCHO$	+	−
14	$HOCH_2COCHO$	++	++
15	$CH_3OCH_2COCHO·H_2O$	++	++
16	$C_2H_5OCH_2COCHO·H_2O$[c]	++	++
17	$C_2H_5OCH_2COCHO·NaHSO_3$[c]	++	+
18	$CH_3CH(OCH_3)COCHO·H_2O$	++	++
19	$CH_3CH(OCH_3)COCHO·NaHSO_3$[c]	++	++
20	$CH_3CH(OC_2H_5)COCHO·H_2O$ (Code No. U-2032)[c]	++	++
21	$CH_3CH(OC_2H_5)COCHO·NaHSO_3$[c]	++	++
22	$CH_3CH(OC_2H_5)COCHO·MgBr$[d]	++	+
23	$CH_3CH(OC_2H_5)C(p\text{-}NHC_6H_4CO_2H)CH(OH)$-$(p\text{-}NHC_6H_4CO_2H)$[c]	++	++
24	$(CH_3)_2C(OC_2H_5)COCHO$[c]	++	++
25	$CH_3CH(OCH(CH_3)_2)COCHO$[e]	++	
26	$CH_3CH(OCH_2CH_2OCH_3)COCHO·H_2O$	++	++
27	$CH_3CH(OCH_2CH_2OCH_3)COCHO·NaHSO_4$[c]	++	++
28	$CH_3CH(OCH_2CH_2OCH_2OCH_3)COCHO$[c]	++	++
29	$CH_3CH(OCOCH_3)COCHO$	++	++
30	$(CH_3)_2NCH_2C(CH_3)_2COCHO·HCl$	−	
31	$C_{28}H_{36}O_6·NaHSO_3$[f]	+	−
32	Acetals of α-ketoaldehydes	−	−
33	Oximes, phenylhydrazones, phenylosazones of α-ketoaldehydes	−	−
34	$(CH_3)_3CCOCH_2CHO$	−	−
35	$HOCH_2CHO$	++	++
36		++	+
37	$HOCH_2CH(OC_2H_5)_2$	−	
38	$CH_3CH(OH)CHO$	−	
39	$HOCH_2CH(OH)CHO$	++	++
40		−	
41	5- and 6-carbon carbohydrates and derivs.	−	−
42	$C_2H_5OCH(CH_3)CH(OH)CH(OC_2H_5)_2$[c]	−	
43	$C_2H_5OCH(CH_3)C(CH_3)(OH)CHO$[c]	−	−
44	$HCl·(CH_3)_2NCH_2CH_2OCH_2CH(OH)CHO$	++	+
45	$C_6H_5OCH_2CH(OH)CHO$	−	
46	$HOCH_2C(CH_3)_2CH(OH)CHO \rightleftarrows$ 	−	−
47	$OCH(CH_2)_3CH(OH)CHO$	++	++
48	$OCH(CH_2)_3CH(OH)CHO·2NaHSO_3$[c]	+	−
49		−	
50	$OCHCH(CH_3)CH_2CH_2C(CH_4)(OH)CHO$	−	
51	$CH_3COCOCOCH_3·H_2O$	+	
52		++	++
53	Ninhydrin	++	++
54	$CH_3COCOCH_3$	−	
55		+	+
56		+	
57		−	+
58		−	
59	Monosodium 2,5-dihydroxy-p-benzoquinone	−	
60	Tetrahydroxy-p-benzoquinone	−	
61	$CH_3COCOCO_2C_2H_5$	+	
62	$(COCO_2Na)_2·4H_2O$	−	
63	Dehydroascorbic acid	−	
64	CH_3COCH_2OH	++	+
65	$CH_3COCH_2OCOCH_3$	−	−
66	$CH_3COCH(CH_3)OH$	−	
67	$CH_3COC(CH_3)_2OH$	−	
68	$HOCH_2COCH_2OH$	++	
69	$CH_3CO_2CH_2COCH_2OH$	+	
70	$HOC(CH_3)_2COCH_2OH$	+	+
71	Scylloinosose	−	
72	$CH_3OCH_2CH_2COCH_2OH$	−	−
73	p-$HCl·H_2NC_6H_4COCH_2OH$	−	−
74	Calcium 5-ketogluconate	−	
75	$HOCOC(OH){=}C(OH)CO_2H$	++	+
76	Ascorbic acid	−	
77	Hexahydroxybenzene	+	+
78	$CH_3CH(OH)CO_2H$	−	
79	$HOCOCH(OH)CO_2H$	+	
80		−	−
81	CH_2COCO_2H	−	
82	$HOCOCH_2CH_2COCO_2H$	+	+
83	CH_3CH_2CHO	−	
84	$CH_3CH{=}CHCHO$	−	
85	$CH_3CH(OC_2H_5)CH_2CHO$[c]	−	
86	$Cl_3CCHO·H_2O$	−	
87	$CH_3CH(OC_2H_5)CHBrCHO$	−	
88	$HBr·(C_2H_5)_2NCH_2COCH_2Br$	++	
89	CH_3COCH_2Cl	−	
90	CH_3COCH_2SH	−	
91	$CH_3COCH_2NH_2·HCl$	−	
92	$(C_2H_5)_2NCH_2COCH_3$	−	
93	$HOCH_2CH(OH)CH(OH)CH_2OH$	−	
94	Inositol	−	
95		−	

