anhydrous diethylamine for four hours. Distillation of the crude reaction product yielded 4.0 g. (55%) of the bis-(diethylamide).

Table IV summarizes the physical constants and analytical data for these compounds.

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[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

A New Synthesis of 1-Glycosylbenzimidazoles[1]

BY JOHN DAVOLL[2] AND GEORGE BOSWORTH BROWN

1-Glycosylbenzimidazoles are prepared in good yield by condensation of polyacetylglycosyl halides with chloromercuribenzimidazoles, followed by deacetylation of the reaction products.

The isolation of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole from hydrolysates of vitamin B_{12},[3] and the demonstration[4] that it, or the β-isomer, will elicit a vitamin B_{12}-like growth response in rats, has aroused interest in the synthesis of this compound and of analogous 1-glycosylbenzimidazoles. Of the three reported syntheses of this type of compound, two proceed by condensation of the appropriate *o*-glycosylaminoaniline with either ethyl formimino ether hydrochloride[3] or sodium dithioformate.[5a] It has also been reported[5] that 1-D-glucopyranosylbenzimidazole can be prepared, in very low yield, from the condensation product of silver 5,6-dimethylbenzimidazole and tetraacetylglucosyl bromide.[5b]

It has now been found that, as in the pure series,[6] the chloromercuri derivatives of benzimidazoles are much superior to the silver salts for use in such condensations. By deacetylation of the condensation products of chloromercuribenzimidazoles with polyacetyl glycosyl halides the 1-β-D-ribofuranosyl and 1-β-D-glucopyranosyl derivatives of benzimidazole and 5,6-dimethylbenzimidazole have been prepared in 29 to 53% yield. The properties of these compounds are set out in Table I. It is assumed that Walden inversion occurs in the condensation reaction, so that the products have the β configuration. This was verified in the case of 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole by comparison of the picrate with authentic specimens of 1-α- and 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole picrates.[3,7]

TABLE I

	Yield, %[a]	M.p., °C.[b]	Formula	$[\alpha]^{25}D$; c = 1% in 0.1 N HCl	Ultraviolet absorption[c] 40 mg./l. in 0.1 N HCl λm mμ	εm	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found
1-β-D-Ribofuranosylbenzimidazole	53	111–112	$C_{12}H_{14}O_4N_2$	+13°	254	5130	57.6	57.5	5.6	5.8	11.2	11.1
					262	5470						
					269	6530						
					275	5660						
1-β-D-Glucopyranosylbenzimidazole	34	141–142	$C_{13}H_{16}O_5N_2$	+19°	253	4970	55.7	56.0	5.7	5.9	10.0	9.9
					261	5290						
					268	6230						
					275	5290						
1-β-D-Ribofuranosyl-5,6-dimethylbenzimidazole	43	192–200	$C_{14}H_{18}O_4N_2$	+16°	278	7770	60.4	60.5	6.5	6.6	10.1	10.2
					286	7440						
1-β-D-Glucopyranosyl-5,6-dimethylbenzimidazole	29	167–168[d] 251–253[e]	$C_{15}H_{20}O_5N_2$	+ 7°	278	7550	58.5	58.3	6.5	6.9	9.1	9.4
					285	6930						

[a] Based upon the benzimidazole. [b] Determined on a heated microscope stage; uncorrected. [c] Determined on a Cary Recording Spectrophotometer. [d] Reference 5a gives m.p. 166–167° for the sesquihydrate. [e] Anhydrous.

Experimental

Chloromercuribenzimidazoles.—A solution of the benzimidazole in hot 10% ethanol (100 ml./g.) containing one equivalent of sodium hydroxide was treated with an ethanolic solution of one molecular proportion of mercuric chloride. After cooling, the white precipitate was collected, washed with water and dried; yield 90–100%.

Like the corresponding purine derivatives,[6] these compounds contained less chlorine than would be expected from

(1) The authors wish to acknowledge the support of the Atomic Energy Commission, Contract AT(30-1)910 and the National Cancer Institute of the United States Public Health Service, Federal Security Agency.

(2) Fellow of the National Cancer Institute of the United States Public Health Service, Federal Security Agency.

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

(5b) When this manuscript was submitted we were not aware of the papers by P. Mamalis, V. Petrow and B. Sturgeon, *J. Pharm. Pharmacol.*, **2**, 503, 512 (1950), and G. Cooley, B. Ellis, P. Mamalis, V. Petrow and B. Sturgeon, *ibid.*, **2**, 579 (1950), describing the synthesis, from silver benzimidazoles, of 1-D-glucopyranosyl-benzimidazole and -5,6-dimethylbenzimidazole. We find a considerably lower melting point (141–142°) for 1-β-D-glucopyranosylbenzimidazole than that (212–213°) reported by the above authors, but the properties of the tetraacetyl derivative (m.p. 152–154°; $[\alpha]^{25}D$ −27° (c = 1.7% in chloroform)) and picrate (m.p. 144–147°) of our material are in fair agreement with those reported by Petrow, *et al.* For 1-tetraacetyl-β-D-glucopyranosyl-5,6-dimethyl-5,6-dimethylbenzimidazole we find m.p. 169–170°, with sintering above 126°, $[\alpha]^{25}D$ −44° (c = 1.7% in chloroform); Petrow, *et al.*, report m.p. 189.5–191°, $[\alpha]^{20}D$ −40.4° (c = 1% in chloroform).

