A Convenient Synthesis of Certain 1-(β-D-Ribofuranosyl)benzotriazoles (1).

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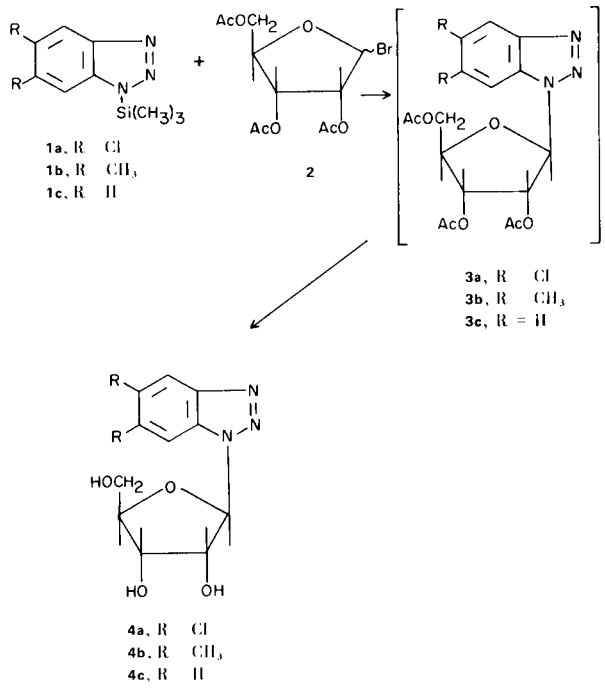
The synthesis of 5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole (**4a**), 5,6-dimethyl-1-(β-D-ribofuranosyl)benzotriazole (**4b**) and 1-(β-D-ribofuranosyl)benzotriazole (**4c**) in good yield has been accomplished by the condensation of the appropriate 1-trimethylsilylbenzotriazole (**1a**, **1b**, and **1c**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) followed by subsequent deacetylation of the reaction products. The assignment of anomeric configuration and site of glycosidation for all nucleosides reported is discussed.

Considerable interest has been evinced in recent years in studying the effect of altering the heterocyclic moiety of a biologically active compound. The effect of replacing the benzimidazole moiety in the benzimidazole glycoside isolated from vitamin B_{12} by benzotriazole analogs prompted the present investigation. The synthesis of 1- and 2-(D-ribofuranosyl)-5,6-dichlorobenzotriazole has been reported (2) and these D-ribofuranosyl derivatives of 5,6-dichlorobenzotriazole have shown (3) some virus inhibitory activity. We now wish to report the preparation of 1-(β-D-ribofuranosyl)benzotriazole, 5,6-dimethyl-1-(β-D-ribofuranosyl)benzotriazole and a more convenient preparation of 5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole.

The silylation of 5,6-dichlorobenzotriazole with hexamethyldisilazane using a catalytic amount of ammonium sulfate, under anhydrous conditions for 15 hours at reflux temperature, has furnished 1-trimethylsilyl-5,6-dichlorobenzotriazole (**1a**) in 89% yield. Since these trimethylsilyl derivatives were extremely susceptible to hydrolysis (cleavage of the N-Si bond) they were always prepared immediately before utilization in the condensation reaction. The condensation of **1a** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) in the presence of a catalytic amount of sodium iodide at 100-105° for 20 minutes afforded a 49.3% yield of nucleoside material (**3a**) as a syrup which was homogeneous by TLC in three different solvent systems. Deacetylation of the carbohydrate moiety of **3a** was accomplished with methanolic ammonia at room temperature to furnish a nucleoside which was established as 5,6-dichloro-1-(β-D-ribofuranosyl)-benzotriazole (**4a**) in 88.7% yield. The site of glycosidation was readily determined as *N*-1 by a comparison between the ultraviolet absorption spectra observed for **4a** (Table

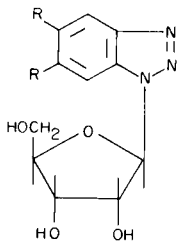


I) and the ultraviolet absorption spectral data reported (4) for the 1- and 2-methyl derivatives of 5,6-dichlorobenzotriazole. The assignment of β for the anomeric configuration of **4a** was established when the specific rotation of **4a** was observed to be $[\alpha]_D^{24}$ -136.4° (C=1, pyridine) in comparison to the reported (2) value of $[\alpha]_D^{21.5}$ -135.9° (C=1, pyridine).

In a like manner, 5,6-dimethylbenzotriazole was silylated with hexamethyldisilazane under anhydrous conditions using a catalytic amount of ammonium sulfate, to furnish 1-trimethylsilyl-5,6-dimethylbenzotriazole (**1b**) as a colorless liquid in quantitative yield. The trimethylsilyl

TABLE I

Ultraviolet Absorption Spectra of 1-(β-D-Ribofuranosyl)benzotriazoles (a).

