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INVESTIGATION ON THE CHEMISTRY OF BERBANS—VIII[1]
SYNTHESIS OF "INSIDE" DEPYRROLO-YOHIMBINE ANALOGUES

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Abstract—Previously known ketonitrile **1** with phosponic acid ester **2** produced the two geometrical isomers **3** and **4** which upon reduction afforded **5b** and **6b**. By hydrolysis and subsequent esterification the two methyl esters **5a** and **6a** were obtained. Dieckmann condensation of **5a** led to **7a** and **7b**. Reduction of the latter compounds yielded the corresponding "inside" yohimbine analogues **8a** and **8b**. Methyl ester **6a** was converted into the ketoester **9**. The stereochemistry of the isomers was proved by physical (H^1 NMR, IR, MS) and by chemical methods.

After the linear synthesis of tetracyclic depyrrolo-yohimbine,[2] reserpine[3] and raunescine stereoisomers,[1] it has been our aim to prepare structure-isomeric "inside" depyrrolo-yohimbines. This task seemed to be all the more attractive, as only the synthesis of "inside" yohimbane stereoisomers unsubstituted in ring E has so far been reported.[4]

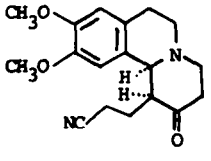
In the course of our earlier studies, the ketonitrile **1** has been prepared, and it has been proved by ^{13}C and ^1H NMR investigations to have a *trans* quinolizidine conformation with an axial substituent at C_1[5].

To build up the fourth ring, ketonitrile **1** was reacted in dimethylformamide in the presence of potassium *tert*-butoxide with phosphonic acid ester **2**, to give the geometrical isomers **3** and **4** in good yield. The structure of the geometrical isomers was determined by ^1H NMR investigations.

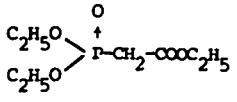
In the (*Z*)-isomer **4**, formed in about 10% yield, the equatorial hydrogen at C_1 gives rise to a multiplet of 18 Hz half width at $\delta = 4.72$ ppm, owing to the deshielding effect of the carbonyl group. When irradiated at $\delta = 1.75$ ppm, this signal is converted into a doublet ($J = 4$ Hz), as a consequence of coupling with the proton at C_{11b}.

It can be mentioned as a further proof of the structures given that, similarly due to the effect of the carbonyl group, the C_{11}-aromatic proton of compound **4** absorbs at a lower field than the corresponding hydrogen of the (*E*) isomer **3**, formed as the main product.[1b] Catalytic hydrogenation of (*E*) and (*Z*) isomers **3** and **4** gave identical products **5b** and **6b**. Interestingly, while the hydrogenation of compound **3** gives nitrile ester **5b** as the main product, and **6b** is formed only in 14% yield, under similar conditions the unsaturated ester **4** yields methyl ester **6b** as the main product and in smaller amount **5b** (in a ratio of 65:35).

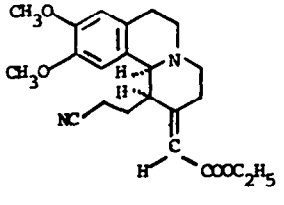
The intensive *Bohlmann* band system[6] in the IR spectra of the saturated compounds **5b** and **6b**, as well as the



