Heterocyclic *N*-Glycosides. III. Synthesis of *N*-Glycosyl-*v*-Triazoles from Glycosyl Azides and Phenylacetylene.

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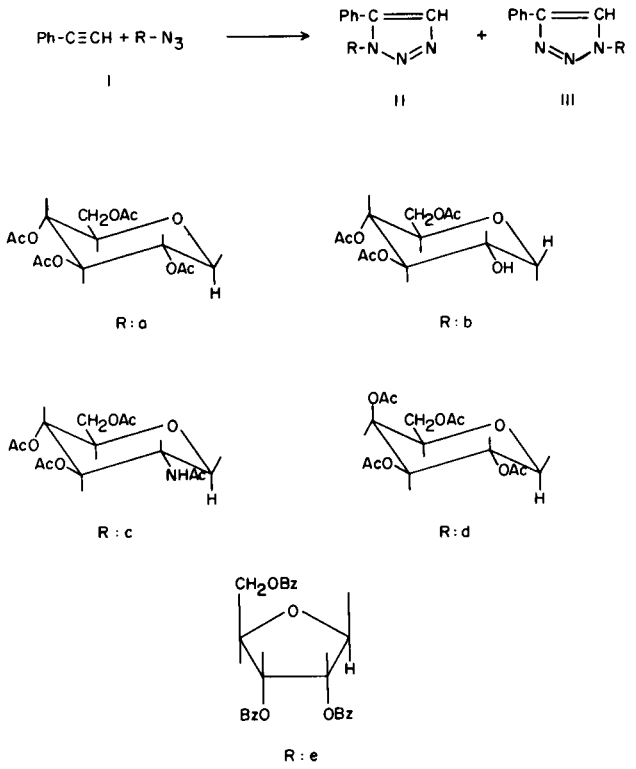
A number of *v*-triazoles were prepared by the 1,3-dipolar cycloaddition of glycosyl azides on phenylacetylene. In all the cases studied, except when 2-*O*-trichloroacetyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl azide was used, the two possible *v*-triazoles were obtained. The assignment of structure and anomeric configuration for all *N*-glycosides obtained is discussed.

Our continued interest in the synthesis of heterocyclic *N*-glycosides (1) has led us to study the reaction between glycosyl azides and phenylacetylene.

It is well known that 1,3-dipolar cycloaddition of azides to acetylenic compounds yields derivatives of 1,2,3-triazole (2). Since the phenylacetylene is an asymmetrical dipolarophile, cycloaddition of glycosyl azides to phenylacetylene would be expected to give a mixture of the two isomeric *v*-triazoles.

F. Michael and G. Baum (3) added 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide to phenylacetylene and isolated in each case only one of the two possible *v*-triazoles, *i.e.*, 4-phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIIa) and 4-phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2,3-triazole (IIId), respectively. The structural assignments were based on the course of the reaction of asymmetric acetylenes with a number of organic azides as studied by Huttel and Moulin (4).



In the present investigation, work of Michael and Baum was repeated and extended to other glycosyl azides, and the structural assignments were confirmed. However, in every case studied we have always obtained the two isomeric *v*-triazoles, the exception being 2-*O*-trichloroacetyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl azide (5) which led to only one of the *v*-triazoles.

It should be noted that generally the two *v*-triazoles were formed almost in equal amounts but sometimes the 1,4-substituted *v*-triazole predominated.

The structures of the *N*-glycosides were established beyond reasonable doubt by means of analysis and NMR spectroscopy. Work in this laboratory (6) has shown that inspection of the NMR spectra of the isomeric *v*-triazoles allows us to distinguish between the 1-substituted 5-phenyl-1,2,3-triazole and the isomeric 1-substituted 4-phenyl-1,2,3-triazole. In the first case the signal corresponding to the five protons of the phenyl group appears as a singlet, while in the second case the aromatic protons give rise to a complex multiplet.