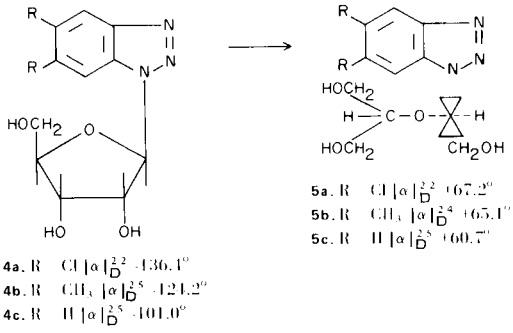


Compound	R	pH 1		Methanol		pH 11	
		λ max mμ	ε	λ max mμ	ε	λ max mμ	ε
4a	Cl	265	8000	264	7360	265	7680
		270	6700	270 (b)	6400	270	6600
		293	4800	293	3200	293	4800
4b	CH_3	265	8650	260	8090	264	8930
		285 (b)	6140	284 (b)	4740	285 (b)	6140
4c	H	255	7280	253	7280	255	7780
		280	4270	280	4270	280	4770

(a) Spectra were obtained with a Beckman DK-2 Ultraviolet Spectrophotometer. (b) Shoulder.

derivative (**1b**) was condensed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) in the presence of a catalytic amount of sodium iodide at 100° which furnished 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzotriazole (**3b**) in 73.7% yield. Removal of the blocking groups from the carbohydrate moiety of this syrup was accomplished with methanolic ammonia at room temperature to furnish 5,6-dimethyl-1-(β-D-ribofuranosyl)benzotriazole (**4b**) in 72.5% yield. The site of glycosidation was established by ultraviolet spectral data (5) (Table I) and the anomeric configuration by specific rotation, $[\alpha]_D^{25}$ -124.2°.

The silylation of benzotriazole with hexamethyldisilazane under anhydrous conditions using a catalytic amount of ammonium sulfate furnished 1-trimethylsilylbenzotriazole (**1c**) in a 95% yield. The condensation of **1c** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) in the presence of a catalytic amount of sodium iodide at 80° for 15 minutes afforded a 74.5% yield of 1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzotriazole (**3c**) as a syrup. Removal of the blocking groups from the carbohydrate moiety of **3c** was accomplished with methanolic ammonia at room temperature to furnish 1-(β-D-ribofuranosyl) benzotriazole (**4c**) in 80.25% yield. The site of glycosidation was ascertained as *N*-1 by a comparison between the ultraviolet absorption spectra observed for **4c** (Table I) and the ultraviolet absorption spectral data reported (5) for 1-alkyl- and 2-alkylbenzotriazoles. The anomeric configuration of **4c** was assigned as β on the basis of the large negative specific rotation $[\alpha]_D^{25}$ -101° (C=1, ethanol). A recent report (6) on the synthesis of 2-substituted ribofuranosylbenzimidazoles suggested that the silylation procedure will usually afford the β-anomer. However, it seemed desirable to utilize pmr to obtain additional support for the above anomeric assignments. In an effort to assign the anomeric configuration on the basis of the coupling constants ($J_{1,2}$) of the anomeric proton, it was observed that the pmr spectra of **4a**, **4b**, and **4c** in dmso-d_6 revealed a $J_{1,2}$ of approximately 6.5 cps in each case. This definitely precluded the use of this method for anomeric assignment since this method is applicable only if the coupling constant for the anomeric proton is less than 3.5 cps (7-9). Therefore, an alternate procedure was investigated in an effort to obtain additional support for the



anomeric assignments of **4a**, **4b**, and **4c**. To corroborate the assigned anomeric configurations, each ribonucleoside was subjected to periodate oxidation followed by reduction with sodium borohydride. By this procedure (10) the dialdehydes are reduced to the corresponding alcohols and the anomeric ribonucleosides are converted to a *dl* pair with optical rotations of opposite sign. Thus, 1-(β-D-ribofuranosyl)benzotriazole (**4c**), $[\alpha]_D^{25}$ -101.0° produced **5c**, $[\alpha]_D^{25}$ +60.7°; 5,6-dimethyl-1-(β-D-ribofuranosyl)-benzotriazole (**4b**), $[\alpha]_D^{25}$ -124.2°, produced **5b**, $[\alpha]_D^{24}$ +65.1°; and 5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole (**4a**), $[\alpha]_D^{22}$ -136.4°, produced **5a**, $[\alpha]_D^{22}$ +67.2°. This data has furnished strong additional support for the assignment of the ribonucleosides **4b** and **4c** as β-anomers.

