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Synthetic Studies in the Alkaloid Field. Part III.* Selective Alkaline Decarboalkoxylative Cyclization of Some *N*-Alkyldihydro- and *N*-Alkyltetrahydropyridines

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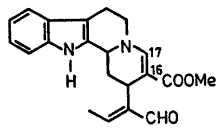
Selective alkaline decarboalkoxylative cyclization of three partially hydrogenated 1-[2-(3-indolyl)ethyl]-3,5-dimethoxycarbonylpyridine derivatives is described. The convenience of the method for the preparation of vallesiachotamine models is discussed.

In continuation of our studies concerning the preparation of indole alkaloid models of vallesiachotamine *1*[1] type we have examined the alkaline decarboalkoxylative cyclization[2] of three recently described,[3] partially hydrogenated 1-[2-(3-indolyl)ethyl]-3,5-dimethoxycarbonylpyridine derivatives *2*, *3*, and *4*. Since heretofore no dimethoxycarbonylpyridine derivative containing both methoxycarbonyl groups directly attached to the heterocyclic ring had been employed in the alkaline decarboalkoxylative cyclization, the preparation of indoloquinolizine derivatives from compounds of this type was of special interest. We hoped to accomplish selective decarboalkoxylation of the methoxycarbonyl group at position 3 of the starting materials while preserving the methoxycarbonyl group at position 5. Moreover, owing to the better conjugation possibility, it was hoped that in compound *4* the double bond would isomerize to the 3,4-position (corresponding to the 16,17-position in the biogenetic nomenclature of vallesiachotamine *1*) of the formed tetracyclic product.



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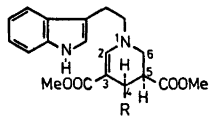
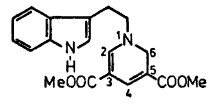


2 R = H

3 R = CH_3



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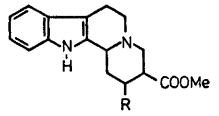
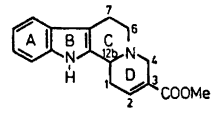


5 R = H

6 R = CH_3



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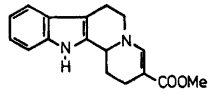

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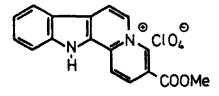

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Heating of the hydropyridine derivatives *2*, *3*, and *4* with aqueous alkali, a reaction known[2] to cause decarboalkoxylative cyclization (hydrolysis, decarboxylation, and cyclization), fol-

* Part II. Lounasmaa, M. and Johansson, C.-J. *Acta Chem. Scand. B 29* (1975) 655.

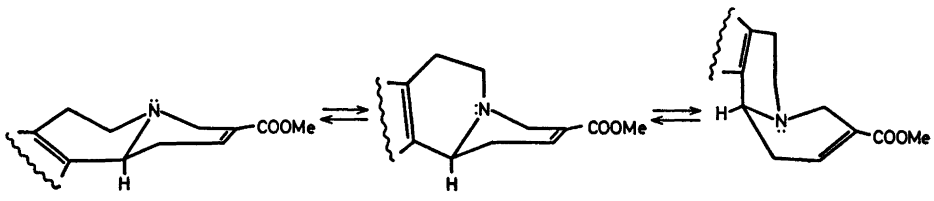
lowed by reesterification with methanolic acid, led to basic compounds which were purified by column chromatography. Compound *2* yielded two diastereoisomers of *5*, designated as *5a* and *5b*, whereas in the case of compound *3* only one of the possible diastereoisomers of 6, designated as *6a* was isolated. Compound *4* afforded *7*.

The correctness of the gross structures proposed for *5a*, *5b*, and *6a* was determined by direct comparison with samples of these substances from unambiguous syntheses.[4] A discussion concerning the stereochemistry of compounds *5a*, *5b*, and *6a* will be published later.