(6) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(7) Kindly supplied by Dr. Karl Folkers, Research Laboratories, Merck and Co., Inc., Rahway, N. J.

the formula RHgCl; this may be due to contamination with derivatives of the type R_2Hg.

1-Glycosylbenzimidazoles.—A suspension of the finely powdered chloromercuri compound in xylene (80 ml./g.) was dried by slow distillation of one-third of the xylene, and to the residual suspension was added a slight excess of triacetyl-D-ribofuranosyl chloride[8] or tetraacetylglucosyl bromide. The mixture was refluxed gently for 1.5–2 hours, then cooled and diluted with two volumes of petroleum ether (b.p. 30–60°). The precipitate was washed with petroleum ether, dried and extracted with cold chloroform. The extract was washed with 30% potassium iodide and with water, dried over sodium sulfate, and evaporated under reduced pressure to a sirup, which was dissolved in methanol and treated with an excess of methanolic ammonia (saturated at 0°). The solution was kept overnight in the refrigerator, then evaporated to dryness and the residual glycosylbenzimidazole crystallized from water or dilute aqueous ethanol. If difficulty was experienced in crystallizing the compound it was isolated as the picrate and regenerated by the use of an anion-exchange resin.[6]

1-β-D-Ribofuranosyl-5,6-dimethylbenzimidazole Picrate.—Prepared in aqueous ethanolic solution, the picrate formed yellow needles, m.p. 172–174°, which did not depress the melting point of an authentic sample, m.p. 169–171° at the same rate of heating. At this rate of heating a sample of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole picrate had m.p. 207–210°.

Anal. Calcd. for $C_{20}H_{21}O_{11}N_5$: N, 13.8. Found: N, 14.1.

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[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

N-Acylamino Acids, A New Class of Resolving Agents[1]

BY H. D. DEWITT AND A. W. INGERSOLL

Various optically active N-acylamino acids were tested as agents for the resolution of racemic bases. N-Acetyl-L-leucine resolved α-phenylethylamine and α-*p*-tolylethylamine. N-Acetyl-3,5-dibromo-L-tyrosine resolved α-phenylethylamine and α-phenyl-*n*-propylamine. Certain other amines were not resolved by these agents. N-Acetyl-3,5-dibromo-DL-tyrosine was resolved by α-phenylethylamines.

The number and structural variety of available acidic resolving agents is quite small. (+)-Tartaric acid, (+)-camphor-10-sulfonic acid and (+)-α-bromocamphor-π-sulfonic acid are extensively used, while fewer than a dozen others have been used a few times. Most of these acids are available mainly in one active form; it is desirable to have both active forms.[2] Also, most of the acids are not physically well suited for convenient preparation and recovery.

It seems feasible to attempt to extend the list of resolving agents considerably by inclusion of suitably chosen N-acylamino acids. Many of these exhibit desirable general properties, particularly chemical stability, moderate acid strength, crystallizing power, and ease of preparation and recovery. Various combinations of parent amino acids with common acyl and sulfonyl groups should provide a desirable range of molecular weights and solubilities. At the outset it has seemed most practical to investigate derivatives of readily available natural acids, such as L-leucine, L-tyrosine and L-glutamic acid, but facile resolutions of the acetyl derivatives of 3,5-dibromo-DL-tyrosine, DL-tyrosine, DL-phenylalanine[3] and other common synthetic amino acids indicate that both active forms can be made available if desired.

Resolutions of *dl*-α-fenchylamine by use of the active acetyl derivatives of leucine,[4] valine[3] and phenylalanine[3] have already been reported. In continuation, acetyl-L-leucine was tested with seven other amines, namely, α-phenylethylamine, α-*p*-tolylethylamine, α-phenyl-*n*-propylamine, α-*p*-chlorophenylethylamine, α-*p*-xenylethylamine, phenylisopropylcarbinamine and β-octylamine. Satisfactory resolutions were obtained with the first two of these; the others formed highly crystalline salts but were not resolved in common solvents. The resolution of α-phenylethylamine is particularly useful, the (+)-form being obtained in 80% yield.

The acetyl and *p*-nitrobenzoyl derivatives of L-glutamic acid did not effect resolutions of any of the amines tested. The salts in general were too soluble or difficult to crystallize, although Howe and Sletzinger[5] recently have used the *p*-nitrobenzoyl derivative for the resolution of isoamidone, the first reported use of this class of agents.

N-Acetyl-L-tyrosine is easily made but is too soluble for convenient purification and recovery. This disadvantage was overcome by dinitration or dibromination of L-tyrosine and subsequent N-acetylation. N-Acetyl-3,5-dinitro-L-tyrosine salts are highly colored and otherwise unsuitable. N-Acetyl-3,5-dibromo-L-tyrosine, however, effected ready resolutions of α-phenyl-*n*-propylamine and α-phenylethylamine. The remaining amines tested formed well crystallized salts but were not resolved. The resolution of α-phenylethylamine gave the (−)-form in 78% yield and is thus complementary to that with acetyl-L-leucine. N-Acetyl-3,5-dibromo-DL-tyrosine, prepared from racemized L-tyrosine, was readily resolved by (−)- and (+)-α-phenylethylamines, thus making both forms available.

The proportion of successful resolutions effected thus far with N-acylamino acids (five of ten tried) is not exceptional but the successful examples fortunately afford convenient procedures for several individually important amines. The work is being continued.

(1) Taken from the Ph.D. thesis of H. D. DeWitt, September, 1950.

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