THE CHEMISTRY OF ANTI-PERNICIOUS ANÆMIA FACTORS

PART IV. BENZIMINAZOLE GLYCOSIDES

(2) SYNTHETIC ROUTES TO THE BENZIMINAZOLE-1-D-GLUCOPYRANOSIDES

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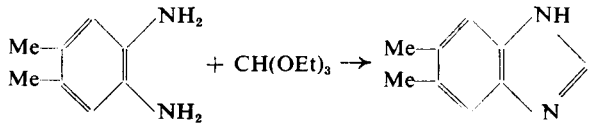
SUCCESSFUL completion of the investigation outlined in the preceding paper (Part IV (I))[1] furnished *o*-phenylenediamine glycosides (e.g., I) suitable for conversion into benziminazole glycosides (e.g., IV). Their instability to acids, however, precluded their conversion into the latter compounds by methods successfully used in Part III[2]. We therefore directed our attention, in the first instance, to the elaboration of milder cyclisation procedures employing *o*-phenylenediamine-tetraacetyl-D-glucopyranoside (I) for these model experiments.

Fundamentally the problem presented in the conversion of (I) into (IV) is the introduction of a methine group between two reactive centres. A similar problem was involved in the synthesis of the carbocyanine dyes from quinaldine alkiodides. Its solution by Hamer[3], who replaced formic acid or formaldehyde by ethyl orthoformate, furnished the essential clue to a new synthesis of benziminazoles[4] which forms the subject of the present communication.

Preliminary experiments showed that *o*-phenylenediamine and its *N*-alkylated derivatives underwent facile conversion into the corresponding benziminazoles on treatment with ethyl orthoformate:



The reaction could be conducted in an excess of the ester at an elevated temperature or in a solvent such as ethyl alcohol or ethyl acetate, the benziminazole being generally obtained in almost quantitative yield.

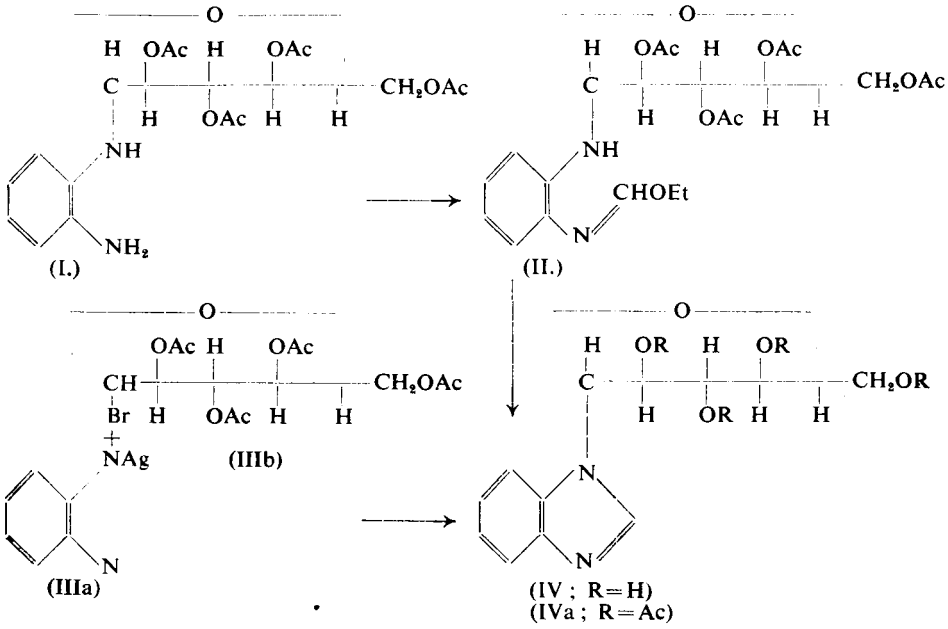
An unexpected difficulty was encountered, however, in the first application of this synthesis to an *o*-phenylenediamine glycoside. Reaction of *o*-phenylenediamine-tetraacetyl-D-glucoside (I) with ethyl orthoformate gave a crystalline product in high yield which, although giving reasonable analytical figures for (IVa), yet failed to exhibit the typical 1-substituted benziminazole absorption spectrum (Fig. I). Elemental analysis and molecular weight determinations finally led to its formulation as a 2-ethoxymethylene-*o*-phenylenediamine-tetraacetyl-D-glucoside (II). The formation of ethyl *iso*formanilides such as (II) from primary arylamines and orthoformates, it may be added, has previously been recorded by a number of workers[5].

