SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XXIV[1]. A NEW REARRANGEMENT OF THE ISOQUINUCLIDINE SKELETON

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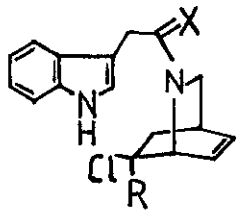
Abstract - A new rearrangement of the isoquinuclidine skeleton under solvolytic conditions was observed. A pentacyclic intermediate was isolated and its structure elucidated.

Recently we have reported the synthesis of deethylcatharanthine via photolytic ring closure of 1a followed by removal of the amide carbonyl group[2].

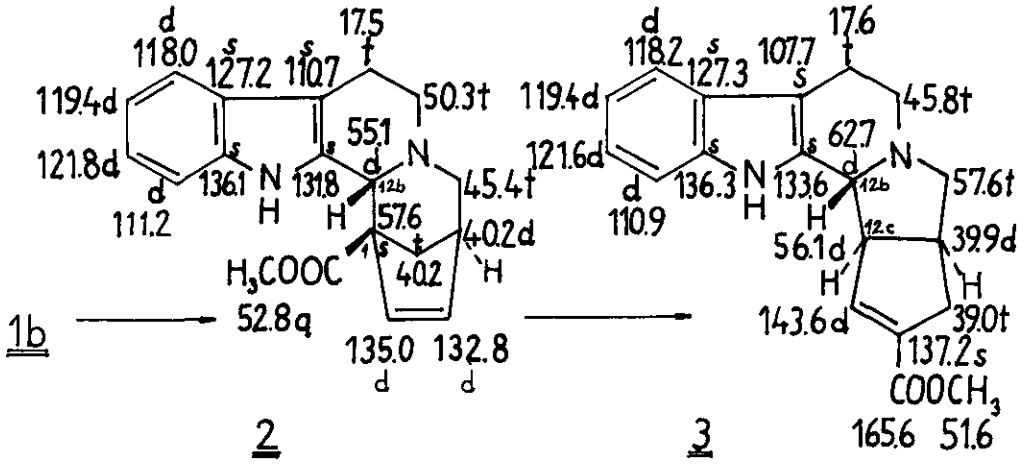


	R	X
1a	$-COOCH_3$	O
1b	$-COOCH_3$	H_2
1c	-CN	H_2

In the course of that work the behaviour of compound 1b[2] was also studied under solvolytic conditions hoping to achieve a ring closure to an iboga-type skeleton.

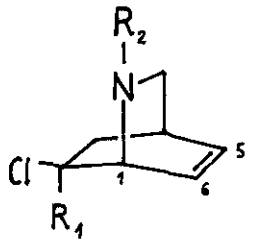
Thus when the indole derivative 1b was boiled in n-butanol for 5 h, the rearranged compound 3 [oil,(IR cm^{-1}): 1720 (C=O), 3320 (indole NH), NMR ($CDCl_3$); δ 3.5 (m, 1H, C_{12c}-H), 3.75 (s, 3H, $-OCH_3$), 4.1 (dt, 1H, C_{12b}-H), 6.81 (dt, 1H, olefinic), 7.04-7.74 (m, 4H, ArH), 8.08 (br s, 1H, indole NH); MS (150°C); m/e, 308.1536 $C_{19}H_{20}N_2O_2$ (15 M), 307 (3), 277 (2), 184 (100), 183 (10), 180 (7), 169 (7), 168 (2), 156 (15)] was obtained in 53% yield after chromatographic separation (Silicagel 60, 0.063-0.2 toluene-chloroform-ethanol = 8:4:2).

A compound with a similar skeleton was obtained by Winterfeldt et al.[3] on a different route.



