Tetrahedron Vol. 23, pp 4653 to 4660 Pergamon Press Ltd. 1967 Printed in Great Britain

GLYCOSYLINDOLES—VII

SYNTHESIS OF 1-(D-β-RIBOFURANOSYL)INDOLE

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(*Received* 17 *February* 1967, *accepted for publication* 29 *March* 1967)

Abstract The first indole analogue of nucleoside 1-(D-β-ribofuranosyl)indole has been prepared by the "indoline indole method"

The condensation of 5-O-tritylribose with indoline resulted in 5-O-tritylribofuranosylindoline (II) whose acetylation led to 1-(D-β-5'-O-trityl-2',3'-di-O-acetylribofuranosyl)indoline (III). The appropriate indole derivative IV was obtained by dehydrogenation of III. The removal of trityl and acetyl protecting groups gave 1-(D-β-ribofuranosyl)indole (VI). The structure of VI was confirmed by $NaIO_4$ oxidation as well as by NMR and IR spectral analysis

1-GLYCOSYLINDOLES are of interest as among the analogues of nucleosides some substances possess high biological activity. Furthermore, the introduction of a glycosyl residue into an indole derivative containing pharmacologically active groups may result in a compound with new valuable properties. This work has been stimulated by the discovery of tubercidine and toyocamycin antibiotics which are pyrrolopyrimidine analogues of nucleosides.[1, 2] The methods used for the synthesis of purine or pyrimidine nucleosides can not be applied to the synthesis of 1-glycosylindoles, but application of the indoline-indole method, for the introduction of substituents into the benzene nucleus of the indole system, made it possible to synthesize 1-(D-β-glucopyranosyl)indole,[3] 1-(D-β-galactopyranosyl)indole, 1-(D-β-ribopyranosyl)-indole[4] as well as 1-(D-β-ribopyranosyl)-6-nitroindole and 1-(D-β-ribopyranosyl)-6-aminoindole.

By boiling 5-O-tritylribose (I) with indoline in alcohol crystalline 1-(D-β-5'-O-tritylribofuranosyl)indoline (II) was obtained and acetylated to 1-(D-β-5'-O-trityl-2', 3'-di-O-acetylribofuranosyl)indoline (III). The latter was dehydrogenated by boiling with dicyandichlorquinone in xylene. When chloranile was used in this reaction only negligible amounts of the indole derivative IV were obtained.

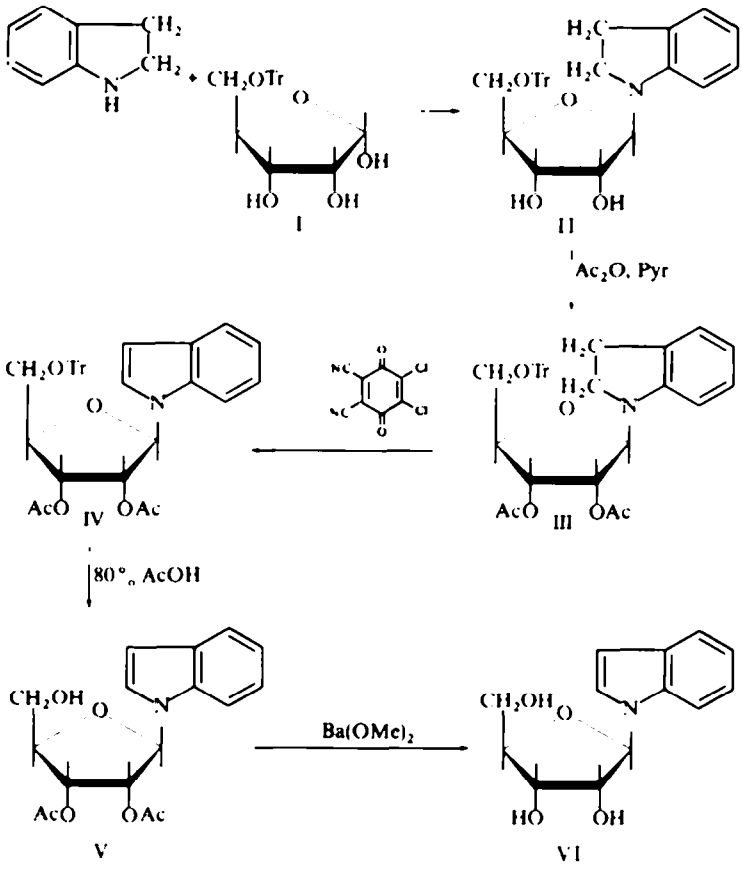
In addition to 1-(D-β-5'-O-trityl-2',3'-di-O-acetyl-ribofuranosyl)indole (IV) a mixture of substances was also obtained in the course of dehydrogenation of III. To separate IV, the reaction mixture was subjected to column chromatography with aqueous silicic acid in benzene and the process was checked by TLC (Fig. 1). The first fractions containing indole substances were not identified. These fractions were followed by triphenylcarbinole, then fractions containing IV and finally fractions