The conversion of (II) into the benziminazole glycoside (IVa) likewise presented considerable initial difficulty[4]. Systematic study led ultimately to the discovery that carefully controlled treatment with very dilute

hydrochloric acid (0·05 to 0·1 N) at 100°C. resulted in smooth conversion into benziminazole-1-tetraacetyl-D-glucoside (IVa).

The constitution assigned to this product was confirmed by its ultraviolet absorption spectrum which bore the characteristics of a 1-substituted benziminazole (Fig. 1). The procedure employed for its synthesis, however, left undefined the stereochemical configuration of the glycosidic centre and the size of the lactol ring.

Two methods have hitherto been employed for the determination of the αβ-configuration of *N*-glycosides. The first, depending upon mutarotation studies[6], is not applicable in this instance owing to the quite remarkable stability of (IV) to acids (*vide infra*). The second depends



upon the interaction of a nitrogenous base, or of its metal derivatives, with an acetohalogeno-sugar and upon the reasonable assumption that a Walden inversion takes place in such a reaction[7]. This assumption appears to be warranted in many cases and is supported indirectly by the kinetic studies of Ingold, Hughes and their collaborators[8] to which Howard has recently drawn attention[9] in this connection. Nevertheless, as the latter author points out (*loc. cit.*), retention of configuration is occasionally encountered in the reaction of certain acetohalogeno-sugars with nucleophilic reagents. In so far as the present evidence allows, however, condensation of α-acetobromglucose with the silver salt of a base appears in general to lead to an *N*-glucoside possessing a β-configuration, and this view has been adopted in the present investigation.

Bearing the above theoretical consideration in mind, we examined the reaction between benziminazole silver[10] (IIIa) and α-acetobromglucose (IIIb) in xylene solution. Facile reaction occurred to give a benzimin-

azole-1 β-tetraacetyl-D-glucoside, identical in m.pt., mixed m.pt. specific rotation, and ultraviolet absorption spectrum (Fig. I) with the product obtained by the "orthoformate route." The latter must, therefore, be assigned the constitution of benziminazole-1-β-tetraacetyl-D-glucopyranoside (IVa).

A number of procedures were examined for the hydrolysis of (IVa), the products being investigated on unidimensional paper chromatograms by

