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The Stereochemistry of Ring C Formation of Tetrahydrocarboline-based Indole Alkaloid Systems*

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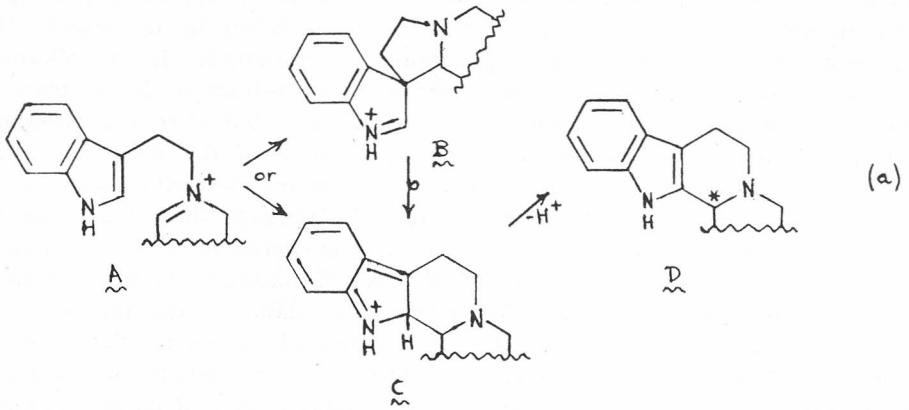
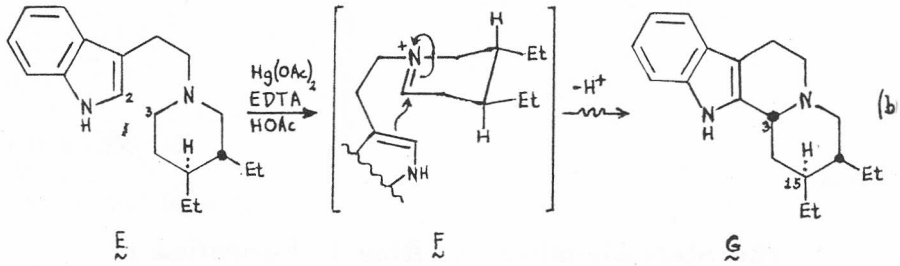
Hydrolyses of alkyl 1-tryptophyl-4-methyl-1,4,5,6-tetrahydronicotinates produced two stereoisomeric methylindoloquinolizidines. Their structures were determined by ^{13}C NMR spectroscopy and their mode of formation described in light of present-day theory.

One of the most popular procedures for the construction of the tetrahydrocarboline ring skeleton consists of the preparation of the immonium salt *A* and its intramolecular condensation depicted in equation (a). Much attention has been paid to the behavior of the indole moiety in the carbon-carbon bond-forming step, *i. e.* with regard to the condensation occurring initially at the indole α-carbon site (leading to intermediate *C*) or β-carbon (*cf.* intermediate *B*) and subsequent Wagner-Meerwein rearrangement.[1] Contrastingly, less attention has been paid to the details of the carbon-carbon bond-forming step with respect to the stereochemistry of the benzylic aminomethine site (starred carbon in *D*) relative to other chiral centers present in the ultimate tetrahydrocarboline system (*D*).Recently, however, the extraordinary preference for H(3)—H(15) *trans* stereochemistry in the production of tetrahydrocarbolines of the indoloquinolizidine type,[2] exemplified by the conversion of



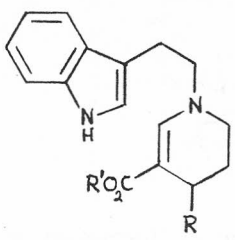
*Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.



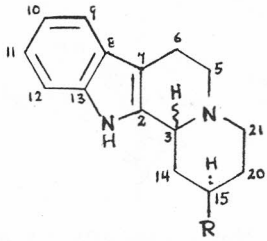
E F G

2,3-secocorynantheane (*E*) into 3-isocorynantheane (*G*) on mercuric acetate oxidation (equation b),[3] has been interpreted in terms of an axial attack of the indole C(α)—C(β) π bond upon the electrophilic carbon of the half-chair piperideinium cation and a concomitant release of the π electrons of the latter to a nitrogen orbital disposed axially to ring D and hence in a coplanar *trans* diaxial orientation with the newly established carbon-carbon bond (conformation *F*).[4,5] This concept, first developed as an explanation for the stereoselectivity observed in the construction of a piperidinotetrahydrocarbazole system,[8] has become the basis for the understanding of the stereochemistry of a vast array of immonium salt cyclizations of the Pictet-Spengler type.[9] In the light of these experiences a recent report[10] on a cyclization of an immonium salt of type *A* not leading to the sterochemically anticipated product came as surprise and required reinterpretation and reinvestigation.