[1] K. Anzai, G. Nakamura and S. Suzaky, *J. Antibiotics, Tokyo* **A10**, 201 (1957).

[2] Y. Mizuno, M. Ikehara and K. A. Watanabe, *Chem. Pharm. Bull., Tokyo* **11** (8), 1091 (1963).

[3] N. N. Suvorov and M. N. Preobrazhenskaya, *ZhOCh* **31**, 1839 (1961); *Chem. Abstr.* **56**, 14386 (1962).

[4] M. N. Preobrazhenskaya, M. M. Vigdorchik and N. N. Suvorov, *Biologically active compounds* p. 60 Izd. "Nauka", Moskva (1965); *Chem. Abstr.* **64**, 790 (1966).



containing unreacted III. 1-D-β-5'-0-Trityl-2',3'-di-0-acetylribofuranosyl)indole (IV) is an amorphous substance without a clearly defined m.p.

The trityl group was removed by boiling IV in 80% acetic acid and the 1-(D-β-2',3'-di-0-acetylribofuranosyl)indole (V) separated by column chromatography with aqueous silicic acid in benzene; the process being checked by TLC (Fig. 1). The first fractions were unidentified indole substances followed by triphenylcarbinole and unreacted IV. The product V was eluated with ethyl acetate as a dark-coloured oil, which according to paper chromatography, contained a small amount of β-pyranoside and, probably, one or two α-anomeres. Crude 1-(D-β-2',3'-di-0-acetylribofuranosyl)indole obtained after column chromatography was deacetylated by the Zemplen method in the presence of barium methylate. 1-(D-β-Ribofuranosyl)indole (VI) was separated by column chromatography with Al_2O_3 in an acetone water system (in ratio 7:1), the fractions being checked by TLC (Fig. 2). It was found that in addition to 1-(D-β-ribofuranosyl)indole (VI) and initial 1-(D-β-2',3'-di-0-acetylribofuranosyl)indole (V) the reaction mixture contained a substance (in a quantity of 1%) for which during TLC on Al_2O_3 an R_f value corresponding to authentic 1-(D-β-ribopyranosyl)indole (Fig. 2) was obtained. In case of the chromatography on paper treated with borate buffer (ph 8·7) in the system n-butanol pyridine water (6:4:3) the R_f value of the by-product agreed with that of authentic 1-(D-β-ribopyranosyl)-

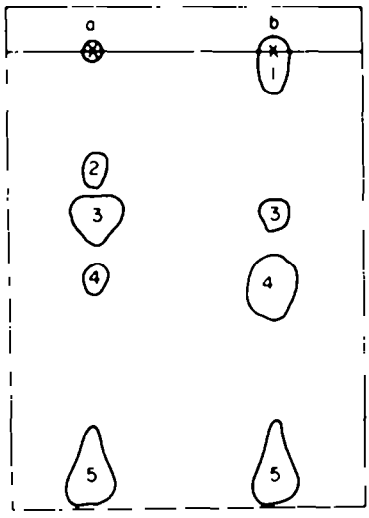


FIG. 1. Chromatogram of products of dehydrogenation (a) and detritylation (b) reactions on a thin layer of silicic acid in benzene. 1. V R_f 0; 2. III R_f 0.25; 3. IV R_f 0.35; 4. Triphenylcarbinole R_f 0.5; 5. Not-identified substances of indole nature R_f 0.95.