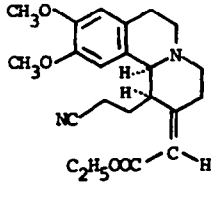
1



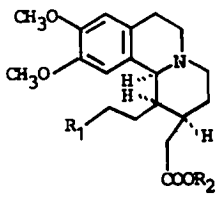
2



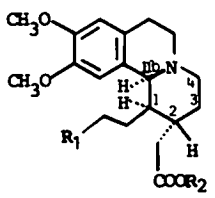
(*E*)
3



(*Z*)
4

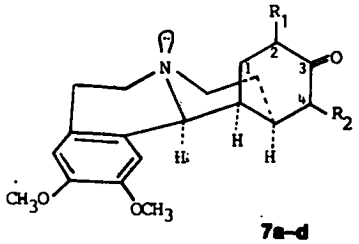


5a,b

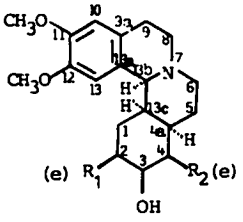


6a,b

5, 6	R_1	R_2
a	$COOCH_3$	CH_3
b	CN	C_2H_5



7a–d



8a–c

7a–d	R_1	R_2
a	$COOCH_3$	H
b	H	$COOCH_3$
c	CN	H
d	H	H

8a–c	R_1	R_2
a	$COOCH_3$	H
b	H	$COOCH_3$
c	CN	H

C_{11b}–H absorption at $\delta = 3.20$ and 3.42 ppm in the ^{1}H NMR spectra of these compounds support the *trans* quinolizidine structure.[7] Coupling constant measurements ($J_{a,e} = 5$ Hz) unambiguously prove that C_1–H is in the α-equatorial position. It follows from this, that compounds **5b** and **6b** differ only in the configuration of C_2.

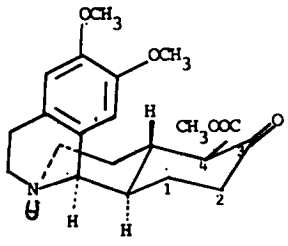
The nitrile esters **5b** and **6b**, when heated with methanolic sulfuric acid, can be converted into dimethyl esters **5a** and **6a**, respectively. The physical properties of the latter compounds are fully in accord with the assumed structure.

Construction of the fourth ring was performed by the *Dieckmann* ring closure of diesters **5a** and **6a**. On boiling for 20 min in benzene solution in the presence of potassium *tert*-butoxide, the diester **5a** gave a mixture of structural-isomers **7a** and **7b** in nearly 1:1 ratio. The structure-isomeric character of these compounds is verified by the observation that both **7a** and **7b** were converted into the same ketone (**7d**) by aqueous hydrochloric acid hydrolysis and decarboxylation.

The tetracyclic ketoesters **7a**, **7b** occur as a mixture of keto-enol forms, with the enol form predominating, both in the crystalline state and in solution. The complex *Bohlmann* band system in the IR spectrum of compounds **7a** and **7b**, as well as the absorptions of C_{13b}–H at $\delta = 3.18$ and 3.30 ppm in their ^{1}H NMR spectrum and coupling constants (J = 5.0 and 4.0 Hz, resp.) indicate that the configuration of carbon atoms C_{13b} and C_{13c} in these compounds, as well as the conformation of the ring system, is the same as in the case of the starting diester **5a**. The position of the methoxycarbonyl group can also be verified by comparison of the ^{1}H NMR spectra of the two substances, as due to the effect of the carbonyl group located in the vicinity of the aromatic ring, the C_{13}–H signal of compound **7a** is observed at a lower field than the corresponding hydrogen of **7b**. This assumption could also be verified by chemical methods.

Based on the assumption that C_1-substitutent occupies an axial position in diester **5a**, and that the *Dieckmann* ring closure is very easy to perform, it may be assumed that compounds **7a** and **7b** have a *cis* C/D ring junction. This is supported also by the absorption at $\delta = 1.7$ and 1.4 ppm, of 9 Hz half-width[4] in their ^{1}H NMR spectra.

The *Dieckmann* ring closure of the dimethyl ester **6a**, containing substitutents in 1,2-diaxial positions, takes place only if conformation transformation, entailing nitrogen inversion and the tilting over of ring C also occurs under the conditions of ring closure. The dimethyl ester **6a** boiled in benzene in the presence of five equivalents of potassium *tert*-butoxide can be converted into compound **9** (in only 25% yield) even after the elapse of 4 h. By preparative layer chromatography during ring closure, only a single structural isomer could be isolated **9**, which did not give an enolic colour reaction with Fe(III) chloride.[8] It follows from the above, that the ester group of compound **9** is located on C_4. This is fully in agreement with the results of mass spectrometric measurements.[9] C_{13b}–H absorption observed in the



9

^{1}H NMR spectrum of compound **9** at $\delta = 4.14$ (J = 6.0 Hz) indicates that the molecule has a *cis*-quinolizidine conformation. This is supported by the fact that no *Bohlmann* bands appear in the IR spectrum of the molecule. Moreover the C/D *trans* ring junction in compound **9** is supported also by the signal system of 6.0 Hz half-width, appearing in the $\delta = 1.4$ ppm range.[4]

For the preparation of the tetracyclic "inside" depyrrolo-yohimbine stereoisomer, ketoester **7a** was reduced with sodium borohydride in methanolic solution, giving a single stereoisomer alcohol **8a** in 86% yield.

