Glycine-d_2 (V).—Two recrystallizations of the amino acid II from water–ethanol effected exchange of the labile protons, producing glycine-d_2 in high yield: λ_{max}^{KBr} 3.15–3.74, 4.45–4.70, 6.24, 6.64, 7.15, and 11.44 μ. Analysis by n.m.r. (DCl, D_2O) showed only absorption due to the exchangeable protons. Paper chromatography indicated a single spot, R_f 0.64.

Anal. Calcd. for $C_2H_3D_2NO_2$: C, 31.16; H, 6.83; N, 18.17. Found: C, 31.12; H, 6.65; N, 18.13.

The hydrogen analysis accounts for 3.92% hydrogen and 5.23% deuterium such that the calculated percentage of hydrogen as obtained by a routine analysis is 6.83%.

Anal. Calcd. for $C_2H_3D_2NO_2$: D, 40.00 atom %. Found: D, 39.9 atom % (99.7%).

Glycine-2-d_2 Ethyl Ester Hydrochloride (III).—Freshly distilled thionyl chloride (3.2 ml., 0.0455 mole) was carefully added to 25 ml. of absolute ethanol. When evolution of sulfur dioxide had ceased, the salt I (5.00 g., 0.0425 mole) was added and the solution was refluxed for 3 hr. After refrigeration, the solid was filtered, washed with anhydrous ether, and dried to afford 5.77 g. (96%) of the ester III. Four recrystallizations from absolute ethanol (30 ml. each) effected complete exchange of hydrogen for deuterium at the labile positions on nitrogen to give 5.06 g. (84%) of the ester III: m.p. 147.5–148°; λ_{max}^{KBr} 3.30, 4.14–4.58, 5.72, 7.58, 8.35, and 11.67 μ. Analysis by n.m.r. (D_2O) showed only signals due to the exchangeable protons and the ethyl moiety.

The ester III was homogeneous as indicated by paper chromatography, R_f 0.82.

Anal. Calcd. for $C_4H_8D_2ClNO_2$: C, 33.93; H, 7.28; Cl, 25.04; N, 9.89. Found: C, 34.19; H, 7.27; Cl, 25.21; N, 10.02.

The hydrogen analysis accounts for 5.69% hydrogen and 2.85% deuterium such that the calculated percentage of hydrogen as obtained by a routine analysis is 7.28%.

Anal. Calcd. for $C_4H_8D_2ClNO_2$: D, 20.00 atom %. Found: D, 19.10 atom % (95.5%).

Glycine-d_4 Ethyl Ester Deuteriochloride (IV).—This material was prepared in 89% yield, m.p. 143–144.5°, by the same procedure as used for compound III except that ethanol-*d* was used as solvent.[7] Recrystallization from this solvent afforded an analytical sample: m.p. 145.5–146.5°; λ_{max}^{KBr} 3.33, 4.37–4.60 5.72, 7.57, 8.43, and 11.67 μ. Analysis by n.m.r. (D_2O) showed only signals due to the ethyl group.

Paper chromatography indicated one spot, R_f 0.82, and a faint trace at R_f 0.63 (glycine).

Anal. Calcd. for $C_4H_5D_5ClNO_2$: C, 33.22; H, 7.36; Cl, 24.52; N, 9.69. Found: C, 32.94; H, 7.08; Cl, 24.32; N, 9.81.

The hydrogen analysis accounts for 3.48% hydrogen and 6.97% deuterium such that the calculated percentage of hydrogen as obtained by a routine analysis is 7.36%.

Anal. Calcd. for $C_4H_5D_5ClNO_2$: D, 50.00 atom %. Found: D, 46.5 atom % (93.0%).

