Hydrolysis of 7. A 34-mg (0.218 mmol) sample of **7** was dissolved in 10 mL of 0.2 N sulfuric acid and heated to reflux. At successive time intervals, 1-mL aliquots were applied to a 2.5 × 90 cm column packed with Dowex AG-50W-X8 resin, H^+ form, 200–400 mesh. After 15 h, a small quantity of precipitate was removed by filtration and identified by NMR as **8**. A 1-mL aliquot applied to the column indicated from retention times and UV spectra mostly unreacted **7** and a small amount of uracil (**2**). After 48 h, more precipitated **8** was removed, and the quantity of **7** was found to have decreased significantly, with an increase in the amount of uracil (**2**) formed.

4,4,10,10-Tetramethyl-2,8-dioxo-1,3,7,9-tetraazaspiroundecane (10). This compound was synthesized according to the procedure of Weinschenk[36] by the condensation of urea and HCl-saturated anhydrous acetone. NMR (Me_2SO-d_6) δ 1.20 (s, 6, 2 CH_3(A)), 1.23 (s, 6, 2 CH_3(B)), 1.87 (A part of AB q, 2, 2 HC**H**), 2.04 (B part of AB q, 2, 2 **H**CH, J = 13.1 Hz), 6.38 (br s, 4, 2 NHC(O)NH); NMR (1:1 Me_2SO-d_6–pyridine-d_5) δ 1.28 (s, 6, 2 CH_3(A)), 1.33 (s, 6, 2 CH_3(B)), 1.91 (A of AB q, 2, 2 HC**H**), 2.17 (B part of AB q, 2, 2 HCH, J = 13.1 Hz), 6.71 (br s, 2, 2 NHC(O)N**H**), 6.83 (br s, 2, 2 **N**HC(O)NH). Our structural assignment for this compound is based on the work of Hatt and Triffett[37] and Hatt, Lichtenwalter, and Riesser.[38,39]

(35) Fissekis, J. D.; Sweet, F. *J. Org. Chem.* **1973**, *38*, 264.
(36) Weinschenk, A. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2185.

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Registry No. 1, 471-25-0; 2, 66-22-8; 3, 71749-93-4; 4, 71749-94-5; 5, 71749-95-6; 6, 71749-96-7; 7, 71749-97-8; 8, 71749-98-9; 10, 4115-66-6; urea, 57-13-6; 5-vinyluracil, 37107-81-6.

(37) Hatt, H. H.; Triffett, A. C. K. *J. Chem. Soc., Chem. Commun.* **1965**, 439.
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(39) The observed chemical shift difference for the methyl groups arises from a conformational flipping between two chair–chair conformers, which is partially frozen out on the NMR time scale, and in which the methyl substituents alternately assume axial- and equatorial-type positions. Similarly, for the methylene protons, this slowed exchange gives rise to the observed AB quartet. The magnetic nonequivalence of these two sets of protons is increased upon the addition of pyridine-d_5, as expected for an aromatic solvent induced shift.[40]
(40) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: New York, 1969; p 246 ff.

Chemistry of Diaminomaleonitrile. 5.[1] Dihydropyrazine Synthesis

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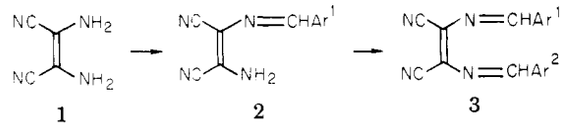
Condensation of aldehydes with diaminomaleonitrile (DAMN) Schiff bases in the presence of triethylamine at temperatures below 20 °C is accompanied by regiospecific hydration of the nitrile groups to give 3-cyanoacrylamide derivatives, which cyclize readily into 1,2-dihydropyrazines (**6** and/or **7**). The substituent effect on the product ratio (**6**/**7**) is examined, and the reaction mechanism is discussed in terms of a new general reaction pattern of DAMN derivatives. Reactions of **6** and **7** by oxidation, reduction, hydantoin formation with isocyanates, and cyanoethylation are also investigated.

Although many Schiff bases **2** have been prepared by the reactions of aldehydes with diaminomaleonitrile (DAMN, **1**) under relatively mild conditions (20–80 °C/ with or without acid catalyst),[1-4] preparation of bis condensation products **3** has been unsuccessful until recently.



An early attempt to condense a second mole of different aldehyde with **2** resulted in displacement of the aldehyde residue of the original derivative to give a new compound **2** (80 °C/8 h/with acid catalyst).[4] Begland[5,6] found that certain aromatic compounds with structure **3** (and its trans isomer), especially when Ar^1 and/or Ar^2 are (dialkylamino)phenyl, possess brilliant colors and are useful as disperse dyes for dying and printing polyesters. Symmetrical compounds **3** (Ar^1 = Ar^2) have been prepared from aldehydes and either **1** or **2** by direct condensation under somewhat more severe conditions (115–120 °C/with acid or base catalyst) than those of the mono condensations.[5] Unsymmetrical compounds **3** ($Ar^1 \neq Ar^2$), on the other hand, have been prepared by oxidation of *N*-benzyl-*N'*-benzylidene derivatives of **1**,[6] since the direct condensation of different aldehydes with **2** gave a product mixture by concomitant displacement of the aldehyde residues to give the symmetrical compounds **3**. In our experience, the reaction of a Schiff base (**2d**, Ar^1 = $Et_2NC_6H_4$) and aldehydes or ketones with piperidine catalyst resulted in exclusive formation of the symmetrical compound (**3**, Ar^1 = Ar^2 = $Et_2NC_6H_4$).

