Monatshefte für Chemie 113, 583—592 (1982)

Monatshefte für Chemie
Chemical Monthly

The *Knoevenagel* Reaction of Malononitrile with Some Cyclic β-Ketocarbothionic Acid Anilides Synthesis of Cycloalkeno-pyridines and Cycloalkeno-thiopyrans

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(Received 1 June 1981. Accepted 8 September 1981)

A new route to the cycloalkeno-pyridines **2** and cycloalkeno-thiopyrans **5** by the reaction of malononitrile with enamines of cyclic β-ketocarbothionic acid anilides is presented. The elucidation of the structure of compounds obtained is based on MS spectral data. The reaction is proposed to be a sequence of addition, elimination and cyclization.

(Keywords: Cycloalkeno[c]pyridines; Cycloalkeno[c]thiopyrans; Reactions with malononitrile)

Die Knoevenagel Reaktion von Malononitril mit einigen cyclischen β-Ketocarbothionsäureaniliden. Synthese von Cycloalkeno-pyridinen und Cycloalkeno-thiopyranen

Es wird ein neuer Zugang zu Cycloalkeno[c]pyridinen (**2**) und Cycloalkeno[c]thiopyranen (**5**) mittels Reaktion von Malononitril mit Enaminen cyclischer β-Ketocarbothionsäureaniliden aufgezeigt. Die Strukturaufklärung der erhaltenen Verbindungen basiert auf massenspektroskopischen Daten. Die Reaktion wird als Folge von Addition, Eliminierung und Cyclisierung diskutiert.

The reaction of β-dicarbonyl compounds with malononitrile, cyanoacetamide and ethylcyanoacetate is one of the most efficient and useful methods for the synthesis of pyridine derivatives. Typical *Knoevenagel* condensation products are generally assumed as intermediates in these reactions[1–6].

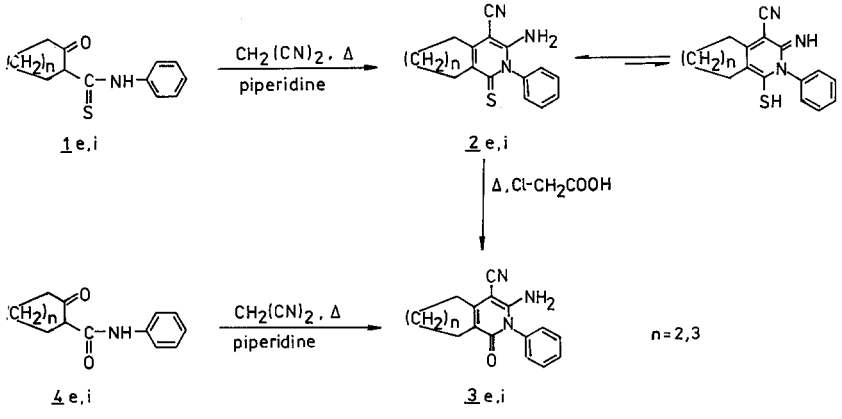
In the course of our study on the chemistry of cyclic β-ketoacid anilides[7,8], the reaction of malononitrile with some cyclic β-ketocarbo-

0026-9247/82/0113/0583/$ 02.00

thionic acid anilides and corresponding enamines were investigated. As a representative case the first studied was the condensation of cyclohexan-2-one-1-carbothionic acid anilide **1e** with malononitrile. The reaction performed in boiling ethanol or benzene in the presence of piperidine afforded compound **2e** in moderate yield (56%), (Scheme 1). The structure of obtained compound was consistent with analytical and IR, ^{1}H-NMR, ^{13}C-NMR and MS spectral data. The identical compound was independently synthesized by *Gewald* et al.[9] in the reaction of cyclohexylidenomalononitrile with phenylisothiocyanate. Similarly, the reaction of anilide **1i** with malononitrile led to cycloheptenopyridine **2i** (51%). Compounds **2e**, **2i** were easily soluble in water-ethanol solution of sodium hydroxide. Acidification of the alkaline solution furnished the unchanged products **2e**, **2i**. Formation of the tautomeric thiolic form seems to be responsible for acidic properties of these compounds.

In order to replace the sulphur atom by the oxygen, compounds **2e** and **2i** were heated with chloroacetic acid. Compounds **3e** and **3i** obtained in this way were identical with these prepared independently by the reaction of anilides **4e** and **4i** with malononitrile. The reaction sequence is shown in Scheme 1.

