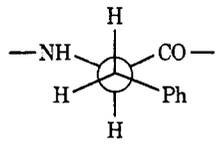
phenylalanyl nitrobenzyl ester and glycyclphenylalanyl-glycine.[25]



XI

(25) A. V. Lakshminarayanan, V. Sasisekharan, and G. M. Ramachandran in "Conformation of Biopolymers," Vol. 1, G. N. Ramachandran, Ed., Academic Press, New York, N. Y., p 61.

In the higher analogs of VI, which contain more than one phenylalanyl residue, overlapping of the β-proton patterns precludes analysis of the β-proton spectra. For trifluoroacetic acid solutions of all of the peptides, the phenylalanyl β protons appear as a doublet in the pmr spectra.

Registry No.—I, 19459-22-4; II, 19459-23-5; III, 19471-37-5; IV, 19459-24-6; V, 6514-26-7; VIa, 7625-14-1; VIb, 19459-27-9; VIc, 19459-28-0; VIIa, 19459-29-1; VIIb, 19459-30-4; VIIc, 19459-31-5.

Heterocyclic Amino Sugar Derivatives. I. Derivatives of 2-Amino-2-deoxy-D-allopyranose[1]

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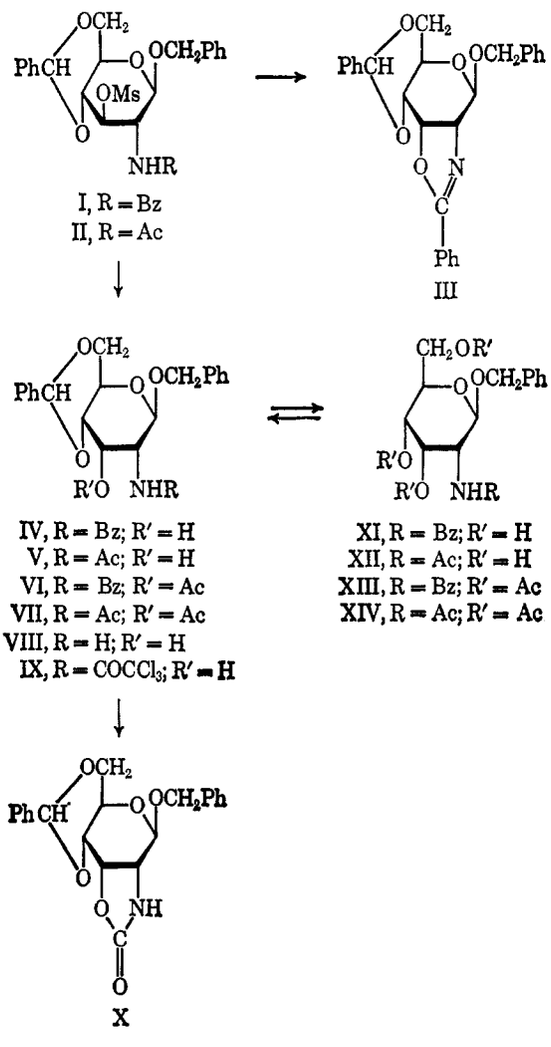
A facile synthetic route from D-glucosamine to benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII) was developed. A number of D-allosamine derivatives were prepared for characterization. Reaction of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII) with phosgene, diphenylcarbonate, *N*,*N*′-carbonyldiimidazole, or hexachloroacetone gave benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X) in excellent yield. A new method developed in this investigation is the utilization of hexachloroacetone to prepare a *N*-trichloroacetamido compound which is subsequently cyclized to give 2-oxazolidone X.

2-Amino-2-deoxy-D-allose (D-allosamine), an amino sugar not as yet found in nature, and some of its derivatives have been previously synthesized.[3-7] In view of the possible use of this amino sugar for the synthesis of antibiotics and nucleosides,[3] two derivatives which should be useful intermediates, benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII), and the cyclic carbamate benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X) have been synthesized (Scheme I). Compound VIII would provide for a variety of anomerically pure, *N*-substituted derivatives, in analogy to corresponding derivatives of D-glucosamine prepared by Gross and Jeanloz,[8] and compound X would provide for an excellent acid-stable, alkali-labile protective group for positions 2 and 3.

