[Chem. Pharm. Bull. 33(3) 937—943 (1985)]

Studies on Heterocyclic Enaminonitriles. VI.[1] Synthesis of 2-Amino-3-cyano-4,5-dihydrofurans

TAKUMI MATSUDA,[a] KENJI YAMAGATA,[b] YUKIHIKO TOMIOKA,[b] and MOTOYOSHI YAMAZAKI*,[b]

Research Laboratories, Hisamitu Pharmaceutical Co., Inc.,[a] 408 Tashiro, Tosu, Saga 841, Japan and Faculty of Pharmaceutical Sciences, Fukuoka University,[b] 8–19–1 Nanakuma, Jonan-ku, Fukuoka 814–01, Japan

(Received May 9, 1984)

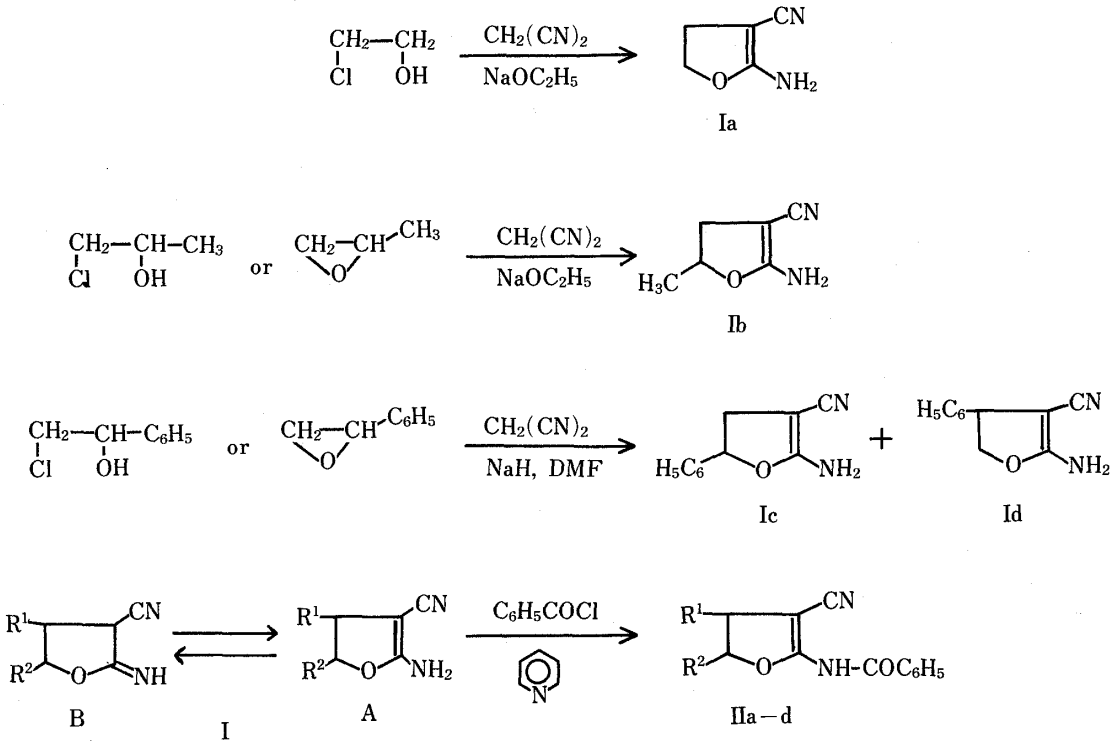
Malononitrile reacts with 2-chloroethanol and 1-chloro-2-propanol (or 2-methyloxirane) in the presence of sodium ethoxide to give 2-amino-3-cyano-4,5-dihydrofuran (Ia) and 2-amino-3-cyano-5-methyl-4,5-dihydrofuran (Ib), respectively. The reaction of malononitrile with 2-phenyloxirane or 2-chloro-1-phenylethanol gave 2-amino-3-cyano-4(and 5)-phenyl-4,5-dihydrofurans (Ic and Id). The 2-benzamido derivatives (IIb—d) of Ib—d were aromatized by treatment with *N*-bromosuccinimide to give the corresponding furans (IIIb—d).

Keywords——malononitrile; *N*-bromosuccinimide; ring opening; 2-amino-3-cyano-4,5-dihydrofuran; aromatization; 2-amino-3-cyanofuran; oxirane

In the previous papers, we showed that malononitrile reacts with 1-ethoxycarbonylaziridines and thiiranes in the presence of sodium hydride to form 2-amino-3-cyano-1-ethoxycarbonyl-4,5-dihydropyrroles[2] and 2-amino-3-cyano-4,5-dihydrothiophenes,[3] respectively. In the present paper, we wish to report a method for the preparation of 2-amino-3-cyano-4,5-dihydrofurans.

