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7- AND 8-MEMBERED RING SUGARS AND RELATED SYSTEMS

7-MEMBERED RINGS FROM DIOLEFINS DERIVED FROM DIOXEPANS VIA DOUBLE MICHAEL CONDENSATIONS

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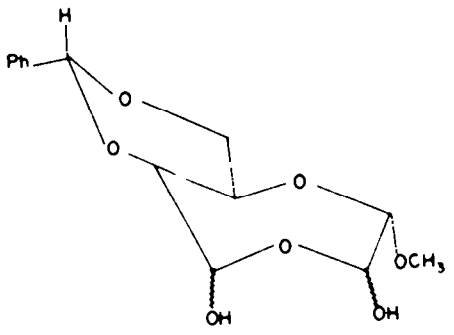
Abstract—The possibilities of cyclisation to 7-membered ring sugars containing nitro- and cyano-functions via double Michael condensations of diolefins derived from sugar dioxepans was investigated. With nitromethane cyclised products were obtained while with the larger ethyl cyanoacetate and malononitrile only one double bond was attacked without cyclisation. Treatment of the diolefins with excess ammonia resulted in cyclisation to novel heterocyclic systems containing oxygen and nitrogen often of known stereochemistry; with butylamine no cyclisation occurred. Treatment with hydrogen sulphide also resulted in cyclisation to novel heterocyclic systems containing sulphur and oxygen often of known stereochemistry. In these systems cyclisation only occurs with the smaller reagents.

The chemistry, stereochemistry and biological activity of furanose and pyranose forms of sugars have been massively studied. In contrast the literature on larger ring analogues is very sparse. The conformational control of reactivity demonstrated originally in cyclohexane and cyclopentane systems has found powerful application in rationalising the reactivity of sugar ring analogues. We have undertaken a programme of synthetic and biochemical work to develop routes to larger ring sugars, to elucidate their chemical and stereochemical properties particularly in the light of gaining knowledge of the stereochemistry of alicyclic analogues, and to study the effect of such changes in ring size upon the interaction of the compounds with enzymes acting upon pyranose analogues. The potential use of such systems chemotherapeutically and in probing enzyme mechanisms are obvious.

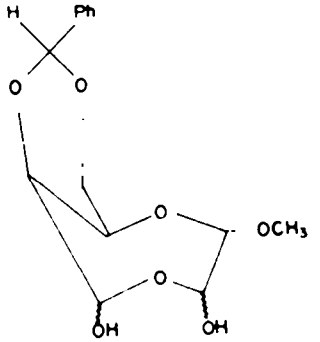
Recently we reported the preparation of nitro- and cyanoseptanoses,[1] potential intermediates in amino-sugar preparations of analogues of some well known antibiotics. We now describe some further work providing alternative routes to septanose systems, and *aza*- and *thia*-analogues. The generation of active points for cyclisation has been achieved in alicyclic chemistry in many ways, but little attention has been paid to the possibility of cyclisation *via* a double Michael condensation. We show here that the route is a useful addition to methods for carbohydrate synthesis.

RESULTS AND DISCUSSION

Treatment of methyl 4,6 - O - benzylidene - α - D - glucopyranoside with periodate gave the dialdehyde isolated as the dihydroxydioxepan (1); another dihydroxydioxepan (2) with different stereochemistry at C-1 and C-4 can be obtained by similar treatment of methyl 4,6 - O - benzylidene - β - D - galactopyranoside. In our earlier work these dihydroxydioxepans were condensed with active methylene compounds to give 7-member ring sugars containing nitro and cyano groups.[1] In the course of other work 1 was condensed with carbethoxy- and acetylmethylenetriphenylphosphoranes to give ethyl 2,3 - didehydro - 2,3 - dideoxy - 4,6 - O - benzylidene - 5 - O - (3' - ethoxycarbonyl - 1' - methoxyl - prop - 2 - enyl) - D - *erythro* - hexonate (3) and 1 - deoxy - 3,4 - didehydro - 3,4 - dideoxy - 5,7 - O - benzylidene - 6 - O - (1' - methoxy - pent - 4 - one - 2 - enyl) - D - *erythro* - heptulose (4) respectively.[2a] Treatment of 2 with carbethoxymethylenetriphenylphosphorane gave the D-*threo* analogue of 3 (5).[2b] In view of the proximity of two electrophilic centres, cyclisation to a 7-membered system was considered to be