[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 activity were derived. [b] The order of activity is indicated broadly as follows: (++) marked activity or 51–100% survivors among the treated eggs, (+) moderate activity or 11–50% survivors and (−) very little or no activity or 0–10% survivors. The compounds were administered at about 85% of the maximum tolerated dose. [c] Preparation described in the Experimental section of this paper. [d] This compound which was prepared by treating an anhydrous ethereal solution of β-ethoxy-α-ketobutyraldehyde[2] with an ethereal solution of anhydrous magnesium bromide was an extremely hygroscopic white solid which appeared to contain one mole of magnesium bromide per mole of β-ethoxy-α-ketobutyraldehyde when assayed for α-ketoaldehyde content (see ref. 5). [e] 3-β-Hydroxy-20-oxo-5-α-pregnan-21-al, compound with sodium hydrogen sulfite, hydrogen succinate. [f] Ribose-5-phosphate (barium salt), D(+)-galactose, D(+)-mannose, D-glucose, D-glucose-1-phosphate (potassium salt), D-glucose-6-phosphate (barium salt), sucrose, D(+)-glucuronic acid, α-galacturonic acid, D-fructose, D-fructose-6-phosphate (barium salt) and D-fructose-1,6-diphosphate.

inactive whereas sodium bisulfite addition compounds (2, 6, 12, 17, 19, 21, 27, 31 and 48), a 1,1-diacetate (4), and anil (23), a carbonate (36), a sulfate (3), a coördination complex (22), etc., are for the most part still moderately active. The retained activity of some of the latter group of derivatives may be due to simple hydrolysis or dissociation in aqueous media rather than to any activity of the derivatives *per se*. Indeed, the activity of sodium bisulfite addition compounds may arise in part from the sodium bisulfite which itself was found to show marked activity.

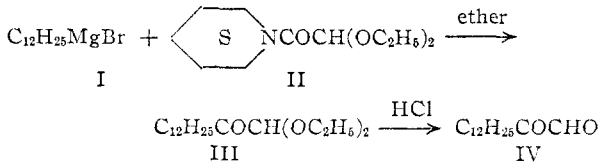
The activity of α-hydroxyaldehydes and α-keto primary alcohols as well as α-ketoaldehydes sug-

(2) L. Rappeu, *J. prakt. Chem.*, **157**, 177 (1941).

gested that the former two were actually precursors to the last and their activity depended upon their ability to become α-ketoaldehydes in the host. To test this hypothesis, we prepared 3-ethoxy-α-hydroxy-β-methylbutyraldehyde (43) in which the α-hydrogen was replaced by a methyl group, thus preventing oxidation to the ketoaldehyde. Another compound, α,δ-dimethyl-α-hydroxy-adipaldehyde (50), was commercially available. The complete inactivity of both of these compounds supported our hypothesis.

