Carbohydrate Research, 30 (1973) 83–89

THE REACTION OF ALLITOL WITH HYDROGEN HALIDES

J. M. BALLARD* AND B. E. STACEY

Department of Chemistry, Sir John Cass School of Science and Technology, City of London Polytechnic, Jewry Street, London EC3N 2EY (Great Britain)

(Received November 6th, 1972; accepted for publication in revised form, March 19th, 1973)

ABSTRACT

The reaction of allitol with fuming hydrochloric acid at 100° afforded 1,4-anhydro-5,6-dichloro-5,6-dideoxy-DL-talitol (**14**) and 1,4-anhydro-6-chloro-6-deoxy-DL-allitol (**3**). 1,4-Anhydro-6-bromo-6-deoxy-DL-allitol (**4**) and 1,4-anhydro-DL-allitol (**6**) were obtained from a similar reaction with excess of hydrogen bromide.

INTRODUCTION

Considerable attention has been focused on the synthesis of carbohydrate derivatives with potential anti-tumour activity[1]. Of the sugar alcohols, ribitol[2], D-arabinitol[2], D- and L-mannitol[2,3], D- and L-iditol[4,5], D-glucitol[2], and galactitol[2,4] have been investigated as carriers of alkylating functions. Examples of cytoactive derivatives include the 1,6-di-*O*-methanesulphonyl, 1,6-dideoxy-1,6-dihalogeno, and 1,2:5,6-dianhydro derivatives of D-mannitol. A marked dependence of biological activity on stereochemistry has been observed. Thus, whereas 1,6-di-*O*-methanesulphonyl-D-mannitol and its tetra-acetate effectively inhibit the growth of the Walker rat carcinoma[2], the L isomer[3,6], and the D-glucitol[2] and galactitol[2,6] analogues show no significant activity.

Allitol (**1**), a hitherto rare hexitol, has recently become readily accessible with the advent of procedures suitable for large-scale preparations of D-allose[7]. The synthesis of terminally substituted derivatives of allitol, particularly the 1,6-dideoxy-1,6-dihalogeno derivatives was therefore attempted. These compounds were also sought as potential intermediates in the synthesis of 1,6-di-*O*-methanesulphonyl- and 1,2:5,6-dianhydro-allitol.

RESULTS AND DISCUSSION

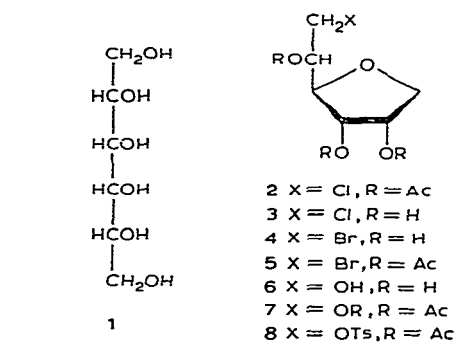
Certain 1,6-dideoxy-1,6-dihalogenohexitols have been prepared by treatment of the hexitol with a large excess of hydrogen halide under suitable conditions. Thus,

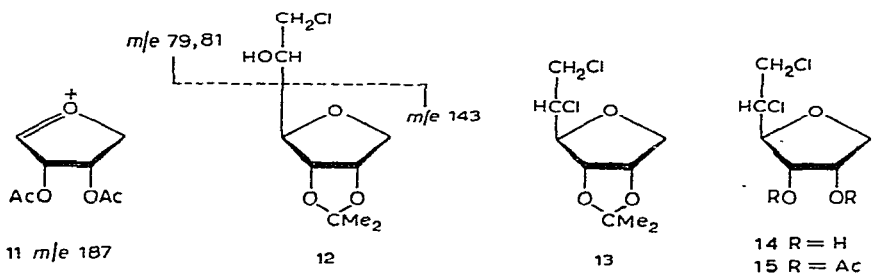
*Present address: Department of Chemistry, Queen Elizabeth College (University of London), Campden Hill, London W. 8.

D-mannitol or galactitol, when heated with fuming hydrobromic acid in sealed tubes, gave the 1,6-dibromides in yields of 40 and 70%, respectively[8]; similar reaction of D-mannitol with fuming hydrochloric acid afforded 1,6-dichloro-1,6-dideoxy-D-mannitol as the major product[9].

