

of ethylene glycol; m. p. 110°; $[\alpha]^{25}_D +38.7^\circ$ (*c*: 1.8 in CHCl_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_{11}\text{N}$: C, 47.38; H, 5.73. Found: C, 47.30; H, 5.75.

Pentaacetyl-*d*-gulonamide.—This compound was prepared from a sample of *d*-gulonic lactone ($[\alpha]^{25}_D -54.4^\circ$), using the method described in the preparation of the galactonic derivative. Recrystallization several times from absolute alcohol gave crystals melting at 162–164°; $[\alpha]^{25}_D +22.7^\circ$ (*c*, 1.6 in CHCl_3).

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_{11}\text{N}$: C, 47.38; H, 5.73. Found: C, 47.19; H, 5.68.

Hexaacetyl-*d*-gluconamide.—Acetic anhydride (50 cc.) and concentrated sulfuric acid (3 cc.) were mixed and cooled to 0°. Gluconamide (6 g.) was added and the reaction was completed as in the case of the pentaacetyl derivatives. The solution was poured into ice water and sodium bicarbonate (10 g.) was added. Chloroform extraction yielded a sirup which crystallized upon standing. Ether was added and it was filtered. Recrystallization from alcohol gave the hexaacetyl-*d*-gluconamide: m. p. 110°; $[\alpha]^{25}_D +25.8^\circ$ (*c*, 1.8 in CHCl_3).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_{12}\text{N}$: C, 48.31; H, 5.64. Found: C, 48.14; H, 5.70.

Hexaacetyl-*d*-galactonamide.—Galactonamide was acetylated in the same manner as for preparation of the

hexaacetyl-*d*-gluconamide. A solid separated upon stirring with ice water and sodium bicarbonate. The material was filtered and recrystallized from benzene: m. p. 149.5–150°; $[\alpha]^{25}_D +19.0^\circ$ (*c*, 1.8 in CHCl_3).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_{12}\text{N}$: C, 48.31; H, 5.64. Found: C, 48.08; H, 5.71.

Summary

1. A general preparation of acetylated sugar acid amides has been indicated. This offers an easier route to obtain the fully acetylated sugar acids.

2. The product of acetylation of amides of sugar acids is governed by the catalyst used. Concentrated sulfuric acid gives a product in which both hydroxyl groups and amide nitrogen are acetylated. Zinc chloride gives a product in which only hydroxyls are acetylated.

3. The above methods have been applied to the preparation of several acetylated amides, of which four are new compounds.

LINCOLN, NEBRASKA

RECEIVED MAY 16, 1938

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & Co., U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

β -Phenylethylamine Derivatives.¹ Tertiary and Quaternary Salts

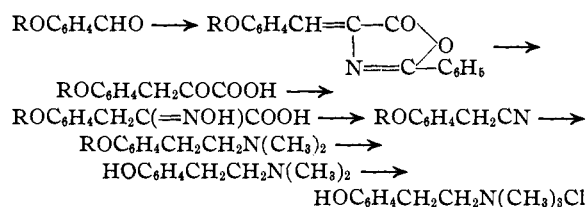
By JOHANNES S. BUCK, RICHARD BALTZLY AND WALTER S. IDE

The present paper describes the preparation and properties of tertiary amine salts and quaternary salts containing the phenylethyl group. One series consists of alkoxy- and hydroxy- β -phenylethyldimethylamine hydrochlorides, of the type of hordenine, the other of the quaternary derivatives of these compounds.

Hordenine has received considerable attention in the literature, and a few related compounds also have been dealt with. For the most part the syntheses are unsatisfactory and not capable of being applied generally. The authors therefore worked out a series of reactions, a composite of various literature methods, which is generally applicable and which gives good yields at each stage. Starting with a substituted benzaldehyde, this is converted successively into the azlactone, the phenylpyruvic acid, the pyruvic acid oxime, and the phenylacetonitrile. This latter is then reduced, in one step, to the alkoxy- β -phenylethyldimethylamine, by catalytic reduction in the pres-

ence of excess dimethylamine. The tertiary amine may be converted readily into the quaternary salt, or O-dealkylated to give the hydroxy compound, which, in turn, easily forms the quaternary compound.

The series of reactions used is as follows



Experimental

The intermediates required were all prepared by the methods given below. A number of them have been described previously in the literature (many prepared by other methods). Only the ones not previously recorded are given (Table I).