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The Preparation of 9-D-Mannofuranosyladenine[1]

LEON M. LERNER AND PAUL KOHN

The Department of Biological Chemistry, University of Illinois at the Medical Center, Chicago, Illinois

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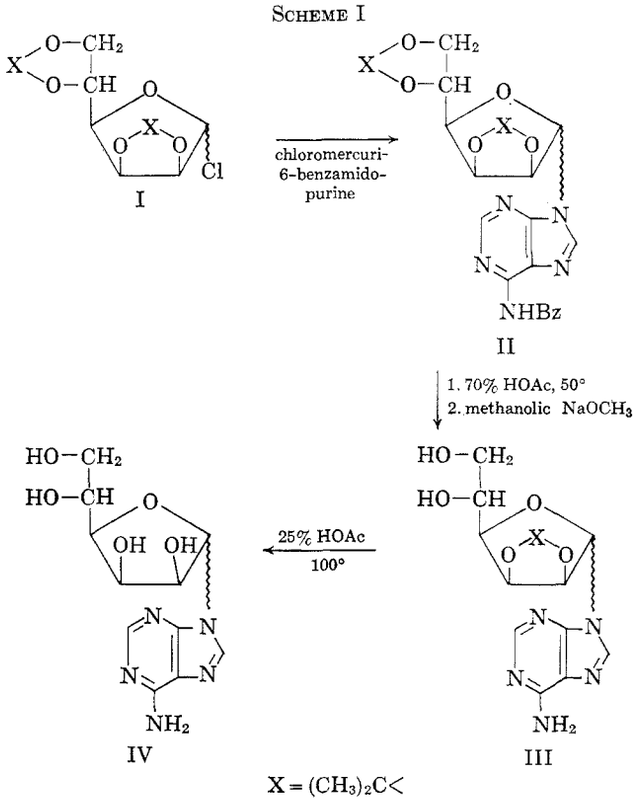
In recent years there has been an interest in the synthesis of hexofuranosyl nucleosides. From the laboratory of the authors has come a general procedure[2] for obtaining furanose derivatives of aldohexoses by using γ-lactones as starting materials. In the pathway, which capitalizes on the presence of the furan ring in γ-lactones, the hydroxyl groups are blocked by acylation and the lactone is reduced to a hemiacetal with bis(3-methyl-2-butyl)borane (disiamylborane). The anomeric hydroxyl group is then acylated, and an acylglycosyl halide is prepared and coupled with the base, from which hexofuranosyl nucleosides are obtained by removal of the blocking acyl groups.

Prior to this, special methods have been required to obtain furanose derivatives of the hexoses. Wolfrom, *et al.*,[3] proceeded by way of dithioacetal formation and furanose thioglycosides to effect the synthesis of gluco- and galactofuranosyl nucleosides. Isopropylidene derivatives of glucose[4] and a number of 6-deoxyhexoses[5] have been used as a means of obtaining furanose rings of six-carbon sugars in order to prepare nucleosides. Before nucleosides were prepared from these derivatives, however, it was necessary to block the 5-hydroxyl, remove the acetone blocking group, acylate the free hydroxyls, and prepare an acylglycosyl halide.

In the present report a synthetic pathway is described (Scheme I) for the preparation of a mannofuranosyl nucleoside which utilizes 2,3:5,6-diisopropylidenemannofuranose as the source of the furanose. It is unique in that the isopropylidene derivative is converted directly to a glycosyl halide and condensed with chloromercuri-6-benzamidopurine to yield a nu-

SCHEME I



(1) (a) Taken in part from a thesis submitted by L. M. Lerner to the University of Illinois Graduate College in partial fulfillment of the requirements for the Ph.D. degree. (b) Supported in part by Grant P-161 from the American Cancer Society and by Training Grant GM-471 from the Division of General Medical Sciences of the U. S. Public Health Service.

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cleoside. Presumably gulofuranosyl nucleosides can be similarly prepared since gulose forms an analogous diisopropylidene derivative.[6]

When D-mannose is treated with acetone under acidic conditions the product formed is 2,3:5,6-di-O-isopropylidene-D-mannofuranose.[7] The anomeric hydroxyl can be exchanged for a chloro by reaction with thionyl chloride in pyridine.[8] When this was done, the analytically pure oil, 2,3:5,6-di-O-isopropylidene-D-mannofuranosyl chloride (I), was formed.

Condensation of I with chloromercuri-6-benzamidopurine was carried out in dry xylene by the method of Davoll and Lowy.[9] A glass (II) was obtained which was treated with 70% aqueous acetic acid at 50°. The acetic acid was evaporated, methanolic sodium methoxide was added, and the solution was refluxed. A 38% yield of 9-(2′,3′-O-isopropylidene)-D-mannofuranosyladenine (III) was obtained. The presence of the isopropylidene group was concluded from the elementary analysis and from the infrared maxima at 7.28 (*gem*-dimethyl) and 11.65 μ (isopropylidene). The position was verified by the determination of formaldehyde after periodate cleavage.

