Synthesis of Imidazo[4,5-*b*]pyrazine Nucleosides †

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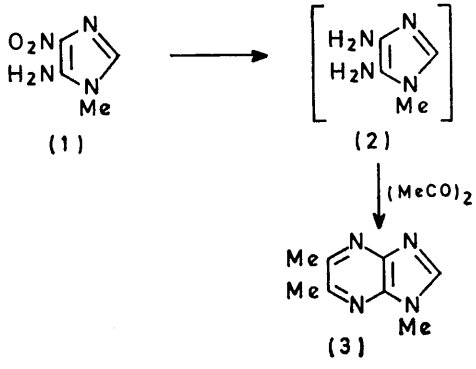
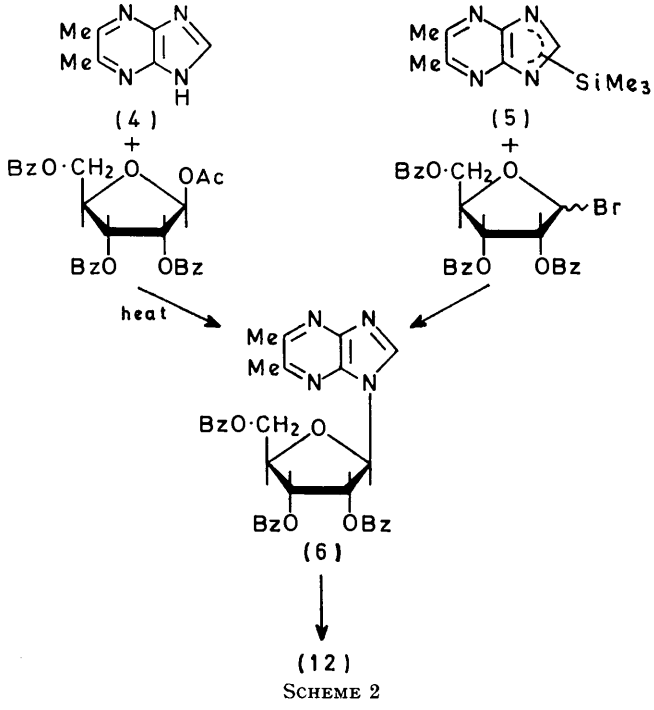
5,6-Dimethyl-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyrazine (12) has been synthesised by three different routes: (*a*) glycosylation of the trimethylsilyl derivative (5) of 5,6-dimethylimidazo[4,5-*b*]pyrazine, (*b*) the fusion procedure, and (*c*) ring closure of an imidazole nucleoside. The assignment of the site of ribosylation and of the anomeric configuration of compound (12) and the imidazo[4,5-*b*]pyrazine nucleosides (10) and (11) is discussed.

NUCLEOSIDES structurally related to the naturally occurring purine ribosides are potential anticancer agents. Examples of structural variations include differences in the position of attachment of the glycosyl bond [*e.g.* 7-(β-D-ribofuranosyl)purines [1a,b] and 3-(β-D-ribofuranosyl)adenine [1c,d]], in the nature of the sugar unit [*e.g.* 6-amino-9-(β-D-arabinofuranosyl)purine [2]], or in the arrangement of the four nitrogen atoms of the bicyclic aglycone. This last category may be divided into two; those with structural modifications in the five-membered ring and those with modifications in the six-membered ring. Examples of the former are formycin,[3a] formycin B,[3a] 4-amino-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine,[3b,c] 4-amino-2-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine,[3b,c] and 1-ribosylallopurinol.[1e,3d] The only reported example of the latter is 4-amino-1-(β-D-ribofuranosyl)imidazo[4,5-*d*]-pyridazine,[4] which is isomeric with adenosine. We have investigated the synthesis of imidazo[4,5-*b*]-pyrazine nucleosides.



SCHEME 1

Our initial approach was made *via* the silylation procedure.[5] Treatment of the trimethylsilyl derivative (5) (Scheme 2) of 5,6-dimethylimidazo[4,5-*b*]pyrazine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetonitrile provided a single nucleoside (t.l.c.) which was isolated as a hard foam. This was debenzoylated with methanolic ammonia. The crystalline product was tentatively identified on the basis of ^{1}H n.m.r.



