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THE SYNTHESIS OF 5,6-DIMETHYL-1-(β-D-RIBOFURANOSYL)IMIDAZO[4,5-b]PYRAZINE BY RING CLOSURE OF AN IMIDAZOLE NUCLEOSIDE, A NEW BICYCLIC NUCLEOSIDE (1)

Raymond P. Panzica (2) and Leroy B. Townsend

Department of Chemistry and Department of Biopharmaceutical Sciences,

University of Utah, Salt Lake City, Utah 84112

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We wish to report a new route for the formation of the imidazo[4,5-b]pyrazine ring system. The previously reported syntheses (3-6) of imidazo[4,5-b]pyrazines have utilized pyrazine precursors while the present synthesis proceeds *via* ring annulation of the appropriate 4,5-diaminoimidazole derivative. This has resulted in the synthesis of 5,6-dimethyl-1-(β-D-ribofuranosyl)-imidazo[4,5-b]pyrazine (IV) which is the first example of an imidazo[4,5-b]pyrazine nucleoside.

5-Bromo-4-nitro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (7) (I) was dissolved in liquid ammonia, placed in a steel reaction vessel and allowed to stand at room temperature for 24 hrs. The excess ammonia was removed at room temperature to provide an orange-yellow solid (II) which was recrystallized (10) from water to afford long needles (mp 197-198°). That removal of the acetyl blocking groups had been accompanied by a nucleophilic displacement of the bromo group was established by pmr spectroscopy (absorption peak at δ7.73, NH_2) and the ultraviolet absorption comparison of the product with 4-nitro-5-amino-1-methylimidazole (8).

The formation of 4,5-diaminoimidazoles by reduction of a 5(4)-nitro-4(5)-aminoimidazole has been reported to be unsuccessful by the usual reduction conditions since they are susceptible toward oxidation. This prompted us to generate the diamino derivative *in situ* followed by ring closure before attempting the isolation of nucleoside material. Catalytic reduction of 5-amino-4-nitro-1-(β-D-ribofuranosyl)imidazole (II) in 70% aqueous ethanol provided III, *in situ*. To the solution containing III was added the calculated amount of diacetyl and the resulting solution then stirred (under N_2) at room temperature for 24 hr. Removal of the solvent *in vacuo* afforded IV (65% yield, II→IV) which was recrystallized from 95% aqueous ethanol, mp 234-245°. Ring closure of III to afford an imidazo[4,5-b]pyrazine derivative rather than a ring opened adduct or imidazo[4,5-d]imidazole derivative was substantiated by a pmr spectrum of the product which showed in addition to the characteristic carbohydrate absorption peaks (δ3.5-6.0), a singlet (6 protons) at δ2.57 (exocyclic methyl groups at C_5 and C_6 of the pyrazine moiety) and a

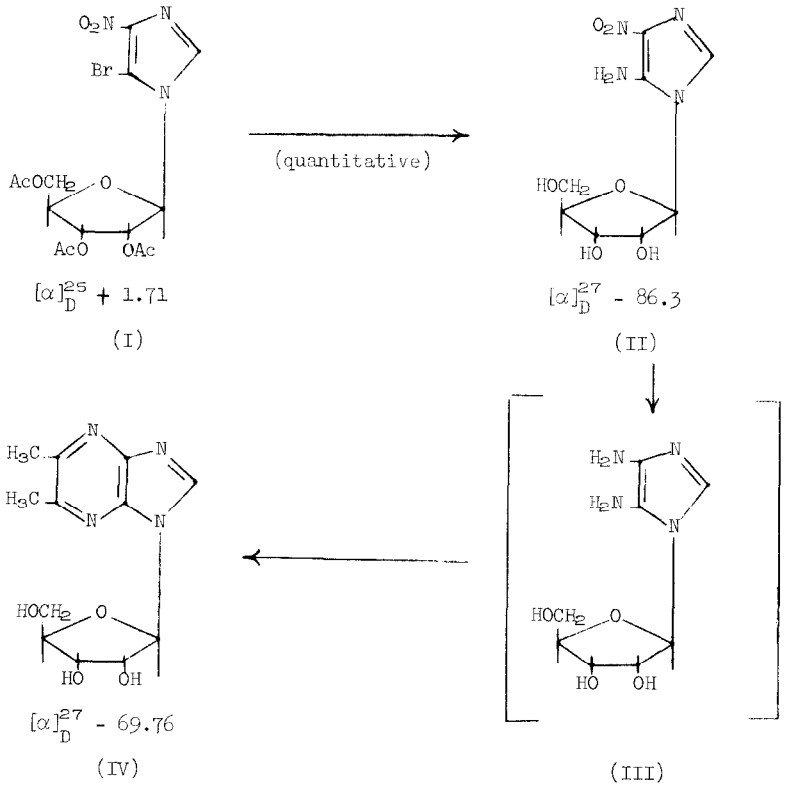

TABLE I

ULTRAVIOLET SPECTRA

	pH 1		MeOH		pH 11	
	λmax	ε max x 10^{-3}	λmax	ε max x 10^{-3}	λmax	ε max x 10^{-3}
I	304	8.10	295	7.20	232 304	9.00 8.55
II	222 366	9.60 13.70	360	13.00	239 366	9.70 13.00
IV	307	12.30	257 310	1.82 12.35	312	13.70

singlet (1 proton) at δ8.77 (aromatic hydrogen on the imidazole moiety at C_2).

The preparation of IV illustrates, once again (7,9,11), the potential of imidazole nucleosides for the synthesis of bicyclic nucleosides unavailable by other routes. This successful preparation of III has provided a new general route for the synthesis of imidazo[4,5-b]pyrazines. Application of this ring closure to the synthesis of other imidazo[4,5-b]pyrazine nucleosides is in progress in our laboratory.

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10. Satisfactory analytical data (C,H,N) were obtained from Heterocyclic Chemical Corp. for all new compounds and they were also found to be homogenous by chromatography.

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