BENZIMIDAZOLE NUCLEOSIDES, NUCLEOTIDES, AND RELATED DERIVATIVES

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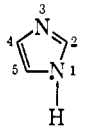
Contents

I. Introduction, Scope, and Nomenclature

The present review covers the area of synthetic and naturally occurring nucleosides and nucleotides of benzimidazoles, benzotriazoles, indazoles, and indoles with a brief discussion of their biochemical significance. The most extensive area covered in this review is that of benzimidazole nucleosides and nucleotides, and they will, therefore, be used to illustrate the nomenclature and numbering system of the nucleosides.

The heterocyclic portion of the benzimidazole ring system has been referred to as glyoxaline,[1] iminazole, 1,3-diazole, and imidazole.[2] Imidazole, which is the term used most frequently, indicates a five-membered heterocyclic ring system containing an imino group and a tertiary nitrogen. The



imidazole

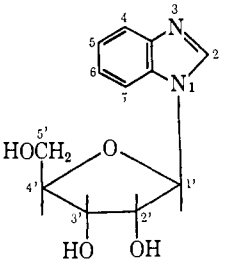
imidazole skeleton is found in several naturally occurring compounds which include the amino acid histidine (a normal constituent of most proteins), histamine, the purines, and biotin. Benzimidazole, a ring system in which a benzene ring is fused to the 4,5 positions of imidazole, is found in an important group of substances which has found practical applications in a wide variety of fields. The terms benziminazole, 1,3-benzodiazole, and benzoglyoxaline are also used in the modern literature with benzimidazole being the most prevalent. The discovery[3,4] that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole was an integral part of the chemical structure of vitamin B_{12} has generated considerable interest in the area of benzimidazole nucleosides and nucleotides.

The term nucleoside was originally[5] used only for the carbohydrate derivatives of purines and pyrimidines isolated from the alkaline hydrolyzates of yeast nucleic acid. This limited the connotation of the term nucleoside, since the major carbohydrate constituents of yeast nucleic acids are either D-ribose or 2-deoxy-D-ribose. However, it has now been generally accepted[6] that the term purine nucleoside refers to all glycosyl derivatives of purines, both synthetic and natural, and it has been proposed[7] that this terminology should cover the entire field of heterocyclic glycosides. Therefore, all glycosyl derivatives of nitrogen heterocycles, regardless of the nature of the carbohydrate moiety, are referred to in this review as nucleosides. Like nucleosides, the term nucleotide was originally applied only to the phosphate esters of certain N-glycosides of purines and pyrimidine bases obtained on hydrolyzing nucleic acids.[8] It is now applied generally to the phosphate

(1) H. Debus, *Ann. Chem.*, 107, 199 (1858).
(2) A. Hantzsch, *ibid.*, 249, 1 (1888).
(3) See R. Bonnett, *Chem. Rev.*, 63, 573 (1963), for a recent and comprehensive review of vitamin B_{12}.
(4) H. H. O. Hill, J. M. Pratt, and R. J. P. Williams, *Chem. Brit.*, 5, 156 (1969).
(5) P. A. Levene and W. A. Jacobs, *Ber.*, 42, 2474 (1909).
(6) J. A. Montgomery and H. J. Thomas, *Advan. Carbohyd. Chem.*, 17, 301 (1962).
(7) L. B. Townsend, *Chem. Rev.*, 67, 533 (1967).
(8) A. R. Todd, *Science*, 127, 787 (1958).

ester of any nucleoside, and in this review the term nucleotide is used when a phosphate ester has been formed on a hydroxy group of the carbohydrate moiety of a heterocyclic nucleoside.

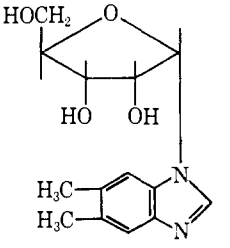
The numbering system will use numerals to designate positions on the heterocyclic aglycon and primed numerals for positions on the carbohydrate moiety. For benzimidazoles, the numbering of the aglycon always begins at the substituted nitrogen and proceeds so that the second nitrogen in the ring is at position 3. Numbering of the carbohydrate moiety originates at the anomeric carbon which is the carbon involved in the glycosidic linkage as illustrated. The nomenclature and numbering system for the benzotriazoles, indazoles, and indoles will be discussed briefly at the beginning of the section in which they are presented.



Several reviews on the chemistry of benzimidazole[9-13] and 2-(*aldo*-polyhydroxyalkyl)benzimidazoles[14-16] have appeared in the literature, but there has never been a complete review on the nucleosides and nucleotides of benzimidazoles, benzotriazoles, indazoles, and indoles, although there has been considerable research reported in each area. This review is designed to summarize and complement previous reports and present a complete and comprehensive review on the above nucleosides and nucleotides. The literature survey pertaining to this review was concluded in December 1968 although a few more recent references have been included.

II. Chemical Synthesis of Benzimidazole Nucleosides and Nucleotides

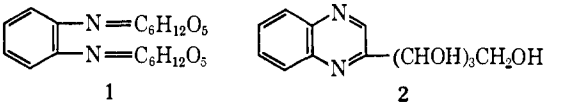
Considerable interest was generated in the area of benzimidazole nucleosides and nucleotides when 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (α-ribazole) and the 3′-phosphate derivative were found among the mineral acid hydrolysis products of vitamin B_{12}.[17-21] In spite of the strong objection raised by Todd and coworkers,[20] the term α-ribazole is still widely used in modern literature. The chemical synthesis of these and other benzimidazole nucleosides and nucleotides is a relatively new area in comparison to the related areas of purine, pyrimidine, and imidazole nucleosides and nucleotides. Certain benzimidazole derivatives have been reported to be superior to hydrazones and osazones for the characterization of sugars;[22] however, the most important single factor which catalyzed the tremendous interest in the synthetic preparation of benzimidazole nucleosides and nucleotides was the discovery that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole



is an integral part of the chemical structure of vitamin B_{12}.

A. BENZIMIDAZOLES CONTAINING A CARBOHYDRATE MOIETY AT POSITION 2

The discovery[23] that phenylhydrazine reacts with carbohydrates to form characteristic derivatives led to an investigation[24] of the reaction of the isomeric compound, *o*-phenylenediamine, with carbohydrates. Thus, a solution of *o*-phenylenediamine (one part by weight) and D-glucose (two parts) in water containing a few drops of hydrochloric acid was allowed to stand for 8 days. The condensed product was isolated and found to be a weak base which crystallized readily from hot water or alcohol. Further investigation[25] revealed that the reaction of *o*-phenylenediamine with D-glucose was more complicated than had been initially assumed[24] and that the results differed according to whether the reaction was carried out in the presence or absence of a mineral acid. In the absence of acid, two molecules of D-glucose condensed with one molecule of *o*-phenylenediamine to form an "*o*-diaminobenzene diglucoside." The same product was obtained[26] by the reaction of D-glucose with *o*-phenylenediamine in pyridine solution. This product was found to be a mixture of tautomeric modifications of N,N′-di-D-glucosyl-*o*-phenylenediamine (**1**).[27] In the presence of acids there was formed a compound which was

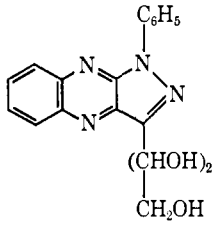


1 2

presumed to be "anhydrogluco-*o*-diaminobenzene,"[25] and was later confirmed by other investigations.[28-30] This compound, which is now referred to as 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**2**), is a weak base, reduces Fehling solu-

(9) J. B. Wright, *Chem. Rev.*, 48, 397 (1951).
(10) K. Hofman, "Heterocyclic Compounds-Imidazole and its Derivatives," Part I, Interscience Publishers, New York, N. Y., 1953, p 247.
(11) S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. V, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 267.
(12) A. Pullman, B. Pullman, and G. Berthier, *C. R. Acad. Sci., Paris*, 243, 380 (1956).
(13) O. E. Polansky and G. Derflinger, *Monatsh. Chem.*, 92, 1114 (1961).
(14) N. K. Richtmyer, *Advan. Carbohyd. Chem.*, 6, 175 (1951).
(15) E. A. Davidson, "Carbohydrate Chemistry," Holt, Rinehart & Winston, Inc., Chicago, Ill., 1967, p 151.
(16) Y. A. Zhdanov and G. M. Dorofeenko, *Usp. Khim.*, 27, 179 (1958); *Chem. Abstr.*, 52, 11077 (1958).
(17) G. H. Beavan, E. R. Holiday, E. A. Johnson, B. Ellis, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, 1, 957 (1949).
(18) G. Cooley, B. Ellis, P. Mamalis, V. Petrow, and B. Sturgeon, *ibid.*, 2, 579 (1950).
(19) N. G. Brink, F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, and K. Folkers, *J. Amer. Chem. Soc.*, 72, 1866 (1950).
(20) J. G. Buchanan, A. W. Johnson, J. A. Mills, and A. R. Todd, *J. Chem. Soc.*, 2845 (1950).
(21) J. G. Buchanan, A. W. Johnson, J. A. Mills, and A. R. Todd, *Chem Ind.* (London), 426 (1950).
(22) S. Moore and K. P. Link, *J. Biol. Chem.*, 133, 293 (1940).
(23) E. Fisher, *Ber.*, 17, 579 (1884).
(24) P. Griess and G. Harrow, *ibid.*, 20, 281 (1887).
(25) P. Griess and G. Harrow, *ibid.*, 20, 2205 (1887).
(26) H. Ohle and J. J. Kruyff, *ibid.*, 77, 507 (1944).
(27) O. Hinsberg, *ibid.*, 20, 495 (1887).
(28) E. Fisher, *ibid.*, 22, 87 (1889).
(29) H. Ohle, *ibid.*, 67, 155 (1934).
(30) H. Erlbach and H. Ohle, *ibid.*, 67, 555 (1934).

tion, and reacts with phenylhydrazine, by oxidation and condensation, to form 1-phenyl-3-(D-*erythro*-trihydroxypropyl)-flavazole (**3**). Various other quinoxalines[26,29-31] and flavazoles[31-37] have been prepared and characterized.



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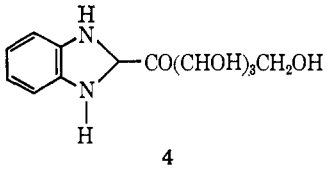
After isolation of **2** from the acidic reaction mixture of D-glucose and *o*-phenylenediamine,[25] concentration of the mother liquor furnished a crystalline compound in low yield which was assigned structure **4**. Although this structure was subsequently found to be incorrect, the properties of the substance as described was sufficiently characteristic to identify it as the first known benzimidazole derivative produced from the reaction between a carbohydrate and *o*-phenylenediamine. This reaction was reinvestigated,[38] and the correct formula was



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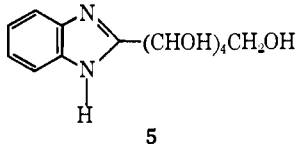

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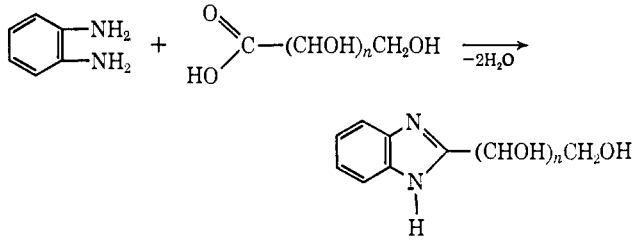
then proposed to be **5**. The low yield of benzimidazoles substituted in the 2 position by carbohydrates was accounted for by the observation that oxidation of the aldose proceeds by two routes, one leading to the formation of an osazone and the other to an aldonic acid. The osazone will then afford quinoxaline derivatives with the diamine while the aldonic acid forms the 2-substituted benzimidazoles.[39,40]

The condensation of *o*-phenylenediamine with L-arabinose and D-galactose, 3,4-diaminotoluene with L-arabinose and D-glucose, and 2,3-diaminobenzoic acid with L-arabinose, D-glucose, D-galactose, and D-maltose has been accomplished to afford crystalline products.[25,41,42] In every case the products were formed in neutral or weakly acidic solutions and were identified as the corresponding 2-substituted benzimidazoles. Conclusive evidence that these compounds were actually 2-substituted benzimidazoles was provided by subjecting the above compounds to oxidative cleavage with permanganate[43] and also by dry distillation.[44] It was an established fact[9] that *o*-phenylenediamine would condense with organic acids including hydroxy acids and should have suggested that the preparation of a benzimidazole from an aldonic acid would be a simple matter. However, it was not until 1939 that this reaction was investigated[22,40,45] by first oxidizing the aldose to an aldonic acid and then condensing the resulting aldonic acid with *o*-phenylenediamine. This general method has been used extensively to prepare benzimidazoles of the general formula **6** in good yield.[45-58] The reaction is usually carried out by heating the aldonic acid and *o*-phenylenediamine in the presence of a mineral acid, *e.g.*, a mixture of hydrochloric acid and phosphoric acid. When the reaction is carried out at 180°



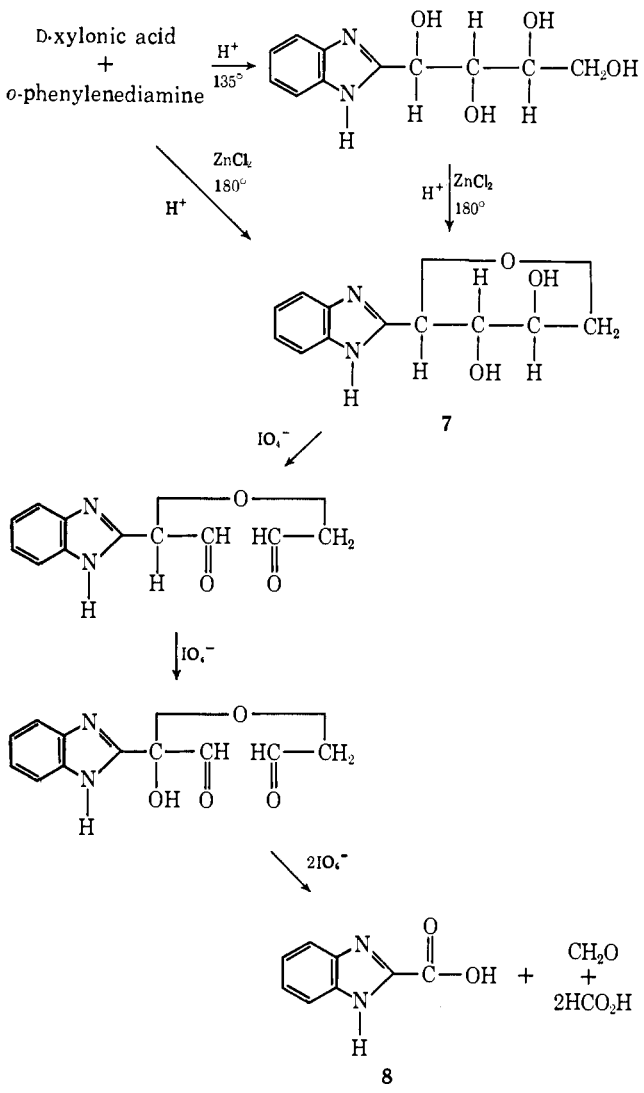
6

in the presence of zinc chloride and hydrochloric acid, the anhydro derivatives are usually formed by the loss of an additional mole of water in the carbohydrate portion of the 2-polyhydroxyalkylbenzimidazole. Thus D-xylonic acid reacts with *o*-phenylenediamine in the presence of zinc chloride and hydrochloric acid to give 2-(1′,4′-anhydro-D-*xylo*-tetrahydroxybutyl)benzimidazole (**7**).[45,53,53a] The structure of **7** was confirmed by periodate oxidation studies which consumed 4 molar equiv of periodate to produce 2-benzimidazolecarboxylic acid (**8**), formaldehyde, and 2 molar equiv of formic acid (Scheme I). This over oxidation has been rationalized[14,53] by assuming that the active hydrogen on the carbon adjacent to the heterocyclic aglycon is oxidized to a hydroxyl group which would then give the products observed.

This conversion of aldopentobenzimidazoles to their 1′,4′-anhydrides at 180° was extended to arabinose, lyxose, and ribose.[53] It was proved conclusively[59] that both D-*ribo*- and D-*arabino*-polyhydroxyalkylbenzimidazoles were formed when the condensation of calcium D-ribonate with *o*-phenylenediamine was carried out in the presence of less than 2 molar

(31) H. Ohle and M. Hielscher, *Ber.*, **74**, 13 (1941).
(32) H. Ohle and G. A. Melkonian, *ibid.*, **74**, 279 (1941).
(33) H. Ohle and G. A. Melkonian, *ibid.*, **74**, 398 (1941).
(34) H. Ohle and R. Liebig, *ibid.*, **75**, 1536 (1942).
(35) H. Ohle and A. Iltgen, *ibid.*, **76**, 1 (1943).
(36) G. Neumüller, *Ark. Kemi, Mineral. Geol.*, **21A**, No. 19, 13 (1946); *Chem. Abstr.*, **41**, 1210 (1947).
(37) U. Rosenqvist, G. Neumüller, and K. Myrbäck, *Ark. Kemi, Mineral Geol.*, **24A**, No. 14, 9 (1946); *Chem. Abstr.*, **42**, 5425 (1948).
(38) O. Hinsberg and F. Funcke, *Ber.*, **26**, 3092 (1893).
(39) C. S. Hudson, O. Hartley, and C. B. Purves, *J. Amer. Chem. Soc.*, **56**, 1248 (1934).
(40) W. T. Haskins and C. S. Hudson, *ibid.*, **61**, 1266 (1939).
(41) P. Griess and G. Harrow, *Ber.*, **20**, 3111 (1887).
(42) D. J. Bell and E. Baldwin, *J. Chem. Soc.*, 125 (1941).
(43) B. Schilling, *Ber.*, **34**, 902 (1901).
(44) R. Kühn and F. Bär, *ibid.*, **67**, 898, 904 (1934).
(45) S. Moore and K. P. Link, *J. Org. Chem.*, **5**, 637 (1940).
(46) P. Karrer, B. Becker, F. Benz, P. Frei, H. Salomon, and K. Schopp, *Helv. Chim. Acta*, **18**, 1435 (1935).
(47) G. R. Barker, K. R. Cooke, and J. M. Gulland, *J. Chem. Soc.*, 339 (1944).
(48) D. J. Bell and E. Baldwin, *Nature*, **146**, 559 (1940).
(49) D. J. Bell and E. Baldwin, *J. Chem. Soc.*, 129 (1941).
(50) J. M. Gulland and G. R. Barker, *ibid.*, 625 (1943).
(51) R. M. Hann, A. T. Merrill, and C. S. Hudson, *J. Amer. Chem. Soc.*, **66**, 1918 (1944).
(52) R. M. Hann, A. T. Merrill, and C. S. Hudson, *ibid.*, 66, 1920 (1944).
(53) G. F. Huebner, R. Lohmar, R. J. Dimler, S. Moore, and K. P. Link, *J. Biol. Chem.*, **159**, 503 (1945).
(53a) This type of compound is usually designated as "C-glycosides," *e.g.*, K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci. U. S.*, **57**, 548 (1967).
(54) A. T. Merrill, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, **65**, 994 (1943).
(55) N. K. Richtmyer and C. S. Hudson, *ibid.*, **64**, 1609 (1942).
(56) N. K. Richtmyer and C. S. Hudson, *ibid.*, **64**, 1612 (1942).
(57) H. Skolnick, J. G. Miller, and A. R. Day, *ibid.*, **65**, 1854 (1943).
(58) T. S. Gardner and E. Wenis, *ibid.*, **73**, 1855 (1951).
(59) G. R. Barker, K. R. Farrar, and J. M. Gulland, *J. Chem. Soc.*, 21 (1947).

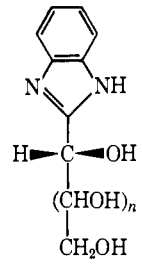
Scheme I



equiv of hydrochloric acid. However, when an excess of hydrochloric acid was used, there was obtained only the D-*ribo*-polyhydroxyalkylbenzimidazole. Epimerization at C-2 of the carbohydrate depends on the concentration of mineral acids used in the reaction[59] and appears to be facilitated at higher temperatures.[45] Aldoses may also be condensed directly with *o*-phenylenediamine to give benzimidazoles, occasionally in good yield, by employing cupric acetate as an oxidizing agent.[60-62] The above procedure was applied to saccharic acids with the products in these cases being bis(benzimidazole) derivatives.[63-66]

Several 2-(*aldo*-polyhydroxyalkyl)benzimidazoles have been isolated as a result of side reactions when ethyl formimidoyl ether hydrochlorides were used as ring-closing agents in the formation of 1-glycosylbenzimidazoles from N-glycosides of 2-aminoanilines.[67,68]

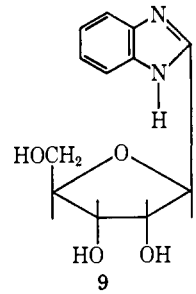
The so-called "benzimidazole rule" has been formulated[69] for the determination of configuration of aldonic acids and related compounds. This rule is expressed in the following manner: whenever the hydroxyl group on the second (or α) carbon atom of an aldonic acid is written on the right in the conventional projection formula, the rotation of the derived benzimidazole is positive and, conversely, when the hydroxyl group is written on the left, the rotation of the benzimidazole derivative is negative. A recent investigation[69a] has equated the stereochemistry at C-1′ of 2-(*n*-polyhydroxyalkyl)benzimidazoles with the Cotton effect observed in the rotatory dispersion spectrum. It was established that a 2-(*n*-polyhydroxyalkyl)benzimidazole which has *S* chirality (**8a**) at C-1′ will exhibit a positive Cotton effect while a 2-(*n*-polyhydroxyalkyl)-benzimidazole with *R* chirality at C-1′ will show a negative Cotton effect. A subsequent report[69b] has also established a method for the assignment of not only the stereochemistry of C-1′ but also C-2′ and C-3′ by ORD spectral measurements.



8a

Benzimidazoles containing the carbohydrate moiety in position 2 have been used for resolving a racemic mixture of tartaric acid[40,70,71] and potassium acid tartrate.[70]

The recent preparation of 2-(β-D-ribofuranosyl)benzimidazole (**9**) has been accomplished[72] by the condensation of 2,5-anhydro-D-allonic acid with *o*-phenylenediamine under acidic conditions. The structure for the carbohydrate moiety was inferred by the method of synthesis and the electrophoretical mobility in a neutral borate buffer solution. This investigation



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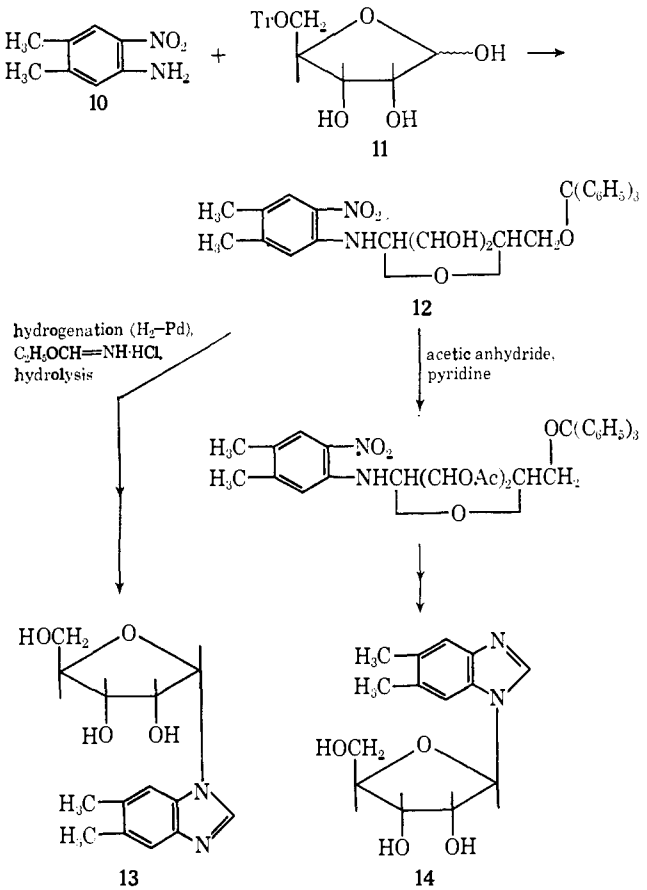
(60) R. J. Dimler and K. P. Link, *J. Biol. Chem.*, 150, 345 (1943).
(61) A. J. Cleaver, A. B. Foster, and W. G. Overend, *J. Chem. Soc.*, 3961 (1957).
(62) R. Weidenhagen, *Ber.*, 69, 2263 (1936).
(63) R. Lohmar, R. J. Dimler, S. Moore, and K. P. Link, *J. Biol. Chem.*, 143, 551 (1942).
(64) C. S. Hudson and H. S. Isbell, *J. Amer. Chem. Soc.*, 51, 2225 (1929).
(65) G. A. Levvy, *Biochem. J.*, 42, 2 (1948).
(66) J. K. Grant and G. F. Marrian, *ibid.*, 47, 1 (1950).
(67) F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, J. B. Lavigne, and K. Folkers, *J. Amer. Chem. Soc.*, 74, 4521 (1952).
(68) D. Heyl, G. Emerson, M. M. Gasser, E. C. Chase, and K. Folkers, *ibid.*, 78, 4491 (1956).
(69) N. K. Richtmyer and C. S. Hudson, *ibid.*, 64, 1612 (1942).
(69a) W. S. Chilton and R. C. Krahn, *ibid.*, 89, 4129 (1967).
(69b) W. S. Chilton and R. C. Krahn, *ibid.*, 90, 1318 (1968).
(70) J. D. Surmatis, U. S. Patent 2,456,752 (Dec 21, 1948); *Chem. Abstr.*, 43, 3031 (1949).
(71) V. O. G. Klingmuller and G. Gedenk, *Nature*, 179, 367 (1957).
(72) M. Bobek and J. Farkas, *Collect. Czech. Chem. Commun.*, 34, 247 (1969).

Scheme II



is of considerable interest and has added a new dimension to the area of 2-substituted benzimidazole nucleosides and nucleotides.

B. BENZIMIDAZOLES CONTAINING A CARBOHYDRATE MOIETY AT POSITION 1

The preparation of 1-glycosylbenzimidazoles has been an area of considerable interest primarily because of the structure elucidation[19,73] of the nucleoside portion of vitamin B_{12} as a 1-glycosylbenzimidazole [5,6-dimethyl-1-(α-D-ribofuranosyl)-benzimidazole (α-ribazole)]. The above structural assignment to this nucleoside was very remarkable in view of the fact that all the naturally occurring nucleosides isolated from various nucleic acids had, up until that time, been found to possess the β configuration. This prompted a tremendous amount of research in efforts to develop better and more facile methods for the synthesis of various 1-glycosylbenzimidazoles of both α and β configuration.

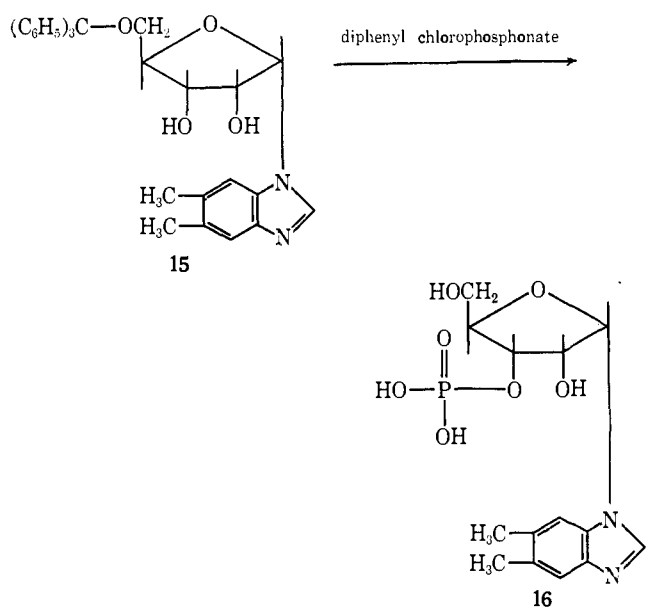
1. Ring Closure of N-Glycosyl-o-phenylenediamine Derivatives

Benzimidazoles containing a carbohydrate moiety at position 1 have been prepared from N-monosubstituted *o*-phenylenediamines where the N substituent was a carbohydrate moiety.

(73) N. G. Brink, F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, and K. Folkers, *J. Amer. Chem. Soc.*, 72, 2820 (1950).

These *o*-diamines were ring closed by conventional methods[9] to furnish a number of benzimidazole nucleosides. The initial synthesis of α-ribazole and the corresponding β anomer was successfully accomplished from the route described above. 2-Nitro-4,5-dimethylaniline (**10**) and 5-*O*-trityl-D-ribose (**11**) were condensed to furnish what was assumed to be 2-nitro-4,5-dimethyl-N-(5′-trityl-D-ribofuranosyl)aniline (**12**) (Scheme II). Hydrogenation of the nitro group and condensation with ethyl formimidoyl ether hydrochloride or isopropyl formimidoyl ether hydrochloride[67,74] was followed by acid hydrolysis to afford 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (**13**) which was isolated as a picrate. However, when **12** was acetylated with acetic anhydride in pyridine prior to hydrogenation, the product isolated after condensation with ethyl formimidoyl ether hydrochloride and deacetylation of the cyclized product was the β anomer of **13** [5,6-dimethyl-1-(β-D-ribofuranosyl)benzimidazole (**14**)] as a picrate. For convenience, the dextrorotatory isomer was termed α-ribazole [5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (**13**)] and the levorotatory isomer β-ribazole [5,6-dimethyl-1-(β-D-ribofuranosyl)benzimidazole (**14**)].