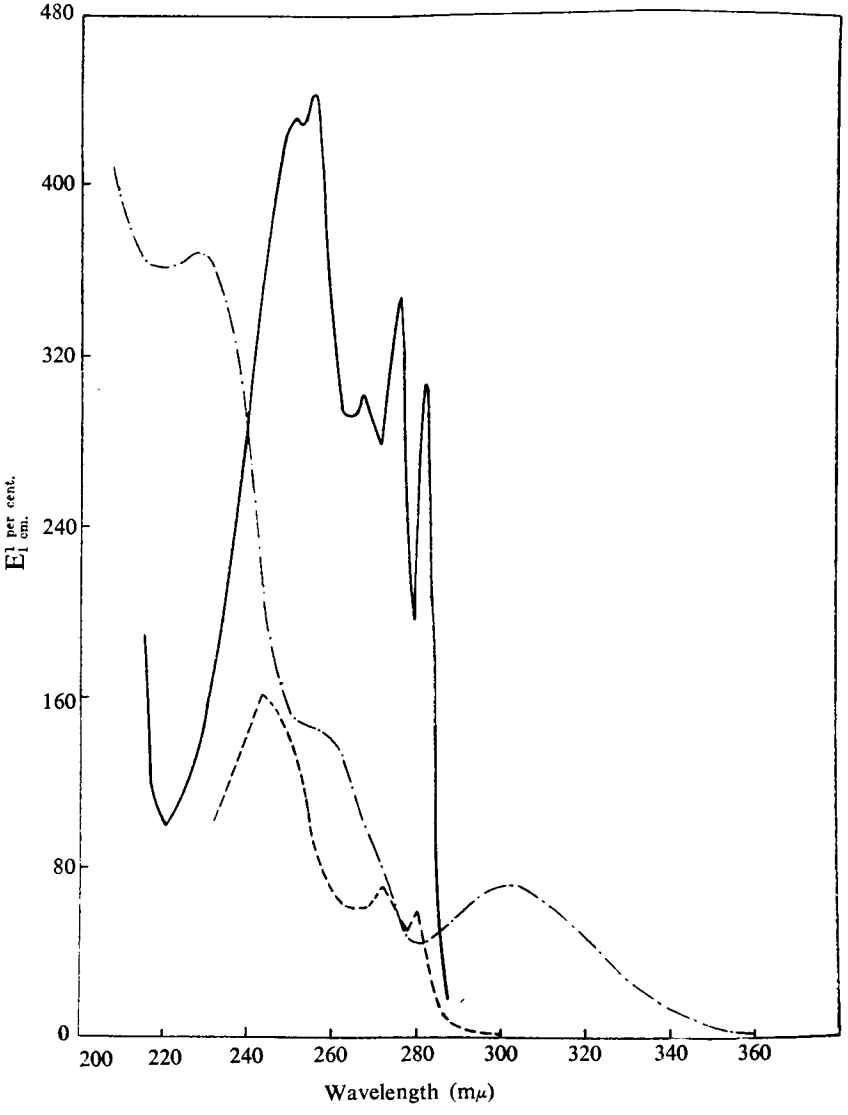


FIG. 1. Absorption curves

——— 1-Methylbenziminazole
—.—.—. 2-Ethoxymethylene-*o*-phenylenediamine-tetraacetyl-D-glucoside
— — — Benziminazole-1-β-tetraacetyl-D-glucopyranoside

Mr. B. Ellis and Mr. G. Cooley of these laboratories. Hydrolysis with sodium ethoxide or ethyl alcoholic ammonia was found to be effective, but had limited practical value owing to the difficulty in separating the glycoside from concomitant inorganic matter. Heating with hydrochloric acid of strength from 2N to 6N at 100°C., however, proved satisfactory in every way, the benziminazole glucopyranoside ring system showing remarkable stability toward acidic reagents, a result in marked contrast to recorded observations in the nucleoside field. Rapid deacetylation occurred giving benziminazole-1-β-glucopyranoside hydrochloride, readily isolated as the monohydrate. Benziminazole-1-β-D-glucopyranoside (IV) itself was obtained by percolating an aqueous solution of the latter compound through the ion-exchange resin "Amberlite IR-4B" and was characterised by formation of the picrate. The pyranoside formulation was supported by periodate titrations when two molecules of the oxidant were consumed.

Having successfully developed two novel routes to the benziminazole glycosides, we next turned our attention to the preparation of some analogues of (IV) with the object of extending the range of synthetic compounds available for study. Both hexose and pentose sugars were employed for these experiments. For convenience, however, discussion of the pentosides is deferred at this stage and is reported upon separately in Part IV (3).

4-Methyl-*o*-phenylenediamine-tetraacetyl-D-glucoside reacted normally with ethyl orthoformate to give the *iso*formanilide derivative, converted by 0·1 N hydrochloric acid into 5-methylbenziminazole-1-tetraacetyl-D-glucoside. The latter compound could not be prepared, however, by the reaction of α-acetobromglucose with 5(6)-methylbenziminazole silver. A mixture of 5- and 6-methylbenziminazole-1-β-tetraacetyl-D-glucopyranosides was obtained from which attempts to isolate either isomer in a state of purity proved unsuccessful. It was thus impossible to determine the configuration of the anomeric centre in the 5-methyl acetylated glycoside by direct experiment. The results obtained with the parent base (IV), however, leave little doubt that this compound, too, must by analogy be formulated as the β-glycoside. Its hydrolysis with 6N hydrochloric acid furnished 5-methylbenziminazole-1-β-D-glucopyranoside.

3:4-Dimethyl-*o*-phenylenediamine-tetraacetyl-D-glucoside, in contrast to the foregoing glycosides, was surprisingly transformed directly into the benziminazole glycoside on heating with ethyl orthoformate. The same compound was also obtained by the action of α-acetobromglucose on 4:5-dimethylbenziminazole silver. It must, therefore, be formulated as 4:5-dimethylbenziminazole-1-β-tetraacetyl-D-glucopyranoside. On deacetylation with acid it gave 4:5-dimethylbenziminazole-1-β-D-glucopyranoside hydrochloride.