SCHEME 2

spectroscopy and a u.v. spectral comparison with compound (4) (Table 2) as 5,6-dimethyl-1-(D-ribofuranosyl)-imidazo[4,5-*b*]pyrazine. To verify that the site of ribosylation was N-1, the synthesis of 1,5,6-trimethylimidazo[4,5-*d*]pyrazine (3) (Scheme 1) was undertaken.

A critical step in this synthesis was the reduction of 5-amino-1-methyl-4-nitroimidazole (1) [6] to 4,5-diamino-1-methylimidazole (2). Preparation of 4,5-diaminoimidazoles by use of the usual methods [7a,b] for reduction of aminonitroimidazoles has been reported to be unsuccessful since the diamines are readily oxidized.

† This work was supported by Drug Research and Development, National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

[1] (*a*) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, 1968, **90**, 2661; (*b*) R. J. Rousseau, R. P. Panzica, S. M. Reddick, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, 1970, **35**, 631 and references cited therein; (*c*) N. Leonard and R. A. Laursen, *Biochemistry*, 1965, **4**, 354; (*d*) C. L. Schmidt and L. B. Townsend, *J. Org. Chem.*, 1972, **37**, 2300; (*e*) T. A, Krenitsky, G. B. Elion, R. A. Strelitz, and G. H. Hitchings, *J. Biol. Chem.*, 1967, **242**, 2675.

[2] E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, 1962, **27**, 3274.

[3] (*a*) R. K. Robins, L. B. Townsend, F. Cassidy, J. F. Gerster, A. F. Lewis, and R. L. Miller, *J. Heterocyclic Chem.*, 1966, **3**, 110; (*b*) G. R. Revankar and L. B. Townsend, *J. Chem. Soc.* (*C*), 1971, 2440; (*c*) J. A. Montgomery, S. J. Clayton, and W. E. Fitzgibbon, *J. Heterocyclic Chem.*, 1964, **1**, 215; (*d*) R. A. Earl, R. P. Panzica, and L. B. Townsend, *J.C.S. Perkin I*, 1972, 2672.

[4] J. A. Carbon, *J. Org. Chem.*, 1960, **25**, 579.

[5] R. P. Panzica and L. B. Townsend, *J. Org. Chem.*, 1971, **35**, 1594, and references cited therein.

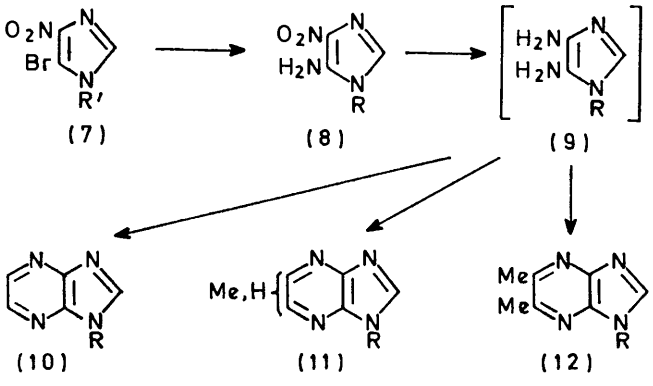
[6] I. E. Balaban, *J. Chem. Soc.*, 1930, 268.

[7] (*a*) P. M. Kochergin, S. G. Verenikina, and K. S. Bushueva, *Khim. geterotsikl. Soedinenii*, 1965, **1**, 765; (*b*) H. Schubert and D. Heydenhauss, *J. prakt. Chem.*, 1963, **22**, 304.

We therefore generated the diamine (2) *in situ* and did not isolate it before ring closure. Condensation of the diamine (2) with biacetyl under neutral conditions afforded the imidazopyrazine (3) in 23·8% overall yield, whereas with addition of 0·1N-hydrochloric acid an overall yield of 40·9% was obtained. Comparison of the u.v. spectra of the product (3) and our synthetic nucleoside confirmed that ribosylation had occurred on N-1.

We could not establish the β-configuration of the nucleoside on the basis of the ^{1}H n.m.r. spectrum, which exhibited a coupling constant ($J_{1',2'}$) of 6 Hz,[8a] nor did we rely on the *trans* rule,[8b] since exceptions to this rule have been reported.[9] We therefore attempted to synthesise 5,6-dimethyl-1-(β-D-ribofuranosyl)imidazo-[4,5-*b*]pyrazine from a nucleoside of known β-configuration by use of the conditions and procedures established for the synthesis of compound (3) (Scheme 3).