Azlactones (2-Phenyl-4-(alkoxybenzal)-oxazolones).—These compounds were prepared in the conventional way from the appropriate benzaldehyde and hippuric acid,² and

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.

(2) Kropf and Decker, *Ber.*, **42**, 1184 (1909); *Org. Syntheses*, **13**, 8 (1933).

TABLE I
 NEW INTERMEDIATES

| Substituent | Appearance | M. p. or b. p., °C. (corr.) | Formula | Analyses, % | | | |
|---|---------------------------------------|-----------------------------------|--|-------------|------|-------|------|
| | | | | Calcd. | | Found | |
| | | | | C | H | C | H |
| Azlactones (2-Phenyl-4-(alkoxybenzal)-oxazolones) | | | | | | | |
| 2-Ethoxy | Lemon-yellow glittering flakes | 186 | C ₁₈ H ₁₆ O ₃ N | 73.69 | 5.16 | 73.64 | 5.12 |
| 3-Ethoxy | Pale yellow felted slender prisms | 123 | C ₁₈ H ₁₆ O ₃ N | 73.69 | 5.16 | 73.60 | 5.23 |
| 4-Ethoxy | Golden-yellow crystalline crusts | 168 | C ₁₈ H ₁₆ O ₃ N | 73.69 | 5.16 | 73.92 | 5.32 |
| 2-Ethoxy-3-methoxy | Large deep yellow flaky prisms | 140 | C ₁₉ H ₁₇ O ₄ N | 70.57 | 5.30 | 70.68 | 5.21 |
| 3,4-Diethoxy | Orange-yellow tiny glittering needles | 161 | C ₂₀ H ₁₈ O ₄ N | 71.19 | 5.68 | 71.06 | 5.83 |
| Alkoxyphenylpyruvic Acids | | | | | | | |
| 2-Methoxy | Small flat pointed prisms | 161 | C ₁₀ H ₁₀ O ₄ | 61.83 | 5.19 | 62.08 | 5.28 |
| 2-Ethoxy | Felted tiny prisms | 164 | C ₁₁ H ₁₂ O ₄ | 63.43 | 5.81 | 63.67 | 6.16 |
| 3-Ethoxy | Meshed small flat needles | 132 | C ₁₁ H ₁₂ O ₄ | 63.43 | 5.81 | 63.67 | 5.93 |
| 4-Ethoxy | Flat chalky thin needles | 182 | C ₁₁ H ₁₂ O ₄ | 63.43 | 5.81 | 63.38 | 5.78 |
| 2-Ethoxy-3-methoxy | Not crystallized | .. | C ₁₂ H ₁₄ O ₅ | 60.48 | 5.93 | | ... |
| 3,4-Diethoxy | Pearly thin felted plates | 164 | C ₁₃ H ₁₆ O ₅ | 61.87 | 6.39 | 61.86 | 6.51 |
| Alkoxyphenylacetoneitriles | | | | | | | |
| 3-Ethoxy | Viscous colorless refractile liquid | 141 (8 mm.) | C ₁₀ H ₁₁ ON | 74.49 | 6.88 | 74.36 | 6.98 |
| 2-Ethoxy-3-methoxy | Faint yellow refractile liquid | 133 (2.0 mm.) | C ₁₁ H ₁₃ O ₂ N | 69.07 | 6.85 | 68.82 | 6.95 |
| 3-Ethoxy-4-methoxy | White crystalline solid m. p. 61.5° | 151 (2.5 mm.) | C ₁₁ H ₁₃ O ₂ N | 69.07 | 6.85 | 68.74 | 6.81 |

were recrystallized from acetic acid, in which they are rather sparingly soluble, until pure. The unrecrystallized material is usually satisfactory for the subsequent hydrolysis. With most aldehydes the yield is from 60 to 70%.

Alkoxyphenylpyruvic Acids.—The azlactones were hydrolyzed by sodium hydroxide and the phenylpyruvic acid separated from benzoic acid by means of sulfur dioxide, followed by washing with ether where the solubility permitted.³ For analysis they were recrystallized until pure, from aqueous acetic acid, aqueous alcohol, or ether-pentane. Ordinarily, the reaction product was used directly for the next step (oximation). Melting points are usually unsharp. The yields vary widely with different acids, from 55 to 90%.