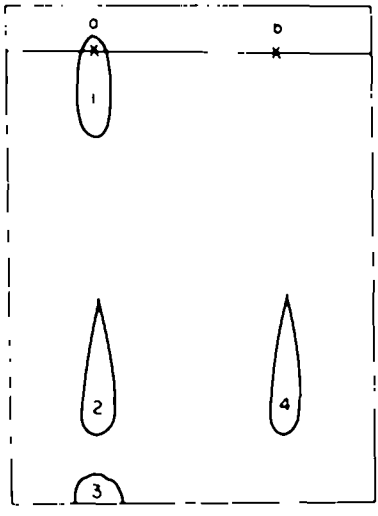


FIG. 2. Chromatogram of reaction products of the deacetylation of product V on a thin layer of Al_2O_3 in the acetone–water (7:1) system.
(a) 1. VI R_f 0.12; 2. By-products R_f 0.82; 3. V R_f 1.0.
(b) 4. 1-(D-β-ribopyranosyl)indole R_f 0.82.

indole (R_f 0.9) (1-(D-β-ribofuranosyl)indole R_f 0.73). In some cases during the chromatography in this system it was possible to observe the formation of another by-product (with R_f 0.32). This by-product and 1-(D-β-ribopyranosyl)indole could not be resolved by TLC on Al_2O_3.

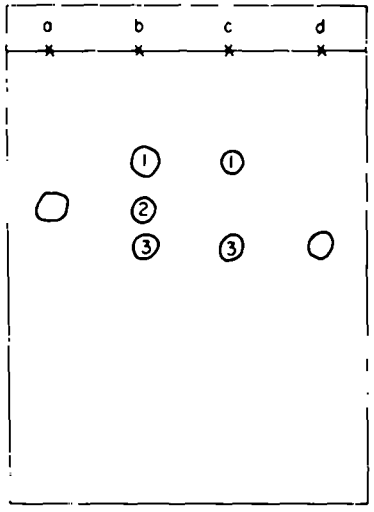
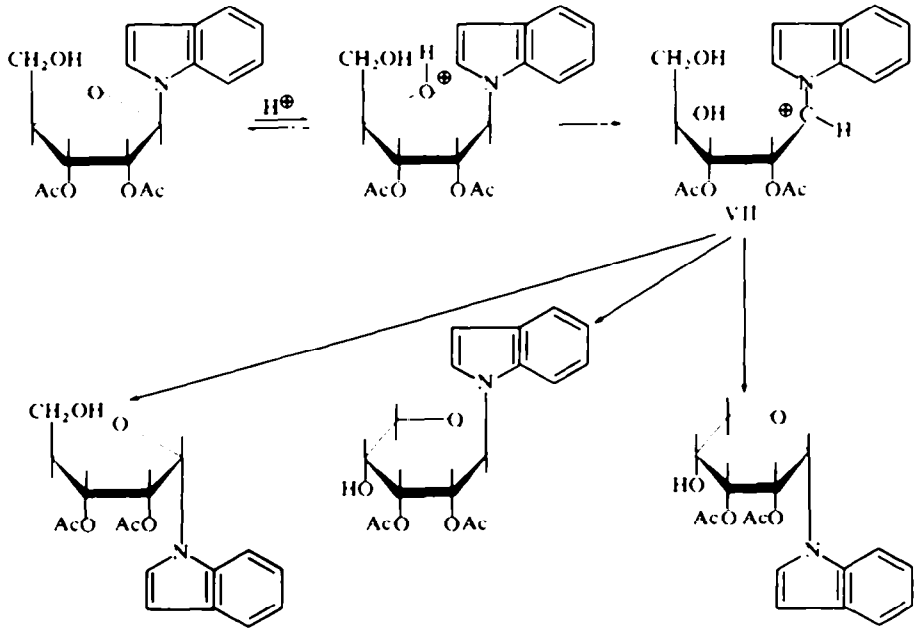