5-Bromo-4-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (7) [1a] reacted with liquid ammonia at room temperature to provide the amine (8) in 90% yield. That complete removal of the acetyl blocking groups had been accompanied by a nucleophilic displacement



SCHEME 3

R′ = tri-*O*-acetyl-β-D-ribofuranosyl
R = β-D-ribofuranosyl

of the bromo group was established by ^{1}H n.m.r. spectroscopy (NH_2 signal) and a u.v. spectral comparison with compound (1). Reduction and condensation with biacetyl gave a crystalline nucleoside [10] identical with that obtained from the silylation procedure, which was thus identified as 5,6-dimethyl-1-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyrazine (12).

In a similar fashion [ring closure of the diamine (9)] we prepared 1-(β-D-ribofuranosyl)imidazo[4,5-*b*]pyrazine (10) and 5(6)-methyl-1-(β-D-ribofuranosyl)imidazo-[4,5-*b*]pyrazine (11). The former is an isomer of the nucleoside antibiotic nebularine.[11] Once again the addition of 0·1N-hydrochloric acid improved the overall yield of the annulation. The yield of compound (10) was low when the diamine (9) was treated with either glyoxal bisulphite adduct (<10%) or glyoxal trimer (23·5%) in neutral medium; however, with the addition of 0·1N-hydrochloric acid in the reaction with glyoxal trimer in aqueous ethanol, a 10% increase in yield was observed. Similarly, the condensation of the diamine (9) with aqueous 30% pyruvaldehyde afforded compound (11) in 38% yield in the presence of acid, as compared with 23% under neutral conditions.

Although the nucleoside (11) was apparently homogeneous by paper chromatography, it was in fact a mixture of the 5-methyl and 6-methyl isomers. The ^{1}H n.m.r. spectrum [60 MHz; $(CD_3)_2SO$] revealed two pairs of singlets in the δ 8·4—9·1 region for the C-5(6) and C-2 protons. Integration of this region (100 MHz spectrum) showed the presence of a 1 : 1 mixture.* It has been reported [12] that the formation of 6-hydroxy- and 7-hydroxy-pteridines by use of pyruvic acid for ring closure under weakly acidic conditions affords an approximately equimolar mixture of these compounds. We therefore expected an isomeric mixture from our reaction with pyruvaldehyde in weakly acidic media, but not the 1 : 1 mixture we obtained, which suggests that the amino-groups on the 4- and 5-positions of the imidazole ring, unlike those on certain diaminopyrimidines,[12] exhibit similar basicities.

We also examined the fusion procedure [1a] for the synthesis of the nucleoside (12). A mixture of 5,6-dimethylimidazo[4,5-*b*]pyrazine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, heated at 190—195° with bis-(*p*-nitrophenyl) phosphate, gave 5,6-dimethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*b*]-pyrazine (6), identified on the basis of elemental analysis, spectral evidence, and subsequent conversion into (12) by treatment with methanolic ammonia.

The overall yields of compound (12) from the silylation, fusion, and ring closure procedures were 44·6, 64·2, and 68·2%, respectively. It would appear that the fusion and silylation methods are to be preferred, since they are not dependent on the generation of a 4,5-diaminoimidazole intermediate. However, the overall yields of these methods are deceptive because they do not reflect the lengthy synthesis of the requisite imidazo-[4,5-*b*]pyrazine. When the availability of starting materials is considered, the third method is the logical choice.

The successful preparation of compounds (2) and (9) represents a new route for the synthesis of the imidazo-[4,5-*b*]pyrazine ring system. The synthesis of the nucleosides (10)—(12) again illustrates the potential of imidazole nucleosides for the synthesis of bicyclic nucleosides which may not be available by other routes.

* The C-5(6) methyl resonances are coincident at δ 2·67.

[8] (*a*) R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.* 1963, **32**, 155; (*b*) B. R. Baker, Ciba Foundation Symposium on the Chemistry and Biology of Purines, 1957, p. 120.

[9] C. L. Schmidt, W. J. Rusho, and L. B. Townsend, *Chem. Comm.*, 1971, 1515.

[10] Preliminary account, R. P. Panzica and L. B. Townsend, *Tetrahedron Letters*, 1970, 1013.

[11] R. J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970, pp. 261—267.

