GLYCOSYLINDOLES

V. 1-(D-β-Ribopyranosyl)-6-Nitroindole and 1-(D-β-Ribopyranosyl)-6-Aminoindole*

M. N. Preobrazhenskaya, L. A. Savel'eva, and N. N. Suvorov

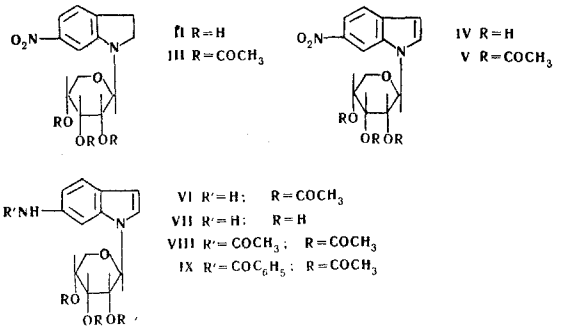
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 4, pp. 692–695, 1967

UDC 547.455.522'751

Reaction of 6-nitroindoline with D-ribose gives 1-(D-β-ribopyranosyl)-6-nitroindoline. Dehydrogenation of the O-acetyl derivative of the latter gives 1-(D-β-tri-O-acetylribopyranosyl)-6-nitroindole, deacetylation of which gives 1-(D-β-ribopyranosyl)-6-nitroindole. The pyranose portion is shown to have a pyranoside structure. Reduction of 1-(D-β-tri-O-acetylribopyranosyl)-6-nitroindole gives 1-(D-β-tri-O-acetylribopyranosyl)-6-aminoindole, and the N-acetyl and N-benzoyl derivatives of the latter are prepared.

The present authors previously reported the synthesis of 1-glycosylated indoles: 1-(D-β-glucopyranosyl)indole [1, 2] and 1-(D-β-ribopyranosyl) indole [3]. Starting from the fact that 1-glycosylindoles are indole analogs of nucleosides, it was of interest to obtain such derivatives of that type as would contain in the indole benzene ring an amino and hydroxy group. Consequently a study was made of methods of synthesizing 1-ribopyranosyl-6-nitroindole, and of passing from it to 1-ribopyranosyl-6-aminoindole.

Reaction of D-ribose with 6-nitroindole (I) [4] in boiling ethanol in the presence of ammonium chloride gave 1-(D-β-ribopyranosyl)-6-nitroindoline (II), acetylated to 1-(D-β-tri-O-acetylribopyranosyl)-6-nitroindoline (III). Compound III can be obtained without isolating pure II. Zemplen deacetylation of III with a catalytic quantity of sodium methoxide in methanol gave II. To pass to 1-(D-β-ribopyranosyl)-6-nitroindole (IV), the corresponding nitroindoline III was refluxed in xylene with 2, 3-dichloro-5, 6-dicyanobenzoquinone. However dehydrogenation did not then proceed to completion, and the product was a mixture of starting III and 1-(D-β-tri-O-acetylribopyranosyl)-6-nitroindole (V), as paper chromatography showed. The conditions for paper chromatography of acetyl derivatives of glycosylindoles were previously ascertained [2]. Zemplen deacetylation of a mixture of III and V gives a mixture of II and IV, and by recrystallizing it was possible to isolate 1-(D-β-ribopyranosyl)-6-nitroindole (IV). Paper chromatography was used to check the purity of reaction products. A ribopyranoside structure for the compounds obtained is confirmed by sodium metaperiodate [5] oxidation of IV giving 1 molecule of formic acid. 1-(D-β-Triacetylribopyranosyl)-6-nitroindole (V), free from traces of acetyl indoline derivative III, was obtained by acetylating IV. Also studied was the dehydrogenation of ribosylindoline II by 2, 3-dichloro-5, 6-dicyanobenzoquinone in dimethylformamide. A pure product of



dehydrogenation of IV was not obtained by chromatographing, but acetylation gave acetylated ribopyranosyl-6-nitroindole V in low yield.

