The Vilsmeier-Haack Reaction of Isoxazolin-5-ones. Synthesis and Reactivity of 2-(Dialkylamino)-1,3-oxazin-6-ones[1]

Egle M. Beccalli and Alessandro Marchesini*

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, 20133 Milano, Italy

Received August 8, 1986

The Vilsmeier-Haack reaction on isoxazolin-5-ones gives 2-(dialkylamino)-1,3-oxazin-6-ones, and a reaction path is proposed depending on substitution pattern of the isoxazolin-5-ones studied. A thermal equilibrium between the oxazinones, imino ketenes, and vinyl isocyanates is hypothesized to explain most of the chemical reactivity of the 2-(dialkylamino)-1,3-oxazin-6-ones.

The Vilsmeier-Haack reaction on heterocyclic compounds as well as the synthesis of heterocycles using this reaction has been widely studied.[2] A report[3] on the reaction between 3-arylisoxazolin-5-ones and DMF-$POCl_3$ excess of $POCl_3$ indicated the formation of 4-(3-aryl-5-isoxazolyl)3-aryl-5-isoxazolones and 3-aryl-5-chloro-4-(dichloromethyl)isoxazoles. These results differ from the findings we described in our preliminary papers.[1]

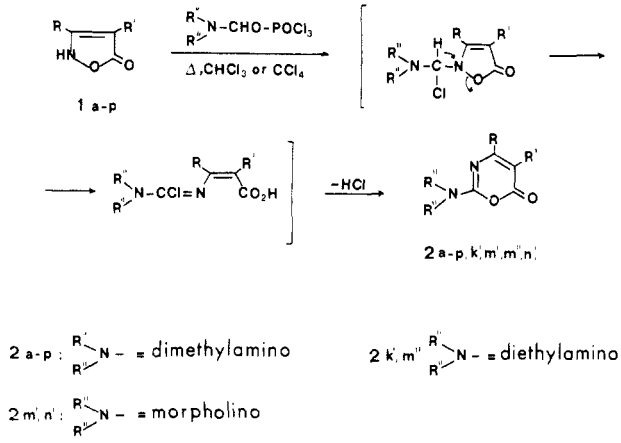
More recently and at the time this work was nearly completed, D. J. Anderson reinvestigated the Vilsmeier-Haack reaction of 3-phenylisoxazolin-5-one[4] and was also not able to reproduce the earlier result. He found instead, 3-phenyl-4-[(dimethylamino)methylene]isoxazolin-5-one and 2-(dimethylamino)-5-formyl-4-phenyl-1,3-oxazin-6-one. The proposed reaction path fits our proposed mechanism.[1]

To the best of our knowledge only two other reports covering the synthesis of 1,3-oxazin-6-ones from isoxazolin-5-ones are available in the literature[5] whereas 2*H*-1,3-oxazines are known to be formed from isoxazolium salts.[6] We now report the synthesis and reactivity of 2-(dialkylamino)-1,3-oxazin-6-ones (**2**), heterocycles which belong to a virtually unknown class,[7] obtained by a Vilsmeier-Haack-type reaction from the readily available isoxazolin-5-ones **1**.

Vilsmeier-Haack Reaction of 3,4-Disubstituted and 3-Unsubstituted Isoxazolin-5-ones. When the Vilsmeier-Haack reaction is carried out on 3,4-disubstituted and 3-unsubstituted isoxazolin-5-ones **1a-p**, the heterocycles **2a-p** are readily obtained in a pure state and in very good yields (Scheme I and Table I). Whereas with the 3,4-disubstituted isoxazolin-5-ones an excess of the Vilsmeier reagent may be used, with the 3-unsubstituted derivatives **1m-p** the reaction must be carried out with a molar amount of the preformed reagent because the first formed 4-unsubstituted oxazines **2m-p** react further with the Vilsmeier reagent (see later).

We suggest that the reaction giving 2-(dialkylamino)-1,3-oxazin-6-ones proceeds by the attack of the Vilsmeier reagent at position 2 of the isoxazolin-5-one, followed by ring opening and cyclization with hydrogen chloride elimination as shown in Scheme I.

Scheme I



Although we were unable to isolate any intermediate, this reaction path is strongly supported by its analogy with the easy cyclization of 1,4-diaryl-1-cyano-2-azabuta-1,3-diene-4-carboxylic acids to give 2,5-diaryl-1,3-oxazin-6-ones, as reported previously.[5b] The 2-(dialkylamino)-1,3-oxazin-6-ones are stable compounds and can be stored indefinitely at room temperature. The structure of the new compounds is based on analytical and spectroscopic data as well as chemical behavior. The structures of the oxazinones **2g**, **2n**, and **2n'** were confirmed by X-ray diffraction analysis.[8] Moreover good yields of oxazinones **2** were also obtained when formamides other than dimethylformamide (e.g., formylmorpholine or diethylformamide) were used (Table I, derivatives **2k'**,**m'**,**m''**,**n'**). The 2-morpholino-5-phenyl-1,3-oxazin-6-one (**2m'**) proved to be identical with the compound previously reported as 6-morpholino-5-phenyl-2*H*-1,3-oxazin-2-one by G. V. Boyd.[9] On the basis of this we also synthesized, using our method, the oxazinone **2k'**, which also proved to be identical with the compound described by Boyd as 4-(diethylamino)-5,6,7,8-tetrahydro-2*H*-3,1-benzoxazin-2-one and synthesized from 2-(diethylcarbamoyl)-3,4,5,6-tetrahydrobenzoyl azide.[9] The structure of compound **2m'** also follows from the chemical behavior.

Vilsmeier-Haack Reaction of 4-Unsubstituted Isoxazolin-5-ones. A more complex reaction pattern is shown by the 4-unsubstituted isoxazolin-5-ones **1q-u** when the Vilsmeier-Haack reaction is applied to these derivatives. Scheme II presents an overall picture of the products so formed.

(1) Preliminary papers: (a) Beccalli, E. M., Marchesini, A. Presented at the 11th European Colloquium on Heterocyclic Chemistry, Ferrara, Italy, 1985. (b) Beccali, E. M.; Marchesini, A.; Molinari, H. *Tetrahedron Lett.* **1986**, 627.

(2) Jutz, C. *Adv. in Org. Chem.* **1976**, *9*(1), 225. Kantlehner, W. *Ibid.* **1976**, *9*(2), 5. Meth-Cohn, O.; Tarnowski, B. *Adv. Heterocycl. Chem.* **1982**, *31*, 207.

(3) Kallury, R. K. M. R.; Devi, P. S. U. *Tetrahedron Lett.* **1977**, 3655.

(4) Anderson, D. J. *J. Org. Chem.* **1986**, *51*, 945.

(5) (a) Risitano, F.; Grassi, G.; Foti, F.; Caruso, F.; Lo Vecchio, G. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1522. (b) Beccalli, E. M.; La Rosa, C.; Marchesini, A. *J. Org. Chem.* **1984**, *49*, 4287.

(6) King, J. F.; Durst, D. *Can. J. Chem.* **1962**, *40*, 882.

(7) Some representatives have been described by: Chuche, J. Presented at the 11th European Colloquium on Heterocyclic Chemistry, Ferrara, Italy, 1985.

(8) Pilati, T., unpublished results (complete data were supplied to the editor for inspecting).

(9) Baydar, A. E.; Boyd, G. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2871.