The configurations of the glycopyranosides at the anomeric carbon atom were established by their NMR spectra and appeared to be the same as those of the azides used as starting materials. This result is not surprising since it is not reasonable to expect a change of configuration in this type of reaction.

For the ribofuranosides obtained from the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (7) with

phenylacetylene, the configuration at the anomeric carbon atom could not be established by means of their NMR spectra. It is well known (8) that this method is applicable to the β-anomer when the coupling constant $J_{1',2'}$ is less than 3.5 cps and that the method is reliable only when the coupling constant is less than about 1.0 cps.

The NMR spectra of IIe and IIIe as well as those of their debenzoylated derivatives showed coupling constants $J_{1',2'}$ larger than 3.5 cps. Nevertheless, considering that in the other reactions studied inversion of configuration at the anomeric carbon atom was not observed regardless of the azide employed, a tentative assignment of β-configuration has been made for IIe and IIIe.

Finally, attention is called to the fact that the only *N*-glucoside obtained from the reaction of 2-*O*-trichloroacetyl-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl azide with phenylacetylene has lost the trichloroacetyl grouping present at the azide.

EXPERIMENTAL

Melting points were taken on a Kofler apparatus. NMR spectra were obtained on a Perkin-Elmer R-10 spectrometer using tetramethylsilane as an internal standard and the ultraviolet spectra with a Perkin-Elmer 350 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter.

T.l.c. was performed with 0.25 mm. chromatoplates of silica gel GF 254 (Merck) and spots were visualized with U.V. light of 254 mμ.

General Procedure for the Preparation of the *N*-Glycosides.

A mixture of 0.06 mole of pure phenylacetylene and 0.02 mole of the glycosyl azide in 30 ml. of dry toluene was heated at reflux temperature for 10-13 hours. After this, the reaction products were separated and purified as specified in each case.

4-Phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIIa) and 5-phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIa).

The precipitate which formed on cooling the reaction mixture at room temperature was removed by filtration and washed with ethanol. T.l.c. of this product showed a single spot. Recrystallization from ethanol gave white needles, m.p. 218°, $[\alpha]_D$ -63.5° (c 1.0, chloroform), yield, 42%, lit. (3) m.p. 218°, $[\alpha]_D$ -65.3° (c 0.95. chloroform); U.V. λ max (ethanol), 243 (ε, 18,000), 260 (ε, 8,400), (sh), 277 mμ (ε, 870) (sh); NMR (deuteriochloroform, τ), 1.99 singlet (H_5), 2.16 and 2.62 multiplets (5H, phenyl group), 4.04 doublet (H_1',$J_{1',2'}$ 9.1 cps), methyl singlets at 7.93 (6H), 7.97 (3H), 8.13 (3H). This product was the *N*-glycoside IIIa.

The solid obtained by evaporation of the mother liquor and washing ethanol was dissolved in a small amount of benzene and chromatographed on a silica gel column; elution was carried out with benzene and mixtures of benzene-ethyl acetate (4:1 and 1:1). Whereupon three products were separated. First, phenylacetylene, next, 0.9 g. of IIIa, and finally, IIa.

This last compound was recrystallized from ethyl acetate-petroleum ether to give white needles, m.p. 135° $[\alpha]_D$ -19.8° (c 1.0, chloroform), yield, 28%; U.V. λ max (ethanol), 242 mμ (ε, 11,000); NMR (deuteriochloroform, τ), 2.30 singlet (H_4), 2.41 singlet (5H, phenyl group), 4.37 doublet (H_1',$J_{1',2'}$ 9.0 cps), methyl singlets at 7.92 (3H), 7.97 (3H), 8.01 (3H), 8.21 (3H).

Anal. Calcd. for $C_{22}H_{25}N_3O_9$: C, 55.58; H, 5.26; N, 8.84. Found: C, 55.57; H, 5.28; N, 9.01.

4-Phenyl-1-(3′,4′,6′-tri-*O*-acetyl-α-D-glucopyranosyl)-1,2,3-triazole (IIIb).

