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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XIV.[1]

A NEW ROUTE TO CYCLOPROPANE CARBOXYLIC ACID DERIVATIVES.

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Abstract - The reaction of α-halogen acrylic esters and α-halogen acrylic nitriles with some enamines gave rise unexpectedly to cyclopropane derivatives.

Earlier we reported[2] the reaction of 1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine with 2-chloroacrylonitrile and methyl-(2-bromo-acrylate) respectively. We established that first an electrophilic alkylation took place, which was then followed by intramolecular nucleophilic substitution at the indol nitrogen leading to 3,4-dehydro-14,15-dihydroeburnamenine derivatives. These results suggested, that with the same reagents the enamines 1 and 2 which lack an ethyl group at C-1 would yield eburnamenine derivatives too.

The enamines 1 and 2 were prepared by known methods[4] from tryptamine and 4-butanolide or methyl-(5-chloropentanoate)[3] and were isolated as the perchlorates (1·$HClO_4$,m.p. >360°C, 2·$HClO_4$,m.p. 227-228°C)[5]. Prior to reaction the enamines were liberated from the pure perchlorate salts.

Contrary to expectations, the reaction of enamines 1 and 2 with either 2-chloro-acrylonitrile or methyl-(2-bromo-acrylate) proceeded in an entirely unusual way and yielded, respectively, 1-cyclopropyl-indolo-indolizine (3,5) and 1-cyclopropyl-indolo-quinolizine (4,6) derivatives. The constitution of the novel products was evidenced by ^{1}H and ^{13}C NMR observations.[6] Proton NMR disclosed the presence of the unchanged indol-NH, the occurrence in the molecule of an "isolated" three-spin system with chemical shift values and coupling constants typical for substituted cyclopropanes[7] while carbon-13 spectra revealed that the products contain a quaternary carbon atom giving its resonance in the sp^3 region (approx.30 ppm). Of further corroborative value were the chemical shifts of carbon atoms encompassed in the cyclopropane ring (for relevant ^1H and ^{13}C NMR data see Table 1.).

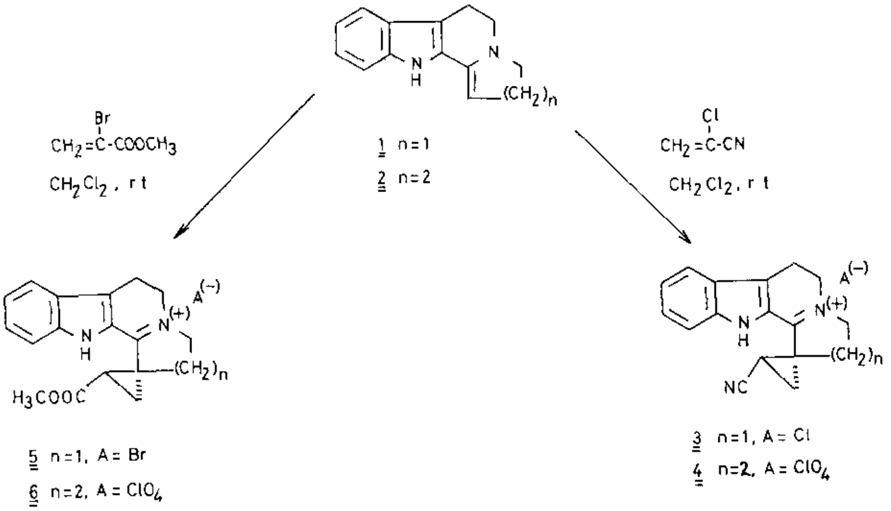
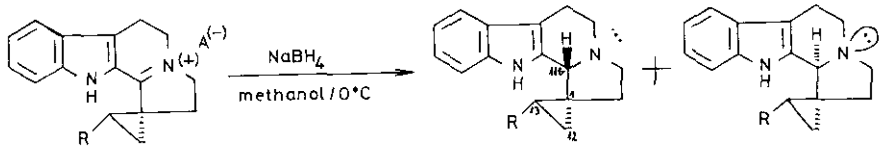


Table 1.

