

## Knoevenagel Reaction of Malononitrile and Its "Dimer" with $\beta$ -Ketoanilides

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The reaction of benzoylacetanilides with malononitrile has been investigated. The structure of the compounds obtained (**2**, **3**, **4**) have been assigned on the basis of chemical properties and spectral data.

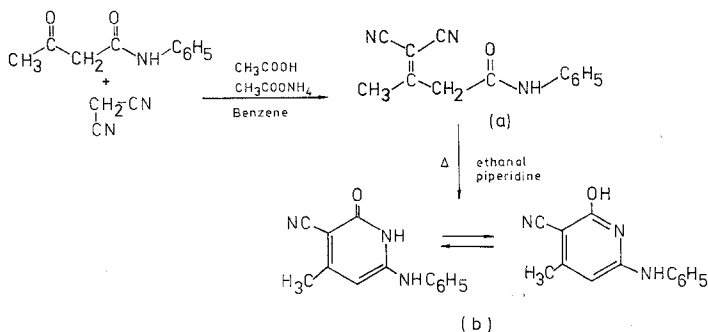
(Keywords: Heterocycles; Knoevenagel reaction)

*Die Knoevenagel-Reaktion von Malodinitril und seinem „Dimer“ mit  $\beta$ -Ketoaniliden*

Die Reaktion von Malodinitril mit Benzoylacetaniliden wurde untersucht. Die Struktur der dabei erhaltenen Verbindungen (**2**—**4**) wurde auf Basis der chemischen und spektroskopischen Eigenschaften zugeordnet.

*J. W. Ducker*<sup>1</sup> has shown that under *Cope-Knoevenagel* reaction conditions acetoacetanilides react with malononitrile in benzene to give the dicyanomethylene compounds (a). The product (a) heating in basic (piperidine) ethanol solution produces the pyridines (b).

Scheme 1



The aim of the present study has been to investigate the condensation of benzoylacetanilides **1 a, b, c, d** with malononitrile.

It was found that the reaction of equimolar amounts of benzoylacetanilides **1** and malononitrile in presence of piperidine in boiling ethanol yielded two compounds (**2** and **3**). They were separated utilizing the far greater solubility of one of them in boiling ethanol.

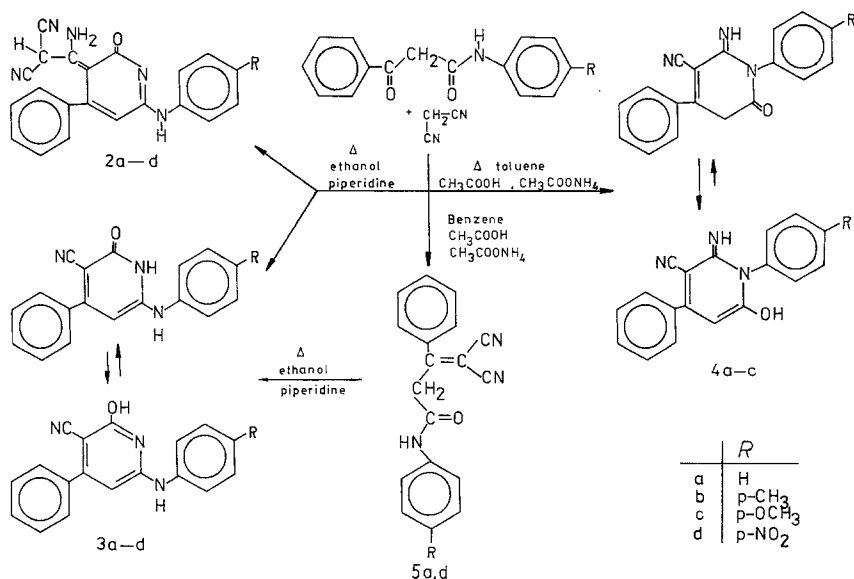
When the proportion of malononitrile was increased **2** was isolated as a main product. The optimum yield of **2** was obtained from two moles of malononitrile and one mole of benzoylacetanilide.

