Tetrahedron. Vol. 33, pp. 1501 to 1507. Pergamon Press 1977. Printed in Great Britain

SEVEN AND EIGHT MEMBERED RING SUGARS AND RELATED SYSTEMS

THE SYNTHESIS OF SOME SEPTANOSE RINGS FROM DIOXEPANS[1,2]

MARTIN E. BUTCHER, JOHN C. IRESON, J. BARRY LEE and MICHAEL J. TYLER

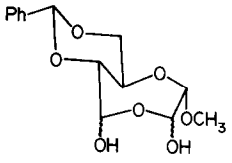
The School of Natural Sciences, The Hatfield Polytechnic, Bayfordbury Research Laboratories, Hertford SG13 8LD, England

(*Received in the UK* 21 *December* 1976; *Accepted for publication* 27 *January* 1977)

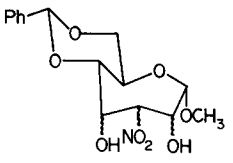
Abstract—The condensation of nitroalkanes with dihydroxydioxepans derived from the periodate oxidation of sugar derivatives has been studied. The nature of the products obtained, namely 3-deoxy-3-nitroheptoseptanosides and 7- and 9-substituted nitroalkyl-dioxepans depended on the nitroalkane used, the basic catalyst and the solvent. Condensations with nitroacetate, cyanoacetate and malonoitrile gave nitro- and cyano-3,4-dideoxyseptanoside derivatives. These reactions could provide routes to novel amino-sugars.

Although pyranose and furanose systems have been extensively studied the larger septanose and octanose rings are hardly known in sugar chemistry. The complex stereochemical effects upon reactivity in the smaller rings have been extensively rationalised and these larger rings offer an interesting challenge both in preparation and in similar rationalisation of reactivity. Biochemical and biological effects may also be observed as an additional spin off.

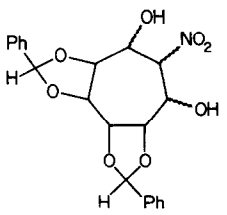
This paper is concerned with the synthesis of some branched-chain 7-member ring sugars containing nitro and cyano groups: these potentially provide routes to novel aminoglycoside systems, analogues of many well-known antibiotics. Their generation by condensations of dioxepans with active methylene compounds is described below together with some interesting effects which govern the formation of dioxepan versus branched chain septanose products.



1



2



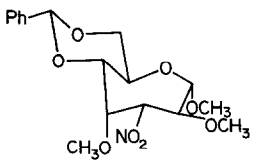
3

RESULTS AND DISCUSSION

Little work appears in the literature relating to the synthesis of glycosides containing the septanoid ring. Baschang[3] in 1963 reported the synthesis of methyl 5,7 - *O* - ethylidene - 3 - deoxy - 3 - nitro - α - D-*manno*-heptoseptanoside in 41% yield from cyclisation of the periodate oxidation product of methyl 4,6 - *O* - ethylidene - α - D - glucopyranoside with nitromethane in the presence of sodium methoxide. Later Wolfrom *et al.*[4] applied the cyclisation method to the periodate oxidation product of 4,6 - *O* - benzylidene - α - D - glucopyranoside **1** to obtain a mixture of four isomeric methyl 5,7 - *O* - benzylidene - 3 - deoxy - 3 - nitroheptoseptanosides **2**. Nitromethane has also been found to cyclise with 2,3:4,5 - di - *O* - benzylidene - L - *manno*-hexodialdose,[5] again in the presence of methoxide ions to give a mixture of 1,2:6,7 - di - *O* - benzylidene - 4 - deoxy - 4 - nitrocycloheptitol diastereoisomers **3**.

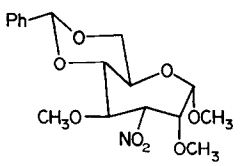
Wolfrom's synthesis of the notroheptoseptanosides was repeated and an 80% overall yield was obtained with the isomer melting at 233–234° being that most readily crystallisable. We also obtained the 2,4-di-*O*-methyl derivative by heating **2** under reflux in methanol. Wolfrom also reported that TLC of the reaction mixture showed the presence of two other products but they were not separated and identified. We separated the major product **4** by crystallisation and subsequent column chromatography of the mother liquor gave two further crystalline products **5** and **6**. Elemental analysis for **5** was consistent with a 2,4-di-*O*-methyl derivative, presumably an isomer of **4**, whereas the elemental analysis of **6** was consistent with a mono-methyl derivative.

Although Wolfrom reported the PMR spectrum for **4** he did not make any structural assignments. The C-3 proton was a doublet of doublets (J 6.0 Hz and 1.5 Hz) at



