Diazepines and Naphthyridines from the Rearrangement of Thienoindolizidinone Oximes

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Thienoindolizidinone oximes previously reported [1] were treated with polyphosphoric acid and led to thienopyrrolidinodiazepines or thienonaphthyridines. The rearrangement depends on the structural form of the starting oxime and the results obtained are discussed.

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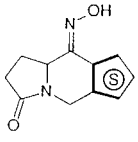
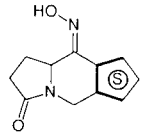
In a preceeding paper [1] we synthesized several ketones by intramolecular Friedel-Crafts acylation of 5-oxo-1-(thienylmethyl)prolines. We wish to report herein the Beckmann rearrangement of the oximes **1a-d** corresponding to these ketones.

In high acidic medium two types of reaction can be observed: the Beckmann rearrangement leading to cyclic lactams **2a-d** or the fragmentation of the oxopyrrolidine ring leading to naphthyridines **3b-d** (see Scheme II).

As previously described [1], oximes **1a-d** may exist in two forms: configuration **A** in which the OH group of the oxime is *syn* to the thiophene ring and configuration **B** in which the OH group is *anti*.



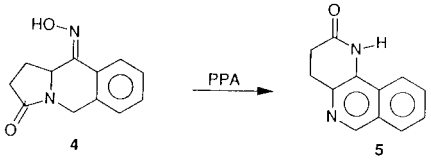
isomer A



isomer B

Previous investigations [2,3] have elucidated that the oxime **4** (isomer **B**) gave only the naphthyridine **5**. Thus it appeared of interest to study oximes annelated to a thiophene ring.

Scheme I



4 5

Therefore, when oximes **1a-d** are heated with polyphosphoric acid at 120° under nitrogen we formed with compound **1a** the diazepine **2a** and with compounds **1b-d** a mixture of diazepines and naphthyridines **3b-d**. All these reactions gave a quantitative yield of the crude products. The results, summarized in Table 1, are in direct correspondance with the configuration of the starting oxime.

Table 1

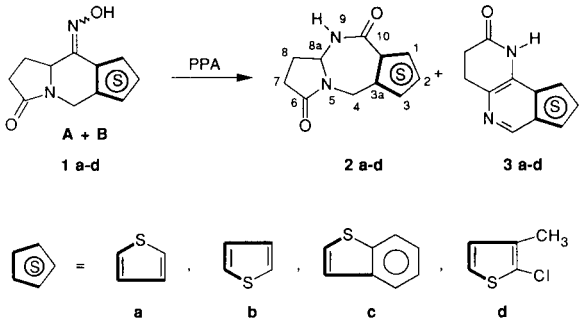
Composition* of starting oximes and lactams after reaction of **1** with PPA.

Oximes	Products (%)	
A = 100% **1a**	100% **2a**	0% **3a**
A = 40% ; B = 60% **1b**	35% **2b**	65% **3b**
A = 81% ; B = 19% **1c**	80% **2c**	20% **3c**
B = 100% **1d**	42% **2d**	58% **3d**

* Determined in the crude product by ^{1}H nmr spectroscopy (200 MHz).

Oxime **1a (A)** afforded exclusively the diazepine **2a** according to the normal Beckmann rearrangement. The structure of **2a** is supported by its ^{1}H nmr spectrum (Table 2). The multiplet at 5.11-5.20 ppm is assigned to proton H_{8a}. It shows a significant chemical shift (+0.7 ppm) from the corresponding ketone [1] (δH_{8a} = 4.50 ppm) because it is influenced by the two nitrogen atoms of the diazepine ring. We also observe that the -N-CH_2- protons of the di-

Scheme II



azepine ring appear as an AB quartet with chemical shifts of 4.42 and 4.83 ppm and a coupling constant J = 17.8 Hz characteristic of methylene protons. We have already observed a non-equivalence of the methylene protons in benzothienothiazocines [4] and thienoindolizidines [1]. Furthermore a ^{13}C nmr spectral evaluation (Table 3) confirms the structure **2a**. Carbon C_{3a} is typically shifted upfield in the diazepine (δ = 139.4 ppm) compared to the corresponding ketone (δ = 149.5 ppm).

Under the same conditions (polyphosphoric acid, 120°) the mixture of oximes **1b** (**A** = 40%, **B** = 60%) led to a mixture of pyrrolo[1,2-*a*]thieno[3,2-*e*][1,3]diazepine **2b** (35%) and naphthyridine **3b** (65%). The oxime **1b** (**A**) afforded, as in the preceeding case, the Beckmann product. In contrast oxime **1b** (**B**) underwent a fragmentation of the oxopyrrolidine ring with formation of the thieno[2,3-*c*]-[1,5]naphthyridine **3b**. These two compounds were easily separated by chromatography on silica gel. The ^{1}H, ^{13}C nmr and ir data (Tables 2 and 3) of **2b** are similar to those of **2a**. For both, we notice constant chemical shifts characteristic of the carbon atoms of the diazepine ring (C_{8a} = 65.9 ppm, C_{3a} = 139.4 ppm). The diazepine corresponding to a migration of the thiophene ring to the nitrogen atom was not found (Beckmann product from **1b** (**B**)) probably due to the fragile character of the lactam linkage of the oxopyrrolidine ring. Compound **3b** was characterized by its H_9 proton δ = 8.72 ppm as a singlet signal. These observations confirm the results obtained elsewhere [2] with oxime **4** (**B**) which afforded, under the same conditions, exclusively the naphthyridine **5**.

