18 hours at room temperature, and then poured into ice, giving 0.99 g. of crystalline material. Recrystallization from ethanol gave 0.95 g. (84%) of pure material, m.p. 177–178.5°, undepressed on admixture with material prepared from D-glucosamine, $[\alpha]^{25}$ +13.6° (*c* 4, U.S.P. chloroform).

Anal. Calcd. for $C_{19}H_{18}O_8S_2N(CH_3CO)_5$ (559.6): C, 42.92; H, 5.94; N, 2.50; S, 11.46; CH_3CO, 38.46. Found: C, 42.88; H, 5.94; N, 2.71; S, 11.44; CH_3CO, 38.91.

The same material was also obtained by substituting methanolic ammonia for aqueous ammonia in the above procedure.

D-Arabinose.—Five grams of the D-*arabo*-3,4,5,6-tetraacetoxy-1,1-bis-(ethanesulfonyl)-hexene-1 (I) was added to 100 ml. of methanol and to this there was added 4.5 ml. of 85% hydrazine hydrate in water. The material dissolved rapidly and, after four hours at room temperature, the solvent was removed at reduced pressure, water (50 ml.) was added, and the mixture extracted four times with 20-ml. portions of chloroform. To the aqueous layer was added 35 ml. of benzaldehyde, 0.5 g. of benzoic acid and 40 ml. of ethanol and the mixture was refluxed for 3 hours. After cooling, the mixture was extracted with three 20-ml. portions of chloroform and then with 20 ml. of ether, and then passed consecutively through columns of Duolite C-3H and Duolite A-2[20] and washed with about 400 ml. of water, after which the effluent gave a negative Fehling test. The percolate was concentrated at reduced pressure (bath temperature below 60°) to a volume of about 10 ml., charcoal was added and the water removed from the filtered solution in a vacuum oven at 40°.[21] To complete the crystallization of the D-arabinose 5 ml. of hot methanol was added, and after 24 hours at +4° the crystalline residue was washed twice with cold methanol by decantation and dried *in vacuo* over calcium chloride. In a typical experiment, there was obtained 1.10 g. (73%) of D-arabinose $[\alpha]^{23}D$ −103.0° (equilibrium, *c* 2, water).

(20) Manufactured by the Chemical Process Company, Redwood City, California; column dimensions 1.4 × 21 cm.

(21) *Cf.* W. Z. Hassid, M. Doudoroff and H. A. Barker, THIS JOURNAL, **66**, 1416 (1944).

The first chloroform extract was dried with Na_2SO_4 and, after removal of the solvent at reduced pressure, the crystalline residue was recrystallized from water giving 1.73 g. (87%) of bis-(ethanesulfonyl)-methane m.p. 102–103°, undepressed on admixture with an authentic sample.

The degradation could also be carried out on the crude disulfone; 5.00 g. of D-glucose diethyl mercaptal pentaacetate was oxidized with monoperphthalic acid as described, and the crude disulfone obtained after concentration of the chloroform extract was degraded exactly as in the case of the pure material. In a typical experiment there was obtained 0.88 g. of D-arabinose (58%) having $[\alpha]^{25}D$ −103.3°.

D-Lyxose.—Five grams of D-*lyxo*-3,4,5,6-tetraacetoxy-1,1-bis-(ethanesulfonyl)-hexene-1 (III) was degraded exactly as in the case of the *arabo*-isomer. To effect crystallization of the D-lyxose, the sirup obtained after concentration in the vacuum oven was dissolved in 3 ml. of hot methanol, seeded, and left at +4°. After crystallization had progressed considerably (24 hours), 3 ml. of isopropyl alcohol was added and after a further 24 hours at +4° the crystals were washed twice by decantation with cold isopropyl alcohol. In a typical experiment there was obtained 0.86 g. (57%) of D-lyxose, $[\alpha]^{24}D$ −14.0° (equilibrium, *c* 3.8, water).

Working up the chloroform extract containing the bis-(ethanesulfonyl)-methane gave, after recrystallization from water, 1.80 g. of material (90%), m.p. 102–103°.