Morgenlie[4] reported a preparation of 2-amino-3-cyano-4,5-dihydrofuran (Ia) from the sodium salt of malononitrile and 2-bromoethanol. However, the yield of Ia is very low (10%). In order to improve this procedure, we examined the reaction of malononitrile with 2-chloroethanol. When a solution of malononitrile, 2-chloroethanol and sodium ethoxide in ethanol was stirred for 2 h at 40—50 °C, Ia was obtained in 62% yield. Similarly, the reaction of malononitrile with 1-chloro-2-propanol gave 2-amino-3-cyano-5-methyl-4,5-dihydrofuran (Ib) in 59% yield. Compound Ib was also synthesized from malononitrile, 2-methyloxirane and sodium ethoxide. Campaigne *et al.*[5] reported that when a mixture of malononitrile, 2-phenyloxirane and sodium hydride in dimethyl sulfoxide (DMSO) is stirred at room temperature for 16 h, and then heated at 60 °C for 3 h, 2-amino-3-cyano-5-phenyl-4,5-dihydrofuran (Ic, mp 95—97 °C) is formed in 55% yield. However, our attempt to synthesize Ic according to Campaigne *et al.* yielded 2-amino-3-cyano-4-phenyl-4,5-dihydrofuran (Id, mp 137—138 °C, 6%) and a 1 : 1 mixture (Ie, mp 104—106 °C, 48%) of Ic and Id.

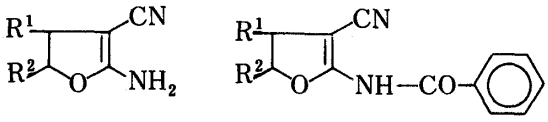
On the other hand, when a mixture of malononitrile, 2-phenyloxirane and sodium hydride in dimethylformamide (DMF) was stirred at room temperature for 2 h, and treated with ice water, Id and Ie were obtained in 66 and 12% yields, respectively. The products after 5 h at 90 °C were Ic (mp 114—116 °C, 23%) and Ie (18%). In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of Ic and Id, the benzylic proton of Ic appeared a doublet of doublets at δ 5.59, while that of Id was observed a multiplet at δ 4.14—4.43. Integration of the spectrum of Ie indicated it to be a 1 : 1 mixture of Ic and Id. Equimolecular amounts of Ic and



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

Chart 1

TABLE I. Some Properties of Ia—d and IIa—d

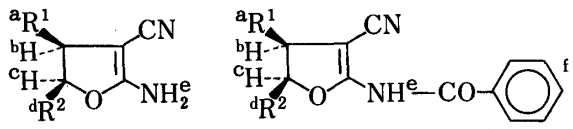


a: $R^1=R^2=H$
b: $R^1=H$, $R^2=CH_3$
c: $R^1=H$, $R^2=C_6H_5$
d: $R^1=C_6H_5$, $R^2=H$

Compd. No.	mp (°C) (Recrystn. solvent)	Appearance (Colorless)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
Ia	111—113 (Acetone–petr. benzin)	Prisms	62	$C_5H_6N_2O$	54.54 (54.26	5.49 5.41	25.44 25.35)
Ib	106—108 (CH_2Cl_2–petr. benzin)	Prisms	59 (46)[a]	$C_6H_8N_2O$	58.05 (58.01	6.50 6.41	22.57 22.60)
Ic	114—116 (CH_2Cl_2–petr. benzin)	Columns	(23)[a]	$C_{11}H_{10}N_2O$	70.95 (70.73	5.41 5.22	15.05 14.82)
Id	137—138 (CH_2Cl_2)	Prisms	60 (66)[a]	$C_{11}H_{10}N_2O$	70.95 (71.16	5.41 5.21	15.05 15.09)
IIa	139—140 (Acetone–petr. benzin)	Needles	81	$C_{12}H_{10}N_2O_2$	67.28 (67.49	4.71 4.94	13.08 12.87)
IIb	123—125 (Acetone–petr. benzin)	Prisms	84	$C_{13}H_{12}N_2O_2$	68.41 (68.78	5.30 5.62	12.27 12.03)
IIc	149—150 (Acetone–petr. benzin)	Columns	86	$C_{18}H_{14}N_2O_2$	74.47 (74.67	4.86 4.68	9.65 9.71)
IId	157—158 (Acetone)	Needles	81	$C_{18}H_{14}N_2O_2$	74.47 (74.68	4.86 4.68	9.65 9.71)

a) Yields from the reactions of oxiranes with malononitrile.