It was found that sulfonate can be eliminated with the 2-methoxyethanol–sodium acetate reagent[4] from benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (II) to give benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (V) in excellent yield without any laborious purification process. This approach seems to be superior to other known methods in large-scale preparations. However, we could not convert by this method the α anomer of II into the α anomer of V. Similarly, Rhoads and Gross[9] observed that eliminations of the sulfonate from benzyl 2-benzyloxycarbonylamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-D-glucopyranosides proceeded only with the β anomer.

SCHEME I



(1) A preliminary communication was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, by K. Miyai and P. H. Gross, Abstracts C-017. Taken from the doctoral thesis of K. Miyai, University of the Pacific, 1968. This work was partially supported by Grant No. GP-4587 of the U. S. National Science Foundation.

(2) To whom inquiries should be directed.

(3) E. J. McEvoy, M. J. Weiss, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 205 (1960).

(4) R. W. Jeanloz, *ibid.*, **79**, 2591 (1957).

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(6) P. H. Gross, K. Brendel, and H. K. Zimmerman, *Ann.*, **683**, 175 (1965).

(7) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1057, 1063 (1964).

(8) P. H. Gross and R. W. Jeanloz, *ibid.*, **32**, 2759 (1967).

(9) W. D. Rhoads, Dissertation, University of the Pacific, 1968.

The elimination of sulfonate from benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (I) gave a mixture of benzyl 4,6-*O*-benzylidene-β-D-allopyranosido-(2′-phenyl)-[2,3:4′,5′]-2′-oxazoline (III) and benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (IV). The cyclic intermediate of the reaction (I → IV), the very stable oxazoline (III), was obtained in high yield, predominating over the formation of the desired compound (IV). The result is in agreement with earlier observations that a stable oxazoline is formed with the N-benzoyl neighboring group.[10] For good yields, it was necessary to prepare IV from the previously known benzyl 2-benzamido-2-deoxy-β-D-allopyranoside (XI)[6] with benzaldehyde–$ZnCl_2$. Formation of a 3,4-*O*-benzylidene compound was not observed in this reaction. Removal of the benzylidene group of IV and V with aqueous acid gave compounds XI and XII. Acetylation into compounds VI, VII, XIII, and XIV posed no special problems, when done at 0° in fairly dilute solutions.

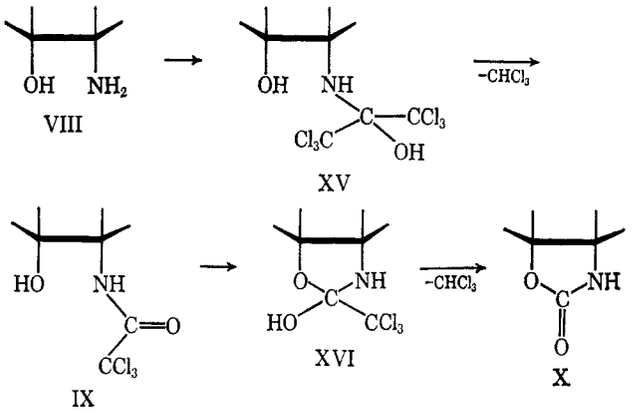
Alkaline hydrolysis of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (V) and of the corresponding *N*-benzoyl compound (IV) gave benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII), unblocked at positions 2 and 3.

When VIII was treated with phosgene in toluene or with diphenyl carbonate, it gave the desired cyclic compound, benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X), in excellent yield. The structure of compound X was supported by its independent synthesis,[9] and by examination of its ir spectrum (amide I at 1750 cm^{-1}, amide II absorption absent).[11,12]

We found only one literature report[13] in which a 2-oxazolidone compound was obtained from a β-amino alcohol with *N*,*N*′-carbonyldiimidazole. When this reagent was used, compound X was obtained quantitatively from VIII.

A new method developed in this investigation is the utilization of hexachloroacetone to prepare a *N*-trichloroacetamido compound which is then cyclized to give a 2-oxazolidone compound. It was observed that hexachloroacetone and amino alcohol VIII initially form a hexachloroacetone–amine adduct. This loses a molecule of chloroform to give the *N*-trichloroacetamido compound. Thus, benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX) was obtained in good yield under mild conditions. The *N*-trichloroacetamido compound, IX, was also prepared with trichloroacetyl chloride to confirm the structure of the product obtained with hexachloroacetone. Base-catalyzed cyclization reaction of benzyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX) yielded benzyl 4,6-*O*-benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X). As a possible interpretation of the observed results, a double haloform cleavage mechanism is proposed (Scheme II). The initially formed addition product (XV), which can

SCHEME II



be isolated, eliminates successively two molecules of chloroform to yield oxazolidone X.