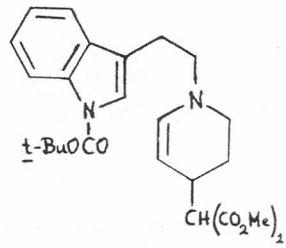
Some time ago we introduced a facile method of *in situ* preparation of cations of type *F* en route to indoloquinolizidines and related alkaloids.[11] It involved a one-operation, sequential hydrolysis, decarboxylation and cyclization of tetrahydronicotinates, *e. g.* the conversion of compounds *1a* or *b* into tetracycle *2a*[11], and led to applications in various areas of alkaloid synthesis.[11,12] As part of a decade-long study of approaches to the synthesis of the indole alkaloid vallesiachotamine,[13,14] based to a large extent on our schemes of indole alkaloid synthesis initiating with *N*-tryptophyl-β-acylpyridinium salt chemistry,[15] Lounasmaa had the occasion to investigate the hydrolysis, decarboxylation and cyclization of compound *1c* in alkaline, aqueous methanol and reported the formation of tetracycle *2c*, instead of its expected isomer *2b*. He interpreted this result and that of related reactions in terms of a SN_2-like, intramolecular displacement of the methoxy group of an intermediate carbinolamine ether (obtained by methoxide addition to the immonium ion *A*) by the indole moiety.[16] Whereas this idea could be dismissed as untenable on the basis of the non-existence of concerted displacements on carbinolamine ethers and a SN_1-like displacement being equivalent to the intermediacy of ion *A (vide supra)*, the claim of the formation of product *2c* could not be taken lightly. A reinspection of the problem became mandatory in the light of the recent report[17] of the methanolic acid-induced transformation of enamine *3* into tetracycle *2d* (and a trace of its stereoisomer *2e*), *i. e.* a stereochemical outcome consistent with present-day theory and opposite to that of Lounasmaa's result.



1a, R = H, R' = Me
b, R = H, R' = t-Bu
c, R = R' = Me
d, R = Me, R' = t-Bu



2a, R = H
b, 3β-H, R = Me
c, 3α-H, R = Me
d, 3β-H, R = $CH(CO_2Me)_2$
e, 3α-H, R = $CH(CO_2Me)_2$



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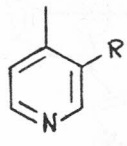
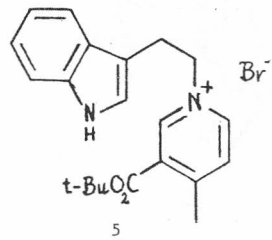
For the repetition of Lounasmaa's experiment and a parallel experiment of the hydrolytic, decarboxylative cyclization of the *t*-butyl ester *1d* methyl γ-methylnicotinate (*4c*) had to be prepared. Whereas it could be produced by laborious methods from γ-picoline[18] or acyclic precursors,[19] it now was found that a two-step, one-operation procedure of permanganate oxidation of β-ethyl-γ-picoline (»β-collidine«) (*4a*)[20] and esterification of the resultant γ-methylnicotinic acid (*4b*) afforded the ester in 45% yield. *t*-Butoxide-induced ester interchange[11a] led to ester *4d*, whose treatment with tryptophyl bromide produced salt *5*. Palladium-catalyzed hydrogenation of the latter in the presence of triethylamine[15] yielded tetrahydropyridine *1d*.



4a, R = Et
b, R = CO_2H
c, R = CO_2Me
d, R = CO_2t-Bu



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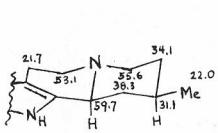
Hydrolysis of ester *1c* in refluxing, alkaline, aqueous methanol gave a 8 : 1 mixture of tetracycles *2c* and *2b* in 52% yield (30% of starting material being recovered). Hydrolysis of ester *1d* in refluxing, aqueous acetic acid produced a 4 : 1 mixture of the same, two compounds in 83% yield. The stereochemistry of the products was established by ^{13}C NMR spectroscopy, which revealed the major product to be identical with Lounasmaa's sole product. Recovery of the minor product (*2b*) in an experiment in which it was exposed to aqueous alkali under conditions identical with those of the hydrolysis of ester *1c* showed the amines (*2b* and *c*) to be kinetic products of the hydrolysis. The lower *2c*/*2b* product ratio from the acid-catalyzed hydrolysis of ester *1d*, conditions more conducive to H(3) isomerization,[21] indicated that the amines formed in this reaction constituted also mostly the kinetic products. Comparison of the non-aromatic carbon shifts of the amine products with those of alkaloids of the indoloquinolizidine type revealed isomer *2c* to possess an equatorial methyl group within a *trans*-quinolizidine framework (*6*) and isomer *2b* to be an equilibrium mixture of *cis*- and *trans*-quinolizidines (*7*) at room temperature.