1



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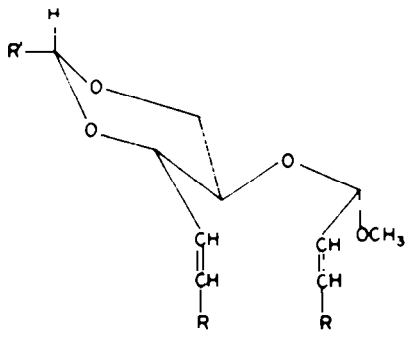
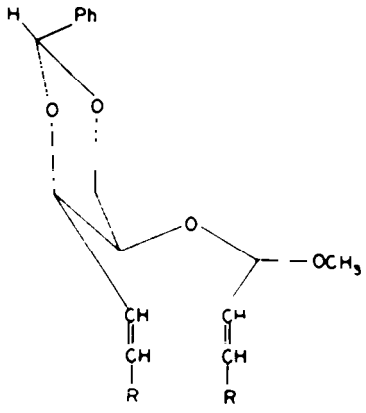
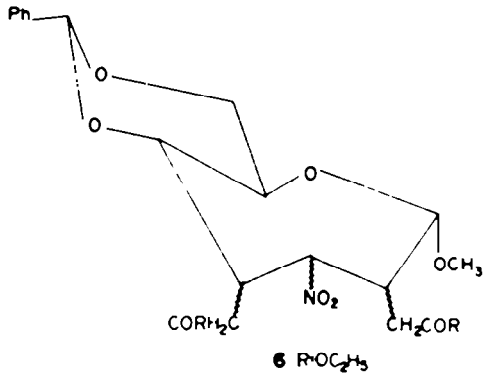


3 R=CO_2Et R'=C_6H_5

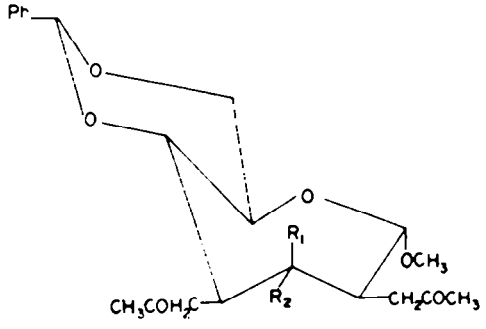
4 R=$COCH_3$ R'=C_6H_5



5 R=CO_2Et



6 R=OC_2H_5



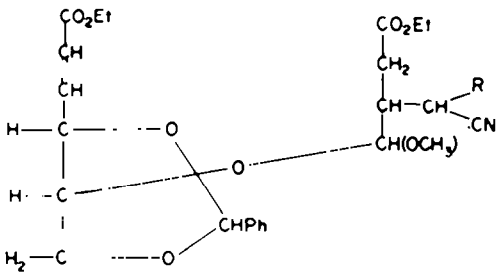
7 R_1=H R_2=NO_2

8 R_1=NO_2 R_2=H

a likely possibility when the Michael reaction was carried out, thus providing an alternative route to the systems described in the earlier paper.

Nitromethane has been added to α,β-unsaturated esters using a variety of catalysts such as diethylamine, di-isopropylamine, benzyltrimethylammonium hydroxide, etc.[3] As the double bond becomes more crowded the yield of the adduct falls off.[4] However it has been reported[5] that nitromethane adds to α,β-unsaturated esters in the presence of 1,1,3,3-tetramethylguanidine giving 40–80% yields of the product. The addition of nitromethane to unsaturated diester, **3**, in the presence of 1,1,3,3-tetramethylguanidine was examined. A potential disadvantage of the route could be addition to one or both bonds independently rather than cyclisation; in practice two isomers of the cyclic methyl 2,4 - di - C - ethoxycarbonylmethyl - 3 - deoxy - 5,7 - O - benzylidene - D - *erythro* - heptoseptanoside (**6**) were formed, but were not separated since the mixture gave a single spot on tlc. Structure **6** was consistent with the elemental analysis. In the PMR spectrum the two singlets at 4.50 and 4.52 τ (1 proton, C_6H_5CH–), the two singlets at 6.60 and 6.65 τ (3 protons, OCH_3) and the two triplets at 8.24 and 8.25 τ (6 protons, J = 7.0 Hz, CH_3CH_2–) showed the presence of two isomers. The IR spectrum showed a saturated ester band at 1730 cm^{-1} and a nitro band at 1500 cm^{-1}.

Treatment of unsaturated ketone, **4**, with nitromethane under similar conditions gave two isomers of the cyclic adduct, methyl 5,7 - O - benzylidene - 3 - deoxy - 3 - nitro - di - C - 2' - oxopropyl - D - *erythro* - heptoseptanoside (**7**, **8**); one isomer was separated by fractional crystallisation and the other by column chromatography of the mother liquor. The analytical and spectroscopic data showed that these compounds had septanose ring structures. The IR spectra of both compounds showed saturated ketone bands; no olefinic protons were present in the PMR spectrum. The PMR spectrum of **7** showed a doublet at 5.31 τ (J = 8.0 Hz) which was assigned to the C-1 proton; the large coupling constant between the C-1 and C-2 protons suggested that the C-2 proton was axial as the C-1 proton was known to be equatorial. The doublet at 4.8 τ (J = 10.0 Hz) was assigned to the C-3 proton; this suggested that the C-3 proton was almost split equally by the C-2 and C-4 protons, and the large coupling constant required them to be axial; thus the groups at C-2, 3, 4 were equatorial. The PMR spectrum of **8** showed doublets due to the C-1 and C-3 protons with the same chemical shift (5.42 τ). The doublet with the larger coupling constant (J = 8.0 Hz) was assigned to the C-1 proton (hence the C-2 proton was axial), and the other with the smaller coupling constant (J = 4.0 Hz) was assigned to the C-3 proton; this suggested that the C-3 proton was equatorial and thus the nitro group was axial. This contrasts with our earlier work[1] where we only separated 3 - nitro - 3 - deoxy - heptoseptanosides having the nitro group equatorial. Clearly interaction with the flanking substitutents in this case narrowed the energy differences between the axial and equatorial possibilities favouring production of a greater proportion of the former. Steric interactions in ring closure are known to be often critical in determining the direction of the reaction. The more sterically demanding ethyl cyanoacetate and malononitrile added smoothly to unsaturated diester **3** to give ethyl 2,3 - didehydro - 2,3 - dideoxy - 4,6 - O - benzylidene - 5 - O - (3' - ethoxycarbonyl - 2' - C - ethoxycarbonylcyanomethyl - 1' - methoxypropyl) - D - *erythro* - hexonate (**9**) and ethyl 2,3 - didehydro - 2,3 -

