# SUBSTITUENT EFFECTS ON THE RATE OF ACID-CATALYSED EPIMERIZATION OF INDOLO[2,3-*a*]QUINOLIZIDINES

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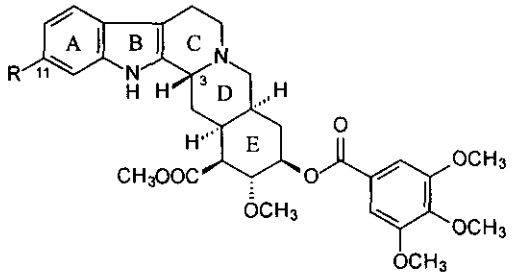
***Abstract*** - 10-Substituted indolo[2,3-*a*]quinolizidine derivatives were prepared to study the effect of substituents on the epimerization rate. Under the conditions employed, electron withdrawing substituents hindered epimerization and electron donating substituents accelerated it.

Acid-catalysed C-3 epimerization[1] has played an important role in indole alkaloid chemistry. It was used in the 1950's as a tool in the structure elucidation of reserpine (**1**).[2] Woodward *et al.* utilized ingeniously the epimerization reaction as the key step in connection with the first total synthesis of reserpine.[1,3]




**1** (R=$OCH_3$)
**2** (R=H)

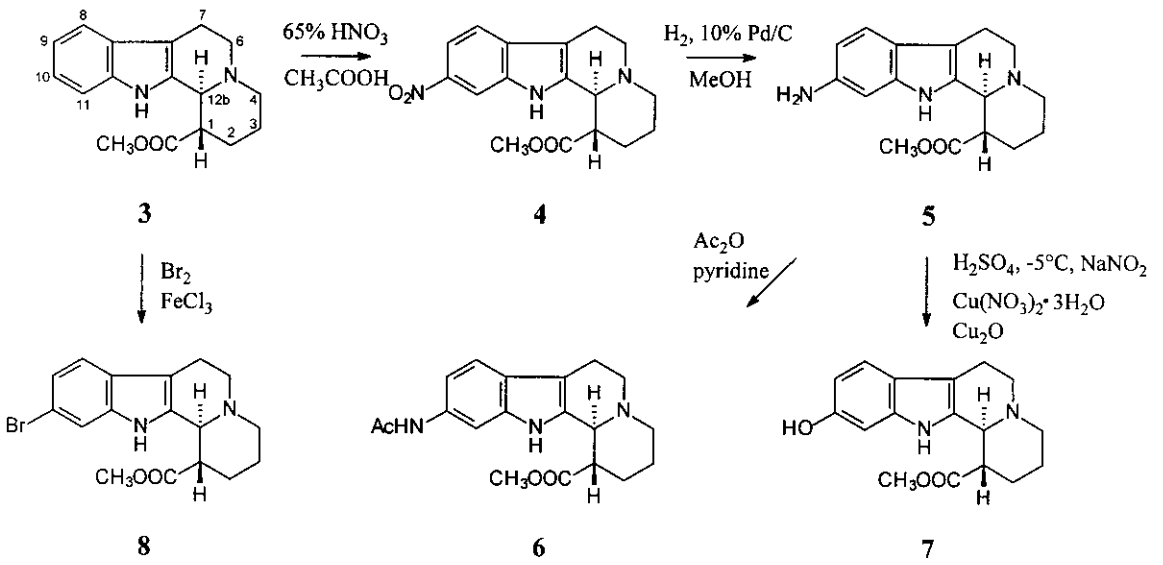
Further synthetic use of the epimerization reaction has been reported. As a representative example, Rapoport and co-workers[4] applied it to obtain an important intermediate for the synthesis of the pharmacologically important indole alkaloid vincamine. Recently, Lounasmaa *et al.*[5] utilized the same tool in the preparation of key intermediates for tacamine-type alkaloids. These various compounds exhibit very different epimerization behaviour: reserpine (**1**), when refluxed in trifluoroacetic acid (TFA), epimerizes within minutes,[6] whereas indolo[2,3-*a*]quinolizidines, which do not contain substituents in the

aromatic ring (A ring), require a much longer reaction time.[7] The apparent reason for the acceleration of the epimerization rate with reserpine seems to be the electron donating methoxy substituent in the A ring. This was already confirmed by MacPhillamy *et al.*,[8] who compared the epimerization rates of reserpine (**1**) and deserpidine (11-demethoxyreserpine (**2**)).