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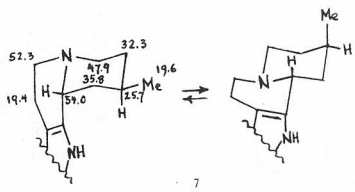
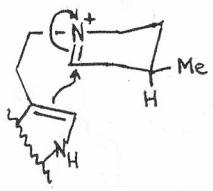


7

While not substantiating the exclusivity of amine *2c* formation in the alkaline hydrolysis of vinylogous urethane *1c*,[10] the above observations reveal the preponderant formation of isomer *2c* in the hydrolysis of vinylogous urethanes *1c* and *d*. Whereas this unexpected result, *i. e.* the product (*2c*) not being a H(3)—H(15) *trans* compound, does not necessitate the abandonment of the theory inherent in the $F \rightarrow G$ transformation (*vide supra*), it requires a subtle rationale. The immonium ion intermediate en route to tetracycles *2b* and *c* differs from most previous cases by possessing only one sidechain attachment (besides the *N*-tryptophyl unit) to the piperideine ring and from the intermediate of the $3 \rightarrow 2d$ conversion by the sole alkyl sidechain, *i. e.* a methyl group, being small in size. Under these circumstances it is conceivable that the 1-alkyl-4-methyl-1-piperideinium ion assumes energetically similar half-chair (*8*) and half-boat (*9*) conformations. Cyclization of the first form would lead to isomer *2b* and ring closure of the latter conformation would result in the production of isomer *2c*.



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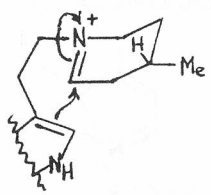

9

EXPERIMENTAL

Melting points were taken on a Reichert micro hotstage and are uncorrected. Ultraviolet spectra of methanol solutions and infrared spectra of KBr mulls were recorded on Perkin-Elmer 550 and 1330 spectrophotometers, respectively. ^{1}H NMR spectra of $CDCl_3$ solutions were obtained on a Varian EM-390 spectrometer and a 360 MHz instrument with a highly modified Varian HR-220 console, an Oxford magnet and a Nicolet 1180-E computer system. ^{13}C NMR spectra of $CDCl_3$ solutions were taken on a Nicolet NT-200 (wide-bore, broad-band, with Oxford magnet) spectrometer, operating at 50.31 MHz in the Fourier transform mode. The carbon shifts are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. The low-resolution mass spectrum was taken on a Finnigan 4021 spectrometer.

Methyl γ-Methylnicotinate (4c)

A mixture of 40.0 g of β-collidine (*4a*) and 192.0 g of potassium permanganate in 1 L of water was stirred at 0 °C for 2 h and then at room temperature for 16 h. The colorless solution was filtered from the resultant brown precipitate and the latter washed with hot water. The combined filtrate and washings were concentrated to 160 mL and the solution brought to pH 6.5 by the addition of 40% sulfuric acid. The resultant potassium sulfate precipitate was filtered, a solution of 68.0 g of cupric acetate in 800 mL of water added to the filtrate and the combined solutions refluxed for 1 h. (A 5 L flask is needed for this operation

to avoid material loss as a consequence of strong frothing.) The precipitated copper salt was filtered and then dissolved in 560 mL of 10% hydrochloric acid solution. Hydrogen sulfide gas was bubbled through the solution for as long as cupric sulfide continued to precipitate. The mixture was filtered and the filtrate evaporated to dryness. A solution of the residual γ-methylnicotinic acid in 400 mL of dry methanol was saturated with hydrogen chloride gas and stirred at room temperature for 4 days. It was evaporated under vacuum and the residue dissolved in the smallest amount of brine solution. The latter was neutralized with solid sodium bicarbonate and extracted exhaustively with benzene. The extract was dried (Na_2SO_4) and evaporated. Distillation of the residual oil yielded 90.0 g (45%) of colorless liquid ester *4c*: b. p. 92—93 °C/3 Torr; ^{1}H NMR δ 2.63 (s, 3, Me), 3.94 (s, 3, OMe), 7.15 (d, 1, J = 6 Hz, H-5), 8.55 (d, 1, J = 6 Hz, H-6), 9.05 (s, 1, H-6); spectrally identical with authentic sample.[11b]

t-Butyl 4-Methyl-1-tryptophylnicotinate Bromide (5)

