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 alkoxyphenylethyldimethylamine 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 RECEIVED MAY 20, 1938

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

Relations of *cis-trans* Isomerism to Asymmetric Oxidation of Sugars[1]

BY M. R. EVERETT AND FAY SHEPPARD

Richtmyer and Hudson[2] 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 $[\alpha]^{20}D$ $-14°$. The *d*- and *meso*-tartaric acids were Central Scientific Co. and Eastman Kodak Co. products with $[\alpha]^{20}D$ $+14$ and $+0.05°$, respectively. The sugar solutions and special reagents[4] 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 Isbell[8] 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 0.1696 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[5] 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).

TABLE I

RELATIVE REDUCING EQUIVALENTS OF SUGARS (*d*-GLUCOSE = 1.00)

Sugars	Folin–Wu tartrate reagents mg./cc.	*d*-	*l*-	*meso*	Sumner reagent (0.5 mg./cc.)
d-Xylose	0.1	0.97	1.02	0.91	1.14
d-Xylose	.2	.985	.995	.94	
l-Xylose	.1	.965	1.05	.955	1.18
l-Xylose	.2	.99	1.05	.955	
d-Lyxose	.1	.96	0.94	.855	1.16
d-Lyxose	.2	.96	.935	.88	
d-Arabinose	.1		.92	.76	1.13
d-Arabinose	.2	.69	.88	.78	
d-Arabinose	.4	.685			
l-Arabinose	.1	.86		.765	1.14
l-Arabinose	.2	.87	.73	.77	
l-Arabinose	.4		.69		
d-Ribose	.1		.84		1.08
d-Ribose	.2	.62	.83	.70	
d-Ribose	.4	.655		.73	
d-Glucose	.1	1.00	.98	1.00	1.00
d-Glucose	.2	1.00	.975	1.00	
d-Mannose	.2	0.45	.56	0.70	0.97
d-Mannose	.4	.57	.63	.68	
d-Galactose	.1	.78			.97
d-Galactose	.2	.79	.64	.755	
d-Galactose	.4		.63	.72	
d-Glucosamine·HCl	.1	.77	.79	.73	.33[a]
d-Glucosamine·HCl	.2	.81	.80	.755	
d-Glycuronic acid	.1			.95	.91
d-Glycuronic acid	.2	.71	.65	.945	
d-Glycuronic acid	.4	.80	.715		
d-Galacturonic acid·H_2O	.2	.655	.45	.58	.87
d-Galacturonic acid·H_2O	.4	.65	.46	.565	
d-Sorbose	.1	.76	.70	.745	.99
d-Sorbose	.2	.80	.71	.785	
l-Sorbose	.1	.80	.795	.785	.95
l-Sorbose	.2	.85	.83	.83	
d-Fructose	.1	.89	.965	.94	.99
d-Fructose	.2	.93	.975	.98	
l-Rhamnose·H_2O	.3	.315	.40	.385	.98
l-Rhamnose·H_2O	.6	.375	.41	.44	
l-Fucose	.3	.45	.53	.475	1.00
l-Fucose	.6	.42	.48	.45	
α-*d*-Mannoheptose	.2	.60	.515	.67	0.83
α-*d*-Mannoheptose	.4	.63	.51	.66	
d-Mannoketoheptose	.2	.68	.605	.75	1.00
d-Mannoketoheptose	.4	.70	.60	.73	
l-Ascorbic acid	.1	.55	.55	.55	0.44
l-Ascorbic acid	.4	.925	.90	.945	
Gentiobiose	.2	.54	.54	.57	.66
Gentiobiose	.4	.535	.535	.57	
Cellobiose	.2	.535	.53	.655	.83
Cellobiose	.4	.52	.51	.645	
Maltose·H_2O	.2	.415	.46	.51	.76
Maltose·H_2O	.4	.425	.44	.51	
Melibiose·$2H_2O$	.2	.495	.52	.50	.63
Melibiose·$2H_2O$	.4	.49	.50	.50	
Lactose·H_2O	.2	.475	.45	.535	.77
Lactose·H_2O	.4	.475	.445	.53	

[a] Used 1 mg./cc.

pentoses with alkaline reagents (Table I) follows epimeric relations; thus, xylose and lyxose (epimeric *trans* types) react almost equally with *d*- and *l*-tartrate reagents, whereas ribose and arabinose (epimeric *cis* types) select opposite enantiomorphs of reagents. Six and seven carbon sugars behave qualitatively like related epimeric pentose types, but deviate quantitatively. Additional

