

INDOLINES THROUGH INTRAMOLECULAR IMINE CYCLIZATIONS

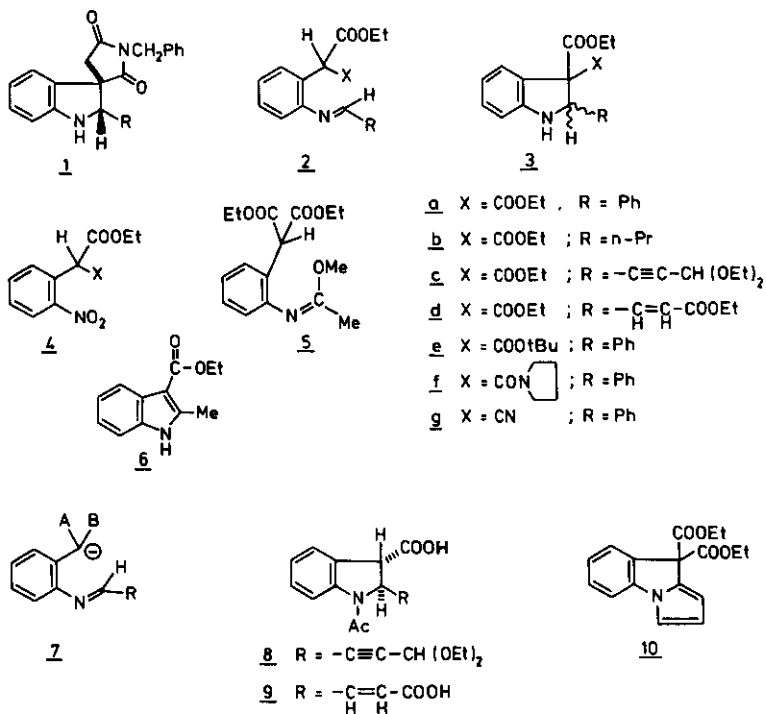
Jan Dijkink, Johannes N. Zonjee, Bart S. de Jong, and W. Nico Speckamp^{*}
 Laboratory of Organic Chemistry, University of Amsterdam
 Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract - Indolines $\mathfrak{3}$ are synthesized by intramolecular base-catalyzed cyclization of imines $\mathfrak{2}$. Controlled basic hydrolysis of $\mathfrak{3}$ affords indoline carboxylic acids $\mathfrak{8}$ and $\mathfrak{9}$. The compounds $\mathfrak{3}$ are also useful for the synthesis of the mitomycin skeleton as exemplified by the preparation of $\mathfrak{10}$.

The stereoselective formation of 3,3-spirocyclic indolines $\mathfrak{1}$ by a presumed 1,5-electrocyclization process¹ invited to the stereocontrolled synthesis of 2,3-disubstituted indolines. Since carbanion additions to anils belong to a well-documented type of reaction², an intramolecular variant of this addition seemed of potential usefulness. Contrary to the facile intermolecular reaction of benzylidene aniline and ethyl phenylacetate³, however, the intramolecular addition of $\mathfrak{2}^4$ (X = H, R = alkyl, aryl) - base treatment under a variety of conditions - did not afford a trace of cyclic product $\mathfrak{3}$. The failure to undergo intramolecular cyclization could be due to (i) unfavorable geometry for a 5-endo-trig ring closure (anti Baldwin process)⁵ or to (ii) incomplete carbanion formation in protic solvents. In order to enhance the acid strength of the C-H bond a number of disubstituted imines $\mathfrak{2}$ (X = COOEt, COOtBt, CN, CONR₂) were investigated. The starting materials $\mathfrak{2}$ could be prepared by nucleophilic aromatic substitution of o-chloronitrobenzene⁶ by the appropriate anion followed by catalytic hydrogenation of the nitro group of $\mathfrak{4}$ in an aprotic solvent and condensation of the so-obtained amine with an aldehyde. As already reported¹ it was found that reaction of $\mathfrak{2}$ (X = COOEt, R = C₆H₅) under a variety of base-catalyzed conditions afforded the indoline $\mathfrak{3a}$, m.p. 70-71°C, in good yield. Other types of imines $\mathfrak{2}$ underwent similar cyclization as shown by the formation of $\mathfrak{3b}$ (MeOH-MeONa, r.t., 5 min) oil, 63%, $\mathfrak{3c}^7$ (EtOH-EtONa, r.t. 5 min) oil, 95% and $\mathfrak{3d}$ (MeOH-MeONa, r.t. 3 min) oil, 100%. An analogous reaction behaviour was observed upon base treatment (tBuOH-tBuOLi, reflux 5 h) of the imino ether $\mathfrak{5}$ prepared by reaction of the amine with 1,1-dimethoxyethene⁸. The product