Alkoxyphenylpyruvic Acid Oximes.—The method of Baker and Robinson⁴ was found to be quite satisfactory for the preparation of these compounds. However, attempts at rigid purification were in general unsuccessful, dehydration and decarboxylation gradually taking place, the corresponding phenylacetoneitrile being obtained ultimately. For this reason, the unpurified oxime, after drying, was used directly for the next step, a procedure for which there is ample precedent.⁵ The yields of the oximes are high, usually well over 80%.

Alkoxyphenylacetoneitriles.—Decarboxylation and dehydration of the oximes were carried out simultaneously by means of acetic anhydride, using not more than 20 g. of oxime for a preparation.⁴ Acetic anhydride is retained persistently by the nitriles so that, after isolation, washing and distillation, they were again washed and redistilled or recrystallized from hexane. The liquid nitriles have only

a faint nitrile-type odor. The yields vary according to the oxime used, but usually are considerably over 80%.

Alkoxyphenylethyldimethylamine Hydrochlorides.—The alkoxyphenylacetoneitrile, in methanol solution, with excess (2.5 mol) of dimethylamine (33% in methanol) was reduced catalytically with a palladium catalyst. This reaction, first used by Kindler and Hesse,⁶ gave excellent results. After reduction was complete the catalyst was removed, excess dimethylamine and methanol distilled off, and the residual oil dissolved in dilute hydrochloric acid. Non-basic material was extracted with ether, and the aqueous solution then cooled in ice and treated with sodium nitrite solution (40 g. nitrite per mole of base). After thorough extraction with ether, the acid solution was made strongly alkaline and the base extracted with ether. After drying the extract over solid potassium hydroxide, the hydrochloride was obtained by passing hydrogen chloride into the ether solution. The crude hydrochlorides were recrystallized twice or more from methyl or ethyl alcohol, with ethyl acetate and/or ether, and were so obtained as well crystallized white salts, readily soluble in alcohol, water and hydrochloric acid and practically insoluble in ether, ethyl acetate, etc. Some of them are hygroscopic.

The palladium catalyst was either the commercial "palladium mohr" or material prepared by the Willstätter-Waldschmidt-Leitz method. The optimum speed of reduction appears to be about 1 g. nitrile per hour (Burgess-Parr apparatus, at room temperature and 3 atm. pressure) and relatively large amounts of catalyst, one-quarter upward of the weight of nitrile, were used to obtain this speed. The nitrile must be very pure.

Hydroxyphenylethyldimethylamine Hydrochlorides.—These compounds were obtained by demethylating the corresponding methoxy hydrochlorides with hydrochloric acid (two hours at 160° in carbon dioxide atmosphere). The acid solution was then evaporated to dryness under reduced pressure and the residue recrystallized as with the

(3) (a) *Org. Syntheses*, **15**, 31 (1935); (b) Buck and Perkin, *J. Chem. Soc.*, **125**, 1675 (1924); (c) Pfeiffer, Quehl and Tappermann, *Ber.*, **63**, 1301 (1930).

(4) (a) Baker and Robinson, *J. Chem. Soc.*, 152 (1929); (b) cf. Edwards, *ibid.*, 740 (1926); (c) cf. Haworth and Richardson, *ibid.*, 120 (1935).

(5) Cf. ref. 3c; Julian and Sturgis, *THIS JOURNAL*, **57**, 1126 (1935); ref. 4c.

(6) Kindler and Hesse, *Arch. Pharm.*, **271**, 439 (1933).