TABLE II

CLASSIFICATION OF PENTOSES, METHYLPENTOSES AND HEXOSES ACCORDING TO *cis-trans* ISOMERISM OF PYRANOID FORMS

trans Forms

d-Xylose group	*l*-Xylose group
d-Isorhamnose	*l*-Isorhamnose
d-Sorbose	*l*-Sorbose
d-Glucose	*l*-Glucose
l-Idose	*d*-Idose

2,3-*cis* Forms

d-Lyxose group	*l*-Lyxose group
d-Rhamnose	*l*-Rhamnose
d-Tagatose	*l*-Tagatose
d-Mannose	*l*-Mannose
l-Gulose	*d*-Gulose

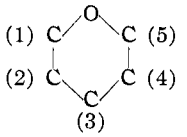
3,4-*cis* Forms

d-Arabinose group	*l*-Arabinose group
l-Fucose	*d*-Fucose
d-Fructose	*l*-Fructose
d-Altrose	*l*-Altrose
l-Galactose	*d*-Galactose

2,3,4-*cis* Forms

d-Ribose group	*l*-Ribose group
Epifucose	Epirhodeose
d-Psicose	*l*-Psicose
d-Allose	*l*-Allose
l-Talose	*d*-Talose

Type formula



Carbon 1 is the characteristic potential carbonyl.

carbon at pyranoid positions 1 or 5 (Table II) limits mobility of the cyclic oxygen, allowing opposite planar arrangements of cyclic oxygen in aldohexoses of each *cis–trans* group and the resultant alteration of *cis–trans* influences at pyranoid position 5.

In our experiments *cis* sugars with opposite extraplanar relationships showed opposing selectivity for asymmetric oxidizing agents. *d*-Mannose and *l*-rhamnose, with 2,3-*cis* hydroxyls *trans* to cyclic oxygen, selected *l*-tartrate reagent, and *d*-galactose, an extraplanar opposite as far as positions 2, 3 and 4 are concerned, selected the *d*-reagent (Table I). The oxidation of sugars is thus influenced by spacial configuration in three dimensions.

In Table III we have listed molar reducing equivalents of sugars and their percentage deviations from the *d*-glucose standard. The molar equivalents have been calculated as percentages