Scheme 1

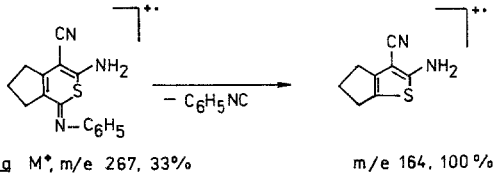


In striking contrast cyclopentan-2-one-1-carbothionic acid anilide **1a** reacted with malononitrile under the same conditions yielding the product **5a**. Although the analytical data of **5a** were in agreement with the expected formula $C_{15}H_{13}N_3S$ its chemical properties were different from these of compounds **2e** and **2i**. Compound **5a** did not exchange sulphur atom by oxygen atom in the reaction with chloroacetic acid.

The IR spectrum of **5a** showed strong absorption bands at 3450-3190 cm^{-1} and 2190 cm^{-1} corresponding to NH and CN groups respectively.

Taking into account analytical as well as IR spectral data it was reasonable to assume, that the obtained compound would be a typical *Knoevenagel* condensation product. On the basis of the ^{1}H-NMR spectrum it was difficult to assign to this compound the appropriate structure. In this case the mass spectrum was particularly helpful. The expected structure of a typical *Knoevenagel* condensation product was rejected, because the mass spectrum did not show the fragmentary ion at *m/e* 135 corresponding to the elimination of C_6H_5NCS fragment, which is characteristic for fragmentation of carbothionic acid anilides and their derivatives. The fragmentation of **5a** began with elimination of phenylisocyanide (C_6H_5NC) and led to the peak at *m/e* 164 (100%) corresponding to the composition $C_8H_8N_2S$. This kind of fragmentation suggest that sulphur atom in **5a** is a part of heterocyclic ring and allows to propose the structure of 1-phenylimino-3-amino-4-cyano-1,5,6,7-tetrahydro-cyclopenta[c]thiopyran (Scheme 2).

Scheme 2



5a M$^+$, m/e 267, 33% m/e 164, 100%

The above reactions of anilidines **1a**, **1e**, **1i** with malononitrile occur by initial formation of *Knoevenagel* condensation products **6** (Scheme 3). These products may cyclize by two different routes. The first occurs by nucleophilic attack of the amino nitrogen atom, and the second by nucleophilic attack of the sulphur atom of the tautomeric thiolic group, on the same carbon atom of the cyano group.

In order to obtain non cyclized condensation products, the reaction with malononitrile was performed at room temperature. The morpholino enamines **7a-7l** were used as starting materials instead of β-ketocarbothionic acid anilides. These enamines are assumed to be intermediates of *Knoevenagel* reactions performed in the presence of *sec.* amines at higher temperature[10].

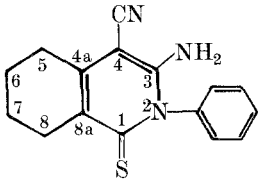
The reactions of enamines **7a-7l** with malononitrile performed in benzene solution at ambient temperature were completed in approxi-

