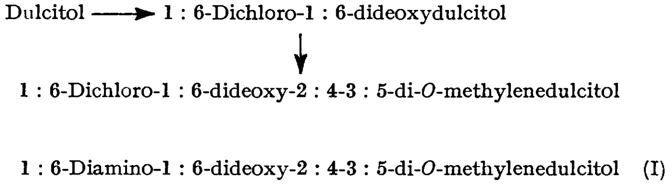
128. *The Structure of Bouchardat's Dichlorodideoxydulcitol and the Synthesis of* 1 : 6-*Diamino*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol.*

By K. Butler and W. A. W. Cummings.

The structure of a dichlorodideoxydulcitol prepared by Bouchardat[1] is proved by synthesis. The preparation of 1 : 6-diamino-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol, together with characteristic derivatives, is described.

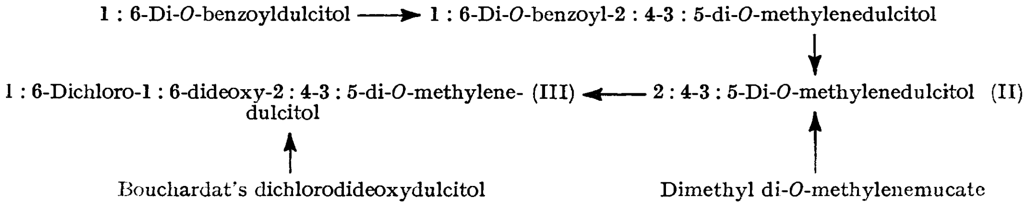
Diamines derived from carbohydrate sources may offer useful monomers for the preparation of polyamides. To obviate cross-linking during the polymerisation process it is necessary to protect the hydroxyl groups, and methylene bridges have been used for this purpose. Further, for the preparation of linear unbranched polymers it is essential that the amino-groups be attached to terminal carbon atoms of the monomer chain. For example, Haworth, Heath, and Wiggins[2] have prepared a fibre-forming polymer from 1 : 6-diamino-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenemannitol and adipic acid.

In the present work the sugar alcohol selected was dulcitol, and a possible route to the required diamine is :



A dichlorodideoxydulcitol first described by Bouchardat[1] was considered by Hamamura[3] to be 1 : 6-disubstituted. Hamamura found that it gave monochloroacetaldehyde (identified as its 2 : 4-dinitrophenylhydrazone) when oxidised with lead tetra-acetate in benzene. With lead tetra-acetate in acetic acid he obtained a compound which he believed to be 2-hydroxy-3 : 4-epoxybutyraldehyde, but which was being further examined. Although this evidence suggests that Bouchardat's compound was 1 : 6-dichloro-1 : 6-dideoxydulcitol, it was necessary to establish the structure unequivocally before proceeding with the amination experiments.

The following synthetic route provides an unambiguous proof of the position of the chlorine atoms.



1 : 6-Di-*O*-benzoyldulcitol (structure proved by Hann, Maclay, and Hudson[4]) on treatment with paraformaldehyde and concentrated sulphuric acid gave 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylenedulcitol. Removal of the benzoyl groups with a catalytic amount of sodium methoxide gave 2 : 4-3 : 5-di-*O*-methylenedulcitol (II), also formed by the reduction of dimethyl di-*O*-methylenemucate[5] with lithium aluminium hydride. The latter

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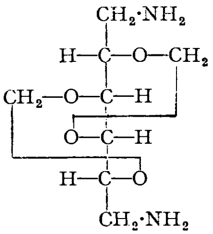
[1] Bouchardat, *Ann. Chim. Phys.*, 1872, **27**, 174.
[2] Haworth, Heath, and Wiggins, *J.*, 1944, 155.
[3] Hamamura, *Bull. Agric. Chem. Soc. Japan*, 1942, **18**, 54.
[4] Hann, Maclay, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 2432.
[5] Personal communication from Prof. M. Stacey.

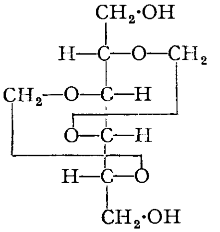
experiment provided an independent confirmation that the primary hydroxyl groups were unsubstituted. Finally, chlorination of the di-*O*-methylene compound, with thionyl chloride in pyridine, yielded 1 : 6-dichloro-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol (III).