The best conditions for the removal of the 2′,3′-isopropylidene group was found to be in 25% aqueous acetic acid at 100°. The product, 9-D-mannofuranosyladenine (IV), was obtained in 52% yield from III. The furanose structure was further verified by periodate oxidation with the finding of 0.98 mole of formaldehyde/mole of nucleoside.

The authors believe this to be the first time that isopropylidene groups or any other acetal blocking groups have been used in the direct condensation reaction in nucleoside synthesis. The results are especially interesting since one would have expected both the α and β anomers to be obtained in the absence of the directive effect that is observed when an ester group is present at carbon 2. However, in these studies it appears that essentially only one isomer was obtained. This is concluded from the observations that after crystallization of III the mother liquor contained only traces of nucleoside other than III, as revealed by paper chromatography in two solvent systems. Furthermore, following the condensation of I with stoichiometric amounts of chloromercuri-6-benzamidopurine, there was recovered from the reaction mixture unreacted amounts of chloromercuri-6-benzamidopurine sufficient to account for almost 60% of the chloromercuri-6-benzamidopurine that had been used. The yield of III (38%), therefore, represented virtually all nucleoside that could have been formed.

The anomeric configuration of IV (or of II or III) has not been unequivocally demonstrated. However, comparison of the molecular rotation (+22,280°) of this substance with the molecular rotations of a variety of glycofuranosides suggests an α configuration. If further work demonstrates that this is indeed the case, the configuration of I would need clarification, since I was assigned an α configuration[7,8] on the basis of its high positive specific rotation ($[\alpha]^{21}D$ +85.7°). If I is indeed the α anomer, it would be difficult to explain an α configuration for II, III, and IV since glycoside formation from glycosyl halides usually proceeds through Walden inversion. Only the β nucleoside would therefore be expected. When Wright, *et al.*,[10] coupled syrupy 5-O-benzyl-D-ribofuranosyl bromide 2,3-carbonate, an ester which has no directive effect due to participation in ortho ester formation, with chloromercuri-6-benzamidopurine, both anomers were obtained. In that case it was suggested that the syrup was a mixture of α and β bromides which reacted through Walden inversion. However, Perlin[11] has shown that 5,6-di-O-acetyl-α-D-mannofuranosyl bromide 2,3-carbonate will give rise to only methyl α-D-mannofuranoside upon treatment with sodium methoxide and he suggested that the configuration may have been retained owing to the existence of an intermediate 1,2-epoxide. If it can be demonstrated on a firmer basis than optical rotation that the glycosyl halide I and the nucleoside derived from it both have an α configuration, a possible explanation might lie in a reaction by an SN1 mechanism with resultant formation of a single isomer as a result of steric hindrance owing to the bulky isopropylidene group.

Experimental Section[12]

Melting points were obtained on a Kofler hot stage and correspond to corrected values. Paper chromatograms of the nucleosides were run by the descending technique and the spots were located with a Mineralight lamp which produced ultraviolet radiation at 254 mμ. Spots were assigned R_{Ad} values which correspond to the ratio of the distance the nucleoside traveled to that which adenine traveled. Infrared spectra were measured on a Perkin-Elmer Infracord spectrophotometer, and ultraviolet spectra were determined on a Beckman Model DU spectrophotometer. Optical rotations were determined in 100-mm. semimicro tubes using a Rudolph polarimeter, Model 70.

2,3:5,6-Di-O-isopropylidene-D-mannofuranose.—D-Mannose was treated with acetone, anhydrous zinc chloride, and phosphoric acid exactly as described for D-gulcose by Blakely.[13] The product had m.p. 122°, $[\alpha]^{21}D$ +16.6° after 10 min. (*c* 2.5, absolute ethanol); lit.[7] m.p. 122°, $[\alpha]^{21}D$ +15.8° after 5 min. (*c* 2.5, absolute ethanol).

