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Vitamin B_{12}. XX. Synthesis of 1-Glycosides of 5,6-Dimethylbenzimidazole

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Four methods for converting 2-amino-4,5-dimethyl-N-glycosylanilines to 1-glycosyl-5,6-dimethylbenzimidazoles are described. The ring closing agents are alkyl formimino ether hydrochlorides, N-(dichloromethyl)-formamidine hydrochloride, ethyl formate and carbon bisulfide and barium hydroxide followed by Raney nickel catalyst for removal of the sulfhydryl group. The glycosyl hydroxyl groups are protected by acetylation. New 1-glycosyl-5,6-dimethylbenzimidazoles include L-arabinofuranosyl and D- and L-lyxopyranosyl derivatives. Vitamin B_{12}-like activities of these and previously described analogs have been estimated in rats.

After the isolation from vitamin B_{12} of α-ribazole (1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole),[1] the synthesis of a number of 1-glycosides of 5,6-dimethylbenzimidazole was undertaken, both for the purpose of exploring synthetic methods, and for comparison of the vitamin B_{12}-like activities of the various glycosides with that of the degradation product, α-ribazole. Syntheses of the four possible ribosides already have been published.[2] Several other papers also have appeared in the literature, describing additional glycosides.[3-6] The glycosides described in this publication include both new ones and known compounds synthesized by new routes.

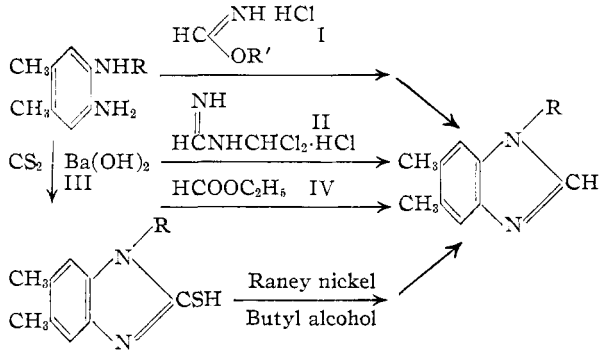
2-Nitro-4,5-dimethyl-N-L-arabinosylaniline was prepared by the literature methods,[3,7] and two isomers were obtained. Acetylation of these isomers resulted in the preparation of two isomeric triacetates which also have been reported.[3] Both these isomers of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline, after catalytic reduction of the nitro group and ring closure, resulted in one and the same form of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole. This compound also has been reported by others.[3]

Three different methods of ring closure have been studied. The best of these is ring closure with ethyl formimino ether hydrochloride (I), a method already described in connection with the preparation of 5,6-dimethylbenzimidazole ribosides.[2] A 75% yield of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole (isolated in part as the picrate) was obtained by use of this reagent, followed by acid hydrolysis of the acetyl groups. The physical properties of the product are in agreement with those previously reported.[3]

N-(Dichloromethyl)-formamidine hydrochloride (II)[8] could be used in place of ethyl formimino ether hydrochloride as ring closing agent. The yield by this method was poor in a few trials.

A third ring closure of the intermediate 2-amino-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline was effected by stirring with carbon bisulfide and barium hydroxide (III). Desulfurization of the intermediate 1-(2',3',4'-triacetyl-L-arabinopyranosyl)-2-sulfhydryl-5,6-dimethylbenzimidazole followed by hydrolysis of the acetyl groups resulted in a 24% yield of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole.

The use of carbon bisulfide and a base for closing benzimidazole rings has been described before,[9] but not for the synthesis of benzimidazole glycosides.



R = acetylated glycosyl group
R' = C_2H_5 or i-C_3H_7

The carbon bisulfide ring closure has been applied successfully to the synthesis of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole, the starting material being 2-nitro-4,5-dimethyl-N-(2',3'-diacetyl-5'-trityl-D-ribofuranosyl)-aniline.[2] The product was isolated as the picrate. The furanose nature of the glycoside ring was determined by periodate titration. No 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole was isolated from this preparation.