When the degradation was carried out on the crude disulfone obtained by oxidation of 5.00 g. of D-galactose diethyl mercaptal pentaacetate, there was obtained 0.93 g. (60%) of D-lyxose showing $[\alpha]^{25}D$ −13.4° (equilibrium, *c* 4.0, water).

Acknowledgments.—The authors are particularly grateful to Miss B. Rolander for carrying out many of the combustion analyses, and to Mr. R. Dorner for the preparation of D-*gluco*-2-acetamino-3,4,5,6 - tetraacetoxy - 1,1 - bis - (ethanesulfonyl)-hexane from D-glucosamine.

BERKELEY 4, CALIFORNIA RECEIVED NOVEMBER 12, 1951

[CONTRIBUTION FROM THE BIOLOGY DIVISION, OAK RIDGE NATIONAL LABORATORY]

The Separation of Sugars by Ion Exchange[1]

BY JOSEPH X. KHYM AND LEONARD P. ZILL

The separation of sugars has been achieved by the elution of their borate complexes from strong-base anion exchangers with boric–borate buffers. Disaccharides are readily separated from the monosaccharides and the components of hexose or pentose mixtures are easily separated. Hexose–pentose mixtures can be analyzed by the techniques presented. The results are consistent with current concepts of the structures of sugar–borate complexes and the reactions of free sugars in aqueous solutions.

Introduction

The lack of simple quantitative methods for the analysis of sugar mixtures has long been recognized. Until recently,[2] the assay of one or more components of a sugar mixture has been somewhat involved and, in some cases, impossible. Although newer methods have overcome to a large extent the fundamental empiricism of reporting sugars as total and reducing sugars, they have certain difficulties of methodology.

The experiments to be described had as their objective the development of a procedure for the quantitative analysis of mixtures of sugars using the technique of ion exchange in a fashion similar to that used in separating nucleotides and related compounds.[3]

Sugars, being very weak electrolytes, have little tendency to react with ion exchangers. However, it has long been known that certain polyhydroxy compounds react with borate ion (from boric acid or its salts) with great ease and rapidity to form borate complexes which are negatively charged ions.[4] Although within a given class of sugars

(1) Biology Division, Oak Ridge National Laboratory, operated under Contract Number W-7405-Eng-26 for the Atomic Energy Commission, Oak Ridge, Tennessee.

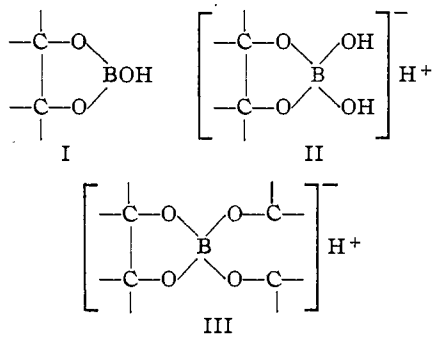
(2) S. Udenfriend and M. Gibbs, *Science*, **110**, 708 (1949); W. W. Binkley and M. L. Wolfrom, Chromatography of Sugars and Related Substances, Sugar Research Foundation, Inc., *Scientific Report Series* #10 (1948); B. W. Lew, M. L. Wolfrom and R. M. Goepp, Jr., THIS JOURNAL, **68**, 1449 (1946); M. Ikawa and C. Niemann, *J. Biol. Chem.*, **180**, 923 (1949); M. Ikawa and C. Nieman, *Arch. Biochem. Biophys.*, **31**, 62 (1951); Z. Dische, L. B. Shettles and M. Osnos, *Arch. Biochem.*, **22**, 169 (1949); S. Hestrin and J. Mager, *Nature*, **158**, 95 (1946); L. Hough, J. K. N. Jones and W. H. Wadman, *J. Chem. Soc.*, 2511 (1949); S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

(3) W. E. Cohn, THIS JOURNAL, **72**, 1471 (1950); E. Volkin, J. X. Khym and W. E. Cohn, *ibid.*, **73**, 1533 (1951).

