

(I.R., mix. m.p.) and trimellitic acid (anhydride, m.p. 161–163°, I.R., mix. m.p.).

From the above results structure (II) and (III) may be tentatively proposed for α - and β -himachalene respectively.

Ar I could be the source of isophthalic acid, Ar II of terephthalic acid and Ar III (R = CH₃) of trimellitic acid, 3,3-dimethylphthalide-5-carboxylic acid (IV), 2,2,6-trimethylpimelic acid (V), and acid C₁₅H₂₀O₂, m.p. 135–137° (Ar III, R = COOH). The himachalenes would then appear to be formed by deprotonation of the cation (I) postulated by Hendrickson to be an intermediate in the transformation of *cis*-farnesol into longifolene³ (and juniperol)⁴. If this assumption is correct the steric orientation of the hydrogen atoms at the asymmetric carbon atoms of (II) and (III) would be as in (I).

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Synthetic Aminosugar Derivatives as Potential Antimicrobials; Oxazolidine Derivatives of 1-Arylamino-1-deoxy-D-fructopyranose

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Amadori compounds such as 1-arylamino-1-deoxy-D-fructoses, which have interested the authors as potential antimicrobials (unpublished work), are known to be labile in solution because of their high reducing power. The first non-reducing derivative of an Amadori compound (1-(4-methylphenyl)-amino-1-deoxy-D-fructose) was prepared by condensation with benzaldehyde and tentatively described as 2,3-O-benzylidene-1-(4-methylphenyl)-amino-1-deoxy-D-fructopyranose¹. Kuhn *et al.*² proved this condensation product to be 1,2-N,O-benzylidene-1-(4-methylphenyl)-amino-1-deoxy-D-fructopyranose (I), using methylation and degradation to 1,3,4,5-tetra-O-methyl-D-fructose. Formula (I) represents an aminosugar derivative in which the reducing function is blocked by ring formation and one of the parent sugar's

biochemically important terminal hydroxyl groups is replaced by a tertiary amino group. These structural features relate the compound (I) to the type of aminosugar derivatives previously studied by the authors as potential antimicrobials³, and it seemed of interest to attempt the synthesis of a series of aminosugar derivatives analogous to (I) with a view to their use in microbiological tests.

The substances (I), (II), and (III) were obtained by refluxing the parent Amadori compounds with benzaldehyde in absolute ethanol. 1-(4-Ethoxyphenyl)-amino-1-deoxy-D-fructose reacted only to a minor degree and the corresponding 2-methylphenyl or 3,4-dimethylphenyl derivatives did not give oxazolidines under the experimental conditions employed. When benzaldehyde was replaced by monophenolic aldehydes (2-, 3-, or 4-hydroxybenzaldehyde, vanillin) substantial quantities of the various Amadori compounds were recovered unchanged. 4-Nitrobenzaldehyde, however, did react by prolonged reflux to give oxazolidines, e.g. substance (IV).

(IV) differs from the reference compound (I) only by the presence of a nitro group, and the size of the heterocyclic rings in this product (IV) could be determined by methylation followed by hydrolysis to 1-(4-methylphenyl)-

amino-1-deoxy-3,4,5-tri-O-methyl-D-fructopyranose hydrochloride, obtained by Kuhn *et al.*² from (I).

To confirm the size of the heterocyclic rings constituting the substances (II) and (III) recourse was had to periodate oxidation, again using (I) as a reference compound, Fig. 1. Periodate first opens the pyranose ring, yielding one mole of monovalent acid and a product which upon reduction with potassium borohydride releases from all three substances ethylene glycol (C₅-C₆ of the sugar moiety), detected by paper chromatography. The periodate uptake (Fig. 1) was, especially under prolonged oxidation, higher than expected, probably because of a certain degree of hydrolytic opening of the oxazolidine ring, initiating secondary oxidation reactions which may also involve the aromatic amine components (coloured products). It should therefore be emphasized that the determination of the size of the rings in (II) and (III) is based upon a comparison with the well known compound (I).

The substances (I), (II) and (III) differ so little as to the character of the substituent R₁ that the uniformity of their molecular rotation (*M_D*) may be interpreted as corresponding to an identical steric configuration of all three compounds. The stereochemistry of oxazolidines formed by condensation of aminoalcohols with aldehydes has been reviewed by Bergmann⁴. It is seen from the formulas that the asymmetry of carbon 2 of the sugar moiety alone would account for the possibility of two diastereoisomers without considering the possible stereochemical contribution of the asymmetric carbon atom introduced in the oxazolidine ring by benzaldehyde. On examination in the polarizing microscope the crystalline reference compound (I) revealed no sign of being a mixture of diastereoisomers. The oxazolidine derivatives of the Amadori compounds probably result from an asymmetric synthesis intimately connected with the non-elucidated mechanism of the ring formation.

The aminosugar derivatives (I), (II), (III), and (IV) were tested as antimicrobials using the same techniques and the same pathogenic micro-organisms as previously described³, but applying the substances as finely ground powder because of their extremely low solubility in water (less than 1:10⁴). No antimicrobial activity could be observed.

Experimental. (All melting points are micro melting points, Kofler's hot-stage microscope. The various Amadori compounds were prepared and identified according to known methods⁵.)