By reduction under similar conditions compound **7b** was converted into alcohol **8b** in 90% yield.

The sharp OH-bands in the IR spectra of alcohols **8a** and **8b** at 3510 cm^{-1}, and further the multiplets of 6,0 Hz half-width appearing in the ^{1}H NMR spectra at $\delta =$ 4.22 ppm indicate that in both compounds the C_3–OH group has a β-axial position, while the C_2- and C_4-methoxycarbonyl groups are arranged β-equatorially.[10] It should be noted that in both compounds **8a**, **8b** C_{13b}–H is clearly visible at $\delta = 3.26$ ppm (J = 6.0 Hz), and at $\delta = 3.22$ ppm (J = 5.0 Hz), respectively.

The ketoester **7a**, reduced at 0° in methanol with sodium borohydride, can be converted into alcohol **8a** in a yield of 86%.

The position of the methoxycarbonyl groups in compounds **7** and **8**, was verified also by the following chemical method. Nitrile ester **5b** was subjected to *Dieckmann* condensation to produce the ketonitrile **7c** in almost quantitative yield which was then converted by reduction with sodium borohydride into nitrile alcohol **8c** in 94% yield. According to physical investigations compounds **7c** and **8c** exist in the *trans* quinolizidine conformation. The multiplet with a coupling constant of J = 6 Hz, appearing at $\delta = 4.16$ ppm in the ^{1}H NMR spectrum of the nitrile alcohol **8c**, points to the presence of equatorial C_2-βCN and axial C_3-βOH groups.

The nitrile alcohol **8c** boiled in methanol containing sulfuric acid is converted into alcohol **8a**, in 3 h in 30% yield, which verifies the position of the methoxycarbonyl group in compounds **7a, b** and **8a, b**.

EXPERIMENTAL

IR spectra were recorded in KBr with Spectronom 2000 spectrophotometer. The ^{1}H NMR spectra were obtained using a Varian XL-100-15 Fourier transform instrument, chemical shifts are reported as ppm (δ) downfield from TMS. Mass spectra (MS) were recorded with an AEI MS 902 instrument (70 eV, ion source temp. 150°, direct insertion). The source of the reaction was checked by qualitative TLC for which DC-Alufolien Kieselgel 60 F 254 (benzene: MeOH, 14:3). For the quantitative separation Kieselgel $PF_{254-366}$, layer 1,5 mm (benzene: MeOH, 14:3 with CH_2Cl_2) indicative absorbents were used. The reactions were carried out under argon; M.ps. were uncorrected.

(E *and* Z)-*Ethyl*-9,10-*dimethoxy*-1β-(2-*cyanoethyl*)-1,3,4,6,7, 11bα-*hexahydro*-2H-*benzo*[a]*quinolizin*-2-*ylideneacetate* **3** *and* **4**

The keto-nitrile **1**(3.8 g, 12.0 mmol) in DMF (24 ml) was added into a mixture of *t*-BuOK (2.8 g, 25.0 mmol) and **2** (5.6 g, 25.0 mmol) in DMF (11 ml). After 2 days at room temp. the reaction mixture was poured into ice water (150 ml) and extracted with ether. The solvent was evaporated and the residue after recrystallisation (MeOH) gave **3** (2.2 g, 48.4%), m.p. 128–129° (MeOH); ($C_{22}H_{28}N_2O_4$ (384, 5) Calc.: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.62; H, 7.31; N, 7.29%; IR (KBr) 2840–2750 (Bohlmann's absorption) 2240 (CN), 1720 (COOEt), 1645 (C=C) 1620 cm^{-1} (aromatic); ^{1}H NMR (C_6D_6) 6.72, 6.48 (2H, s, aromatic), 6.02 (1H, s, –CH=), 4.12 (2H, q, J = 7 Hz, $COO\underline{CH_2}$–CH_3) 3.74, 3.52 (6H, s, OCH_3), 3.29 (1H, m, J = 6 Hz, C_{11b}–H), 1.06 (3H, t, $COOCH_2$–$\underline{CH_3}$); MS (*m/e*): 384 (34), 383 (17), 369 (0, 5), 355 (2, 1), 344 (100), 339 (12), 330 (3, 8), 311 (7, 2), 297 (1, 6), 270 (2, 5), 205 (17), 203 (10), 192 (21), 191 (13), 190 (15), 176 (6, 7), 153 (6), 125 (21). The methanolic mother liquor was separated by chromatography. $R_f3 > R_f4$ Total yield of **3**: 2.4 g (52.8%) **4** 1.27 g (28.0%) m.p. 116–18° (MeOH); ($C_{22}H_{28}N_2O_4$ (384, 5) Calc.: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.70; H, 7.40; N, 7.30%); IR (KBr) 2840–2720 (Bohlmann's absorption), 2240 (CN), 1705 (COOEt), 1640 (C=C), 1620 cm^{-1} (aromatic); ^{1}H NMR (C_6D_6) 6.94, 6.48 (2H, s, aromatic), 5.78 (1H, d, J = 2Hz, =CH–) 4.72 (1H, m, J = 18 Hz, C_1-eqH), 4.10 (2H, q, J = 7 Hz, $COO\underline{CH_2}CH_3$), 3.68, 3.52 (6H, s, OCH_3) 3.24 (1H, m, J = 6 Hz, C_{11b}-H), 1.08 (3H, t, $COOCH_2\underline{CH_3}$); MS (*m/e*): 384 (38), 383 (19), 369 (0, 7), 355 (2, 2), 344 (100), 339 (11), 330 (4, 1), 311 (6, 4), 297 (1, 7), 270 (2, 1), 205 (14), 203 (8, 4), 192 (15), 191 (8, 9), 190 (14), 176 (4, 7), 153 (3, 8), 125 (13).