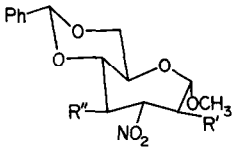
4a

D-Glycero-α-D-Altro



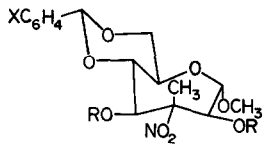
4b

D-Glycero-α-D-Gulo



5 R′=R″=OCH_3
6 R′=OH, R″=OCH_3 or R′=OCH_3, R″=OH

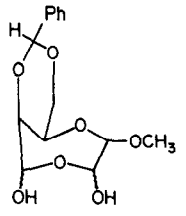
5.13τ; these coupling constants indicated that the dihedral angle of one adjacent proton was large and the other was smaller (axial–axial and axial–equatorial coupling respectively) suggesting either the D-*glycero*-α-D-*altro* **4a** or D-*glycero*-α-D-*gulo* **4b** configurations assuming the bulky nitro group occupies the more favourable equatorial position. The C-1 proton resonated as a doublet at 5.10τ ($J_{1,2}$ 6 Hz); as the C-1 proton is equatorial the coupling constant suggested a large dihedral angle and thus that the C-2 proton was pseudo axial allowing for some deformation of the ring. With the C-2 proton axial $J_{2,3}$ would have the larger coupling constant (6 Hz) and $J_{3,4}$ would have the smaller one (1.5 Hz) and thus **4** would have the D-*glycero*-α-D-*altro* configuration. The *altro* configuration is more favourable since considerable steric crowding of the methoxy groups at C-1 and C-2 (both axial) occurs in the *gulo* case. The stereochemistry of **5** could not be determined directly from its PMR spectrum. Treatment with *N*-bromosuccinimide under standard conditions gave the 5 - *O* - benzoyl - 7 - bromo - 7 - deoxy compound. This compound showed three distinct singlets, assignable to the three methoxy groups at 6.4, 6.55 and 6.65τ. The C-5 proton (which is axial) resonated at 4.73τ as a doublet of doublets (J 10.0 Hz and 8.5 Hz) which suggested that H_6 and H_4 were psuedo axial as the large coupling constants require dihedral angles approaching 180°. The C-3 proton resonated at 5.2τ as a doublet (J 10 Hz) which suggested that both H_2 and H_4 split H_3 to an equal extent and the large coupling constant again indicated a dihedral angle close to 180°; as H_4 is already fixed as pseudo axial, both H_2 and H_3 must also be pseudo axial. Thus the methoxy groups at C-2 and C-4 and the nitro group must lie equatorially, therefore **5** has the D-*glycero*-α-D-*ido* configuration. The PMR spectrum of **6** showed two methoxy resonances at 6.5 and 6.6τ; it also showed a double at 5.45τ (J 9.0 Hz) assigned to H-3 and a doublet at 5.40τ ($J_{1,2}$ 5.5 Hz) assigned to H_1. The coupling constant between H_1 and H_2 suggested that H_2 is pseudo axial as H_1 was fixed as equatorial; the fact that H_3 was equally split by H_2 and H_4 and that the coupling constant was large indicated that H-3 and H-4 were also pseudo axial, and hence the groups at C-2,3 and 4 were all equatorial, i.e. the D-*glycero*-α-D-*ido* configuration. It was not possible from the PMR spectrum to determine whether C-2 or C-4 carried the methoxy group. Nitroethane is known to condense with sugar dialdehydes giving 3 - deoxy - 3 - *C* - methyl - 3 - nitro-hexopyranosides.[6] A smooth reaction between **1** and nitroethane occurred in methanol in the presence of sodium methoxide giving a single isomer **7**, the stereochemistry of which could not be assigned from the PMR spectrum. However acetylation gave the 2,4-di-*O*-acetyl derivative **8**; the PMR spectrum of **8** showed the C-2 and C-4 protons at low field, as doublets, both with large coupling constants ($J_{1,2}$ 7 Hz and $J_{4,5}$ 9 Hz). H_5 is known to lie axially thus the large coupling constant with H_4 indicated a large dihedral angle with H_4 lying axially (thus the large acetyl group equatorial). Similarly H_1 is known to lie equatorial, and the coupling constant indicated that H_2 lies axially (and thus the large acetyl group is again equatorial). Also the acetyl protons showed coincident resonances at 8.03τ which indicated similar steric dispositions.



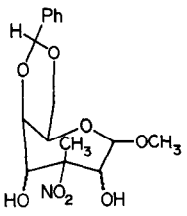
7 R=H, X=H
8 R=CH_3CO, X=H
12 R=H, X=NO_2

The stereochemistry at C-3 however cannot be determined from the PMR spectrum; **7** and **8** have either D-*glycero*-α-D-*ido* or D-*glycero*-α-D-*talo* configurations. The larger size of the nitro group will presumably favour, a pseudo-equatorial rather than axial arrangement. Treatment of the dioxepan from methyl 4,6-benzylidene-β-D-galactopyranoside **9** with nitroethane under the same conditions gave isomers of methyl 5,7 - *O* - benzylidene - 3 - deoxy - 3 - *C* - methyl - 3 - nitro - β - D - heptoseptanoside **10**. Acetylation gave the 2,4 - di - *O* - acetyl derivative which crystallised; its broad melting point suggested that it was more than one isomer. This galactose derivative differs from that from glucose in the stereochemistry of the ring fusion of the benzylidene group and the stereochemistry of the anomeric centre.

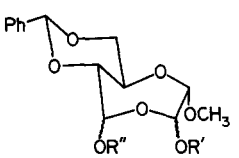
Treatment of **1** with 1-nitromethyl cyclohexene and sodium methoxide in methanol gave 9 - hydroxy - 6 - α - methoxy - 7 - methoxy - 2 - phenyl - *trans* - *m* - dioxano - (5,4 - *e*)(1,4) - dioxepan or the 9 - methoxy - 7 - hydroxy isomer **11**, that is, the dialdehyde methanolate.[7] This compound is known to be formed when the dialdehyde is heated under reflux with methanol. It would appear that the formation of methanolate completes with the active methylene condensation, and bulky compounds such as 1-nitromethyl cyclohexene do not react sufficiently rapidly. Compound **11** was the sole product when condensations with ω-nitrostyrene and ethyl nitroacetate were attempted. This reaction has not previously been reported under such mild consitions (0° in methanol); further investigation showed that quantitative yields of **11** could be obtained by reaction of **1** with an equivalent amount of sodium methoxide for about 30 min at 0°.



9

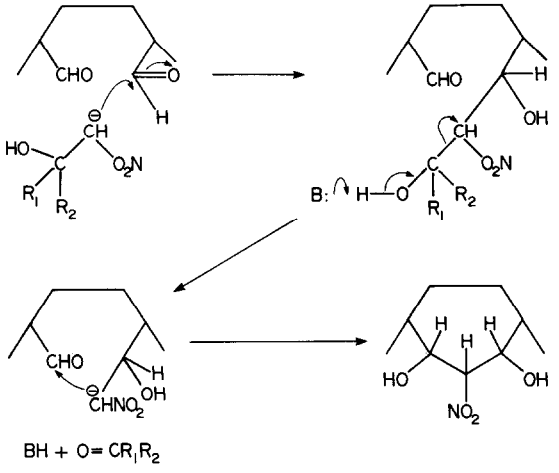


10



11 R′=CH_3, R″=H or R′=H, R″=CH_3

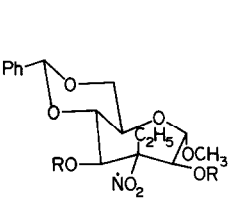
Treatment of **1** in methanol with the sodium salt of 1-nitromethyl cyclohexanol give a yellow oil which smelt of cyclohexanone, the presence of which was confirmed by TLC. Also the oil was shown to contain the known isomers of methyl 5,7 - *O* - benzylidene - 3 - deoxy - 3 - nitro - α - D - heptoseptanosides **2**. Reaction of other β-hydroxynitro compounds such as 1 - nitropentan - 2 - ol and 1 - nitrohexan - 2,6 - diol gave isomers of **2** together with the appropriate carbonyl compound. Base attack on the hydroxy group subsequent to condensation of the nitro compound with one of the aldehydic groups is a possible mechanism for this breakdown.



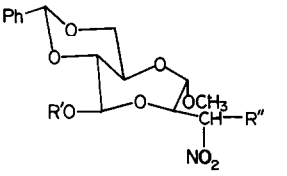
Scheme 1.

