NUCLEOPHILIC REPLACEMENT REACTIONS OF SULPHONATES

PART VII[1] SELECTIVE TOSYLATION OF METHYL 2-BENZAMIDO-2-DEOXY-α-D-GLUCOPYRANOSIDE AND A SYNTHESIS OF METHYL 2-BENZAMIDO-2,3,6-TRIDEOXY-α-D-*ribo*-HEXOPYRANOSIDE

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ABSTRACT

Selective tosylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside at room temperature gave a mixture of the 6-sulphonate and the 3,6- and 4,6-disulphonates in yields of 25, 20, and 12%, respectively Treatment of the 4-acetate of the 3,6-disulphonate with iodide ion gave the 3,6-di-iodo-D-*gluco* derivative, with overall retention of configuration involving participation of the 2-benzamido substituent in the substitution of the 3-tosyl group and formation of an intermediary oxazolinium ion Reduction of the 3,6-di-iodo derivative gave methyl 2-benzamido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside The disulphonates, characterised as their monoacetates, were synthesised from methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside by unambiguous routes, each of which was superior to selective tosylation

INTRODUCTION

Apart from derivatives encountered in the synthesis of kasuganobiosamine[2], 2-amino-2,3,6-trideoxyhexoses are unknown, although several isomers occur naturally[3] and have been synthesised[4,5], including 2-amino-2,4,6-trideoxy-D-*xylo*-hexose[6] Ring opening of 2,3,6-trideoxy-2,3-epimino-α-D-allopyranoside[7] is a possible route to the required 2-aminotrideoxyhexoses A more-promising route appeared to be *via* selective tosylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside, which would be expected to yield the 3,6- and 4,6-di-*O*-tosyl derivatives by analogy with selective benzoylation[8], followed by sequential nucleophilic substitution with iodide ion and reduction of the 3,6- and 4,6-substituents

RESULTS AND DISCUSSION

Selective tosylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[9] in pyridine afforded a mixture containing three major products which were subsequently

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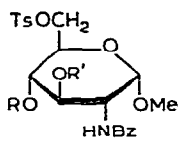
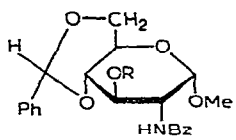
separated and identified as the 6-sulphonate[10] (25%), the 3,6-disulphonate (20%), and the 4,6-disulphonate **1** (12%) The relative reactivities of the hydroxyl groups in methyl 2-benzamido-2-deoxy-α-D-glucopyranoside are therefore in the order HO-6 > HO-3 > HO-4 Studies[11,12] of the selective benzoylation of hexopyranosides have shown that the 4-hydroxyl group is the least reactive because of steric hindrance from the large substituent at C-5, and parallel results were reported[8] for methyl 2-benzamido-2-deoxy-α-D-glucopyranosides

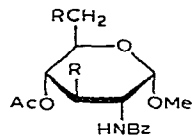
Acetylation of the 3,6-disulphonate gave methyl 4-*O*-acetyl-2-benzamido-2-deoxy-3,6-di-*O*-tosyl-α-D-glucopyranoside (**2**) and, likewise, the 4,6-disulphonate afforded the 3-*O*-acetyl derivative **3** The structures of the acetates **2** and **3** were confirmed by their n m r spectra and by unequivocal syntheses from methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside[10] and methyl 3-*O*-acetyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**4**), respectively In each case, these syntheses were better than those based on selective tosylation Thus, hydrolysis of the benzylidene group of **4** with aqueous acetic acid, followed by tosylation at 4°, gave the 4,6-disulphonate **3** Similar hydrolysis of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside[13], followed by selective tosylation at HO-6 and then acetylation, gave the 3,6-disulphonate **2** Comparison of the n m r spectra of the 4,6-diester **3** with the 3,6-diester **2** revealed that the H-3 signal for **3** appeared at lower field strength, and that the aryl methyl protons for **2** gave two distinct signals, whereas for **3** the signals overlapped