Table 1. *1-Thioxo-2-phenyl-3-amino-4-cyano-1,2-dihydro-cycloalkeno[c]pyridines*

2	*n*	*X*	Yield %	m.p. °C	IR (Nujol) cm^{-1}	^{1}H-NMR [$(CD_3)_2CO$] ppm	M.S. *m/e*	M^+
a	1	H	81	248–250	3 430 3 330 3 220 NH 2 215 C≡N	1.25–1.37 m 2H 2.72–2.88 m 4H 6.25 s 2H NH_2 7.23–7.62 m 5 H arom.	267	100%
b	1	CH_3	79	245–248	3 450 3 320 3 210 NH 2 210 C≡N	2.40 s 3H CH_3 2.70–3.05 m 6H 6.30 s 2 H NH_2 7.05–7.42 2d 4H arom.	281	100%
c	1	Cl	83	214–215	3 460 3 330 3 220 NH 2 205 C≡N	2.70–3.05 m 6H 6.52 s 2H NH_2 7.20–7.62 2d 4H arom.	301	100%
d	1	Br	87	203–205	3 420 3 330 3 220 NH 2 205 C≡N	2.67–3.05 m 6H 6.55 s 2H NH_2 7.17–7.77 2d 4H arom.	345	100%
e	2	H	94	257–259	3 460 3 330 3 240 NH 2 210 C≡N	1.70–1.95 m 4H 2.82–3.12 m 4H 5.25 s 2H NH_2 7.37–7.87 m 5H arom.	281	100%
f	2	CH_3	72	234–236	3 470 3 310 3 210 NH 2 210 C≡N	1.72–1.90 m 4H 2.45 s 3H CH_3 2.68–2.84 m 4H 4.95 s 2H NH_2 7.05–7.45 m 4H arom.	295	100%
g	2	Cl	87	209–211	3 430 3 310 3 230 NH 2 220 C≡N	1.48–1.95 m 4H 3.25–3.42 m 4H 6.82 s 2H NH_2 7.15–7.68 2d 4H arom.	315	100%
h	2	Br	69	222–223	3 420 3 310 3 210 NH 2 210 C≡N	1.52–1.97 m 4H 3.07–3.51 m 4H 6.78 s 2H NH_2 7.12–7.57 2d 4H arom.	359	100%
i	3	H	78	223–225	3 470 3 320 3 220 NH 2 220 C≡N	1.37–1.98 m 6H 2.80–2.92 m 2H 3.17–3.30 m 2H 7.12–7.62 m 5H arom.	295	100%
j	3	CH_3	67	197–198	3 470 3 310 3 230 NH 2 220 C≡N	1.32–1.82 m 6H 2.67–2.95 m 4H 2.30 s 3H CH_3 5.02 s 2H NH_2 7.12–7.62 m 4H arom.	309	100%

Table 1 (continued)

2	*n*	*X*	Yield %	m.p. °C	IR (Nujol) cm^{-1}	^{1}H-NMR [$(CD_3)_2CO$] ppm	M.S. *m/e*	M^+
k	3	Cl	88	210–211	3450 3320 3200 NH 2210 C≡N	1.27–1.48 m 6H 2.82–3.25 m 4H 4.92 s 2H NH_2 7.17–7.62 m 4H arom.	329	100%
l	3	Br	83	215–216	3460 3320 3230 NH 2210 C≡N	1.38–1.97 m 6H 2.71–3.05 m 4H 6.74 s 2H NH_2 7.21–7.70 2d 4H arom.	373	100%

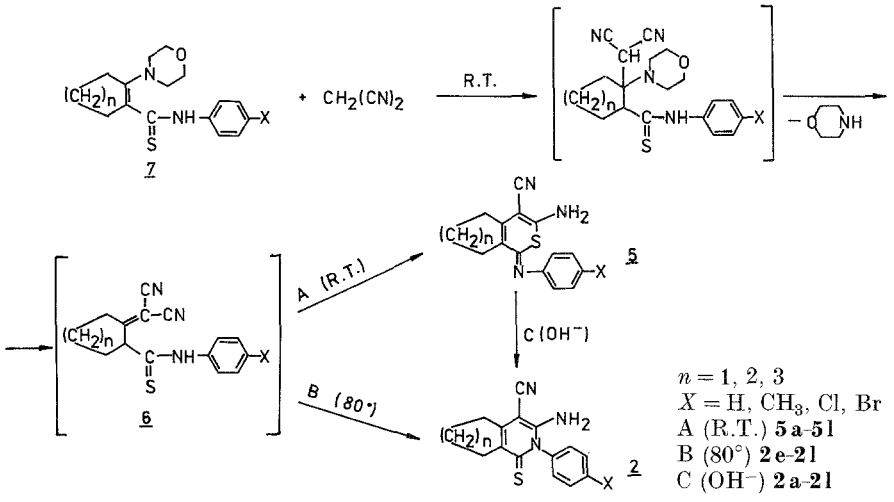


^{13}C-NMR ($CDCl_3$) ppm

21.64 C-5	153.02 C-3	128.18	2C-ar.
22.81 C-8	138.97 C-8a	129.74	C-ar.
29.05 C-7	144.76 C-4a	130.13	2C-ar.
29.25 C-6	183.44 C-1	130.98	C-ar.
153.15 C-4	116.16 C≡N		

mately 20–40 min giving yellowish coloured products in moderate to good yield (56–90%). Analytical data of all obtained products **5a–5l** were in agreement with the expected formulas for typical condensation products and showed that enamines reacted with malononitrile in

Scheme 3



molar ratio 1:1. The initial step of these reactions is an addition of malononitrile to C=C bond of enamine[11], followed by elimination of morpholine and formation of *Knoevenagel* condensation product **6**, which in turn may form thiopyran or pyridine derivatives. Thus, in this reaction two isomers **5** and **2** might have been expected (Scheme 3).