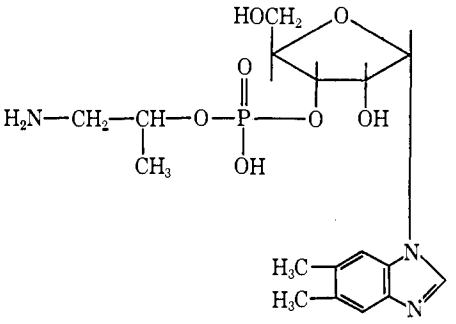
One of the hydrolytic (acid) products of vitamin B_{12} [5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole 3′-phosphate (**16**, α-ribazole phosphate)] was prepared by starting with the direct phosphorylation of 5′-trityl-α-ribazole (**15**) with diphenyl chlorophosphonate.[75,76] Removal of trityl and phenyl



groups by acid hydrolysis furnished α-ribazole phosphate which was isolated as the lead salt and then converted to the free base with hydrogen sulfide. The phosphorylation of 5′-*O*-trityl-α-ribazole was also effected by means of dibenzyl chlorophosphonate in a carbon tetrachloride and pyridine solution.[75,76] The benzyl groups were subsequently removed by hydrogenolysis with palladium on carbon and the product was purified as the crystalline dibrucine salt. This nucleotide was formulated tentatively as the 3′-phosphate derivative on

(74) F. W. Holly, C. H. Shunk, J. J. Cahill, and K. Folkers, U. S. Patent 2,644,817 (July 7, 1953); *Chem. Abstr.*, 48, 8267 (1954).
(75) E. A. Kaczka, D. Heyl, W. H. Jones, and K. Folkers, *J. Amer. Chem. Soc.*, 74, 5549 (1952).
(76) D. Heyl, C. H. Shunk, and K. Folkers, U. S. Patent 2,667,479 (Jan 26, 1954); *Chem. Abstr.*, 49, 1817 (1955).

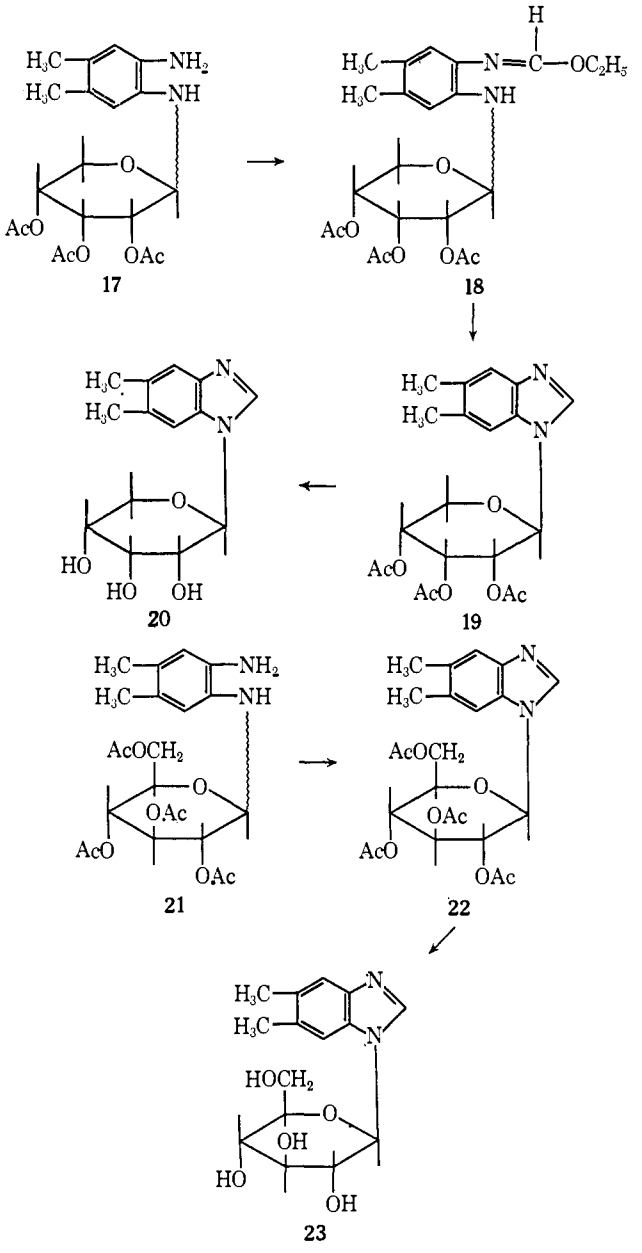
the basis of chromatographic behavior.[77] Careful spectroscopic,[78,79] acid hydrolysis,[80] and X-ray[81-86] studies on vitamin B_{12} and on the synthetic nucleotide proved unequivocally that the benzimidazole nucleotide was α-ribazole 3′-phosphate.[3] The phosphoric acid diester (**16a**) was prepared from 1-amino-



16a

2-propanol and the 2′,3′-cyclic phosphate of 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole.[87] The 2′-phosphoric acid diester was also formed and isolated from the same reaction mixture.

The importance of this synthetic route for the preparation of benzimidazole nucleosides was again demonstrated[88] by the successful synthesis of 5,6-dimethyl-1-(β-D-ribopyranosyl)-benzimidazole (**20**) from the reaction of 4,5-dimethyl-N-(2′,3′,4′-tri-*O*-acetyl-D-ribopyranosyl)-*o*-phenylenediamine (**17**) with ethyl orthoformate which afforded the ethoxymethylene derivative **18**. The conversion of **18** to 5,6-dimethyl-1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)benzimidazole (**19**) was accomplished with dilute hydrochloric acid, and subsequent deblocking of the carbohydrate moiety gave **20**.[67,88,89] The character of the lactol ring was confirmed as being pyranose by periodate titration. Similarly, 5,6-dimethyl-1-(β-D-glucopyranosyl)benzimidazole (**23**) was synthesized by the ring closure of 2-amino-4,5-dimethyl-N-(2′,3′,4′,6′-tetra-*O*-acetyl-D-glucopyranosyl)aniline (**21**) with isopropyl formimidoyl ether hydrochloride[67] or by ethyl orthoformate[90] to afford 5,6-dimethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)benzimidazole (**22**) which on deacetylation afforded **23**. The site of glycosylation in **23** was confirmed as N-1 by a comparison of the ultraviolet absorption spectral data for **23** with the ultraviolet spectral data for other 1-substituted

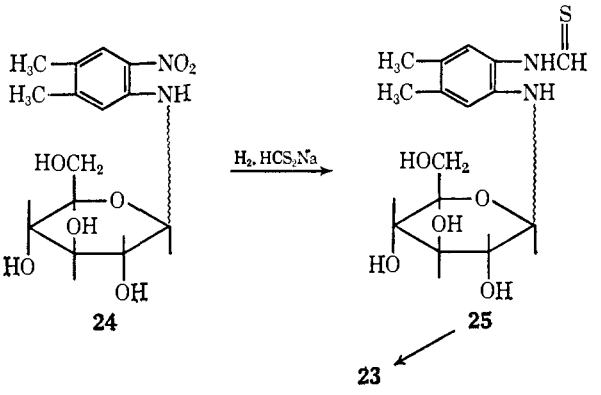


benzimidazoles. Attempts to convert 2-amino-N-(tetra-*O*-acetyl-D-galactosyl)aniline into the corresponding benzimidazole was reported to be unsuccessful.[90,91]

Several different methods of ring closure for N-glycosyl-*o*-phenylenediamine derivatives were studied.[92] The ring-closure reagents used in addition to alkyl formimidoyl ether hydrochlorides were N-(dichloromethyl)formamidine hydrochloride, ethyl formate, and carbon disulfide. The carbon disulfide ring closure was followed by treatment with Raney nickel catalyst for the removal of the exocyclic sulfhydryl group. Ethyl formimidoyl ether hydrochloride was found to be the reagent of choice for these ring closures.

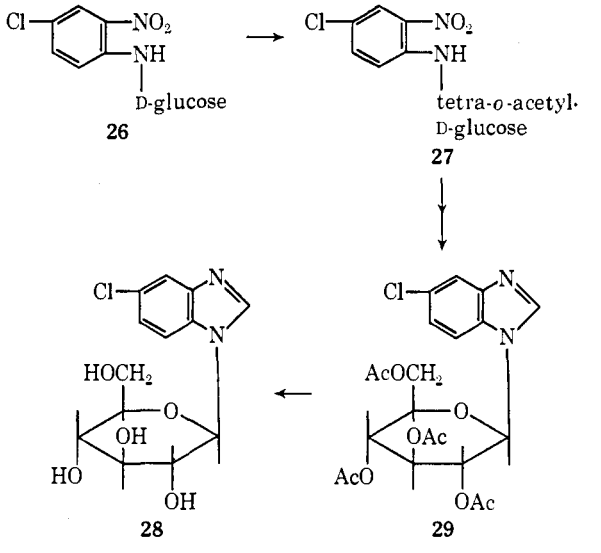
The synthesis of 5,6-dimethyl-1-(β-D-glucopyranosyl)benzimidazole (**23**) by a method similar to that used for the synthesis of certain purine glycosides was also reported.[93] This

(77) E. A. Kaczka and K. Folkers, *J. Amer. Chem. Soc.*, **75**, 6317 (1953).
(78) G. H. Beavan, E. R. Holiday, E. A. Johnson, B. Ellis, and V. Petrow, *J. Pharm. Pharmacol.*, **2**, 944 (1950).
(79) G. Cooley, B. Ellis, V. Petrow, G. H. Beavan, E. R. Holiday, and E. A. Johnson, *ibid.*, **3**, 271 (1951).
(80) J. B. Armitage, J. R. Cannon, A. W. Johnson, L. F. J. Parker, E. L. Smith, W. H. Stafford, and A. R. Todd, *J. Chem. Soc.*, 3849 (1953).
(81) C. Brink, D. C. Hodgkin, J. Lindsey, J. Pickworth, J. H. Robertson, and J. G. White, *Nature*, **174**, 1169 (1954).
(82) D. C. Hodgkin, J. Kamper, J. Lindsey, M. MacKay, J. Pickworth, J. H. Robertson, C. B. Shoemaker, J. G. White, R. L. Prosen, and K. N. Trueblood, *Proc. Roy. Soc.*, **A242**, 228 (1957).
(83) D. C. Hodgkin, J. Lindsey, M. MacKay, and K. N. Trueblood, *ibid.*, **A266**, 475 (1962).
(84) P. G. Lenhert and D. C. Hodgkin, *Nature*, **192**, 937 (1961).
(85) D. C. Hodgkin, J. Lindsey, R. A. Sparkes, K. N. Trueblood, and J. G. White, *ibid.*, **A266**, 494 (1962).
(86) J. G. White, *ibid.*, **A266**, 440 (1962).
(87) W. Friedrich, G. Gross, K. Bernhauer, and P. Zeller, *Helv. Chim. Acta*, **43**, 704 (1960).
(88) G. Cooley, B. Ellis, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **2**, 579 (1950).
(89) P. Mamalis, V. Petrow, and B. Sturgeon, *ibid.*, **2**, 491 (1950).
(90) P. Mamalis, V. Petrow, and B. Sturgeon, *ibid.*, **2**, 503 (1950).
(91) A. J. Cleaver, A. B. Foster, and W. G. Overend, *J. Chem. Soc.*, 409 (1959).
(92) D. Heyl, E. C. Chase, C. H. Shunk, M. U. Moore, G. A. Emerson, and K. Folkers, *J. Amer. Chem. Soc.*, **76**, 1355 (1954).
(93) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, **318** (1944), and preceding papers.



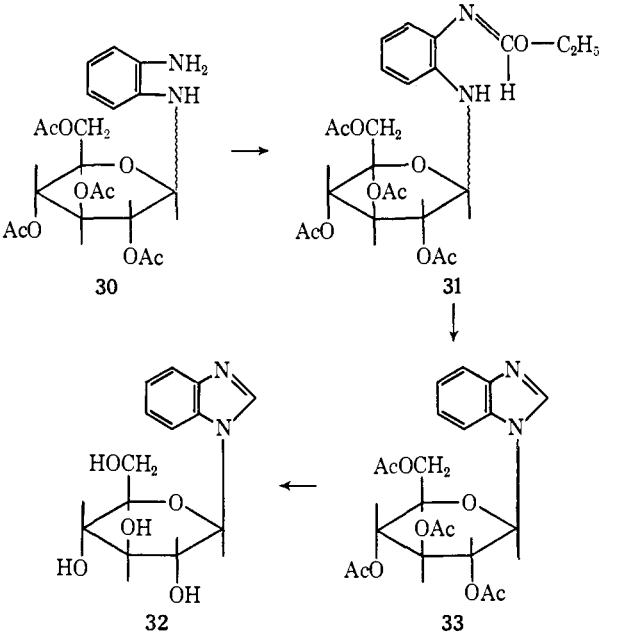
route proceeds *via* the cyclization of the 2-thioformamidoaniline glucoside (**25**) to furnish **23**.

This versatile method was also used[94] for the preparation of 5-chloro-1-(β-D-glucopyranosyl)benzimidazole (**28**) by condensing 4-chloro-2-nitroaniline with D-glucose in ethanol containing ammonium chloride to obtain a mixture of N-D-glucosyl derivatives (**26**). Acetylation of the mixture (**26**) was accomplished with acetic anhydride to obtain a mixture of the tetra-*O*-acetyl derivatives (**27**). Catalytic hydrogenation (5% Pd–C) followed by treatment with ethyl orthoformate furnished only 5-chloro-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)benzimidazole (**29**), from which **28** was obtained by deacetylation with sodium ethoxide. The preparation of 2-methyl- and 2,5-dimethyl-1-(β-D-glucopyranosyl)benzimid-



azoles has been achieved[94] in a similar manner by treatment of the corresponding N-(tetra-*O*-acetyl-D-glucopyranosyl)-*o*-phenylenediamine with ethyl orthoacetate to obtain the acetimidate in good yield. Dilute hydrochloric acid then effected a facile ring closure and deacetylation furnished 2-methyl- and 2,5-dimethyl-1-(β-D-glucopyranosyl)benzimidazoles. Similarly, 2-methyl- and 2,5-dimethyl-1-(β-D-xylopyranosyl)benzimidazoles were prepared.

The reaction of N-(tetra-*O*-acetyl-D-glucopyranosyl)-*o*-phenylenediamine (**30**) with ethyl orthoformate gave a crystalline product which was assigned structure **31**.[90,95] Careful treatment of **31** with dilute hydrochloric acid (0.05–0.1 *N*) at 100° for 15 min in the presence of a few drops of ethanol resulted in a smooth conversion of **31** into 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)benzimidazole (**33**). Deacetylation of **33**



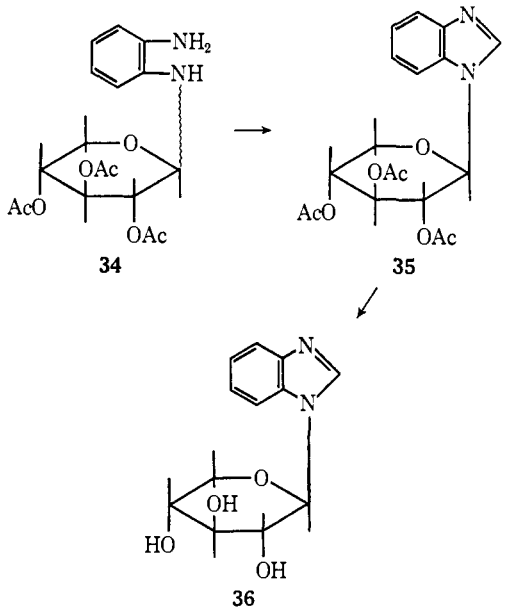
with 6 *N* hydrochloric acid at 100° for 3 hr afforded 1-(β-D-glucopyranosyl)benzimidazole (**32**). Similarly, 4-methyl-N-(tetra-*O*-acetyl-D-glucopyranosyl)-*o*-phenylenediamine reacted with ethyl orthoformate to give the isoformanilide derivative which was converted by 0.1 *N* hydrochloric acid or by an ethanolic picric acid solution into 5-methyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)benzimidazole. Deacetylation with 6 *N* hydrochloric acid under the above conditions furnished 5-methyl-1-(β-D-glucopyranosyl)benzimidazole. 3,4-Dimethyl-N-(tetra-*O*-acetyl-D-glucopyranosyl)-*o*-phenylenediamine was also transformed directly into an acetylated benzimidazole glycoside on heating with ethyl orthoformate. On deacetylation with hydrochloric acid there was obtained 4,5-dimethyl-1-(β-D-glucopyranosyl)benzimidazole hydrochloride.[90]

N-(2′,3′,4′-Tri-*O*-acetyl-D-xylopyranosyl)-*o*-phenylenediamine (**34**) was ring closed with ethyl orthoformate to afford 1-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)benzimidazole (**35**).[95,96] Deacetylation of **35** furnished 1-(β-D-xylopyranosyl)-benzimidazole (**36**), and the pyranose character of the lactol ring was established by periodate studies. 4-Methyl-N-(2′,3′,4′-tri-*O*-acetyl-D-xylopyranosyl)-*o*-phenylenediamine was converted into 5-methyl-1-(β-D-xylopyranosyl)benzimidazole in a similar manner. The preparation of benzimidazole-L-arabinosides by the orthoformate route was not as successful. The reaction of N-(tri-*O*-acetyl-L-arabinosyl)-*o*-phenylenediamine and its 4-methyl derivative with ethyl orthoformate, with or without subsequent treatment with 0.1 *N* hydrochloric acid, invariably gave intractable gums from which a crystalline product could not be isolated. When 4,5-dimethyl-N-(tri-*O*-acetyl-L-arabinosyl)-*o*-phenylenediamine was employed, only a poor yield of 5,6-dimethyl-1-(tri-*O*-acetyl-α-L-arabinopyranosyl)benzimidazole was obtained.[96] 5,6-Dimethyl-1-(tri-*O*-acetyl-L-rhamnopyranosyl)benzimidazole was prepared

(94) H. Antaki and V. Petrow, *J. Chem. Soc.*, 2873 (1951).

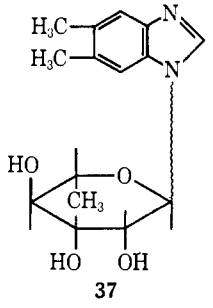
(95) P. Mamalis, V. Petrow, and B. Sturgeon, British Patent 690,119 (April 15, 1953); *Chem. Abstr.*, 48, 6470 (1954).

(96) P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, 2, 512 (1950).



34 35 36

in excellent yield by the orthoformate route and was deacetylated to give 5,6-dimethyl-1-(L-rhamnopyranosyl)benzimidazole (**37**); the structure of the carbohydrate moiety was confirmed by periodate titration.



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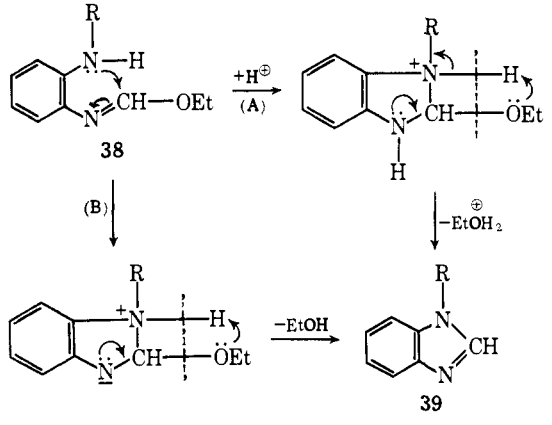
The ring closure with ethyl orthoformate has been proposed[96] to proceed by the following mechanism. The first stage in the reaction between an *o*-phenylenediamine glycoside and ethyl orthoformate is assumed to be the formation of a 2-

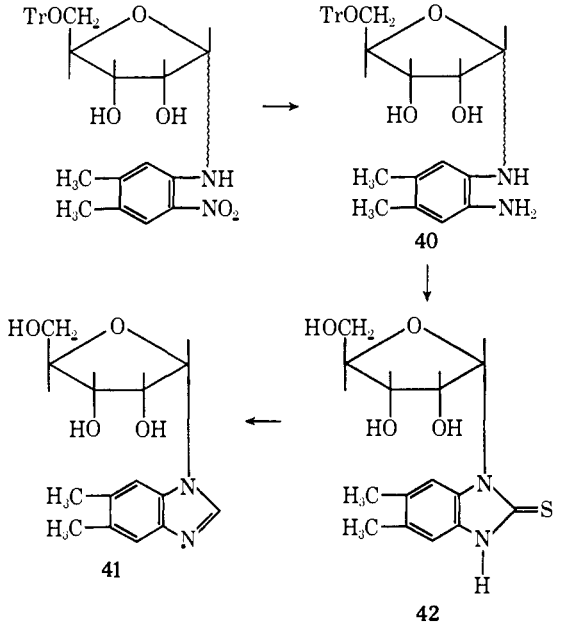


38 39

R = hexose or pentose

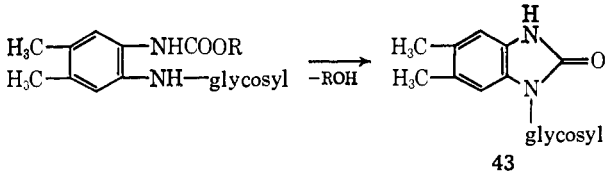
ethoxymethylene-*o*-phenylenediamine glycoside (**38**). Reaction of the latter compound with hydrogen ions, supplied by picric acid or by hydrochloric acid, leads to the formation of the benzimidazole glycoside (**39**) with concomitant elimination of ethyl alcohol. The isoformanilide derived from 3,4-dimethyl-N-(tetra-*O*-acetyl-D-glucopyranosyl)-*o*-phenylenediamine, however, proceeds spontaneously to the benzimidazole glycoside on heating at 100° in an excess of ethyl orthoformate. This ring closure presumably occurs by an alternate mechanism (route B above).

The preparation of α isomers of 1-glycosylbenzimidazoles was reported[97] to occur by treating the corresponding N-glycosyl-*o*-phenylenediamine with carbon disulfide and barium hydroxide in an inert solvent to produce 1-glycosyl-2-mercaptobenzimidazole. Desulfurization with Raney nickel gave the corresponding 1-glycosylbenzimidazole. Thus, the condensation of 5-*O*-trityl-D-ribose with 2-nitro-4,5-dimethylaniline in benzene containing a catalytic amount of acetic acid afforded what was assumed to be 2-nitro-4,5-dimethyl-N-(5′-*O*-trityl-D-ribofuranosyl)aniline which on hydrogenation in the presence of Pd–Darco catalyst gave **40**. Treatment of **40** with carbon disulfide in benzene in the presence of barium hydroxide afforded 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole-2-thione (**42**). Desulfurization of **42** with Raney nickel in butanol gave 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (**41**), isolated as a picrate. The 1-D-glucosyl- and 1-L-arabinosylbenzimidazoles have been prepared by the same procedure.



40 41 42

Several 2-hydroxybenzimidazole nucleosides (**43**) have been obtained as by products in the synthesis of flavins.[98-102] These



43

(97) D. Heyl, U. S. Patent 2,606,187 (Aug 5, 1952); *Chem. Abstr.*, 47, 6987 (1953).

(98) H. Euler, P. Karrer, M. Malmberg, K. Schopp, F. Benz, B. Becker and P. Frei, *Helv. Chim. Acta*, 18, 522 (1935).

(99) P. Karrer, K. Schopp, F. Benz, and K. Pfaehler, *ibid.*, 18, 69 (1935).

(100) P. Karrer, H. Salomon, K. Schopp, F. Benz, and B. Becker, *ibid.*, 18, 908 (1935).

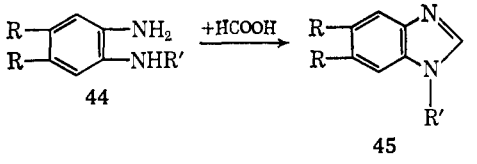
(101) P. Karrer and F. M. Strong, *ibid.*, 18, 1343 (1935).

(102) P. Karrer and F. M. Strong, *ibid.*, 19, 487 (1936).

compounds were obtained by ring closure of the appropriate N^1-glycosyl-substituted N^2-carbalkoxy-*o*-phenylenediamines.

2. *Ring Closure of N-Glycityl-o-phenylenediamine Derivatives*

A series of 1-(1′-glycityl)benzimidazoles (**45**) have been prepared[103] from N-glycityl-*o*-phenylenediamines (**44**). Ring closure of the substituted *o*-diamines was effected by formic



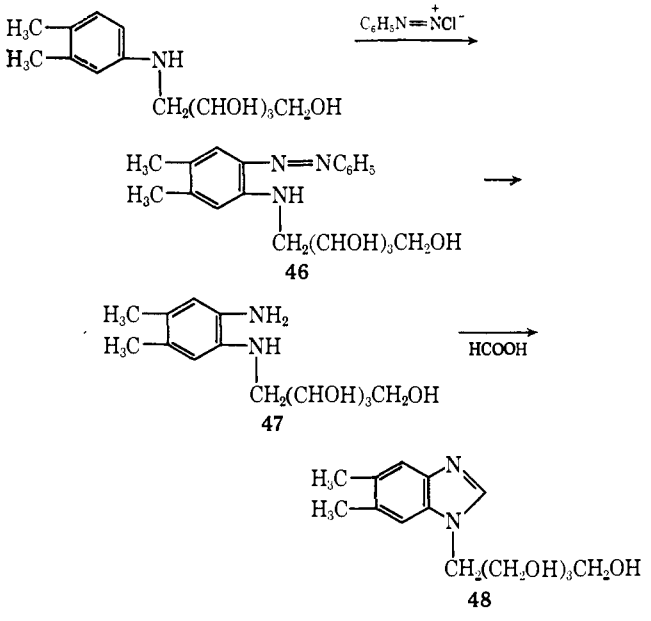
44 **45**

R = CH_3 or Cl;
R′ = ribityl, glucityl, arabityl, or xylityl

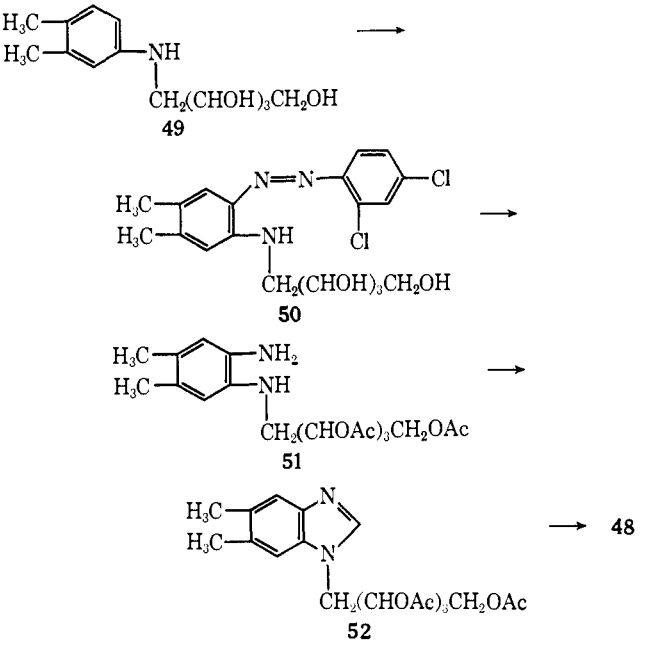
acid in 4 *N* hydrochloric acid solution.[104] This procedure was used for the preparation of 5,6-dimethyl-1-(1′-D-ribityl)benzimidazole, 5,6-dichloro-1-(1′-D-glucityl)benzimidazole, 5,6-dichloro-1-(1′-D-arabityl)benzimidazole, and 5,6-dichloro-1-(1′-D-xylityl)benzimidazole.

5,6-Dimethyl-1-(1′-D-ribityl)benzimidazole (**48**) has also been prepared[20] according to Scheme III. 4,5-Dimethyl-2-

Scheme III



(D-ribitylamino)phenylazobenzene (**46**)[105] in ethanol was reduced by sodium dithionite, and the resulting amine (**47**) was treated with formic acid (98%) in 4 *N* hydrochloric acid at reflux temperature to obtain **48**. Similarly, N-D-ribityl-*o*-4-xylidine (**49**) was condensed with 2,4-dichlorophenyldiazonium chloride to afford 3,4-dimethyl-6-(2,4-dichlorophenylazo)-N-ribitylaniline (**50**) in excellent yield.[18] Acetylation of **50**, followed by reduction with zinc dust and acetic acid in an ethyl acetate solution, furnished tetra-*O*-acetyl-D-ribityl-4,5-dimethyl-*o*-phenylenediamine (**51**). The latter compound was not isolated but was condensed *in situ* with ethyl orthoformate

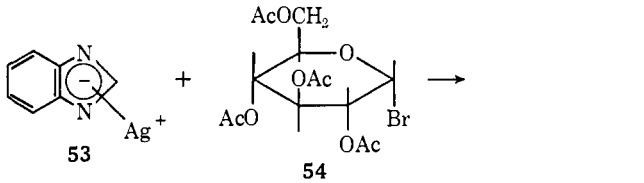


to give 5,6-dimethyl-1-(tetra-*O*-acetyl-1′-D-ribityl)benzimidazole (**52**) which was isolated as the picrate. Deacetylation of **52** furnished 5,6-dimethyl-1-(1′-D-ribityl)benzimidazole (**48**).