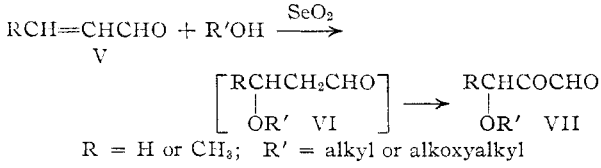
It is interesting that the 5- and 6-carbon carbohydrates (41) appear to be inactive whereas glycolaldehyde (35) and glyceraldehyde (39) are active.

Many of the compounds used in this study have been described previously, but often not in a pure state nor adequately characterized. A number of the compounds are new. Dodecylglyoxal, a new compound, was prepared by the action of dodecylmagnesium bromide (I) on diethoxyacetylpiperidine (II) followed by hydrolysis of the resulting dodecylglyoxal diethylacetal III to the glyoxal IV.



Two alicyclic glyoxals, cyclopentylglyoxal and cyclohexylglyoxal, were prepared by similar procedures. They were also obtained by the oxidation of the corresponding methyl ketone with selenium dioxide. The intermediate ketones are well known but have not been prepared previously by the action of a Grignard on acetic anhydride at low temperatures.[3] It was found that the crude cyclohexylglyoxal obtained by selenium dioxide oxidation essentially as described by Rubin, Paist and Elderfield[4] could be purified in the form of its crystalline hydrate. This cyclohexylglyoxal also gave a previously unknown sodium bisulfite addition compound. The tetraethylacetal of a bis-glyoxal, 1,1,5,5-tetraethoxy-2,4-pentanedione, was synthesized by the condensation of ethyl diethoxyacetate with pyruvaldehyde diethylacetal.

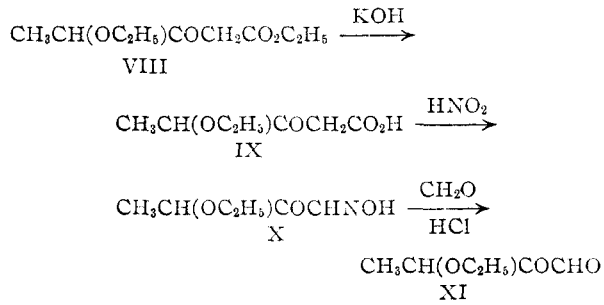
A number of β-alkoxy-α-ketoaldehydes were prepared readily according to the procedure of Rappen[2] by the selenium dioxide oxidation of a mixture of the appropriate alcohol and α,β-unsaturated aldehyde. The isolation of the pure products,



R = H or CH_3; R′ = alkyl or alkoxyalkyl

however, presented many problems. Contrary to Rappen's experience, no β-alkoxy-α-ketoaldehyde was prepared sufficiently pure to afford satisfactory elemental analyses. All were very hygroscopic oils which partially decomposed upon distillation and polymerized quickly upon standing. According to Friedemann's procedure,[5] which proved reliable for the determination of pure crystalline glyoxals, we found that these β-alkoxy-α-ketoaldehyde preparations usually had a glyoxal content corresponding to no more than 60 to 80% purity. A wide variety of procedures, both physical and chemical, for their purification was investigated. The most successful involved conversion to the hydrates. Although none of the hydrates were crystalline, some could be obtained as tacky sirups which gave nearly correct analyses for the monohydrate.

Efforts to improve the quality of the β-alkoxy-α-ketoaldehydes by chemical methods included (1) the investigation of other synthetic routes and (2) conversion of the α-ketoaldehydes to various functional derivatives from which they might be regenerated. β-Ethoxy-α-ketobutyraldehyde (XI), for example, was prepared by the following route designed to avoid selenium dioxide oxidation