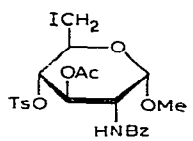
1 R = Ts, R' = H
2 R = Ac, R = Ts
3 R = Ts, R' = Ac



4 R = Ac



5 R = I, R = OTs
6 R = H, R = OTs
7 R = R = I
8 R = R = H



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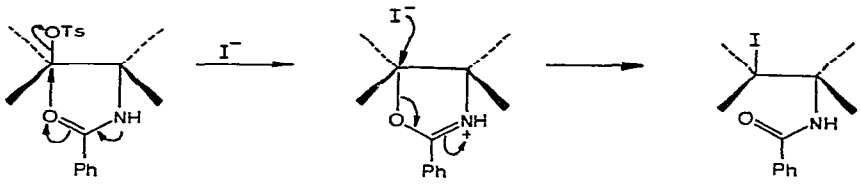
Replacement of the primary sulphonate group in **2** by treatment with sodium iodide in butanone was selective, giving the expected 6-deoxy-6-iodo derivative **5** which was converted into the 6-deoxy derivative **6** by reduction with Raney nickel In the n m r spectrum of **6**, the signal for Me-6 appeared as a doublet at τ 8 8 ($J_{5,6}$ 6.4 Hz) Under more-forcing conditions, the secondary sulphonate group in **2** (and **5**) was replaced by iodide to give the 3,6-dideoxy-3,6-di-iodo derivative **7** The structure of **7** was confirmed by its 100-MHz spectrum, H-1 appearing as a doublet at τ 5 39, H-3 as a triplet at 5 86, and H-4 as a quartet to lower field at 5 06 because of the deshielding effect of the 4-acetoxyl group The derived first-order coupling constants ($J_{1,2}$ 3 3, $J_{3,4}$ 11 0, $J_{4,5}$ 9 0, and $J_{5,6}$ 6 0 Hz) provided proof for the *gluco* configuration and the C_1^4 conformation for **7** Clearly, the 2-benzamido group participated in the elimination of the neighbouring *trans*-3-tosyloxy substituents of **2** (and **5**) to give a cyclic oxazolinium cation intermediate, which then underwent ring-opening

by nucleophilic attack at C-3 to give the 3,6-di-iodo derivative **7** with overall retention of configuration



10 **11** **12**

Examples of the solvolysis of sulphonyloxy groups by participation of neighbouring *trans*-acylamido groups are well-established[14], but there are few examples[15] where an oxazolinium intermediate is implicated giving a product with retention of configuration Reduction of the 3,6-di-iodo substituents of **7** with Raney nickel afforded methyl 2-benzamido-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (**8**) The n m r spectrum revealed first-order coupling constants ($J_{1\,2}$ 3 4, $J_{3e\,4}$ 5 0, $J_{3e,3a}$ 11 0, $J_{4\,5}$ 10 0, $J_{5\,6}$ 6 0, and $J_{NH\,CH}$ 9 0 Hz) that were consistent with the structure **8** and the C_1^4 conformation

The 4,6-disulphonate **3** underwent selective, nucleophilic substitution with sodium iodide in butanone to give the 6-deoxy-6-iodo derivative **9**

EXPERIMENTAL

The general experimental data are as described previously[16].

Tosylation of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside — To a solution of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[9] (20 g) in pyridine (400 ml) was added toluene-*p*-sulphonyl chloride (50 g) in pyridine (50 ml) at 15° over a period of 2 h The solution was stored at room temperature for 24 h, and t l c (chloroform–acetone, 4 1) then revealed three major products along with a minor, fast-moving component After addition of water (10 ml), the solution was concentrated to a thick syrup A solution of this residue in chloroform was washed successively with 2M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated The residue was eluted from a column of silica gel (Mallinckrodt, 800 g) with chloroform–light petroleum (10 1) to give two major fractions The first, after several crystallisations from ethanol, afforded methyl 2-benzamido-2-deoxy-4,6-di-*O*-tosyl-α-D-glucopyranoside (**1**), (5 g, 12%), m p 102–104°, $[\alpha]_D$ +56 4° (*c* 1 3, chloroform) (Found C, 55 1, H, 5 0, N, 2 3, S, 11 0 $C_{28}H_{31}NO_{10}S_2$ calc C, 55 5, H, 5 1, N, 2 3, S, 10 6%)