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



Ia—d IIa—d

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

Compd. No.	IR ν_{max}^{KBr} cm^{-1}			^{1}H-NMR spectra ppm (J in Hz)						MS
	NH	CN	CO	H^a	H^b	H^c	H^d	H^e	H^f	m/z (M^+)
Ia	3390 3310 3270	2170		a) —2.90— (t)		—4.47— (t)		4.95 (br s)		110
				(J=8.5)						
Ib	3420 3320 3270	2175		a) 2.99 (dd)	2.49 (dd)	4.60—5.00 (m)	1.37 (d)	5.10 (br s)		124
				($J_{a,b}$=12, $J_{a,c}$=8.5, $J_{b,c}$=7, $J_{c,d}$=6.5)						
Ic	3440 3330 3270	2190		a) 3.28 (dd)	2.88 (dd)	5.59 (dd)	7.33 (s)	5.03 (br s)		186
				($J_{a,b}$=12, $J_{a,c}$=9, $J_{b,c}$=8)						
Id	3450 3325 3270	2190		a) 7.13—7.45 (m)	4.60—4.89 (m)	4.14—4.43 (m)		5.07 (br s)		186
IIa	3290	2205	1683	a) —3.03— (t)		—4.54— (t)		8.29 (br s)	7.33—7.65 (3H, m) 7.78—8.00 (2H, m)	214
				(J=9)						
IIb	3220	2210	1700	a) 3.06 (dd)	2.53 (dd)	4.58—4.98 (m)	1.31 (d)	9.06 (br s)	7.27—7.60 (3H, m) 7.79—8.03 (2H, m)	228
				($J_{a,b}$=13.5, $J_{a,c}$=9.5, $J_{b,c}$=8, $J_{c,d}$=6)						
IIc	3260	2200	1685	b) 3.50 (dd)	2.96 (dd)	5.85 (dd)	7.44 (s)	11.20 (br s)	7.23—7.63 (3H, m) 7.84—8.00 (2H, m)	290
				($J_{a,b}$=13, $J_{a,c}$=10, $J_{b,c}$=8)						
IId	3290	2210	1692	b) 7.37 (s)	4.92 (dd)	4.30—4.72 (m)		11.25 (br s)	7.46—7.73 (3H, m) 7.99—8.07 (2H, m)	290
				($J_{b,c}$=7, $J_{b,d}$=9)						

Abbreviations: br s, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; t, triplet. *a*) In $CDCl_3$. *b*) In $(CD_3)_2SO$.

Id were dissolved in ether to provide "synthetic" Ie. Separation of Ie was attempted by column chromatography on alumina and recrystallization, but was not successful. On benzoylation, Ie was converted to 2-benzamido-3-cyano-5-phenyl-(and 4-phenyl)-4,5-dihydrofurans (IIc and IId), which could be separated by fractional crystallization. The reaction of 2-chloro-1-phenylethanol with malononitrile resulted in the formation of Id and Ie. On the basis of this finding, it seems likely that 2-chloroethanol, 1-chloro-2-propanol or 2-chloro-1-phenylethanol was converted to oxirane, 2-methyloxirane or 2-phenyloxirane on reaction with a base, and then a malononitrile anion attacked at C-2 of oxirane, at C-3 of 2-methyloxirane, or at C-3 and C-2 of 2-phenyloxirane to form Ia, Ib or Ic and Id.

The infrared (IR) spectra of Ia—d displayed bands in the 2170—2190 cm^{-1} region due to a conjugated cyano group and in the 3270—3450 cm^{-1} region indicative of a primary amino group. The ^{1}H-NMR spectra showed a broad two-proton singlet at near δ 5 attributable to an amino group. These observations are consistent with the enamine structures (A) rather than

the imine structures (B). On benzoylation with benzoyl chloride, Ia—d gave the corresponding 2-benzamido derivatives (IIa—d). Some properties of Ia—d and IIa—d are shown in Table I, and the spectral data are listed in Table II.

In order to confirm the structures of Ib—d, we aromatized IIb—d by the use of *N*-bromosuccinimide (NBS).[2,3,6] When a solution of 2-benzamido-3-cyano-5-methyl-4,5-dihydrofuran (IIb), NBS, and benzoyl peroxide in carbon tetrachloride was refluxed, 2-benzamido-3-cyano-5-methylfuran (IIIb) was obtained. Gewald[7] has reported that the reaction of 1-hydroxy-2-propanone with malononitrile in the presence of potassium hydroxide yields 2-amino-3-cyano-4-methylfuran (IV). Isidor *et al.*[8] concluded that the above reaction product is not IV, but its dimer, 2,4-diamino-3,5-dicyano-3*a*,6-dimethyl-3*a*-4,7,7*a*-tetrahydro-*endo*-4,7-epoxybenzofuran (IV′, mp 156—158 °C) formed by the Diels–Alder reaction of IV with itself. When diethylamine was used in place of potassium hydroxide, IV (mp 108—109 °C) was obtained. The structure assignment of IV was made on the basis of elemental analysis and the spectral data. Compound IV was heated at 130—135 °C for 30 min to furnish its dimer, IV′. On benzoylation with benzoic anhydride, IV gave 2-benzamido-3-cyano-4-methylfuran (V).