Attempts were made to parallel formation of **2** or **3** by the reaction of 4,4-dicyano-3-phenyl-N-phenyl-but-3-enamide with malononitrile in presence of piperidine in boiling ethanol but only the product **3** was formed.

The attempt to synthesize **2** from **3** and malononitrile in the molecular ration 1:1 was unsuccessful.

The analytical and IR (Table 1), MS spectral data observed for compounds **3 a, b, c, d** show good agreement with compound (b) to which the structure of 6-anilino-2-hydroxy-4-methyl-pyridine-3-carbonitrile was assigned by *Ducker*<sup>1</sup>.

Scheme 2



The structure of **2 a** was elucidated on the basis of chemical and analytical data, and IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, MS spectral data. Com-

Table 1. IR spectral data of compounds **2-5** (cm<sup>-1</sup>)

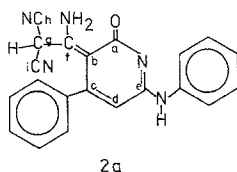
Compound	—C=C—	C=O	C=N	C≡N	N—H
<b>2 a</b>	1620	1670		2200	3490
				2190	3370
<b>2 b</b>	1610	1660		2200	3480
				2180	3440
					3280
<b>2 c</b>	1600	1660		2200	3480
				2180	3440
					3280
<b>2 d</b>	1620	1670		2200	3450
				2180	3380
<b>3 a</b>	1610	1690	1670	2220	3270
					3490 m
<b>3 b</b>	1610	1670	1650	2220	3280 w
					3440 m
<b>3 c</b>	1600	1680	1660	2210	3300 w
					3440 m
<b>3 d</b>	1620	1670	1640	2210	3330 w
					3460 m
<b>4 a</b>	1620	1700	1660	2210	3330 w
					3280
<b>4 b</b>	1620	1670	1660	2210	3200 w
					3280 m
<b>4 c</b>	1620	1670	1650	2210	3200 w
					3270 m
<b>4 e</b>	1620	1670	1650	2210	3100 w
					3280
<b>5 a</b>	1620	1670		2220	3300
<b>5 d</b>	1610	1670		2220	3280

ound **2 a** has basic properties, it is easily soluble in alkalies and yields salts with acids.

The infrared spectrum of compounds **2** showed typically strong NH absorption at 3 240, 3 370 cm<sup>-1</sup> and 3 490 cm<sup>-1</sup>, unconjugated nitrile bands 2 200 cm<sup>-1</sup> and 2 180 cm<sup>-1</sup> a strong carbonyl band at 1 670 cm<sup>-1</sup>, and a band at 1 620 cm<sup>-1</sup> (siehe Table 1).

The <sup>1</sup>H-NMR (*DMSO-d*<sub>6</sub>) spectrum of **2** showed a characteristic one proton singlet for the group —CH(CN)<sub>2</sub> and broad multiplet for NH groups (Table 2).

The <sup>13</sup>C-NMR spectrum showed, besides the aromatic carbon resonances, one amide carbonyl resonance at 167.77 ppm<sup>2</sup>. The nitrile carbons resonated at 117.92 ppm and 101.95 ppm whereas carbon carrying them at 40.43 ppm. The down field shift of one of the CN signals was caused probably by steric hindrance from the benzene ring.