TABLE II
 PHENYLETHYLDIMETHYLAMINE HYDROCHLORIDES

| Substituent | Appearance | M. p., °C. (corr.) | Formula | Analyses, % | | | |
|----------------------------|-------------------------------------|-----------------------|--|-------------|------|-------|------|
| | | | | Calcd. | | Found | |
| | | | | C | H | C | H |
| None ⁷ | Large silky leaves | 165 | C ₁₀ H ₁₆ NCl | 64.66 | 8.69 | 64.74 | 8.75 |
| 2-Methoxy | Glittering silky leaves | 159.5 | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.45 | 8.33 |
| 3-Methoxy | Felted silky leaves | 135 | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.32 | 8.56 |
| 4-Methoxy ⁸ | Small glittering rectangular prisms | 176.5 | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.11 | 8.34 |
| 2,3-Dimethoxy | Dull tiny nodules of prisms | 140 | C ₁₂ H ₂₀ O ₂ NCl | 58.63 | 8.21 | 58.79 | 8.22 |
| 3,4-Dimethoxy ⁸ | Chalk-white tiny meshed prisms | 197 | C ₁₂ H ₂₀ O ₂ NCl | 58.63 | 8.21 | 58.76 | 8.33 |
| 2-Ethoxy | Felted slender silky needles | 143 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.78 | 8.74 |
| 3-Ethoxy ⁹ | Clumps of small stout prisms | 137 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.89 | 9.00 |
| 4-Ethoxy ¹⁰ | Glittering tiny flat prisms | 175 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.67 | 8.69 |
| 2-Ethoxy-3-methoxy | Slender meshed needles | 145 | C ₁₃ H ₂₂ O ₂ NCl | 60.08 | 8.54 | 60.41 | 8.73 |
| 3-Methoxy-4-ethoxy | Small pearly leaves | 151 | C ₁₃ H ₂₂ O ₂ NCl | 60.08 | 8.54 | 59.94 | 8.79 |
| 3-Ethoxy-4-methoxy | Small glittering irregular plates | 161.5 | C ₁₃ H ₂₂ O ₂ NCl | 60.08 | 8.54 | 60.26 | 8.65 |
| 3,4-Diethoxy | Tiny meshed flat prisms | 138 | C ₁₄ H ₂₄ O ₂ NCl | 61.39 | 8.84 | 61.46 | 8.84 |
| 2-Hydroxy ¹¹ | Leaves | 108 | C ₁₀ H ₁₆ ONCl | 59.53 | 8.00 | 59.68 | 8.05 |
| 3-Hydroxy ⁹ | Small glittering stout prisms | 164 | C ₁₀ H ₁₆ ONCl | 59.53 | 8.00 | 59.71 | 8.23 |
| 4-Hydroxy ¹² | Silky tiny leaves | 181 | C ₁₀ H ₁₆ ONCl | 59.53 | 8.00 | 59.53 | 8.02 |
| 2,3-Dihydroxy | Small grayish nodules | 96 | C ₁₀ H ₁₆ O ₂ NCl | 55.15 | 7.41 | 55.23 | 7.55 |
| 3,4-Dihydroxy ⁸ | Small grayish glittering leaves | 127 | C ₁₀ H ₁₆ O ₂ NCl | 55.15 | 7.41 | 55.25 | 7.57 |

 TABLE III
 PHENYLETHYLTRIMETHYLAMINE CHLORIDES

| Substituent | Appearance | M. p., °C. (corr.) | Formula | Analyses, % | | | |
|-----------------------------|-------------------------------|-----------------------|--|-------------|------|-------|------|
| | | | | Calcd. | | Found | |
| | | | | C | H | C | H |
| None ¹³ | Masses of minute plates | 192 | C ₁₁ H ₁₈ NCl | 66.13 | 9.09 | 66.34 | 9.28 |
| 2-Methoxy | Glittering stout leaves | 221 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.80 | 9.01 |
| 3-Methoxy | Small powdery prisms | 158 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.92 | 9.01 |
| 4-Methoxy ¹⁴ | Chalky tiny meshed needles | 206 | C ₁₂ H ₂₀ ONCl | 62.71 | 8.78 | 62.62 | 8.74 |
| 2,3-Dimethoxy | Stout prisms | 180 | C ₁₃ H ₂₂ O ₂ NCl | 60.08 | 8.54 | 60.15 | 8.57 |
| 3,4-Dimethoxy | Tiny glittering flat prisms | 206 | C ₁₃ H ₂₂ O ₂ NCl | 60.08 | 8.54 | 59.99 | 8.64 |
| 2-Ethoxy | Small glittering leaves | 211 | C ₁₃ H ₂₂ ONCl | 64.03 | 9.10 | 64.13 | 9.15 |
| 3-Ethoxy ¹⁵ | Dull powdery plates | 160 | C ₁₃ H ₂₂ ONCl | 64.03 | 9.10 | 64.10 | 8.99 |
| 4-Ethoxy | Powder of small prisms | 193 | C ₁₃ H ₂₂ ONCl | 64.03 | 9.10 | 64.16 | 9.24 |
| 2-Ethoxy-3-methoxy | Glittering irregular plates | 182 | C ₁₄ H ₂₄ O ₂ NCl | 61.39 | 8.84 | 61.64 | 9.16 |
| 3-Methoxy-4-ethoxy | Glittering prism clusters | 173 | C ₁₄ H ₂₄ O ₂ NCl | 61.39 | 8.84 | 61.59 | 9.02 |
| 3-Ethoxy-4-methoxy | Obscure prisms | 162 | C ₁₄ H ₂₄ O ₂ NCl | 61.39 | 8.84 | 61.59 | 9.10 |
| 3,4-Diethoxy | Tiny glittering needle prisms | 125 | C ₁₆ H ₂₆ O ₂ NCl | 62.57 | 9.11 | 62.55 | 9.30 |
| 2-Hydroxy ¹⁶ | Clumps of tiny prisms | 254 dec. | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.35 | 8.59 |
| 3-Hydroxy | Nodules of small spindles | 220 | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.25 | 8.35 |
| 4-Hydroxy ¹⁵ | Glittering small leaves | 287 dec. | C ₁₁ H ₁₈ ONCl | 61.22 | 8.41 | 61.09 | 8.42 |
| 2,3-Dihydroxy | Clumps of small prisms | 225 | C ₁₁ H ₁₈ O ₂ NCl | 56.99 | 7.82 | 57.09 | 7.75 |
| 3,4-Dihydroxy ¹⁷ | Small stout obscure prisms | 263 dec. | C ₁₁ H ₁₈ O ₂ NCl | 56.99 | 7.82 | 56.93 | 7.83 |

