SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. XXXIII[1]. FORMATION OF A NEW RING SYSTEM VIA ADDITION OF METHYL ACRYLATE TO INDOLOQUINOLIZINE DERIVATIVES

Lajos Szabó[a)], Pál Kolonits[a)], György Kalaus[a)], Alajos Kálmán[b)], László Párkányi[b)], and Csaba Szántay[b)]*

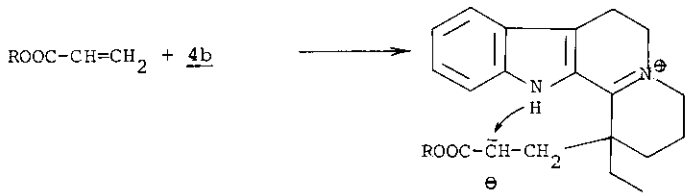
a) Institute of Organic Chemistry, Technical University, H-1521, Budapest

b) Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525, Budapest, P.O.Box 17, Hungary

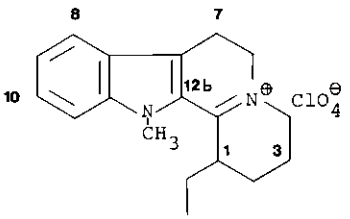
Abstract - While acrylic acid esters alkylate enamine 4b with free indole NH group at position C-1, indole N-Me containing analogues react in a different way. The structure of the new products (1a and 2) has been elucidated by X-ray crystallography.

When Gilbert Stork in 1954 started his work with enamines reporting that the alkylation of the pyrrolidine enamine of cyclohexanone with methyl iodide followed by acid hydrolysis led to the monoalkylated ketone, he opened up a new field in synthetic organic chemistry[2]. In the years which followed enamine chemistry proved to be a valuable contribution to preparative chemistry, among others to alkaloid chemistry.

In the course of our studies aiming at the total synthesis of indole alkaloids and analogues it has been demonstrated that Michael addition to the enamines represents a key step in these syntheses[3]. Therefore we were interested in the detailed mechanism of this addition. For instance, using acrylic ester and Wenkert enamine (4b)[4] as reacting partners in the first elementary step a zwitter-ion should be formed and in the second one the carbanion is protonated by the indole NH group:



In order to learn what happens if that proton is not available, 4b was methylated with methyl iodide in acetone, in the presence of powdered KOH[5]. The main product (70 %) was isolated as its perchlorate (3)[6]. In addition to that some quaternery salt 5[7] was also isolated. Reduction of 3 by $NaBH_4$ afforded 6[8] in 73 % yield.



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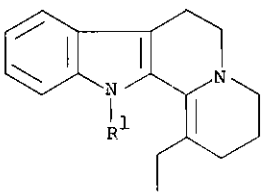

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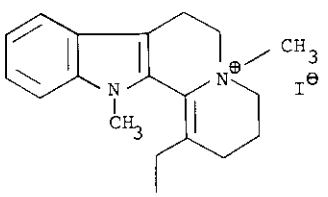
	R^1
4a	CH_3
4b	H



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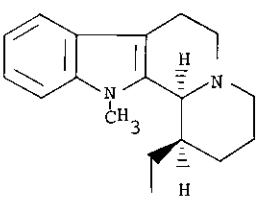

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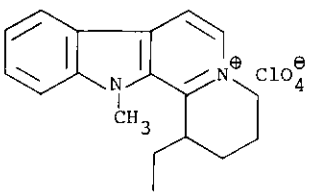
The enamine 4a prepared from 3 by treatment of its solution in CH_2Cl_2 with NaOH (10 % sol. in water), unlike 4b did not react with methyl acrylate at ambient temperature. Interaction occurred only on boiling the components in toluene in the presence of tert -butanol for 30-40 h. Two products were isolated, 1a[9] in 29 %, and 2[10] in 1.5 % yield. Due to redox side reaction, compounds 7[11] and 6 were also isolated from the reaction mixture.



