785. 2-(*Polyhydroxyalkyl*)*benziminazoles Derived from* 2-*Deoxy-sugars.*

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Of the methods for synthesis of 2-(polyhydroxyalkyl)benziminazoles from 2-deoxy-sugars the most satisfactory is shown to be direct condensation of the sugar with *o*-phenylenediamine in the presence of cupric acetate. The " benziminazole rule " relating specific rotation to configuration is extended to this class of compound.

CONDENSATION of aldonic acids with *o*-phenylenediamine affords 2-(polyhydroxyalkyl)-benziminazoles [I; R = $^-$(CH·OH)$_n$·CH$_2$·OH], which are usually suitable for characterization of sugars (for a review see Richtmyer [1]). We have examined application of this method of characterization to 2-deoxy-sugars. Only one benziminazole derived from a 2-deoxy-sugar (digitoxose) has been described previously.[2]

Haskins and Hudson's procedure [3] was studied initially. 2-Deoxy-D-galactose was oxidized to the lactone (characterized by conversion into crystalline 2-deoxy-*N*-phenyl-D-galactonohydrazide) which was heated at 100° for 7 hr. with a slight excess of *o*-phenylenediamine. 2-(D-*lyxo*-2 : 3 : 4 : 5-Tetrahydroxypentyl)benziminazole (I; R = a) (" 2-deoxy-galactobenziminazole," see ref. 1) was isolated in low yield. A much improved yield was

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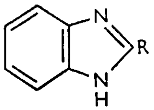
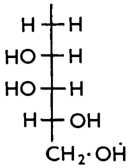
[1] Richtmyer, *Adv. Carbohydrate Chem.*, 1951, **6**, 175.
[2] Dimler and Link, *J. Biol. Chem.*, 1943, **150**, 345.
[3] Haskins and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1266.

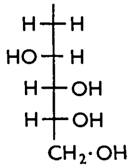
obtained if hydrochloric acid (2 equiv.) was added to the reaction mixture (cf. Haskins and Hudson[3]). Oxidation of this compound by permanganate[4] afforded benziminazole-2-carboxylic acid identical with a sample obtained by the known[1] oxidation of 2-(L-*arabo*-1 : 4-epoxy-2 : 3-dihydroxybutyl)benziminazole. Decarboxylation yielded benziminazole, thereby demonstrating the formation of this nucleus in the condensation.



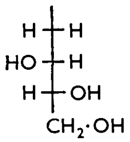
(I)



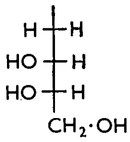
(a) +24·5°



(b) +29·3°



(c) +40·5°



(d) +36·3°

Dimler and Link[2] developed a method for the direct oxidative condensation of a sugar and *o*-phenylenediamine. This method was satisfactory with 2-deoxy-D-galactose and proved to be the best procedure for the synthesis of compounds of type (I) from 2-deoxy-sugars generally. Yields were better than are obtained normally with hexoses. (However the method fails with maltose and lactose.) The formation of a (polyhydroxyalkyl)-benziminazole from a sugar involves an oxidation and the fact that 2-deoxy-D-galactose is oxidized more rapidly than D-galactose[5] may account for the higher yields obtained with the 2-deoxy-sugars. We find that lactose, D-galactose, and 2-deoxy-D-galactose reduce cupric acetate in dilute acetic acid in the presence of *o*-phenylenediamine, the deoxy-sugar doing so immediately. In the absence of the base the deoxy-sugar did not give a precipitate of cuprous oxide after 17 hr. at 51° and then 1 hr. at 100°, but on addition of the diamine the precipitate was again formed immediately. It may be that the deoxy-sugar and the base react to give a substance which is readily oxidizable, and indeed we have evidence[6] that *o*-phenylenediamine and tetra-*O*-acetyl-2-deoxy*aldehydo*-D-galactose condense to give a dihydrobenziminazole derivative.

