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THE SYNTHESIS OF RHAZINILAM

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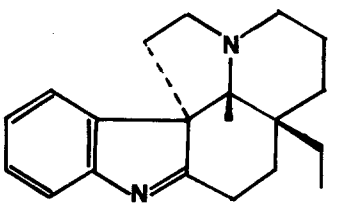
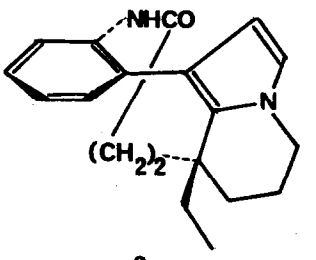
We wish to report a partial synthesis of (-)-rhazinilam (2) from (+)-1,2-dehydroaspidospermidine (1), and a total synthesis of (±)-rhazinilam (10). The alkaloidal artefact[2] (-)-rhazinilam has been isolated by several authors from a number of different plant species[1] and its structure strongly suggests a derivation from a relatively simple Aspidosperma alkaloid.

Partial Synthesis of (-)-Rhazinilam.

The above hypothesis gains some support from our current observation that (+)-1,2-dehydroaspidospermidine (1) when treated with m-chloroperbenzoic acid, then with aqueous iron (II) sulphate, gives a moderate yield of (-)-rhazinilam (2) (ca. 30% from 1: the reaction conditions have not yet been optimised; identity established by mixed m.p., tlc., spectral behaviour and optical rotation measurements). This correlation gives the absolute configuration of (-)-rhazinilam shown in 2[3].

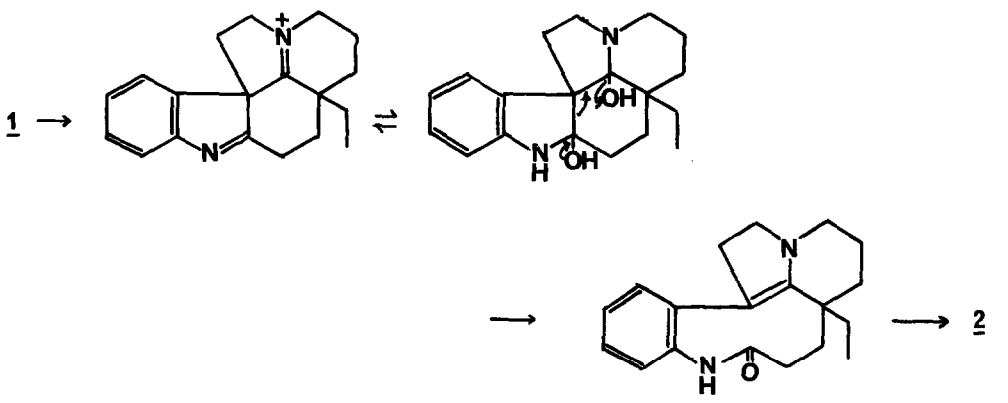


1



2

Initial studies indicate the oxidation reaction is complex and a detailed description will be given in a subsequent publication. A plausible reaction sequence for the conversion is given below.

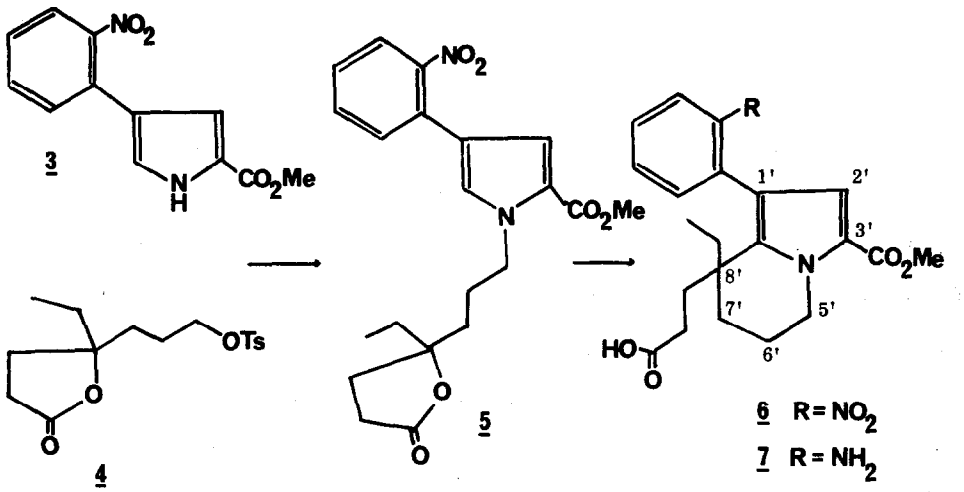


Total Synthesis of (±)-Rhazinilam.

