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Studies on Heterocyclic Enaminonitriles. IX.[1] Ring Opening of 2-Amino-3-cyano-4,5-dihydrofurans by the Use of Benzoyl(and Acetyl) Chlorides

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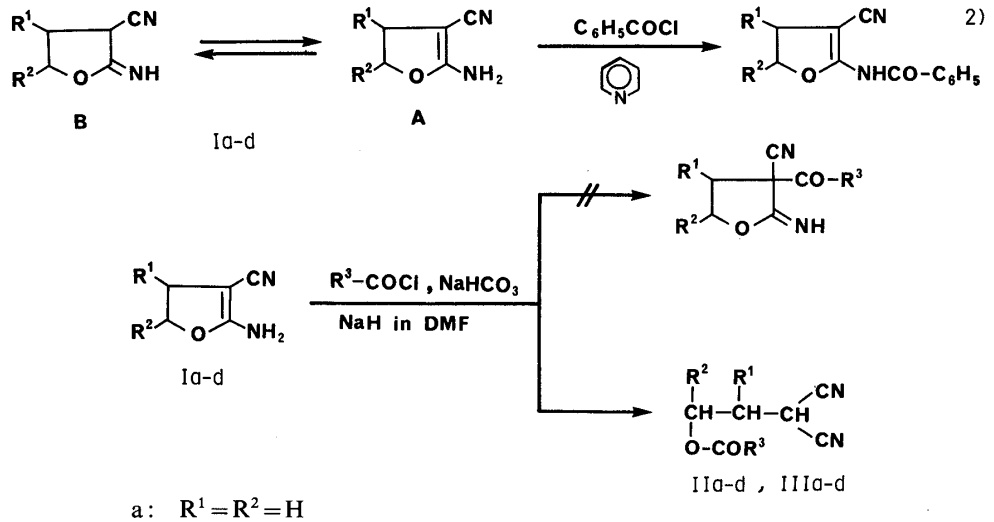
The reaction of 2-amino-3-cyano-4,5-dihydrofuran (Ia) with benzoyl(or acetyl) chloride in the presence of sodium hydride and sodium hydrogen carbonate gave 2-benzoyloxy(or acetoxy)ethylmalononitrile (IIa or IIIa). Similarly, 2-amino-3-cyano-5-methyl-4,5-dihydrofuran (Ib) and 2-amino-3-cyano-4-phenyl(or 5-phenyl)-4,5-dihydrofuran (Ic or Id) reacted with benzoyl(or acetyl)-chloride to form the corresponding malononitrile derivatives (IIb—d or IIIb—d). On the other hand, the reaction of Ia with phenacyl bromide gave 3-cyano-2-imino-3-phenacyltetrahydrofuran (IV).

Keywords——ring opening; 2-amino-3-cyano-4,5-dihydrofuran; 2-benzoyloxyethylmalononitrile; benzoyl chloride; acetyl chloride

In the previous paper, we reported that benzoyl chloride in pyridine attacks the enamino nitrogen of 2-amino-3-cyano-4,5-dihydrofurans (Ia—d), which exist as the enamine forms (A) rather than the imine forms (B), to give 2-benzamido-3-cyano-4,5-dihydrofurans.[2] However, it is well known that acylation of an enamine occurs in principle at the carbon atom β to nitrogen.[3] Therefore, we examined the acylation at the 3-position of Ia—d, and different results were obtained.