The yield was poor in the final step and the product was of no better quality than that obtained by the selenium dioxide method. β-Ethoxy-α-ketobutyraldehyde was converted to a variety of derivatives in the hope that these could be purified and a glyoxal of higher quality regenerated from them. These derivatives included the sodium bisulfite addition compound, the condensation product with *p*-aminobenzoic acid, the phenylosazone, the 2,4-dinitrophenylosazone and several acetals. Condensation with glycine, methyl *p*-aminobenzoate, *p*-aminophenylacetic acid, aniline, ethylenediamine, ethanolamine, *n*-octylamine and *o*-phenylenediamine gave only intractable oils. All but the acetals and many of the amines gave crystalline products which could be purified reasonably well. The free glyoxals could not be regenerated from any of these solids under the conditions tried. This was especially surprising in the case of the sodium bisulfite addition compound. It failed to undergo an exchange reaction with glyoxal and apparently remained intact in 4 *N* hydrochloric acid at room temperature. In aqueous bicarbonate solution the ketoaldehyde was destroyed. The sodium bisulfite addition compounds were valuable derivatives, nevertheless, because they were nicely crystalline, stable, and very water soluble. A modification of the Friedemann analysis of glyoxals offered a convenient analysis for these sodium bisulfite addition

(3) M. S. Newman and W. T. Booth, THIS JOURNAL, **67**, 154 (1945).

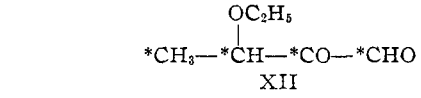
(4) M. Rubin, W. D. Paist and R. C. Elderfield, *J. Org. Chem.*, **6**, 260 (1941).

(5) T. E. Friedemann, *J. Biol. Chem.*, **73**, 331 (1927). Friedemann's procedure for the determination of glyoxals employs the oxidation of the glyoxal with alkaline hydrogen peroxide solution followed by titration of the resulting two acid fragments.

compounds.[6] β-Ethoxy-α-ketobutyraldehyde also formed a crystalline complex with magnesium bromide in ether, but this very hygroscopic solid was not obtained pure enough for satisfactory analysis.

In efforts to reduce β-ethoxy-α-ketobutyraldehyde to the corresponding glycol, neither catalytic hydrogenation nor reduction with lithium aluminum hydride gave material that was free of carbonyl. β-Ethoxy-α-ketobutyraldehyde diethylacetal was, however, reduced successfully to β-ethoxy-α-hydroxybutyraldehyde diethylacetal.

A sample (6.58 g.) of radioactive β-ethoxy-α-ketobutyraldehyde monohydrate labeled with carbon-14 as shown (XII) was prepared from doubly labeled acetaldehyde for biological studies.[7]



XII

Acknowledgments.—We wish to express our appreciation to Mr. Arthur Barton of our Department of Chemistry for technical assistance.

Experimental[8]

Dodecylglyoxal Diethylacetal.—Dodecylmagnesium bromide was prepared from 15.2 g. (0.625 g.-atom) of magnesium, 110 g. (0.37 mole) of dodecyl bromide and 225 ml. of anhydrous ether. To the stirred Grignard reagent 53.3 g. (0.25 mole) of diethoxyacetylpiperidine[9] was added dropwise at 0–5°. After 2 hours without cooling and 3 hours under reflux the mixture was decomposed with 20% ammonium chloride at 0–5°. The ether layer plus an ether extract of the residue were combined, dried, concentrated and distilled through a short column, giving 68.2 g. (92%) of a colorless liquid, b.p. 140–150° (0.7 mm.). Redistillation gave 48.7 g., b.p. 141–143° (0.7 mm.), $n^{20}D$ 1.4355.

Anal. Calcd. for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.14; H, 12.04.

Dodecylglyoxal.—A solution of 23 g. (0.077 mole) of dodecylglyoxal diethylacetal and 15 ml. of 9 *N* sulfuric acid in 150 ml. of ethanol was heated under reflux for 18 hours. It was then concentrated, diluted with 250 ml. of water and extracted with ether. The ether extracts were dried and distilled to yield 5.0 g. of oil, b.p. 114° (0.9 mm.), which partially solidified. Recrystallization of this from ethanol gave 3.0 g. (17%) of white solid, m.p. 54–56°, which contained 66% dodecylglyoxal.[5]

Dodecylglyoxal monosodium bisulfite addition compound was prepared from 0.0050 mole of the above dodecylglyoxal (only 66% pure) in 20 ml. of tetrahydrofuran–water (3:1) and recrystallized from hot water giving 50 mg. of platelets.

Anal. Calcd. for $C_{14}H_{27}NaSO_5$: C, 50.90; H, 8.24. Found: C, 50.73; H, 8.21.