Table 2.  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ) data for compounds **2** (ppm)

Compound	CH—	—NH	H <sub>aromat</sub>	—OCH <sub>3</sub>	—CH <sub>3</sub>
<b>2a</b>	6.37 (1H, s)	6.85 (3H)	7.45-7.73 (11H, m)	—	—
<b>2b</b>	6.37 (1H, s)	6.82 (3H)	7.47-7.25 (10H, m)	—	2.37 (3H, s)
<b>2c</b>	6.37 (1H, s)	6.62 (3H)	7.17-7.62 (10H, m)	3.87 (3H, s)	—
<b>2d</b>	6.37 (1H, s)	6.83 (3H)	7.15-7.58 (10H, m)	—	—

Table 3. Chemical shifts (ppm from  $\text{SiMe}_4$ ) in the  $^{13}\text{C-NMR}$  of **2a** (aromatic carbon resonances not shown)

Compound	C <sub>a</sub>	C <sub>b,c,e,f</sub>	C <sub>d</sub>	C <sub>g</sub>	C <sub>h,i</sub>
<b>2a</b>	167.77	138.27 134.77 132.17 131.08	105.46	40.43	117.92 101.95

The off-resonance noise decoupling revealed the nature of C<sub>g</sub>, the signal for this methine carbon showed doublet at 40.43 ppm. The next doublet 105.46 ppm was assigned to the carbon C<sub>d</sub> of heterocyclic ring.

Further evidence confirming the proposed structure of **2a** was obtained by the measurement of mass spectra (Table 4).

The basic breakdown pathway of compounds **2** is connected with the elimination of  $\text{CH}_2(\text{CN})_2$  [ $\text{M}^+ - 66$ ] and  $\text{NH}_3$  [ $\text{M}^+ - 17$ ]. The next intensive peak present in the spectra of all compounds **2** correspond to ions  $m/e$  155 [ $\text{C}_{10}\text{H}_5\text{NO}$ ]<sup>+</sup> and  $m/e$  140 [ $\text{C}_{10}\text{H}_6\text{N}$ ]<sup>+</sup>. They were formed by cleavage of heterocyclic pyridine ring on two different<sup>3</sup> fragmentation pathways of parent ion.

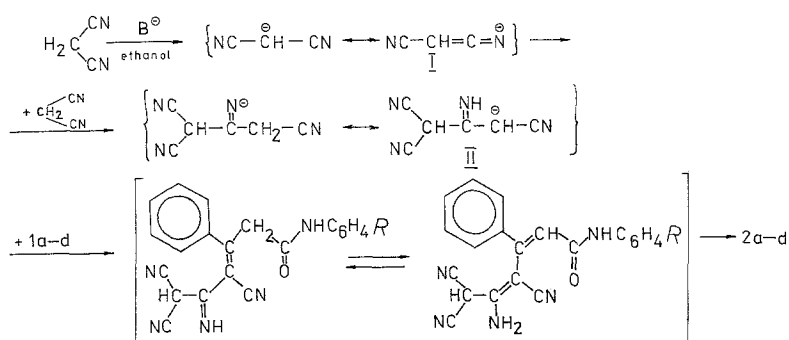
All spectra showed characteristic peaks corresponding to ions [ $\text{ArNH}$ ]<sup>+</sup>.

On the basis of these considerations the 6-arylamino-2,3-dihydro-2-oxo-4-phenyl-3-( $\alpha$ -amino- $\beta$ -dicyano)ethylideno-pyridine structure could be ascribed to compounds **2**.

This difference from the described route of the reaction of benzoyl-acetanilides with malononitrile may be explained on the basis of literature reports<sup>4-6</sup> regarding the dimerization of malononitrile.

In the presence of basic catalyst in ethanol solution malononitrile undergoes self-condensation to form dimers. The  $\alpha$ -methylene group in malononitrile is sufficiently acidic to afford a carboanion I which reacts to produce a very reactive carboanion II.

Scheme 3



The next step of reaction is connected with nucleophilic attack of carboanion II on the carbonyl atom of the benzoyl group. The *Knoevenagel* condensation product is formed as an intermediate. In the next step the intramolecular cyclization to the N-phenyl derivative occurs. It may be explained by the mechanism postulated by *Bogdanowicz-Szved*<sup>9</sup> for cyclization of dicyanomethylene compound (a).