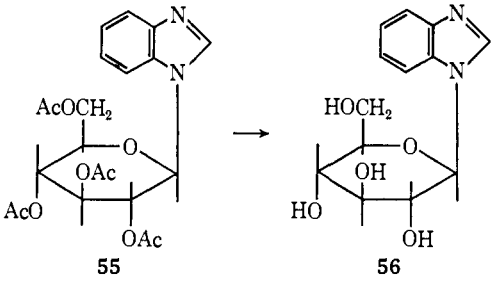
3. *Condensation of Silver Salts of Preformed Benzimidazoles with Polyacylglycosyl Halides*

A general method for the preparation of benzimidazole glycosides has been devised[106] by reacting a silver salt of the appropriate benzimidazole with an acylated glycosyl halide followed by deacylation of the condensation product. Thus, condensation of the silver salt of benzimidazole (**53**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**54**) in boiling xylene gave crystalline 1-(tetra-*O*-acetyl-β-D-glucopyranosyl)benzimidazole (**55**) in good yield. Deacetylation of **55** with sodium methoxide in methanol gave 1-(β-D-glucopyranosyl)benzimidazole (**56**), identical in all respects with the nucleoside (**32**) prepared by the ring-closure method.[90] It is of interest to note that while a condensation of the silver salt of 5(6)-methylbenzimidazole with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide gave a mixture of 5- and 6-methyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-benzimidazoles which could not be resolved,[90] a similar condensation with the silver salt of 4,5(6,7)-dimethylbenzimidazole afforded, after deacetylation, only 4,5-dimethyl-1-(β-D-glucopyranosyl)benzimidazole.[107] The preparation of 5,6-dimethyl-1-(β-D-glucopyranosyl)benzimidazole (**23**) has been

(103) F. W. Holly, E. W. Peel, J. J. Cahill, and K. Folkers, *J. Amer. Chem. Soc.*, 73, 332 (1951).
(104) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).
(105) F. Bergel, A. Cohen, and J. W. Haworth, *ibid.*, 165 (1954).
(106) F. Weygand, A. Wacker, and F. Wirth, *Z. Naturforsch.*, **6b**, 25 (1951).
(107) P. Mamalis, V. Petrow and B. Sturgeon, British Patent 682,960 (Nov 19, 1952); *Chem. Abstr.*, 48, 2120 (1954).



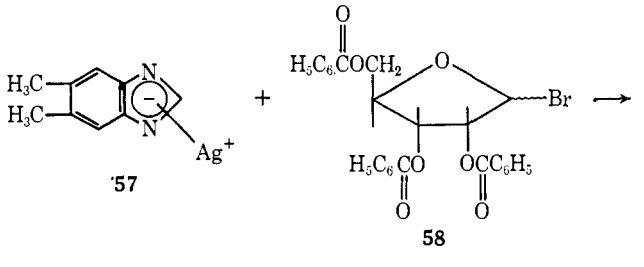
53 54



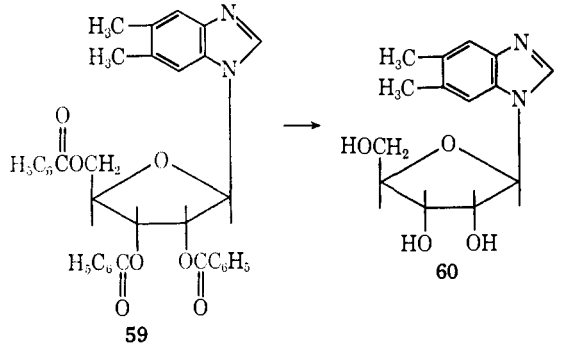
55 56

accomplished[90,106,108] by condensing the silver salt of 5,6-dimethylbenzimidazole with α-acetobromoglucose in boiling xylene followed by deblocking of the carbohydrate moiety of the condensed product. This nucleoside was found to be identical with the nucleoside prepared by the ring-closure method. In a like manner, 5,6-dimethyl-1-(β-D-xylopyranosyl)benzimidazole, 5,6-dichloro-1-(β-D-glucopyranosyl)benzimidazole, and 5,6-dibromo-1-(β-D-glucopyranosyl)benzimidazole have been prepared.[106]

The synthesis of 5,6-dimethyl-1-(β-D-ribofuranosyl)benzimidazole (β-ribazole) (**60**) was accomplished[109-111] by the following procedure. A condensation of the silver salt of 5,6-dimethylbenzimidazole (**57**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**58**) in dry xylene at reflux temperature afforded 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (**59**). Debenzoylation of the carbohydrate moiety of **59** with boiling 6 *N* hydrochloric acid gave **60** identical with the nucleoside (**14**) prepared by the ring-closure method.



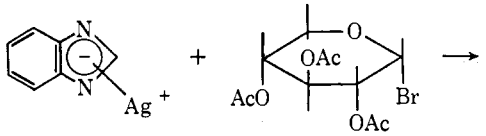
57 58



59 60

The poor yields usually obtained from the silver salt method are largely attributable to the heterogeneous nature of the initial reactions.[112] In the condensations of metal derivatives of benzimidazoles with a poly-*O*-acylglycosyl bromide, the occurrence of a Walden inversion or a acetoxonium ion intermediate has been assumed,[113] and the condensed products have accordingly been formulated as poly-*O*-acyl-β-D-glycosylbenzimidazoles.

A condensation of the silver salt of benzimidazole with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**61**) furnished 1-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)benzimidazole (**62**) which on deacetylation afforded 1-(β-D-xylopyranosyl)-benzimidazole (**63**) identical in all respects with the nucleoside (**36**) prepared by a ring-closure method. The condensation of α-acetobromoxylose with the silver salt of 5(6)-methylbenzimidazole was not successful and failed to yield any nucleoside material. However, when the silver salt of 5,6-di-



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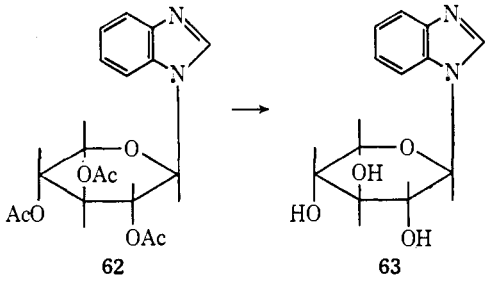
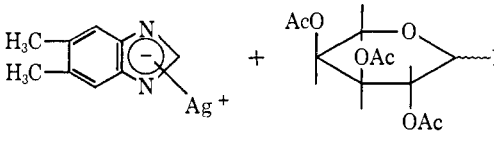


62 63

methylbenzimidazole was allowed to react with 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl bromide (**64**), a good yield of 5,6-dimethyl-1-(2′,3′,4′-tri-*O*-acetyl-α-L-arabinopyranosyl)benzimidazole (**65**) was obtained. Deacetylation of **65** with sodium methoxide in absolute ethanol or with dilute hydrochloric acid afforded 5,6-dimethyl-1-(α-L-arabinopyranosyl)benzimidazole (**66**), which was isolated as the picrate.[108] Similarly, the condensation of the silver salt of 5,6-dimethylbenzimidazole



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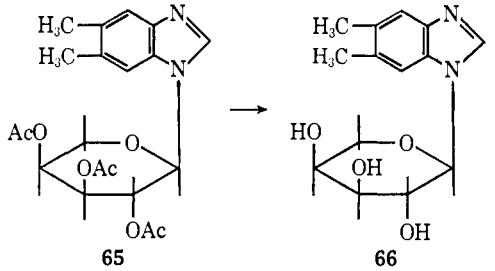
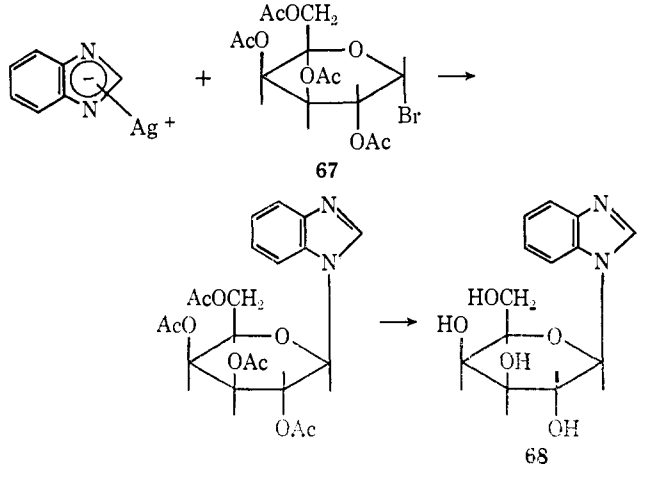


65 66

(108) F. W. Holly, C. H. Shunk, and K. Folkers, U. S. Patent 2,662,883 (Dec 15, 1953); *Chem. Abstr.*, **49**, 3265 (1954).
(109) F. Weygand and F. Wirth, *Chem. Ber.*, **85**, 1000 (1952).
(110) A. Wacker and F. Weygand, *Z. Naturforsch.*, **76**, 488 (1952).
(111) F. Weygand and F. Wirth, German Patent 940,833 (March 29, 1956); *Chem. Abstr.*, **52**, 14702 (1958).
(112) A. W. Johnson, G. W. Miller, J. A. Mills, and A. R. Todd, *J. Chem. Soc.*, 3061 (1953).
(113) G. A. Howard, *ibid.*, 1045 (1950).

with 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl chloride followed by deacetylation of the condensed product (**65**) gave **66**, which was also isolated as the picrate. The silver salt method also gave good yields of 1-(2′,3′,4′-tri-*O*-acetyl-α-D-arabinopyranosyl)benzimidazole (from β-acetobromo-D-arabinose), 1-(tri-*O*-acetyl-α-L-arabinopyranosyl)benzimidazole, and 5(6)-methyl-1-(tri-*O*-acetyl-α-L-arabinopyranosyl)benzimidazole. The latter result is of particular interest as previous attempts to employ the silver salt of 5(6)-methylbenzimidazole had invariably provided a mixture of isomers which had not proved to be amenable toward separation. Deacetylation of the above blocked nucleosides with boiling 6 *N* hydrochloric acid furnished the corresponding benzimidazole arabinopyranosides. These results would suggest that the condensation of the silver salt of 5(6)-methylbenzimidazole and α-acetobromoxylose should be reinvestigated.

2,3,4,6-Tetra-*O*-acetyl-α-D-galactosyl bromide (**67**) was condensed with the silver salt of benzimidazole to give a dark reaction mixture which on deacetylation[114] afforded crystalline 1-(β-D-galactosyl)benzimidazole (**68**).[91] The condensation of crude 3,4,6-tri-*O*-acetyl-2-deoxy-D-galactosyl bromide with the silver salt of benzimidazole in xylene at reflux temperature gave, after deacetylation, a levorotatory form of 1-(2′-deoxy-D-galactosyl)benzimidazole.[91,115] However, the same condensation in dioxane yielded, not only the above compound, but also a larger quantity of a dextrorotatory isomer.[116,117] Treatment of 3,4-di-*O*-acetyl-2,6-dideoxy-D-galactosyl chloride with the silver salt of benzimidazole in dry boiling xylene gave 1-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-D-galactosyl)benzimidazole, which was deacetylated to obtain 1-(2′,6′-dideoxy-D-galactosyl)benzimidazole.[91] Similarly, 1-(di-*O*-acetyl-2′-deoxy-L-ribosyl)benzimidazole, 1-(2′-deoxy-D-glucosyl)benzimidazole, as well as the D-galactosyl and 2-deoxy-D-galactosyl derivatives of 5,6-dimethylbenzimidazole were obtained by this method.



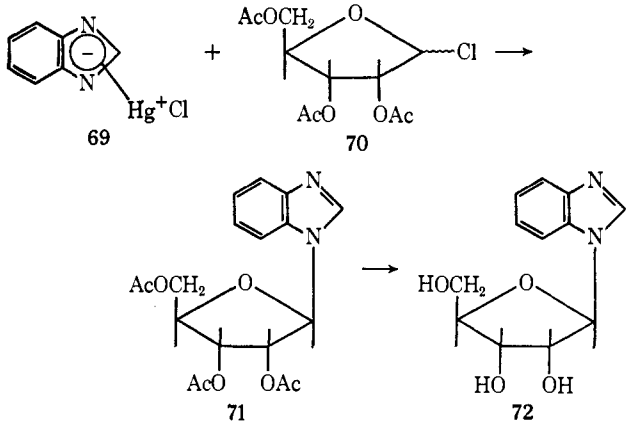
The reaction of 1-bromo-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucose with the silver salt of 5,6-dimethylbenzimidazole gave a noncrystalline mixture of α and β anomers which could not be resolved by standard fractionation procedures. However, deacetylation of the mixture was followed by treatment with picric acid to give a crystalline 5,6-dimethyl-1-(2′-deoxy-D-glucopyranosyl)benzimidazole picrate from which, by acetylation, 5,6-dimethyl-1-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-D-glucopyranosyl)benzimidazole was obtained in crystalline form. Deacetylation furnished what was assumed to be a pure anomer of 5,6-dimethyl-1-(2′-deoxy-D-glucopyranosyl)benzimidazole. The other anomer was not isolated and no anomeric assignments were given for either anomer.[18] In contrast to these results, the reaction between the silver salt of 5,6-dimethylbenzimidazole and 1-chloro-3,4-di-*O*-acetyl-2-deoxy-D-ribose in xylene solution at 100° readily gave 5,6-dimethyl-1-(3′,4′-di-*O*-acetyl-2′-deoxy-D-ribopyranosyl)benzimidazole. Deacetylation furnished 5,6-dimethyl-1-(2′-deoxy-D-ribopyranosyl)benzimidazole which was without an assignment of anomeric configuration. Similar results were obtained by the reaction between the silver salt of benzimidazole and 1-chloro-3,4-di-*O*-acetyl-2-deoxy-D-ribose which gave crystalline 1-(3′,4′-di-*O*-acetyl-2′-deoxy-D-ribopyranosyl)benzimidazole picrate. Deacetylation with hydrochloric acid gave 1-(2′-deoxy-D-ribopyranosyl)benzimidazole which was isolated as the hydrochloride. Condensation of the silver salt of 5,6-dimethylbenzimidazole and α-acetobromoribopyranose in xylene at 140° afforded 5,6-dimethyl-1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)benzimidazole, which on deacetylation with hydrochloric acid gave 5,6-dimethyl-1-(β-D-ribopyranosyl)benzimidazole.

Recently, various 2-thiazolylbenzimidazole glycosides have been reported[118-120] to be active anthelmintics, anticoccids, bactericides, nematocides, fungicides, and antiviral agents. These 2-thiazolylbenzimidazole glycosides were prepared by condensing the silver salt of the appropriate benzimidazole with the acylglycosyl halide followed by deacetylation of the condensed product with methanolic ammonia. However, there were presented no physical or biological data for these nucleosides.

4. *Condensation of Halomercury Salts of Preformed Benzimidazoles with Polyacylglycosyl Halides*

It has been found[121] that the chloromercury derivatives of benzimidazole are much superior to the silver salts for use in the condensation reaction with poly-*O*-acylglycosyl halides. Thus, the condensation of chloromercury benzimidazole (**69**) with 1-chloro-2,3,5-tri-*O*-acetyl-D-ribofuranose (**70**)[122] in xylene at reflux temperature gave 1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**71**). Deacetylation of **71** with methanolic ammonia afforded 1-(β-D-ribofuranosyl)benzimidazole (**72**), in an overall yield of 53%. Similarly, 1-(β-D-glucopyranosyl)benzimidazole, 5,6-dimethyl-1-(β-D-ribofuranosyl)-benzimidazole, and 5,6-dimethyl-1-(β-D-glucopyranosyl)benzimidazole have been prepared in good yield. It was assumed that either a Walden inversion occurs or the *trans* rule[123] is in effect in the condensation reaction and that the products all

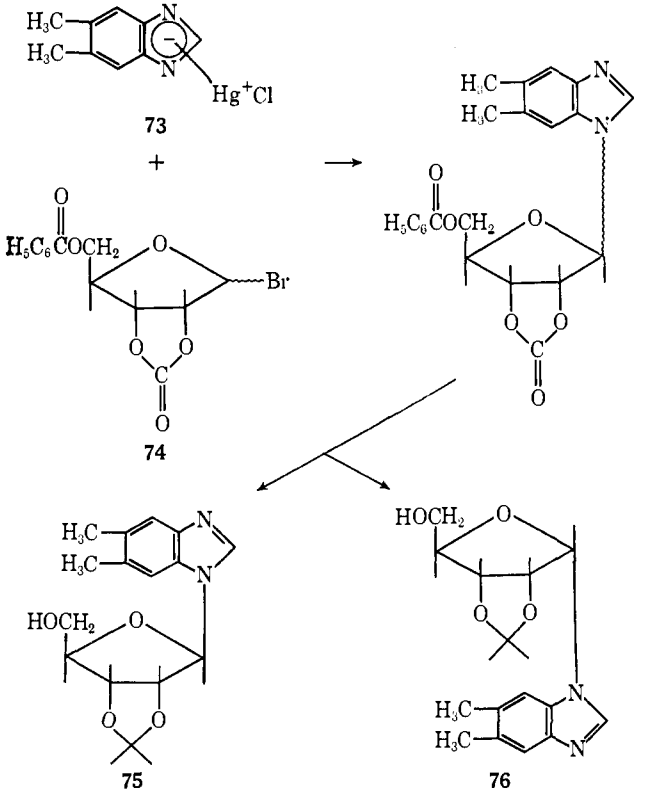
(114) G. Zemplen and E. Pacsu, *Ber.*, 62, 1613 (1929).
(115) A. J. Cleaver, A. B. Foster, E. J. Hedgley, and W. G. Overend, *J. Chem. Soc.*, 2578 (1959).
(116) R. J. Ferrier and W. G. Overend, *ibid.*, 3638 (1959).
(117) R. Bonnett, J. G. Buchanan, A. W. Johnson, and A. R. Todd, *ibid.*, 1168 (1957).
(118) French Patent 1,476,535 (April 14, 1967); *Chem. Abstr.*, 68, 11092 (1968).
(119) French Patent 1,476,537 (April 14, 1967); *Chem. Abstr.*, 68, 10198 (1968).
(120) French Patent 1,476,557 (April 14, 1967); *Chem. Abstr.*, 68, 10199 (1968).
(121) J. Davoll and G. B. Brown, *J. Amer. Chem. Soc.*, 73, 5781 (1951).
(122) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).
(123) B. R. Baker, *Chem. Biol. Purines, Ciba Found. Symp., 1956*, 120 (1957).



have the β configuration. The configuration and the site of glycosidation in the case of 5,6-dimethyl-1-(β-D-ribofuranosyl)benzimidazole was verified by a comparison of the picrate with authentic samples of 1-α- and 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole picrates. The 5′-phosphate and 5′-triphosphate of 1-(β-D-ribofuranosyl)benzimidazole have been prepared[124,125] and reported to possess ATP-like pharmacological activity.

In an attempt[126] to prepare α-ribazole, the chloromercury derivative of 5,6-dimethylbenzimidazole (**73**) was condensed with 5-*O*-benzoyl-D-ribofuranosyl bromide 2,3-cyclic carbonate (**74**), in xylene containing acid-washed Celite, at reflux temperature to afford an anomeric mixture. Only very low

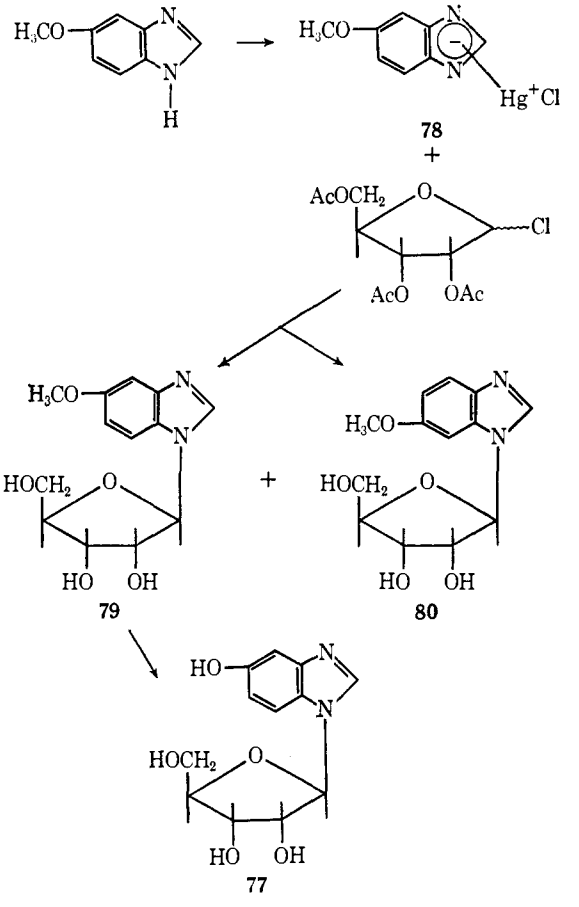
Scheme IV



yields of the α and β anomers of 5,6-dimethyl-1-(D-ribofuranosyl)benzimidazole were obtained as the crystalline 2′,3′-isopropylidene derivatives with the α anomer (**76**) being the predominant anomer (Scheme IV). The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide with chloromercury benzimidazole in boiling xylene followed by deacetylation gave a 23% yield of the expected galactosylbenzimidazole.[91]

The acid hydrolytic product of factor III, supposedly 5-hydroxy-1-(α-D-ribofuranosyl)benzimidazole, was not isolated in a crystalline form but was purified by paper chromatography using a 1-butanol–acetic acid–water (4:1:5) system.[127–129] The synthesis of the other anomer, 5-hydroxy-1-(β-D-ribofuranosyl)benzimidazole (**77**), was accomplished[130] by the sequence of Scheme V. Condensation of the chloro-

Scheme V

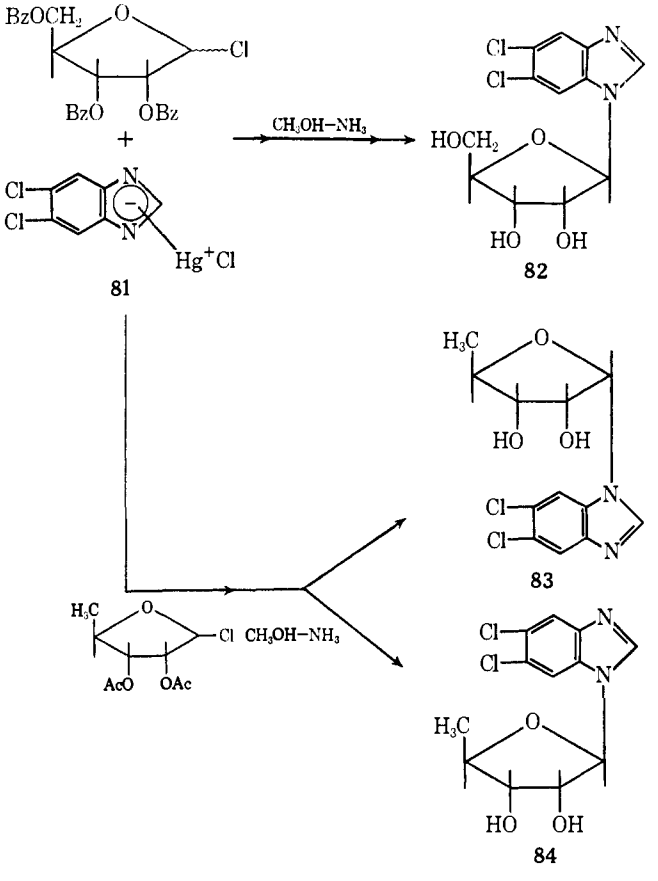


mercury derivative (**78**) of 5-methoxybenzimidazole (probably a mixture of 1-chloromercury-5- and -6-methoxybenzimidazole) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride was followed by deacetylation to afford two nucleosides (**79** and **80**) which were purified by countercurrent distribution in a butanol–water system and separated as their picrates. Regeneration of the free nucleosides using an IR-45 resin gave

(124) M. Ikehara, Japan Patent 11,384 (June 22, 1964); *Chem. Abstr.*, **61**, 14771 (1964).
(125) C. W. Woenckhaus, *Chem. Ber.*, **97**, 2439 (1964).
(126) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Amer. Chem. Soc.*, 80, 2004 (1958).
(127) F. M. Robinson, I. M. Miller, J. F. McPherson, and K. Folkers, *ibid.*, 77, 5192 (1955).
(128) W. Friedrich and K. Bernhauer, *Angew. Chem.*, **67**, 619 (1955).
(129) W. Friedrich and K. Bernhauer, *Z. Naturforsch.*, **9b**, 686 (1954).
(130) C. H. Shunk, F. M. Robinson, J. F. McPherson, M. M. Gasser, and K. Folkers, *J. Amer. Chem. Soc.*, 78, 3228 (1956).

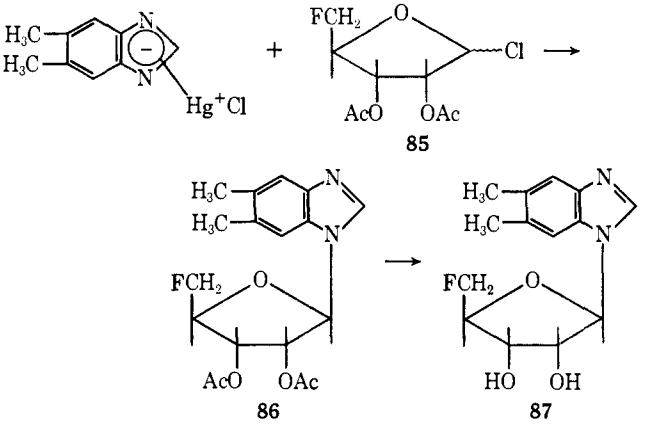
crystalline 5-methoxy-1-(β-D-ribofuranosyl)benzimidazole (79) and the noncrystalline 6-methoxy isomer (80). Hydrolysis of the methoxy group of 79 afforded the noncrystalline 5-hydroxy-1-(β-D-ribofuranosyl)benzimidazole (77) which was purified by paper chromatography.

5,6-Dichloro-1-(β-D-ribofuranosyl)benzimidazole (82) as well as the α and β anomers of 5,6-dichloro-1-(5′-deoxy-D-ribofuranosyl)benzimidazole (83 and 84) were synthesized[131] by the reaction of the chloromercury derivative of 5,6-dichlorobenzimidazole (81) with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride and 2,3-di-O-acetyl-5-deoxy-D-ribofuranosyl chloride, respectively, in boiling xylene. The gummy reaction products were subsequently deblocked with methanolic ammonia. The formation of 83 was of interest, even though



there was obtained only a very low yield, since this was an exception to the *trans* rule. Similarly, the synthesis[132] of a series of 5,6-dihalo-1-(D-ribofuranosyl)benzimidazoles was accomplished by condensing the halomercury salt of various 5,6-dihalobenzimidazoles with 1-halo-2,3,5-tri-O-substituted D-ribofuranose and subsequent deblocking of the condensed product. Thus, 5,6-dichloro-1-(2′,3′,5′-tri-O-acetyl-D-ribofuranosyl)benzimidazole, 5,6-dichloro-1-(2′,3′,5′-tri-O-butyryl-D-ribofuranosyl)benzimidazole, 5,6-dibromo-1-(2′,3′,5′-tri-O-propionyl-D-ribofuranosyl)benzimidazole, and 5,6-dibromo-1-(2′,3′,5′-tri-O-benzoyl-D-ribofuranosyl)benzimidazole have been prepared which on removal of the blocking groups with methanolic ammonia afforded the corresponding nucleosides. Likewise, the condensation of the chloromercury salt of 4(7),5,6-trichlorobenzimidazole with 2,3,5-tri-O-acetyl-D-ribofuranosyl chloride in dry xylene at reflux temperature gave 4(7),5,6-trichloro-1-(2′,3′,5′-tri-O-acetyl-D-ribofuranosyl)benzimidazole as a syrup[133] which on deacetylation with methanolic ammonia furnished crystalline 4(7),5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole.[134] The preparation of 4(7),5,6-tribromo-1-(β-D-ribofuranosyl)benzimidazole and 5-(6)-bromo-4,6(5,7)-dichloro-1-(β- and α-D-ribofuranosyl)-benzimidazole have been reported.[134-136]

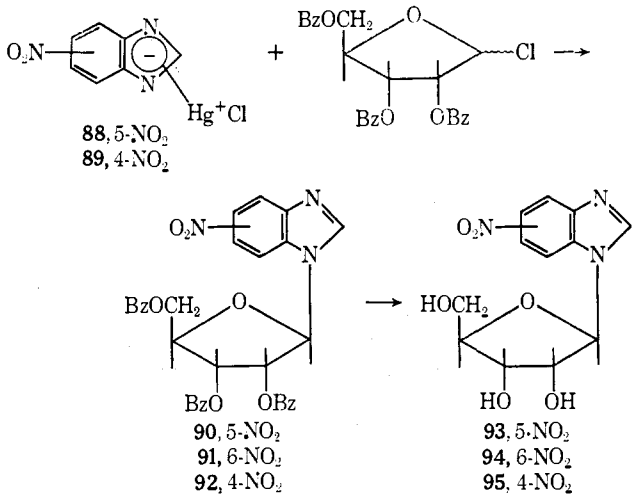
The chemical synthesis of 5′-deoxy-5′-fluoro-β-ribazole [5,6-dimethyl-1-(5′-deoxy-5′-fluoro-β-D-ribofuranosyl)benzimidazole (87)] has been accomplished[137] by condensing the chloromercury salt of 5,6-dimethylbenzimidazole with 2,3-di-O-acetyl-5-deoxy-5-fluoro-D-ribofuranosyl chloride (85) in refluxing xylene to afford 5,6-dimethyl-1-(2′,3′-di-O-acetyl-5′-deoxy-5′-fluoro-β-D-ribofuranosyl)benzimidazole (86) as a syrup. This nucleoside (86) was deacetylated with methanolic sodium methoxide to yield crystalline 5′-deoxy-5′-fluoro-β-ribazole in an overall yield of 38%. The reaction of tri-O-acetyl-2-deoxy-D-galactosyl bromide with chloromercury benzimidazole in xylene gave after deacetylation a levorotatory form of 1-(2′-deoxy-D-galactosyl)benzimidazole in only 5% yield. The condensation of the chloromercury salt of benzimidazole with 2,3,6-tri-O-acetyl-4-deoxy-D-*xylo*-hexosyl bromide



in the presence of Celite gave the crystalline 1-(2′,3′,6′-tri-O-acetyl-4′-deoxy-β-D-*xylo*-hexosyl)benzimidazole[138] which on deacetylation with sodium methoxide at room temperature gave 1-(4′-deoxy-β-D-*xylo*-hexopyranosyl)benzimidazole.