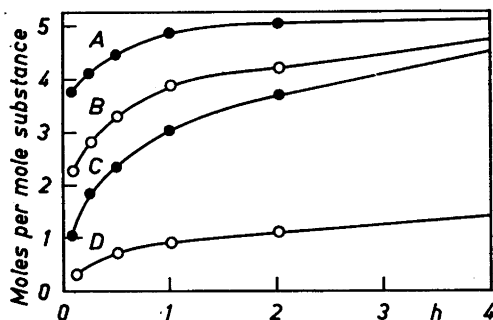


Fig. 1. Periodate oxidation of compounds I, II, and III. Curves A, B, and C represent the periodate uptake of the substances III, II, and I, respectively. Curve D represents the amount of monovalent acid liberated from each of the three compounds. Experimental conditions: test substance, 10⁻⁵ mole (5 ml, 50% ethanol) + sodium metaperiodate, 5 × 10⁻⁵ mole (5 ml) at room temperature; periodate uptake by the arsenite method, acidity by direct titration after adding ethylene glycol.

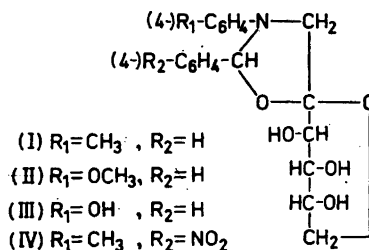
1,2-N,O-benzylidene-1-(4-methylphenyl)-amino-1-deoxy-D-fructopyranose (I). The following method was preferred to the direct condensation method without any solvent^{1,2}. The parent Amadori compound (10^{-2} mole) was refluxed for 6–8 h with benzaldehyde (2×10^{-2} mole) dissolved in absolute ethanol (25 ml). The crude product separating on cooling was washed with light petroleum and suspended in water (50–60°) to dissolve unreacted Amadori compound. Recrystallizations from acetone-methanol 2:1 to constant m.p. 198–200°. Yield 30%. $[\alpha]_D^{20} -149.6$ ($c = 0.4612$, pyridine). $M_D -534$. The product crystallizes in rods or needles with parallel extinction and elongation negative or positive. $a = 1.567$ (20°) and $\gamma = 1.617$ (20°) measured on rods with negative elongation (flash figure in convergent polarized light). β not observable with accuracy. Crushed material with random orientation showed all indices between a and γ .

1,2-N,O-benzylidene-1-(4-methoxyphenyl)-amino-1-deoxy-D-fructopyranose (II). Preparation as above (yield 35%), m.p. 210–212°. $[\alpha]_D^{20} -157.0^\circ$ ($c = 0.4056$, pyridine) $M_D -586$. (Found: C 63.24; H 6.36; N 3.69. $C_{20}H_{25}O_6N$ requires C 64.33; H 6.21; N 3.75.)

1,2-N,O-benzylidene-1-(4-hydroxyphenyl)-amino-1-deoxy-D-fructopyranose (III). Preparation as above (yield 30%), m.p. 204–206°. $[\alpha]_D^{20} -142.3^\circ$ ($c = 0.288$, pyridine). $M_D -511$. (Found: C 63.59; H 5.87; N 3.89. $C_{19}H_{21}O_6N$ requires C 63.49; H 5.89; N 3.90.)

1,2-N,O-4-nitrobenzylidene-1-(4-methylphenyl)-amino-1-deoxy-D-fructopyranose (IV). Preparation as above (yield 40%, reflux 14–16 h), m.p. 210–212°. $[\alpha]_D -79.7^\circ$ ($c = 0.419$, pyridine). (Found: C 59.98; H 5.52; N 7.06. $C_{20}H_{23}O_7N_2$ requires C 59.70; H 5.51; N 6.96.) Methylation² introduced three methoxyl groups (syrupy product which crystallized when kept, m.p. 100–110°), (Found: MeO 20.7; $C_{23}H_{28}O_7N_2$ requires MeO 20.94). The methylated product was hydrolyzed in methanolic hydrochloric acid and the liberated 4-nitrobenzaldehyde removed (after dilution with water) by extraction with benzene-light petroleum. The remaining 1-(4-methylphenyl)-amino-1-deoxy-3,4,5-tri-O-methyl-D-fructopyranose hydrochloride² was recrystallized from methanol: m.p. 133–135° (decomp.). $[\alpha]_D^{20} -59.1^\circ$ (initial) $\rightarrow -55.1^\circ$ (constant, after 1 h), ($c = 0.843$, dimethylformamide). (Found: MeO 26.3; $C_{16}H_{25}O_5N$; HCl requires MeO 26.77).

Oxidation with periodate of the benzaldehyde condensation products (I) (II) (III). a) Experi-



mental conditions and results of the quantitative analyses are given in Fig. 1. b) 2.5×10^{-5} mole of the oxazolidine derivatives dissolved in ethanol (1 ml) + 10^{-4} mole of sodium metaperiodate (1 ml). After 2 h add potassium borohydride (30 mg) in water (1 ml) and leave overnight. Acidify with hydrochloric acid (0.5 N, 1.2 ml) and shake with silver carbonate (0.5 g). The filtrate is concentrated to dryness under reduced pressure, the residue extracted with ethanol (2 ml) and examined by paper chromatography (ethyl acetate:pyridine:water, 7:2:1 v/v) giving spots which could not be distinguished from those of ethylene glycol and of an intensity estimated to about one third of the amount of ethylene glycol corresponding to an opening of the pyranose ring not disturbed by secondary reactions. The technique employed is with some modification based upon the method given by Viscontini *et al.*⁶

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