Start. mat.		Prod-ucts	Yield(%) m.p.(C°)	IR (KBr) ν_{max} (cm^{-1})	^1H and ^{13}C-NMR data
1	CH_2 C-Cl CN	3	36,6 231-232 (MeOH)	3300(ind NH) 2285 (-CN) 1618 (>C=N=) (+)	^1H NMR($CDCl_3$): δ 1.72($12H_A$), 2.98 ($12H_B$), 3.54(13H)ppm: J_{gem}=4.5Hz, J_{trans}=6.2Hz, J_{cis}=9.5Hz. ^{13}C NMR ($CDCl_3$+TFA): δ 15.54(C13), 22.94 (C12), 35.71(C1)ppm.
	CH_2 C-Br $COOCH_3$	5	52,1 220-221 (MeOH)	3340(ind NH) 1720(>CO) 1615(>C=N=) (+)	^1H NMR($CDCl_3$): δ 1.80($12H_A$), 2.83 ($12H_B$), 3.60(13H)ppm; J_{gem}=4.5Hz, J_{trans}=6.2Hz, J_{cis}=9.2Hz. ^{13}C NMR ($CDCl_3$+TFA): δ 30.37(C13), 23.61 (C12), 37.23(C1)ppm.
2	CH_2 C-Cl CN	4	64,9 210-211 (MeOH)	3260(ind NH) 2280(-CN) 1600-1620 (>C=N=) (+)	^{13}C NMR(DMSO-D_6+$CDCl_3$): δ 15.69 (C14), 23.42(C13), 27.24(C1)ppm.
	CH_2 C-Br $COOCH_3$	6	43,9 200-202 (MeOH)	3300(ind NH) 1724(>CO) 1618-1638 (>C=N=) (+)	^1H NMR($CDCl_3$): δ 1.97($13H_A$), 2.51 ($13H_B$), 2.88(14H)ppm; J_{gem}=6.6Hz, J_{trans}=7.5Hz, J_{cis}=9Hz. ^{13}C NMR ($CDCl_3$+TFA): δ 31.37(C14), 23.25 (C13), 29.86(C1)ppm.

The sodium-borohydride reduction (in MeOH at 0°C) of the (C11b)=N double bond of 3 and 5 afforded the respective isomeric pairs 7, 8 and 9, 10 (see Table 2.).



3 R=CN, A=Cl
5 R=$COOCH_3$, A=Br

7 R=CN
9 R=$COOCH_3$

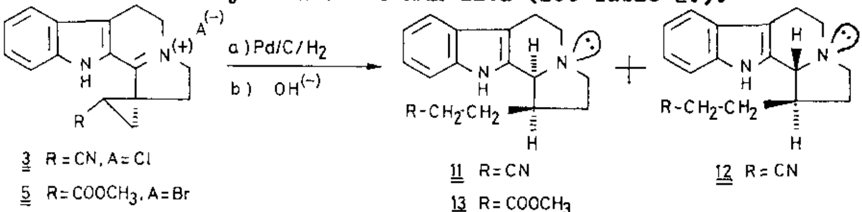
8 R=CN
10 R=$COOCH_3$

Table 2.

