the solution of chlorinated imino ester. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature with periodic testing for active chlorine. After being stirred for 3 hr, the mixture still contained active chlorine. In spite of this fact, the reaction mixture was poured into 2 *N* hydrochloric acid and the aqueous layer was separated, refluxed for 5 hr, and evaporated to dryness. Isolation of the product in a manner similar to that used in the isolation of α-aminophenylacetic acid yielded 1.7 g (21%) of β-phenylalanine.

β-Phenylalanine (6, R = $C_6H_5CH_2$) (Using Potassium *t*-Butoxide).—To a stirred solution of potassium *t*-butoxide prepared from 4.6 g (0.12 g-atom) of potassium and 50 ml of anhydrous *t*-butyl alcohol was added dropwise a solution of ethyl N-chlorohydrocinnamimidate prepared as described in the preceding preparation from 9.80 g (0.0553 mole) of the imino ester and 6.00 g (0.0553 mole) of *t*-butyl hypochlorite. The reaction mixture was cooled in a cold-water bath. The resulting yellow mixture gave a negative starch–iodide test as soon as all of the chloro compound had been added. The hydrochloric acid extract of this mixture, after being heated under reflux and worked up as described in the previous experiment, yielded 5.5 g (60%) of β-phenylalanine.

Alanine (7, R = CH_3).—The following procedure is considered represent the optimum conditions developed thus far for the amino acids cited in Table I. A mixture of 150 ml of dry *t*-butyl alcohol and 5.80 g (0.148 mole) of metallic potassium was heated under reflux with stirring until all of the potassium had dissolved (about 3 hr), then cooled in an ice bath until the alcohol started to freeze.

While the foregoing solution was being heated, a solution of methyl N-chloropropionimidate was prepared. A solution of 20 g (0.50 mole) of sodium hydroxide in 200 ml of water was cooled in an ice–salt bath and treated with 16.7 g (0.23 mole) of chlorine gas at a rate such that the temperature remained below 10°. After the addition of the chlorine was completed, 5 ml of glacial acetic acid was added to the solution. To the resulting stirred and cooled solution 12.35 g (0.1000 mole) of methyl iminopropionimidate hydrochloride was added slowly through a powder funnel, the resulting mixture was stirred an additional 10 min, and then extracted once with a 50-ml portion and twice with 25-ml portions of *n*-pentane. The combined pentane extracts were dried ($MgSO_4$) in the refrigerator for at least 1 hr.

The dried pentane solution containing the methyl N-chloropropionimidate was filtered and added dropwise during a period of 25 min to the cooled potassium *t*-butoxide solution. As soon as the addition was completed, the ice bath was removed and the mixture was stirred at room temperature until 1 drop of mixture when placed on acidified starch–iodide paper, caused no color change. This required about 70 min. The reaction mixture was then poured into 100 ml of 2 *N* hydrochloric acid, the organic layer was separated and washed twice with 25-ml portions of 2 *N* hydrochloric acid, and the combined aqueous extracts were evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml of 2 *N* hydrochloric acid, and the solution was heated under reflux for 2 hr, then evaporated to dryness. This residue was extracted with one 50-ml portion and two 25-ml portions of boiling 95% ethanol. The combined alcoholic extracts were cooled to room temperature and filtered, 5 ml of water was added, and the resulting solution was treated with 6 ml of pyridine. The resulting mixture was cooled in the refrigerator for 1 day and filtered, and the resulting solid was washed with 25 ml of 95% ethanol and dried under vacuum giving 4.9 g (55%) of alanine.

In another experiment the procedure described above for ethyl N-chlorophenylacetimidate was followed, and a sample of ethyl N-chloropropionimidate was prepared from 21.23 g (0.05 mole of ethyl propionimidate hydrochloride. The *n*-pentane was evaporated, and the crude N-chloro compound was distilled under reduced pressure giving a 64.4% yield of a more nearly pure product, bp 60–61° (14 mm). The distillate showed no absorption in the 5.7-μ region of the infrared spectrum.[12] Analysis as described for ethyl N-chlorophenylacetimidate indicated an active chlorine content of 97.7%. Upon treatment of 6.98 g (0.050 mole) of this product with the potassium *t*-butoxide from 2.61 g (0.067 g-atom) of potassium and 50 ml of *t*-butyl alcohol as described above, 3.5 g (78%, based on the N-chloro compound) of alanine was isolated.

