FORMATION OF [7](2,6)PYRIDINOPHANES BY RING ENLARGEMENT OF A PYRIDO[1,2-*a*]AZEPINONE [1, #]

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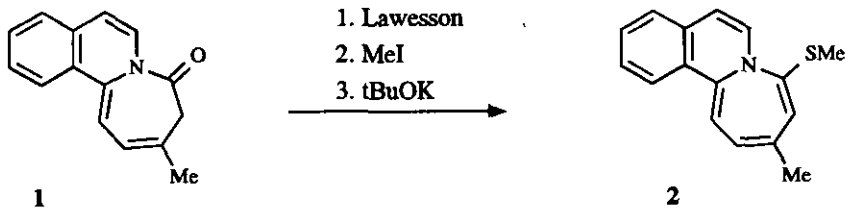
Abstract - Pyrido[1,2-*a*]azepinone (**4**) is deprotonated from the pyridine unit by lithium diisopropylamide affording lithium salt (**7**), which is trapped by electrophiles like D_2O, benzoyl chloride and aldehydes. In the latter case subsequent intramolecular attack of the intermediate alkoxide to the lactam moiety leads to [7](2,6]pyridinophanes (**9a,b**). On reaction of **4** with the lithium-free phosphazene base **tBu-P5** deprotonation takes place at the α–carbonyl position of the azepinone ring affording the enolate (**6**).

Recently we reported on the isolation of the 1,2-naphtho annulated azepine (**2**), which is the first derivative of the potential antiaromatic pyrido[1,2-*a*]azepine system.[2] The synthesis was performed by a route which involves sequential transformation of the naphthoazepinone (**1**) into the corresponding thiolactam, formation of the methylsulfonium salt and subsequent proton elimination.

