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STEREOSELECTIVE TOTAL SYNTHESIS OF (+)-VINCAMINE

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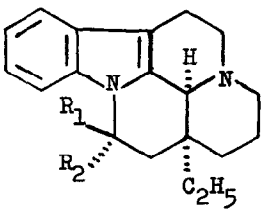
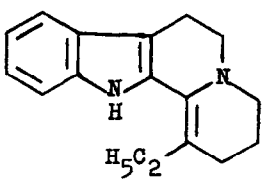
Two non-stereoselective syntheses of the racemic form of vincamine (1a), a therapeutically useful[1] alkaloid, are described in the literature[2,3]. The purpose of our present work was a stereoselective synthesis of this compound

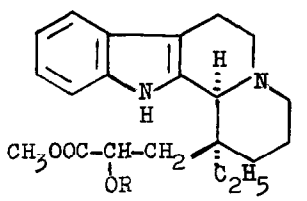


1a R_1= OH R_2= $COOCH_3$

1b R_1= $COOCH_3$ R_2= OH



2a



3a R = $COCH_3$

3b R = H

The reaction of the enamine 2, described by Wenkert[4], with methyl acrylate gave an adduct in excellent yield. However, either catalytic (Pd) or chemical ($NaBH_4$) reduction of the adduct yielded the two possible stereoisomers, prepared earlier by Kuehne[2], in a ratio almost 1:1.

If the addition reaction was carried out with α-acetoxyacrylic acid methyl ester[5] instead of acrylic acid ester, and the product [perchlorate salt mp. 152-154°, IR ν_{max}^{KBr} (cm^{-1}): 3570, 3480 (NH), 1740, 1736 (CO), 1630, 1525 (C=N)] was reduced catalytically (Pd-methanol), only one stereoisomer (3a) [mp. 144° from methanol, IR ν_{max}^{KBr} (cm^{-1}): 3420 (NH), 2800-2730 (weak Bohlmann bands), 1740 (CO)] was obtained in a good yield.

Using $NaBH_4$ as a reducing agent, 3a was accompanied by a small amount of another epimer which, after deacetylation, had mp. 165-167° [IR ν_{max}^{KBr} (cm^{-1}): 3450 (NH), 3380 (OH), 2800-2730 (strong Bohlmann bands), 1745 (CO)].

Deacetylation of 3a by sodium methoxide in methanol furnished the alcohol 3b, which had mp. 234° [IR ν_{max}^{KBr} (cm^{-1}): 3420 (broad, NH, OH), 2820-2720 (weak Bohlmann bands), 1745 (CO)]; this is 30° higher than the mp. reported by Gibson and Saxton[3], so probably 3b and the earlier described compound, are epimers on the carbon atom bearing the hydroxyl function.

The alcohol 3b was readily oxidized by Ag_2CO_3/Celite [Fétizon reagent] in benzene to a mixture of vincamine and 14-epivincamine. However, if the oxidation was carried out at the boiling point of xylene, vincamine was obtained as the main product.

When 14-epivincamine (1b) was boiled in xylene in the presence of Fétizon reagent or another Ag^+ or Hg^+ compound, it readily epimerized to a mixture containing about 80% vincamine and 20% 14-epivincamine. Epimerization can be best achieved by using sodium methoxide in methanol, when the conversion 1b ⟶ 1a is practically quantitative.

Thus a fully stereoselective synthesis of vincamine has been achieved.

The resolution of racemic vincamine was effected with dibenzoyltartaric acid in methanol.

(+)-Vincamine was oxidized at room temperature in acetic acid by $K_2Cr_2O_7$ to 3,4-dehydrovincamine, isolated as the perchlorate salt [mp. 185-186°, IR ν_{max}^{KBr} (cm^{-1}): 3400 (OH), 1740 (CO), 1580 (C=N)]. 3,4-Dehyrovincamine could not be reduced to vincamine, but only to 3-epivincamine which has the thermodynamically more stable trans C/D ring junction [mp. 189-190°, IR $\nu_{max}^{CHCl_3}$: 2750-2805 cm^{-1}, (Bohlmann bands)]. 3-Epivincamine is also a natural alkaloid isolated by Cava et al.[6]

References

1. L. Szporny and K. Szász, Arch. Exp. Path. Pharm., 236, 296 (1959).
2. M.E. Kuehne, J. Amer. Chem. Soc., 86, 2946 (1964); Lloydia 27, 435 (1964).
3. K.H. Gibson and J.E. Saxton, Chem. Commun., 1969, 1490.
4. E. Wenkert and B. Wieckberg, J. Amer. Chem. Soc., 87, 1580 (1965).
5. J. Wolinsky and R. Novak, J. Org. Chem., 29, 3596 (1964).
6. M.P. Cava, S.S. Tjoa, R.A. Ahmed and A.I. DaRocha, J. Org. Chem., 33, 1055 (1968).