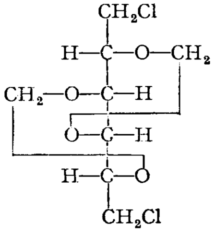
Interaction of Bouchardat's dichlorodideoxydulcitol with paraformaldehyde and concentrated sulphuric acid gave a di-*O*-methylene derivative identical with the product (III). Bouchardat's compound must therefore be 1 : 6-dichloro-1 : 6-dideoxydulcitol.

The orientation of the methylene groups has not been proved, but from the rules deduced by Barker, Bourne, and Whiffen[6] they probably bridge positions 2 : 4 and 3 : 5.

Treatment of the dichloride (III) with a large excess of 30% aqueous ammonia solution in an autoclave gave an amine hydrochloride, from which 1 : 6-diamino-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol (I) was isolated by treatment with excess of barium hydroxide. A yield of 60% of distilled diamine was obtained. It formed a crystalline dihydrochloride and dipicrate. If heating of the dichloro-compound and ammonia was continued for too long, a spongy halogen-free compound was produced (probably a cross-linked polyamine), and the yield of diamine was reduced. After 5 days' heating, for example, 40% of the weight of starting material had been converted into the polymer, and the yield of amine was only 20%.


(I)


(II)


(III)

The diamine was also synthesised by an alternative route in which 1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylene-1 : 6-diphthalimidodulcitol was the intermediate, but the overall yield was lower. The diphthalimido-compound was prepared by heating together the dichloride (III) and potassium phthalimide. When glycerol was used as the reaction medium a low yield (25%) was obtained, but in *NN*-dimethylformamide the yield was 85%. Hydrolysis of the diphthalimido-compound by means of hydrazine[7] gave the diamine, but in low yield. When condensed with phthalic anhydride this gave a 1 : 6-diphthalimido-derivative identical with that obtained from dichlorodimethylenedulcitol and potassium phthalimide.

Other routes to 1 : 6-diamino-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol were explored, but, as in each case the yields in the initial stages were low, none was pursued to completion. Three methods were considered : (*a*) conversion of mucic acid into 2 : 4-3 : 5-di-*O*-methylenemucamide[8] (overall yield about 50%) which on interaction with thionyl chloride gave 2 : 4-3 : 5-di-*O*-methylenemuconitrile (19%) ; (*b*) if dulcitol could be converted into 1 : 6-di-*O*-benzoyldulcitol in high yield, the method used to prove the structure of 1 : 6-dichloro-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol might afford a useful synthetic route : the yield, however, was only 11% ; in (*c*), dulcitol was converted into 1 : 4-3 : 6-di-*O*-methylenedulcitol[9] which, unlike *iso*propylidene derivatives,[4] did not rearrange on benzoylation in the presence of quinoline to give the required 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylenedulcitol. Instead, 2 : 5-di-*O*-benzoyl-1 : 4-3 : 6-di-*O*-methylenedulcitol was formed.

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[6] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.

[7] Ing and Manske, *J.*, 1926, 2348.

[8] Butler and Lawrance, unpublished work.

[9] Weber and Tollens, *Ber.*, 1897, **30**, 2511; *Annalen*, 1898, **299**, 318.

EXPERIMENTAL

Bouchardat's Dichlorodideoxydulcitol.—Dulcitol (120 g.) was dissolved in fuming hydrochloric acid (*d* 1·19; 1200 ml.) and sealed off in six glass tubes. These were enclosed in screw-cap iron tubes and heated in an air-oven for 48 hr. at 100°. Only a slight pressure was noticed when the tubes were opened. The brown solution produced was filtered and cooled to 0° for 24 hr., giving yellow-brown crystals of dichlorodideoxydulcitol (27·25 g.), m. p. 183—184° (decomp.). Evaporation of the mother-liquors to about 900 ml. at <50° under diminished pressure gave a further 8·65 g., m. p. 183—185° (decomp.) (total yield 24%). Evaporation to dryness left a residue (77·1 g.) which was dissolved in fuming hydrochloric acid (770 ml.) and sealed up as before. The solution was heated to 100° during 7 hr. and then maintained at 100° for 48 hr. Isolation by the foregoing procedure gave a further batch of dichlorodideoxydulcitol (16·5 g., 10%), m. p. 182—183° (decomp.) (Found: C, 32·8; H, 5·3; Cl, 31·6. Calc. for $C_6H_{12}O_4Cl_2$: C, 32·9; H, 5·5; Cl, 32·4%).