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EXPERIMENTAL

M.p.s were determined with a Thomas–Hoover capillary apparatus. ^{1}H N.m.r. spectra were obtained with Varian A-56/60 and XL-100 spectrometers (sodium 2,2-dimethyl-2-silapentane-5-sulphonate as internal standard and [$^2H_6$]-dimethyl sulphoxide as solvent unless otherwise stated). I.r. spectra were determined for potassium bromide discs with a Beckman IR-8 spectrophotometer and u.v. spectra were recorded on a Beckman DK-2 spectrophotometer. Optical rotations were obtained with a Perkin-Elmer model 141 automatic digital readout polarimeter. T.l.c. was run on glass plates coated (250 μm) with SilicAR 7 GF (Mallinckrodt). Silica gel suitable for chromatographic use was purchased from J. T. Baker Chemical Co. All solvent proportions are quoted by volume. Evaporations were performed under diminished pressure at 40° with a Büchi Rotovapor unless otherwise stated. The Raney nickel used for reductions was purchased from W. R. Grace and Co., South Pittsburgh, Tennessee and elemental analyses were preformed by Heterocyclic Chemical Corp., Harrisonville, Missouri.

The trimethylsilyl derivative of 5,6-dimethylimidazo-[4,5-b]pyrazine was prepared by the general procedure of Wittenburg.[13] 5,6-Dimethylimidazo[4,5-*b*]pyrazine [14] was heated at reflux temperature (130°) in an excess of hexamethyldisilazane with a catalytic quantity of ammonium sulphate under anhydrous conditions for 18 h. The excess of hexamethyldisilazane was removed under reduced pressure and the crystalline residue was used without further purification.

5-*Amino*-1-*methyl*-4-*nitroimidazole* (1).—5-Chloro-1-methyl-4-nitroimidazole [15] (10·0 g, 0·062 mol) dissolved in liquid ammonia (100 ml) was kept in a stainless steel vessel at room temperature for 24 h. The excess of ammonia was allowed to evaporate and the yellow solid was recrystallized from hot water (1·2 l) to give the amine (1) (8·4 g, 95·5%), m.p. 304—306° (decomp.) [lit.,[6] 303° (decomp.)], δ 7·84br (2H, s, NH_2), 7·25 (1H, s, 2-H), and 3·48 (3H, s, Me), $\nu_{max.}$ 1673 (NH_2) and 1541 cm^{-1} (NO_2) (Found: N, 39·3. Calc. for $C_4H_6N_4O_2$: N, 39·4%).

1,5,6-*Trimethylimidazo*[4,5-b]*pyrazine* (3).—A suspension of compound (1) (1·0 g, 7·05 mmol) in methanol–water (7 : 3; 50 ml) containing Raney nickel (1·5 g; washed with methanol and weighed wet) was hydrogenated at 30 lb in^{-2} for 4·5 h. The catalyst was filtered off under nitrogen and washed with methanol (*ca.* 30 ml). Biacetyl (0·69 g, 8·04 mmol) and 0·1N-hydrochloric acid (6 ml) were then added to the combined filtrate and washings, and the mixture was stirred under nitrogen for 36 h at room temperature. The solvent was removed *in vacuo* to give a syrup, which was dissolved in the minimum of chloroform and applied to a silica gel column (2·2 × 60 cm). The column was eluted with chloroform (450 ml) and then chloroform–ethanol (20 : 1; 800 ml). Fractions of 100 ml were collected and fractions 9—11 were combined and evaporated. The residue was dissolved in acetonitrile * (15 ml), treated with charcoal, and left at 4° for 18 h to yield *crystals* (466 mg, 40·9%), m.p. 189—190°, δ ($CDCl_3$) 8·10 (1H, s, 2-H), 3·87 (3H, s, NMe), and 2·62 (6H, s, 5- and 6-Me) (Found: C, 59·5; H, 6·35; N, 34·3. $C_8H_{10}N_4$ requires C, 59·25; H, 6·2; N, 34·55%).