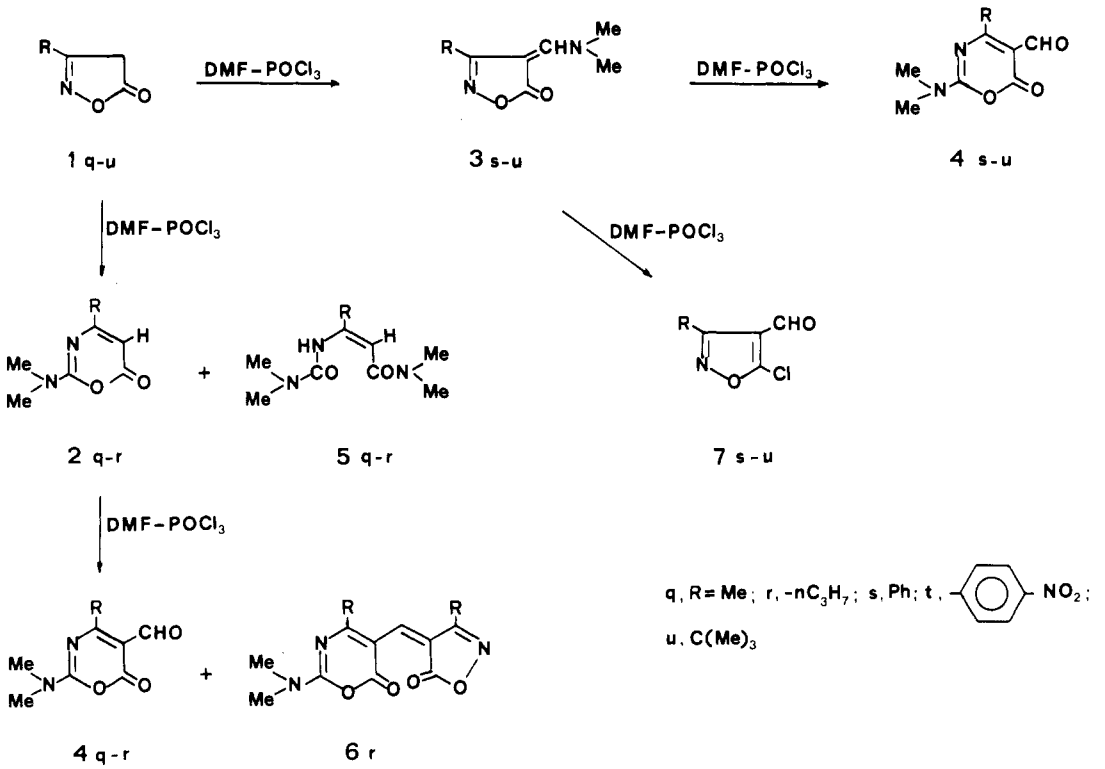
0022-3263/87/1952-3426$01.50/0

Table I. 2-(Dimethylamino)-1,3-oxazin-6-ones 2 from Isoxazolin-5-ones 1

start matrl	R	R′	product (% yield)	eluant	mp, °C	reacn time, h
1a[22]	Me	Ph	**2a** (73)	CH_2Cl_2–Et_2O (20:1)	79–80[a]	2.5
1b[23]	Ph	Me	**2b** (87)		115–116[a]	6
1c[24]	Me	CH_2Ph	**2c** (80)		96–97[a]	5
1d[25]	CO_2Et	Me	**2d** (70)		60–61[a]	3
1e[26]	Me	CH_2CO_2Me	**2e** (62)	CH_2Cl_2–Et_2O (20:1)	77–78[a]	3
1f[26]	Me	n-$C_{16}H_{33}$	**2f** (77)	CH_2Cl_2–hexane (1:2)	63–64[b]	8
1g[27]	Ph	CO_2Et	**2g** (74)		121–122[c]	2
1h[28]	Ph	n-C_8H_{17}	**2h** (90)	CH_2Cl_2–hexane (1:1)	41–42[a]	12
1i[26]	Me	CH_2CH_2Ph	**2i** (87)	CH_2Cl_2–Et_2O (20:1)	105–106[a]	2
1j[29]	Ph	Et	**2j** (72)		126–127[d]	4
1k[10]		$(CH_2)_4$	**2k** (85)	CH_2Cl_2–Et_2O (20:1)	98–99[a]	3
1k		$(CH_2)_4$	**2k′** (85)	Et_2O–hexane (3:1)	43–44[d]	1.5
1l[30]	Ph	CH_2Ph	**2l** (62)		107–108[d]	2
1m[31]	H	C_6H_5	**2m** (69)	Et_2O–hexane (4:1)	109–110[c]	1.5
1m	H	C_6H_5	**2m′** (60)	CH_2Cl_2–Et_2O (20:1)	149–150[c]	2
1m	H	C_6H_5	**2m″** (93)	CH_2Cl_2–hexane (1:1)	73–74[a]	2
1n[5b]	H	C_6H_4Me-*o*	**2n** (87)	CH_2Cl_2–hexane (3:1)	104–105[a]	3
1n	H	C_6H_4Me-*o*	**2n′** (45)	CH_2Cl_2–Et_2O (20:1)	124–125[a]	2
1o[5b]	H	C_6H_4Cl-*p*	**2o** (62)	CH_2Cl_2	154–155[d]	1
1p[32]	H	CO_2Et	**2p** (69)	CH_2Cl_2–Et_2O (20:1)	114–115[c]	1.5

[a] Et_2O–hexane. [b] Hexane. [c] CH_2Cl_2–Et_2O. [d] Et_2O.

Scheme II



We carried out the reaction with 1 and 2 mol of the Vilsmeier reagent, respectively. The results are reported in Table II and clearly show the effect of the steric hindrance of group R on the reaction path. For the alkyl-substituted isoxazolones **1q,r**, in which the steric hindrance at position 2 is low, the main products of the reaction with 1 mol of the Vilsmeier reagent are the oxazinones **2q,r** (see Table II) arising from the attack of the reagent at position 2 of the isoxazolone nucleus; this is in agreement with the behavior of disubstituted isoxazolones. In the same reaction byproducts **5q,r** were also formed, and a small amount of derivatives **4q,r** were isolated: these products respectively arise from **2q,r** and dimethylamine and from the attack of the Vilsmeier reagent at position 5 of the main products **2q,r**, as shown in a separate experiment.

As shown in Table II, and as expected, compounds **4q,r** became the main products when an excess of the Vilsmeier reagent was used; when R = n-C_3H_7, **6r** was also formed as a condensation product of **4r** and the starting isoxazolone **1r**.

In the case of isoxazolones **1s–u**, where a more bulky substituent is present, the main products of the reaction with a molar amount of the Vilsmeier reagent are the [(dimethylamino)methylene]isoxazolones **3s–u**, resulting from the attack of the reagent at position 4 of the isoxazolone ring. In the case of **1s**, also **4s** and a minor amount of **7s** were also isolated; starting from **1u** a minor amount of **7u** was formed.

With an excess of the reagent, compounds **4s–u** and the chloroisoxazolaldehydes **7s–u** became the favored products. The 2-(dimethylamino)-5-formyl-1,3-oxazin-6-ones **4s–u** arise from the attack of the Vilsmeier reagent at position 2 of the [(dimethylamino)methylene]isoxazolones **3s–u** (as also verified by Anderson for **4s**),[4] whereas the chloroisoxazolaldehydes **7s–u** arise from the attack of the reagent on the carbonylic oxygen atom of compounds **3s–u**,

Table II. Products from Vilsmeier-Haack Reaction of Isoxazolin-5-ones 1q–u

start matrl	products	eluant	% yields a	% yields b	mp, °C [bp, °C (mm)]	reacn time, h a	reacn time, h b
1q[10]	2q	Et_2O–hexane (2:1)	53	16	103–104[c]	1	2
	4q		5	42	177–178[d]		
	5q		9	6	88–89[d]		
1r[33]	2r	Et_2O–hexane (1:1)	62	0	[135–140 (0.2)]	1.5	2
	4r		6	66	77–78[e]		
	5r		6	0	38–39[c]		
	6r		0	11	132[d]		
1s[34]	4s	CH_2Cl_2–Et_2O (20:1)	15	80	158–159[d]	1.5	2
	3s		50	0	143–144[b]		
	7s		4	15	44–45[f]		
1t[35]	4t	CH_2Cl_2–Et_2O (3:1)	0	54	208–210[d]	1.5	4
	3t		67	22	195–196[d]		
	7t		0	11	116–117[d]		
1u[10]	4u	CH_2Cl_2–Et_2O (10:1)	0	17	83–84[f]	1	2
	3u		70	0	92–93[e]		
	7u		4	64	[105–110 (15)]		

[a] Reaction with 1 mol of Vilsmeier reagent. [b] Reaction with 2 mol of Vilsmeier reagent. [c] Hexane. [d] CH_2Cl_2–Et_2O. [e] Et_2O. [f] Et_2O–hexane.

