Heterocyclic *N*-Glycosyl Derivatives. XII. The Reaction of Glycosyl Azides with α,β-Unsaturated Esters

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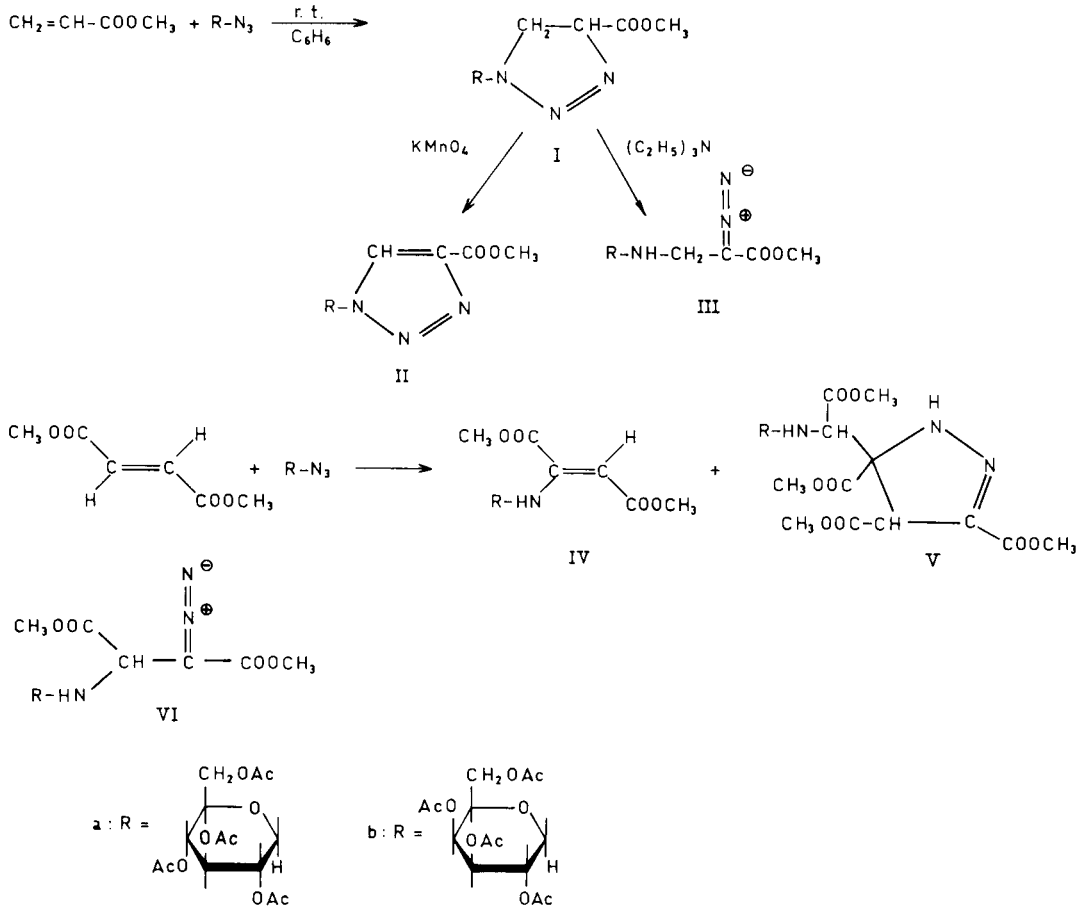
Because of their interest as possible anticancer agents nucleoside analog derivatives of five-membered heterocyclic systems other than imidazole have recently received considerable attention. As a consequence, interest has been focused on *N*- and *C*-glycosyl triazole derivatives, many of which have been prepared both by 1,3-dipolar cycloaddition reaction of suitable acetylenic and azido precursors (1) and by the silylation procedure (2).

From the extensive work of Huisgen *et al.* (3) and L'abbé *et al.* (4), α,β-unsaturated esters are known to react with aryl azides and *n*-butyl azide to give Δ^2-1,2,3-triazolines which can be easily converted into the corresponding ring-opened isomers, namely, *N*-substituted 3-amino-2-diazoesters. The present study was undertaken to examine the extension of these reactions to glycosyl azides.

Condensation of methyl acrylate with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide in benzene at room temperature gave the Δ^2-1,2,3-triazoline Ia in 32% yield. The structure of this compound was established on the basis of its elemental analysis, spectroscopic data and chemical evidence. Since the infrared spectrum of Ia did not show



absorption in the diazo region it was assumed that this compound was the expected cycloaddition adduct. In the nmr spectrum of Ia the anomeric proton appeared as a doublet at 4.2 τ with a coupling constant ($J_{1',2'}$ = 9.5 Hz) indicative of the axial disposition of H-1'. Finally, confirmation for the assigned structure was obtained by a chemical method. Oxidation of Ia with potassium permanganate gave 4-carbomethoxy-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (IIa), which was identical with a sample prepared from methyl propiolate and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (Id).