Having used the epimerization reaction as a synthetic tool we became interested in the effect of A ring substituents on this phenomenon. It is important to know how different substituents affect the epimerization rate in order to decide whether to conduct the epimerization before or after a certain aromatic substitution reaction.

## RESULTS AND DISCUSSION

We prepared five 10-substituted indolo[2,3-*a*]quinolizidines to study the effect of substituents on the epimerization rate (Scheme 1).[9] The reactions were based on aromatic substitution of ester (**3**), whose preparation has been described previously.[10,11]

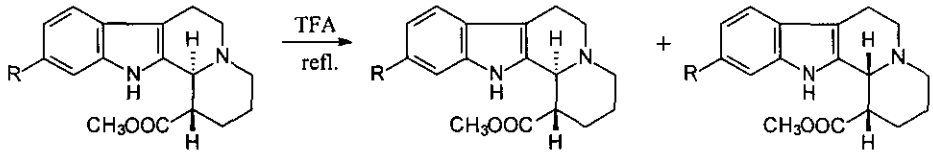



Scheme 1

When the nitration of ester (**3**) was performed with 65% nitric acid,[12] 10-nitro ester (**4**) was isolated in 40% yield. The residue contained the corresponding 8-nitro ester, which could not be isolated in pure state. In an attempt to improve the yield of ester (**4**), ester (**3**) was BOC protected. However, the nitration of the BOC protected ester improved the ratio of 10-nitro ester (**4**) and 8-nitro ester only slightly and this route was abandoned.

Nitro ester (**4**) was then reduced to amino ester (**5**), which was acetylated to amido ester (**6**). Hydroxy ester (**7**) was obtained *via* diazotization of compound (**5**). Finally, 10-bromo ester (**8**) was chosen as an example of a halogen substituted indolo[2,3-*a*]quinolizidine.[13] Compound (**8**), in addition to 9-bromo ester and polybrominated products, was obtained by direct bromination of ester (**3**).[14]

Unsubstituted ester (**3**) and the 10-substituted compounds (H-1/H-12b *trans*) nitro ester (**4**), amino ester (**5**), amido ester (**6**), hydroxy ester (**7**) and bromo ester (**8**) were all submitted to epimerization conditions. The esters were refluxed (90°C) in TFA for 60 minutes. After alkaline work-up, $^1$H NMR spectra of the crude products were recorded showing how far the epimerization had advanced (Table 1).



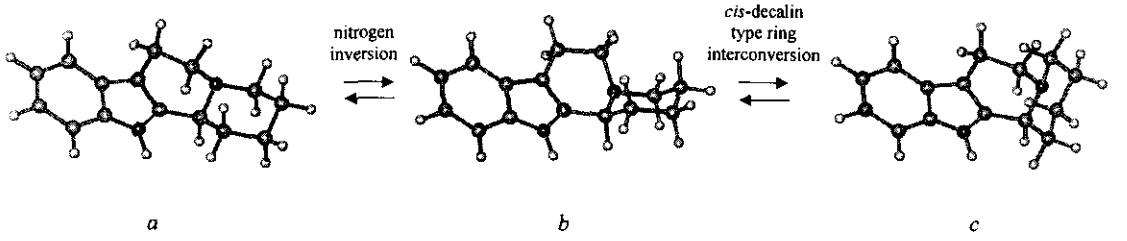

| Starting ester | R | *trans*:*cis* ratio |
|---|---|---|
| **3** | H | 74:26 |
| **4** | $NO_2$ | no epimerization |
| **5** | $NH_2$ | no epimerization |
| **6** | NHAc | traces of *cis* epimer |
| **7** | OH | 32:68 |
| **8** | Br | traces of *cis* epimer |