Table III

start matrl	MeOH–TEA[f] reacn time	MeOH–TEA[f] products	MeOH–TEA[f] % yields	MeOH reacn time	MeOH products	MeOH % yields	mp, °C
2a	24 h	8a	38[a]	3 days	8a	0	144–145[d]
		9a	41		9a	97	114[d]
2b	24 h	8b	74[a]	4 days	8b	3	111–112[d]
		9b	13		9b	72	134–135[d]
2c	10 h	8c	35[b]	3 days	8c	0	46–47[d]
		9c	21		9c	70	123[d]
2d	2 h	8d	80[a]	4 days	8d	11	102–103[d]
		9d	2		9d	52	96–97[d]
2e	24 h	8e	46[a]	5 days	8e	0	72–73[d]
		9e	20		9e	78	86–87[d]
2f	6 h	8f	68[c]	3 days	8f	0	71–72[e]
		9f	6		9f	85	64[e]
2g	0.5 h	8g	67[a]	2 h	8g	53	92–93[d]
		9g	34		9g	30	68–69[d]
2h	2 h	8h	60	4 days	8h	0	47–48[d]
		9h	0		9h	95	59–60[e]
2i	6 h	8i	85	4 days	8i	0	53–54[d]
		9i	0		9i	85	109–110[d]
2j	6 h	8j	53[a]	4 days	8j	4	93–94[d]
		9j	3		9j	58	123–124[d]
2k	3 h	8k	71	4 days	8k	15[a]	69–70[e]
		9k	0		9k	40	105–106[d]
2l	24 h	8l	50[a]	3 days	8l	0	106–107[d]
		9l	18		9l	90	109–110[d]
2m	0.5 h	8m	65	2 days	8m	0	112–113[d]
		9m	0		9m	72	85–86[d]
2n	0.5 h	8n	73	2 days	8n	0	82–83[d]
		9n	0		9n	80	81–82[d]
2o	0.5 h	8o	82	2 days	8o	0	115–116[d]
		9o	0		9o	42	111–112[d]
2p	0.5 h	8p	75	2.5 h	8p	0	81–82[d]
		9p	0		9p	81	117–118[d]

[a] Column chromatography eluant: CH_2Cl_2–Et_2O (30:1). [b] Column chromatography eluant: Et_2O–hexane (1:1). [c] Column chromatography eluant: CH_2Cl_2. [d] Crystallization solvent: Et_2O–hexane. [e] Crystallization solvent: hexane. [f] Similar results were obtained with acidic catalyst (*p*-toluenesulfonic acid).

as could also be shown in a separate experiment (Scheme III). The ratio between derivatives **4** and **7** also reflects the steric hindrance of group R: when R = t-C_4H_9 the chloroisoxazolaldehyde **7u** is the main product. Compounds **3s**, **7s**, and **4s** are identical with those previously reported.[4]

In principle, besides the steric effects, a change in the tautomeric composition of the 4-unsubstituted isoxazolin-5-one as a consequence of the kind of the substituent may also be considered in explaining the regiochemistry of the reaction of the Vilsmeier reagent with the isoxazolones **1q–u**. However this latter effect can be ruled out since Katritzky showed that the tautomeric equilibrium composition of isoxazolin-5-ones with a single substituent in the 3-position changes according to the ionic strength of the medium independently of the nature of the substituent present.[10]

Reactivity of 4,5-Disubstituted and 4-Unsubstituted 2-(Dialkylamino)-1,3-oxazin-6-ones (Scheme IV). (a) Reaction with MeOH. By refluxing in methanol with either acid (*p*-toluensulfonic acid) or base (triethylamine) as catalyst, the 4,5-disubstituted 2-(dimethylamino)-1,3-oxazin-6-ones **2a–l** gave a mixture of two derivatives **8** and **9**, the **8** to **9** ratio being variable and compounds **8** being generally more abundant. In the case of **2h,i,k** only **8h,i,k**

(10) Katritzky, A. R.; Oksne, S.; Boulton, A. J. *Tetrahedron* **1962**, *18*, 777.

Scheme III

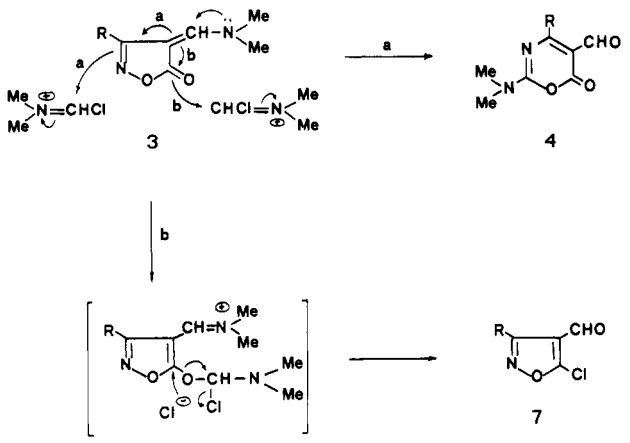


Table IV

start matrl	product (% yield)	mp, °C	start matrl	product (% yield)	mp, °C
2a	**10a** (36)	80–81[a]	**2e**	**10e** (26)	oil
9a	**10a** (45)		**9e**	**10e** (0)	
2b	**10b** (62)	86–87[b]	**2h**	**10h** (57)	oil
9b	**10b** (41)		**9h**	**10h** (62)	
2c	**10c** (67)	oil	**2l**	**10l** (80)	105–106[b]
9c	**10c** (71)		**9l**	**10l** (76)	

[a] Et_2O–hexane. [b] CH_2Cl_2–Et_2O.

Table V. Alkaline Hydrolysis of Oxazinones 2

start matrl	product (% yield)	mp, °C[a]	reacn time, h
2a	**11a** (90)	107–110[b]	2.5
2b	**11b** (46)	102–103[c]	3
2c	**11c** (50)	86–89[d]	3
2f	**11f** (60)	72–76[e]	18
2h	**11h** (71)	76–77[f]	7
2i	**11i** (79)	93–95[e]	6
2j	**11j** (80)	99–100[b]	6
2k	**11k** (90)	111–112[b]	2
2k′	**11k′** (60)	102–105[e]	2
2l	**11l** (50)	104–107[c]	3
2m	**11m** (57)	163–165[b]	3
2m′	**11m′** (86)	189–190[g]	2
2n	**11n** (71)	183–185[b]	3
2o	**11o** (68)	167–170[b]	3

[a] All derivatives melt with decomposition. [b] CH_2Cl_2–Et_2O. [c] Et_2O. [d] CH_2Cl_2–hexane. [e] Et_2O–hexane. [f] Hexane. [g] THF.

were formed (Table III). On the other hand by refluxing in methanol with no added catalyst, the oxazinones **2a–l** gave, very slowly but in high yields, the corresponding amido esters **9**. Only in the case of **2d,g,k** was an appreciable amount of esters **8d,g,k** also formed (Table III). In the reaction with methanol the 4-unsubstituted oxazinones **2m–p** gave only the esters **8m–p** in the presence of a catalyst, whereas with no added catalyst only the amido esters **9m–p** were formed. In this case both reactions are faster than the corresponding reactions of 4,5-disubstituted oxazinones (Table III). Analytical and spectral data support structures **8** and **9**. Acidic hydrolysis of the amido esters **9** afforded the corresponding β-keto acids dimethyl amides **10** (Scheme IV and Table IV), and the amide **10a** has already been reported.[11] The structure of the amido ester **9m** has been confirmed by X-ray diffraction analysis.[8,12]

Table VI

start matrl	product (% yield)	mp, °C	reacn time, h
2a	**14a** (60)	226[a]	1
14a	**15a** (55)	100–101[d]	
2b	**14b** (65)	192–193[b]	1
2c	**14c** (57)	138–139[c]	1
14c	**15c** (40)	93–94[d]	
2d	**14d** (60)	94–95[d]	1
14d	**15d** (42)	80–82[d]	
2e	**14e** (26)	98–100[b]	1
2f	**14f** (65)	106–107[d]	0.3
2h	**14h** (76)	98–99[d]	2.5
14h	**15h** (60)	82–83[d]	
2i	**14i** (62)	174–176[b]	1
2j	**14j** (55)	108–109[d]	1.5
2k	**14k** (36)	151–152[d]	0.3
2l	**14l** (74)	152–153[b]	2.5
14l	**15l** (75)	117–118[d]	

[a] CH_2Cl_2. [b] CH_2Cl_2–hexane. [c] Et_2O. [d] Et_2O–hexane.

