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GENERAL METHODS OF ALKALOID SYNTHESIS. AMBIDENT NUCLEOPHILICITY OF VINYLOGOUS URETHANES. SYNTHESIS OF (±)-LUPININE AND A FUNCTIONALISED HYDROJULOLIDINE DERIVATIVE.

By G.C. Gerrans*, A.S. Howard*, and B.S. Orlek.
(Department of Chemistry, University of the Witwatersrand, Johannesburg 2001. South Africa)

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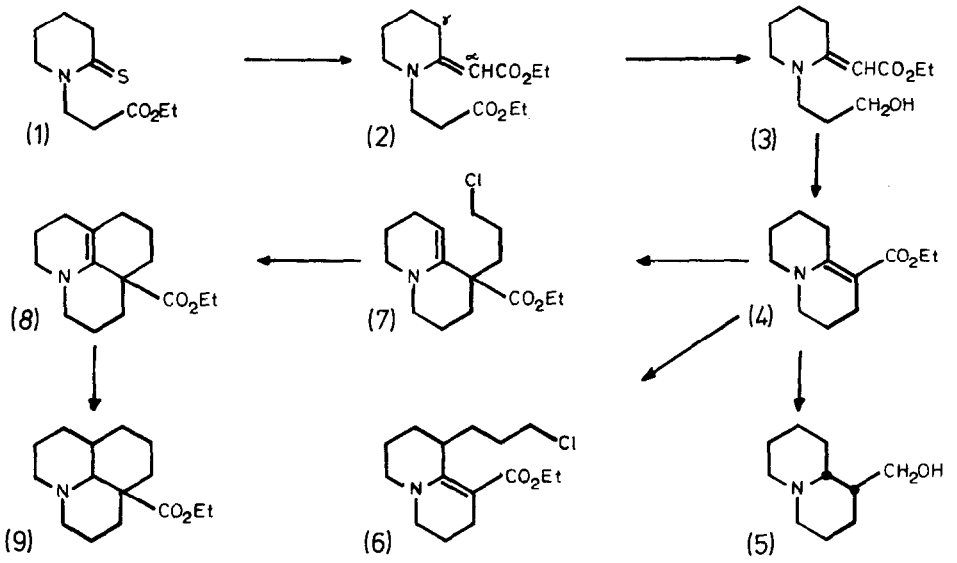
Many alkaloid structures incorporate variously substituted pyrrolizidine, indolizidine, and quinolizidine ring systems. Consequently, development of a general method for the synthesis of functionalised derivatives of these ring systems, suitable for elaboration into a variety of alkaloids, appealed to us a worthwhile objective[1]. The key steps in our approach involve the selective use of the ambident nucleophilicity of the vinylogous urethane group at the α- and γ-C atoms. Some of our initial investigations are in the area of functionalised quinolizidines, and we report here the synthesis of the Lupin alkaloid, (±)-lupinine (5), and of the hydrojulolidine derivative (8).

2-Thiopiperidone was treated with ethyl acrylate in the presence of a catalytic amount of NaH[2] to give the N-alkyl derivative (1),[3] b.p. 110-115°/1 x 10^{-4} torr; IR (film): 1730, 1515, cm^{-1}; NMR ($CDCl_3$): 1,25(t) 3H, 4.18(q) 2H; (94%). Reaction of (1) with ethyl bromoacetate followed by Et_3N/Ph_3P[4] gave the vinylogous urethane (2), b.p. 130-137°/0.001 torr; IR (film): 1725, 1670, 1560 cm^{-1}; NMR ($CDCl_3$): 4.53(s) 1H; UV (EtOH): 289 nm (ε 18,300); (70%). The saturated ester group was selectively reduced with $LiAlH_3OEt$ to the alcohol (3), m.p. 47-48°; IR (KBr): 3410, 1640, 1550 cm^{-1}; NMR ($CDCl_3$): 4.53(s) 1H, 2.52(s) 1H - exchanges with D_2O; UV (EtOH): 290 nm (ε 27,700); (71%) which, on treatment with NaH/pTsCl followed by warming in CH_3CN, gave directly the bicyclic vinylogous urethane (4)[5], b.p. 98-100°/0.03 torr; IR (film): 1660, 1560 cm^{-1}; NMR ($CDCl_3$): no 1H singlet in the vinyl region; UV (EtOH): 304 nm (ε 19,900); (60%). Conversion of this compound to (±)-lupinine (5), m.p. 58.5-59.5°; IR (KBr): 3200 cm^{-1}; NMR ($CDCl_3$): 5.05(s) 1H - exchanges with D_2O; was effected in 65% yield by the method of Goldberg[6] using $NaBH_4$ followed by $LiAlH_4$.

Treatment of (4) with n-BuLi[7] in THF and 1-bromo-3-chloropropane gave a mixture of α- and γ-substituted products which were separated by column chromatography into the vinylogous urethane (6), IR (film): 1665, 1550 cm^{-1}; NMR ($CDCl_3$): no 1H singlet in the vinyl region; UV (EtOH): 304 nm (ε 22,400); (10%), and the endocyclic enamine (7), IR (film): 1725, 1640 cm^{-1}; NMR ($CDCl_3$): 4.6 (t) 1H; UV (EtOH): 223 nm (ε 3,900); (67%). The preponderance of the α-substituted product was surprising in the light of model studies carried out in this laboratory[8] and of published results[7,9]. Cyclisation of the major product, (7), to the tetrahydrojulolidine derivative, (8), b.p. 90-100°/ 4 x 10^{-4} torr; IR (film): 1720, 1665 cm^{-1}; NMR ($CDCl_3$): No 1H singlet in the vinyl region; UV (EtOH): 224 nm (ε 4,200); (25%-yield not optimised) was brought about by

reaction with NaI in acetone followed by warming in CH_3CN. The minor product (6) did not cyclise under these conditions. Catalytic reduction (H_2 - PtO_2/EtOH) of (8) gave a stereoisomeric mixture of hexahydrojulolidine derivatives (9), IR (film): 1725 cm^{-1}; shown by g.l.c. to be comprised of three components, one of which constituted ~75% of the total.



Extension of this sequence using other three-carbon fragments to give Lycopodine hydrojulolidines and application of the general scheme to the synthesis of functionalised pyrrolizidines and indolizidines are both under investigation.

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