THE MADELUNG SYNTHESIS OF DIHYDRO-1H-PYRROLO- AND TETRAHYDROPYRIDO[1,2-a]-INDOLES UNDER MILD CONDITIONS

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Abstract. Benzeneacetonitriles substituted with lactam moieties in the ortho-position cyclize under the influence of a base, dependent on the ring-size of the lactam function, to dihydropyrrolo-, tetrahydropyrido[1,2-a]indole or dihydro-1-benzazepin derivatives, respectively.

The Madelung reaction, *viz.* the intramolecular cyclization of *N*-acylated-*ortho*-alkylanilines in the presence of a strong base and at elevated temperatures (200-400 °C), represents a useful method for the synthesis of indoles.¹ The corresponding cyclization of *N*-acylated-*ortho*-alkylanilines of which the benzylic carbon atom possesses an electron-withdrawing group may be regarded as a modification of this reaction.^{2,3} To the best of our knowledge no examples are known of similar systems containing a *cyclic* amide moiety.

In previous papers^{4,5} we have described the synthesis of 2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole-9-carbonitriles, which could not be converted into the corresponding 2,3-dihydro compounds by elimination of hydrogen cyanide. Generally, the pyrrolo[1,2-a]indoles⁶ are of synthetic interest because they form the basic skeleton of the mitomycins. In the present paper we wish to present our preliminary results of a novel and facile synthesis of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles via a Madelung reaction under mild conditions of *N*-acylated-*ortho*-alkylanilines **1** that contain both a cyclic amide function and an electron-withdrawing

Scheme I

group at the benzylic position. The scope of this cyclization reaction with respect to the ring-size of the cyclic amide function will be discussed.

The starting materials **4** were prepared as depicted in Scheme I. Reaction of the anilines **1**⁷ with the appropriate acid chloride **2**¹⁰ in the presence of ethyldiisopropylamine in tetrahydrofuran at room temperature for 0.5 h afforded the acylated aniline derivatives **3**^{11,12} in yields of 79-96%. Subsequent cyclization according to Manhas and Jeng¹³ with 1.5 equiv. of sodium amide in liquid ammonia gave the compounds **4**¹⁴ in yields of 68-87%.

At higher temperatures [sodium hydride (NaH)] or in the presence of a stronger base [potassium *tert*-butoxide (KOt-Bu)] the 2-(2-oxo-1-pyrrolidinyl)benzeneacetonitriles **4a-d** underwent intramolecular cyclization to the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **5a-d** which could be purified by column chromatography (silica gel, ethyl acetate/methanol, 95:5). The 4,5-dimethoxy-2-(2-oxo-1-piperidinyl)benzeneacetonitrile (**4f**) reacted similarly to give the corresponding 6,7,8,9-tetrahydropyrrolo[1,2-*a*]indole (**6**). Reaction with NaH (~ 5 equiv.) in toluene (method A) required temperatures of 100-110 °C to complete the reaction. The reaction time appeared to be critical because too long reaction times gave lower yields owing to the formation of polymeric material. Reaction with KOt-Bu (2.2 equiv.) in tetrahydrofuran (method B) occurred at room temperature and did not show this drawback; the reaction products **5a-d** and **6** were obtained in good yields. The results of both methods are summarized in the Table.

Table. Intramolecular cyclization of **4a-d,f**.

Compd	R ¹	R ²	Mp (°C)	Method A		Method B	
				Time (h)	Yield (%)	Time (min)	Yield (%)
5a	H	H	110-133 (dec) (toluene)	48	< 1 ^a	10	88
5b	OCH ₃	OCH ₃	206-208 (ethanol) ^b	22	69	120	83
5c	OCH ₃	CH ₃	170-172 (ethanol) ^c	2	61	90	75
5d	OCH ₃	H	142-152 (dec) (ethanol)	0.75	79	90	69
6			173-174 (ethyl acetate)	0.75	82	20	85

^aOnly polymeric material was obtained. ^bLit.¹⁵ mp 203-203.5 °C.

^cLit.¹⁶ mp 173-173.5 °C ; lit.¹⁵ mp 174-174.5 °C.

