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THE VILSMEIER-HAACK REACTION OF N-ALKYL-1,2,3,4-TETRAHYDROCARBAZOLES AND THE SYNTHETIC APPLICATION TO OLIVACINE AND ELLIPTICINE

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Abstract: The mechanism of the formation of products resulting from the Vilsmeier-Haack reaction of N-alkyl-1,2,3,4-tetrahydrocarbazoles, and the synthetic application to olivacine and ellipticine, are described.

Bruck[1] has reported that the Vilsmeier-Haack(V-H) reaction of N-methyl-1,2,3,4-tetrahydrocarbazole(1a, N-methyl-THC) gave quite an abnormal product (2a). Recently Murakami and Ishii[2], on the basis of the experiment using 6-chloro-N-methyl-THC as a substrate, suggested that the possible intermediates were the 1-formyl-THC(3a) and 1-methyl-carbazole(4a). We wish to report here a more reasonable mechanism derived from the results of the V-H reaction of N-benzyl-THC (1b), and the total syntheses of two anti-tumour indole alkaloids, olivacine(5a) and ellipticine(5b), by using the expected products(2b,c) obtained from 1b,c.

When 1b was allowed to react with $POCl_3$ in DMF under various conditions, the product distribution varied greatly as is shown in the table. The reaction at 120°C gave the desired aldehyde(2b), with a by-product, amine(6)(Runs 1,2, and 3), whereas at 0°C only 3b was obtained in a good yield(Run 5). It is

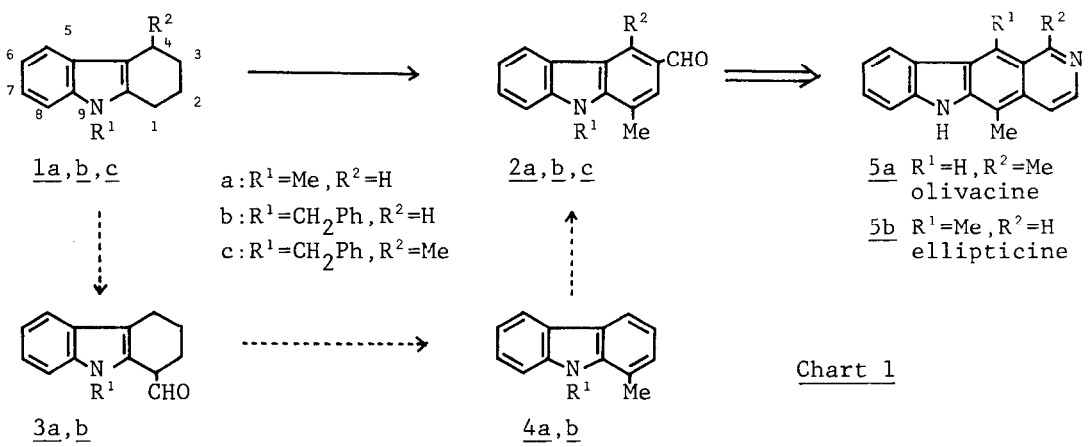


Chart 1

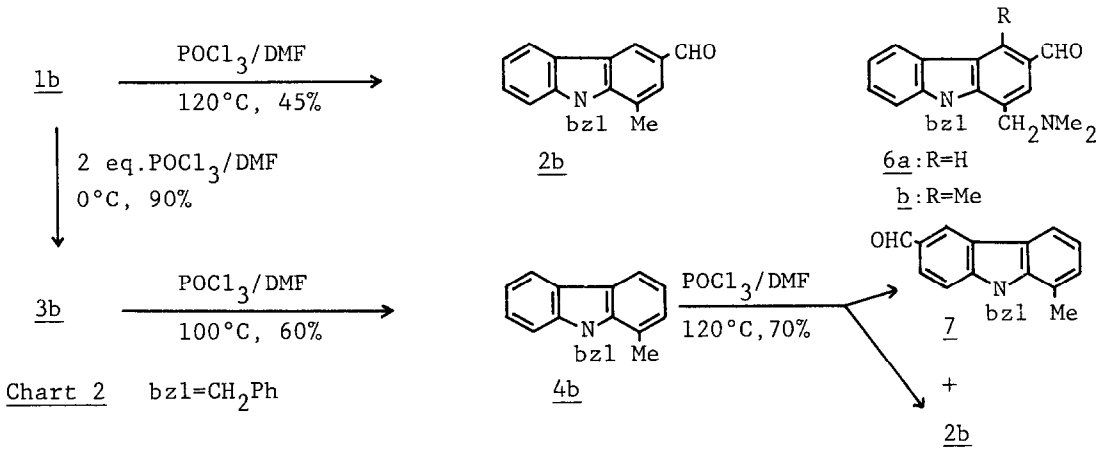


Chart 2

Table The Vilsmeier-Haack Reaction of N-Benzyl-1,2,3,4-tetrahydrocarbazole(1b)