The reaction of allitol with fuming hydrochloric acid (sealed tube, 100°, 22 h) yielded a syrupy mixture of four components (*A–D*) which were separated by preparative layer chromatography.

Component *D* was a syrupy anhydrochlorodeoxyhexitol, the crystalline triacetate of which had an EI mass spectrum containing peaks at *m/e* 309, 311 (intensity ratio ~3:1) for $(M+1)^+$ due to ^{35}Cl and ^{37}Cl isotopes. The presence of a 1,4-anhydro ring was indicated by an intense peak at *m/e* 187 due to the stable oxycarbonium ion **11** formed by cleavage of the C-4–C-5 bond[10]. The triacetate was identified as 2,3,5-tri-*O*-acetyl-1,4-anhydro-6-chloro-6-deoxy-DL-allitol (**2**) by comparison with an authentic sample prepared from 2,3,5-tri-*O*-acetyl-1,4-anhydro-6-*O*-tosyl-DL-allitol (**8**) by treatment with lithium chloride–acetic anhydride.





Component *B* was crystalline, and elemental analysis indicated the molecular formula $C_9H_{15}ClO_4$. The i.r. spectrum of *B* showed a strong hydroxyl absorption and *B* formed a crystalline acetate **10**. The mass spectrum of *B* contained weak peaks for the molecular ions *m/e* 222 and 224 (intensity ratio ~3:1), and an intense peak at *m/e* 207 for $(M-15)^+$ characteristic of an isopropylidene group[11]. There were also strong peaks at *m/e* 143 ($C_7H_{11}O_3$) and *m/e* 79, 81 (C_2H_4ClO, Cl isotope ratio ~3:1),

corresponding to the fragments formed by cleavage of the C-4–C-5 bond (**12**). Further evidence for the presence of an isopropylidene group in *B* was provided by the n.m.r. spectrum which showed, *inter alia*, two 3-proton signals (τ 8.45, 8.65) which were shown by double irradiation techniques not to be coupled with other protons and were therefore assigned to non-equivalent methyl groups. A 1-proton doublet (τ 4.7, J 6 Hz; further split by a small, unresolved coupling of ~1 Hz) was assigned to H-3, and the small value (~1 Hz) of $J_{3,4}$ indicated a *trans* arrangement. H-2 appeared as a 1-proton multiplet at τ 5.1 due to coupling with H-3 ($J_{2,3}$ 6 Hz), H-1 *cis* ($J_{1,2}$ 4.5 Hz), and H-1 *trans* ($J_{1,2}$ 1.5 Hz) (*cf.* ref. 12). These data support the identification of *B* as 1,4-anhydro-6-chloro-6-deoxy-2,3-*O*-isopropylidene-DL-allitol (**9**).

Chemical evidence for the structure of *B* was provided by its conversion into **2**, *via* mild hydrolysis with acid and acetylation. The reaction of *D* with 2,2-dimethoxypropane afforded a single product which appeared to be identical (t.l.c.) with *B*. The isolation of *B* as an isopropylidene derivative is incompatible with the initial reaction conditions, and the acetal formation must have occurred during trituration with acetone in the isolation procedure (see Experimental).

Compound *A* was crystalline, and the molecular formula $C_9H_{14}Cl_2O_3$ suggested that it was related to *B* by substitution of Cl for HO, since the i.r. spectrum did not contain an hydroxyl absorption. The mass spectrum did not exhibit a molecular ion peak but the expected strong peak of *m/e* 225 (M − 15), indicating loss of Me from an isopropylidene group, was present. The n.m.r. spectrum was similar to that of *B* but more complicated, and the ring protons could not be assigned. However, two 3-proton singlets (τ 8.5, 8.7) were clearly due to non-equivalent methyl groups. Mild hydrolysis with acid converted *A* into a single product, slower moving on t.l.c., which was reconverted into the starting material (t.l.c.) by reaction with 2,2-dimethoxypropane. Although the location of the two chlorine atoms could not be deduced with certainty, it is reasonable to assume that *A* was formed by further chlorination of 1,4-anhydro-6-chloro-6-deoxy-DL-allitol at C-5 with acetalation occurring in the isolation procedure.

