contained a brown, viscous sirup with odor of caramel which made crystallization difficult. Subsequent recrystallizations of the commercial β-methylaspartic acid with the same conditions used for our product resulted in poor recovery of amino acid. The simplicity of the synthesis, however, offsets to some extent the low yield of pure product obtained.

Experimental

Diethyl β-methyl-α-ketosuccinate was prepared by the condensation of diethyl oxalate (4 moles) with ethyl propionate (1 mole) in the presence of sodium ethoxide (1 mole).[8] The product distilled at 85–88° (2 mm.). Attempts to prepare an oxime derivative were unsuccessful, but prolonged treatment with phenylhydrazine on a steam bath led to the formation of the pyrazolone derivative[8] (ethyl 1-phenyl-4-methyl-5-pyrazolone-3-carboxylate), m.p. 148–148.1° (white crystals from chloroform–petroleum ether).

The keto ester gave qualitative reactions which indicated a high enol content: It rapidly decolorized bromine in carbon tetrachloride and gave a deep red coloration with ferric chloride solution.

Preparation of Amino Acid.—A mixture of diethyl β-methyl-α-ketosuccinate (20.2 g., 0.10 mole), 90% formic acid (18.5 g., 0.36 mole), and 99% formamide (18.0 g., 0.40 mole) was heated under reflux for 17 hr. During the first half hour, some volatile liquid with an ester odor (ethyl formate?) was removed to keep the temperature near 135°, where it remained throughout the refluxing period. Concentrated hydrochloric acid (20 ml.) was added, and heating was continued to hydrolyze formamide and ester. After 3 hr., 30 ml. of water was added; the pH of the mixture was about 4–5. More acid (20 ml. of conc. hydrochloric acid and 10 ml. of water) was added to lower the pH to about 2, and the brown mixture was then boiled for 8 hr. longer.

It was poured into a crystallizing dish and set on a steam bath to evaporate. A grayish tan crystalline residue with some sticky material remained; weight, 31.7 g. A portion (26.8 g.) of this crude material was dissolved in water. When the solution was concentrated on a steam bath, 11 g. of pure ammonium chloride was obtained. The filtrate was diluted with 95% ethyl alcohol and was chilled at 4° for a week. White crystals, which proved to be essentially pure β-methylaspartic acid, separated from the solution and were collected with suction; yield 2.0 g. (16%). An appreciable amount of β-methylaspartic acid remained in the filtrate. A paper chromatogram of the filtrate gave strongly positive ninhydrin tests for both β-methylaspartic acid and α-aminobutyric acid (solvent, *n*-butyl alcohol–formic acid–water, 4:1:1 v./v.).

Identification of β-Methylaspartic Acid Product.—The white crystals obtained from the alcohol solution showed 100% amino acid in a quantitative ninhydrin test, with both L-aspartic acid and commercial β-methyl-DL-aspartic acid being used as standards. Paper chromatography R_f values for both the amino acid and its *N*-(2,4-dinitrophenyl) derivative were identical with those for known standards. (Chromatography solvent for amino acid was *n*-butyl alcohol–formic acid–water, 4:1:1 v./v.; that for the *N*-(2,4-dinitrophenyl) derivative was *t*-amyl alcohol saturated with 0.1 *M* phthalate buffer, pH 6.) This same comparison enabled us to identify both β-methylaspartic acid and α-aminobutyric acid in the alcoholic filtrate.

Anal.[9] Calcd. for $C_5H_9NO_4$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.27; H, 6.26; N, 9.42.

The synthesized β-methylaspartic acid was shown to have the *threo* configuration by enzymatic resolution of the DL-acid with β-methylaspartase prepared from sonic lysates of *Bacterium cadaveris*.[1] This enzyme deaminates only the L-isomer. β-Methyl-D-aspartic acid was recovered from the mixture; $[\alpha]^{22}D$ +14.8° (*c* 1.42 mg./ml., in water). Repetition of the resolution with a commercial sample of *threo*-β-methyl-DL-aspartic acid[3] gave D-acid with +12.6° (*c* 3.88 mg./ml., in water). The specific rotation reported for *threo*-β-methyl-D-aspartic acid is $[\alpha]^{25}D$ +11.7 ± 2°[6]; that for *threo*-β-methyl-L-aspartic acid is −12.4°[10]; and that for *erythro*-β-methyl-D-aspartic acid is −24.5 ± 3°,[6] all in water solutions.

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Preparation and Polymerization of 6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose[1]

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1 - *O* - Vinyl - 2,3;4,5 - di - *O* - isopropylidene-D-fructose[4] has been prepared by treating in an autoclave 2,3;4,5-di-*O*-isopropylidene-D-fructose with acetylene diluted with nitrogen in the presence of small amounts of potassium hydroxide catalyst. Best reactions occurred at 150–160° during a period of 18.5 hours. Similarly there has been obtained 3,5,6-tri-*O*-vinyl-1,2-isopropylidene-D-glucose[5] and 3-*O*-vinyl-1,2;5,6-di-*O*-isopropylidene-D-glucose.[6] Acetylene has been found to react readily at 100° and atmospheric pressure with fatty alcohols to produce the corresponding vinyl ethers.[7] The vinylation of methyl α-D-glucopyranoside with acetylene at 150° and 375 p.s.i.g. has recently been discussed.[8]

Herein we describe the vinylation of 1,2;3,4-di-*O*-isopropylidene-D-galactopyranose to obtain the 6-*O*-vinyl derivative. Reaction is accomplished by bubbling acetylene through the melt for 16 hours at atmospheric pressure in the presence of dry, powdered potassium hydroxide. Identity of the product is established by reduction to the 6-*O*-ethyl derivative which can be hydrolyzed to

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6-*O*-ethyl-D-galactose. The vinyl ether does not polymerize easily with usual free radical initiators, but homopolymerizes readily with ionic initiators.