Table VII. Products from Vilsmeier–Haack Reaction on Isoxazolin-5-ones 1m–p with 2 mol of the Reagent

start matrl	products (% yield)	mp, °C
1m	**2m** (73)	
	16m (11)	98–99[a]
1n	**2n** (28)	
	16n (57)	142–144[b]
1o	**2o** (48)	
	16o (49)	107–108[a]
1p	**2p** (8)	
	16p (76)	88–89[b]

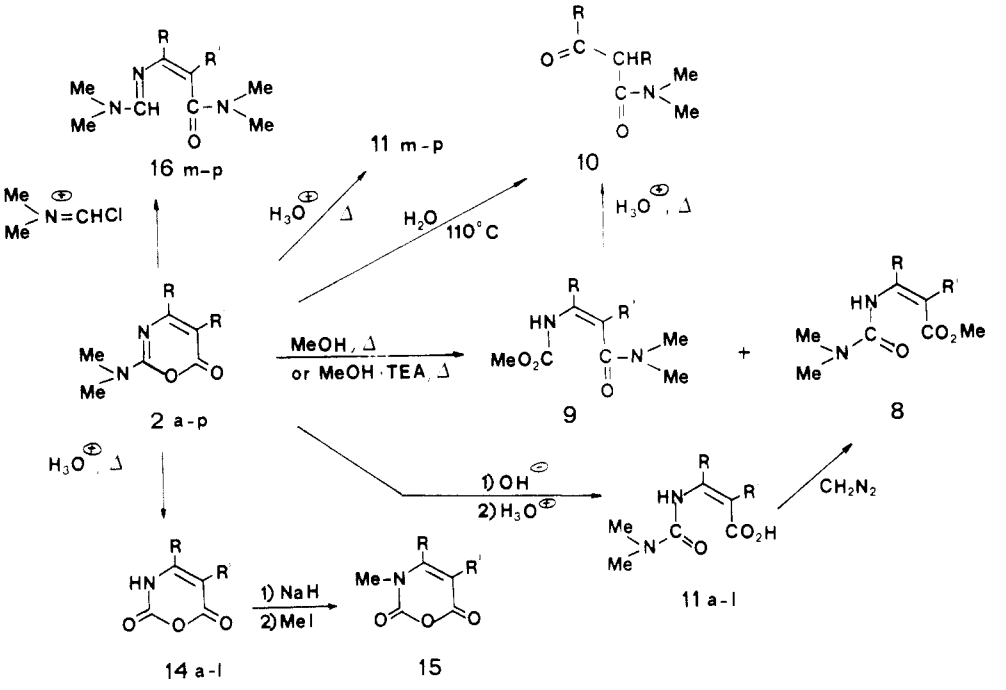
[a] Et_2O. [b] CH_2Cl_2–Et_2O.

(b) Alkaline Hydrolysis. Room temperature alkaline hydrolysis of the oxazinone **2** gave in good yields the ureido acids **11** (Scheme IV and Table V). The previously reported esters **8** may be obtained also by diazomethane esterification of these acids. An example of the reactivity of the acids **11** as well as of the esters **8** is shown in Scheme V for the acid **11m′** and the ester **8m′**. The reported reactions have been used for a further confirmation by chemical methods of the structure of the oxazinone **2m′**. Acidic hydrolysis of the acid **11m′** afforded the aldehyde **12**[13] and carbamylmorpholine. The unsaturated aldehyde **12** arises from phenyl acetaldehyde, as proved in a separate experiment. From acidic hydrolysis of ester **8m′** we were able to isolate, besides carbamylmorpholine, the methyl 2-formyl-2-phenylacetate (**13**), identical with an authentic sample.[14]

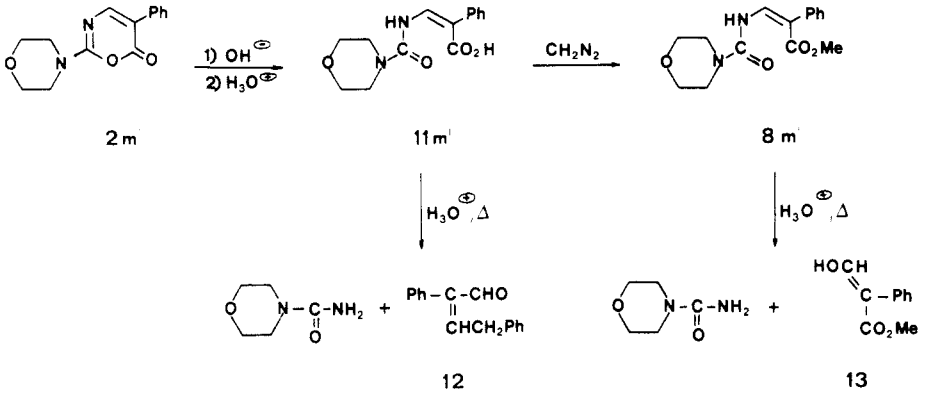
(c) Acidic Hydrolysis (Scheme IV and Table VI). Acidic treatment of 4,5-disubstituted 1,3-oxazin-6-ones **2a–l** gave the corresponding 1,3-oxazin-2,6-diones **14**. This reaction greatly extends the range of the substitution pattern for these biologically interesting heterocycles[15] which are obtained in a pure state and in good yields (Table VI). From **14** the 3-methyl derivatives **15** were easily obtained by reaction with sodium hydride and methyl iodide. The structures of **14** and **15** follow from analytical and spectroscopic data and are confirmed by the fact that compound **14d** proved to be identical with an authentic sample synthesized by a reported method.[15] The acidic treatment of the 4-unsubstituted oxazinones **2m–o** gave the same ureido acids **11** already obtained by room temperature alkaline hydrolysis of the same oxazinones.

(11) Butke, G. P.; Jimenez, F.; Michalik, J.; Gorski, R. A. *J. Org. Chem.* **1978**, *43*, 954.
(12) Previously we assigned the incorrect structure of 2-(dimethylamino)-2-methoxy-2,3-dihydro-1,3-oxazin-6-ones[1] to compounds **9**.
(13) Chelpanova, L. F.; Komer, V. A. *Zh. Obshch. Khim.* **1955**, *25*, 1513; *Chem. Abstr.* **1956**, *50*, 4872f.
(14) Wislicenus, W. *Justus Liebigs Ann. Chem.* **1916**, *413*, 206.
(15) Washburne, S. S.; Park, K. K. *Tetrahedron Lett.* **1976**, 243 and references cited therein.

Scheme IV



Scheme V

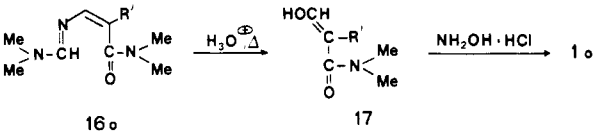


(d) Reaction with H_2O. The oxazinones **2** react with water only in a sealed tube at 110 °C for 16 h. Thus from the oxazinones **2a–c,e,h,l** the corresponding β-keto amides **10** (Table IV) were obtained.

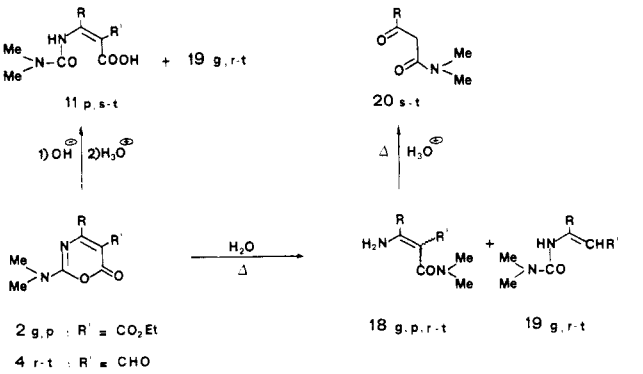
(e) Reaction with the Vilsmeier Reagent. When the Vilsmeier–Haack reaction was carried out on 2-(dimethylamino)-5-carbethoxy-1,3-oxazin-6-one (**2p**) the corresponding 2-azabuta-1,3-diene **16p** was formed. Since 2 mol of the reagent are used to convert the primarily formed oxazinone to products **16**, the Vilsmeier–Haack reaction on the isoxazolones **1m–p** must be carried out with 1 mol of the reagent to obtain good yields of the corresponding oxazinones. Accordingly, starting from **1m–p** and working with 2 mol of Vilsmeier reagent, the azadienes **16m–p** were obtained as well as the oxazinones **2m–p** (Table VII).

The structure of compounds **16** is verified by analytical and spectroscopic data as well as by the fact that acidic hydrolysis of **16o** gave the corresponding amido aldehyde **17**, from which by reaction with $NH_2OHxHCl$, the starting isoxazolone **1o** was formed (Scheme VI).

Scheme VI



Scheme VII



Reactivity of 2-(Dialkylamino)-1,3-oxazin-6-ones Bearing an Electron-Withdrawing Group in Position 5. The oxazinones bearing an electron-withdrawing group in position 5 (e.g., **2g,p** and **4r–t**) exhibit a peculiar reactivity (Scheme VII). These derivatives react with water at 100 °C in a maximum time of 2 h and give the dimethyl amides of substituted 3-aminopropenoic acids **18** (Table VIII) together with a small amount of compounds **19**.