A distinction between the two possible isomeric products was made from mass spectral analysis of all obtained compounds. The mass spectra of compounds **5a–5l** exhibited the characteristic fragmentation patterns which unambiguously confirmed their structure as cycloalkeno-thiopyran derivatives. These spectra showed parent ions calculated for the expected formulas (Table 2). In each cases the fragmentation began with the loss of phenylisocyanide (X—C_6H_4NC, $X = H$, M^+—103; $X = CH_3$, M^+—117; $X = Cl$, M^+—137; $X = Br$, M^+—181) yielding fragmentary ions, which appeared as base peaks ($n = 1$, $m/e = 164$; $n = 2$, $m/e = 178$; $n = 3$, $m/e = 192$). It should be noted, that the samples of compound **5a** obtained in the reaction of thioanilide **1a** or enamine **7a** with malononitrile were found to be identical and their MS spectra exhibited the same characteristic fragmentation.

All obtained cycloalkeno-thiopyrans were stable under acidic conditions and yielded dark yellow or orange coloured salts with hydrochloric or acetic acid.

In some cases the reaction of enamine with malononitrile was exotermic and the mixture of two isomeric compounds of type **2** and **5** was formed (Table 1). Two isomers were easily separated by column chromatography.

When the reaction of malononitrile with enamine derivatives of six- and seven-membered β-keto-carbothionic acid anilides **7e–7l** were performed in boiling benzene, only cyclohexeno- or cycloheptenopyridines **2e–2l** were formed. In contrast, enamines **7a–7d**, derivatives of five-membered β-ketocarbothionic acid anilides, reacted with malononitrile in boiling benzene yielding exclusively cyclopenteno-thiopyran derivatives **5a–5d**.

Taking into account the above reactions it was found, that the course of cyclization of initially formed *Knoevenagel* products **6** depended on the temperature of the reaction and on the size of cycloalkene ring. It should be noted that thiopyran derivatives were formed easier than pyridine ones, because the formation of the latter required the increase in temperature of the reaction.

In further experiments it was interesting to study the possibilities of isomerization of cycloalkeno-thiopyrans **5** to cycloalkeno-pyridines **2**. The attempts to isomerization of **5** to **2** in boiling benzene or ethanol in the presence of morpholine were unsuccessful. The transformation of

