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Note

Additions of acetylenecarboxylates to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose oxime*

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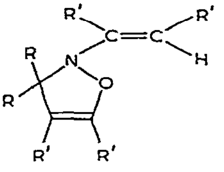
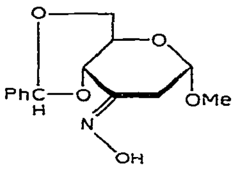
Ketoximes ($R_2C{=}NOH$) react with dimethyl acetylenedicarboxylate to give, in high yield, 1:2-adducts possessing the dihydroisoxazole structures[1] (**1**). An analogous reaction with oximes of glycopyranosiduloses should lead to products with the dihydroisoxazole ring spiro-linked to a pyranoid ring. These compounds might serve as precursors of branched-chain amino sugars with the amino group located at the branch point. Hence the possibility of applying this reaction in carbohydrate chemistry has been examined by studying the reactions of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose oxime (**2**) with dimethyl acetylenedicarboxylate and with ethyl propiolate (ethyl propynoate).



1 R′ = MeOC=O



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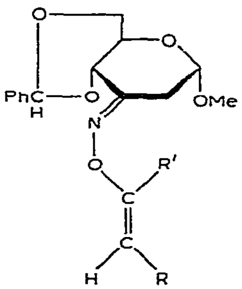
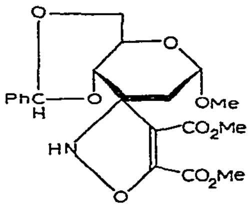


3 R = R′ = $MeCO_2$
5 R = $EtCO_2$, R = H



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The oxime **2** was prepared as described by Collins *et al.*[2]. Alternatively, it could be obtained in good yield by treatment of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose phenylhydrazone with a large excess of hydroxylamine hydrochloride in hot pyridine solution. Experiments with other phenylhydrazones

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*Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.

from glycosiduloses indicate that this route may be generally useful for the preparation of sugar oximes.

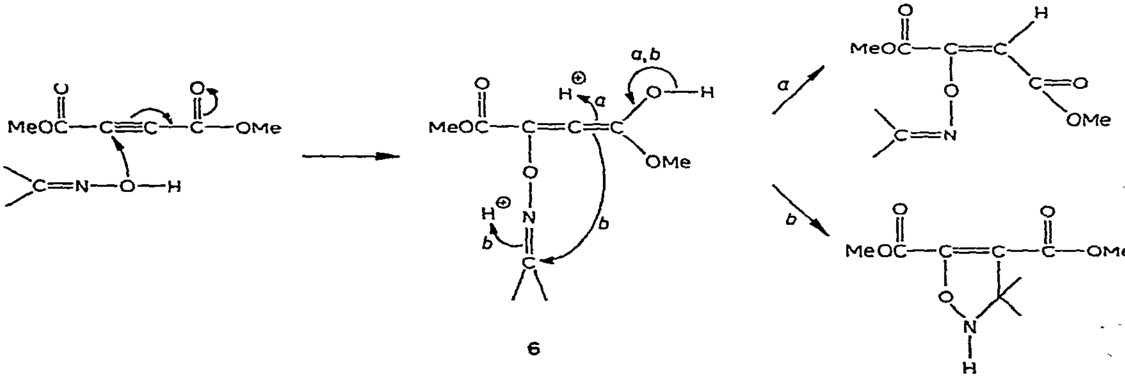
After treatment of the oxime **2** with dimethyl acetylenedicarboxylate in methyl sulphoxide for 4 days at room temperature, two solid products [*A*, m.p. 160° (major product); and *B*, m.p. 131–132°] were isolated. Attempts to accelerate the reaction by heating led to discolouration and decomposition.

On the basis of its elemental analysis, infrared absorption ($\alpha\beta$-unsaturated ester band), and n.m.r. spectra, compound *A* was considered to be the 1:1-adduct (**3**). The minor product *B* was shown to be the spiro-addition product (**4**), on the basis of its elemental analysis and spectral characteristics. This product is also a 1:1 adduct. The configuration at the spiro centre is not known.

The oxime **2** did not react with ethyl propiolate in methyl sulphoxide in the absence of catalyst, but in the presence of 1,4-diazabicyclo[2.2.2]octane, the *O*-substituted oxime **5** was formed in an exothermic reaction. The structure of **5** was also based on analytical and spectral evidence (see Experimental section). A cyclic addition product was not isolated in this reaction.

Thus, the reaction of the carbohydrate oxime **2** with acetylenecarboxylates differs from that of cyclohexanone oxime[1]. The formation of the cyclic 1:1 adduct with the dicarboxylate is more analogous, however, to the result obtained for the condensation of formaldehyde oxime with $\alpha\beta$-unsaturated esters[3], which has been shown to produce not only saturated, cyclic 2:1 adducts corresponding to **1**, but also some saturated 1:1 adducts corresponding to **4**. The reaction with oximes of carbohydrate derivatives now described differs from the earlier work most markedly, however, in leading to the formation of large amounts of addition products (*i.e.*, **3** and **5**). Compounds of this type were not observed with aliphatic oximes[1,3].

A route by which both of our products *A* and *B* could arise is shown in Scheme 1. The intermediate **6** formed by addition of the two reactants could be protonated as shown in path *a* or, after cyclisation, as shown in path *b*.



Scheme 1.

The low yield of cyclic product made this route to amino sugars unattractive and it was not pursued further.