A sodium *t*-butoxide solution (from 6.60 g of sodium hydride and 230 mL of *t*-butanol) was added dropwise to a solution of 16.50 g of ester *4c* in 5 mL of dry benzene over a 30-min period and the mixture then refluxed for 2 h. The solvent, 200 mL, was evaporated (evaporation to dryness lowering the product yield), 36 g of ice and 30 mL of methylene chloride added and the mixture shaken vigorously until all solids had dissolved. The layers were separated and the aqueous solution extracted with methylene chloride. The combined organic solutions were dried (Na_2SO_4) and evaporated. Distillation of the residue, 10.9 g (containing 4% of starting ester *4c*), gave 9.86 g (47%) of colorless liquid ester *4d*: b. p. 90 °C/1.5 Torr; ^{1}H NMR δ 1.60 (s, 9, *t*-Bu methyls), 2.55 (s, 3, Me), 7.10 (d, 1, J = 6 Hz, H-5), 8.50 (d, 1, J = 6 Hz, H-6), 9.02 (s, 1, H-2).

A solution of 2.10 g (11 mmol) of ester *4d* and 2.50 g (11 mmol) of tryptophyl bromide in 7 mL of dry methanol was stirred under nitrogen at room temperature for ca. 4 days (until the disappearance of starting bromide as shown by TLC). The mixture was filtered and the solid washed with dry ether, leading to 3.10 g (68%) of crystalline salt *5*: m. p. 168—170 °C; UV λ_{max} 215 nm (log ε 4.58), 265 (3.81); IR NH 3400 (m), C=O 1720 (s), C=C 1635 (m), 1602 (m) cm^{-1}; ^{1}H NMR δ (d_6-DMSO) 1.50 (s, 9, *t*-Bu methyls), 2.82 (s, 3, Me), 3.36 (t, 2, J = 6 Hz, benzyl Hs), 4.89 (t, 2, J = 6 Hz, NCH_2), 6.8—7.5 (m, 5, indole Hs), 8.08 (d, 1, J = 6 Hz, H-5), 8.92 (s, 1, H-2), 9.00 (d, 1, J = 6 Hz, H-6).

Anal. Calcd for $C_{21}H_{25}O_2N_2Br$: N, 6.71. Found: N, 6.56.

t-Butyl 4-Methyl-1-tryptophyl-1,4,5,6-tetrahydronicotinate (1d)

A mixture of 2.09 g (5 mmol) of salt *5*, 0.40 g of 10% palladium-charcoal and 0.84 mL of triethylamine in 50 mL of dry methanol and 50 mL of anhydrous benzene was hydrogenated at 50 psi for 24 h. It then was filtered through Celite and evaporated. A benzene solution of the residue was filtered and the filtrate passed through a short alumina column and evaporated. Crystallization of the residue from benzene-hexane gave 881 mg (52%) of crystalline vinylogous urethane *1d:* m. p. 187—188 °C; UV λ_{max} 218 nm (log ε 4.43), 290 (4.38); IR NH 3300 (m), C=O 1660 (s), 1620 (s) cm^{-1}; ^{1}H NMR δ 0.97 (d, 3, J = 6 Hz, Me), 1.42 (s, 9, *t*-Bu methyls), 1.4—1.8 (m, 2, CH_2), 2.5—3.5 (m, 7, CH, methylenes), 6.9—7.7 (m, 6, aromatic, olefinic Hs); ^{13}C NMR δ tryptophyl: 24.8 (benzyl CH_2), 56.1 (NCH_2), 111.2 (C-7), 112.1 (C-3), 118.2 (C-4), 119.0 (C-5), 121.7 (C-6), 122.0 (C-2), 126.9 (C-3a), 136.2 (C-7a); nicotinyl: 21.8 (4-Me), 24.0 (C-4), 27.8 (C-5), 28.5 (*t*-Bu methyls), 41.5 (C-6), 77.7 (*t*-Bu C), 100.7 (C-3), 144.6 (C-2), 168.4 (C=O); *m/e* 340 (25%, M$^+$), 284 (10), 210 (27), 154 (base), 144 (25), 130 (30), 108 (20), 94 (10), 78 (22), 57 (23).