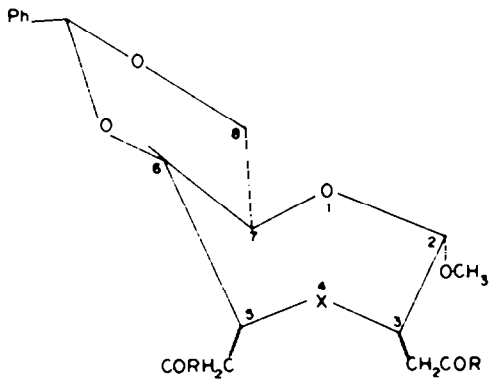


9 R=$CO_2C_2H_5$
10 R=CN

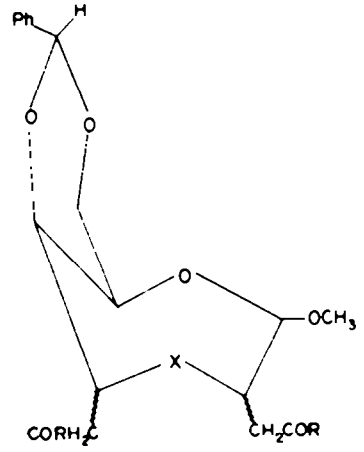
dideoxy - 4,6 - O - benzylidene - 5 - O - (3' - ethoxycarbonyl - 2' - C - dicyanomethyl - 1' - methoxypropyl) - D - *erythro* - hexonate (**10**) and its isomers (where attack occurred at C-3) in the case of the latter. These structures were confirmed by elemental analyses and IR and PMR spectra. Although **9** appeared to be homogeneous on tlc, the PMR spectrum suggested that it was a mixture of isomers (presumably at the new asymmetric centre, C-2'); the benzylidene proton signal was seen as two singlets which integrated for one proton. It also contained two olefinic protons showing that cyclisation had not occurred. The fact that the C-1' proton shifted upfield (as compared with unsaturated diester, **3**) showed that attack occurred at C-2'. **10** gave four spots on tlc and as might be expected the PMR spectrum was poorly resolved but it did show the presence of two olefinic protons, again showing that cyclisation had not occurred.

A similar steric effect was demonstrated in attempts to prepare *aza*-analogues; Michael reactions with ammonia and n-butylamine were examined. Treatment of unsaturated diester (**3**) with excess ammonia resulted in cyclisation. From analytical and spectroscopic data the product was assigned structure, **11** (i.e. 3,5 - diethoxycarbonylmethyl - 6,8 - O - benzylidene - 2 - α - methoxy - 1,4 - oxazepan). It is interesting to note the lack of reactivity of the ester groups with ammonia under these conditions. The IR spectrum showed the presence of a saturated ester CO band. The PMR spectrum showed the presence of two ester groups and it also showed the product to be a mixture of three isomers (the benzylidene proton and the OMe protons both showed two singlets, one having a shoulder). Reaction of excess ammonia with **5** gave one isomer of 3,5 - diethoxycarbonylmethyl - 6,8 - O - benzylidene - 2 - β - methoxy - 1,4 - oxazepan (**12**) in 80% yield; this is an analogue of **11** which differs in its stereochemistry at C-2 and C-6. Presumably in this case these differences precluded the formation of the other isomers in detectable amounts. Again the IR spectrum showed an ester CO band; also the PMR spectrum showed the presence of two ester groups. In suitable cases this cyclisation can lead to novel 7-membered heterocyclic systems containing N and O of known stereochemistry, and we are investigating the extension of this route to the smaller and larger ring systems.

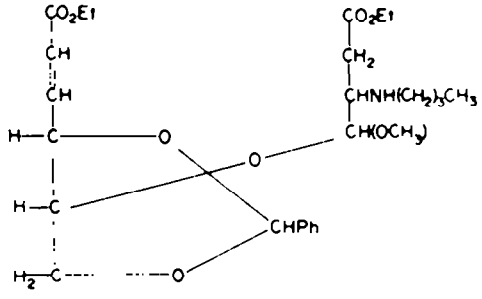
When **3** was treated with an equimolar amount of n-butylamine, addition occurred to one double bond only and no cyclic product could be detected; the isolated product was ethyl 2,3 - didehydro - 2,3 - dideoxy - 4,6 - O - benzylidene - 5 - O - (3' - ethoxycarbonyl - 2' - n - butylamino - 1' - methoxypropyl) - D - *erythro* - hexonate (**13**) in which attack was restricted to the less hindered electrophilic centre. The IR spectrum showed both saturated and unsaturated ester CO bands. The PMR spectrum showed only two olefinic protons; the upfield shift of the C-1' proton confirmed that the attack was at C-2'. Treatment of **3** with a large excess of n-butylamine still yielded no cyclic product; three amine residues were found in the product, the amine having added onto the two double bonds and also formed an amide with one ester group. Whether the material isolated was the n-butyl 2,3 - dideoxy - 3 - n - butylamino - 4,6 - O -



