of compounds I through VI were compared (by R.D.H.) with samples of compounds having the same structure prepared previously. Mixed melting points were undepressed and the crystal forms (microscopic examination) were the same when appropriate pairs were examined, and the compounds were identical, structurally as well as stereochemically, in each case.

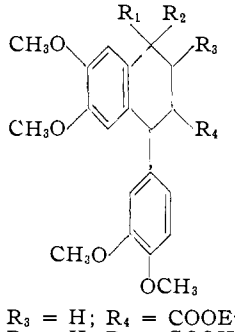
Lactone VII, obtained in the later work by dehydration of acid V in the presence of acetic acid,[2] was identical with the "β-lactone," for which structure VIII was suggested,[3,5] which was prepared earlier by aluminum amalgam reduction of the glyoxylic ester derivative of I followed by thermal dehydration of the resulting hydroxy acid,[3] as well as by another method.[5] In the light of this new evidence, the revised structure VII may be advanced for the "β-lactone."

TABLE I

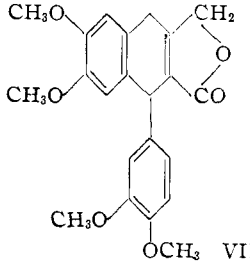
Compound number	References	Haworth, m.p.,[a] °C.	Walker m.p.,[a] °C.	Mixed m.p.,[a] °C.
I	1,3	130–131	130–132	130–131
II	1,3	202–203	205–207	204–207
III	1,3	184–185	182–184	182–185
IV	2,3	164–166	172–176	165–173
V	2,3	195–201	209–210	200–208
VI[b]	2,4,5	220–223	225–228	221–226
VII	2,3,5	209–210 (β-lactone)	206–208	207–209
VIII	2,3	186–187 (α-lactone)	187–188	186–187

[a] Uncorrected. [b] Anhydrous form.

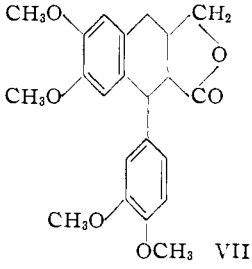
Lactone VIII, prepared by hydrogenation and dehydration of V in the presence of palladium–charcoal in acetic acid,[2] was identical with the "α-lactone," having structure VIII, prepared previously by sodium amalgam reduction of IV



I, R_1R_2 = O; R_3 = H; R_4 = COOEt
II, R_1R_2 = O; R_3 = H; R_4 = COOH
III, R_1 = R_2 = R_3 = H; R_4 = COOH
IV, R_1R_2 = O; R_3 = CHO; R_4 = COOEt
V, R_1 = H; R_2 = OH; R_3 = CH_2OH; R_4 = COOH
VI, R_1 = R_2 = H; R_3 = CH_3; R_4 = COOH



VII



VIII

followed by thermal dehydration.[3] The nature of the implied reductive lactonization set forth in the earlier paper is still obscure, but the new results provide welcome confirmation of the structure VIII suggested for the "α-lactone."

THE UNIVERSITY
SHEFFIELD, ENGLAND, AND
LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS
NATIONAL HEART INSTITUTE
BETHESDA 14, MARYLAND

Active Hydrogen in Aldehydes

BY JOHN A. KING

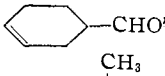
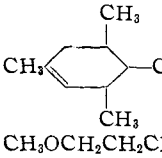
RECEIVED MARCH 9, 1954

In connection with the elucidation of the structure of a natural product it became of interest to verify the prediction that a probably secondary aldehyde group or a β-alkoxy aldehyde would show active hydrogen as it is usually determined.[1] There appears to be no information in the literature on the latter point and the only thing found that is at all pertinent to the former is the report by Young and Roberts[2] of the reduction of isobutyraldehyde by *sec*-butylmagnesium bromide; one can assume that the amount of isobutyraldehyde they recovered (22%) was a measure of enolization of the aldehyde by the reagent.

To test these possibilities, active hydrogen determinations were made on the compounds in Table I, with the indicated results.