Hydrogenating V at room temperature and atmospheric pressure using Adams catalyst in the presence of triethylamine [6], gives 1-(D-β-tri-O-acetylribopyranosyl)-6-aminoindole (VI). Acetylation of VI gave the 6-acetamino derivative VIII, benzoylation the 6-benzoylamino derivative IX. Zemplen deacetylation of 1-(D-β-tri-O-acetylribopyranosyl)-6-aminoindole (VI) gave 1-(D-β-ribopyranosyl)-6-aminoindole (VII). The formation of compounds VIII and IX by acylation of VI shows that when 5 was hydrogenated using Adams catalyst in the presence of triethylamine, the ribopyranose structure is preserved. From the results of earlier work [1, 2] a β configuration could be ascribed to the compounds prepared, but unfortunately it was not possible to confirm these data by analysis of the IR spectra, because C_1—H deformation vibrations (890–900 cm^{-1}), characteristic of β sugars, (axial hydrogen at the glucoside carbon atom) here masked the out-of-plane deformation vibrations of C—H in the 1, 2, 4-tri-substituted benzene ring [7].

EXPERIMENTAL

All IR spectra were determined with a UR-10 instrument, using vaseline mulls, and UV spectra were determined with a SF-4 instrument, on EtOH solutions.

1-(D-β-Ribopyranosyl)-6-nitroindoline (II). a) A mixture of 2.64 g 6-nitroindoline I, 1.8 g ribose, 0.8 g ammonium chloride and 70 ml absolute EtOH was stirred and refluxed for 1 1/2 hr, then left for 24 hr at room temperature. The products were column chromatographed on alumina (22 × 2.5 cm). Elution with absolute EtOH gave a first portion containing unreacted 6-nitroindoline (0.94 g), after which II was eluted out. Recrystallization from absolute EtOH gave 2.18 g (61.3%) orange II. Sometimes it was possible to isolate II without chromatographing, by evaporating the products to small volume, then

*For Part IV see [1]

cooling. The substance was recrystallized from EtOH and EtOH–ether, mp 109°–110° C. Found: C 52.87; H 5.69%, calculated for $C_{13}H_{16}O_6N_2$: C 52.70; H 5.45%. IR spectrum: 3550 cm^{-1} (OH), 1520 cm^{-1} (NO_2). UV spectrum: λ_{max} 256 nm in MeOH. (lg ε 4.18), λ_{max} 394 nm in MeOH (lg ε 3.28). R_f 0.62. Ehrlich's reagent as the visualizer gave a yellow spot.

Time, hr	Vol. of alkali used in titrating, ml
0.5	0.85
1	0.90
2	0.95
4	0.95
24	0.95

b) 0.5 g 1-(D-β-tri-O-acetylribopyranosyl)-6-nitroindoline III was suspended in dry MeOH, and a solution of MeONa added dropwise, with stirring, until the solid dissolved completely. The solution was evaporated to small volume, and cooled, when 0.26 g (72.4%) orange II was obtained, mp 115°–116° C, undepressed mixed mp with the compound prepared by method *a*, and R_f, and the IR and UV spectra were also identical.

1-(D-β-Tri-O-acetylribopyranosyl)-6-nitroindoline (III). 1 g II was dissolved in 20 ml dry pyridine, the solution stirred, and 20 ml Ac_2O added. The products were left for 24 hr at room temperature, then poured onto ice, and the yellow crystalline precipitate of III filtered off. Yield 1.26 g (88%), mp 198.5°–199° C (ex MeOH). Found: C 54.35; H 5.26; N 6.52%, calculated for $C_{19}H_{22}N_2O_9$: C 54.00; H 5.25; N 6.64%. UV spectrum 1750 cm^{-1} (CO): 1520 cm^{-1} (NO_2) nm in MeOH in cyclohexane on paper impregnated with formamide – acetone (1:1).