11 R=OC_2H_5 X=NH
15 R=OC_2H_5 X=S
16 R=CH_3 X=S

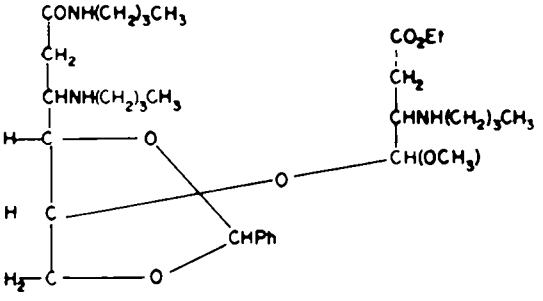


12 R=OC_2H_5 X=NH
17 R=OC_2H_5 X=S



13

benzylidene - 5 - O - (3' - ethoxycarbonyl - 2' - n - butylamino - 1' - methoxypropyl) - D - *erythro* - hexonamide (**14**) or its isomer where the amide is formed from the other ester group remains to be determined although the latter is less hindered. Steric hindrance presumably prevented the reaction of **14** with a further molecule of n-butylamine.



14

Hydrogen sulphide[6] has been reported to add smoothly to α,β-unsaturated carbonyl compounds although anomalous reactions have been noted. Treatment of **3** and **4** with hydrogen sulphide gave the expected novel cyclised 7-membered rings containing both O and S atoms, namely 3,5 - diethoxycarbonylmethyl - 6,8 - O - benzylidene - 2 - α - methoxy - 1,4 - thiaoxepan (**15**) and 3,5 - di - C - 2' - oxopropyl - 6,8 - O - benzylidene - 2 - α - methoxy - 1,4 - thiaoxepan (**16**) respectively. Compound **15** was a syrup, apparently a mixture of isomers from the PMR data; the benzylidene proton was not very sharp and the OMe signal showed two shoulders. One isomer of **16** could be isolated as a crystalline compound by column chromatography. In the PMR spectrum this isomer showed a doublet at 5.65 τ (J = 9.0 Hz) which was assigned to the C-2 proton; the high coupling constant between the C-2 and C-3 protons suggested that the C-3 proton was axial, as the former was equatorial, and thus the 2' - oxopropyl group at C-3 was equatorial. The stereochemistry at C-5 remains to be determined. Treatment of **5** with hydrogen sulphide gave 3,5 - diethoxycarbonylmethyl - 6,8 - O - benzylidene - 2 - β - methoxy - 1,4 - thiaoxepan (**17**), an analogue of **15**; this product was a single isomer. Again in suitable cases this cyclisation can provide a route to novel 7-membered heterocyclic systems containing O and S of known stereochemistry.

From these additions it can be concluded that smaller reagents, such as nitromethane, ammonia and hydrogen sulphide add to both double bonds giving a cyclic product, whereas bulkier reagents such as methyl cyanoacetate, malononitrile, and n-butylamine added to only one double bond and cyclisation was prevented, possibly sterically. Even under forcing conditions using a large excess of n-butylamine cyclisation did not occur. It would be interesting to investigate the effect of compounds intermediate in size between ammonia and n-butylamine such as methylamine, ethylamine and n-propylamine.

These reactions offer routes to novel septanose sugars and also to related *aza* and *thia* analogues which can in certain cases give ready routes to novel heterocyclic systems of known stereochemistry. The chemistry of these novel structures is under active investigation and will form the subject of subsequent communications.

EXPERIMENTAL

Elemental analyses were carried out at either the National Physical Laboratory, Teddington, Middx. or at Pfizers Ltd., Sandwich, Kent.

M.ps were taken using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 spectrophotometer, solids as nujol mulls and liquids as thin films. PMR spectra were recorded on either a Varian A60A or HA100 spectrometer using tetramethylsilane as an internal standard in various solvents at 27°. Column chromatography was carried out on B.D.H. 60–120 mesh silica gel, thin layer and preparative layer chromatography on Kiesel gel G (type 60); detection was with iodine. Solvents were dried, where required, by standard methods.

7,9 - *Didhydroxy* - 6 - *α* - *methoxy* - 2 - *phenyl* - trans - m - *dioxano* (5,4 - e)(1,4) - *dioxepan hydrate* (**1**). This was prepared by the literature procedure[7] (78% yield, m.p. 142–143° (lit. m.p. 143–144°)). This procedure was used to obtain the periodate oxidation product of *methyl* 4,6 - O - *benzylidene* - *β* - D - *galactopyranoside* (**2**, yield 79% m.p. 116°–118° (lit.[8] m.p. 118–119°)).

