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2-AMINO-2,5-ANHYDRO-2-DEOXY-DL-RIBITOL: AN AMINO SUGAR DERIVATIVE HAVING NITROGEN IN THE RING[1]

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ABSTRACT

A direct, high-yielding route for synthesis of a pyrrolidine analog of a 2-deoxy-*erythro*-pentose is reported. The synthesis involves modification of pyrrole-2-carboxylic acid by reduction followed by a hydroxylation step. The structure and stereochemistry of 2,5-anhydro-2-deoxy-2-*p*-toluenesulfonamido-DL-ribitol (**5a**) was established by chemical transformations and by ^{13}C n.m.r. data.

INTRODUCTION

There has been considerable interest in recent years in the synthesis of monosaccharide derivatives in which the ring oxygen atom is replaced by another heteroatom. Much of this work has been motivated by the hope that this type of structural change would be accompanied by biological activity of significance in both the modified sugar and in derived nucleosides.

In the course of work on synthesis of puromycin analogs, we required the hitherto unknown pyrrolidine derivative **5**. Although several examples of furanose sugars having nitrogen as the ring atom have been reported[2–9], they have all been obtained by multi-step transformations from naturally occurring monosaccharides. We report here a direct, high-yielding synthesis of **5** from a non-carbohydrate precursor.

RESULTS AND DISCUSSION

The point of departure was pyrrole-2-carboxylic acid (**1**), a compound available from natural sources and which possesses the framework necessary for modification to a simple amino sugar. The first step involved reduction of **1** with gaseous hydrogen iodide and aqueous hypophosphorous acid in acetic acid[10] to give the imino acid, dehydro-DL-proline (**2**). 3,4-Dehydro-*N*-*p*-tolylsulfonyl-DL-proline methyl ester (**3**) was prepared in almost quantitative yield from **2** by *N*-*p*-tolylsulfonylation followed

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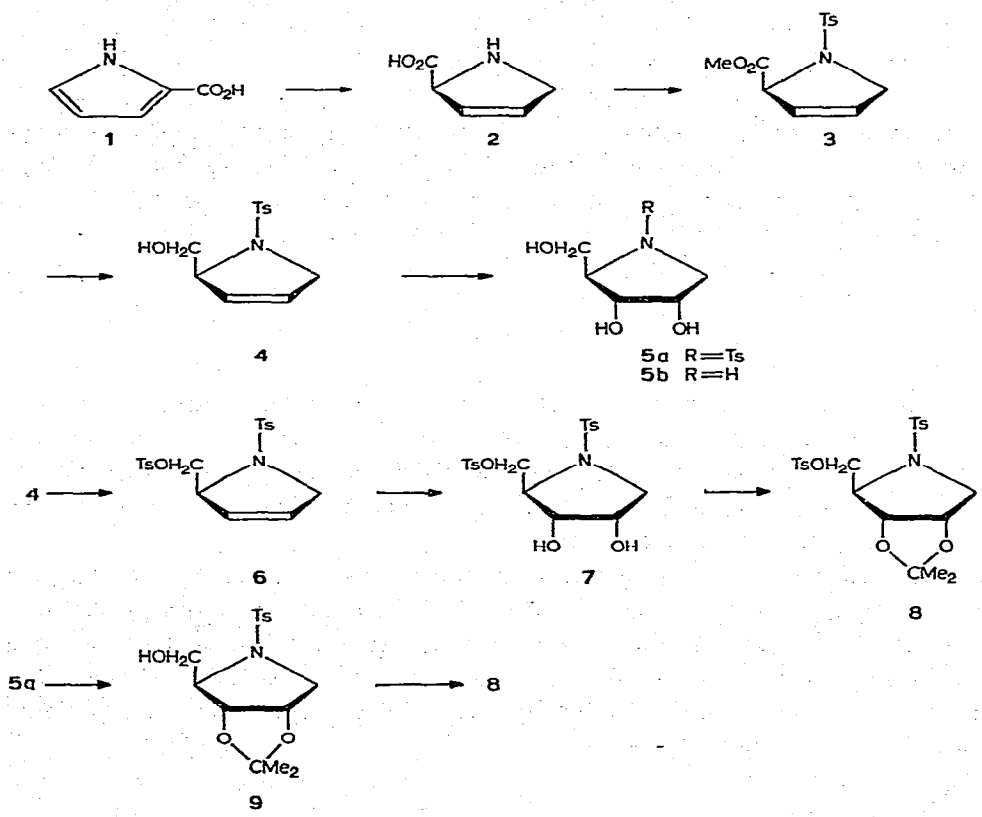
by methylation with diazomethane[11]. The ester group in **3** was then reduced almost quantitatively by lithium borohydride in tetrahydrofuran to give 3,4-dehydro-*N*-*p*-tolylsulfonyl-DL-prolinol (**4**) as a viscous oil. Hydroxylation of **4** with osmium tetraoxide gave a single compound, the diol **5a**, in quantitative yield. Desulfonylation of (**5a**) with sodium metal in liquid ammonia gave **5b**, which appeared to be extremely unstable. Electrolytic desulfonylation[12] was unsuccessful. The data recorded for this pyrrolidine sugar are therefore those of its derivative **5a**. Interestingly, the solubility and chromatographic properties of **5a** resembled closely those of mono-*p*-toluenesulfonylated ribofuranosides.