A further example of the direct conversion of an *o*-phenylenediamine glycoside into a benziminazole glycoside was encountered during experiments employing 4:5-dimethyl-*o*-phenylenediamine tetraacetyl-D-glucosides, *isomers A* and *B* (see Part IV (I)). Both compounds gave the same 5:6-dimethyl-benziminazole-1-β-tetraacetyl-D-glucopyranoside, the

constitution of which followed from its alternative preparation from α-acetobromglucose and 5:6-dimethylbenziminazole silver. Only *isomer B*, however, yielded the intermediate ethyl*iso*formanilide on treatment with ethyl orthoformate. Hydrolysis furnished 5:6-dimethylbenziminazole-1-β-D-glucopyranoside, characterised by formation of the picrate.

Attempts to convert *o*-phenylenediamine-tetraacetyl-D-galactoside into the corresponding benziminazole proved unsuccessful, resinification taking place. The reason for this failure is not evident, particularly as Andrews, Kenner and Todd[11] observed no difficulty in the preparation of 2-methylthioadenine-9-D-galactopyranoside. The results obtained in this and the succeeding communication, however, lead to the conclusion that the factors governing the synthesis of benziminazoles by the "orthoformate route" are exceedingly complex and cannot readily be defined at this stage.

EXPERIMENTAL

Melting points are corrected. Microanalyses and molecular weight determination are by Drs. Weiler and Strauss, Oxford.

Experiments on the Synthesis of Benziminazole Glycosides from o-Phenylenediamine Glycosides employing Sodium Dithioformate. (i) a methyl alcoholic solution of *o*-phenylenediamine-tetraacetyl-D-glucoside (prepared by catalytic reduction of 5 g. of the corresponding nitro-compound in the presence of palladium/charcoal; see Part IV (I) preceding communication) was treated with technical sodium dithioformate (for which the authors are indebted to Prof. A. R. Todd, F.R.S., and Dr. F. Bergel) (4·5 g.) in methyl alcohol (40 ml.), followed at once by acetic acid (1·3 g., 1 mol.). After standing at room temperature for 3 days, the mixture was boiled for 1 hour, filtered and evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate and the extract chromatographed on a column of alumina which was thoroughly washed with ethyl acetate. The crude thioformyl derivative (1 g.), isolated by evaporation to dryness, could not be crystallised and was, therefore, cyclised direct by heating under reflux for 5 hours with potassium acetate (5 g.) in acetonitrile (20 ml.). After filtration and evaporation *in vacuo* the product was isolated as the picrate (90 mg.) which crystallised from alcohol (95 per cent.) in yellow needles m.pt. 167°C. This was probably an impure sample of *benziminazole-1-β-tetraacetyl-D-glucopyranoside picrate* (Found: C, 48·1; H, 3·8; N, 10·7. $C_{21}H_{24}O_9N_2$, $C_6H_3O_7N_3$ requires C, 47·2; H, 4·0; N, 11·6 per cent.) as it showed no depression of the melting point in admixture with an authentic sample (see below).

(ii) 4:5-Dimethyl-*o*-phenylenediamine-tetraacetyl-D-glucopyranoside (1·6 g.) was converted into a resinous thioformyl-derivative (1·1 g.) by the procedure outlined above. This intermediate (500 mg.) was cyclised by heating with sodium methoxide (110 mg.) in absolute alcohol (20ml.) for 4 hours. The neutralised solution was taken to dryness and an alcoholic extract of the residue treated with picric acid. The picrate so obtained (120 mg.) was presumably 5:6-*dimethylbenziminazole*-1-β-D-*glucopyranoside picrate* as it did not depress the melting-point of an

authentic sample (see below), but repeated crystallisation failed to raise the m.p. above 228°C. (decomp.). Found: C, 45·8; H, 4·4; N, 13·2. $C_{15}H_{20}O_5N_2$, $C_6H_3O_7N_3$ requires C, 46·9; H, 4·2; N, 13·0 per cent.

2-Ethoxymethylene-o-phenylenediamine-tetraacetyl-D-glucoside. A solution of *o*-nitroaniline-tetraacetyl-D-glucopyranoside (5 g.) in ethyl acetate (50 ml.) was shaken in hydrogen in the presence of palladium/charcoal until reduction was complete, whereafter the catalyst was filtered and the filtrate evaporated on the steam bath for 2 to 3 hours with ethyl orthoformate (8 ml.). The solvents were removed *in vacuo* and the residue recrystallised from a mixture of benzene and light petroleum. The product (4·5 g.) separated in colourless needles, m.p. 141° to 142°C. $[\alpha]_D^{26°C.}$ − 84·6° (in chloroform c = 1). Found: C, 55·5; H, 6·1; N, 5·9; Mol.Wt. 497. $C_{23}H_{30}O_{10}N_2$ requires C, 55·6; H, 6·1; N, 5·7 per cent.; Mol.Wt. 494.