Ethyl 2,3 - *didehydro* - 2,3 - *dideoxy* - 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxycarbonyl* - 1' - *methoxyprop* - 2' - *enyl*) - D - erythro - *hexonate* (**3**). Dialdehyde **1** (3.16 g, 0.01 mole) and carbethoxymethylenetriphenylphosphorane (10.44 g, 0.03 mole) in DMF (90 ml) were heated together at 90–5° for 3 hr. The solvent was removed *in vacuo*. Triphenylphosphine oxide was removed by complexation with lithium bromide. The syrupy residue was chromatographed on silica gel (60 g). The title compound was obtained as a homogeneous syrup when the column was eluted with 4:96 acetone:petrol–ether (v/v), yield 3.48 g (66.9%). Found: C, 63.1; H, 6.8. $C_{22}H_{28}O_8$ required: C, 62.9; H, 6.9%). ν_{max}: 3060 and 3040 (w, olefinic and aromatic), 1727 (s, C=O), 1667 (s, C=C), 710 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.57 (m, 5H, C_6H_5); 2.82–4.1 (m, 4H, 2 × CH–CH); 4.44 (s, 1H, C_6H_5CH); 4.91 (dd, 1H, J 4 Hz and 1.3 Hz, $C(OCH_3)H$); 5.78 (q, 4H, J 7.0 Hz, 2 × CH_2CH_3, overlapping some other protons); 8.73 (t, 6H, J 7.0 Hz, 2 × CH_2CH_3), 6.64 (s, 3H, OCH_3) and 5.5–6.7 (m, 11H, including 4 protons from CH_2CH_3 groups and 3 from OCH_3 group. **2** was reacted with carbethoxymethylenetriphenylphosphorane in a similar way to give *ethyl* 2,3 - *didehydro* - 2,3 - *dideoxy* 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxy-carbonyl* - 1' - *methoxy-prop* - 2 - *enyl* - D - threo - *hexonoate* (**5**) (*yield* 41%, *syrup*).

1 - *Deoxy* - 3,4 - *didehydro* - 3,4 - *dideoxy* - 5,7 - O - *benzylidene* - 6 - O - (1' - *methoxy-pent* - 4 - *one* - 2 - *enyl*) - D - erythro - *heptulose* (**4**). Dialdehyde **1** (2.1 g, 0.0067 mole), acetylmethylenetriphenylphosphorane (5.36 g, 0.02 mole) and DMF (90 ml) were heated at 90–95° for 3 hr. The solvent was evaporated under vacuum. Triphenylphosphine oxide was removed by complexation with LiBr. The solid residue was crystallised from ether at 0°. The title compound was obtained as a white crystalline material, yield 1.2 g (50.2%) m.p. 78–79°. (Found: C, 66.7; H, 6.7. $C_{20}H_{24}O_6$ requires: C, 66.7; H, 6.7%). ν_{max}: 3050 (w, C=C); 1678 (s, C=O), 1660 (s, C=C), 772 (s) and 710 (s) (aromatic) cm $^{-1}$. τ ($CDCl_3$): 2.98 (m, 5H, C_6H_5); 2.7–3.7 (m, 4H, 2 × CH=CH); 4.38 (s, 1H, C_6H_5CH); 4.87 (d, 1H, J 3.0 Hz, H-1'), 6.6 (s, 3H, OCH_3); 7.7 (s, 6H, 2 × $COCH_3$) and 5.48–6.4 (m, 4H, H-4,5,6).

Methyl 2,4 - *di* - C - *ethoxycarbonylmethyl* - 3 - *deoxy* - 3 - *nitro* - 5,7 - O - *benzylidene* - D - erythro - *heptoseptanoside* (**6**). Unsaturated diester **3** (2.1 g, 0.005 mole), nitromethane (1.5 g, 0.0246 mole) and tetramethylguanidine (0.23 g, 0.002 mole) were stirred at room temp. for 3 days. The solvent and the catalyst were evaporated under vacuum. A dark brown syrup (2.5 g) was obtained. A part (0.5 g) of the syrup was chromatographed on silica gel (50 g) and eluted with increasing proportions of acetone in petrol–ether. When the column was eluted with 4:96 acetone:petrol–ether (v/v) the title compound (0.23 g) was obtained as a homogenous (tlc) syrup, total yield 1.15 g (43.7%). (Found: C, 57.5; H, 6.5; N, 2.8. $C_{23}H_{31}NO_{10}$ Requires: C, 57.4; H, 6.5; N, 2.9%), ν_{max}: 1730 (s, $COOC_2H_5$), 1550 (s) and 1372 (m) (NO_2), 755 (s) and 700 (m) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.52 (s, 5H, C_5H_5); 4.5 and 4.52 (2 singlets, 1H, C_6H_5CH); 4.82–6.5 (m,

10H); 6.6 and 6.65 (2 singlets, 3H, OCH_3); 6.78–7.24 (m, 6H) and 8.55–8.94 (m, 6H, $2\times CH_3CH_2$).