In our experiments Moore and Link's general method[7] gave only small yields. An attempt to condense barium 2-deoxy-D-galactonate directly with *o*-phenylenediamine in the presence of concentrated hydrochloric acid at 135° resulted in much decomposition and only traces of benziminazole. Condensing 2-deoxy-D-galactonic acid with the diamine in the presence of hydrochloric acid at 100° or of hydrochloric and phosphoric acid at 135°, gave some of the benziminazole but there was also much decomposition. From 2-deoxy-D-galactonolactone the 5 : 6-dimethylbenziminazole was prepared, and 2-deoxy-D-gluconolactone was converted into 2-(D-*arabo*-2 : 3 : 4 : 5-tetrahydroxypentyl)benziminazole (I; R = b). With the less accessible 2-deoxypentoses direct oxidative condensation afforded 2-(D-*threo*- and 2-(L-*erythro*-2 : 3 : 4-trihydroxybutyl)benziminazole (I; R = c and d) from 2-deoxy-D-xylose and 2-deoxy-L-ribose respectively.

Richtmyer and Hudson[8] observed that when the 2-hydroxyl group of the aldonic acid was on the right in the conventional projection formula, the optical rotation of the derived benziminazole was positive. This relation (the " benziminazole rule ") holds for a large number of compounds and has been used reliably for deciding the configuration of new sugars made by Fischer cyanohydrin syntheses.[9]

The rule cannot be applied directly to the new compounds described because they lack this hydroxyl group. However, of the limited number of compounds examined, whenever the 3-hydroxyl group in the 2-deoxyaldonic acid (or 2-deoxy-sugar) is disposed to the left in the conventional projection formula, the optical rotation of the derived benziminazole is

[4] Bistrzycki and Przeworski, *Ber.*, 1912, **45**, 3483.

[5] Overend, Shafizadeh, and Stacey, *J.*, 1951, 2062.

[6] Cleaver, Foster, and Overend, unpublished results.

[7] Moore and Link, *J. Biol. Chem.*, 1940, **133**, 293.

[8] Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 1612.

[9] Zissis, Richtmyer, and Hudson, *ibid.*, 1950, **72**, 3882; Rosenfeld, Richtmyer, and Hudson, *ibid.*, 1951, **73**, 4907; Rosenfeld, Pratt, Richtmyer, and Hudson, *ibid.*, p. 5907.

positive, and when disposed to the right the rotation is negative. [The change $-CH_2{\cdot}OH$ to $-CH_3$ in digitoxose is unlikely to exercise any influence since it is known that 6-deoxy-D-glucose (D-glucomethylose) and 6-deoxy-L-mannose (L-mannomethylose) both obey the benziminazole rule.] The latter statement is based on the fact that Dimler and Link[2] reported that the benziminazole derivative obtained from D-digitoxose (2 : 6-dideoxy-D-allose) had a negative rotation.

The new compounds described are being examined for carcinolytic activity [cf. Folkers and his colleagues[10] who reported that some substituted 2-(polyhydroxyalkyl)-benziminazoles inhibit growth of lymphosarcomata in mice].

EXPERIMENTAL

*2-Deoxy-*D*-galactonolactone.*—Oxidation of 2-deoxy-D-galactose (5 g.) with bromine (5 ml.) in water (50 ml.) at 30° afforded the lactone (3 g., 61%) which recrystallized from acetone as colourless prisms, m. p. 97—98°, $[\alpha]_D^{16}$ −33·5° (*c* 1·01 in H_2O) (lit.,[11] m. p. 97—98°, $[\alpha]_D$ −33° in H_2O). The lactone (0·5 g.) was converted into *2-deoxy-*N*-phenyl-*D*-galactonohydrazide* (0·4 g., 48%) by phenylhydrazine (0·37 g.) at 100° in 1 hr. After recrystallization from ethanol leaflets, m. p. 144°, $[\alpha]_D^{25}$ −18·2° (*c* 1·54 in pyridine) (Found: C, 53·6; H, 6·6; N, 10·7. $C_{12}H_{18}O_5N_2$ requires C, 53·3; H, 6·7; N, 10·4%), were obtained.