A drawback to condensations with **1** is the fact that it is not very soluble in alcohols and competitive reaction with alkoxide ion occurs. The reaction of **1** with nitroethane in pyridine and in DMF in the presence of an equivalent of sodium methoxide was investigated. In pyridine a superior yield of **7** as a single isomer was obtained; reaction in DMF proceeded identically but in slightly lower yield. Treatment of the periodate oxidation product of methyl 4,6 - *O* - *p* - nitrobenzylidene - α - D - glucopyranoside in pyridine gave a single isomer of **12** in good yield. Treatment of **1** with nitromethane in pyridine gave the four known isomers of **2** as in methanol. Reaction of nitromethane in pyridine with **9** (derived from methyl 4,6 - *O* - benzylidene - β - D - galactopyranoside) gave two isomers of the expected product, one of which was isolated by recrystallisation. Reaction of nitroethane in pyridine with the periodate oxidation products of methyl 4,6 - *O* - *m*- and methyl 4,6 - *O* - *p* - nitrobenzylidene - α - D - glucopyranosides gave in one case two isomers which could not be separated and in the other two isomers of the expected product one of which was isolated on recrystallisation respectively.

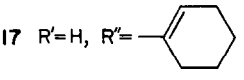
In contrast, when reaction of **1** with 1-nitropropane and sodium methoxide in pyridine was examined, whilst the major product was found to be the expected methyl 5,7 - *O* - benzylidene - 3 - deoxy - *C* - ethyl - 3 - nitro - α - D - heptoseptanoside **13** in addition a second product, shown to have the dioxepan structure **14** was formed in reasonable amount. Acetylation of **13** gave the 2,4 - di - *O* - acetyl derivative **15** the PMR spectrum of which was similar to **8** (the 3 - *C* - methyl analogue); the spectrum showed that the acetyl groups were again equatorial. Inspection of a model of **13** showed that, when the ethyl group was axial and the nitro group equatorial, the ethyl group would experience serious steric crowding from neighbouring groups thus restricting free rotation. This is supported by the PMR spectrum which shows a complex signal for the CH_2 group of the ethyl group rather than the usual sharp quartet; Lichtenthaler *et al.*[8] has reported that the cyclisation of 1-nitropropane with gluteraldehyde to give 1 - nitro - 1 - ethyl-cyclohexanediol; in this case where steric crowding is negligible the ethyl CH_2 group is seen as a sharp quartet. This indicates that **13** has the configuration with the ethyl group axial. As a methyl group is less bulky than an ethyl group it is almost certain that **8** (the 3 - *C* - methyl analogue) has the configuration with the methyl group axial.



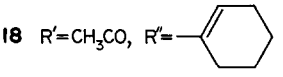
13 R=H
15 R=CH_3CO



14 R'=H, R''=C_2H_5
16 R'=CH_3CO, R''=C_2H_5



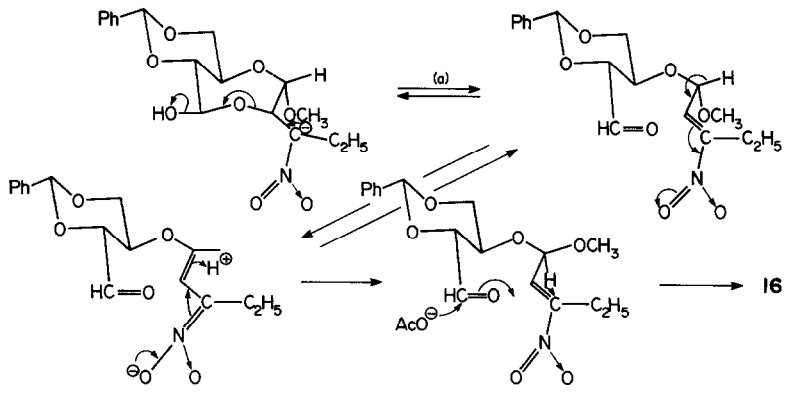
17 R'=H, R''=



18 R'=CH_3CO, R''=

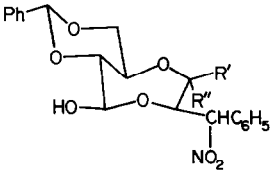
The second product was the dioxepan derivative **14**. The formation of this in the nitropropyl case but not in the nitroethyl case is clearly because this structure **14** gives some relief of the steric crowding resulting from the exchange of ethyl for methyl; this presumably shifts the balance of thermodynamic stability more in favour of the dioxepan structure in this case. The PMR spectrum of **14** showed H_6 and H_7 to be coupled by 6 Hz which indicated a fairly large dihedral angle and thus the large 1-nitropropyl side chain in the more favourable equatorial position. Acetylation of **14** gave the mono-acetoxy derivative **16**; in the PMR spectrum H-6 was not coupled to the proton on the carbon atom bearing the acetoxy group thus ruling out the alternative possible dioxepan structure (the 9 - (1 - nitropropyl) - 7 - hydroxy compound). The coupling constant of 8 Hz for H_9 suggested that the acetyl group was also equatorial. Close examination of the spectrum revealed the presence of two methoxy singlets at 6.55 and 6.64τ indicative of the presence of the 6α and 6β compounds respectively; the coupling constants between H_1 and H_2 were consistent with the 1-nitropropyl group being equatorial. The presence of the 6α and 6β compounds was confirmed by TLC. When acetylation was carried out under acidic conditions the 6α-anomer was the sole product, thus the epimerisation must have been base catalysed. A possible mechanism is postulated; analogies to the first step (a) are found in base catalysed epimerisation at the α-carbon found[9] in certain nitrohexopyranoside systems.

When attempts were made to react nitro-compounds containing larger groups with the dialdehyde under the same conditions, i.e. with one mol of methoxide present, reaction with methoxide again became dominant. Thus 1-nitromethyl cyclohexene failed to react with **1** in the presence of sodium methoxide in pyridine. When the sodium salt of 1-nitromethyl cyclohexene in pyridine was used under otherwise similar conditions, a

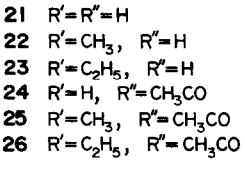


Scheme 2.

30% yield of the 9 - hydroxy - 7 - (cyclohexenyl-nitromethyl) dioxepan **17** was obtained. The PMR spectrum showed H_6 as a doublet at 5.25τ ($J_{6,7}$ 7 Hz) which indicated that the cyclohexenylnitromethyl group was pseudo axial as the C-6 proton is known to be equatorial. The nitromethine proton was a doublet of doublets split by the olefinic ring proton and H_7 (J 7 and 2 Hz). Acetylation in pyridine again gave a mixture of the 6α- and 6β-methoxy epimers **18** as in the 7(1 - nitropropyl) - dioxepan case. The proton on the carbon carrying the acetoxy group was again not coupled to H_6 confirming that **17** was the 9 - hydroxy - 7 - (cyclohexenylnitromethyl) isomer. This further supports the suggestion that nitro compounds containing a large bulky group tend to condense directly with only one of the aldehydic groups of **1**. When sodio-phenyl nitromethane and **1** were reacted in pyridine, the 7-substituted dioxepan structure was again obtained, but in this case a mixture of the 6α**19**- and 6β**20**-isomers were formed (the α-form being slightly more abundant); these were separated by column chromatography. The epimerisation in this case probably takes place faster than in the cases of **14** and **17** because of the increased stability of the unsaturated intermediate. In the PMR spectrum the methoxy CH_3 resonances of the α and β forms were seen at 6.55τ and 7.27τ respectively, the large difference as compared with the cases of **15** and **18** being the result of shielding by the aromatic ring; Guthrie *et al.*[10] observed a similar intramolecular shielding effect due to the 2-tosyl group on the β-methoxy group of methyl 4,6 - *O* - benzylidene - 2 - *O* - (4 - tolylsulphonyl) - β - D - allopyranoxide, but no effect is shown on the α-epimer. Acetylation of a mixture of **19** and **20** (in pyridine) gave mainly the β-epimer; in the PMR spectrum the coupling constant of 8.0 Hz for H_9 at 4.15τ indicated that the acetoxy group was equatorial.