Run	Reaction Temp.(°C)	$POCl_3$(eq.)	Products(%) 2b	6a	3b	S.M.(1c) recov.
1	120	1.0	18	5	0	22
2	120	2.0	45	18	0	0
3	120	3.0	37	24	0	0
4	0	1.0	0	0	46	48
5	0	2.0	0	0	90	0

noteworthy that this reaction required 2 eq. of $POCl_3$ in spite of the introduction of only one formyl group into the C-1(Runs 4 and 5).

The 1-formyl compound(3b) was next allowed to react under the V-H reaction conditions. Dehydration and subsequent aromatization occurred to give 1-methylcarbazole(4b)(1.2 eq. of $POCl_3$ in DMF at 100°C, 60 % yield). Unexpectedly this compound(4b) was formylated nonregiospecifically under V-H conditions to give a mixture of 3-formyl-(2b) and 6-formyl-(7) derivatives(total yield, 70 %; 2b:7= 3:2; Chart 2). Contrary to the previous suggestion[2], this result indicated that 3b and 4b were not the real intermediates in the direct conversion of 1b into 2b, because this conversion did not give the isomer(7) at all. Thus we propose the following mechanism in order to explain all of the above results reasonably(Chart 3): THC(1b) was attacked by 2 eq. of V-H reagents to produce the key intermediate(B) via (A) which had been formed by an initial attack of the reagent on the electron-rich C-4a. Then the intermediate(B) was converted into 3b during the work-up(path a). On the other hand, at a high temperature, the $-CH=\overset{+}{N}Me_2$ group at C-4a was rearranged to C-3 with proton transfer(path b), thus producing 2b regiospecifically. Recently, an abnormally high reactivity of the side chain at C-2 of indoles(C-1 of THC) has been reported.[3] It has

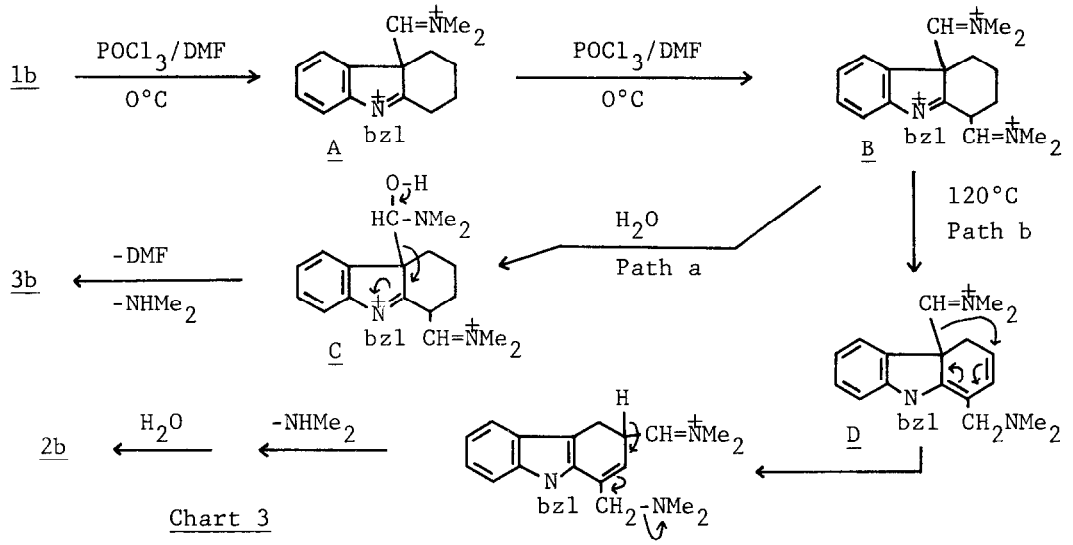
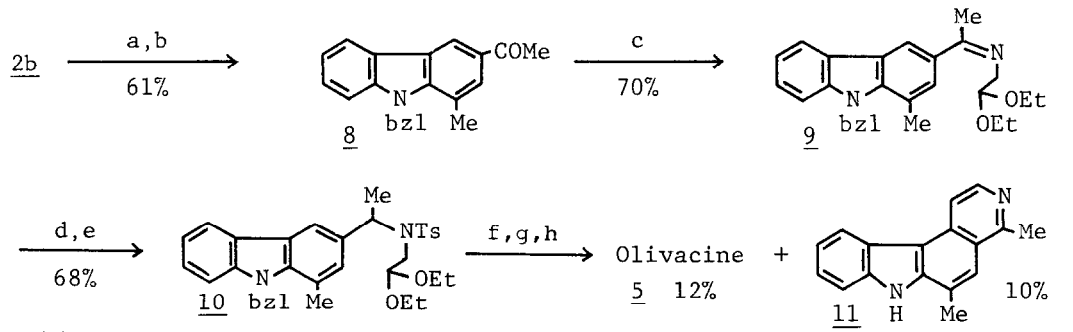