(4) J. Böeseken in "Advances in Carbohydrate Chemistry," edited by W. W. Pigman and M. L. Wolfrom, Academic Press, Inc., New York, N. Y., 1949, Vol. 4, p. 189.

(*e.g.*, the monosaccharides) one would expect the sugar–borate compounds to possess very similar properties, it was thought that since ion exchange columns can resolve compounds which are very similar, the separation of a mixture of these sugar–borate complexes could be achieved.

Information concerning the character of these compounds has been derived from the measurement of changes in optical rotation, conductivity, acidity, freezing point and solubility.[5] The structures which have been postulated from this kind of data are shown. There is good evidence that some sugars can form complexes of each type represented



but, for any single diol, it has not been possible to separate all three compounds in crystalline form.[5] The evidence suggests that, when the three types of complexes are possible, they are in equilibrium; this equilibrium is dependent upon *p*H, ratio of borate to sugar, and the absolute concentration of the latter.[5]

According to the data of Isbell, *et al.*,[5] structures of type II should predominate in dilute solutions containing large quantities of borate and little sugar. In the separations of the monosaccharides to be presented, these conditions are fulfilled, and thus it seems reasonable to assume that we are dealing to a large extent with sugar–borate complexes of type II. In the separation of some of the disaccharides, the structure of the borate–diol compounds involved is probably analogous to type I.

For the separation of substances by ion exchange, it is necessary to find sets of conditions in which each substance exhibits a different degree of affinity for the exchanger. Control of *p*H and direct ion replacement of the sugar–borate complexes by borate ion were selected as the simplest method of exploiting any differences in the affinity of these complexes for the resin. All the separations described here were carried out using borate solutions as the eluting agents at *p*H's between 8 and 9 (the *pK* of boric acid is about 9.2). A high *p*H minimizes the total borate required and the use of borate as the replacing ion shifts the equilibrium so as to favor the complex form of the sugar.

Experimental

Apparatus.—The type of column is described elsewhere.[6,7] An automatic sample changer was used to collect serial samples of 30 to 50 ml. each. The hexoses and disaccharides were assayed according to the anthrone method[8,9] and the pentoses by the orcinol method,[10] using Coleman or Evelyn colorimeters at 620 mμ for both methods. Paper chromatography was used for the identification of material isolated by the exchangers[11]; however, to obtain characteristic and reproducible papergrams, it was found necessary to remove the alkali cations from the concentrated borate–sugar solutions. This was easily accomplished by passing the sugar–borate solution through a strong acid exchanger in the hydrogen form (Dowex-50), thereby giving a saturated boric acid solution of the sugar which has been found to give a characteristic papergram.

Ion Exchangers.—All separation experiments were performed with 200–400 mesh strong-base anion exchanger (Dowex-1). The exchanger was washed free of fines by decantation, slurried into columns, and washed with 1 *N* hydrochloric acid. The columns were then converted to the borate form by allowing 0.1 *M* potassium tetraborate to pass through until the effluent showed only a faint test for chloride ion. A water wash then removed excess borate from the column.

Test Substances.—Most of the sugars were obtained from commercial sources.

Procedure.—After the columns had been converted to the borate form and excess borate removed, they were washed with dilute borate solution depending upon the particular experiment (*e.g.*, for the separation of disaccharides, about 50 ml. of 0.005 *M* borate was washed through the column prior to passing through sugars). Following this wash, the test material (usually about 10 mg. of each component) was absorbed on the column from 10 ml. of dilute borate solution. It was our practice to give the column another 10 ml. wash with dilute borate before elution with the desired reagent was commenced.

The reaction between the borate ion and the sugar molecule to form the complex is quite rapid and it did not seem to alter column separations whether these sugar–borate solutions were allowed to stand 5 minutes or 24 hours before adsorption of the test material on the column.