Dehydrogenation of compound *8*, prepared by sodium dithionite reduction of the recently described 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl pyridinium bromide [3] followed by acid-induced cyclization,[4] with palladium in aqueous maleic acid solution [5] yielded a hexadehydro compound, isolated as the perchlorate *9*. Reduction of the latter with sodium borohydride afforded a sample of *7* (*cf.* Ref. 5), which proved to be identical with *7* obtained from the alkaline decarboalkoxylative cyclization and reesterification of *4*. On the other hand, catalytic hydrogenation of the perchlorate *9*, which this time was prepared by palladium-maleic acid dehydrogenation of compound *7*, afforded compound *8*. Thus a reciprocal conversion between compounds *7* and *8* was accomplished.

Compound *7* can exist in three conformations, which are in equilibrium by nitrogen inversion and half-chair ring interconversion (Scheme 1, only one enantiomer is illustrated). The conformation with a *trans* diaxial C/D ring juncture is not possible. In all conformations examined, rings C and D are assumed by analogy with cyclohexene to be in the half-chair conformations.[6] Strictly speaking, however, this is a simplification, because rings C and D cannot both be at the same time exactly in the half-chair conformation. This becomes evident if one considers, for instance, conformer *a* (Scheme 1) where, with no deformation of the valence angles and overlooking the small difference between the C–N and C–C bond distances, the relationship between the C(12b) hydrogen and the lone electron pair of the basic nitrogen would be simultaneously *trans* diaxial (considering ring D) and *trans* pseudoaxial-axial (considering ring C). Thus, a slight deformation of the ideal half-chairs is to be expected.

Compounds of the above indoloquinolizine-type, possessing in their preferred conformation the C(12b) hydrogen and at least one more adjacent C hydrogen *trans* diaxial to the lone electron pair of the basic nitrogen, are known [7–11] to exhibit so-called Bohlmann bands in their IR spectra. The preference of the ring C of indoloquinolizines for the half-chair conformation (*cf.* above) tends to force the C(12b) substituents to pseudoaxial and pseudoequatorial positions. As a consequence, for most indoloquinolizines in the conformation where the relationship between the C(12b) hydrogen and the lone electron pair of the basic nitrogen is said to be *trans* diaxial, the relationship is not exactly *trans* diaxial but slightly deformed. This deformation, which is dependent *inter alia* on the ring D and its substituents, may have a slight influence on the intensity of the Bohlmann bands. However, this deformation has no practical meaning when the Bohlmann bands are being used for the determination of preferred conformations. The presence of Bohlmann bands in the IR spectrum of compound *7* indicates that conformer *a*, which possesses *trans*-



a b c

Scheme 1.

quinolizine juncture of the C/D rings, dominates the conformational equilibrium between *a*, *b*, and *c* (Scheme 1).

A study of the nonbonded interactions of each conformer, made with the aid of Dreiding models, reveals that in conformer *b* there is an interaction between the C(1) pseudoaxial hydrogen and the C(6) axial hydrogen, and in conformer *c* between the C(4) pseudoaxial hydrogen and the C(7) pseudoaxial hydrogen, whereas in conformer *a* no appreciable nonbonded interactions are present.

The preponderance of conformer *a* is also supported by the ^{1}H NMR. The absence of any signal downfield from δ 3.8 that could be assigned to the C(12b) hydrogen is characteristic of *trans*-quinolizine juncture (conformer *a*).[8, 10–13]

The selective decarboalkoxylation of the methoxycarbonyl groups at C(3) of the starting materials *2*, *3*, and *4*, with the preservation of the methoxycarbonyl groups at C(5), has thus been accomplished in all three cases. On the other hand, the desired direct isomerization of the double bond of compound *4* to the 3,4-position (enamine position) of the formed tetracyclic product did not take place. This isomerization could not be achieved by various modifications of the reaction conditions, nor could it be induced by treatment of the tetracyclic product *7* with *t*-BuOK in DMSO under carefully controlled conditions.[14] However, the conversion of compound *7* to compound *8* by dehydrogenation with palladium in aqueous maleic acid followed by catalytic hydrogenation indicates the applicability of the selective alkaline decarboalkoxylative cyclization method described above to the preparation of vallesiachotamine *1* models containing a $\Delta^{3(4)}$ double bond.