Experimental Section

Melting points were taken in a Thomas–Hoover melting point apparatus, Model 6404H. All the melting points reported herein are uncorrected. Optical rotations were measured with a O. C. Rudolph and Sons, Inc., Model No. 956 polarimeter. Infrared spectra were recorded with Perkin-Elmer spectrophotometers (Models 137 and 337) using the KBr pellet technique. The homogeneity of the compounds synthesized was determined by thin layer chromatography using silica gel G (Merck) and silica gel GF (Merck). The plates were developed with chloroform containing a sufficient portion of ethanol or *n*-hexane to produce R_f values between 0.2 and 0.7. The compounds were detected with ultraviolet light and also by subsequent spraying with 10–15% sulfuric acid–methanol and heating about 15 min at 120°. All the compounds reported herein are chromatographically homogeneous. The microanalyses were performed by Alfred Bernhardt of Mikroanalytisches Laboratorium im Max-Plank-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

Benzyl 4,6-*O*-Benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-phenyl-2′-oxazoline (III).—A solution of benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (I, 1 g, 0.0018 mol)[14] and sodium acetate trihydrate (1 g) in 2-methoxyethanol (60 ml) containing water (3 ml) was refluxed for 33 hr. The solvent was evaporated *in vacuo*, water was added and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from methanol to give 536 mg (67.1%): mp 160.5–161°, $[\alpha]^{23}D$ +31.8° (*c* 2.17, pyridine).

Anal. Calcd for $C_{27}H_{25}NO_5$ (443.5): C, 73.12; H, 5.69; N, 3.16; O, 18.02. Found: C, 73.59; H, 5.74; N, 3.18; O, 17.76.

From the mother liquor of the crystallization, 7% IV could be isolated by fractional crystallization from absolute ethanol–ether.

Benzyl 2-Benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (IV). A.—Intensively dried compound XI (10.5 g, 0.0281 mol) was shaken 25 hr in a solution of freshly prepared anhydrous zinc chloride (4 g) in distilled benzaldehyde (65 ml). Diethyl ether was added and the mixture was kept several hours at 0°. The precipitate was filtered off and washed with cold diethyl ether. The filtrate was treated with water to obtain additional crude product. The combined product was recrystallized from absolute dioxane, then from absolute ethanol to give 11.3 g (86.8%): mp 240–240.5°; $[\alpha]^{30}D$ −169.5° (*c* 1.0, pyridine).

Anal. Calcd for $C_{27}H_{27}NO_6$ (461.5): C, 70.26; H, 5.90; N, 3.04; O, 20.55. Found: C, 70.10, H, 5.97; N, 3.58; O, 20.55.

B.—The compound was also prepared from III by following a procedure similar to that described for the preparation of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII). Fractional crystallization from absolute ethanol–diethyl ether gave IV in 12% yield plus a 70% recovery of the starting material.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyran-

(10) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967).
(11) M. E. Dyen and D. Swern, *Chem. Rev.* **67**, 197 (1967).
(12) S. Pinchas and D. Ben-Ishai, *J. Amer. Chem. Soc.*, **79**, 4099 (1957).
(13) W. B. Wright, *J. Heterocycl. Chem.*, **2**, 41 (1965).
(14) K. Miyai, P. H. Gross, and H. K. Zimmerman, *Ann.*, in press.

oside (V).—A solution of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-β-D-glucopyranoside (II, 28 g, 0.058 mol)[8] and sodium acetate trihydrate (28 g) in 2-methoxyethanol (750 ml) containing water (28 ml) was refluxed 50 hr. The solvent was evaporated *in vacuo*. Water was added to the remaining syrup and the mixture was kept at 0°.

The precipitate was filtered off, dried, and recrystallized from absolute ethanol to give 19.8g (85%): mp 260–260.5°; $[\alpha]^{24}D$ −115.6° (*c* 1.27, chloroform).

Anal. Calcd for $C_{22}H_{25}NO_6$ (399.5): C, 66.14; H, 6.31; N, 3.51; O, 24.03. Found: C, 66.29; H, 6.40; N, 4.05; O, 23.77.