Results

The separations that are shown in Figs. 1 to 6 are for the more common sugars, although any group of sugars able to form a borate complex would probably behave in a similar manner. Recoveries of sugars are essentially quantitative. In Fig. 1 is shown the separation of a hexose mixture. If mannose and fructose are both present in a hexose mixture, no separation of these two is obtained under the conditions of Fig. 1. However, a separation of mannose and fructose can be obtained at a lower *p*H and lower tetraborate concentration as demonstrated in Fig. 2.

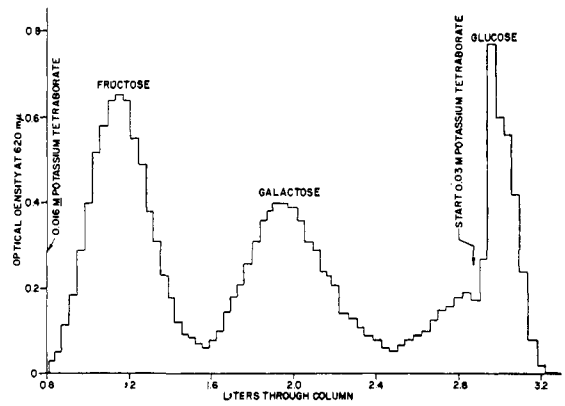


Fig. 1.—Separation of hexose mixture: exchanger, 0.85 sq. cm. × 13 cm., strong-base anion resin, *ca.* 300 mesh, borate form; eluting agent, borate solutions as shown at 1 ml./min.; test material, 10 mg. of each sugar in 10 ml. of 0.01 *M* potassium tetraborate.

(5) H. S. Isbell, J. F. Brewster, N. B. Holt and H. L. Frush, *J. Research Natl. Bur. Standards*, **40**, 129 (1948).

(6) E. R. Tompkins, J. X. Khym and W. E. Cohn, THIS JOURNAL, **69**, 2769 (1947).

(7) E. R. Tompkins, *J. Chem. Educ.*, **26**, 32 (1949).

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(10) A. H. Brown, *Arch. Biochem.*, **11**, 269 (1946).

(11) S. M. Partridge, *Biochem. J.*, **42**, 238 (1948).

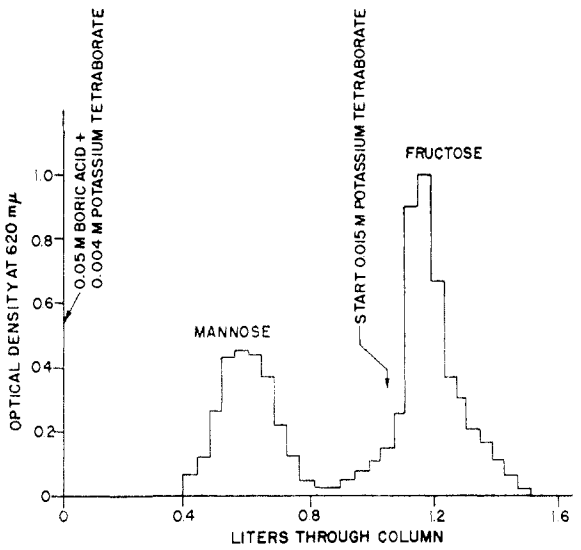


Fig. 2.—Separation of mannose and fructose: exchanger, 0.85 sq. cm. × 12 cm., strong-base anion resin, *ca.* 300 mesh, borate form; eluting agent, borate solutions as shown at 1 ml./min.; test material, 10 mg. each of fructose and mannose in 10 ml. of 0.01 *M* potassium tetraborate.

Two procedures for the separation of pentoses have been developed. In Fig. 3 is illustrated a separation which closely parallels the conditions of elution for the hexoses; however, the pentoses can be removed from the column sooner and with a higher degree of separation if ribose and arabinose are eluted at a lower pH_k (0.08 *M* boric acid +0.004 *M* potassium tetraborate) and then xylose is eluted with 0.03 *M* potassium tetraborate.