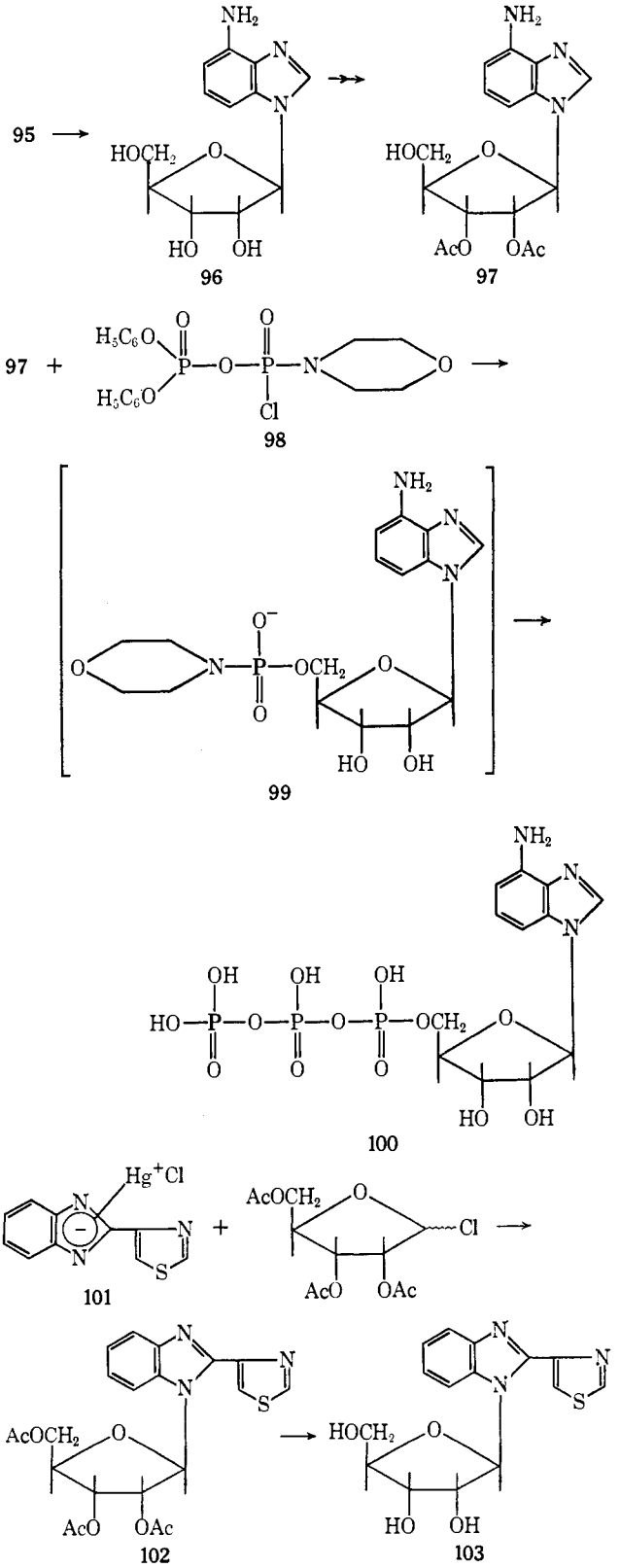
This synthetic route for the preparation of 1-glycosylbenzimidazoles was also applied to the synthesis of 4-, 5-, and 6-nitrobenzimidazole ribofuranosides.[139] The condensation of the chloromercury salt of the corresponding nitrobenzimidazole with 2,3,5-tri-O-benzoyl-D-ribofuranosyl chloride[140] was accomplished by the standard procedure.[141] Thus,

(131) H. M. Kissman, R. G. Child, and M. J. Weiss, *J. Amer. Chem. Soc.*, 79, 1185 (1957).
(132) K. Folkers and C. H. Shunk, U. S. Patent 2,860,131 (Nov 11, 1958); *Chem. Abstr.*, 53, 7201 (1959).
(133) Merck and Co., Inc., British Patent 783,306 (Sept 18, 1957); *Chem. Abstr.*, 52, 9219 (1958).
(134) K. Folkers and C. H. Shunk, U. S. Patent 2,876,230 (March 3, 1959); *Chem. Abstr.*, 53, 18060 (1959).
(135) C. H. Shunk and K. Folkers, U. S. Patent 2,935,508 (May 3, 1960); *Chem. Abstr.*, 54, 21134 (1960).
(136) H. Mizuntani, T. Komai, and D. Mizuno, *Jap. J. Med. Sci. Biol.*, 13, 147 (1960).
(137) H. M. Kissman and M. J. Weiss, *J. Amer. Chem. Soc.*, 80, 5559 (1958).
(138) A. F. Cook and W. G. Overend, *J. Chem. Soc., C*, 1549 (1966).
(139) Y. Mizuno, M. Ikehara, F. Ishikawa, and H. Ikehara, *Chem. Pharm. Bull.* (Tokyo), 10, 761 (1962).
(140) F. Ishikawa, A. Nomura, T. Ueda, M. Ikehara, and Y. Mizuno, *ibid.*, 8, 380 (1960).
(141) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, 73, 1650 (1951).

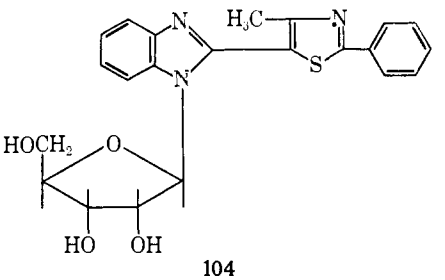


the condensation of the chloromercury salt of 5(6)-nitrobenzimidazole (**88**)[142,143] with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride afforded a mixture of 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-5- and -6-nitrobenzimidazoles. This isomeric mixture was separated by column chromatography on alumina and fractional crystallization into the two crystalline nucleosides, 5-nitro-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (**90**) (15.6%) and 6-nitro-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (**91**) (24.2%). Debenzoylation of these blocked nucleosides with methanolic ammonia gave the corresponding nucleosides (**93** and **94**). Similarly, the chloromercury salt of 4(7)-nitrobenzimidazole (**89**) was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride, to afford crystalline 4-nitro-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (22%) (**92**) after purification by alumina column chromatography. Debenzoylation of **92** gave crystalline 4-nitro-1-(β-D-ribofuranosyl)benzimidazole (**95**). The anomeric configurations of these nitrobenzimidazole ribofuranosides were assigned as β on the basis of optical rotation values and the *trans* rule.[123,144] Catalytic hydrogenation[145,146] of **95** in the presence of a palladium on carbon catalyst gave a 70% yield of 1,3-dideazaadenosine, 4-amino-1-(β-D-ribofuranosyl)benzimidazole (**96**). The preparation of 4-amino-1-(2′,3′-di-*O*-acetyl-β-D-ribofuranosyl)benzimidazole (**97**) was accomplished with trityl chloride and acetic anhydride[147] which on phosphorylation with P-diphenyl P′-morpholino pyrophosphorochloridate (**98**) afforded the intermediate **99**. Treatment of **99** with bis(tri-*n*-butylammonium) pyrophosphate gave 4-amino-1-(β-D-ribofuranosyl)benzimidazole 5′-triphosphate (**100**).

A recent French patent has described[118] the preparation of various 2-thiazolylbenzimidazole glycosides. The condensation of the chloromercury salt of preformed 2-thiazolylbenzimidazole (**101**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride in boiling xylene afforded 1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2-thiazolylbenzimidazole (**102**) which on deacetylation with methanolic ammonia gave 1-(β-D-ribofuranosyl)-2-thiazolylbenzimidazole (**103**). Similarly, 1-(β-D-ribofuranosyl)-2-thiazolyl-4,5,6-trichlorobenzimidazole, 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-2-thiazolylbenzimidazole, 1-(D-glucopyranosyl)-2-thiazolylbenzimidazole, 1-(D-xylopyranosyl)-2-thiazolylbenzimidazole, and 1-(D-mannopyranosyl)-2-thiazolylbenzimidazole have been prepared. Also prepared were the 1-(β-D-ribofuranosyl) derivatives of 2-(2′-phenyl-4′-methyl-5′-thiazolyl)benzimidazole (**104**) and 2-(4′-thiadiazolyl)benzimidazole (**105**) with no physical or biological data given.



(142) E. Bamberger and B. Berle, *Ann. Chem.*, **273**, 340 (1893).
(143) O. Fisher and W. Hess, *Ber.*, **36**, 3769 (1903).
(144) B. R. Baker, *J. Org. Chem.*, **19**, 1786 (1954).
(145) M. Ikehara, E. Ohtsuka, S. Kitagawa, and Y. Tonomura, *Biochim. Biophys. Acta*, **82**, 74 (1964).
(146) S. R. Jenkins, F. W. Holly, and R. K. Robins, *J. Med. Chem.*, **11**, 910 (1968).
(147) H. Bredereck, *Ber.*, **73**, 269 (1940).



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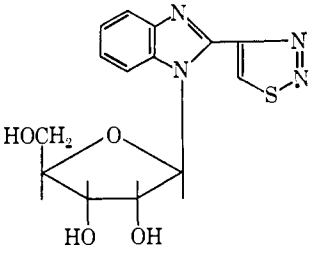


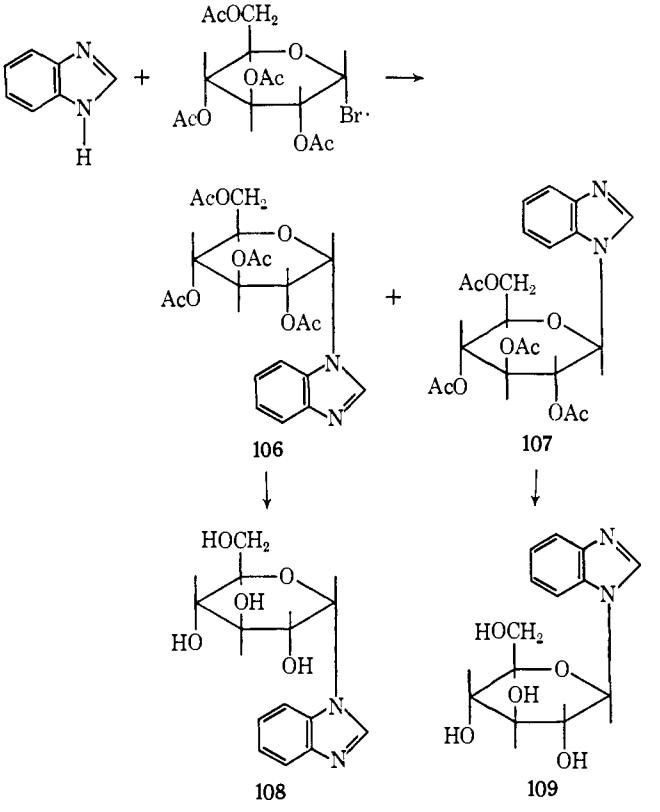
105

5. *Direct Alkylation of a Preformed Benzimidazole with a Polyacylglycosyl Halide*

In an attempt to improve the synthesis of N-glycosylbenzimidazoles, an alternate route was investigated[112] which involved the reaction between a poly-*O*-acylglycosyl halide and a metal-free benzimidazole. This reaction is similar to the Hilbert-Johnson method used for the synthesis of pyrimidine nucleosides[148,149] which involves the condensation of a poly-*O*-acylglycosyl halide with 2,4-diethoxypyrimidine. This proceeds by elimination of ethyl halide from the quaternary salt which is initially formed. This method has the advantage of simplicity and was attractive in the case of 5,6-dimethylbenzimidazole and other 5,6-disubstituted benzimidazoles since their symmetrical structure eliminates the main drawback to such methods, *viz.*, ambiguity as regards the position of the entering carbohydrate moiety.

The reaction between 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide and benzimidazole was accomplished[112] in dioxane solution at 100°, and the crude 1-(2′,3′,4′,6′-tetra-*O*-acetyl-D-glucopyranosyl)benzimidazoles (**106** and **107**) were deacetylated to afford **108** and **109**. The hydrogen bromide liberated in the reaction was removed as a salt by maintaining an excess of benzimidazole in the reaction mixture. The α anomer [1-(α-D-glucopyranosyl)benzimidazole (**108**)] (3.7%) and the β anomer (**109**) (21%) were separated by fractional crystallization.[149a] The reaction of 5,6-dimethylbenzimidazole with acetobromoglucose by the above method yielded both anomers with the α anomer being isolated in a 5.1% yield and the β anomer in 20% yield.

A more recent method[150] involves the condensation of benzimidazole with acetobromoglucose in dry nitromethane containing mercuric cyanide to give a 63% yield of **107** as an amorphous powder. Deacetylation of **107** with methanolic ammonia at 0° afforded a good yield of **109**. A condensation



106 107 108 109

of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with 5,6-dimethylbenzimidazole was achieved in dioxane, and the two anomers were separated chromatographically, the β anomer (10%) being more abundant than the α isomer (2%). When 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide was used,[148] the yield of the α anomer compound was not improved and the use of acetonitrile as a solvent also furnished no increase in the yield of the α anomer.

This method has been used for the preparation of 1-β-D-galactopyranosylbenzimidazole by the condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide with an excess of benzimidazole in dry dioxane, followed by deacetylation. Undesired side reactions, probably base-catalyzed reactions, leading to products of the *O*-acetylglycoseen and the *O*-acetyl-1,6-anhydroglucose type were reported to occur. An attempt[91] to condense the galactosyl halide with benzimidazole at room temperature using the Koenigs-Knorr technique[151] was also unsuccessful. However, the treatment of tri-*O*-acetyl-2-deoxy-D-galactosyl bromide with an excess of benzimidazole in dioxane at 100° afforded after deacetylation, a small amount of the levorotatory 1-(2′-deoxy-D-galactosyl)benzimidazole, together with a larger quantity (30%) of a dextrorotatory compound. The formation of two different nucleosides, which are probably α and β anomers, was not unexpected in view of the undetermined configuration at the anomeric carbon of the *O*-acetylglycosyl halide employed and the absence of a participating group at position 2. The dextrorotatory compound was converted into the levorotatory compound by boiling with dilute mineral acid.

The reaction of 5,6-dimethylbenzimidazole with 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride has been the subject of

(148) G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 1052 (1947).

(149) G. W. Kenner, B. Lythgoe, and A. R. Todd, *ibid.*, 957 (1948).

(149a) A reinvestigation of this condensation has provided a 45% yield of β and 31% yield of α; see ref 23 contained in ref 152.

(150) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, 30, 149 (1965).

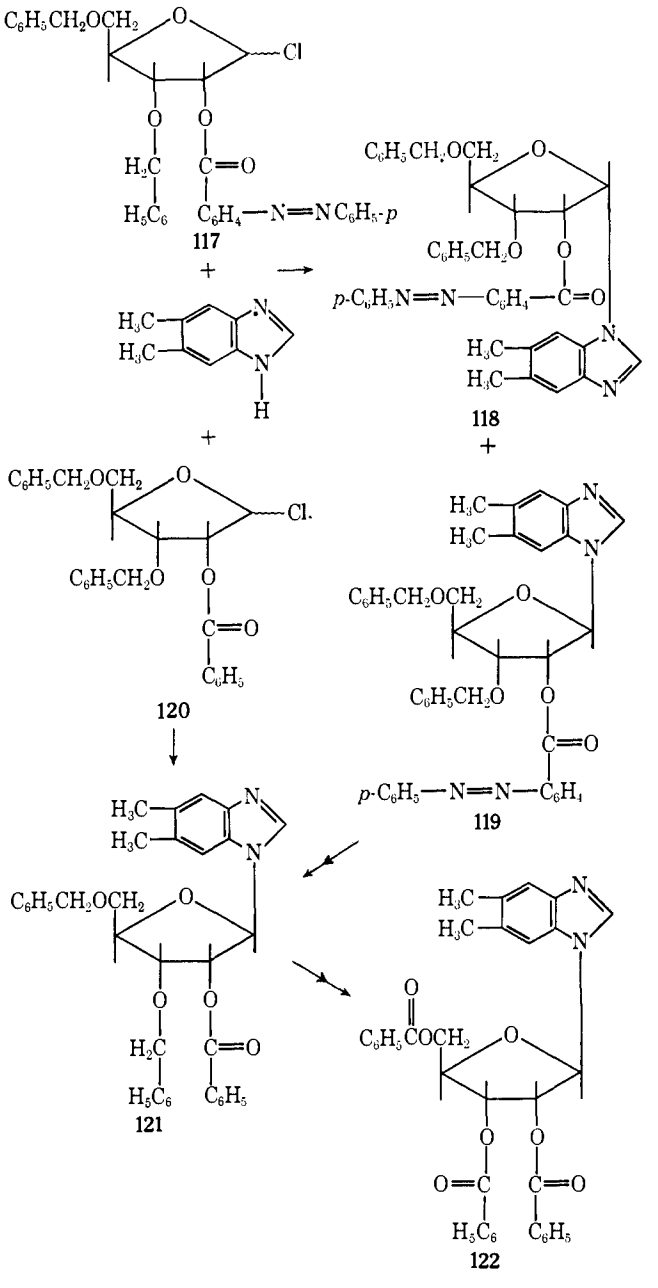
(151) D. D. Reynolds and W. L. Evans, *J. Amer. Chem. Soc.*, 60, 2559 (1938).

some recent investigations.[152] Condensation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**110**) in a dioxane solution with slightly more than a 2 molar equiv of 5,6-dimethylbenzimidazole gave, after chromatography, a good yield (66%) of 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-benzyl-α-D-ribofuranosyl)benzimidazole (**111**). Catalytic debenzylation of **111** with palladium on charcoal (10%) and palladium chloride in a hydrogen atmosphere in methanol afforded 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole (α-ribazole, **112**). For further structural proof, **112** was converted to a picrate and then to the isopropylidene derivative, 5,6-dimethyl-1-(2′,3′-*O*-isopropylidene-α-D-ribofuranosyl)benzimidazole (**113**). It was found that the use of acetonitrile as a solvent instead of dioxane gave a lower yield of **111** (46%). When the silver salt of 5,6-dimethylbenzimidazole was used as a suspension in acetonitrile, the yield decreased to 25%. Condensation of the amorphous 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**114**) with an excess of 5,6-dimethylbenzimidazole in a dry dioxane solution at 100° led, after extensive chromatography, to the isolation of the crystalline picrate of 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (**115**) in a 51% yield. The amorphous picrate of the α anomer was also isolated in a 28% yield. The structural assignments of these picrates were established by their conversion into the respective deblocked nucleosides (ribazoles) followed by a comparison with the known derivatives. Their yields are considerably higher than those reported in the previous literature.[112,121] From the above results, it would appear that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**110**) is the carbohydrate derivative of choice for the synthesis of α-D-ribofuranosyl nucleosides while 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**114**) is preferable for the synthesis of the β-D-ribofuranosyl nucleosides. This can presumably be ascribed primarily to the difference in the substituents at position 2, the reaction conditions (solvent, temperature, etc.), and the configuration of the halogen atom at C-1′.

A route for the synthesis of ribonucleosides in which C-2′ bears one type of substituent while C-3′ and C-5′ bear another type has also been recently reported.[153] For this purpose, 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl chloride (**117**) was selected. Condensation of **117** with an excess of 5,6-dimethylbenzimidazole in boiling dioxane solution afforded a mixture of four products from which a 61% yield of crystalline 5,6-dimethyl-1-(3′,5′-di-*O*-benzyl-2′-*O*-*p*-phenylazobenzoyl-β-D-ribofuranosyl)benzimidazole (**119**) and a 10% yield of 5,6-dimethyl-1-(3′,5′-di-*O*-benzyl-2′-*O*-*p*-phenylazobenzoyl-α-D-ribofuranosyl)benzimidazole (**118**) as a syrup were isolated. A similar condensation of **117** with 5,6-dimethylbenzimidazole in dioxane at room temperature for 72 hr gave a 32% yield of **119** and a 9% yield of **118**. Deblocking of **119** followed by benzoylation afforded 5,6-dimethyl-1-(2′-*O*-benzoyl-3′,5′-di-*O*-benzyl-β-D-ribofuranosyl)benzimidazole (**121**) which was characterized as a crystalline picrate and was found to be identical in all respects with the compound prepared by condensing 5,6-dimethylbenzimidazole with 2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranosyl chloride (**120**). Catalytic hydrogenolysis of **121** gave 5,6-dimethyl-1-(2′-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole, which was benzoylated to furnish 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)benzimidazole (**122**), isolated as a crystalline picrate. The condensation of 3,5-di-*O*-benzyl-D-ribofuranosyl chloride with 5,6-dimethylbenzimidazole in dichloromethane solution at room temperature afforded a mixture which was then benzoylated with benzoic anhydride in pyridine. Preparative tlc yielded two nucleosides as syrups, one of which gave a crystalline picrate identical with **121**. The structure of the other product was established as 1-(2′-*O*-benzoyl-3′,5′-di-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole.

(152) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

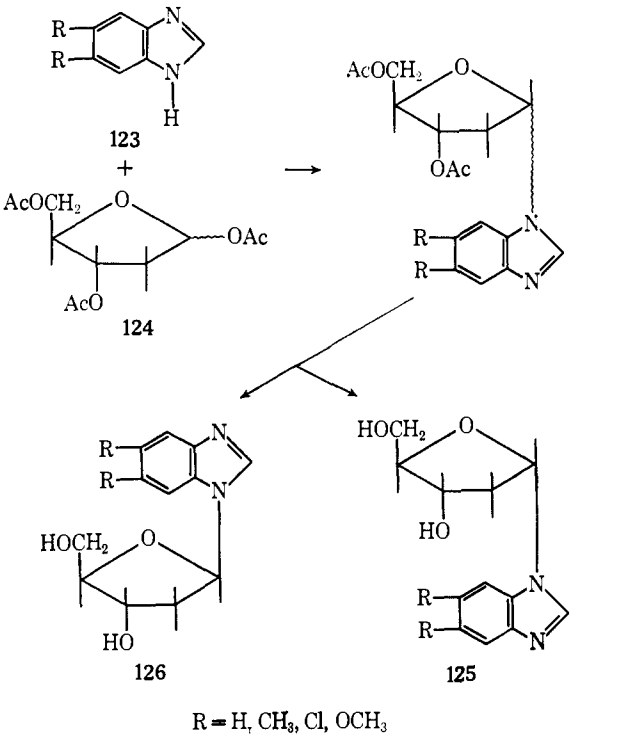
(153) M. Haga, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **33**, 1810 (1968).



6. *Acid-Catalyzed Fusion Procedure*

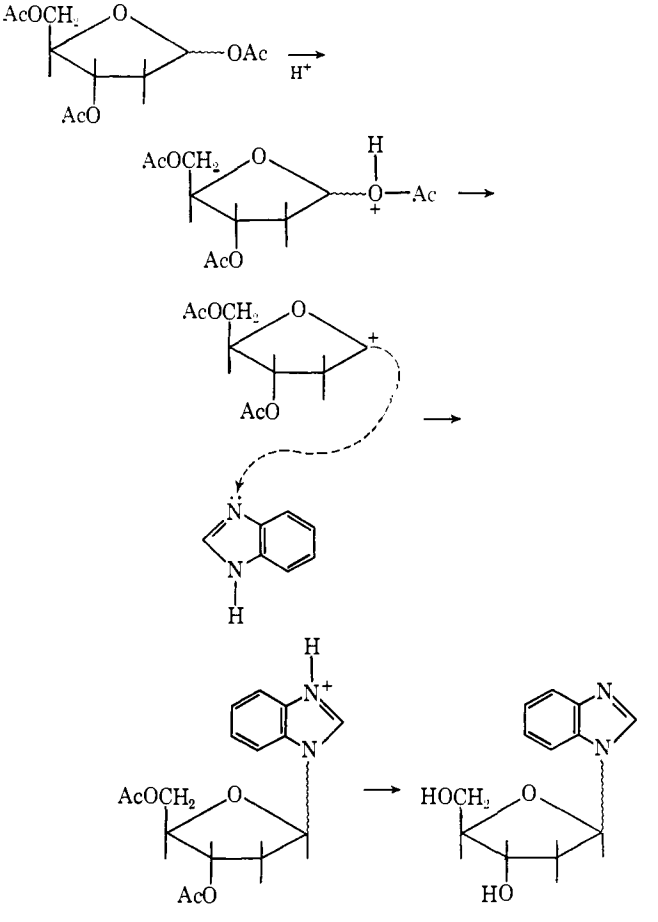
A recent advance in the field of nucleoside synthesis was the advent of acid-catalyzed fusions. This technique was first used in the area of nucleoside synthesis[154] to produce N-glycosylpurines and has subsequently been applied to various other heterocyclic systems.[7]

The only glycosylbenzimidazoles prepared by the acid-catalyzed fusion method were reported[155] in an investigation involving the synthesis of 2′-deoxyribofuranosylbenzimidazoles. Various substituted 1-(2′-deoxy-α- and -β-D-ribofuranosyl)benzimidazoles (**125** and **126**) have been prepared in excellent yield by a simple fusion at 160° of the requisite benzimidazole (**123**) and 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose (**124**) in the presence of chloroacetic acid as a catalyst. This was followed by the subsequent deblocking of the carbohydrate moiety, and the α and β anomers were then separated by fractional crystallization and column chromatography on alumina. The benzimidazoles which are most basic (least acidic, pK_a = 6.1 to 4.74) reacted most readily



R = H, CH_3, Cl, OCH_3

Scheme VI



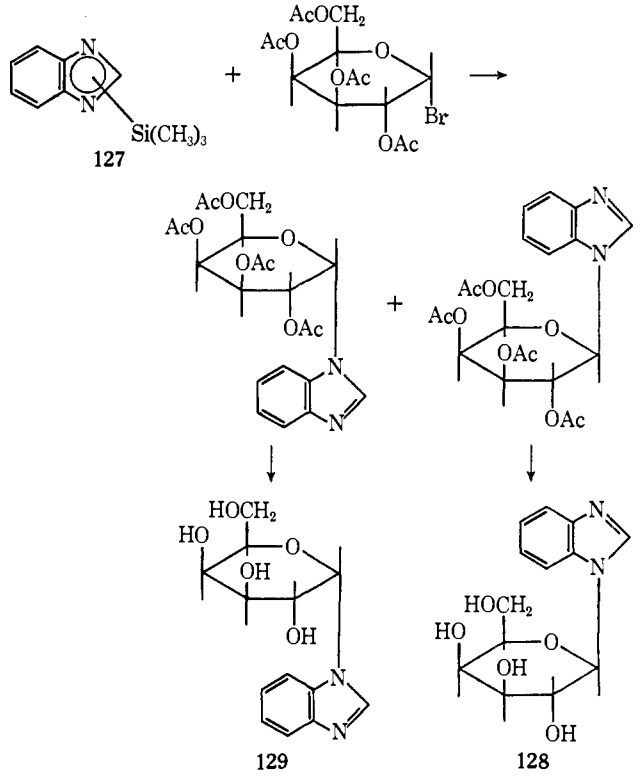
(154) T. Sato, T. Shimidate and Y. Ishido, *J. Chem. Soc. Jap., Ind. Chem. Sect.*, 81, 1440 (1960), and subsequent papers.

(155) C. P. Whittle and R. K. Robins, *J. Amer. Chem. Soc.*, 87, 4940 (1965).

with 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose in the fusion process. There was proposed[155] a reaction mechanism (Scheme VI) involving alkylation of the benzimidazole nitrogen (tertiary nitrogen with the lone electron pair) by a 3,5-di-*O*-acetyl-2-deoxy-D-ribofuranosyl-1-carbonium ion intermediate. This mechanism predicts that the more basic benzimidazoles should be glycosylated much more rapidly than the acidic benzimidazoles. The acid-catalyzed fusion procedure for the preparation of benzimidazole ribofuranosides using various reaction conditions and acidic catalysts has been found[156] to be rather unfruitful.