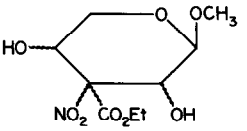


19 R′=H, R″=OCH_3
20 R′=OCH_3, R″=H



21 R′=R″=H
22 R′=CH_3, R″=H
23 R′=C_2H_5, R″=H
24 R′=H, R″=CH_3CO
25 R′=CH_3, R″=CH_3CO
26 R′=C_2H_5, R″=CH_3CO

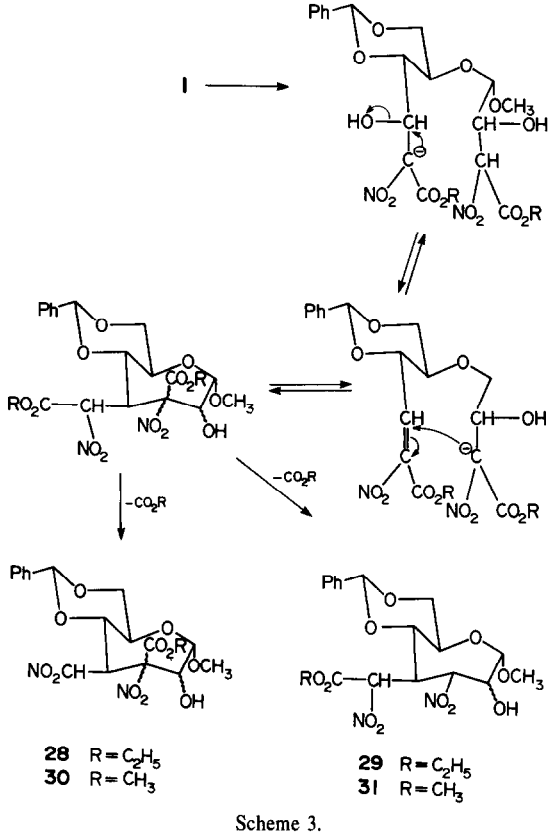
Since the strength and type of the base catalyst could conceivably affect the reaction, the use of aqueous potassium hydroxide instead of methoxide was examined. Reaction of **1** with nitromethane, nitroethane and nitropropane gave rise to a series of 7 - hydroxy - 9 - (1 - nitroalkyl) dioxepan derivatives (**21–23**) which were mono-acetylated to give **24–26**. In the cases of **22** and **23** two isomers presumably of different configuration at C-7 (in view of the bulk of the nitroalkyl side chain at C-9) were formed which were separated by PLC. In the case of **21** only one isomer was formed together with small amounts of three of the isomeric forms of **2**; the latter were separated by fractional crystallisation from ethanol. The PMR spectrum of **22** (the nitroethane product) showed a methyl signal at 8.4τ as a doublet (J 7 Hz) which clearly showed that it was part of the side chain. On acetylation of **21–23** in pyridine, no epimerisation at C-6 was observed indicating that the branched chain was at C-9. The PMR spectra of these monoacetoxy derivatives (**24–26**) showed in each case that the proton on the carbon carrying the acetoxy was coupled to H_6 and was pseudo equatorial (J 6–7 Hz), and thus that the branched chains were at C-9. The reason for the formation of the two different substituted form of dioxepan is obscure, but it is clear that, with condensation of **1** with nitroalkanes, the nature of the products is greatly affected by steric effects, the nature of the products is greatly affected by steric effects, the nature of the base catalyst and the solvent. The addition of ethyl nitroacetate to sugar dialdehydes has been reported in the hexose series giving 3 - deoxy - 3 - ethoxycarbonyl - 3 - nitropyranosides; Yanagisawa's group[11] have condensed the periodate oxidation product of β-L-arabinopyranoside with ethyl nitroacetate to give isomeric mixtures with the general formula **27**. However such additions to **1** have not been reported; this would appear to be a convenient route to sugar systems containing both amino and carboxylic functions.



27

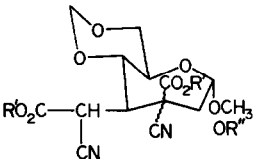
Ethyl nitroacetate did not react with **1** in methanol using methoxide as base because of the competitive formation of the dialdehyde methanolate (see earlier),

but the reaction proceeded smoothly in pyridine when the sodium salt of the nitro compound was used. In sharp contrast to the reactions with nitroalkanes two equivalents of nitroacetate condensed with one mole of **1** to give a crystalline product, which was shown to be a mixture of two components (**28**, **29**). The components were separated by column chromatography and crystallisation from ethanol; the ratio of isolated compounds **28**–**29** was 13:1. Elemental analysis showed two nitro groups to be present, but only one ester group; this was confirmed by mass spectroscopy (molecular ion at *m/e* 456). A possible reaction mechanism which involves condensation with 2 moles of ethyl nitroacetate, cyclisation and decarboxylation is outlined. The major product was assigned structure **28** as follows. The PMR spectrum of ethyl nitroacetate itself shows the CH_3 ethyl ester signal as a triplet at 8.75τ. In the structure **28** the ester group is directly attached to the ring and will be under considerable steric strain which will have the effect of pushing the methyl signal upfield; the major product **28** did show a triplet at 9.13τ. Conversely the minor product **29** where the ester is less hindered showed a triplet at 8.75τ. The major product **28** showed in its PMR spectrum two doublets (integrating for 2 protons) at 5.04 and 4.88τ which were assigned to the non-equivalent methylene protons at C-4 (J 10 Hz). It is very likely that the bulky branched chain at C-4 in both cases was pseudo equatorial.

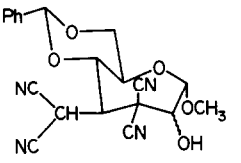


Scheme 3.