Table 1

Ester (**3**), which does not have substituents in the aromatic ring, represents a reference compound for this study. In earlier work, treatment with TFA overnight resulted in an equilibrium mixture of ester (**3**) and its *cis*-epimer (22:78).[15] Under the present conditions (*vide supra*), however, the ratio was 74:26. The electron withdrawing, strongly deactivating nitro group in ester (**4**) was expected to decrease the epimerization rate. Surprisingly, the deactivating effect of the nitro group not only decreased but completely blocked the epimerization reaction. The amino group in compound (**5**), originally electron donating and strongly activating, changes upon protonation to the opposite ($H_3N^+$-), which prevented the epimerization. Even acetylation of the amino group scarcely increased the epimerization rate, which can be explained by the delocalization of the nitrogen lone pair over the protonated N-C-O system. In contrast, electron releasing properties were retained in the phenolic hydroxy group of compound (**7**),

pushing the epimerization equilibrium well over to the *cis* side (32:68). Finally, the electronegative bromo group in ester (**8**) deactivates the aromatic ring and thus decreased the epimerization rate considerably.

Another interesting feature of the epimerization reactions is related to the different conformations of indolo[2,3-*a*]quinolizidines. The indolo[2,3-*a*]quinolizidine system can exist in three main conformations (conformations *a*, *b* and *c*), which are in equilibrium by nitrogen inversion and *cis*-decalin type ring interconversion. Ring C is considered to be in a half chair conformation and ring D in chair conformation (Scheme 2).[16,17]

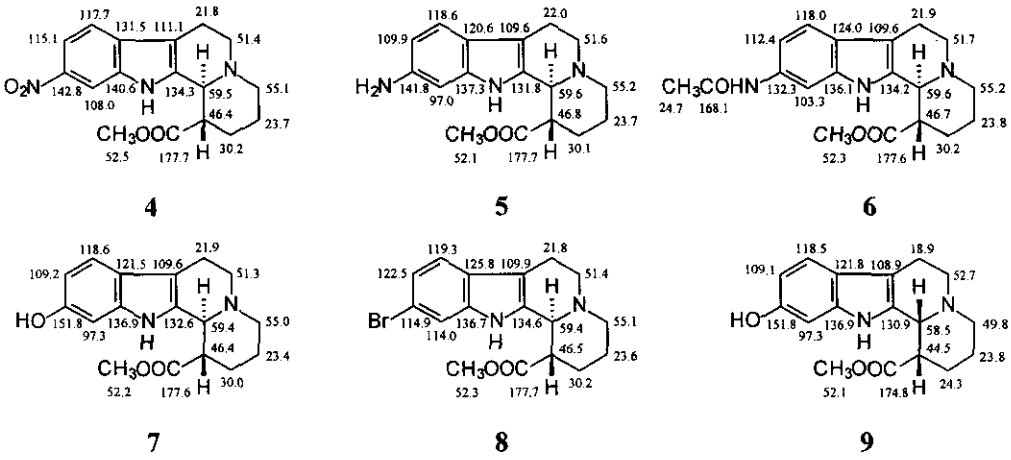



Scheme 2

When observing different conformations involved in the epimerization reactions it is of importance to notice the overwhelming contribution of conformer *a* to the conformational equilibrium of the *trans* products (equatorial ester group) (*cf.* Chart and Refs. 16 and 17). This means that the steric interaction of an ester group with the indolic part of the molecule is not a critical factor in the conformational equilibrium (in striking contrast to an ethyl group[7]). Accordingly, the ester group does not oppose the preponderant contribution of conformer *c* to the conformational equilibrium of *cis* products (equatorial ester group).