FIG. 3. Paper chromatogram of acetylated ribosilindoles (the dimethylformamide–cyclohexane, moving phase).
(a) Acetylated 1-(D-β-ribofuranosyl)indole R_f 0·35
(b) Products of the acetylation of crude product V: 1. R_f 0·26; 2. R_f 0·35; 3. R_f 0·43
(c) Acetylated by-products after isolation of product VI: 1. R_f 0·26; 2. R_f 0·43
(d) 1-(D-β-tri-O-acetylribopyranosyl)indole R_f 0·43

The acetylation of 1-(D-β-ribofuranosyl)indole and 1-(D-β-ribopyranosyl)indole yielded the respective acetates, which analysed by chromatography on paper impregnated with dimethylformamide in cyclohexane showed R_f values of the known 1-(D-β-2',3',4'-tri-O-acetylribopyranosyl)indole and acetylated 1-(D-β-ribofuranosyl)-indole (Fig. 3). Fig. 3 also presents a chromatogram of a product obtained during



acetylation of a detritylated substance (not participating in the deacetylation reaction). As it can be seen from the chromatogram that in addition to the acetylated 1-(D-β-ribofuranosyl)indole, the mixture also contained acetylated 1-(D-β-ribopyranosyl)-indole, as well as a spot corresponding to a substance whose structure was not identified. These by-products are not formed during deacetylation of V, but occur during removal of the trityl group in acid media. It is possible that in addition to the recyclization with the formation of a ribopyranose derivative anomerization also can take place. The mechanism of recyclization seems to be due to the formation of an acyclic carbonium ion (VII)[5] which closes again. The yields of α-anomers of furanose or pyranose can not be high due to conformational and configurational difficulties.

1-(D-β-Ribofuranosyl)indole is an amorphous powder which retains traces of solvent.

The oxidation of VI in accordance with the Malaprade method confirmed its furanose structure. Although indole could be oxidized with $NaIO_4$,[6] at room temperature this process proceeds very slowly (from 8 to 24 hr). In the course of oxidation of 1-glycosylindole, the α-diole part of a molecule is probably attacked first. This was supported by results obtained during oxidation of 1-(D-β-glucopyranosyl)indole, 1-(D-β-ribopyranosyl)indole, 1-(D-β-ribopyranosyl)-6-nitroindole and 1-(D-β-ribofuranosyl)indole (VI). Table I shows the relationship between the structure of 1-glycosylindole and the number of moles of an alkali required for titration of the acid formed during oxidation. The relationship is given with respect to time intervals after mixing the oxidant and the substrate.

TABLE 1

Time	Relationship between glycoside and alkali required for titration of acid formed during oxidation, moles		
	1-(D-β-gluco-pyranosyl)indole	1-(D-β-ribo-pyranosyl)indole	1-(D-β-ribo-furanosyl)indole
15 min	1:0·992	1:0·995	1:0·03
1 hr	1:1·041	1:0·995	1:0·03
2 hr	1:1·13	1:0·995	1:0·19
3 hr	1:1·26	1:1·03	1:0·25
24 hr	1:1·32	1:1·39	1:0·40

During the first hour the formation of one mole of formic acid was observed in the case of glycopyranosylindoles but not in case of ribofuranosylindole.