(1) Part 4: Ohtsuka, Y. *J. Org. Chem.* **1979**, *44*, 827.
(2) (a) Hinckel, L. E.; Richards, G. O.; Thomas, O. *J. Chem. Soc.* **1937**, 1432. (b) Onoda, K. *Nippon Nogei Kagaku Kaishi* **1962**, *36*, 255. (c) Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W. *J. Org. Chem.* **1974**, *39*, 2341. (d) Rasshofer, W.; Vögtle, F. *J. Chem. Res. (S)* **1977**, 265.
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(4) Robertson, P. S.; Vaughan, J. *J. Am. Chem. Soc.* **1958**, *80*, 2691.
(5) Begland, R. W. U.S. Patent 3 914 276, 1976.
(6) Begland, R. W. U.S. Patent 3 912 724, 1976.

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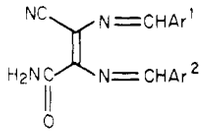
Table I. Selected Examples of 3-Cyanoacrylamides (4)[a]



4a-d

	Ar^1	Ar^2	reaction time, h	yield, %	mp, °C dec
a	Ph	Ph	2	80	179-181
b	Ph	4-MeC_6H_4	3	68	154-155
c	4-MeC_6H_4	Ph	4	79	169-170
d	4-MeC_6H_4	4-MeC_6H_4	4	73	150-151

[a] All compounds showed elemental analyses consistent with their structures.

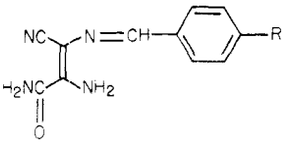
We noticed that the displacement of aldehyde residues was a slow reaction at room temperature and that the aldehyde condensation with **2** under mild conditions had the potential for the selective formation of unsymmetrical compound **3**. The possibility has been pursued, and, as described in detail in this report, unexpected results were obtained. The reaction of **2** and aldehyde at −5 to 20 °C in the presence of triethylamine did not follow the simple course of condensation but afforded dihydropyrazines. The results demonstrate a new reaction pattern of DAMN derivatives in which hydration of the neighboring nitrile group is concerted with the amine–aldehyde condensation.

Results and Discussion

Condensation of Aldehyde with DAMN Schiff Bases. The Schiff bases (**2a**,[4] **2b**,[1] **2c**, **2d**,[5] and **2e**;[2c] see Table II for Ar^1 in each compound) were allowed to react with aryl aldehydes in the presence of triethylamine[7] at 5 to −5 °C. When the reaction was carried out in an appropriate solvent (alcohols, acetonitrile or benzene), 2,3-bis(arylideneamino)-3-cyanoacrylamides (**4**) were isolated as bright yellow precipitates (Scheme I). Several examples of **4** are shown in Table I. Gross structures **4a–d** were supported by spectral data: ^1H NMR (freshly prepared solution in Me_2SO-d_6) δ 8.41–8.48 and 8.64–8.71 (two kinds of azomethine protons); IR (KBr) 2200–2210 (C≡N), 1680–1703 cm^{-1} (C=O). The strong tendency toward cyclization (see later) and the mild conditions of the preparation indicate the *Z* structure in respect to the central C=C bonds.

The reaction of **2a** (Ar^1 = Ph) with *p*-tolualdehyde gave **4b**, and the reaction of **2b** (Ar^1 = *p*-$CH_3C_6H_4$) with benzaldehyde gave a different product, **4c**. Similarly, the product by successive reactions of **1** with benzaldehyde followed by *p*-isopropylbenzaldehyde was different from the product obtained by the reverse sequence. These results show that a regioselective hydration of nitrile groups in **2** occurs during the aldehyde condensation.

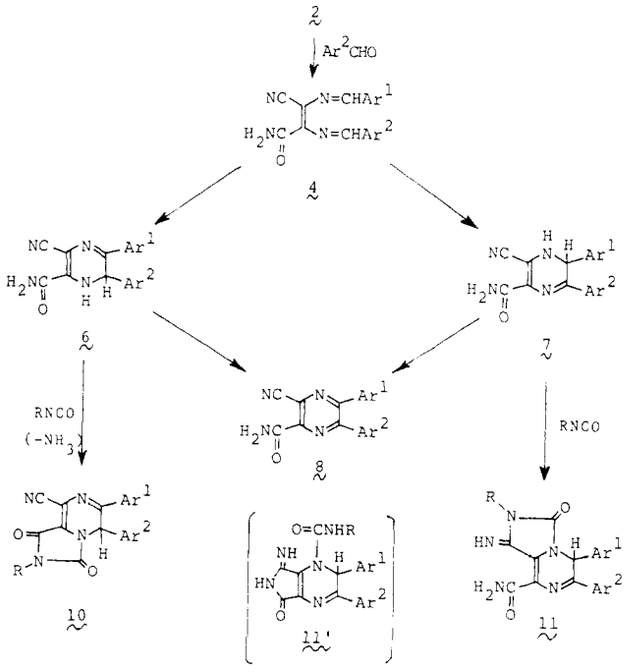
The stereochemistry of the product **4** was determined on the basis of the following reactions. We have previously reported the partial hydration of **2** to give amides **5**, of



5a, R = H
b, R = CH_3

(7) Instead of triethylamine, piperidine can be used to give the equivalent results.

Scheme I



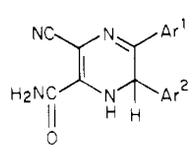
which structures can be determined by ^{13}C NMR spectroscopy.[1] Hydrolyses of azomethine linkages in **4b** and **4c** with H_2O_2 in acetic acid afforded the amides **5a** and **5b**, respectively. The formation of **5** can only be explained by selective elimination of the aldehyde residue, Ar^2CH:, from the structure **4**.

