SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. III.[1]
STEREOSELECTIVE SYNTHESIS OF ISOVINCINE.

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When enamine 2a was reacted with methyl α-acetoxy--acrylate, and the adduct obtained was reduced, 8a was formed stereoselectively. Deacetylation of 8a and subsequent oxidation furnished isovincine (1c).

Previously we have published our stereoselective and asymmetric synthesis of vincamine[1].

Vinca minor contains, in addition to vincamine (1a), its methoxy-containing analogue vincine[2] (1b) along with other alkaloids. Vincine possesses interesting pharmacological properties[3].

For investigation of the relationship of biological effect to structure an isomer of vincine has been synthesised, in which the methoxy-group occupies position 10 instead of 11 (1c), thus showing closer similarity to the biologically extremely active serotonin.

As the starting material 5-methoxytryptamine was used, prepared according our previously described method[4].

The key intermediate 2 was prepared from 5-methoxytryptamine and the lactone 3 [1], in two different ways.

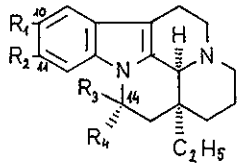
In the first approach 3 was treated with boiling hydrobromic acid (48 %, 4-5 hrs.), and the resulting acid was esterfied (methanol/H_2SO_4) to give 4[5] in 66 % yield. After boiling 4 with 5-methoxytryptamine in xylene (64 hrs.) the lactam 5 was obtained in 47 % yield [m.p. 119-121°; ir ν_{max}^{KBr} cm^{-1}: 1610, 3200; nmr (τ in $CDCl_3$): 1,60 (1H, s, ind-NH), 2,58-3,25 (3H, m, aromatic protons), 6,15 (3H, s, $-OCH_3$), 9,05 (3H, t, $-CH_2-\underline{CH_3}$)].

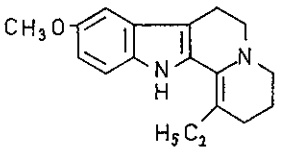
The lactam 5 was treated with boiling $POCl_3$ (5 hrs.) and excess reagent was distilled. After working up the residue, the perchlorate 2b was isolated in 64 % yield (m.p. 216-217°; ir ν_{max}^{KBr} cm^{-1} 1620, 3350).

A second route proved to be easier. A solution of the lactone 3 and 5-methoxytryptamine in chlorobenzene was boiled for 8 hrs. After removal of the solvent and the unreacted amine, the crude amide 6 was treated with $POCl_3$ as above, yielding 2b (31 %).

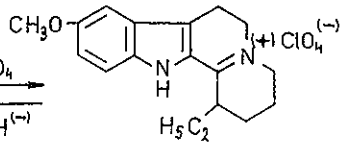
The liberated base 2a was reacted with methyl α-acetoxyacrylate in CH_2Cl_2 in the presence of a small amount of tert.-butanol as proton source (48 hrs.) and the product was isolated in the form of its perchlorate [(30 %, m.p. 180-181°; ir ν_{max}^{KBr} cm^{-1}: 1625, 1750, 1770, 3300)].

Catalytic reduction of the salt 7a (Pd/C, methanol) proceeded with high stereoselectivity. According to our earlier[1] experiments with the closely related compound 7b the ester 8c having cis C/D ring junction is formed as the major product, so it is reasonable to presume that the structure 8a is correct also in this case. The acetoxy-group was hydrolyzed easily during the workup, so it was convenient to analyze the beautifully crystalline hydroxy-ester 8b. Complete deacetylation was achieved by the use of methanolic sodium



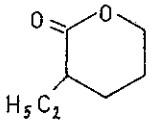


2a



2b

	R_1	R_2	R_3	R_4
1a	H	H	OH	$COOCH_3$
b	H	OCH_3	OH	$COOCH_3$
c	OCH_3	H	OH	$COOCH_3$
d	OCH_3	H	$COOCH_3$	OH



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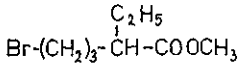

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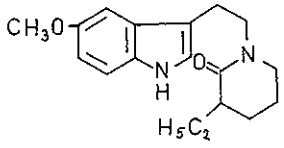

