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SYNTHESIS AND EPIMERIZATION OF 11b-SUBSTITUTED-INDOLIZINO-[8,7-b]INDOLE-5-CARBOXYLIC ACID METHYL ESTERS

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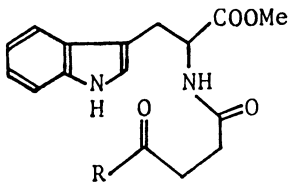
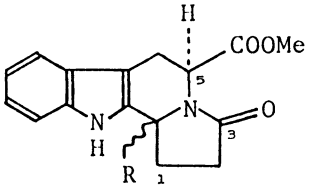
The methoxide-catalyzed epimerization at C-5 of the 11b-substituted-indolizino[8,7-b]indole-5-carboxylic acid methyl esters was in line with the stereochemical relationship of the substituent on C-11b and the methoxycarbonyl group on C-5.

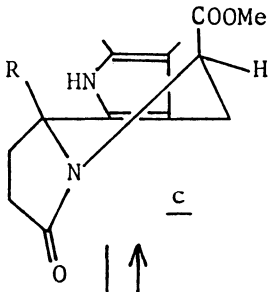
In a previous paper, we reported the isolation of four carboxylic acids as the methyl esters (1c R=β-H, 1t R=α-H, 2c R=β-COOMe, and 2t R=α-COOMe) from Clerodendron trichotomum Thunb. Epimerization of 1t and 2t gave the enantiomers of 1c and 2c, respectively.[1] This paper describes the synthesis and methoxide-catalyzed epimerization at C-5 of the 11b-substituted-indolizino[8,7-b]indole-5-carboxylic acid methyl esters (3c,t–6c,t, 7t, and 8t).



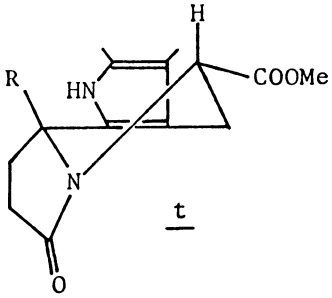
3a R = Me
4a R = Et
5a R = n-Pr
6a R = Ph
7a R = i-Pr
8a R = t-Bu



1c,t R = H
2c,t R = COOMe
3c,t R = Me
4c,t R = Et
5c,t R = n-Pr
6c,t R = Ph
7t R = i-Pr
8t R = t-Bu



c



t

The amides 3a–8a were prepared from L-tryptophan methyl ester and the corresponding γ-keto-carboxylic acids.[2] Treatment of 3a–6a with 13% HCl-MeOH afforded 3c and 3t (r.t., 20 h, in a ratio of 2:1), 4c and 4t (r.t., 20 h, 1:2), 5c and 5t (r.t., 20 h, 1:2), and 6c and 6t (reflux, 2 h, 1:20), which were separated by column chromatography, respectively.[3] Cyclization of 7a and 8a under the similar conditions yielded the respective 7t and 8t. The stereoselective formation of 7t and 8t seems to be due to the interaction between the methoxycarbonyl and the R group in the cyclization intermediates.[4]

As shown in Table 1, the ^{1}H NMR spectra of 1c–6c indicated the signals at 5.23–5.48 ppm (1H, dd, J=6.6–8.1 and 1.5–2.1 Hz), which suggested the equatorial orientations of the C-5 proton in these compounds. On the other hand, the double doublet signals in 1t–8t were observed at 3.88–4.51 ppm (1H, J=10.0–11.1 and 5.1–5.8 Hz), indicating the axial orientations of the C-5 proton. The characteristic ABX-signals observed for the C-5 and -6 protons in 1t–8t were similar to those for the C-3 and -4 protons in the ^{1}H NMR spectra of the 1,3-cis-disubstituted-1,2,3,4-tetrahydro-β-carbolines.[5,6] The proton signals of the methoxycarbonyl group in 1c–6c were found at higher-field than those in 1t–6t, respectively.