Preparation of Methyl α-Aminopropionate Hydrochloride (6, R = CH_3).—A *n*-pentane solution of methyl N-chloropropionimidate prepared from 12.35 g (0.100 mole) of methyl propionimidate hydrochloride was allowed to react with a solution of potassium *t*-butoxide as described in the foregoing procedure. As soon as the reaction mixture had given a negative starch–iodide test, it was poured into a mixture of 50 ml of 4 *N* hydrochloric acid and 50 g of ice. The aqueous layer was separated from the pentane layer and the former was evaporated to dryness under vacuum at a temperature below 45°. The resulting residue was extracted with boiling methanol and the filtrate was again evaporated to dryness. The residue was purified by dissolving it in the minimum amount of methanol and adding 100 ml of anhydrous ether with stirring. The resulting precipitate was collected and dried under reduced pressure giving 7.7 g of colorless powder. Evaporation of the filtrate to dryness and purification of the residue produced an additional 0.41 g of the product. The total yield of methyl α-aminopropionate hydrochloride was 8.1 g (58%), mp 157°.[15]

(15) See Table I, footnote *e*, mp 158°.

Synthesis of a D-Glucofuranosyl Nucleoside Derivative through an Oxazoline[1]

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A novel synthesis of crystalline 3′,5′,6′-tri-*O*-acetyl-2-methyl-α-D-glucofurano[2′,1′:4,5]-2-oxazoline (II) was effected by the action of chlorine on ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside. This 2-methyloxazoline derivative was utilized in acid-catalyzed fusion techniques to synthesize a phenolic glycoside and a nucleoside derivative of 2-amino-2-deoxy-D-glucofuranose.

Acyl migrations from oxygen to nitrogen[2] and from nitrogen to oxygen[3] have been established in the 2-amino-2-deoxy-D-glucose structure and for this an oxazoline derivative has been postulated as an intermediate.[4] Such intermediates have indeed been isolated as crystalline compounds for the 2-phenyl-2-oxazoline derivative in several cases[5–8] and utilized in glycoside synthesis.[6,7,9] Although a 2-methyloxazoline derivative of 2-amino-2-deoxy-D-glucose was once claimed,[4] it was later disproved.[10,11] We describe herein the crystalline 3′,5′,6′-

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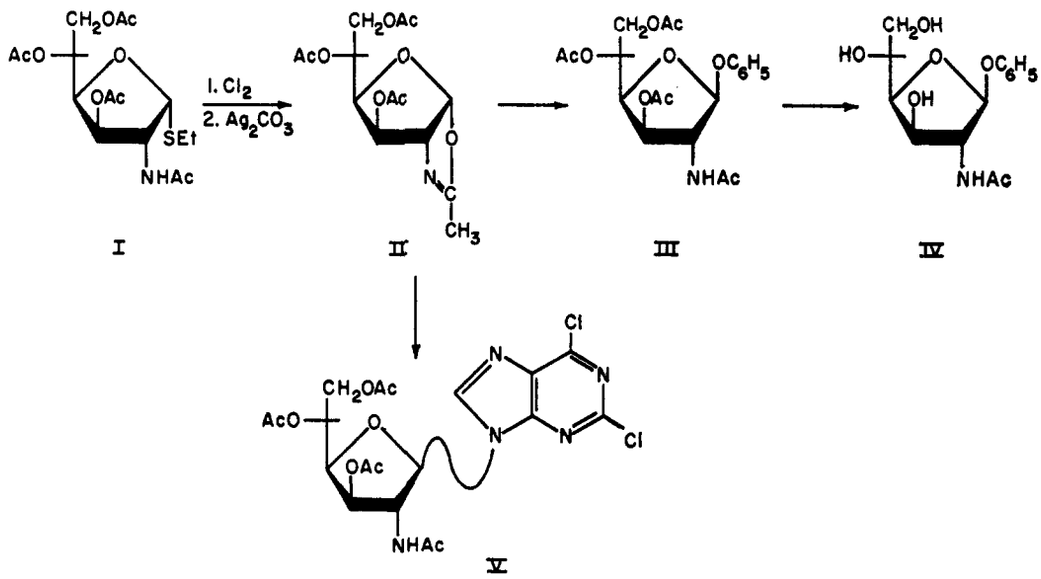