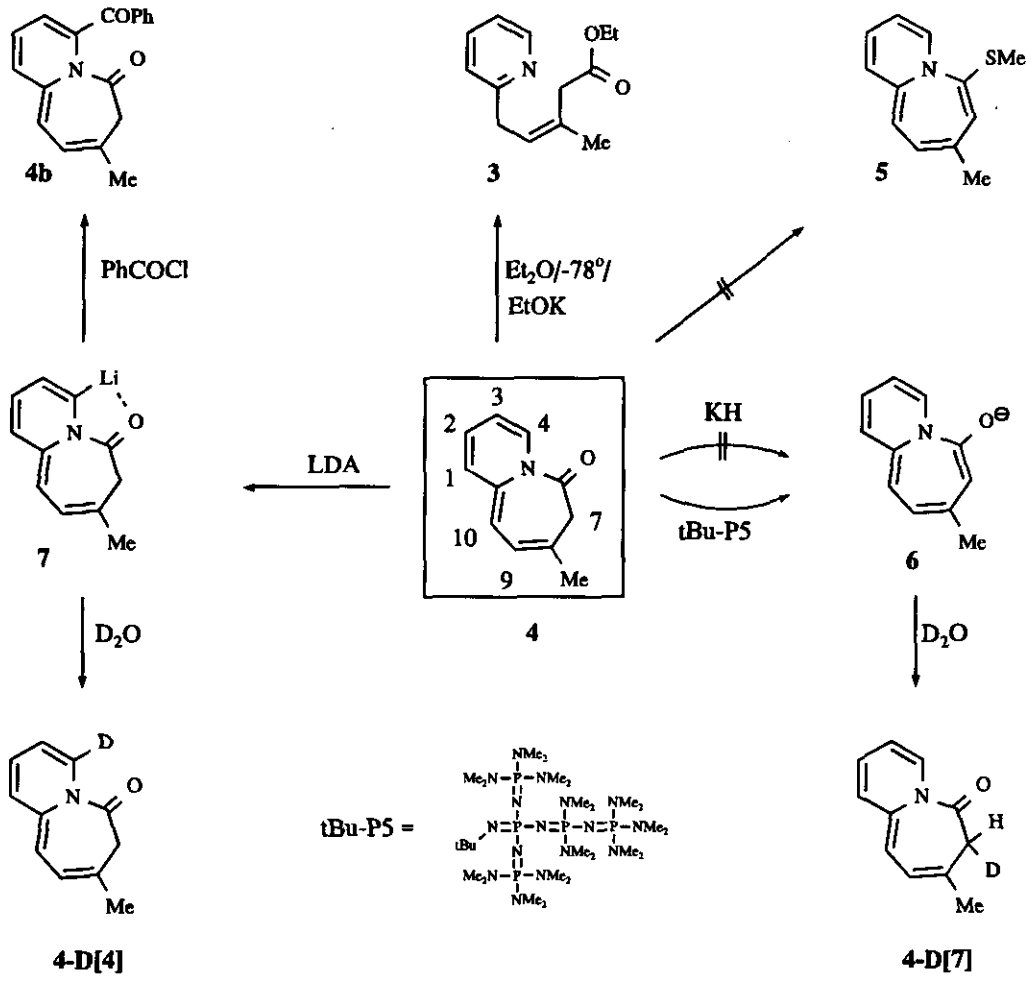


1 **2**

All attempts to apply the same procedure to the preparation of the 12π, non-annulated pyrido[1,2-*a*]azepine (**5**) failed due to the surprisingly facile cleavage of the lactam bond of **4** affording pyridine derivatives; e.g. with C_2H_5OH as reagent and catalytic amount of *p*-TosOH the ethyl pyridyl-pentenecarboxylate (**3**) is readily formed at 20°C.[2,3]

Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.

With regard to enolization experiments with monocyclic 2-[5] and 3-azepinones,[6] respectively, which likewise show a strong resistance against formation of the cyclic conjugated, antiaromatic 8π-systems, we investigated the behaviour of **4** against bases in some detail with the special aim to trap the enolate (**6**).

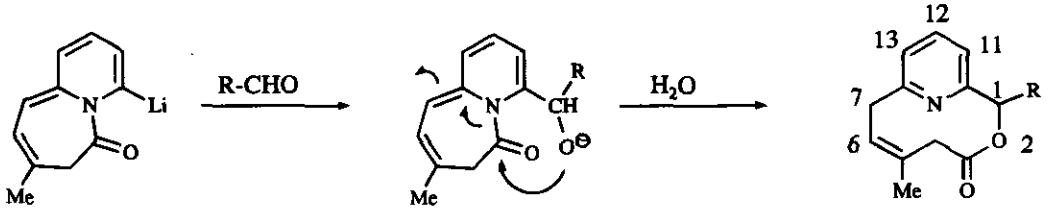


It turned out that treatment of an ether suspension of **4** with KH[7] at varying temperatures (-78 to +20°C) was ineffective; after quenching with D_2O the starting material was reisolated with no deuterium incorporation at all. On the other hand, using potassium ethoxide in ether at room temperature (5 min) or even at -78°C (45 min), a clean reaction took place to afford the carboxylic ester (**3**), which was identical with the product obtained by acid catalysed ethanol addition at room temperature.[2] Obviously the nucleophilic attack to the carbonyl group followed by rearomatization of the pyridine ring is again the dominating process.

Therefore lithium diisopropylamide as a strong and less nucleophilic base was used. On reaction with **4** at -78°C the tetrahydrofuran solution immediately turned deeply red. After addition of D_2O and workup the pyridoazepinone (**4-D[4]**) was isolated as single monomeric product in 51% yield, which unexpectedly showed almost quantitative uptake of deuterium at C-4 of the six membered ring; however, no H/D-exchange at the α-carbonyl position (C-7) has occurred! This result can be explained partly by the above mentioned reduced acidity of the methylene protons, partly on the basis of the "*complex induced proximity*" (*CIP*) effect[8] which facilitates the metalation at the vinyl position by coordination of the lithium with the carbonyl oxygen[9] (see structure **7**). Indeed, when the azepinone (**4**) reacted with the very strong, lithium-free phosphazene base **tBu-P5**[10] and subsequently was treated with D_2O, deuterium labelling was exclusively observed at C-7 (ca. 80%; see structure **4-D[7]**); careful ^{1}H-nmr analysis revealed no indications for an exchange at C-4. Interestingly, the occurrence of a different anionic species after addition of **tBu-P5** was indicated by a green color of the solution in this case. Quenching of the enolate (**6**) with triisopropylsilyl chloride (TIPS-Cl) resulted in the formation of a very unstable compound which could not be isolated in pure form; on the basis of the ^{1}H-nmr spectral data the structure of the corresponding silyl enol ether was proposed.[1]

While experiments towards functionalization of the C-4 lithiated derivative (**7**) using TMS-Cl or methyl iodide as electrophiles were unsuccessful because of their low reactivity at -78°C (at higher temperature the lithium compound is not stable any more), reaction with benzoyl chloride afforded the 4-benzoyl derivative (**4b**) as the only monomeric product (21% after repeated chromatographic purification).

By taking advantage of both the *CIP* effect and the unusual high reactivity of the lactam bond of the benzoazepinone (**4**) a novel synthesis of [2,6]pyridinophanes using a domino route has been uncovered.



