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# INDOLINES THROUGH INTRAMOLECULAR IMINE CYCLIZATIONS

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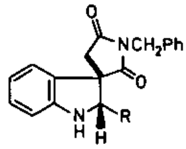
Abstract – Indolines 3 are synthesized by intramolecular base-catalyzed cyclization of imines 2. Controlled basic hydrolysis of 3 affords indoline carboxylic acids 8 and 9. The compounds 3 are also useful for the synthesis of the mitomycin skeleton as exemplified by the preparation of 10.

The stereoselective formation of 3,3-spirocyclic indolines 1 by a presumed 1,5-electrocyclization process[1] invited to the stereocontrolled synthesis of 2,3-disubstituted indolines. Since carbanion additions to anils belong to a well-documented type of reaction[2], an intramolecular variant of this addition seemed of potential usefulness. Contrary to the facile intermolecular reaction of benzylidene aniline and ethyl phenylacetate[3], however, the intramolecular addition of 2[4] (X = H, R = alkyl, aryl) - base treatment under a variety of conditions - did not afford a trace of cyclic product 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 2 (X = COOEt, COOtBt, CN, $CONR_2$) were investigated. The starting materials 2 could be prepared by nucleophilic aromatic substitution of o-chloro nitrobenzene[6] by the appropriate anion followed by catalytic hydrogenation of the nitro group of 4 in an aprotic solvent and condensation of the so-obtained amine with an aldehyde. As already reported[1] it was found that reaction of 2 (X = COOEt, R = $C_6H_5$) under a variety of base-catalyzed conditions afforded the indoline 3a, m.p. 70-71°C, in good yield. Other types of imines 2 underwent similar cyclization as shown by the formation of 3b (MeOH-MeONa, r.t., 5 min) oil, 63%, 3c[7] (EtOH-EtONa, r.t. 5 min) oil, 95% and 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 5 prepared by reaction of the amine with 1,1-dimethoxyethene[8]. The product obtained in 60% yield, m.p. 130-132°C, proved to be ethyl 2-methylindole-3-carboxylate (6)[9] and most probably results from a base-catalyzed decarboxylative aromatization of the initially formed indoline. As compared to well-established indole syntheses[10] the relatively mild reaction conditions are noteworthy. In order to prepare the indolines 3e, 3f and 3g and to evaluate the influence of different substituents X, the corresponding imines 2 ($R = C_6H_5$) were also subjected to base treatment. For the t-Bu ester 3e 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 $CH_3$ absorption[11]. 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 7. In accordance with the slightly diminished charge-stabilizing capacity of the amide group in 2f the ring closure leading to indoline 3f 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 2f proved also possible under Lewis acid catalysis (five days; $Zn(OAc)_2$-EtOH, r.t.), furnishing indoline 3f in 80% yield also with a cis-trans ratio 2:3[12]. Lastly, the cyano derivative 4 (X = CN), upon successive hydrogenation (Pd/C, $PhCH_3$-EtOH) and imine formation ($PhCH_3$, r.t.) underwent spontaneous cyclization in absence of external base and directly afforded a 3:7 mixture of the cis and trans isomers of 3g in a yield of 72%. Crystallization (ether-hexane) gave the pure trans isomer, m.p. 105-108°C, in 36% yield. $^1H$ NMR δ ($CDCl_3$): 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 mechanism[13]. From a synthetic viewpoint, however, the compounds are valuable intermediates in syntheses of substituted indolines as is also evidenced by the following transformations of 3c and 3d. After acylation the diester 3c was saponified (KOH/EtOH-$H_2O$/0°C) to produce the trans indoline carboxylic acid 8 in 90% yield, m.p. 138-141°C. $^1H$ NMR δ($CDCl_3$): 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 3d was converted to the



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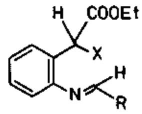

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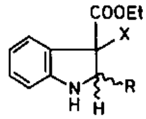

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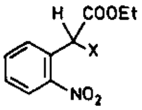
a X = COOEt , R = Ph
b X = COOEt ; R = n-Pr
c X = COOEt ; R = –C≡C–CH(OEt)$_2$
d X = COOEt ; R = –CH=CH–COOEt
e X = COOtBu ; R = Ph
f X = CON(pyrrolidinyl) ; R = Ph
g X = CN ; R = Ph



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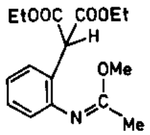

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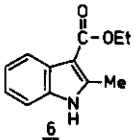

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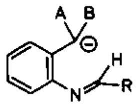

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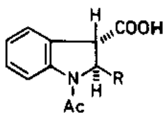
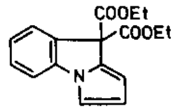


8 R = –C≡C–CH(OEt)$_2$
9 R = –CH=CH–COOH



10

dicarboxylic acid **9**. $^1$H NMR δ(CD$_3$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 **3c** into the pyrrolo[1,2-a]indole **10** by Lindlar hydrogenation of **3c** and acid treatment (AcOH ; r.t., 2 h) of the resulting (Z)-olefinic acetal. Data of **10**: m.p. 113-115°C. $^1$H NMR δ(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.

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4. **2** was prepared by condensing the appropriate aldehyde with ethyl orthoamino-

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11. Triplet of $CH_3CH_2O$ cis to C-2 phenyl is shifted upfield **3e** ($CDCl_3$) 0.81; **3f** ($CDCl_3$) 0.82; **3g** ($CDCl_3$) 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.

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15. Elemental analysis of **10** Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.20; H, 5.87; N, 4.71.

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