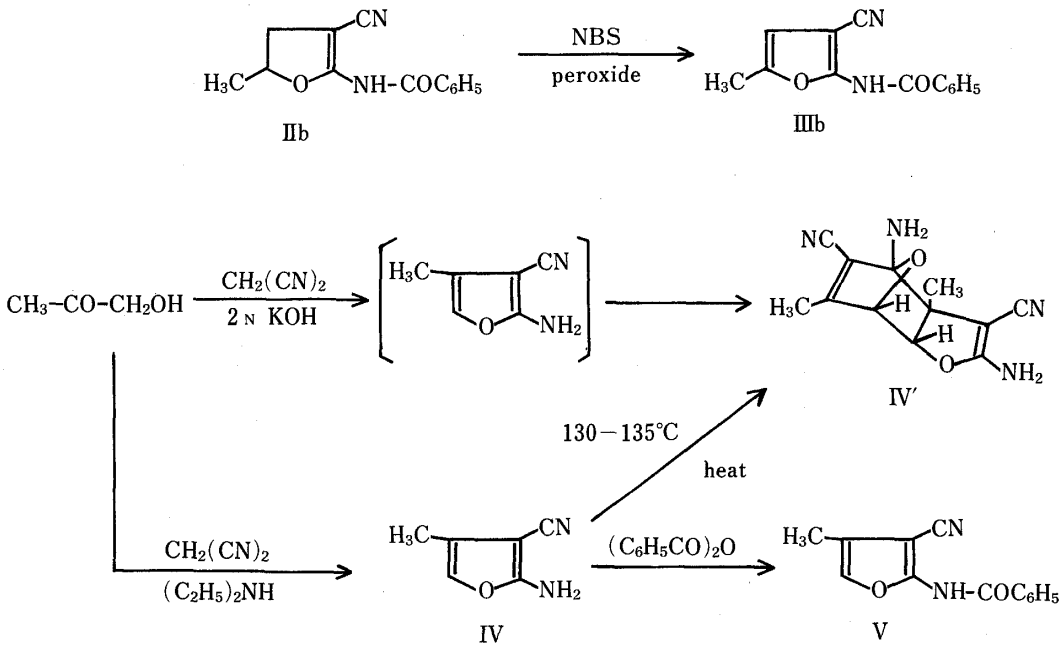


Chart 2

In the ^{1}H-NMR spectra of IIIb and V, the aromatic proton signal at C-4 in IIIb appeared at higher magnetic field than the proton signal at C-5 in V (δ 6.50 and δ 7.46 for IIIb and V, respectively). On the other hand, the methyl protons at C-5 in IIIb absorbed at lower field than the methyl protons at C-4 in V (δ 2.29 and δ 2.12 for IIIb and V, respectively). On the basis of these spectral data, IIIb was assigned as 2-benzamido-3-cyano-5-methylfuran.

Subsequently, the reaction of 2-benzamido-3-cyano-5-phenyl-4,5-dihydrofuran (IIc) with NBS gave 2-benzamido-3-cyano-5-phenylfuran (IIIc), which was proved to be identical with an authentic sample prepared from 2-amino-3-cyano-5-phenylfuran (VI) and benzoyl chloride. Temnikova *et al.*[9] showed that treatment of phenacylmalononitrile[10] with a base results in cyclization to VI, although no experimental details were given. Phenacylmalononitrile was cyclized to VI by treatment with piperidine in refluxing ethanol.

Finally, the reaction of IId with NBS gave 2-benzamido-3-cyano-4-phenylfuran (IIId) together with 2-benzamido-5-bromo-3-cyano-4-phenylfuran (VII). The structure of IIId was