If the chlorination at C-5 were effected by an S_N1 mechanism, a mixture of the DL-*talo* and DL-*allo* isomers of 1,4-anhydro-5,6-dichloro-5,6-dideoxyhexitol would have been expected; if the S_N2 mechanism were operative, only the DL-*talo* product should be formed. Since *A* appeared to be a pure compound (sharp melting point, homogeneous on t.l.c.) and no other dichloride was detected, it is presumed to be 1,4-anhydro-5,6-dichloro-5,6-dideoxy-2,3-*O*-isopropylidene-DL-talitol (**13**).

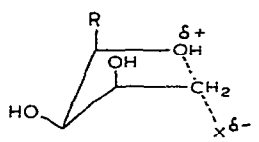
Component *C* and its diacetate (**15**) were syrups. However, treatment of *C* with 2,2-dimethoxypropane gave *A*, and *C* is therefore 1,4-anhydro-5,6-dichloro-5,6-dideoxy-DL-talitol (**14**).

Reaction of allitol with fuming hydrobromic acid afforded two products, isolated as syrups by p.l.c. Acetylation of the faster moving component gave 2,3,5-tri-*O*-acetyl-1,4-anhydro-6-bromo-6-deoxy-DL-allitol (**5**), identical with an authentic sample prepared from **8** by reaction with sodium bromide–acetic anhydride. The second component was 1,4-anhydro-DL-allitol and yielded a crystalline tetra-acetate

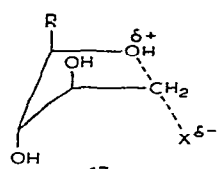
(7) previously known only as a syrup[13]. An intense peak at *m/e* 187, due to the oxycarbonium ion **11**, occurred in the mass spectra of both **5** and **7**.

With a much larger concentration of hydrogen bromide, allitol gave an anhydrodibromodideoxyhexitol and a crystalline anhydrohexitol which have not yet been characterised.

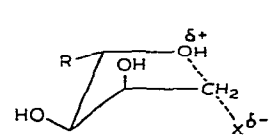
Although 1,6-dichloro-1,6-dideoxy-D-mannitol was the major product from the reaction of D-mannitol with fuming hydrochloric acid in a sealed tube[9], products thought to be the 6-chloro and 2,6- or 5,6-dichloro derivatives of 1,4-anhydro-D-mannitol and a chloro derivative of 1,4:3,6-dianhydro-D-mannitol were also obtained[14]. It was concluded that the 1,4-anhydrohexitol was initially formed under dehydration conditions and was readily converted into the 1,4:3,6-dianhydrohexitol, which underwent ring opening on reaction with excess of hydrogen chloride. Since allitol does not form a 1,4:3,6-dianhydride, because of the steric strain involved in the formation of two *trans*-fused tetrahydrofuran rings[15], the reaction of allitol with hydrogen halides under pressure results in the sequential formation of 1,4-anhydro-DL-allitol and 1,4-anhydro-6-deoxy-6-halogeno-DL-allitol (**3**, **4**). Further halogenation of **3** (or **4**) may then occur in the presence of a large excess of hydrogen halide, but our results show that ring opening to give a 1,6-dideoxy-1,6-dihalogenoallitol is not favoured. The ease of opening of a 1,4-anhydro ring by hydrogen halide appears to be dependent on the relative spatial dispositions of HO-2 and the side chain (R) at C-4. Assuming that the transition state for ring opening with hydrogen halide is similar to that involved in anhydro ring formation[16], ring opening in the *manno* (**16**) and *galacto* (**17**) compounds is facilitated by the relief of the strong *syn*-axial interaction between O-2 and the side chain, R, whereas this interaction is not present in the *allo* compound **18**.



16



17



18

EXPERIMENTAL

General. — Organic solutions were dried over anhydrous sodium sulphate and concentrated below 40° under reduced pressure. Thin-layer chromatography (t.l.c.) was performed on Kieselgel G (Merck), using (*A*) ethyl acetate–light petroleum (3:1) or (*B*) ethyl acetate–ethanol–water (10:3:2). Mass spectra were recorded by P.C.M.U., Harwell, using an AEI MS-902 instrument operating at 70 eV with a direct-insertion system. Infrared spectra were obtained for Nujol mulls on a Perkin–Elmer Model 237 spectrometer. N.m.r. spectra were recorded at 60 MHz for solutions in pyridine containing tetramethylsilane as internal standard.

