Tetrahedron Letters No. 24, pp 2287 - 2290. 0040-4039/79/0608-2287$02.00/0

AZEPINES.I : THE FORMATION AND REACTIVITY OF THE ANION OF 2-DIETHYLAMINO-5-PHENYL-3H-AZEPINE

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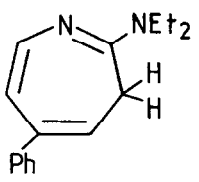
Summary: Deprotonation of 2-diethylamino-5-phenyl-3H-azepine with strong bases affords a highly coloured anion, which reacts with deuterium oxide or with an appropriate electrophile to give an azepine bearing the new substituent at C-3.

During the last decades several papers have appeared dealing with anions of seven-membered ring systems, e.g. of cycloheptatrienes[1] and of 1,2-diazepines[2,3]. These negatively charged 8π-systems are antiaromatic. Since to our knowledge no work has been carried out with the anions, derived from azepines, we started a study on the formation of the anion of 2-diethylamino-5-phenyl-3H-azepine (1) and on its reactivity towards electrophiles.

On addition of a solution of 1 in 1,2-dimethoxyethane to a solution of 4 eq. of lithium diisopropylamide (Li-DIA) in ether at room temperature under nitrogen an intensive blackviolet coloured solution was obtained. When this solution was quenched with water 1 was regained, but treatment with D_2O gave 3 with 75% deuterium incorporation at position 3 (3, X=D). The results indicate that Li-DIA is able to deprotonate 1 into the cyclic 8π-system 2.



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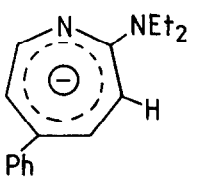

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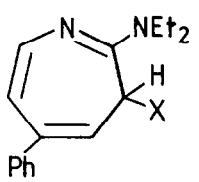

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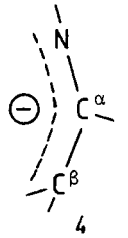

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When 2 was generated as described before and then methyl iodide was added 3 (X=Me) was obtained in a reasonable yield (see Table 1). This convenient one-step conversion of 1 into the 3-methyl derivative (3, X=Me) via the intermediary existence of 2 prompted us to investigate the generality of this reaction, providing a useful entry into 3-substituted 3H-azepines. It was found that reaction of 2 with dimethyl disulfide gave 3 (X=SMe) and that with benzyl bromide, compound 3 ($X=CH_2C_6H_5$) was formed. Quite similar results were obtained when potassium amide in liquid ammonia instead of Li-DIA was used as reagent fot the deprotonation of 1. In all the above-mentioned reactions no indication was found for N-alkylation. This is in agreement with results obtained on alkylation of aldimine anions (4), showing that in these systems alkylation takes

place only at C-β and not at the nitrogen[4]. Similar results were recently obtained with the anion of 1,2-4H-diazepines[3].

Table 1. 3-X-2-diethylamino-5-phenyl-3H-azepines (3)[a]

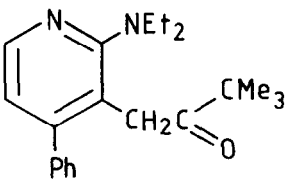
Product	Yield	M.p.(solvent)	^{1}H-NMR data ($CDCl_3$) ; δ (ppm)[b]				
			H(C-3)	H(C-4)	H(C-6)	H(C-7)	X
X=CH_3	60-65%	88.5-89.5°/C (ethanol)	4.22(m)	5.36(d)	5.84(d)	7.30(m)[c]	0.81(d)
X=SCH_3	60-65%	109.5-110.5°/C (aq.ethanol)	5.21(d)	5.46(d)	5.97(d)	7.30(m)[c]	2.07(s)
X=$CH_2C_6H_5$	60-65%	124-125°/C (ethanol)	4.22(m)	5.20(d)	5.90(d)	7.10-7.30(m)[c]	2.45(d)

a) All compounds have a satisfactory microanalysis (C ± 0.3, H ± 0.2).

b) All compounds show the CH_3-triplet signal and the CH_2-quartet signal of the diethylamino group around 0.99-1.17 and 3.18-3.41 resp. The protons of the phenyl group lie between 7.10 and 7.30(m).

c) This is partly overlapped by the phenyl protons.

When to the solution of 2, prepared from 1 and 2 eq. of Li-DIA, methyl pivalate was added not the expected 3H-azepine 3 (X=COC$(CH_3)_3$) but the pyridine derivative 5 was obtained. The presence of the pyridine ring was indicated by the two low field doublets at δ = 6.77 and 8.21 (H(C-5) and H(C-6) resp.) and the presence of a methylene group at δ = 3.85 (s,2H,CH_2CO). We suppose that in this ring contraction 3 (X=COC$(CH_3)_3$) is probably an intermediate. This should be in agreement with the reported ring contraction of 3H-azepines, containing at C-3 the C(=O)-R (R=OMe,C_6H_5) group, into 3-(CH_2-C(=O)-R) pyridines[5,6]. When instead of methyl pivalate ethyl trifluoroacetate was added, ring contraction also occurred, leading to the pyridine derivative 6. The presence of the enol side-chain was strongly indicated by the absence of the C=O stretching vibration and the presence of an OH-absorption in the NMR spectrum (δ = 14.90). Addition of D_2O immediately led to disappearance of this signal and that of δ = 5.81 (CH=) (see Table 2).



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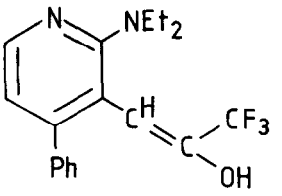

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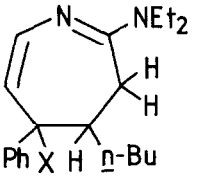

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Table 2. 3-X-2-diethylamino-4-phenylpyridines (5) and (6)[a]

Product	Yield	M.p.	^{1}H-NMR data ;δ(ppm)[b]		
			H(C-5)	H(C-6)	X
5[c]	40%	oil, picrate 143.5-144.5 and 155-156°/C	6.77(d)	8.21(d)	3.85(s) 0.99(t)
6[d]	40%	55-57°/C	7.13(d)	8.37(d)	5.81(s) 14.90(s)

a) These components have a satisfactory microanalysis (C ± 0.3, H ± 0.2).

b) These components show the CH_3-triplet and the CH_2-quartet signal of the diethylamino group around 0.99-1.10 and 3.03-3.30 resp. The protons of the phenyl group lie between 7.20-7.38.

c) measured in $CHCl_3$-CCl_4(1:1).

d) measured in acetone-d_6.

When reacting 1 in THF with 4 eq. of n-BuLi/t-BuOK at -70°C and quenching the solution with ethanol, besides 1 (15%) a compound was isolated (about 45%) to which structure 7 (X=H) was assigned, based on physical (NMR and IR) and microanalytical data. When the reaction mixture was quenched with deuterated methanol (CH_3OD) 3 (X=D,94%) and 7 (X=D,94%) were formed. It is evident that by this reagent besides deprotonation of 1 into 2, addition across the (C-4)-(C-5) double bond occurs. This addition across the C=C bond is quite different from the one of n-BuLi across the C=N bond in 1,2-4H-diazepines[2].

The investigation will be continued.

Acknowledgement

The authors are indebted to Drs.C.A.Landheer and to Mr.W.C.Combé for mass spectrometrical data, to Mr.H.Jongejan for carrying out the microanalyses and to Dr.P.Smit and Mr.A.van Veldhuizen for advice on ^{1}H-NMR analyses.

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(Received in UK 3 April 1979)