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SEVEN MEMBERED RING SUGARS. APPLICATIONS OF KNOEVENAGEL TYPE REACTIONS TO SUGARS.

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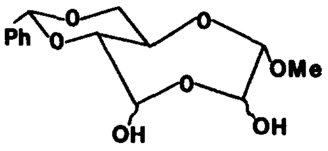
Although widely applied in aliphatic chemistry[1], little application of Knoevenagel-type reactions to sugars has been reported[2]. Glucose in suitably protected form, is readily converted to the hydrated dialdehyde (1) by periodate oxidation and we report double and single Knoevenagel reactions upon this compound as a means of formation of branched chain septanosides and dioxepans.

When compound (1) was treated with ethyl nitroacetate in the presence of sodium methoxide in methanol at 0°C, condensation did not occur. Various modifications of the reaction conditions were examined and finally the desired condensation was achieved by reaction of (1) with the sodium salt of ethyl nitroacetate in pyridine at room temperature. Under these conditions both potential aldehyde groups of compound (1) reacted with the nitroacetate, subsequent ring closure occuring to give a mixture of two products. The H^1nmr spectrum of the major product shows only one ethyl ester triplet at 9.1τ whereas microanalytical figures and mass spectral data show two nitro groups to be present. This suggests that this compound is the di-nitro septanoside (2) which has arisen by decarboxylation in the branched chain at C-4. Infra-red and microanalytical data indicate a molecule of water of crystallisation to be present. Similarly the minor product is found to be the anhydrous compound (3) in which the alternative decarboxylation at C-3 has occured. The H^1nmr spectrum of this compound reveals a triplet due to the ester group at 8.75τ. Methyl nitroacetate gave analogous products.

Ethyl and methyl cyanoacetates were also found to condense smoothly with compound (1) in pyridine, with either aqueous ammonium acetate or aqueous potassium hydroxide as base, although the latter gave superior yields. Initial condensation with both aldehyde groups with subsequent cyclisation, in analogous manner to the nitroacetate condensation, was observed, but no decarboxylation was found to occur. Single products were obtained in both cases, respectively the di-cyano sugars (4) and (5). The H^1nmr spectrum of compound (4) shows the C-3 ethyl ester triplet at 9.1τ and the C-4 branched chain ester triplet at 8.67τ. Furthermore the mass spectrum reveals a molecular ion and a major peak corresponding to loss of the branched chain at C-4. Malononitrile condensed with compound (1) in a similar fashion to give a high yield of the analogous tetra-cyano septanoside (6). In contrast diethyl malonate and cyanoacetamide did not react under these conditions which suggest that di-addition occurs when there are two strongly electron withdrawing groups attached to the methylene moiety of the condensing agent. This may be compared to the situation with nitroalkanes[3], having only one activating group which have been found to give only mono addition compounds.

It was also interesting to discover that attempts to introduce a very bulky group, viz. ethyl benzoyl acetate, into the same system, led to the substituted dioxepan (7) or (8) in low yield. At present there is insufficient evidence to establish which of these alternative structures corresponds to that of the isolated material. Ethyl phenyl acetate failed to react under similar conditions.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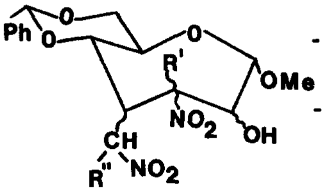
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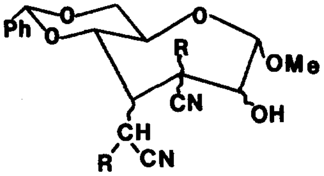
$R'' = H$
-3- $R' = H$
$R'' = CO_2Et$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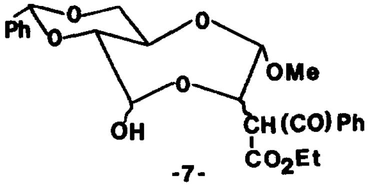
-5- $R = CO_2Me$
-6- $R = CN$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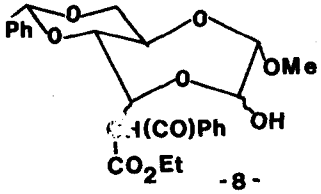
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