The reduction of D-allose (13 g) dissolved in water (85 ml) with sodium borohydride (4 g), followed by deionisation and removal of boric acid by co-distillation with methanol, gave allitol (**1**; 11.3 g, 87%), m.p. 149–150°; lit.[17] m.p. 150–151°. The hexa-acetate had m.p. 59–61° (from aqueous ethanol); lit.[18] m.p. 61°.

Reaction of allitol with fuming hydrochloric acid. — Hydrogen chloride was passed for ~2 h into conc. hydrochloric acid (40 ml, 35%) cooled in ice. Allitol (5 g) was dissolved in this solution which was then heated in a sealed Pyrex tube at 100°. Some decomposition had occurred after 22 h when the reaction was terminated. The dark-red solution was concentrated and several aliquots of water were added to, and evaporated from, the residue. Decolorisation of the resulting aqueous solution with charcoal, followed by evaporation, gave a pale-yellow syrup (5.1 g) containing the following four components (t.l.c) which were isolated by p.l.c. with chloroform–methanol (15:1). *A* (384 mg, 6%) was crystallised from light petroleum to yield 1,4-anhydro-5,6-dichloro-5,6-dideoxy-2,3-*O*-isopropylidene-DL-talitol (**13**, 233 mg), m.p. 50–51.5°, R_F 0.71 (solvent *A*), ν_{max} 1375 cm^{-1} (CMe_2). N.m.r. data: τ 5.1 (m, 4 protons), 5.5 (m, 2 protons), 6.25 (m, 3 protons), 8.5, 8.7 (s, CMe_2). Mass spectrum: *m/e* 225, 227, and 229 (Cl isotope ratio 57:39:7, $(M-CH_3)$], 165, 167, and 169 [48:27:5, $(M-CH_3-HOAc)$, metastable ions at 121, 123], 59 (57, $Me_2\overset{+}{C}OH$), 43 (100, $CH_3\overset{+}{C}O$). Accurate mass measurement on the peak at *m/e* 225 gave the formula $C_8H_{11}Cl_2O_3$.

Anal. Calc. for $C_9H_{14}Cl_2O_3$: C, 44.8; H, 5.8; Cl, 29.4. Found: C, 44.4; H, 5.7; Cl, 29.0.

90% Aqueous trifluoroacetic acid (room temperature, 0.25 h) converted **13** into a single product, R_F 0.50 (solvent *A*); concentration of the mixture and reaction of the residue with 2,2-dimethoxypropane regenerated **13** (t.l.c.).

B (1.1 g, 18%) was crystallised from light petroleum (b.p. 60–80°) to give 1,4-anhydro-6-chloro-6-deoxy-2,3-*O*-isopropylidene-DL-allitol (**9**, 470 mg), m.p. 78–81°, ν_{max} 3380 (sharp, OH), 1375 cm^{-1} (CMe_2).

Anal. Calc. for $C_9H_{15}ClO_4$: C, 48.5; H, 6.75; Cl, 15.9. Found: C, 48.3; H, 6.5; Cl, 16.1.

The 5-acetate (**10**) of **9** had m.p. 33–36° (from aqueous ethanol), ν_{max} 1755, 1740 (C=O), 1375 cm^{-1} (CMe_2). Mass spectrum: *m/e* 249, 251 [chlorine isotope ratio 53:18), $(M-CH_3)^+$], 143 (22), 59 (31, Me_2COH), 43 (100, $CH_3\overset{+}{C}O$).

Anal. Calc. for $C_{11}H_{17}ClO_5$: C, 49.8; H, 6.4; Cl, 13.4. Found C, 49.4; H, 6.2; Cl, 13.7.

Compound **9** (250 mg) was stored with 90% aqueous trifluoroacetic acid (4 ml) for 1 h. Concentration of the solution gave a syrup which was acetylated to yield 2,3,5-tri-*O*-acetyl-1,4-anhydro-6-chloro-6-deoxy-DL-allitol (**2**, 70 mg), m.p. 80–83°, identical (i.r., t.l.c.) with the authentic compound described below.

C (1.1 g, 20%) was syrupy 1,4-anhydro-5,6-dichloro-5,6-dideoxy-DL-talitol (**14**), R_F 0.48 (solvent *A*) ν_{max} 3370 (broad) cm^{-1} (OH).