Ethyl-9,10-*dimethoxy*-1β-(2-*cyanoethyl*)-1, 3, 4, 6, 7, 11bα-*hexahydro*-2H-*benzo*[a]*quinolizin*-(2β)-*yl acetate* **5b** *and Ethyl*-9,10-*dimethoxy*-1β-(2-*cyanoethyl*)-1, 3, 4, 6, 7, 11bα-*hexahydro*-2H-*benzo*[a]*quinolizin*-(2α)-*yl acetate* **6b**. (A) Unsaturated nitril-ester **3** (2.5 g, 6.5 mmol) in MeOH (20 ml) was hydrogenated in presence of Pd–C catalyst (1.0 g). After removing the catalyst the MeOH was distilled off and the residue was recrystallised from MeOH to give **5b**, (1.9 g). The mother liquor yielded **5b** (0.12 g) and **6b** (0.28 g) by chromatography R_f**5b** > R_f**6b**. **5b** 2.02 g (80.4%); m.p. 135–136°; (MeOH); ($C_{22}H_{30}N_2O_4$ (386.5); Calc.: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.80; N, 7.24%); IR (KBr) 2800-2750 (Bohlmann's absorption) 2240 (C=N) 1725 ($COOC_2H_5$), 1608 cm^{-1} (aromatic); ^{1}H NMR (C_6D_6) 6.76, 6.43 (2H, s, aromatic H), 4.10 (2H, q, J = 7 Hz, $COO\underline{CH_2}CH_3$), 3.72, 3.50 (6H, s, OCH_3), 3.20 (1H, m, J = 5 Hz, C_{11b}–H), 1.08 (3H, t, $COOCH_2$-$\underline{CH_3}$); MS (*m/e*): 386 (34), 385 (18), 372 (0, 8), 371 (0, 9), 357 (1, 7), 346 (100), 344 (6, 7), 341 (11), 332 (2, 9), 299 (53), 218 (34), 205 (13), 191 (15), 190 (9, 4), 176 (5, 8). **6b** 0.28 g (11.1%) m.p. 93–94°; (MeOH); ($C_{22}H_{30}N_2O_4$ (386.5) Calc.: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40: H, 7.81; N, 7.26%): IR (KBr) 2856–2750 (Bohlmann's-absorption) 2240 (CN), 1730 ($COOC_2H_5$) 1610 cm^{-1} (aromatic); ^{1}H NMR (C_6D_6): 6.80, 6.48 (2H, s, aromatic H), 4.14 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 3.80, 3.52 (6H, s, OCH_3), 3.41 (1H, m, J = 5 Hz, C_{11b}–H) 1.1 (3H, t, $COOCH_2\underline{CH_3}$), MS (*m/e*): 386 (40), 385 (19), 372 (0, 5), 371 (0, 8), 357 (2, 6), 346 (100), 344 (1, 4), 341 (12), 332 (1, 4), 299 (54), 218 (36), 205 (14), 191 (14), 190 (8, 2), 176 (5, 8).