5-*Amino*-4-*nitro*-1-(β-D-*ribofuranosyl*)*imidazole* (8).—5-Bromo-4-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (7) [1a] (18·3 g, 40·6 mmol) dissolved in liquid ammonia (100 ml) was kept in a stainless steel vessel at room temperature for 24 h. The excess of ammonia was allowed to evaporate at room temperature to leave an orange syrup. The residual ammonia was removed *in vacuo* and the syrup solidified. The orange-yellow solid was triturated with ethanol (150 ml) and then left at 4° for 20 h. The solid was filtered off, air-dried, and recrystallized from water to provide long *needles* (10·2 g, 90%), m.p. 197—198°, $[\alpha]_D^{27}$ −86·3 (*c* 1·03 in H_2O), δ 7·75br (2H, s, NH_2), 7·53 (1H, s, 2H), δ [$(CD_3)_2SO$–D_2O] 5·63 (1H, d, $J_{1'2'}$ 6·5 Hz, 1′-H), $\nu_{max.}$ 1650 (NH_2) and 1534 cm^{-1} (NO_2) (Found: C, 34·4; H, 5·1; N, 20·15. $C_8H_{12}N_4O_6,H_2O$ requires C, 34·5; H, 5·05; N, 20·15%).

1-(β-D-*Ribofuranosyl*)*imidazo*[4,5-b]*pyrazine* (10).—A solution of 5-amino-4-nitro-1-(β-D-ribofuranosyl)imidazole (8) (2·00 g, 7·18 mmol) in ethanol–water (7 : 3; 80 ml) containing fresh Raney nickel (2·0 g; washed with ethanol and weighed wet) was hydrogenated at 20 lb in^{-2} for 3 h.

The catalyst was filtered off under nitrogen and washed with ethanol (3 × 10 ml). The combined filtrate and washings were added to a stirred solution of glyoxal trimer (Matheson, Coleman, and Bell) (1·4 g, 8·04 mmol) in ethanol (10 ml) and 0·1N-hydrochloric acid (12 ml). The mixture was stirred under nitrogen for 24 h, then evaporated to a syrup, which was dissolved in the minimum amount of methanol and applied to a silica gel column (2·2 × 70 cm). The column was eluted with chloroform (500 ml) and then chloroform–methanol (8 : 2; 1 l). Fractions of 50 ml were collected; fractions 16—18 were combined and evaporated to dryness to give material (0·60 g, overall yield 33·1%) of m.p. 201—203°. Recrystallization from ethanol–water provided the *nucleoside* (10), m.p. 206—208°, $[\alpha]_D^{27}$ −45·8° (*c* 1·01 in H_2O), δ 9·11 (1H, s, 2-H), 8·63 and 8·51 (2H, ABq, J_{AB} 2·5 Hz, 5- and 6-H), and 6·13 (1H, d, $J_{1'.2'}$ 5·5 Hz, 1′-H) (Found: C, 47·7; H, 5·0; N, 22·0. $C_{10}H_{12}N_4O_4$ requires C, 47·6; H, 4·8; N, 22·2%).

5(6)-*Methyl*-1-(β-D-*ribofuranosyl*)*imidazo*[4,5-b]*pyrazine* (11).—A solution of compound (8) (1·00 g, 3·59 mmol) in ethanol–water (7 : 3; 50 ml) was hydrogenated at 20 lb in^{-2} for 3 h over Raney nickel (1·00 g; washed with ethanol and weighed wet). The catalyst was filtered off under nitrogen and washed with ethanol (3 × 10 ml). The combined filtrate and washings were stirred with aqueous 30% pyruvaldehyde (1·0 g, 4·16 mmol) and 0·1N-hydrochloric acid (4·4 ml) for 36 h at room temperature (under nitrogen). The solvent was removed to afford a syrup, which was dissolved in a small amount of ethanol and applied to a silica gel column (2·0 × 75 cm). The column was eluted with chloroform (300 ml) and then chloroform–ethanol (8 : 2; 1 l). Fractions of 50 ml were collected; fractions 17—20 yielded material (0·362 g, overall yield 37·8%) of m.p. 160—162°. Recrystallization from ethanol–water gave the nucleoside (11), m.p. 164—166°, $[\alpha]_D^{27}$ −56·5° (*c* 1·02 in H_2O), δ 9·09(s) and 9·06(s) (1H, 5-H, 6-H), 8·58(s) and 8·47 (s) (1H, 2-H), 6·15 (1H, d, $J_{1',2'}$ 5·8 Hz, 1′-H), and 2·67 [3H, s, 5(6)-Me] (Found: C, 48·0; H, 5·25; N, 20·7. Calc. for $C_{11}H_{14}N_4O_4$, 0·5 H_2O: C, 48·0; H, 5·5; N, 20·35%).