Cyclopentylglyoxal Diethylacetal.—In a manner similar to that described above for dodecylglyoxal, this was prepared from 17.0 g. (0.74 g.-atom) of magnesium, 73.3 g. (0.7 mole) of cyclopentyl chloride, 107.5 g. (0.5 mole) of diethoxyacetylpiperidine[9] and 400 ml. of absolute ether. The product was distilled through an efficient column giving 90.2 g. (90%) of colorless liquid, b.p. 90° (2 mm.), $n^{25}D$ 1.4388.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.00; H, 10.19.

Cyclopentylglyoxal.—To 40 g. (0.2 mole) of cyclopentylglyoxal diethylacetal was added 264 ml. of 3A ethanol, 50 ml. of concentrated hydrochloric acid, and water to make the volume 500 ml. Periodically samples were withdrawn, neutralized, and assayed.[5] During 24 hours at room temperature, the glyoxal content increased to 37%. After 3 hours longer at 50° this increased to 55.6% but fell to 49.5% during the next 3 hours. The solution was cooled below 0°, rendered slightly basic, and extracted with methylene chloride and with ether. Distillation of the dried extracts through a short column gave 8.8 g. (35%) of yellow liquid, b.p. 47–56° (12 mm.), which assayed 86.4%.[5]

The 2,4-dinitrophenylosazone of cyclopentylglyoxal melted at 250–267° dec. after recrystallization from dimethylformamide.

Anal. Calcd. for $C_{19}H_{18}N_8O_8$: C, 46.91; H, 3.73; N, 23.04. Found: C, 47.17; H, 3.80; N, 22.74.

Cyclopentyl methyl ketone was prepared in 47.8% yield by the general procedure of Newman and Booth[3] from 314 g. (3.0 moles) of cyclopentyl chloride, 80 g. (3.3 g.-atoms) of magnesium, 408 g. (377 ml., 4 moles) of acetic anhydride and 2 l. of absolute ether.

Oxidation of this ketone by selenium dioxide to the glyoxal did not give results superior to the above preparation.

Cyclohexyl methyl ketone was prepared by the same method in 61% yield from 415 g. (3.5 moles) of cyclohexyl chloride, 87.6 g. (3.6 g.-atoms) of magnesium, 510 g. (472 ml., 5 moles) of acetic anhydride and 2 l. of absolute ether.[3]

Cyclohexylglyoxal Hemihydrate.—The above cyclohexyl methyl ketone was oxidized with selenium dioxide.[4] The distilled product, a yellow oil, yielded 245 g. of a white crystalline hemihydrate, m.p. 110–120°, upon heating with 1.4 l. of water and cooling. Additional material was recovered as the sodium bisulfite addition compound (as below).

Anal. Calcd. for $C_8H_{12}O_2 \cdot {}^1/_2H_2O$: C, 64.40; H, 8.75; equiv. wt., 74.59. Found: C, 64.42; H, 8.62; equiv. wt.,[5] 73.8.

Cyclohexylglyoxal monosodium bisulfite addition compound was prepared from 3.5 g. (0.023 mole) of the above hydrate in aqueous ethanol and recrystallized from water, giving 4.65 g. (76%) of white crystals, m.p. 179–180° dec.

Anal. Calcd. for $C_8H_{13}NaO_5S \cdot {}^1/_2H_2O$: C, 37.94; H, 5.57; Na, 9.08; equiv. wt., 84.41. Found: C, 37.61; H, 5.71; Na, 9.34; equiv. wt.,[6] 84.07.

Cyclohexylglyoxal Diethylacetal.—In a manner similar to that described above for dodecylglyoxal diethylacetal this was prepared from 17 g. (0.74 g.-atom) of magnesium, 80 g. (0.7 mole) of cyclohexyl chloride, 108 g. (0.5 mole) of diethoxyacetylpiperidine[9] and 250 ml. of anhydrous ether. The product was twice fractionated through an efficient column to give 80.2 g. (75%) of oil, b.p. 85° (1.5 mm.), $n^{25}D$ 1.4435.[4]

Using a procedure similar to that described for the cyclopentyl analog, the acetal above was hydrolyzed to **cyclohexylglyoxal** which gave the same hemihydrate as described above but in lower over-all yield.