a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$
d: $R^1=H$, $R^2=C_6H_5$

II: $R^3=C_6H_5$
III: $R^3=CH_3$

Chart 1

When a solution of 2-amino-3-cyano-4,5-dihydrofuran (Ia) and sodium hydride in dimethylformamide (DMF) was treated with benzoyl chloride and sodium hydrogen carbonate, 2-benzoyloxyethylmalononitrile (IIa) was obtained in 69% yield, and the expected 3-benzoyl-3-cyano-2-iminotetrahydrofuran was not isolated. The infrared (IR) spectrum of IIa exhibited bands due to a nonconjugated cyano group at 2255 cm^{-1} and a carbonyl group at 1720 cm^{-1}, and no band indicative of an amino group was observed. The proton magnetic resonance (^{1}H-NMR) spectrum showed a one-proton triplet at δ 4.02 assignable to a methine group, a two-proton triplet at δ 4.56 and a two-proton multiplet at δ 2.36—2.65 indicative of two methylene groups, besides the signals due to five aromatic protons. The treatment of IIa with potassium carbonate gave Ia in 47% yield. This finding suggests that IIa was initially hydrolyzed to 2-hydroxyethylmalononitrile, which then underwent cyclization to form Ia. The structure of IIa was confirmed by direct comparison with an authentic sample prepared by the reaction of 2-bromoethyl benzoate with malononitrile.

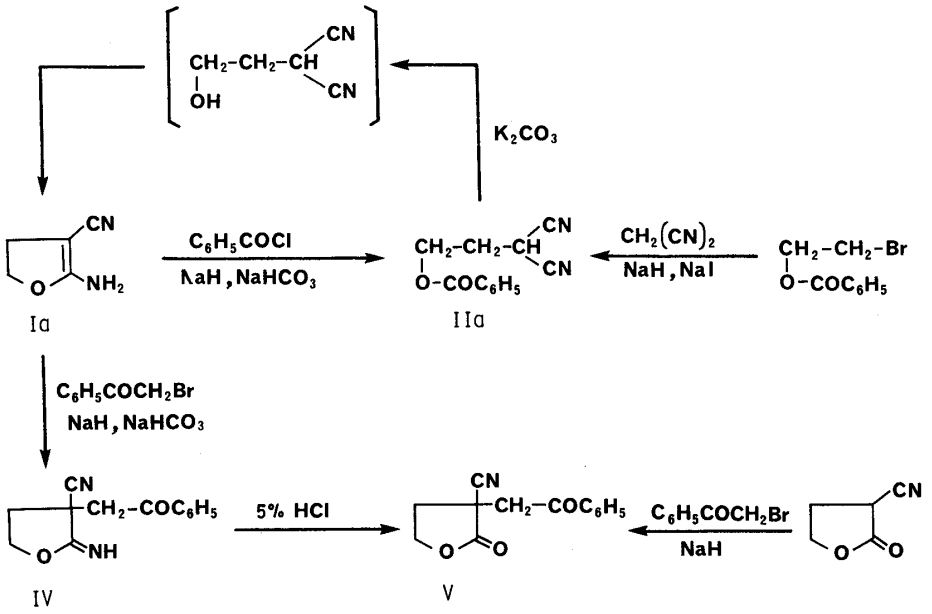


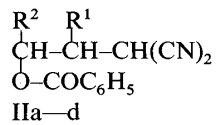
Chart 2

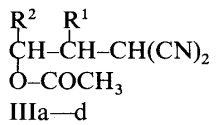
2-Amino-3-cyano-5-methyl-4,5-dihydrofuran (Ib) and 2-amino-3-cyano-4-phenyl(or 5-phenyl)-4,5-dihydrofuran (Ic or Id) reacted with benzoyl chloride under the same conditions to provide the corresponding malononitrile derivatives (IIb—d) in yields of 69, 51 and 57%, respectively. When the reaction of Ic with benzoyl chloride was carried out in the absence of sodium hydrogen carbonate, the yield of IIc decreased to 31%. In a similar manner, the reactions of Ia—d with acetyl chloride resulted in the formation of the corresponding 2-acetoxyethylmalononitriles (IIIa—d). The structural assignments of IIb—d and IIIa—d were made on the basis of elemental analysis (Table I) and the spectral data (Table II). The structures of IIIa and IIIc were confirmed by direct comparison with authentic specimens prepared from malononitrile and 2-bromoethyl acetate or 2-chloro-2-phenylethyl acetate.