1-(D-β-Ribopyranosyl)-6-nitroindole (IV). 1.26 g Triacetylindoline derivative III was dissolved by heating with 40 ml xylene, the solution stirred, and 0.75 g 2, 3-dichloro-5, 6-dicyanobenzoquinone added. The mixture was refluxed for 4 hr, the products cooled and the dark precipate of dichlorodicyanohydroquinone removed by filtration. The xylene filtrate was evaporated to dryness, and the residue recrystallized from EtOH, to give 0.75 g mixed triacetates of ribopyranosyl-6-nitroindole (V) and -indoline (III). (Chromatography on paper impregnated with formamide–acetone 1:1, with cyclohexane as the mobile phase, gave 2 spots, R_f 0.07 and 0.21). A MeONa solution was added dropwise to a stirred suspension of mixed V and II in 10 ml EtOH until the solid dissolved completely. The solution was vacuum evaporated to small volume, then on cooling crystals of 1-(D-β-ribopyranosyl)-6-nitroindole IV were obtained. Yield of orange crystals mp 213.5°–215° C, 0.17 g (19.3%). Found: C 53.26; H 4.63; N 9.60%, calculated for $C_{13}H_{14}N_2O_6$: C 53.10; H 4.79; N 9.52%. UV spectrum: λ_{max} 248 nm in MeOH (lg ε 3.98), λ_{max} 326 nm in MeOH (lg ε 3.90). R_f 0.62. Erlich's reagent as the visualizer gave a raspberry-red spot.

Oxidation of 1-(D-β-ribopyranosyl)-6-nitroindole (IV). Aqueous solutions of 0.2943 g (0.001 M) ribosylindole (IV) and 0.6418 g (0.003 M) sodium metaperiodiate were mixed. The mixture was diluted with 0.1 N NaOH, from time to time, using methyl red as an indicator.

When oxidation of IV liberates an equimolecular amount of formic acid, 50 ml solution should require 1 ml 0.1 N NaOH. In the present case, therefore, oxidation of 1 mole IV gave 0.95 mole formic acid.

1-(D-β-Tri-O-acetylribopyranosyl)-6-nitroindole (V). a) The ribosylindole IV was acetylated in the same way as II. Yield 88%, mp 168.5°–169.5° C. Found: C 53.97; H 4.90; N 6.63%, calculated for $C_{19}H_{20}N_2O_9$: C 54.28; H 4.79; N 6.66%. IR spectrum 1750 cm^{-1} (CO). UV spectrum λ_{max} 246 nm in cyclohexane (1g ε 3.96), λ_{max} 316 nm in cyclohexane (lg ε 3.90). R_f 0.07, using paper impregnated with formamide–acetone (1:1).

b) 1 g Ribosylindoline (II) and 0.8 g 2, 3-dichloro-5, 6-dicyanobenzoquinone were dissolved in 50 ml freshly-distilled dimethylformamide and the mixture heated on a steam bath for 4 hr. The solvent was vacuum distilled off, the residue dissolved in absolute EtOH, and column chromatographed on alumina (12 × 2.5 cm). Elution with absolute EtOH gave dichlorodicyanohydroquinone, 6-nitroindoline, 6-nitroindole, and the starting ribosylindoline II, detected by paper chromatographing a MeOH solution. This was followed by elution with MeOH, the MeOH fraction evaporated to dryness to give 0.3 g material which was acetylated in the usual way. A small amount of V (0.05 g) was obtained. The two lots of compound had the same R_f and mp, and the same IR and UV spectra.

1-(D-β-Tri-O-acetylribopyranosyl)-6-aminoindole (VI). 3.54 g Nitroindole V was dissolved in 100 ml EtOAc, 8.25 ml Et_3N added to the solution, and 0.59 g Adams catalyst added. The mixture was shaken with hydrogen at 1 atm and room temperature until the reaction mixture was completely decolorized. The catalyst was filtered off, the filtrate evaporated to dryness, and the residue recrystallized from EtOH. Yield 3.11 g (94.5%) white crystalline product, mp 173.5°–175° C, $[\alpha]_D^{20}$ + 54.81° C ($CHCl_3$, c 3.78). Found: C 58.73 H 5.68; N 6.92%, calculated for $C_{19}H_{22}N_2O_7$: C 58.50; H 5.67; N 7.17%. IR spectrum: 3400, 3490 cm^{-1} (NH_2), 1730–1750 cm^{-1} (CO).