Analogously, addition of the sodium salt of methyl nitroacetate to **1** gave two products, **30** and **31**, methyl analogues of **28** and **29**. These findings suggest that a carbanion reagent which contains two strongly electron widtdrawing groups will react with both aldehyde groups of dialdehyde **1**. The sodium salt of a nitroacetamide was found not to react at all. The addition of alkyl cyanoacetates, which in basic conditions also give a carbanion (to which is attached two electron withdrawing groups), to "sugar dialdehydes" or dioxepans such as **1** has not been reported. Ethyl cyanoacetate reacted smoothly at 0° with **1** in pyridine containing one equivalent of aqueous potassium hydroxide, but no reaction took place when sodium methoxide was used as base. The sole product was bound to be methyl 5,7 - *O* - benzylidene - 3 - cyano - 2,4 - dideoxy - 3 - ethoxycarbonyl - 4 - ethoxycarbonylcyanomethyl - α - D - heptoseptanoside **32** in one isomeric form. Elemental analysis and the PMR spectrum showed the presence of two nitro and two ester groups; the mass spectrum showed the molecular ion at *m/e* 488. This emphasises the difference in stability between nitroacetates and cyanoacetates. As before the triplet at 9.10τ was assigned to the ethyl ester at C-3 and the one at 8.67τ to the ethyl ester in the branched chain at C-4. The amoneric proton was observed clearly at 5.25τ as a doublet ($J_{1,2}$ 6.5 Hz) indicating that the hydroxy group at C-2 is pseudo equatorial; presumably because of its bulk, the branched side chain at C-4 will also be pseudo equatorial. Methyl cyanoacetate reacted in a similar manner to give **33** which was acetylated to give **34**. The PMR spectrum showed H_2 to be coupled to H_1 ($J_{1,2}$ 7 Hz) confirming that the acetoxy group was at C-2 ruling out the alternative structure with the methoxycarbonylcyanomethyl group at C-2. Similar treatment of the periodate oxidation product of methyl 4,6 - *O* - *p* - nitrobenzylidene - α - D - glucopyranoside with methyl cyanoacetate under the same conditions also gave a single isomer of the product; the periodate oxidation product of methyl 4,6 - *O* - benzylidene - β - D - galactopyranoside **9** under the same conditions gave an oil. We have often found that the products derived from galactose are more difficult to handle.



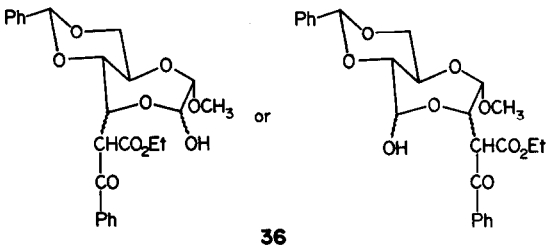
32 R′=C_2H_5, R″=H
33 R′=CH_3, R″=H
34 R′=CH_3, R″=CH_3CO



35

Malononitrile also readily condensed with the dialdehyde **1** under the influence of potassium hydroxide giving a high yield (90%) of one isomer of methyl 5,7 - *O* - benzylidene - 3,4 - dideoxy - 3 - dicyano - 4 - dicyanomethyl - α - D - heptoseptanoside **35**. Again the carbanion has condensed with both aldehyde groups. The PMR spectrum showed the anomeric proton at 5.37τ as a doublet (J 6.5 Hz) indicating that the hydroxyl group at C-2 was pseudo equatorial; because of its bulk the dicyanomethyl group at C-4 will also be pseudo equatorial. Diethyl malonate did not condense at all with dialdehyde **1** under the influence of potassium hydroxide. Ethyl benzoylacetate, which stabilises the carbanion to a slightly greater extent than diethyl malonate condensed with in the presence of potassium hydroxide to give a low yield of the monoaddition product **36**. The PMR spectrum could not distinguish between the two possible isomers; all attempts to acetylate **36** led to decom-

position. By analogy to the nitroalkanes, the 9-substituted isomer is the most likely structure. The behaviour of ethyl benzoylacetate is in contrast to that of alkyl cyano- and nitroacetates and malononitrile but presumably the increased size of the benzoyl group prevents the occurrence of the dicondensation.



36

Compounds which do give carbanions but do not condense with **1** are ethyl acetoacetate, ethyl benzylacetate, 2-nitrobenzylacetate, phenyl acetonitrile (contrast with phenyl nitromethane) and 4-chlorophenyl acetonitrile.

This work, in general terms, shows that the usual activation criteria in carbanion condensations apply in these examples with dioxepans, but stereochemical factors also show large effects in determining the structure of the products formed, as does the use of different base systems. These reactions also provide routes to novel sugar derivatives (particularly amino sugars).

EXPERIMENTAL

Elemental analyses were carried out either at the National Physical Laboratory, Teddington, Middx. or at Pfizer Ltd, Sandwich, Kent. Melting points were taken using a Kofler hot-stage apparatus and are all uncorrected. IR spectra were recorded on a Perkin–Elmer 257 spectrophotometer. Solids were examined as Nujol mulls and liquids as thin films. PMR spectra were recorded on a Varian A60A spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used in recording these spectra: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet, hex, sextet; m, multiplet. Sodium methoxide solutions refers to 3 g of sodium dissolved in 100 ml of methanol. Solvents were dried, where required, by standard methods. Petroleum ether refers to the 60–80° boiling range. TLC and PLC were performed on Kieselgel G (type 60); detection of spots was with iodine. The solvent systems were: (a) methanol:benzene 1:9 (b) ethylacetate:petroleum ether 1:1.

Reaction of methyl 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - *nitro* - *α* - D - *heptoseptanosides* **2** *with methanol*

The isomeric mixture of methyl 5,7 - *O* - benzylidene - 3 - deoxy - 3 - nitro - *α* - D - heptoseptanosides **2** (2.5 g) was heated under reflux in methanol for 72 h. The solvent was removed giving a pale yellow oil from which was crystallised the known methyl 5,7 - *O* - benzylidene - 3 - deoxy - 2,4 - di - *O* - methyl - 3 - nitro - *α* - D - heptoseptanoside **4** (840 mg, 31%) m.p. 183–185° (lit.[4] 184–185°) ν_{max}: 1550 (NO_2), 760 and 737 (Ar) cm^{-1}. τ ($CDCl_3$): 6.58, 6.54 and 6.41 (9H, 3xs, OCH_3), 6.3–5.0 (8H, m, H_{1-7}) 5.44 (1H, s, C_6H_5CH) and 2.75–2.5 (5H, m, C_6H_5).

The mother liquors were evaporated and chromatographed on a silica gel column eluted with chloroform and petroleum ether to give a white crystalline material (67 mg, 2.5%) m.p. 148–150° which was shown to be a different isomeric form of methyl 5,7 - *O* - benzylidene - 3 - deoxy - 2,4 - di - *O* - methyl - 3 - nitro - *α* - D - heptoseptanoside **5**. ν_{max}: 1565 (NO_2), 760 and 750 (Ar) cm^{-1}. τ ($CDCl_3$): 6.55 (6H, s, 2 × OCH_3), 6.45 (3H, s, OCH_3), 6.4–5.0 (8H, m, H_{1-7}) 4.5 (1H, s, C_6H_5CH), 2.6 (5M, s, C_6H_5). (Found: C, 55.21; H, 6.29; N, 3.58. $C_{17}H_{23}NO_8$ requires: C, 55.29; H, 6.23; N, 3.79%).