The initial adducts **4** have marginal stabilities and undergo ready cyclization during attempts at purification by recrystallization. In practice, heating **4** in Me_2SO for a short time followed by fractional crystallization from hot benzene gave 1,2-dihydropyrazines **6** and **7**, as shown in Table II.

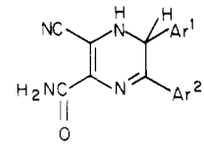
The two types of dihydropyrazines were distinguished from each other by TLC and physical properties. The lower melting isomers (**6**) were isolated from the more soluble fractions of the hot benzene crystallizations and exhibit IR absorptions at 2200–2210 (C≡N) and 1682–1700 cm^{-1} (C=O). The higher melting isomers (**7**), which are sparingly soluble in most organic solvents, have higher C≡N frequencies at 2220–2230 cm^{-1} and lower C=O frequencies at 1665–1670 cm^{-1}. The lower frequency bands were attributed to the groups (C≡N or $CONH_2$) conjugated with the ring NH on the basis of the previous study of open-chain compounds **2** and **5**.[1] As shown in Scheme I, this assignment has been confirmed by reaction of isocyanates with **6** and **7** (vide infra). Further information on the structures of **6h** and **7j** was obtained from their D_2O-exchanged ^1H NMR spectra by the couplings between the ring CH and α-protons in (cyclo)alkyl substituents to give doublets (δ 4.65–4.68, J = 4 Hz).

Selected examples of electronic spectra of dihydropyrazines (**6** and **7**) are shown in Table III. These compounds possess two absorption maxima at 254–275 nm (band A) and at 383–430 nm (band B). The band A of **7a**, having the Ph—C=N—C=C—CN (Ph~CN) conjugation, is observed at longer wavelength than that of **6a** having the Ph~$CONH_2$ conjugation. Replacement of the phenyl group by *p*-tolyl in both the conjugation systems of Ar~CN (**7a** and **7c** vs. **7b**) and Ar~$CONH_2$ (**6a** and **6b** vs. **6c**) shifts the band A to longer wavelength by 10–11 nm. Introduction of electron-withdrawing substituents on the phenyl ring in the Ar~CN system (**7k** and **7l**) shifts the band B to longer wavelength. Table III also indicates that

Table II. Dihydropyrazines[a]



6



7

Ar[1]	Ar[2]	starting matl	cond solv	prod[b]	yield,[c] %	mp, °C dec	prod[b]	yield,[c] %	mp, °C dec
Ph	Ph	2a	MeOH	6a	68	191-192[d,e]	7a	10	232-233[i]
Ph	4-MeC_6H_4	2a	MeOH	6b	54	205-207[d,e]	7b	6	234-236[j]
4-MeC_6H_4	Ph	2b	MeOH	6c	62	182-184[d,c]	7c	14	230-232[i]
4-MeC_6H_4	4-MeC_6H_4	2b	MeOH	6d	57	199-200[f]	7d	11	226-227[j]
Ph	4-*i*-PrC_6H_4	2a	MeOH	6e	40	180-182[g]	7e	3	224-225[d]
4-*i*-PrC_6H_4	Ph	2c	MeOH	6f	44	175-176[e,g]	7f	8	249-250[k]
Ph	4-ClC_6H_4	2a	EtOH	6g	56	172-173[g]	7g	37	256-257[h]
Ph	c-C_6H_{11}	2a	EtOH	6h	45	189-190[h]			
4-$Et_2NC_6H_4$	4-ClC_6H_4	2d	MeCN				7i	40	258-259[j,l]
i-Pr	4-$NO_2C_6H_4$	2e	benzene				7j	90	217-218[j]
Ph	4-$NO_2C_6H_4$	2a	EtOH				7k	77	253-255[i]
Ph	4-CNC_6H_4	2a	EtOH				7l	76	253-255[j]
4-MeC_6H_4	4-CNC_6H_4	2b	MeOH				7m	78	252-253[j]
4-*i*-PrC_6H_4	4-CNC_6H_4	2c	MeOH				7n	71	262-263[f]

[a] Satisfactory elemental analyses (±0.4% for C, H, N, and Cl) were obtained for all new compounds. [b] For spectral data see supplementary material. [c] Net yield based on **2**. Crystallization solvents: [d] ethyl acetate, [e] *n*-hexane, [f] ethanol, [g] benzene, [h] methanol, [i] nitromethane, [j] acetonitrile, [k] butanol, and [l] DMF.

Table III. Electronic Spectra of Dihydropyrazines

compd	absorption[a] λ_{max}, nm (log ϵ)	fluorescence[a,b] λ_{max}, nm
6a	254 (4.24), 383 (3.97)	508
7a	261.5 (4.34), 383 (4.04)	509
6b	254 (4.25), 383 (3.97)	508
7b	272.5 (4.30), 390 (4.04)	506
6c	265 (4.26), 386 (4.02)	510
7c	262.5 (4.26), 385 (3.93)	507
7k	260 (4.35), 430 (4.16)	535
7l	265 (4.34), 409 (4.04)	538

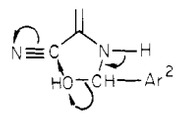
[a] MeOH solution. [b] Excitation at 260 nm.

these compounds exhibit green fluorescences. The intensities are about $^1/_{10}$th those of pyrazines **8**.