Table VIII. Products from Reaction with H_2O of Oxazinones 2g,p and 4r–t

start matrl	products (% yields)	eluant	mp, °C	reacn time, h
2g	**18g** (59)		162–164[a]	2
	19g (33)	CH_2Cl_2–Et_2O (10:1)	oil	
2p	**18p** (85)		124–125[d]	0.5
4r	**18r** (64)		72–76[b]	
	19r (7)	CH_2Cl_2–Et_2O (3:1)	36[a]	2
4s	**18s** (65)		168–170[d]	
	19s (4)	CH_2Cl_2–MeOH (100:1)	68–69[c]	0.3
4t	**18t** (60)		178–182[d]	
	19t (3)	CH_2Cl_2–MeOH (50:1)	138–139[e]	0.3

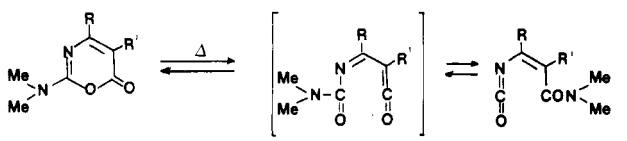
[a] Hexane. [b] Et_2O. [c] Et_2O–hexane. [d] CH_2Cl_2–Et_2O. [e] CH_2Cl_2–hexane.

Table IX. Products from Alkaline Hydrolysis of Oxazinones 2g,p and 4r–t

start matrl	products (% yields)	mp, °C	eluant	reacn time, min
2g	**19g** (27)	oil	CH_2Cl_2	180
2p	**11p** (24)	107–109 dec		60
4r	**19r** (64)		Et_2O–hexane (1:2)	20
	11r (0)			
4s	**19s** (7)		CH_2Cl_2–Et_2O (5:1)	20
	11s (73)	101–103[a]		
4t	**19t** (5)		CH_2Cl_2–Et_2O (1:1)	20
	11t (48)	115–116 dec[b]		

[a] Et_2O. [b] CH_2Cl_2–Et_2O.

Scheme VIII



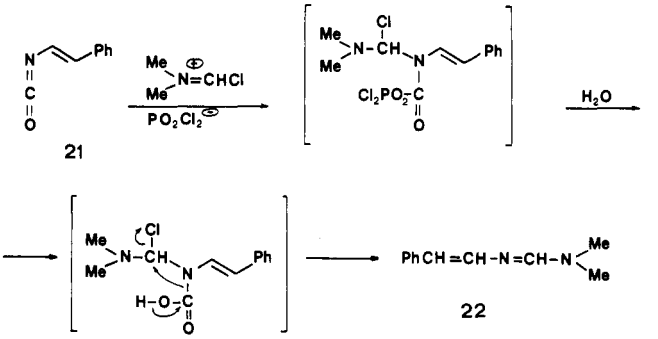
2 a b

Derivatives **18** are a near 1:1 mixture of the *E* and *Z* isomers (^1H NMR) and by acidic hydrolysis afford the β-keto acids dimethyl amides **20**. The amide **20s** has been previously reported.[16] The isolation of compounds **18** demonstrates the intermediacy of enamine amides in the hydrolysis of oxazinones **2** to keto amides **10**. Room temperature alkaline hydrolysis of oxazinones **4s–t** gave acids **11s–t**, together with the corresponding decarboxylation products **19s–t**. In the case of **2g** and **4r** only derivatives **19g** and **19r** were obtained, while **11p** was obtained in low yields only by this way (Table IX). The reaction with methanol of **2g** and **2p** is very fast if compared with the same reaction of the other member of the group (Table III); also the 5-formyl oxazinones **4** react very fast with methanol, but they give very complex mixtures of compounds from which we were unable to isolate pure products.

Proposed Mechanism for Ring-Opening Reactions of Oxazinones 2. A thermal equilibrium between the oxazinones **2** and the corresponding vinyl isocyanates b, probably via the intermediacy of an imino ketene a (Scheme VIII), can account for the formation of most products obtained in the reaction of 2-(dimethylamino)-1,3-oxazin-6-ones **2**, and we suggest that there is an initial

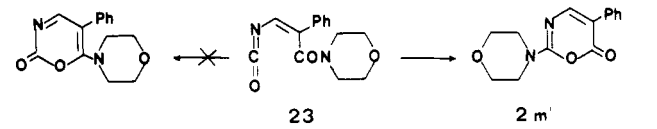
(16) Oishi, T.; Ochiai, M.; Nagai, M.; Ban, Y. *Tetrahedron Lett.* **1968**, 497.

Scheme IX



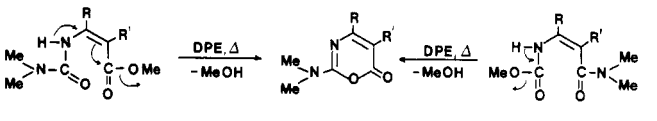
21 22

Scheme X



23 2m′

Scheme XI



8 2 9

valence isomerization to an imino ketene followed by a [1,5]-shift of the dimethylamino group to form a vinyl isocyanate.

The amido esters **9** arise from methanol addition to b; also compounds **10** and **18** clearly arise from water addition to b followed by decarboxylation and in the case of **18** enaminė hydrolysis. We suggest that also the formation of the 2-azabuta-1,3-dienes **16** may be rationalized via an attack of the Vilsmeier reagent at the nitrogen atom of the vinyl isocyanates b followed by hydrolysis and HCl and CO_2 elimination. An indirect support to this hypothesis was given by the isolation in very low yields of 1-(dimethylamino)-4-phenyl-2-azabuta-1,3-diene **22** from the Vilsmeier–Haack reaction of the phenylethenyl isocyanate **21**[17] (Scheme IX).

That an equilibrium between oxazinones **2** and vinyl isocyanates b exists is firmly confirmed by two facts: (i) the cyclization of Boyd's vinyl isocyanates (e.g., **23**) affords the 1,3-oxazin-6-ones (e.g., **2m′**) rather than 1,3-oxazin-2-ones as previously reported[9] (Scheme X); (ii) flash vacuum pyrolysis of the "1,3-oxazin-2-ones" (that are indeed 1,3-oxazin-6-ones) gave vinyl isocyanates; moreover the same substrates on reaction with 1-(diethylamino)propyne gave products arising from Diels–Alder addition and $2\pi + 2\pi$ cycloaddition of the ynamine to a vinyl isocyanate.[18] Moreover it is known that 2-ethoxy-4-methyl-1,3-oxazin-6-one exists in equilibrium with β-isocyanocrotonate,[19] and in the 1,3,5-oxadiazin-2-one series there is IR spectroscopic evidence of the formation of instable isocyanates following thermolysis.[20]

Although we have no evidence of the intermediacy of an imino ketene in the equilibrium **2** ⇄ **b** (Scheme VIII), we point out that this hypothesis is strongly substantiated by the fact that oxazinones **2** can be obtained by thermal cyclization of ureido esters **8** with a reaction that parallels

(17) Jones, L. W.; Wason, J. P. *J. Am. Chem. Soc.* **1927**, *49*, 2528.
(18) Baydar, A. E.; Boyd, G. V.; Lindley, P. F.; Watson, F.; Manley, P. W.; Storr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2878.
(19) Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 128.
(20) Gompper, R.; Towae, F. *Synthesis* **1975**, 522.

the behavior of the 2-(acylamino)crotonic esters and that may occur by way of ketene intermediates[21] (Scheme XI). Oxazinones **2** can also be obtained by thermal cyclization of derivatives **9**.

The formation of the ureido esters **8** from oxazinones **2** by reaction with MeOH (with or without catalyst) cannot be considered an indication that intermediate imino ketenes will be formed. In all the cases studied the derivatives **8** were sterically unitary, whereas if they originated from the MeOH addition to a ketene it would be reasonable to expect that, at least in some cases, both isomers *E* and *Z* would be formed. It is more probable that products **8** arise from MeOH nucleophilic attack at C_6 of the oxazinone system.

Our results suggest that the nature of the substituents on the oxazinone ring influences the cycloreversion reaction, which, we believe, is the initial stage of the thermal reactivity of the 2-(dialkylamino)-1,3-oxazin-6-ones.

On the assumption that this fact could be correlated to the molecular parameters we are now trying to determine these parameters by the X-ray diffraction analysis of a large number of 2-(dialkylamino)-1,3-oxazin-6-ones. The Vilsmeier–Haack reaction of 4-alkylidenisoxazolin-5-ones is also being studied.

Experimental Section

Melting and boiling points are uncorrected. IR spectra were determined with a Perkin-Elmer 298 instrument, in Nujol mull for solids and liquid film for oils. NMR spectra were recorded on a Varian EM-390 or on a Bruker WP80SY spectrometer with tetramethylsilane as an internal standard. Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Magnesium sulfate was used as drying agent. Evaporation was carried out under vacuum in a rotary evaporator. Satisfactory combustion analysis (±0.3%) for C, H, and N were obtained. Only representative spectral data are reported. Spectral data of other products are collected in Table X (supplementary material).