TABLE I

ACTIVE HYDROGEN, %

Compound	Calcd. for one	Found	Ionization[d] of compound, %
$(CH_3)_2CHCHO$[a]	1.40	0.19, 0.23	14, 16
 [b]	0.92	0.06, 0.08	7, 9
 [b]	0.66	0.06, 0.11	9, 17
$CH_3OCH_2CH_2CHO$[c]	1.14	0.40, 0.41	35, 36
n-$C_4H_9OCH_2CH_2CHO$[b]	0.77	0.24, 0.26	31, 34

[a] Eastman Chemical Products, Inc. [b] Carbide and Carbon Chemicals Co. [c] Shell Development Company. [d] "Ionization" is used instead of "enolization" to satisfy the concept that release of α-hydrogen is preliminary to either enolization or β-elimination and that the measured active hydrogen content is the sum of these two processes which are mutually exclusive.

The results make it clear that: (1) secondary aldehydes do enolize with methyl Grignard reagent but the ratio of addition to ionization is about 10:1; (2) when there is an electron-attracting group in the β-position (compounds that undergo β-elimination) the ratio of addition to ionization of primary aldehydes is about 2:1; and (3) active hydrogen determinations on compounds of unknown structure must be treated with caution.

(1) Aromatic aldehydes show some active hydrogen, presumably because of condensation to benzoins; *cf.* M. Lieff, G. F. Wright and H. Hibbert, THIS JOURNAL, **61**, 865 (1939).

(2) W. G. Young and J. D. Roberts, *ibid.*, **67**, 1040 (1945).

Experimental

Each of the substances gave ultimate analyses[3] for carbon and hydrogen that were within the usually accepted limits, indicating the absence of significant amounts of extraneous material or moisture. As a further check, each was analyzed[4] for moisture with the Karl Fischer reagent and showed a maximum moisture content of 0.01%. The active hydrogen determinations were made[3] using *methyl Grignard* reagent in the customary manner with 7–8 mg. samples.

(3) By Drs. G. Weiler and F. B. Strauss, Oxford, England.

(4) By Miss Linda Einstein of these laboratories.

WARNER-CHILCOTT RESEARCH LABORATORIES
113 WEST 18th STREET
NEW YORK 11, N. Y.

The Synthesis of Glucofuranosides

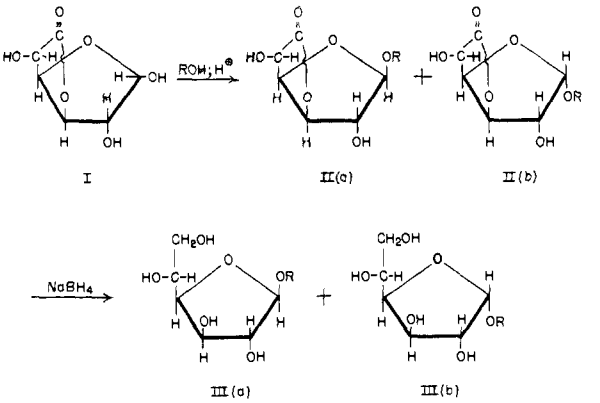
BY DONALD D. PHILLIPS

RECEIVED FEBRUARY 27, 1954

A short and convenient synthesis of glucofuranosides of general formula III was needed in these laboratories. A survey of the recorded methods indicated that none was applicable in a general way to the preparation of substantial quantities of the desired furanosides. For example, the original Fischer procedure for glycoside formation usually yields an inseparable sirupy mixture of isomeric glycosides from which a crystalline glycofuranoside has been separated only in rare instances.[1] Haworth and co-workers have developed another method involving the use of carbonates and acetonides as protecting groups but the procedure is long and over-all yields are quite low.[2] More recently it has been shown[1b] that the selective removal of thioalkyl groups from sugar mercaptals by the action of mercuric salts may give rise to glycofuranosides but yields are often poor and the sirupy mixture obtained in the case of the ethyl D-glucofuranosides (IIIa and b, R = C_2H_5) could not be crystallized, although both epimers are known to be crystalline.[2a]

Since the principal difficulty in all of these synthetic schemes rests in the formation of a furanose ring in a sugar that exists preferentially in a pyranose structure, it seemed probable to us that if a readily available intermediate containing a *preformed* furanose ring could be found, this difficulty might be circumvented. Such an intermediate is D-glucuronolactone (I), which has recently become commercially available in this country.[3] The furanose nature of this compound has been adequately demonstrated[4] and we have found it to be most useful for the preparation of furanosides.