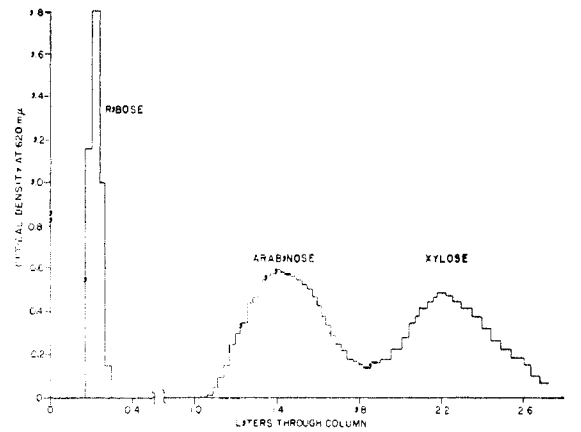


Fig. 3.—Pentose separation: exchanger, 0.85 sq. cm. × 11 cm. strong base anion resin, *ca.* 300 mesh, borate form; eluting agent, 0.015 *M* potassium tetraborate at 1 ml./min.; test material, 10 mg. of each pentose in 10 ml. of 0.01 *M* potassium tetraborate.

If lyxose is present in a pentose mixture, it is eluted in the same position as ribose under the conditions shown. A partial separation of lyxose and ribose is obtained using 0.01 *M* boric acid plus 0.001 *M* potassium tetraborate as the eluting agent.

Inspection of Figs. 1 and 3 shows that ribose can be separate from other components of a hexose–pentose mixture whereas the bulk of arabinose is eluted with fructose, and xylose with galactose. Even though a complete separation of all commonly occurring hexoses and pentoses is not possible under the conditions thus far presented, identification and approximate assay of such a mixture can be accomplished by a combination of the orcinol and anthrone color reactions. If the concentrations of sugars are of the same order of magnitude, the degree of cross interference by applying both tests to a given hexose–pentose pair is not too great; this is illustrated in Table I which shows the results of both color tests as applied to standard pentose and hexose solutions and mixtures of these. A single column run was made on a hexose–pentose mixture and both the anthrone and orcinol tests were made on each fraction as removed from the column. The results of this run are shown in Fig. 4.

TABLE I

ORCINOL AND ANTHRONE COLOR TESTS ON HEXOSE AND PENTOSE SOLUTIONS AND MIXTURES

Sample	μg./cc.	Optical density	Color test
Arabinose	20	0.62	Orcinol
Arabinose + Fructose	20 40	.68	Orcinol
Fructose	40	.07	Orcinol
Fructose	20	.48	Anthrone
Fructose + Arabinose	20 40	.54	Anthrone
Arabinose	40	.04	Anthrone
Xylose	20	.56	Orcinol
Xylose + Galactose	20 40	.67	Orcinol
Galactose	40	.14	Orcinol
Galactose	20	.24	Anthrone
Galactose + Xylose	20 40	.30	Anthrone
Xylose	40	.06	Anthrone

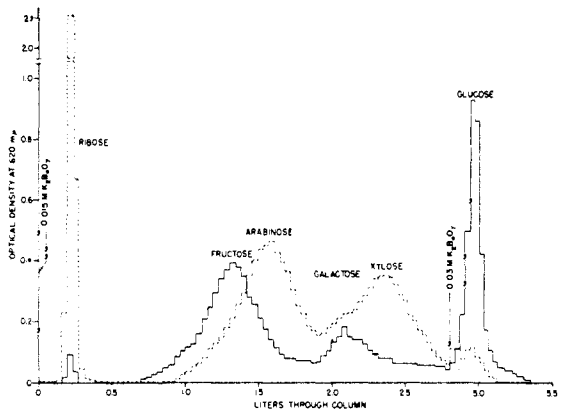


Fig. 4.—Separation of sugars by use of ion exchange: exchanger, 0.84 sq. cm. × 11 cm. strong-base anion resin, *ca.* 300 mesh, borate form; eluting agent, potassium tetraborate as shown at flow rate of 1 ml./min.; test material, 10 ml. of 0.01 *M* $K_2B_4O_7$ containing 2.5 mg. ribose, 5 mg. fructose, 5 mg. galactose, 5 mg. glucose, 5 mg. xylose, and 5 mg. arabinose; solid line —, anthrone optical density broken line - -, orcinol optical density.