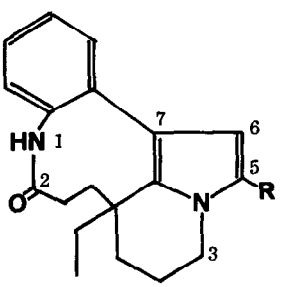
The two crucial steps in the total synthesis involved the alkylation of 2-methoxycarbonyl-4-(2'-nitrophenyl) pyrrole (3) as the sodium salt by 4-ethyl-4-hydroxy-7-tosyloxyheptanoic acid γ-lactone (4) to give 4-ethyl-4-hydroxy-7-(1'-[2'-methoxycarbonyl-4'-(2"-nitrophenyl)pyrrolyl]) heptanoic acid γ-lactone, $C_{21}H_{24}N_2O_6$ (5) (90% yield), which on cyclisation by anhydrous aluminium chloride in nitromethane gave 3-(8'-[1'-(2"-nitrophenyl)-3'-methoxycarbonyl - 8'-ethyl-5', 6', 7', 8'-tetrahydroindolizinyl]) propanoic acid, $C_{21}H_{24}N_2O_6$ (6) (50% yield from 5).

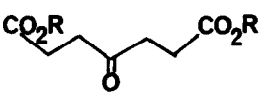
The carboxylic acid 6 contains the entire carbon skeleton of rhazinilam and an extra carbon atom as the carbomethoxy group whose function in the lactone 5 is simply to direct the subsequent cyclisation in the desired way.

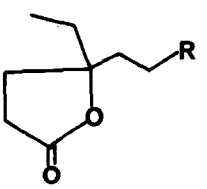
The synthesis was completed in four steps by reduction of the nitro group in 6 using H_2/Adams PtO_2/EtOAc[4] to give 3-(8'-[1'-(2"-aminophenyl)-3'-methoxycarbonyl-8'-ethyl-5', 6', 7', 8'-tetrahydroindolizinyl]) propanoic acid, $C_{21}H_{26}N_2O_4$ (7) (86% yield), which was then lactamised by dicyclohexylcarbodiimide in THF[5] to give (±)-5-methoxycarbonylrhazinilam, $C_{21}H_{24}N_2O_3$ (8) m.p.



254-5° (> 95% yield) saponification of the ester function in (8) with aqueous methanolic sodium hydroxide at 50° gave (±)-rhazinilam-5-carboxylic acid (9)*, decarboxylation of which occurred smoothly at







8 (R = -COOCH$_3$)

9 (R = -COOH)

10 (R = -H)

11 (R = -Et)

12 (R = 2-ethylhexyl)

13 (R = -COOEt)

14 (R = -COOH)

15 (R = -COCl)

16 (R = -CHO)

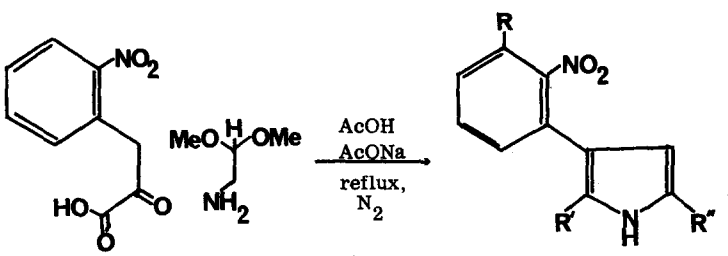
17 (R = -CH$_2$OH)

18 (R = -CH(NPh)(NPh))

*Numbering follows that of Aspidosperma alkaloids, cf Ref. 1.

240°/0.05 mm to give (±)-rhazinilam, $C_{19}H_{22}N_2O$ (10) (88% yield from 8), as a white crystalline sublimate m.p. 222-3°. The identity of the racemic product with (-)-rhazinilam (2) from Rhazya stricta was established by complete identity of their UV, IR, 100 M.Hz NMR and mass spectra, together with identical TLC behaviour in four different systems.