(B) The unsaturated nitril-ester **4** (90 mg, 0.23 mmol) in methanol (10 ml) was hydrogenated in presence of Pd–C (50 mg) catalyst and yielded **5b** (23.6 mg, 26.2%) and **6b** (49.6 mg, 55.1%).

Methyl - 9,10 - *dimethoxy* - 2β - (*methoxycarbonyl* - *methyl*) - 1, 3, 4, 6, 7, 11bα - *hexahydro* - 2H - *benzo*[a]*quinolizin* - (1β) - *yl propionate* **5a** *and methyl* - 9,10 - *dimethoxy* - 2α - (*methoxycarbonyl* - *methyl*) - 1, 3, 4, 6, 7, 11bα - *hexahydro* - 2H - *benzo*[a]*quinolizin* - *yl propionate* **5a**. (A) In a mixture of conc. H_2SO_4 (2.19 ml) and MeOH (6.14 ml) nitrile-ester **5b** was refluxed for 5 h. The reaction mixture was poured into ice water (50 ml) alkalized (pH = 9) with 10% NaOH and extracted with ether. The etheral soln was dried over $MgSO_4$, filtered and evaporated. The residue after recristallisation from MeOH gave **5a** (1,2 g, 71.5%) m.p. 105–106°; (MeOH); ($C_{22}H_{31}NO_6$ (405.5) Calc.: C, 65.16; H, 7.71; N, 3.45. Found: C, 65.02; H, 7.75; N, 3.27%); IR (KBr) 2800–2750 (Bohlmann's absorption), 1732, 1722 ($COOCH_3$) 1610 cm^{-1} (aromatic); ^{1}H NMR ($CDCl_3$) 6.67, 6.57 (2H, s, aromatic H) 3.84, 3.71, 3.54 (12H, s, $COOCH_3$, OCH_3) 3.29 (1H, m, J = 5 Hz, C_{11b}–H); MS (*m/e*): 405 (33), 404 (24), 390 (2, 0), 374 (13), 372 (3, 3), 346 (2, 5), 332 (100), 330 (3, 6), 318 (2, 2), 299 (5, 2), 218 (46), 205 (25), 191 (22), 190 (9, 8), 176 (7, 1).

(B) The nitrile-ester **6b** (0.12 g, 0.31 mmol) with the above method gave **6a** (0.101 g, 80.4%) oil. ($C_{22}N_{31}NO_6$ (405.5) Calc.: C, 65.16; H, 7.71; N, 3.45. Found: C, 65.21; H, 7.71; N, 3.32%); IR (Nujol) 2850-2750 (Bohlmann's absorption) 1735 ($COOCH_3$) 1610 cm^{-1} (aromatic); ^{1}H NMR ($CDCl_3$) 6.58, 6.56 (2H, s, aromatic H) 3.84, 3.71, 3.58 (12H, s, $COOCH_3$, OCH_3) 3.44 (1H, m, J = 5 Hz, C_{11b}–H); MS (*m/e*): 405 (42), 404 (29), 390 (2, 2), 374 (16), 346 (2, 3), 332 (100), 318 (2, 2), 244 (2, 3), 218 (40), 205 (17), 191 (18), 190 (6, 3), 176 (4, 4).

