The Synthesis of Certain Ribofuranosylindazoles (1)

Ganapathi R. Revankar and Leroy B. Townsend

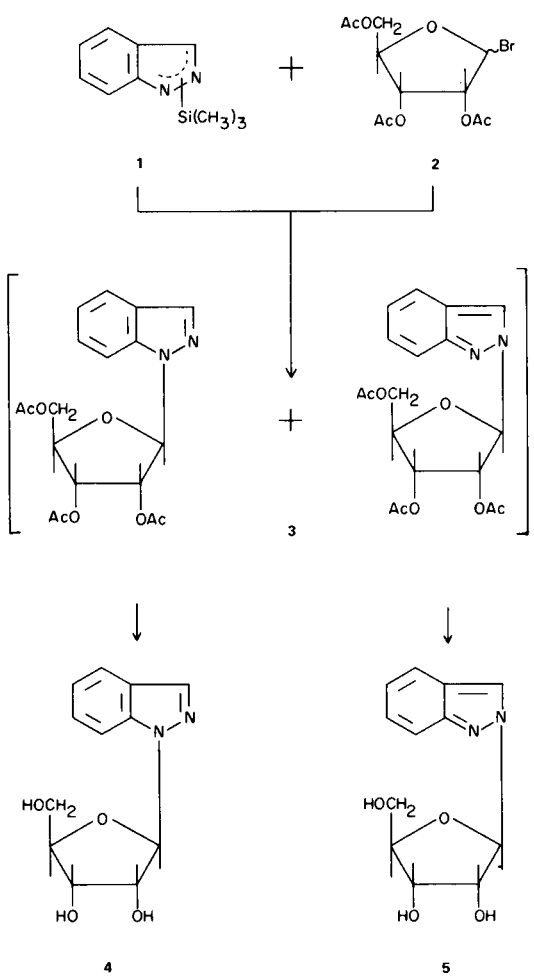
Department of Chemistry and Department of Biopharmaceutical Sciences
University of Utah

The synthesis of 1-(β-D-ribofuranosyl)indazole (**4**), 2-(β-D-ribofuranosyl)indazole (**5**) and 6-, 5-, and 4-nitro-2-(β-D-ribofuranosyl)indazole (**8a**, **8b**, and **8c**, respectively), has been accomplished in good yield by the condensation of the appropriate *N*-trimethylsilylindazole (**1**, **6a**, **6b**, and **6c**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) followed by subsequent deacetylation of the reaction products. The site of ribosylation and the assignment of anomeric configuration for all nucleosides reported is discussed. This has furnished the first indazole nucleosides with assigned anomeric configurations and the site of ribosylation has been established on the basis of uv comparisons with model methyl compounds.

The structural elucidation (2) of the nucleoside moiety of Vitamin B_{12} as a benzimidazole nucleoside has generated tremendous interest in not only the chemical synthesis (3,4) and biochemical action of benzimidazole nucleosides but has also prompted a number of investigations involving the synthesis of closely related nucleosides (5,6). Therefore, it was of considerable interest that a thorough review (7) of the literature revealed only one previous investigation (8) in the area of indazole nucleosides. In fact, there was only one indazole nucleoside (2-D-glucopyranosylindazole) reported (8) and this nucleoside was without an assignment of anomeric configuration. This isolation of only one isomer was of interest since the alkylation of indazole and various substituted indazoles have been reported (9) to afford, in general, a mixture of the corresponding 1- and 2- alkylated indazoles. This prompted the present investigation in an effort to determine the effect a change in the heterocyclic precursor would have not only on the site of ribosylation but also on the isomer ratio.

The silylation of indazole has furnished *N*-trimethylsilylindazole (**1**) in quantitative yield. The condensation of **1** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**) afforded an 80% yield of a mixture of two (detected by TLC) nucleosides (**3**) as a syrup. This was of interest since in the previous investigation under similar conditions with a polyacylglucosyl halide there was obtained only one isomer. Complete deacetylation of the carbohydrate moiety of **3** was accomplished with methanolic ammonia to furnish a mixture of the two deblocked nucleosides. The separation of this mixture was effected by chromatography on an alumina column. 1-(β-D-Ribofuranosyl)-indazole (**4**) was isolated from the initial fractions and