Methyl 5,7 - O - *benzylidene* - 3 - *deoxy* - 3 - *nitro* - 2,4 - *di* - C - 2' - *oxopropyl* - D - erythro - *heptoseptanoside* (**7**, **8**). A soln of **4** (0.9 g, 0.0025 mole), nitromethane (0.7 g) and MeOH (15 ml) was made alkaline to litmus paper by adding a conc. soln of NaOMe. The solution was left at room temp. for 7 days. Amberlite resin IR-120 (H^+) (5.0 g) was added and the suspension was stirred for 0.5 hr. The suspension was filtered and the filtrate was concentrated. A crystalline substance separated which was collected and found to be an isomer (**7**) of the title compound, yield 0.06 g (5.7%); m.p. 205°. (Found: C, 59.4; H, 6.5; N, 3.1. $C_{21}H_{27}NO_8$ Requires: C, 59.8; H, 6.4; N, 3.3%). ν_{max}: 1720 (s, C=O), 1550 (s) and 1367 (m) (NO_2), 750 (s) and 700 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.57 (s, 5H, C_6H_5); 4.55 (s, 1H, C_6H_5CH); 6.66 (s, 3H, OCH_3); 7.9 and 7.97 (2 singlets, 6H, $2\times COCH_3$); 4.8 (d, 1H, J, 10 Hz, H-3); 5.31 (d, 1H, J 8.0 Hz, H-1) and 6.83–7.76 (m, 6H, H-2, 4 and $2\times CH_2CO$). The mother liquor was evaporated and the residue was chromatographed on silica gel (50 g). Elution with 4:96 acetone in petrol–ether (v/v) gave 0.22 g of a syrup which was crystallised from EtOH to give isomer, **8**, yield 0.1 g (9.5%); m.p. 170–171°. (Found: C, 59.7; H, 6.7; N, 3.2. $C_{21}H_{27}NO_8$ Requires: C, 59.9; H, 6.4; N, 3.3%). ν_{max}: 1708 (s, C=O), 1580 (NO_2) cm^{-1}. τ ($CDCl_3$): 2.62 (s, 5H, C_6H_5); 4.54 (s, 1H, $C_6H_5CH_A$); 4.54 (s, 1H, $C_6H_5CH_B$); 5.42 (d, 1H, J 8.0 Hz, H-1); 5.42 (d, 1H, J 4.0 Hz, H-3'); 6.77 (s, 3H, OCH_3); 7.85 and 7.90 (2 singlets, 6H, $2\times COCH_3$); 5.8–6.5 (m, 4H, H-5, 6, 7) and 6.89–7.48 (m, H-2, 4 and $2\times CH_2CO$).

Ethyl 2,3 - *didehydro* - 2,3 - *dideoxy* - 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxycarbonyl* - 2' - C - *ethoxycarbonylcyanomethyl* - 1' - *methoxypropyl*) - D - erythro - *hexonoate* (**9**). Ethyl cyanoacetate (0.113 g, 0.001 mole) was added to a soln of NaOEt (0.23 g, 0.001 mole of Na in 15 ml of abs EtOH). After 10 min the solvent was evaporated and quickly replaced by pyridine (15 ml). Unsaturated diester **3** (0.42 g, 0.001 mole) in pyridine (15 ml) was added. The resulting soln was kept at room temp. for 48 hr. The solvent was evaporated under vacuum. The syrupy residue was dissolved in chloroform and washed with dilute AcOH and water. The dried chloroform layer was evaporated. The syrupy residue was chromatographed on silica gel (25 g) and eluted with increasing proportions of acetone in petrol–ether. When it was eluted with 4:96 acetone:petrol–ether (v/v) the title compound was obtained as a homogenous syrup, yield 0.25 g (46.9%). (Found: C, 61.0; H, 6.8; N, 2.8. $C_{27}H_{31}NO_{10}$ Requires: C, 60.8; H, 6.6; N, 2.6%). ν_{max}: 2250 (w, C≡N), 1730 (s, $COOC_2H_5$), 1660 (w, C=C), 762 and 708 (aromatic) cm^{-1}. τ ($CDCl_3$): 2.6 (m, 5H, C_6H_5); 2.89–4.17 (m, 2H, CH_A=CH_B); 4.42 and 4.53 (2 singlets, 1H, C_6H_5CH); 5.3–6.52 (m, 12H); 6.62 (singlet with 2 shoulders, 3H, OCH_3); 7.3–7.55 (m, 2H, CH_2CO) and 8.53–9.0 (m, 10H, $3\times CH_3$ and H-2').

Ethyl 2,3 - *didehydro* - 2,3 - *dideoxy* - 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxycarbonyl* - 2' - C - *dicyanomethyl* - 1' - *methoxypropyl*) - D - erythro - *hexonoate* (**10**) (*or its isomer*). Unsaturated diester **3** (0.42 g, 0.001 mole) in pyridine (15 ml) was treated with Na-salt of malononitrile (0.066 g, 0.001 mole). The soln was kept at room temp. for 60 hr. After evaporating the solvent the residue was found to be a complex mixture. It was chromatographed on silica gel and eluted with acetone:petrol–ether mixture. When it was eluted with 4:96 acetone:petrol–ether (v/v) starting material (0.06 g) was recovered, followed by a syrup which gave 4 spots on tlc 1:19 MeOH:benzene (v/v). These are probably the isomers of the title compound, yield 0.2 g (41.2%). (Found: C, 61.0; H, 6.1; N, 5.4. $C_{25}H_{30}N_2O_8$ Requires: C, 61.7; H, 6.2; N, 5.8%). ν_{max}: 2255 (w, CN), 1730 (s, $COOC_2H_5$), 1660 (w, C=C); 760 (s) and 705 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.62 (s, 5H, C_6H_5); 3.0–4.1 (m, 2H, CH_A=CH_B); 4.42 and 4.62 (2 singlets, 1H, C_6H_5CH); 6.62 (s, 3H, OCH_3); 5.32–6.55 (m, 10H); 7.0–7.3 (m, 2H, CH_2CO); 7.5–7.8 (m, 1H) and 8.55–9.0.