Methyl - 11,12 - *dimethoxy* - 3 - *oxo* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (2)] - *yl carboxylate* **7a**[11] *and methyl* - 11,12 - *dimethoxy* - 3 - *oxo* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (4)] - *yl carboxylate* **7b**. Potassium *t*-butoxide (0.4 g; 3.6 mmol) was added to a benzene (8 ml) soln of dimethyl ester **5a** (0.8 g, 1.97 mmol) and the reaction mixture was stirred and refluxed for 20 min. At room temp. the reaction mixture was neutralized with acetic acid and the solvent was evaporated *in vacuo*. Water (10 ml) was added to the residue and the soln was made alkaline with 5% Na_2CO_3 (pH = 8.5), and extracted with CH_2Cl_2. The organic soln after drying ($MgSO_4$) was evaporated. The residue was separated by chromatography. R_f**7a** > R_f**7b**. **7a** 0.29 g (39.5%) m.p. 171–172°; (MeOH); ($C_{21}H_{27}NO_5$ (373.4) Calc.: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.39; H, 7.21; N, 3.68%); IR (KBr) 2800-2750 (Bohlmann's absorption), 1740, 1715 ($COOCH_3$, C=O), 1660 (conjugated $COOCH_3$), 1615 cm^{-1} (C=C); ^1H NMR (C_6D_6) 12.76 (1H, s, enol OH) 6.76, 6.40 (2H, s, aromatic H), 3.58, 3.45, 3.15, (9H, s, $COOCH_3$, OCH_3), 3.18 (1H, m, J = 5 Hz, C_{13b}–H); MS (*m/e*): 373 (100), 372 (43), 358 (2, 4), 342 (13), 341 (13), 340 (29), 314 (30), 258 (3, 3), 246 (4, 2), 245 (4, 3), 244 (6, 7), 218 (83), 205 (59), 191 (70), 190 (18), 176 (18). **7b** 0.3 g (40.8%) m.p. 162–163° ($C_{21}H_{27}NO_5$ (373.4) Calc.: C, 67.54; H, 7.29: N, 3.75. Found: C, 67.49; H, 7.29; N, 3.74%); IR (KBr) 2850-2750 (Bohlmann's absorption) 1660 (conjugated $COOCH_3$) 1620 cm^{-1} (C=C); ^1H NMR (C_6D_6) 12.8 (1H, s, enol OH) 6.60, 6.48, (2H, s, aromatic H), 3.56, 3.50, 3.44 (9H, s, $COOCH_3$, OCH_3), 3.30 (1H, m, J = 4 Hz, C_{13b}–H); MS (*m/e*): 373 (59), 372 (17), 358 (0, 8), 342 (4, 1), 341 (4, 1), 340 (13), 314 (6, 5), 258 (1, 3), 244 (1, 1), 218 (100), 205 (95), 191 (80), 190 (16), 176 (17).

11,12 - *Dimethoxy* - 3 - *oxo* - *cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c-*decahydro* - 13bα H - *dibenzo*[a, h]*quinolizin* **7a**. (a) The keto-ester **7a** (50 mg, 0.13 mmol) was heated in 10% HCl (5 ml) at 100° for 5 h. The cold soln was made alkaline with 10% NaOH (pH = 9), the precipitate was filtered and recrystallized from MeOH. **7d** 30 mg (71%) m.p. 160–161°; (MeOH); ($C_{19}H_{25}NO_3$ (315.4) Calc.: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.50; H, 7.81; N, 4.36%); IR (KBr) 2850-2750 (Bohlmann's absorption) 1705 (C=O), 1610 cm^{-1} (aromatic); ^1H NMR (C_6D_6) 6.70, 6.48 (2H, s, aromatic H), 3.62, 3.50 (6H, s, OCH_3), 3.16 (1H, m, J = 5 Hz, C_{13b}–H); MS (*m/e*): 315 (100), 314 (88), 300 (2, 2), 298 (2, 1), 286 (1, 6), 272 (2, 8), 258 (3, 5), 246 (5, 4), 218 (86), 205 (72), 191 (71), 190 (20), 176 (15).

(b) Keto-ester **7b** (50 mg, 0.13 mmol) with the method described above yielded 29.5 g (70%) **7d**.

Methyl - 11,12 - *dimethoxy* - 3β - *hydroxy* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (2β)] - *yl carboxylate* **8a**. Keto-ester **7a** (37 mg; 0.1 mmol) was stirred in abs. MeOH (5 ml) at 0° and $NaBH_4$ (30 mg; 0.65 mmol) was added to the reaction-mixture. After 1 h stirring at 0° acetic acid (2 drops) was added to the mixture and evaporated. Water (5 ml) was added to the residue, and the mixture was made alkaline with 5% Na_2CO_3 (pH = 8.5). The precipitate was filtered and recrystallized from MeOH to yield. **8a** 32 mg (86.5%) m.p. 206–207°; (MeOH); ($C_{21}H_{29}NO_5$ (375.4) Calc.: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.07; H, 7.68; N, 3.70%); IR (KBr) 3510 (OH) 2800-2750 (Bohlmann's absorption), 1735 ($COOCH_3$) 1610 cm^{-1} (aromatic); ^1H NMR (C_6D_6) 6.76, 6,42 (2H, s, aromatic), 4.22 (1H, m, J = 7 Hz, C_3-eq H) 3.61, 3.54, 3.05 (9H, s, $COOCH_3$, OCH_3), 3.25 (1H, m, J = 6 Hz, C_{13b}–H); MS (*m/e*); 375 (72), 374 (59), 360 (3, 4)358 (3, 7), 344 (6, 0), 316 (4, 9), 258 (0, 9), 244 (1, 3), 218 (62), 205 (100), 191 (46), 190 (17), 176 (12).