Facile reactions of **2** with benzaldehydes having electron-withdrawing substituents resulted in exclusive formation of one type of dihydropyrazine, **7j-l**. The condensation of **2a** and cyclohexanecarboxaldehyde afforded only the other type of dihydropyrazine **6h**. These results indicate that the cyclization reaction is directed by substituents Ar^1 and Ar^2 to give the compound in which the more negative substituent is located at the "methine" carbon in the dihydropyrazine ring. When Ar^1 and Ar^2 are similar in electronic character, the reaction gives a mixture of dihydropyrazines in the ratio **6a-f**/**7a-f** = 8:2 to 9:1, probably because of stabilization of **6** by hydrogen bonding between $CONH_2$ and the ring NH. The reaction of **2a** and *p*-chlorobenzaldehyde may be a borderline case, giving the ratio **6g**/**7g** = 6:4.

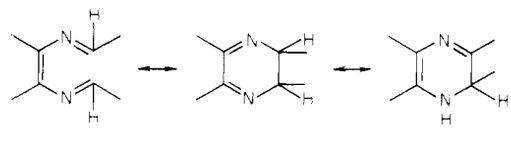
The condensation failed with the following pairs of reactants: Schiff base **2a** and aldehydes with electron-donating substituents (Ar^2 = *p*-$Et_2NC_6H_4$, *p*-$Me_2NC_6H_4$, and *p*-$MeOC_6H_4$); Schiff bases **2** with electron-withdrawing substituents (Ar^1 = *p*-$NO_2C_6H_4$ and *p*-CNC_6H_4) and aldehydes. The successful and unsuccessful results agree with the expectation that the reaction is initiated by nucleophilic attack of NH_2 in **2** on the aldehyde carbon.

The present results show that the base-catalyzed aldehyde condensation with **2** at the amino group is accompanied by highly regioselective hydration of the α-nitrile group. The net reaction proceeds in a low-temperature range, and no better result was obtained at temperatures higher than 20 °C. In contrast, the simple condensation of aldehydes with **2** to give **3** requires higher reaction temperatures.[5] The comparison suggests the importance of the entropy factor for the reaction. By the addition-elimination mechanism of imine formation, it is generally recognized that elimination of water from the carbinolamine intermediate is the rate-determining step in mildly basic solution.[8] As for the present reaction, it is very likely that the aldehyde condensation is assisted by a rate enhancement of the dehydration process through direct transfer of water to the α-nitrile from the carbinolamine



A similar cyclic compound formed from a carbinolamine and a nitrile function has been isolated by the reaction of **1** and acetaldehyde.[9] The mechanism has also been proposed in our studies on α-nitrile hydrations of DAMN derivatives.[1,3] Moreover, partial hydrations of nitrile groups during heterocyclic syntheses from *N*-acyl derivatives of **1**[10,11] may be rationalized by this mechanism. Such an intramolecular nitrile hydration should be a general mechanism for reactions of DAMN derivatives.

The facile cyclization of **4** into 1,2-dihydropyrazines **6** and **7** provides a new example of the diaza Cope rearrangement.[12] The resulting 2,3-dihydropyrazines would rearrange into 1,2-dihydropyrazines under the influence of substituents.[13]



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(11) Linstead, R. P.; Noble, E. G.; Wright, J. M. *J. Chem. Soc.* **1937**, 911.
(12) (a) Padwa, A.; Glazer, E. *J. Am. Chem. Soc.* **1972**, *94*, 7788. (b) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 767. (c) Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1.

Table IV. 5,6-Disubstituted 3-Cyano-2-pyrazinecarboxamides (8)[a]

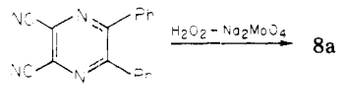
starting compd	prod	5-subst (Ar^1)	6-subst (Ar^2)	method[b]	yield, %	mp, C dec[c]
6a, 7a[d]	8a	Ph	Ph	A	80	178–179
				B	30	
6b, 7b[d]	8b	Ph	4-MeC_6H_4	A	96	212–213
				B	13	
7b				A	91	
6c, 7c[d]	8c	4-MeC_6H_4	Ph	A	82	263–265
				B	30	
6h	8d	Ph	c-C_6H_{11}	A	65	265–267
7k	8e	Ph	4-$NO_2C_6H_4$	B	94	252–254
7l	8f	Ph	4-CNC_6H_4	B	94	277–279
7m	8g	4-MeC_6H_4	4-CNC_6H_4	B	95	218–220

[a] All products showed spectral properties and elemental analyses consistent with their structures. [b] Method A, oxidation with MnO_2; method B, oxidation with H_2O_2. [c] Recrystallization from MeOH. [d] Product mixture of the cyclization of 4.

The driving factors may be the stability of the β-cyanoacrylamide partial structure and the increase of conjugation with aromatic substituent, Ar^1 or Ar^2. No remarkable solvent effect was observed when the cyclization of **4a** was carried out in several polar solvents (MeOH, MeCN, $MeNO_2$, acetone, and DMF).

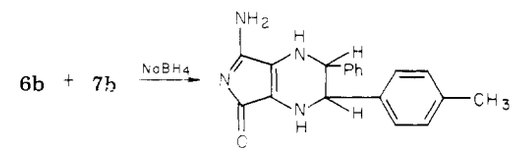
It is interesting to note the difference in chemical behavior between two types of enediimines, **3** and **4**. The dicyano compound **3** undergoes facile isomerization around the C=C bond to the trans compound, and no dihydropyrazine formation from **3** has been reported.[5,6] In contrast, all our attempts to isomerize the cyano carboxamides **4** into the respective trans (*E*) isomers failed because of the formation of dihydropyrazines. The difference may be attributed to the intramolecular interaction between CN and $CONH_2$ groups in **4** to prevent the rotation around the C=C bond. Such an interaction is suggested from the result that the cyano carboxamide **5** undergoes facile cyclization of CN and $CONH_2$ to give a pyrrolone,[1] while the corresponding reaction has never observed for Schiff base **2**.