The mother liquor from the crystallisation of **1** was concentrated to a syrup (8 g, 20%) which could not be crystallised Consequently, it was acetylated in pyridine (100 ml), using acetic anhydride (16 ml) at room temperature for 40 h The reaction mixture was then poured into ice–water, and the precipitate was collected, washed well with water, and dried at 30° *in vacuo* The residue, on crystallisation from ethanol,

gave methyl 4-*O*-acetyl-2-benzamido-2-deoxy-3,6-di-*O*-tosyl-α-D-glucopyranoside (**2**) (8 g, 93%), m p 171–172°, $[\alpha]_D$ +126° (*c* 2 07, methylene chloride) (Found . C, 55 7, H, 5 2; N, 2 2, S, 11.6 $C_{30}H_{33}NO_{11}S_2$ calc C, 55 6; H, 5 1, N, 2 2, S, 9 9%)

N m r (60 MHz) data τ 5 16 (*d*, 1 proton, $J_{1\,2}$ 3 5 Hz, H-1), 4 87 (*t*, 1 proton, $J_{3\,4}$ 9 0 Hz, H-3), 5 02 (*t*, 1 proton, $J_{4\,5}$ 9 0 Hz, H-4), 3 37 (*d*, 1 proton, $J_{NH\,CH}$ 8 6 Hz, H–N), 6 65 (*s*, 3 protons, OMe), 7 56, 7 7 (2 *s*, 6 protons, 2 Me–Ph), and 8 09 (*s*, 3 protons, Ac)

The second fraction afforded syrupy methyl 2-benzamido-2-deoxy-6-*O*-tosyl-α-D-glucopyranoside (8 g, 25%), which was characterised as the 3,4-di-*O*-acetyl derivative[10], m p and mixed m p 129–131°, $[\alpha]_D$ +115° (*c* 1.39, chloroform)

Methyl 3-O-acetyl-2-benzamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (**4**) — Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[9] (3 g) in pyridine (20 ml) was treated with acetic anhydride (8 ml) at room temperature for 20 h The reaction mixture was worked up as described above to give a solid residue Crystallisation from acetone gave **4** (2 g, 60%), m p 225–226° $[\alpha]_D$ +75 6° (*c* 2 82, methylene chloride) (Found C, 64 6, H, 5 7; N, 3 6 $C_{23}H_{25}NO_7$ calc C, 64 6, H, 5 9, N, 3 3%)

Methyl 3-O-acetyl-2-benzamido-2-deoxy-4,6-di-O-tosyl-α-D-glucopyranoside (**3**). — (*a*) The 4,6-disulphonate **1** (4 g) in pyridine (50 ml) was treated with acetic anhydride (10 ml) at room temperature for 40 h The reaction mixture was poured on to ice–water, and the precipitate was filtered off, washed well with water, and dried overnight at 30° *in vacuo* Recrystallisation from ethanol gave the 3-acetate **3** (4 1 g, 93%), m p 162–163°, $[\alpha]_D$ +82 5° (*c* 1 88, chloroform) (Found C, 55 5, H, 5 0, N, 2 0; S, 11 7 $C_{30}H_{33}NO_{11}S$ calc C, 55 6, H, 5 1, N, 2 2, S, 9 9%)

N m r (60 MHz) data τ 5 36 (*d*, 1 proton, $J_{1,2}$ 3 3 Hz, H-1), 4 71 (*q*, 1 proton, $J_{3\,4}$ 10 0 Hz, H-3), 5 41 (*t*, 1 proton, $J_{4\,5}$ 10 0 Hz, H-4), 3 75 (*d*, 1 proton, $J_{NH,CH}$ 9.0 Hz, H–N), 6 75 (*s*, 3 protons, OMe), 7 58 (*s*, 6 protons, Me-Ph), 8 23 (*s*, 3 protons), Ac)

