NOVEL APPLICATIONS OF THE MODIFIED POLONOVSKI REACTION - VIII[1]
SYNTHETIC STUDIES IN THE PSEUDOVINCAMINE SERIES

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Abstract - 1β-Ethyl-(2'-methoxycarbonyl)-3α-ethyloctahydro-1,2,3,4,6,7,12,12b-indolo[2,3-a]quinolizine 7, a potential intermediate in the pseudovincamine series, was synthesized via the modified Polonovski reaction. Conformational considerations are presented.

INTRODUCTION

The significant therapeutical value of several vincamine derivatives[2-4] has prompted an intensive search for feasible total syntheses of these compounds. Pseudovincamines are vincamine isomers in the Iboga series, and for them, too, interesting pharmacological properties can be predicted. The possible existence of pseudovincamines was proposed several years ago[5] but the first natural representatives of the series, the tacamines, were isolated just recently.[6,7]

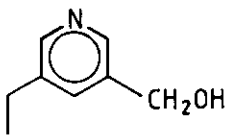
In connection with our work on therapeutically valuable indole alkaloid derivatives we became interested in the preparation of vincamine and pseudovincamine derivatives and their synthetic intermediates[8] by the modified Polonovski reaction.[9-12]

RESULTS AND DISCUSSION

We describe the preparation of 1β-ethyl-(2'-methoxycarbonyl)-3α-ethyloctahydro-1,2,3,4,6,7,12,12b-indole[2,3-a]quinolizine 7, which seems to be a potential intermediate in the pseudovincamine series (e.g. (±)-14-epihomotacamonine[13]).

Carbinol 1[14] was dehydrogenated (MnO_2) to the corresponding aldehyde 2, which was reacted with malonic acid. Esterification of the resulting acid to 3 and alkylation of this with tryptophyl bromide yielded the corresponding pyridinium salt 4. Catalytic hydrogenation of 4 furnished the N-tryptophylpiperidine 5a. After protection of the indole N with the t-butyloxy-

carbonyl (Boc) group, compound 5b was formed. The corresponding N-oxide was subjected to the modified Polonovski reaction conditions,[9-12] followed by cyanide trapping, to furnish the α-aminonitriles 6a and 6b. Treatment of 6a with $AgBF_4$ and then with methanol presaturated with HCl yielded nearly exclusively (except tarry material) the indolo[2,3-a]quinolizine 7.



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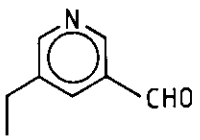

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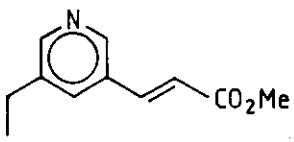

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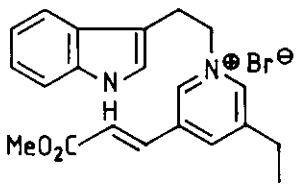

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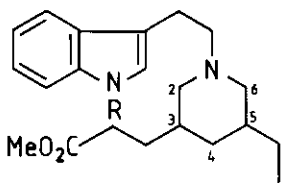
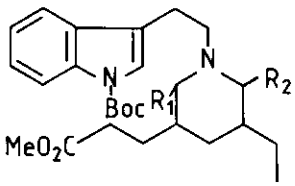
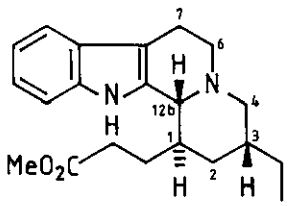