7. *Trimethylsilyl Procedure*

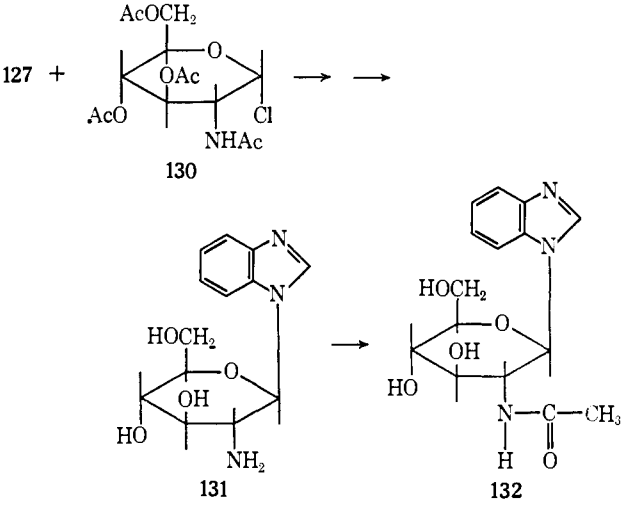
An improved method and probably the most significant advance in the synthesis of benzimidazole nucleosides is based on the activation of the heterocyclic ring nitrogens by silylation.[157-165] 1-Trimethylsilylbenzimidazole[157] (**127**) was fused with powdered tetra-*O*-acetyl-α-D-galactopyranosyl bromide at 110–130° *in vacuo*, to afford a noncrystalline anomeric mixture which on deacetylation with 20% hydrochloric acid at



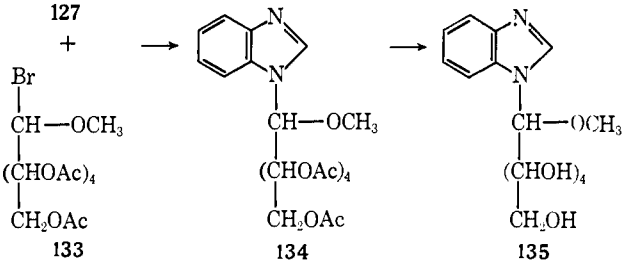
reflux temperature for 3 hr, gave a 33% yield of 1-(β-D-galactopyranosyl)benzimidazole (**128**) and a 25% yield of 1-(α-D-galactopyranosyl)benzimidazole (**129**). Similarly, **127** was condensed with α-acetobromoglucose and β-acetobromo-L-arabinose to obtain the corresponding nucleosides. The reaction of **127** with acetobromo-D-glucofuranose[166,167] at 110–130° gave after deacetylation a mixture of 1-α- and 1-β-D-glucofuranosylbenzimidazoles in good yield.

It was shown earlier[168,169] that the nucleosides (furanosides with participating groups at position 2) prepared by this method possessed the β configuration in general, although there were some exceptions. Other investigators[161] were able to isolate the 1-α- and 1-β-nucleosides in the case of 1-D-galactopyranosylbenzimidazole, 1-D-glucopyranosylbenzimidazole, 1-L-arabinopyranosylbenzimidazole, and 1-D-glucofuranosylbenzimidazole.

The preparation of 1-(2′-amino-2′-deoxy-β-D-glucopyranosyl)benzimidazole (**131**) was accomplished by reacting **127** with 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-D-glucopyranosyl chloride (**130**)[170] followed by deacetylation.[168] Controlled acetylation of **131** gave 1-(2′-acetamido-2′-deoxy-β-D-glucopyranosyl)benzimidazole (**132**) in 96% yield. The synthesis of 1-(1′-benzimidazolyl)-1-methoxy-*aldehydo*-D-galactose (**135**) has been accomplished by condensing **127** with 1-bromo-1-

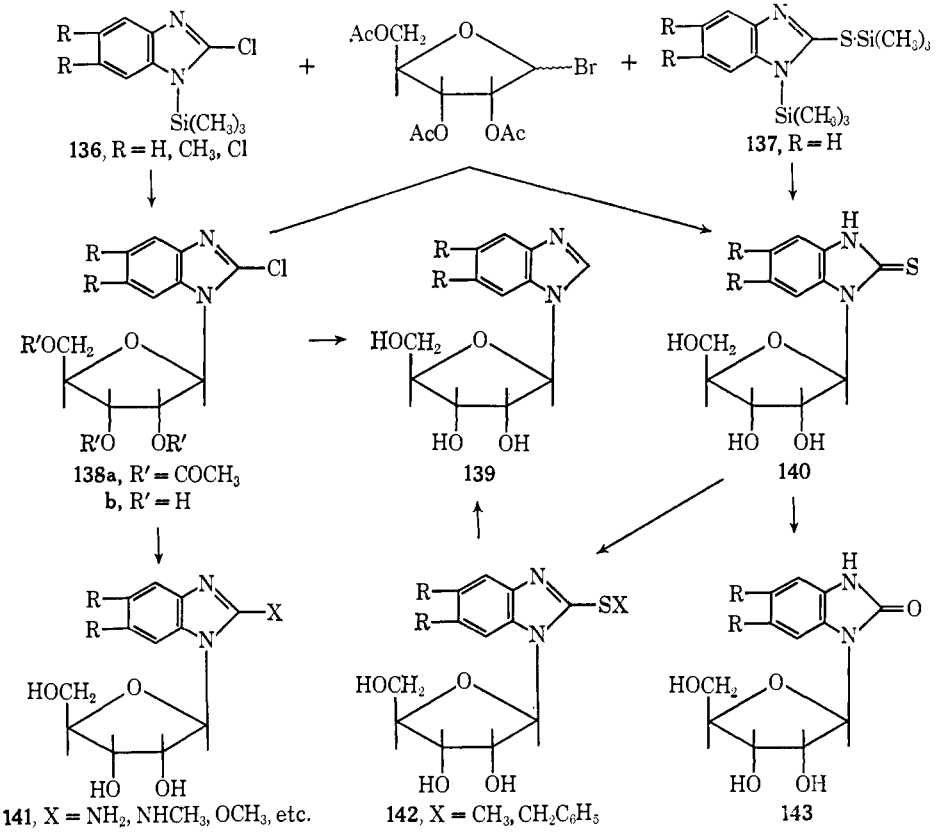


methoxy-*aldehydo*-D-galactose penta-*O*-acetate (**133**).[171] This furnished a 29% yield of crystalline 1-(1′-benzimidazolyl)-1-methoxy-*aldehydo*-D-galactose penta-*O*-acetate (**134**) which



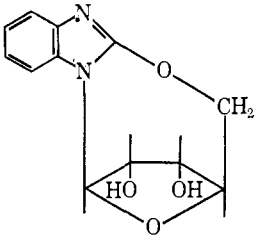
on deacetylation gave **135**. The by-products formed during the preparation of benzimidazole nucleosides from N-trimethyl-

(156) G. R. Revankar and L. B. Townsend, unpublished observations.
(157) L. Birkofer, P. Richter, and A. Ritter, *Chem. Ber.*, **93**, 2804 (1960).
(158) L. Birkofer, H. P. Kuhlthau, and A. Ritter, *Angew. Chem.*, **75**, 209 (1964).
(159) L. Birkofer, H. P. Kuhlthau, and A. Ritter, *Chem. Ber.*, **93**, 2810 (1960).
(160) L. Birkofer, H. P. Kuhlthau, and A. Ritter, *ibid.*, **97**, 934 (1964).
(161) H. Bräuniger and A. Koine, *Arch. Pharm.*, **296**, 668 (1963).
(162) H. Bräuniger and A. Koine, *ibid.*, **298**, 641 (1965).
(163) H. Bräuniger and A. Koine, *ibid.*, **298**, 644 (1965).
(164) H. Bräuniger and A. Koine, *ibid.*, **298**, 708 (1965).
(165) H. Bräuniger and A. Koine, *ibid.*, **298**, 712 (1965).
(166) F. Weygand and H. Ziemann, *Ann. Chem.*, **657**, 179 (1962).
(167) M. L. Wolfrom, P. McWain, R. Pagnucco, and H. Thompson, *J. Org. Chem.*, **29**, 454 (1964).
(168) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **11**, 1470 (1963).
(169) T. Nishimura, B. Shimizu, and I. Iwai, *ibid.*, **12**, 1471 (1964).
(170) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).
(171) F. Weygand, H. Ziemann, and H. J. Bestman, *Chem. Ber.*, **91**, 2534 (1958).



silylbenzimidazole have been isolated and shown to be 1,3-diglycosylbenzimidazolium compounds.

The preparation of benzimidazole ribofuranosides by this facile synthetic route was recently demonstrated[172-174] by the successful preparation of a series of 2-substituted benzimidazole nucleosides. The synthesis of 1-(β-D-ribofuranosyl) derivatives of 2-chloro-, 2-chloro-5,6-dimethyl-, and 2,5,6-trichlorobenzimidazoles has been accomplished in excellent yield. This was accomplished by a condensation of the appropriate 1-trimethylsilylbenzimidazole (**136**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, followed by deacetylation of the condensed product (**138a**) with methanolic ammonia at room temperature to obtain **138b**. Removal of the 2-chloro group from **138b** with palladium on carbon (10%) in a hydrogen atmosphere in aqueous ammonium hydroxide solution afforded the corresponding 1-(β-D-ribofuranosyl)benzimidazoles (**139**). A comparison of **139** with an authentic sample of **139** established the actual site of ribosylation and the β configuration. Displacement of the 2-chloro group of **138b** was accomplished with thiourea in ethanol to furnish 1-(β-D-ribofuranosyl)benzimidazole-2-thione (**140**) which was also prepared by condensing the disilylated derivative of benzimidazole-2-thione (**137**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide followed by deacetylation. Treatment of **140** in an aqueous ammoniacal solution with methyl iodide or benzyl chloride furnished 2-methylthio- and 2-benzylthio-1-(β-D-ribofuranosyl)benzimidazole, respectively (**142**). Treatment of **140** with alkaline hydrogen peroxide gave 1-(β-D-ribofuranosyl)benzimidazol-2-one (**143**). Nucleophilic displacement of the 2-chloro group from **138b** produced a number of interesting 2-substituted 1-(β-D-ribofuranosyl)benzimidazoles (**141**). A small amount of the high-melting cyclonucleoside (**144**) was isolated[172] from the deacetylation product



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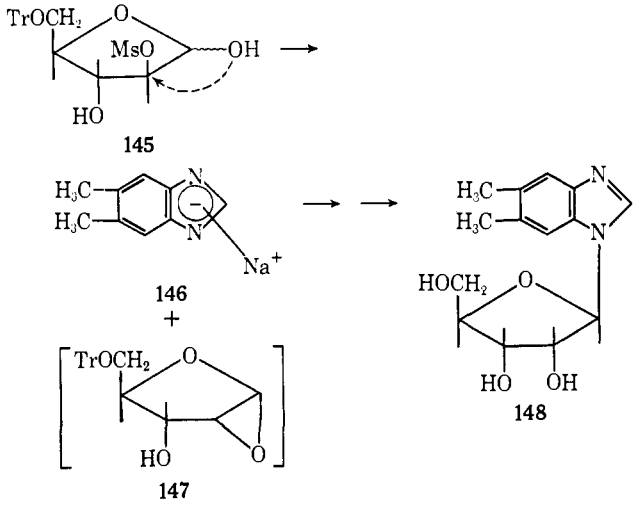
of **138a** with methanolic ammonia at room temperature.

8. *Miscellaneous Methods*

The preparation of a benzimidazole nucleoside has been reported[175] by a rather novel method. Tritylation of 2-*O*-methanesulfonyl-D-arabinose has furnished 5-*O*-trityl-2-*O*-mesyl-D-arabinose (**145**) which then precludes the formation of a pyranoside derivative. Treatment of **145** under basic conditions effected a facile displacement of the 2-*O*-mesyl group to furnish the intermediate (**147**) *in situ*, which was then condensed with the sodium salt of 5,6-dimethylbenzimidazole (**146**) to afford **148** after detritylation. A variation of the principle has been used for the recent[176] glycosylation of

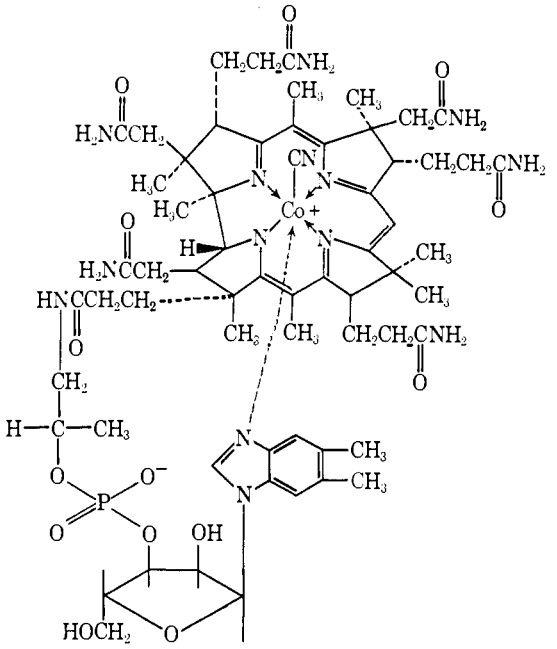
(172) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **5**, 477 (1968).
(173) G. R. Revankar and L. B. Townsend, *ibid.*, **5**, 615 (1968).
(174) G. R. Revankar and L. B. Townsend, in press.
(175) W. Schroeder, U. S. Patent 2,993,039 (July 18, 1961).
(176) N. K. Kochetkov, A. F. Bochkov, and T. A. Sokolorskaia, *Dokl. Akad. Nauk, SSSR*, **187**, 96 (1969), and references cited therein.



various heterocycles by what has been termed the orthoacetate (1, 2) procedure.

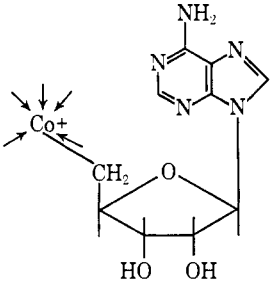
III. Naturally Occurring Benzimidazole Nucleosides and Nucleotides Involved in Vitamin B_{12} Biosynthesis

The importance of vitamin B_{12} in various metabolic processes (*e.g.*, intramolecular isomerizations, enzymatic methylations, the reduction of ribonucleotides to 2′-deoxyribonucleotides, as well as the reduction of other vicinal diol compounds, etc.) has been well documented.[3,4,177-181] This has created considerable interest in the area of vitamin B_{12}, vitamin B_{12} coenzymes, pseudovitamin B_{12}, and related analogs. The tremendous interest in the area of benzimidazole nucleosides must be related to the structural elucidation of vitamin B_{12} (**149**). A number of fragments from vitamin B_{12} were identified in the initial elucidation studies [*e.g.*, D-1-aminopropan-2-ol,[182-184] 5,6-dimethylbenzimidazole,[17,185] the nucleoside of 5,6-dimethylbenzimidazole,[67,112,186] which was established as possessing the α anomeric configuration in direct contrast to the nucleosides (β anomeric configuration) isolated from nucleic acids, and the nucleotide[20,75] of 5,6-dimethylbenzimidazole where the phosphate group was suggested[20,75,117] to be on the 3′-hydroxyl group in the intact molecule although on basic hydrolysis some migration will usually occur to provide some of the 2′-phosphate derivative]. Other chemical studies[80] revealed several salient features of the total structure and a correlation of these various chemical and spectroscopic (ultraviolet and infrared) studies along with X-ray analyses[187] provided the final structural elucidation of vitamin B_{12} (**149**). A



149, vitamin B_{12}

vitamin B_{12} analog was subsequently isolated[188,189] and shown[84] to possess not only the 5,6-dimethylbenzimidazole nucleotide (α anomer) but also in addition the adenine riboside (**150**) which possessed a β anomeric configuration with the carbohydrate moiety at N-9. It was established that this purine nucleoside (5′-deoxyadenosyl) had replaced the cyano group as a ligand with the structure of the remaining molecule apparently being very similar to that of vitamin B_{12}.



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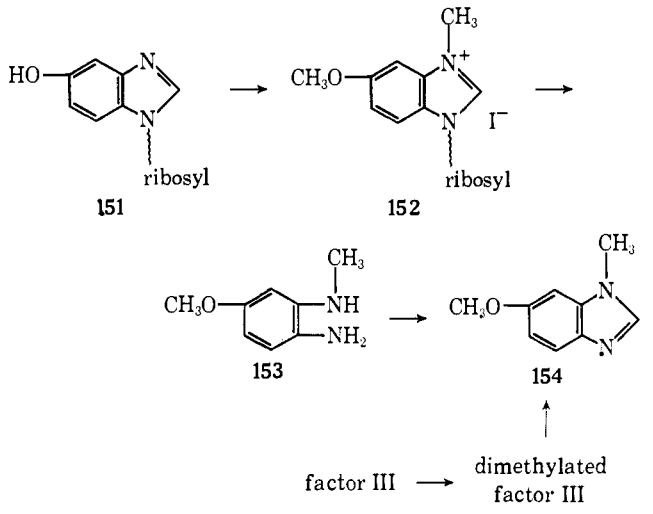
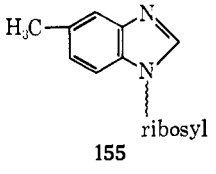
There have also been additional benzimidazole nucleosides isolated from vitamin B_{12} analogs. The hydrolysis of factor III [α-(5-hydroxybenzimidazolyl)cobamide cyanide] established that the heterocyclic portion of the nucleoside was 5-hydroxybenzimidazole.[127,128] The site of ribosyl attachment was established by methylation and degradation studies. Methylation of factor III,[190] *per se*, and the nucleoside[130] isolated from factor III (**151**) has furnished a dimethylated derivative in each instance. The dimethylated derivative of factor III was degraded to furnish 6-methoxy-1-methylbenzimidazole (**154**). However, treatment of the methiodide of the dimethylated derivative of the nucleoside from factor III (**152**) with methanolic sodium hydroxide effected not only a loss of the ribosyl moiety but also a facile ring opening. This

(177) K. Bernhauer, O. Muller, and F. Wagner, *Angew. Chem. Intern. Ed. Engl.*, 3, 200 (1964).
(178) J. M. Buchanan, H. L. Elford, R. E. Loughlin, B. M. McDougall, and S. Rosenthal, *Ann. N. Y. Acad. Sci.*, 112, 756 (1964).
(179) H. Weissbach and H. Dickerman, *Physiol. Rev.*, 45, 80 (1965).
(180) R. L. Blakely and H. A. Barker, *Biochem. Biophys. Res. Commun.*, 16, 391 (1964).
(181) R. Abrams and S. Duraiswami, *ibid.*, 18, 409 (1965).
(182) G. Cooley, B. Ellis, and V. Petrow, *J. Pharm. Pharmcol.*, 2, 128 (1950).
(183) B. Ellis, V. Petrow, and G. F. Snook, *ibid.*, 1, 950 (1949).
(184) D. E. Wolf, W. H. Jones, H. Valiant, and K. Folkers, *J. Amer. Chem. Soc.*, 72, 2820 (1950).
(185) N. G. Brink and K. Folkers, *ibid.*, 72, 4442 (1950).
(186) N. G. Brink and K. Folkers, *ibid.*, 74, 2856 (1952).
(187) D. C. Hodgkin, J. Kamper, M. MacKay, J. Pickworth, K. N. Trueblood, and J. G. White, *Nature*, 178, 64 (1956).
(188) H. A. Barker, H. Weissbach, and R. D. Smyth, *Proc. Nat. Acad. Sci. U. S.*, 44, 1093 (1958).
(189) H. Weissbach, J. Tookey, and H. A. Barker, *ibid.*, 45, 521 (1959).
(190) W. Friedrich and K. Bernhauer, *Chem. Ber.*, 89, 2030 (1956).



resulted in the isolation of 2-methylamino-4-methoxyaniline (**153**) which was then ring closed with formic acid to afford **154**. This proved that the nucleoside from factor III was a 1-ribosyl-5-hydroxybenzimidazole (**151**), and while the anomeric assignment was not made unequivocally, it was postulated to be an α-D-ribofuranoside. 5-Methylbenzimidazole and 5-methylbenzimidazole-α-riboside (**155**) were isolated[191] from the degradation of another vitamin B_{12} factor which was assigned the name α-(5-methylbenzimidazole)cobamide cyanide. The site of ribosyl attachment was ascertained by methylation studies[192] very similar to those discussed above for the 5-hydroxybenzimidazole nucleoside while the anomeric con-



figuration was again postulated to be α. Another factor containing a benzimidazole nucleoside was α-benzimidazolylcobamide cyanide.[191,192] The site of ribosyl attachment was not a problem in this case since a visual inspection of benzimidazole reveals a symmetrical structure. The anomeric configuration was not established unequivocally but was postulated to be α.

There are a number of naturally occurring vitamin B_{12} analogs where the heterocyclic aglycon is not 5,6-dimethylbenzimidazole. The most interesting series of these vitamin B_{12} analogs is those containing purine bases.[177] Pseudovitamin B_{12} contains the purine base (adenine) as the 7-α-D-ribosyl derivative, while other analogs (factor A, factor G, etc.) contain other purine bases which have also been postulated to exist as the 7-α-D-ribosyl derivatives. This has created considerable interest in the chemical synthesis of 7-ribosylpurines.[193-197] In fact, the 2′-deoxy derivative [7-(2′-deoxy-α-D-ribofuranosyl)-6-purinone] has been recently prepared[198] from an appropriate imidazole nucleoside and is presumed to be the 2′-deoxy derivative of the nucleoside from factor G.[198a] These vitamin B_{12} analogs are of especial interest, since it has been demonstrated that certain ones can function as precursors of vitamin B_{12} and the conversion to vitamin B_{12} is effected in the presence of *Propionibacterium shermanii* and 5,6-dimethylbenzimidazole. This is of interest in view of recent investigations[199-204] which have established the identity of a new vitamin B_{12} analog as vitamin B_{12} 5′-phosphate. This analog has been converted to vitamin B_{12} with heat or by an enzyme and has resulted in the formulation of two separate and distinct pathways for the formation of vitamin B_{12} 5′-phosphate. One pathway would be by the direct insertion of a α-5′-nucleotide for or instead of the normal α-nucleoside. It has been previously demonstrated[205,206] that *P. shermanii* possesses a phosphoribosyl transferase which can be used for the formation of N-α-glycosidic 5′-ribonucleotides of several benzimidazoles. This has provided strong support for the above postulation that the formation of vitamin B_{12} occurs as a direct replacement of or for a heterocyclic α-nucleoside by a heterocyclic α-5′-nucleotide with subsequent dephosphorylation to provide vitamin B_{12}. Of interest in this respect is the report[207] that GDP (cobinamide coenzyme in the cell-free system isolated from *E. coli* 113-3) is converted into vitamin B_{12} in the presence of 5,6-dimethylbenzimidazole but not the corresponding riboside. It would be of considerable interest to see if the 5′-nucleotide would function satisfactorily as a substrate under these same conditions.

An alternate pathway for the formation of vitamin B_{12} 5′-phosphate has received little support since it would entail a breakdown of complete corrinoids to cobinamide derivatives.

The primary importance of benzimidazole nucleosides and especially nucleotides in this area may be the possibility of incorporation with the formation of a corrinoid. This would appear to be of especial importance for heterocycles which are not symmetrical since it has been shown that the stereospecificity of these enzymes may not be complete. The incorporation of 5(6)-methylbenzimidazole by *P. shermanii* affords[192] primarily the 6-methylbenzimidazole compound, but there is also observed a small amount of the 5-methylbenzimidazole compound. However, if the 5′-nucleotide could be incorporated without transformation, then the juxtaposition between the carbohydrate moiety and exocyclic groups on the heterocyclic moiety would remain constant and could provide the basis for some very interesting investigations.

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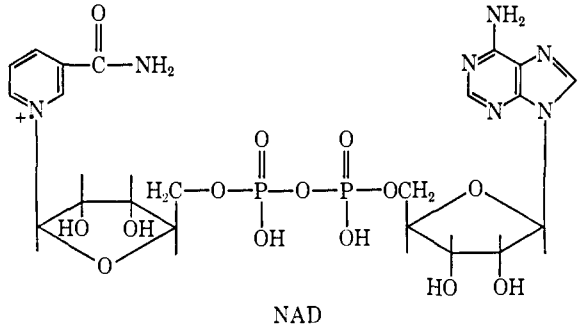
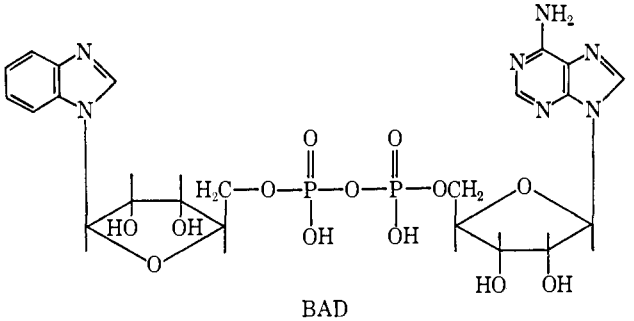
(192) W. Friedrich and K. Bernhauer, *ibid.*, **91**, 1665 (1958).
(193) R. J. Rousseau and L. B. Townsend, *J. Org. Chem.*, **33**, 2828 (1968).
(194) R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Chem. Commun.*, 265 (1966).
(195) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **90**, 2661 (1968).
(196) R. J. Rousseau, R. P. Panzica, S. M. Reddick, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **35**, 631 (1970).
(197) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, 87, 5442 (1965); *J. Heterocycl. Chem.*, **5**, 303 (1968); *J. Org. Chem.*, **34**, 2646 (1969).
(198) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, in press.
(198a) The synthesis of the nucleoside from factor G has been reported; see ref 197.
(199) H. C. Friedmann and D. L. Harris, *Biochem. Biophys. Res. Commun.*, 8, 164 (1962).
(200) K. Ohlenroth and H. C. Friedmann, *Biochim. Biophys. Acta*, 170, 465 (1968).
(201) H. C. Friedmann, *J. Biol. Chem.*, **243**, 2065 (1968).
(202) C. L. Coveter, S. W. Haekinson, and H. C. Friedmann, *Biochim. Biophys. Acta*, 177, 293 (1969).
(203) P. Renz, *Angew. Chem. Intern. Ed. Engl.*, **6**, 368 (1967).
(204) P. Renz, *Z. Phys. Chem.*, **349**, 979 (1968).
(205) H. C. Friedmann, *J. Biol. Chem.*, **240**, 413 (1965).
(206) H. C. Friedmann and D. L. Harris, *ibid.*, 240, 406 (1965).
(207) W. Walerych, T. Kato, and J. Pawelkiewicz, *Biochem. Biophys. Res. Commun.*, **31**, 328 (1968).

IV. Other Naturally Occurring Benzimidazole Nucleosides and Nucleotides

It has been demonstrated that benzimidazole effects a significant inhibition[208] of the enzyme orotidine 5′-phosphate pyrophosphorylase from the embryos of wheat seedlings. This has been explained on the basis of benzimidazole being in direct competition with orotate for PRPP which indicated the presence of another enzyme (benzimidazole nucleotide pyrophosphorylase). This was further supported by the isolation of a radioactive benzimidazole mononucleotide upon the administration of benzimidazole-2-^{14}C to wheat embryo homogenates. A benzimidazole nucleoside has been previously[209] isolated from wheat leaves which were fed benzimidazole, and this has now been postulated to have originally occurred as the nucleotide with the phosphate bond being hydrolyzed during isolation. Another possible origin for this benzimidazole nucleoside can be based on the report[210] that the reaction between nicotinamide adenine dinucleotide (NAD) and benzimidazole furnished a benzimidazole nucleoside. This was unexpected since it has been previously reported[211] that a very similar reaction furnished benzimidazole adenine dinucleotide (BAD). The fact that benzimidazole nucleoside rather than BAD was isolated from the enzymatic reaction using a glycohydrolase from a certain fraction of wheat embryos has been rationalized by the suggestion that there must be another enzyme (presumably a 5′-nucleotidase) in this fraction which cleaves the bond between the phosphate group and the ribosyl group attached to benzimidazole.



NAD

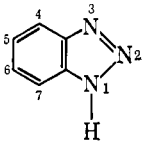


BAD

V. Chemical Synthesis of Benzotriazole, Indazole, and Indole Nucleosides and Nucleotides

A. BENZOTRIAZOLE NUCLEOSIDES AND NUCLEOTIDES

Benzotriazole (benzeneazimide) is a heterocyclic ring system in which a benzene ring is fused to the 4,5 positions of a 1,2,3-triazole (*v*-triazole) ring (a five-membered doubly unsaturated heterocycle). The *v*-triazole ring is composed of three sequentially linked nitrogen atoms and two carbon atoms.[212] The universally adopted numbering system of benzotriazole is indicated in **156**.[213] Benzotriazole derivatives, excluding nucleosides, have found some use as chemotherapeutic agents.[214,215] The reason for this absence of reported chemotherapeutic activity for benzotriazole nucleosides is probably due to the paucity of these derivatives.



156

The first chemical synthesis[216] of a benzotriazole nucleoside was accomplished by a condensation of the silver salt of 5,6-dichlorobenzotriazole (**157**)[217] with 3,5-di-*O*-benzoyl-D-ribofuranosyl chloride (**158**) in boiling xylene which produced four crystalline (isomeric and anomeric) nucleosides (**159**, **160**, **161**, **162**) which were separated by fractional crystallization. Debenzoylation of these nucleosides with methanolic ammonia afforded the corresponding nucleosides [5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole (**163**), 5,6-dichloro-1-(α-D-ribofuranosyl)benzotriazole (**164**), 5,6-dichloro-2-(β-D-ribofuranosyl)benzotriazole (**165**), and 5,6-dichloro-2-(α-D-ribofuranosyl)benzotriazole (**166**)].