REACTION SCHEME I



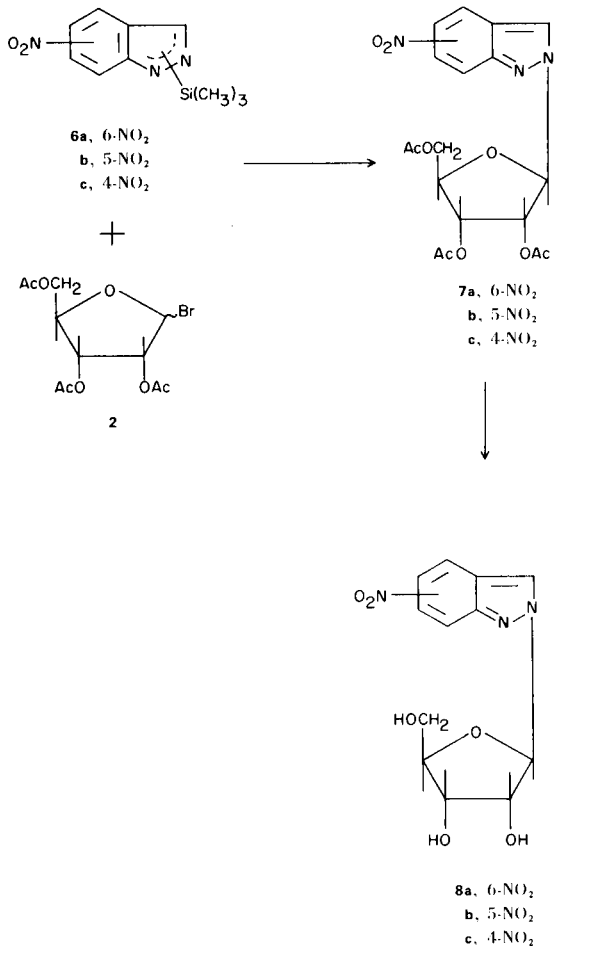
2-(β-D-ribofuranosyl)indazole (**5**) from subsequent fractions with the yield of **5** being approximately five times that of **4**. The site of ribosylation was readily determined by a comparison between the ultraviolet absorption spectra observed for **4** and **5** with the ultraviolet absorption spectral data reported (10,11,12) for the 1- and 2-methyl derivatives of indazole.

The anomeric configuration of **4** has been *tentatively* assigned as *beta* on the basis of the *trans* rule (13) and a comparison of the specific rotation ($[\alpha]_D^{23}$ + 9.20°) obtained for **4** with that reported (3) ($[\alpha]_D^{25}$ + 16.0° for 1-(β-D-ribofuranosyl)benzimidazole. The anomeric configuration of **5** was ascertained as *beta* on the basis of a comparison of the specific rotation of **5** with the data obtained for 2-(β-D-ribofuranosyl)-6-nitroindazole (**8a**) and the products (**10a**, **10c**) following the oxidation-reduction procedure, *vide infra.*

The silylation of 6-nitroindazole furnished *N*-trimethylsilyl-6-nitroindazole (**6a**) as a yellow liquid in quantitative yield. The condensation of **6a** with **2** afforded a 66.7% yield of nucleoside material which was subsequently assigned the structure 2-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-6-nitroindazole (**7a**). Deacetylation of **7a** with methanolic ammonia furnished a nucleoside which was assigned the structure 2-(β-D-ribofuranosyl)-6-nitroindazole (**8a**) on the basis of the following data. The site of ribosylation was readily ascertained as *N*-2 by a comparison between the ultraviolet absorption spectra observed for **8a** and that of 2-methyl-6-nitroindazole and 1-methyl-6-nitroindazole (11,14) (Table I). The anomeric configuration of **8a** was tentatively assigned as *beta* on the basis of the *trans* rule (13). Although **8a** exhibited a large negative specific rotation ($[\alpha]_D^{30}$ - 71.0°) this could not be used for the unequivocal assignment of anomeric configuration since there were no indazole nucleosides available for comparison (8). Therefore, it seemed desirable to utilize pmr spectroscopy to obtain additional support for the above anomeric assignment. The pmr spectra of **8a** in dmso-d_6/deuterium oxide revealed a doublet centered at δ 6.2 with a $J_{1,2}$ of approximately 3.5 Hz which still left some doubt as to the unequivocal anomeric assignment since this method is applicable only if the coupling constant for the anomeric proton is less than 3.5 Hz (15,16,17).