Reactions of Dihydropyrazines. Dihydropyrazines **6** and **7** are relatively stable toward oxidation. Only a few compounds were spontaneously oxidized to pyrazines on long standing of their solutions. Oxidation with MnO_2 in DMF (method A) or with H_2O_2 in MeOH (method B) gave 5,6-disubstituted 3-cyano-2-pyrazinecarboxamides (**8**) in excellent yields (Table IV and Scheme I). This new synthesis of pyrazines from 1 and 2 mol of aldehyde affords compounds of unequivocal structures which may be useful as intermediates to pyrazinamides, pteridines, and other related compounds. 3-Cyano-5,6-diphenyl-2-pyrazinecarboxamide (**8a**) was synthesized by an alternative route from 5,6-diphenyl-2,3-pyrazinedicarbonitrile.[2a]



8a

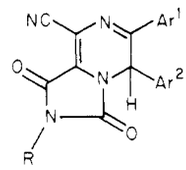
Reduction of a dihydropyrazine mixture, **6b** and **7b** (the cyclization product of **4b**), with sodium borohydride gave the cyclized tetrahydropyrazine **9**.



9

(13) The relative stability of isomeric dihydropyrazines depends on the substituents on the rings: Katritzky, A. R.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1972**, *14*, 182.

Table V. 1,3-Dioxo-1,2,3,5-tetrahydroimidazo[1,5-*a*]pyrazine-8-carbonitriles (Hydantoin Derivatives)[a]



10a–e

compd[b]	Ar^1	Ar^2	R	yield, %	mp, °C dec
a	Ph	4-MeC_6H_4	Ph	75	217–218[c]
b	4-MeC_6H_4	Ph	Ph	86	210–211[c]
c	4-MeC_6H_4	4-MeC_6H_4	*i*-Pr	94	225–226[d]
d	Ph	4-ClC_6H_4	*n*-Bu	87	211–212[c]
e	Ph	c-C_6H_{11}	Ph	99	190–191[c]

[a] Satisfactory elemental analyses (±0.4% for C, H, N, and Cl) were obtained for all new compounds. [b] For spectral data see the supplementary material. Recrystallization solvent: [c] ethanol, [d] methanol.

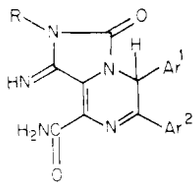
Reaction with isocyanates provides an interesting example of a structure-differentiating reaction between dihydropyrazines **6** and **7** (Scheme I). One mole of ammonia was eliminated by the reaction of **6** with an excess of isocyanate in the presence of triethylamine to give hydantoin derivatives **10** (Table V). Structures **10** are consistent with their IR spectra (1770–1788 and 1730–1740 cm^{-1} for C=O and 2220–2225 cm^{-1} for C≡N), ^1H NMR spectra (δ 5.75–6.97 for ring CH), and their microanalytical data. The C=O frequencies of these compounds correspond to those for reported hydantoins obtained from azole-2-carboxamides and isocyanates under similar reaction conditions.[14]

Dihydropyrazines **7** reacted more readily with 1 mol of isocyanate in DMF or in the presence of triethylamine in acetone, and the 1:1 adducts were obtained (Table VI). These products are assigned the structure of iminohydantoins **11** or open-chain ureas **11′** on the basis of IR spectra (1738–1765, 1672–1685, 1640–1650 cm^{-1}, and no nitrile absorption), ^1H NMR spectra (δ 5.59–6.83 for ring CH), and microanalytical data. The structure **11**, rather than the structure **11′**, was prefered for the products by the following observations: (i) the ^1H NMR spectrum of **11e** (R = CH_3) contains a sharp methyl singlet (δ 3.0) and three uncoupled NH peaks;[15] (ii) the ^{13}C chemical shift of

(14) (a) Papadopoulos, E. P.; Habiby, H. S. *J. Org. Chem.* **1966**, *31*, 327. (b) Papadopoulos, E. P.; Bedrosian, S. B. *Ibid.* **1968**, *33*, 4551. (c) Papadopoulos, E. P. *Ibid.* **1977**, *42*, 3925. (d) Papadopoulos, E. P.; Schupbach, C. M. *Ibid.* **1979**, *44*, 99.

(15) The result was compared with that of a methylurea derivative of 1, $H_2NC(CN)=C(CN)NHCONHCH_3$,[3] that shows a doublet methyl signal (at δ 2.6, J = 4.4 Hz), which becomes a singlet peak either by irradiation at δ 6.27 (NH) or by the addition of D_2O to the sample solution.

