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1-GLYCOSYLINDAZOLES

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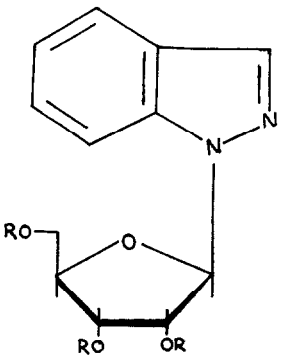
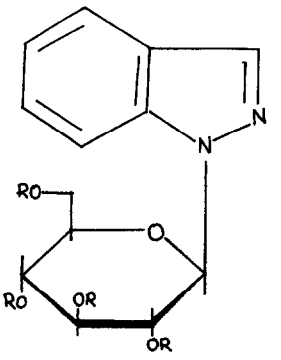
Glycosylation of indazole, 4-, 5- and 6-nitroindazoles, 3-cyanoindazole via "trimethylsilyl" or "$Hg(CN)_2$-nitromethane" methods afforded corresponding 2-glycosylindazoles[1-4]. In this paper we describe the methods of synthesis of 1-glycosylindazoles. These nucleosides are more interesting than the 2-isomers as potential antimetabolites because of their greater structural similarity to the naturally occuring purine nucleosides.

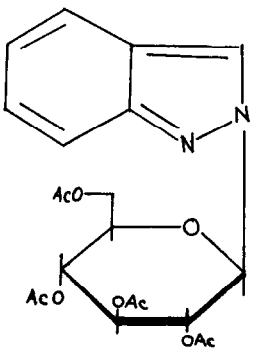
Fusion of indazole with tetra-O-acetyl-β-D-ribofuranose or with penta-O-acetyl-β-D-glucopyranose in vacuo at 160° in the presence of I_2 gave in 70% yield 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)indazole (I), syrup, $[\alpha]_D^{25}$ -43° (1.2, $CHCl_3$) or 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indazole (II), m.p. 164-165°, $[\alpha]_D^{25}$ -51°(1.0, $CHCl_3$). Deacetylation of I and II with methanolic ammonia furnished 1-(β-D-ribofuranosyl)indazole (III), m.p. 174-175°, $[\alpha]_D^{25}$-136° (1.36, pyridine) and 1-(β-D-glucopyranosyl)indazole (IV), m.p. 205-207°, $[\alpha]_D^{25}$ -27°(1.0, pyridine). UV-spectral data for I-IV are similar : λ_{max}^{EtOH} 250(ε 4800), 257(ε 4200), 288(ε 4100), 299(ε 4600) nm. The site of glycosylation was readily determined as 1-N by comparison between these data with the UV-spectral data reported for 1- and 2-methylindazoles and 2-glycosylindazoles[2,4,5]. PMR-spectral data also confirm the identification of I-IV as 1-glycosylindazoles. The values of $\Delta\delta = \delta_{d\text{-DMSO}} - \delta_{CDCl_3}$ of C_3H for I and II (0.12 ppm and 0.23 ppm) are close to 0.1 ppm for 1-methylindazole, whereas those for 2-methylindazole and 2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indazole (V) are 0.47 ppm and 0.37 ppm[4,6]. In PMR spectra of



I R=Ac, III R=H



II R=Ac, IV R=H



V

Table. PMR spectra (JNM 4H-100 instrument, TMS internal standart).

	Chemical Shifts (δ ppm)								J_{vic}(Hz)		
Comp.	C_3H	C_1,H	C_2,H	C_3,H	C_4,H	C_5,H	C_6,H	CH_3CO-	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$ ($J_{4',5'}$)
I[a]	8.24	6.53	5.99	5.72	3.95 – 4.50			1.89;2.05; 2.13	3.0		
I[b]	8.01	6.26	6.07	5.82	4.00 – 4.50			1.96;2.06; 2.08	3.2		
II[a]	8.12	6.38	5.76;	5.52;	5.16	4.36	4.11	1.63;1.96; 1.96;2.05	8.6	8.6	8.6 (8.6)
II[b]	8.00	5.15 – 6.10				3.80 – 4.35		1.69;2.00; 2.03;2.06			
III[c]	8.03	6.62	5.36	4.95	4.59	4.06			4.2	4.0	4.0
IV[c]	8.05	6.10	5.00	3.95 – 4.45					8.0	9.0	
V[c]	8.02	6.70	5.02	4.70		3.94			6.3		
VII[a]	8.31	6.74	5.45	6.42	5.18	3.70	4.45	1.65;1.90; 1.98;2.02	6.0	10.0	9.0 (10.0)
VIII[c]	7.98	6.58	4.50	4.35	4.05 – 4.35				6.0	9.7	7.0

