127. Synthesis of Substituted 2-Amino-6*H*-1,3-oxazin-6-ones[1][2])

by **Haukur Kristinsson**[a])*, **Tammo Winkler**[b]), **Grety Rihs**[b]), and **Hans Fritz**[b])

Agricultural Division[a]) and Central Function Research, Physics Department[b]), *Ciba-Geigy AG*, CH-4002 Basel

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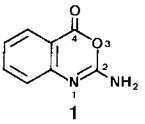
Derivatives of the unknown 2-amino-6*H*-1,3-oxazin-6-one **2** have been synthesized for the first time in two steps and in excellent yields, starting from *N*-cyanocarbonimidates **3a–c** and cyanoacetates. The structures of **2a–c** are assigned by NMR-spectroscopic methods and corroborated by an X-ray structure analysis of **2c**.

1. Introduction. – 2-Amino-4*H*-3,1-benzoxazin-4-one (**1**) has been known for a long time and is readily prepared in a single step by reacting bromine or chlorine cyanide with the Na salt of anthranilic acid [2]. A method for the construction of the non-annellated 2-amino-6*H*-1,3-oxazin-6-one (**2**) or its derivatives, however, has, to the best of our knowledge, never been described in the literature. We now report on the synthesis of 5-cyano-4-heteroalkyl derivatives of **2**, obtained in two steps from cyanoacetates and the readily available *N*-cyanocarbonimidates **3a–c** [3]. The novel heterocycles **2a–c** are obtained in excellent yields.



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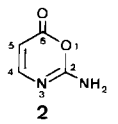

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The structures of the new compounds were elucidated with the aid of ^{13}C- and ^{15}N-NMR spectra in combination with an X-ray analysis of **2c**. Recently, the preparation and reactivity of the related 2-phenyl-6*H*-1,3-oxazin-6-ones and 6-thiones carrying the same substituents in the 4 and 5 position as our **2c** have been described [4]. Indeed, relatively few 6*H*-1,3-oxazines are known [5].

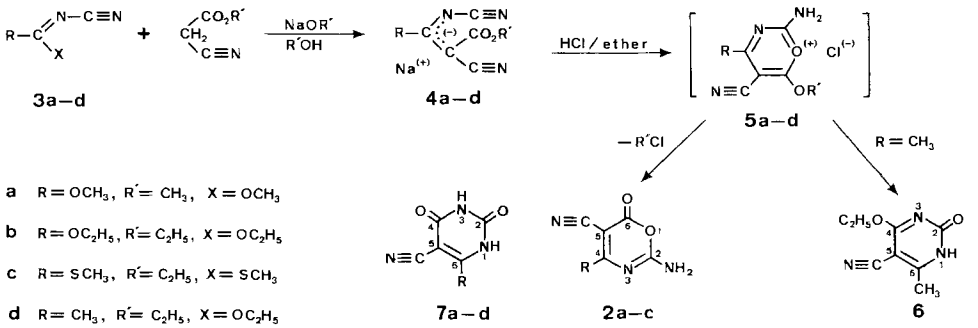
2. Results and Discussion. – The synthesis of the novel compounds is outlined in the *Scheme*. *N*-Cyanocarbonimidates **3a–c** were reacted with the Na salt of ethyl or methyl cyanoacetate in the corresponding alcohol (see *Exper. Part*) at room temperature, yielding the sodium salts **4a–c** in high yields. The Na salts **4a–c** are stable, non-hygroscopic compounds. Treatment of **4a–c** with HCl in Et_2O at 0° results in the formation of 2-amino-6*H*-1,3-oxazin-6-ones **2a–c** in almost quantitative yield.

It is proposed that the reaction proceeds *via* the 1,3-oxazinium (3-azapyrylium) salts **5a–c** as intermediates. An ether cleavage of the ketene-acetal moiety of **5** would then lead to **2a–c**. The cleavage reactions of ketene acetals with HCl giving esters and alkyl chlorides are well-established [6]. 1,3-Oxazinium salts are well-known and have been used

[1]) Synthesis of Heterocycles, Part VIII. Part VII: [1].

[2]) Presented at the Autumn Meeting of the Swiss Chemical Society, Bern, October 19, 1984.

Scheme



for the preparation of a number of 5- and 6-membered heterocycles by a ring transformation with nucleophiles [7].

Curiously, 4-alkyl-5-cyano derivatives of **2** , however, cannot be prepared by our route. Thus, the Na salt **4d**, readily prepared from the ethyl *N*-cyanoacetimidate **3d** [3] and the Na salt of ethyl cyanoacetate, reacts with HCl in Et_2O to give the pyrimidin-2(1*H*)-one **6**. This cyclization should also proceed *via* the 1,3-oxazinium salt intermediate **5d**. In contrast to the heteroalkyl substituted intermediates **5a–c**, the CH_3-substituted **5d** undergoes a *Dimroth* rearrangement to yield **6**.