Table 2. *1-Phenylimino-3-amino-4-cyano-1H-cycloalkeno[c]thiopyrans*

5	*n*	*X*	Yield %	m.p.	IR (Nujol) cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm	M.S. *m/e*	M^-
a	1	H	73	203-204	3450, 3420 3330, 3190 NH 2190 C≡N	1.87-2.12 m 2H 2.75-2.95 m 4H 5.20 s 2H NH_2 6.77-7.35 m 5H arom.	267 164	33% 100%
b	1	CH_3	67	213-215	3430, 3415 3330, 3230 NH 2195 C≡N	2.27 m 2H 2.63-2.77 m 4H 2.95 s 3H CH_3 7.10 s 2H NH_2 6.95-7.20 2d 4H arom.	281 164	33% 100%
c	1	Cl	89	212-215	3430, 3420 3330, 3220 NH 2190 C≡N	2.77-2.98 m 6H 7.17 s 2H NH_2 6.80-7.44 2d 4H arom.	301 164	29% 100%
d	1	Br	90	208-210	3430, 3410 3330, 3230 NH 2195 C≡N	2.67-2.97 m 6H 7.15 s 2H NH_2 6.80-7.42 2d 4H arom.	345 164	22% 100%
e	2	H	85	171-173	3460, 3420 3330, 3210 NH 2195 C≡N	1.67-1.82 m 2H 2.29-2.58 m 4H 2.83-2.97 m 2H 7.78 s 2H NH_2 6.45-6.73 m 5H arom.	281 178	24% 100%
f	2	CH_3	76	170-173	3460, 3430 3330, 3220 NH 2190 C≡N	1.75-1.82 m 4H 2.52-2.75 m 4H 2.42 s 3H CH_3 5.25 s 2H NH_2 7.02-7.45 2d 4H arom.	295 178	67% 100%
g	2	Cl	53 28 **2g**	155-157	3450, 3410 3320, 3210 NH 2195 C≡N	1.48-1.95 m 4H 3.25-3.42 m 4H 6.82 s 2H NH_2 7.15-7.68 2d 4H arom.	315 178	26% 100%
h	2	Br	79	170-172	3460, 3420 3330, 3220 NH 2190 C≡N	1.62-1.87 m 4H 2.32-2.96 m 4H 7.98 s 2H NH_2 6.65-7.55 2d 4H arom.	359 178	21% 100%
i	3	H	56 31 **2i**	203-205	3470, 3320 3215, 3190 NH 2190 C≡N	1.63-1.92 m 6H 2.42-2.78 m 4H 6.82 s 2H NH_2 7.58-7.87 m 5H arom.	295 192	24% 100%
j	3	CH_3	73	175-178	3440, 3380 3300, 3190 NH 2190 C≡N	1.26-1.80 m 6H 2.30 s 3H CH_3 2.75-2.95 m 4H 6.87 s 2H NH_2 6.57-7.20 2d 4H arom.	309 192	22% 100%
k	3	Cl	72 17 **2k**	178-180	3440, 3410 3320, 3200 NH 2195 C≡N	1.62-1.82 m 6H 2.48-2.62 m 4H 6.88 s 2H NH_2 6.30-6.73 2d 4H arom.	329 192	21% 100%
l	3	Br	58 34 **2i**	179-181	3460, 3325 3290, 3230 NH 2190 C≡N	1.30-1.83 m 6H 2.83-2.94 m 4H 7.46 s 2H NH_2 6.42-7.12 2d 4H arom.	373 192	12% 100%

compounds **5** to **2** occured readily with quantitative yield in ethanolic solution under the influence of sodium hydroxide[12]. The cyclohexeno- and cycloheptenо-pyridine derivatives **2e–2l** obtained in this way were in all respects identical with these obtained from the reactions of enamines **7e–7l** with malononitrile in boiling benzene. The isomerization of cyclopenteno-thiopyrans **5a–5d** under the influence of sodium hydroxide afforded cyclopenteno-pyridines **2a–2d**, which were not formed in the reactions of enamines **7a–7d** with malononitrile even at higher temperature. In this way the second series of compounds derivatives of cyclopenteno-pyridine was completed (Scheme 3). The MS spectra of compounds **2a–2d** exhibited the fragmentation characteristic for this series of compounds.

The above procedure offers a simple method for the synthesis of *o*-aminonitriles derivatives of cycloalkeno-thiopyran and cycloalkeno-pyridine, which in turn could provide ready access to a variety of useful systems.

Experimental

Melting points are uncorrected. IR spectra were recorded on UR-10 (Zeiss, Jena) spectrophotometer in Nujol mulls. ^{1}H-NMR spectra were taken on Tesla BS-487 spectrometer for solutions in deuterochloroform and in deuteroacetone, ^{13}C-NMR spectrum was recorded with a Varian XL-100 spectrometer (*TMS* as internal standard). Mass spectra were taken on LKB-9000S spectrometer. Elemental analyses were performed in Regional Laboratory of Phisico-Chemical Analyses and Structural Studies in Kraków. The analytical data for C, H, N, S (**2a–2l**, **5a–5l**) are in full agreement with the proposed structures.

Enamines **7a–7l** were prepared according to the method described in Ref.[13].

1-Phenylimino-3-amino-4-cyano-1H-cycloalkeno[c]thiopyran **5a–5l**

General Procedure

A solution of malononitrile (0.02 mol) in benzene (10 ml) was added to a solution of enamine **7** (0.2 mol) in benzene (100 ml). The mixture was stirred for 20-30 min at room temperature. The precipitated crystalline yellow product was isolated by filtration and washed with benzene. Evaporation of benzene solution gave an additional amount of product. The combined solids were purified by crystallization from ethanol or methanol. Yellow prisms, average yield 56-90%.