2,3:5,6-Di-O-isopropylidene-D-mannofuranosyl Chloride (I).—This compound was prepared from 2,3:5,6-di-O-isopropylidene-D-mannofuranose by the reaction of thionyl chloride in pyridine as described by Freudenberg, and co-workers.[8] The product was an oil which was distilled *in vacuo*, b.p. 112–114° (4 mm.), lit.[8] b.p. 112–115° (1 mm.). Analytically pure material was obtained after two additional distillations.

Anal. Calcd. for $C_{12}H_{19}ClO_5$: C, 51.70; H, 6.09; Cl, 12.72. Found: C, 51.57; H, 6.20; Cl, 12.52.

6-Benzamido-9-(2′,3′:5′,6′-di-O-isopropylidene-D-mannofuranosyl)purine (II).—Chloromercuri-6-benzamidopurine[9] (9.4 g., 19.8 mmoles), 9.4 g. of Celite-535, and 400 ml. of dry xylene were mixed and 80 ml. of this mixture was distilled to remove traces of moisture. To this mixture was added 5.5 g. of I dissolved in 100 ml. of dry xylene, and the well-stirred mixture was refluxed, protected from moisture, for 4 hr.[9] The mixture was filtered while still warm, the filter cake was washed with chloroform (200 ml.), and the solvents were removed *in vacuo* (45°). The residue was dissolved in 300 ml. of chloroform, filtered, and washed three times with 100-ml. portions of 30% potassium iodide and three times with 100-ml. portions of water. The solution was dried over sodium sulfate, concentrated to a yellow syrup weighing 13.9 g., and dissolved in a little warm benzene. After standing for 3 hr. a small amount of solid ma-

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terial was removed by filtration and the filtrate was distilled, leaving a glass.

9-(2′,3′-O-Isopropylidene-D-mannofuranosyl)adenine (III).—The glass (II) was dissolved in 150 ml. of 70% acetic acid at 50° and permitted to stand at this temperature for 2.5 hr., after which the solution was evaporated to a syrup and absolute ethanol was added and removed three times. Addition and removal of toluene gave a glass which was treated with 20 ml. of 1 *N* methanolic sodium methoxide in 100 ml. of absolute methanol, refluxed 50 min., and neutralized with glacial acetic acid. The solution was filtered and the solvent was removed *in vacuo* (45°). The residue was partitioned between 130 ml. each of water and chloroform, and the chloroform layer was further extracted five times with 50-ml. portions of water. The aqueous extracts were combined and the water was removed under reduced pressure (45°). During this process crystallization took place. The product was removed by filtration and recrystallized from water: yield 1.96 g. (29%). Two additional crops brought the total yield to 2.56 g. (38%). The product softened between 240 and 246°, m.p. 249–250°, $[\alpha]^{21}D$ +32.5° (*c* 1.26, 0.1 *N* HCl) after 3 min. No change was observed after 1 hr. Paper chromatography with 5% aqueous disodium hydrogen phosphate[14] (without the organic phase) on Whatman No. 1 paper gave one spot, R_{Ad} 1.41 and 1.53 in *n*-butyl alcohol–acetic acid–water (4:1:5 v./v.).

Ultraviolet and infrared spectra showed the following: $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,200); λ_{max}^{KBr} 2.9, 3.0 (OH, NH), 6.0, 6.12, 6.3, 6.4 (NH and purine ring), 7.28 (CH_3), 8.95, 9.2, 9.4, 9.5 (C–O–C, C–O–H), 11.65 (isopropylidene) μ.

Anal. Calcd. for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76. Found: C, 49.91; H, 5.63; N, 20.88.

The nucleoside was treated with excess periodate and formaldehyde was determined by the dimedone test[15] (0.81 mole HCHO/mole of nucleoside).

9-D-Mannofuranosyladenine (IV).—To 118 ml. of 25% acetic acid solution was added 2.36 g. (7 mmoles) of III. The mixture was stirred at 100° for 3.5 hr., cooled quickly to room temperature, and allowed to stand an additional 0.5 hr. The solvent was removed *in vacuo* (45°) to leave a white residue. This material was recrystallized from ethanol–water to give beautiful tiny rods: 1.09 g. (52%); m.p. 237–237.5°; $[\alpha]^{21}D$ +74.8° (*c* 3.05, 1 *N* HCl); R_{Ad} 1.53 in 5% aqueous disodium hydrogen phosphate,[14] 0.15 in water-saturated butanol, and 0.49 in *n*-butyl alcohol–acetic acid–water (4:1:5 v./v.).