## CONCLUSIONS

The results collected in Table 1 clearly demonstrate that, in the aromatic ring of indolo[2,3-*a*]quinolizidines, electron withdrawing substituents such as the nitro group prevent or at least slow down the epimerization. Electron donating substituents such as the hydroxy group, in turn, accelerate the epimerization rate. Halogens such as bromine decrease the rate. Thus, the various aromatic substituents have a surprisingly powerful influence on the epimerization process: electron withdrawal from the indole ring appears to slow down dramatically the acid-catalysed epimerization taking place at C-12b (C-3). This underlines the critical role of the aromatic π-system in the mechanism.



Chart

## EXPERIMENTAL

Except where otherwise stated, all reactions were carried out under argon. Alkaline work-up comprised addition of sat. aq $NaHCO_3$, extraction with $CH_2Cl_2$ (3x), drying of the combined organic layers with $Na_2SO_4$, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra ($cm^{-1}$, in $CHCl_3$ unless otherwise noted) were recorded on a Perkin-Elmer 700 spectrophotometer. $^1H$ NMR (399.958 MHz, reference: TMS, $\delta_H$ = 0.0 ppm) and $^{13}C$ NMR (100.578 MHz, reference: $CDCl_3$, $\delta_C$ = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ used as solvent. Coupling constants ($J$) are given in Hz. Signal assignments are based on standard APT, COSY, NOE, and HETCOR experiments. For the $^{1h}C$ NMR data of the compounds (**4** – **9**), see Chart. EI and HR MS spectra (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography. In the epimerization experiments the temperature of the oil bath was kept at (90±5)°C and the obtained *trans/cis* ratios were determined by $^1H$ NMR integration.

**Nitration of Ester (3) with 65% Nitric Acid.** *Ester* (**3**) *(251 mg, 0.88 mmol)* was dissolved in glacial acetic acid (10 mL). To the solution was slowly added at rt a mixture (6 mL) of 65% nitric acid and glacial acetic acid (1:1). The solution was stirred for 15 min and then poured into a beaker containing ice and subjected to alkaline work-up (25% $NH_3$). The crude product was purified by column chromatography ($CH_2Cl_2$:MeOH, 99:1) and preparative TLC (hexane:acetone, 25:75), which gave 116 mg (40%) of amorphous 10-nitro ester (**4**); IR: 2850-2780 (Wenkert-Bohlmann bands), 1720 (C=O), 1520 ($NO_2$); $^1H$ NMR: δ 8.79 (1H, br s, NH), 8.25 (1H, d, $J$ = 2, H-11), 7.98 (1H, dd, $J$ = 9 and 2, H-9), 7.48 (1H, d, $J$ = 9, H-8), 3.85 (1H, d, $J$ = 10.5, H-12b), 3.84 (3H, s, -$COOCH_3$); MS: 329 ($M^+$, 96), 328 (100), 298 (24), 243 (32), 242 (90), 215 (43), 214 (46), 168 (28); HR-MS: calcd for $C_{17}H_{19}N_3O_4$: 329.1376, found: 329.1355; Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.84; H, 5.66; N, 12.62.

**Catalytic Hydrogenation of 10-Nitro Ester (4).** 10-Nitro ester (**4**) (135.1 mg, 0.41 mmol) was hydrogenated for 17 h in MeOH (20 mL) using 10% Pd/C (19.7 mg) as catalyst. The catalyst was removed by filtration and the solvent was evaporated. The crude product was purified by column chromatography ($CH_2Cl_2$:MeOH, 98:2), which yielded 96.6 mg (79%) of amorphous 10-amino ester (**5**); IR: 2850-2780 (Wenkert-Bohlmann bands), 1720 (C=O); $^1$H NMR: δ 7.83 (1H, br s, NH), 7.23 (1H, d, $J$ = 8, H-8), 6.58 (1H, d, $J$ = 2, H-11), 6.52 (1H, dd, $J$ = 8 and 2, H-9), 3.78 (3H, s, -$COOCH_3$), 3.77 (1H, d, $J$ = 10.5 Hz, H-12b), 3.32 (2H, br s, -$NH_2$); MS: 299 ($M^+$, 74), 298 (100), 212 (33), 185 (53), 184 (32); HR-MS: calcd for $C_{17}H_{21}N_3O_2$: 299.1634, found: 299.1624; Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 67.82; H, 7.67; N, 13.86.