TABLE III

MOLAR REDUCING EQUIVALENTS AND PERCENTAGE DEVIATIONS OF SUGARS RELATIVE TO *d*-GLUCOSE

Sugars	mg./cc.	Folin-Wu equivalents *d*-Reag.	*l*-Reag.	*m*-Reag.	Deviation, % X	Y	Z	Sumner equivalent[a]	Deviation, %
d-Xylose	0.1	0.81	0.85	0.76	− 4	−15	−24	0.95	− 5
d-Xylose	.2	.82	.83	.78	− 1	−17	−22		
l-Xylose	.1	.805	.875	.795	− 7	−12.5	−20.5	.98	− 2
l-Xylose	.2	.825	.875	.795	− 5	−12.5	−20.5		
d-Glucose	.1	1.00	.98	1.00	+ 2	0	0	1.00	0
d-Glucose	.2	1.00	.975	1.00	+ 2.5	0	0		
d-Glucosamine	.1	0.92	.95	0.875	− 3	− 5	−12.5	0.395	−60.5
d-Glucosamine	.2	.97	.96	.905	+ 1	− 4	− 9.5		
d-Glycuronic acid	.1			1.025			+ 2.5	.98	− 2
d-Glycuronic acid	.2	.765	.70	1.02	+ 6.5	−23.5	+ 2		
d-Glycuronic acid	.4	.86	.77		+ 9	−14			
d-Sorbose	.1	.76	.70	0.745	+ 6	−24	−25.5	.99	− 1
d-Sorbose	.2	.80	.71	.785	+ 9	−20	−21.5		
l-Sorbose	.1	.80	.795	.785	+ 0.5	−20	−21.5	.95	− 5
l-Sorbose	.2	.85	.83	.83	+ 2	−15	−17		
d-Lyxose	.1	.80	.78	.71	+ 2	−20	−29	.965	− 3.5
d-Lyxose	.2	.80	.78	.73	+ 2	−20	−27		
d-Mannose	.2	.45	.56	.70	−11	−44	−30	.97	− 3
d-Mannose	.4	.57	.63	.68	− 6	−37	−32		
l-Rhamnose	.3	.32	.405	.39	− 8.5	−59.5	−61	.99	− 1
l-Rhamnose	.6	.38	.415	.445	− 3.5	−58.5	−55.5		
d-Mannoketoheptose	.2	.79	.71	.875	+ 8	−21	−12.5	1.16	+16
d-Mannoketoheptose	.4	.82	.70	.85	+12	−18	−15		
d-Arabinose	.1		.77	.63		−23	−37	0.94	− 6
d-Arabinose	.2	.575	.73	.65	−15.5	−27	−35		
d-Arabinose	.4	.57							
l-Arabinose	.1	.72		.64		−28	−36	.95	− 5
l-Arabinose	.2	.725	.61	.64	+11.5	−27.5	−36		
l-Arabinose	.4		.575						
d-Galactose	.1	.78				−22		.97	− 3
d-Galactose	.2	.79	.64	.755	+15	−21	−24.5		
d-Galactose	.4		.63	.72			−28		
d-Galacturonic acid	.2	.77	.53	.68	+24	−23	−32	1.025	+ 2.5
d-Galacturonic acid	.4	.765	.54	.665	+22.5	−23.5	−33.5		
d-Fructose	.1	.89	.965	.94	− 7.5	− 3.5	− 6	0.99	− 1
d-Fructose	.2	.93	.975	.98	− 4.5	− 2.5	− 2		
l-Fucose	.3	.41	.48	.43	− 7	−52	−57	.91	− 9
l-Fucose	.6	.38	.44	.41	− 6	−56	−59		
α-*d*-Mannoheptose	.2	.70	.60	.78	+10	−30	−22	.97	− 3
α-*d*-Mannoheptose	.4	.735	.595	.77	+14	−26.5	−23		
d-Ribose	.1		.70			−30		.90	−10
d-Ribose	.2	.52	.69	.58	−17	−31	−42		
d-Ribose	.4	.54		.61			−39		
l-Ascorbic acid	.1	.56	.56	.56	0	−44	−44	.45	−55
l-Ascorbic acid	.4	.945	.92	.965	+ 2.5	− 5.5	− 4.5		
Gentiobiose	.2	1.03	1.03	1.08	0	+ 3	+ 8	1.25	+25
Gentiobiose	.4	1.02	1.02	1.08	0	+ 2	+ 8		
Cellobiose	.2	1.02	1.01	1.24	+ 1	+ 2	+24	1.57	+57
Cellobiose	.4	0.99	0.97	1.23	+ 2	− 1	+23		
Maltose	.2	.83	.92	1.02	− 9	− 8	+ 2	1.52	+52
Maltose	.4	.85	.88	1.02	− 3	−12	+ 2		
Melibiose	.2	1.04	1.09	1.05	− 5	+ 9	+ 5	1.32	+32
Melibiose	.4	1.03	1.05	1.05	− 2	+ 5	+ 5		
Lactose	.2	0.95	0.90	1.07	+ 5	− 5	+ 7	1.54	+54
Lactose	.4	.95	.89	1.06	+ 6	− 5	+ 6		

[a] Concentrations as in Table I.

of the reduction of *d*-tartrate reagent by *d*-glucose. The deviations are defined as follows: X, representing planar influences for *trans* reagents, is the molar equivalent for the *d*-reagent minus that for the *l*-reagent. Y, representing extraplanar influences for *trans* reagents, is the equivalent for that *trans* reagent most reduced by any particular sugar minus the equivalent of the *trans* sugar, *d*-glucose, for the *d*-reagent. Z, representing the total influence upon the *meso* reagent, is the equivalent for this reagent minus that of *d*-glucose for the *d*-reagent.

The deviations of monosaccharides with *trans* tartrate reagents reveal that epimerized *d*-glucose, *d*-glucosamine, *d*-xylose, *d*-lyxose and *l*-sorbose are most symmetrical in a planar sense, since their X deviations approach zero. However, these *trans* sugars have average Y deviations of 0, −4.5, −16, −20 and −17.5, respectively. The presence of the CH_2OH group at position 5 in *d*-glucose therefore increases the *trans* characteristics of the pyranoid molecule. In the three-dimensional strainless model of *d*-glucopyranose, viewed from the plane of the ring, the additional hydroxyl group of carbon 6 balances the other oxygens in both a planar (right and left) and an extraplanar (polar) sense. In *l*-sorbose and *d*-xylose models the oxygens are well balanced in a planar sense but not in an extraplanar sense, since there is no CH_2OH group at pyranoid position 5.