Chart 3

also been suggested[3a,b] that this reactivity might be caused by an initial attack of the electrophile on C-3(C-4a of THC) of indoles. Our results provide new evidence which strongly supports the above mechanism, showing a general reactivity of the side chain at C-2 of indoles. Although the subsequent unique sigmatropic type rearrangement has no experimental evidence for it, the present mechanism can clearly explain the regiospecific formation of 2b.

Syntheses of olivacine(5a) and ellipticine(5b) were accomplished, as is shown in Charts 4 and 5 respectively, in a way similar to Jackson's route[4]. The aldehyde(2b) was converted into the acetal(10), whose subseqent cyclization, followed by debenzylation and aromatization, gave olivacine(5a, mp 320-324 °C) and an anticipated isomer(11, mp 313-316°C).

The synthesis of ellipticine was started from 4-methyl-THC(1c). Presence



a)MeLi/THF at -78°C, b)Jones' Oxidation, c)$H_2NCH_2CH(OEt)_2$, d)$NaBH_4$/EtOH, e)TsCl/pyridine, f)6N-HCl in dioxane, g)Na/liq.NH_3 in THF, h)Pd-C/tetralin

Chart 4

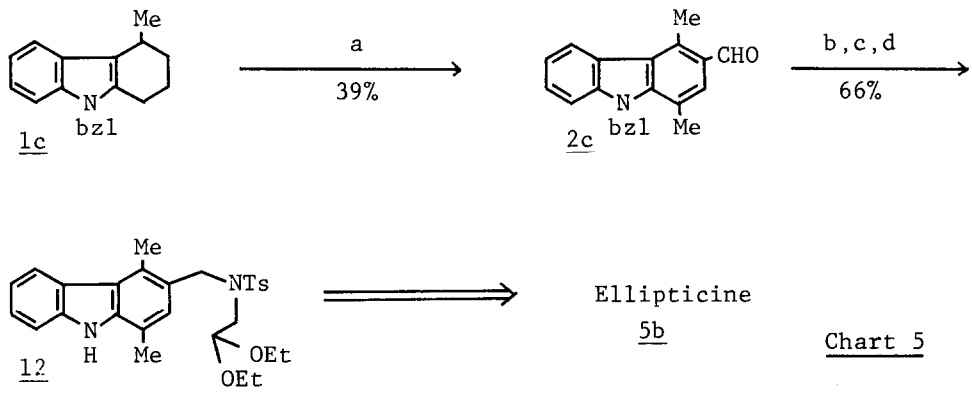


Chart 5

a) 2.6 eq. $POCl_3$/DMF, 100°C, b) $H_2NCH_2CH(OEt)_2$, c) Li/liq.NH_3 in THF, d) TsCl/$NaHCO_3$aq.

of the C_4-methyl group in 1c did not affect the reactivity of the V-H reaction; i.e., 2c was obtained (39 % yield) regiospecifically, accompanied by the amine (5b, 21 %) as a by-product. The aldehyde (2c) was converted in 3 steps into the acetal (12), which had previously been converted[4], in one step, into ellipticine in a high yield (86 %). Thus the very efficient formal total synthesis of ellipticine (5b) was accomplished in only 5 steps (overall yield, 22.4 % from 1b). All the physical and spectral data of olivacine (5a)[5] and the acetal (12)[4,6] were in accord with previously reported values.

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References and Notes

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6) We converted the acetal (12) into ellipticine (5b) [mp 308-312°C(dec.)], whose spectral data coincided with the previously reported data[4] [mp 306-309°C(dec.)].

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