The starting point for the synthesis of the lactone 4 was the interaction of diethyl 4-ketopimelate (11) and ethyl magnesium bromide. This reaction is reported[6] to give a high yield of 4-ethyl-4-hydroxyheptane-1,7-dioic acid ethyl ester γ-lactone (13) using one molar proportion of the Grignard reagent: we were unable to obtain a high yield under these conditions. In our hands, using 1.5 molar equivalents of the Grignard reagent, the maximal yield (after hydrolysis) of the corresponding acid 14 was only 40%. This behaviour is parallelled by previous work on the interaction of di-(2-ethylhexyl)-4-ketopimelate (12) and methyl magnesium iodide[7]. The lactone acid 14 was converted into 4-ethyl-4,7-dihydroxyheptanoic acid γ-lactone (17) by way of 4-ethyl-4-hydroxy-6-chlorocarbonyl hexanoic acid γ-lactone (15) which on Rosenmund reduction[8] gave 4-ethyl-4-hydroxyheptan-7-aloic acid γ-lactone*, $C_9H_{14}O_3$ (16) which was further reduced by $NaBH_4$ to the alcohol 17**, $C_9H_{16}O_3$ (70% yield from 14). Tosyl chloride in pyridine at 25° converted the alcohol 17 into the tosylate 4, $C_{16}H_{22}O_5S$ (78% yield).



19 (R = R' = R" = -H)

20 (R = R" = -H, R' = -COOH)

21 (R = -Cl, R' = R" = -H)

22 (R = R" = -H, R' = -CHO)

23 (R = R' = -H, R" = -CHO)

24 (R = R' = -H, R" = -COOH)

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*Characterised also as the N,N'-diphenylimidazolidine derivative 18, m.p. 137-9°.
**Characterised also as the acetate, 3,5-dinitrobenzoate and α-napthylurethane (all non-crystalline).

Synthesis of the pyrrole 3 started with the ring synthesis of 3-(2'-nitrophenyl)pyrrole, $C_{10}H_8N_2O_2$ (19), obtained together with the easily decarboxylated carboxylic acid 20, $C_{11}H_8N_2O_4$, (combined yield 20%) following the method described for the synthesis of the pyrrolnitrin analogue 21[9a)-9d)].

The pyrrole 19 was formylated by the Vilsmeier method to give a 1:4 mixture of 2-formyl-3-(2'-nitrophenyl)pyrrole (22) and 2-formyl-4-(2'-nitrophenyl)pyrrole, $C_{11}H_8N_2O_3$ (23), (combined yield 80%): the major isomer 23 (m.p. 145-7°) was easily separated from the mixture by crystallisation. Oxidation of the formyl pyrrole 23 using silver oxide in aqueous methanol[10] gave the corresponding 4-(2'-nitrophenyl)pyrrole-2-carboxylic acid, $C_{11}H_8N_2O_4$ (24), which on treatment with diazomethane gave the pyrrole 3, $C_{12}H_{10}N_2O_3$, m.p. 114° (82% yield from 23).

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REFERENCES

1. H.A. Linde, Helv. Chim. Acta, 48, 1822, (1965); A. Banerji, P.L. Majumder and A. Chatterjee, Phytochemistry, 9, 1491, (1970); K.T. De Silva, A.H. Ratcliffe, G.F. Smith and G.N. Smith, Tet. Letters, 913, (1972); D.J. Abraham, R.D. Rosenstein, R.L. Lyon and H.H.S. Fong, Tet. Letters, 917, (1972).
2. A.H. Ratcliffe, G.F. Smith and G.N. Smith, unpublished results.
3. W. Klyne, R.J. Swan, B.W. Bycroft and H. Schmid, Helv. Chim. Acta., 48, 443, (1965).
4. G.H. Cooper and R.L. Rickards, J. Chem. Soc. (C), 3759, (1971).
5. Fieser and Fieser, Reagents For Organic Synthesis, Wiley, 1967, vol. 1, p.231.
6. T. Mizuno, Kumanto Univ. J. Science, 7(1), 17, (1965).
7. J.W. Westfahl, J. Amer. Chem. Soc., 80, 3428, (1958).
8. E. Mosettig and R. Mozingo, Organic Reactions, 8, 218, (1954).

9. a) S. Umio, K. Kariyone and K. Tanaka (Fujisawa Pharmaceutical Co. Ltd.), Japan 69-10, 263, (Chem. Abs., 71, 38799, (1967).); b) S. Umio, K. Kariyone and K. Tanaka (Fujisawa Pharmaceutical Co. Ltd.), Japan 70-14, 065, (Chem. Abs., 73, 45326, (1970).); c) S. Umio K. Kariyone and K. Tanaka (Fujisawa Pharmaceutical Co. Ltd.), Japan 72-07, 548; (Chem. Abs., 77, 5322, (1972).); d) K. Tanaka, K. Kariyone and S. Umio, Chem. Pharm. Bull. (Tokyo), 17(3), 622, (1969).

10. P. Hodge and R. Rickards, J. Chem. Soc. (C), 2543, (1963).