Benzyl 3-*O*-Acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VI).—Compound IV (3 g, 0.0065 mol) in absolute pyridine (50 ml) was acetylated at 0° with acetic anhydride (6 ml) for 24 hr. The mixture was poured into ice–water and kept at 0°. The precipitate was filtered off, washed with water, and recrystallized from dioxane–diisopropyl ether, then from absolute ethanol to give 2.8 g (87.5%): mp 247–248°; $[\alpha]^{21}D$ −125.6° (*c* 1.04, pyridine).

Anal. Calcd for $C_{29}H_{29}NO_7$ (503.6): C, 69.17; H, 5.80; N, 2.78; O, 22.24. Found: C, 69.29; H, 5.78; N, 2.89; O, 22.53.

Benzyl 2-Acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VII).—Compound V (2 g, 0.005 mol) was dissolved in absolute pyridine (40 ml) at 50–60°. The solution was cooled rapidly to 0° and acetic anhydride (6 ml) was dropped in with stirring. Stirring was continued for 1 additional hr at 0–5° and 4 days at room temperature. The mixture was concentrated *in vacuo* to 20 ml and poured into ice–water. The precipitate was filtered off, washed with water, dried, and recrystallized from absolute ethanol–diethyl ether–*n*-hexane to give 2.0 g (90.9%): mp 171–171.5°; $[\alpha]^{22}D$ −137.9° (*c* 1.03, pyridine).

Anal. Calcd for $C_{24}H_{27}NO_7$ (441.5): C, 65.29; H, 6.17; N, 3.18; O, 25.37. Found: C, 65.49; H, 6.08; N, 3.53; O, 24.93.

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside (VIII). A.—A solution of V (16 g, 0.040 mol) in a hot mixture of potassium hydroxide (60 g, 86.7% assay) and 95% ethanol (200 ml) was refluxed for 9–10 hr at 87°. The mixture was diluted with 400 ml of hot water, allowed to cool to room temperature, and kept at 0°. The precipitate was filtered off, washed with water, and dried *in vacuo* at room temperature. Recrystallization from absolute ethanol gave 12.5 g (87.5%): mp 141–142°; $[\alpha]^{25}D$ −77.3° (*c* 1.01, pyridine).

Anal. Calcd for $C_{20}H_{23}NO_5$ (357.4): C, 67.20; H, 6.49; N, 3.92; O, 22.39. Found: C, 66.87; H, 6.55; N, 4.01; O, 22.55.

B.—Starting from X, a 95% yield of VIII was obtained. Compound IV was completely de-N-benzoylated only after 27 hr at 87° to give VIII (67%).

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-trichloroacetamido-β-D-allopyranoside (IX). A.—Compound VIII (1 g, 0.0027 mol) was refluxed with hexachloroacetone (5 g) and dimethylmesidine (1.5 ml) in absolute chloroform (100 ml). Precipitation of the initial hexachloroacetone adduct occurred after 10–15 min refluxing. Refluxing was continued for 6 hr and after addition of 1.5 ml of hexachloroacetone for 8 hr. The solvent was evaporated *in vacuo* and the remaining syrup was dissolved in ethanol which was again evaporated. Hot ethanol (5 ml) was added, followed by addition of warm water. The mixture was kept at 0° and the precipitate filtered off. Careful recrystallization from absolute ethanol gave 1.1 g (78.5%): mp 173–175° (sintering at 170°); $[\alpha]^{23}D$ −89.0° (*c* 1.09, pyridine).

Anal. Calcd for $C_{22}H_{22}NO_6Cl_3$ (502.8): C, 52.55; H, 4.41; N, 2.78; O, 19.10; Cl, 21.16. Found: C, 52.42; H, 4.52; N, 2.78; O, 19.26; Cl, 21.01.

B.—This compound was also prepared by treating compound VIII with trichloroacetyl chloride in pyridine under normal acylation conditions (yield 42%).

Benzyl 4,6-*O*-Benzylidene-β-D-allopyranosido[2,3:4′,5′]-2′-oxazolidone (X). A.—To a solution of VIII (3.57 g, 0.01 mol) in absolute pyridine (50 ml) was added dropwise a solution of phosgene (2.1 g) in dry toluene (20 ml). The mixture was stirred at room temperature for 5 hr, poured into ice water–petroleum ether (bp 30–60°), and kept at 0°. The precipitate was filtered off, washed with cold water, dried, and recrystallized from absolute ethanol to give 3.37 g (88%): mp 208.5–209.5°; $[\alpha]^{27}D$ +17.2° (*c* 1.04, pyridine).