1,1,5,5-Tetraethoxy-2,4-pentanedione.—Sodium shot (12.9 g.) was suspended in 285 ml. of dry benzene and 126 g. of ethyl diethoxyacetate was added with stirring at −5 to 0°, followed by 94.2 g. of pyruvaldehyde diethylacetal over a period of 30 minutes. After 3 hours at 0 to 5° and 16 hours at 10° the mixture was concentrated below 40° and the residue treated cautiously with 140 ml. of water, followed by 33.8 g. of acetic acid. An ether extract of this was washed, dried, and distilled for a yield of 39.7 g. (24%) of a very light yellow liquid, b.p. 115° (0.47 mm.), $n^{20}D$ 1.4524. Infrared spectral studies indicated that the product was an equilibrium mixture of the dione and its enol forms.

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.50; H, 8.76. Found: C, 56.58; H, 8.49.

3-Ethoxy-3-methylbutanone-2.—To a solution of 10 g. of mercuric sulfate in 60 ml. of water was added 10 ml. of concentrated sulfuric acid and then 100 ml. of 95% ethanol. A yellow precipitate formed. Then 112.2 g. (1 mole) of 3-

(6) Friedemann's analysis of glyoxals[5] was adapted to the analysis of sodium bisulfite addition compounds of glyoxals simply by omitting the initial neutralization step. In the case of these compounds, which contained only one mole of sodium bisulfite, oxidation with alkaline hydrogen peroxide produced three equivalents of acid. Thus, the effective equivalent weight was one-third of the molecular weight.

(7) D. H. Simonsen, J. H. Hunter, S. J. Musser and J. B. Wright, to be published.

(8) All melting points reported are uncorrected and taken in capillary tubes unless otherwise indicated. Microanalyses were performed by William A. Struck and associates of our Department of Physics and by Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were obtained and interpreted by Dr. James L. Johnson and associates of our Department of Physics when structures were in doubt.

(9) A. Wohl and M. Lange, *Ber.*, **41**, 3612 (1908).

ethoxy-3-methylbutyne-1[10] was added dropwise with stirring over a period of 30 minutes. A gray precipitate replaced the yellow solid. The temperature rose to reflux which was maintained by heating 1 hour more. The mixture was neutralized with 20% sodium hydroxide solution. An ether extract of the mixture was washed twice with saturated salt solution, dried over potassium carbonate and distilled through an efficient column to give 105.6 g. (81%) of colorless liquid, b.p. 72–74° (94 mm.), $n^{25}D$ 1.4037.[11]

β-Ethoxy-α-ketoisovaleraldehyde.—A mixture of 27.8 g. (0.25 mole) of selenium dioxide, 50 ml. of dioxane, 15 ml. of water and 32.6 g. (0.25 mole) of 3-ethoxy-3-methylbutanone-2 was heated under reflux for 2 hours and the precipitated selenium removed by filtration. The filtrate was distilled three times through a short column to yield 7.0 g. of dark yellow liquid which assayed[5] 93% β-ethoxy-α-ketoisovaleraldehyde. On the refractometer the index of refraction changed rapidly from $n^{24}D$ 1.4490 to $n^{24}D$ 1.4537 in about 30 minutes.

The 2,4-dinitrophenylosazone melted at 246–248° dec. after recrystallization from dioxane.

Anal. Calcd. for $C_{19}H_{20}N_8O_9$: C, 45.24; H, 4.00; N, 22.21. Found: C, 44.97; H, 3.80; N, 22.21.

