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

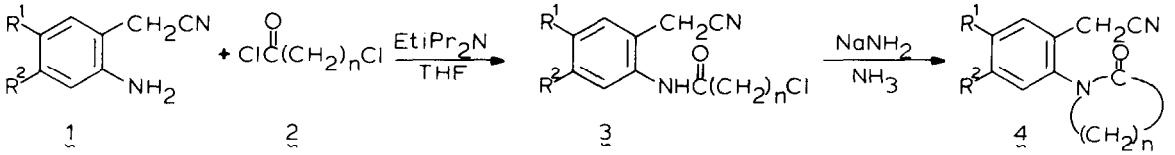
W. Verboom, H.J. Berga, W.P. Trompenaars and D.N. Reinhoudt*

Laboratory of Organic Chemistry, Twente University of Technology,
Enschede, The Netherlands

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*-1*H*-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*]indoles[6] 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*-1*H*-pyrrolo[1,2-*a*]indoles via a Madelung reaction under mild conditions of *N*-acylated-*ortho*-alkylanilines 4 that contain both a cyclic amide function and an electron-withdrawing



1 2 3 4

1 a, $R^1=R^2=H$
b, $R^1=R^2=OCH_3$
c, $R^1=OCH_3$, $R^2=CH_3$
d, $R^1=OCH_3$, $R^2=H$

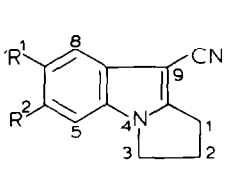
2 a, n=3; $R^1=R^2=H$
b, n=3; $R^1=R^2=OCH_3$
c, n=3; $R^1=OCH_3$, $R^2=CH_3$
d, n=3; $R^1=OCH_3$, $R^2=H$
e, n=2; $R^1=R^2=OCH_3$
f, n=4; $R^1=R^2=OCH_3$

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 Jeng[13] 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 (KO*t*-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-tetrahydropyrido[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 KO*t*-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.



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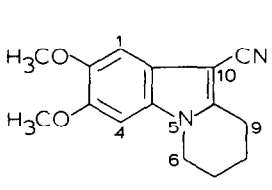

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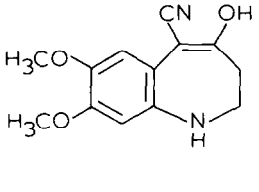

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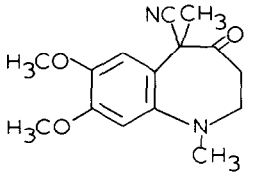

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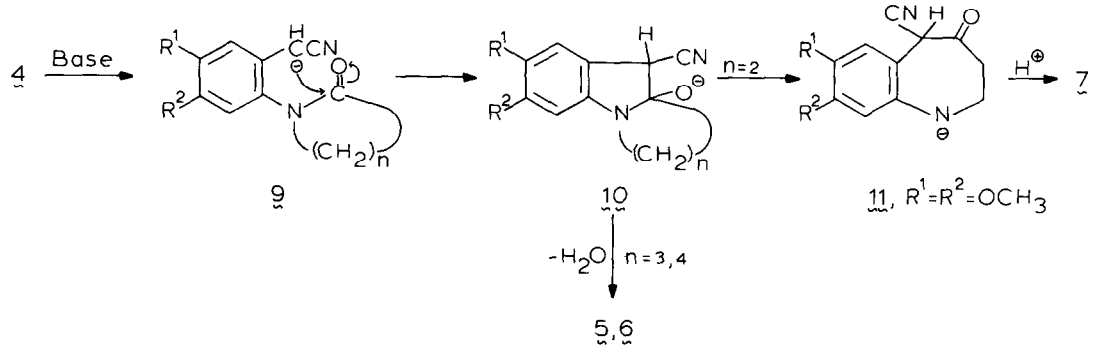
Table. Intramolecular cyclization of 4a-d,f.

Compd	R^1	R^2	Mp (°C)	Method A Time (h)	Method A Yield (%)	Method B Time (min)	Method B 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

[a] Only polymeric material was obtained. [b] Lit.[15] mp 203-203.5 °C.
[c] Lit.[16] mp 173-173.5 °C ; lit.[15] mp 174-174.5 °C.

Reaction of 4,5-dimethoxy-2-(2-oxo-1-azetidinyl)benzeneacetonitrile (4e) with KO*t*-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 159-165 °C; IR (KBr) 3290 (NH), 2700-2400 (OH), 2200 (CN) cm^{-1}; ^1H NMR (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, CH_2C=); ^{13}C NMR (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

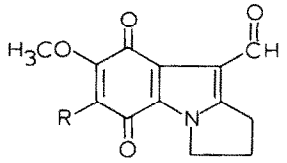


Scheme II

workup. In the case of KO*t*-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 Flitsch[18] 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 = CH_3
b, R = H

into the corresponding quinone 12a by nitration, reduction of the nitro group and subsequent oxidation of the resulting aniline derivative by Fremy's salt.[15] In a similar way we have modified compound 5d to the corresponding 2,3-dihydro-7-methoxy-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (12b) [mp 247-248 °C (ethanol); mass spectrum, *m/e* 245.069 (M^+, calcd, 245.069); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1 H, HC=O), 5.70 (s, 1 H, H-6), 4.4-4.15 (m, 2 H, NCH_2), 3.85 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) 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, OCH_3), 47.4 (t, NCH_2)].

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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6. For a review see: T. Kametani and K. Takahashi, *Heterocycles* 9, 293 (1978).
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.
8. V. Rousseau and H.G. Lindwall, *J. Am. Chem. Soc.* 72, 3047 (1950).
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10. Commercially available.
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.
13. M.S. Manhas and S.J. Jeng, *J. Org. Chem.* 32, 1246 (1967).
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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17. Compound 7 could not be recrystallized, therefore no satisfactory elemental analysis was obtained.
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