A NEW REARRANGEMENT IN THE METHYLATION OF 2-(DIETHYLAMINO)-3-(ETHOXYCARBONYL)-5-PHENYLAZEPINYL ANION[1]

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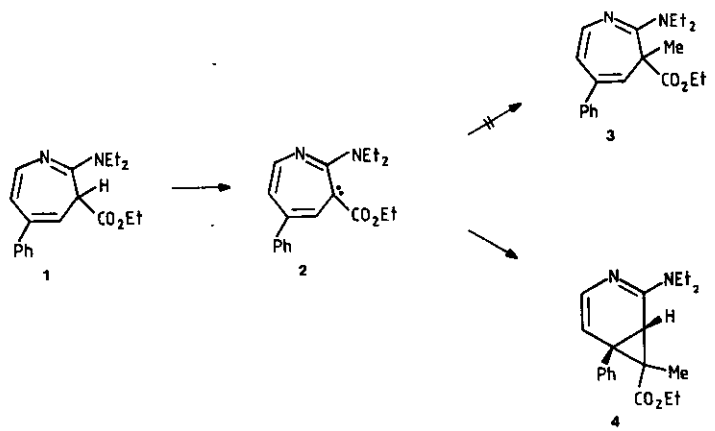
Abstract - Treatment of the anion of 2-(diethylamino)-3-(ethoxycarbonyl)-5-phenyl-3H-azepine with methyl iodide leads to the formation of 2-(diethylamino)-7-(ethoxycarbonyl)-7-methyl-3,4-dihydro-3,4-methano-4-phenylpyridine, the structure of which was confirmed by an X-ray analysis of its picrate. The mechanism of this rearrangement reaction will be discussed.

Our general interest in the reactivity of azepinyl anions induced us to investigate the behaviour of anion **2**, obtained from 2-(diethylamino)-3-(ethoxycarbonyl)-5-phenyl-3H-azepine (**1**) by treatment with lithium 2,2,6,6-tetramethylpiperidide in THF, towards alkylating agents.

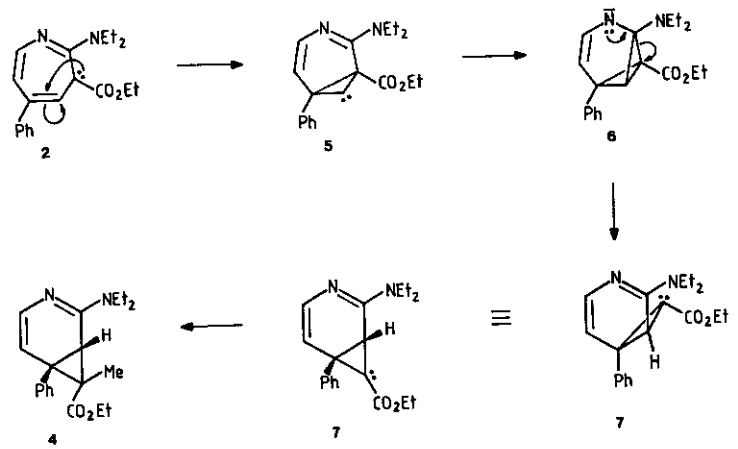
In this paper we wanted to publish a new rearrangement reaction, which took place on reacting **2** with methyl iodide. In this reaction a product was isolated (50% yield), which according to mass spectrometric data and microanalysis of its picrate showed to have the empirical formula $C_{20}H_{26}N_2O_2$, indicating that a methyl group has been introduced into **2**. ^1H- and ^{13}C-NMR data gave clear indications that this product is not the 3-methylazepinyl derivative **3**, as evidenced by the absence of the characteristic chemical shift of H-4 of the azepine ring around 5.3-5.5 ppm as well as the absence of the C-4 doublet around 108-113 ppm (J = 150-165 cps) and the C-2 singlet at 140-150 ppm in the proton-coupled ^{13}C-spectrum.[3] Instead, the ^1H-NMR spectrum features among other peaks an absorption at 3.33 ppm and the ^{13}C-spectrum shows a singlet at 45.3 ppm and a doublet at 30.2 ppm. These NMR data seem to suggest that we deal here with a valence tautomer of **3**, probably an azanorcaradiene, containing the pyridine ring, fused with a three-membered carbocycle. In order to establish the structure of this valence isomer more firmly we carried out an X-ray analysis. From this analysis it became evident that this compound is indeed an azanorcaradiene, i.e. 2-(diethylamino-)-7-(ethoxycarbonyl)-7-methyl-3,4-dihydro-3,4-methano-4-phenylpyridine (**4**). The formation of **4** from **2** indicates that during treatment of **2** with methyl

iodide a new rearrangement has taken place. This unexpected result induced us to investigate whether the structure of our starting material 1 was correct: an X-ray analysis confirmed its structure.[4]



Scheme 1

The formation of **4** from 1 can be explained if one assumes that two sequential 1,2-carbanionic shifts occur: the first 1,2-carbanion shift, possibly occurring pericyclicly converts anion **2** into 5, followed by a second shift converting 5 into 7, probably via **6**. Methylation of **7** yields **4**.