2-Nitro-4,5-dimethyl-N-D-arabinosylaniline and its triacetate were synthesized by the methods used in the L-series. Two isomers of each compound were obtained. One of each of these has not been reported before in the D-series. Hydrogenation, ring closure by means of ethyl formimino ether hydrochloride and hydrolysis to form 1-D-arabinopyranosyl-5,6-dimethylbenzimidazole were carried out as in the L-series.

1-(3',4'-Isopropylidene-D-arabinopyranosyl)-5,6-

(1) N. G. Brink, F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill and K. Folkers, THIS JOURNAL, **72**, 1866 (1950).

(2) F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, J. B. Lavigne and K. Folkers, *ibid.*, **74**, 4521 (1952).

(3) P. Mamalis, V. Petrow and B. Sturgeon, *J. Pharm. Pharmacol.*, **2**, 491 (1950).

(4) G. Cooley, B. Ellis, P. Mamalis, V. Petrow and B. Sturgeon, *ibid.*, **2**, 579 (1950).

(5) J. G. Buchanan, A. W. Johnson, J. A. Mills and A. R. Todd, *J. Chem. Soc.*, 2845 (1950).

(6) F. Weygand, A. Wacker and F. Wirth, *Z. Naturforsch.*, **6b**, 25 (1951).

(7) R. Kuhn and R. Ströbele, *Ber.*, **70**, 773 (1937).

(8) L. E. Hinkel and R. T. Dunn, *J. Chem. Soc.*, 1834 (1930). F. B. Dains (*Ber.*, **35**, 2503 (1902)) obtained benzimidazole by condensation of o-phenylenediamine with this reagent.

(9) W. G. Bywater, D. A. McGinty and N. D. Jenesel, *J. Pharmacol. Exp. Therap.*, **85**, 14 (1945).

dimethylbenzimidazole and the corresponding compound in the L-series were prepared in connection with some other work. They are described here as derivatives of the 5,6-dimethylbenzimidazole arabinopyranosides.

1-L-Arabinofuranosyl-5,6-dimethylbenzimidazole was prepared by the usual sequence of acetylation, catalytic hydrogenation, ring closure with ethyl formimino ether hydrochloride and hydrolysis of 2-nitro-4,5-dimethyl-N-(5'-trityl-L-arabinofuranosyl)-aniline, which was prepared according to the directions of Kuhn and Ströbele[7] for preparation of the corresponding D-mannose derivative.

1-D-Lyxopyranosyl-5,6-dimethylbenzimidazole was prepared from the usual intermediates and *via* the ethyl formimino ether hydrochloride ring closure method. The pyranoside nature of the product was shown by its consumption of 1.97 moles of periodate. The corresponding compounds in the L-lyxose series were prepared by parallel experiments.

2-Nitro-4,5-dimethyl-N-D-xylosylaniline and its triacetate were obtained as oils, probably because of the presence of a mixture of isomers. Mamalis, Petrow and Sturgeon[3] isolated one isomer of each compound in crystalline form. A fourth ring closing agent, ethyl formate (IV), was used to convert the reduced triacetate to the benzimidazole. 1-D-Xylopyranosyl-5,6-dimethylbenzimidazole was isolated in poor yield as the picrate. A free base has been described before.[6]

The synthesis of 1-D-(2'-desoxyribopyranosyl)-5,6-dimethylbenzimidazole was very similar to the one already reported.[4] The physical properties were in good agreement with the published ones.

Tests for vitamin B_{12} activity were carried out as previously described.[10] The results are summarized in Table I, and are directly comparable with previously reported activities.[10,11] The one compound that showed activity according to this assay was 1-L-arabinofuranosyl-5,6-dimethylbenzimidazole, which is the only furanoside in the group. Although this compound was tested at a higher level, the activity may be of the same order as that of α-ribazole, which produced a weight increment of 69 g. in a similar experiment[10] when fed at a dosage level of 100 μg. This dosage level produces a response close to the maximum, so that a higher dosage might be expected to result in an insignificant increase in weight.