Experimental

1,2;3,4-Di-*O*-isopropylidene-D-galactopyranose.—This compound was prepared from D-galactose according to the methods described by Ohle and Behrend[9] and by Levine and Meyer.[10] It had an optical rotation of $[\alpha]^{25}D$ −54.7° (*c*, 3.5 in chloroform) and was chromatographically pure.

6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose.—For vinylation, 100 g. of the above product and 5 g. of dry powdered potassium hydroxide were placed in a cylindrical reaction vessel provided with a fritted glass bottom and with a gas inlet tube sealed beneath the fritted glass. The vessel was placed in an oil bath at 160°, and flushed with nitrogen. The nitrogen stream was discontinued, and acetylene was bubbled through the reaction mixture at 160–180° for a period of 16 hr. at a rate of approximately 0.2–0.3 l./min. Effluent gases were passed through a cool chamber before discard. The reaction mixture was extracted with chloroform and the extract was combined with material which condensed on the walls of the cooling chamber. After distillation of the chloroform, the resulting sirup was mixed with powdered potassium hydroxide and distilled at 12–15 mm. pressure without fractionation. It was distilled through a Vigreux column. The main fraction distilled at 154–156° and 10–11 mm; yield 64 g. (58% of theoretical).

The clear distillate produced a single spot when chromatographed on dimethylformamide treated paper irrigated with acetone–dimethylformamide (4:1 v./v.); $[\alpha]^{25}D$ −81.2° (*c*, 1.90 in chloroform).

Anal. Calcd. for $C_{14}H_{22}O_6$: 1 C, 58.73; H, 7.74. Found: C, 58.89; H, 7.86.

6-*O*-Ethyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose.—Five grams of 6-*O*-vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose was dissolved in 50 ml. of 99% ethanol and mixed with 2 g. of Girdler nickel catalyst (Girdler 6–49A, 65.5% Ni)[11] in a 100-ml. rocking autoclave. Hydrogen was added to a pressure of 100 p.s.i.g. and the autoclave heated for 8 hr. at 80°. The reaction mixture was filtered and the filtrate concentrated to a sirup which was distilled in a micro distillation apparatus. The main fraction distilled at 89–93° at 0.2 mm. pressure; yield was 3.3 g. (66%) of a colorless liquid. The infrared spectra of this product showed no trace of the absorption bond characteristic of double bonds; $[\alpha]^{25}D$ −60.6° (*c*, 1.45 in chloroform).

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.31; H, 8.38. Found: C, 58.17; H, 8.23.

6-*O*-Ethyl-D-galactopyranose.—6-*O*-Ethyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose was hydrolyzed as described by McKeown and Hayward.[12] The product melted at 106°. Its X-ray diffraction pattern was identical to that of an authentic sample of 6-*O*-ethyl-D-galactopyranose.

Homopolymerizations.—6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactose did not polymerize with free radical initiators and was thus similar to other vinyl ethers. Initiators tested were 2,4-dichlorobenzoyl peroxide, benzoyl peroxide, and azobisdiisobutyronitrile. They were tested in concentrations up to 1% in methanol solutions of monomer at 3.5% concentration.

With ionic initiators polymerization took place rapidly at room temperature. Polymers were produced in 3.5% methanolic solution with trace addition of titanium tetrachloride, stannic chloride, and boron trifluoride etherate. Polymers precipitated immediately from the reaction mixture and were insoluble in methanol, ethanol, hexane, cyclohexane, ethylene dichloride, benzene, and pyridine.

Copolymerizations.—Copolymers of 6-*O*-vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose were readily made with methyl methacrylate, vinyl acetate, and acrylonitrile in methanol solutions with the ionic initiators mentioned above.

Copolymers involving vinyl acetate could be produced with free radical initiators although the incorporation of the sugar derivative into the copolymer did not exceed 30% as estimated from infrared spectra (potassium bromide pellets). Limited incorporation of vinyl ethers had previously been observed in copolymerizations of various vinyl ethers and vinyl acetate.[13] 6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose did not copolymerize with methyl methacrylate in the presence of free radical initiators. Infrared patterns of the polymer products were identical with those of polymethylmethacrylate.

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Antineoplastic Agents. VIII. Bis(2-chloroethyl)amine Condensation Reactions. Part A[1,2]

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The facility with which bis(2-chloroethyl)amines will undergo certain intra- and intermolecular reactions under neutral or basic conditions is well established.[3] A detailed knowledge of these transformations, however, is essential both to developing efficient synthetic routes to nitrogen mustards, and to understanding their biological role in cancer chemotherapy.[4] While a number of investigations have dealt with various aspects of this problem, there remains a pressing need for additional basic information. For this reason, we have undertaken a study of intramolecular reactions involving nitrogen mustard.

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