1 : 6-*Dichloro*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol.*—Dichlorodideoxydulcitol (23 g.) was intimately mixed with paraformaldehyde (23 g.), concentrated sulphuric acid (15 ml.) added, and the paste heated to about 60° with shaking. The product was extracted by shaking for 3 hr. with chloroform (250 ml.) and then twice for 1 hr. with fresh chloroform (250 ml.). The combined extracts were washed successively with 5% ammonia solution and water, and then dried ($MgSO_4$). Evaporation of the extracts to dryness gave 1 : 6-*dichloro*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol* (19·2 g., 76%) which crystallised from absolute ethanol as needles, m. p. 77—78° (Found: C, 39·3; H, 4·8. $C_8H_{12}O_4Cl_2$ requires C, 39·5; H, 4·9%).

1 : 6-*Di*-O-*benzoyl*-2 : 4-3 : 5-*di*-O-iso*propylidenedulcitol.*—Dulcitol (25 g.) was shaken with acetone (490 ml.) containing dry hydrogen chloride (12 g.) for 24 hr. After unchanged dulcitol had been filtered off, sodium carbonate (anhyd.; 50 g.) was added, and the mixture stirred for 3 hr. and set aside overnight. The filtered solution was concentrated to 140 ml. and the insoluble product collected. This mixture of di-*O*-*iso*propylidenedulcitols (21·5 g.) was shaken with quinoline (23·2 g.) and benzoyl chloride (23·2 g.) and then heated at 100° for 6 hr. Excess of benzoyl chloride was removed by addition of ethanol (250 ml.) and then by heating for 30 min. at 100°. After cooling of the reactants, the solid was collected, washed with ethanol, and dried, giving a colourless powder (26 g., 65%), m. p. 182—183°, which crystallised from carbon tetrachloride as irregular prisms, m. p. 185—187° (lit., 185—186°) (Found: C, 66·0; H, 6·3. Calc. for $C_{26}H_{30}O_8$: C, 66·4; H, 6·4%).

1 : 6-*Di*-O-*benzoyldulcitol.*—1 : 6-Di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-*iso*propylidenedulcitol (13 g.) was heated with 80% acetic acid (300 ml.) for 45 min. On cooling, 1 : 6-di-*O*-benzoyldulcitol crystallised as plates (10 g., 100%), m. p. 205—208°. Recrystallisation from acetic acid afforded the pure compound, m. p. 209—210° [lit., 209° (corr.)] (Found: C, 61·5; H, 5·4. Calc. for $C_{20}H_{22}O_8$: C, 61·5; H, 5·6%).

1 : 6-*Di*-O-*benzoyl*-2 : 4-3 : 5-*di*-O-*methylenedulcitol.*—1 : 6-Di-*O*-benzoyldulcitol (5 g.), paraformaldehyde (5 g.), and concentrated sulphuric acid (3·75 ml.) were treated in a similar manner to that described for 1 : 6-dichloro-1 : 6-dideoxy-2 : 4-3 : 5-di-*O*-methylenedulcitol. Three crystallisations of the crude product from absolute ethanol gave 1 : 6-*di*-O-*benzoyl*-2 : 4-3 : 5-*di*-O-*methylenedulcitol* (2·75 g., 52%) as needles, m. p. 109·5—110·5° (Found: C, 64·0; H, 5·2. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·3%).

2 : 4-3 : 5-*Di*-O-*methylenedulcitol.*—To a solution of 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylenedulcitol (2 g.) in chloroform (50 ml.) at 0°, sodium methoxide solution (0·1N; 5 ml.) was added and the mixture set aside overnight. After evaporation of the solvent and removal of methyl benzoate by ether-extraction, 2 : 4-3 : 5-*di*-O-*methylenedulcitol* remained, which crystallised from absolute ethanol as needles (0·6 g., 66%), m. p. 104—104·5° (Found: C, 46·3; H, 6·7. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%).