The trimethylsilyl procedure has been recently extended for the preparation of benzotriazole nucleosides.[218] Treatment of N-trimethylsilylbenzotriazole (**167**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide at 110–130° under high vacuum produced a 39% yield of 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)benzotriazole (**168**). Complete deblocking of the carbohydrate moiety of **168** was accomplished with barium methylate in methanol to obtain 1-(β-D-glucopyranosyl)benzotriazole (**169**). The site of glucosylation was readily determined as N-1 by a comparison between the ultraviolet absorption spectra observed for **169** and the ultraviolet absorption spectral data reported for 1-methylbenzotriazole and 2-methylbenzotriazole. The anomeric configuration (β) for **169** was assigned on the basis of the large negative specific rotation and was confirmed by periodate oxidation studies. Similarly, the condensation of **167** with 3,4,6-tri-*O*-acetyl-2-deoxy-2-acetamido-α-D-glucopyranosyl chloride produced a

(208) M. Kapoor and E. R. Waygood, *Can. J. Biochem.*, **43**, 153 (1965); 2-aminobenzimidazole and 2-methylbenzimidazole are not as effective.
(209) D. Wang, unpublished observations.
(210) M. Kapoor and E. R. Waygood, *Can. J. Biochem.*, **43**, 165 (1965).
(211) S. G. A. Alivasatos, L. Lamantia, and B. L. Natijovitch, *Biochem. Biophys. Acta*, 58, 201 (1962).
(212) F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).
(213) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 355.
(214) K. Elbs, O. Hirschel, F. Wagner, K. Himmler, W. Turk, A. Henrich, and E. Lehmann, *J. Prakt. Chem.*, **108**, 209 (1924).
(215) R. W. Cunningham, E. J. Fellows, and A. E. Livingston, *J. Pharmacol.*, **73**, 312 (1941).
(216) P. E. Wittreich, K. Folkers, and F. M. Robinson, U. S. Patent 3,138,582 (June 23, 1964); *Chem. Abstr.*, **61**, 7091 (1964).
(217) R. H. Wiley and K. F. Hussung, *J. Amer. Chem. Soc.*, **79**, 4395 (1957).
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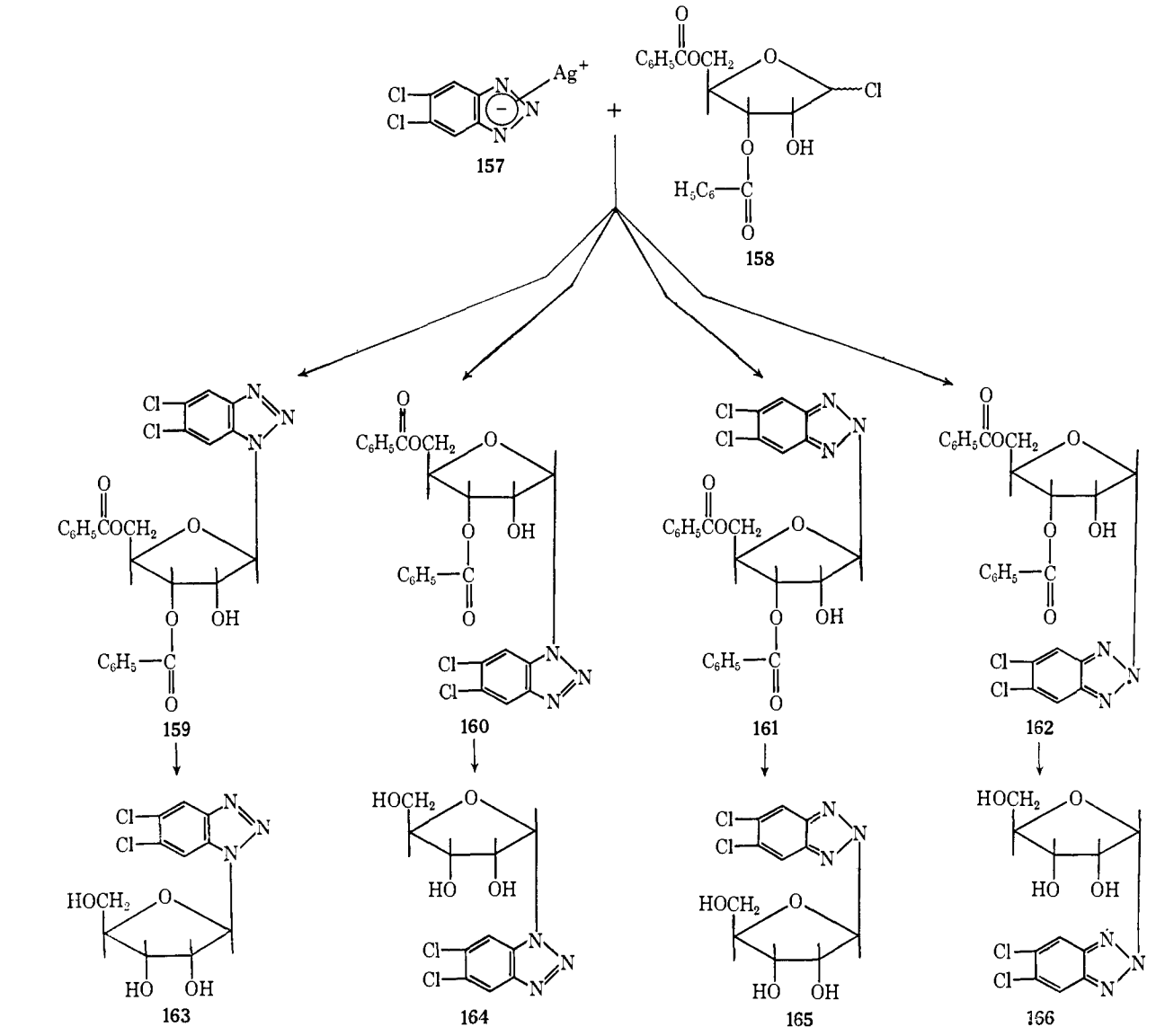
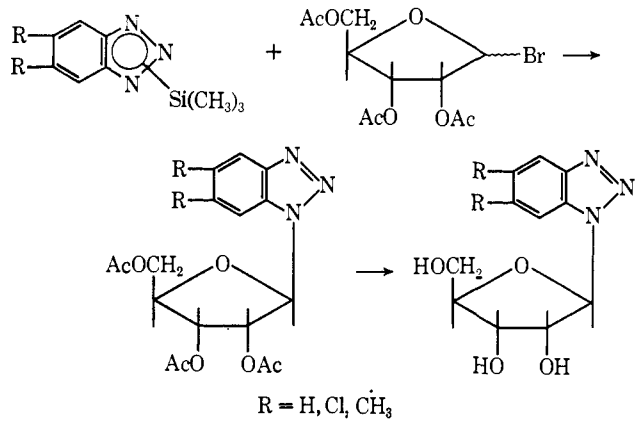


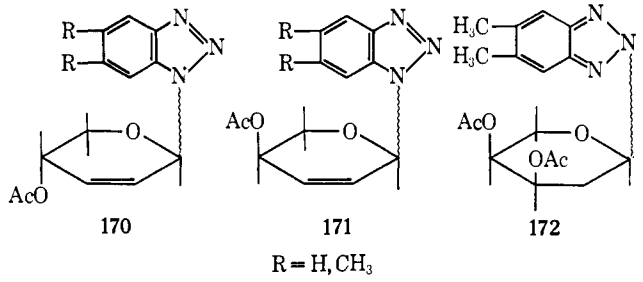
60% yield of crystalline 1-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-acetamido-β-D-glucopyranosyl)benzotriazole.[163] Deacetylation of the carbohydrate moiety with barium methylate in methanol produced 1-(2′-deoxy-2′-acetamido-β-D-glucopyranosyl)benzotriazole. The site of glucosylation and anomeric configuration were established as in the case of **169**. In a like manner, **167** with 1-bromo-1-methoxy-D-galactose pentaacetate gave crystalline 1-(1′-benzotriazolyl)-1-methoxy-D-galactose pentaacetate[164] which on deacetylation with methanolic barium methylate produced 1-(1′-benzotriazolyl)-1-methoxy-D-galactose.

The importance and generality of this procedure for the preparation of benzotriazole ribofuranosides was demonstrated by the successful preparation of several 1-(β-D-ribofuranosyl)benzotriazoles.[219] The synthesis of 5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole, 5,6-dimethyl-1-(β-D-ribofuranosyl)benzotriazole, and 1-(β-D-ribofuranosyl)benzotriazole was achieved in good yield by the condensation of the appropriate N-trimethylsilylbenzotriazole with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide, followed by subsequent deacetylation of the reaction products. The site of ribosylation was established as N-1 by a comparison between the ultraviolet absorption spectra observed for these nucleosides and those reported for model methyl compounds. The β configuration was established by large negative specific rotation, the *trans* rule, and by periodate oxidation and sodium borohydride reduction studies.

(219) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, **5**, 785 (1968).



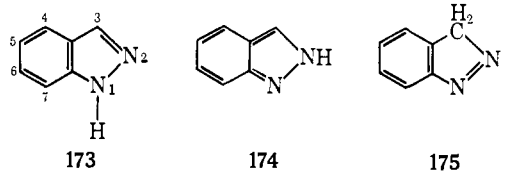
The reaction of 3,4-di-*O*-acetyl-D-xylal and 3,4-di-*O*-acetyl-L-arabinal with benzotriazole and 5,6-dimethylbenzotriazole, in ethyl acetate and in the presence of trifluoracetic acid, has also been studied.[220] The treatment of benzotriazole with 3,4-di-*O*-acetyl-D-xylal[221] in ethyl acetate containing a few drops of trifluoracetic acid in a sealed tube at 110° produced crystalline 1-(4′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxy-D-*glycero*-pyranosyl)benzotriazole (**170**, R = H). A similar reaction with 3,4-di-*O*-acetyl-L-arabinal[222] gave 1-(4′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxy-L-*glycero*-pyranosyl)benzotriazole (**171**, R = H). Condensation of 5,6-dimethylbenzotriazole with 3,4-di-*O*-acetyl-D-xylal and 3,4-di-*O*-acetyl-L-arabinal



produced 5,6-dimethyl-1-(4′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxy-D-*glycero*-pyranosyl)benzotriazole (**170**, R = CH_3) and 5,6-dimethyl-1-(4′-*O*-acetyl-2′,3′-didehydro-2′,3′-dideoxy-L *glycero*-pyranosyl)benzotriazole (**171**, R = CH_3), respectively. However, with 3,4-di-*O*-acetyl-L-arabinal a small amount of another crystalline product was isolated which was assigned structure **172**.

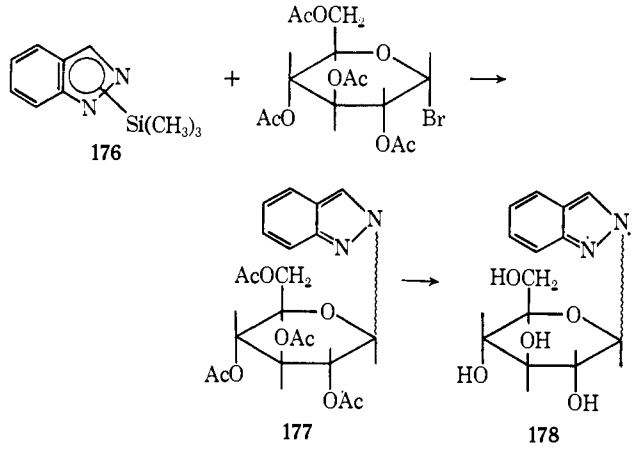
B. INDAZOLE NUCLEOSIDES AND NUCLEOTIDES

Indazole, a heterocyclic ring system in which a benzene ring is fused to two carbon atoms of a pyrazole ring, is capable of existing in three tautomeric forms (**173**, **174**, **175**).[223] The



numbering system universally adopted is indicated in **173**. Although the chemistry of indazoles has been extensively studied, they have not been found in natural products and are at the present time of little commercial use.

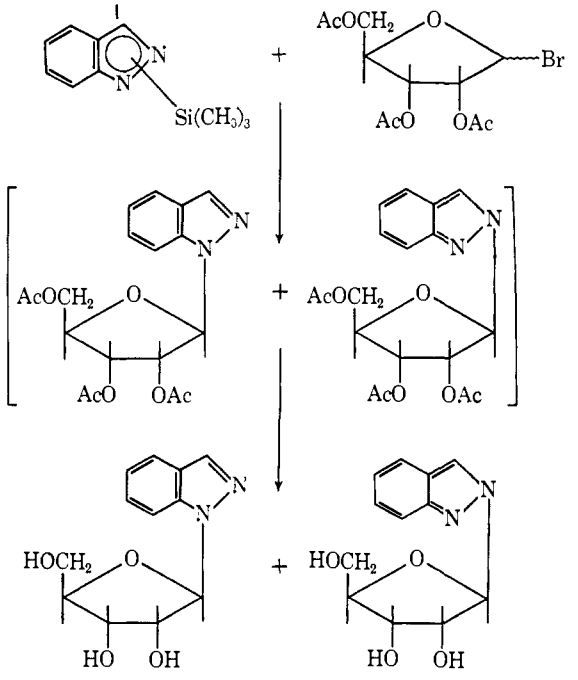
An examination of the literature revealed that the only reported examples of N-glycosylindazoles were 2-D-glucopyranosylindazole[224] and certain indazole ribofuranosides.[225] The synthetic approach used by these workers involved the reaction of N-trimethylsilylindazoles with acylglycosyl bromides to obtain the corresponding indazole glycosides. Thus, the condensation of an equimolar proportion of N-trimethylsilylindazole (**176**) with α-acetobromoglucose at 130° under reduced pressure produced a 39% yield of crystalline 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)indazole (**177**).[224] Complete deacetylation of the carbohydrate moiety



of **177** was accomplished with methanolic barium methylate to obtain 2-(D-glucopyranosyl)indazole (**178**) isolated as the monohydrate. Although the anomeric configuration of **178** was inferred to be β on the basis of specific rotation, the exact configuration was not assigned. Similarly, the treatment of **176** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in the presence of potassium iodide at 75–80° under reduced pressure produced a syrupy mixture of nucleoside material. Deacetylation of this syrup with methanolic ammonia at room temperature and separation of the isomers by column chromatography on alumina gave two nucleosides which were assigned the structures 1-(β-D-ribofuranosyl)indazole (**179**) and 2-(β-D-ribofuranosyl)indazole (**180**).[225] The yield of **180** was about five times that of **179**. The site of ribosylation was determined by a comparison between the ultraviolet absorption spectra observed for **179** and **180** with the ultraviolet absorption spectral data reported[226] for the 1- and 2-methyl derivatives of indazole. The anomeric configuration of **180** was established as β by periodate oxidation and borohydride reduction studies while the anomeric configuration of **179** was assigned *tentatively* on the basis of specific rotation and the *trans* rule.

In a like manner, the trimethylsilyl derivatives of 4-, 5-, and 6-nitroindazoles were condensed with tri-*O*-acetyl-D-ribofuranosyl bromide followed by deacetylation of the condensed product with methanolic ammonia to obtain the corresponding 2-(β-D-ribofuranosyl)nitroindazoles[225] in good yield. The

(220) M. Fuertes, G. Gareia-Mofioz, M. Lora-Tamayo, R. Madrofiero, and M. Stud, *Tetrahedron Lett.*, 4089 (1968).
(221) M. Gehrke and F. Obst, *Chem. Ber.*, **64**, 1724 (1931).
(222) L. Vargha and J. Kuszmann, *ibid.*, **96**, 411 (1963).
(223) R. C. Elderfield, ref 11, p 162.
(224) H. Brauniger and A. Koine, *Pharmazie*, 20, 457 (1965).
(225) G. R. Revankar and L. B. Townsend, *J. Heterocycl. Chem.*, 7, 117 (1970).
(226) V. Rousseau and H. G. Lindwall, *J. Amer. Chem. Soc.*, 72, 3047 (1950).



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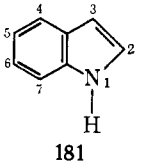
site of ribosylation in all these nucleosides was established to be N-2 by a comparison between the ultraviolet absorption spectra obtained for these nucleosides and that of 1-methyl and 2-methyl model compounds. The anomeric configuration of these nucleosides was assigned as β from the large negative optical rotation values and the *trans* rule and was further confirmed by the periodate oxidation and sodium borohydride reduction studies. These assignments were confirmed by pmr studies which revealed a $J_{1,2}$ of less than 1 Hz for the 2',3'-*O*-isopropylidene derivative of 6-nitro-2-(β-D-ribofuranosyl)-indazole.

C. INDOLE NUCLEOSIDES AND NUCLEOTIDES

Indole (1-benzo[*b*]pyrrole),[227] a ring system in which a benzene ring is fused at the 2,3 position of the pyrrole ring has been found in a large number of alkaloids and other natural products;[228-230] the numbering system of indole is indicated in **181**. Although, indole chemistry has occupied a prominent place



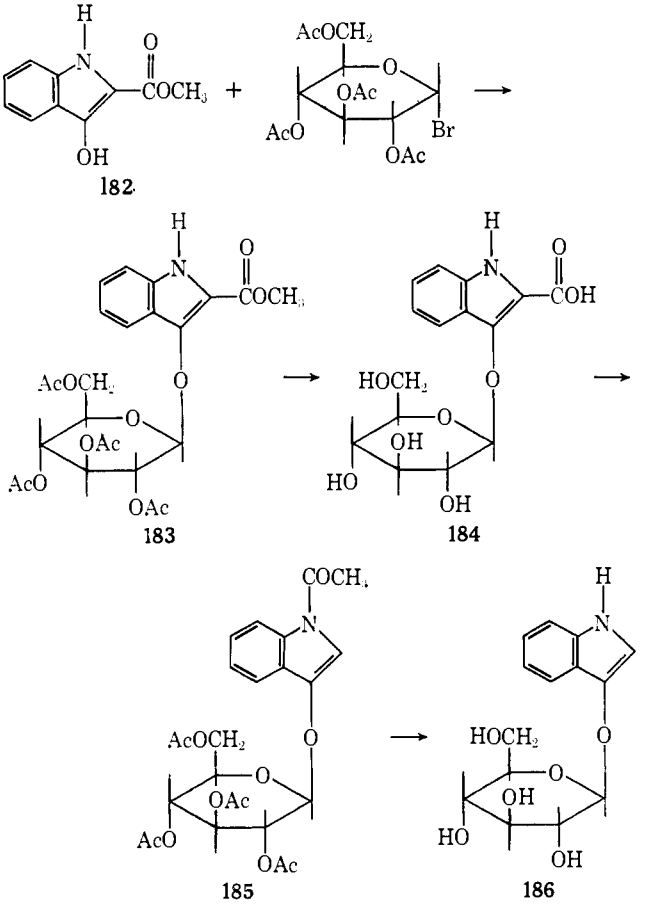
181

in numerous laboratories since 1866, very little work has been reported on glycosylindoles. The object of this section is to present very briefly what has been published in the area of indole nucleosides and nucleotides.

1. Indoles Containing a Carbohydrate Moiety at Position 3

The naturally occurring indole glucoside "indican" (3-β-D-glucosidoxyindole, **186**)[231-234] was synthesized[235] by the reaction of methyl 3-hydroxyindole-2-carboxylate (**182**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in acetone containing potassium hydroxide; methyl 3-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucosyloxy)indole-2-carboxylate (**183**) was obtained. Hydrolysis of **183** with methanolic potassium hydroxide afforded 3-β-D-glucosidoxyindole-2-carboxylic acid (**184**) which on subsequent acetylation with sodium acetate and acetic anhydride gave 1-acetyl-3-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucosyloxy)indole (**185**). Complete deacetylation of **185** with methanolic ammonia produced indican (**186**), identical in all respects with the natural product.[236] Similarly, 6-bromoindican was prepared starting with methyl 6-bromo-3-hydroxyindole-2-carboxylate.[237]

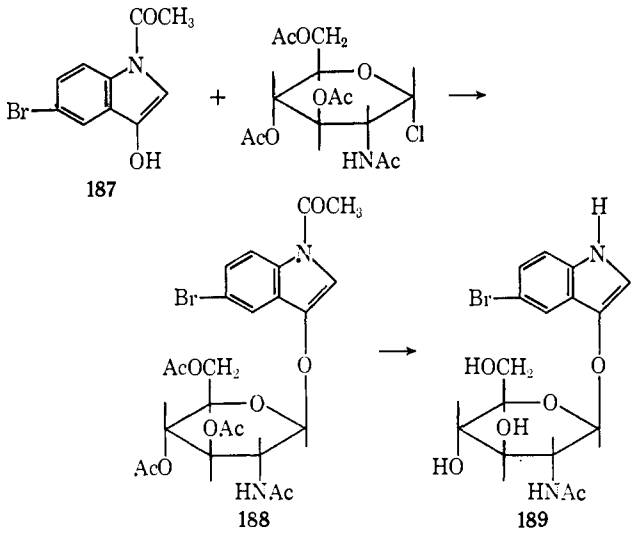
The preparation of 5-bromo-3-(2'-acetamido-2'-deoxy-β-D-glucosyloxy)indole (**189**) has been reported.[238] This was accomplished by the condensation of 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-glucopyranosyl chloride with 1-acetyl-3-hydroxy-5-bromoindole (**187**),[239] affording a 29% yield of



182 183 184 185 186

(227) A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p 128.
(228) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 1.
(229) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds," Interscience Publishers, New York, N. Y., 1954, p 1.
(230) R. M. Acheson, "Chemistry of Heterocyclic Compounds," Interscience Publishers, New York, N. Y.: (a) 1960, p 127; (b) 2nd ed, 1967, p 151.
(231) A. G. Perkin and W. P. Bloxam, *J. Chem. Soc.*, 91, 1715 (1907).
(232) A. G. Perkin and R. Thomas, *ibid.*, 95, 793 (1909).
(233) F. Thomas, W. P. Bloxam, and A. G. Perkin, *ibid.*, 95, 824 (1909).
(234) A. K. Macbeth and J. Pryde, *ibid.*, 121, 1660 (1922).
(235) A. Robertson, *ibid.*, 1937 (1927).
(236) A. Robertson and R. B. Waters, *ibid.*, 30 (1933).
(237) A. Robertson and R. B. Waters, *ibid.*, 72 (1931).
(238) F. B. Anderson and D. H. Leaback, *Tetrahedron*, 12, 236 (1961).
(239) S. J. Holt, A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 1217 (1958).

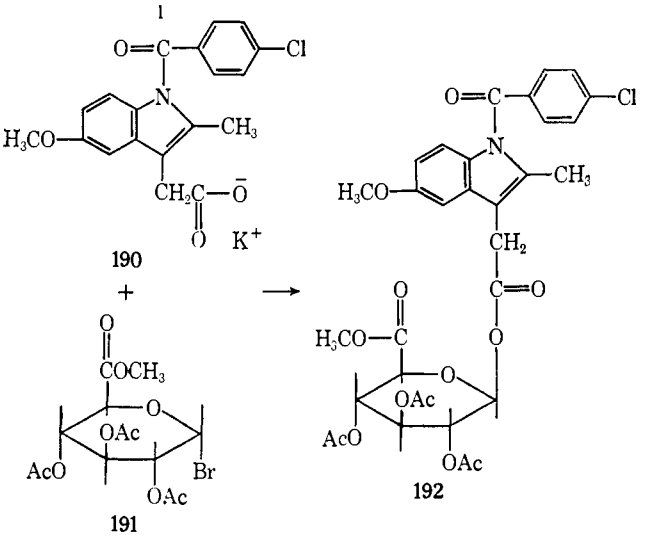
5-bromo-1-acetyl-3-(2′-acetamido-2′-deoxy-3′,4′,6′-tri-*O*-acetyl-β-D-glucosyloxy)indole (**188**). Deacetylation of **188** with sodium methoxide in methanol gave **189**. In a like manner, the



corresponding β-D-galactoside was prepared,[240] but attempts to prepare the β-D-glucuronide from acetobromo-[241] or acetoiodo-[242] methylglucuronate under a variety of conditions were unsuccessful. Attempts to prepare 3-β-D-glucuronidoxy-5-bromoindole by catalytic oxidation of the corresponding β-D-glucoside were also unsuccessful. An extension of the above method for the preparation of some dihalogeno-3-indolyl-β-D-glycosides has been published.[243-245]

The acyl glucuronide (**192**) of indomethacin (**190**, 1-*p*-chlorobenzoyl-5-methoxy-2-methyl-3-indolylacetic acid), which is rapidly excreted in the urine by man,[246] was synthesized[247] by condensing the potassium salt of **190** with methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (**191**)[248] in acetone. Similarly, the condensation of methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate with 3-indoleacetic acid or 5-benzyloxy-3-indoleacetic acid in dichloromethane furnished the corresponding 1-*O*-acyl-D-glucopyranuronates[249] similar in structure to **192**.

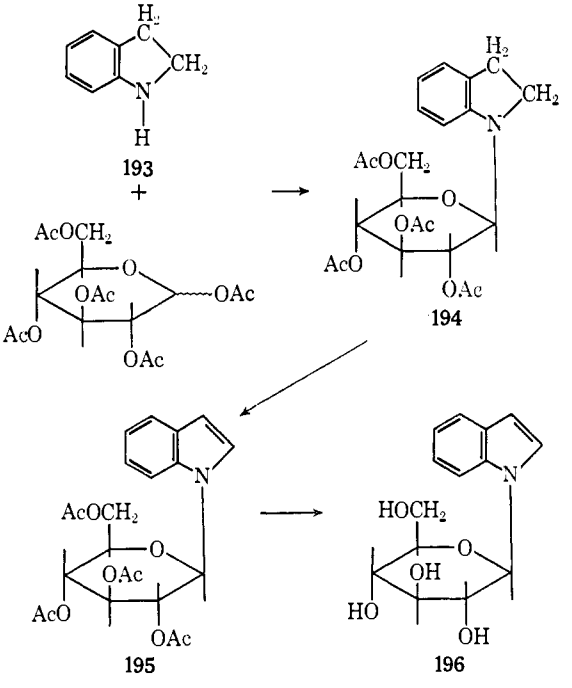
It is of interest that treatment of indolylmagnesium bromide with a poly-*O*-acetylglycosyl chloride gives 3-glycosylindoles.[250] Thus, treatment of indolylmagnesium bromide with tetra-*O*-acetylglucopyranosyl chloride in ether at reflux temperature, followed by decomposition of the Mg-organic complex with water and acetic acid, furnished 3-glucopyranosyl-



indole. Acetylation with acetic anhydride in pyridine afforded the crystalline 3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)indole. Similarly the corresponding galactopyranosyl and xylopyranosyl derivatives have been prepared.[250] These indole glycosides were reported to be C-C derivatives and not N-glycosides which was confirmed by the presence of active H and $KMnO_4$ oxidation studies.

2. *Indoles Containing a Carbohydrate Moiety at Position 1*

Indoles containing a glycosyl residue at N-1 were prepared for the first time by the "indoline-indole" method.[251] Treatment of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose with 2 mol of indoline (**193**) in ethanol containing glacial acetic acid fur-

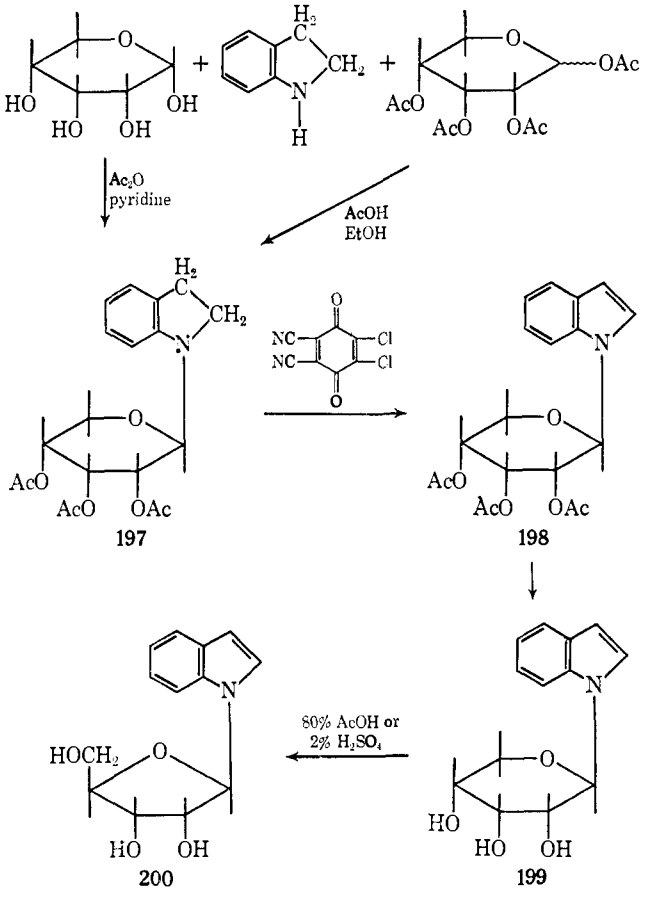


nished 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)indoline (**194**), 77.5% yield. **194** was also prepared in 57% yield

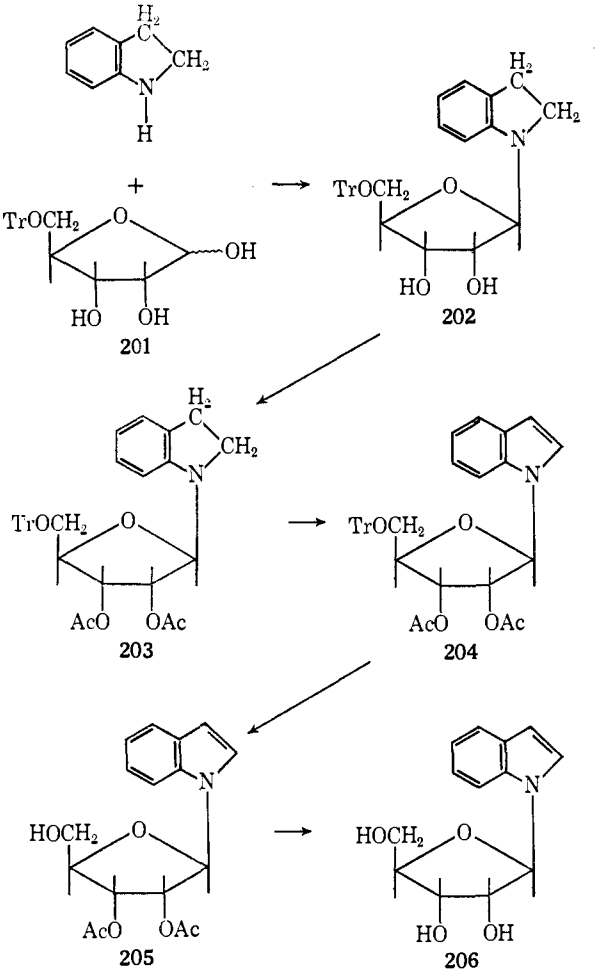
(240) B. Pearson, M. Andrews and F. Grose, *Proc. Soc. Exptl. Biol. Med.*, 108, 619 (1961).
(241) G. N. Bollenback, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *J. Amer. Chem. Soc.*, 77, 3310 (1955).
(242) F. B. Anderson and D. H. Leaback, *Chem. Ind.* (London), 967 (1960).
(243) J. P. Horwitz, J. Chua, R. J. Curby, A. J. Tomson, M. A. DaRooge, B. E. Fisher, J. Maurieio, and I. Klundt, *J. Med. Chem.*, 7, 574 (1964).
(244) P. L. Wolf, J. P. Horwitz, J. Vazquez, J. Chua, and M. A. DaRooge, *Amer. J. Clin. Pathol.*, 44, 307 (1965).
(245) B. Pearson, P. L. Wolf, and J. Vazquez, *Lab. Invest.*, 12, 1249 (1963).
(246) M. M. Airaksinen, T. A. Miettinen, and J. Huttunen, *Biochem. Pharmacol.*, 14, 1019 (1965).
(247) R. G. Strachan, M. A. P. Meisinger, W. V. Ruyle, R. Hirschmann, and T. Y. Shen, *J. Med. Chem.*, 7, 799 (1964).
(248) W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, 111, 347 (1935).
(249) N. Pravdie' and D. Keglević, *J. Chem. Soc.*, 4633 (1964).
(250) Yu. A. Zhdanov, G. N. Dorofeenko, and N. V. Ivanchenko, *Chem. Abstr.*, 55, 2607 (1961).
(251) N. N. Suvorov and M. N. Preobrazhenskaya, *Zh. Obshch. Khim.*, 30, 2434 (1960); *Chem. Abstr.*, 55, 8383 (1961).

from α-acetobromoglucose and indoline in boiling benzene. The intermediate **194** was then oxidized with chloranil in dry boiling xylene to afford 1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)indole (**195**) which was subsequently deacetylated with sodium methoxide in methanol to furnish 1-β-D-glucopyranosylindole (**196**). The assignment of β-anomeric configuration to **196** was made[252] on the basis of the *trans* rule, the thermodynamic preference for the equatorial rather than axial conformation of the indoline moiety which would provide the β configuration, and the magnitude of the specific rotation observed for the product. Indoline was also treated with tetra-*O*-benzyl-D-glucopyranosyl bromide in ether to give a 78% yield of 1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)indoline. Oxidation of this product with 2,3-dichloro-5,6-dicyanobenzoquinone in boiling xylene gave a quantitative yield of 1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)indole.[253] Debenzylation was effected with Raney nickel in ethanol to afford 1-(β-D-glucopyranosyl)indole.