Several disaccharides have been investigated; with one exception (melibiose) they were not firmly bound to the resin and were rapidly removed from the exchanger at very

TABLE II

ELUTION ORDER OF SOME DISACCHARIDES

Column size: 0.85 sq. cm. × 11 cm. strong-base anion resin

Disaccharide	$K_2B_4O_7$, eluting agent, *M*	Ml. to peak
Sucrose	0.005	175
Trehalose	.005	370
Cellobiose	.005	660
Maltose	.005	750
Lactose	.005	810
Melibiose*	...	...

* Eluted after glucose with 0.015 *M* $K_2B_4O_7$.

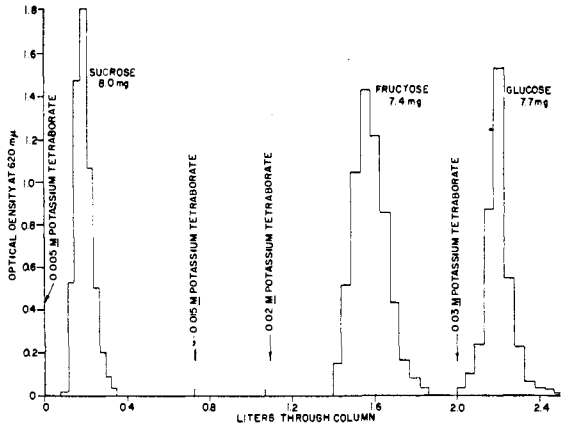


Fig. 5.—Separation of incomplete hydrolysis mixture of sucrose: exchanger, 0.85 sq. cm. × 11 cm., strong-base anion resin, *ca*, 300 mesh, borate form; eluting agent, potassium tetraborate as shown at 1 ml./min.; test material, 23 mg. incompletely hydrolyzed sucrose in 6 ml. of 0.005 *M* potassium tetraborate.

dilute borate concentrations. The separation of components of an incomplete sucrose hydrolysate (Fig. 5) illustrates the ease of differentiating between a disaccharide and its constituent monosaccharides. Some of the more common disaccharides can be separated with dilute borate as demonstrated in Fig. 6 and Table II.

Discussion

The theoretical implications of these results have not been fully explored, hence the nature of the reactions involved in the separation of the sugar–borate complexes cannot be stated with assurance. This lack of assurance is not only due to the purpose and design of the experiments presented but also to the considerable uncertainty in regard to the character of the sugar–borate compounds in aqueous solutions. However, even in these initial experiments, certain implications of the results can be explained with a viewpoint that is consistent with the present theory of sugar–borate complexes[4,5] and of the nature of sugars in aqueous solutions.

Structural formulas for the existence of three types of diverse borate–diol compounds have already been given. In the case of sucrose and trehalose, non-reducing sugars which have no adjacent *cis* hydroxyl groups, the borate–diol compounds are presumably of the type represented by structure I (1,3-diols are analogous to this type). The weak affinity of sucrose and trehalose for the exchanger is consistent with the evidence that compounds of type I are only slightly ionized. Cellobiose, maltose, lactose and melibiose are reducing sugars and have the possibility of adjacent *cis* hydroxyl groups through the mechanism of mutarotation (an additional pair of adjacent *cis* hydroxyl groups is present in the non-reducing residue of lactose and melibiose); hence, they can form the borate–diol compounds represented by structures II or III. These structures are thought to be highly ionized and this is in conformity with the fact that the reducing disaccharides show a greater affinity for the exchanger than do sucrose and trehalose.