(All products are DL forms)

On mechanistic grounds, *cis*-hydroxylation with the sterically large osmium tetraoxide–pyridine complex would be expected to occur preferentially from the less-hindered face of dehydroprolinol to give 1,3-*trans*, 3,4-*cis* isomer (**5a**). Favored attack from the less-hindered face has been observed for both proline and dehydroproline derivatives[13,14]. Further confirmation of the stereochemistry was provided by the fact that acetonation gave only one product. As *cis*-hydroxylation of alkenes with osmium tetraoxide is well documented, the only possible stereochemistry in the final product other than **5a** would be the 1,3-*cis*, 3,4-*cis* isomer. The 1,3-*cis*, 3,4-*cis*

isomer would be expected to give a mixture of the 1,3- and 3,4-isopropylideneacetals, whereas **5a** would form only the one acetal, as was observed. In addition, hydroxylation of the highly hindered di-*p*-tolylsulfonyldehydroprolinol (**6**), followed by acetonation, gave a product identical with compound **8**, which had been obtained from **5a** in several steps. Indirect evidence from ^{13}C n.m.r. spectroscopy also confirmed the stereochemistry. It is known that the geometry of hydroxyl groups in sugars affects their ^{13}C chemical shifts. For example, the chemical shifts of the 2′ and 3′ carbon atoms in adenosine vary noticably from those in 9-β-D-arabinofuranosyladenine. As the chemical shifts of sugar carbon atoms in nucleosides are relatively invariant with respect to the nitrogen heterocycle[15], the chemical-shift difference must be due to geometry. Thus, the formation of more than one isomer in the hydroxylation reaction should be detectable by ^{13}C n.m.r. spectroscopy. This evidence, in conjunction with that provided by the acetonation reaction, clearly indicates that hydroxylation results in the formation of only one stereoisomer (**5a**).

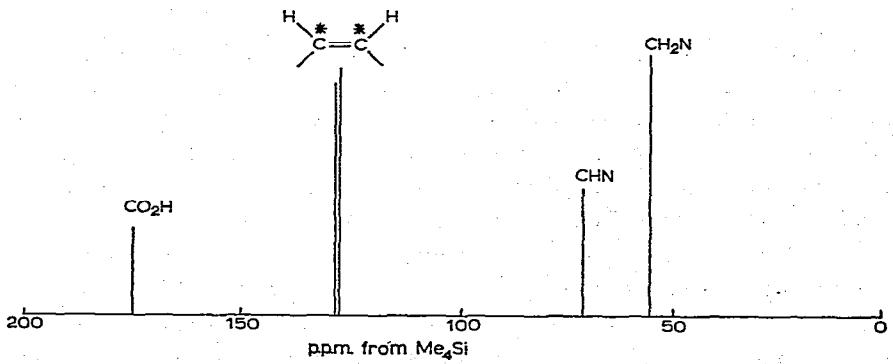


Fig. 1. The ^{13}C n.m.r. spectrum of compound **2**.

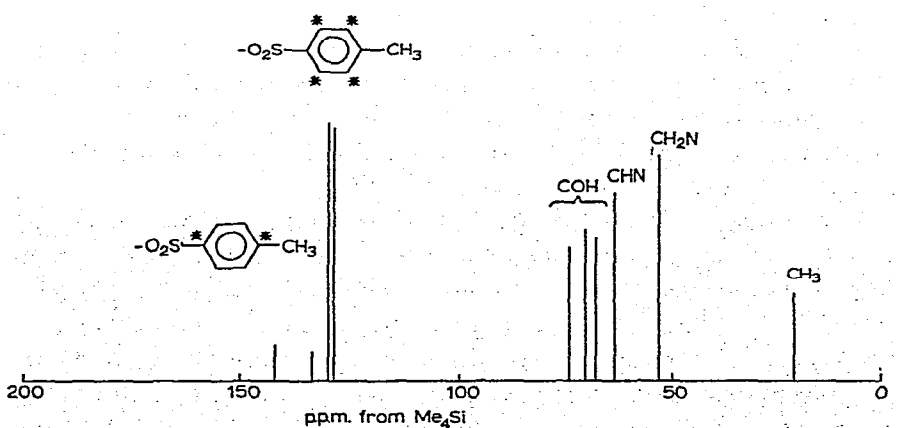


Fig. 2. The ^{13}C n.m.r. spectrum of compound **5a**.