This prompted the preparation of the 2′,3′-*O*-isopropylidene derivative of **8a** in an effort to change the conformation of the furanose ring and to reduce the magnitude of the coupling constant ($J_{1,2}$) to within the acceptable limits (17). Treatment of **8a** with 70% perchloric acid and 2,2-dimethoxypropane furnished an excellent yield of 2-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-6-nitroindazole. The pmr spectrum (dmso-d_6/deuterium oxide) of the above isopropylidene derivative revealed an absorption

REACTION SCHEME II

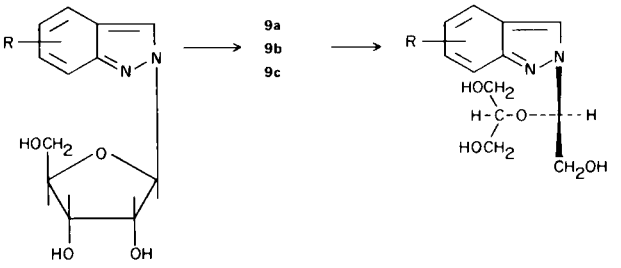


peak at δ 6.45 with a coupling constant of less than 1.0 Hz which was assigned to the anomeric proton. Therefore, the anomeric assignment for the isopropylidene derivative of **8a** and hence **8a** was unequivocally assigned as *beta* on the basis of this coupling constant (17).

5-Nitroindazole was silylated to furnish *N*-trimethylsilyl-5-nitroindazole (**6b**). The trimethylsilyl derivative **6b** was condensed with **2** to afford nucleoside material, in 71.5% yield, and was assigned the structure 2-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-nitroindazole (**7b**). Deacetylation of **7b** with methanolic ammonia furnished 2-(β-D-ribofuranosyl)-5-nitroindazole (**8b**). The actual site of ribosylation was established as *N*-2 by a comparison between the ultraviolet absorption spectra observed for **8b** and that of 2-methyl-5-nitroindazole and 1-methyl-5-nitroindazole (18) (Table I). The anomeric configuration was established as *beta* on the basis of the *trans* rule (13) and the oxidation-reduction procedure, *vide infra.* Similarly, 4-nitroindazole was silylated and then condensed with **2** to afford chromatographically homogeneous 2-(2′,3′,5′-

tri-*O*-acetyl-β-D-ribofuranosyl)-4-nitroindazole (**7c**) as a syrup. Removal of the blocking groups from the carbohydrate moiety of **7c** was accomplished with methanolic ammonia to furnish 2-(β-D-ribofuranosyl)-4-nitroindazole (**8c**). The site of ribosylation was ascertained as *N*-2 by a comparison between the ultraviolet absorption spectra observed for **8c** and that of the 1- and 2-methyl derivatives of 4-nitroindazole (14,19,20) (Table I). The anomeric configuration of **8c** was tentatively assigned as *beta* on the basis of the *trans* rule (13) and the large negative specific rotation, $[\alpha]_D^{28}$ - 74.0° (C = 1, pyridine).

Although the coupling constants ($J_{1,2}$) observed for **8b** (3.5 Hz), **8c** (3.5 Hz) and **5** (3.4 Hz) could most likely be reduced to within acceptable limits (17) by the formation of an isopropylidene derivative, an alternate procedure was investigated which would require a much smaller amount of nucleoside material. Therefore, **8a** (40 mg.) was subjected to periodate oxidation followed by reduction with sodium borohydride. By this procedure (6) the dialdehydes are reduced to the corresponding alcohols and the



8a, R = 6-NO_2, $[\alpha]_D^{30}$ -71.0°
8b, R = 5-NO_2, $[\alpha]_D^{30}$ -114.0°
5 R = H, $[\alpha]_D^{28}$ -92.0°

10a, R = 6-NO_2, $[\alpha]_D^{22}$ +14.9°
10b, R = 5-NO_2, $[\alpha]_D^{22}$ +7.6°
10c, R = H, $[\alpha]_D^{22}$ +15.2°

TABLE I

Ultraviolet Absorption Spectral Data for
Certain Ribofuranosylindazoles and Methylindazoles (a)