β-Ethoxy-α-ketopropionaldehyde.—Two hundred and six grams (245 ml., 3.67 moles) of acrolein (stabilized with hydroquinone) was stirred at reflux temperature while 165 g. (1.49 moles) of selenium dioxide dissolved in 300 ml. of commercial anhydrous ethanol was added dropwise during 1 hour. After an additional 5 hours under reflux, the mixture was cooled, filtered to remove selenium, and distilled twice through a short column, giving 61.0 g. (35%) of yellow oil, b.p. 58–59° (15 mm.), which contained 81% β-ethoxy-α-ketopropionaldehyde.[5,12]

Purification of β-Ethoxy-α-ketopropionaldehyde as the Monohydrate.—A solution of 75 g. (actually 60.6 g., 0.521 mole) of 81% β-ethoxy-α-ketopropionaldehyde in 375 ml. of water was treated with Darco G-60, filtered, extracted with *n*-pentane, and passed through 40 ml. of Amberlite IR-45 resin. Concentration under reduced pressure at 50° gave 142 ml. of pale yellow sirup which assayed[5] 402 mg. of monohydrate per ml., corresponding to a yield of 57.2 g. (82%). Evaporation of a sample overnight at 25° and 1 mm. pressure gave a viscous residue which assayed 100 ± 2% monohydrate.[5]

β-Ethoxy-α-ketopropionaldehyde Monosodium Bisulfite Addition Compound.—A solution of 45.9 g. (actually 37.1 g., 0.320 mole) of 81% β-ethoxy-α-ketopropionaldehyde in 45 ml. of ethanol was added to a freshly prepared solution of sodium bisulfite[13] (prepared by passing sulfur dioxide into a solution of 15.4 g. (0.145 mole) of anhydrous sodium carbonate in 60 ml. of water). Filtration and evaporation under reduced pressure at 30° gave a powder which was rendered anhydrous by adding and distilling off portions of absolute ethanol. Upon triturating with ethanol and filtering this yielded 44.0 g. (63%) of white crystals, m.p. 122–128° dec. with darkening below this temperature.

Anal. Calcd. for $C_5H_9NaO_6S$: C, 27.27; H, 4.12; Na, 10.44; S, 14.56; equiv. wt., 73.4. Found: C, 26.78; H, 4.22; Na, 10.52; S, 15.28; equiv. wt.,[6] 73.0.

β-Alkoxy-α-ketoaldehydes.—The following β-alkoxy-α-ketoaldehydes and their hydrates and sodium bisulfite addition compounds were prepared essentially as described above for β-ethoxy-α-ketopropionaldehyde, using acrolein or crotonaldehyde and the appropriate alcohol: **a. β-Methoxy-α-ketopropionaldehyde** was obtained in 51% yield as a yellow oil,[12] b.p. 58.5° (16–19 mm.). **b. β-Butoxy-α-ketopropionaldehyde** was obtained in 13% yield as a yellow oil,[12] b.p. 86–88° (11 mm.), which assayed[5] 69.5% pure. **c. β-Methoxy-α-ketobutyraldehyde** was obtained in 42% yield as a yellow oil,[12] b.p. 60–66° (24 mm.), which assayed[5] 80% pure and gave a **monosodium bisulfite addition compound.** *Anal.* Calcd. for $C_5H_9NaO_6S$: equiv. wt.,[6] 73.4. Found: equiv. wt.,[6] 73.4. **d. β-Methoxyethoxy-α-ketobutyraldehyde** was obtained in 37% yield as a yellow oil,[12] b.p. 62–66° (9 mm.), which assayed[5] 79% pure and gave a **monosodium bisulfite addition compound.** *Anal.* Calcd. for $C_{17}H_{13}NaO_7S$: equiv. wt.,[6] 88.1. Found: equiv. wt.,[6] 89.0. **e. β-Methoxymethoxyethoxy-α-ketobutyraldehyde** was obtained as an oil,[12] b.p. 93–95° (0.25 mm.), which assayed[5] 66% pure. **f. β-Ethoxy-α-ketobutyraldehyde,** which was also described by Rappen,[2] was obtained in 43% yield as a yellow oil,[12] b.p. 47–50° (11 mm.), which assayed 81% pure and gave a purified 51% aqueous solution of the monohydrate in 93% recovery. (Isolating and purifying the intermediate β-ethoxybutyraldehyde diethylacetal[14] in this process improved neither the yield nor the quality of the product.) Essentially all traces of selenium could be removed from crude β-ethoxy-α-ketobutyraldehyde by long stirring with neutral Raney nickel. Concentration of some of the aqueous solution of the hydrate under 1 mm. pressure at 25° gave a pale yellow viscous sirup which assayed 95–97% **β-ethoxy-α-ketobutyraldehyde monohydrate.**

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found: C, 49.05; H, 8.08.

