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# SOME COMMENTS ON AN ALLEGEDLY "FACILE SYNTHESIS OF NOJIRIMYCIN"

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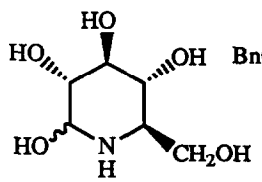
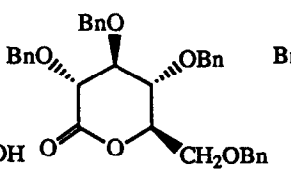
Difficulties in repeating a short synthesis of nojirimycin from 2,3,4,6-tetra-O-benzyl-D-glucono-δ-lactone are reported.

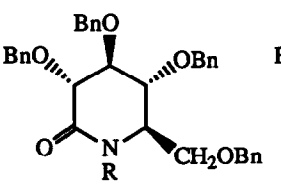
Recently, a short synthesis of nojirimycin (1) from tetra-O-benzyl-glucono-δ–lactone[1] contained only two simple - but remarkable - steps. First, the reaction of the lactone (2) with amines under mild conditions gave the corresponding lactams in which nitrogen had replaced oxygen at C-5 with retention of configuration; for example, treatment with benzylamine in toluene in the presence of molecular sieve and catalytic amounts of ion exchange resin gave the pentabenzyl-δ–lactam (3) in 80% yield and with aqueous ammonia in dioxane afforded the lactam (4). Secondly, hydrogenation of the N-benzyl lactam (3) in the presence of 5% palladium on carbon in acetic acid gave nojirimycin (1) in 72% yield. This paper reports the synthesis of the pentabenzyl lactam (3) by benzylation of the dibenzyl lactam (5); when the lactone (2) was reacted with benzylamine under a number of conditions, none of the expected lactam (3) was detected, the only product isolated being the secondary amide (7). Also, hydrogenation of the lactam (3) in the presence of palladium catalysts resulted in partial debenzylation, or complete debenzylation to give nojirimycin lactam (6); there was no evidence to indicate the formation of nojirimycin or deoxynojirimycin (9) in the reaction mixture.



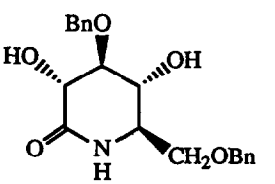
(1)



(2)

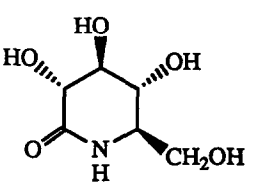


(3) R = Bn
(4) R = H

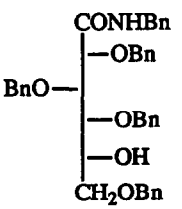


(5)

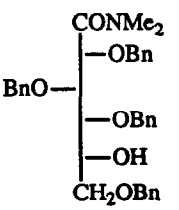
Bn = $CH_2Ph$



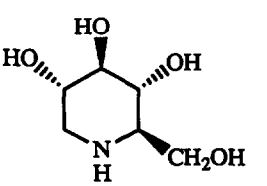
(6)



(7)



(8)



(9)

Preparation of pentabenzyl lactam (3). The dibenzyl lactam (5)[2] was added to a suspension of powdered potassium hydroxide in dry dimethyl sulphoxide and the reaction mixture stirred at room temperature for 30 min; benzyl chloride (10 equivalents) was added and after one hour the reaction was quenched with water and extracted with ether. The ether layer was then washed with brine, dried and the solvent removed to give, after purification by flash chromatography (ether/hexane 1:3 to ether/hexane 1:1), the pentabenzyl lactam (3)[3] in 40 % yield together with a more polar product (36% yield) corresponding to an unidentified tetrabenzyl lactam.[4]