On the other hand, in the reaction of Ia with phenacyl bromide under the same conditions, phenacyl bromide attacked the 3-position of Ia to furnish 3-cyano-2-imino-3-phenacyltetrahydrofuran (IV) in 63% yield. On hydrolysis with 5% hydrochloric acid, IV gave 3-cyano-2-oxo-3-phenacyltetrahydrofuran (V), the identity of which was confirmed by direct comparison with an authentic sample prepared from 3-cyano-2-oxotetrahydrofuran[4] and phenacyl bromide.

The formation of IIa—d and IIIa—d can be explained in terms of the scheme shown in

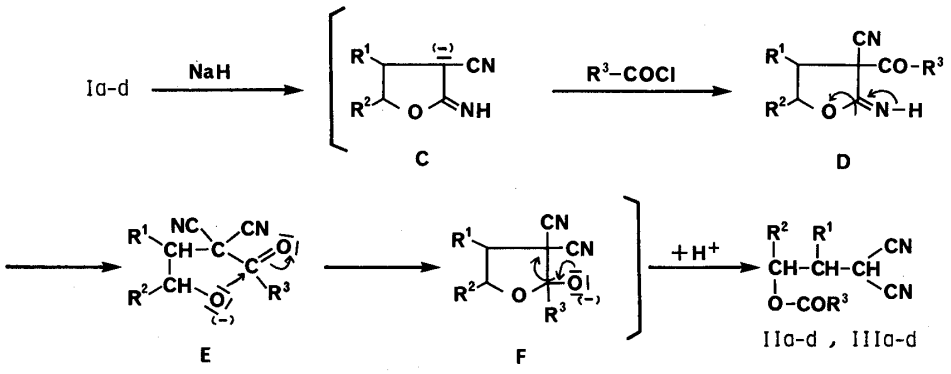
TABLE I. Yields, Melting Points, and Elemental Analyses of IIa—d and IIIa—d


IIa—d


IIIa—d

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$
d: $R^1=H$, $R^2=C_6H_5$

Compd. No.	Yield (%)	mp (°C) (Recrystallization solvent)	Appearance (Colorless)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
IIa	69	63—64 (Ether–petr. ether)	Needles	$C_{12}H_{10}N_2O_2$	67.28 (67.24	4.71 4.58	13.08 12.88)
IIb	69	60—61 (Ether–petr. ether)	Prisms	$C_{13}H_{12}N_2O_2$	68.41 (68.45	5.30 5.24	12.27 12.10)
IIc	51	112—114 (Acetone–petr. ether)	Columns	$C_{18}H_{14}N_2O_2$	74.47 (74.12	4.86 4.54	9.65 9.60)
IId	57	89—90 (Acetone–petr. ether)	Prisms	$C_{18}H_{14}N_2O_2$	74.47 (74.53	4.86 4.76	9.65 9.58)
IIIa	55	115—118/2 mmHg	Oil	$C_7H_8N_2O_2$	55.25 (54.76	5.30 5.34	18.41 18.34)
IIIb	67	35—36 (Ether–petr. ether)	Prisms	$C_8H_{10}N_2O_2$	57.82 (57.67	6.07 6.14	16.86 16.95)
IIIc	62	62—63 (Ether–petr. ether)	Prisms	$C_{13}H_{12}N_2O_2$	68.41 (68.16	5.30 5.25	12.27 12.18)
IIId	66	69—70 (Ether–petr. ether)	Columns	$C_{13}H_{12}N_2O_2$	68.41 (68.41	5.30 5.22	12.27 12.12)



a: $R^1=R^2=H$, b: $R^1=H$, $R^2=CH_3$, c: $R^1=C_6H_5$, $R^2=H$
d: $R^1=H$, $R^2=C_6H_5$

II: $R^3=C_6H_5$, III: $R^3=CH_3$

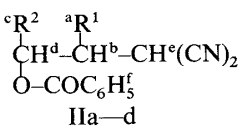
Chart 3

Chart 3. Sodium hydride abstracts a proton from Ia—d to give the anions (C), and an acyl chloride attacks C to provide 3-acyl-3-cyano-2-iminotetrahydrofurans (D), which undergo ring opening by a base to produce the alkoxide ions (E). The alkoxide ions attack the carbon atom of the carbonyl group to form (F), and then F are converted to IIa—d or IIIa—d.