3,5 - *Diethoxycarbonylmethyl* - 6,8 - O - *benzylidene* - 2 - *α* - *methoxy* - 1,4 - *oxazepan* **11**. Abs EtOH (40 ml) containing ammonia (0.5 g, 0.003 mole) was added to **3** (1.00 g, 0.0024 mole) in abs EtOH (10 ml). The soln was kept at room temp. for 12 days. The soln and the unreacted ammonia were evaporated. A syrupy residue (1.0 g) was obtained, a part of which (0.15 g) was put onto a preparative tlc plate which was eluted twice in 1.5:98.5 MeOH:benzene (v/v). Small portions of the plate were developed with iodine in CCl_4. The middle band was scraped from the plate and eluted with $CHCl_3$. The solvent was evaporated and a syrupy residue (0.108 g) which was found to be a mixture of three isomers of the title compound was obtained, total yield 0.72 g (69.2%). (Found: C, 59.9; H, 7.4; N, 3.0. $C_{22}H_{31}NO_8$ Requires: C, 60.2; H, 7.1; N, 3.2%). ν_{max}: 3340 (m, NH), 1730 (b, $COOC_2H_5$), 760 and 708 (aromatic) cm^{-1}. τ ($CDCl_3$): 2.6 (m, 5H, C_6H_5); 4.52 and 4.58 (2 singlets with a shoulder at 4.5, 1H, C_6H_5CH); 8.75 (3 triplets, 6H, J 7.0 Hz, CH_2CH_3); 6.59, 6.62 (2 singlets with a shoulder at 6.64, 3H, OCH_3); 5.5–6.5 (m, 9H) and 6.7–7.7 (m, 7H). Reaction of ammonia with **5** under similar conditions gave an isomer of 3,5 - *diethoxycarbonyl methyl* - 6,8 - O - *benzylidene* - 2 - *β* - *methoxy* - 1,4 - *oxazepan* (**12**) in 80% yield (syrup). (Found: C, 60.7; H, 7.1; N, 3.1. $C_{22}H_{31}O_8N$ Requires: C, 60.4; H, 7.2; N, 3.2%). ν_{max}: 3360 (N-H), 1725 (C=O), 750 and 703 (aromatic) cm^{-1}. τ ($CDCl_3$): 2.24–2.58 (m, 5H, C_6H_5), 4.52 (s, 1H, C_6H_5CH), 5.98 (q, 2H, J 7.5 Hz, CH_2CH_3), 6.00 (q, 2H, J 7.5 Hz), CH_2CH_3), 6.54 (s, 3H, OCH_3), 6.96 (s, 1H, NH, exchangeable with D_2O), 8.73 (t, 3H, J 7.5 Hz, CH_2CH_3) and 8.75 (t, 3H, J 7.5 Hz, CH_2CH_3).

Ethyl 2,3 - *didehydro* - 2,3 - *dideoxy* - 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxycarbonyl* - 2' - n-*butylamino* - 1' - *methoxypropyl* - D - erythro - *hexonate* (**13**). Unsaturated diester **3** (2.1 g, 0.005 mole), n-butylamine (0.37 g, 0.005 mole) and abs EtOH (20 ml) were kept at room temp. for 10 days. The solvent was evaporated and the resultant syrup was left under vacuum over P_2O_5 to remove traces of the amine. The syrup thus obtained was not further purified. A mixture of the configurational isomers at C-2' was obtained, yield 2.30 g (93.0%). (Found: C, 63.6; H, 7.7; N, 2.8. $C_{26}H_{39}NO_6$ Requires: C, 63.3; H, 8.0; N, 2.8%). ν_{max}: 3400 (w, NH), 1733 (s, saturated $COOC_2H_5$), 1720 (s, conjugated $COOC_2H_5$), 1600 (m, C=C), 752 (b) and 698 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.5 (m, 5H, C_6H_5); 2.8–3.9 (m, 2H, CH_A=CH_B); 4.4 (s, 1H, C_6H_5CH); 5.4–6.6 (m, 12H); 6.7–7.77 (m, 6H) and 8.25–9.0 (m, 13H, $2\times CH_2CH_3$ and C_3H_7).