Table 2

^{1}H NMR Chemical Shifts of Pyrrolothieno[1,3]diazepines **2a-d** in DMSO-d_6, δ (ppm)

Compound No.	$(CH_2)_3$	H_{8a}	H_4	NH	H_{arom}	J,Hz
2a	1.98-2.27 m	5.11-5.20 m	4.83 d, 4.42 d	8.68 *s*	7.75 d (H_2), 7.05 d (H_3)	5.1 (H_2, H_3), 17.8 (H_4 gem)
2b	1.95-2.57 m	5.10-5.21 m	4.75 d, 4.63 d	8.77 d	7.49 d (H_2), 7.29 d (H_1)	5.2 (H_1, H_2), 16.7 (H_4 gem)
2c	2.00-2.62 m	5.32-5.45 m	5.23 d, 4.72 d	9.05 *s*	8.03 d (1H), 7.94 d (1H) 7.50 m (2H)	7.8 (H_{arom}), 7.5 (H_{arom}) 18.4 (H_4 gem)
2d [a]	1.88-2.58 m	5.03-5.15 m	4.74 d, 4.31 d	8.94 d		15.9 (H_4 gem)

[a] 2.21 (*s*, 3H, CH_3).

Table 3

^{13}C NMR Chemical Shifts of Pyrrolothieno[1,3]diazepines **2a-d** in DMSO-d_6, δ (ppm)

Compound No.	C_8	C_7	C_4	C_{8a}	C_{3a}	C_3	C_2	C_1	C_{10a}	C_{10}	C_6
2a	24.7	28.7	42.6	65.9	139.4	128.7	131.7	–	134.6	164.1	173.4
2b	23.8	29.6	40.4	65.9	139.5	–	124.7	129.4	135.1	165.7	172.6
2c [a]	25.0	28.6	41.6	65.8	134.8	137.9	139.1	–	133.8	164.4	173.7
2d [b]	22.9	30.1	39.0	65.8	135.1	–	122.5	135.6	134.4	165.4	171.9

[a] 122.6, 123.2, 124.9, 127.1 (C_{arom}). [b] 12.9 (CH_3).

The results obtained from oxime **1d** are interesting. This one, exclusively with configuration **B** (100%), gave a mixture of naphthyrine **3d** (58%) and diazepine **2d** (42%). According to the preceeding results and to the literature cited [2] the naphthyridine is the normal rearrangement product. The formation of diazepine **2d** can be explained by an initial isomerization of the oxime in acidic medium followed by the Beckmann rearrangement. This isomerization has been previously reported elsewhere [5] during the formation of benzothienoazocine. On the other hand, we did not observe the formation of a nitrile product as in the benzene series [2]. Compounds **2d** and **3d** were also separated by chromatography and easily identified from their spectral data (ir, ^1H and ^{13}C nmr). There is a perfect analogy of the chemical shift of carbons C_{3a} and C_{8a} respectively δ = 135.1 and 65.8 ppm, with those of diazepines **2a** and **2b** (see Tables 2 and 3).

From these results it was of interest to study an oxime annelated to a benzothiophene system. Thus, oxime **1c** was allowed to react with polyphosphoric acid at 120° to afford a mixture of diazepine and naphthyridine. Oxime **1c (A)** gave the expected diazepine **2c** (80%) and oxime **1c (B)** gave naphthyridine **3c** (20%). These percentages are in agreement with those of starting products **1c (A)** = 81% and **1c (B)** = 19%. As previously, both compounds **2c** and **3c** were separated by chromatography on silica gel (R_f values are given in the Experimental). The spectral data are summarized in Tables 2 and 3. As with the oxime **1a (A)**, oxime **1c (A)** afforded exclusively the diazepine **2c** corresponding to the Beckmann rearrangement and as oxime **4 (B)**, oxime **1c (B)** led to the naphthyridine **3c**. We did not observe an isomerization product or a nitrile product.

In conclusion, it seems that the intramolecular interaction between the hydrogen of the hydroxyl group and the sulfur atom would control the regioselectivity of the Beckmann rearrangement. Thus it is a convenient route to the new tetrahydropyrrolothienodiazepine system. Further investigations with a pyrrolidine or a piperidine ring instead of oxopyrrolidine are in progress and the results will be published soon.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Beckman IR 20 spectrometer. The nmr spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in DMSO-d_6 using tetramethylsilane (^1H) or DMSO-d_6 (^{13}C, δ = 39.5 ppm) as the internal standards. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M^T. S^T. Aignan. The starting oximes **1a-d** were prepared according to a reported procedure [1].