Compound	*p*H1		Methanol		*p*H 11	
	λ_{nm}^{Max}	ϵ	λ_{nm}^{Max}	ϵ	λ_{nm}^{Max}	ϵ
1-(β-D-Ribofuranosyl)indazole, **4**	249	5,500	250	5,750	249	5,500
	255 (b)	5,000	257 (b)	5,000	256 (b)	5,000
	288	4,500	288	4,750	288	4,500
			299 (b)	3,500	298 (b)	3,500
2-(β-D-Ribofuranosyl)indazole, **5**	266	7,000	274	7,500	274	7,250
	294	5,500	293	6,250	293	6,000
2-(β-D-Ribofuranosyl)-4-nitroindazole, **8c**	315 (b)	7,375	312 (b)	6,785	315 (b)	5,900
	550 (b)	6,200	525	7,670	545 (b)	6,200
	685	7,670	680	8,260	680	7,670
2-Methyl-4-nitroindazole	316 (b)	4,600	314 (b)	3,000	318 (b)	4,425
	550 (b)	3,890	524	4,425	540 (b)	3,540
	684	4,600	680	4,600	680	4,425
1-Methyl-4-nitroindazole	237.5	8,850	235.5	8,320	237	8,690
	352	10,800	352	10,800	351	10,800
	675	6,725	650	6,200	660	6,725
2-(β-D-Ribofuranosyl)-5-nitroindazole, **8b**	262	21,600	262	22,700	262	21,600
	306	7,375	305	7,080	306	7,670
2-Methyl-5-nitroindazole	263	9,025	262	10,400	262.5	9,550
	306	6,100	306	6,200	307	6,550
1-Methyl-5-nitroindazole	231	12,390	230	13,190	232	11,860
	261	16,450	258	10,100	261	16,450
	314 (b)	6,020	305	6,460	314 (b)	6,020
2-(β-D-Ribofuranosyl)-6-nitroindazole, **8a**	264	18,880	262	27,700	264	18,880
2-Methyl-6-nitroindazole	263.5	8,850	262	11,330	263	9,160
	297 (b)	4,425			296 (b)	4,780
1-Methyl-6-nitroindazole	257	13,980	255	15,230	257	13,270
	292	9,115	286	9,160	292	8,850

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

anomeric ribofuranosides are converted to a pair of enantiomorphs with optical rotations of equal but opposite sign. 2-(β-D-Ribofuranosyl)-6-nitroindazole (**8a**), $[\alpha]_D^{30}$ - 71.0°, produced **10a**, $[\alpha]_D^{30}$ + 14.9°; 2-(β-D-ribofuranosyl)-5-nitroindazole (**8b**), $[\alpha]_D^{30}$ - 114.0°, produced **10b**, $[\alpha]_D^{22}$ + 7.6°, and 2-(β-D-ribofuranosyl)indazole (**5**), $[\alpha]_D^{28}$ - 92.0°, produced **10c**, $[\alpha]_D^{22}$ + 15.2°. Since the anomeric configuration of **8a** has been unequivocally established by pmr spectral data, the above findings support the previous assignment of anomeric configuration of *beta* for **8b** and **5**. The specific rotation for **8c** ($[\alpha]_D^{28}$ - 74.0°) is almost identical to that observed for **8a** and was used for supporting the initial assignment of anomeric configuration (*beta*).

This investigation has furnished the first indazole nucleosides with assigned anomeric configurations and has established that the site of ribosylation can be ascertained on the basis of model methyl compounds. This has provided a firm basis for future investigations in the area of indazole nucleosides.

EXPERIMENTAL (21)

1-(β-D-Ribofuranosyl)indazole (**4**) and 2-(β-D-Ribofuranosyl)-indazole (**5**).