The structure of VI was confirmed by IR and NMR spectra. The IR spectrum of VI differs from that of 1-(D-β-ribopyranosyl)indole in the "fingerprint" region. In the spectrum of VI the absorption assigned to the symmetrical ring-breaking of the furanose is observed in the region of 930 cm^{-1}. Other absorption regions typical for furanoses are masked by the presence of the indole ring.[7, 8]

[5] P. Nuhn and G. Wagner, *Die Pharmazie* **21**, No. 5, 261 (1966).

[6] L. J. Dolby and D. L. Booth, *J. Am. Chem. Soc.* **88**, 1049 (1966).

[7] S. A. Barker and R. Stephens, *J. Chem. Soc.* 4550 (1954).

[8] P. Nanasi, F. Nemes Nanasi and E. Cerletti, *Gazz. Chim. Ital.* **95**, 966, 975 (1965).

The NMR spectrum of 1-(D-β-ribopyranosyl)indole (Fig. 4) is characterized by the presence of a doublet with chemical shift $\tau = 4{\cdot}4$ ppm and $J = 9$ c/s belonging to anomere proton. The value J indicates a β-configuration of the glycoside. Taking into account the constants of spin-spin interaction of other protons of the ring, conformation CI can be ascribed to the 1-(D-β-ribopyranosyl)indole. The NMR spectrum of VI is analogous to the spectra of nucleosides and resembles that of 9-(D-β-ribofuranosyl)-purine (antiobiotic nebularine[9]). The chemical shift of the anomere proton lies in a weaker field than in case of 1-(D-β-ribopyranosyl)indole ($\tau = 4{\cdot}1$ ppm, $J = 5$ c/s). The presence of a multiplet in the region of a strong field $\tau = 6{\cdot}27$ ppm belonging to