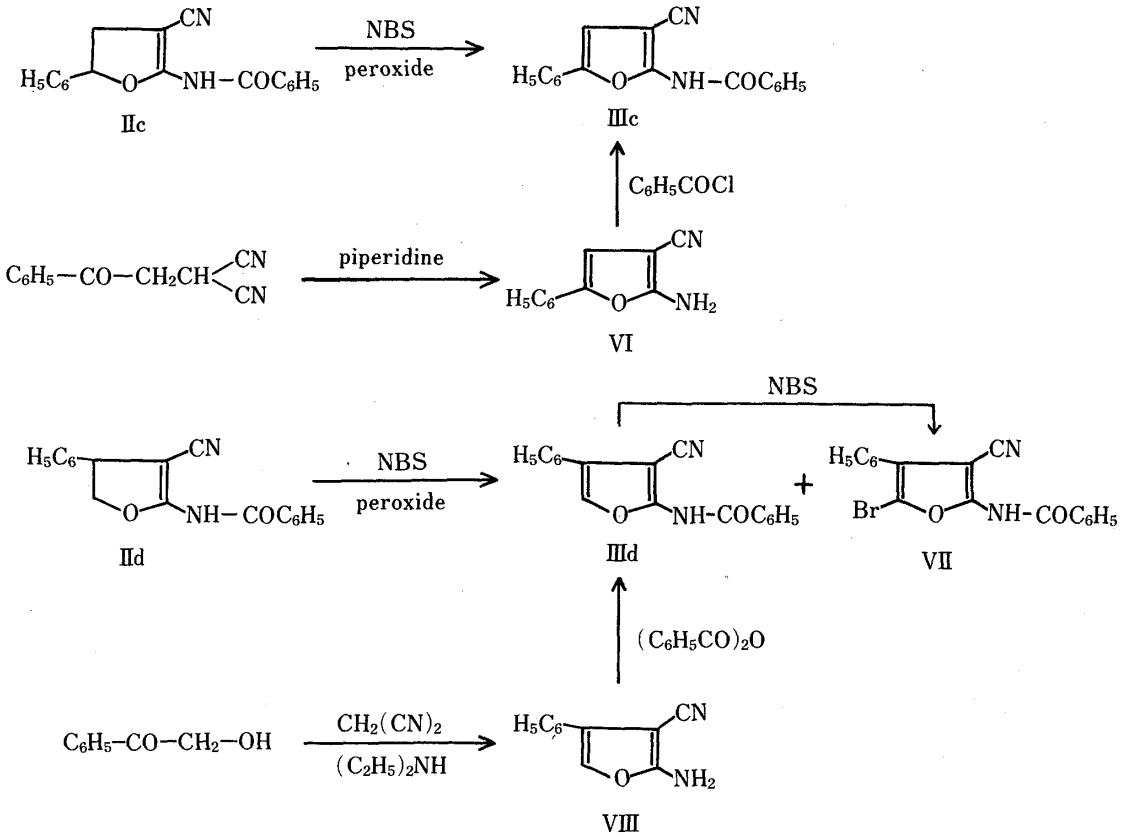


Chart 3

confirmed by direct comparison with an authentic sample prepared from 2-amino-3-cyano-4-phenylfuran (VIII) and benzoic anhydride. 2-Hydroxyacetophenone reacted with malononitrile in the presence of diethylamine to give VIII, which was converted to IIId on heating with benzoic anhydride. Compound VII was formed by bromination of IIId with NBS.

Experimental

DMF was prepared by distillation from calcium hydride and stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 or a JASCO A-302 spectrometer. ^{1}H-NMR spectra were taken on a Hitachi R-22 (90 MHz) or a JNM-MH-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL JMS-01SG spectrometer.

Reaction of Malononitrile with 2-Chloroethanol or 1-Chloro-2-propanol——A solution of 2-chloroethanol or 1-chloro-2-propanol (0.2 mol) in abs. EtOH (20 ml) was added dropwise to a stirred solution of malononitrile (0.2 mol) and sodium ethoxide (0.2 mol) in abs. EtOH (80 ml) at 40—50 °C. The resulting mixture was warmed for 2 h at 40—50 °C with stirring. The NaCl was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was poured into ice water, and salted out with NaCl. The deposited crystals were collected, washed with cold water, dried, and recrystallized from the solvent listed in Table I.

Reaction of Malononitrile with 2-Methyloxirane——A solution of 2-methyloxirane (0.2 mol) in abs. EtOH (20 ml) was added dropwise to a stirred solution of malononitrile (0.3 mol) and sodium ethoxide (0.2 mol) in abs. EtOH (80 ml) at a temperature below 35 °C. After 2 h of heating at 40—50 °C, the EtOH was removed *in vacuo*, and the residue was poured into ice water, and salted out with NaCl. The precipitate was collected, washed with cold water, and dried. Recrystallization from CH_2Cl_2–petr. benzin gave Ib (11.36 g, 46%).

Reaction of Malononitrile with 2-Phenyloxirane——(a) The reaction of malononitrile (14.5 g, 0.22 mol) with 2-phenyloxirane (12 g, 0.1 mol) in DMSO was carried out according to the method described by Campaigne *et al.*[5] When the reaction was complete, the cooled mixture was poured into ice water (*ca.* 800 ml), salted out with NaCl, and kept in a refrigerator overnight. The precipitate was collected, successively washed with water and petr. benzin, dried, and then dissolved in $CHCl_3$ (*ca.* 150 ml). The $CHCl_3$-insoluble material was removed by filtration. The filtrate was concentrated *in vacuo*. The residue was chromatographed on alumina with $CHCl_3$ as the eluent to give a mixture of 2-amino-3-cyano-4(and 5)-phenyl-4,5-dihydrofurans (Id and Ic). Fractional crystallization from ether–petr. ether gave

colorless columns (1.05 g, 6%) of the less soluble compound (Id, mp 137—138 °C) and colorless columns (8.94 g, 48%) of the more soluble one (a 1 : 1 mixture (Ie) of Ic and Id, mp 104—106 °C).