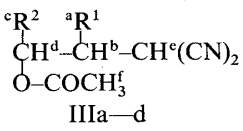
Experimental

DMF was distilled under reduced pressure and stored over molecular sieves 4A. All melting points are uncorrected. IR spectra were recorded on a JASCO A-302 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi

TABLE II. Spectral Data for IIa—d and IIIa—d



IIa—d



IIIa—d

a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=C_6H_5$, $R^2=H$
d: $R^1=H$, $R^2=C_6H_5$

Compd. No.	IR ν_{max}^{KBr} cm^{-1}		^{1}H-NMR spectra (ppm) (J in Hz)					
	CN	CO	H^a	H^b	H^c	H^d	H^e	H^f
IIa	2255	1720	[b]	2.36—2.65 (m)	4.56 (t, J=5.5)		4.02 (t, J=7)	7.32—7.70 (3H, m) 7.93—8.13 (2H, m)
IIb	2260	1712	[c]	2.51 (t, J=6.5)	1.39 (d) (J=6.5)	5.26 (sext) (J=6.5)	5.03 (t) (J=6.5)	7.40—7.78 (3H, m) 7.98—8.15 (2H, m)
IIc	2265	1723	[c] 7.35—7.78 (m)	4.01—4.23 (m)	4.71 (d) (J=6.5)		5.60 (d) (J=7)	7.35—7.78 (8H, m)[d] 7.98—8.13 (2H, m)
IId	2255	1710	[c]	2.64—2.93 (m)	7.30—7.81 (m)	6.13 (dd) (J=9.5, 4.5)	5.09 (dd) (J=7, 6)	7.30—7.81 (8H, m)[e] 8.05—8.23 (2H, m)
IIIa	2260[a]	1735[a]	[b]	2.26—2.49 (m)	4.33 (t, J=5.5)		4.01 (t, J=7)	2.09 (s)
IIIb	2260	1738	[b]	2.29 (t, J=6.5)	1.35 (d, J=6.5)	5.11 (sext) (J=6.5)	3.95 (t, J=6.5)	2.09 (s)
IIIc	2255	1732	[c] 7.41 (s)	3.78—4.01 (m)	4.44 (d) (J=6.5)		5.38 (d) (J=7)	2.03 (s)
IIId	2255	1745	[c]	2.49—2.70[f] (m)	7.36 (s)	5.86 (dd) (J=8.5, 5)	4.98 (t) (J=6.5)	2.09 (s)

Abbreviations: d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; sext, sextet; t, triplet. *a*) Neat. *b*) In $CDCl_3$. *c*) In DMSO-d_6. *d*) Overlapping with the H^a signal. *e*) Overlapping with the H^c signal. *f*) Overlapping with the solvent signal.

R-22 (90 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL model JMS-D 300 mass spectrometer.

Reactions of 2-Amino-3-cyano-4,5-dihydrofurans (Ia—d) with Acyl Halides. General Procedure——Compound Ia—d (10 mmol) was dissolved in DMF (15 ml), and 60% NaH (10 mmol) was added with stirring and cooling. After 30 min of stirring, acyl halide (10 mmol) and $NaHCO_3$ (10 mmol) were added, and the mixture was stirred at room temperature for 4 h, then poured into water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIa—d or IIIa—d in the yields shown in Table I.