**Preparation of 10-Amido Ester (6).** 10-Amino ester (**5**) (38.0 mg, 0.13 mmol) was dissolved in acetic anhydride (1 mL) and pyridine (1 mL) and the mixture was stirred at rt for 16 h. After evaporation, alkaline work-up was performed. The crude product was purified by column chromatography ($CH_2Cl_2$:MeOH, 98:2-97:3) to give 27.1 mg (63%) of amorphous (**6**); IR: 2850-2780 (Wenkert-Bohlmann bands), 1715 (C=O), 1670 (NH*CO*); $^1$H NMR: δ 8.15 (1H, br s, indole NH), 7.90 (1H, d, $J$ = 1.5, H-11), 7.34 (1H, d, $J$ = 8, H-8), 7.30 (1H, br s, amide NH), 6.78 (1H, dd, $J$ = 8 and 1.5, H-9), 3.80 (3H, s, -$COOCH_3$), 3.79 (1H, d, $J$ = 10, H-12b); MS: 341 ($M^+$, 85), 340 (100), 254 (43), 227 (40), 184 (18); HR-MS: calcd for $C_{19}H_{23}N_3O_3$: 341.1739, found 341.1657; Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.72; H, 6.67; N, 12.16.

**Preparation of 10-Hydroxy Ester (7).** 10-Amino ester (**5**) (378.6 mg, 1.3 mmol) was dissolved in 35% sulphuric acid (9 mL) and the solution was cooled to -5 °C. Ice (5 g) and a cooled $NaNO_2$ solution (156.4 mg (2.3 mmol) dissolved in 4 mL of distilled water) were then added. The mixture was stirred in an ice bath for 20 min, after which $Cu(NO_3)_2{\cdot}3H_2O$-solution (5.0 g (20.8 mmol) dissolved in 53 mL of distilled water) was added, and then with vigorous stirring $Cu_2O$ (196.3 mg, 1.4 mmol). Stirring was continued for an additional 5 min, after which alkaline work-up (EtOAc as extraction solvent) was performed. The crude product was purified by column chromatography ($CH_2Cl_2$:MeOH, 98.5:1.5), which yielded 58.5 mg (15%) of 10-hydroxy ester (**7**); mp 169-171 °C (toluene); IR: 2850-2780 (Wenkert-Bohlmann bands), 1715 (C=O); $^1$H NMR: δ 7.87 (1H, br s, NH), 7.24 (1H, d, $J$ = 8.5, H-8), 6.65 (1H, d, $J$ = 2, H-11), 6.61 (1H, dd, $J$ = 8.5 and 2, H-9), 3.82 (1H, d, $J$ = 9, H-12b), 3.78 (3H, s, -$COOCH_3$); MS: 300 ($M^+$, 77), 299 (100), 213 (44), 186 (38), 185 (26); HR-MS: calcd for $C_{17}H_{20}N_2O_3$: 300.1474, found 300.1477; Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.68; H, 6.62; N, 9.18.