2-(D-lyxo-2 : 3 : 4 : *5-Tetrahydroxypentyl)benziminazole.*—(a) *Condensation of 2-deoxy-*D*-galactonolactone with* o*-phenylenediamine.* (i) Treating the lactone (1·0 g.) in water (1·5 ml.) with *o*-phenylenediamine (0·68 g.) according to Haskin and Hudson's method[3] afforded 2-(D-lyxo-2 : 3 : 4 : *5-tetrahydroxypentyl)benziminazole* (*2-deoxy-*D*-galactobenziminazole*) (0·132 g., 8·9%), m. p. 212° (decomp.), $[\alpha]_D^{16}$ +24·5° (*c* 1·06 in N-HCl) (Found: C, 56·9; H, 6·2; N, 11·2. $C_{12}H_{16}O_4N_2$ requires C, 57·1; H, 6·4; N, 11·1%).

(ii) From a solution of 2-deoxy-D-galactonolactone (1·7 g.) and *o*-phenylenediamine (1·16 g.) in concentrated hydrochloric acid (2·1 ml.) and water (4·5 ml.) heated at 100° for 7 hr. deoxy-D-galactobenziminazole (1·32 g., 50%), m. p. 212° (decomp.), was isolated. Its *hydrochloride monohydrate* had m. p. 172—173° (Found: N, 8·8; Cl, 11·5. $C_{12}H_{16}O_4N_2,HCl,H_2O$ requires N, 9·1; Cl, 11·6%).

(b) *Oxidative condensation of 2-deoxy-*D*-galactose and the diamine. o*-Phenylenediamine (0·60 g., 1·1 mol.) and 2-deoxy-D-galactose (0·82 g., 1 mol.) were added to a solution of cupric acetate monohydrate (2·0 g.) in water (40 ml.) and acetic acid (14 ml.) kept at 55° for 16 hr. 2-Deoxy-D-galactobenziminazole (0·56 g., 44%), m. p. 212° (decomp.), $[\alpha]_D^{17}$ +23·7° (*c* 1·8 in N-HCl), was then isolated by Moore and Link's method.[12]

*5 : 6-Dimethyl-2-(*D-lyxo-2 : 3 : 4 : *5-tetrahydroxypentyl)benziminazole.*—2-Deoxy-D-galactonolactone (0·65 g.) and 4 : 5-dimethylphenylenediamine (0·557 g.) were heated in water (5 ml.) and concentrated hydrochloric acid (0·81 ml.) at 100° for 7 hr. 5 : *6-Dimethyl-2-(*D-lyxo-2 : 3 : 4 : *5-tetrahydroxypentyl)benziminazole* (0·65 g.) was isolated as needles, m. p. 201·5° (decomp.), $[\alpha]_D^{19}$ +24·7° (*c* 1·46 in N-HCl) (Found: C, 59·6; H, 6·9; N, 10·3. $C_{14}H_{20}O_4N_2$ requires C, 60·0; H, 7·2; N, 10·0%). The *picrate* crystallized from aqueous ethanol as yellow needles, m. p. 182—183° (Found: N, 13·6. $C_{14}H_{20}O_4N_2,C_6H_3O_7N_3$ requires N, 13·75%).

2-Deoxy-D-gluconolactone (0·65 g.) and *o*-phenylenediamine (0·44 g.) in water (1·5 ml.) and concentrated hydrochloric acid (0·81 ml.) at 100° for 7 hr. gave 2-(D-arabo-2 : 3 : 4 : *5-tetrahydroxypentyl)benziminazole* (0·17 g.), needles (from aqueous ethanol), m. p. 216° (decomp.), $[\alpha]_D^{18}$ +29·3° (*c* 1·16 in N-HCl) (Found: C, 57·4; H, 6·3; N, 11·4. $C_{12}H_{16}O_4N_2$ requires C, 57·1; H, 6·4; N, 11·1%).