Reaction of 4,5-dimethoxy-2-(2-oxo-1-azetidiny)benzeneacetonitrile (4e) with $\text{KO}t\text{-Bu}$ in tetrahydrofuran at 5°C for 15 min afforded after trituration of the crude reaction mixture with chloroform, 2,3-dihydro-4-hydroxy-7,8-dimethoxy-1*H*-1-benzazepin-5-carbonitrile (7)¹⁷ [mp $159\text{--}165^\circ\text{C}$; IR (KBr) 3290 (NH), $2700\text{--}2400$ (OH), 2200 (CN) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 10.58 (br s, 1 H, NH), 6.89 and 6.43 (s, 1 H, Ar H), 5.60 (br s, 1 H, OH), 3.68 and 3.66 (s, 3 H, OCH_3), 3.2–3.1 (m, 2 H, NCH_2), 2.7–2.6 (m, 2 H, $\text{CH}_2\text{C=}$); ^{13}C NMR ($\text{DMSO}-d_6$) δ 170.4 (s, C-4), 88.6 (s, C-5), 43.5 (t, C-2), 37.9 (t, C-3)] in a yield of 45%. Methylation of 7 with excess iodomethane in acetone in the presence of potassium carbonate for 21 h gave after column chromatography (silica gel, ethyl acetate/methanol, 95:5) 2,3-dihydro-7,8-dimethoxy-1,5-dimethyl-4-oxo-1*H*-1-benzazepin-5-carbonitrile (8) [oil; mass spectrum, m/e 274.131 (M^+ , calcd, 274.132); IR (KBr) 2240 (CN), 1730 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 7.07 and 6.73 (s, 1 H, Ar H), 3.92 and 3.91 (s, 3 H, OCH_3), 3.3–2.5 (m, 4 H, NCH_2 and CH_2CO), 2.74 (s, 3 H, NCH_3), 1.77 (s, 3 H, CH_3); ^{13}C NMR (CDCl_3) δ 202.4 (s, C=O), 56.6 (t, C-2), 52.3 (s, C-5), 41.8 (q, NCH_3), 38.5 (t, C-3), 23.6 (q, CH_3)] in a yield of 37%, indicating that both the nitrogen atom and the carbon atom at the 5-position had been methylated.

We can explain the formation of 5, 6 and 7 as depicted in Scheme II. In all cases intramolecular addition of the benzylic carbanion to the carbonyl moiety leads to the intermediate 10. In the cases of 4a–d and 4f with $n=3$ and 4, respectively, elimination of water ultimately gives the compounds 5 and 6. When NaH is used the protonation could be by unreacted 4 or during the aqueous

Scheme II

workup. In the case of $\text{KO}t\text{-Bu}$ when at least 2 equiv. of base are necessary, the protonation can also be performed by the *tert*-butanol formed. In the case of 4e dehydration would lead to a highly strained tricyclic compound. Therefore the reaction proceeds by cleavage of the N-CO bond to give 11 which after protonation can be isolated as 7.

A somewhat related method for the synthesis of dihydro-1*H*-pyrrolo[1,2-*a*]indoles, via an intramolecular Wittig olefination, has recently been published by the groups of Flitsch¹⁸ and Zimmer.¹⁹

This new method represents a very useful synthesis of substituted 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles, in which a quinone function can easily be introduced. Compound 5c, after reduction of the cyano to an aldehyde group, has been converted

12a, R = CH₃

b, R = H

OCH₃); ¹³C NMR (CDCl₃) δ 186.7 (d, HC=O), 178.1 and 177.3 (s, C=O), 160.6 (s, C-7), 105.5 (d, C-6), 56.7 (q, OCH₃), 47.4 (t, NCH₂)].

Further work on the application of this method for the synthesis of mitomycin analogues is in progress.

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References and notes

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7. The anilines **1a**⁸ and **1b**⁹ were prepared as described. Compounds **1c** and **1d** were prepared starting from 2-methyl-5-chloroaniline and 3-chlorophenol, respectively.
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11. Compound **3a**: yield 79%, mp 98-99 °C (toluene); **3b**: yield 96%, mp 136-138 °C (ethyl acetate); **3c**: yield 88%, mp 144-145 °C (diisopropyl ether); **3d**: yield 83%, mp 93-94 °C (toluene); **3e**: yield 91%, mp 165-167 °C (ethyl acetate); **3f**: yield 94%, mp 132.5-133.5 °C (ethyl acetate).
12. Satisfactory elemental analyses and spectral data (as far as not mentioned) were obtained for all new compounds.
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14. Compound **4a**: yield 68%, mp 67.5-68.5 °C (toluene); **4b**: yield 87%, mp 158-159 °C (ethyl acetate); **4c**: yield 68%, mp 164-169 °C (dec) (ethyl acetate); **4d**: yield 80%, mp 99-100 °C (ethyl acetate, -20 °C); **4e**: yield 82%, mp 126-128 °C (ethanol); **4f**: yield 80%, mp 116-117 °C (ethanol).
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