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Synthesis of Vinca Alkaloids and Related Compounds VI[1]

Syntheses of Eburnamonine and Isoeburnamonine.

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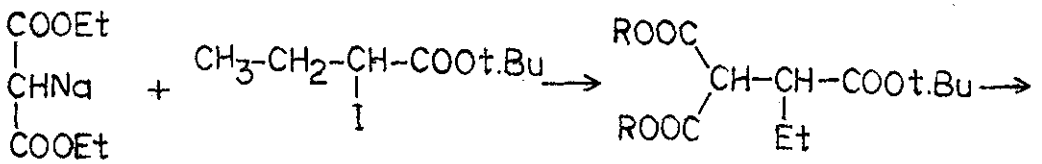
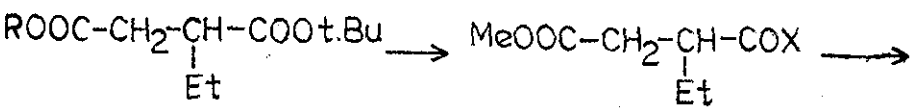
Eburnamonine and isoeburnamonine are synthesized in five steps starting from 3,4-dihydro-β-carboline.

Recently attention has been focused on the pentacyclic indole alkaloids which occur naturally in various plants, because vincamine and eburnamonine possess potent antihypertensive and sedative effects. Many conceptually different routes to eburnamonine /16/ have been employed with considerable success[2]. We now report a new approach in which the intramolecular cyclization of β-carboline derivative[3] derived from 3,4-dihydro-β-carboline and α,β-unsaturated ketone plays a central role.

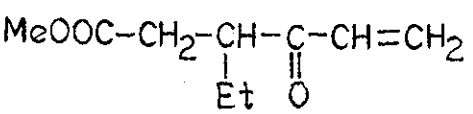
Treatment of the sodium salt of ethyl malonate with iodo-ester 2[4] gave the tri-ester 3, [bp 128°/1 mm] in 85 % yield [NMR /$CDCl_3$/δ 0.95 /t, J=6Hz, $\underline{CH_3}$-CH_2/, 1,3 /t, J=6Hz, CH_3-$\underline{CH_2}$/, 1,45 /s, $\underline{CH_3}$-C/, 1,6 /m, -CH-$\underline{CH_2}$-CH_3/, 2,95 /m, -CH-$\underline{CH}$-CH_2/, 3,7 /d, MeOOC-$\underline{CH}$-COOMe/, 4,2 /q, O-CH_2-/_7[5]. Partial hydrolysis of the ester groups in 3 /potassium hydroxide, dioxane, water; 100°/ followed by decarboxylation of the resulting carboxylic acid 4 /92 %, mp 68°/ /pyridine ; reflux/ afforded the t-butyl ester 5 which - without foregoing purification - was converted /dimethyl sulfate, sodium hydroxide, water/ to the diester 6 [70 %; bp 83-84°/1 mm; NMR /$CDCl_3$/ 0,92 /t, J=6Hz, $\underline{CH_3}$-CH_2/, 1,42 /s, $\underline{CH_3}$-C/, 2,55 /m, -$\underline{CH}$-CH_2-/, 3,62 /s, OCH_3//. Cleavage of the t-butyl ester group /p-TsOH, benzene: reflux/ gave rise to the acid 7 [90 %; bp 128-130°/1 mm; NMR /$CDCl_3$/ 0,98 /t, J=6Hz, $\underline{CH_3}$-CH_2-/, 1,7 /m, CH_3-$\underline{CH_2}$-/, 2,65 /m, CH_2-$\underline{CH}$-/, 3,65 /s, O-CH_3/_7[6], which was converted to the acid chloride 8 /90 %; bp 86-87°/1 mm/ by chlorination with thionyl chloride at 40° for 3 hr. The reaction of 8 with ethylene in the presence of catalyst /aluminium chloride, ethylene chloride; 40°/ yielded the enone 9 [65 %; bp 82°/0,4 mm; NMR /$CDCl_3$/ 0,95 /t, J=6Hz, $\underline{CH_3}$-CH_2/, 1,65 /m, CH_3-$\underline{CH_2}$/, 2,5-3,1 /m, $\underline{CH_2}$-$\underline{CH}$/, 3,7 /s, O-CH_3/, 5,85 /m, -$\underline{CH}$/, 6,45 /m, =$\underline{CH_2}$/_7[7].