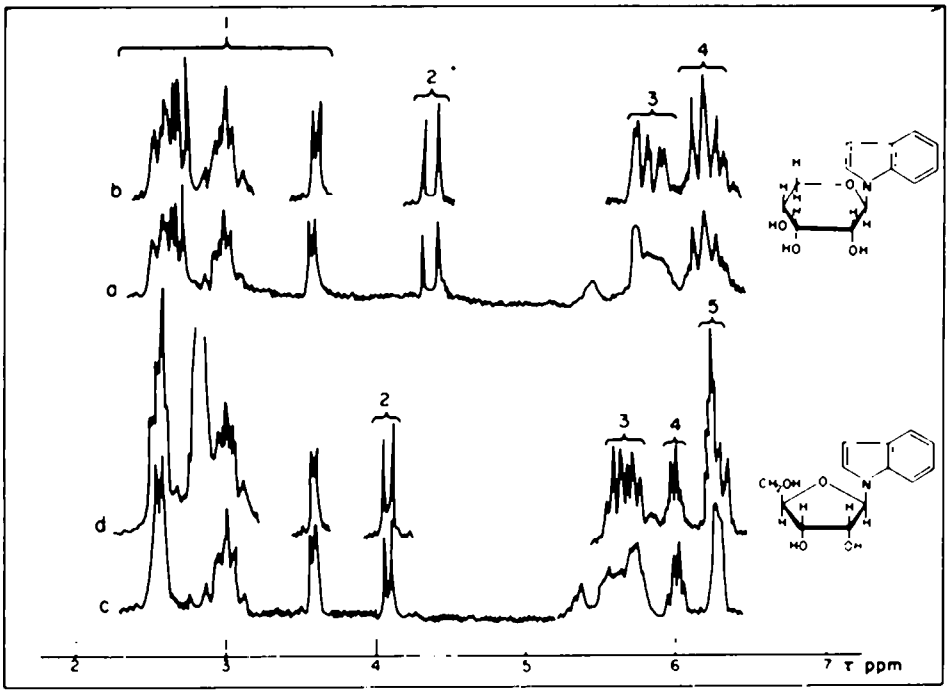


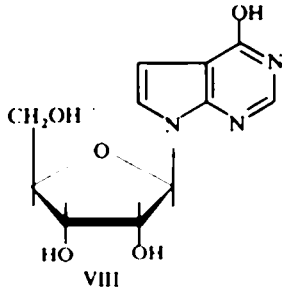
FIG. 4 NMR spectra of 1-(D-β-ribopyranosyl)indole (a and b) and 1-(D-β-ribofuranosyl)indole (c and d). a and c in CD_3COCD_3, b and d in $CD_3COCD_3 \cdot CF_3COOH$
(b) 1 Protons of indole nucleus; 2 H^1; 3 H^2, H^3; 4 H^4, H^5
(d) 1 Protons of indole nucleus; 2 H^1; 3 H^2, H^3; 4 H^4; 5 H^5, H^5

protons at C_5 is noteworthy. The values of constants of spin-spin interaction do not contradict the C_2-*endo* conformation inherent in natural purine nucleosides. The values of $[\alpha]_D$ and $[M]_D$ of VI are close to the $[\alpha]_D$ and $[M]_D$ values of a condensed pyrrole nucleoside (VIII).[10]

For (VI): $[\alpha]_D^{20} = -7{\cdot}1°$, $[M]_D^{20} = -7{\cdot}1 \times 249{\cdot}2 = -1769{\cdot}32$

For (VIII): $[\alpha]_D^{20} = -6{\cdot}7°$, $[M]_D^{20} = -6{\cdot}7 \times 269{\cdot}2 = -1803{\cdot}64$

[9] T. Hashisume and H. Iwamura *Tetrahedron Letters* No. 6, 643 (1966).
[10] Y. Mizuno, M. Ikehara, K. A. Watanabe and S. Suzaky, *J. Org. Chem* **28**, 3331 (1963).



VIII

According to the data obtained by Jardetzky, unlike the pyrimidine nucleoside with C_3-*endo* conformation and positive specific rotation,[11,12] the purine nucleosides have C_2-*endo* conformation and negative specific rotation. As the value $[\alpha]_D$ of condensed pyrrole nucleosides is smaller than that of the purine nucleosides, it may be supposed that in case of condensed pyrrole nucleosides C_2 the ribose atom lies just outside the plane of the furanose ring.

EXPERIMENTAL

The NMR spectra were measured with TMS as internal standard using a JNM4H100 instrument possessing operating frequency of 100 mc.

1-(D-β-5'-O-*tritylribofuranosyl)indoline* (II). Indoline (2·1 ml) was added to a boiling soln of 5-O-tritylribose (3·0 g) in abs. EtOH (75 ml) and the mixture was heated under reflux for 3 hr and then evaporated *in vacuo* to ⅓th of its initial volume and kept in a refrigerator overnight. The ppt was recrystallized from abs EtOH with activated charcoal, yielding 2·4 g (63·5%) of II, m.p. 132–135°. $[\alpha]_D^{20}$ −28·3° (*c* 3, $CHCl_3$). (Found: C, 77·78; H, 6·33; N, 2·83. $C_{32}H_{31}NO_4$ requires: C, 77·98; H, 6·18; N, 2·88%.)

1-(D-β-5'-O-*trityl*-2',3'-*di*-O-*acetylribofuranosyl)indoline* (III). Acetic anhydride (30 ml) was added to the soln of II (2·4 g) in dry pyridine (48 ml) and the mixture incubated for 6 hr at 20° and for 12 hr at 0°. The soln was then poured into 2 l. of ice-water and the ppt filtered, washed with water and dried at 40°, yielding 2·4 g (86%) of III, m.p. 65–67°. The sample for analysis was obtained by recrystallization from EtOH–water (5:1) with charcoal, m.p. 70–71°. $[\alpha]_D^{20}$ +7·36° (*c* 4, $CHCl_3$). (Found: C, 74·88; H, 6·03; N, 2·38. $C_{36}H_{35}NO_6$ requires: C, 74·86; H, 6·10; N, 2·42%.)

