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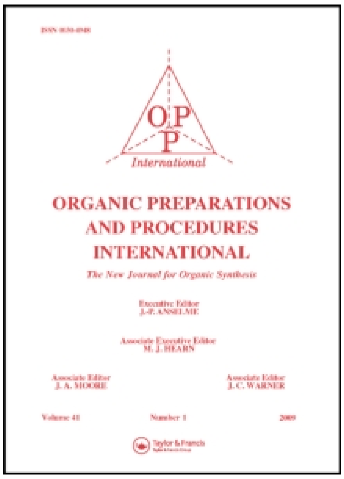

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SOME BENZIMIDAZOLE DERIVATIVES

Submitted by (3/21/74) Edgar A. Steck[1] and R. Pauline Brundage

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1-Substituted benzimidazoles (Table I) were obtained by subjecting a benzimidazole to the Mannich reaction[2] with an appropriate piperidine or piperazine unsubstituted at position 1. Two 2-(D-arabo-2,3,4,5-tetrahydroxyamyl) benzimidazoles were prepared from o-phenylenediamine (or, 4-chloro-o-phenylenediamine) by reaction with 2-deoxy-D-glucose in the presence of copper (I) acetate.[3] 2-Chloromethyl-1-methyl-2-benzimidazole was reacted with piperazine to form 1,4-bis-(1-methyl-2-benzimidazolyl-methyl)piperazine and with tropine to give 8-(1-methyl-2-benzimidazolyl) methyl tropinium chloride.

EXPERIMENTAL[4,5]

A. Intermediates. - In general, the benzimidazoles were prepared by the method of Phillips,[6] from the appropriate o-phenylenediamine and formic acid or chloroacetic acid in 4 N hydrochloric acid. Included were: benzimidazole,[6] 5(6)-chlorobenzimidazole,[7] 5,6-dichlorobenzimidazole,[8] and 2-chloromethyl-1-methylbenzimidazole.[9] The diamines were obtained by catalytic reduction (Raney nickel) of the amino-nitro or dinitro compounds in ethanol.

Nipecotamide was prepared in 93% yield by reduction of niacinamide (pyridine-3-carboxamide) in ethanol at 135° under 1900 psi of hydrogen pressure with Raney nickel catalyst.[10]

TABLE I. - 1-Substituted Benzimidazole

R_1	$R_{5/6}$	Appearance	Mp., °C[a]	Solvent[b]	Yield, %
$-CH_2N(CH_3)_2$	Cl	Fine needles	85.5-86.5	Pe	77.5
$-CH_2(Pip^{e}-3-CONH_2)$	H	Microcryst	182-183.5	M-E	66.5
$-CH_2(Pip^{e}-3-CONEt_2)$	H	Blades	110-111	E	87
$-CH_2-(Pz^{f})-CH_2-$	H	Needles	253-254d	Cs-W	97.5
	[c]	Creamy needles	>300	M-E	
$-CH_2-(Pz^{f}-4-CH_2CH_2OH)$	H[d]	Creamy needles	190.5-192	iPr-E	80.5
$-CH_2-(Pz^{f}-4-COOEt)$	H	Prisms	112.5-113.5	Ch	96
	Cl	Needles	132.5-133.5	Hp	88.5
	Cl_2	Light tan microcrystals	165.5-167	M	85

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[a] d signifies decomposition.

[b] Legend: Ch, cyclohexane; Cs, 2-methoxyethanol; E, ether; Hp, heptane; iPr, propanol-2; M, methanol; Pe, pentane.

[c] Hexahydrochloride.

[d] Tetrahydrochloride, obtained directly from the oily base; yield given for crude salt.

[e] Pip, signifies 1-piperidyl.

[f] Pz, signifies piperazinyl.

The base boiled at 120-122° (0.25 mm) and solidified to a mass of rosettes of needles, mp. 95-97°.

N,N-Diethyl nipecotamide. - Nikethamide (N,N-diethyl nicotinamide) was made by a composite of patented procedures.[11,12] The yield of amide was 62.5%; bp. 87-92° (0.1-0.2 mm). It was reduced in ethanol with Raney nickel catalyst at 115° under 2100 psi of hydrogen to a 97% yield of the hexahydro compound,[13-15] bp. 107-109° (1 mm); n_D^{25} 1.4855.