EXPERIMENTAL (11)

5,6-Dichloro-1-(β-D-ribofuranosyl)benzotriazole (**4a**).

A mixture of dry 5,6-dichlorobenzotriazole (4) (5.65 g.), freshly distilled hexamethyldisilazane (6 g.) and a catalytic amount of ammonium sulfate (approximately 10 mg.) was heated at 125° with the exclusion of moisture. Within 15 minutes a clear dark brown solution was obtained followed by a profusion of ammonia. The heating was continued for an additional 15 hours with efficient stirring and the reaction mixture then fractionated by distillation *in vacuo* to obtain 1-trimethylsilyl-5,6-dichlorobenzotriazole (**1a**) as a colorless liquid which solidified on cooling, b.p. 140-142°/1.5 mm (7.0 g., 89.6%). This material was used in the following condensation reaction immediately after distillation. 1-Trimethylsilyl-5,6-dichlorobenzotriazole (**1a**, 2.6 g.) was intimately mixed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (12) (**2**, 3.5 g.) and a few crystals of sodium iodide (approximately 10 mg.). The mixture was heated at 100-105° (oil bath temperature) for 20 minutes *in vacuo* (1.5 mm) with good stirring. The cold reaction mixture was dissolved in chloroform (100 ml.) and the insoluble material (0.15 g.) removed by filtration and discarded. The filtrate was washed with cold saturated aqueous sodium bicarbonate solution (4 x 50 ml.), cold water (4 x 50 ml.), dried over anhydrous sodium sulfate and then evaporated *in vacuo* at 35° to a brown syrup. The syrup was dissolved in boiling methanol (150 ml.), treated with norit and the methanol then evaporated to dryness under reduced pressure to obtain 5,6-dichloro-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl) benzotriazole (**3a**) as a syrup. The syrup (2.2 g., 49.3%) was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 100 ml.) and the solution allowed to stand at room temperature for 25 hours with occasional shaking. The solution was filtered and the filtrate evaporated *in vacuo* on a steam bath to a syrup. The syrup was triturated with ice cold water (20 ml.) for two hours. The solid which had separated was collected by filtration, washed with cold water (3 x 20 ml.) and crystallized from ethanol, with the aid of norit, to obtain 5,6-dichloro-1-(β-D-ribofuranosyl)benzotriazole (**4a**) as colorless needles, 1.4 g. (88.7%). A small sample was recrystallized from ethanol for analysis, m.p. 180°, $[\alpha]_D^{22}$ -136.4° (C=1, pyridine) ([lit. (2) $[\alpha]_D^{21.5}$ -135.9° (C=1, pyridine); m.p. 177°]).

Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_4$: C, 41.26; H, 3.43; N, 13.12. Found: C, 41.48; H, 3.33; N, 13.21.

5,6-Dimethyl-1-(β-D-ribofuranosyl)benzotriazole (**4b**).

A mixture of dry 5,6-dimethylbenzotriazole (13) (5 g.), freshly distilled hexamethyldisilazane (6 g.) and a catalytic amount of ammonium sulfate (approximately 10 mg.) was heated at reflux temperature (125°) with the exclusion of moisture. Within 10 minutes a clear reaction mixture was obtained and the heating was then continued for an additional 15 hours with stirring. The clear reaction mixture was fractionated by distillation under reduced pressure to obtain what was assumed to be 1-trimethylsilyl-5,6-dimethylbenzotriazole (**1b**) as a colorless liquid which solidified on cooling, b.p. 135°/1.5 mm (7.45 g., 100%). Since this material was found to be very susceptible to hydrolysis, it was used in the following condensation reaction immediately after distillation. 1-Trimethylsilyl-5,6-dimethylbenzotriazole (**1b**, 4.4 g.) was intimately mixed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**, 7.0 g.) and a few crystals of sodium iodide (approximately 10 mg.). The mixture was heated at 100° (oil bath temperature) for 15 minutes *in vacuo* (1.5 mm) with good stirring. The cold reaction mixture was dissolved in chloroform (150 ml.) and a small amount of insoluble material (0.25 g.) was removed by filtration. The chloroform solution was washed with cold saturated aqueous sodium bicarbonate solution (4 x 100 ml.) and then with cold water (4 x 100 ml.). The chloroform phase was dried over anhydrous sodium sulfate and then evaporated *in vacuo* to a syrup. The syrup was dissolved in boiling methanol (100 ml.), decolorized with norit and the methanolic solution then taken to dryness under reduced pressure to obtain 5,6-dimethyl-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)benzotriazole (**3b**). The syrupy **3b** (6 g., 73.7%) was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 200 ml.) and the solution allowed to stand at room temperature for 25 hours with occasional shaking. The methanolic ammonia was removed *in vacuo* on a steam bath to afford a syrup which was triturated with ice cold water (25 ml.) for one hour. The solid which had separated was removed by filtration, washed with cold water (2 x 20 ml.) and crystallized from a mixture of water and ethanol to obtain 5,6-dimethyl-1-(β-D-ribofuranosyl)benzotriazole (**4b**) as colorless needles, 3.0 g. (72.5%). A small sample was recrystallized from the above solvent pair for analysis m.p. 180°, $[\alpha]_D^{25}$ -124.2° (C=1, pyridine).