Reaction of Oximes **1a-d** with Polyphosphoric Acid. General Procedure.

Finely powdered oxime **1a-d** (5 mmoles) was added to hot (120°) stirred polyphosphoric acid (20 g) within 5 minutes. The mixture was stirred under nitrogen for 30 minutes. The hot solution was decanted over crushed ice (200 ml) and the resulting mixture was basified to *p*H 8 with 50% sodium hydroxide solution. Extraction with chloroform (3 x 50 ml), followed by the usual work up of the organic layer, gave a solid residue. The crude product was processed according to one of the following procedures.

A. The less soluble heterocycles **2a** and **3b** were obtained by crystallization from ethanol. The mother liquor was concentrated *in vacuo*.

B. The mixture of diazepines **2b-d** and naphthyridines **3b-d** were separated by column chromatography on silica gel (100 g for 1 g of crude product) eluting with chloroform/acetone (8:2). The thieno[*c*][1,5]naphthyridines **3b-d** were obtained as the first eluted products. Further elution afforded the pyrrolothienodiazepines **2b-d**. The R_F values (chloroform/acetone = 8/2) are: 0.21 (**2a**), 0.22 (**2b**), 0.29 (**2c**), 0.34 (**2d**), 0.36 (**3b**), 0.43 (**3c**), and 0.58 (**3d**).

4,7,8,8a-Tetrahydropyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepine-6,10-(9*H*)-dione (**2a**).

This compound was obtained in 63% yield, mp 273-275° (from ethanol); ir: 1674 (CO), 1700 (CO) cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.54; N, 12.61. Found: C, 53.87; H, 4.14; N, 12.42.

5a,6,7,10-Tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*][1,3]diazepine-4(5*H*),8-dione (**2b**).

This compound was obtained in 42% yield, mp 210-211° (from benzene-cyclohexane); ir: 1644 (CO), 1704 (CO) cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.03; H, 4.54; N, 12.61. Found: C, 53.83; H, 4.42; N, 12.47.

1,2,5,12a-Tetrahydropyrrolo[1,2-*a*]benzo[*b*]thieno[2,3-*e*][1,3]diazepine-3,11(12*H*)-dione (**2c**).

This compound was obtained in 45% yield, mp 263-264° (from ethanol); ir: 1645 (CO), 1710 (CO) cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.74; H, 4.45; N, 10.29. Found: C, 61.42; H, 4.17; N, 10.10.

2-Chloro-3-methyl-5a,6,7,10-tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*][1,3]diazepine-4(5*H*),8-dione (**2d**).

This compound was obtained in 18% yield, mp 226-227° (from ethanol); ir: 1645 (CO), 1698 (CO) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}N_2O_2SCl$: C, 48.79; H, 4.10; N, 10.35. Found: C, 48.53; H, 3.98; N, 10.13.

The ^1H and ^{13}C nmr spectra of diazepines **2a-d** are given in Tables 2 and 3.

6,7-Dihydrothieno[2,3-*c*][1,5]naphthyridin-5(4*H*)-one (**3b**).

This compound was obtained in 68% yield, mp 268-270° (from ethanol); ir: 1684 (CO) cm^{-1}; ^1H nmr: δ 2.62 (t, 2 H, CH_2CO), 3.09 (t, 2 H, CH_2, J = 8.2 Hz), 7.82 (d, 1 H, H_3, J = 5.5 Hz), 7.97 (d, 1 H, H_2), 8.72 (s, 1 H, H_9), 10.53 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.80; H, 3.96; N, 13.72. Found: C, 58.53; H, 3.93; N, 13.45.

3,4-Dihydrobenzo[*b*]thieno[3,2-*c*][1,5]naphthyridin-2(1*H*)-one (**3c**).

This compound was obtained in 36% yield, mp >280°; ir: 1668 (CO) cm^{-1}; ^1H nmr: δ 2.72 (t, 2 H, CH_2CO), 3.22 (t, 2 H, CH_2, J = 8.0 Hz), 7.50-7.62 (m, 2 H, H_8 and H_9), 8.10-8.19 (m, 1 H, H_7), 8.40-8.48 (m, 1 H, H_{10}), 9.16 (s, 1 H, H_6), 10.66 (br s, 1 H, NH).

Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.11; H, 3.97; N, 11.02. Found: C, 66.03; H, 3.90; N, 11.02.

2-Chloro-6,7-dihydro-3-methylthieno[2,3-*c*][1,5]naphthyridin-5(4*H*)-one (**3d**).

This compound was obtained in a yield of 36%, mp 219-221° (from ethanol); ir: 1650 (CO) cm^{-1}; ^1H nmr: δ 2.58 (s, 3 H, CH_3), 2.64 (t, 2 H, CH_2CO), 3.11 (t, 2 H, CH_2, J = 8.0 Hz), 8.69 (s, 1 H, H_9), 10.66 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_9N_2OSCl$: C, 52.57; H, 3.60; N, 11.09. Found: C, 52.37; H, 3.50; N, 10.96.

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