1-Carbethoxypiperazine[16] and 1-(2-hydroxyethyl)piperazine[17] were prepared by published procedures, as also was 2-deoxy-*D*-glucose.[18]

B. 1-Substituted Benzimidazoles. - Mannich reactions of the several benzimidazoles were performed in much the way described by Bachman and Heisey.[2] The resulting series of 1-substituted benzimidazoles is listed in Table I.

C. 2-Substituted Benzimidazoles

2-(D-Arabo-2,3,4,5-tetrahydroxyamyl)benzimidazole. - *o*-Phenylenediamine (10.8 g, 0.1 mole) was added to 16.8 g (0.102 mole) of 2-deoxy-*D*-glucose in 50 ml of water, and then stirred with a solution of 42.0 g (0.21 mole) of copper (II) acetate monohydrate. The entire mixture was warmed to 90° during 15 min. and kept at 87-92° for one half-hour longer. It was then filtered hot and the green, gelatinous filtrates were diluted with 900 ml of water and heated at 80° for *ca* one half-hour. Hydrogen sulfide was passed through the hot solution which was then filtered. The brown liquors were concentrated *in vacuo* to *ca* 200 ml and diluted with two volumes of ethanol, to precipitate a tan solid, mp. 220-225°. The crude product was twice crystallized (charcoal) from ethanol-water to give 20.0 g (80%) of amorphous, slightly pink compound, mp. 221-222° (dec.). Additional product was recovered from the liquors (1.9 g; mp. 220-221.5°, (dec.)).

2-(D-Arabo-2,3,4,5-tetrahydroxyamyl)-5/6-chlorobenzimidazole hydrochloride. - The procedure for the preparation of 2-(D-arabo-2,3,4,5-tetrahydroxyamyl) benzimidazole was applied to 4-chloro-o-phenylenediamine.[19] A 42% yield of purified product was obtained from 4:3 water-ethanol; mp. 231.5-232°, (dec.). It was converted to the hydrochloride and crystallized from ethanol. The pale cream-colored microcrystals melted with intumescence at 271-272°.

1,4-bis-(1-Methyl-2-benzimidazolylmethyl)piperazine. - To a stirred solution of 12.6 g (0.07 mole) of 2-chloromethyl-1-methylbenzimidazole in 20 ml of absolute ethanol at 25° was added (during ca 10 min.) a solution of 6.0 g (0.07 mole) of piperazine in 15 ml of absolute ethanol. It was kept at room temperature for several hours, then refluxed for one hour and concentrated in vacuo. The residue was rubbed with water and dried, giving 12.7 g (97%) of crude product. The 1,4-bis(1-methyl-2-benzimidazolylmethyl)piperazine was obtained from ethanol as white, prismatic needles, mp. 251-253°.

8-(1-Methyl-2-benzimidazolylmethyl) tropinium chloride. - Three and one-half g (0.025 mole) of tropine was dissolved in the minimal amount of boiling acetone and a solution of 5.0 g (0.0278 mole) 2-chloromethyl-1-methylbenzimidazole in 75 ml of boiling acetone was added. The mixture was refluxed for one half-hour and was allowed to stand for a day, then chilled. Several crystallizations of the compound from methanol-ether and one from methanol-acetone-ether (5:2:3) were required to obtain the quaternary salt as white microcrystals (4.2 g, 52% yield); mp. 252-253°.

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SYNTHESIS OF METHYL 2,3,4-TRI-O-ACETYL-6-DEOXY-6-IODO-α-D-GLUCOPYRANOSIDE

Submitted by
3/26/74

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An improved synthesis of iodo sugar IV, an important precursor for the synthesis of naturally occurring amino nucleosides,[1,2] starts from I. Tosylation of I with tosyl chloride in pyridine[3,4] was followed by acetylation of the free hydroxyl groups on II with acetic anhydride added directly to the reaction mixture. Removal of volatile materials under reduced pressure afforded III[5,6] in excellent yield