Solvent at 50°C : a d-DMSO, b $CDCl_3$, c C_5D_5N. Shifts for benzene nucleus protons in range of 6.90 -7.90 ppm.

glucosides II and IV the values of J_{vic} for protons of glucopyranose fragment indicate their β-configuration in conformation C1. Periodate oxidation followed by reduction with $NaBH_4$ of both glucoside IV and riboside III gave products with approximately equal large positive $[M]_D^{25}$(+60° for IV and +70° for III). This allows to conclude on β-configuration of riboside III. Both nucleosides III and IV demonstrate negative long-wavelength Cotton-effect in CD spectra.

The fusion method may be considered as a general method for synthesis of 1-N-glycosides of fused pyrazoles - indazoles, pyrazolo(3,4-b)pyridines and pyrazolo(3,4-b)pyrazines[7-9]. The formation of 1-glycosides at 160-170° in the presence of I_2 may be determined by their greater termostability compared to 2-isomers as well as by I_2 catalysis. This suggestion is confirmed by the fact, demonstrated in our experiments, that by heating at 160° in the presence of I_2 during 25 min 2-glucosylindazole V was completely isomerizated to 1-isomer II. We have also found that it is the addition of molecular sieve (Zeosorb 4 Å) to a solution of indazole, acetobromglucose and $Hg(CN)_2$ in boiling nitromethane that produced II in 70% yield. Experiments without addition of molecular sieve yielded only 2-glucoside V[4]. Recently molecular-sieve catalysed N→N glycosyl migration was demonstrated for vic-triazolo(4,5-d)pyrimidines[10].

By deacetylation of the mother liquors of crystllisation of I we prepared in 1% yield the isomer of riboside III the glycoside VI, m.p. 202°, $[\alpha]_D^{25}$ +90° (2.3, pyridine). Respectively while obtaining II we separated the minor product tetraacetate VII, $[\alpha]_D^{25}$ +56°(3.6, pyridine), which when deacetylated produced glycosylindazole VIII, m.p. 200°, $[\alpha]_D^{25}$ +60°(0.2, pyridine).UV-spectral data of VI-VIII indicate that they are 1-glycosylindazoles. The values of $[M]_D^{25}$ of periodate oxidation - $NaBH_4$ reduction products for VI (-60°) and VIII(-70°) are equal in magnitude and opposite in signs to those for III and IV respectively. These data permit to conclude that glycosides III and VI, IV and VIII are C-1' epimers. One can suppose that VI is 1-(α-D-ribofuranosyl)indazole and VIII is 1-(α-D-glucopyranosyl)indazole. However it is difficult to explain a large magnitude of $J_{1',2'}$(6.0 Hz) observed for VIII. J_{vic} for other carbohydrate protons are 9-10 Hz, this indicates to their trans-diaxial orientation. Recently large values of $J_{1',2'}$ (5.7 Hz and 5.3 Hz) was observed for 1-(α-D-glucopyrano-

syl)imidazole and for its tetra-acetate[11]. Glycoside VI gave a metaperiodate-benzydine test[12] typical of ribonucleosides. Both glycosides VI and VIII demonstrate negative long-wavelength Cotton-effect in CD spectra.

It is interesting that Revancar and Townsend [2] have described their "1-(β -D-ribofuranosyl)indazole", m.p. 205°, $[\alpha]_D^{23}$ +9.22° (1.0, pyridine) isolated in 5% yield as minor product by ribosylation of N-trimethylsilyl-indazole. The anomeric configuration of that compound was tentatively assigned as β- on the basis of trans-rule and a comparison of its specific rotation with that (+16.0°) reported for 1-(β -D-ribofuranosyl)benzimidazole. The 1-(β -D-ribofuranosyl)indazole (III) obtained in our experiments differs from Revancar and Townsend's compound in the values of m.p. and $[\alpha]_D$.

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