Benziminazole-1-β-tetraacetyl-D-glucopyranoside. (i) The foregoing *iso*-formanilide (5 g.), 0·1N hydrochloric acid (30 ml.), water (15 ml.) and a few drops of absolute alcohol were heated at 100°C. for 15 minutes with stirring. The solution was neutralised with potassium bicarbonate and cooled. *Benziminazole-1-β-tetraacetyl-D-glucopyranoside* 2·5 g.) separated and was recrystallised from a mixture of ethylacetate and light petroleum forming feathery needles, m.p. 151° to 152°C. $(\alpha)_D^{24·6°C}$ − 22·8° (in chloroform c = 1). Found: C, 55·8; H, 5·7; N, 6·0. $C_{21}H_{24}O_9N_2$ requires C, 56·2; H, 5·4; N, 6·3 per cent.

(ii) A suspension of the silver salt of benziminazole (4·0 g., thoroughly dried and then finely ground) in dry xylene (120 ml.) was dried by azeotropic distillation of half of the solvent. α-Acetobromglucose (7·35 g.) was added, the mixture heated under reflux for 4 hours, and filtered from silver bromide. The product was isolated by evaporation of the filtrate *in vacuo,* purified by passage of a chloroform solution through a column of alumina, and finally converted into the picrate. Benziminazole-1-β-tetraacetyl-D-glucopyranoside picrate (2·5 g.) crystallised from ethyl alcohol in felted yellow needles, m.p. 170° to 171°C. Found: N, 11·4; Calc. for $C_{21}H_{24}O_9N_2$, $C_6H_3O_7N_3$: N, 11·6 per cent. The picrate was conveniently decomposed by passing a chloroform solution through alumina. On treating the evaporated eluate with light petroleum, the base separated in felted white needles, m.p. 151° to 152°C., identical in all respects with the material prepared by method (i). Found: C, 55·2; H, 5·5; N, 6·0 per cent.

Benziminazole-1-β-D-glucopyranoside. The foregoing tetraacetate (2·5 g.) and 6N hydrochloric acid (90 ml.) were heated at 100°C. for 3 hours. The solution was concentrated under reduced pressure until the product began to separate, when acetone was added. The hydrochloride (1·6 g.) separated as colourless needles of the mono-hydrate from water and acetone, m.p. 196°C. (with foaming), $(\alpha)_D^{24·6°C.}$ + 17·3° (in water, c = 1). Found: C, 46·7; H, 6·0; N, 8·4; Cl, 10·6. $C_{13}H_{16}O_5N_2$, HCl. H_2O requires C, 46·7 H, 5·7; N, 8·4; Cl, 10·6 per cent.

A solution of the hydrochloride (1·0 g.) in distilled water (100 ml.) was percolated through a column of Amberlite IR-4B and the filtrate and

washings taken to dryness. The residue was dried at 100°C. (0·1 mm.) and crystallised once from a mixture of absolute alcohol and benzene, and subsequently from absolute alcohol. *Benziminazole-1-β-D-glucoside* (800 mg.) separated in fine colourless needles, m.pt. 212° to 213°C. $[\alpha]_D^{22\,C.}$ − 3·4° (in water, c = 1·2). Found: C, 55·8; H, 5·9; N, 10·3. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·7; N, 10·0 per cent. The *picrate* crystallised from water in flat yellow needles, m.pt. 146° to 148°C. (decomp). Found: C, 44·8; H, 4·0; N, 13·3. $C_{13}H_{16}O_5N_2$, $C_6H_3O_7N_3$ requires C, 44·8; H, 3·7; N, 13·8 per cent.

Periodate titrations. The glycoside (20 to 200 mg.) was dissolved in water, 0·242N periodic acid solution (50 to 100 per cent. excess) was added, and the solution diluted to a standard volume. At intervals, aliquots were withdrawn, and the remaining periodic acid determined by the method of Barneby[12]. Oxidation was generally complete within 72 to 96 hours.

Benziminazole-1-β-D-glucopyranoside consumed 2·01 moles. of periodic acid under these conditions, whilst the hydrochloride consumed 1·98 moles.