Reduction of Dimethyl Di-O-*methylenemucate.*—The ester (13·1 g.), contained in a Soxhlet thimble, was added during 24 hr. to a suspension of lithium aluminium hydride (5 g.) in boiling ether (400 ml.). Water (150 ml.) and then 10% sulphuric acid (150 ml.) were gradually added and the ether layer was removed. The aqueous layer was almost neutralised (sodium carbonate), concentrated to 100 ml., and extracted with ether. The combined ethereal solutions were evaporated, giving crude 2 : 4-3 : 5-*di*-O-*methylenedulcitol* (8·35 g., 81%), m. p. 99—103°, which, on crystallisation from absolute ethanol, afforded plates, m. p. 104—104·5° not depressed on admixture with a sample prepared by hydrolysis of 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylenedulcitol (Found: C, 46·6; H, 6·5. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8%).

1 : 6-*Dichloro*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol.*— 2 : 4-3 : 5-Di-*O*-methylenedulcitol (0·5 g.) was suspended in pyridine (2 ml.), and thionyl chloride (1·3 ml.) added. The

mixture was heated on the steam-bath for 2 hr., poured on ice, and chloroform (50 ml.) added. The brown precipitate was filtered off and washed with chloroform (50 ml.). The aqueous layer in the filtrate was separated and twice extracted with chloroform (50 ml.). The combined extracts were washed successively with saturated sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation to dryness gave a yellow-brown gum, which, on being dissolved in absolute ethanol, treated with charcoal, and concentrated to 5 ml., gave 1 : 6-*dichloro*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol* (0·16 g., 27%) as needles, m. p. 75—77°. After recrystallisation from absolute ethanol the pure compound was obtained, having m. p. 77—78°, undepressed on admixture with the compound from Bouchardat's dichlorodideoxydulcitol (Found : C, 39·4; H, 4·7. $C_8H_{12}O_4Cl_2$ requires C, 39·5; H, 4·9%).

1 : 6-*Diamino*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol*.—Dichlorodimethylenedulcitol (110 g.) and 30% ammonia solution (1980 ml.) were heated in an autoclave with stirring for 24 hr. at 110—115°. Subsequent operations were carried out in an atmosphere of nitrogen. The resulting brown solution was evaporated to dryness, hydrated barium hydroxide (143 g.) and water (1100 ml.) were added, and the mixture was heated under reflux for 1 hr. It was then evaporated to dryness and the amine extracted by boiling six times with chloroform (6 × 1400 ml.). The combined extracts were dried ($MgSO_4$), and the solvent was removed. The residual brown oil was purified by several distillations under reduced pressure. The pure 1 : 6-*diamine* (56·25 g., 61%) was obtained as a colourless oil, b. p. 120—124°/0·07 mm., which solidified (Found : C, 46·7; H, 7·8; N, 13·5; Amine equivs./10^6 g., 9790. $C_8H_{16}O_4N_2$ requires C, 47·1; H, 7·8; N, 13·7%; Amine equivs./10^6 g., 9803).

The *dihydrochloride* formed needles (from aqueous ethanol), m. p. *ca.* 270° (decomp.) (Found : C, 34·7; H, 6·7; N, 10·3. $C_8H_{16}O_4N_2,2HCl$ requires C, 34·7; H, 6·5; N, 10·1%), and the *dipicrate*, yellow needles (from aqueous ethanol), m. p. 271—273° (decomp.) (Found : C, 36·1; H, 3·4; N, 16·8. $C_8H_{16}O_4N_2,2C_6H_3O_7N_3$ requires C, 36·2; H, 3·3; N, 16·9%).

