Ring Transformation of 4-Amino and 4-*N*-(Substituted)amino-1*H*-1,5-benzodiazepine-3-carbonitriles with Hydroxylamine. A New Synthesis of Benzimidazolidine and Isoxazole Derivatives

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The reaction of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **1** with hydroxylamine provided the ring-opened hydroxylamine adduct **2** which was converted to 2-benzimidazolidinylidene-3-hydroxyiminopropionitrile **4** in hydrochloric acid. The reaction of 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile **6a** or *N*-(3-cyano-1*H*-1,5-benzodiazepin-4-yl)-*N'*-ethylurea **6b** with hydroxylamine afforded 5-(*o*-aminoanilino)-4-cyanoisoxazole **3** which underwent a facile rearrangement into **4** with a base.

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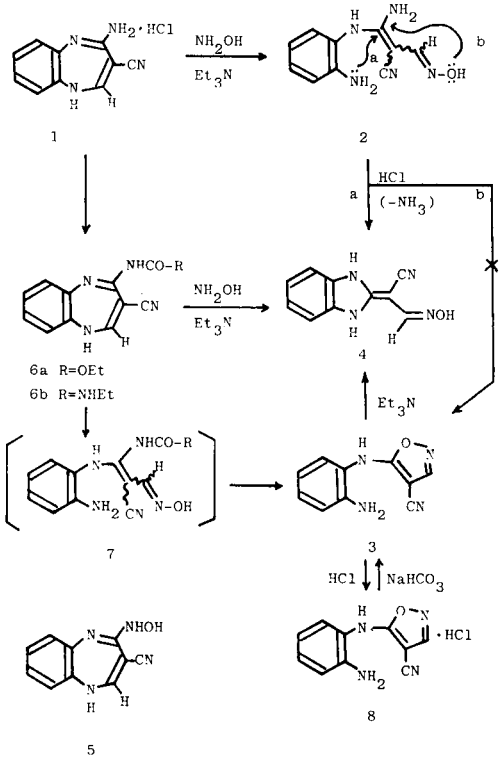
In a series of studying the ring transformation of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **1** [2], we reported that the reaction of **1** with hydroxylamine in the presence of sodium hydroxide in water gave the ring-opened hydroxylamine adduct **2** which readily converted to 5-(*o*-aminoanilino)-4-cyanoisoxazole **3** under acidic conditions [3]. In continuation of this kind of work, the structure of the compound **3** was found to be 2-benzimidazolidinylidene-3-hydroxyiminopropionitrile **4**, but not the isoxazole ring **3**. Herein, we would like to revise the result described in the previous paper [3], where the wrong isoxazole structure **3** was proposed instead of the benzimidazolidine structure **4**. This paper describes the ring transformation of **1** with hydroxylamine, especially a new synthesis of **3** and its isomerization to **4**.

Scheme 1



When the benzodiazepine **1** was heated with hydroxylamine hydrochloride in the presence of triethylamine in methanol, compound **2** was obtained in 54% yield (Scheme 1). All analytical data for **2** were coincided with those of the compound which was obtained using sodium hydroxide as a base and water as a solvent in the reaction as described in our previous paper [3]. No change in **2** was observed when heated in ethanol in the presence of a base such as triethylamine or 1,4-diazabicyclo[2,2,2]octane (DABCO). On treatment with diluted hydrochloric acid, **2** was converted to a deaminated compound. Although the structure **3** was once considered to be the deaminated compound [3], another structure **4** may also be considered from the spectral data. Moreover, since the compound can not form a hydrochloride salt and is soluble in an aqueous alkaline solution, structure **3** must be excluded. Namely, in hydrochloric acid, the *o*-amino group in **2** exclusively attacks the amidino carbon, giving the benzimidazolidine ring system **4** (Scheme 1, reaction a). To confirm the above result, we attempted to obtain the compound **3**. When 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbo-

Table I

Physical Data for Compounds **3** and **4**

Compound No.	Mp (°C)	Solubility	Molecular Formula	Analyses Calcd. (%) Found (%) C	H	N
3	188-189 dec	soluble in 10% HCl	$C_{10}H_6N_4O$ (200.20)	59.99 59.87	4.03 4.01	27.99 27.87
4	264-265 dec	insoluble in 10% HCl	$C_{10}H_6N_4O$ (200.20)	59.99 59.71	4.03 4.11	27.99 27.83

Table II

Spectral Data for Compounds **3** and **4**

Compound No.	MS (intensity) m/z	IR (cm^{-1}) KBr	^{1}H-NMR (ppm) DMSO-d_6)
3	200 (91 (M^+) 183 (100) 155 (39) 118 (22) 103 (25)	2190 (CN) weak	7.00-7.56 (m, 4H, Ph-H) 7.2-7.8 (br, 2H, NH_2) 8.63 (s, 1H, -CH=) 11.3-12.3 (br, 1H, NH)
4	200 (100) (M^+) 183 (92) 155 (98) 129 (44) 103 (92)	2190 (CN) strong	6.32 (br, s, 1H, NH) 7.00-7.60 (m, 5H, Ph-H and -CH=) 12.17 (br, 2H, NH and OH)

nitrile **6a** [5,6] or *N*-(3-cyano-1*H*-1,5-benzodiazepin-4-yl)-*N'*-ethylurea **6b** [7] was reacted with hydroxylamine hydrochloride in methanol in the presence of an equimolecular amount of triethylamine, **3** was obtained. The characterization of **3** is summarized in Tables I and II. In the ^{1}H-nmr spectrum of **3**, a signal due to the olefinic proton was observed at 8.64 ppm which is lower than that of **6a** (7.23 ppm) (Table II). This difference in the chemical shifts excluded structure **5** which could arise by simple substitution with hydroxylamine at the 4-position of **6a**. Other signals in the ^{1}H-nmr spectrum were in good agreement with the proposed structure **3**. Furthermore, compound **3** is soluble in dilute hydrochloric acid and gave the monohydrochloride **8** which again gave the free base on treatment with an aqueous sodium bicarbonate solution. Compound **3** was readily converted to **4** in quantitative yield under refluxing in ethanol in the presence of excess triethylamine.