**Preparation of 10-Bromo Ester (8).** Ester (**3**) (170 mg, 0.60 mmol) was dissolved in $CHCl_3$ (3 mL) and cooled with an ice bath. Anhydrous $FeCl_3$ (110 mg, 0.68 mmol) was added, followed by $Br_2$ (0.037 mL, 0.72 mmol). The mixture was stirred overnight. 15% $NH_3$ (5 mL) was added and the solution was filtered. The filtrate was extracted with $CH_2Cl_2$ and the solid was washed with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$) and the solvents were evaporated. The crude mixture (165 mg) was purified by preparative TLC (petroleum ether:EtOAc, 25:75) to give 46 mg (21%) of amorphous bromo ester (**8**); IR: 2850-2780 (Wenkert-Bohlmann bands), 1710 (C=O); $^1$H NMR: δ 8.22 (1H, br s, NH), 7.43 (1H, d, $J$ = 1.5, H-11), 7.31 (1H, d, $J$ = 8.5, H-8), 7.16 (1H, dd, $J$ = 8.5 and 1.5, H-9), 3.81 (1H, d, $J$ = 9.5, H-12b),

3.80 (3H, s, -$COOCH_3$); MS: 364 ($M^+$+2, 82), 363 (100), 362 ($M^+$, 81), 361 (85), 277 (37), 275 (40), 248 (26); HR-MS: calcd for $C_{17}H_{19}N_2O_2$ $^{79}Br$: 362.0630, found 362.0654; Anal. Calcd for $C_{17}H_{19}N_2O_2Br$: C, 56.21; H, 5.27; N, 7.71. Found: C, 56.08; H, 5.12; N, 7.48.

**Acid-Catalysed Epimerization of 10-Hydroxy Ester (7).** 10-Hydroxy ester (**7**) (9.1 mg, 0.03 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up (EtOAc as extraction solvent) was performed on the residue. The $^1H$ NMR spectrum showed a ratio of 32:68 (*trans*-hydroxy ester:*cis*-hydroxy ester). The neutralized residue was purified by column chromatography ($CH_2Cl_2$:MeOH, 98.5:1.5-97:3) to give 4.8 mg (53%) of amorphous *cis*-epimer (**9**) and 1.4 mg (15%) of **7**; IR: 1710 (C=O); $^1H$ NMR: δ 8.26 (1H, br s, NH), 7.28 (1H, d, $J$ = 8.5, H-8), 6.78 (1H, d, $J$ = 2, H-11), 6.65 (1H, dd, $J$ = 8.5 and 2, H-9), 4.18 (1H, br s, H-12b), 3.66 (3H, s, -$COOCH_3$); MS: 300 ($M^+$, 76), 299 (100), 213 (47), 186 (50), 185 (37); HR-MS: calcd for $C_{17}H_{20}N_2O_3$: 300.1474, found: 300.1475; Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.68; H, 6.55; N, 9.12.

**Acid-Catalysed Epimerization of Ester (3).** Ester (**3**) (9.8 mg, 0.03 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up was performed on the residue. The $^1H$ NMR spectrum showed a ratio of 74:26 (*trans*-ester:*cis*-ester[15]).

**Acid-Catalysed Epimerization of 10-Nitro Ester (4).** 10-Nitro ester (**4**) (16.0 mg, 0.05 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up was performed on the residue. The $^1H$ NMR spectrum showed that epimerization had not occurred.

**Acid-Catalysed Epimerization of 10-Amino Ester (5).** 10-Amino ester (**5**) (17.9 mg, 0.06 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up was performed on the residue. The $^1H$ NMR spectrum showed that epimerization had not occurred.

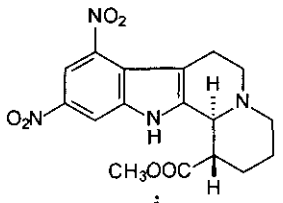
**Acid-Catalysed Epimerization of 10-Amido Ester (6).** 10-Amido ester (**6**) (13.4 mg, 0.04 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up was performed on the residue. The $^1H$ NMR spectrum showed only traces of the corresponding *cis*-epimer.

**Acid-Catalysed Epimerization of 10-Bromo Ester (8).** 10-Bromo ester (**8**) (4.6 mg, 0.01 mmol) was refluxed in TFA (4 mL) for 60 min. The acid was evaporated and alkaline work-up was performed on the residue. The $^1H$ NMR spectrum showed only traces of the corresponding *cis*-epimer.