Lengthening the carbon chain therefore results in appreciable alteration of extraplanar influences, which are interrelated with planar influences. The interrelation is demonstrated by the fact that *d*- and *l*-isomerism can be represented alternately as a polar phenomenon relative to the pyranoid cyclic oxygen. Inversion of strainless pyranoid models of *l*-sugars, whose ring systems are thus viewed as identical with those of *d*-sugars, reveals polar interchanges between carbons 1 and 5 and between carbons 2 and 4. Relating sugar antipodes in this fashion facilitates comparisons which are difficult with the usual right and left disymmetric formulas. Since planar and extraplanar influences have a common space coördinate, the substitution of CH_2OH or COOH groups at pyranoid positions 1 or 5 affects both *cis–trans* (Y) and planar (X) influences, the latter causing a "shift to the right" in reagent selection by ketoses and alduronic acids. (Compare these with related aldohexoses in Table III.)

Of the monosaccharides studied, *d*-glucose gives rise to the most symmetrical three-dimensional epimeric system. In a planar sense, epimerized *d*-glucosamine, *d*-xylose, *l*-sorbose and *d*-lyxose are just as symmetrical, while *d*-galacturonic acid, *d*-ribose, *d*-arabinose and *d*-galactose (3,4-*cis* types) are most unsymmetrical. In an extraplanar sense, *d*-glucose, *d*-glucosamine and *d*-fructose are most symmetrical, the latter evidently going to a balanced epimeric system by a Lobry de Bruyn rearrangement; methylpentoses are most unsymmetrical and reduce less copper than other sugars.

The *trans* arrangement of epimerized *d*-glucose and its relatives, *d*-fructose and *d*-glycuronic acid, is also the most favorable influence for reduction of *meso*-tartrate reagent (Table III). With aldopentoses, extraplanar deviations (Y) for *trans* reagents are uniformly less than the total deviations (Z) for the *meso* reagent, and the latter is not always reduced equally by planar antipodes. (See xylose and sorbose in Table III.) Analogous smaller deviations occur even with the nonasymmetric Sumner reagent.

The fact that *d*-glucose reduces *meso* reagent 23% more than does *d*-xylose, indicates again that mutarotation and epimerization of the *trans* pentose are insufficient to balance its molecule in all dimensions and that terminal CH_2OH groups are active. Certain sugars which are not optical antipodes reduce the *meso* reagent equally (*d*-xylose and *d*-sorbose, also *d*-mannose and *d*-galacturonic acid); others (*d*-glucose, *l*-ascorbic acid, the methylpentoses and ketohexoses) have approximately equal Y and Z deviations.

More detailed correlation is problematical because the concentration of certain sugars affects their oxidation. Notable instances are *d*-mannose and *d*-glycuronic acid with *trans* tartrate reagents (Table III), but the most remarkable example is α-glucosan with *d*-tartrate.[7]

The β-glucose-glucosides, cellobiose and gentiobiose, resemble the parent monosaccharide with *trans* reagents, but differ in their effects upon *meso* reagent. Cellobiose presents a space arrangement for *meso* oxidation markedly superior to that of any sugar studied (Table III). The marked reduction of Sumner's reagent by disaccharides is significant.

We have called attention previously to the usefulness of Sumner/Folin–Wu ratios of glucose equivalents for differentiating sugars in solution.[7,9]

(9) Everett, Edwards and Sheppard, *J. Biol. Chem.*, **104**, 11 (1934).

The present study provides a more scientific basis for these ratios and correlates them with sugar structure.

Summary

1. Quantitative studies have been made of the oxidation of twenty-five sugars by *d*-, *l*- and *meso*-tartrate modifications of the Folin–Wu alkaline copper reagent and by Sumner's dinitrosalicylate reagent.

2. The behavior of reducing sugars is determined by the entire sugar molecule, but intramolecular influences can be conveniently classified as planar and extraplanar, *cis–trans* relations being important extraplanar influences.