The ^{13}C n.m.r. spectra for these compounds are simple to interpret and evaluate, as compared with the corresponding proton spectra and provide excellent evidence of structure and purity. For example, the p.m.r. spectra of dehydroproline and derivatives of it are extremely complex[16,17], and analysis of the spectrum of the amide of **2** shows it to be an ABMXX′ spin-system containing over 100 lines. However, the broad-band ^{1}H-decoupled ^{13}C n.m.r. spectrum of **2** (Fig. 1) exhibits five lines, corresponding to the five carbon atoms in the molecule. The ^{13}C spectrum of **5a** (Fig. 2) confirmed both its assigned structure and purity[18].

EXPERIMENTAL

General methods. — Melting points are uncorrected. The i.r. spectra were recorded on a Beckman IR-20A spectrometer. The p.m.r. spectra were obtained with Varian A-60 and HA-100 instruments. The carbon-13 spectra were recorded on a Bruker HX-90E Pulse Fourier Transform instrument interfaced with a Nicolet 1080 computer.

*3,4-Dehydro-*DL*-proline* (**2**). — A stirred mixture of acetic acid (150 ml) and 50% hypophosphorus acid (60 g) was cooled to −10° in an ice–salt bath. Gaseous hydrogen iodide was bubbled into the mixture until saturation was attained and the solution had turned dark brown (~30 min). Pyrrole-2-carboxylic acid (**1**, 25.28 g, 224 mmol) was then added with stirring to the reaction mixture and a continuous, gentle stream of hydrogen iodide was bubbled into the reaction mixture for 4 h. The reaction mixture was then filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in water and passed through a column packed with CGC-240 cation-exchange resin (H^+ form) (Baker Chemical Co.). The column was washed with water until the eluate was neutral, and then the product was removed by elution with 2M ammonium hydroxide. Removal of the solvent from the ammoniacal eluate and crystallization of the residue from 10:1 ethanol–water gave 3,4-dehydro-DL-proline (**2**); yield 15.37 g (62%); m.p. 236° (lit.[10] m.p. 236–237°); ^{13}C n.m.r. $\delta^{D_2O}_{Me_4Si}$: 53.30, 69.44, 121.38, 126.52, and 173.17.

*3,4-Dehydro-*N-p-*tolylsulfonyl-*DL*-proline methyl ester* (**3**). — 3,4-Dehydro-DL-proline (**2**, 5.65 g, 50 mmol) dissolved in M sodium hydroxide was sulfonylated with *p*-toluenesulfonyl chloride. Treatment of the crude product with ethereal diazomethane gave 13.49 g (96%) of 3,4-dehydro-*N*-*p*-tolylsulfonyl-DL-proline methyl ester (**3**) as white prisms, m.p. 97.5–99° (lit.[11] m.p. 97.5–98.5°).

*3,4-Dehydro-*N-p-*tolylsulfonyl-*DL*-prolinol* (**4**). — Lithium borohydride (1.32 g, 60 mmol) in 40 ml of dry tetrahydrofuran was placed in a three-necked flask fitted with a condenser and a magnetic stirrer. Compound **3** (5.62 g, 20 mmol) in tetrahydrofuran (50 ml) was added slowly, and when the addition was complete, the reaction mixture was heated for 7 h at reflux with constant stirring. The solution was then cooled, the solvent was removed *in vacuo*, and 100 g of ice containing 10 ml of concentrated hydrochloric acid was added. After the bubbling had ceased, 100 ml of dichloromethane was added, followed by 100 ml of saturated sodium chloride

solution, and the entire mixture was then transferred to a separatory funnel and shaken. The organic layer was removed, and the aqueous layer was extracted with dichloromethane (3 × 100 ml). The organic extracts were then combined, dried (sodium sulfate) and evaporated *in vacuo* to give a pink oil. The product was purified by chromatography on silica gel to give 4.39 g (87%) of the 3,4-dehydro-*N*-*p*-tolylsulfonyl-DL-prolinol (**4**) as a clear yellow oil, ν_{max} 3500, 1660, 1330, 1160, and 815 cm^{-1}; n.m.r. $\delta^{CDCl_3}_{Me_4Si}$: 2.42 (s, 3 H), 2.74–3.12 (s, 1 H, exchanged by D_2O), 3.70–3.87 (d, unresolved, 2H), 4.08–4.30 (m, 2 H), 4.30–4.65 (m, 1 H), 5.45–5.87 (m, 2 H), and 7.22–7.90 (q, 4 H).