Scheme 2

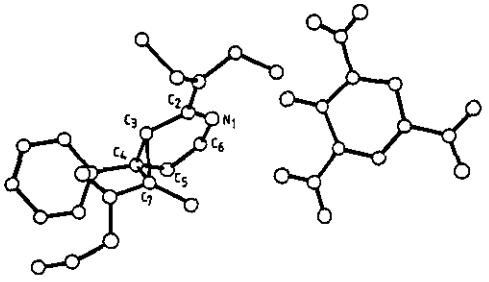
This result seems to indicate that probably the bicyclic system 7 is an intermediate in the formation of 3-alkoxy(or alkyl)carbonylmethylenepyridines from 3-alkoxy(or alkyl)carbonyl-3H-azepines under basic conditions.[5,6]

Crystallographic Determination of Structure 4

The reflections were collected on a Syntex $P2_1$ diffractometer using graphite-monochromatized moKα radiation (λ = 0.7107 Å) and the ω scan technique up to 2θ = 47°. The structures were solved by direct methods using the MULTAN 80[7] computer system and refined by the SHELX 76[8] programme. Coordinates and molecular dimensions are available from the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

Crystal Data of the Picrate of 4

$C_{20}H_{26}N_2O_2 \cdot C_6H_3N_3O_7$, triclinic, space group $P\bar{1}$; cell dimensions a = 7.705(2), b = 11.596(4), c = 16.538(7)Å, α = 104.95(3), β = 101.68(3), γ = 93.21(2)°; V = 1388.9(9)Å^3; Z = 2. 4091 measured and 1446 observed reflections. Final R: 0.113.



EXPERIMENTAL

Preparation of 4

All glasware used was dried at 100-140°C prior to use. The experiment was performed under nitrogen. 2,2,6,6-Tetramethylpiperidine (TMP, Aldrich) was stored over molecular sieves (A4) previously dried at 300°C. Tetrahydrofuran (25 mL) was distilled from calcium hydride under nitrogen into a 250 mL three-necked flask containing 1 (1.26 mmol, 0.394 g). The flask was placed in a bath at 20°C and TMP (0.5 mL, 0.42 g, 3.0 mmol) was added using a syringe. After 5 min. stirring 1.32 M n-butyllithium in hexane (1 mL, 1.3 mmol), was added, again using a syringe. A black-violet colour was formed; After 30 min. 2 mL of methyl iodide was added at once. After 180 min. at 20°C ethanol was added, the solvent was evaporated off and the product was isolated in

50-60% yield by preparative TLC (silica gel/petroleumether (60/80°C)-ethyl acetate-methanol (ratio 10:9:1, R_F = 0.37).

4, oil; ir (chloroform): 1725 cm^{-1} (C = O); ^1H NMR (deuteriochloroform): δ 7.18 (s, 5H, Ph); 6.62 (d, $J_{5,6}$ = 6.9 Hz, 1H, H-6); 5.02 (d, $J_{5,6}$ = 6.9 Hz, $J_{3,5}$ = 0.7 Hz, 1H, H-5); 3.95-3.30 (m, 6H, CH_2); 3.33 (s, $J_{3,5}$ = 0.7 Hz, 1H, H-3); 1.30-0.80 (m, 12H, CH_3); ^{13}C NMR (deuteriochloroform): δ 172.9 (C = O); 157.2 (C-2); 141.6 (C-Ph_1); 136.1 (J = 174 Hz, C-6); 128.2, 128.2, 126.9 (C-$Ph_{o.m.p.}$); 105.5 (J = 168 Hz, C-5); 60.9 (OCH_2); 45.3 (C-4); 42.3 (NCH_2); 30.2 (J = 165 Hz, C-3); 24.1 (C-7); 13.8, 10.7 (CH_3); ms: accurate mass theor. 326.1994 for $C_{20}H_{26}N_2O_2$; exp. 326.1991.

Picrate, mp 138.0-139.5°C (ethanol, -30°C); ^1H NMR (acetone-d_6): δ 8.70 (s, 2H, H-Ph picric acid); 7.35 (s, 5H, H-Ph); 6.58 (d, $J_{5,6}$ = 7.8 Hz, 1H, H-6); 5.60 (d, $J_{5,6}$ = 7.8 Hz, $J_{3,5}$ = 0.9 Hz, 1H, H-5); 4.15-3.75 (m, 6H, CH_2); 3.78 (s, $J_{3,5}$ = 0.9 Hz, 1H, H-3); 1.57-1.23 (m, 9H, CH_3); 0.93 (t, 1H, CH_3).

Anal. Calcd. for $C_{20}H_{26}N_2O_2.C_6H_3N_3O_7$: C, 56.21; H, 5.26. Found: C, 56.04; H, 4.98.

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REFERENCES AND NOTES

1. Part 5 on azepines from this laboratory. See for part 4 ref. 2.
2. J.W. Streef and H.C. van der Plas, Heterocycles, 1985, **23**, 2715.
3. J.W. Streef, H.C. van der Plas, A. van Veldhuizen and K. Goubitz, Recl. Trav. Chim. Pays-Baa, 1984, **103**, 225.
4. C.H. Stam, unpublished results.
5. M. Anderson and A.W. Johnson, J. Chem. Soc.(C), 1966, 1075.
6. J.W. Streef and H.C. van der Plas, Tetrahedron Lett., 1979, **20**, 2287.
7. P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq and M.M. Woolfson, 1980, MULTAN 80. A System of Computer Programmes for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data. Universities of York (England) and Louvain-la-Neuve (Belgium).
8. G.M. Sheldrick, 1976, SHELX 76. Program for Crystal Structure Determination. University of Cambridge, England.

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