The ^{13}C NMR signals for C-5 and -11b in 1c–6c appeared at higher-field than those in the corresponding 1t–6t, indicating the axial orientations of the methoxy-

Table 1. ^{1}H and ^{13}C NMR spectral data ($CDCl_3$, δ-values)

Compound	5-H		-OCH_3		C-5		C-11b	
	c[a)]	t[b)]	c	t	c	t	c	t
1 R = H	5.34	4.12	3.63	3.82	49.5	54.7	52.5	56.3
2 R = COOMe	5.48	4.39	3.59	3.83[c)]	49.2	53.4	63.9	66.6
3 R = Me	5.40	4.09	3.66	3.79	48.7	52.2	59.8	61.9
4 R = Et	5.39	4.07	3.68	3.83	48.9	52.1	63.1	64.9
5 R = n-Pr	5.37	4.10	3.69	3.82	48.9	52.2	62.9	64.6
6 R = Ph	5.23	3.88	2.89	3.74	48.3	52.1	64.4	68.1
7 R = i-Pr		4.15		3.81		51.8		67.7
8 R = t-Bu		4.51		3.78		53.9		70.5

a) Double doublet, J=6.6–8.1 and 1.5–2.1 Hz. b) Double doublet, J=10.0–11.1 and 5.1–5.8 Hz. c) Assignment may be interchangeable with the singlet at 3.87 ppm (3H).

Table 2. Equilibrations(%) at C-5[a)]

		c	t
1	R = H	>99	<1
2	R = COOMe	90	10
3	R = Me	81	19
4	R = Et	65	35
5	R = n-Pr	70	30
6	R = Ph	54	46
7	R = i-Pr	≃0[b)]	≃100
8	R = t-Bu	≃0[b)]	≃100

a) The ratios determined by HPLC.

b) No isomer was detected.

carbonyl group on C-5 in 1c–6c and the equatorial orientations of that in 1t–6t.[7)] In the ^{13}C NMR spectra of 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines, the signals for C-1 and -3 in the trans-isomers were found at higher-field than those in the corresponding cis-isomers.[8)]

The proton signals of the methoxycarbonyl group in 1c–5c were observed at 3.59–3.69 ppm, while that in 6c appeared at 2.89 ppm because of the magnetic anisotropic effect of the phenyl group on C-11b.[6)] The proton signals for 5-H (3.88 ppm) in 6t were found at higher-field than those in 1t–5t. The characteristic of the ^{1}H NMR spectra of 6c and 6t was in accord with the cis-relationships of the substituent on C-11b and the methoxycarbonyl group on C-5 in 1c–6c, and the trans-relationships of those in 1t–8t.

In order to examine the 11b-substituent effect on the epimerization at C-5, each compound 1c–6c, 1t–8t was treated with 0.1 M NaOMe in MeOH at room temperature for a few days, and the ratio of cis/trans isomers at equilibrium was determined by HPLC, JASCO Fine SIL-5 ($CHCl_3$–hexane). The results are shown in Table 2. The compound 1c was thermodynamically more stable than 1t, and existed to the extent of more than 99%. Assuming the cis-fusion of the indolizinone ring,[9)] the conformer c might be assigned to 1c–6c and the conformer t to the epimerization isomers of 1c–6c, respectively. The compound 1t seems to be destabilized by the interaction between the amido carbonyl and the methoxycarbonyl group on C-5 as shown in the conformer t. Epimerization at C-5 in 2c–6c seems to be affected by the interaction between the bulky 11b-substituent and the methoxycarbonyl group on C-5. No epimerization isomers of 7t and 8t were detected either by ^{1}H NMR or HPLC.

The equilibrations shown in Table 2 were in line with the stereochemical assignments of 1c–6c and 1t–8t.

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3) The figures 3c,t, 4c,t, and 6c,t show the relative configurations of the methoxycarbonyl and the R group because of the epimerization at C-5.

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