The reaction mixture was evaporated to dryness *in vacuo* and the residual product chromatographed on a silica gel column which was eluted with a mixture of benzene-ethanol (9:1) to give a white solid. Upon recrystallization from ethyl acetate-petroleum ether, m.p. 207°, $[\alpha]_D$ +149° (c 0.98, chloroform), yield, 72%; I.R., 3,450 cm^{-1} (OH group); U.V. λ max (ethanol), 243 (ε, 15,900), 275 mμ (ε, 800) (sh); NMR (deuteriochloroform, τ), 2.00 singlet (H_5), 2.16 and 2.56 multiplets (5H, phenyl group), 3.78 doublet (H_1',$J_{1',2'}$ 5.5 cps), methyl singlets at 7.91 (3H), 7.95 (3H), 7.98 (3H).

Anal. Calcd. for $C_{20}H_{23}N_3O_8$: C, 55.39; H, 5.34; N, 9.65. Found: C, 54.91; H, 4.91; N, 9.84.

4-Phenyl-1-(2′-acetamido-2′-deoxy-3′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIIc) and 5-Phenyl-1-(2′-acetamido-2′-deoxy-3′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIc).

The solid which separated after cooling the reaction mixture was collected by filtration and washed with ethanol. It was purified by recrystallization from ethanol to give white needles, m.p. 285-286°, $[\alpha]_D$ -94.6° (c 1.0, pyridine), yield, 49%; U.V. λ max (ethanol), 242 (ε, 19,900), 247 (ε, 1,085) (sh), 285 mμ (ε, 217) (sh); NMR (trifluoroacetic acid, τ), 1.08 singlet (H_5), 2.29 multiplet (5H, phenyl group), 3.55 doublet (H_1',$J_{1',2'}$ 9.6 cps), methyl singlets at 7.70 (9H), 7.88 (3H). This product was IIIc.

Anal. Calcd. for $C_{22}H_{26}N_4O_8$: C, 55.68; H, 5.52; N, 11.81. Found: C, 55.60; H, 5.91; N, 12.22.

The combined filtrate and washings were evaporated and the solid residue was dissolved in ethyl acetate and chromatographed on a silica gel column using ethyl acetate as eluent, whereupon four products were separated: phenylacetylene, an unidentified compound, IIIc, and finally a white solid. This solid was recrystallized from ethyl acetate-petroleum ether, m.p. 199°, $[\alpha]_D$ -20.6° (c 1.0, chloroform), yield, 41%; U.V. λ max (ethanol), 242 mμ (ε, 10,400); NMR (deuteriochloroform, τ), 2.36 singlet (H_4), 2.52 singlet (5H, phenyl group), 3.64 doublet (H_1', $J_{1',2'}$ 9.6 cps), methyl singlets at 7.94 (3H), 8.00 (6H), 8.31 (3H). These data indicated that the product was IIc.

Anal. Calcd. for $C_{22}H_{26}N_4O_8$: C, 55.68; H, 5.52; N, 11.81. Found: C, 55.75; H, 5.57; N, 12.05.

4-Phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-galactopyranosyl)-1,2,3-triazole (IIId) and 5-Phenyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2,3-triazole (IId).

The brown residue from evaporation of the toluene was dissolved in a small amount of ethyl acetate and the solution was applied to a column of silica gel. Elution was accomplished with a mixture of ethyl acetate-petroleum ether (1:1). By this procedure three compounds were obtained: phenylacetylene, IIId, and IId.

The *N*-glycoside IIId was recrystallized from methanol, m.p. 203°, $[\alpha]_D$ -40° (c 0.9, chloroform), yield, 38%, lit. (3) m.p. 203°, $[\alpha]_D$ -41.2° (c 1.0, chloroform); U.V. λ max (ethanol), 243 (ε, 17,350), 247 mμ (ε, 756) (sh); NMR (deuteriochloroform, τ), 1.95 singlet (H_5), 2.15 and 2.62 multiplets (5H, phenyl group), 4.05 doublet (H_1',$J_{1',2'}$ 8.6 cps), methyl singlets at 7.78 (3H), 7.99 (6H), 8.12 (3H).