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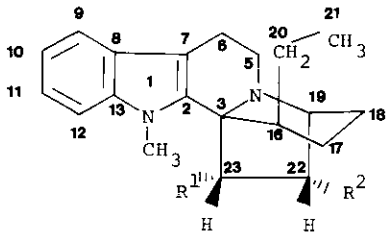


1a -c, 2

	R^1	R^2
1a	$-CO_2CH_3$	H
1b	$-CO_2Bu^t$	H
1c	-COOH	H
2	H	$-CO_2CH_3$

Using tert -butyl acrylate instead of methyl acrylate as a reaction partner with 4a, 1b[12] was isolated in 13 % yield, which upon hydrolysis gave 1c[13] carboxylic acid[14]. The latter compound was transformed to 1a by using diazomethane.

STRUCTURE ELUCIDATION BY X-RAY

In addition to the usual spectroscopic methods[15], structure of 1a and 2 was proved by X-ray investigations as well.

The structure of compounds 1a.$HClO_4$ and 2.$HClO_4$ differing only in the position of the methoxycarbonyl group (C23 for 1a and C22 for 2) are depicted in Figure 1.

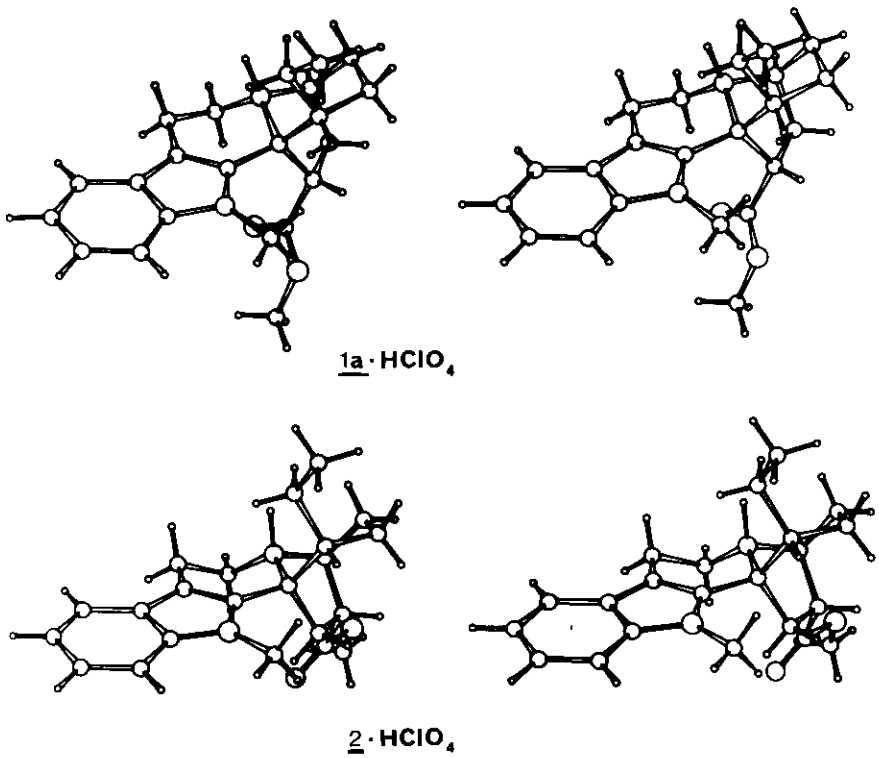


Figure 1. A stereoscopic view of the molecular structure of 1a.$HClO_4$ and 2.$HClO_4$

Accordingly, the configurations of the chiral centres (including the protonated N4 atom) are as follows:

	C3	N4	C16	C19	C22	C23
1a.$HClO_4$	R*	R*	R*	S*	-	S*
2. $HClO_4$	S*	R*	R*	S*	R*	-

Of course, the shift of the methoxycarbonyl group from C23 to C22 alters the chirality of C3. The conformations of the des-E-eburnamenine skeleton are essentially the same. Only the puckering[16] of the flexible C ring having a double bond at the B/C junction differs slightly. While in 1a it is a half chair in 2 it is shifted towards an envelope form with C5 on the flap. This in turn has an impact on the shape of the five-membered E ring through the cis- C/E ring junction.

