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SYNTHETIC STUDIES IN THE ALKALOID FIELD - XII[1]

VALLESIACHOTAMINE MODELS

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Our continuing interest in preparing indole alkaloid models of vallesiachotamine 1[2] type has led us to investigate the sodium dithionite reduction of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-(α-methoxycarbonylpropenyl)pyridinium bromide 2. The results obtained are the subject of the present communication.

Alkylation of the recently described[3,4] diester 3 with tryptophyl bromide[5] yielded 2.

Pyridinium bromide 2. Yield 85 %. Amorphous mass. IR (KBr): NH 3400 (m), C=O 1735 (s) cm^{-1}.

Sodium dithionite treatment [2] of 2 in aqueous methanol afforded 4 and 5.

Tetrahydropyridine 4. Yield 25 %. Viscous oil. IR (film): NH 3340 (m), C=O 1730 (s), 1675 (s), C=C 1615 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.50 (3 H, d, J 7 Hz, -C=CH-$\underline{CH_3}$)[6], 3.68 (3 H, s, -$COOCH_3$), 3.70 (3 H, s, -$COOCH_3$), 6.96 (1 H, d, J 2 Hz, indolyl α-H), 7.50 (1 H, s, C-2-H), 8.20 (1 H, s, NH). MS: 382 (M), 252, 144, 130.

(±)-19,20-Dihydro-20-desformyl-20-methoxycarbonylvallesiachotamine 5 (biogenetic numbering). Yield 5 %. M.p. 203-205 °C (MeOH). IR, MS and TLC were identical with those of the sample described earlier (Ref. 2, compound 4b).

The isolation of 5, although in low yield, indicated that an alternative synthetic route to this recently described[2] vallesiachotamine 1 model was in hand.

Aware of the strong reducing power of sodium dithionite,[7-11] we expected at the beginning of our study that the propenyl side chain of 2 would probably

be totally reduced.[12] However, the isolation of 4 showed that this was not the case. Unfortunately thinking of a possible route to 20-desformyl-20-methoxycarbonylvallesiachotamine 6 the conservation of the propenyl side chain in this dithionite treatment was intimately connected with the reduction of the pyridine ring to the tetrahydropyridine stage.

Buffering the sodium dithionite reaction medium[2] with sodium bicarbonate led to the hydropyridine derivatives 7a-b (a mixture of E and Z isomers) and 8.

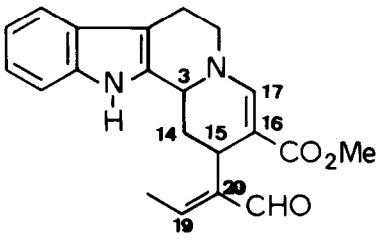
Hydropyridines 7a-b. Yield 15 %. Viscous oil. IR ($CHCl_3$): C=O 1725 (s), 1675 (s), C=C 1615 (m), 1590 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.24 (3 H, t, J 7 Hz, =C-CH_2-CH_3), 3.00 and 3.02 (2 H, 2xq, J 7 Hz, =C-CH_2-CH_3), 3.48, 3.65, 3.67 and 3.68 (6 H, 4xs, -$COOCH_3$ groups), 4.66 and 4.70 (1 H, 2xd, J 8 Hz, C-5-H), 5.64 and 5.66 (1 H, 2xdd, J_1 8 Hz, J_2 2 Hz, C-6-H), 6.95 (1 H, br d, J 2Hz, indolyl α-H), 7.10 and 7.20 (1 H, 2xd, J 2 Hz, C-2-H), 8.20 (1 H, br s, NH). MS: 380 (M), 352, 321, 144, 130.

Hydropyridine 8. Yield 12 %. Viscous oil. IR, MS and TLC were identical with those of the sample described earlier (Ref. 2, compound 9b).

Acid-induced cyclization[2] of 7a-b yielded 9a-b.

Indoloquinolizines 9a-b. Yield 45 %. Paste. IR ($CHCl_3$): C=O 1725 (s), 1675 (m), C=C 1605 (m) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (3 H, br t, J 7 Hz, =C-CH_2-CH_3), 3.02 (2 H, m, =C-CH_2-CH_3), 3.70, 3.74, 3.93 and 3.95 (6 H, 4xs, -$COOCH_3$ groups), 4.40 (1 H, m, C-12b-H), 7.40 and 7.43 (1 H, 2xs, C-4-H), 9.24 and 9.34 (1 H, 2xbr s, NH). MS: 380 (M), 352, 321.

The isolation of hydropyridines 7a-b is of great interest, because, it apparently represents the first example of a dithionite reduction of a pyridinium salt where an exocyclic double bond assists in the formation of the reduction products. The generality of this new phenomenon and its applicability to the syntheses of other indole alkaloids is under investigation.



