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THE SYNTHESIS OF 1-AZATWISTANE*

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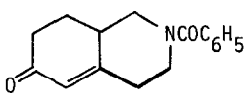
As part of our continuing interest (1,2,3) in the synthesis of the twistane skeleton, we wish now to report the synthesis of 1-azatwistane (1-azatricyclo $[4.4.0.0^{3,8}]$decane).

Catalytic reduction (Pd/C 10%, ethanol-HCl 3N) of the readily available enone amide 1 (4) gave a mixture of the dihydro derivatives 2 and 3 (ratio about 3:2) which could be separated by preparative layer chromatography (PLC) with silica gel. The cis structure 2 for the major isomer [m.p. 153°C***, litt. (4) m.p. 148-149°C] was ascertained by providing a



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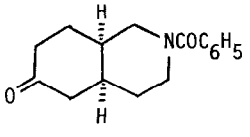

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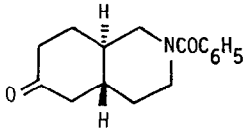

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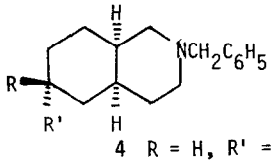
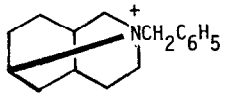


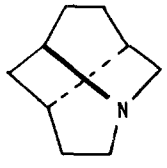
4 R = H, R' = OH

5 R = OH, R' = H

6 R = H, R' = CH_3SO_3



7 $CH_3SO_3^-$



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*** All Compounds gave satisfactory analytical and mass spectral data. I.R. and N.M.R. ($CDCl_3$-TMS) spectra are consistent with the structures proposed.

rigourous chemical proof for the structure of the minor isomer [m.p. 164-165°C, litt. (4) m.p. 159-160°C]: chemical reduction (Li/NH_3, 1 min) of 1 gave a mixture of two neutral products which were separated (PLC) and respectively identified as the starting material 1 and the minor isomer (m.p. 164-165°C) of the preceeding experiment. This result shows that the minor isomer possesses the trans structure 3 (5).

Reduction of keto amide 2 ($LiAlH_4$ in THF) gave a mixture (ratio about 1:3) of compound 4 [picrate, m.p. 163-164°C] and compound 5 [picrate, m.p. 77-79°C] which were separated by PLC.

Mesylation (CH_3SO_2Cl-pyridine in CH_2Cl_2) of the cis alcool 4 gave the mesylate 6 [τ 2.73 (5H, singlet, C_6H_5), 5.15 (1H, broad multiplet, CH_3SO_3CH), 6.55 (2H, singlet, $C_6H_5CH_2$) and 7.02 p.p.m. (3H, singlet, CH_3SO_3); hydrochloride, m.p. 166-167°C]. A solution of 6 in toluene was heated to reflux for 20 h to give the crystalline salt 7 [86%; m.p. 188°C; τ, 2.53 (5H, multiplet, C_6H_5), 5.28 (2H, singlet, $C_6H_5CH_2$), 5.78-6.70 (5H, multiplets, $-CH-\overset{+}{N}(CH_2-)_2$) and 7.20 p.p.m. (3H, singlet, $CH_3SO_3^-$)].

Hydrogenolysis of 7 (Pd/C 10%, ethanol) gave a quantitative yield of 1-azatwistane (8) [hydrochloride, m.p. 310°C dec]. This product 8 and its hydrochloride were shown to be completly identical (IR, NMR, VPC, and TLC) to samples of 1-azatwistane and its hydrochloride salt prepared by a different route (6).

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6. We are pleased to acknowledge that Dr. K. Heusler (Woodward Research Institute) informed us of his synthesis of 1-azatwistane and provided us with a sample of the hydrochloride salt (see accompanying communication).