* Acetonitrile was also found to be an effective solvent for recrystallization of 5,6-dimethylimidazo[4,5-*b*]pyrazine.

[13] E. Wittenburg, *Z. Chem.*, 1964, **4**, 303.

[14] E. Schipper and A. R. Day, *J. Amer. Chem. Soc.*, 1952, **74**, 350.

[15] J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713.

5,6-Dimethyl-1-(β-D-ribofuranosyl)imidazo[4,5-b]pyrazine (12).—*Method* 1. Compound (8) (1·0 g, 3·59 mmol) was hydrogenated as in the preceding experiment, and the product was treated with biacetyl (0·62, 7·20 mmol). The solution was stirred under nitrogen for 24 h at room temperature. The solvent was removed *in vacuo* and the syrup was triturated with ethanol. After 6 h at 4° the precipitate was collected, air-dried, and recrystallized twice from ethanol–water (9 : 1) to afford the nucleoside (12) (0·687 g, overall yield 68·2%), m.p. 243—245°, $[\alpha]_D^{27}$ −69·8° (*c* 1·04 in H_2O), δ 8·77 (1H, s, 2-H), 6·02 (1H, d, $J_{1'2'}$ 6 Hz, 1'-H), and 2·57 (6H, s, 5- and 6-Me) (Found: C, 51·45; H, 5·65; N, 20·4. $C_{12}H_{16}N_4O_4$ requires C, 51·4; H, 5·75; N, 20·0%).

Method 2. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [16] [from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1·51 g, 3·0 mmol)] in acetonitrile (10 ml) was added to the trimethylsilyl derivative (5) [from 5,6-dimethylimidazo[4,5-*b*]pyrazine (4) (444 mg, 3·0 mmol)]. The solution was protected from moisture and stirred at room temperature for 8 days. A white residue (31 mg) was then filtered off and washed with acetonitrile (5 ml). The combined filtrate and washings were evaporated and the resulting syrup, dissolved in benzene, was washed with cold, saturated sodium hydrogen carbonate solution (2 × 25 ml) and then water (3 × 25 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in ethanol and evaporated *in vacuo* to provide a hard foam. The foam (*ca.* 1·50 g) was dissolved in methanol (25 ml) which had been previously saturated at −5° with ammonia, and the solution was kept at room temperature for 4 days in a pressure bottle. The solvent was removed and the resulting syrup was triturated with carbon tetrachloride (2 × 25 ml); the solvent was decanted and the semi-solid was dissolved in ethanol (15 ml) and kept at 4° for 16 h. The precipitate was filtered off, air-dried, and recrystallized from ethanol–water (9 : 1) to afford the nucleoside (12) (375 mg, 44·6%) as needles, m.p. 238—240°, $[\alpha]_D^{27}$ −68·7° (*c* 0·44 in H_2O).

Method 3. A dry, finely powdered mixture of 5,6-dimethylimidazo[4,5-*b*]pyrazine (4) (148 mg, 1·0 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (510 mg, 1·01 mmol) was heated at 195°. After 5 min, bis-(*p*-nitrophenyl) phosphate (3 mg) was added to the clear melt, a vacuum (*ca.* 14 mmHg) was applied, and heating was continued for 10 min. The residue, dissolved in warm benzene (30 ml), was washed with cold, saturated sodium hydrogen carbonate solution (2 × 25 ml) and then water (3 × 25 ml), dried ($MgSO_4$), and evaporated *in vacuo* to a hard foam. The foam (550 mg) was dissolved in chloroform and applied to a silica gel column (1·5 × 53 cm; packed in chloroform). The column was eluted with chloroform (300 ml) and then chloroform–methanol (49 : 1; 400 ml) with 100 ml fractions being collected. Fraction 5 (homogeneous on t.l.c. in chloroform–methanol, 16 : 1) was evaporated to yield *5,6-dimethyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)imidazo[4,5-b]pyrazine* (6) as a foam (447 mg, 84·5%), m.p. (73—75° sinters) 88—90°, $[\alpha]_D^{27}$ −52·4° (*c* 1·01 in EtOH), δ ($CDCl_3$) 8·33 (1H, s, 2-H), 6·45 (1H, d, $J_{1'.2'}$ 2·6 Hz, 1'-H) and 2·61 (6H, d, 5- and 6-Me) (Found: C, 66·85; H, 4·8; N, 9·5. $C_{38}H_{28}N_4O_7$ requires C, 66·9; H, 4·75; N, 9·45%).