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.09; N, 15.05. Found: C, 55.70; H, 5.94; N, 15.06.

1-(β-D-Ribofuranosyl)benzotriazole (**4c**).

A mixture of dry benzotriazole (14) (7.2 g.), freshly distilled hexamethyldisilazane (10 g.) and a few crystals of ammonium sulfate (approximately 50 mg.) was heated at reflux temperature (125°) under anhydrous conditions with good stirring. Within 15 minutes a clear reaction mixture was obtained and heating was then continued for an additional 15 hours. The clear brown reaction mixture was fractionated *in vacuo* to obtain 1-trimethylsilylbenzotriazole (**1c**) (11.0 g., 95.2%) as a colorless liquid, b.p.

100-102°/1.5 mm. This material (**1c**) was always prepared immediately before utilization in the condensation reaction.

1-Trimethylsilylbenzotriazole (**1c**, 9.55 g.) was thoroughly mixed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (12) (**2**, 17.5 g.), a catalytic amount of sodium iodide (20 mg.), and the mixture heated at 80° (oil bath temperature) for 15 minutes *in vacuo* (1.5 mm) with efficient stirring. The cold reaction mixture was dissolved in chloroform (200 ml.) and a small amount of insoluble material (0.4 g.) removed by filtration. The chloroform solution was washed with cold saturated aqueous sodium bicarbonate solution (4 x 100 ml. portions), cold water (4 x 100 ml. portions), dried over anhydrous sodium sulfate, and then evaporated *in vacuo* at 35° to a brown syrup. The residual syrup was dissolved in boiling methanol (100 ml.), treated with norit, and the methanolic solution then evaporated to dryness under reduced pressure to obtain 1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-benzotriazole (**3c**) as a syrup. The syrup (14.0 g., 74.5%) was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 500 ml.) and this solution then allowed to stand at room temperature for 30 hours with occasional shaking. The solution was filtered and the filtrate evaporated *in vacuo* on a steam bath to a syrup. The residual syrup was dissolved in dichloromethane (150 ml.) and the solution allowed to stand at -20° for four hours. The colorless solid which had separated from solution was removed by filtration and washed with cold dichloromethane (3 x 30 ml.). The solid was crystallized from a mixture of dichloromethane and ethanol to obtain 1-(β-D-ribofuranosyl)benzotriazole (**4c**) as colorless needles, 7.5 g. (80%). A small sample was recrystallized from the same solvent mixture for analysis, m.p. 135°, $[\alpha]_D^{25}$ -101.0° (C=1, ethanol).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.60; H, 5.17; N, 16.73. Found: C, 52.40; H, 5.08; N, 16.91.

Periodate Oxidation and Sodium Borohydride Reduction of 1-(β-D-Ribofuranosyl)benzotriazoles.

To 40 mg. of 1-(β-D-ribofuranosyl)benzotriazole (**4c**) was added 4.0 ml. of 0.08 *M* sodium periodate solution and the mixture stirred at room temperature for 15 minutes. Sodium borohydride (120 mg.) was then added and the resulting solution allowed to stand at room temperature for another 30 minutes after which excess reducing agent was destroyed by dropwise addition of 10% acetic acid (1.4 ml.) until gas evolution ceased. The optical rotation was determined on this solution as $[\alpha]_D^{25}$ +60.7° based on the original weight of **4c**.

In a like manner, 40 mg. of 5,6-dimethyl-1-(β-D-ribofuranosyl)-benzotriazole (**4b**) was treated with 4.0 ml. of 0.08 *M* sodium periodate solution followed by 120 mg. of sodium borohydride and neutralization with 1.8 ml. of 10% aqueous acetic acid. The optical rotation of this solution was determined as $[\alpha]_D^{24}$ +65.1° based on the original weight of **4b**.

A similar treatment of 40 mg. of 5,6-dichloro-1-(β-D-ribofuranosyl)-benzotriazole (**4a**) with 4.0 ml. of 0.08 *M* sodium periodate solution followed by 120 mg. of sodium borohydride resulted in a solution, after neutralization with 1.4 ml. of 10% aqueous acetic acid, which gave an optical rotation of $[\alpha]_D^{22}$ +67.2° based on the original weight of **4a**.

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