Table VI.
1-Imino-3-oxo-1,2,3,5-tetrahydroimidazo[1,5-*a*]pyrazine-8-carboxamides (Iminohydantoin Derivatives)[a]

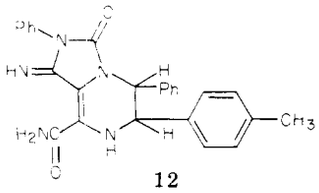


11a-g

compd[b]	Ar^1	Ar^2	R	yield, %	mp, °C dec
a	Ph	4-MeC_6H_4	Ph	69	242-244[c]
b	4-MeC_6H_4	4-MeC_6H_4	*i*-Pr	92	250-251[d]
c	Ph	4-ClC_6H_4	Ph	74	235-236[c]
d	*i*-Pr	4-$NO_2C_6H_4$	Ph	80	231-232[d]
e	Ph	4-$NO_2C_6H_4$	Me	94	235-237[c]
f	Ph	4-$NO_2C_6H_4$	*n*-Bu	79	219-220[d]
g	Ph	4-$NO_2C_6H_4$	Ph	74	224-226[c]

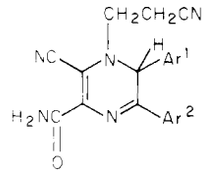
[a] Satisfactory elemental analyses (±0.4% for C, H, N, and Cl) were obtained for all new compounds. [b] For spectral data see the supplementary material. Recrystallization solvent: [c] acetonitrile, [d] ethanol.

the amide carbon in **11e** (δ 166) is similar to that of the respective carbon in **7k** (δ 164); (iii) the products are more chemically stable than those that would be expected from the structure **11′**, being recovered unchanged by both refluxing in ethanol for 3 h and reprecipitation with HCl from their solutions in aqueous NaOH. Also, attempted oxidative cleavage of **11c** by treatment with MnO_2 in DMF (60 °C/12 h) resulted in recovery of the original compound. Sodium borohydride reduction of **11a** gave the tetrahydropyrazine derivative **12**.



12

The results of cyanoethylation also favor the assignment **11**. Treatment of dihydropyrazines **7j** and **7n** with acrylonitrile in the presence of triethylamine did not give cyclization products similar to **11′** but gave the simple adducts **13a** and **13b**, respectively. These compounds **13**



13a, Ar^1 = Me_2CH; Ar^2 = 4-$NO_2C_6H_4$
b, Ar^1 = 4-$Me_2CHC_6H_4$; Ar^2 = 4-CNC_6H_4

are colored similarly to dihydropyrazines **6** and **7** (yellow), and attempted further cyclizations have been unsuccessful.

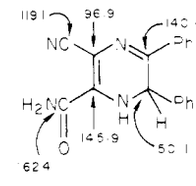
Experimental Section[16]

Diaminomaleonitrile (DAMN, **1**) used in this experiment was the product of Nippon Soda Co., Ltd. (grade A; 98% purity). DAMN Schiff bases (**2a**,[4] **2b**,[1] **2c**,[17] **2d**,[5] and **2e**[2c]) were prepared from **1** and aldehydes with H_2SO_4 catalyst after the general procedure described in a previous report.[1]

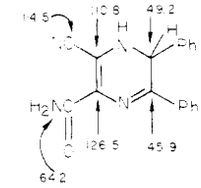
General Procedure for Preparation of 4 from Schiff Bases 2 and Aldehydes. 2,3-Bis(benzylideneamino)-3-cyanoacrylamide (4a). To a mixture of 19.6 g of benzylidenediaminomaleonitrile (**2a**) and 10.6 g of benzaldehyde in 700 mL of methanol at 5 to −5 °C was added 10.1 g of triethylamine. After the mixture was stirred for 2 h, the yellow precipitate which formed was filtered and washed repeatedly with MeOH. Adducts **4b,c** were prepared similarly with the duration of reaction time listed in Table I. These products had sufficient purity for consistent microanalytical and spectral data. Initial adducts of the reactions for the preparations of **6** and **7** (Table II) were isolated by the above procedure. These adducts underwent ready cyclization by heating their solutions. Rapid cyclization also occurred by addition of water to their cold solutions in Me_2SO.

Preparation of Dihydropyrazines 6a-g and 7a-g. A mixture of 3.0 g of the adduct **4** and 15 mL of Me_2SO was stirred on a bath at 80 °C. After 10 min, the resulting solution was poured into 150 mL of ice–water. Filtration and washing with water gave yellow powder. Compounds **6h** and **7i–n** were isolated by recrystallization of the products. In other cases, the above reaction gave a mixture of the two dihydropyrazines **6** and **7**. Thus, the product mixture (1.5 g) was refluxed in 200 mL of benzene for 10 min, and the insoluble solid (**7**) was separated quickly by filtration. Evaporation of the filtrate to dryness gave **6**. When an oily evaporation residue was obtained, the product was crystallized from ethyl ether. The separation could be traced by TLC [silica gel/benzene (twice), acetonitrile (once)], and, if necessary, the above procedure was repeated until the pure compounds **6** and **7** were obtained. Results on isolated compounds, **6** and **7**, are shown in Table II and in the supplementary material.

^{13}C chemical shifts (ppm from Me_4Si) assigned to the following carbons in **6a** and **7a** are



6a



7a

Hydrolytic Cleavage of 4b and 4c. To a mixture of 0.5 g of 3-(benzylideneamino)-3-cyano-2-(4-methylbenzylideneamino)-acrylamide (**4b**) and 7 mL of acetic acid was added at room temperature 1 mL of 30% aqueous H_2O_2. The solid dissolved, and a new precipitate was separated after a few minutes. The reaction mixture was chilled after 15 min, and the solid was filtered and washed with water to give 0.3 g of white powder. The product was recrystallized from ethanol to give pale yellow crystals, mp 197–198 °C dec. The IR spectrum of the compound was identical with that of 2-amino-3-(benzylideneamino)-3-cyanoacrylamide (**5a**).[1] Hydrolysis of 2-(benzylideneamino)-3-cyano-(4-methylbenzylideneamino)acrylamide (**4c**) was carried out as described for **4b**. From 0.8 g of **4c** there was obtained 0.43 g of 2-amino-3-(4-methylbenzylideneamino)-3-cyanoacrylamide (**5b**), confirmed by IR spectra.

