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REARRANGEMENT OF THE CYANOMETHYL GROUP IN CYCLOAMMONIUM ZWITTERIONS GENERATED FROM SPIRO-4-CYANOMETHYL-3-METHYL-1,2,3,4,5,6-HEXAHYDROBENZO[*f*]ISOQUINOLINIUM-1,2'-(1',2',3',4'-TETRAHYDRONAPHTHALEN-1'-ONE) CHLORIDE

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Keywords: spiro-4-cyanomethyl-3-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinolinium-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) chloride, intramolecular electrophilic transcyanomethylation, [1,2]- and [1,4]-sigmatropic shifts.

In the presence of sodium hydride the 4-aryl-1-methyl-1-ethoxycarbonylmethyl-1,2,3,6-tetrahydropyridine halide [1] and N-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinolinium alkyl halide [2] quaternary salts give exocyclic ylides which are converted *in situ* with contraction of the six membered heterocycle to a pyrrole [1], with expansion to a tetrahydro-1H-3-benzazepine [1, 2], or with Hofmann fission [2]. In this work we have studied the reaction of the more complex substrate **1** which also contains 4-aryltetrahydropyridine and hexahydroisoquinoline fragments. It was assumed that the cyano group would stabilize the exocyclic anhydrobase in the same way and the reaction would proceed by the route indicated above (besides Hofmann β-elimination). However, the reaction of quaternary salt **1** under similar conditions did not give the expected transformation of the piperidine ring. Chromatography of the reaction mixture gave the two isomeric reaction products **2** and **3** in 18.7 and 6.5% yields respectively. Their structures were unambiguously proved by X-ray analysis and by ^{1}H NMR and chromato mass spectrometry. Evidently their formation must precede the endocyclic zwitterion **A** stabilized in two mesomeric forms. Localization of the negative charge on the C(4) atom (in the case of the cycloammonium ylide) leads to a [1,2]-sigmatropic shift of the cyanomethyl group. In the case of the cyclic 1,4-zwitterion a [1,4] rearrangement of the CH_2CN group occurs to the γ-position of the heterocycle with migration of the double bond to position C(4)–C(4a) to form compound **3**.

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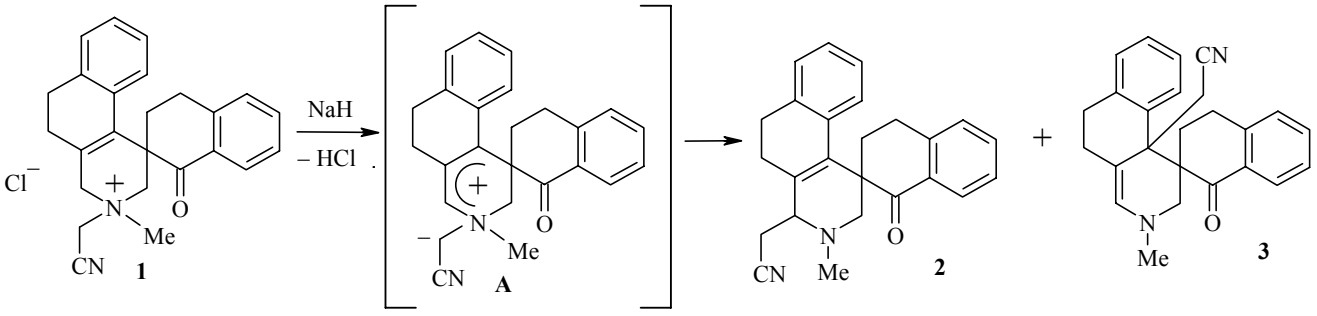

The observed change in the types of rearrangement processes for compound **1** (an intramolecular electrophilic transalkylation occurring in place of the expected recyclization) evidently relates to an increase in the stability of the tetrahydropyridine ring due to spiro conjugation. A detailed X-ray analysis of the molecular structure of substances **2** and **3** will be presented in a separate study.

The ^{1}H NMR spectra were recorded on a Bruker WP-400 (400 MHz) spectrometer using DMSO-d_6 (compound **1**) or $CDCl_3$ (compounds **2** and **3**) with the residual deuterated solvent protons as internal standard. IR Spectra were taken on an Infralum FT-801 spectrometer for KBr tablets. An Agilent 1100 liquid chromatograph with DAD, ELSD Sedex 75 detectors combined with an Agilent LC/MSD VL mass spectrometer with electrospray ionization was used to monitor the reaction mixtures and the purity of the separated compounds **2** and **3**. X-ray structural analysis of compounds **2** and **3** was carried out by a direct method on a Bruker SMART 1000 CCD diffractometer with MoKα radiation, graphite monochromator, and with θ- and ω-scanning. The starting spiro-3-methyl-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) was prepared by method [3].