To a mixture of dry indazole (**22**) (5.9 g.) and freshly distilled hexamethyldisilazane (8.0 g.) was added a catalytic amount of ammonium sulfate (approximately 10 mg.) and the reaction mixture heated at 125° with the exclusion of moisture. Within 20 minutes a clear brown solution was obtained followed by a profusion of ammonia. The reaction mixture was heated at this temperature for an additional 15 hours with vigorous stirring. The reaction mixture was then fractionated by distillation *in vacuo* to obtain *N*-trimethylsilylindazole (**1**) as a colorless liquid, b.p. 90°/1.5 mm. (9.45 g., quantitative yield). This material was always used in the following condensation reaction immediately after distillation. *N*-Trimethylsilylindazole (**1**, 7.6 g.) was mixed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**23**) (**2**, 14.0 g.) and a few crystals of sodium iodide (approximately 10 mg.). The mixture was heated at 75-80° (oil bath temperature) for 30 minutes *in vacuo* (1.5 mm.) with stirring. The reaction mixture was cooled, dissolved in chloroform (200 ml.) and the chloroform phase washed with cold saturated aqueous sodium bicarbonate solution (4 X 75 ml.) followed by cold water (3 X 100 ml.). After drying over anhydrous sodium sulfate for 18 hours, the chloroform was removed under reduced pressure at 35° to afford a brown syrup. This syrup was dissolved in boiling methanol (200 ml.), treated with Norit and the methanol then evaporated to dryness under reduced pressure to furnish a syrup (**3**). This syrup was found to be a mixture of two components on TLC plates. The syrupy mixture of what was assumed to be blocked nucleosides (**3**, 12.0 g., 80%) was dissolved in methanolic ammonia (methanol saturated with ammonia at 0°, 400 ml.) and the solution then allowed to stand at room temperature for 25 hours with occasional shaking. A small amount of insoluble material was removed by filtration and the filtrate evaporated *in vacuo* on a steam bath to a syrup. This syrup was placed on a column (5 cm X 20 cm) of neutral alumina (200 g., Merck) and a mixture of ethanol and water (70:30, v/v) was used as eluent with 20 ml. fractions being collected. This gave chromatographically homogeneous 1-(β-D-ribofuranosyl)indazole (**4**, 0.8 g.) in fractions 10-25. The solvent was removed *in vacuo* and a small sample was recrystallized from ethanol for analysis, m.p. 205°, $[\alpha]_D^{23}$ + 9.22° (C = 1, pyridine).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.71; H, 5.74; N, 11.29.

The fractions 30-50 from the preceding column were collected and evaporated to dryness under reduced pressure. The residue was crystallized from dichloromethane containing a very small amount of methanol to obtain 2-(β-D-ribofuranosyl)indazole (**5**, 4.2 g.). A small sample was recrystallized from methanol for analysis, m.p. 135°, $[\alpha]_D^{28}$ - 92.0° (C = 1, pyridine).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.48; H, 5.37; N, 11.36.

2-(β-D-Ribofuranosyl)-4-nitroindazole (**8c**).

A mixture of dry 4-nitroindazole (**24**) (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 15 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 *N*-trimethylsilyl-4-nitroindazole (**6c**) as a yellow liquid which solidified on cooling, b.p. 148-150°/1.5 mm. (7.0 g., 100%). This material (**6c**) was used in the following condensation reaction immediately after distillation. *N*-Trimethylsilyl-4-nitroindazole (**6c**, 2.35 g.) was thoroughly mixed with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**, 3.5 g.) and a few crystals of sodium iodide (approximately 10 mg.). The mixture was fused at 105-110° (oil bath temperature) for 20 minutes *in vacuo* (1.5 mm.) with good stirring. The reaction mixture was cooled and then dissolved in chloroform (150 ml.) and the chloroform phase washed with cold saturated aqueous sodium bicarbonate solution (3 X 50 ml.) followed by cold water (3 X 50 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 filtrate taken to dryness under reduced pressure to obtain 2-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-4-nitroindazole (**7c**). This nucleoside material (**7c**, 3 g.) 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 methanolic ammonia was removed *in vacuo* on a steam bath. The residual semisolid was collected by filtration and washed with a very small amount of methanol. The solid was crystallized from methanol with the aid of Norit, to obtain 2-(β-D-ribofuranosyl)-4-nitroindazole (**8c**) as needles, m.p. 184°, 65%, $[\alpha]_D^{28}$ - 74.0° (C = 1, pyridine).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.40; N, 14.23. Found: C, 48.90; H, 4.38; N, 14.31.

2-(β-D-Ribofuranosyl)-5-nitroindazole (**8b**).