5a R=H
b R=Boc



6a R_1 = CN R_2 = H
b R_1 = H R_2 = CN



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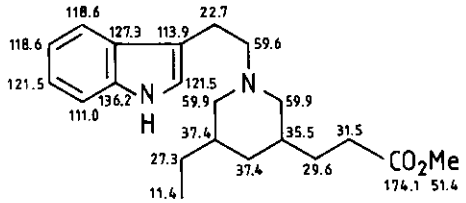
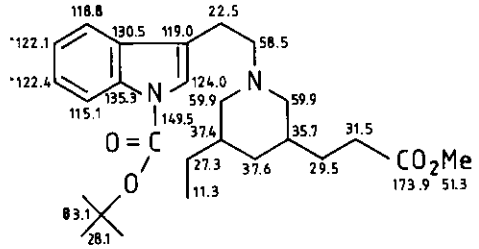
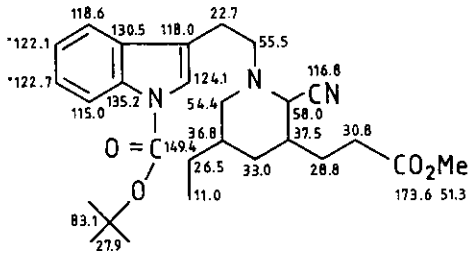
^{13}C NMR spectra of compounds 5a, 5b, 6a and 6b provide strong evidence that the 3,5-substituents are cis to each other and occupy equatorial positions in the predominant conformation. They also indicate that the cyano group of 6a and 6b is axially oriented. These findings are in good agreement with earlier results.[14]



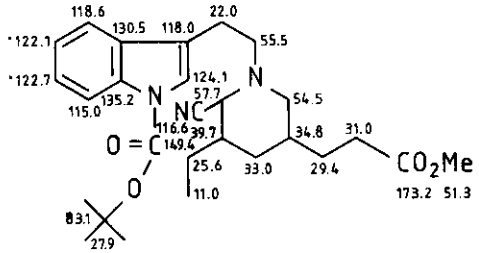
5a



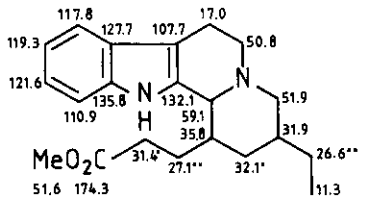
5b



6a



6b



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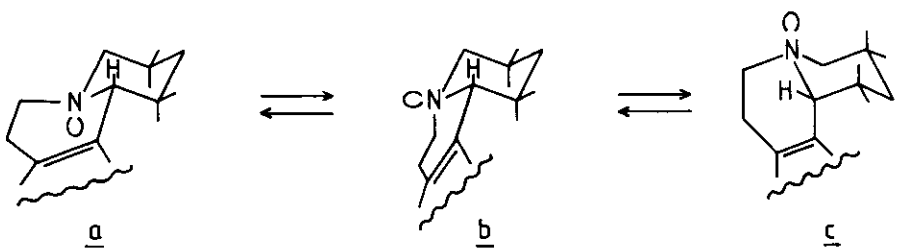
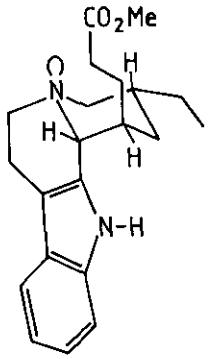
The indolo[2,3-a]quinolizine 7 can exist in three conformations, which are in equilibrium by nitrogen inversion and cis-decalin type ring inversion (Scheme 1). Ring C is assumed to be in the half chair conformation and only the chair forms of ring D are considered.



a b c

Scheme 1.

The stereostructure of the pseudovincamine derivative 7 could be determined from spectroscopical data. The absence of Bohlmann bands in the IR spectrum and presence of the ^1H NMR signal of C(12b)-H at δ = 4.35 ppm (>3.8 ppm) suggested that compound 7 exists predominantly in a cis-fused C/D ring conformation (conformation c). The value of C-7 at δ = 17.0 ppm in the ^{13}C NMR spectrum further proved that compound 7 exists almost totally in conformation c. This means that the C-1 substituent is axially oriented (to avoid steric interactions with the indolic part) and the C-3 substituent is equatorially oriented.[8] Thus the two substituents are trans to each other (vide supra). As a consequence, an epimerisation must have taken place prior to the cyclisation to the indolo[2,3-a]quinolizine 7. This can be explained by the cleavage of the cyanide ion, followed by the iminium-enamine equilibration and the retrapping of the cyanide ion on the opposite side of the C-3 substituent (C-1 substituent in the cyclized product). The cyanide ion is then replaced by a nucleophile (e.g. MeO^- from the solvent) in a normal S_N2 displacement, followed by cyclisation on the opposite side to the axial leaving group. This leads straight to the predominant conformation c.



