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Synthesis of the Tricyclic Nucleus of the Alkaloid Stemofoline: X-Ray Crystal Structure of (4*RS*,5*RS*,7*SR*,10*RS*)-10-Butyl-5-hydroxy-1-azatricyclo[5.3.0.0^{4,10}]decan-2-one

Roy L. Beddoes, Michael P. H. Davies and Eric J. Thomas*

The Department of Chemistry, The University of Manchester, Manchester M13 9PL, UK

The tricyclic lactams **20** and **21** have been synthesized using iminium ion cyclisations and formation of the third ring *via* halogen metal exchange; oxidation of the lactam **22** using lead(*iv*) acetate gave the tetracyclic ether **27** regioselectively.

Stemofoline 1, a complex alkaloid with insecticidal activity against silk worm larvae,^{1,2} has not been synthesized despite its novel structure and biological activity. A key step in one possible approach to stemofoline was identified as the remote oxidation of alcohol 3, since molecular modelling studies indicated that the tricyclic nucleus of the alcohol 3 is distorted so that the *endo*-hydrogen at C(9) is closer to the hydroxy group than the *endo*-hydrogen at C(8), 2.31 *vs*. 2.85 Å. Remote oxidation³ of the alcohol 3 should, therefore, provide regioselective access to the hydroxyketone 2 (Scheme 1). We now report a synthesis of the tricyclic hydroxylactam 22, and its oxidation to the tetracyclic ether 27 using lead(1v) acetate. The structure of this ether corresponds to the tetracyclic core of stemofoline.

Ketones 5 and 6 were prepared from 5-propenylpyrrolidinone 4,^{4,5} and were converted into the cyclic imines 7 and 8 using trifluoroacetic acid in dichloromethane. The imines were cyclised stereoselectively to the tropanones 9 and 10 by treatment with methyl or 2,2,2-trichloroethyl chloroformate and triethylamine (overall yields, 50–70%),^{6–8} the structures, specifically the stereochemistry, of the products being established by spectroscopic methods and by an X-ray diffraction study of 10.[†]

Reduction of the ketone 9 using zinc borohydride gave a

mixture of the alcohols 11 and 12, ratio 38:62. Protection of the axial alcohol and further reduction using an excess of diisobutylaluminium hydride (DIBAL-H), gave the alcohol 16 together with the tricyclic product 15 formed by reduction of the carbamate and interception of the intermediate iminium ion by the primary alcohol. The formation of the tricyclic product 15 could be avoided by use of lower temperatures and less reagent.



[†] The details of this X-ray structure will be reported in a full paper.





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Scheme 2 Reagents: i, trifluoroacetic acid, CH₂Cl₂, 0 - 20 °C, 3 h; ii, methyl or 2,2,2-trichloroethyl chloroformate, CH_2Cl_2 , -78 °C, 10 min, then triethylamine, -78 °C, 12 h (9, 71% from 5:10, 51% from 6); iii, Zn(BH₄)₂·Et₂O, 0 °C, 1 h (90%); iv, 13, phenylmethyl 2,2,2-trichloroacetimidate, trifluoromethanesulfonic acid, cyclohex-ane, dichloromethane, 20 °C, 12 h (95%); 14, *tert*-butyldimethylsilyl trifluoromethanesulfonate, lutidine, dichoromethane, 1 h (86%); v, DIBAL-H, hexane, -78 °C, 1 h (16, 75%; 17, 78%); vi, iodine, triphenylphosphine, imidazole, dichloromethane, 3 h (18, 71%; 19, 83%); vii, tert-butyllithium, tetrahydrofuran (THF), -78 °C; viii, tetrabutylammonium fluoride, THF, 12 h (100%) (Bn = PhCH₂)





Fig. 1 PLUTO9 diagram of lactam 22

Treatment of the iodide 18, available from the alcohol 16, with tert-butyllithium at -78 °C, gave mixtures of the tricyclic lactam 20 and the bicyclic ester 23. The yields of these products were found to depend upon the reaction time. If the reaction was quenched by the addition of acid after 1 min, the amino ester 23 was the major product (70%). However, if the reaction was left for 30 min at -78 °C before being quenched, the tricyclic lactam 20 was the major product (86%). These observations are consistent with the participation of the tricyclic alkyllithiumcarbamate adduct 24, which on being quenched with acid gives the amino ester 23. However, if addition of the acid is delayed, elimination of lithium methoxide takes place to give the tricyclic lactam. The silvlated hydroxylactam 21 was similarly prepared (Scheme 2).

The structure of the hydroxylactam 22 was confirmed by an X-ray crystal structure determination, see Fig. 1.9[‡] The amide functionality is significantly nonplanar, the nitrogen lone-pair being in the plane of the carbonyl group, and the carboxyl carbon-nitrogen bond length is 1.432 Å.10 The predicted twist in the tropanone system is apparent with the oxygen of the hydroxy group being 2.97 and 2.32 Å from the endohydrogens at C(8) and C(9), respectively.

These structural features influence the spectroscopic and chemical properties of the tricyclic lactams. Their IR amide carbonyl stretching absorptions are at 1746 cm⁻¹, and reduction of 20 using lithium aluminium hydride gave the alcohol 25 as a single diastereoisomer, characterised as its acetate 26. To test the regioselectivity of the proposed remote oxidation, the alcohol 22 was treated with lead(IV) acetate (Scheme 3).11 This gave the bridged ether 27 (35%) together with a small amount of the ketone 28. No product corresponding to oxidation at C(8) was isolated.

Crystal data for 22: C₁₃H₂₁NO₂, colourless, prismatic, m.p. 86–88 °C, crystal dimensions $0.280 \times 0.280 \times 0.560$ mm, triclinic, a =12.452(1), $\dot{b} = 16.234(1)$, c = 6.443(1) Å; $\alpha = 100.362(9)$, $\beta =$ $P_{0.57(1), \gamma} = 98.543(6)^{\circ}, U = 1266.1(2)$ Å³, space group *P*I (No. 2), *Z* = 4, *F*(000) = 488. ω -20 scans of (1.21 + 0.30 tan0)^o were made at a speed of 32.0° min⁻¹ at 297(1) K; 3958 reflections were collected with $0^{\circ} < 2\theta < 120.0^{\circ}$; of these, 3755 were unique and 2771 with $F > 10^{\circ}$ $3.0\sigma(F)$ were used in the analysis. The data were collected on a Rigaku AFC5R diffractometer using graphite monochromated Cu-Ka radiation. Lorentz, polarisation and linear intensity drift (maximum 0.99%) corrections were applied. The structure was solved by direct methods. Two crystallographically distinct molecules were found, but these differed only in the conformation of the butyl side-chain. The refinement converged with R = 0.063, $R_w = 0.086$. All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation, 1985.12 Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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The structure of the tetracyclic ether 27 corresponds to the tetracyclic core of stemofoline, and establishes the viability of the proposed remote oxidation for the regioselective introduction of the hydroxy substituent at C(9). This work is being continued to complete a synthesis of stemofoline.

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