A further white crystalline solid was then obtained (63 mg, 2.3%) m.p. 190–192° which was shown to be either methyl 5,7 - *O* - benzylidene - 3 - deoxy - 2 - *O* - methyl - 3 - nitro - *α* - D - heptoseptanoside or the 4-*O*-methyl isomer **6** ν_{max}: 3480 (OH) and 1575 (NO_2) cm^{-1}. τ (DMSO-d_6): 6.6 (3H, s, OCH_3), 6.5 (3H, s, OCH_3), 6.5–5.0 (8H, m, H_{1-7}) 4.45 (1H, s, C_6H_5CH), 3.75 (1H, d, J 6.5 Hz, OH) and 2.6 (5H, s, C_6H_5). (Found: C, 53.74; H, 6.00; N, 3.86. $C_{16}H_{21}NO_8$ requires: C, 54.08; H, 5.96; N, 3.94%).

Methyl 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - C - *methyl* - 3 - *nitro* - *α* - D - *heptoseptanoside* **7**

Dialdehyde **1** (632 mg, 0.002 mole) and nitroethane (150 mg, 0.002 mole) were stirred at 0° in methanol (15 ml); sodium methoxide solution (1.5 ml) was added dropwise, and the solution gradually became clear. After stirring for a further 2 h and deionisation with resin, removal of the solvent gave a yellow oil from which the desired product was recrystallised from chloroform and petroleum ether (261 mg, 38%) m.p. 219–221°. TLC (solvents a and b) showed only one isomer to be present. ν_{max}: 3420 (OH) and 1560 (NO_2) cm^{-1}. τ (DMSO-d_6): 8.3 (3H, s, CH_3), 6.6 (3H, s, OCH_3), 5.6–6.5 (8H, m, H_{1-7} and 2 × OH), 5.6 (1H, d, J 7 Hz, H_1), 4.5 (1H, s, C_6H_5CH) and 2.6 (5H, m, C_6H_5). (Found: C, 53.75; H, 5.84. $C_{16}H_{21}O_8N$ requires: C, 54.08; H, 5.92%).

Acetylation in pyridine at 5° gave the diacetyl derivative, *methyl* - 2,4 - *di* - O - *acetyl* - 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - C - *methyl* - 3 - *nitro* - *α* - D - *heptoseptanoside* **8** which was recrystallised from ethanol m.p. 187–189°. ν_{max}: 1770, 1760 (C=O), 1555 (NO_2) and 770 (Ar) cm^{-1}. τ ($CDCl_3$): 8.15 (3H, s, CH_3), 8.05 (6H, s, $OCOCH_3$), 6.6 (3H, s, OCH_3), 5.7–6.5 (4H, m, $H_{5,7}$), 5.5 (1H, d, $J_{1,2}$ 7 Hz H_1), 4.55 (1H, s, C_6H_5CH), 4.1 (1H, d, $J_{2,1}$ 7 Hz H_2), 3.95 (1H, d, $J_{4,5}$ 9 Hz, H_4) and 2.6 (5H, s, C_6H_5). (Found: C, 53.41; H, 6.03. $C_{20}H_{25}O_{10}N$ requires: C, 53.21; H, 6.03%).

Attempted reaction between **1** *and* 1-*nitromethyl cyclohexane in methanol*

Sodium methoxide solution (1.5 ml) was added dropwise to dialdehyde **1** (632 mg) and 1-nitromethyl cyclohexene (282 mg) in dry methanol (30 ml) which was then stirred for 1.5 h. After deionisation and removal of the solvent, the crude reaction product gave unchanged 1-nitromethyl cyclohexene and 9 - *hydroxy* - 6 - *α* - *methoxy* - 7 - *methoxy* - 2 - *phenyl* - trans - m - *dioxano* - (5,4 - e) (1,4) - *dioxepan* or its 9 - *methoxy* - 7 - *hydroxy* isomer **11** (402 mg, 64%) m.p. 153–154° (lit.[7] 153°). (Found: C, 57.87; H, 6.42. Calc. for $C_{15}H_{20}O_7$: C, 57.69; H, 6.41%). ν_{max}: 3420 (OH) 760 and 710 (Ar) cm^{-1}. τ (DMSO-d_6): 6.6 and 6.65 (6H, 2 × s, OCH_3), 5.0–6.5 (8H, m), 4.45 (1H, s, C_6H_5CH) and 2.6 (5H, s, C_6H_5). Condensations with *ω*-nitrostyrene and ethyl nitroacetate gave **11** as the sole product.

Condensation between **1** *and* 1-*nitromethyl cyclohexanol in methanol*

Reaction under the conditions of the previous experiment gave cyclohexanone and the isomeric *methyl* 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - *nitro* - *α* - D - *heptoseptanosides* **2**.

Preparation of methyl 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - C - *methyl* - 3 - *nitro* - *α* - D - *heptoseptanoside* **7** *in pyridine*

Sodium methoxide solution (1.5 ml) was added dropwise to a stirred solution of dialdehyde **1** (632 mg) and nitroethane (150 mg) in pyridine (15 ml); the solution became cloudy and pale yellow in colour. After 0.5 h water (5 ml) was added (the solution became clear), and stirring was continued for a further 0.5 h. After deionisation the solution was poured into cold 1 M H_2SO_4 (200 ml) followed by extraction with chloroform (3 × 75 ml); the extract afforded a 60% yield of **7**. A 52% yield of **7** was obtained using DMF as the solvent.

Reaction between **1** *and* 1-*nitropropane in pyridine using sodium methoxide as base*

This reaction was carried out as in the previous experiment. The crude reaction product was fractionally crystallised from ethanol giving two products. The first was identified as *methyl* 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - C - *ethyl* - 3 - *nitro* - *α* - D - *heptoseptanoside* **13** (184 mg, 34.3%) m.p. 188–190°. (Found: C, 54.85; H, 6.09; N, 3.24. $C_{17}H_{23}O_8N$ requires: C, 55.14; H, 6.22; N, 3.78%). ν_{max}: 3400 (OH), 1550 (NO_2) and 748 (Ar) cm^{-1}. τ ($CDCl_3$): 8.97 (3H, t, J 7 Hz, CH_2CH_3), 7.86 (2H, m, CH_2CH_3), 6.5

(3H, s, OCH_3), 5.55 (1H, d, $J_{1,2}$ 6 Hz, H_2), 5.2 (1H, d, $J_{2,1}$ 6 Hz, H_1), 4.47 (1H, s, C_6H_5CH) and 2.5 (5H, s, C_6H_5).