4,5-Disubstituted 2-(Dialkylamino)-1,3-oxazin-6-ones 2a–l from Isoxazolin-5-ones 1a–l. General Procedure. To a solution in CCl_4 (40 mL) of the isoxazolin-5-one **1** (10 mmol) were added dimethylformamide (or diethylformamide for the synthesis of **2k′**) (30 mmol) and phosphorus oxychloride (20 mmol) at room temperature under stirring. The reaction mixture was stirred under reflux for the reported time (Table I). After cooling, the reaction mixture was evaporated, ice–water (50 mL) added, and the mixture neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 40 mL). The organic layer was dried, filtered, and evaporated. The residue was purified by crystallization or by column chromatography (see Table I).

2i: IR 1728, 1608 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (m, 5 H), 3.15 (s, 6 H), 2.76 (m, 4 H), 1.98 (s, 3 H). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.75; H, 7.05; N, 10.91.

2k′: IR 1740, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (q, *J* = 7 Hz, 4 H), 2.4 (m, 4 H), 1.73 (m, 4 H), 1.25 (t, *J* = 7 Hz, 6 H). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.90; H, 8.15; N, 12.67.

3-Unsubstituted 2-(Dialkylamino)-1,3-oxazin-6-ones 2m–p from Isoxazolin-5-ones 1m–p. General Procedure. Chloroform (50 mL, EtOH free) was cooled in an ice bath, and the appropriate formamide (10 mmol) and phosphorus oxychloride (10 mmol) were added. The isoxazolin-5-one **1** (10 mmol) dissolved in chloroform (10 mL) was then added. After warming to room temperature, the reaction mixture was stirred under reflux for the reported time. The reaction mixture was evaporated, water (60 mL) added, and the mixture neutralized with $NaHCO_3$ and extracted with methylene chloride (2 × 40 mL). The organic layer was dried, filtered, and evaporated. Column chromatography of the residue gave pure oxazinones **2** (Table I).

2m′: IR 1732, 1582 cm^{-1}; NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.6 (m, 2 H), 7.35 (m, 3 H), 3.8 (s, 8 H). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.17; H, 5.49; N, 10.91.

2o: IR 1750, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.82 (s, 1 H), 7.53 (d, *J* = 8 Hz, 2 H), 7.31 (d, *J* = 8 Hz, 2 H), 3.25 (s, 6 H). Anal. Calcd for $C_{12}H_{11}N_2O_2Cl$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.42; H, 4.44; N, 11.19.

Vilsmeier–Haack Reaction of 4-Unsubstituted Isoxazolin-5-ones 1q–n with 1 mol of Vilsmeier Reagent. General Procedure. CCl_4 (60 mL) was cooled in an ice bath, and DMF (10 mmol) and phosphorus oxychloride (10 mmol) were added. The isoxazolin-5-one **1** (10 mmol) was then added and the reaction, after warming at room temperature, stirred under reflux for the reported time. The reaction mixture was evaporated, water (60 mL) added, and the mixture neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 40 mL). The organic layer was dried, filtered, and evaporated. Column chromatography of the residue gave the pure compounds (Table II).

2q: IR 1728, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 5.4 (s, 1 H), 3.22 (s, 6 H), 2.18 (s, 3 H). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.55; H, 6.56; N, 18.20.

3t: IR 1708, 1634 cm^{-1}; NMR ($CDCl_3$) δ 8.38 (d, *J* = 9 Hz, 2 H), 7.87 (d, *J* = 9 Hz, 2 H), 7.55 (s, 1 H), 4.69 (s, 3 H), 4.42 (s, 3 H). Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.20; H, 4.25; N, 16.12.

Vilsmeier–Haack Reaction of 4-Unsubstituted Isoxazolin-5-ones 1q–n with 2 mol of Vilsmeier Reagent. General Procedure. The reaction was carried out as described, on 10 mmol of isoxazolin-5-ones **1**, but 20 mmol of DMF and 20 mmol of $POCl_3$ were used (Table II).

4q: IR 1760, 1655, 1612 cm^{-1}; NMR ($CDCl_3$) δ 10.13 (s, 1 H), 3.38 (s, 3 H), 3.3 (s, 3 H), 2.64 (s, 3 H). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.80; H, 5.51; N, 15.40.

7u: IR 1693, 1557 cm^{-1}; NMR ($CDCl_3$) δ 9.98 (s, 1 H), 1.46 (s, 9 H). Anal. Calcd for $C_8H_{10}NO_2Cl$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.20; H, 5.34; N, 7.50.

Ring Opening of Oxazinones 2a–p with MeOH. A solution of the oxazin-6-one **2** (1 mmol) in MeOH (25 mL) was heated under reflux for the reported time (Table III). The residue from the solvent evaporation was crystallized to obtain derivatives **9** or separated by column chromatography, and pure compounds **8** and **9** crystallized (Table III).

9e: IR 3220, 1745, 1730, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (br s, 1 H, exchanged by D_2O), 3.68 (s, 6 H), 3.3 (s, 2 H), 3 (s, 6 H), 2.15 (s, 3 H). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.03; N, 10.85. Found: C, 51.06; H, 7.01; N, 10.87.

9m: IR 3200, 1723, 1658, 1615 cm^{-1}; NMR ($CDCl_3$) δ 8.2 (br s, 1 H, exchanged in D_2O), 7.25 (m, 6 H), 3.8 (s, 3 H), 2.85 (br s, 6 H). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.80; H, 6.52; N, 11.31.

Ring Opening of Oxazinones 2a–p with MeOH–TEA. The reaction was carried out as described above, but a drop of triethylamine was added to the reaction mixture (Table III).

8e: IR 3440, 1730, 1685 cm^{-1}; NMR ($CDCl_3$) δ 11.63 (s, 1 H, exchanged in D_2O), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.37 (s, 2 H), 3.12 (s, 6 H), 2.5 (s, 3 H). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.03; N, 10.85. Found: C, 51.17; H, 7.04; N, 10.89.

(21) Eiden, F.; Nagar, B. S. *Naturweissenschaften* **1963**, *50*, 403. Steglich, W.; Bushmann, E.; Hollitzer, O. *Angew. Chem., Int. Ed. Engl.* **1978**, *13*, 533. Maier, G.; Schäfer, U. *Tetrahedron Lett.* **1977**, 1053.
(22) Jacquier, R.; Petrus, C.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1970**, 2685.
(23) Boulton, A. J.; Katritzky, A. R. *Tetrahedron* **1961**, *12*, 41.
(24) Silveira, A., Jr.; Satra, S. K. *J. Org. Chem.* **1978**, *44*, 873.
(25) Adembri, G.; Todeschi, P. *Bull. Sci. Fac. Chim. Ind. (Bologna)* **1965**, *23*, 203; *Chem. Abstr.* **1965**, *63*, 13235b.
(26) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *J. Org. Chem.* **1987**, *52*, 1666.
(27) Stagno D'Alcontres, G.; Lo Vecchio, G.; La Monica, G. *Gazz. Chim. Ital.* **1961**, *91*, 1005.
(28) Baldoli, C.; Beccalli, E. M.; Licandro, E.; Marchesini, A. *Gazz. Chim. Ital.* **1981**, *111*, 347.
(29) Wallingford, V. H.; Homeyer, A. M.; Jones, D. M. *J. Am. Chem. Soc.* **1941**, *63*, 2252.
(30) Dorlars, A.; Neunez, O.; Schellhammer, C. W.; Schroeder, J. (Bayer, A.-G.) Ger. Offen. 2816028, **1980**; *Chem. Abstr.* **1980**, *92*, 78110e.
(31) De Sarlo, F.; Dini, G. *J. Heterocycl. Chem.* **1967**, *4*, 533.
(32) Claisen, L. *Justus Liebigs Ann. Chem.* **1897**, *297*, 75.
(33) Kurkov, V. P. (Chevron Research Co.) U.S. Pat. 4504486, 1985; *Chem. Abstr.* **1985**, *103*, P54064n.
(34) Hantzch, H. *Chem. Ber.* **1891**, *24*, 495.
(35) Jacobsen, N.; Kolind Andersen, H.; Christensen, J. *Can. J. Chem.* **1984**, *62*, 1940.

8m: IR 3320, 1678, 1665, 1605 cm^{-1}; NMR ($CDCl_3$) δ 10.8 (d, J = 10.5 Hz, 1 H, exchanged in D_2O), 7.73 (d, J = 10.5 Hz, 1 H, s after D_2O), 7.3 (s, 5 H), 3.8 (s, 3 H), 3.12 (s, 6 H). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.83; H, 6.51; N, 11.29.