The structure elucidation of the novel compounds is based on their ^{13}C- and ^{15}N-NMR spectra (see *Table 1* and *2*).

Table 1. *^{13}C-NMR Chemical Shifts* (in ppm) *of* **2a–c, 7a–d,** *and* **6** *in (D$_6$)DMSO*

Compound	C(2)	C(4)	C(5)	C(6)	CN	Remaining C-atoms
2a	161.7	175.1	63.0	158.6	114.3	55.7
2b	161.6	174.6	63.1	158.7	114.4	64.7, 14.3
2c	159.7	181.1	75.4	155.8	114.8	12.6
7a[a])	149.5	162.0	69.8	167.8	114.0	59.0
7b[a])	149.4	162.0	70.2	167.0	114.0	68.6, 14.3
7c[a])	149.3	159.9	84.8	165.7	114.2	14.2
7d[a])	149.6	161.1	86.5	163.6	114.7	18.3
6	154.4	168.9	80.2	165.6	113.6	63.5 and 13.9 (OC_2H_5), 17.9 (CH_3–C(6))

[a]) *i*) N(1)–H: **7a**: 10.95, **7b**: 11.47, **7c**: 11.66, **7d**: 11.7 ppm. *ii*) Preparation of **7a** and **7b** analogous to that of **7c, d** [8]. *iii*) ^{15}N-NMR data of **7c**: 271.19 (CN), 153.48 and 144.58 (ring N-atoms).

Table 2. *^{15}N-NMR Data of* **2a–c, 1,** *and* **6** *in (D$_6$)DMSO*

Compound	N(3)	^3J(N(3),NH_2)	CN	NH_2	^{1}J(NH_2)	$^{14}NH_2$
2a	170.74	n.d.[a])	265.98	101.48	n.d.	9.27 and 9.15
2b	170.75	6.1; 0	265.77	100.80	90.5	9.19 and 9.06
2c	186.84	6.6; 0	272.19	100.47	90.5	9.17 and 9.07
1[b])	[c])		–	77.81	~ 90	7.5 (*s*)
6[d])	221.63	–	269.49	–	–	–

[a]) n.d.: not determined. [b]) ^{13}C-NMR data: [9]. [c]) N(1): 168.19 ppm. [d]) N(1): 161.32 ppm, $^1J(NH) \approx 88$ Hz.

Chemical shifts of the ring C-atoms and of the NH protons of **2a–c** differ distinctly from those of the isomeric 5-cyano-uracils **7a–c** (see *Table 1* and the *Scheme*). Moreover, their proton-coupled ^{15}N-NMR spectra show a triplet at *ca.* 100 ppm ($^1J_{NH}$ = 90.5 Hz) proving the presence of an NH_2 group. Its chemical shift is similar to that of the NH_2 group in benzamide (105.4 ppm) or benzenesulfonamide (94.3 ppm) in agreement with its acidity[3]) and different from that of aniline (55.4 ppm) [10]. The electron demand of the heterocycle responsible for this acidity of the NH_2 group leads also to the formation of a partial double bond between the amino N-atom and C(2) as shown by the two chemical shifts of the NH_2 protons *(Table 2)*, of which only the *trans*-configurated one couples with the N(3) atom (6.1 Hz in **2b** or 6.6 Hz in **2c**).

The structures of **2a–c** were, furthermore, confirmed by the X-ray structure analysis of **2c** *(Fig.)*.

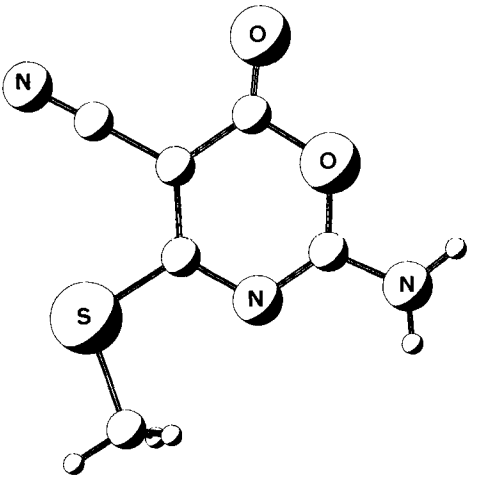


Fig. *A perspective view of* **2c**

The structure of **6** has been assigned by comparing its ^{13}C-NMR data with those of 2- and 4-alkoxy-pyrimidines [11]. In this context, the C-atom carrying the alkoxy group and the carbonyl C-atom can be distinguished in the proton-coupled ^{13}C-NMR spectrum by the presence or absence of long-range coupling to the side-chain protons. The position of the NH proton was established with a proton-coupled ^{15}N-NMR spectrum showing N(3) as a single sharp line excluding a CH_3 group in 4-position by the absence of long-range coupling with the CH_3 protons and showing, furthermore, a broad doublet for N(1) due to coupling with its proton under slow intermolecular exchange conditions. After addition of CF_3COOH, the exchange speeds up, and a broadened quartet due to long-range coupling with the CH_3 group in 6-position is observed.