(*b*) A suspension of the 4,6-*O*-benzylidene derivative **4** (1 5 g) in 50% aqueous acetic acid was refluxed for 5 min The solution was cooled to room temperature and concentrated to a mobile syrup which was washed with light petroleum to remove benzaldehyde, and dried overnight at 30° *in vacuo* The syrup was then dissolved in pyridine (15 ml) and treated at 4° with toluene-*p*-sulphonyl chloride in pyridine The reaction mixture was stored at room temperature for 48 h and worked up in the usual way to give a syrup which was crystallised from ethanol, yield, 800 mg (35%) Recrystallisation afforded needles of **3**, m p and mixed m p 161–163°, $[\alpha]_D$ +82 9° (*c* 2 09, chloroform) The n m r spectrum was identical with that of the previously prepared sample

Methyl 4-O-acetyl-2-benzamido-2-deoxy-3,6-di-O-tosyl-α-D-glucopyranoside (**2**) — Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside[13] {1 g; m p 193–195°, $[\alpha]_D$ +30° (chloroform)} was treated with boiling 50% aqueous acetic acid for 5 min The solution was concentrated, and the residue was washed well with light petroleum and dried overnight at 30° *in vacuo*. A cooled (−10°) solution of

the syrup in pyridine was then treated with toluene-*p*-sulphonyl chloride (1 g) for 24 h at 0°. The reaction was worked up as previously to give a syrup (800 mg, 71%), $[\alpha]_D$ +90° (*c* 1 77, methylene chloride) A solution of the syrup in pyridine (10 ml) was then acetylated using acetic anhydride (2 ml), and the reaction mixture, after storage at room temperature for 48 h, was poured on to ice–water The precipitate was collected, washed well with water, dried, and crystallised from ethanol to give **2** (750 mg, 87%), m p and mixed m p 171–172°, $[\alpha]_D$ +126° (*c* 1 88, methylene chloride), the n m r spectrum of which was identical with that of the sample prepared previously

Methyl 4-O-acetyl-2-benzamido-2,6-dideoxy-6-iodo-3-O-tosyl-α-D-glucopyranoside (**5**) — The 3,6-disulphonate **2** (1 g) was treated with a boiling solution of sodium iodide (1 mol) in butanone (50 ml) for 24 h Sodium toluene-*p*-sulphonate was filtered off and the filtrate concentrated to dryness The residue was partitioned between water and chloroform The chloroform layer was washed with aqueous sodium thiosulphate and water, dried (Na_2SO_4), and concentrated The resulting, colourless syrup was crystallised from ethanol to give the 6-iodo derivative **5** as fine needles (700 mg, 75%), m p 173–175°, $[\alpha]_D$ +114° (*c* 1 46, methylene chloride) (Found C, 46 0, H, 4 3, I, 21 0, N, 2 2, S, 5 2 $C_{23}H_{26}INO_8S$ calc C, 45 8, H, 4 3, I, 21 0, N, 2 3, S, 5 3%)

N m r (100 MHz) data· τ 5 16 (*d*, 1 proton, $J_{1\ 2}$ 3 3 Hz, H-1), 5 54 (*m*, 1 proton, H-2), 4 9 (*t*, 1 proton, $J_{3\ 4}$ 9 0 Hz, H-3), 6 29 (*m*, 1 proton, $J_{5\ 6}$ 8 0 Hz, H-5), 6 95 (*q*, 1 proton, $J_{6\ 6'}$ 10 5 Hz, H-6), 6 75 (*q*, 1 proton, $J_{5\ 6'}$ 3 0 Hz, H-6'), 3 18 (*d*, 1 proton, $J_{NH\ CH}$ 9 0 Hz, H–N), 6 6 (*s*, 3 protons, OMe), 7 76 (*s*, 3 protons, Me–Ph), 8 08 (*s*, 3 protons, Ac)