5-Methylbenziminazole-1-tetraacetyl-D-glucopyranoside. 4-Methyl-*o*-phenylenediamine-tetraacetyl-D-glucopyranoside (4·5 g.) was heated at 100°C. with ethyl orthoformate (10 ml.). Evaporation to dryness left a crystalline product which proved extremely soluble in the common organic solvents and could not be satisfactorily purified. It was, therefore, converted direct into the benziminazole by heating at 100°C. with 0·1N hydrochloric acid (30 ml.) After basification with potassium bicarbonate, the product was extracted with chloroform and converted into the *picrate* (3·0 g.), which crystallised from alcohol in yellow needles, m.pt. 185° to 186°C. Found: C, 49·0; H, 4·5; N, 10·0. $C_{22}H_{26}O_9N_2$,$C_6H_3O_7N_3$ requires C, 48·6; H, 4·2; N, 10·1 per cent. The regenerated *5-methylbenziminazole-1-tetraacetyl-D-glucopyranoside* crystallised from a mixture of chloroform and light petroleum in colourless needles, m.pt. 175°C. $(\alpha)_D^{21°C.}$ − 37·8 (in chloroform c = 1. Found: C, 57·0; H, 5·6; N, 6·0. $C_{22}H_{26}O_9N_2$ requires C, 57·1; H, 5·6; N, 6·1 per cent.

5-Methylbenziminazole-1-D-glucopyranoside. The foregoing tetra-acetate (500 mg.) was dissolved in 6N hydrochloric acid (20 ml.) and the solution heated at 100°C. for 90 minutes. The residue left on evaporation was freed from hydrogen chloride by evaporation with water and then dissolved in distilled water and passed through a column of ion exchange resin. Evaporation gave *5-methylbenziminazole-1-D-glucopyranoside* (300 mg.), octahedra from alcohol, m.pt. 275° to 276°C. (decomp.), $(\alpha)_D^{25°C.}$ − 33·6° (in pyridine, c = 1). Found: C, 57·1; H, 6·1; N, 9·5. $C_{14}H_{18}O_5N_2$ requires C, 57·1; H, 6·1; N, 9·5 per cent. This compound consumed 1·97 moles of periodic acid.

5:6-Dimethylbenziminazole-1-β-tetraacetyl-D-glucopyranoside. (i) An ethyl acetate solution of 4:5-diamethyl-*o*-phenylenediamine tetraacetyl-D-glucopyranoside (isomer B), m.pt. 128° to 129°C. (2 g.) was heated under reflux for 3 hours with ethyl orthoformate (6 ml.) The

solvents were removed under reduced pressure and the residue heated on the steam bath with 0·05N hydrochloric acid (15 ml.) for 2 hours, by which time the resinous product had solidified. 5:6-*Dimethylbenziminazole*-1-β-*tetraacetyl*-D-*glucopyranoside* (800 mg.) crystallised from a mixture of benzene and light petroleum in cream-coloured needles, m.pt. 189, 5° to 191°C., $(\alpha)_D^{29°C.}$ – 40·4° (in chloroform, c = 1). Found: C, 57·5; H, 6·2; N, 6·0. $C_{23}H_{28}O_9N_2$ requires C, 58·0; H, 5·8; N, 5·9 per cent.

(ii) The silver salt of 5:6-dimethylbenziminazole (4·75 g.) was reacted with α-acetobromglucose (7·75 g.) in xylene solution in the manner described above. After chromatography of the crude product, the glucoside crystallised and was purified from a mixture of benzene and light petroleum, forming cream-coloured needles, m.pt. 190° to 191°C., not depressed in admixture with the compound obtained by method (i) above. Found: C, 58·7; H, 5·8; N, 5·8 per cent.

(iii) The mother liquor from the crystallisation of 4:5-dimethyl-*o*-phenylenediamine-*N* : *N'*-di-(tetraacetyl-D-glucopyranoside) (preceding paper) was evaporated at 100°C. with ethyl orthoformate (6 ml.) for 3 hours. A crystalline solid separated on cooling and was identified as 5:6-dimethylbenziminazole-1-β-tetraacetyl-D-glucoside, m.pt. 189° to 190°C., $(\alpha)_D^{20°C.}$ – 37·4°, after crystallisation from a mixture of chloroform and light petroleum. After the separation of this glucoside, 5:6-dimethylbenziminazole was isolated from the mother liquor as the picrate (cf. preceding paper). A trial experiment showed that 4:5-dimethyl-*o*-phenylenediamine-*N* : *N'*-di(tetraacetyl-D-glucopyranoside) failed to react with ethyl orthoformate.