3. Epimeric sugars have related behaviors, the glucose epimeric system being most symmetrical in all dimensions. *cis*-Sugars are most unsymmetrical in a planar sense and methylpentoses in an extraplanar sense.

4. *meso*-Tartrate reagent is susceptible to both planar and extraplanar influences.

OKLAHOMA CITY, OKLA. RECEIVED JANUARY 7, 1938

[CONTRIBUTION NO. 134 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Hydantoins Derived from the Analogs of 1,3-Dichloroisopropoxyethyl Methyl Ketone[1]

BY BRUCE B. ALLEN WITH HENRY R. HENZE

As a continuation of attempts to prepare substances possessing soporific properties, attention has now been directed to the synthesis of 5,5-disubstituted hydantoins in which one of the substituents is of the halogenoalkoxyalkyl type. In this Laboratory, the application of Bucherer's[2] hydantoin synthesis has been extended to the preparation of disubstituted heterocyclic compounds from such bifunctional carbonyl substances as alkoxymethyl alkyl (or aryl) ketones[3] and phenoxymethyl alkyl (or aryl) ketones,[4] and has been shown to be advantageous over other accepted methods as regards yield, ease of execution, and degree of purity of product. In the present investigation, then, successful use of the Bucherer method in hydantoin formation from dichloroisopropoxyethyl alkyl or aryl ketones resulted in further extension of the application of the method. The ketones used were, with one exception, of the type $(CH_2Cl)_2CH\text{-}O\text{-}CH(CH_3)\text{-}COR$ where R represents alkyl and includes those groups which have been shown most active physiologically; the preparation and characterization of these ketones have been described by us previously.[5] Since the hydantoin derived from the phenyl analog of this series of ketones represents a halogenoalkoxyl derivative of Nirvanol (5-ethyl-5-phenylhydantoin), a substance shown to possess useful medicinal value,[6] it was deemed pertinent to effect its preparation and subsequent conversion into the corresponding hydantoin.

Experimental

Preparation of α-1,3-Dichloroisopropoxyethyl Alkyl Ketones.—The eight ketones of this series which were employed were prepared from α-1,3-dichloroisopropoxypropionitrile by means of the Grignard reaction, these preparations having been described previously.[5]

Preparation of α-1,3-Dichloroisopropoxyethyl Phenyl Ketone.—The general method as described for the preparation of the alkyl analogs was employed in the synthesis of this ketone. The Grignard reagent from 48.1 g. (0.31 mole) of phenyl bromide, 7.3 g. (0.3 atom) of magnesium in the form of turnings, and 250 cc. of anhydrous ether was treated with the solution of 45.5 g. (0.25 mole) of α-1,3-dichloroisopropoxypropionitrile in an equal volume of ether. Although vigorous reaction occurred throughout the nitrile addition, completion was ensured by refluxing for two hours over a steam-cone. The addition product, which separated as a gray-colored solid, was decomposed in the usual manner with chilled, dilute hydrochloric acid and crushed ice; the resulting ether layer was separated, washed with dilute sodium carbonate solution and then water, and finally dried over anhydrous calcium chloride. The crude material was freed of ether by evaporation and then purified by two fractionations under 4 mm. pressure; the pure ketone is a colorless, almost odorless, quite viscous liquid which develops a deep red coloration upon standing; yield, 45.4 g. (69.6%); b. p. 169° (4 mm.); d^{20}_4 1.2356; $n^{20}D$ 1.5398; *MR* calcd., 66.18;[7] *MR* found, 65.31; γ^{20} 35.53 dynes/cm.; *P* calcd. (Sugden's atomic constants), 538.4; *P* found, 516.0.

(1) From a portion of a dissertation presented by Bruce B. Allen to the Faculty of the Graduate School of the University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1938.

(2) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(3) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936).

(4) Whitney with Henze, *ibid.*, **60**, 1148 (1938).

(5) Allen with Henze, *ibid.*, **59**, 540 (1937).

(6) De Rudder, *Chem. Zentr.*, **99**, I, 2628 (1926); Poynton and Schlesinger, *Lancet*, II, 267 (1929); Pilcher and Gerstenberger, *Am. J. Diseases Children*, **40**, 1239 (1930); Jones and Jacobs, *J. Am. Med. Assoc.*, **99**, 18 (1932).

(7) This summation includes the exaltation value due to the C_6H_5-CO- grouping which has been determined for acetophenone by Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **84**, 20 (1911).