Acetonation of a portion (500 mg) of *C* with 2,2-dimethoxypropane (6 ml)

catalysed by toluene-*p*-sulphonic acid gave 1,4-anhydro-5,6-dichloro-5,6-dideoxy-2,3-*O*-isopropylidene-DL-talitol (310 mg), m.p. 52–54°, which was identical (i.r. and mass spectra) with **13** described above.

Acetylation of *C* gave syrupy 2,3-di-*O*-acetyl-1,4-anhydro-5,6-dichloro-5,6-dideoxy-DL-talitol (**15**), b.p. 160–170°/0.02 mmHg, ν_{max} 1745 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{14}Cl_2O_5$: C, 42.1; H, 4.9; Cl, 24.9. Found: C, 42.0; H, 4.8; Cl, 24.8.

D (261 mg, 5%) was a syrup having ν_{max} 3350 (broad) cm^{-1} (OH). Acetylation gave 2,3,5-tri-*O*-acetyl-1,4-anhydro-6-chloro-6-deoxy-DL-allitol (**2**; 166 mg, 38%), m.p. 82–84°, identical (i.r. and t.l.c.) with the authentic material described below.

Acetonation of *D* with 2,2-dimethoxypropane, as described above, gave one major product, R_F 0.57 (solvent *A*), which exhibited behaviour on t.l.c. identical with that of **9**.

Reaction of allitol with fuming hydrobromic acid. — A solution of allitol (5 g) in ~60% hydrobromic acid (25 ml) was heated at 70° for 5 h in a sealed glass tube; concentration then afforded a dark-red syrup (6.8 g) containing two major components, R_F 0.79, 0.57 (solvent *B*) which were separated by p.l.c. (solvent *B*).

The faster moving component was syrupy 1,4-anhydro-6-bromo-6-deoxy-DL-allitol (**4**; 3.1 g, 50%); R_F 0.79, ν_{max} 3350 (broad) cm^{-1} (OH). Acetylation of a portion (306 mg) gave the 2,3,5-triacetate **5** (167 mg), m.p. 84–86° (from aqueous ethanol), ν_{max} 1755, 1738 cm^{-1} (C=O). Mass spectrum: *m/e* 353, 355 [Br isotope ratio 0.1:0.1, (M+1)], 187 (88), 127 (30, a metastable peak at 86.4 was observed for this step); 85 (64), 43 (100, $CH_3\overset{+}{C}O$).

Anal. Calc. for $C_{12}H_{17}BrO_7$: C, 40.7; H, 4.8. Found: C, 40.6; H, 4.7.

The second component was 1,4-anhydro-DL-allitol (**6**; 1.2 g, 27%), m.p. 80–83° (from ethanol), ν_{max} 3360 (broad) cm^{-1} (OH); lit.[14] m.p. 83–85°. Mass spectrum: *m/e* 146 [2, $(M-H_2O)$], 133 [3, $(M-CH_2OH)$], 103 (100, $C_4H_7O_3$).

The 2,3,5,6-tetra-acetate (**7**) of **6** had m.p. 62–64° (from aqueous ethanol), ν_{max} 1755, 1734 cm^{-1} (C=O). Mass spectrum: *m/e* 332 (0.7, M); 187 (80), 43 (100, $CH_3\overset{+}{C}O$).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.6; H, 6.0; OAc, 51.9. Found: C, 50.3; H, 6.0; OAc, 50.9.

1,4-Anhydro-DL-allitol (**6**). — A solution[19] of allitol (5 g) in water (190 ml) containing conc. sulphuric acid (10 ml) was heated under reflux for 30 h. The cooled solution was neutralised ($BaCO_3$), filtered, concentrated to a small volume, and deionised by passage through a column of Biodeminrolit mixed-bed resin. Concentration of the eluate and crystallisation of the residue from ethanol gave **6** (2.5 g, 56%), m.p. 80–83°, ν_{max} 3360 (broad) cm^{-1} (OH).

A second crop (1.1 g) was obtained by dilution of the mother liquors with ether.