tri-*O*-acetyl-2-methyl-α-D-glucofurano[2′,1′:4,5]-2-oxazoline (II) and its use in the synthesis of a phenolic glycoside and of a nucleoside derivative by acid-catalyzed fusion techniques.

Treatment of ethyl 2-acetamido-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside (I)[12] with chlorine in dichloromethane solution, followed by reaction with silver carbonate, produced the oxazoline II. The assignment of this structure was based on its reactions, elemental analyses, and infrared spectrum. This spectrum shows the disappearance of the NH frequency at 3.10 and the NHAc frequencies at 6.05, 6.48 and the appearance of a C=N frequency at 5.98 μ.

Phenolic glycosides have been prepared by fusion of fully acetylated sugars,[13] including amino sugars,[14] with phenols and a trace of *p*-toluenesulfonic acid or zinc chloride. Fusion of the oxazoline II with phenol in the presence of *p*-toluenesulfonic acid produced a crystalline, acetylated phenyl glycoside III. The nuclear magnetic resonance (nmr) data established that only one anomer was present since in the anomeric region of the spectrum a lone doublet at δ 5.68 ppm was observed. The first-order coupling constant ($J_{1,2}$) between the C-1 and C-2 protons was 1 cps, indicating, but not establishing, a β-D configuratiion.[15] The compound melted over a range and repeated crystallizations failed to improve the melting point. It was surmised that a "liquid crystal" phenomenon was probably being observed. *O*-Deacetylation produced crystalline phenyl 2-acetamido-2-deoxy-β-D-glucofuranoside (IV) in good yield. The high negative optical rotations of IV (−104°) and its precursor III (−80°) confirmed that both III and IV were β-D anomers.

Fusion of II with 2,6-dichloropurine[16,17] in the presence of *p*-toluenesulfonic acid produced a nucleoside derivative, 9-(2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-D-glucofuranosyl)-2,6-dichloropurine (V). The nmr spectrum revealed a lone doublet at δ 6.40 ppm. The first-order coupling constant ($J_{1,2}$) between the C-1 and C-2 protons was 4 cps. While the anomeric configuration could not be assigned definitively from these data,[15] the spectrum again establishes the presence of a single anomer. The optical rotation, $[\alpha]^{25}D$ +7°, also gave little information about the anomeric configuration. Its mode of formation[18] would be expected to give predominantly a β-D anomer.

Further work on the synthesis of nucleosides of 2-amino-2-deoxy-D-glucofuranose along somewhat different lines is now is progress.

Experimental Section[19]

3′,5′,6′-Tri-*O*-acetyl-2-methyl-α-D-glucofurano[2′,1′:4,5]-2-oxazoline (II).—Dry chlorine gas was passed into a solution of I[12] (10 g) in dichloromethane (previously dried over Drierite, 100 ml), protected from moisture for 10 min at 0°. The solution was evaporated to dryness at 30° and the residue was dissolved in dichloromethane (100 ml). To this solution was added excess silver carbonate (15 g), portionwise, with stirring and cooling in ice and water. After effervescence had largely ceased, the mixture was stirred for a further 30 min at room temperature. The silver salts were removed by centrifugation and repeated filtration through sintered glass. The resulting clear, yellow solution was evaporated at 30° to a syrup which was crystallized from ether, yield 4.73 g (56%), mp 84–89°. Several recrystallizations produced pure material: mp 96–97°; $[\alpha]^{20}D$ +25 ± 1° (*c* 6.96, chloroform); λ_{max}^{KBr} 5.74 (OAc) and 5.98 μ (C=N); X-ray powder diffraction data, 8.67 m, 8.19 s (2), 6.15 w, 5.57 s, 5.27 s (1), 4.67 s (2), 4.43 m, 4.19 m, 3.98 s, 3.73 m, 3.52 s (3), 3.33 m, 3.04 w, 2.99 w, and 2.91 vw.

Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.10; H, 5.82; N, 4.26. Found: C, 51.00; H, 6.14; N, 4.42.

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This compound was homogeneous by thin layer chromatography, using ethyl acetate as developer. It gave a negative ninhydrin test. It was unstable at room temperature but could be stored, under dry conditions, for several weeks.

Phenyl 2-Acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-β-D-glucofuranoside (III).—Crude II (7.2 g) and phenol (8.2 g) were gently fused and *p*-toluenesulfonic acid (100 mg) was added to the melt. The melt was heated, with stirring, for 1 hr at 110–115°. After cooling, the residue was extracted with chloroform and the extract was washed repeatedly with 1 *N* sodium hydroxide and water. The dried (magnesium sulfate) chloroform solution was evaporated to dryness and the residue was dissolved in methanol. This solution was decolorized with activated carbon and the solvent was evaporated. The colorless syrup remaining was crystallized from ether: yield 1.60 g (17%); mp 72–85° (several recrystallizations from methanol–ether failed to improve the melting point); $[\alpha]^{18}D$ −80 ± 2° (*c* 2.37, chloroform); λ_{max}^{KBr} 3.1 (NH), 5.74 (OAc), 6.03, 6.42 (NHAc), 6.25, 6.71 (aryl C=C), and 14.47 μ (substituted benzene); nmr data (deuteriochloroform), δ 1.95, 2.00, 2.04 (12 protons, OAc, NAc), 3.82–4.82 (four protons, sugar ring), 5.12–5.57 (two protons, sugar ring), 5.68 (one-proton doublet, $J_{1,2}$ = 1 cps, H1′), 6.82–7.67 (seven protons, phenyl and NH) ppm; X-ray powder diffraction data, 16.06 w, 12.27 m, 9.21 s (3), 6.10 m, 5.30 s (1), 4.90 w, 4.59 vw, 4.27 m, and 4.00 s (2).

Anal. Calcd for $C_{20}H_{25}NO_9$: C, 56.71; H, 5.95; N, 3.31. Found: C, 56.44; H, 6.25; N, 3.51.

This compound was homogeneous by thin layer chromatography using ethyl acetate as developer.

Phenyl 2-Acetamido-2-deoxy-β-D-glucofuranoside (IV).—To the fully acetylated phenyl glycoside (III, 1.49 g) in anhydrous methanol (50 ml) was added sodium (0.1 g) and the solution was maintained for 2 hr at room temperature. The solution was neutralized to pH 7 by the addition of Amberlite IR-120 (H^+) resin. The resin was removed by filtration and washed with methanol. The filtrate and washings were evaporated to dryness. The residue was dissolved in ethanol and the solution was decolorized with activated carbon. The syrup obtained on solvent removal was crystallized from ethyl acetate, yield 0.78 g (79%), mp 136–138°. Recrystallization from methanol–ethyl acetate yielded pure material: mp 137–138°; $[\alpha]^{21}D$ −104 ± 2° (*c* 1.46, acetone); λ_{max}^{KBr} 2.9–3.1 (OH,NH), 6.05, 6.48 (NHAc), 6.15, 6.35, 6.71 (aryl C=C), and 14.47 μ (substituted benzene); X-ray powder diffraction data, 14.48 w, 10.04 m, 9.40 m, 8.58 vw, 7.43 w, 7.02 m, 6.46 vw, 6.06 m, 5.15 s (3), 4.92 vw, 4.64 s, 4.43 s(1), 4.21 vw, 4.07 s (2), 4.05 m, 3.67 m, 3.56 m, 3.37 vw, and 3.29 w.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.70; H, 6.44; N, 4.71. Found: C, 56.63; H, 6.48; N, 4.75.

This compound was homogeneous by thin layer chromatography using ethyl acetate–methanol (4:1) as developer.