Recent work of Osman, *et al.*,[5] has shown that D-glucuronolactone (I) gives rise to two epimeric glycosides in the presence of methanol when the reaction is catalyzed by a cationic exchange resin. A similar result has been found in these laboratories



when the more usual methanolic hydrogen chloride procedure is employed. The mixture consisted principally of the β-form (IIa, R = CH_3), but a small amount of the α-isomer (IIb, R = CH_3) could be recovered from the mother liquor by mechanical separation of the two crystalline products. These glucofururonosides were reduced by sodium borohydride to the corresponding glucofuranosides (IIIa and b, R = CH_3) according to the procedure of Wolfrom and Wood.[6a] The properties of the furanosides were in excellent agreement with those recorded in the literature.

The use of ethanol in the scheme above gave rise to a sirupy mixture of ethyl D-glucofururonosides (IIa and b, R = C_2H_5) which also contained principally the β-isomer as indicated by the reduction to crystalline ethyl β-D-glucofuranoside (IIIa, R = C_2H_5). None of the α-isomer could be isolated from either reaction.

We are currently preparing a series of glucofuranosides by this convenient two-step procedure and the hydrolysis and mutarotation studies will form the basis for a future communication.

Acknowledgment.—We wish to thank the Corn Products Refining Company, New York, for providing the D-glucuronolactone used in this work.

Experimental[7]

Methyl α- and β-D-Glucofururonoside (IIa and b, R = CH_3).—A mixture of 61.3 g. (0.35 mole) of D-glucuronolactone in 450 ml. of anhydrous 0.5% methanolic hydrogen chloride was allowed to stand with occasional shaking at room temperature for three days. The homogeneous solution was neutralized with silver carbonate, the silver chloride filtered off and the filtrate concentrated under reduced pressure to a clear, colorless sirup. Trituration of this residue with ether containing a small amount of ethyl acetate gave 62.5 g. of crude glycoside, m.p. 120–138°. Recrystallization from ethyl acetate gave 37.0 g. (56%) of methyl β-D-glucofururonoside as stout prisms, m.p. 138–139°, $[\alpha]^{20}D$ −58° (*c* 2.8, water), λ_{max}^{nujol} 5.61 μ; lit.[6] $[\alpha]^{23}D$ −59° (*c* 1.0, water).

Anal. Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.29. Found: C, 44.33; H, 5.29.

The filtrate was concentrated to a sirup which was taken up and decolorized in absolute ethanol and 6.0 g. of a second

(1) (a) E. Fischer, *Ber.*, **26**, 2400 (1893); **47**, 1980 (1914); (b) J. W. Green and E. Pacsu, THIS JOURNAL, **59**, 1205 (1937).

(2) (a) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929); 649 (1930); (b) W. N. Haworth, C. R. Porter and A. C. Waine, *ibid.*, 2254 (1932).

(3) D-Glucuronolactone is a product of the Chemical Division, Corn Products Sales Co., 17 Battery Place, New York 4, N. Y.

(4) F. Smith, *J. Chem. Soc.*, 584 (1944).

(5) E. M. Osman, K. C. Hobbs and W. E. Walston, THIS JOURNAL, **73**, 2726 (1951).

(6) (a) M. L. Wolfrom and H. B. Wood, *ibid.*, **73**, 2933 (1951). (b) After this paper had been submitted, R. E. Reeves, THIS JOURNAL, **76**, 934 (1954), reported a similar reduction of 2,5-dimethyl-α-D-glucurone to the corresponding furanoside using lithium aluminum hydride.

(7) Melting points were obtained on a Nalge-Axelrod melting block and are uncorrected. Analyses are by the Du-Good Labs., St. Louis, Mo.