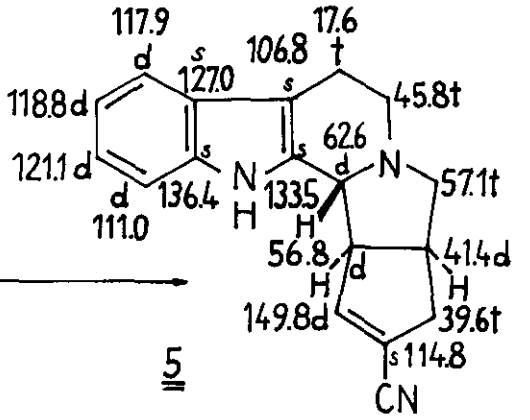
At lower temperature e.g. on boiling 1b in t-butanol for 24 h compound 2 [oil, IR (cm^{-1}): 1720 (C=O), 3340 (indole NH), NMR ($CDCl_3$); δ 3.95 (s, 3H, $-OCH_3$), 4.6 (br s, 1H, C_{12b}-H), 6.05-6.32 (2xdd, 2H, olefinic), 7.0-7.55 (m, 4H, ArH), 8.5 (br s, 1H, indole NH), MS (150°C); m/e, 308.1536 $C_{19}H_{20}N_2O_2$ (12 M), 307 (3), 277 (2), 184 (100), 183 (10), 169 (7), 168 (2), 156 (20), 149 (10)] was isolated by chromatography in 28.4% yield. The compound 2 was supposed to be an intermediate on the way to 3. Indeed on further heating of 2 in different solvents (e.g. in n-butanol) it was transformed into the thermodinamically more stable end-product 3.

In order to investigate the influence of the size of group R in 1 on the rearrangement, compound 4a [HBr salt, mp 224-226°C, IR (cm^{-1}, KBr): 2220 (C≡N), NMR ($CDCl_3$); δ 3.84 (dd, 1H, C_1-H), 6.5-6.7 (m, 2H, C_5H and C_6-H)] was prepared in a similar way as described for 4b[2]. After alkylation of 4a with tryptophyl bromide (methanol, r.t., triethylamine) nitrile 1c [mp 126-128°C from methanol, IR (cm^{-1}, KBr): 2230 (C≡N), 3300 (indole NH), NMR ($CDCl_3$); δ 3.76 (dd, 1H, C_1-H), 6.39, 6.62 (2x td, 2H, C_5-H and C_6-H), 7.05-7.7 (m, 5H, ArH and indole C_2-H), 7.88 (br s, 1H, indole NH)] was obtained in 55% yield. The nitrile 1c behaved in exactly the same way as did the corresponding ester. On heating it in diethyleneglycol (160°C, 20 min), the rearranged product 5 [mp 234-237°C from diethyleneglycol-acetone, IR (cm^{-1}, KBr): 2230 (C≡N), 3320 (indole NH), NMR ($CDCl_3$+DMSO-d_6); δ 3.64 (m, 1H, C_{12c}-H), 4.07 (dt, 1H, C_{12b}-H), 6.83 (dt, 1H, olefinic), 6.95-7.5 (m, 4H, ArH), 9.82 (br s, 1H, indole NH), MS (180°C): m/e, 276 (10), 275 (23 M), 274 (6), 185 (23), 184 (100), 183 (11.2), 169 (7.2), 157 (12.8), 156 (23), 28 (23)] was obtained. Further the stereostructure of 5 was confirmed by the X-ray analysis.