Acidic Hydrolysis of the Amido Esters 9. The amido ester **9** (150 mg) was dissolved in dioxane (10 mL), and then 4.5% H_2SO_4 (5 mL) was added. The reaction mixture was heated under reflux for 12 h. After solvent evaporation, water (20 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 20 mL). The usual workup gave pure **10a–c,e,h,l**.

10b: IR 1685, 1627 cm^{-1}; NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.5 (m, 3 H), 4.5 (q, J = 7.5 Hz, 1 H), 3.09 (s, 3 H), 3.04 (s, 3 H), 1.56 (d, J = 7.5 Hz, 3 H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.29; H, 7.35; N, 6.79.

10l: IR 1688, 1629 cm^{-1}; NMR ($CDCl_3$) δ 7.9 (m, 2 H), 7.47 (m, 3 H), 7.27 (s, 5 H), 4.67 (t, J = 7.5 Hz, 1 H), 3.42 (d, J = 7.5 Hz, 2 H), 2.98 (s, 3 H), 2.85 (s, 3 H). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.81; H, 6.83; N, 5.01.

Alkaline Hydrolysis of Oxazinones 2. Ureido Acids 11. General Procedure. The oxazin-6-one **2** (4 mmol) was dissolved in dioxane (60 mL), and a solution of NaOH (20 mmol) in water (30 mL) was then added. The reaction mixture was stirred at room temperature. After the reported time the solvent was evaporated (45 °C), water (50 mL) added, and the solution, after cooling in an ice bath, acidified with 16% HCl (7 mL). The resultant precipitate was filtered, washed with water, dried, and crystallized to give pure acids **11a–c,f,h–o** (Table V).

11a: IR 3200–2600, 1660, 1590 cm^{-1}; NMR ($CDCl_3$) δ 11.5 (s, 1 H, exchanged in D_2O), 10.6 (br s, 1 H, exchanged in D_2O), 7.3 (m, 5 H), 3.03 (s, 6 H), 1.23 (s, 3 H). Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.74; H, 6.48; N, 11.21.

11k′: IR 3100 (br), 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 11.3 (s, 1 H, exchanged in D_2O), 10.9 (br s, 1 H, exchanged in D_2O), 3.4 (q, J = 7.5 Hz, 4 H), 3.03 (m, 2 H), 2.33 (m, 2 H), 1.66 (m, 4 H), 1.23 (t, J = 7.5 Hz, 6 H). Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 58.98; H, 8.39; N, 11.66. Found: C, 58.83; H, 8.33; N, 11.61.

Acidic Hydrolysis of 4,5-Disubstituted 2-(Dimethylamino)-1,3-oxazin-6-ones 2. 1,3-Oxazine-2,6-diones 14. General Procedure. The 1,3-oxazin-6-one **2** (2 mmol) was dissolved in dioxane (30 mL), and then 4.5% H_2SO_4 (10 mL) was added. The reaction mixture was heated under reflux for the reported time, the solvent evaporated, water (40 mL) added, and then the mixture extracted with CH_2Cl_2 (2 × 40 mL). The organic layer was dried, filtered, and evaporated. The residue was crystallized to give pure 1,3-oxazin-2,6-diones (Table VI).

14h: IR 3250, 3160, 1780, 1715 cm^{-1}; NMR ($CDCl_3$) δ 8.8 (br s, 1 H, exchanged in D_2O), 7.5 (m, 5 H), 2.3 (m, 2 H), 1.23 (m, 12 H), 0.88 (m, 3 H). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.69; H, 7.67; N, 4.63.

14l: IR 3230, 3150, 1780, 1735 cm^{-1}; NMR ($CDCl_3$) δ 9.1 (br s, 1 H, exchanged in D_2O), 7.4 (m, 10 H), 3.72 (s, 2 H). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.07; H, 4.67; N, 5.04.

3-Methyl-1,3-oxazine-2,6-diones 15. The 1,3-oxazine-2,6-dione **14** (2 mmol) was dissolved in dry THF and NaH (4 mmol as 80% suspension) was added. After the mixture was stirred at room temperature for 10 min, MeI (3 mL) was added and the reaction mixture stirred at 40 °C for 24 h. After cooling, the solution was evaporated, cold 2% HCl (40 mL) added, and the mixture extracted with CH_2Cl_2 (40 mL). The organic layer was dried, filtered, and evaporated. Crystallization of the residue gave pure 3-methyl-1,3-oxazine-2,6-diones **15** (Table VI).

15h: IR 1765, 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.55 (m, 3 H), 7.28 (m, 2 H), 3.08 (s, 3 H), 2.05 (m, 2 H), 1.2 (m, 12 H), 0.82 (m, 3 H). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.39; H, 8.01; N, 4.42.

15l: IR 1785, 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.55 (m, 3 H), 7.2 (m, 5 H), 6.9 (m, 2 H), 3.5 (s, 2 H), 3.1 (s, 3 H). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.75; H, 5.17; N, 4.81.

Ester 8m′ from Diazomethane Esterification of 11m′. A THF solution of the acid **11m′** (400 mg) was esterified with an ethereal solution of diazomethane to give in quantitative yield the corresponding ester **8m′**: mp 144–145 °C (Et_2O–hexane); IR 3320, 1690, 1662 cm^{-1}; NMR ($CDCl_3$) δ 10.83 (d, J = 12 Hz, 1 H), 7.73 (d, J = 12 Hz, 1 H), 7.3 (m, 5 H), 3.83 (s, 3 H), 3.78 (m, 4 H), 3.6 (m, 4 H). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.11; H, 6.27; N, 9.67.

Acidic Hydrolysis of the Acid 11m′. The acid **11m′** (400 mg) was dissolved in dioxane (30 mL), and then 10% H_2SO_4 (10 mL) was added. The reaction mixture was heated under reflux for 2 h. After evaporation of the solvent water was added (20 mL) and the mixture extracted with Et_2O (2 × 25 mL). The organic layer was dried, filtered and evaporated. Column chromatography of the residue (eluant CH_2Cl_2–hexane, 1:1) gave pure **12**: 25 mg; mp 36–37 °C (Et_2O–hexane); IR 1683, 1627, 1595 cm^{-1}; NMR ($CDCl_3$) δ 9.7 (s, 1 H), 7.35 (m, 10 H), 6.83 (t, J = 7 Hz, 1 H), 3.78 (d, J = 7 Hz, 2 H). The original aqueous extract was neutralized with $NaHCO_3$ and evaporated to dryness. The solid residue was extracted with boiling AcOEt (3 × 30 mL). Solvent evaporation gave carbamyl morpholine: 85 mg; mp 110–111 °C (CH_2Cl_2–Et_2O).

2,4-Diphenyl-2-butenal 12 from Phenylacetaldehyde. Phenylacetaldehyde (1 g) was dissolved in dioxane (50 mL), and then 10% H_2SO_4 (15 mL) was added. The reaction mixture was heated under reflux for 3 h. Workup as previously described gave, after column chromatography (eluant Et_2O–hexane, 1:2) pure aldehyde **12** (250 mg).

Acidic Hydrolysis of the Ester 8m′. The ester **8m′** (350 mg) was treated as described for the acid **11m′**. After analogous workup the methyl 2-formyl-2-phenylacetate (**13**) (54 mg, after column chromatography, eluant CH_2Cl_2) and carbamylmorpholine (78 mg) were isolated.

Ring Opening of Oxazinones 2 with Water. The oxazinone **2** (200 mg) was dissolved in dioxane (4 mL), and then water (2 mL) was added. The reaction was carried out in a sealed tube at 110 °C for 16 h. After solvent evaporation, water (10 mL) was added and the mixture extracted with CH_2Cl_2 (15 mL). The organic layer was dried, filtered, and evaporated. Column chromatography of the residue (eluant CH_2Cl_2–Et_2O, 20:1) gave pure β-keto acids dimethyl amides **10a–c,e,h,l** (Table IV).

Vilsmeier–Haack Reaction on 2-(Dimethylamino)-5-carbethoxy-1,3-oxazin-6-one (2p). To CCl_4 (30 mL) were added dimethylformamide (5 mmol) and phosphorus oxychloride (5 mmol) and then the oxazin-6-one **2p** (5 mmol). The reaction was stirred under reflux for 2 h. Workup as described previously gave pure **16p** (510 mg). No unreacted oxazinone **2p** was recovered.