EXPERIMENTAL

General methods. — I.r. spectra were measured on solid samples dispersed in potassium bromide, with a Perkin–Elmer Infracord Model 137. Optical rotations were measured for solutions in chloroform with a Bellingham and Stanley polarimeter. N.m.r. spectra at 60 and 100 MHz were determined, respectively, with Varian A-60D and HA-100D instruments. T.l.c. was carried out on silica gel with benzene–ethyl acetate (4:1).

*Methyl 4,6-O-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose oxime* (**2**). — (*a*) Prepared according to the method of Collins *et al.*[2], the oxime had m.p. 207°, $[\alpha]_D$ +200° (*c* 1).

(*b*) Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose phenylhydrazone (0.7 g; mixture of *syn* and *anti* forms) and hydroxylamine hydrochloride (4.2 g) were dissolved in pyridine (25 ml) and heated at 100° for 1 h. The solution was poured into water (200 ml), and the precipitate was collected, washed with water, and recrystallised from ethanol to give the oxime **2** (0.4 g, 73%) identical in all respects with the authentic material in (*a*).

Addition reactions of the oxime **2**. — (*a*) *With dimethyl acetylenedicarboxylate.* — The oxime (1.4 g) and dimethyl acetylenedicarboxylate (8.1 g) were dissolved in methyl sulphoxide (10 ml). After storage for 4 days at room temperature, most of the oxime had disappeared and two new main components were detectable (t.l.c.). The solution was diluted with dichloromethane (100 ml), washed with water (4 × 100 ml), dried ($MgSO_4$), filtered, and concentrated to a syrup. Crystallisation from toluene (50 ml) gave unreacted oxime (0.6 g). The mother liquors were concentrated to remove toluene, and excess of dimethyl acetylenedicarboxylate (5.3 g recovered) was eliminated by heating at 60° (bath)/0.01 mmHg. The residual syrup was again crystallised from toluene (10 ml) to give chromatographically homogeneous compound *A* (0.3 g) which, after recrystallisation from toluene, had m.p. 160° (dec.), $[\alpha]_D^{24}$ +123° (*c* 2); ν_{max} 1755, 1745, and 1650 cm^{-1} (strong bands), but no OH or NH absorption. The n.m.r. spectrum of *A* was similar to that of the oxime precursor, but in place of the hydroxyl-proton resonance there were three new singlets at τ 4.13 (vinylic proton), 6.13 and 6.30 (2Me of ester groups).

Anal. Calc. for $C_{20}H_{23}NO_9$: C, 57.0; H, 5.5; N, 3.3. Found: C, 57.2; H, 5.3; N, 3.3.

The mother liquors from the crystallisation were concentrated to a syrup from which minor impurities were removed by chromatography on a column of silica gel (200 g) with toluene–ethyl acetate (3:1). More of component *A* (0.6 g) was obtained together with a second substance (*B*). Repeated recrystallisation from dichloromethane–light petroleum, followed by ethanol–water, gave pure *B* (0.05 g), m.p. 131–132°, ν_{max} 3200 (N-H), 1750 s and 1650 cm^{-1} (unsaturated ester). The n.m.r. spectrum was consistent with a 1:1 adduct: τ 5.24 (*d*, $J_{1,2ax}$ 4.0, $J_{1,2eq}$<0.5 Hz, H-1); 7.90 (*d*, $J_{2eq,2ax}$ 14.5 Hz, H-2_{eq}) and 7.27 (*q*, $J_{2ax,1}$ 4.0, $J_{2ax,2eq}$ 14.5 Hz, H-2_{ax}); 6.0–5.5 (pyranoid H-4,5,6,6′); 4.4 (*s*, benzylidene); 3.2–3.5 (aromatic H); 6.14, 6.25, and 6.63 (3*s*, 3OMe); no vinylic protons.

Anal. Calc. for $C_{20}H_{23}NO_9$: C, 57.0; H, 5.5; N, 3.3. Found: C, 57.0; H, 5.4; N, 3.3.

(*b*) *With ethyl propiolate.* — When a solution of the oxime **2** (2.8 g) and ethyl propiolate (5 g) in methyl sulphoxide (10 ml) was kept for 3 days at ambient temperature, no reaction was detectable and so 1,4-diazabicyclo[2.2.2]octane (5 mg) was added. The solution immediately became hot and set solid. The cooled mixture was diluted with dichloromethane (150 ml) to give a clear solution which was washed with water (4 × 100 ml) and dried (Na_2SO_4). T.l.c. revealed no starting material and only one product. Evaporation yielded crystals which were recrystallised from ethanol and then twice from methanol. The product (1.6 g) had m.p. 158–159°, $[\alpha]_D^{24}$ +160° (*c* 2); ν_{max} strong bands at 1730, 1680, and 1650 cm^{-1}, but no NH or OH absorptions. The n.m.r. spectrum was similar to that of the oxime precursor, except that resonances for the ethyl ester function gave rise to a 3-proton triplet at τ 8.77 and a 2-proton doublet at τ 5.85. Two vinylic proton doublets were observed at τ 4.47 and 1.98, with a mutual coupling of 13.0 Hz which was taken to indicate *trans* disposition of these protons.

Anal. Calc. for $C_{19}H_{23}NO_7$: C, 60.5; H, 6.1; N, 3.7. Found: C, 60.4; H, 5.95; N, 4.0.

ACKNOWLEDGMENT

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