	R_1	R_2
4a	-CN	H
4b	$-COOCH_3$	H
4c	$-COOCH_3$	n-Bu

1c



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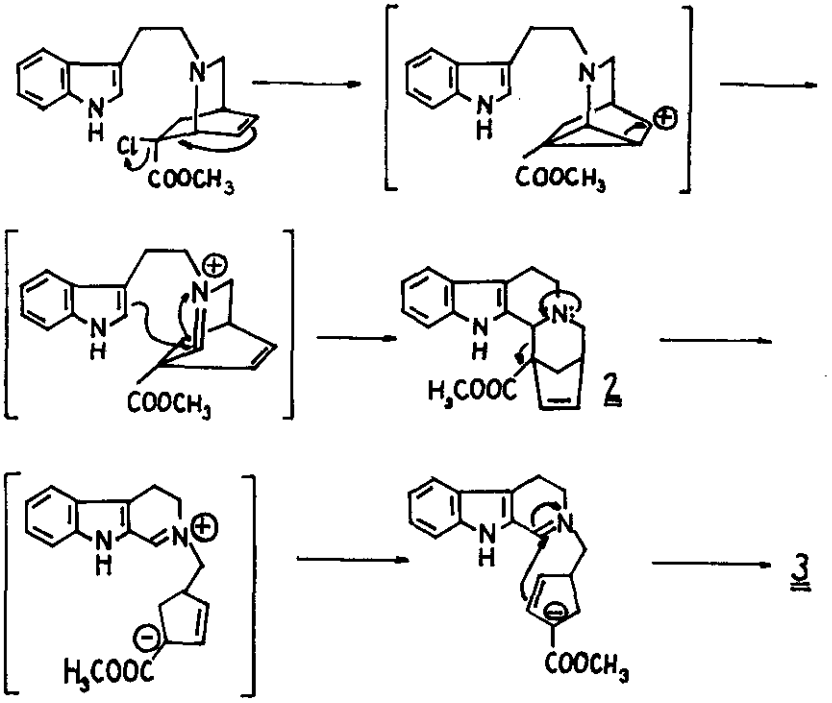
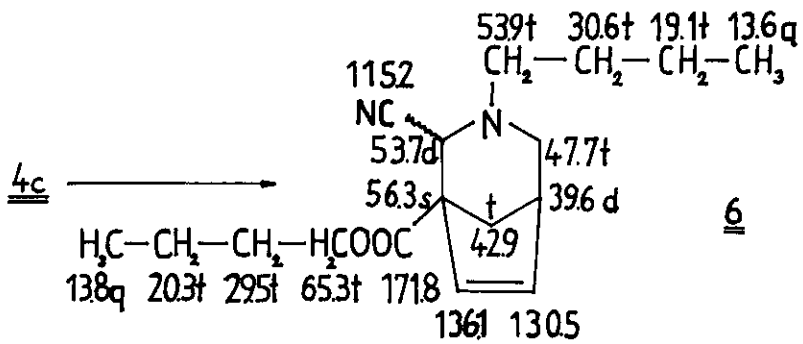
The rearrangement requires a substantial basicity of the nitrogen in the isoquinuclidine ring system. On heating the acylated derivative 1a no reaction occurred under the above conditions.

One possible mechanism of the rearrangement is the following. In the first step a carbocation stabilized by the double bond is formed. In the second step this cation rearranges to the thermodinamically more stable iminium salt which possesses the sufficient lifetime to allow an electrophilic attack at C(3) of the indole nucleus. The labile intermediate rearranges to the first stable product 2 with



indolo-quinolizidine skeleton. On heating, 2 produces by heterolytic fission an 1,5-dipole which, after rotation, furnishes the thermodinamically most stable end-product 3 .

In order to test whether the rearrangement is a general feature of the isoquinuclidine skeleton and can proceed even in the absence of the indole nucleus, 4c [oil, IR (cm^{-1}): 1720 (C=O), NMR ($CDCl_3$); δ 3.75 (s, 3H, $-OCH_3$), 3.85 (dd, 1H, C_1-H), 6.1 (td, 1H, C_6-H), 6.4 (td, 1H, C_5-H)] was prepared by butylation of 4b (n-butyl bromide, methanol, triethylamine, r.t. 48 h) in 24% yield. On refluxing 4c in n-butanol/DMF for 1 h in the presence of cyanide ion nucleophile, rearrangement accompanied by transesterification took place and compound 6 [oil, IR (cm^{-1}): 1720 (C=O), 2220 (C≡N), NMR ($CDCl_3$); δ 3.96 (d, 1H, C_2-H), 4.2 (t, 2H, $-COO-CH_2$), 5.78 and 6.1 (2dd, 2H, C_6-H, C_7-H), MS; m/e, 290 (21M), 275 (0.8), 263 (1.7), 261 (2.8), 247 (75), 233 (12), 222 (8.9), 217 (6.8), 191 (5.2), 188 (6.1), 124 (38), 123 (35), 82 (100), 77 (29)] was isolated in 57.5% yield. ^{13}C NMR data can be seen on the formulas.



Evidence presented in this paper suggests that the new rearrangement is a general characteristic of the isoquinuclidine skeleton. Further investigations concerning the factors influencing the above reactions are in progress.

ACKNOWLEDGEMENT

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