The versatility of this synthetic "indoline–indole" route for the preparation of indole nucleosides has been demonstrated[254,255] by the successful synthesis of 1-(β-D-ribopyranosyl)indole (**199**). The reaction of D-ribopyranose with indoline in pyridine containing acetic anhydride was found to afford 1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)indoline (**197**). The same nucleoside (**197**) was also obtained by the condensation



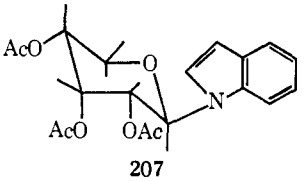
of indoline with tetra-*O*-acetyl-D-ribopyranose in ethanol containing acetic acid.[256] Oxidation of **197** with 2,3-dichloro-5,6-dicyanobenzoquinone furnished 1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)indole (**198**) which on deacetylation gave **199**. The action of boiling 80% acetic acid or 2% sulfuric acid on **199** produced a 6.6% yield of 1-(β-D-ribofuranosyl)indole (**200**).[255] This formation of **200** has been postulated to occur by protonization of the ring oxygen followed by a shift of the positive charge from the oxygen atom to C-1 with a simultaneous ring opening. The subsequent ring closure then results in the formation of both ring structures, furanose and pyranose.[255] The preparation of 1-(β-D-ribofuranosyl)indole (**200**) by an alternate method has been accomplished[257] using the following sequence of reactions. Treatment of 5-*O*-trityl-D-ribose (**201**) with indoline in boiling ethanol produced crystalline 1-(5′-*O*-trityl-β-D-ribofuranosyl)indoline (**202**) which on acetylation with acetic anhydride in pyridine gave 1-(2′,3′-di-*O*-acetyl-5′-*O*-trityl-β-D-ribofuranosyl)indoline (**203**). Dehydrogenation of **203** was accomplished with di-



chlorodicyanobenzoquinone in xylene to give 1-(2′,3′-di-*O*-acetyl-5′-*O*-trityl-β-D-ribofuranosyl)indole (**204**). The trityl group of **204** was removed by 80% acetic acid to furnish 1-(2′,3′-di-*O*-acetyl-β-D-ribofuranosyl)indole (**205**) which was isolated by column chromatography on silicic acid. Deblocking of **205** was accomplished by the Zemplen method in the

(252) N. N. Suvorov and M. N. Preobrazhenskaya, *Zh. Obshch. Khim.*, **31**, 2839 (1961); *Chem. Abstr.*, **56**, 14386 (1962).
(253) M. N. Preobrazhenskaya and N. N. Suvorov, *Zh. Obshch. Khim.*, **35**, 893 (1965); *Chem. Abstr.*, **63**, 14953 (1965).
(254) M. N. Preobrazhenskaya, M. M. Vigdorchik, and N. N. Suvorov, *Chem. Abstr.*, **64**, 790 (1966).
(255) M. N. Preobrazhenskaya, M. M. Vigdorchik, and N. N. Suvorov, *Khim. Prir. Soedin.*, **4**, 128 (1968); *Chem. Abstr.*, **69**, 6330 (1968).
(256) E. Walton, F. W. Holly, and S. R. Jenkins, *J. Org. Chem.*, **33**, 192 (1968).
(257) M. N. Preobrazhenskaya, M. M. Vigdorchik, and N. N. Suvorov, *Tetrahedron*, **23**, 4653 (1967).

presence of barium methylate. However, during the removal of the trityl group of **204**, a small amount of β-pyranoside and presumably either one or two of the α anomers were formed.[157] These minor nucleosides were removed by column chromatography to furnish pure **206**. The oxidation of **206** in accordance with the Malaprade method confirmed the furanose structure which was further substantiated by ir and pmr spectral studies.[258] A recent study[259] on the conformation and configuration of several indole nucleosides has established that the majority of the pyranosides studied exist in the C-1 conformation [*e.g.*, 1-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)indole, **207**]. This is the same conformation previously reported[260] for certain ribopyranosylpurines. The assignment of



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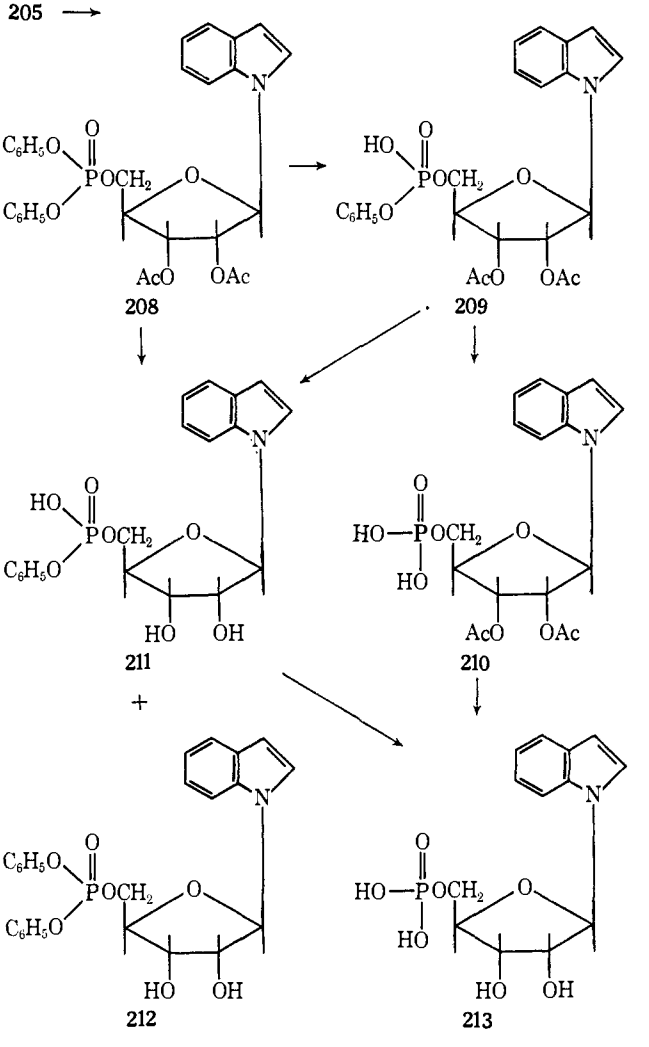
anomeric configuration for pyranosides can be ascertained with very little difficulty by pmr spectroscopy.

Phosphorylation of **205** with diphenylphosphoryl chloride in pyridine at 37–40° gave a 47% yield of the 5′-diphenylphosphate derivative (**208**).[261] Hydrogenation of **208** with Adams platinum oxide catalyst removed only one phenyl group to give the monophenyl ester (**209**). The structure of **209** was confirmed by pmr and electrophoresis studies. Treatment of **208** with basic agents (CH_3OH–NH_3, CH_3OH–NaOH, CH_3OH–$NaOCH_3$) furnished a mixture of the 5′-monophenylphosphate and 5′-diphenylphosphate derivatives of 1-(β-D-ribofuranosyl)indole (**211** and **212**, respectively). **211** was also obtained by alkali hydrolysis of **209**. Incubation of **209** with snake venom or phosphodiesterase in the presence of Mg^+ at 37° and a pH of 9.2 furnished 1-(2′,3′-di-*O*-acetyl-β-D-ribofuranosyl)indole 5′-phosphate (**210**). Treatment of **210** with methanolic ammonia gave 1-(β-D-ribofuranosyl)indole 5′-phosphate (**213**).[261]

The reaction of indoline with 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose furnished the corresponding acetylated indolines.[256] These indolines were then oxidized to the corresponding indoles with 2,3-dichloro-5,6-dicyanobenzoquinone. Application of essentially the same reaction scheme with 4-benzamidoindoline and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose afforded 4-amino-1-(β-D-ribofuranosyl)indole, the 1,3,7-trideaza analog of adenosine. Through a combination of pmr studies, periodate oxidation, and ORD determination, the β-anomeric configuration has been assigned to all these nucleosides.



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VI. Appendix

In this section the following tables are included: (I) Physical Properties of Some 1- and 2-Polyhydroxyalkylbenzimidazoles; (II) Method of Preparation and Physical Properties of Certain 1-Glycosylbenzimidazoles; (III) Physical Properties of Certain Glycosylbenzotriazoles, (IV) Physical Properties of Certain Glycosylindazoles, (V) Physical Properties of 3-Glycosylindoles, and (VI) Physical Properties of 1-Glycosylindoles and 1-Glycosylindolines.

(258) T. Hashisume and H. Iwamura, *Tetrahedron Lett.*, 643 (1966).
(259) M. N. Preobrazhenskaya, M. M. Vigdorchik, N. P. Kostychenko, and F. N. Sheenker, *Dokl. Akad. Nauk. SSSR*, 185, 617 (1969).
(260) Y. H. Pan, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, 4, 246 (1967).
(261) M. M. Vigdorchik, M. N. Preobrazhenskaya, and N. N. Suvorov, *Tetrahedron Lett.*, 4645 (1968).

Table I

Physical Properties of Some 1- and 2-Polyhydroxyalkylbenzimidazoles

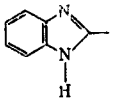
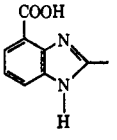
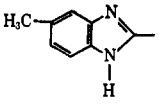
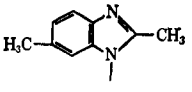
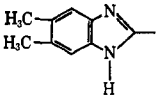
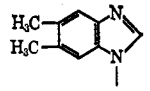
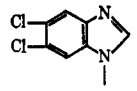
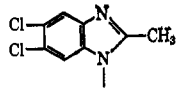
Benzimidazole moiety	*Sugar moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent[a])*	*Ref*
	D-*arabino*-1,2,3,4-Tetrahydroxybutyl	240–241	Water	−49.5 (a)	22, 56, 59, 60
	L-*arabino*-1,2,3,4-Tetrahydroxybutyl	235 dec	Water	+49.8 (a)	22, 29, 41, 55, 56
	D-*lyxo*-1,2,3,4-Tetrahydroxybutyl	189	Water	−12.8 (b)	22
	D-*ribo*-1,2,3,4-Tetrahydroxybutyl	190 dec	Water	+22.5 (a)	47, 56, 59, 60
	D-*ribo*-2,3,4-Trihydroxypentyl	207–209	Water	−45.7 (a)	60
	D-*xylo*-1,2,3,4-Tetrahydroxybutyl	141–143	Butanol	+20.0 (a)	45, 53
	L-*galacto*-1,2,3,4-Tetrahydroxypentyl	248–249	Water	−41.2 (a)	60
	D-*gluco*-1,2,3,4-Tetrahydroxypentyl	190 dec	Ethanol	+9.5 (b)	22, 56
	L-*manno*-1,2,3,4-Tetrahydroxypentyl	210 dec	Ethanol	+29.1 (a)	22, 40
	D-*altro*-1,2,3,4,5-Pentahydroxypentyl	198 dec	Ethanol	−48.1 (a)	40
	D-*galacto*-1,2,3,4,5-Pentahydroxypentyl	246 dec	Ethanol	+45.1 (a)	22, 40, 41, 56
	L-*galacto*-1,2,3,4,5-Pentahydroxypentyl	250 dec	Water	−45.0 (a)	56
	D-*gluco*-1,2,3,4,5-Pentahydroxypentyl	210 dec	Ethanol	+8.9 (a)	22, 25, 40, 56
	L-*gluco*-1,2,3,4,5-Pentahydroxypentyl	215 dec	Water	−9.0 (a)	55, 56
	D-*manno*-1,2,3,4,5-Pentahydroxypentyl	224 dec	Ethanol	−23.7 (a)	22, 40
	1-Methoxy-D-*galacto*	58–62	Ethanol–water	+4.5 (c)	164
	L-*arabino*-1,2,3,4-Tetrahydroxybutyl	235 dec	Water		41
	D-*gluco*-1,2,3,4,5-Pentahydroxypentyl	243	Methanol		25, 43
	L-*arabino*-1,2,3,4-Tetrahydroxybutyl	238	Water		41
	D-*gluco*-1,2,3,4,5-Pentahydroxypentyl	212–214 dec	Water	+9.2 (a)	25
	D-Sorbityl	226	Water	−46.4 ± 5 (e)	99
	L-Arabityl	235–236	Water	−56.3 ± 2 (e)	99
	D-*ribo*-1,2,3,4-Tetrahydroxybutyl	231–233	Methanol		67

Table I (Continued)

Benzimidazole moiety	*Sugar moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent[a])*	*Ref*
	D-Ribityl	210–212	Ethanol–water		20, 88, 103
	D-Arabityl	204–206	Ethanol–water		103
	L-Arabityl	191	Ethanol–water		94
	D-Ribityl	187	Ethanol–water		94
	D-Sorbityl	206–207	Acetic acid–water		94, 103
	D-Xylityl	245–250	Acetic acid–ether		103
	L-Arabityl	247	Ethanol–water		94
	D-Ribityl	207	Ethanol–water		94
	D-Sorbityl	225	Ethanol–water		94

[a] Solvents used in the determination of optical rotations appear as letters in parentheses: (a) 1 *N* hydrochloric acid, (b) 5% citric acid, (c) pyridine, (d) methanol, and (e) water.

Table II

Method of Preparation and Physical Properties of Certain 1-Glycosylbenzimidazoles

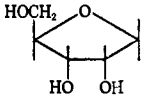
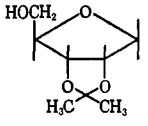
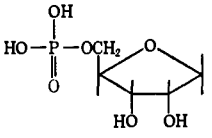
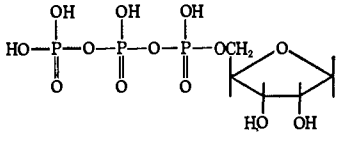
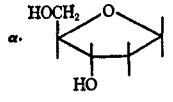
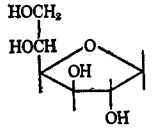
Benzimidazole moiety[a]	*Glycosyl moiety[b]*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra[c]*	*Method of prepn[d]*	*Ref*
		111–112	Ethanol–water	+16.0 (0.1 *N* HCl)	Uv, nmr	III, VI	121, 172
		136				III	124
					Uv	III	125
						III	124
	 α-Configuration	181–182	Ethanol–ethyl acetate	+106.5 (methanol)	Uv, nmr	V	155
	β-Configuration	154.5	Ethanol–ethyl acetate	−30.5 (methanol)	Uv, nmr	V	155
		158–159	Water	−70.9 (pyridine)		VI	162
	Picrate	179–183	Ethanol	−42.1 (pyridine)		VI	162

Table II (Continued)

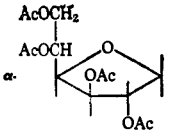
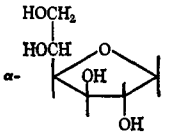
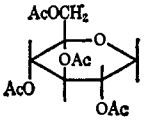
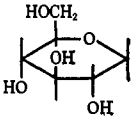
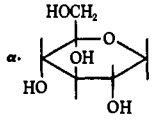
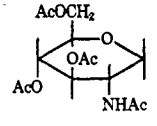
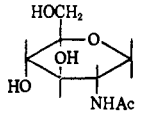
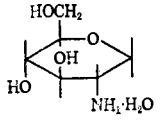
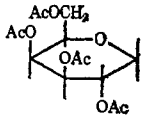
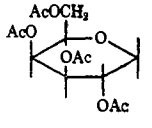
Benzimidazole moiety[a]	Glycosyl moiety[b]	Mp, °C	Recrystn solvent	[α]D, deg (solvent)	Spectra[c]	Method of prepn[d]	Ref
		246–250	Chloroform	+7.5 (pyridine)		VI	162
		172–173	Water	−41.4 (pyridine)		VI	162
	Picrate·H_2O	92–94	Water	−23.3 (pyridine)		VI	162
		156–157	Ethanol	−27.9 (chloroform)		II, VI	90, 106, 161
	Monohydrate	141–142	Water	+19.0 (water)		I, III	20, 121
	Picrate	170–171	Ethanol			I	90
		210–212	Ethanol–benzene	−28.0 (water)		I, II, IV, VI	90, 95, 106, 112 150, 161
	Picrate	145–148	Water	−18.0 (water)		I, II	90, 112
	Hydrochloride	196	Water–acetone	+17.3 (water)		I	90, 95
		178–179	Ethanol	+170.0 (pyridine)		II, VI	112, 161
	Hydrochloride	185–187		+207.2 (water)		VI	161
		160–162	Ethanol–water	−38.1 (chloroform)		VI	163
		236–240	Ethanol–water	−28.4 (pyridine)		VI	163
		136–139	Methanol	−12.1 (pyridine)		VI	163
				−13.4 (chloroform)		III, VI	91, 161
				−17.6 (chloroform)		III	91

Table II (Continued)

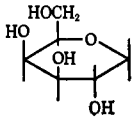
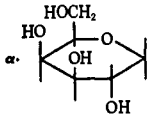
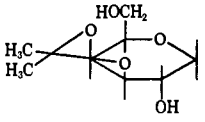
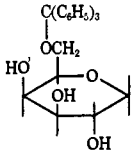
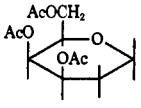
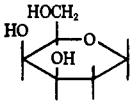
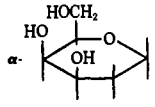
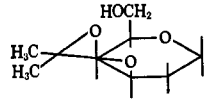
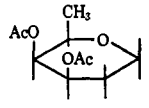
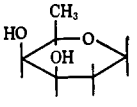
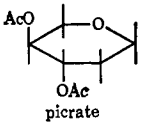
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp*, °C	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		265–267	Water	−31.5 (pyridine)		III, VI	91, 161
	Picrate	169–170	Water	−15.3 (pyridine)		III	91
		230	Isopropyl alcohol	+117.7 (pyridine)		VI	161
	Hydrate	130–136	Water	+115.0 (water)		VI	161
		240–241 dec	Ethanol–water	+43.8 (pyridine)		III	91
		234	Methanol	−15.8 (methanol)		III	91
	 picrate	158				III	91
		214	Water	−18.9 (pyridine)		III	91
	Picrate	160	Water	−9.07 (pyridine)		III	91
		199–200		+21.6 (pyridine)		III	91, 116
		218–219 dec	Ethanol–water	−11.5 (pyridine)		III	91
		206–207	Ethanol–pet. ether	+201.7 (chloroform)		III	91
	Picrate	168	Water	+107.8 (pyridine)		III	91
		185–186	Water	−52.4 (pyridine)		III	91
	Picrate	161–162 dec	Water			III	91
	 picrate	167–168	Ethanol	−8.6 (pyridine)		I	88

Table II (Continued)

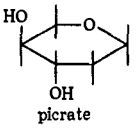
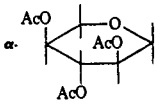
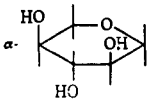
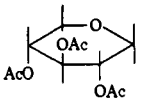
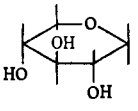
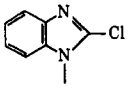
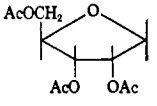
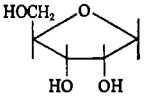
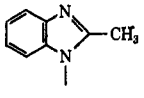
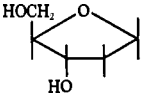
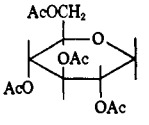
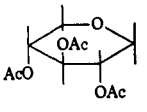
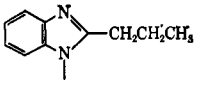
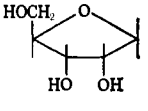
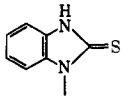
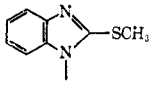
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
	 picrate	170	Ethanol	−14.8 (pyridine)		I	88
	Hydrochloride	150	Ethanol	−34.5 (water)		I	88
		165	Benzene–pet. ether	−3.7 (chloroform)		I, VI	96, 161
	Picrate	182–185	Ethanol			I	96
		226	Ethanol–pet. ether	−63.5 (pyridine)		I, VI	96, 161
	β-Configuration	231	Water	−57.4 (pyridine)		VI	161
		163	Chloroform–pet. ether	−44.8 (chloroform)		I	95, 96
		237–238	Ethanol–benzene	−89.1 (pyridine)		I	95, 96
	Hydrochloride	148–150	Acetone–water	−25.4 (water)		I	95, 96
		117–118	Methanol–pet. ether	−54.4 (ethanol)	Uv, nmr	VI	172
		173	Ethanol–water	−94.5 (ethanol)	Uv, nmr	VI	172
		206–207	Ethanol	+34.3 (methanol)	Uv, nmr	V	155
		202	Ethanol–pet. ether	−30.2 (chloroform)		I	94
		228	Ethanol–water	−76.3 (chloroform)		I	94
		63.5–64.5			Uv	I	136
		120	Ethanol–water	−35.4 (ethanol)	Uv, ir, nmr	VI	172
		99–100	Water	−36.6 (ethanol)	Uv, nmr	VI	172

Table II (Continued)

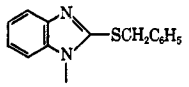
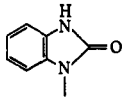
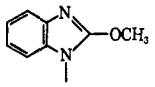
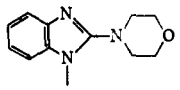
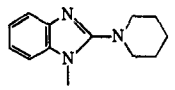
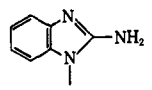
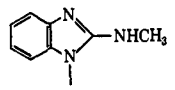
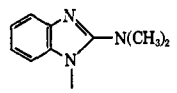
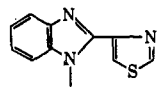
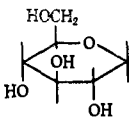
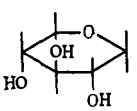
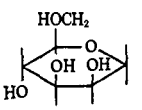
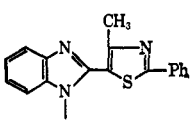
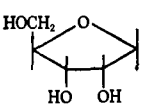
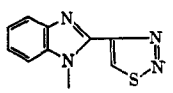
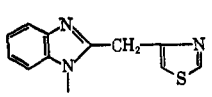
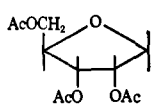
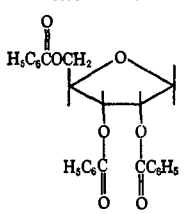
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		132	Ethyl acetate–pet. ether	−102.9 (ethanol)	Uv, nmr	VI	172
		120 (foaming)	Methanol–acetone		Uv, ir, nmr	VI	172
		200	Acetone–water	−56.8 (ethanol)	Uv	VI	172
		230	Ethanol–water	−8.1 (ethanol)	Uv	VI	172
		226	Ethanol–water	−26.1 (ethanol)	Uv	VI	172
		>120	Water		Uv	VI	172
		130–132	Methanol		Uv	VI	172
		130 dec	Methanol–acetone	−44.1 (methanol)	Uv	VI	172
						III	118
						III	118
						III	118
						III	118
						III	118
						III	118
						II	119
						II	119

Table II (Continued)

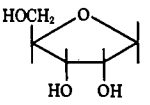
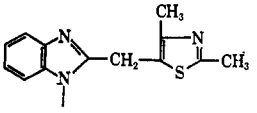
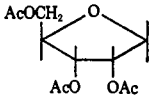
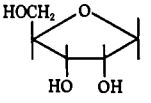
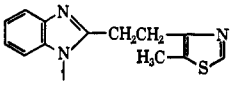
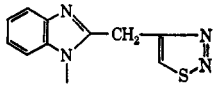
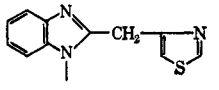
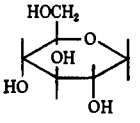
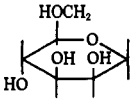
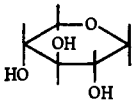
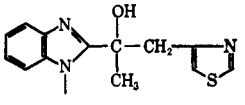
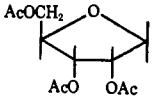
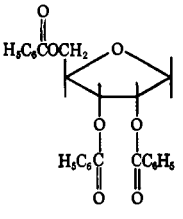
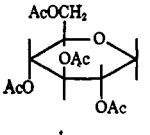
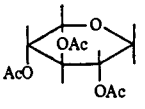
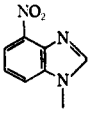
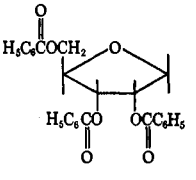
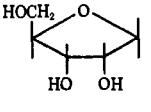
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
						II	119
						II	119
						II	119
						II	119
						II	119
						II	119
						II	119
						II	119
						II	120
						II	120
						II	120
						II	120
		124–125	Ether	−94.3 (chloroform)	Uv	III	139
		192–194	Water	−2.8 (1 *N* HCl)	Uv	III	139

Table II (Continued)

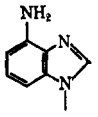
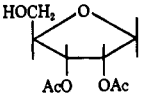
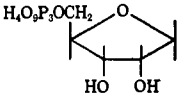
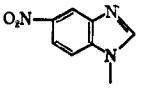
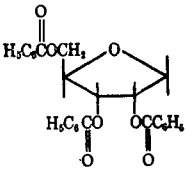
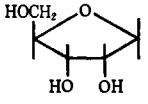
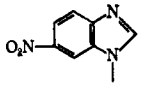
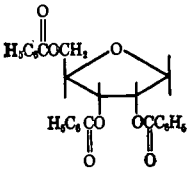
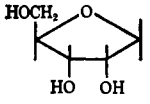
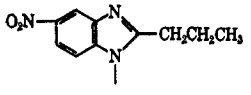
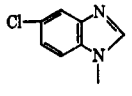
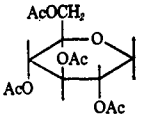
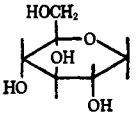
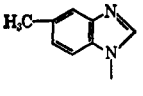
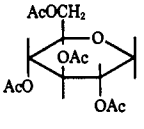
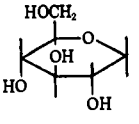
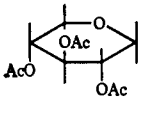
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		137–138	Water	−49.0 (water)	Uv, nmr, ORD	III	145, 146
							145
							145
		139–140	Methanol–chloroform	−83.4 (chloroform)	Uv	III	139
		169–170	Water	+13.9 (1*N* HCl)	Uv	III	139
		137–138	Ether–hexane	−56.0 (chloroform)	Uv	III	139
		200–201	Water	+27.7 (1*N* HCl)	Uv	III	139
		160–161			Uv		136
		156	Ethyl acetate–pet. ether	−39.0 (chloroform)		I	94
	Picrate	173	Ethanol			I	94
		247	Ethanol–water	−24.6 (pyridine)		I	94
		175	Chloroform–pet. ether	−37.8 (chloroform)		I	90, 95
		275–276 dec	Ethanol	−33.6 (pyridine)		I	90, 95
		183	Chloroform–pet. ether	−67.0 (chloroform)		I	95, 96

Table II (Continued)