alkoxy hydrochlorides. The *p*-hydroxy compound was identical with authentic hordenine. The properties of the compounds (hydroxy and alkoxy) are given in Table II.

(7) Johnson and Guest, *THIS JOURNAL*, **32**, 761 (1910); Tiffeneau and Fuhrer, *Bull. soc. chim.*, [4] **15**, 162 (1914).

(8) Kindler and Hesse, *Arch. Pharm.*, **271**, 439 (1933). No hydrochloride.

(9) German Patent 233,069. Base only.

(10) German Patent 234,795. Base mentioned.

(11) Cf. v. Braun and Bayer, *Ber.*, **57**, 913 (1924).

(12) Léger, *Bull. soc. chim.*, [3] **35**, 235 (1906). German Patent 233,069.

(13) Cf. Beilstein's "Handbuch," **12***, 473. No chloride.

(14) Cf. Rosenmund, *Ber.*, **43**, 306 (1910). Iodide.

(15) German Patent 233,069.

(16) Cf. Pschorr and Einbeck, *Ber.*, **38**, 2067 (1905). Iodide.

(17) Cf. Barger and Ewins, *J. Chem. Soc.*, **97**, 2253 (1910).

Alkoxy- and Hydroxyphenylethyltrimethylamine Chlorides.—The quaternary salts were prepared from the tertiary amines, this method being preferable to using the primary amine. The starting hydrochloride was dissolved in water and the base liberated by potassium carbonate solution, extracted with (or, if solid, dissolved in) benzene, and dried with solid potassium hydroxide (for the alkoxy bases) or sodium sulfate (for the hydroxy bases). A considerable excess of methyl iodide was added, when the quaternary iodide rapidly separated out. After some hours ether was added to the usually gelatinous mass, and the solid filtered off, washed with ether, dissolved in water, and converted into the chloride by silver chloride. The aqueous solution was evaporated to dryness under reduced pressure and the residue recrystallized from alcohol-ether.

The chlorides form well-crystallized compounds, soluble in water, alcohol and hydrochloric acid, and practically insoluble in ether, ethyl acetate, etc. They are unusually difficult to analyze. Their properties are described in Table III.

Summary

A series of hydroxy- and alkoxyphenylethyldi-

methylamine hydrochlorides (18 compounds) and a series of hydroxy- and alkoxyphenylethyltrimethylamine chlorides (18 compounds) have been prepared, all by the same sequence of reactions, which appears to be general. The preparation of the intermediates also is described.