Reaction of gluconolactone (2) with benzylamine. The reaction of sugar lactones with ammonia and other amines in general gives the corresponding open chain amides which are readily recyclised to the starting lactone; for example, treatment of (2) with dimethylamine gives the tertiary amide (8) which with Amberlite in dioxan reverts to the lactone (2).[5] The lactone (2)[6] was treated with benzylamine under the conditions described by Rajanikanth and Seshadri.[1] The lactone (2) (50 mg) was dissolved in dry toluene (3 ml) and treated with molecular sieve, catalytic Amberlite IR 120 $H^+$, and benzylamine (15 µl) and the mixture was heated under reflux for three hours under dry nitrogen. The reaction mixture was then cooled and filtered through a celite plug and the filter cake washed with toluene (2 x 5 ml). The solvents were removed and the residue dissolved in dichloromethane (10 ml) and the resulting solution washed with aqueous hydrochloric acid (2M, 10 ml) and water (10 ml). The solution was dried (magnesium sulphate) and the solvents removed under reduced pressure to give after purification, by flash chromatography (gradient elution, 1:3 ether:hexane to ether), the open chain secondary amide (7) (13 mg, 21%)[7] together with starting lactone (36 mg, 72%). This reaction was repeated using 45 µl of benzylamine and refluxing the reaction mixture for 12 h; under these conditions, the open chain amide (7) was isolated in 82% yield. The open chain amide (7) was also prepared by reacting the lactone (2) with benzylamine in dry ether to give an identical product to that prepared under the above conditions.

The authentic lactam (3) was a much less polar compound than the secondary amide (7) and it was clear that none of the lactam (3) was formed under either of these sets of reaction conditions. In comparing the $^{13}C$ NMR spectra of the two compounds, both have relatively high field triplets [δ 48.3 for lactam (3) and δ 43.4 for the open chain amide (7)] corresponding to the $NCH_2Ph$ group and also both display low field resonances corresponding to the amide carbonyl functions [δ 169.9 for lactam (3) and δ 170.9 for the open chain amide (7)]; a significant difference occurs in the presence of a relatively high field doublet [δ 59.0], corresponding to C-5, in the lactam (3) whereas the highest field doublet in (7) is at δ 77.5. The $^1H$ NMR spectra of the two compounds are both complex; a distinctive difference is the relatively low field signal [δ 5.25] in the lactam (3) whereas there are no signals below δ 4.9 in the spectrum of the amide (7). Further confirmation for the the structure of the secondary amide (7) is provided by both the ammonia DCI and positive ion FAB mass spectra. These both show abundant quasi molecular ions $MH^+$ m/z 646 together with a fragment ion at m/z 628 for the loss of $H_2O$ from the $MH^+$ ion which are only consistent with the secondary amide (7). The microanalytical data for the compound reported by Rajanikanth and Seshadri to be the lactam (3) approximates to that required for the open chain amide (7) [TABLE]; also the specific rotation reported by Rajanikanth and Seshadri agrees closely with that found for (7). The $^1H$ NMR spectrum reported by Rajanikanth and Seshadri for (3) is: δ 7.5 (25H, m) and 4.90 - 3.7 (15H, m), which also fits the data for (7) more closely than that for (3), in that the two proton signal at lower field than δ 5 is not present in the $^1H$ NMR spectrum of their compound.

TABLE

| | Found (%) | | | Required (%) | | | m.p.°C | $[\alpha]_D$ ° (c.,in $CHCl_3$) | |
|---|---|---|---|---|---|---|---|---|---|
| | C | H | N | C | H | N | | | |
| lactam (3) | 78.54 | 6.86 | 2.09 | 78.44 | 6.58 | 2.23 | oil | +62.0 | (0.97) |
| open chain amide (7) | 76.09 | 6.63 | 2.29 | 76.25 | 6.71 | 2.17 | 81-82 | +15.9 | (1.0) |
| data for (3) reported by Rajanikanth and Seshadri | 75.58 | 6.77 | 2.27 | | | | 62-64 | +14 | (1.0) |

The possible interconversion of the secondary amide (7) into lactam (3) was investigated. The secondary amide (7) (26 mg, 0.04 mmol) was dissolved in dioxane (5 ml) and a catalytic amount of Amberlite IR 120 $H^+$ was added. The reaction mixture was refluxed for 3 h when TLC (ether:hexane, 1:1) showed the absence of starting material (Rf 0.1) and a single less polar product ($R_f$ 0.6); this product was isolated and purified by flash chromatography (ether:hexane,1:3) to give, as expected, tetrabenzyl gluconolactone (2), (19 mg, 88%), There was no evidence for the formation of the lactam (3) under these conditions.