On the basis of these results, we propose a pathway of **6a**, or **6b**, to **3** where hydroxylamine first attacks at the 2-position of **6** to give the ring-opened intermediate **7**. The liberation of urethane (or ethylurea) from **7** affords **3**. It is worth noting that the substitution of the amino proton by the electron attracting group in compound **2** brings about the nucleophilic attack of the terminal hydroxyl group to the amidino carbon to generate the isoxazole ring system. In compound **3**, the *o*-amino group attacks the carbon at 5-position of the isoxazole ring to give the benzimidazolidine derivative **4**. This conversion was also observed during the ^{1}H- and ^{13}C-nmr measurements.

EXPERIMENTAL

Melting points were determined using a Yamato Scientific stirred liquid apparatus and are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO A-102 spectrometer. Proton magnetic resonance (pmr) spectra were measured with a JNX-PMX 60 spectrometer (JEOL) with tetramethylsilane as an internal standard. The ^{13}C-nmr spectra were obtained from a Varian VXR-300 spectrometer. Mass spectra (ms) were taken on a JMS-DX 300 spectrometer (JEOL). Elementary analyses were performed on a Perkin-Elmer model 240B machine.

3-Amino-3-(*o*-aminoanilino)-2-cyano-2-propenaloxime (**2**).

A mixture of **1** (hydrochloride, 1.32 g, 6 mmoles), hydroxylamine hydrochloride (0.84 g, 12 mmoles) and triethylamine (3.0 g, 30 mmoles) in methanol (30 ml) was refluxed for 1 hour. After removal of the solvent, the residue was treated with water (60 ml). The crystalline precipitate was collected by filtration, and washed with water. Recrystallization from ethanol gave **2** (0.7 g, 54%), mp 193-194° dec, which was identified by comparison of its ir spectrum with that of the authentic sample (lit [3] mp 193-194°).

2-Benzimidazolidinylidene-3-hydroxyiminopropionitrile (**4**).

Method A.

A solution of **2** (0.44 g, 2 mmoles) in 3% hydrochloric acid (30 ml) was heated on a water bath for 15 minutes. The crystalline precipitate was collected, washed with water and recrystallized from *N,N*-dimethylformamide/ethanol to yield **4** (0.27 g, 68%).

Method B.

A solution of **3** (0.4 g, 2 mmoles) and triethylamine (0.6 g, 6 mmoles) in ethanol (12 ml) was refluxed for 1 hour. The crystalline precipitate was collected by filtration, washed with ethanol and dried to yield **4** (0.38 g, 95%) which was practically pure without further recrystallization.

Method C.

A mixture of **6a** (0.77 g, 3 mmoles), hydroxylamine hydrochloride (0.42 g, 6 mmoles) and triethylamine (1.2 g, 12 mmoles) in methanol (15 ml) was refluxed for 2 hours. The precipitate was collected, washed with methanol and recrystallized from *N,N*-dimethylformamide/ethanol to give **4** (0.26 g, 43%). Some analytical data are given in Tables I and II.

5-(*o*-aminoanilino)-4-cyanoisoxazole (**3**).

A mixture of **6a** or **6b** (3 mmoles), hydroxylamine hydrochloride (0.42 g, 6 mmoles) and triethylamine (0.61 g, 6 mmoles) in methanol (15 ml) was refluxed for 10 minutes. After removal of the solvent the residue was treated with water (30 ml), and the crystalline precipitate was collected, washed with water and recrystallized from water/ethanol to yield **3** (0.35 g, 58% from **6a**; 0.39 g, 65% from **6b**); ^{13}C-nmr (deuterated dimethyl sulfoxide): 84.077 (nitrile), 110.572, 117.559, 121.402, 121.487, 133.783, and 143.614 (benzene ring), 146.445 (4-C of isoxazole ring), 148.862 (3-C of isoxazole ring), 168.488 (5-C of isoxazole ring). Some analytical data are also given in Tables I and II.

Monohydrochloride of **3** (**8**).

Compound **3** (0.4 g, 2 mmoles) was dissolved in a hot solution of 2.5% hydrochloric acid on a water bath. The resulting solution was filtered and the filtrate gave colorless crystals after cooling. Recrystallization from water afforded the monohydrochloride of **3** (0.28 g, 59%), mp 254-246° dec; ms: m/z (relative intensity) 200 (95), 183 (100), 155 (29), 118 (13), 103 (15).

Anal. Calcd. for $C_{10}H_8N_4O \cdot HCl$: C, 50.79; H, 3.41; N, 23.69. Found: C, 51.20; H, 3.65; N, 24.02.

REFERENCES AND NOTES

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