In 1a it is of a transitional state between twist chair and envelope, while in 2 it assumes envelope form with N4 on the flap. As shown by the lowest asymmetry factors[17] (fC_s(C17) = 3.8 pm for 1a and 1.6 pm for 2) for the seven-membered rings (F) they possess in both structures boat conformation with C17 on the bowsprit.

In each structure the 16-ethyl group is bound β-axially (C20-C16-C17-C18 = -77(1) and 80(1)°, respectively) to ring D having a chair form. Presumably due to the steric effect of three β-axial protons belonging to C6, N4 and C18, the terminal C21-methyl groups point out from the molecules with similar orientation (C21-C20--C16-C17 = -80 (1)° and -79 (1)°, respectively). The methoxycarbonyl groups exhibit α-pseudoaxial orientation. In 1a C24 assumes syn position with C2 about the C23-C3 bond. In 2 the C23-C22 bond lies in the best plane of the planar methoxycarbonyl moiety.

X-Ray Crystallographic Data for 1a.$HClO_4$ and 2.$HClO_4$: $C_{22}H_{29}ClN_2O_6$, M. W. = 452.94. Crystals of 1a are orthorhombic, space group $P2_12_12_1$, a = 9.753(3), b = 13.710 (4), c = 16.234(5) Å, Z = 4, d_c = 1.39 gcm^{-3}, μ = 19.1 cm^{-1}. Crystals of 2 are monoclinic, space group $P2_1/n$, a = 12.124(3), b = 11.551(2), c = 16.623(2) Å, β = 106.78 (2)°, Z = 4, d_c = 1.35 gcm^{-3}, μ = 18.6 cm^{-1}.

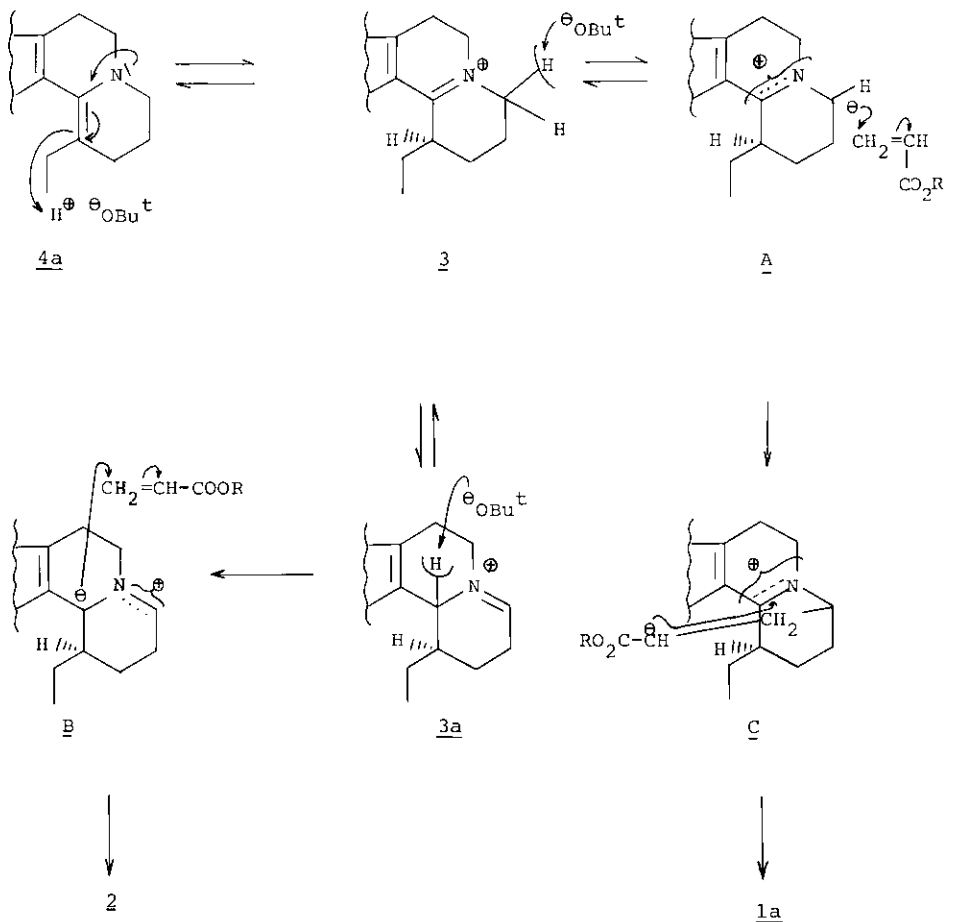
Intensities of both isomers 1a and 2 were collected on an Enraf-Nonius CAD-4 diffractometer at 23(1) C° with graphite monochromated Cu-K_α radiation (λ = = 1.54184 Å) using an ω-2θ scan in the range $1.5 < \theta < 75.0°$ with a scan width α + 0.14tanθ (where α was 0.4 for 1a and 0.5 for 2). In each case the lattice parameters were determined by least-squares from the setting angles of 25 reflections. Three standard reflections were monitored in every hour. They remained constant within experimental error throughout data collection which resulted in 1623 unique reflections for 1a and 3218 for 2. The phase problems were solved for both structures by direct methods using the MULTAN[18] program. In the course of the least-squares refinement of the positional parameters an empirical absorption correction was calculated for both data sets using program DIFABS[19]. The hydrogens were entered in calculated positions except H(N4) which was located in both structures by difference Fourier map. The H positions with a mean isotropic temperature factor were only included in structure factor calculations. The anisotropic refinements were terminated for 1a at R = 0.057 using 908