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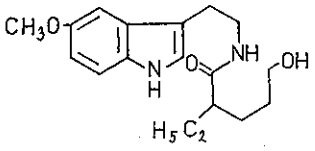

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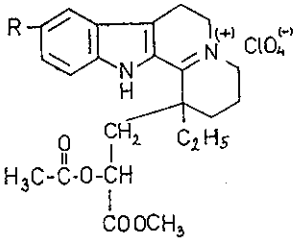
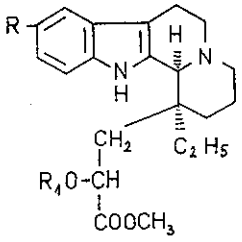


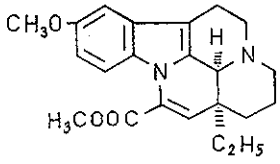
7 a R = OCH_3

b R = H



8

	R_1	R
a	$COCH_3$	OCH_3
b	H	OCH_3
c	$COCH_3$	H



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methoxide (30 min.) [8b, m.p. 206-207°, in 47 % yield from methanol; ir ν_{max}^{KBr} cm^{-1}: 1740, 3250; nmr ($CDCl_3$): 2,05 (1H, s, -OH), 2,30 (1H, s, ind-NH), 2,60-3,35 (3H, m, aromatic protons), 6,15 (3H, s, $-OCH_3$), 6,36 (3H, s, $-COOCH_3$), 6,62 (1H, s, 12bH); mass m/e 386 (M^+), 371 (M^+-15), 327 (M^+-59), 325 (M^+-61), 297 (M^+-89)].

During the oxidation of 8b with Fétizon-reagent (Ag_2CO_3 precipitated on celite) the same phenomenon was observed as in the vincamine synthesis[1].

Reaction of 8b (0.7 g) with Fétizon-reagent (3,50 g) in boiling benzene was monitored by TLC (Al_2O_3 PF_{254}, CH_2Cl_2-methanol 10:0,1). After 44 hr the mixture was worked up and the components separated by preparative TLC (Al_2O_3 PF_{254}, CH_2Cl_2-methanol 10:0,1, elution with hot CH_2Cl_2).

The thermodynamically less stable 14-epi-isovincine [1d, m.p. 171-172° from benzene; ir ν_{max}^{KBr} cm^{-1}: 1745; nmr ($CDCl_3$): 2,52-3,32 (3H, m, aromatic protons), 6,16 (3H, s, $-OCH_3$), 6,28 (3H, s, $-COOCH_3$), 9,16 (3H, t, $-CH_2-CH_3$)] was obtained in 46 % yield and the more stable isovincine [1c, m.p. 164-165° from methanol; ir ν_{max}^{KBr} cm^{-1}: 1742; nmr ($CDCl_3$): 2,60-3,16 (3H, m, aromatic protons), 5,35 (1H, s, -OH), 5,75 (1H, s, 3αH), 6,15 (3H, s, $-OCH_3$), 6,17 (3H, s, $-COOCH_3$), 6,52 (2H, s, C-15-CH_2-); mass m/e 384 (M^+), 383 (M^+-1), 369 (M^+-15), 355 (M^+-29), 337 (M^+-47), 325 (M^+-59), 314 (M^+-70), 297 (M^+-87), 282 (M^+-102)] in 18 % yield.

Epimerization of 1d to 1c was brought about by methanolic NaOMe. The relation between 1d and 1c was also proved by dehydration of each with acetic anhydride to give the same compound, 11-methoxy-apovincamine [9, m.p. 163-164°, in 63 % yield from methanol; ir ν_{max}^{KBr} cm^{-1}: 1740, 1730; nmr ($CDCl_3$): 2,60-3,15 (3H, m, aromatic protons), 3,82 (1H, s, >C=CH-), 5,85 (1H, s, 3αH), 6,02 (3H, s, $-OCH_3$), 6,11 (3H, s, $-COOCH_3$)].

The catalysis of the 1d⇌1c epimerisation was also achieved by silver ions.

Using boiling xylene instead of benzene in the oxidation of 8b by Fétizon-reagent, 1d was gradually converted to 1c as a major component of the mixture and iso-vincine was isolated (after 5 hr) in 50 % yield.

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References.

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