(b) Malononitrile (13.2 g, 0.2 mol) was dissolved in DMF (80 ml) and 60% NaH (5 g, 0.125 mol) was added with stirring and cooling. The stirring was continued until evolution of gas ceased. The mixture was heated at 90 °C, and then a solution of 2-phenyloxirane (12 g, 0.1 mol) in DMF (20 ml) was added dropwise over a period of 10 min. The whole was heated at 90 °C for 5 h. After work-up as noted in (a), a mixture of Ic and Id was obtained. Fractional crystallization from CH_2Cl_2–petr. benzin gave colorless columns (4.2 g, 23%) of the less soluble compound (Ic, mp 114—116 °C), and colorless columns (3.36 g, 18%) of the more soluble one (Ie).

(c) A solution of 2-phenyloxirane (12 g, 0.1 mol) in DMF (20 ml) was added dropwise to a stirred mixture of malononitrile (13.2 g, 0.2 mol) and 60% NaH (4 g, 0.1 mol) in DMF (80 ml) at a temperature below 15 °C. The resulting mixture was stirred for 2 h at room temperature, poured into ice water (*ca.* 800 ml), allowed to stand in a refrigerator overnight, and salted out with NaCl. The precipitate was collected, successively washed with water and petr. benzin, and dried. Recrystallization from $CHCl_3$ or CH_2Cl_2 gave Id (12.35 g, 66%). The mother liquor of the recrystallization of Id was evaporated to dryness and the residue was recrystallized from ether–petr. ether to give Ie (2.22 g, 12%).

Reaction of Malononitrile with 2-Chloro-1-phenylethanol——A solution of 2-chloro-1-phenylethanol (15.7 g, 0.1 mol) in DMF (20 ml) was added dropwise to a stirred mixture of malononitrile (13.2 g, 0.2 mol) and 60% NaH (8 g, 0.2 mol) in DMF (80 ml) at 10—15 °C. The reaction mixture was stirred for 2 h at room temperature. Work-up of the reaction mixture as described above (c) gave Id (11.2 g, 60%) and Ie (2.3 g, 12%).

Preparation of Ie——When petr. ether was added to a solution of Ic (0.25 g) and Id (0.25 g) in ether (30 ml), Ie (0.48 g) was obtained as colorless columns, mp 104—106 °C.

Benzoylation of Ia, b or d——A mixture of Ia, b or d (0.05 mol) and benzoyl chloride (0.055 mol) in pyridine (15 ml) was heated at 40—50 °C for 2 h with stirring. The reaction mixture was poured into ice-aq. $NaHCO_3$. The deposited crystals (IIa, b or d) were collected, washed with water, dried, and recrystallized from an appropriate solvent (Table I).

Benzoylation of Ic——A mixture of Ic (4.65 g) and benzoyl chloride (3.86 g) in pyridine (10 ml) was heated at 40—50 °C for 2 h. Work-up of the reaction mixture as described above gave IIc (6.22 g, 86%).

Benzoylation of Ie——A mixture of Ie (9.3 g, 0.05 mol) and benzoyl chloride (7.73 g, 0.055 mol) in pyridine (20 ml) was heated at 40—50 °C for 1 h. The reaction mixture was poured into ice-aq. $NaHCO_3$. The precipitate was collected, washed with water, and dried. The precipitate was chromatographed on silica gel. Elution with $CHCl_3$ gave a mixture of IIc and IId. Fractional crystallization from acetone–petr. benzin gave colorless needles (3.83 g) of the less soluble compound (IId, mp 157—158 °C) and colorless columns (3.58 g) of the more soluble one (IIc, mp 149—150 °C).

Reaction of IIb with NBS——A solution of IIb (1.14 g, 5 mmol) in $CHCl_3$ (20 ml) was added dropwise to a refluxed solution of NBS (980 mg, 5.5 mmol) and benzoyl peroxide (100 mg) in CCl_4 (100 ml) over a period of 10 min. After 30 min of refluxing, triethylamine (1.1 g) was added, and the whole was refluxed for another 1 h. The reaction mixture was basified with aq. $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was 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 IIIb (270 mg, 24%). 2-Benzamido-3-cyano-5-methylfuran was recrystallized from acetone–petr. benzin to give colorless needles, mp 196—197 °C. *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.98; H, 4.32; N, 12.42. IR ν_{max}^{KBr} cm^{-1}: 3240 (≥NH), 2220 (CN), 1669 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 2.29 (3H, d, J=1 Hz, C_5-C<u>H</u>$_3$), 6.50 (1H, q, J=1 Hz, C_4-H), 7.44—7.67 (5H, m, aromatic H), 11.22 (1H, br s, ≥N<u>H</u>).