The *N*-glycoside (IId) was recrystallized from ethyl acetate-petroleum ether, m.p. 189-190°, $[\alpha]_D$ -8° (c 1.0, chloroform),

yield, 28%; U.V. λ max (ethanol), 241 mμ (ε, 10,025); NMR (deuteriochloroform, τ), 2.29 singlet (H_4), 2.46 singlet (5H, phenyl group), methyl singlets at 7.92 (6H), 8.05 (3H), 8.18 (3H).

Anal. Calcd. for $C_{22}H_{25}N_3O_9$: C, 55.58; H, 5.26; N, 8.84. Found: C, 55.62; H, 5.26; N, 8.91.

4-Phenyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole (IIIe) and 5-Phenyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole (IIe).

The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and applied to a column of silica gel. The column was eluted with benzene and mixtures of benzene-ethyl acetate (9:1, 4:1, and 3:1). By this procedure three products were obtained: phenylacetylene, IIIe, and IIe.

The *N*-glycoside (IIIe) was recrystallized from ethanol, m.p. 161°, $[\alpha]_D$ -113° (c, 1.04, chloroform), yield, 26%; U.V. λ max (ethanol), 232 (ε, 47,100), 275 (ε, 3,925) (sh), 281 mμ (ε, 2,890); NMR (deuteriochloroform, τ), 2.07 (H_5), 2.00 and 2.57 multiplets (20 H, phenyl groups), 3.48 doublet (H_1', $J_{1',2'}$ 3.4 cps).

Anal. Calcd. for $C_{34}H_{27}N_3O_7$: C, 69.26; H, 4.58; N, 7.13. Found: C, 69.12; H, 4.48; N, 6.90.

The other glycoside (IIe) was further purified by preparative t.l.c. on silica gel PF_{254} plates of 2 mm. thickness. The plates were developed in a mixture of petroleum ether-ethyl acetate (2:1) allowing the solvent to run the total length of the plates and dried. This procedure was repeated four times. Finally, the compound was recrystallized from ethanol-water, m.p. 65°, $[\alpha]_D$ -6.2 (c 0.61, chloroform), yield, 15%; U.V. λ max (ethanol), 231 mμ (ε, 44,500); NMR (deuteriochloroform, τ), 2.26 singlet (H_4), 2.04 and 2.56 multiplets (20 H, phenyl groups).

Anal. Calcd. for $C_{34}H_{27}N_3O_7$: C, 69.26; H, 4.58; N, 7.13. Found: C, 69.22; H, 4.49; N, 6.80.

Deacetylation and Debenzoylation of the Above *N*-Glycosides.

The protected *N*-glycosides (0.01 mole) were dissolved in 60 ml. of dry methanolic ammonia (methanol saturated with ammonia at 0°) and the resulting solution was allowed to stand at room temperature for 24 hours. After removal of the methanol the compounds were recrystallized as indicated in each case.

4-Phenyl-1-β-D-glucopyranosyl-1,2,3-triazole.

This product was obtained as a white solid, from IIIa; m.p. 235° (water), $[\alpha]_D$ -7.0° (c 1.0, water), yield, 52%, lit. (3), m.p. 234°, $[\alpha]_D$ 0° (c 1.0, water); U.V. λ max (ethanol), 241 mμ (ε, 17,350); NMR (dimethylsulfoxide, τ), 1.23 singlet (H_5), 2.12 and 2.57 multiplets (5H, phenyl group), 4.39 doublet (H_1', $J_{1',2'}$ 8.7 cps).

5-Phenyl-1-β-D-glucopyranosyl-1,2,3-triazole.