Some slight activity might be claimed for 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole and 1-D-(2'-desoxyribopyranosyl)-5,6-dimethylbenzimidazole. The other compounds were inactive.

TABLE I

RESULTS OF VITAMIN B_{12} ACTIVITY TESTS IN RATS

	Quantity fed daily, μg.	No. of rats	Weight increment ± S.E., g., 15 days
Controls (undosed)		8	28.8 ± 3.9
Vitamin B_{12}	0.063	10	45.5 ± 3.5
Vitamin B_{12}	0.125	9	53.8 ± 3.7
5,6-Dimethylbenzimidazoles			
1-L-Arabinopyranosyl-	100	10	41.7 ± 3.5
1-D-Arabinopyranosyl-	100	10	34.0 ± 3.5
1-L-Arabinofuranosyl-	287	10	69.5 ± 3.5
1-D-Lyxopyranosyl-	100	9	32.7 ± 3.7
1-L-Lyxopyranosyl-	100	8	30.6 ± 3.9
1-D-(2'-Desoxyribopyranosyl)-	50	8	37.2 ± 3.9

(10) G. Emerson, F. W. Holly, C. H. Shunk, N. G. Brink and K. Folkers, THIS JOURNAL, **73**, 1069 (1951).

(11) G. Emerson, N. G. Brink, F. W. Holly, F. Koniuszy, D. Heyl and K. Folkers, *ibid.*, **72**, 3084 (1950).

Experimental[12]

2-Nitro-4,5-dimethyl-N-L-arabinosylaniline.—This material was made approximately according to the method of Kuhn and Ströbele,[7] and the two isomers described by them and by Mamalis, Petrow and Sturgeon[3] were separated by fractional crystallization.

2-Nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline.—Acetylation of both isomers of 2-nitro-4,5-dimethyl-N-L-arabinosylaniline was carried out with acetic anhydride in pyridine as described by Kuhn and Ströbele[7] for one of the D-isomers, with the exception that the acetylation mixture was not heated to boiling. The two isomers reported by Mamalis, Petrow and Sturgeon[3] were obtained.

The 1-L-Arabinopyranosyl-5,6-dimethylbenzimidazole (Method I).—2-Nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline (1.66 g., m.p. 202–204°) dissolved in 50 ml. of ethyl acetate was hydrogenated by shaking with 0.5 g. of 10% palladium–Darco catalyst under 2–3 atmospheres of hydrogen until there was no further absorption of hydrogen. After collection of the catalyst, the ethyl acetate was removed by distillation under reduced pressure, and the water was removed from the residue by distillation with toluene. The product, 2-amino-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline, was obtained as a colorless gum. A solution of this material in 50 ml. of dry benzene was stirred for 24 hours at room temperature with 0.43 g. of ethyl formimino ether hydrochloride.[13] After removal of the benzene, hydrolysis of the acetyl groups was effected by refluxing for two hours with 40 ml. of 1.5 *N* 40% alcoholic hydrochloric acid. Most of the alcohol was then removed by distillation. The remaining colorless solution was cooled in ice and made alkaline (*p*H 8–9) with sodium hydroxide. The resulting thick oil was separated by decanting, and crystallized after brief heating with alcohol; yield of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole, 0.20 g. After one recrystallization from water, the material melted at 278–280° dec., $[\alpha]^{23}D$ −83 ± 10° (*c* 0.2 in pyridine).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.76; H, 6.19; N, 10.08.

The aqueous alkaline solution above was extracted four times with chloroform. After five days, the crystalline product present in the chloroform extract was collected. It was the same benzimidazole (0.44 g.); total yield 59%.