Spiro-4-cyanomethyl-3-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinolinium-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) chloride (1). Chloroacetonitrile (1.36 g, 1.15 ml, 20 mmol) was added with stirring to a solution of spiro-3-methyl-1,2,3,4,5,6-hexahydrobenzo[f]isoquinoline-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) (3.0 g, 10 mmol) in dichloromethane (50 ml). The mixture was refluxed for 5 h under nitrogen. Hexane (100 ml) was added to the cooled mixture and the precipitate was separated, washed with ether, and dried in air to give beige crystals (2.73 g, 67%) of salt **1**; mp 174-175ºC. IR spectrum, ν, cm^{-1}: 2362 (C≡N), 1672 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03, 2.21, and 2.44 (each 1H, all m, C-CH_2); 2.65-3.27 (5H, m, C–CH_2); 3.52 (3H, s, NCH_3); 4.26 and 4.33 (each 1H, d, J = 10.8, NCH_2); 4.63 and 4.87 (each 1H, both d, J = 12.7, CH_2CN); 4.93 and 5.22 (each 1H, both d, J = 16.2, NCH_2); 6.63, 7.05, 7.15, and 7.24 (each 1H, ABCD system, ^3J = 7.7, 7.4, and 7.2, H arom.). 7.47, 7.53, 7.82, and 8.14 (each 1H, ABCD system, ^3J = 7.8, 7.6, and 7.1, H arom.). Mass spectrum, *m/z* (I_{rel}, %): (HPLC-MS, proton ionization): 369 $[M\text{-}Cl]^+$. Found, %: N 6.52; Cl 8.97. $C_{25}H_{25}ClN_2O$. Calculated, %: N 6.92; Cl 8.77. M 404.5.

Spiro-4-cyanomethyl-3-methyl-1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinoline-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) (2) and **Spiro-10b-cyanomethyl-3-methyl-1,2,3,5,6,10b-hexahydrobenzo[*f*]isoquinoline-1,2'-(1',2',3',4'-tetrahydronaphthalen-1'-one) (3)**. Sodium hydride (60% suspension in toluene, 0.36 g, 8.9 mmol) was added to a suspension of the quaternary salt **1** (3.0 g, 7.4 mmol) in absolute dioxane (50 ml) and the mixture obtained was refluxed for 3 h. Methanol (2 ml) was added to the mixture, solvent was distilled *in vacuo*, and the residue was treated with water (70 ml) and extracted with ether. The extract was dried over $MgSO_4$, solvent was evaporated, and the residue was chromatographed on silica using hexane-ethyl acetate with a gradient from 1:0 to 1:10. The 4-cyanomethyl derivative **2** (0.53 g, 19%) was eluted first followed by the 10b-cyanomethyl derivative **3** (0.19 g, 6.5%).

Compound 2. Light-beige crystals; mp 148-150ºC. IR spectrum, ν, cm^{-1}: 2246 (C≡N), 1692 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83, 2.20, and 2.45 (each 1H, all m, C–CH_2); 2.48 (3H, s, NCH_3); 2.72 (5H, m,

C–CH_2); 2.93 and 3.20 (each 1H, both d, J = 12.0, N–CH_2); 2.98 and 3.15 (each 1H, both m, C–CH_2); 3.38 (1H, t, J = 3.6, H-4); 6.74, 6.99, 7.05, and 7.15 (each 1H, ABCD system, ^3J = 8.0, 7.6, and 6.8, H arom); 7.30, 7.40, 7.55, and 8.23 (each 1H, ABCD system, ^3J = 8.0 and 7.7, H arom). Mass spectrum, *m/z* (HPLC-MS, proton ionization): 369 $[M+H]^+$. Found, %: C 81.31; H 6.61; N 7.47. $C_{25}H_{24}N_2O$. Calculated, %: C 81.52; H 6.52; N 7.6. M 368.

Compound 3. Yellow crystals; mp 141-142ºC. IR spectrum, ν, cm^{-1}: 2239 (C≡N), 1677 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.64 and 1.93, 2.20 and 2.35 (each 1H, all m, C–CH_2); 2.62-2.78 (4H, m, C–CH_2); 2.89 and 3.65 (each 1H, both d, J = 12.8, CH_2CN); 3.48 and 3.55 (each 1H, both d, J = 16.4, NCH_2); 5.92 (1H, s, H-4); 6.85-7.40 (7H, m, H arom.); 8.06 (1H, d, ^3J = 7.6 and ^4J = 1.2, H-8'). Mass spectrum, *m/z* (HPLC-MS, proton ionization): 369 $[M+H]^+$. Found, C 81.40; H 6.65; N 7.65. $C_{25}H_{24}N_2O$. Calculated, %: C 81.52; H 6.52; N 7.6. M 368.

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