Experimental Part

1. General. – Melting points (m.p.) are uncorrected. NMR spectra were recorded on a *Bruker WM 400* or on *Varian EM 360, XL 100,* or *XL 300* spectrometers. The ^{15}N chemical shifts were measured with respect to external CH_3NO_2 and converted to the anh. liq. NH_3 scale ($\delta_{CH_3NO_2}$ = 380.23) [10]. No correction for diamagnetic susceptibility differences was applied. Further experimental details of the measurement of the ^{15}N-NMR spectra can be found in [12].

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[3]) The pK_a value of **2a** was found to be close to 10. An exact determination of pK_a is not possible due to the ring opening of **2a** upon deprotonation. The reactivity of **2a–c** are currently being investigated.

2. Preparation of Na Salts 4a–d. – 2.1. *General Procedure.* To a soln. of Na (23 g, 1 mol) in either EtOH or MeOH (1000 ml), ethyl or methyl cyanoacetate (1 mol) was added. After cooling to 0–5°, **3** (1 mol) was added dropwise or in portions and the mixture stirred overnight at r.t. The product **4** was separated and collected by filtration and dried *in vacuo* at r.t.

2.2. *Methyl 2-Cyano-3-(cyanoamino)-3-methoxyacrylate Sodium Salt* (**4a**). Following *Procedure 2.1,* 114 g (1 mol) of **3a** and methyl cyanoacetate in MeOH yielded 183 g (90%) **5a**. Dec. 254–256°. ^{13}C-NMR ((D$_6$)DMSO): 174.0 (C(3)); 166.1 (C(1)); 121.0, 115.4 (CN); 60.9 (C(2)); 54.2 (*C*H$_3$O–C(3)); 50.1 (*C*H$_3$OCO). Anal. calc. for $C_7H_6N_3O_3Na$ (203.13): C 41.39, H 2.98, N 20.69, Na 11.32; found: C 40.2, H 3.2, N 20.2, Na 11.1.

2.3. *Ethyl 2-Cyano-3-(cyanoamino)-3-ethoxyacrylate Sodium Salt* (**4b**). Following *Procedure 2.1,* 142 g (1 mol) of **3b** and ethyl cyanoacetate in EtOH yielded 182 g (79%) **4b**. M.p. 216–218°. ^{13}C-NMR ((D$_6$)DMSO): 173.6 (C(3)); 165.3 (C(1)); 120.8, 115.1 (CN); 62.1 (CH$_3$*C*H$_2$O–C(3)); 60.8 (C(2)); 57.7 (CH$_3$*C*H$_2$OCO); 14.6 (*C*H$_3$CH$_2$OCO); 14.4 (*C*H$_3$CH$_2$O–C(3)). Anal. calc. for $C_9H_{10}N_3O_3Na$ (231.19): C 46.76, H 4.36, N 18.18, Na 9.95; found: C 46.7, H 4.3, N 18.2, Na 9.6.

2.4. *Ethyl 2-Cyano-3-(cyanoamino)-3-(methylthio)acrylate Sodium Salt* (**4c**). Following *Procedure 2.1,* 146 g (1 mol) of **3c** and ethyl cyanoacetate in EtOH yielded 212 g (91%) of **4c**. Dec. 246–248°. ^{13}C-NMR ((D$_6$)DMSO): 177.8 (C(3)); 165.3 (C(1)); 119.1, 115.2 (CN); 73.4 (C(2)); 58.3 (CH$_2$O); 14.5 (CH$_2$*C*H$_3$); 14.3 (CH$_3$S). Anal. calc. for $C_8H_8N_3O_2SNa$ (233.22): C 41.2, H 3.46, N 18.02, S 13.75, Na 9.86; found: C 41.1, H 3.6, N 17.7, S 13.4, Na 9.66.

2.5. *Ethyl 2-Cyano-3-(cyanoamino)crotonate Sodium Salt* (**4d**). Following *Procedure 2.1,* 112 g (1 mol) of **3d** and ethyl cyanoacetate in EtOH yielded 175 g (87%) **4d**. Dec. 254–256°. ^{13}C-NMR ((D$_6$)DMSO): 182.1 (C(3)); 166.5 (C(1)); 120.4, 119.6 (CN); 74.4 (C(2)); 58.2 (CH$_3$*C*H$_2$); 21.5 (*C*H$_3$–C(3)); 14.6 (*C*H$_3$CH$_2$). Anal. calc. for $C_8H_8N_3O_2Na$ (201.16): C 47.77, H 4.01, N 20.89, Na 11.43; found: C 47.6, H 4.0, N 20.5, Na 11.0.