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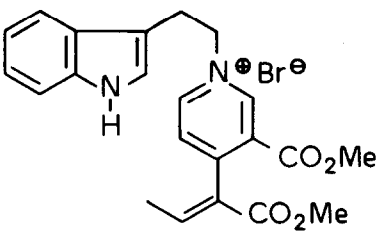

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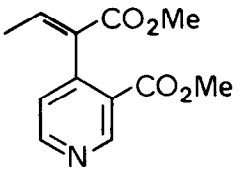

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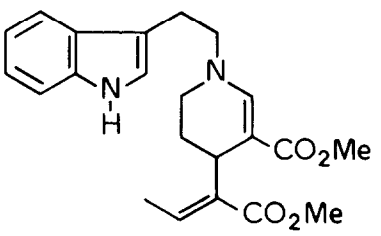

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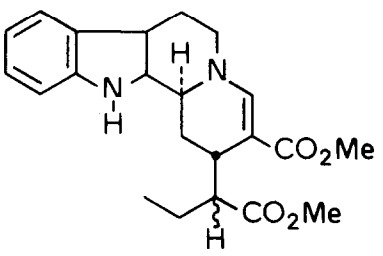

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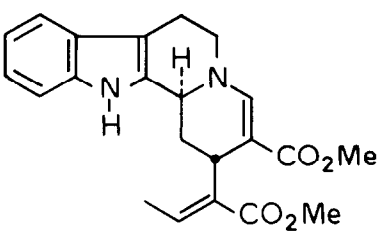

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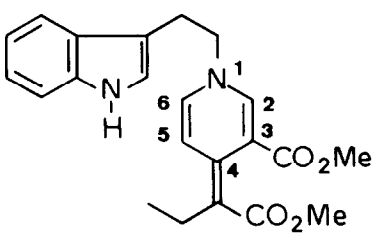
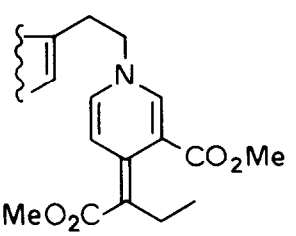
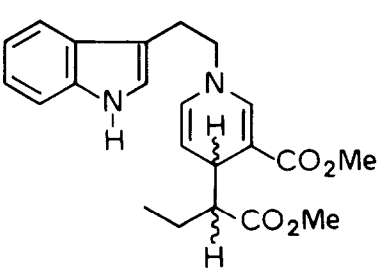


7a



7b



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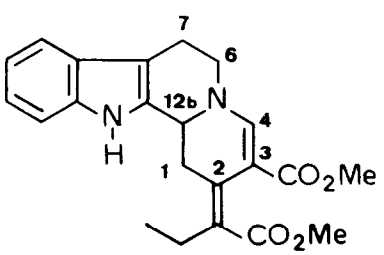

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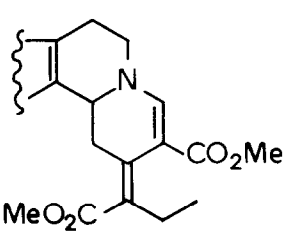

9b

REFERENCES and NOTES

1. Part XI: M. Lounasmaa and M. Puhakka, Planta Medica. In press.
2. M. Lounasmaa, P. Juutinen and P. Kairisalo, Tetrahedron. In press.
3. E. Wenkert, P.W. Sprague and R.L. Webb, J. Org. Chem. 38, 4305 (1973).
4. In accordance with the earlier results[3] the diester obtained consisted of two isomers in about 9:1 ratio. Assuming the normal stereochemical course of an aldol type condensation we assign the structure depicted on formula 3 to the major isomer.
5. T. Hoshino and K. Shimodaira, Justus Liebigs Ann. Chem. 520, 19 (1935).
6. The weak doublet at δ 1.38 (J 7 Hz) in the ^{1}H NMR spectrum of 4 is probably due to the presence of a small amount of the other geometrical isomer of the propenyl side chain (cf. Ref. 3 and Note 4).
7. R.F. Hutton and F.H. Westheimer, Tetrahedron 3, 73 (1958).
8. R.E. Lutz and S.M. King, J. Org. Chem. 17, 1519 (1952).
9. C.G. Overberger, M. Valentine and J.-P. Anselme, J. Am. Chem. Soc. 91, 687 (1969).
10. J.G. de Vries, T.J. van Bergen and R.M. Kellogg, Synthesis, 246 (1977).
11. H. Minato, S. Fujie, K. Okuma and M. Kobayashi, Chem. Lett. 1091 (1977).
12. Owing to the formation of hydropyridine derivatives, the hydride transfer mechanism must be taken into consideration as well; D.M. Hedstrand, W.H. Kruizinga and R.M. Kellogg, Tetrahedron Lett. 1255 (1978) and references therein.

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