2,3,5-Tri-O-acetyl-1,4-anhydro-6-O-tosyl-DL-allitol (**8**). — A solution of **6** (2.31 g) and toluene-*p*-sulphonyl chloride (2.7 g, 5% excess) in pyridine (40 ml) was stirred for 21 h at room temperature. Acetic anhydride (10 ml) was then added to the cooled solution and, after 24 h, the reaction mixture was treated with excess of ice–

water. Chloroform extraction afforded a syrup (6.1 g), which partially crystallised from ethanol. Recrystallisation of the product from the same solvent gave **8** (1.37 g, 22%), m.p. 73–75°, ν_{max} 1753, 1741 (C=O), 1600 cm^{-1} (C=C, aromatic).

Anal. Calc. for $C_{19}H_{24}O_{10}S$: C, 51.5; H, 5.4; S, 7.2. Found: C, 51.3; H, 5.4; S, 7.0.

2,3,5-Tri-O-acetyl-1,4-anhydro-6-bromo-6-deoxy-DL-allitol (**5**). — A solution of **8** (400 mg) in acetic anhydride (15 ml) containing sodium bromide (500 mg) was heated under reflux for 5 h. The reaction was diluted with ice–water and extracted with chloroform to yield a syrup (340 mg) which crystallised from ethanol. Recrystallisation of the product from the same solvent gave **5** (84 mg, 26%), m.p. 81–83°, ν_{max} 1755, 1738 cm^{-1} (C=O).

Anal. Calc. for $C_{12}H_{17}BrO_7$: C, 40.7; H, 4.8; Br, 22.6. Found: C, 41.8; H, 4.9; Br, 19.9.

2,3,5-Tri-O-acetyl-1,4-anhydro-6-chloro-6-deoxy-DL-allitol (**2**). — Reaction of **8** (407 mg) with anhydrous lithium chloride (505 mg) in acetic anhydride (15 ml) for 24 h, as described above, gave **2** (145 mg, 51%), m.p. 75–77° (from aqueous ethanol), ν_{max} 1740, 1735 cm^{-1} (C=O).

Anal. Calc. for $C_{12}H_{17}ClO_7$: C, 46.7; H, 5.5; Cl, 11.5. Found: C, 47.2; H, 5.7; Cl, 10.8.

ACKNOWLEDGMENTS

The authors thank Dr. R. F. M. White for determining the n.m.r. spectra, and Mr. B. Saunderson for performing the microanalyses. This work was supported by a grant from the Cancer Research Campaign.

REFERENCES

1 W. C. J. Ross, *Biological Alkylating Agents*, Butterworths, London, 1962, pp. 137–140.
2 G. M. Timmis and S. S. Brown, *Biochem. Pharmacol.*, 3 (1960) 247.
3 B. Kellner and L. Nemeth, *Brit. J. Cancer*, 13 (1959) 469.
4 J. Kuszmann and L. Vargha, *Carbohyd. Res.*, 16 (1971) 261.
5 T. Horvath and L. Vargha, *Carbohyd. Res.*, 16 (1971) 253.
6 L. Vargha, O. Feher, T. Horvath, L. Toldy, and J. Kuszmann, *Acta Chim. Hung.*, 25 (1960) 361.
7 W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, 44 (1966) 836; V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, 43 (1965) 3452.
8 L. Institoris, I. P. Horvath, and E. Csanyi, *Arzneimittel-Forsch.*, 17 (1967) 145.
9 W. N. Haworth, R. L. Heath, and L. F. Wiggins, *J. Chem. Soc.*, (1944) 155.
10 D. C. DeJongh and K. Biemann, *J. Amer. Chem. Soc.*, 86 (1964) 67.
11 N. K. Kochetkov and O. S. Chizhov, *Advan. Carbohyd. Chem.*, 21 (1966) 39.
12 S. J. Angyal, V. A. Pickles, and R. Ahluwalia, *Carbohyd. Res.*, 3 (1967) 300.
13 R. Barker, *J. Org. Chem.*, 29 (1964) 869.
14 R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, (1948) 2204.
15 L. F. Wiggins, *Advan. Carbohyd. Chem.*, 5 (1950) 191.
16 B. G. Hudson and R. Barker, *J. Org. Chem.*, 32 (1967) 3650; R. Barker, *ibid.*, 35 (1970) 461.
17 M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 19 (1936) 188.
18 J. Wiemann, *Ann. Chim. (Paris)*, 5 (1936) 267.
19 J. Baddiley, J. G. Buchanan, and B. Carss, *J. Chem. Soc.*, (1957) 4138.