1 2 3 R=Et 4 R=H



5 R=H 6 R=Me 7 X=OH 8 X=Cl



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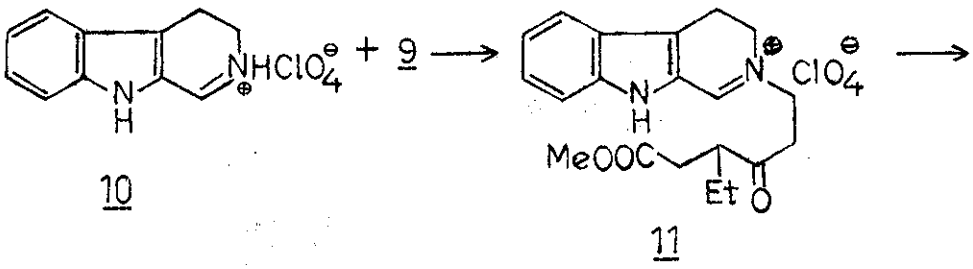
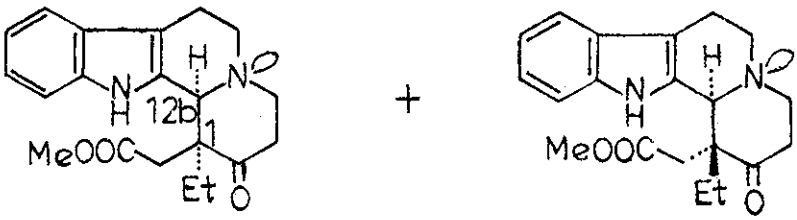
The reaction of 3,4 dihydro-β-carboline salt 10 with the enone 9 afforded the β-carbolinium salt 11 [~55 %; mp 142°, ν_{max}/KBr/ 3350, 1720, 1712, and 1635 cm^{-1}], which was treated with triethylamine /methanol, room temperature; 4 days/, and two tetracyclic compounds, 12 and 13 /26 and 22 %, respectively/, were isolated by alumina column chromatoghraphy in about equal quantity.

The assignment of configurations at C_{-1} and C_{-12b} of 12 and 13 were based on IR and NMR studies. The IR spectrum of compound 12 showed Bohlmann bands [ν_{max}/KBr/ 3360, 2820, 2750, 1710, and 1695 cm^{-1}]and its NMR spectrum showed no one-proton signal above 4 attributable to the angular 12b-proton [NMR /$DMSO_{-d_6}$/ 0,85 /t, J=6Hz, $\underline{CH_3}$-CH_2/, 3,78 /s, -$\underline{CH}$- /, 3,85 /s, O-$\underline{CH_3}$/, 7-7,6 /m, aromatic protons/]. The IR and NMR spectra of compound 13 were closely similar to those for 12 [ν_{max}/KBr/ 3360, 2810, 2730, 1730, and 1710 cm^{-1}; NMR /$CDCl_3$/ 0,85 /t, J=6Hz, $\underline{CH_3}$-CH_2- /, 3,75 /s, -$\underline{CH}$ /, 3,85 /s, O-$\underline{CH_3}$/, 7-7,5 /m, aromatic protons/].

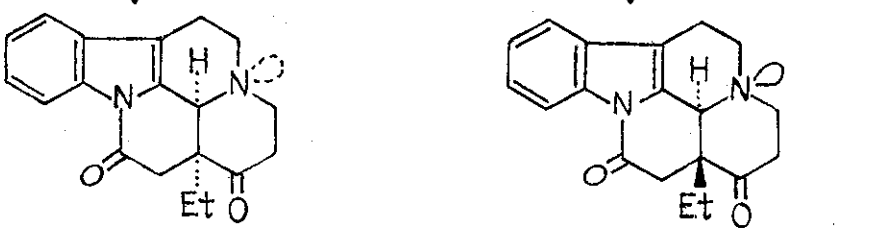
Next, the tetracyclic ester 12 was cyclized at room temperature in toluene for 0,5 hr using sodium t-butoxide / 3 equiv / to form 1-oxo--eburnamonine /14/, in 40 % yield[8].
The lack of Bohlmann bands in its IR spectrum [ν_{max}/KBr/ 1705 and 1635 cm^{-1}] and its NMR spectrum in which one of four aromatic proton signals observed appeared at lower field /δ 8,3 / than usual, indicating that it is forced into the deshielding zone of oxogroup owing to the ring formation, provided confirmation of the structure [NMR /$CDCl_3$/ 1,1 /t, $\underline{CH_3}$-CH_2/, 4,5 /s, -$\underline{CH}$- /, 7,5