## REFERENCES AND NOTES

1. For a review, see: M. Lounasmaa, M. Berner, and A. Tolvanen, *Heterocycles*, 1998, **48**, 1275.
2. For a review, see: E. Schlittler, "*Rauwolfia* Alkaloids with Special Reference to the Chemistry of Reserpine", in *The Alkaloids*, Vol. 8, ed. by R. H. F. Manske, Academic Press, New York, 1965, pp. 287-334.

3. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1.
4. P. Gmeiner, P. L. Feldman, M. Y. Chu-Moyer, and H. Rapoport, *J. Org. Chem.*, 1990, **55**, 3068.
5. D. Din Belle, A. Tolvanen, and M. Lounasmaa, *Tetrahedron*, 1996, **52**, 11361.
6. M. Lounasmaa, M. Berner, and A. Tolvanen, unpublished results.
7. M. Lounasmaa, L. Miikki, and A. Tolvanen, *Tetrahedron*, 1997, **53**, 5349.
8. H. B. MacPhillamy, C. F. Huebner, E. Schlittler, A. F. St. André, and P. R. Ulshafer, *J. Am. Chem. Soc.*, 1955, **77**, 4335. See also: A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.
9. P. Sarlet and J. Hannart, *Bull. Soc. Chim. Belg.*, 1979, **88**, 93.
10. E. Wenkert, K. G. Dave, and F. Haglid, *J. Am. Chem. Soc.*, 1965, **87**, 5461.
11. M. Lounasmaa and C.-J. Johansson, *Acta Chem. Scand. B*, 1975, **29**, 655.
12. Nitration of ester (**3**) with fuming nitric acid resulted mainly in 8,10-dinitro ester (**i**); mp 197-198 °C (methanol); IR: 2870-2780 (Wenkert-Bohlmann bands), 1700 (C=O), 1520 ($NO_2$); $^1$H NMR: δ 9.62 (1H, br s, NH), 8.78 (1H, d, $J$ = 2, H-9), 8.49 (1H, d, $J$ = 2, H-11), 3.90 (1H, d, $J$ = 10, H-12b), 3.86 (3H, s, -$COOCH_3$); $^{13}$C NMR: δ 178.1, 145.5 (2C?), 140.6, 136.7, 123.4, 112.9, 112.4, 111.6, 59.7, 55.1, 52.7, 51.5, 46.4, 30.4, 24.9, 23.7; MS: 374 ($M^+$, 72), 374 (22), 357 (60), 327 (32), 288 (37), 287 (100), 243 (44), 167 (50); HR-MS: calcd for $C_{17}H_{18}N_4O_6$: 374.1226, found: 374.1232.




**i**

13. For a recent study of brominated indolo[2,3-*a*]quinolizidines of marine origin, see: B. E. A. Burm, M. M. Meijler, J. Korver, M. J. Wanner, and G.-J. Koomen, *Tetrahedron*, 1998, **54**, 6135.
14. Bromination of ester (**3**) was performed according to L. Szabó, L. Dobay, G. Kalaus, E. Gács-Baitz, J. Tamás, and C. Szántay, *Arch. Pharm. (Weinheim, Ger.)*, 1987, **320**, 781. The amount of bromine turned out to be critical: excess of this reagent led to complex mixtures of dibromo and tribromo products.
15. M. Lounasmaa, L. Miikki, and A. Tolvanen, *Tetrahedron*, 1996, **52**, 9925.
16. (a) G. W. Gribble and R. B. Nelson, *J. Org. Chem.*, 1973, **38**, 2831; (b) G. W. Gribble, R. B. Nelson, J. L. Johnson, and G. C. Levy, *J. Org. Chem.*, 1975, **40**, 3720. See also: E. Wenkert, C.-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.*, 1976, **98**, 3645 (note 55).
17. M. Lounasmaa, *Curr. Org. Chem.*, 1998, **2**, 63, and references therein.

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