The particular order of elution of the sugars suggests that several factors which affect the affinity of the sugar–borates for the exchanger are

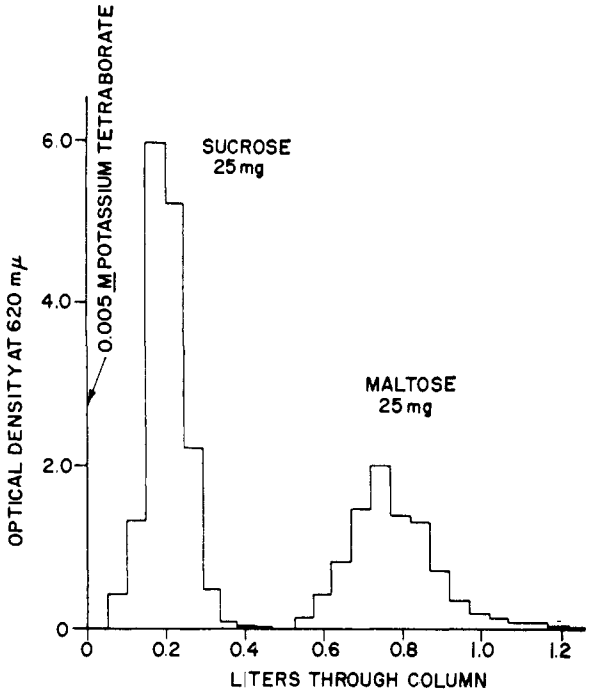


Fig. 6.—Separation of sucrose and maltose: exchanger, 0.85 sq. cm. × 11 cm., strong-base anion resin, *ca*. 300 mesh, borate form; eluting agent, potassium tetraborate as shown at 1 ml./min.; test material, 25 mg. sucrose plus 25 mg. maltose in 10 ml. of 0.005 *M* potassium tetraborate.

involved. Mutarotation and furanose–pyranose interconversion are undoubtedly important as to the degree of formation of a sugar–borate diol; in fact, Böeseken[4] strongly emphasizes that the furanose structure of carbohydrates is the form that is most favorable for the formation of a sugar–borate complex. The affinity for the exchanger of the borate diols of the 1,4-disaccharides, maltose, lactose and cellobiose, which cannot pass into furanose isomers, is much less than the affinity of those monosaccharides here studied, all of which can form furanose structures. The importance of furanose–pyranose interconversion as a factor in elution order is more strongly implicated in the behavior of melibiose, which, due to its 1,6-linkage, is the only one of all the disaccharides studied capable of passing into a furanose isomer. The affinity of its borate complex for the exchanger parallels that of the monosaccharides. The ease of mutarotation of a sugar is another factor that could affect the rate of reaction of a borate diol with the exchanger, and it appears significant that, among the monosaccharides, the sugars having the highest mutarotation constants are the ones most easily eluted and that these constants, when compared, correspond roughly with the elution order of the pentoses and hexoses.

The above implications suggest that definite equilibria are involved as the sugar–borate complexes move down the column, not only between the borate complex and the exchanger but also with the sugar–borate complex and various forms of the free sugars.

These studies have established the general applicability of this method of analysis and define condi-

tions under which a given separation can be made. It is anticipated that as the method is more fully explored, broader applications will suggest themselves. Its usefulness in radiochemical investigations and as a means for the isolation of pure sugars in high yield has already been demonstrated.[12]

(12) L. P. Zill and G. R. Noggle, 1951, work to be published.

Acknowledgments.—The authors wish to express appreciation to Dr. G. R. Noggle for his advice and assistance given to us throughout these experiments, and to Dr. W. E. Cohn for his criticisms and many constructive suggestions pertaining to the preparation of this manuscript.

Oak Ridge, Tennessee Received October 26, 1951

[Contribution from the Rohm and Haas Company]

The OXO Reaction of Camphene. Structure of the Aldehyde and Derivatives

By J. C. LoCicero and R. T. Johnson

Camphene undergoes the OXO reaction without rearrangement giving an aldehyde which has been shown to be structurally related to isocamphenilanaldehyde by several methods of degradation. Oxidation of the aldehyde gives an acid which is shown to be disastereoisomeric with homocamphenilanic acid previously prepared from camphene *via* the Prins reaction.