General Procedure for Preparation of 5,6-Disubstituted 3-Cyano-2-pyrazinecarboxamides (8). Method A. A mixture of 0.5 mmol of dihydropyrazine (**6** and/or **7**), 0.15 g of MnO_2, and 15 mL of *N,N*-dimethylformamide (DMF) was kept at around 60 °C for 12 h with occasional shaking. The solid was then removed by filtration and rinsed with a small quantity of DMF. The combined filtrate and washing were diluted with 50 mL of water. The resulting precipitate was filtered, washed with water, and dried to give pyrazine **8**.

Method B. To a solution of 3 mmol of dihydropyrazine (**6** and/or **7**) in 10–20 mL of methanol was added 4 mL of 30% aqueous H_2O_2. After the mixture was stirred for 8 h at 50–55 °C,

(16) All melting points were measured on a Yanagimoto MP-21 micro-hot-stage apparatus (calibrated) and are uncorrected. Spectra were recorded on the following instruments: IR spectra, Hitachi EPI-G3 infrared spectrometer; mass spectra, Hitachi RMU-6E mass spectrometer; ^1H NMR spectra, Varian HA-100 spectrometer; ^{13}C NMR spectra, Varian XL-100 spectrometer with a Nicolet TT-100 computer. The ^{13}C chemical shifts were determined on 500–700 mg/3 mL of Me_2SO-d_6 solutions containing 10 mg of $Cr(acac)_3$ with Me_4Si as internal standard.

(17) Prepared from **1** and cuminaldehyde with an 85% yield; mp 174–175 °C (from toluene).

the resulting pyrazine 8 was isolated by filtration. The results are summarized in Table IV. These compounds were identified from IR data for amide and nitrile absorptions at 1690–1700 and 2220–2230 cm^{-1}, respectively, and consistent microanalytical data.

Independent Synthesis of 3-Cyano-5,6-diphenyl-2-pyrazinecarboxamide (8a). To a stirred mixture of 50.0 g (0.18 mol) of 5,6-diphenyl-2,3-pyrazinedicarbonitrile,[2a] 3 L of ethanol, and 1 L of acetone were added successively 300 mL of a 1% (w/w) aqueous solution of sodium molybdate and 300 mL of 30% aqueous hydrogen peroxide. After the mixture was stirred at 60–65 °C for 4 days, the resulting precipitate was filtered, washed with water, and dried to give 42.3 g (79.6% yield) of the product, which was identical (IR) with the compound **8a** obtained by the oxidation of **6a** and/or **7a**.

Reduction of Dihydropyrazines 6b and 7b. To an ice-cooled mixture of 1.0 g of the 9:1 mixture of **6b** and **7b** (the product of cyclization of **4b**) and 20 mL of methanol was added portionwise 1.0 g of sodium borohydride during a period of 15 min. The reaction mixture was stirred for an additional 15 min at room temperature and poured into 100 mL of ice–water. The resulting solid was filtered, washed with water, and dried to give 0.95 g of the product. Recrystallization from ethanol gave 3-amino-6-(4-methylphenyl)-5-phenyl-1,4,5,6,7-pentahydropyrrolo[3,4-*b*]-pyrazin-1-one (**9**): mp 205–207 °C dec; orange-yellow powder; IR (KBr) 3410, 3330, 3290, 1704, 1675, 1650 cm^{-1}; ^1H NMR δ 6.53 (d, J = 4 Hz, 1 H, NH), 5.71 (d, J = 4 Hz, 1 H, NH), 4.43 (br s, 2 H, CH); mass spectrum, m/e (rel intensity) 318 (100).

Anal. Calcd for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60. Found: C, 71.55; H, 5.71; N, 17.47.

Reaction of Isocyanates with Dihydropyrazines 6 (Table V). A mixture of 2.5 mmol of dihydropyrazines **6** (**6b–d,g,h**), 7.5 mmol of isocyanate, 2.5 mmol of triethylamine, and 30 mL of acetone was refluxed for 4 h. The solvent was then removed on a rotary evaporator, and the residue was triturated with ethanol to give yellow crystalline solid 2,5,6-trisubstituted 1,3-dioxo-1,2,3,5-tetrahydroimidazo[1,5-*a*]pyrazine-8-carbonitriles **10a–e**. Spectral data are listed in the supplementary material.

Reaction of Isocyanates with Dihydropyrazines 7 (Table VI). A mixture of 2.0 mmol of dihydropyrazines **7** (**7b,c,g,j**), 2.5 mmol of isocyanate, 2.0 mmol of triethylamine, and 30 mL of acetone was refluxed for 1.5 h and then worked up as described above. The reactions of **7k** were carried out by the following procedure. A solution of 2.0 mmol of **7k** and 3 mmol of isocyanate in 5–10 mL of DMF was warmed at 50–55 °C to induce crystallization of the product. After 1 h, chilling the reaction mixture followed by filtration and washing with acetonitrile gave the product.

These products were assigned the structures of 2,5,6-trisubstituted 1-imino-3-oxo-1,2,3,5-tetrahydroimidazo[1,5-*a*]-pyrazine-8-carboxamides **11a–g** on the basis of the discussion described before. Spectral data are listed in the supplementary material.