A different course of reaction of benzoylacetanilides and acetyloacetanilide with malononitrile was observed when the reaction was carried out in the presence of acetic acid and ammonium acetate (compounds 4).

The derivatives 4 were identical on the basis of their analytical and spectral properties (Table 1, 4, 5).

4 showed strong bands in IR for the NH group at  $3280\text{ cm}^{-1}$ . The conjugated nitrile showed a strong absorption at  $2210\text{ cm}^{-1}$ . There was a weak band at  $1620\text{ cm}^{-1}$  assigned to the carbon-carbon double band, a strong carbonyl band at  $1670\text{ cm}^{-1}$  and a conjugated  $\text{C}=\text{N}$  band at  $1650\text{ cm}^{-1}$ .

The analysis of the mass spectrum showed the fragmentation characteristic for pyridine rings:  $m/e$  140  $[\text{C}_{10}\text{H}_6\text{N}]^+$ ,  $m/e$  150  $[\text{C}_{10}\text{H}_5\text{NO}]^+$  and ion  $[\text{M} - 28]^+$ .

Table 4. *m/e* Values of characteristic ions and their relative intensities for **2-5**

Compound	$M^+$		$M^+ - 17$		$M^+ - 66$		$M^+ - CO^+$		$C_{10}H_5NO^+$		$C_{10}H_6N^+$		$ArNH^+$	
	<i>m/e</i>	%	<i>m/e</i>	%	<i>m/e</i>	%	<i>m/e</i>	%	<i>m/e</i>	%	<i>m/e</i>	%	<i>m/e</i>	%
<b>2 a</b>	353	100	336	66.0	287	20	325	3.0	155	14.0	140	15.1	92	2.3
<b>2 b</b>	367	100	350	6.4	301	62.9	339	4.5	155	28.0	140	21.4	106	6.4
<b>2 c</b>	387	15.0	336	6.0	317	100	359	2.5	155	14.5	140	15.2	122	5.0
<b>2 d</b>	398	20.0	381	5.0	333	100	370	3.8	155	24.3	140	33.0	138	2.5
<b>3 a</b>	287	68.2					259	100	155	36.4	140	24.5	92	3.6
<b>3 b</b>	301	67.0					273	100	155	38.0	140	28.4	106	11.6
<b>3 c</b>	317	100					289	59.8	155	16.3	140	18.1	122	4.5
<b>3 d</b>	332	100					304	93.7	155	26.3	140	36.2	138	2.5
<b>4 a*</b>	287	100					259	12.3	155	5.4	140	12.3	92	2.9
<b>4 b</b>	301	100					273	5.3	155	4.9	140	11.3	106	3.0
<b>4 c</b>	317	100					289	5.1	155	6.0	140	19.3	122	2.1
<b>4 e*</b>	225	100					197	7.7	93	17.8	78	20.0	92	5.1
<b>5 a</b>	317	100											92	62.8
<b>5 d</b>	332	100											138	31.2

\* In addition *m/e* 93 for **4 e** [ $C_5H_3NO$ ] and *m/e* 78 for **4 a** [ $C_5H_4N$ ].

Table 5. *Physical properties and yields for 2-5\**

Compound	m.p. °C	Yield %	Crystalline form
<b>2 a</b>	302	70	Yellow prisms
<b>2 b</b>	279	75	Yellow prisms
<b>2 c</b>	270	80	Yellow prisms
<b>2 d</b>	300	50	Yellow prisms
<b>3 a</b>	286	18	Colorless needles
<b>3 b</b>	301	10	Light yellow needles
<b>3 c</b>	306	15	Colorless needles
<b>3 d</b>	301	20	Colorless needles
<b>4 a</b>	234	30	Colorless plates
<b>4 b</b>	241	40	Colorless needles
<b>4 c</b>	245	52	Colorless needles
<b>4 d</b>	142	30	Yellow needles
<b>4 e</b>	205	70	Colorless plates
<b>5 a</b>	115	75	Light yellow needles

\* Elemental analyses are in full agreement with the proposed structures.