reflections with $F^2 > 2.0\sigma(F^2)$ and for 2 at R = 0.072 using 1880 reflections with the same criterion. The highest peaks in the final difference maps were 0.19 (4) and 0.41(6) e.$\AA^{-3}$, respectively. The atomic scattering factors were taken from standard tables[20]. Coordinates, thermal parameters, bond lengths and bond angles have been deposited with the Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, England.

MECHANISM

The structure of 1a and 2 being clarified (the compounds can also be regarded as a combination of indoloquinolizidine and tropane skeleton), one may wonder about the reaction sequence leading to the end products.

Scheme 1.



Presumably the iminium salt 3 present in equilibrium would release a proton from C-4 and the zwitter-ion A would react with the acrylic acid ester. The intermediate 1,5-dipole C forms the new ring system (Scheme 1). If the isomeric iminium salt 3a is present in the equilibrium, the proton from position C-12b can be released, and again the same zwitter-ion is formed which is now presented in another mesomeric form (B). The indicated attack on acrylic ester leads to the minor product in a similar way as described above. The attack on C-4 may require less activation energy than on C-12b because of steric reasons, which explaines the product ratio. Instead of a stepwise mechanism a concerted addition on the 1,3-dipole (A,B) is also feasible. The results strongly support the assumption that the intermediate zwitter-ion indeed abstracts the proton of the indole NH group. If it is available the reaction takes a different course.

Methylation of the indole NH group thus prevents the alkylation at C-1, because proton transfer from that group is excluded. Another factor could be a simple steric hinderance between the N-Me group and the entering alkylating agent. But certainly the formation of the two carbanions (A and B) would be highly unlikely in the presence of an acidic indole NH in the molecule.

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6. Compound 3: mp 225 °C (methanol); IR (KBr): 1610 and 1525 cm^{-1} (C=N); (HCl salt): MS m/z (%) 266 (M^+, 50.1), 251 (100), 237 (41.0); ^1H NMR (DMSO-d_6) δ (ppm) 0.98 (3H, t, J = 7.2 Hz, $-CH_2-CH_3$), 3.97 (3H, s, indole-N-CH_3), 3.90 (2H, m,

H_2 (4)), 4.05 (2H, m, H_2 (6)), 7.78-7.23 (4H, m, aromatic).