1-(D-β-5'-O-*trityl*-2',3'-*di*-O-*acetylribofuranosyl)indole* (IV). Compound III (2·4 g) was dissolved in hot dry xylene (80 ml) and 25 ml of the xylene were then distilled off from the soln to remove traces of moisture. Dicyandichlorquinone (1·0 g) was added to the residue and the mixture stirred for 1 hr at 60–70° and then heated under reflux for 3 min. The colour changed from red to brown and a ppt of dicyandichlorhydroquinone was produced. After keeping in a refrigerator overnight the mass was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in 7 ml of benzene and placed on a column with aqueous silicic acid (L = 30 cm, d = 30 mm). The product was eluated with benzene and a check made by chromatography on a thin layer of silicic acid in benzene (Fig. 1). The evaporation of the fractions containing only IV yielded an oil which was dissolved in 5 ml of EtOH and poured into 100 ml of ice-water. A ppt of IV (1·2 g; 50%) in the form of amorphous powder was obtained. $[\alpha]_D^{20}$ +18·4° (*c* 1·5, $CHCl_3$). (Found: C, 75·19; H, 5·98; N, 2·21. $C_{36}H_{33}NO_6$ requires: C, 75·11; H, 5·78; N, 2·43%.)

1-(D-β-2',3'-*Di*-O-*acetylribofuranosyl)indole* (V). A mixture containing 1·2 g of IV and 30 ml 80% AcOH was heated under reflux for 15 min and then incubated for 48 hr at 20°. The AcOH was distilled off *in vacuo*. MeOH was added several times to the residue and also evaporated. Finally the residue was dissolved in 5 ml benzene and placed on a column with aqueous silicic acid (L = 25 cm, d = 30 mm). The fractions eluted were checked by chromatography in a thin layer of silicic acid in benzene (Fig. 1). After the by-products and IV had been removed, benzene was replaced by AcOEt and product V eluted. Evaporation of the AcOEt yielded V (0·4 g) in the form of a dark-coloured oil.

[11] Ch. D. Jardetzky, *J. Am. Chem. Soc.* **82**, 229 (1960).
[12] Ch. D. Jardetzky, *J. Am. Chem. Soc.* **84**, 62 (1962).

1-(D-β-Ribofuranosyl)indole (VI). 4 Drops of barium methylate soln were added to V dissolved in 7 ml of abs. MeOH and the mixture kept for 12 hr at 20°. Water (7 ml) and 0·1N H_2SO_4 (ca 1 ml) were added until the soln had a pH of 5·5–6. After mixing thoroughly for 20 min 0·5 g of $BaCO_3$ was added and the mixture stirred for 10 min and then filtered. The filtrate was treated with 0·1 g activated neutral charcoal and evaporated *in vacuo*. The residue was dissolved in 3 ml of acetone–water (7:1) mixture and placed on a column with Al_2O_3 (L = 40 cm, d = 20 mm). The fractions eluted were checked by TLC (Fig. 2). The fractions containing only VI were collected and after evaporation yielded 0·12 g of VI (23% starting from IV) in the form of amorphous substance slowly soluble in water and perfectly soluble in alcohol and acetone. $[\alpha]_D^{20}$ −7·1° (*c* 2·8, CH_3OH). (Found: C, 62·00; H, 6·20; N, 5·65. $C_{13}H_{15}NO_4$ requires: C, 62·64; H, 6·06; N, 5·61%.)

Oxidation of glycosilindoles. 1-(D-β-Glucopyranosyl)indole (0·5407 g) and $NaIO_4$ (1·23 g) were dissolved in 50 ml of distilled water. 10 ml-samples of the reaction mixture were titrated with 0·1 N NaOH in the presence of methyl-red.

1-(D-β-Ribopyranosyl)indole and 1-(D-β-ribofuranosyl)-indole were oxidized under similar conditions. See Table 1.

Acknowledgements—The authors are greatly indebted to Professor Yu. N. Sheynker and Dr. K. F. Turchin for the study and valuable discussion of NMR spectra.