The remaining aqueous solution was then acidified (*p*H 3–4) with hydrochloric acid and treated with an excess of aqueous picric acid. Crystallization of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole picrate was brought about by heating, then cooling; yield 0.32 g. (16%). After one recrystallization from methanol, the picrate melted at 210–212° dec., $[\alpha]^{23}D$ −27 ± 2° (*c* 2 in pyridine).

Anal. Calcd. for $C_{20}H_{21}N_5O_{11}$: C, 47.34; H, 4.17; N, 13.80. Found: C, 46.70; H, 4.37; N, 13.45.

This picrate was identical with a sample of picrate prepared from the free benzimidazole.

The 1-L-Arabinopyranosyl-5,6-dimethylbenzimidazole (Method II).—Two grams of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline (m.p. 133–136°) was hydrogenated as described in method I, with the exception that benzene instead of ethyl acetate was used as solvent. The resulting amine, after drying, was stirred for three days with 50 ml. of benzene, 1.6 g. of finely ground barium hydroxide and 10 ml. of carbon bisulfide. The mixture was then concentrated under reduced pressure to a residue which was taken up in 40 ml. of water. The *p*H was adjusted to 2 with 6 *N* sulfuric acid, and a stream of air blown through

(12) We are indebted to Mr. Richard Boos and his associates for the microanalyses.

(13) L. F. Cavalieri, J. F. Tinker and A. Bendich, THIS JOURNAL, **71**, 533 (1949).

the mixture to remove hydrogen sulfide. The solid material was collected on a filter and washed with water. It was then taken up in alcohol and the insoluble barium sulfate removed by centrifuging. Attempts to crystallize the 1-(2',3',4'-triacetyl-L-arabinopyranosyl)-2-sulfhydryl-5,6-dimethylbenzimidazole contained in this solution were unsuccessful. Consequently, a solution of the residue in 200 ml. of *n*-butyl alcohol was refluxed with 9 g. of Raney nickel catalyst for 3 hours. After removal of the nickel, the filtrate was concentrated to dryness, and the residue hydrolyzed with dilute alcoholic hydrochloric acid as described in method I. 1-L-Arabinopyranosyl-5,6-dimethylbenzimidazole was isolated as the picrate; yield 0.61 g. (26%). After recrystallization from methanol, the m.p. was 209–210°, which was unchanged when the material was mixed with a sample prepared by method I; $[\alpha]^{24}D$ −34 ± 2° (*c* 2 in pyridine).

The 1-L-Arabinopyranosyl-5,6-dimethylbenzimidazole (Method III).—The hydrogenation of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline was carried out as described in method II. The ring closure and hydrolysis were carried out as described in method I, with the exception that N-(dichloromethyl)-formamidine hydrochloride[8] was used in place of ethyl formimino ether hydrochloride. The concentrated hydrolysis product was black and was extracted several times with chloroform before being made alkaline. The resulting alkaline solution was also extracted several times with chloroform. 1-L-Arabinopyranosyl-5,6-dimethylbenzimidazole picrate was obtained in low yield by acidification of the aqueous solution with hydrochloric acid and treatment with aqueous picric acid. After recrystallization from aqueous ethyl alcohol, the picrate melted at 213–214° dec. The melting point of a mixture of this picrate and the one obtained by method I was not depressed.

1-(3',4'-Isopropylidene-L-arabinopyranosyl)-5,6-dimethylbenzimidazole.—Treatment of 1.32 g. of 1-L-arabinopyranosyl-5,6-dimethylbenzimidazole with acetone and concentrated sulfuric acid as described below for the D-isomer gave 1-(3',4'-isopropylidene-L-arabinopyranosyl)-5,6-dimethylbenzimidazole in 60% yield. After recrystallization from isopropyl alcohol–ether–petroleum ether (b.p. 30–60°), the m.p. was 261–262°; $[\alpha]^{25}D$ +11 ± 2° (*c* 1 in pyridine).

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.25; H, 6.82; N, 9.00.