1-(D-β-Ribopyranosyl)-6-aminoindole (VII). 1-(D-β-Tri-O-acetylribopyranosyl)-6-aminoindole VI was deacetylated in the same way as III. 2.61 g compound VI gave 1.71 g VII (96.5%). The compound darkened at about 195° C, mp 208° C (decomp), $[\alpha]_D^{20}$ + 20.28° C, (dimethylformamide, c 2.81). Found: C 59.04; H 6.40; N 10.61%, calculated for $C_{13}H_{16}N_2O_4$: C 59.07; H 6.10; N 10.60%. IR spectrum 3300, 3380, 3580 cm^{-1} (OH, NH_2).

1-(D-β-Tri-O-acetylribopyranosyl)-6-acetylaminoindole (VIII). Triacetylribopyranosyl-6-aminoindole (VI) was acetylated as in the case of II. Pouring the products onto ice gave an oily product which was extracted with $CHCl_3$. The extract was taken to dryness and the residue triturated with aqueous EtOH. The rose-colored crystals were filtered off and recrystallized from aqueous EtOH, using decolorizing charcoal. The white crystalline product was dried in a vacuum desiccator over P_2O_5. 0.4 g VI gave 0.20 g (45.5%) VIII. The compound softened at 97° C, mp 97°–104° C. $[\alpha]_D^{20}$ + 75° C (dimethylformamide, c 1.04). $[\alpha]_D^{20}$ + 71.72° C ($CHCl_3$, c 0.98). Found: C 57.37; H 5.61; N 6.35%, calculated for $C_{21}H_{24}N_2O_8 \cdot 0.5H_2O$: C 57.13; H 5.71; N 6.34%. IR spectrum: 3200–3700 cm^{-1} (broad band characteristic of an associated hydroxyl group), 1750 cm^{-1} (CO).

1-(D-β-Tri-O-acetylribopyranosyl)-6-benzoylaminoindole (IX). 0.5 g Triacetylribopyranosyl-6-aminoindole VI was dissolved in dry pyridine and 0.4 ml benzoyl chloride added at room temperature. The mixture was left overnight, and the products poured onto ice, the oil obtained was triturated with aqueous EtOH, and the crystalline material was recrystallized from aqueous EtOH, using decolorizing charcoal. The solid was vacuum dried at 60° C over P_2O_5. Yield 0.52 g (63.33%) IX, mp 103°–105° C. $[\alpha]_D$ + + 54.54° C (dimethylformamide, c 2.42). Found: C 62.08; H 5.56; N 5.51; H_2O 1.29%, calculated for $C_{26}H_{26}N_2O_8 \cdot 0.5H_2O$; C 62.02; H 5.42; N 5.56; H_2O 1.79%. IR spectrum 3700–3200 cm^{-1} (wide band characteristic of an associated hydroxyl group), 1760 cm^{-1} (CO).

REFERENCES

1. M. N. Preobrazhenskaya and N. N. Suvorov, ZhOKh, 35, 893, 1965.

2. N. N. Suvorov and M. N. Preobrazhenskaya, ZhOKh, 31, 2839, 1961.

3. M. N. Preobrazhenskaya, M. M. Vigdorchik, A. S. Bobkov, and G. M. Sorokina, ZhOKh, 29, 2541, 1959.

4. A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, ZhOKh, 29, 2541, 1959.

5. L. Jackson and C. S. Hudson, J. Am. Chem. Soc., 61, 1530, 1939.

6. R. Kuhn and R. Ströbele, Chem. Ber., 70, 747, 1937.

7. K. Nakanisi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Mir, Moscow, 32, 42, 1965.

16 November 1965

Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific Research Institute, Moscow