In the case of enamines **7** (**g**, **i**, **k**, **l**) two isomeric products **5** (**g**, **i**, **k**, **l**) and **2** (**g**, **i**, **k**, **l**) were formed simultanously. The crude solids were dissolved in chloroform and isomers **5** and **2** were separated on Al_2O_3 column. Evaporation of chloroform gave yellow semisolid residues, which were crystallized from ethanol. All cycloalkeno-thiopyrans have lower melting points than isomeric cycloalkeno-pyridines.

1-Thioxo-2-phenyl-3-amino-4-cyano-1,2-dihydro-cycloalkeno[c]pyridine **2**

a. Reactions of Enamines with Malononitrile (**2e–2l**)

To a benzene solution (100 ml) of enamine **7e–7l** (0.02 mol) malononitrile (0.02 mol) was added. The reaction mixture was refluxed for 2 h and then

filtered. The filtrate was concentrated and the resinous mass was treated with 30 ml of methanol. The crude product was filtered off and recrystallized from ethanol. Yellow prisms, yield 67–94%.

b. Reaction of Anilide **1e** or **1i** with Malononitrile (**2e**, **2i**)

A mixture of appropriate anilide (0.02 mol), malononitrile (0.02 mol) and 0.5 g of piperidine was refluxed in 150 ml of benzene or ethanol for 2 h. After cooling the precipitated solid was filtered off and crystallized from ethanol. Yield (56% **2e**), (51% **2i**).

c. Isomerization of Compounds **5** to **2**

To a solution of compounds **5** (0.05 mol) in 30 ml of ethanol 2 ml of 5% solution of sodium hydroxide was added. The reaction mixture was refluxed for 20 min. The intensive yellow solution was poured into 100 ml of ice water and the aqueous suspension was neutralized with dilute hydrochloric acid. The precipitate was filtered off, washed with water and purified by crystallization from ethanol. Yield 80–92%. Compounds **2a–2d** were obtained only in this manner.

1-Oxo-2-phenyl-3-amino-4-cyano-1,2,5,6,7,8-hexahydroisoquinoline **3e**

a. By Desulfuration of Compound **2e**

The mixture of **2e** (0.56 g, 0.002 mol), chloroacetic acid (5 g) and water (2 ml) was heated on a steam-bath under reflux for 30 min. The resulting intensive yellow solution was poured into 100 ml of ice water and neutralized with a solution of sodium hydroxide. The precipitated solid was filtered off and crystallized from methanol. Colourless needles, m.p. 272–274 °C. Yield 0,32 g (60%).

b. By Condensation of Anilide **4e** with Malononitrile

A mixture of anilide **4e** (6.5 g, 0.03 mol), malononitrile (2 g, 0.03 mol), piperidine (0.5 g) was refluxed for 10 h in ethanol (150 ml). Ethanol was distilled off and the precipitate was separated and crystallized from ethanol. Colourless prisms, m.p. 272–274 °C. Yield 2,4 g (30%). The identity samples obtained by the method a and b was confirmed by m.p., mixed m.p. and comparison of IR spectra.

$C_{16}H_{15}N_3O$ (265.3). Calc. C 72,43, H 5,70, N 15,84.
Found C 72,45, H 5,79, N 15,81.

IR (Nujol): 3450, 3330 (NH_2); 2205 cm^{-1} (CN).

1-Oxo-2-phenyl-3-amino-4-cyano-1,2,6,7,8,9-hexahydro-5H-cyclohepta[c]pyridine **3i**

a. By Desulfuration of Compound **2i**

The mixture of **2i** (1.5 g, 0.005 mol), chloroacetic acid (15 g) and water (10 ml) was heated under reflux for 1 h. The reaction mixture was worked up in a similar manner as described above for **3e** in a. Colourless prisms from ethanol, m.p. 245–246 °C. Yield 0.8 g (57%).

b. By Condensation of Anilide **4i** with Malononitrile

The reaction was performed in a similar manner as for compound **3e** described in b. The mixture of anilide **4i** (6.9 g, 0.03 mol), malononitrile (2 g,

0.03 mol) and piperidine (0.5 g) gave 2.1 g (25%) of **3i**. Colourless prisms from ethanol, m.p. 245–246 °C.

$C_{17}H_{17}N_3O$ (279.3). Calc. C 73,09, H 6,13, N 15,04.
Found C 72,98, H 6,05, N 15,06.

IR (Nujol): 3460, 3350 (NH_2), 2200 cm^{-1} (CN).

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