The silylation of 5-nitroindazole with hexamethyldisilazane in the presence of ammonium sulfate, following the method as described in the preparation of **6c**, gave *N*-trimethylsilyl-5-nitroindazole (**6b**) as a pale yellow liquid which solidified on cooling, b.p. 145-147°/1.0 mm., in quantitative yield. The condensation of **6b** (7.0 g.) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (**2**, 12.0 g.) in the presence of sodium iodide, adopting the procedure described for **7c** gave syrupy, chromatographically homogeneous 2-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-5-nitroindazole (**7b**) (9.0 g., 71.5%). Deacetylation of **7b** (8.0 g.) with methanolic ammonia

(250 ml.) at room temperature and working up as in the case of **8c**, furnished 2-(β-D-ribofuranosyl)-5-nitroindazole (**8b**) which was recrystallized from methanol as needles with the aid of Norit (4.5 g., 80.3%). A small sample was recrystallized from methanol for analysis, m.p. 205-206°, $[\alpha]_D^{30}$ - 114.0° (C = 1, pyridine).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.40; N, 14.23. Found: C, 48.85; H, 4.38; N, 14.37.

2(-β-D-Ribofuranosyl)-6-nitroindazole (**8a**).

The silylation of 6-nitroindazole with hexamethyldisilazane using ammonium sulfate as the catalyst and following the procedure described for **6c**, gave *N*-trimethylsilyl-6-nitroindazole (**6a**) as a yellow liquid, b.p. 135°/1.0 mm., in quantitative yield. The product solidified on standing. The condensation of **6a** (9.2 g.) with 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl bromide (**2**, 14.0 g.) in the presence of sodium iodide and following the procedure described for **8c**, furnished 2-(β-D-ribofuranosyl)-6-nitroindazole (**8a**) which was crystallized from methanol (6.5 g., 84.2%). A small sample was recrystallized from methanol for analysis, m.p. 215°, $[\alpha]_D^{30}$ - 71.0° (C = 1, pyridine).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.40; N, 14.23. Found: C, 49.02; H, 4.68; N, 14.28.

2-(2',3'-*O*-Isopropylidene-β-D-ribofuranosyl)-6-nitroindazole.

To 400 ml. of acetone was added 1.5 ml. of 2,2-dimethoxypropane and 2.0 ml. of 70% perchloric acid. The mixture was protected from moisture with stirring at room temperature for 5 minutes and then 1.20 g. of 2-(β-D-ribofuranosyl)-6-nitroindazole (**8a**) was added in one portion. Pyridine (1.50 ml.) was added after the mixture had been stirred for 45 minutes. The volume was reduced to 50 ml. *in vacuo* and 20 ml. of 10% aqueous sodium carbonate was added before the remaining acetone was removed. Cold water (50 ml.) was added to the aqueous solution and the solution was then allowed to stand at 5° for 12 hours. The yellow solid which had separated from solution was collected by filtration and washed with cold water. Recrystallization from a mixture of ethanol and water afforded 1.0 g. (73.4%) of yellow needles, m.p. 135°.

Anal. Calcd. for $C_{15}H_{17}N_3O_6$: C, 53.74; H, 5.07; N, 12.54. Found: C, 53.59; H, 5.05; N, 12.65.

Methylindazoles.

The 1- and 2-methyl derivatives of 4-nitro- (13), 5-nitro- (15), and 6-nitroindazole (10) have been prepared according to the methods reported in the literature. The ultraviolet absorption spectral data for these compounds were obtained and are included in Table I since this data was used to establish the actual site of glycosydation for the reported nucleosides.

Periodate Oxidation and Sodium Borohydride Reduction.

To 40 mg. of 2-(β-D-ribofuranosyl)indazole (**5**) 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. The excess reducing agent was then destroyed by dropwise addition of 10% acetic acid (1.4 ml.) until gas evolution ceased. The optical rotation was determined on this solution as $[\alpha]_D^{22}$ + 15.2° based on the original weight of **5**.

In a like manner, 40 mg. of 2-(β-D-ribofuranosyl)-5-nitroindazole (**8b**) was treated with 4.0 ml. of 0.08 *M* sodium periodate solution followed by 120 mg. of sodium borohydride and neutralization with 1.5 ml. of 10% aqueous acetic acid. The optical rotation of this solution was determined as $[\alpha]_D^{22}$ + 7.6° based on the original weight of **8b**.

A similar treatment of 40 mg. of 2-(β-D-ribofuranosyl)-6-nitroindazole (**8a**) 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 $[\alpha]_D^{22}$ + 14.9° based on the original weight of **8c**.

Acknowledgment.

The authors wish to thank Professor Roland K. Robins for his encouragement.

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Received September 2, 1969 Salt Lake City, Utah 84112