7. Compound 5: mp 241-243 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 1.14 (3H, t, J=7.2, $-CH_2-C\underline{H}_3$), 3.40 (3H, s, N-$C\underline{H}_3$), 3.62 (3H, s, indole-N-$C\underline{H}_3$), 4.96-3.76 (4H, m, H_2 (4) and H_2 (6)), 7.59-7.12 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 12.4 (q, $CH_2-\underline{C}H_3$), 17.3$^+$ (t, C_7), 18.5$^+$ (t, C_3), 27.2^X (t, C_2), 28.2^X (t, $-\underline{C}H_2-CH_3$), 34.0 (q, indole-N-$\underline{C}H_3$), 48.6 (q, $N^{\oplus}-\underline{C}H_3$), 64.2 (t, C_4), 66.9 (t, C_6), 108.9 (s, C_{7a}), 110.8 (d, C_{11}), 119.2 (d, C_8), 120.9 (d, C_9), 124.4 (d, C_{10}), 125.4§ (s, C_{7b}), 127.8§ (s, C_{12a}), 127.8§ (s, C_1), 138.1 (s, C_{11a}), 140.7 (s, C_{12b}).

8. Compound 6: mp 76 °C (methanol); MS m/z (%) 268 (M^+, 70), 267 (100), 253 (13.4), 239 (11.8), 183 (42.1), 168 (25.7); ^{1}H NMR ($CDCl_3$) δ (ppm) 0.74 (3H, t, J = 7 Hz, $-CH_2-C\underline{H}_3$), 3.55 (1H, m, W 1/2 = 6 Hz, H (12b)), 3.65 (3H, s, indole-N-$C\underline{H}_3$), 7.50-7.00 (4H, m, aromatic).

9. Methyl 1-methyl-3α, 19α-ethano-des-E-eburnamenine-23-syn-carboxylate (1a).$HClO_4$ salt: mp 160 °C (methanol); IR (KBr) 1738 cm^{-1} (ester CO); (HCl salt): mp 237 °C (methanol-ether), MS m/z (%) 352 (M^+, 78), 351 (100), 337 (7.7), 321 (5.5), 293 (36.6), 282 (11.5); ^{1}H NMR ($CDCl_3$, base) δ (ppm) 0.69 (3H, t, J = 7.0 Hz, $-CH_2-C\underline{H}_3$), 3.14 (3H, s, indole-N-$C\underline{H}_3$), 3.20-3.70 (4H, m), 3.78 (3H, s, $-CO_2C\underline{H}_3$), 6.90-7.60 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 12.9 (q , C_{21}), 20.7 (t, C_{20}), 21.7 (t, C_6), 22.1 (t, C_{18}), 28.5 (t, C_{17}), 32.6 (q, C_{14}), 33.2 (t, C_{22}), 46.3 (d, C_{16}), 46.9 (t, C_5), 51.4 (q, $OC\underline{H}_3$), 53.9 (d, C_{23}), 63.8 (d, C_{19}) 73.6 (s, C_3), 108.4 (d, C_{12}), 111.5 (s, C_7), 118.3 (d, C_9), 118.7 (d, C_{11}), 121.2 (d, C_{10}), 126.2 (s, C_8), 134.3 (s, C_2), 138.0 (s, C_{13}), 175.6 (s, $\underline{C}OO-$).

10. Compound 2 ($HClO_4$ salt): mp 232 °C (methanol); IR(KBr): 1738 cm^{-1} (ester CO); MS m/z (%, base) 352 (M^+, 73.3), 351 (100), 337 (5.1), 321 (5.1), 293 (56.6), 282 (11.6); ^{1}H NMR ($CDCl_3$, base) δ (ppm) 0.68 (3H, t, J=7 Hz, $-CH_2-C\underline{H}_3$), 3.67 (3H, s, indole-N-$C\underline{H}_3$), 3.72 (3H, s, $-OC\underline{H}_3$), 3.81 (1H, m, 23-H), 6.9-7.5 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.0 (q, C_{21}), 20.9 (t, C_{20}), 21.9 (t, C_6), 22.3 (t, C_{18}), 29.0 (t, C_{17}), 31.7 (q, C_{14}), 36.9 (t, C_{22}), 44.7 (d, C_{16}), 48.5 (d, C_{22}), 48.5 (t, C_5), 52.1 (q, $-OC\underline{H}_3$), 67.0 (d, C_{19}), 69.5 (s, C_3), 108.7 (d, C_{12}), 109.6 (s, C_7), 118.0 (d, C_9), 119.0 (d, C_{11}), 120.9 (d, C_{10}), 126.3 (s, C_8), 137.7 (s, C_{13}), 138.8 (s, C_2), 176.1 (s, $\underline{C}OO-$).