The base-catalyzed isomerization of Ia proceeded smoothly at room temperature to give the diazo derivative IIIa. Its infrared spectrum showed strong absorption at 2,105 cm^{-1} (diazo group), 1,685 cm^{-1} (-$COOCH_3$) and 3,360 cm^{-1} (NH). Likewise, methyl 3-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-diazopropionate (IIIb) was prepared in 37% yield starting from methyl acrylate and 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide. The intermediate Δ^2-1,2,3-triazoline was not isolated but was isomerized directly under basic conditions to the desired diazo derivative IIIb. This type of diazo compounds is of special interest as possible cytotoxic agents.

When methyl acrylate was substituted for dimethyl fumarate and the reaction run in benzene at reflux temperature, it was found that 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide yielded a mixture of the enamine IVa and the pyrazoline derivative Va. Structural assignment of IVa was based on microanalytical data and nmr evidence. This compound displayed a single vinyl proton resonance at 4.5 τ which is in close agreement with reported values for related fumarate compounds (5). The doublet at 1.56 τ ($J_{NH,1'}$ = 10 Hz) was assigned to the intramolecularly bonded amino proton on the basis of a comparison with the chemical shifts reported by Gómez Sánchez *et al.* (6) for several ethyl 3-(glycosylamino)crotonates in which the ethoxycarbonyl and the amino groups were *cis* oriented. In accordance with earlier studies (3,4), the second product of the above reaction was identified as the pyrazoline Va. The obtention of this latter compound can be rationalized as proceeding through the formation of VI *via* the corresponding Δ^2-1,2,3-triazoline (5,7) and further reaction of the diazoester VI with dimethyl fumarate.

On the other hand, considering that in previously studied cycloaddition reactions using β-glycosyl azides (Ic,d,e,f) inversion was not observed at the anomeric carbon atom, a tentative β configuration assignment has been made for the enamine IVa and the pyrazoline Va.

From the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide with dimethyl fumarate in refluxing benzene the pyrazoline Vb was isolated in about 46% yield. On the other hand, a significantly lower yield (~ 15%) of Vb was obtained when the two above reactants were allowed to stand at room temperature in benzene solution for two months.

EXPERIMENTAL

Melting points are not corrected. Nmr spectra were determined on a Perkin-Elmer R-12 spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter. Tlc was performed with 0.25 mm chromatoplates of silica gel GF_{254} (Merck) and spots were visualized with uv light of 254 mμ.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-carbomethoxy-Δ^2-1,2,3-triazoline (Ia).

A solution of 1.5 g. (4 mmoles) of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide and 1.37 g. (16 mmoles) of methyl acrylate in 30 ml. of benzene was kept at room temperature for 45 days. After removing the solvent *in vacuo*, the remaining solid was recrystallized twice from ethyl acetate-petroleum ether to give 0.64 g. of pure Ia (32% yield), m.p. 139-140°, $[\alpha]_D$ -107° (c 0.53, chloroform); nmr (DMSO-d_6, τ) 4.2 doublet ($H\text{-}1'_{1',2'}$ 9.5 Hz).

Anal. Calcd. for $C_{18}H_{25}N_3O_{11}$: C, 47.05; H, 5.44; N, 9.15. Found: C, 47.35; H, 5.54; N, 9.36.

4-Carbomethoxy-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazole (IIa).

To a solution of 0.138 g. of Ia in 0.5 ml. of pure acetone was added dropwise a solution of 0.145 g. of potassium permanganate in 3 ml. of acetone. The mixture was allowed to stand for 15 minutes at room temperature and then the excess of potassium permanganate was decomposed with hot methanol. The manganese dioxide was removed by filtration and washed with acetone and the combined filtrate was evaporated to yield a solid residue. The R_f values (tlc spots were detected with 30% sulfuric acid in ethanol) of this material in several solvent systems (chloroform, ethyl acetate-petroleum ether 1:1, and chloroform-ethyl acetate 4:1) were identical with those of an authentic sample of IIa (Id).

Methyl 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)-2-diazopropionate (IIIa).

A solution of 0.46 g. of the Δ^2-1,2,3-triazoline Ia in 10 ml. of benzene containing 0.5 ml. of triethylamine was maintained at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue recrystallized from ethyl acetate-petroleum ether yielding 0.36 g. of yellow crystals, m.p. 116°, $[\alpha]_D$ -10.4° (c 0.7, chloroform); uv λ max (ethanol), 260 mμ (ε, 9,884); ir (nujol), 3,330 (NH), 2,100 (diazo group), 1680 cm^{-1} (-$COOCH_3$).