5:6-*Dimethylbenziminazole*-1-β-D-*glucopyranoside*. The foregoing tetraacetate was deacetylated in the usual manner. The *glucoside* crystallised from alcohol in cream-coloured octahedra, m.pt. 246° to 248°C. Found: C, 58·1; H, 6·7; N, 8·9. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1 per cent. The *picrate* separated from water containing a little alcohol in yellow needles, m.pt. 236°C. Found: C, 46·2; H, 4·7. $C_{15}H_{20}O_5N_2$, $C_6H_3O_7N_3$ requires C, 46·9; H, 4·3 per cent.

4:5-*Dimethylbenziminazole*-1-β-*tetraacetyl*-D-*glucopyranoside*. (i) 3:4-Dimethyl-*o*-phenylenediamine-tetraacetyl-D-glucopyranoside (2·0 g.) and ethyl orthoformate (6 ml.) were heated under reflux for 4 hours. The crystalline residue remaining after evaporation was recrystallised from a mixture of ethyl acetate and light petroleum giving 4:5-*dimethylbenziminazole*-1-β-*tetraacetyl*-D-*glucopyranoside* (1·5 g.) in colourless needles, m.pt. 177·5° to 178·5°C. $(\alpha)_D^{25°C.}$ – 35·7° (in chloroform, c = 1). Found: C, 57·8; H, 5·5; N, 6·1. $C_{23}H_{28}O_9N_2$ requires C, 58·0; H, 5·8; N, 5·9 per cent.

(ii) 4:5-Dimethylbenziminazole silver (3·5 g.) and α-acetobromglucose (6·1 g.) were condensed in boiling xylene solution and the product isolated in the usual way. The *picrate* (3·5 g.) which crystallised from alcohol in yellow needles, m.pt. 148° to 150°C. (decomp.) (Found: N, 9·8. $C_{23}H_{28}O_9N_2$, $C_6H_3O_7N_3$ requires N, 9·9 per cent.), gave a tetraacetylglucoside in slender needles from a mixture of benzene and light

petroleum, m.pt. 178° to 178·5°C. Found: C, 58·3; H, 6·1 per cent., identical with the compound prepared by the "orthoformate route" (i) (above).

4:5-*Dimethylbenziminazole*-1-β-D-*glucopyranoside*. Hydrolysis of the foregoing tetraacetate afforded 4:5-*dimethylbenziminazole*-1-β-D-*glucopyranoside hydrochloride*, prismatic needles from aqueous alcohol, m.pt. 216° to 217°C. (decomp.), $(\alpha)_D^{27°C.}$ +11·5° (c=1, in water). Found: C, 52·2; H, 6·3; N, 8·1. $C_{15}H_{20}O_5N_2$, HCl requires C, 52·2; H, 6·; N, 8·1 per cent. This compound consumed 2·06 moles of periodic acid per mole. The *picrate* formed needles from water, m.pt. 202° to 204°C. Found: C, 45·2; H, 4·6; $C_{15}H_{20}O_5N_2$, $C_6H_3O_7N_3$, H_2O requires C, 45·4; H, 4·6 per cent.

SUMMARY AND CONCLUSIONS

1. By heating *o*-phenylenediamine-tetraacetyl-D-glucoside with ethyl orthoformate, 2-ethoxymethylene-*o*-phenylenediamine tetraacetyl-D-glucoside has been obtained.

2. The foregoing ethyl *iso*formanilide has been converted into benziminazole-1-β-tetraacetyl-D-glucopyranoside by the action of hot dilute hydrochloric acid.

3. The constitution assigned to this compound has been confirmed by an alternative synthesis from benziminazole silver and α-acetobromglucose.

4. Benziminazole-1-β-D-glucopyranoside has been obtained by hydrolysis of the acetylated glucoside with 6N hydrochloric acid and the pyranoside character of the lactol ring confirmed by periodate titrations.

5. The foregoing novel synthetic methods have been applied to the preparation of 5-methyl-, 4:5-dimethyl-, and 5:6-dimethylbenziminazole glucosides.

6. In certain cases reaction between an *o*-phenylenediamine acetylglucoside and ethyl orthoformate has led directly to the formation of the benziminazole acetylglucoside.

7. The benziminazole glucopyranosides prepared in the course of this work showed unexpected stability towards hot 6N hydrochloric acid.

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