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In addition to the above data, the substituent effects in the ^{13}C NMR spectrum of compound 7 confirm the axiality of the C-1 substituent and the equatoriality of C-3 substituent.[14,15]

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 spectrophotometer using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration. Bands yielding structural information are reported. ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS as internal standard δ = 0) on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS where s, d, t, q and m designate singlet, doublet, triplet, quartet and multiplet, respectively.

Coupling constants J are given in Hz. Mass spectrometry was performed on a Jeol JMS-D-100 apparatus and Kratos MS 80 RFA Autoconsole/DS 55 apparatus (high resolution spectra).

Compound 2

Carbinol 1[14] (1.3 g, 9.5 mmol) and freshly prepared MnO_2 (6.0 g) in CH_2Cl_2 (15 ml) were refluxed for 6 h. The progress of the reaction was followed by TLC. When there was no more carbinol to be seen the inorganic material was centrifuged away. Y: 74%. ir 1700 (-CHO), pmr 1.31 (3H, t, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 2.79 (2H, q, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 8.01-8.92 (3H, m, arom. H), 10.11 (1H, s, -CHO), cmr 14.67 ($-CH_2\underline{CH_3}$), 25.58 ($-\underline{CH_2}CH_3$), 130.96 (C-3), 134.28 (C-4), 139.73 (C-5), 149.34 (C-2), 154.34 (C-6), 190.70 (-CHO), m/z 135 (M^+) (100%), 134, 120, 106. Found: C, 71.01; H, 6.66; N, 10.22. Calc. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36.

Compound 3

Aldehyde 2 (0.95 g, 7.0 mmol), malonic acid (1.46 g, 2 ekv), pyridine (3 ml) and piperidine (0.1 ml) were refluxed for 1 h at 90°C and for 3 h at 130°C and then evaporated to dryness. Conc. H_2SO_4 (1.0 ml), MeOH (3.2 ml) and benzene (5 ml) were added and refluxing was continued for 20 h. Ice-water (10 ml) was added to the cooled mixture and the mixture was neutralised with ammonia. The water phase was extracted with ether and the combined organic phases were dried over Na_2SO_4. The crude product mixture was separated by column chromatography on silica (chloroform-methanol, 90:10). Essentially pure 3 was obtained as an orange viscous oil. Y: 45%. ir 1715 (C=O), pmr 1.30 (3H, t, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 2.71 (2H, q, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 3.84 (3H, s, $-CO_2CH_3$), 6.53 (1H, d, J = 16 Hz, α-H), 7.71 (1H, d, J = 16 Hz, β-H), 7.68-8.58 (3H, m, arom. H), cmr 14.87 ($-CH_2\underline{CH_3}$), 26.65 ($-\underline{CH_2}CH_3$), 51.49 ($-CO_2CH_3$), 119.34 (α-C), 129.40 (C-3), 133.11 (C-4), 139.08 (C-5), 141.03 (β-C), 146.87 (C-6), 150.84 (C-2), 166.42 (C=O), m/z 191 (M^+), 190, 176, 160 (100%). Found: C, 68.98; H, 6.75; N, 7.21. Calc. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.86; N, 7.32.

Compounds 4, 5a and 5b

Alkylation of compound 3 with tryptophyl bromide afforded the corresponding pyridinium salt 4, whose catalytic hydrogenation (PtO_2, 3 d) yielded compound 5a as a semi-solid oil. Y: 91%. ir 1740 (C=O), pmr 0.91 (3H, t, J = 5.5 Hz, $-CH_2\underline{CH_3}$), 1.63 (2H, q, J = 5.5 Hz, $-\underline{CH_2}CH_3$), 3.66 (3H, s, $-CO_2CH_3$), 6.99 (1H, s, ind. α-H), 7.20-7.68 (4H, m, arom. H), 8.26 (1H, br s, NH), m/z 342 (M^+), 327, 311, 212, 144, 130 (100%). Found: 342.2303 (mass spectrometry). Calc. for $C_{21}H_{30}N_2O_2$: 342.2309.