3. Preparation of 6*H*-1,3-Oxazin-6-ones 2a–c. – 3.1. *General Procedure.* To a soln. of HCl (20–60 g) in Et$_2$O (450 ml), **4** (0.15 mol) was added at 0–5° in portions. The resulting mixture was stirred at r.t. overnight. After evaporation, the solid material was treated with H$_2$O, then collected by filtration and dried *in vacuo* at 60°.

3.2. *2-Amino-4-methoxy-6-oxo-6*H*-1,3-oxazine-5-carbonitrile* (**2a**). Following *Procedure 3.1,* 32.6 g (0.15 mol) **4a** and HCl (20 g) yielded 23.3 g (93%) **2a**. M.p. 212°. ^{1}H-NMR ((D$_6$)DMSO): 3.96 (*s*, CH$_3$O); 9.15, 9.27 (2*s*, NH$_2$). Anal. calc. for $C_6H_5N_3O_3$ (167.12): C 43.12, H 3.02, N 25.14, O 28.72; found: C 43.2, H 3.1, N 25.0, O 28.8.

3.3. *2-Amino-4-ethoxy-6-oxo-6*H*-1,3-oxazine-5-carbonitrile* (**2b**). Following *Procedure 3.1,* 34.7 g (0.15 mol) **4b** and HCl (40 g) yielded 26.1 g (96%) **2b**. M.p. 209°. ^{1}H-NMR ((D$_6$)DMSO): 1.2 (*t*, CH$_3$); 4.4 (*q*, CH$_2$); 9.06, 9.19 (2*s*, NH$_2$). Anal. calc. for $C_7H_7N_3O_3$ (181.15): C 46.41, H 3.90, N 23.20, O 26.50; found: C 46.6, H 4.1, N 23.2, O 26.7.

3.4. *2-Amino-4-(methylthio)-6-oxo-6*H*-1,3-oxazine-5-carbonitrile* (**2c**). Following *Procedure 3.1,* 34.9 g (0.15 mol) **4c** and HCl (60 g) yielded 25.2 g (92%) **2c**. Dec. 260°. **2c** can be recrystallized from MeCN. ^{1}H-NMR ((D$_6$)DMSO): 2.54 (*s*, CH$_3$S); 9.07, 9.17 (2*s*, NH$_2$). Anal. calc. for $C_6H_5N_3O_2S$ (183.19): C 39.24, H 2.75, N 22.94, O 17.47, S 17.50; found: C 40.0, H 2.9, N 22.8, O 17.6, S 17.0.

3.5. *4-Ethoxy-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carbonitrile* (**6**). To a soln. of HCl (45 g) in Et$_2$O (450 ml) was added 30.2 g (0.15 mol) **4d** at 0–5° in portions. The resulting mixture was stirred at r.t. overnight. After evaporation, the solid material was treated with H$_2$O, then collected by filtration and dried *in vacuo* at 60° yielding 19.6 g (73%) **6**. M.p. 249–251°. ^{1}H-NMR ((D$_6$)DMSO): 1.3 (*t*, *C*H$_3$CH$_2$); 2.36 (*s*, CH$_3$); 4.4 (*q*, CH$_3$C*H*$_2$). Anal. calc. for $C_8H_9N_3O_2$ (179.18): C 53.63, H 5.06, N 23.45, O 17.86; found: C 53.6, H 5.1, N 23.6, O 17.9.

4. X-Ray Structure Analysis of 2c[4]). – Crystals are triclinic, space group $P_{\bar{1}}$, $a = 7.429$ Å, $b = 8.682$ Å, $c = 13.399$ Å, $\alpha = 88.25°$, $\beta = 94.05°$, $\gamma = 115.28°$, $Z = 4$. On a *Philips PW 1100* diffractometer 3574 independent reflections were measured of which 2940 were considered observed ($I > 2\sigma(I)$). The structure was solved by direct methods using the program system MULTAN [13]. All the H-atoms could be located in difference maps and included in the refinement with isotropic temperature factors. For all the other atoms anisotropic temperature factors were introduced. The refinement converged to a final value of $R = 0.041$. The two molecules of the asymmetric unit show no significant differences.

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[4]) Atomic coordinates for **2c** have been deposited with the *Crystallographic Data Centre, Cambridge University, University Chemical Lab, Cambridge CB2 1EW, England* or are available, together with bond lengths and bond angles, on request from *G. R.*

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