Acetylation with acetic anhydride in pyridine gave the 2,4 - *di* - O - *acetyl* derivative **15** m.p. 165–167°. (Found: C, 55.28; H, 6.01; N, 3.31. $C_{21}H_{27}O_{10}N$ requires: C, 55.63; H, 5.96; N, 3.09%). ν_{max}: 1765, 1755 (C=O), 1555 (NO_2) and 1215 cm^{-1}. τ ($CDCl_3$): 8.75 (3H, t, J 7 Hz, CH_2CH_3), 8.0 (6H, s, $OCOCH_3$), 7.5 (2H, m, CH_2CH_3), 6.6 (3H, s, OCH_3), 6.5–5.5 (4H, m, $H_{5,7}$), 5.35 (1H, d, $J_{1,2}$ 7 Hz, H_1), 4.53 (1H, s, C_6H_5CH), 4.07 (1H, d, $J_{2,1}$ 7 Hz, H_2), 4.04 (1H, d, $J_{4,5}$ 9 Hz, H_4) and 2.57 (5H, s, C_6H_5). The second product was identified as 9 - *hydroxy* - 6 - *α* - *methoxy* - 7 - (*nitropropyl*) - 2 - *phenyl* - trans - m - *dioxano* - (5,4 - e)(1,4) - *dioxepan* **14** (61 mg, 11.3%) m.p. 168–170°. (Found: C, 54.95; H, 6.08; N, 3.56. $C_{17}H_{23}O_8N$ requires: C, 55.14; H, 6.22; N, 3.78%). ν_{max}: 3400 (OH), 1550 (NO_2) and 750 (Ar) cm^{-1}. τ (DMSO-d_6): 9.0 (3H, t, J 7 Hz, CH_2CH_3), 7.9 (2H, m, CH_2CH_3), 6.44 (3H, s, OCH_3), 6.5–5.0 (8H, m, $H_{4,6,7,9,10}$ and $CHNO_2$), 4.5 (1H, s, C_6H_5CH), 3.1 (1H, d, J 6.5 Hz, OH) and 2.6 (5H, s, C_6H_5).

Acetylation gave a mixture of the 9 - *acetoxy* - 6*α* - *methoxy* and 9 - *acetoxy* - 6*β* - *methoxy* derivatives **16** m.p. 170–175°. (Found: C, 56.02; H, 6.12; N, 2.96. $C_{19}H_{25}O_9N$ requires: C, 55.57; H, 6.13; N, 3.46%). ν_{max}: 1755 (C=O) and 1555 (NO_2) cm^{-1}. ($CDCl_3$): 9.04 (3H, t, J 7 Hz, CH_2CH_3), 7.95 (2H, m, CH_2CH_3), 7.85 (3H, s, $OCOCH_3$), 6.65 (1H, s, *β*OCH_3), 6.55 (2H, s, *α*OCH_3), 5.25 (0.6H, d, $J_{1,2}$ 10 Hz, H_6, *α*-isomer), 5.21 (0.4H, d, $J_{1,2}$ 7 Hz, H_6, *β*-isomer), 4.48 (1H, s, C_6H_5CH), 4.33 (1H, d, J 8 Hz, H_9) and 2.5 (5H, s, C_6H_5).

Reaction between **1** *and the sodium salt of phenyl nitromethane in pyridine*

The condensation was carried out as in the previous experiment. Two isomers were formed which were separated by fractional crystallisation from ethanol. The faster running isomer on TLC (solvent b) was found to be 9 - *hydroxy* - 6 - *methoxy* - 2 - *phenyl* - 7 - (*phenylnitromethyl*) - trans - m - *dioxano* - (5,4 - e)(1,4) - *dioxepan* **20** (154 *mg*, 19%), m.p. 179–181°. (Found: C, 60.23; H, 5.49; N, 3.44. $C_{21}H_{23}O_8N$ requires: C, 60.42; H, 5.55; N, 3.36%). ν_{max}: 3350 (OH), 1565 (NO_2), 750, 723 and 697 (Ar) cm^{-1}. τ (DMSO-d_6): 7.3 (3H, s, *β*OCH_3), 4.47 (1H, s, C_6H_5CH), 4.2 (1H, d, J 8.5 Hz, $CHNO_2$) and 2.5 (10H, m, $2\times C_6H_5$).

The slower moving isomer was shown to be the 6*α*-*methoxy* isomer as the hydrate **19** (160 mg, 20%) m.p. 160–162°. (Found: C, 58.27; H, 5.74; N, 3.11. $C_{21}H_{25}O_9N$ requires: C, 58.06; H, 5.75; N, 3.22%). ν_{max}: 3470 (OH), 3220, 1650 (H_2O), 1554 (NO_2), 750 and 695 (Ar) cm^{-1}. τ (DMSO-d_6): 6.6 (3H, s, *α*OCH_3), the remainder of the spectrum being similar to the *β*-isomer.

Reaction between **1** *and* 1-*nitropropane using potassium hydroxide as base*

40% Potassium hydroxide solution (1.5 ml) was added to dialdehyde **1** (632 mg) and 1-nitropropane (178 mg) stirred in pyridine (15 ml) stirred at 0°, followed by water (6 ml) to make the solution clear. The solution was poured into 0.5 m H_2SO_4 (400 ml) followed by extraction with chloroform (3×75 ml). The extract afforded a white solid which was recrystallised from ethanol (290 mg, 35%) m.p. 148–162° (TLC (solvent b) revealed two close-running spots). PLC separation (solvent b) afforded the two isomeric 7 - *hydroxy* - 6 - *methoxy* - 9 - (1 - *nitropropyl*) - 2 - *phenyl* - trans - m - *dioxano* - (5,4 - e)(1,4) - *dioxepans* **23** m.p. 161–163° (80%) and m.p. 153–155° (20%). ν_{max}: 3400 (OH), 1560 (NO_2) and 750 (Ar) cm^{-1}. (Found: C, 55.68; H, 6.05; N, 3.56. $C_{17}H_{23}O_8N$ requires: C, 55.14; H, 6.22; N, 3.78%).

The major isomer was acetylated with acetic anhydride in pyridine to give the 7-*acetoxy* derivative **26** m.p. 183–184°. (Found: C, 55.38; H, 6.08; N, 3.21. $C_{19}H_{25}O_9N$ requires: C, 55.47; H, 6.13; N, 3.46%). ν_{max}: 1755 (C=O) and 1558 (NO_2) cm^{-1}. τ ($CDCl_3$): 9.05 (3H, t, J 7 Hz, CH_2CH_3), 8.0 (2H, m, CH_3CH_3), 7.9 (3H, s, $OCOCH_3$), 6.55 (3H, s, OCH_3), 5.38 (1H, d, $J_{6,7}$ 6.5 Hz, H_6), 4.5 (1H, s, C_6H_5CH), 4.45 (1H, d, $J_{7,6}$ 6.5 Hz, H_7) and 2.55 (5H, s, C_6H_5).