2-Nitro-4,5-dimethyl-N-D-arabinosylaniline.—The method of Kuhn and Ströbele[7] for preparation of the L-isomer was employed for preparation of this material. In addition to the D-isomer obtained by them, a higher melting one corresponding to the isomer described by both these authors and by Mamalis, Petrow and Sturgeon[3] in the L-series was obtained. In the D-series, this isomer has not been described. The m.p. was 181–182°, $[\alpha]^{25}D$ −72 ± 2° (*c* 2 in pyridine).

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.37; H, 6.41; N, 9.35.

2-Nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-D-arabinosyl)-aniline.—Acetylation of both isomers of 2-nitro-4,5-dimethyl-N-D-arabinosylaniline was carried out in the same manner as in the L-series, and both isomers of the triacetate were obtained. The lower melting one has not been described before; m.p. 137–138°, $[\alpha]^{24}D$ −18 ± 2° (*c* 2 in chloroform).

Anal. Calcd. for $C_{19}H_{24}N_2O_9$: C, 53.77; H, 5.70; N, 6.60. Found: C, 54.25; H, 5.66; N, 6.81.

1-D-Arabinopyranosyl-5,6-dimethylbenzimidazole.—The preparation was exactly parallel with that of the L-isomer as described under method I. The product melted at 280–281° dec., $[\alpha]^{25}D$ +75 ± 2° (*c* 1 in pyridine).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.14; H, 6.64; N, 10.22.

1-(3',4'-Isopropylidene-D-arabinopyranosyl)-5,6-dimethylbenzimidazole.—A mixture of 1.63 g. of 1-D-arabinopyranosyl-5,6-dimethylbenzimidazole and 105 ml. of anhydrous acetone was cooled in ice. To this mixture was added a cold solution of 6 ml. of concentrated sulfuric acid in 105 ml. of anhydrous acetone. The mixture was stirred at room temperature for 4.5 hours. It was then added slowly with stirring to an ice-cold solution of 27.0 g. of sodium carbonate in 200 ml. of water. The resulting mixture was concentrated under reduced pressure until the acetone had been removed. The precipitate of 1-(3',4'-isopropylidene-D-arabinopyranosyl)-5,6-dimethylbenzimidazole was collected on a filter, washed well with cold water and dried; yield 1.17 g. (62%). After recrystallization from isopropyl alcohol–ether–petroleum ether (b.p. 30–60°), the m.p. was 261.5–262.5°, $[\alpha]^{25}D$ −11 ± 2° (*c* 1 in pyridine).

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.18; H, 6.91; N, 8.97.

1-L-Arabinofuranosyl-5,6-dimethylbenzimidazole Picrate.—2-Nitro-4,5-dimethyl-N-(5'-trityl-L-arabinofuranosyl)-aniline was prepared by the method described by Kuhn and Ströbele[7] for the preparation of the corresponding derivative of D-mannose, and was obtained as an oil. This material was acetylated by the method described above for the preparation of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline, and yielded an oil, 2-nitro-4,5-dimethyl-N-(2',3'-diacetyl-5'-trityl-L-arabinofuranosyl)-aniline. A solution of 5.0 g. of the latter compound in 150 ml. of dry benzene was shaken with 2 g. of 10% palladium–Darco catalyst under 2–3 atmospheres of hydrogen. After 2 hours another 3 g. of catalyst was added, and the shaking continued for 1.25 hours. After removal of the catalyst, water was removed from the filtrate by distillation with benzene. The residual solution was diluted to 150 ml. with dry benzene, treated with 2.6 g. of ethyl formimino ether hydrochloride, and refluxed for 3.25 hours. After distillation of the benzene under reduced pressure, the acetyl and trityl groups were removed from the residue by refluxing with 80 ml. of 1.5 *N* 40% alcoholic hydrochloric acid for 2 hours. The resulting solution, concentrated to half its original volume, was extracted four times with chloroform. The aqueous solution, cooled in an ice-bath, was made alkaline with 6 *N* sodium hydroxide. The solution was decanted from the oil and extracted once with chloroform. After removal of the excess chloroform under reduced pressure, the aqueous solution was treated with aqueous picric acid, which caused the precipitation of 0.8 g. (20%) of 1-L-arabinofuranosyl-5,6-dimethylbenzimidazole picrate. After two recrystallizations from methanol, the picrate melted at 177–178°, $[\alpha]^{23}D$ −48 ± 2° (*c* 1.5 in pyridine).