EXPERIMENTAL

The UV spectra were measured on a Perkin-Elmer 137 UV apparatus and the IR spectra on a Perkin-Elmer 237 apparatus. The NMR spectra were taken with either a Varian A-60 instrument or a Jeol JNM-PMX 60 instrument using TMS as internal standard. The mass spectra were recorded on a Perkin-Elmer 270 mass spectrometer at 70 eV using direct sample insertion into the ion source whose temperature was 80–90 °C. The melting points were determined in a capillary melting point apparatus (Büchi) and are uncorrected.

Decarboalkoxylative cyclizations

General procedure: A mixture of the tetrahydro- or dihydropyridine derivative and potassium hydroxide in methanol and water was refluxed with stirring under nitrogen for 45 h. The solvents were evaporated under vacuum and the residue dried in a vacuum desiccator for 18 h. The residue was then dissolved in abs. methanol and the solution saturated with dry hydrogen chloride gas during 2 h. The mixture was allowed to stand for 70 h and then slowly poured into a suspension of excess of sodium hydrogencarbonate in 200 ml of dichloromethane. The mixture was filtered and the filtrate evaporated under vacuum. The residue was extracted with dichloromethane and purified by column chromatography (Al_2O_3; act. IV).

Tetrahydropyridines. Reaction between 388 mg of diester *2* and 2.0 g of potassium hydroxide in 10 ml of methanol and 10 ml of water gave a mixture of two isomers which were separated by column chromatography.

5a. Yield 165 mg. M.p. 192–194 °C (methanol). IR, UV, NMR, MS, and TLC were identical with those of an authentic sample.[4]

5b. Yield 44 mg. M.p. 223–225 °C (methanol). IR, UV, NMR, MS, and TLC were identical with those of an authentic sample.[4]

Reaction between 334 mg of diester *3* and 2.0 g of potassium hydroxide in 10 ml of methanol and 10 ml of water gave a mixture which was fractionated by column chromatography and preparative layer chromatography.

6a. Yield 87 mg. M.p. 173–175 °C (methanol). IR, UV, NMR, MS, and TLC were identical with those of an authentic sample.[4]

A small fraction, which proved to be identical (IR, NMR, MS, and TLC) with the 60/40 mixture of the two diastereoisomers recently described (Ref. 3., gross structure XXIII), was also isolated.

Dihydropyridine. Reaction between 580 mg of diester *4* and 2.0 g of potassium hydroxide in 10 ml of methanol and 10 ml of water gave a tarry mixture which was fractionated by column chromatography and preparative layer chromatography.

7. Yield 28 mg. M.p. 180–182 °C (methanol). IR (KBr) NH 3370 (s), Bohlmann bands 2820 and 2765, C=O 1695 (s), C=C 1650 (m) cm^{-1}. IR ($CHCl_3$) Bohlmann bands 2820 and 2770, C=O 1710 (s), C=C 1660 (m) cm^{-1}. UV (EtOH 94 %) λ_{max} 205 (infl.) (ε 29 200), 224 (ε 40 700), 284 (ε 9140), and 292 (ε 8230) nm. λ_{min} 206 (infl.), 250, and 289 nm. NMR ($CDCl_3$) δ 3.75 (3H, s, $-COOCH_3$) and δ 7.78 (1 H, br s, ind. N–H). MS M^+ at *m/e* 282

corresponding to $C_{17}H_{18}N_2O_2$. Other important peaks at *m/e* 281, 170, and 169.

Small amounts of *5a*, *5b*, and 3,5-dimethyl dinicotinate (Ref. 3., structure VII) were also found, due to disproportionation.

Conversion between compounds *7* and *8*.