Reaction between **1** *and the sodium salt of ethyl nitroacetate in pyridine*

The condensation of dialdehyde **1** (632 mg, 0.002 mole) and the sodium salt of ethyl nitroacetate (620 mg, 0.004 mole) in pyridine (15 ml) was carried out in the usual way. Crystallisation of the crude reaction product from chloroform and petroleum ether gave a white crystalline solid (480 mg, 53%) m.p. 100–130° which was chromatographed on silica gel. Elution with an acetone–petroleum ether gradient gave two products. One product was *methyl* 5,7 - O - *benzylidene* - 3,4 - *dideoxy* - 3 - *ethoxycarbonyl* - 3 - *nitro* - 4 - *nitromethyl* - *α* - D - *heptoseptanoside hydrate* **28** (390 mg, 42.89%) m.p. 136–137° from ethanol. (Found: C, 48.59; H, 5.15; N, 6.23. $C_{19}H_{26}O_{12}N_2$ requires: C, 48.10; H, 5.52; N, 5.91%). ν_{max}: 3450 (OH), 1760 (C=O), 1565 (NO_2), 780 and 715 (Ar) cm^{-1}. τ ($CDCl_3$): 9.12 (3H, t, J 7 Hz, CH_2CH_3), 6.4–5.2 (8H, m, H_{1-7} and OH), 5.02 and 4.83 (2H, $2\times$d, J 10 Hz, CH_2NO_2), 4.55 (1H, s, C_6H_5CH) and 2.55 (5H, s, C_6H_5). The second product was *methyl* - 5,7 - O - *benzylidene* - 3,4 - *dideoxy* - 4 - *ethoxycarbonylnitromethyl* - 3 - *nitro* - *α* - D - *heptoseptanoside* **29** (30 mg, 3.3%) m.p. 84–86°. ν_{max}: 3450 (OH), 1765 (C=O), 1575 (NO_2), 750 and 720 (Ar) cm^{-1}. τ ($CDCl_3$): 8.77 (3H, t, J 7 Hz), 6.57 (3H, s, OCH_3), 4.57 (1H, s, C_6H_5CH) and 2.55 (5H, s, C_6H_5).

Preparation of methyl 5,7 - O - *benzylidene* - 3 - *cyano* - 3,4 - *dideoxy* - 3 - *ethoxycarbonyl* - 4 - *ethoxycarbonylcyanomethyl* - *α* - D - *heptoseptanoside* **32** *in pyridine using potassium hydroxide as base*

40% Aqueous potassium hydroxide (1.5 ml) was added dropwise to dialdehyde **1** (632 mg, 0.002 mole) and ethyl cyanoacetate (452 mg, 0.004 mole) stirred at 0° in pyridine (15 ml) and water (5 ml); stirring was continued for 0.5 h. The solution was then poured into cold 1 M H_2SO_4 (250 ml) and extracted with chloroform (3×75 ml). The extract afforded crystalline **32** from chloroform–petroleum ether (584 mg, 60%) m.p. 184–186°. (Found: C, 59.51; H, 5.79; N, 6.09. $C_{24}H_{28}O_9N_2$ requires: C, 59.02; H, 5.78; N, 5.74%). ν_{max}: 3440 (OH), 2280 (CN), 1760 (C=O) and 740 (Ar) cm^{-1}. τ ($CDCl_3$): 9.07 (3H, t, J 7 Hz, $CO_2CH_2CH_3$ at C_3), 8.65 (3H, t, J 7 Hz, $CO_2CH_2CH_3$ at C_4), 6.7 (1H, d, J 7.5 Hz, CHCN), 6.5 (3H, s, OCH_3), 6.5–5.4 (11H, m, H_{2-7}, $2\times CH_2CH_3$ and OH), 5.25 (1H, d, J 6.5 Hz, H_1), 4.45 (1H, s, C_6H_5CH) and 2.6 (5H, s, C_6H_5).

Preparation of methyl 5,7 - O - *benzylidene* - 3 - *dicyano* - 4 - *dicyanomethyl* - 3,4 - *dideoxy* - *α* - D - *heptoseptanoside* **35** *in pyridine using potassium hydroxide as base*

The condensation was carried out as in the previous experiment using malononitrite instead of ethyl cyanoacetate. Recrystallisation of the crude reaction mixture from chloroform–petroleum ether gave pure **35** (720 mg, 93%) m.p. 148–150°. (Found: C, 60.68; H, 4.58; N, 13.99. $C_{20}H_{18}O_5N_4$ requires: C, 60.91; H, 4.60; N, 14.21%). ν_{max}: 3440 (OH), 2295, 2285, 2270 (CN), 770 and 705 (Ar) cm^{-1}. τ ($CDCl_3$): 6.55 (3H, s, OCH_3), 6.5–5.5 (7H, m, H_{2-7}), 5.37 (1H, d, J 6.5 Hz, H_1), 6.85 (1H, s, OH), 4.35 (1H, s, C_6H_5CH) and 2.6 (5H, m, C_6H_5).

Acknowledgement—The SRC is thanked for financial support to M.J.T.

REFERENCES

[1]M. E. Butcher and J. B. Lee, *Chem. Comm.* 1010 (1974).
[2]M. E. Butcher and J. B. Lee, *Tetrahedron Letters* 2663 (1974).
[3]G. Baschang, *Ann.* **663**, 167 (1963).
[4]M. L. Wolfrom, G. E. Nayak and T. Radford, *Proc. Nat. Acad. Sci. U.S.A.* **58**, 1848 (1967).
[5]I. Dijong and R. Bonn, *Tetrahedron Letters* 1485 (1971).
[6]S. W. Gunner, W. G. Overend and W. R. Williams, *Chem. and Ind. (London)* 1523 (1966); H. H. Baer and G. V. Rao, *Ann.* 210 (1963); *Chem. and Ind. (London)* 137 (1965).
[7]R. D. Guthrie and J. Honeyman, *J. Chem. Soc.* 2441 (1959); *Chem. and Ind. (London)* 388 (1958).
[8]F. W. Lichtenthaler, H. Leinert and U. Scheideggar, *Chem. Ber.* **101**, 1819 (1968).
[9]H. H. Baer, *Nitro-compounds-Proc. Intern. Symposium, Warsaw*, 263 (1964); H. O. L. Fisher and H. H. Baer, *Ann.* **619**, 53 (1958).
[10]R. D. Guthrie, A. M. Prior and S. E. Creasey, *J. Chem. Soc* (C), 1963 (1970).
[11]S. Umezawa, M. Kinoshita and H. Yanagisawa, *Asahi. Garasu Kogyo Gijutsu Shoereikai Kenkya Hokoku* **16**, 83 (1970).