Anal. Calcd. for $C_{18}H_{25}N_3O_{11}$: C, 47.05; H, 5.44; N, 9.15. Found: C, 47.23; H, 5.48; N, 9.39.

Methyl 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosylamino)-2-diazopropionate (IIIb).

A mixture of 1.5 g. (4 mmoles) of methyl acrylate and 1.37 g. (16 mmoles) of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide in 30 ml. of benzene was kept at room temperature for 20 days. After this time 2 ml. of triethylamine was added and the solution was allowed to stand at room temperature for two days. The solvent was distilled *in vacuo* and the residue chromatographed over silica gel (Merck). Elution with ethyl acetate gave 0.543 g. of IIIb, m.p. 112° (from ethyl acetate-petroleum ether), $[\alpha]_D$ -25.6° (c 0.5, chloroform); uv λ max (ethanol), 260 mμ (ε, 8,725); ir (nujol), 3,330 (NH), 2,100 (diazo group), 1680 cm^{-1} ($COOCH_3$).

Anal. Calcd. for $C_{18}H_{25}N_3O_{11}$: C, 47.05; H, 5.44; N, 9.15. Found: C, 47.28; H, 5.71; N, 8.91.

Dimethyl 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)fumarate (IVa) and Methyl *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(3,4,5-tricarbomethoxy-Δ^2-pyrazolin-5-yl)glycinate (Va).

A mixture of 2 g. (0.013 mole) of dimethyl fumarate and 2.6 g. (0.0069 mole) of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide in 40 ml. of benzene was heated to reflux temperature for 30 hours. After removing the solvent *in vacuo*, the residue was dissolved in a small amount of ethyl acetate and the solution was applied to 30 preparative tlc plates (20 x 20 cm and 2 mm thickness, silica gel PF_{254}, Merck). The plates were developed three times in a mixture of ether-petroleum ether 3:1 and five times in a mixture of ether-petroleum ether 5:1 resulting in the separation of the two major bands which were detected by uv light (254 mμ). The faster moving band gave a pale yellow syrup which was shown to be formed by a complex mixture of products. The crude product thus obtained was subjected to thick-layer chromatography (benzene-ethanol, 15:1, eight developments). The main fraction furnished a syrup which was crystallized from ether-cyclohexane to give 0.134 g. of IVa, m.p. 98°, $[\alpha]_D$ -20° (c 0.5, chloroform); uv λ max (ethanol), 285 mμ (ε, 7,120); nmr (deuteriochloroform, τ) 4.5 singlet (1H, vinylic proton), 1.56 (1H, NH group, $J_{NH,1'}$ 10 Hz).

Anal. Calcd. for $C_{20}H_{27}NO_{13}$: C, 49.07; H, 5.52; N, 2.86. Found: C, 49.23; H, 5.78; N, 3.08.

The slower moving band gave 1.94 g. of a colorless syrup. Subsequent purification of this product tlc using benzene-ethanol 15:1 afforded pure Va as a glass which could not be induced to crystallize, $[\alpha]_D$ -19.3° (c 0.8, chloroform); uv λ max (ethanol), 286 mμ (ε, 7,730); ir (nujol), 3,330 (NH), 1,560 cm^{-1} (C=N).

Anal. Calcd. for $C_{26}H_{35}N_3O_{17}$: C, 47.27; H, 5.33; N, 6.36. Found: C, 46.78; H, 5.31; N, 6.20.

Methyl *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-1-(3,4,5-tricarbomethoxy-Δ^2-pyrazolin-5-yl)glycinate (Vb).

A solution of 2 g. (0.013 mole) of dimethyl fumarate and 2.6 g. (0.0069 mole) of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide in 40 ml. of benzene was refluxed for 30 hours. The residue obtained after the removal of the solvent was purified by thick-layer chromatography (silica gel PF_{254}, Merck). After two consecutive developments with a mixture of ether-cyclohexane 5:1, from the slower moving band visualized with a uv lamp (254 mμ) a syrup was obtained. This material was rechromatographed (tlc benzene-ethanol 10:1) to give 2.07 g. (55% yield) of pure Vb which could not be crystallized, [α] -16° (c 0.7, chloroform); uv λ max (ethanol) 286 mμ (ε, 8,335); ir (nujol), 3.335 (NH), 1565 cm^{-1} (C=N).

Anal. Calcd. for $C_{26}H_{35}N_3O_{17}$: C, 47.27; H, 5.33; N, 6.36. Found: C, 47.22; H, 5.21; N, 6.41.

The same pyrazoline Vb was obtained when the glycosyl azide and the dimethyl fumarate were allowed to react in benzene at room temperature for two months, yield 15.5%.

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