This compound was prepared by deacetylation of IIa, m.p. 76° (methanol-ether), $[\alpha]_D$ -3° (c 1.0, water), yield, 76%; U.V. (ethanol), 241 mμ (ε, 12,000); NMR (deuterium oxide, τ), 2.18 singlet (H_4), 2.53 singlet (5H, phenyl group), 4.62 doublet (H_1', $J_{1',2'}$, 9.9 cps).

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.53; N, 13.68. Found: C, 54.48; H, 5.32; N, 13.54.

4-Phenyl-1-α-D-glucopyranosyl-1,2,3-triazole.

This compound was prepared by deacetylation of IIIb; m.p. 226-227° (water), $[\alpha]_D$ +69° (c 0.43, ethanol), yield, 80%; NMR (dimethylsulfoxide-d_6, τ), 1.33 singlet (H_5), 2.11 and 2.56 multiplets (5H, phenyl group), 2.81 doublet (H_1',$J_{1',2'}$ 5.5 cps).

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.53; N, 13.68. Found: C, 54.48; H, 5.32; N, 13.58.

4-Phenyl-1-(2′-acetamido-2′-deoxy-β-D-glucopyranosyl)-1,2,3-triazole.

This compound was prepared from IIIc; m.p. 266-267° (water), $[\alpha]_D$ -54.1° (c 1.0, pyridine), yield, 86%; U.V. λ max (ethanol), 245 (ε, 19,000), 275 (ε, 863) (sh), 286 mμ (ε, 211) (sh).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.78; N, 16.08. Found: C, 54.95; H, 6.64; N, 16.35.

5-Phenyl-1-(2′-acetamido-2′-deoxy-β-D-glycopyranosyl)-1,2,3-triazole.

This compound was obtained from IIc; m.p. 227° (methanol-ether), $[\alpha]_D$ -2.5° (c 1.0, water), yield, 77%; U.V. λ max (ethanol), 243 mμ (ε, 14,200).

Anal. Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.78; N, 16.08. Found: C, 55.29; H, 5.38; N, 16.45.

4-Phenyl-1-β-D-galactopyranosyl-1,2,3-triazole.

This compound was prepared from IIId; m.p. 217° (water), $[\alpha]_D$ +26° (c 1.0, water), yield, 53%, lit. (3) m.p. 218°, $[\alpha]_D$ +25° (c 0.9, water); U.V. λ max (ethanol), 243 (ε, 16,600), 274 mμ (ε, 992) (sh).

5-Phenyl-1-β-D-galactopyranosyl-1,2,3-triazole.

This compound was obtained from IId; m.p. 201° (methanol-ether), $[\alpha]_D$ -6.8° (c 0.25, ethanol), yield, 26%; U.V. λ max (ethanol), 242 mμ (ε, 10,500).

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.53; N, 13.68. Found: C, 54.46; H, 5.68; N, 13.86.

4-Phenyl-1-β-D-ribofuranosyl-1,2,3-triazole.

This compound was obtained from IIIe; m.p. 222° (water), $[\alpha]_D$ -25.5° (c 0.09, ethanol), yield, 70%; U.V. λ max (ethanol), 274 (ε, 13,900), 284 mμ (ε, 500); NMR (dimethylsulfoxide, τ), 1.24 singlet (H_5), 2.13 and 2.57 multiplets (5H, phenyl group), 3.96 doublet (H_1',$J_{1',2'}$ 4.4 cps).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.41; N, 15.16. Found: C, 56.53; H, 5.33; N, 15.05.

5-Phenyl-1-β-D-ribofuranosyl-1,2,3-triazole.

This compound was obtained from IIe; m.p. 148° (ethanol), $[\alpha]_D$ -87° (c 0.5, ethanol), yield, 62%; U.V. λ max (ethanol), 235 mμ (ε, 11,000); NMR (dimethylsulfoxide-d_6, τ), 2.09 singlet (H_4), 2.47 singlet (5H, phenyl group), 4.37 doublet (H_1',$J_{1',2'}$ 3.0 cps).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.41. Found: C, 56.44; H, 5.69.

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