Anal. Calc. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.69; H, 5.94; N, 5.83.

2,5-Anhydro-2-deoxy-2-p-*toluenesulfonamido*-DL-*ribitol* (**5a**). — Compound **4** (1.50 g, 6 mmol) was dissolved in 25 ml of dry pyridine and stirred overnight with 1.09 g (4.30 mmol) of osmium tetraoxide in a sealed container. A solution of 10 ml of pyridine, 30 ml of water and 1.8 g of sodium hydrogen sulfite was then added, and the reaction mixture was stirred until a clear orange color appeared (5–30 min). This solution was then extracted with chloroform (4 × 50 ml)[19]. The combined chloroform layers were dried (sodium sulfate). After removal of solvent *in vacuo*, the residual brown oil was crystallized from dichloromethane–pentane to give 1.23 g (99%) of white, crystalline **5a**, m.p. 139–139.5°; ν^{Nujol}_{max} 3590, 3300, 1600, 1360, 1160, and 818 cm^{-1}; n.m.r. $\delta^{CDCl_3}_{Me_4Si}$: 2.42 (s, 3 H), 2.90–4.48 (m, 1OH, 3 H exchanged by D_2O), and 7.24–7.90 (q, 4 H); mass spectrum, 70 eV, direct inlet, 130°, *m/e* 256 (M − CH_2OH), 223 (M − SO_2), 155 (Ts), 124, 101 (M − Ts − CH_2OH), 91 (tropylium ion), 58 (HN=CH–CH=OH), 43 ($\dot{C}H_2$–NH^+=CH_2), 42, and 28 ($CH{\equiv}NH)^+$; ^{13}C n.m.r. $\delta^{(CD_3)_2CO}_{Me_4Si}$: 20.79, 52.46, 62.94, 67.57, 69.70, 73.32, 128.02, 129.47, 134.76, and 143.67.

Anal. Calc. for $C_{12}H_{17}NO_5S$: C, 50.20; H, 5.96; N, 4.87. Found: C, 50.24; H, 5.93; N, 4.81.

3,4-Dehydro-N,O-*di*-p-*tolylsulfonyl*-DL-*prolinol* (**6**). — 3,4-Dehydro-*N*-*p*-tolylsulfonyl-DL-prolinol (**4**) (500 mg, 1.98 mmol) and *p*-toluenesulfonyl chloride (416 mg, 2.18 mmol) were dissolved in 15 ml of dry pyridine and stirred in a closed vessel for 45 h. Hydrochloric acid (2M, 100 ml) was then added and the mixture was extracted with ethyl acetate (5 × 50 ml). The organic extracts were dried (sodium sulfate) and evaporated to a yellow oil. This oil was then purified by preparative-layer chromatography on silica gel (PF-254), with 10% dichloromethane in ether as developer. After removal of the solvent and drying (vacuum pump), 598 mg (75%) of compound **5** was isolated as a brown oil; n.m.r. $\delta^{CDCl_3}_{Me_4Si}$ 2.40 (s, 3 H), 2.45 (s, 3 H), 3.96–4.82 (m, 5 H), 5.67 (bs, 2 H), and 7.18–8.00 (m, 8 H).

Anal. Calc. for $C_{19}H_{21}NO_5S_2$: C, 56.00; H, 5.19; N, 3.44. Found: C, 56.24; H, 5.31; N, 3.51.