The monosodium bisulfite addition compound was obtained as a white crystalline solid.

Anal. Calcd. for $C_6H_{11}NaO_6S$: equiv. wt.,[6] 78.1. Found: equiv. wt.,[6] 78.1.

The phenylosazone melted at 106–108° after recrystallization from 80% ethanol.

Anal. Calcd. for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.15; N, 18.05. Found: C, 69.92; H, 6.94; N, 17.49.

The 2,4-dinitrophenylosazone was obtained as a mixture of red and yellow crystals, m.p. 224–227° dec.

Anal. Calcd. for $C_{18}H_{18}N_8O_9$: C, 44.08; H, 3.70; N, 22.85. Found: C, 44.12; H, 3.57; N, 22.28.

A condensation product with *p*-aminobenzoic acid resulted when a solution of 30 g. (0.20 mole) of *p*-aminobenzoic acid and 14 g. (0.10 mole) of β-ethoxy-α-ketobutyraldehyde monohydrate in 50 ml. of tetrahydrofuran was boiled gently for 30 minutes. The product separated as 23.5 g. (61%) of pale yellow platelets, m.p. 183–184° dec.

Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.41; H, 5.77; N, 7.28; neut. equiv., 193. Found: C, 62.15; H, 5.70; N, 6.93; neut. equiv., 197.

Both the sodium bisulfite addition compound and the condensation product above could be converted directly to the 2,4-dinitrophenylosazone, m.p. 224–227°, identical to that described above.

β-Ethoxy-α-ketobutyraldehyde was also prepared by the following indirect route which was devised in order to avoid the selenium dioxide oxidation of Rappen's procedure[2]: To a stirred solution of 8.7 g. (0.155 mole) of potassium hydroxide in 325 ml. of water was added 25.0 g. (0.133 mole) of γ-methyl-γ-ethoxyacetoacetic ester and the stirring was continued for about 1 hour until homogeneous. After standing overnight the solution was treated with a solution of 10.8 g. of sodium nitrite in 33 ml. of water, then cooled in ice, and a cold solution of 8.7 ml. of sulfuric acid in 76.5 ml. of water was added very slowly keeping the temperature below 2°. Stirring was continued 2 hours while

(10) G. F. Hennion and D. E. Maloney, THIS JOURNAL, **73**, 4737 (1951).

(11) I. N. Nazarov, *Bull. Acad. Sci. U.S.S.R. Classe Sci. Chem.*, 203 (1940); *C. A.*, **36**, 744 (1942).

(12) The β-alkoxy-α-ketoaldehydes were fluid golden yellow oils very readily miscible with water when freshly distilled. Upon standing they slowly polymerized and became progressively more viscous, paler in color and less soluble in water, although old samples largely dissolved slowly upon long shaking. The samples were usually 60 to 80% pure according to the analysis of Friedemann[5] and these values remained essentially unchanged as the samples became highly polymerized gums. Redistillation failed to increase the α-ketoaldehyde content of any sample beyond about 80%. Even at very low pressures *no distillation occurred until depolymerization* (and partial decomposition) took place at a characteristic temperature and then the material virtually flash-distilled without any effective fractionation. Refractive indices determined with the usual Abbe refractometer are of questionable value because of their rapid change. A typical sample of β-ethoxy-α-keto-butyraldehyde had $n^{23.7}D$ 1.4348 when first applied to the prisms and $n^{23.7}D$ 1.4442 only 15 minutes later. Infrared analyses of typical samples always indicated the presence of hydroxyl as well as carbonyl and single carbon–oxygen bond. Older samples showed an increase of hydroxyl absorption at the expense of the carbonyl. Molecular weight determinations gave such widely varying results that they were of little value.

(13) It was necessary to use freshly prepared sodium bisulfite because no commercial reagent which was free of sodium sulfate was available and the latter could not be removed from the extremely water-soluble product if once allowed to contaminate it.

(14) G. Meier, *Ber.*, **76B**, 1016 (1943).

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.

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

Antiviral Compounds. II. Aromatic Glyoxals

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RECEIVED JUNE 12, 1956

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.