Methyl - 11,12 - *dimethoxy* - 3β - *hydroxy* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (4β)] - *yl carboxylate* **8b**. The keto-ester **7b** gave **8b** (90% yield) using the same procedure described for **8a**. **8b** m.p. 156–157°; (MeOH); ($C_{21}H_{29}NO_5$ (375.4) Calc.: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.17; H, 7.80; N, 3.61%); IR (KBr) 3510 (OH), 2800-2740 (Bohlmann's absorption), 1725 ($COOCH_3$), 1620 cm^{-1} (aromatic); ^1H NMR (C_6D_6) 6.70, 6.50 (2H, s, aromatic), 4.22 (1H, m, J = 6 Hz, C_3-eq H) 3.62, 3.52, 3.38 (9H, s, $COOCH_3$, OCH_3), 3.22 (1H, m, J = 5 Hz, C_{13b}–H); MS (*m/e*): 375 (79), 374 (79), 360 (3, 4), 358 (2, 2), 344 (6, 5), 316 (2, 7), 258 (3, 1), 246 (1, 3), 244 (1, 9), 218 (100), 205 (71), 191 (58), 190 (18), 176 (14).

11,12 - *Dimethoxy* - 3 - *oxo* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (2)] - *yl carbonitrile* **7c**. A mixture of nitrile-ester **5b** (50 mg, 0.13 mmol) and *t*-BuOK (40 mg, 0.36 mmol) in benzene (5 ml) was stirred and refluxed for 30 min. At room temp. the reaction mixture was neutralized with acetic acid and the solvent was evaporated *in vacuo*. Water (5 ml) was added to the residue, alkalized with 5% Na_2CO_3(pH = 8) and extracted with CH_2Cl_2. The organic soln, after drying ($MgSO_4$), was evaporated and the residue was recristallized from MeOH. **7c** 41.2 mg (93.8%) m.p. 233–34°; (MeOH); ($C_{20}H_{22}N_2O_3$ (340.4) Calc.: C, 70.54; H, 7.10; N, 8.29. Found: C, 70.32; H, 7.07; N, 8.15%); IR (KBr) 2800-2750 (Bohlmann's absorption), 2240 (C=N), 1735 (C=O), 1610 cm^{-1} (aromatic); MS (*m/e*): 340 (100), 339 (84), 325 (4, 0), 323 (1, 8), 297 (3, 3) 272 (6, 8), 258 (11), 246 (15), 218 (90), 205 (81), 191 (57), 190 (21), 176 (14).

11,12 - *Dimethoxy* - 3β - *hydroxy* - [*cis,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (2β)] - *yl carbonitrile* **8c**. The keto-nitrile **7a** (32 mg, 0.09 mmol) was stirred in MeOH (5 ml) at 0° and $NaBH_4$ (20 mg, 0.43 mmol) was added to the reaction mixture. After 0.5 h stirring acetic acid (2 drops) was added to the soln and evaporated. Water (5 ml) was added to the residue made alkaline with 5% Na_2CO_3 (pH = 8.5), the precipitate was filtered and recristallized from MeOH. **8c** 30 mg (93.7%) m.p. 239–40°; (MeOH); ($C_{20}H_{26}N_2O_3$ (342.5) Calc.: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.07; H, 7.52; N, 8.27%); IR (KBr) 3450 (OH), 2800-2750 (Bohlmann's absorption), 2217 (C ≡ N), 1610 cm^{-1} (aromatic); ^1H NMR (C_6D_6 + DMSO): 6.78, 6.56 (2H, s, aromatic), 5.32 (1H, d, J = 5 Hz, OH) 4.16 (1H, m, J = 6 Hz, C_{13b}–H); MS (*m/e*): 342 (82), 341 (93), 327 (1, 8), 325 (4, 8), 272 (2, 5), 258 (2, 8), 246 (2, 2), 244 (1, 8), 218 (100), 205 (58), 191 (71), 190 (20), 176 (16).