A solution of compound (6) (447 mg, 0·756 mmol) in

[16] J. D. Stevens, R. K. Ness, and H. G. Fletcher, jun., *J. Org. Chem.*, 1968, **33**, 1806.

TABLE 1

R_F Values of imidazoles and imidazo[4,5-*b*]pyrazines [a,b]

Compound	Solvent systems [c] A	B	C	D	E
(8)	0·69	0·29	0·55	0·75	
(10)	0·79	0·29	0·67	0·71	
(11)	0·77	0·35	0·74	0·76	0·40
(12)	0·74	0·48	0·79	0·77	0·48
(6)	0·00	0·89	0·94	0·82	0·95
(1)	0·67	0·28	0·66	0·67	0·42
(3)	0·71	0·69	0·82	0·81	

[a] Whatman No. 1 paper; descending technique. [b] U.v, light (254 nm) was used to detect the spots. [c] A, aqueous 5% ammonium hydrogen carbonate (w/w); B, butan-1-ol saturated with water; C, propan-1-ol–ammonium hydroxide (*d* 0·90)–water (6 : 3 : 1 v/v); D, ethanol–water (7 : 3 v/v); E, ethyl acetate–propan-1-ol–water (4 : 1 : 2 v/v), upper phase).

TABLE 2

U.v. absorptions of imidazoles and imidazo[4,5-*b*]pyrazines

Compound	pH	$\lambda_{max.}$/nm	ε × 10^{-3}	$\lambda_{min.}$/nm	ε × 10^{-3}
(8) [a]	1	222	12·10		
		366	14·77	290	1·11
	MeOH	223	10·02		
		360	14·13	283	0·70
	11	234	7·09		
		265sh	4·85	295	0·97
		366	14·47		
(1)	1	218	9·88		
		257sh	3·91	295	0·64
		364	13·66		
	MeOH	220	11·01		
		360	13·36	290	0·71
	11	268	5·83	250	4·77
		369	13·50	300	0·71
(10)	1	252sh	2·52	235	1·89
		288	9·96		
		303sh	7·06		
	MeOH	259sh	3·28	235	1·51
		290	11·35		
	11	250	3·78		
		289	10·72	263	3·53
		304sh	7·57		
		312sh	5·55		
(11) [c]	1	301	11·04	257	2·86
		310sh	10·46		
	MeOH	260sh	2·70	235	1·40
		294·5	11·78		
		309	9·08		
	11	297sh	11·04	265	3·16
		305	11·48		
		319sh	7·98		
(12)	1	290sh	9·98	254	2·27
		306	13·09		
	MeOH	258	2·63	234	1·37
		295sh	10·73	265	2·52
		309	12·25		
	11	245·5	3·50	231	3·03
		295sh	9·67	265	2·63
		312	13·54		
(3)	1	285sh	8·68	253	1·07
		304	14·16		
	MeOH	260	2·24	236·5	1·24
		298sh	11·11	265	2·19
		309	12·77		
	11	295sh	8·35		
		313	14·68		
(4)	1	285sh	8·04	251·5	0·87
		304	12·09		
	MeOH	241	1·33	228	0·93
		295sh	9·13	262	0·36
		309	10·48		
	11	302sh	7·19	252·5	0·74
		323	13·34		

[a] Monohydrate. [b] Cary 15 spectrophotometer. [c] Hemihydrate.

methanolic ammonia (25 ml; saturated at −5°) was kept at room temperature for 4 days in a pressure bottle. The solvent was removed, the resulting syrup was triturated with chloroform (2 × 25 ml), and the chloroform was decanted. The residual solid was dissolved in ethanol (15 ml) and kept at 4° for 16 h. The crystalline nucleoside (12) was filtered off and recrystallized from ethanol–water (9 : 1) to give needles (180 mg, 85·3%), m.p. 242—244°, $[\alpha]_D^{27}$ −67·3° (*c* 0·51 in H_2O).

The nucleosides (12) obtained by all three methods were identical (u.v. and i.r. spectra, chromatographic mobilities, and mixed m.p.s).

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