2,5-Anhydro-2-deoxy-2-p-*toluenesulfonamido-5*-O-p-*tolylsulfonyl*-DL-*ribitol* (**7**). — Compound **6** (1.95 g, 4.79 mmol) was dissolved in 25 ml of dry pyridine and stirred with 1.00 g (3.94 mmol) of osmium tetraoxide in a sealed vessel for ~12 h. To this mixture was added, with stirring, a solution of 1.8 g of sodium hydrogen

sulfite, 30 ml of water, and 10 ml of pyridine, so that the ratio of sodium hydrogen sulfite, water, and pyridine in the final solution was about 2:30:35. When a clear orange solution was obtained (5–30 min) it was extracted with chloroform (5 × 50 ml). The combined chloroform layers were dried (sodium sulfate), the solvent was removed, and the remaining oil was further dried (vacuum pump). Purification was effected by preparative-layer chromatography on silica gel plates with acetone as the developing solvent. The diol **6** (1.86 g, 87%) was isolated after removal of solvent as a clear viscous oil: n.m.r. $\delta^{CDCl_3}_{Me_4Si}$ 2.37 (s, 3 H), 2.43 (s, 2 H), 2.85–3.82 (m, 5 H, exchanged by D_2O removes 2 H), 3.98–4.52 (m, 4 H), and 7.17–8.00 (m, 8 H).

Anal. Calc. for $C_{19}H_{23}NO_7S_2$: C, 51.69; H, 5.25; N, 3.17. Found: C, 51.47; H, 4.92; N, 3.20.

*2,5-Anhydro-2-deoxy-3,4-*O*-isopropylidene-2-*p*-toluenesulfonamido-1-*O*-p-tolylsulfonyl-*DL*-ribitol* (**8**) *from* 7. — To 120 mg (0.272 mmol) of compound 7 dissolved in 5 ml of acetone was added 0.5 ml of dimethoxypropane and one drop of concentrated sulfuric acid. After stirring in a sealed vessel for 23.5 h, 250 mg of sodium carbonate was added to neutralize the acid. After 15 min of stirring the sodium carbonate was filtered off and the filtrate concentrated to a brown oil that crystallized from ether–pentane giving 80 mg (61%) of compound **8** as light tan crystals, m.p. 141.5–144°. A mixed melting point with compound **8** prepared from **5a** (m.p. 142.5–143.5°) showed no depression, indicating that the samples were identical. The i.r. and n.m.r. spectra of the compounds obtained by both routes were also identical.

*2,5-Anhydro-2-deoxy-3,4-*O*-isopropylidene-2-*p*-toluenesulfonamido-*DL*-ribitol* (**9**). — Compound **5a** (441 mg, 1.57 mmol) was dissolved in 12 ml dry acetone together with two drops of concentrated sulfuric acid and 1.3 ml of dimethoxypropane, and the mixture was stirred overnight. An excess of sodium carbonate (1 g) was then added to the solution to neutralize the acid. After stirring for 10 min, the sodium carbonate was filtered off, the acetone extracts evaporated *in vacuo*, and the residue dried (vacuum pump). Crystallization from ether–pentane gave 451 mg (87%) of tan colored crystals: m.p. 110–111°; n.m.r. $\delta^{CDCl_3}_{Me_4Si}$ 0.85 (s, 3 H), 1.18 (s, 3 H), 2.41 (s, 3 H), 2.60 (bs, 1 H, exchanged by D_2O), 3.52–4.07 (m, 5 H), 4.44–4.86 (m, 2 H), and 7.20–7.95 (q, 4 H); *m/e* (70 eV): 327 (M^+).

Anal. Calc. for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found: C, 55.24; H, 6.56; N, 4.30.

*2,5-Anhydro-2-deoxy-3,4-*O*-isopropylidene-2-*p*-toluenesulfonamido-5-*O*-p-tolylsulfonyl-*DL*-ribitol* (**8**) *from* **9**. — Compound **9** (327 mg, 1 mmol) was dissolved in 15 ml of pyridine, and then *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) was added and the reaction mixture was stirred at room temperature for 65 h in a closed flask. After quenching the reaction by adding 100 ml of 2M hydrochloric acid mixture was extracted with ethyl acetate (4 × 50 ml). The extracts were dried (sodium sulfate) and then evaporated *in vacuo* to a yellow oil. Crystallization from dichloromethane–pentane gave 268 mg (57%) of white crystals, m.p. 142.5–143.5; n.m.r. $\delta^{CDCl_3}_{Me_4Si}$ 0.82 (s, 3 H), 1.15 (s, 3 H), 2.40 (s, 3 H), 2.46 (s, 3 H), 3.47–4.84 (m, 7 H), and 7.15–7.93 (m, 8 H); ν^{KBr}_{max} 2980, 2940, 1600, 1405, 1385, 1365, 1193, 1180, 1165, and 820 cm^{-1}.

Anal. Calc. for $C_{22}H_{27}NO_7S$: C, 54.87; H, 5.65; N, 2.91. Found: C, 54.52; H, 5.73; N, 2.89.

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