11. Compound 7: mp 213 °C (methanol); IR (KBr) 1628 cm^{-1} (aromatic); (HCl salt): MS m/z 265 (M^+); ^1H NMR ($CDCl_3$) δ (ppm) 1.13 (3H, t, J = 7Hz, $-CH_2-CH_3$), 1.77 (2H, q, J = 7Hz, $-CH_2-CH_3$), 4.30 (3H, s, indole-N-CH_3), 4.98 (2H, m, H_2 (4)), 8.25-7.28 (4H, m, aromatic), 8.35 (1H, d, J = 6.4Hz, H (7)), 8.68 (1H, d, J = 6.4 Hz, H (6)).

12. Compound 1b (HCl salt): mp 180 °C (methanol); IR (KBr): 1735 cm^{-1} (ester CO); MS m/z (%) 394 (M^+, 22.6), 337 (45.5), 293 (52.3), 237 (48.3), 223 (67.1), 57 (100); ^1H NMR ($CDCl_3$, base) δ (ppm) 0.70 (3H, t, J = 7.0 Hz, $-CH_2-CH_3$), 0.91 (9H, s, $-C(CH_3)_3$), 3.79 (3H, s, indole-N-CH_3), 6.9-7.5 (4H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ (ppm) 13.0 (q, C_{21}), 20.4 (t, C_{20}), 21.6 (t, C_6), 21.9 (t, C_{18}), 27.3 (q, $C(CH_3)_3$), 28.4 (t, C_{17}), 33.0 (q, C_{14}), 33.3 (t, C_{22}), 45.9 (d, C_{16}), 46.7 (t, C_5), 55.4 (d, C_{23}), 63.5 (d, C_{19}), 73.1 (s, C_3), 80.3 (s, $-C(CH_3)_3$), 108.3 (d, C_{12}), 110.9 (s, C_7), 118.1 (d, C_9), 118.5 (d, C_{11}), 121.0 (d, C_{10}), 126.1 (s, C_8), 134.6 (s, C_2), 137.6 (s, C_{13}), 174.2 (s, COO-).

13. Compound 1c: mp 175 °C (methanol); IR (KBr): 3340 cm^{-1} (OH), 1590 cm^{-1} (COO^-); MS m/z (%) 338 (M^+, 58), 337 (18.7), 336 (100), 293 (37.9), 281 (21.8), 266 (37.4), 237 (32.2), 223 (20.4); ^{13}C NMR (DMSO-d_6) δ (ppm) 12.5 (q, C_{21}), 20.2 (t, C_{20}), 21.5 (t, C_6), 21.9 (t, C_{18}), 28.0 (t, C_{17}), 32.7 (q, C_{14}), 32.9 (t, C_{22}), 45.1 (d, C_{16}), 46.1 (t, C_5), 53.1 (d, C_{23}),62.9 (d, C_{19}), 72.6 (s, C_3), 108.9 (d, C_{12}), 110.0 (s, C_7), 117.6 (d, C_9), 118.3 (d, C_{11}), 120.6 (d, C_{10}), 125.6 (s, C_8), 135.1 (s, C_2), 137.5 (s, C_{13}), 176.0 (s, COOH).

14. All products gave satisfactory elemental analysis.

15. All NMR measurements were performed on a Jeol FX-100 instrument; + x § Assigments may be interchanged.

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