Anal. Calcd for $C_{21}H_{28}O_2N_2$: C 74.10; H 8.20; N 8.20.
Found: C 73.95; H 8.19; N 8.09.

Cyclizations of Vinylogous Urethanes 1c and 1d

A solution of 1.10 g of ester *1c* and 14.0 g of potassium hydroxide in 90 mL of methanol and 60 mL of water was refluxed under nitrogen for 72 h. It then was poured into 100 mL of water and the mixture extracted with methylene

chloride. The organic solution was extracted with 0.3 M citric acid solution and the extract kept, while the organic solution was dried (Na_2SO_4) and evaporated. The crystalline residue, 330 mg (30%), was starting ester *1c*. Solid sodium bicarbonate was added to the citric acid solution for neutralization and the mixture extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated. Preparative TLC of the residue on silica gel and development by 7 : 1 ether--methanol gave 400 mg (66%, based on utilized ester *1c*) of amine *2c* [m. p. 164—166 °C (from hexane-dichloromethane) (lit.[10] m. p. 165—166 °C); ^{1}H NMR δ 1.03 (d, 3, $J = 7$ Hz, Me), 3.04 (dd, 1, $J = 11$, 2 Hz, H-3; ^{13}C NMR δ (indole) 107.9 (C-7), 110.6 (C-12), 118.0 (C-9), 119.2 (C-10), 121.6 (C-11), 127.4 (C-8), 134.9 (C-2), 135.8 (C-13)] and 58 mg (9%, based on utilized ester *1c*) of amine *2b*: m. p. 110—112 °C (from hexane-benzene); ^{1}H NMR δ 1.07 (d, 1, $J = 6$ Hz, Me), 3.8—4.0 (m, 1, H-3); ^{13}C NMR δ (indole) 107.9 (C-7), 110.6 (C-12), 117.9 (C-9), 119.3 (C-10), 121.2 (C-11), 127.4 (C-8), 134.0 (C-2), 135.6 (C-13). Exact mass (M^+—H peak): *m/e* 239.1548 (Calcd. for $C_{16}H_{19}N_2$: *m/e* 239.1548).

A solution of 840 mg of ester *1d* in 20 mL of methanol was added dropwise to a refluxing 5% acetic acid solution (200 mL) over a 2-h period and the heating continued for 4 h. The mixture was concentrated under vacuum to 30 mL, made alkaline with 5% sodium hydroxide solution and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated. Preparative TLC of the residue as above gave 405 mg (67%) of amine *2c* and 94 mg (16%) of amine *2b*.

Attempted Isomerization of Amine 2b

A solution of 50 mg of amine *2b* and 0.70 g of potassium hydroxide in 3 mL of water and 4.5 mL of methanol was refluxed under nitrogen for 30 h. Work-up as above gave back 47 mg of starting amine, no isomer being detected.

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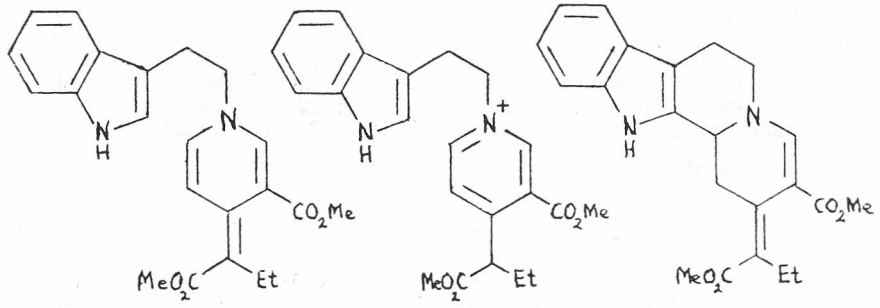

verts them into pyridinium salts (e. g. *i*→*ii*)[6], the recent claim of the acid-catalyzed cyclization of ester *i* into tetracycle *iii*[7] cannot be accepted.

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IZVOD

Stereohemija formiranja prstena C kod tetrahidrokarbolinskih indol-alkaloidnih sistema

Ernest Wenkert, Ai-Li Han i Enrique L. Michelotti

Hidrolizom alkil-1-triptofil-4-metil-1,4,5,6-tetrahidronikotinata postaju dva stereoizomerna metil-indolohinolizidina. Njihove strukture određene su ^{13}C-NMR spektroskopijom a način njihovog formiranja opisan je u svetlosti savremene teorije.