obtained in 60% yield, m.p. 130-132°C, proved to be ethyl 2-methylindole-3-carboxylate (β)⁹ and most probably results from a base-catalyzed decarboxylative aromatization of the initially formed indoline. As compared to well-established indole syntheses¹⁰ the relatively mild reaction conditions are noteworthy. In order to prepare the indolines β , β and β and to evaluate the influence of different substituents X, the corresponding imines λ (R = C₆H₅) were also subjected to base treatment. For the t-Bu ester β a similar reaction as with the ethyl ester was observed, although in this case a cis-trans mixture of two C-2 isomers was formed in a ratio of 1:2. Characterization of the isomers was easily possible by ¹H NMR analysis showing marked differences in the ester CH₃ absorption¹¹. The formation of two isomers is understandable in view of the small differences between the groups A and B resulting in the cyclization via two energetically almost equivalent conformations of anion λ . In accordance with the slightly diminished charge-stabilizing capacity of the amide group in β the ring closure leading to indoline β was slower and heating was necessary to complete the reaction (EtOH-EtONa, 50°C, 4 h). Again two C-2 isomers were formed in a ratio of 2:3 (cis:trans) in a combined yield of 65%. The ring closure of amide β proved also possible under Lewis acid catalysis (five days; Zn(OAc)₂-EtOH, r.t.), furnishing indoline β in 80% yield also with a cis-trans ratio 2:3¹². Lastly, the cyano derivative λ (X = CN), upon successive hydrogenation (Pd/C, PhCH₃-EtOH) and imine formation (PhCH₃, r.t.) underwent spontaneous cyclization in absence of external base and directly afforded a 3:7 mixture of the cis and trans isomers of β in a yield of 72%. Crystallization (ether-hexane) gave the pure trans isomer, m.p. 105-108°C, in 36% yield. ¹H NMR δ (CDCl₃): 1.38 t (3H); 3.2-4.0 m (1H); 4.25-4.6 m (2H); 5.67 s (1H); 6.7-7.0 m (2H); 7.15-7.7 m (7H). The latter result clearly indicates the importance of a sufficient acid strength in this type of intramolecular condensation.

The obvious lack of stereoselectivity in the imine cyclization reactions described precludes a definite conclusion on its actual mechanism¹³. From a synthetic viewpoint, however, the compounds are valuable intermediates in syntheses of substituted indolines as is also evidenced by the following transformations of β and β . After acylation the diester β was saponified (KOH/EtOH-H₂O/0°C) to produce the trans indoline carboxylic acid β in 90% yield, m.p. 138-141°C. ¹H NMR δ (CDCl₃): 1.20 t (6H); 2.45 s (3H); 3.4-3.8 (4H); 4.30 m (1H); 5.24 d (1H); 5.57 m (1H); 7.0-7.52 m (3H); 8.0 m (1H); 8.0-8.35 m (1H). Similarly β was converted to the



dicarboxylic acid $\underline{9}$. $^1\text{H NMR } \delta(\text{CD}_3\text{OD})$: 2.28 s (3H); 4.00 d (1H); 5.57 m (1H); 5.88 dd $J=16$, $J=1$ Hz (1H); 6.95 dd $J=5.5$ Hz (1H); 7.0-7.52 (3H); 8.10 m (1H).

Finally, the methodology outlined herein is being developed as a novel approach to the synthesis of mitomycins ¹⁴. The potential value of the compounds described is illustrated by the quantitative conversion of $\underline{3c}$ into the pyrrolo[1,2-a]indole $\underline{10}$ by Lindlar hydrogenation of $\underline{3c}$ and acid treatment (AcOH; r.t., 2 h) of the resulting (Z)-olefinic acetal. Data of $\underline{10}$: m.p. 113-115°C. $^1\text{H NMR } \delta(\text{CDCl}_3)$: 1.29 t (6H); 4.25 q (4H); 6.42 m (2H); 7.0-7.5 m (4H); 7.73 m (1H) ¹⁵. Further progress will be reported in due course.

LITERATURE AND REFERENCES

- W.N. Speckamp, S.J. Veenstra, J. Dijkink and R. Fortgens, J. Amer. Chem. Soc., 1981, **103**, 4643.
- R.W. Layer, Chem. Rev., 1963, **63**, 489.
- a. E.J. Wayne and J.B. Cohen, J. Chem. Soc., 1925, **127**, 450.
b. E. Simova and B. Kurtev, Monatsh. für Chemie, 1965, **96**, 722.
- $\underline{9}$ was prepared by condensing the appropriate aldehyde with ethyl orthoamino-

phenylacetate.

5. J. Baldwin, J.C.S. Chem. Comm., 1976, 734.
6. J. Bourdais and C. Germain, Tetrahedron Lett., 1970, 195.
7. The corresponding aldehyde was prepared according to A. Gorgues and A. le Coq, Tetrahedron Lett., 1979, 4825.
8. H.M. Barnes, D. Kundiger, and S.M. McElvain, J. Amer. Chem. Soc., 1940, 62, 1281.
9. S. Saeki, M. Hayashida, T. Sukamoto, and M. Hamana, Heterocycles, 1974, 2, 445.
10. R.K. Brown, 'Heterocyclic Compounds', Indoles Part I, W.J. Houlihan Ed., J. Wiley, 1972, pp 385-396.
11. Triplet of $\text{CH}_3\text{CH}_2\text{O}$ cis to C-2 phenyl is shifted upfield δ_e (CDCl_3) 0.81; δ_f (CDCl_3) 0.82; δ_g (CDCl_3) 0.66.
12. As expected the cis-trans ratio is markedly dependent on the solvents used. A ratio of 3:1 was found in DMSO-NaOEt, r.t., while in DMSO-tBuOH, r.t., a 1:1 ratio was obtained.
13. The occurrence of a ring closure through a 1,5-electrocyclization process is strongly indicated especially with regard to the differences observed in the ring closures of mono and disubstituted imines 2. Investigations to solve this question, especially on the influence of the size and electronic character of the substituent X in 2, are currently underway.
14. R.W. Franck, Fortschr. Chem. Org. Naturst., 1979, 38, 1.
15. Elemental analysis of 10 Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.20; H, 5.87; N, 4.71.

Received, 28th February, 1983