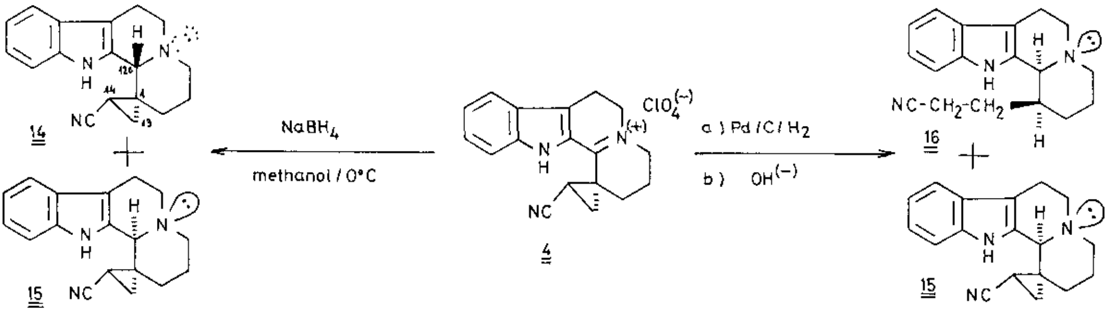
Start mat.	Reduct. type	Products ratio m.p. C°	IR (KBr) ν_{max} (cm^{-1})	^1H and ^{13}C-NMR data
3	$NaBH_4$	7+8 36:64 123-124 106-107 (MeOH)	7: 3310(ind NH) 2300(CN)	^1H NMR($CDCl_3$+DMSO-D_6): δ 4.10(11bH)ppm. ^{13}C NMR($CDCl_3$+DMSO-D_6): δ 6.50(C13),18.06 (C12),19.49(C6),31.05(C2),33.08(C1),46.88 (C5),50.90(C3),61.77(C11b),120.52(-CN)ppm.
			8: 3320(ind NH) 2305(CN)	^1H NMR($CDCl_3$+DMSO-D_6): δ 4.08(11bH)ppm. ^{13}C NMR($CDCl_3$+DMSO-D_6): δ 7.57(C13),15.46 (C12),20.26(C6),30.68(C2),32.82(C1), 47.01(C5),51.66(C3),61.47(C11b),119.94 (-CN)ppm.
	H_2/Pd	11+12 59:41 79-80 149-150 (MeOH)	11: 3290(ind NH) 2290(CN)	^1H-NMR($CDCl_3$): δ 3.68(11bH)ppm. ^{13}C NMR ($CDCl_3$+DMSO-D_6): δ 15.20(C13),21.20(C6), 27.67(C12),28.06(C2),38.95(C1),48.45(C5), 51.48(C3),62.85(C11b),120.14(-CN)ppm.
			12: 3310(ind NH) 2280(CN)	^1H NMR($CDCl_3$): δ 3.98(11bH)ppm. ^{13}C NMR ($CDCl_3$+DMSO-D_6): δ 15.50(C13),17.26(C6), 29.81(C2),30.75(C12),42.88(C1),45.66(C5), 48.93(C3),62.04(C11b),120.09(-CN)ppm.
5	$NaBH_4$	9 + 10 39:61 205-206 60-64 (MeOH)	9: 3298(ind NH) 1710(CO)	^1H NMR($CDCl_3$): δ 3.72($-COOCH_3$),3.98(11bH) ppm. ^{13}C NMR($CDCl_3$+DMSO-D_6): δ 18.89(C12), 20.03(C6),22.32(C13),29.60(C2),35.30(C1), 47.25(C5),51.42(C3,$-COO\underline{CH}_3$), 62.66(C11b), 173.30($-\underline{CO}OCH_3$)ppm.
			10: 3350(ind NH) 1732(CO)	^1H NMR($CDCl_3$): δ 3.63($-COOCH_3$), 3.86(11bH) ppm. ^{13}C NMR($CDCl_3$+DMSO-D_6): δ 16.25(C12), 20.22(C6),23.20(C13),29.11(C2),35.00(C1), 46.96(C5),51.42($-COO\underline{CH}_3$),51.60(C3),62.99 (C11b),172.66($-\underline{CO}OCH_3$)ppm.
	H_2/Pd	10+13 70:30 60-64 117-118 (MeOH)	13: 3340(ind NH) 1728(CO)	^1H NMR($CDCl_3$): δ 3.70(11bH)ppm. ^{13}C NMR ($CDCl_3$+DMSO-D_6): δ 21.10(C6),27.12(C12), 28.34(C2),32.29(C13),39.51(C1),48.46(C5), 51.11($-COO\underline{CH}_3$),51.35(C3),63.08(C11b),173.73 ($-\underline{CO}OCH_3$)ppm.

Their relative stereochemistries, as shown, were inferred from the carbon-13 NMR spectra. In particular, the chemical shift values for the carbon atoms C6 and C11b were indicative of the common trans C/D ring junction[8] while changes in that of C13 for a given pair of isomers were consistent with an altered configuration at C11b. Since the chemical shift of the nitrile carbon remains largely unaffected by changes in the configuration, it seems reasonable to assume that the substituent of the cyclopropane ring assumes a steric position such that it points away from the indole moiety. As the reduction leaves the spiro carbon atom unaffected, this conclusion applies for the unsaturated products (3, 5) as well.

The reduction of 3 and 5 through catalytic hydrogenation (Pd/C/H_2, ambient temp., normal pressure) yielded 11, 12 and 13.[9] The cleavage of the cyclopropane ring, as well as the relative stereochemistries of the reduction products were evidenced by ^1H and ^{13}C NMR data (see Table 2.).

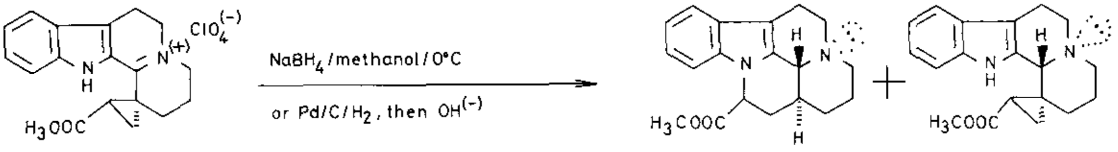


Conversion of the indolo-quinolizine derivatives 4 and 6 by sodium borohydride reduction or catalytic hydrogenation followed a less regular pattern, and led to products the constitution and relative stereochemistries of which appeared to be related to the nature of the substituent of the cyclopropane ring.