Anal. Calcd. for $C_{20}H_{21}N_5O_{11}$: C, 47.34; H, 4.17; N, 13.80. Found: C, 47.04; H, 3.95; N, 13.50.

The free base was made in solution for physiological testing. Removal of picric acid by continuous chloroform extraction of an aqueous solution of the picrate which had been treated with an equivalent of hydrochloric acid was followed by neutralization of the hydrochloride with sodium bicarbonate.

2-Nitro-4,5-dimethyl-N-D-lyxosylaniline.—A mixture of 1.00 g. of D-lyxose, 1.11 g. of 2-nitro-4,5-dimethylaniline,[14] 0.2 g. of ammonium chloride and 50 ml. of anhydrous alcohol was refluxed for 2.5 hours. After cooling, the solid material was collected on a filter and washed thoroughly with benzene. It consisted of 0.74 g. (37%) of crude 2-nitro-4,5-dimethyl-N-D-lyxosylaniline. After recrystallization from alcohol, the material melted at 198–199°, $[\alpha]^{23}D$ −109 ± 3° (*c* 1 in pyridine).

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.45; H, 5.99; N, 9.45.

2-Nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-D-lyxosyl)-aniline.—2-Nitro-4,5-dimethyl-N-D-lyxosylaniline (0.18 g.) was acetylated in the manner described for the preparation of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-L-arabinosyl)-aniline, the yield being 0.21 g. (82%) of 2-nitro-4,5-dimethyl-N-(2',3',4'-triacetyl-D-lyxosyl)-aniline. After recrystallization from alcohol, the material melted at 190–191°, $[\alpha]^{24}D$ −154 ± 2° (*c* 2 in pyridine).

Anal. Calcd. for $C_{19}H_{24}N_2O_9$: C, 53.77; H, 5.70; N, 6.60. Found: C, 53.61; H, 5.47; N, 6.82.

1-D-Lyxopyranosyl-5,6-dimethylbenzimidazole.—Method I was used. The reduction of 2-nitro-4,5-dimethyl-N-(2',-3',4'-triacetyl-D-lyxosyl)-aniline (1.97 g.) was carried out in benzene. In the final step, the addition of sodium hydroxide precipitated a gum which crystallized when the aqueous mixture was stirred with chloroform. After recrystallization from water, the 1-D-lyxopyranosyl-5,6-dimethylbenzimidazole was obtained in a yield of 0.44 g. (34%), m.p. 258–258.5°, $[\alpha]^{25}D$ +54 ± 3° (*c* 1 in pyridine). The material consumed 1.97 moles of sodium periodate, and was therefore in the pyranose form.

(14) E. Noelting, A. Braun and E. Thesmar, *Ber.*, **34**, 2242 (1901).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.64; H, 6.90; N, 10.37.

2-Nitro-4,5-dimethyl-N-L-lyxosylaniline.—L-Lyxose[15,16] was condensed with 2-nitro-4,5-dimethylaniline in the manner already described for D-lyxose. The 2-nitro-4,5-dimethyl-N-L-lyxosylaniline melted at 195–196°, $[\alpha]^{23}D$ +112 ± 2° (*c* 1 in pyridine).

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.30; H, 6.06; N, 9.34.