2-(D-threo-2 : 3 : *4-Trihydroxybutyl)benziminazole.*—From a mixture of cupric acetate monohydrate (3·4 g.) in water (40 ml.) and glacial acetic acid (2·0 ml.) and *o*-phenylenediamine (1·04 g.) to which 2-deoxy-D-xylose (1·15 g.) in water (20 ml.) had been added 2-(D-threo-2 : 3 : *4-trihydroxybutyl)benziminazole* (0·792 g., 42%) was obtained, having m. p. 199—200° (decomp.), $[\alpha]_D^{21}$ +40·5° (*c* 2·32 in N-HCl) (Found: C, 59·2; H, 6·4; N, 12·5. $C_{11}H_{14}O_3N_2$ requires C, 59·4; H, 6·35; N, 12·6%) [*hydrochloride*, m. p. 180—181° (Found: N, 10·9; Cl, 13·7. $C_{11}H_{14}O_3N_2,HCl$ requires N, 10·8; Cl, 13·7%)].

Likewise from 2-deoxy-L-ribose (0·536 g.), 2-(L-erythro-2 : 3 : *4-trihydroxybutyl)benziminazole*

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[10] Heyl, Emerson, Gasser, Chase, and Folkers, *J. Amer. Chem. Soc.*, 1956, **78**, 4491.
[11] Overend, Shafizadeh, and Stacey, *J.*, 1950, 671.
[12] Moore and Link, *J. Org. Chem.*, 1940, **5**, 642.

(0·548 g., 62%) was obtained as prisms, m. p. 185—186° (decomp.), $[\alpha]_D^{21}$ +36·3° (*c* 2·48 in N-HCl) (Found: C, 59·1; H, 6·3; N, 11·9%).

Benziminazole-2-carboxylic Acid.—(a) 2-(L-*arabo*-1 : 4-Epoxy-2 : 3-dihydroxybutyl)benziminazole (1·1 g.) (kindly supplied by Dr. J. T. Edward) and anhydrous sodium carbonate (2 g.) were dissolved in hot water (100 ml.). To the solution, at 80°, potassium permanganate solution (2%) was added dropwise with stirring until a faint permanent pink colour was produced. After 30 min. at 100° the solution was filtered and the filtrate was acidified with acetic acid. Benziminazole-2-carboxylic acid (0·38 g.), m. p. 169° (decomp.), crystallized.

(b) 2-(D-*lyxo*-2 : 3 : 4 : 5-Tetrahydroxypentyl)benziminazole (1·26 g.) was stirred with 2% sodium carbonate solution (100 ml.) at 80° and 2% potassium permanganate was added as in the previous experiment. Impure benziminazole-2-carboxylic acid (0·36 g.) was isolated and purified with some difficulty. This solid (42 mg.) was heated at 180° for 15 min., effervescence then ceasing. The melt solidified on cooling and crystallized from water as plates (18 mg.), m. p. 172—174° alone or in admixture with benziminazole.

Reducing Action of Sugars on Cupric Acetate in Dilute Acetic Acid in the Presence and Absence of o-*Phenylenediamine.*—Cupric acetate monohydrate (8 g.) was dissolved in acetic acid (4·6 ml.) and water (150 ml.). Each sugar (1 millimol.) was dissolved in the reagent (7·5 ml.) at room temperature and *o*-phenylenediamine (0·12 g.) was added. In parallel experiments the *o*-phenylenediamine was omitted. The concentrations were similar to those employed in the preparation of 2-(polyhydroxyalkyl)benziminazoles by oxidative condensation. The solutions were kept for 17 hr. at 51° and then for 1 hr. at 100°. Tests were performed in duplicate: results are tabulated.

Sugar	Diamine added (g.)	Results after 17 hr. at 51°	Result after a further 1 hr. at 100°
D-Galactose	—	Red ppt.	No change
2-Deoxy-D-galactose	—	No change	No change *
Lactose	—	No change	Red ppt.
—	0·12	Black ppt.	No change
D-Galactose	0·12	Red and black ppt. †	—
2-Deoxy-D-galactose	0·12	,, ‡	—
Lactose	0·12	,,	—

* When *o*-phenylenediamine was added to the warm mixture a red precipitate was formed immediately. † This mixture contained much gelatinous material. ‡ The 2-deoxy-D-galactose–diamine mixture was unique in that it gave a red precipitate immediately on warming.

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