## Experimental

Melting points are uncorrected. IR spectra were recorded on UR-10 (Carl Zeiss, Jena) spectrophotometer in KBr disk.  $^1\text{H-NMR}$  spectra were taken on Tesla BS-487 spectrometer using *TMS* as internal reference, in *DMSO* as a solvent.  $^{13}\text{C-NMR}$  spectra was measured on Bruker WH 90 in *DMSO-d*<sub>6</sub> as a solvent. Mass spectral molecular weight were determined with LKB-9000 S spectrometer. Elemental analyses were performed in Regional Laboratory of Physico-Chemical Analyses and Structural Studies in Kraków.

*6-Anilino-2-oxo-3-( $\alpha$ -amino- $\beta$ -dicyano)-ethylideno-4-phenyl-2,3-dihydropyridine (2a)*

*6-Anilino-2-hydroxy-3-carbonitrile-4-phenyl-pyridine (3a)*

A stirred mixture of 2.4 g (0.01 mol) benzoylacetanilide (**1a**) and 1.3 g (0.02 mol) malononitrile in dry ethanol 35 cm<sup>3</sup> containing piperidine (0.1 cm<sup>3</sup>) was heated under reflux for 10 h. The solid which precipitated from hot solution was filtered off, and recrystallized from dimethylformamide and ethanol mixture (1:1). Yellow prisms of **2a**, m.p. 302°. Yield (3 g) 70%.

After cooling, the precipitated solid was filtered off.

Recrystallization from dilute ethanol produced colorless needles of **3a**, m.p. 286°. Yield (0.7 g) 18%.

Procedure as above using 0.01 mol of anilide **1a**, **1b**, **1c**, **1a** and 0.02 mol of malononitrile was used to synthesize: **2b** and **3b**, **2c** and **3c**, **2d** and **3d**.

Properties for all compounds are listed in Table 5.

*2-Imino-4-phenyl-6-hydroxy-3-carbonitrile-N-phenyl-pyridine (4a)*

A mixture of 2.4 g (0.01 mol) benzoylacetanilide (**1a**), 0.7 g (0.01 mol) malononitrile, ammonium acetate 0.4 g, and 4 cm<sup>3</sup> acetic acid in 120 cm<sup>3</sup> toluene was heated under reflux for 20 h. The reaction mixture was concentrated in vacuo, and residual precipitated was recrystallized from benzene.

Colorless needles m.p. 234°. Yield 30%.

An analogous procedure was applied for compounds **4b**, **4c**, **4d** (see Tab. 4).

*2-Imino-4-methyl-6-hydroxy-3-carbonitrile-N-phenyl-pyridine (4e)*

The reaction was carried out in similar manner as that described above for **4a**. A mixture of 1.8 g (0.01 mol) acetoacetanilide, 1.7 g (0.01 mol) malononitrile, ammonium acetate 0.4 g, and 4 cm<sup>3</sup> acetic acid in 120 cm<sup>3</sup> toluene was heated under reflux for 20 h. Colorless plates, m.p. 205°. Yield 70%.

*4,4-Dicyano-3-phenyl-N-phenylbut-3-enamide (5a)*

A mixture of benzoylacetanilide (**1a**) 12 g (0.05 mol), malononitrile 3.3 g (0.05 mol), and ammonium acetate 0.78 g in acetic acid 0.6 g and benzene 80 cm<sup>3</sup> was heated under reflux with continuous water separation for 4 h.

The precipitated solid was filtered off and recrystallized from benzene. **5d** was prepared in analogy to **4a**.

*Reaction of 5a with malononitrile*

A stirred mixture of **5a** with equimolar amounts of malononitrile (1 g of **5a** and 0.2 g of malononitrile) in 10 cm<sup>3</sup> of dry ethanol containing 2 drops of piperidine was heated under reflux for 7 h. Compound **3a** was obtained.

### References

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