Our experiments indicate that the major product from the reaction of benzylamine with the gluconolactone (2) is the secondary amide (7); in our hands, the lactam (3) was not formed - neither in the reaction of benzylamine with the lactone (2), nor from the open chain secondary amide.

Hydrogenation of the per-benzylated lactam (3). The second remarkable step in the preparation of nojirimycin reported by Rajanikanth and Seshadri was the hydrogenation of (3) to give the expected removal of the benzyl protecting groups together with the novel reduction of a lactam to a 2-hydroxypiperidine; normally, amides are not reduced at all by catalytic hydrogenation in the presence of palladium but additionally the product, nojirimycin, might have been expected to undergo further reduction to deoxynojirimycin (9).[8] In order to investigate this reduction, the benzylated lactam (3) was dissolved in glacial acetic acid and then hydrogenated in the presence of 10% palladium on carbon for 40 h; the solvent was removed and examination of the crude reaction mixture by 1H NMR indicated that the removal of the benzyl groups was incomplete. Accordingly, the lactam (3) was hydrogenated in methanol in the presence of palladium black and a small amount of hydrochloric acid. Under these conditions, all the benzyl groups were removed and nojirimycin lactam (6),[9] identical to an authentic sample,[2] was formed in good yield. There was no evidence for the formation of either nojirimycin or deoxynojirimycin under the conditions of this reaction.

In summary, we have found difficulties in repeating the novel chemistry reported by Rajanikanth and Seshadri[1] for the preparation of nojirimycin; in our hands, the reaction of benzylamine with the protected gluconolactone (2) affords the expected open chain secondary amide (7) rather than the reported[1] lactam (3) and furthermore authentic lactam (3) on hydrogenation gives the expected deprotected lactam (6) rather than the reported[1] nojirimycin. If the strategy reported by Rajanikanth and Seshadri for the synthesis of nojirimycin were general, then very easy routes to a number of polyhydroxylated piperidines would be available giving easy access to this important class of amino sugar glycosidase inhibitors;[10] however, the work reported in this paper indicates that further study of the procedures indicated by Rajanikanth and Seshadri is necessary before the viability of that strategy has been demonstrated.

Acknowledgments. We are grateful to Drs. Rajanikanth and Seshadri for copies of spectra of compounds reported by them. This project has been supported by the Science and Engineering Research Council (to NGR) and G. D. Searle Monsanto (to NMC and SP).

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1 Rajanikanth, B., Seshadri, R., *Tetrahedron Lett.*, **30**, 755 (1989).

2 Fleet, G. W. J., Carpenter, N. M., Petursson, S., Ramsden, N. G., *Tetrahedron Lett.*, accompanying paper

3 Analytical data for pentabenzyllactam (3): $[\alpha]_D^{20}$ 62.0° (*c*, 0.97 in $CHCl_3$), m/z (DCI, $NH_3$): 628 ($M+H^+$, 20%), 91 ($C_7H_7^+$, 100%); $\nu_{max}$ (film): 1670 $cm^{-1}$; $^{13}C$ NMR: ($CDCl_3$, 62.5 MHz): δ 169.9 (s), 138.3 (s), 137.9 (s), 137.5 (s), 136.8 (s), 128.5, 128.3, 128.4, 127.9, 127.8, 127.7, 127.6 and 127.4 (8 x d, ArCH), 82.1 (d), 78.5 (d), 74.5 (d), 73.9 (t), 73.3 (t), 72.3 (t), 67.9 (t), 60.3 (t), 59.0 (d), 48.3 (t). $^1H$ NMR: ($CDCl_3$, 300 MHz): δ 7.4-7.2 (25H, m, ArH), 5.25 (2H, dd). 4.9-4.1 (9H, m), 3.89 (2H, m), 3.51 (2H, m) and 3.36 (1H, m). (Found: C, 78.54; H, 6.86; N, 2.09%. $C_{41}H_{41}NO_5$ requires: C, 78.47; H, 6.54; N, 2.23%).