7 **8** **9a** (R = Ph)
9b (R = Me)

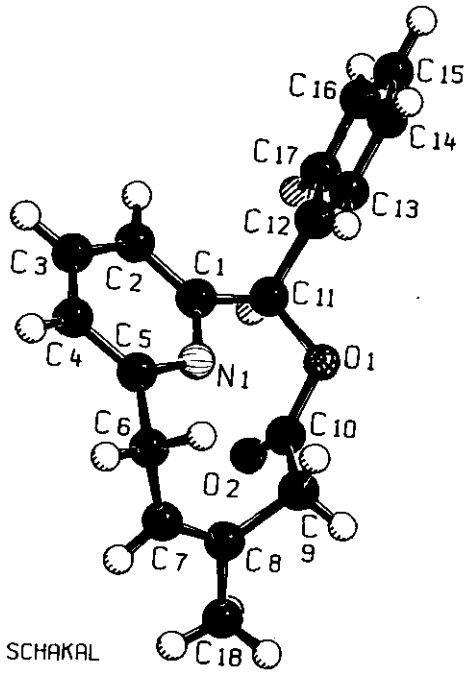
The procedure consists of the reaction of the lithiated compound **7** with an aldehyde affording the alkoxide (**8**), which subsequently undergoes intramolecular nucleophilic bond cleavage to give heterocyclophanes (**9**). With

benzaldehyde and acetaldehyde, respectively, the [7](2,6)pyridinophanes (**9a**) and (**9b**) were obtained in about 50% yield.

The phane structure of the products is clearly confirmed by the ^{1}H-nmr spectra in which the presence of the aromatic pyridine nucleus is shown by signals between 6.8 and 7.5 ppm (see experimental part). Furthermore, the absorptions of four methylene protons, but for only one olefinic hydrogen correspond with the newly developed bridge. As indicated by the coupling constants of the methylene protons (13.5/15 Hz for $J_{4a,4b}$ and $J_{7a,7b}$, respectively) conformational changes of the bridge must be fast.

In addition to the spectroscopic data a crystal structure analysis has been performed with the phenyl derivative **9a**[11] (see Table).

Table. Selected X-ray crystallographic data for **9a** (atom numbers are related to the SCHAKAL drawing)



bond distances [Å]			
C1-C11	1.522(2)	C11-O1	1.462(1)
O1-C10	1.367(1)	C10-C9	1.511(2)
C9-C8	1.515(2)	C8-C7	1.332(2)
C7-C6	1.510(3)	C6-C5	1.513(2)
intramolecular distances [Å]			
N1-O1	2.451(1)	N1-C10	2.386(2)
N1-C9	2.761(2)	N1-C8	3.040(2)
bond angles [°]			
N1-C1-C11	112.9(1)	C2-C1-C11	125.3(1)
C9-C8-C18	114.3(2)	C7-C8-C9	125.5(2)
N1-C5-C6	111.8(1)	C4-C5-C6	128.1(2)
O1-C10-C9	115.3(1)	C6-C7-C8	130.9(2)
torsion angles [°]			
C6-C7-C8-C9	-0.5(0.2)	C6-C7-C8-C18	-179.6(0.4)

cell constants: a = 10.096 (2)Å, b = 10.399 (2)Å, c = 8.121 (3)Å, α = 111.07 (2)°, β = 96.29 (1)°, γ =70.56 (2)°, V=751.1 (4)Å^3, crystal system: triclinic, P-$\bar{1}$(N2), molecules per unit cell: Z = 2, R = 0.045, Rw = 0.038, total reflections 4808, observed reflections 3157 (I>2σ(I)), number of parameters 258.

It is shown by the data that the double bond is not twisted and that the angles around both the double bond (C6-C7-C8/C7-C8-C9 = 131°/125.5°) and the bridgehead positions (C4-C5-C6/C2-C1-C11 = 128°/125°) are significantly larger than 120°; the distance between the α-carbonyl carbon and the pyridine nitrogen amounts to 2.76 Å. In contrast to the suggestion in case of the saturated [7](2,6)pyridinophane[12] the pyridine ring of **9a** is planar.

The ring enlargement of *pyrido*[1,2-*a*]*azepinones* is an attractive alternative to other syntheses of pyridinophanes,[13] a class of naturally occurring compounds with muscopyridine as a particularly prominent representative.[14] Although the preparation of [6](2,6)pyridinophane (the member with the shortest bridge so far) has been successfully accomplished[14] the double bond of **9a,b** is a rather unusual structural element within this class.