Methyl 4-O-acetyl-2-benzamido-2,6-dideoxy-3-O-tosyl-α-D-glucopyranoside (**6**) — A solution of **5** (500 mg) in ethanol (50 ml) containing freshly prepared Raney nickel (2 g) was refluxed for 5 h T l c (chloroform) revealed that the product **6** and starting material **5** were coincident but distinguishable by the marked difference in colour formation with sulphuric acid The catalyst was filtered off, and the filtrate was concentrated Recrystallisation of the residue from ether–light petroleum afforded **6** (250 mg, 63%), m p 159–160°, $[\alpha]_D$ +114 4° (*c* 1 89, methylene chloride) (Found C, 57 8, H, 5 7; N, 3 1, S, 6 5 $C_{23}H_{27}NO_8S$ calc C, 57 9, H, 5 7, N, 2 9, S, 6 7%)

N m r (60 MHz) data τ 5 16 (*d*, 1 proton, $J_{1\ 2}$ 3 3 Hz, H-1), 6 16 (*m*, 1 proton, $J_{5\ 6}$ 6 4 Hz, H-5), 3 34 (*d*, 1 proton, $J_{NH\ CH}$ 8 5 Hz, H-N), 6 63 (*s*, 3 protons, OMe), 8 8 (*d*, 3 protons, $J_{5\ 6}$ 6 4 Hz, Me-5), 7 71 (*s*, 3 protons, Me–Ph), 8 08 (*s*, 3 protons, Ac)

Methyl 4-O-acetyl-2-benzamido-2,3,6-trideoxy-3,6-di-iodo-α-D-glucopyranoside (**7**) — A solution of the 3,6-disulphonate **2** (3 g) in *N*,*N*-dimethylformamide–butanone (100 ml, 1 1) containing sodium iodide (2 g) was refluxed at 125–130° for 6 days The solution was then concentrated to dryness by codistillation with toluene, and traces of *N*,*N*-dimethylformamide were removed by storing overnight at 30° *in vacuo* The reaction mixture was worked up as described previously, and the syrup obtained after concentration of the chloroform extract was crystallised from ethanol–light petroleum to give **7** (1 g, 39%), m p 235–237°, $[\alpha]_D$ +113 2° (*c*, 1 76 chloroform)

(Found: C, 34 4; H, 3 4, I, 44 4; N, 2 3, $C_{16}H_{19}I_2NO_5$ calc C, 34 4, H, 3 4, I, 45 4; N, 2 5%)

N m r data (100 MHz) τ 5 39 (*d*, 1 proton, $J_{1,2}$ 3 3, H-1), 5 86 (*t*, 1 proton, $J_{3\,4}$ 11 0 Hz, H-3), 5 06 (*q*, 1 proton, $J_{4\,5}$ 9 0 Hz, H-4), 6 49 (*o*, 1 proton, $J_{5,6}$ 9 0 Hz, $J_{5,6'}$ 3.0 Hz, H-5), 6.99 (*q*, 1 proton, $J_{6,6}$ 11 0 Hz, H-6), 9 81 (*q*, 1 proton, *J* 3 0 and 11 0 Hz, H-6'), 7 94 (*s*, 3 protons, Ac)

*Methyl 4-O-acetyl-2-benzamido-2,3,6-trideoxy-α-*D*-ribo-hexopyranoside* (**8**) — A solution of the 3,6-di-iodo derivative 7 (500 mg) in methanol (50 ml) was refluxed with freshly prepared Raney nickel (*ca* 2 g) for 12 h The catalyst was filtered off and the filtrate concentrated to dryness A solution of the residue in chloroform was washed with water, dried (Na_2SO_4), and concentrated to a syrup which crystallised from ether–light petroleum (150 mg, 54%), m p 193–194°, $[\alpha]_D$ +138 8° (*c* 1 38, methylene chloride) (Found C, 62 2; H, 6 6, N, 4 9 $C_{16}H_{21}NO_5$ calc C, 62 5, H, 6 8, N, 4 6%)