Anal. Calcd for $C_{21}H_{21}NO_6$ (383.4): C, 65.78; H, 5.52; N, 3.66; O, 25.04. Found: C, 65.55; H, 5.83; N, 3.66; O, 24.97.

B.—Compound VIII (0.357 g, 0.001 mol) was heated in *N,N*-dimethylformamide (7 ml) with diphenyl carbonate (0.25 g) and sodium phenoxide (0.03 g) for 15 hr at 110°, and the mixture poured into excess ice–water. The precipitate was recrystallized by decolorization with charcoal from absolute ethanol to give 0.271 g (76%).

C.—Compound IX (0.5 g, 0.001 mol) was heated in *N,N*-dimethylformamide (10 ml) with 1,5-diazabicyclo[4.3.0]-5-nonene (0.25 g) for 15 hr at 110–115° and worked up as above to give 0.35 g (91%). Sodium methoxide or sodium phenoxide can also be used as the base catalyst in the reaction.

D.—Compound VIII (1.78 g, 0.0049 mol) in absolute tetrahydrofuran (40 ml) was mixed with a solution of *N,N′*-carbonyldiimidazole (1.62 g) in absolute tetrahydrofuran (40 ml) with exclusion of moisture, and the solution was stirred at room temperature for 15 hr. The solvent was evaporated *in vacuo*, excess water was added and the mixture kept at 0°. The precipitate was filtered off, dried, and recrystallized from absolute ethanol to give 1.80 g (96%).

Benzyl 2-Acetamido-2-deoxy-β-D-allopyranoside (XII).—A solution of compound V (4 g, 0.01 mol) in glacial acetic acid (120 ml) was heated to 90° and water (80 ml) was added dropwise over a period of 30 min. The mixture was stirred 70 min at 80–85°. The solvent was evaporated *in vacuo*, followed by repeated coevaporation with water and finally with toluene. Petroleum ether (bp 30–60°) was added to the remaining syrup and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from methylene chloride and ethanol–petroleum ether to give 2.6 g (85%): mp 156–158°; $[\alpha]^{25}D$ −114° (*c* 1.4, pyridine).

Anal. Calcd for $C_{15}H_{21}NO_6$ (311.3): C, 57.88; H, 6.80; N, 4.50; O, 30.84. Found: C, 57.79; H, 6.80; N, 4.07; O, 31.49.

Benzyl 3,4,6-Tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-allopyranoside (XIII).—Compound XI (1 g, 0.0026 mol) in absolute pyridine (15 ml) was treated with acetic anhydride (3 ml). The mixture was kept at room temperature overnight, poured into ice–water, and kept at 0°. The precipitate was filtered off, dried, and recrystallized from pyridine–water to give long needles, melting at 149.5–151°, which may be a hydrate. This product was recrystallized again from dry toluene–petroleum ether to give 1.2 g (92.3%): mp 165.5–166°; $[\alpha]^{25}D$ −27.9° (*c* 0.6, pyridine).

Anal. Calcd for $C_{26}H_{29}NO_9$ (499.5): C, 62.51; H, 5.85; N, 2.80; O, 28.82. Found: C, 62.47; H, 5.79; N, 3.05; O, 28.70.

Benzyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-allopyranoside (XIV).—Compound XII (0.62 g, 0.002 mol) in absolute pyridine (8 ml) was treated with acetic anhydride (1.5 ml). The mixture was kept at room temperature overnight and poured into ice–water. The product was extracted with chloroform which was then evaporated *in vacuo*. *n*-Heptane was added to the remaining syrup and the mixture was kept at 0°. The precipitate was filtered off, dried, and recrystallized from chloroform–petroleum ether to give 0.61 g (70%): mp 106–108°; $[\alpha]^{25}D$ −54.4° (*c* 1.0, pyridine).

Anal. Calcd for $C_{21}H_{27}NO_9$ (437.4): C, 57.66; H, 6.22; N, 3.21; O, 32.92. Found: C, 57.58; H, 6.35; N, 3.40; O, 32.76.

Registry No.—III, 19398-20-0; IV, 19374-63-1; V, 19374-64-2; VI, 19374-65-3; VII, 19374-66-4; VIII, 19374-67-5; IX, 19374-68-6; X, 19374-69-7; XII, 19374-70-0; XIII, 19374-71-1; XIV, 19374-72-2.