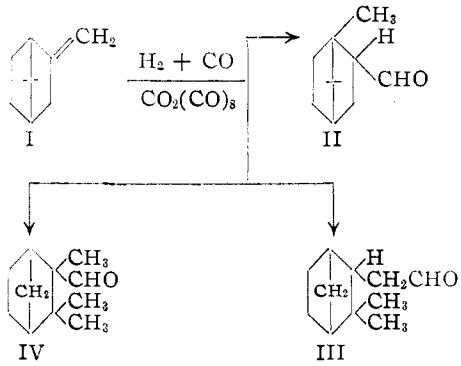
The preparation of aldehydes from olefins by the reaction of carbon monoxide, hydrogen and a cobalt catalyst under pressure has been the subject of some recent publications.[1-4a]

It has been shown[3] that under the conditions of the reaction, migration of the double bond occurs in an olefinic compound. The rearranged olefinic structure then gives rise to additional isomeric aldehydes, *e.g.*, pentene-1 gives not only hexanal and 2-methylvaleraldehyde but 2-ethylbutyraldehyde as well. With increased chain length the number of possible isomers increases accordingly depending on the number of isomeric olefins possible by the shifting of the double bond in the starting olefin.

Camphene (I) appeared to be an interesting substrate for the hydroformylation reaction because of its well known tendency to undergo the Wagner rearrangement under acidic conditions. Cobalt carbonyl hydride, which is believed to be the catalyst of the reaction,[4] is acidic and can be titrated.[5] The aldehydic product that might result on hydroformylation could be camphene 2-aldehyde (II) or an isomer.

Assuming no rearrangement to occur, the product might have the structure (III) or (IV). In view of the factors[3] which appear to regulate the position of the entering aldehyde group, structure (IV) did not appear likely.

It was found that camphene (I) underwent the OXO reaction smoothly when diluted with an equal volume of benzene using dicobalt octacarbonyl[4a] giving a liquid aldehyde (V) of constant boiling point in 65% yields. Oxidation of the aldehyde (V) with air or oxygen gives a single acid (VI) m.p. 56–57° of the same chain length. Oxidative decarboxylation of the α-hydroxy acid (VII) from



the acid (VI) as well as thermal decomposition of the α-methoxy acid (IX) by the method of Darzens and Lévy[6] give isocamphenilanaldehyde (X) which is differentiated from camphenilanaldehyde solely by its oxidation in air to isocamphenilanic acid[7,8] (XI) m.p. 116–117° compared to 65° for camphenilanic acid; both aldehydes give the same semicarbazone which on hydrolysis yields isocamphenilanaldehyde.[8] Chemical oxidation of either aldehyde with potassium permanganate yields isocamphenilanic acid.[7] Recrystallization of camphenilanic acid from nitric acid gives isocamphenilanic acid.

A novel and more direct method for degrading the aldehyde (V), attended by higher yields, was found to be the oxidation of the enamine (XII) with potassium permanganate in acetone to give isocamphenilanic acid (XI).

The preceding reactions show conclusively that the hydroformylation of (I) gives a single aldehyde homologous with isocamphenilanaldehyde showing the absence of any rearrangement during the reaction. The structure of the aldehyde (V) must be that corresponding to (III).

Since the aldehyde from camphene (V = III) has been related structurally to isocamphenilanic acid, we shall refer to it henceforth as homoisocamphenilanaldehyde.

(1) O. Roelen, U. S. Patent 2,327,000 (1943).

(2) Fiat Final Report 1000. The OXO Process. Issued by the Office of Military Government for Germany through the Office of Technical Services of the U. S. Department of Commerce, PB 81383.

(3) A. I. M. Keulemans, A. Kwantes and T. Van Bavel, *Rec. trav. chim.*, **67**, 299 (1948).

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(5) W. Reppe, "New Developments in the Chemistry of Acetylene and Carbon Monoxide," Springer-Verlag, Berlin, Göttingen, Heidelberg 1949.

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