2-Nitro-4,5-dimethyl-N-(2′,3′,4′-triacetyl-L-lyxosyl)-aniline.—2-Nitro-4,5-dimethyl-N-L-lyxosylaniline (3.70 g.) was acetylated as described above for the L-arabinose analog. The yield of 2-nitro-4,5-dimethyl-N-(2′,3′,4′-triacetyl-L-lyxosyl)-aniline was 4.94 g. (95%), $[\alpha]^{23}D$ +155 ± 2° (*c* 2 in pyridine), m.p. 184–185°. The m.p. of this compound was as high as 192–193° in other preparations. The discrepancy may be due to the presence of another isomer.

Anal. Calcd. for $C_{19}H_{24}N_2O_9$: C, 53.77; H, 5.70; N, 6.60. Found: C, 53.50; H, 5.54; N, 6.61.

1-L-Lyxopyranosyl-5,6-dimethylbenzimidazole.—The reduction of 0.78 g. of 2-nitro-4,5-dimethyl-N-(2′,3′,4′-triacetyl-L-lyxosyl)-aniline and ring closure to the benzimidazole were carried out as already described under method I, except that benzene was used in place of ethyl acetate as solvent for the hydrogenation, and isopropyl formimino ether hydrochloride[17] was used in place of the ethyl analog for ring closure. 1-L-Lyxopyranosyl-5,6-dimethylbenzimidazole crystallized from the alkaline solution; yield 0.11 g. (22%); m.p. after two recrystallizations from alcohol, 260–261°; $[\alpha]^{23}D$ −64 ± 8° (*c* 0.3 in pyridine).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.80; N, 10.17.

1-D-Xylopyranosyl-5,6-dimethylbenzimidazole Picrate.—A mixture of 25 g. of 2-nitro-4,5-dimethylaniline,[14] 22.6 g. of D-xylose, 1.5 g. of ammonium chloride and 200 ml. of absolute alcohol was refluxed for 2 hours. 2-Nitro-4,5-dimethyl-N-D-xylosylaniline was purified by chromatography by the method described by Kuhn and Ströbele[7] for the purification of 2-nitro-4,5-dimethyl-N-D-arabinosylaniline. The product, which was obtained as an oil, was acetylated as described above for the preparation of 2-nitro-4,5-dimethyl-N-(2′,3′,4′-triacetyl-L-arabinosyl)-aniline. The crude oil obtained after removal of acetic anhydride and solvents was dissolved in benzene. This solution was extracted twice with water and dried over sodium sulfate. The solution was purified by passage over 1 kg. of acid-washed alumina, and the product was eluted completely with benzene. Distillation of the benzene yielded 32 g. of 2-nitro-4,5-dimethyl-N-(2′,3′,4′-triacetyl-D-xylosyl)-aniline as an amber oil.

Two grams of the above material was hydrogenated in 30 ml. of ethyl acetate with 1.3 g. of 5% palladium–Darco catalyst. After separation of the catalyst, the solvent was distilled under reduced pressure and the ethyl acetate completely removed by distillation of two portions of xylene. The residual oil in a solution of 40 ml. of xylene and 5 ml. of ethyl formate was refluxed for 18 hours under a nitrogen atmosphere. After distillation of the solvent under reduced pressure, the residual oil was refluxed for 2 hours with a mixture of 10 ml. of alcohol, 3 ml. of 12 *N* hydrochloric acid and 20 ml. of water, for hydrolysis of the acetyl groups. The resulting solution was concentrated to half the initial volume, made alkaline with dilute sodium hydroxide and extracted twice with chloroform. The aqueous layer was acidified with dilute hydrochloric acid and treated with an excess of aqueous picric acid. Warming the mixture on the steam-bath and filtering gave a clear solution (50 ml.). The solid which separated on cooling was collected and recrystallized from water. The 75 mg. of small yellow prisms of 1-D-xylopyranosyl-5,6-dimethylbenzimidazole picrate was again recrystallized from water; m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{21}N_5O_{11}$: C, 47.34; H, 4.17; N, 13.80. Found: C, 47.46; H, 4.20; N, 14.26.