TUCKAHOE, NEW YORK

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[CONTRIBUTION FROM THE BIOCHEMISTRY LABORATORY OF THE UNIVERSITY OF OKLAHOMA MEDICAL SCHOOL]

Relations of *cis-trans* Isomerism to Asymmetric Oxidation of Sugars¹

BY M. R. EVERETT AND FAY SHEPPARD

Richtmyer and Hudson² recently reported the interesting phenomenon of unequal quantitative reduction of alkaline copper reagents by *d*- and *l*-forms of aldoses, when *d*- or *l*-tartaric acids were used in Shaffer-Hartman-Somogyi reagents. We have now completed similar experiments with *d*-, *l*- and *meso*-tartrate Folin-Wu reagents.³ The *l*-tartaric acid employed was prepared by the method described by Richtmyer and Hudson, and had the correct $[\alpha]^{20D} - 14^\circ$. The *d*- and *meso*-tartaric acids were Central Scientific Co. and Eastman Kodak Co. products with $[\alpha]^{20D} + 14$ and $+0.05^\circ$, respectively. The sugar solutions and special reagents⁴ were freshly prepared, immediately before analysis. Several concentrations of each sugar were investigated and compared with suitable *d*-glucose standards. Determinations were made under strictly comparable conditions.

The results reported in Table I are the reducing equivalents relative to *d*-glucose and *d*-tartrate reagent taken as 1.00 and are averages of four or more determinations. Corrections for moisture content of sugars and proportionality of the analytical method have been applied. The reagents employed by us appear to be somewhat more sensitive to spacial configuration than the

copper reagents used by Richtmyer and Hudson, but both investigations show that *d*-forms of arabinose, fructose and mannose and *l*-forms of fucose and rhamnose select the *l*-tartrate reagent; *d*-forms of galactose, lactose and mannoketoheptose and *l*-arabinose select the *d*-tartrate reagent; and *d*-forms of glucose and xylose show little selectivity. For sugars not investigated by Richtmyer and Hudson, we find that *d*-forms of maltose, melibiose and ribose select the *l*-tartrate reagent; *d*-forms of galacturonic and glycuronic acids, mannoheptose and sorbose select the *d*-reagent; *d*-forms of cellobiose, gentiobiose, glucosamine and lyxose and *l*-forms of ascorbic acid, sorbose and xylose are not very selective. Our *meso*-tartrate reagent is reduced more than either of the *trans* reagents by *d*-forms of cellobiose, gentiobiose, glycuronic acid, lactose, maltose, α -mannoheptose, mannoketoheptose and mannose.

It is evident from these results that asymmetric oxidation of sugars bears no simple relation to ordinary optical or planar isomerism, and is influenced by extraplanar molecular relations (group substitution, *cis-trans* relations, etc.). The reducing values of Table I are definitely related to the *cis-trans* classification of sugars suggested by the authors.^{6,7} This arrangement of sugars in eight *cis-trans* groups, corresponding to the eight aldopentoses, is reproduced in Table II.

Oxidation in alkaline solution is complicated by mutarotation and epimerization, and recently Isbell⁸ has shown that mutarotation is correlated with *cis-trans* configuration. The behavior of

(1) Aided by a grant from the Research Fund of the University of Oklahoma Medical School. The authors also wish to acknowledge the following gifts: α -*d*-mannoheptose and *d*-mannoketoheptose from Dr. C. S. Hudson and *d*-galacturonic acid from Dr. Karl Link.

(2) Richtmyer and Hudson, THIS JOURNAL, **58**, 2540 (1936).

(3) Folin and Wu, J. Biol. Chem., **67**, 357 (1926).

(4) For each 20 cc. of alkaline tartrate reagent we used 0.1096 g. of tartaric acid (*d*-, *l*- or *meso*-), 3 cc. of distilled water, 2 cc. of 1.125 *N* sodium hydroxide and 15 cc. of buffer solution (containing 4.667% sodium carbonate and 1.467% sodium bicarbonate); 18 cc. of this solution was then mixed with 2 cc. of 5% cupric sulfate solution. The time of heating was uniformly seven and one-half minutes on the boiling water-bath. The Folin's acid reagent was used for color development.

(5) Folin, J. Biol. Chem., **82**, 83 (1929).

(6) Everett and Sheppard, Proc. Okla. Acad. Sci., November, 1936.

(7) Everett and Sheppard, "The Oxidation of Carbohydrates in Acid Solution," University of Oklahoma Medical School Monograph, 1936.

(8) Isbell, J. Research Natl. Bur. Standards, **18**, 505 (1937).