Preparation of 2-Amino-3-cyano-4-methylfuran (IV)——Diethylamine (10 ml) was added dropwise to a stirred solution of malononitrile (19.8 g, 0.3 mol) and 1-hydroxy-2-propanone (14.8 g, 0.2 mol) in MeOH (50 ml) at a temperature below 40 °C. The reaction mixture was stirred for 2 h at 30—35 °C, poured into ice water, and salted out with NaCl. The precipitate was collected, washed with water, dried, and recrystallized from ether–petr. ether to furnish IV as colorless prisms, 15.37 g (63%), mp 108—109 °C. *Anal.* Calcd for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.14; H, 4.99; N, 23.04. MS *m/z*: 122 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3420, 3320, 3260 (NH_2), 2200 (CN). ^{1}H-NMR (in $CDCl_3$) δ: 2.01 (3H, d, J=1.5 Hz, C_4-C<u>H</u>$_3$), 5.06 (2H, br s, -N<u>H</u>$_2$), 6.54 (1H, q, J=1.5 Hz, C_5-H).

Dimerization of IV——Compound IV (1.22 g) was heated at 130—135 °C for 30 min. During this time IV melted and its dimer (IV′) gradually solidified. Recrystallization from nitromethane gave IV′ (860 mg, 70%, mp 157—159 °C, lit.,[7] mp 156—158 °C), which was identical with an authentic sample by mixed melting point determination and comparison of the IR spectra.

2-Benzamido-3-cyano-4-methylfuran (V)——A mixture of IV (1.22 g) and benzoic anhydride (2.7 g) in toluene (3 ml) was refluxed for 5 h. After the solvent had been removed *in vacuo*, the residue was basified with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by column chromatography on silica gel with $CHCl_3$ as the eluent. Recrystallization from acetone–petr. benzin gave V (670 mg, 30%) as colorless columns, mp 187—189 °C. *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.83; H, 4.12; N, 12.31. IR ν_{max}^{KBr} cm^{-1}: 3260 (≥NH), 2240 (CN), 1660 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 2.12 (3H, d, J=1.5 Hz, C_4-C<u>H</u>$_3$), 7.46 (1H, q, J=1.5 Hz, C_5-H), 7.53—7.69 (3H, m, aromatic H), 7.91—8.16 (2H, m, aromatic H), 11.54 (1H, br s, ≥N<u>H</u>).

Reaction of IIc or d with NBS——A solution of IIc or d (5 mmol) and benzoyl peroxide (50 mg) in $CHCl_3$ (30 ml) was added dropwise to a refluxed solution of NBS (5.5 mmol) and benzoyl peroxide (100 mg) in CCl_4 (100 ml) over a period of 10 min. After 30 min of refluxing, triethylamine (1.1 g) was added, and the reaction mixture was refluxed for another 1 h. The solvent was removed *in vacuo*, and the residue was made alkaline with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and concentrated *in vacuo*.

(i) For IIc: The residue was washed with ether, and recrystallized from acetone to give IIIc (570 mg, 40%) as colorless needles, mp 213—214 °C. *Anal.* Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.52; H, 3.85; N, 9.70. MS *m/z*: 288 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3400 (≥NH), 2240 (CN), 1673 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 7.40 (1H, s, C_4-H), 7.35—7.76 (8H, m, aromatic H), 7.98—8.10 (2H, m, aromatic H), 11.73 (1H, br s, ≥NH).

(ii) For IId: The residue was chromatographed on silica gel. The first fraction eluted with $CHCl_3$ gave VII (140 mg, 8%), which was recrystallized from CH_2Cl_2–petr. benzin to provide colorless needles, mp 177—178 °C (dec.). The second product to appear was IIId (350 mg, 24%), which was identical with an authentic sample prepared from VIII by mixed melting point determination and comparison of the IR spectra.

Preparation of 2-Amino-3-cyano-5-phenylfuran (VI)——A mixture of phenacylmalononitrile[10] (3.68 g) and piperidine (5 ml) in abs. EtOH (50 ml) was refluxed for 1 h. The EtOH was removed *in vacuo*, and the residue was poured into ice water. The precipitate was collected, dried, and recrystallized from MeOH to afford VI (1.84 g, 50%) as colorless scales, mp 196—198 °C. *Anal.* Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.68; H, 4.02; N, 15.28. IR ν_{max}^{KBr} cm^{-1}: 3400, 3320, 3240 (NH_2), 2200 (CN). ^{1}H-NMR (in DMSO-d_6) δ: 6.94 (1H, s, C_4-H), 7.18—7.55 (5H, m, aromatic H), 7.56 (2H, br s, $-NH_2$).