50% aq. NaOH (2.5 ml) was added to compound 5a (320 mg, 0.94 mmol) in toluene (5 ml) containing tetrabutylammonium hydrogen sulphate (100 mg). The two phase system was stirred under argon for 5 min. Di-t-butyl dicarbonate (415 mg, 1.90 mmol) in toluene (3 ml) was added during 10 min and stirring was continued for another 10 min. The organic layer was separated and the aqueous layer was washed several times with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give 5b. Y: 98%. ir 1730 (C=O), pmr 0.91 (3H, t, J = 5.5 Hz, $-CH_2\underline{CH_3}$), 1.65 (9H, s, $-C(CH_3)_3$), 3.65 (3H, s, $-CO_2CH_3$), 7.39 (1H, s, ind. α-H), m/z 442 (M^+, 1%), 212 (100%), 144, 130. Found: 442.2828 (mass spectrometry). Calc. for $C_{26}H_{38}N_2O_4$: 442.2833.

Compounds 6a and 6b

Compound 5b (400 mg, 0.90 mmol) was reacted with H_2O_2 (30%, 0.3 ml) in $CHCl_3$-MeOH (1:1) (8 ml) (55°C, 3 d) to give after the usual workup the corresponding N-oxide in 89% yield.

The N-oxide (370 mg, 0.80 mmol) in dry CH_2Cl_2 (3 ml) was stirred at 0°C (Ar-atm) and TFAA (0.30 ml, 2.5 ekv) was added during 15 min. Stirring was continued for 1 h at 0°C and 15 min at rt after which KCN (85 mg) in H_2O (2 ml) was added and the pH of the aqueous layer was adjusted to pH 5 by the addition of NaOAc. The mixture was stirred at rt for 0.5 h, basified to pH 10 with 10% aq. Na_2CO_3 and extracted with CH_2Cl_2 several times. The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Y: 75% (6a + 6b, 1:1) after purification through a short column of alumina (CH_2Cl_2-hexane, 4:6). Compounds 6a and 6b were separated by repeated TLC (Silica gel, $CHCl_3$-MeOH, 85:15).

6a: ir 2270 (CN), 1740 (C=O), pmr 0.88 (3H, t, J = 5.5 Hz, $-CH_2\underline{CH_3}$), 1.67 (9H, s, $-C(CH_3)_3$), 3.66 (3H, s, $-CO_2CH_3$), 3.82 (1H, br, >CH-CN), 7.43 (1H, s, ind. α-H), m/z 467 (M^+, 1%), 441, 436, 237, 210 (100%), 143, 130. Found: 467.2780 (mass spectrometry). Calc. for $C_{27}H_{37}N_3O_4$: 467.2786.
6b: ir 2270 (CN), 1730 (C=O), pmr 0.90 (3H, t, J = 5.5 Hz, $-CH_2-\underline{CH_3}$), 1.67 (9H, s, $-C(CH_3)_3$), 3.66 (3H, s, $-CO_2CH_3$), 3.90 (1H, br, >CH-CN), 7.43 (1H, s, ind. α-H), m/z 467 (M^+, 1%), 441, 436, 237, 210 (100%), 143, 130. Found: 467.2778 (mass spectrometry). Calc. for $C_{27}H_{37}N_3O_4$: 467.2786.

Compound 7

$AgBF_4$ (156 mg, 0.80 mmol) in dry THF (2 ml) was added to 6a (350 mg, 0.75 mmol, containing some 6b) in dry THF (8 ml) (Ar-atm). The reaction mixture was stirred for 1 h and evaporated to dryness. MeOH (30 ml) presaturated with dry HCl was added and the reaction mixture was stirred at 60°C for 22 h. It was then diluted with ice-water and the aqueous solution was neutralised with $NaHCO_3$

and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water and dried over Na_2SO_4. Essentially pure 7 was obtained after preparative TLC on silica ($CHCl_3$-MeOH, 85:15). Y: 50%. ir 3300 (br, NH), 1720 (C=O), pmr 0.95 (t, J = 6.0 Hz, $-CH_2-\underline{CH_3}$), 3.71 (3H, s, $-CO_2\underline{CH_3}$), 4.35 (1H, br, H-12b), 7.03-7.54 (4H, m, arom. H), 8.50 (1H, br s, NH), m/z 340 (M^+) (100%), 339, 325, 311, 309, 170, 169. Found: 340.2149 (mass spectrometry). Calc. for $C_{21}H_{28}N_2O_2$: 340.2152.

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