4 m/z (DCI, $NH_3$): 538 ($M+H^+$, 20%), 91 ($C_7H_7^+$, 100%); $\nu_{max}$ (film): 3400 (br,OH), 1700 (C=O) $cm^{-1}$.

5 Kuzuhara, H., Fletcher, H. G., *J. Org. Chem.*, **32**, 2531 (1967)

6 2,3,4,6-Tetra-O-benzyl-glucono-δ-lactone was prepared as previously described in reference 5.

7 Analytical data for secondary amide (7): m.p. 81°-82°C (from ether), $[\alpha]_D^{20}$ +15.9° (*c*, 1.0 in $CHCl_3$), m/z (FAB+ ex DTTDTE): 646 ($M+H^+$), 628 ($M-H_2O+H^+$), 556 ($M-C_7H_7+H^+$), 538 ($M-C_7H_7-H_2O+H^+$), 91 ($C_7H_7^+$, 100%); $\nu_{max}$ (film): 3600 - 3200 (NH, OH), 1670 (C=O) $cm^{-1}$; $^{13}C$ NMR: ($CDCl_3$, 62.5 MHz): δ 170.9 (s), 138.3 (s), 138.0 (s), 136.8 (s), 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, (10 x d, ArCH), 80.8 (d), 80.3 (d), 77.7 (d), 77.2 (d), 75.1 (t), 74.1 (t), 73.5 (t), 71.5 (t), 71.3 (t), 43.4 (t). $^1H$ NMR: ($CDCl_3$, 300 MHz): δ 7.4-7.2 (25H, m, ArH), 6.96 (1H, br m), 4.73 - 4.45 (9H, m), 4.35-4.24 (2H, m), 4.10 (1H, m), 3.96 (1H, m), 3.89 (1H, m), 3.67 (2H, m), and 2.92 (1H, m). (Found: C, 76.09; H, 6.63; N, 2.29%. $C_{41}H_{43}NO_6$ requires: C, 76.28; H, 6.67; N, 2.17%).

8 Inouye, S., Tsuruoka, T., Ito, T., Niida, T., *Tetrahedron*, **24**, 2125 (1968)

9 Analytical data for nojirimycin lactam (6): m.p. 204°-205°C, $[\alpha]_D^{20}$ +57° (*c*, 0.63 in $H_2O$). $\nu_{max}$ (KBr): 3600 - 3000 (broad signal with peaks at 3180, 3260, 3370, 3430, (NH and OH), 1645 (br, C=O) $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 3.15 (1H, m), 3.48-3.65 (4H, m), 3.80 (1H, m); $^{13}C$ NMR ($D_2O$): δ 174.38 (s, C=O), 74.06 (d), 71.39 (d), 68.25 (d), 57.66 (d), 61.04 (t). m/z ($NH_3$,DCI): 195 ($M+NH_4^+$, 12%), 178 ($M+H^+$, 100%). (Found: C;40.41; H, 6.49; N, 7.53. $C_6H_{11}NO_5$ requires C, 40.68; H, 6.26; N, 7.91%.)

10 Fellows, L. E., Fleet, G. W. J., Alkaloidal Glycosidase Inhibitors from Plants, Chap. 13 in *Natural Product Isolation*, (ed. G. H. Wagman and R. Cooper), p. 540, Elsevier, Amsterdam, 1988.

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