9-(2-Acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-D-glucofuranosyl)-2,6-dichloropurine (V).—Finely ground II (4.73 g) and 2,6-dichloropurine (2.30 g) were mixed and fused at 110–120°. *p*-Toluenesulfonic acid (60 mg) was added and the melt was well stirred and heated for 10 min at 110–120°. The cooled melt was extracted with chloroform and the extract was filtered. The filtrate was washed successively with cold, saturated, aqueous sodium bicarbonate solution and water and dried (magnesium sulfate). The residue obtained on solvent removal at 40° was dissolved in methanol and the solution was decolorized with activated carbon. The solution was evaporated to a syrup, which was crystallzed from methanol–ether, yield 0.75 g (10%), mp 148–150°. Further recrystallizations produced pure material: mp 152–153°; $[\alpha]^{25}D$ + 7 ± 1° (*c* 1.56, methanol); λ_{max}^{KBr} 3.1 (NH), 5.68 (OAc), 6.05, 6.25, 6.42, and 6.75 μ (NHAc, purine); λ_{max}^{MeOH} 253 mμ (sh, ε 4960), 274 mμ (ε 9410); nmr data (deuterioacetone), δ 2.03, 2.06, 2.08, 2.17 (12 protons, NAc, OAc), 4.00–5.05 (four protons, sugar ring), 5.37–5.83 (two protons, sugar ring), 6.40 (one-proton doublet, $J_{1,2}$ = 4 cps, H1′), 8.09 (one-proton broad doublet, NH at 2′), 8.86 (one-proton singlet, H-8) ppm; X-ray powder diffraction data, 13.39 m, 11.48 s (3), 9.61 m, 8.50 s (2), 7.76 w, 6.91 w, 6.41 s (2), 5.86 w, 5.43 w, 5.21 vw, 4.71 w, 4.69 s (1), 4.25 vw, 4.17 vw, 4.00 vw, and 3.90 m.

Anal. Calcd for $C_{19}H_{21}Cl_2N_5O_8$: C, 44.02; H, 4.08; Cl, 13.68; N, 13.51. Found: C, 43.55; H, 4.29; Cl, 13.89; N, 13.75.

This compound was homogeneous by thin layer chromatography using ethyl acetate as developer.

Attempts to remove the *O*-acetyl groups and to replace the chlorine atoms in this nucleoside derivative did not lead to crystalline products.

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The Synthesis of Aldehydes from the Reaction of Amines with Butadiene

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The interaction of butadiene and amines in the presence of alkali metal compounds, such as hydrides and amides, has been found to give aldimine products. Upon acid hydrolysis, the major component was a novel C_{12} aldehyde (I) containing a quaternary carbon system. A structural assignment has been made from infrared and nmr spectroscopy and by the independent synthesis of an amine derivative. The formation of this aldehyde can be directed to high yields by the utilization of *t*-butylamine and certain aldimine reactants.

The alkali metal initiated addition of ammonia and amines to conjugated diolefins was first described in 1929.[1] Since then a number of related investigations have been reported.[2] For the most part, the reactions of secondary amines with 1,3-butadiene afforded good yields of simple butenyl compounds, whereas the major products from primary amines were of a higher molecular weight; *i.e.*, they contained more than 2 moles of butadiene per mole of amine.

Upon infrared examination of the products obtained from the reaction of butadiene and some primary amines, we observed absorption bands characteristic of aldimine compounds, and were able to isolate aldehydes after hydrolysis. The preparation, isolation, and structural proof of these compounds will be described herein, along with related reactions.

The interaction of methylamine, butadiene (1:1 molar ratio), and a catalytic quantity of an alkali metal compound, such as sodium hydride, was found to give a mixture of amines and aldimine materials. Separation of these materials was obtained by steam distillation from a dilute acid solution (Scheme I).

SCHEME I

$$CH_2{=}CH{-}CH{=}CH_2 + CH_3NH_2 \xrightarrow{NaH} \xrightarrow[\text{steam distillation}]{H^+}$$

steam volatiles + acid solubles
C_8 aldehyde, $CH_3NHC_4H_7$, $CH_3N(C_4H_7)_2$,
C_{12} aldehyde I high-boiling amines

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