In the case of 4, the former reaction afforded the pair of isomers 14 and 15 which, according to their NMR characteristics, differed in their relative configurations at the angular carbon atom (C12b). By contrast, catalytic hydrogenation of the same molecule afforded only one isomer having its cyclopropane ring cleaved while the other product isolated from the reaction mixture proved to be 15.

A more significant alteration in the reaction route was observed upon changing the nitrile group to carbomethoxy function. Thus, treatment of 6 either by sodium borohydride or catalytic hydrogenation afforded the same two products, one of which (18) contained the cyclopropane ring and proved sterically identical with 14.



6 17 18

The ^1H NMR of the other product, 17, exhibited no resonance attributable to the indol-NH proton and, besides the signal due to C(12b)H, showed another methine resonance in the region characteristic of CH group adjacent to hetero-atom (5.04 ppm). These findings clearly showed the occurrence of the intramolecular ring closure and the chemical shift values and off-resonance multiplicities of carbon atoms furnished full support for the eburnamenin structure 17. According to the magnitude of the vicinal coupling between C(12b)H and C(1)H, the geometry of the C/D and D/E ring junctions in 17 is trans-trans.

Table 3.

Start. mat.	Reduct. type	Products ratio, m.p.	IR (KBr) ν_{max} (cm^{-1})	^1H and ^{13}C-NMR data
4	$NaBH_4$	14+15 8:92 225-226 203-204 (MeOH)	14 3250(ind NH) 2270(CN)	^1H NMR($CDCl_3$): δ 3.49(12bH)ppm. ^{13}C NMR ($CDCl_3$+DMSO-D_6): δ 7.65(C14), 18.13(C13), 18.63(C7), 23.21(C3), 27.28 (C1), 28.13(C2), 47.34(C4), 49.78(C6), 60.82(C12b), 120.33(-CN)ppm.
			15 3320(ind NH) 2280(CN)	^1H NMR($CDCl_3$): δ 3.52(12bH)ppm. ^{13}C NMR($CDCl_3$+DMSO-D_6): δ 7.13(C14), 18.07 (C13), 19.72(C7), 22.61(C3), 27.52(C1), 30.22(C2), 49.31(C6), 50.79(C4), 60.45 (C12b), 120.35(-CN)ppm.

Start. mat.	Reduct. type	Products ratio, m.p.	IR (KBr) ν_{max}(cm^{-1})	^{1}H and ^{13}C NMR data
4	H_2/Pd	16+15 55:45 131-132 203-204 (MeOH)	16 3315(ind NH) 2275(CN)	^{1}H NMR($CDCl_3$): δ 3.45(12bH)ppm. ^{13}C NMR($CDCl_3$): δ 15.42(C14),20.93(C7),21.65(C3),22.53(C13),27.12(C2),35.65(C1),53.40(C6),56.36(C4),63.64(C12b),120.30(-CN)ppm.
6	$NaBH_4$	17+18 23:77 186-187 128-129 (MeOH)	17 1760;1738 (CO)	^{1}H NMR($CDCl_3$): δ 3.15(d,J=7.6Hz,12bH),3.53(s,$-COOCH_3$),5.04(m,ΣJ~7.8Hz,14H)ppm. ^{13}C NMR($CDCl_3$): δ 21.46(C7),25.54(C3),29.91(C2),32.37(C13),33.04(C1),52.07($-COO\underline{CH}_3$),53.33(C6),55.10(C14),55.15(C4),63.91(C12b),171.78($-\underline{CO}OCH_3$)ppm.
	H_2/Pd	17+18 10:90	18 3410(ind NH) 1710(CO)	^{1}H NMR($CDCl_3$): δ 3.48(12bH),3.83($-COOCH_3$)ppm. ^{13}C NMR($CDCl_3$): δ 17.21(C13),17.83(C7),24.53(C3),24.66(C2),25.04(C14),29.30(C1),45.73(C4),51.00(C6),51.99($C-COO\underline{CH}_3$),62.91(C12b),171.27($-\underline{CO}OCH_3$)ppm.

A more detailed account of these and related studies will be published elsewhere.

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