Salt 9. A mixture of 150 mg of *8*,[4] 130 mg of maleic acid and 150 mg of palladium-charcoal (10 %) in 15 ml of water was refluxed for 18 h under a stream of nitrogen. The solution was filtered and the filtrate evaporated under vacuum. The residue was dissolved in a saturated solution of sodium perchlorate to yield 90 mg of the salt *9*. M.p. 274–276 °C (dec.) (methanol). IR (KBr) NH 3280 (m), C=O 1730 (s), C=C 1635 (s) and 1555 (s) cm^{-1}.

A similar treatment of a mixture of 54 mg of *7*, 48 mg of maleic acid and 54 mg of palladium-charcoal (10 %) in 5 ml of water yielded 48 mg of the salt *9*.

1,4,6,7,12,12b-Hexahydro-3-methoxycarbonylindolo[2,3-a]-quinolizine 7. 130 mg of the salt *9* was dissolved in 30 ml of methanol and 300 mg of sodium borohydride was added portionwise. The mixture was stirred for *ca.* 2.5 h and the solution was evaporated under vacuum. The residue was dried in a vacuum desiccator overnight and then dissolved in 50 ml of abs. methanol. Dry hydrogen chloride gas was passed into the solution for 2 h and the mixture was allowed to stand at room temperature for 60 h. The solution was neutralized in a mixture of dichloromethane and sodium hydrogencarbonate. The inorganic materials were filtered off and the filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV) to yield 12 mg of ester *7*. M.p. 180–182 °C (methanol). IR, UV, NMR, MS, and TLC were identical with those of the sample above.

1,2,6,7,12,12b-Hexahydro-3-methoxycarbonylindolo[2,3-a]-quinolizine 8. A mixture of 110 mg of the salt *9*, 200 mg of palladium-charcoal (10 %) and 0.2 ml of triethylamine in 200 ml of abs. methanol was hydrogenated for 24 h at atmospheric pressure. The catalyst was filtered off, the filtrate evaporated under vacuum and the residue extracted with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was chromatographed on alumina (act. IV) to yield 20 mg of ester *8*. M.p. 170–172 °C (methanol). IR, UV, NMR, MS, and TLC were identical with those of an authentic sample.[4]

REFERENCES

1. Djerassi, C., Monteiro, H. J., Walser, A. and Durham, L. J. *J. Amer. Chem. Soc. 88* (1966) 1792.
2. Wenkert, E. *Accounts Chem. Res. 1* (1968) 78, and references therein.
3. Lounasmaa, M. and Johansson, C.-J. *Acta Chem. Scand. B 29* (1975) 655.
4. Lounasmaa, M. and Johansson, C.-J. *Forthcoming publication.*
5. Wenkert, E. and Roychaudhuri, D. K. *J. Amer. Chem. Soc. 80* (1958) 1613.
6. Beckett, C. W., Freeman, N. K. and Pitzer, K. S. *J. Amer. Chem. Soc. 70* (1948) 4227.
7. Bohlmann, F. *Chem. Ber. 92* (1959) 1798.
8. Uskokovic, M., Bruderer, H., von Planta, C., Williams, T. and Brossi, A. *J. Amer. Chem. Soc. 86* (1964) 3364.
9. Crabb, T. A., Newton, R. F. and Jackson, D. *Chem. Rev. 71* (1971) 109, and references therein.
10. Imbert, T., Thal, C., Husson, H.-P. and Potier, P. *Bull. Soc. Chim. Fr.* (1973) 2705.
11. Gribble, G. E. and Nelson, R. B. *J. Org. Chem. 38* (1973) 2831.
12. Wenkert, E. and Wickberg, B. *J. Amer. Chem. Soc. 84* (1962) 4914.
13. Husson, H.-P., Imbert, T., Thal. C. and Potier, P. *Bull. Soc. Chim. Fr.* (1973) 2013.
14. Price, C. C. and Snyder, W. H. *J. Amer. Chem. Soc. 83* (1961) 1773.

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