2-Benzamido-3-cyano-5-phenylfuran (IIIc)——A mixture of VI (920 mg) and benzoyl chloride (840 mg) in pyridine (5 ml) was heated at 60 °C for 2 h. The reaction mixture was poured into ice water. The precipitate was collected, washed with water, dried, and recrystallized from acetone to give IIIc (1.41 g, 73%) as colorless needles, mp 213—214 °C.

Preparation of 2-Amino-3-cyano-4-phenylfuran (VIII)——Diethylamine (2.5 ml) was added dropwise to a stirred solution of 2-hydroxyacetophenone (6.8 g) and malononitrile (4.95 g) in MeOH (15 ml) at a temperature below 40 °C. After the whole had been stirred for 1 h at 30—35 °C, the reaction mixture was poured into ice water. The deposited crystals were collected, washed with water, and dried. Recrystallization from CH_2Cl_2–petr. benzin gave VIII (7.86 g, 85%) as colorless columns, mp 88—89 °C. *Anal.* Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.36; H, 4.05; N, 15.07. IR ν_{max}^{KBr} cm^{-1}: 3420, 3320, 3240 (NH_2), 2200 (CN). ^{1}H-NMR (in $CDCl_3$) δ: 5.00 (2H, br s, $-NH_2$), 6.96 (1H, s, C_5-H), 7.27—7.60 (5H, m, aromatic H).

2-Benzamido-3-cyano-4-phenylfuran (IIId)——A mixture of VIII (1.84 g) and benzoic anhydride (2.7 g) in toluene (3 ml) was refluxed for 5 h. The toluene was removed *in vacuo*, and the residue was basified with aq. $NaHCO_3$. The precipitate was collected, washed with water and ether, and dried. Recrystallization from acetone–petr. benzin gave IIId (1.32 g, 46%) as colorless needles, mp 191—192 °C. *Anal.* Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.73; H, 3.83; N, 9.74. IR ν_{max}^{KBr} cm^{-1}: 3230 (≥NH), 2220 (CN), 1670 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 7.38—7.78 (8H, m, aromatic H), 7.93—8.16 (2H, m, aromatic H), 8.09 (1H, s, C_5-H), 11.62 (1H, br s, ≥NH).

2-Benzamido-5-bromo-3-cyano-4-phenylfuran (VII)——A solution of IIId (288 mg) and NBS (196 mg) in $CHCl_3$ (30 ml) was refluxed for 1 h. The reaction mixture was basified with aq. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–petr. benzin to give VII (320 mg, 87%) as colorless needles, mp 177—178 °C (dec.). *Anal.* Calcd for $C_{18}H_{11}BrN_2O_2$: C, 58.87; H, 3.02; N, 7.63. Found: C, 58.83; H, 2.83; N, 7.15. MS *m/z*: 366 (M^+), 368 ($M^+ + 2$). IR ν_{max}^{KBr} cm^{-1}: 3220 (≥NH), 2240 (CN), 1680 (CO). ^{1}H-NMR (in DMSO-d_6) δ: 7.40—7.78 (8H, m, aromatic H), 7.96—8.12 (2H, m, aromatic H), 11.82 (1H, br s, ≥NH).

Acknowledgement The authors thank the staff of the Analytical Center of the Faculty of Pharmaceutical Sciences, Fukuoka University, for NMR spectra, MS and elemental analyses.

References

1) Part V: H. Matsunaga, M. Sonoda, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, **32**, 2596 (1984).
2) M. Sonoda, N. Kuriyama, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, **30**, 2357 (1982).
3) K. Yamagata, Y. Tomioka, M. Yamazaki, and K. Noda, *Chem. Pharm. Bull.*, **30**, 4396 (1982).
4) S. Morgenlie, *Acta Chem. Scand.*, **24**, 365 (1970).
5) E. Campaigne, R. L. Ellis, and M. Bradford, *J. Heterocycl. Chem.*, **6**, 159 (1969).
6) *a*) W. Forest, "Newer Methods of Organic Chemistry," Vol. II, Academic Press, New York and London, 1964, p. 165; *b*) G. Bianchi and P. Grunanger, *Tetrahedron*, **22**, 817 (1965).
7) K. Gewald, *Chem. Ber.*, **99**, 1002 (1966).
8) J. L. Isidor, M. S. Brookhart, and R. L. Mckee, *J. Org. Chem.*, **38**, 612 (1973).
9) T. I. Temnikova, Y. A. Sharanin, and V. S. Karavan, *Zh. Org. Khim.*, **3**, 596 (1967).
10) T. I. Temnikova and Y. A. Sharanin, *Zh. Org. Khim.*, **2**, 2018 (1966).