8a. A mixture of nitrile-alcohol **8c** (20 mg, 0.06 mmol) MeOH (0.63 ml) and conc. H_2SO_4 (0.21 ml) was refluxed at 100° for 4 h. The reaction mixture was poured into ice water (5 ml) made alkaline with 10% NaOH (pH = 9) and extracted with CH_2Cl_2. The organic soln after drying ($MgSO_4$) was evaporated and the residue was purified by chromatography. **8a** 7 mg (31%) m.p. 206–207°.

Methyl - 11,12 - *dimethoxy* - 3 - *oxo* - [*trans,syn* - 1, 2, 3, 4, 4a, 5, 6, 8, 9, 13c - *decahydro* - 13bα H - *dibenzo*[a,h]*quinolizin* - (4)] - *yl carboxylate* **9**. A mixture of dimethyl-ester **6a** (30 mg, 0.09 mmol) *t*-BuOK (50 mg, 0.45 mmol) in benzene (2 ml) was stirred and refluxed for 4 h. The cold reaction mixture was neutralized with acetic acid and evaporated. Water (3 ml) was added to the residue, made alkaline with 5% Na_2CO_3 (pH = 8.5) and extracted with CH_2Cl_2. The organic soln after drying ($MgSO_4$) was evaporated and the residue was purified by chromatography. **9** 7 mg (25%); IR (Nujol) 1740, 1715 ($COOCH_3$, CO), 1620 cm^{-1} (aromatic); ^1H NMR (C_6D_6) 6.58, 6.48 (2H, s, aromatic), 4.14 (1H, m, J = 6 Hz, C_{13b}–H), 3.56, 3.48 (9H, s, OCH_3, $COOCH_3$); MS (*m/e*): 373 (55), 372 (34), 342 (6, 7), 340 (3, 5), 314 (8, 9), 279 (2, 7), 273 (1, 2), 272 (2, 3), 258 (2, 6), 244 (1, 6), 218 (57), 205 (100), 191 (50), 190 (12), 176 (9, 4).

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REFERENCES

[1]I. Tóth, L. Szabó, L. Radics, E. Baitz-Gács, M. Kajtár-Peredy and Cs. Szántay, *Tetrahedron* **34**, 2113 (1978).
[2a]L. Szabó, K. Honty, L. Töke, I. Tóth and Cs. Szántay, *Chem. Ber.* **105**, 3215 (1972); [b]L. Szabó, K. Honty, L. Töke and Cs. Szántay, *Ibid.* **105**, 3231 (1972). [c]L. Szabó, I. Tóth, K. Honty, J. Tamás and Cs. Szántay, *Ibid.* **109**, 1724 (1976).

[3]L. Szabó, L. Tóth, L. Töke, J. Tamás and Cs. Szántay, *Liebigs Ann. Chem.*, 642 (1977).
[4]G. C. Morrison, W. A. Cetenko and I. Shavel, *J. Org. Chem.* 32, 2768 (1967).
[5]L. Szabó, K. Nógrádi, I. Tóth, Cs. Szántay, L. Radics, S. Virág and E. Kanyó, *Acta Chim. (Budapest)* 99, 73 (1979).
[6]F. Bohlmann, *Angew. Chem.* 69, 541 (1957), *Chem. Ber.* 91, 2157 (1958).
[7]M. Uskokovic, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *J. Am. Chem. Soc.* 86, 3364 (1964).
[8a]It is known that in the case of yohimbines with *trans* C/D ring function there is no possibility for enolization, due to the so called "peri-effect". [b]G. Stork and R. K. Hill, *J. Am. Chem. Soc.* 76, 949 (1954); *Ibid.* 79, 495 (1957). [c]M. D. Soffer, R. A. Stewart and G. L. Smith, *J. Am. Chem. Soc.* 74, 1556 (1952). [d]M. M. Janot, R. Goutarel, E. Warnhoff and A. LeHir, *Bull. Soc. Chim. (France)* 637 (1961).
[9]J. Tamás, I. Tóth, L. Szabó and Cs. Szántay, To be published in *Org. Mass Spektrom.*
[10a]J. L. Pierre, M. Vincens and M. Vidal, *Bull. Soc. Chim. (France)* 1755 (1971). [b]B. Casu, M. Reggiani, G. C. Gallo and A. Vigevani, *Tetrahedron* 22, 3061 (1966).
[11]*Cis* and *trans* refer to the relationship of the hydrogens at C_{4a} and C_{13c} *syn* and *anti* refer to the hydrogens at C_{13c} and C_{13b}.