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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XII[1]
AN UNUSUAL RACEMIZATION. CHROMIC EFFECT.

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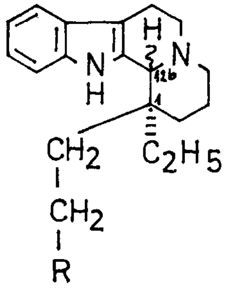
Abstract: Oxidation of the quinolizine derivative 1a by sodium dichromate is accompanied by racemization not observable with other oxidizing agents.

1α-Ethyl-1β-(methoxycarbonyl-ethyl)octahydro-indolo[2,3-a]quinolizine (1a) is a key intermediate in the synthesis of the cerebral vasodilator alkaloid vincamine[2,3].

For the synthesis of the natural product the levorotatory 1a ester is required, the dextrorotatory enantiomer being discarded after resolution of the racemic compound. Thus the economy of the synthesis could be much improved by the racemization of the unwanted enantiomer of the two chiral centers (C_1 and C_{12b}). C_1 linked to four other carbon atoms seems to be the main obstacle to an intended racemization. For its inversion namely one of these bonds must be broken.

We chose to investigate oxidation procedures to form the iminium salt 2. When Hg^{II}acetate[4] or Pb^{IV}acetate[5] was used as oxidizing agent, the optically active 2a was isolated as a perchlorate in 55 % and 57 % yield, respectively, [m.p. 162-168°, $[\alpha]_D$= -34° (c=2, CH_2Cl_2)]. Re-reduction of the salt 2c (Pd/C in methanol) gave the isomers 1a and 1b, which were separated



	R	12b-H
a	$COOCH_3$	α
b	$COOCH_3$	β
c	CN	α
d	CN	β

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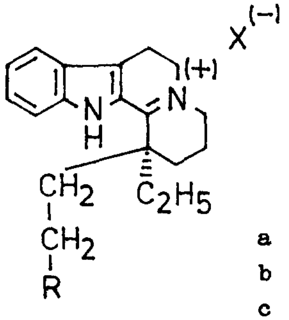

	R	X
a	$COOCH_3$	ClO_4
b	CN	ClO_4
c	$COOCH_3$	Cl

2

by TLC on silicagel. The optical rotation of 1a was identical with that of the starting material ($[\alpha]_D = -123{,}3^\circ$, c=1, CH_2Cl_2).

However, when the perchlorate salt of 1a was oxidised with sodium dichromate in acetic acid, the racemic salt 2a crystallized from the solvent in 53 % yield, which on reduction yielded racemic 1a.

On treating the optically active salt 2a under the same condition with sodium dichromate, *no racemization was observable*, i.e. the bond-breaking must have occured *during* the oxidation process.

To investigate the role of the ester group in the racemization of the unknown intermediate, the nitrile derivatives[1] were also subjected to the same treatment. Resolution was carried out by dibenzoyl tartaric acid in methanol [(-)1c nitrile base m.p. 165-166°, $[\alpha]_D = -152^\circ$, (c=1, CH_3OH)].

The oxidation was again performed with sodium dichromate and the iminium salt (2b, 63 %; $[\alpha]_D = -13^\circ$, c=1, CH_3OH; m.p. 190°) was reduced in order to establish the optical purity. The diastereomers 1c and 1d were separated by TLC (silicagel, ratio 4:6). The rotatory power for 1c ($[\alpha]_D = -35^\circ$, c=1, CH_2Cl_2) revealed that though some racemization occurred it was incomplete (remaining e.e. 23 %).

All the above facts suggest that during the oxidation of compound 1a chromium-containing radical is formed in which the C_1-C_{12b} bond is homolytically broken causing the racemization.

This unusual "chromic effect" using other models too, is being investigated.

References

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