1-D-(2′-Desoxyribopyranosyl)-5,6-dimethylbenzimidazole.—3,4-Diacetyl-D-arabinal[18] was converted to 1-chloro-3,4-diacetyl-D-2-desoxyribose.[19] This material was treated with silver 5,6-dimethylbenzimidazole[20] approximately as described by Cooley, Ellis, Mamalis, Petrow and Sturgeon.[4] The acetyl groups were removed by acid hydrolysis. 1-D-(2′-Desoxyribopyranosyl)-5,6-dimethylbenzimidazole was isolated as the picrate, melting, after recrystallization from methyl alcohol–water, at 200–201° dec., $[\alpha]^{25}D$ +27 ± 2° (*c* 0.5 in pyridine).

Anal. Calcd. for $C_{20}H_{21}N_5O_{10}$: C, 48.88; H, 4.31; N, 14.25. Found: C, 48.96; H, 4.25; N, 14.07.

1-D-(2′-Desoxyribopyranosyl)-5,6-dimethylbenzimidazole was obtained after continuous chloroform extraction of a dilute hydrochloric acid suspension of the picrate and neutralization. After two recrystallizations from water, the m.p. was 158–159°. The material consumed 0.94 mole of sodium periodate.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.30; H, 6.69; N, 10.44.

1-α-D-Ribofuranosyl-5,6-dimethylbenzimidazole Picrate.—Five grams of 2-nitro-4,5-dimethyl-N-(2′,3′-diacetyl-5′-trityl-D-ribofuranosyl)-aniline[2] dissolved in 100 ml. of benzene was reduced to 2-amino-4,5-dimethyl-N-(2′,3′-diacetyl-5′-trityl-D-ribofuranosyl)-aniline by shaking with 1.5 g. of palladium–Darco catalyst under 2–3 atmospheres of hydrogen. After removal of the catalyst and solvent, a solution of the sirupy amine in 50 ml. of dry benzene was stirred for two days with 20 ml. of carbon bisulfide and 2.52 g. of finely ground barium hydroxide. The residue, after removal of the volatile material, was partitioned between chloroform and dilute sulfuric acid. The sulfuric acid fraction was extracted three times with chloroform, and the combined chloroform extract washed three times with water. The chloroform solution, dried over sodium sulfate, was concentrated to dryness, and the residue, containing 1-(2′,3′-diacetyl-5′-trityl-D-ribofuranosyl)-2-sulfhydryl-5,6-dimethylbenzimidazole, was dissolved in 200 ml. of butyl alcohol. This solution was refluxed for 3 hours with 9 g. of Raney nickel catalyst. The butyl alcohol, after removal of the Raney nickel, was distilled under reduced pressure, and a mixture of the residue, 15 ml. of ethyl alcohol and 40 ml. of 0.67 *N* hydrochloric acid, was refluxed for 2 hours. The resulting solution was concentrated to half its original volume, then extracted three times with chloroform. The aqueous solution, cooled in an ice-bath and made alkaline with sodium hydroxide, was extracted four times with chloroform. The almost colorless aqueous layer was cooled, reacidified with hydrochloric acid, decolorized with a little Darco and concentrated to remove the chloroform. Addition of aqueous picric acid precipitated 0.43 g. (11%) of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole picrate. After recrystallization from ethyl alcohol the product melted at 201–202°, $[\alpha]^{25}D$ +12 ± 2° (*c* 1.6 in pyridine). The melting point (in a capillary) of an authentic specimen of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole picrate[21] was 206–207°, the mixed m.p. of the two substances 201–202°. All three melting points were determined simultaneously. The previously reported[2] rotation was $[\alpha]^{23}D$ +9° (*c* 4 in pyridine). That the picrate was a furanoside was evidenced by its consuming 0.99 mole of periodate.

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(21) We are indebted to Dr. Frederick W. Holly for this material,