Reduction of Iminohydantoin 11a. To a mixture of 0.1 g of **11a**, 20 mL of MeOH, and a few drops of water was added 0.1 g of $NaBH_4$. After the mixture was stirred at room temperature for 20 min, the reaction mixture was poured into 80 mL of water. The resulting crystals were filtered, washed with water, and dried to give 0.08 g of the product. Recrystallization from EtOH gave 1-imino-6-(4-methylphenyl)-3-oxo-2,5-diphenyl-1,2,3,5,6-pentahydroimidazo[1,5-*a*]pyrazine-8-carboxamide (**12**) as slightly yellow fine needles: mp 237–238 °C dec; IR (KBr) 1750, 1638 cm^{-1}; mass spectrum, m/e (rel intensity) 438 (32), 437 (100, M^+).

Anal. Calcd for $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.01. Found: C, 71.22; H, 5.29; N, 15.92.

Cyanoethylation of Dihydropyrazines 7. 3-Cyano-4-(2-cyanoethyl)-5-isopropyl-6-(4-nitrophenyl)-4,5-dihydro-2-pyrazinecarboxamide (13a). A mixture of 3.14 g (10 mmol) of **7j**, 1.06 g (20 mmol) of acrylonitrile in 10 mL of Me_2SO, and 1 mL of H_2O was stirred at room temperature for 64 h. The reaction mixture was poured into water to give 3.22 g (88% yield) of the product. Recrystallization from methanol gave **13a**: mp 214–216 °C dec; yellow product; IR (KBr) 2240, 2220, 1680, 1600, 1528 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.84 (t, J = 6 Hz, 2 H, β-CH_2), 3.82 (dt, J^3 = 6 Hz, J^2 = 15 Hz, 1 H, α-CH), 4.13 (dt, J^3 = 6 Hz, J^2 = 15 Hz, 1 H, α-CH), 5.15 (d, J = 10 Hz, 1 H, ring CH), 7.49 (br s, 1 H, NH), 7.86 (br s, 1 H, NH); mass spectrum, m/e (rel intensity) 366 (9, M^+), 323 (100).

Anal. Calcd for $C_{18}H_{18}N_6O_3$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.16; H, 5.05; N, 22.78.

3-Cyano-4-(2-cyanoethyl)-6-(4-cyanophenyl)-5-(4-isopropylphenyl)-4,5-dihydro-2-pyrazinecarboxamide (13b) was prepared from 1.85 g (5 mmol) of **7n**, 1.0 g (20 mmol) of acrylonitrile, 0.3 mL of triethylamine, and 10 mL of Me_2SO by the same procedure as for **13a**. Recrystallization from DMF–ethanol–*n*-hexane gave **13b**: mp 241–243 °C dec; yellow powder; IR (KBr) 3430, 2950, 2240, 2225, 1675, 1588, 1528 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.90 (t, 2 H, β-CH_2), 4.2 (m, 2 H, α-CH_2), 6.28 (br s, 1 H, ring CH), 6.95 (br s, ~1 H, NH), 7.37 (br s, 1 H, NH); mass spectrum, m/e (rel intensity) 423 (14), 422 (44, M^+).

Anal. Calcd for $C_{25}H_{22}N_6O$: C, 71.07; H, 5.25; N, 19.89. Found: C, 70.55; H, 5.23; N, 19.60.

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Registry No. 1, 1187-42-4; **2a**, 56029-18-6; **2b**, 66371-27-5; **2c**, 66371-41-3; **2d**, 66371-43-5; **2e**, 51801-87-7; **4a**, 66371-72-0; **4b**, 66371-28-6; **4c**, 66371-26-4; **4d**, 71871-40-4; **6a**, 66371-73-1; **6b**, 66371-31-1; **6c**, 66371-29-7; **6d**, 71871-41-5; **6e**, 66371-44-6; **6f**, 66371-45-7; **6g**, 68271-12-5; **6h**, 71871-42-6; **7a**, 66371-74-2; **7b**, 66371-32-2; **7c**, 66371-30-0; **7d**, 71871-43-7; **7e**, 66371-60-6; **7f**, 66371-61-7; **7g**, 71871-44-8; **7i**, 71885-35-3; **7j**, 71871-14-2; **7k**, 71871-15-3; **7l**, 71871-16-4; **7m**, 71871-17-5; **7n**, 71871-18-6; **8a**, 66371-68-4; **8b**, 71871-19-7; **8c**, 71871-20-0; **8d**, 71871-21-1; **8e**, 71871-22-2; **8f**, 71871-23-3; **8g**, 71871-24-4; **9**, 71871-25-5; **10a**, 71871-26-6; **10b**, 71871-27-7; **10c**, 71871-28-8; **10d**, 71871-29-9; **10e**, 71871-30-2; **11a**, 71885-50-2; **11b**, 71871-31-3; **11c**, 71871-32-4; **11d**, 71871-33-5; **11e**, 71871-34-6; **11f**, 71871-35-7; **11g**, 71871-36-8; **12**, 71871-37-9; **13a**, 71871-38-0; **13b**, 71871-39-1; benzaldehyde, 100-52-7; 4-methylbenzaldehyde, 104-87-0; 5,6-diphenyl-2,3-pyrazinedicarbonitrile, 52197-23-6; phenyl isocyanate, 103-71-9; 2-isocyanatopropane, 1795-48-8; 1-isocyanatobutane, 111-36-4; isocyanatomethane, 624-83-9; acrylonitrile, 107-13-1.

Supplementary Material Available: Spectral data for compounds **6**, **7**, **10**, and **11** (2 pages). Ordering information is given on any current masthead page.