N m r (100 MHz) data τ 5 42 (*d*, 1 proton, $J_{1\,2}$ 3 4 Hz, H-1), 7 74 (*sx*, 1 proton, $J_{3e\,4}$ 5 0 Hz, $J_{3a\,3e}$ 11 0 Hz, H-3e), 8 24 (*p*, 1 proton, $J_{3a,3e}$ 11 0 Hz, H-3a), 5 42 (*sx*, 1 proton, $J_{4\,5}$ 10 0 Hz, H-4), 3 76 (*d*, 1 proton, $J_{NH,CH}$ 9 0 Hz, H–N), 6 63 (*s*, 3 protons, OMe), 8 83 (*d*, 3 protons, $J_{5,6}$ 6 0 Hz, Me-5), 8 0 (*s*, 3 protons, Ac)

*Methyl 3-O-acetyl-2-benzamido-2,6-dideoxy-6-iodo-4-O-tosyl-α-*D*-glucopyranoside* (**9**) — The 4,6-disulphonate 3 (900 mg) was treated with a boiling solution of sodium iodide (1 mol) in butanone (20 ml) for 24 h T l c (chloroform) revealed a fast-moving product The reaction was worked up as described previously to give a syrup which was crystallised from acetone–light petroleum to yield **9** (500 mg, 59%), m p 78–81°, $[\alpha]_D$ +74 5° (*c* 2 51, methylene chloride) (Found C, 45 5; H, 4 1, I, 21 3, N, 2 2, S, 5 1. $C_{23}H_{26}INO_8S$ calc C, 45 8, H, 4 3, I, 21 0, N, 2 3, S, 5 3%)

N m r (60 MHz) data τ 5 23 (*d*, 1 proton, $J_{1,2}$ 3 4 Hz, H-1), 4 7 (*q*, 1 proton, $J_{3\,4}$ 8 7 Hz, H-3), 5 25 (*t*, $J_{4\,5}$ 8 7 Hz, H-4), 6 6 (*s*, 3 protons, OMe), 7 6 (*s*, 3 protons, Me–Ph), 8 27 (*s*, 3 protons, Ac)

REFERENCES

1 PART VI A C. RICHARDSON, *Carbohyd Res*, 10 (1969) 395
2 M NAKAJIMA, H SHIBATA, K KITAHARA, S TAKAHASMI, and A HASEGAWA, *Tetrahedron Lett*, (1968) 2271
3 J D DUTCHER, *Advan Carbohyd Chem*, 18 (1963) 259
4 A C RICHARDSON, *Carbohyd Res*, 4 (1967) 422
5 J P MARSH, C N MOCCER, E M ACTON, and L GOODMAN, *Chem Commun*, (1967) 973
6 J HILL and L HOUGH, *Carbohyd Res*, 8 (1968) 398
7 C F GIBBS, L HOUGH, A C RICHARDSON, AND J TJEBBES, *Carbohyd Res*, 8 (1968) 405
8 M W HORNER, L HOUGH, AND A C RICHARDSON, *J Chem Soc, C*, (1970) 1336
9 C F GIBBS, L HOUGH, AND A C RICHARDSON, *Carbohyd Res*, 1 (1965) 290
10 R KHAN AND L HOUGH, *Carbohyd Res*, 24 (1972) 147
11 J M WILLIAMS AND A C RICHARDSON, *Tetrahedron*, 23 (1967) 1369, 1641
12 A C. RICHARDSON, *Carbohyd Res*, 4 (1967) 415
13 C F GIBBS, Ph D Thesis, University of Bristol, 1967
14 B R BAKER AND P. E SCHAUB, *J Org Chem*, 19 (1954) 646, A C RICHARDSON AND H O L FISCHER, *J Amer Chem Soc*, 83 (1961) 1132, A C RICHARDSON AND K A MCLAUCHLAN, *J. Chem. Soc*, (1962) 2499, R D GUTHRIE AND G. P MUTTER, *ibid*, (1964) 5364
15 A C RICHARDSON, *J. Chem Soc*, (1964) 5364
16 C H BOLTON, L HOUGH, AND R KHAN, *Carbohyd Res*, 21 (1972) 133