Hydrolysis of IIa——A mixture of IIa (5 mmol) and potassium carbonate (5 mmol) in methanol (20 ml) and water (10 ml) was warmed for 0.5 h at 60 °C. After removal of the solvent *in vacuo*, the residue was poured into ice water, and salted out with NaCl. The deposited crystals were collected, washed with cold water, and dried. Recfystallization from acetone–petr. benzin gave 2-amino-3-cyano-4,5-dihydrofuran (Ia: 260 mg, 47%) as colorless prisms, mp 111—113 °C. This compound was shown to be identical with an authentic sample[2] by mixed melting point determination and comparison of the IR spectra.

Reactions of 2-Bromoethyl Benzoate, 2-Bromoethyl Acetate and 2-Chloro-2-phenylethyl Acetate with Malononitrile. General Procedure——Malononitrile (40 mmol) was added dropwise to a stirred suspension of 60% NaH (10 mmol) in DMF (20 ml). The stirring was continued until evolution of gas ceased. 2-Bromoethyl benzoate, 2-bromoethyl acetate or 2-chloro-2-phenylethyl acetate (10 mmol) and NaI (10 mmol) were added, and the mixture was heated at 70 °C for 2 h with stirring, then poured into ice water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give IIa (78%), IIIa (64%) or IIIc (21%).

Reaction of Ia with Phenacyl Bromide——Compound Ia (20 mmol) was dissolved in DMF (20 ml), and 60% NaH (20 mmol) was added with stirring and cooling. After 30 min of stirring, phenacyl bromide (20 mmol) and $NaHCO_3$ (20 mmol) were added, and the mixture was stirred at room temperature for 4 h, then poured into ice water. The precipitate was collected, dried, and recrystallized from acetone–petr. ether to give 3-cyano-2-imino-3-phenacyltetrahydrofuran (IV: 2.86 g, 63%) as colorless needles, mp 137—138 °C. *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.62; H, 5.43; N, 12.28. MS *m/z*: 228 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3300, 3260 (NH), 2250 (CN), 1684 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 2.44 (1H, dt, J=13, 8.5 Hz, C_4-H), 3.04 (1H, dt, J=13, 4.5 Hz, C_4-H), 3.47 and 4.03 (each 1H, each d, J=18 Hz, $-CH_2-COC_6H_5$), 4.43 (2H, dd, J=8.5, 4.5 Hz, C_5-H), 7.29—7.83 (4H, m, >NH and aromatic H), 7.82—8.04 (2H, m, aromatic H).

Hydrolysis of IV——A suspension of IV (5 mmol) in 40 ml of 5% HCl was stirred for 1 h at 40 °C. The reaction mixture was cooled, and the deposited crystals were collected, washed with water, and dried. Recrystallization from CH_2Cl_2–petr. ether gave 3-cyano-2-oxo-3-phenacyltetrahydrofuran (V: 0.99 g, 86%) as colorless needles, mp 103—104 °C. *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.90; H, 4.83; N, 6.16. MS *m/z*: 229 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2250 (CN), 1775, 1686 (CO). ^{1}H-NMR (in $CDCl_3$) δ: 2.49—3.10 (2H, m, C_4-H), 3.16 and 3.95 (each 1H, each d, J=18 Hz, $-CH_2-COC_6H_5$), 4.47—4.68 (2H, m, C_5-H), 7.33—7.73 (3H, m, aromatic H), 7.82—8.00 (2H, m, aromatic H).

Reaction of 3-Cyano-2-oxotetrahydrofuran with Phenacyl Bromide——3-Cyano-2-oxotetrahydrofuran (5 mmol) was dissolved in DMF (5 ml) and 60% NaH (5 mmol) was added with stirring and cooling. The stirring was continued until evolution of gas ceased. Phenacyl bromide (5 mmol) was then added, and the mixture was heated at 60 °C for 1 h. The solvent was removed *in vacuo*, and the residue was poured into ice water. The deposited crystals were collected, washed with water, dried, and recrystallized from CH_2Cl_2–petr. ether to give 3-cyano-2-oxo-3-phenacyltetrahydrofuran (V: 0.96 g, 84%), which was identical with an authentic sample prepared from IV on the basis of mixed melting point determination and comparison of the IR spectra.

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