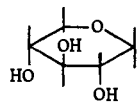
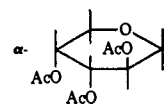
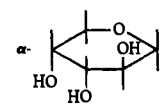
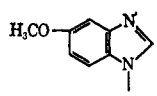
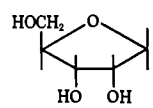
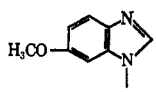
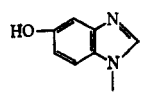
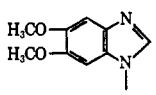
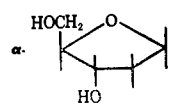
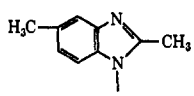
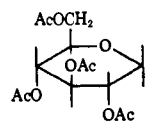
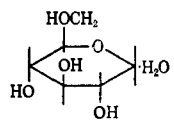
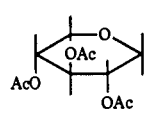
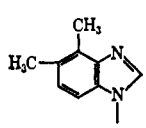
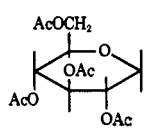
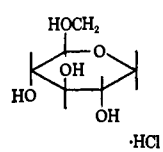
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		215–216	Ethanol	−50.7 (water)		I	95, 96
		181–183	Ethyl acetate–pet. ether	−15.7 (pyridine)		I, II	96, 107
		229	Ethanol–pet. ether	+14.8 (pyridine)		I	96
		162–164		−33.0		III	130
	Picrate	144–146				III	130
		Gum		−36.0		III	130
	Picrate	78–82				III	130
				−59.0	Uv	III	130
	α-Configuration			−11.0	Uv	III	130
		190–191	Methanol–ethyl acetate	+109.6 (methanol)	Uv, nmr	V	155
		220	Ethanol	−43.4 (chloroform)		I	94
		236 dec	Acetone–water	+20.0 (water)		I	94
		258	Ethanol	−93.9 (chloroform)		I	94
		177.5–178.5	Ethyl acetate–pet. ether	−35.7 (pyridine)		I, II	90, 107
	Picrate	148–150 dec	Ethanol			I, II	90, 107
		216–217 dec	Ethanol–water	+11.5 (water)		I	90
	Picrate	202–204	Water			I	90

Table II (Continued)

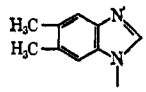
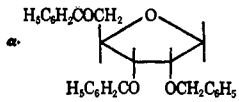
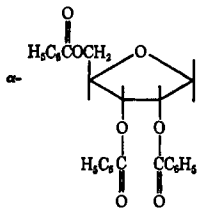
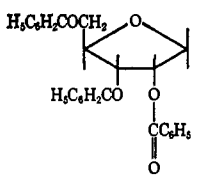
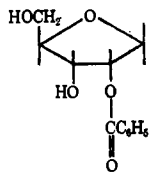
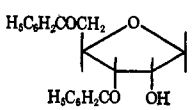
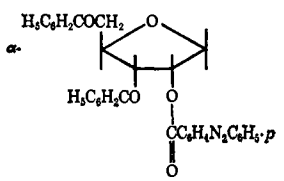
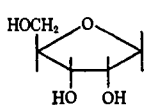
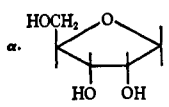
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
	 α-			+56.7 (chloroform)	Nmr	IV	152
	 α-			−53.8 (chloroform)	Nmr	IV	152
	β-Configuration	136–137	Ethanol	−121.0 (chloroform)	Nmr	IV	152
	Picrate	160–161	Ethanol–ethyl acetate	−85.8 (chloroform)		IV	152
		165–167	Ethanol–ethyl acetate	−8.9 (dichloromethane)		IV	153
		228–230	Ethyl acetate	−76.4 (methanol)		IV	153
		142–143		−5.4 (dichloromethane)		IV	153
	 α-	113–114	Ethanol–pentane	−164.0 (dichloromethane)	Nmr	IV	153
	β-Configuration	103–106	Ether–pentane	−93.5 (dichloromethane)	Nmr	IV	153
	Picrate	196–198	Ethanol–chloroform	−47.5 (dichloromethane)		IV	153
		190–192	Water	−44.0 (pyridine)	Uv, nmr	I, II, III, IV, VI	67, 74, 109, 111, 112, 121, 152, 173
	Picrate	175–177	Water	−24 ± 2 (pyridine)	Uv, nmr	I, II, III	67, 74, 96, 109, 111, 121
	 α-	198–199	Water	+14.0 (pyridine)	Uv, ir, nmr	I, II, IV	67, 74, 97, 112, 152

Table II (Continued)

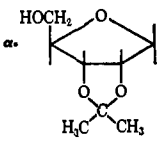
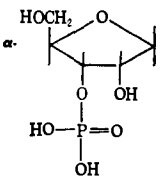
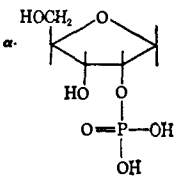
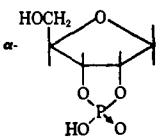
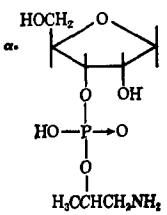
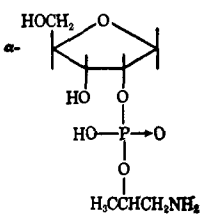
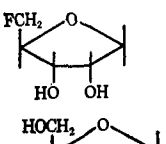
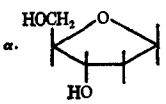
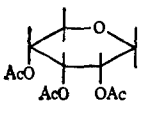
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp*, °C	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
	Picrate	218–220	Ethanol	+9.1 ± 1 (pyridine)	Uv, nmr	I, II, IV	67, 74, 92, 96, 97, 112, 152
		180–180.5	Acetone	−76.0 (chloroform)	Nmr	I, III, IV	67, 126, 152
	β-Configuration	191–192	Acetone	−28.0 (chloroform)	Nmr	I, III, IV	67, 126, 152
		240–241	Acetone–water		Uv, ir	I	75, 76, 117
		226–228 dec	Acetone–water		Uv, ir		117
	Dibrucine salt	169–175	Water			I	75, 76
					Uv		179
					Uv		179
					Uv		179
		175–176	Ethyl acetate–acetone	−43.3 (methanol)	Uv	III	137
		225–226	Methanol	+109.6 (methanol)	Uv, nmr	V	155
	β-Configuration	158–160	Ethyl acetate–ethanol	−32.2 (methanol)	Uv, nmr	V	155
		155	Chloroform–pet. ether	−40.4 (chloroform)		I, II	88, 107

Table II (Continued)

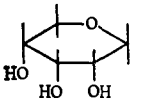
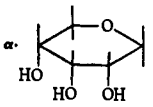
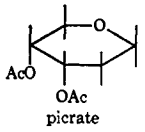
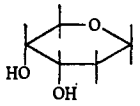
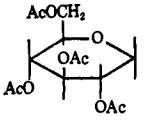
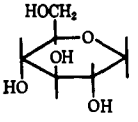
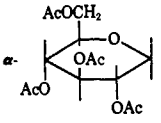
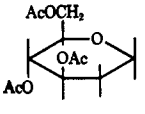
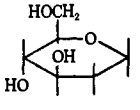
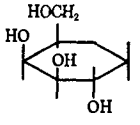
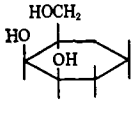
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp,* °C	*Recrystn solvent*	[α]D, *deg (solvent)*	*Method Spectra*[c]	*of prepn*[d]	*Ref*
	Picrate	186	Ethanol			I, II	88, 107
		250–251 dec	Ethanol–pet. ether	−75.0 (pyridine)		I, II	88, 109
		185–188	Methanol	−4.4 ± 4		I	67, 74, 88
	 picrate	203	Ethanol–chloroform			I	88
		160	Ethanol–pet. ether	+30.9 (pyridine)		I	88, 92
	Picrate	203	Ethanol	+27 ± 2 (pyridine)		I	88, 92
		189–191	Benzene–pet. ether	−40.4 (chloroform)		I, II	90, 95, 106, 107
		167–168	Ethanol	+7.0 (1 *N* HCl)	Uv	I, II, III	20, 67, 90, 106, 121
	Picrate	235–236	Ethanol–water	−16.0 (pyridine)		I	67, 74, 90
	Sesquihydrate	166–167	Water		Uv	I	20
		176	Water	+171.0 (chloroform)		II	112
	Picrate	205	Ethanol–water	+101.0 (chloroform)		II	112
		125–127	Chloroform–pet. ether	−39.4 (chloroform)		I	88
		250	Methanol–pet. ether			I	88
	Picrate	189 dec	Ethanol	−4.9 (pyridine)		I	88
		269	Ethanol	−29.4 (pyridine)		I	91
		225	Ethanol–water	−32.4 (pyridine)		I	91

Table II (Continued)

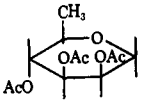
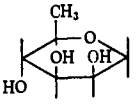
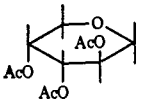
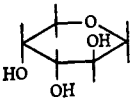
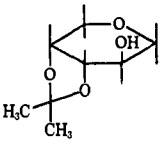
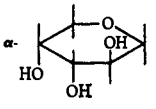
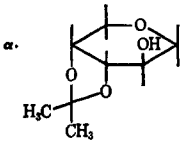
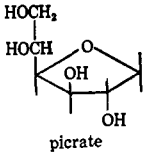
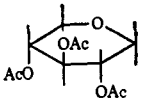
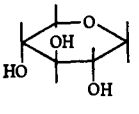
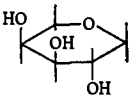
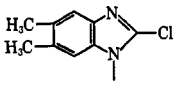
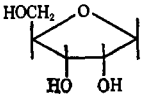
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	$[\alpha]D$, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		92–95	Pet. ether			I	96
	Picrate	184	Ethanol			I	96
		252	Ethanol–pet. ether			I	95, 96
		141–143	Benzene–pet. ether	−31.9 (chloroform)		I, II	96, 107
		280–281	Ethanol–pet. ether	−70.5 (pyridine)		I, II	74, 92, 95, 96, 108
	Picrate	216–217	Ethanol	−27 ± 2 (pyridine)		I	74, 92, 95
		261–262	Isopropyl alcohol–ether–pet. ether	+11.0 ± 2 (pyridine)		I	92
		280–281		+75.0 ± 2 (pyridine)		I	92
		261.5–262.5	Isopropyl alcohol–ether–pet. ether	−11.0 ± 2 (pyridine)		I	92
	 picrate	177–178	Methanol	−48.0 (pyridine)		I, II	92, 97, 108
		199	Pet. ether–pyridine	−51.5 (pyridine)		II	106
		254	Ethanol	−91.0 (pyridine)		II	106
	Picrate	120–122	Water			I	74, 92
		258–258.5	Water	+54.0 ± 3 (pyridine)		I	92
		182	Ethanol–water	−67.90 (ethanol)	Uv, nmr	VI	173

Table II (Continued)

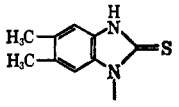
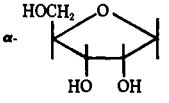
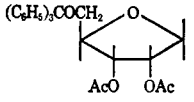
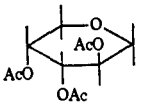
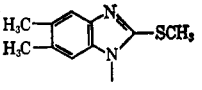
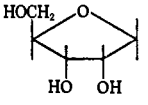
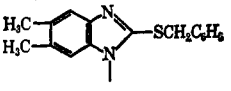
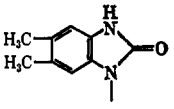
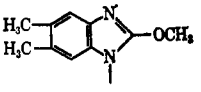
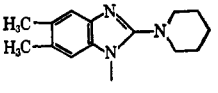
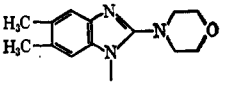
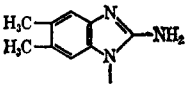
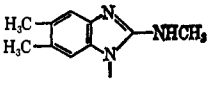
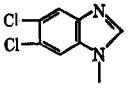
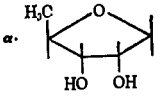
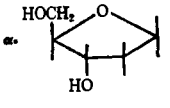
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		241–242	Ethanol–water	−15.06 (ethanol)	Uv, ir, nmr	VI	173
						I	97
						I	97
						I	97
		150	Water	−45.0 (ethanol)	Uv, nmr	VI	173
		208	Ethanol–ethyl acetate	−8.0 (ethanol)	Uv	VI	173
		>210	Methanol	−21.0 (ethanol)	Uv, ir	VI	173
		205	Methanol	−51.1 (ethanol)	Uv	VI	173
		233	Ethanol	−11.8 (ethanol)	Uv	VI	173
		243–244	Ethanol	−22.5 (ethanol)	Uv	VI	173
		135	Methanol	−3.6 (ethanol)	Uv	VI	173
		254–255	Ethanol–water	−2.2 (ethanol)	Uv	VI	173
		215–216	Ethanol	−63.3 (pyridine)	Uv, nmr	III, VI	131, 132, 174
		182–183	Chloroform	+12.1 (ethanol)	Uv	III	131
	β-Configuration	131–132	Ether–dichloromethane	−20.3 (ethanol)	Uv	III	131
		179.5–180	Ethyl acetate	+107.5 (methanol)	Uv, nmr	V	155
	β-Configuration	168–169	Ethyl acetate	−31.0 (methanol)	Uv, nmr	V	155

Table II (Continued)

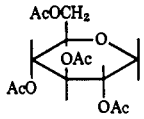
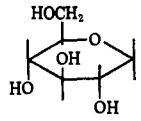
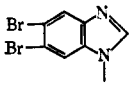
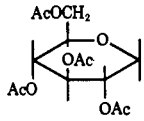
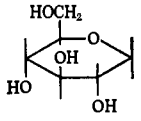
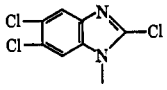
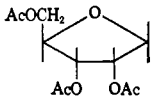
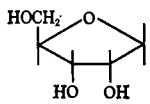
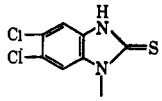
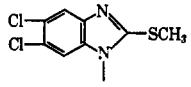
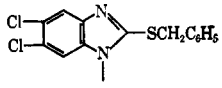
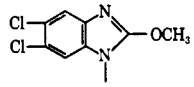
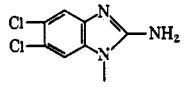
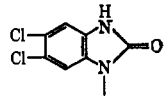
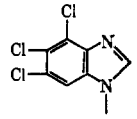
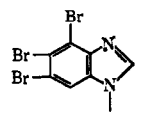
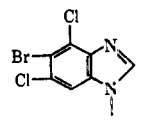
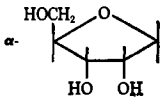
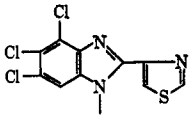
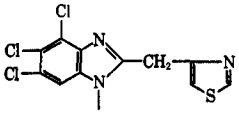
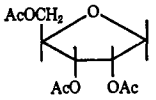
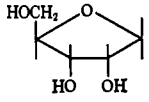
Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
		197–198	Pyridine–pet. ether	−55.7 (pyridine)		II	106
		247	Pyridine–pet. ether	−35.0 (pyridine)		II	106
		195	Ethanol	−49.3 (pyridine)		II	106
		257	Ethanol	−28.0 (pyridine)		II	106
		146–147	Methanol		Uv, nmr	VI	174
		188–189	Ethanol–water	−79.6 (ethanol)	Uv, nmr	VI	174
					Uv, ir, nmr	VI	174
					Uv, nmr	VI	174
					Uv, nmr	VI	174
					Uv	VI	174
					Uv	VI	174
					Uv	VI	174
		230–232	Ethanol–water			III	133, 134
		230–235	Methanol	−57.0 (pyridine)		III	134, 135
		217–219	Ethanol–water	−61.0 ± 2 (pyridine)		III	134, 135

Table II (Continued)

Benzimidazole moiety[a]	*Glycosyl moiety*[b]	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*[c]	*Method of prepn*[d]	*Ref*
	 α-	193–196	Methanol	+34.0 ± 2 (pyridine)		III	135
	β-Configuration					III	118
						II	119
						II	119

[a] The position of glycosidic attachment to the benzimidazole moiety can be easily determined by visual inspection, and all compounds are of the β configuration unless they are specifically designated. [b] The abbreviation -OAc denotes $-OCOCH_3$ and -Bz denotes $-CH_2C_6H_5$. [c] Uv = ultraviolet; ir = infrared; nmr = nuclear magnetic resonance; ORD = optical rotatory dispersion. [d] Key to the method of preparation: I, ring closure of N-glycosyl-*o*-phenylenediamine derivatives; II, condensation of silver salts of preformed benzimidazoles with acylglycosyl halides; III, condensation of halomercury salts of preformed benzimidazoles with acylglycosyl halides; IV, direct alkylation of a preformed benzimidazole with an acylglycosyl halide; V, acid-catalyzed fusion; VI, trimethylsilyl procedure.

Table III

Physical Properties of Certain Glycosylbenzotriazoles

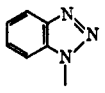
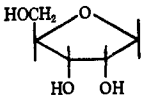
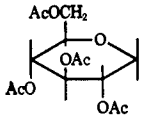
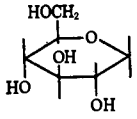
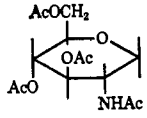
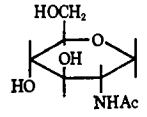
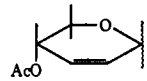
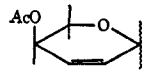
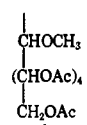
Benzotriazole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*	*Ref*
		135	Ethanol–dichloromethane	−101.0 (ethanol)	Uv, nmr	219
						218
						218
		183–185	Ethanol–water	−66.9 (chloroform)		163
		231–232	Ethanol	−68.6 (pyridine)		163
		144–145	Ethyl acetate–pet. ether	+120.7	Uv, nmr	220
		144–145	Ethyl acetate–pet. ether	−122.4	Uv, nmr	220
	 *galacto*-	62–64	Ethanol–water	−23.7 (chloroform)	Ir	164

Table III (Continued)

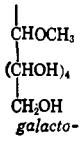
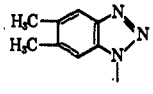
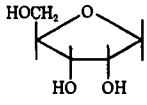
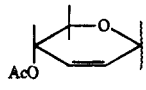
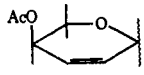
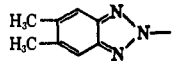
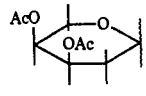
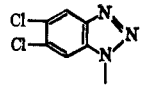
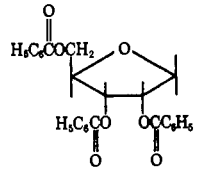
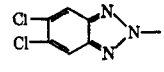
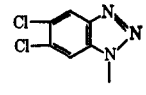
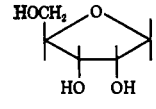
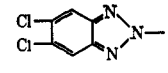
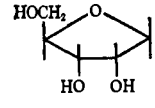
Benzotriazole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*	*Ref*
	 *galacto-*	184–187	Methanol	−22.2 (pyridine)	Ir	164
		180	Ethanol–water	−124.2 (pyridine)	Uv, nmr	219
		147–148	Ethyl acetate–pet. ether	+22.6	Uv, nmr	220
		147–148	Ethyl acetate–pet. ether	−22.4	Uv, nmr	220
		172–173	Ethyl acetate–pet. ether	+87.4	Uv, nmr	220
		233–235	Acetone–water	−104.2 (pyridine)		216
		186–188	Acetone–water	−82.8 (pyridine)		216
	α-Configuration	163–164	Acetone–water	+35.8 (pyridine)		216
	α-Configuration	155–156	Acetone–water	+77.7 (pyridine)		216
		180	Ethanol	−136.4 (pyridine)	Uv, nmr	216, 219
	α-Configuration	166–168	Water	+115.8 (pyridine)		216
		149–151	Water	−89.0 (pyridine)		216
	α-Configuration	112–114	Water	+5.2 (pyridine)		216

Table IV

Physical Properties of Certain Glycosylindazoles

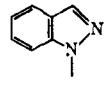
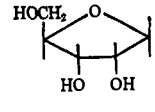
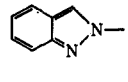
Indazole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*	*Ref*
		205	Ethanol	−9.22 (pyridine)	Uv, nmr	225
		135	Dichloromethane	−92.0 (pyridine)	Uv, nmr	225

Table IV (Continued)

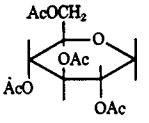
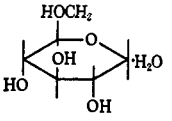
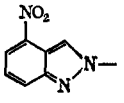
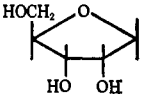
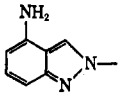
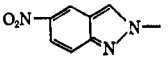
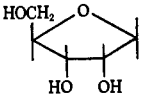
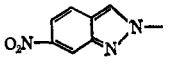
Indazole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*	*Ref*
		164–165	Ethanol	−40.3 (chloroform)		224
		127–130	Water	−32.5 (pyridine)		224
		184	Methanol	−74.0 (pyridine)	Uv, nmr	225
	Hydrochloride		Ether–ethanol		Uv	225
		205–206	Methanol	−114.0 (pyridine)	Uv, nmr	225
		215	Methanol	−71.0 (pyridine)	Uv, nmr	225

Table V

Physical Properties of 3-Glycosylindoles

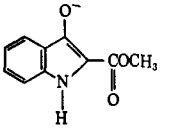
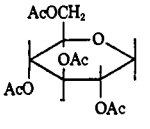
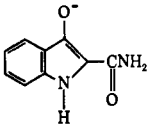
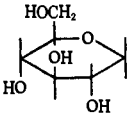
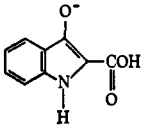
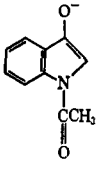
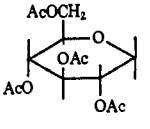
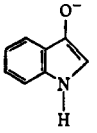
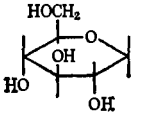
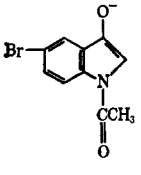
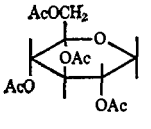
Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg (solvent)*	*Spectra*	*Ref*
		229–230	Methanol			235
		254–256 dec	Water			235
		230–231	Water			235
		148	Ethanol			235
		176–178	Water			235
		157–158	Ethanol	−47.0 (chloroform)		238

Table V (Continued)

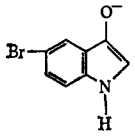
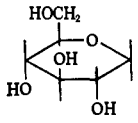
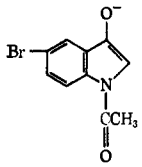
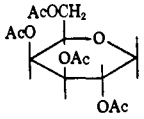
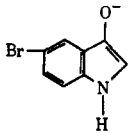
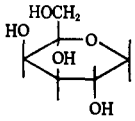
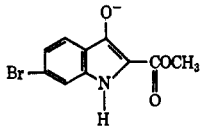
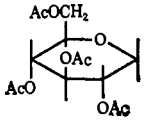
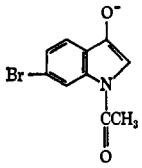
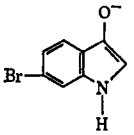
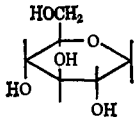
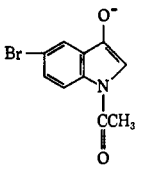
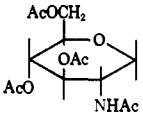
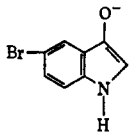
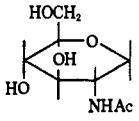
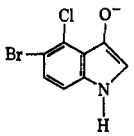
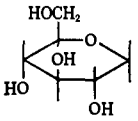
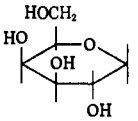
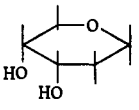
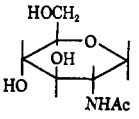
Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*	*Ref*
		259–260	Water	−77.0 (methanol)		238
		175–176	Ethanol	−26.0 (chloroform)		238
		195	Ethanol–chloroform	−70.0 (ethanol)		238
		171	Methanol	−59.7 (acetone)		237
		159	Methanol	−48.8 (acetone)		237
		177	Water	−6.4 (acetone)		237
		245–246	Ethanol	−35.5 (acetone)		238
		246–247	Water	−42.0 (methanol)		238
		240–243 dec	Methanol	−89.0 (DMF)		243
		237–239 dec	Methanol	−69.0 (DMF)		243
		211–212	Ethanol	−106.0 (ethanol)		243
		246–248 dec	Water	−63.0 (DMF)		244

Table V (Continued)

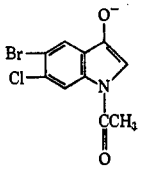
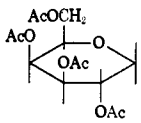
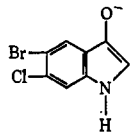
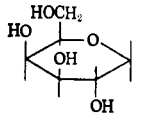
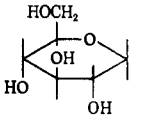
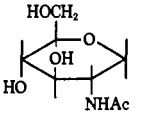
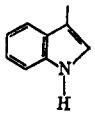
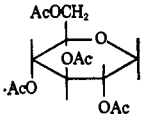
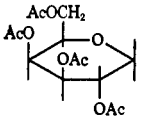
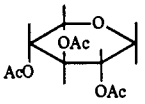
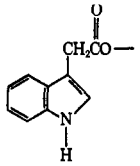
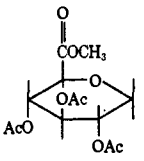
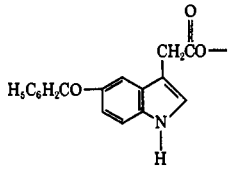
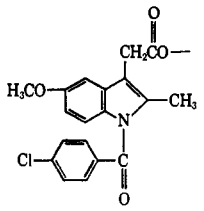
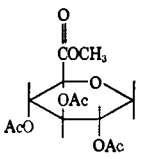
Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*	*Ref*
		178–179	Ethanol	−20.0 (acetone)		243
		180–181	Ether	−41.0 (ethanol)		243
		196–198	Methanol	−60.0 (acetone)		243
		260–262 dec	Water	−51.0 (DMF)		244
		120–122	Ethanol–water			250
		135–140	Ethanol–water			250
		140–145	Ethanol–water			250
		104–108	Ether–pet. ether	−19.0		249
		152–153	Ethanol	−32.0		249
		151–152	Ether–hexane		Uv, ir	247

Table VI

Physical Properties of 1-Glycosylindoles and 1-Glycosylindolines

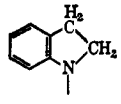
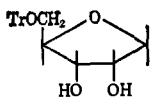
Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*	*Ref*
		132–135	Ethanol	−28.3 (chloroform)		257

Table VI (Continued)

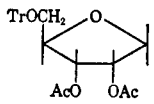
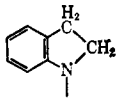
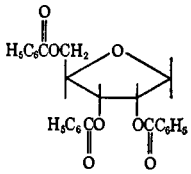
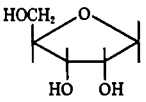
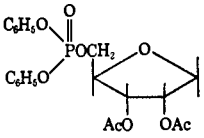
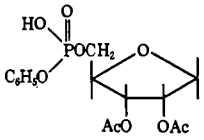
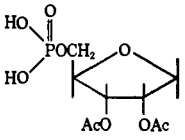
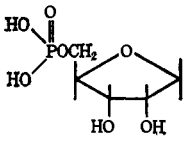
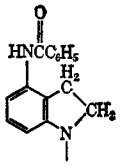
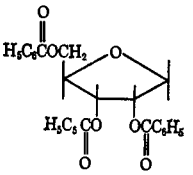
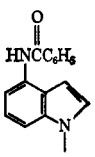
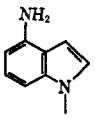
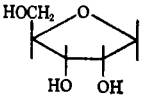
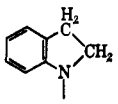
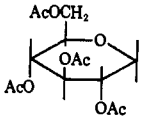
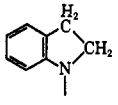
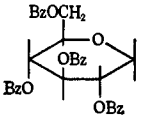
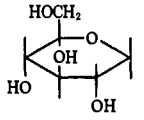
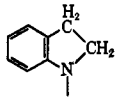
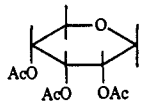
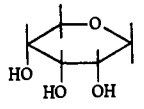
Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	[α]D, *deg* (*solvent*)	*Spectra*	*Ref*
		70–71	Ethanol–water	+7.36 (chloroform)		257
			Ethanol–water	+18.4 (chloroform)		257
		Glass		−26.0 (chloroform)	Uv	256
		Glass		−57.0 (chloroform)	Uv	256
		143–145	Water	−94.0 (water)	Uv, ir, nmr, ORD	255–257
					Nmr	261
					Nmr	261
					Nmr	261
					Nmr	261
		163–165	Ether	−68.0 (chloroform)	Uv, ir	256
		163–165	Ethyl acetate–pet. ether	−112.0 (chloroform)	Uv, ir	256
				−46.0 (methanol)	Uv, ir, nmr, ORD	256

Table VI (Continued)

Indole moiety	*Glycosyl moiety*	*Mp, °C*	*Recrystn solvent*	*[α]D, deg (solvent)*	*Spectra*	*Ref*
		117.8–118.5		+5.5 (carbon tetrachloride)	Uv	251, 252
		148.5–149	Ethanol	+1.5 (chloroform)	Uv	251–253
		129.5–130		−33.8		253
		101.5–102.5		−36.9		253
		80–100	Water	−28.0 (water)	Uv, ir, nmr	252, 253, 256
		151–153	Ethanol	+76.0 (chloroform)	Uv, ir	254, 256
		169–171	Ethanol	+40.0 (chloroform)	Uv	254, 256
		Glass		−20.0 (dichloromethane)	Uv, nmr	254, 256