n - *Butyl* 2,3 - *dideoxy* - 3 - *n-butylamine* - 4,6 - O - *benzylidene* - 5 - O - (3' - *ethoxycarbonyl* - 2' - *n* - *butylamino* - 1' - *methoxypropyl*) - D - erythro - *hexonamide* (**14**) (*or its isomer*). Unsaturated diester **3** (2.1 g, 0.005 mole), n-butylamine (3.65 g, 0.05 mole) and abs EtOH (20 ml) were kept at room temp. for 20 days. The solvent and the unreacted amine were distilled, and the resultant syrup was kept under vacuum over P_2O_5 for a few days to remove the last traces of the amine. The syrup thus obtained was not further purified. It was found to be an isomeric mixture of the title compound, yield 2.6 g (92.2%). (Found: C, 65.2; H, 9.4; N, 8.8. $C_{34}H_{60}N_4O_6$ Requires: C, 65.7; H, 9.7; N, 9.0%). ν_{max}: 330 (b, bonded NH), 1730 (s, $COOC_2H_5$), 1650 (b, CONH), 1542 (m, NH) and 700 (aromatic) cm^{-1}. τ ($CDCl_3$): 2.5 (m, 5H, C_6H_5); 4.5 (s, 1H, C_6H_5CH); 5.3–6.5 (m, 10H); 6.7–8.0 (m, 15H three of which are exchangeable with D_2O) and 8.3–9.1 (m, 24H, CH_3CH_2 and $3\times C_3H_7$).

3,5 - *Diethoxycarbonylmethyl* - 6,8 - O - *benzylidene* - 2 - *α* - *methoxy* - 1,4 - *thiaoxepan* (**15**). H_2S was bubbled for 6 hr through **3** (0.8 g) in pyridine (3 ml) and triethylamine (1 ml). The coloured soln was poured onto iced-water whereby an emulsion was formed. It was de-emulsified by adding NaCl and then filtered. The residue was washed with water, dried and chromatographed. It was eluted with increasing proportions of acetone in petrol–ether. The title compound was obtained as a syrup with 4:96 acetone:petrol–ether (v/v), yield 0.35 g (40.5%). (Found: C, 57.9; H, 6.5. $C_{22}H_{30}O_8S$ Requires: C, 58.1; H, 6.7; S, 4.9%). ν_{max}: 1730 (s, $COOC_2H_5$), 760 (s) and 705 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.60 (s, 5H, C_6H_5); 4.50 (s, 1H, C_6H_5CH); 6.60 (s, 3H, OCH_3); 8.75 (t, 6H, J 7.0 Hz, CH_3CH_2); 6.75–7.68 (m, 4H, CH_2CO) and 5.33–6.52 (m, 14H). Treatment of **5** under similar conditions gave a single isomer of 3,5 - *diethoxycarbonyl* - 6,8 - O - *benzylidene* - 2 - *β* - *methoxy* - 1,4 - *thiaoxepan* (**17**). Found: C, 58.2; H, 6.9; S, 7.1. $C_{22}H_{30}O_8S$ Requires: C, 58.1; H, 6.7; S, 7.1%). ν_{max}: 1745 (C=O), 740 and 695 (aromatic) cm^{-1}. τ ($CDCl_3$): 2.36–2.68 (m, 5H, C_6H_5); 4.48 (s, 1M, C_6H_5CH); 5.82 (q, 4H, J 7 Hz, $2\times CH_2CH_3$); 6.52 (s, 3H, OCH_3); 8.75 (t, 3H, J 7 Hz, CH_2CH_3) and 8.78 (t, 3H, J 7 Hz, CH_2CH_3).

3,5 - *Di* - C - 2' - *exopropyl* - 6,8 - O - *benzylidene* - 2 - *α* - *methoxy* - 1,4 - *thiaoxepan* (**16**). H_2S was bubbled for 6 hr through a soln of **4** (1.0 g) in pyridine (4 ml) and triethylamine (1.3 ml). The coloured soln was poured onto iced water. It was de-emulsified by adding NaCl and filtered. The residue was washed with water, dried and chromatographed. When it was eluted with 1:9 acetone:petrol–ether (v/v), 0.16 g of one isomer A of the title compound was obtained. It was crystallised from EtOH. On being further eluted, 0.2 g of a crystalline material was obtained which was found (IR, PMR and microanalysis) to be a mixture of isomers of the title compound. It was crystallised from EtOH.

First crystalline material, yield 0.16 g (15%); m.p. 187–190°. (Found: C, 60.6; H, 6.6. $C_{20}H_{26}O_6S$ Requires: C, 60.9; H, 6.6; S, 8.1%). ν_{max}: 1710 (s, C=O), 762 (s) and 708 (s) (aromatic) cm^{-1}. τ ($CDCl_3$): 2.62 (s, 5H, C_6H_5); 4.52 (s, 1H, C_6H_5CH); 6.52 (s, 3H, OCH_3); 7.82 and 7.88 (2 singlets, 6H, $2\times CH_3CO$); 6.8–7.01 (m, 2H, CH_3CO); 7.3–7.55 (m, 2H, CH_2CO); 5.65 (d, 1H, J 9.0 Hz, H-2) and 5.72–6.55 (m, 6H).

The other crystalline material isolated, yield 0.2 g (18%); m.p. 125–179°. (Found: C, 60.8; H, 6.6%). ν_{max}: 1710 (C=O), 762 and 708 (aromatic) cm^{-1}. The finger-print region is almost identical to that of the first material. PMR spectrum of this compound was identical to that of isomer A except that the peaks were less well resolved and the singlet at 4.49 τ had a shoulder at 4.51 τ.

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