From a different point of view the lactam unit of the bicyclic system (**4**) can be regarded as an acyl transfer reagent.[15] Further applications of this methodology are in progress.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-Nmr spectra were recorded on Bruker WM 250 (250 MHz) and Bruker AM 400 (400 MHz), with tetramethylsilane as internal standard. Ir spectra were measured on a Perkin Elmer 457 infracord. Ms were taken with a Finnigan MAT 44S spectrometer. X-ray crystallographic data were performed on a Enraf-Nonius CAD-4 diffractometer. The structure was calculated with a MOLen program. All reactions were performed in anhydrous solvents under nitrogen atmosphere.

Treatment of 4 with potassium ethanolate

A slurry of 173 mg (1 mmol) of **4** and 340 mg of a 35% oil-suspension of potassium hydride (3 mmol) in 30 ml of Et_2O was cooled to -78°C and treated dropwise with ethanol until complete consumption of KH. After 45 min 20 ml of water were added and the reaction mixture was allowed to warm up to room temp. Ether extraction and removal of the solvent *in vacuo* gave an oily residue which was submitted to silica gel column chromatography with ethyl acetate/cyclohexane (1:1). The main fraction contained 191 mg (87%) of the known (Z)-ethyl 3-methyl-5-(2'pyridyl)pent-3-enecarboxylate (**3**).[2]

^{1}H-Nmr($CDCl_3$) δ 8.51 (m, 6'-H), 7.60 (m, 4'-H), 7.18 (m, 3'-H), 7.10 (m, 5'-H), 5.68 (t, J = 7 Hz, 4-H [*NOE* on 3-CH_3]), 4.14 (q, 2 H, J = 7.5 Hz, $OC\underline{H}_2CH_3$), 3.60 (d, 2 H, J = 7 Hz, 5-H [*NOE* on 2-H]), 3.17 (s, 2 H, 2-H [*NOE* on 5-H]), 1.84 (s, 3 H, 3-CH_3 [*NOE* on 4-H]), 1.26 (t, 3 H, J = 7.5, $OCH_2C\underline{H}_3$).

7-Deutero-8-methylpyrido[1,2-*a*]azepin-6(7*H*)-one (4-D[7])

The yellow solution of 87 mg (0.5 mmol) of **4** in 10 ml of anhydrous THF was added to the phosphazene base **tBu-P5**[10] in 10 ml of THF; the color of the solution immediately turned to green. After 15 min 1 ml of D_2O was added, and the yellow color of the azepinone reappeared. The solution was allowed to warm to room temperature, then water was added. After ether extraction the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel with cyclohexane/ethyl acetate (10:1) gave 63 mg (74%) of the azepinones **4/4-D(7)**. ^{1}H-Nmr analysis of the mixture showed exclusive H/D-exchange at position 7 (deuteration grade >80%).

^{1}H-Nmr($CDCl_3$) δ 7.90 (d, $J_{3,4}$ = 7.5 Hz, 4-H), 6.66 (d, $J_{1,2}$ = 9.0 Hz, 1-H), 6.25 (dd, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 6.0 Hz, 2-H), 6.09 (m, 9-H), 5.90 (m, 3-H), 5.81 (d, $J_{9,10}$ = 5.5 Hz, 10-H), 2.55 (br, 1 H, 7-CDH), 2.04 (3 H, CH_3).

4-Deutero-8-methylpyrido[1,2-*a*]azepin-6(7*H*)-one (4-D[4])

The yellow solution of 87 mg (0.5 mmol) of **4** in 10 ml of anhydrous Et_2O was added at -78 °C to LDA (0.55 mmol) in 10 ml of Et_2O; an immediate color change to red occurred. After 15 min 1 ml of D_2O was added and reaction mixture was worked up as described above to afford 45 mg (51 %) of the azepinones **4/4-D(4)**. ^{1}H-Nmr analysis of the mixture showed exclusive H/D-exchange at position 4 (deuteration grade >90%).

^{1}H-Nmr(250MHz; $CDCl_3$) δ 6.66 (d, $J_{1,2}$ = 9.0 Hz, 1-H), 6.25 (dd, $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 6.0 Hz, 2-H), 6.09 (m, 9-H), 5.90 (br m, $J_{2,3}$ = 6.0 Hz, 3-H), 5.81 (d, $J_{9,10}$ = 5.5 Hz, 10-H), 2.59 (br, 2 H, 7-H), 2.04 (3 H, CH_3).