Ultraviolet and infrared spectra showed the following: $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,800); λ_{max}^{KBr} 2.95 (OH, NH), 6.2, 6.3, 6.7 (NH and purine ring), 9.1, 9.2, 9.35, 9.6 (C–O–C, C–O–H) μ.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.36; H, 5.12; N, 23.33.

A formaldehyde determination with the dimedone reagent,[15] after treatment with excess periodate, yielded 0.98 mole of HCHO/mole of nucleoside.

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Free-Radical Chemistry of Peptide Bonds. II. Conversion of Lactams to Imides

H. L. NEEDLES AND R. E. WHITFIELD

Western Regional Research Laboratory,[1] Albany, California

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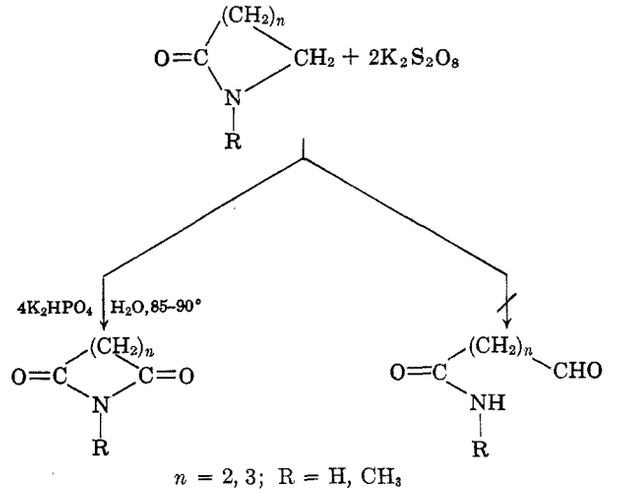
Recently, N-dealkylation of N-alkyl- and N,N-dialkylamides by persulfate was reported.[2,3] These dealkylations were believed to proceed *via* free-radical attack of the methylene adjacent to the amide nitrogen. It appeared that this dealkylation might provide a novel method for opening lactam rings to produce the corresponding ω-aldehydoamides; however, reactions of five- and six-membered lactams with persulfate yielded imides as the primary product (23–61%).



n = 2, 3; R = H, CH_3

In contrast, caprolactam with aqueous persulfate gave a low molecular weight polymer in 76% yield as the only isolable product. The 2,5-diketopiperazines, 2,5-piperazinedione and 1,4-dimethyl-2,5-piperazinedione (which contain two amide groups in the ring), were fairly stable to persulfate attack and were recovered from the reaction mixture in 89 and 82% yield, respectively. Low yields of carbon dioxide and ammonia were also found, and some formaldehyde (8%) was liberated from 1,4-dimethyl-2,5-piperazinedione. Products and yields from these reactions are listed in Table I.

TABLE I
PERSULFATE OXIDATION PRODUCTS

Reactant	Products	% yield
2-Pyrrolidinone	Succinimide	61
	Carbon dioxide	2
1-Methyl-2-pyrrolidinone	N-Methylsuccinimide	35
2-Piperidone	Glutarimide	23
1-Methyl-3-piperidone	N-Methylglutarimide	47
Caprolactam	Polymer	76
	Carbon dioxide	3
2,5-Piperazinedione[a]	Carbon dioxide	15
	Ammonia	11
1,4-Dimethyl-2,5-piperazinedione[b]	Carbon dioxide	3
	Ammonia	3
	Formaldehyde	8

[a] 89% recovery of starting material. [b] 82% recovery of starting material.

In the absence of persulfate, recoveries of known amounts of imide from the reaction mixture were 70% or better. Control experiments with imides in the presence of persulfate showed that attack by persulfate on imide lowered recoveries of imide from solution to some extent and formed water-soluble tars that could not be purified. Gas–liquid partition chromatography of crude oils from the action of persulfate on the five- and six-membered lactams showed imides to be greater than 95% of the volatile reaction products present.

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.
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