1 : 6-*Dideoxy*-2 : 4-3 : 5-*di*-O-*methylene*-1 : 6-*diphthalimidodulcitol*.—Dichlorodimethylenedulcitol (10 g.), potassium phthalimide (20 g.), and *NN*-dimethylformamide (50 ml.) were heated for 6 hr. at 180°. The cold mixture was poured into water, giving a solid (17·75 g.). This was extracted (Soxhlet) with chloroform, leaving the 1 : 6-*diphthalimido-derivative* (16·2 g., 85%) which crystallised from chloroform–light petroleum (b.p. 60—80°) as needles, m. p. 277—279° (decomp.) (Found : C, 61·4; H, 4·5; N, 6·0. $C_{24}H_{20}O_8N_2$ requires C, 62·1; H, 4·3; N, 6·0%).

Hydrolysis.—(*a*) The 1 : 6-diphthalimido-compound (4·64 g.) was heated for 2 hr. at 100° with absolute ethanol (20 ml.) and 50% hydrazine hydrate (2·5 ml.). The solvent was removed by distillation, the residual mixture made acid to Congo-red with 2N-hydrochloric acid, and the precipitate of phthalhydrazide filtered off. The filtrate was evaporated to dryness, heated under reflux with barium hydroxide solution, again evaporated to dryness, and extracted with hot chloroform. The crude diamine so obtained was converted into the dihydrochloride, which crystallised from ethanol–water as needles (0·35 g., 13%), m. p. *ca.* 270° (decomp) (Found : C, 34·4; H, 6·0%).

(*b*) In a similar experiment, with the diphthalimido-compound (16·2 g.), hydrazine hydrate (8 ml.), and absolute ethanol (50 ml.), the pure diamine was isolated by distillation as a pale-yellow oil (1·8 g., 26%), b. p. 140—148° (air-bath)/0·5—1 mm.

Condensation of 1 : 6-*Diamino*-1 : 6-*dideoxy*-2 : 4-3 : 5-*di*-O-*methylenedulcitol with Phthalic Anhydride*.—The diamine (1·04 g.) was heated with phthalic anhydride (1·46 g.) at 160° for 2 hr. Some frothing occurred at first and a solid cake was soon produced. The product was then extracted (Soxhlet) with chloroform. The extract was diluted with more chloroform, boiled with charcoal, and filtered, and light petroleum (b. p. 60—80°) was added. The 1 : 6-diphthalimido-compound (0·55 g., 23%) separated from the cold solution as needles (Found : N, 6·0%), m. p. 280—281°, not depressed on admixture with the previous product.

2 : 4-3 : 5-*Di*-O-*methylenemuconitrile*.—2 : 4-3 : 5-Di-*O*-methylenemucamide (10 g.) and freshly distilled thionyl chloride (20 ml.) were heated at 100° for 6 hr. Excess of thionyl chloride was removed *in vacuo*, and finally by drying over potassium hydroxide in a desiccator. Two crystallisations of the product from absolute alcohol gave the *dinitrile* (1·6 g., 19%) as needles, m. p. 126—128° (Found : C, 49·2; H, 4·2. $C_8H_8O_4N_2$ requires C, 49·0; H, 4·1%).

1 : 6-*Di*-O-*benzoyldulcitol*.—To a suspension of dulcitol (9·1 g.) in quinoline (12·95 ml.) at 100°, benzoyl chloride (11·55 ml.) was added, and the mixture was shaken vigorously and then heated for 6 hr. Excess of benzoyl chloride was removed by addition of absolute ethanol (60 ml.) and heating for 30 min. at 100°. The solid was filtered off, washed with ethanol and ether, and crystallised from glacial acetic acid, giving colourless 1 : 6-di-*O*-benzoyldulcitol (2·05 g., 11%), m. p. and mixed m. p. 209—210°.

Attempted Preparation of 1 : 6-*Di*-O-*benzoyl*-2 : 4-3 : 5-*di*-O-*methylenedulcitol from* 1 : 3-4 : 6-*Di*-O-*methylenedulcitol*.—The 1 : 3-4 : 6-compound (5·15 g.), suspended in quinoline (6·5 ml.), was heated on the steam-bath and benzoyl chloride (5·8 ml.) added. The mixture was heated for 6 hr., ethanol (45 ml.) added, and heating continued for a further 30 min. The colourless crystals (7·45 g., 72%), when washed with ethanol, had m. p. 220—224° [lit., 228—231° for the 2 : 5-di-*O*-benzoyl derivative; 1 : 6-derivative (see above), m. p. 109·5—110·5°].

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