4-Benzoyl-8-methylpyrido[1,2-*a*]azepin-6(7*H*)-one (4b)

The solution of 4-lithio-8-methylpyrido[1,2-*a*]azepin-6(7*H*)-one 7 [generated as described above from 173 mg (1 mmol) of **4** and LDA (1.1 mmol)] in 20 ml of ether was treated at -78 °C with a solution of 210 mg (1.5 mmol) of benzoyl chloride in 10 ml of ether and stirred for 1h at the same temperature. After addition of 20 ml of water the mixture was allowed to warm up to room temperature. Ether extraction and concentration of the dried organic layers ($MgSO_4$) afforded a yellow residue, which was purified by repeated flash chromatography on silica gel with cyclohexane/ethyl acetate (3:1) to afford 58 mg (21%) of **4b**.

Ir (CCl_4) 1675, 1655 cm^{-1} (CO, NCO); ^{1}H-nmr ($CDCl_3$) δ 7.76 (m, 2 phenyl-H), 7.33-7.45 (m, 3 phenyl-H), 6.73 (d, $J_{1,2}$ = 9 Hz, 1-H), 6.43 (m, $J_{2,3}$ = 6 Hz, 3-H), 6.33 (dd, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 6 Hz, 2-H), 6.13 (m, $J_{9,10}$ = 5.5 Hz, 9-H), 6.09 (d, $J_{9,10}$ = 5.5 Hz, 10-H), 2.58 (br, 2 H, 7-CH_2), 1.80 (3 H, CH_3); Hrms m/z: calcd for $C_{18}H_{15}NO_2$ (M^+): 277.1103. Found: 277.1101.

5-Methyl-1-phenyl-2-oxa-[7](2,6)pyridinophane-5(Z)-en-3-one (9a) and **1,5-dimethyl-2-oxa-[7](2,6)pyridinophane-5(Z)-en-3-one (9b)**

The solution of 4-lithio-8-methylpyrido[1,2-*a*]azepin-6(7*H*)-one 7 [generated as described above from 173 mg (1 mmol) of **4** and LDA (1.1 mmol)] in 20 ml of ether was treated at -78°C with solutions of aldehydes [160 mg (1.5 mmol) of benzaldehyde and 66 mg (1.5 mmol) of acetaldehyde, respectively] in 10 ml of ether and stirred for 1h at the same temperature. After addition of 20 ml of water the mixture was allowed to warm up to room temperature. Ether extraction and concentration of the dried organic layers ($MgSO_4$) afforded **9a,b**, which were purified by flash chromatography on silica gel with cyclohexane/ethyl acetate (1:1) and crystallization.

(9a): 128 mg (46%); colorless prisms, mp 93°C (Et_2O/hexane); ir (CCl_4) 1730 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) δ 7.38-7.50 (m, 6 H, 5 phenyl-H, 12-H), 7.02 (s, 1-H), 6.99, 6.75 (2 H, 11-H, 13-H), 5.78 (m, 6-H), 4.03 (d, $J_{4a,4b}$ = 13.5 Hz, 4a-H), 3.64 (m, 7a-H), 3.30 (dd, $J_{7a,7b}$ = 15 Hz, $J_{7b,6}$ = 9 Hz, 7b-H), 3.08 (d, $J_{4a,4b}$ = 13.5 Hz, 4b-H), 2.14 (m, 3 H, CH_3); EIms: *m/z* 279 (76 %, M^+), 234 (100 %, M^+-COOH). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 76.87; H, 6.15; N, 4.97.

(9b): 98 mg (45%); colorless prisms, mp 103°C (Et_2O/hexane); ir (CCl_4) 1720 cm^{-1} (C=O); ^{1}H-nmr ($CDCl_3$) δ 7.56 (m, 12-H), 7.00 (m, 2 H, 11-H, 13-H), 6.21 (q, J_{1,CH_3} = 7 Hz, 1-H), 5.73 (m, 6-H), 3.84 (d, $J_{4a,4b}$ = 13.5 Hz, 4a-H), 3.57 (m, 7a-H), 3.27 (dd, $J_{7a,7b}$ = 15 Hz, $J_{7b,6}$ = 9 Hz, 7b-H), 3.02 (d, $J_{4a,4b}$ = 13.5 Hz, 4b-H), 2.11 (3 H, 5-CH_3), 1.71 (d, 3 H, J_{1,CH_3} = 7 Hz, 1-CH_3). Anal. Calcd for $C_{13}H_{15}NO_2$ (217.3): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.44; H, 7.02; N 6.34.

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