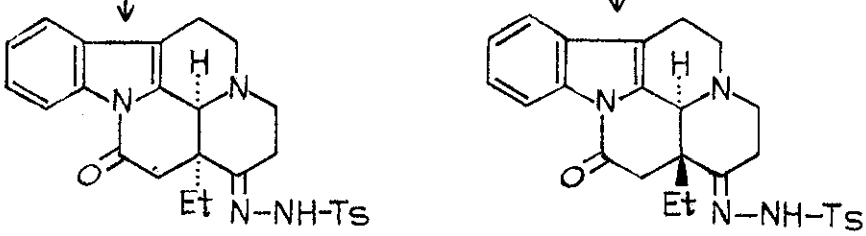
10 11



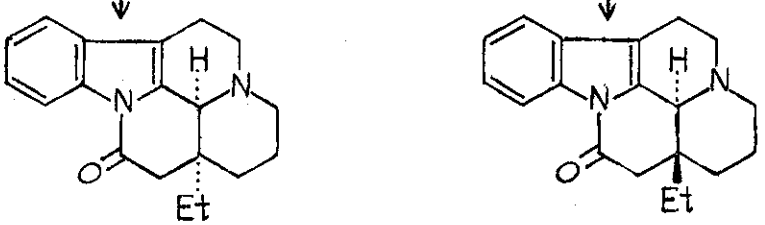
12 13



14 17



15 18



16 19

/m, aromatic protons/, 8,2 /m, C_{-10} proton/_7.

Reaction of 14 with p-toluenesulfonylhydrazide /1N HCl, room temperature; 3 hr/ gave the corresponding tosyl hydrazone 15 [ν_{max}/KBr/ 3180, 3130, 1700, 1630, and 1600 cm^{-1}_7, which was subjected to reaction with sodium cyanoborohydride /dimethylformamide - sulfolane, TsOH; 110°, 2 hr /to give dl-eburnamonine /16; mp 206-207°, 45 % yield from 14/.

Optical resolution of 16 was achieved by means of salt formation with /-/-0,0-dibenzoyltartaric acid in methanol solution, when the salt corresponding to /-/-eburnamonine separated in cristalline form [62 %, mp 210-211°, $/\alpha/_D^{20}$= -83°, C=0,3 , chloroform-methanol; /-/-16 : 58 %; mp 181-182°, $/\alpha/_D^{20}$= -94°, C=0,51 , chloroform_7. When the salt formation was carried out with /+/-0,0-dibenzoyltartaric acid the salt of /+/-eburnamonine crystallized [59 %; mp 207°, $/\alpha/_D^{20}$= +95°, C=0,3 , chloroform-methanol; /+/-16: 55 %; mp 174-175°, $/\alpha/_D^{20}$= +102°, C=0,51 , chloroform_7.

In a similar manner, treatment of the other isomer /13/ with sodium t-butoxide afforded 1--oxo-isoeburnamonine 17; [ν_{max}/KBr/ 2810, 1730,

1708, and 1655 cm^{-1}; NMR/$CDCl_3$/ 0,8 /t, J=6Hz, CH_3-CH_2/, 7,3 /m, aromatic protons/, 8,4 /m, C_{-10} proton /_7, which was directly converted /Ts-NH-NH_2-HCl followed by $NaCNBH_3$/ via the tosyl hydrazone 18 to dl-isoeburnamonine /19; mp 133-135°/.

References:

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5. Satisfactory analytical /C, H and N/ data were obtained for all new compounds.

6. Compound 7 could be purified by conversion to the dicyclohexylamine salt, followed by recrystallization /mp 112°/.

7. The reaction product was isolated simply by quenching the mixture with ice-water, washing the organic layer with aqueous sodium carbonate, evaporation of the solvent and distilled twice from anhydrous sodium carbonate. Because of the relative instability of the corresponding chloroethyl ketone, its conversion to 9 was carried out without delay.

8. The pentacyclic compounds 14 and 17 were also obtained directly, without the isolation of esters, by utilising a longer reaction period or elevated temperature, but the yields were rather moderate.

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