Vilsmeier–Haack Reaction on 3-Unsubstituted Isoxazolin-5-ones 1m–p with 2 mol of the Vilsmeier Reagent. General Procedure. To CCl_4 (50 mL) were added dimethylformamide (10 mmol) and phosphorus oxychloride (10 mmol) and then the isoxazolin-5-one **1** (5 mmol). The reaction was stirred under reflux for 2 h and then evaporated. Water was added (40 mL) and the mixture extracted with CH_2Cl_2 (2 × 30 mL). Elaboration of the organic layer, as described previously, gave the oxazinone **2**. The original aqueous extract was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 30 mL). Workup of the organic layer gave the 2-azabuta-1,3-dienes **16** purified by crystallization (Table VII).

16n: IR 1630, 1608 cm^{-1}; NMR ($CDCl_3$) δ 7.6 (s, 1 H), 7.3 (m, 5 H), 2.98 (s, 6 H), 2.84 (s, 6 H), 2.3 (s, 3 H). Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.21. Found: C, 69.41; H, 8.17; N, 16.26.

16p: IR 1678, 1640 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (s, 1 H), 7.66 (s, 1 H), 4.25 (q, J = 7.5 Hz, 2 H), 3.13 (s, 6 H), 3.08 (s, 3 H), 3 (s, 3 H), 1.3 (t, J = 7.5 Hz, 3 H). Anal. Calcd for $C_{11}H_{19}N_3O_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.71; H, 7.92; N, 17.47.

Acidic Hydrolysis of *N*,*N*-Dimethyl-1-(dimethylamino)-4-(*p*-chlorophenyl)-2-azabuta-1,3-diene-4-carboxamide (16o). The compound **16o** (800 mg) was dissolved in 5% H_2SO_4 (20 mL) and the solution heated under reflux for 1.5 h. After cooling, the mixture was extracted with CH_2Cl_2 (2 × 20 mL).

The organic layer was dried, filtered, and evaporated to give pure 2-formyl-2-(*p*-chlorophenyl)-1-(dimethylamino)acetamide **17**: 610 mg; mp 100–104 °C (*i*-Pr_2O–hexane); IR 3320, 3160, 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 9.87 (d, J = 3 Hz, 1 H), 7.37 (m, 4 H), 4.6 (d, J = 3 Hz, 1 H), 3.06 (s, 3 H), 2.97 (s, 3 H).

Reaction with Water of the Oxazinones 2g,p and 4r–t. The oxazinone (5 mmol) was dissolved in dioxane (40 mL), and then water (15 mL) was added. The reaction mixture was heated under reflux for the reported time. After solvent evaporation, water (40 mL) was added and the mixture extracted with CH_2Cl_2 (2 ×

30 mL). The organic layer was dried, filtered, and evaporated. Column chromatography of the residue gave pure derivatives **18** and **19** (Table VIII).

18r: IR 3280, 3080, 1685, 1605 cm^{-1}; NMR ($CDCl_3$) δ 10.6 (br s, 1 H, exchanged in D_2O), 9.15 (s, 1 H), 6.72 (br s, 1 H, exchanged in D_2O), 3.13 (s, 3 H), 3.05 (s, 3 H), 2.5 (t, J = 7 Hz, 2 H), 1.66 (m, 2 H), 1 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.47; H, 10.33; N, 17.98.

19r: IR 1685, 1620 cm^{-1}; NMR ($CDCl_3$) δ 12.4 (br s, 1 H, exchanged in D_2O), 9.26 (d, J = 1.5 Hz, 1 H), 5.35 (d, J = 1.5 Hz, 1 H), 3.14 (s, 6 H), 2.86 (t, J = 7 Hz, 2 H), 1.67 (m, 2 H), 1.02 (t, J = 7Hz, 3 H). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.47; H, 10.31; N, 17.95.

18t: IR 3310, 3170, 1640, 1628 cm^{-1}; NMR ($CDCl_3$) δ 10.6 (br s, 1 H, exchanged in D_2O), 9.4 (s, 0.66 H), 8.8 (s, 0.34 H), 8.32 (m, 2 H), 7.72 (m, 3 H, 2 H after D_2O), 3.13 (s, 2 H), 2.8 (s, 4 H). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.19; H, 5.55; N, 17.89.

19t: IR 3260, 1662, 1652, 1610 cm^{-1}; NMR ($CDCl_3$) δ 11.9 (br s, 1 H, exchanged in D_2O), 9.49 (d, J = 2 Hz, 1 H), 8.2 (d, J = 9 Hz, 2 H), 7.52 (d, J = 9 Hz, 2 H), 5.5 (d, J = 2 Hz, 1 H), 3.1 (s, 6 H). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.19; H, 5.58; N, 17.87.

Acidic Hydrolysis of Derivatives 18r–t: β-Keto Amides 20r–t. Compound **18** (2 mmol) was dissolved in dioxane (15 mL), and then 4.5% H_2SO_4 (15 mL) was added. The reaction mixture was heated under reflux for 1.5 h. After solvent evaporation, water was added (30 mL) and the mixture extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried, filtered, and evaporated. The residue was crystallized to give pure **20r–t**. Compound **20r** was purified by column chromatography (eluant hexane–Et_2O, 1:1).

20r: undistilled oil (83%); IR 1708, 1633 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (s, 2 H), 3.08 (s, 3 H), 3.03 (s, 3 H), 2.6 (t, J = 7 Hz, 2 H), 1.63 (m, 2 H), 0.96 (t, J = 7 Hz, 3 H).

20s: mp 82–83 °C (CH_2Cl_2–hexane (71%)).

20t: mp 153–154 °C (CH_2Cl_2–Et_2O (65%)); IR 3400–3200, 1605, 1588 cm^{-1}; NMR ($CDCl_3$) δ 15.56 (s, 1 H, exchanged in D_2O), 8.31 (d, J = 9 Hz, 2 H), 7.99 (d, J = 9 Hz, 2 H), 5.92 (s, 1 H), 3.2 (s, 6 H). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.91; H, 5.13; N, 11.89.

Alkaline Hydrolysis of Oxazinones 2g,p and 4r–t. The oxazinone (5 mmol) was dissolved in dioxane (60 mL) and then NaOH (25 mmol) in water (30 mL) was added. The reaction mixture was stirred at room temperature for 20 min. The solvent was evaporated (45 °C), water added (30 mL), and the solution, cooled in an ice bath, acidified carefully with 8% HCl. The resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were dried, filtered, and evaporated. Column chromatography of the residue afforded pure compounds **11** and **19** (Table IX).

Synthesis of 1-(Dimethylamino)-5-phenyl-2-azabuta-1,3-diene (22). Chloroform (70 mL) was cooled in an ice bath, and dimethylformamide (20 mmol) and phosphorus oxychloride (20 mmol) were added. The styryl isocyanate (**21**) (20 mmol) was then added dissolved in $CHCl_3$ (20 mL). The reaction was stirred at room temperature for 10 min and then under reflux for 2 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (70 mL) and water (40 mL). The water layer was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 40 mL). The methylene chloride was dried, filtered, and evaporated. The residue was purified by column chromatography (eluant CH_2Cl_2 and CH_2Cl_2–MeOH, 100:1) to give pure **22** (210 mg, 6%): undistilled oil; IR 1655, 1612, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.57 (s, 1 H), 7.3 (m, 6 H), 6.35 (d, J = 14 Hz, 1 H), 3.03 (s, 6 H).

Thermal Cyclization of the Ureido Esters 8f,i,l. Oxazinones 2f,i,l. The ureido ester **8** (250 mg) in diphenyl ether (20 mL) was heated at 255 °C for 20 min, while nitrogen gas was bubbled through the solution. The diphenyl ether was distilled off under vacuum to yield crude oxazinone **2**. Silica gel column chromatography (eluant CH_2Cl_2) gave pure oxazinones **2f,i,l** (yields 42–60%).

Thermal Cyclization of the Amido Esters 9f,i,l. Oxazinones 2f,i,l. The reactions were carried out as described above, and after 1 h at 255 °C, pure oxazinones **2f,i,l** were obtained (yields 46–64%) after silica gel column chromatography.

Registry No. **1a**, 29879-48-9; **1b**, 29879-49-0; **1c**, 87927-86-4; **1d**, 84280-59-1; **1e**, 108471-22-3; **1f**, 108471-23-4; **1g**, 108471-24-5; **1h**, 108471-25-6; **1i**, 108471-26-7; **1j**, 108471-27-8; **1k**, 29879-50-3; **1l**, 89114-09-0; **1m**, 17147-69-2; **1n**, 91632-31-4; **1o**, 91632-27-8; **1p**, 54535-14-7; **1q**, 1517-96-0; **1r**, 108471-28-9; **1s**, 1076-59-1; **1t**, 39214-83-0; **1u**, 75914-61-3; **2a**, 106013-78-9; **2b**, 106013-79-0; **2c**, 106013-80-3; **2d**, 106013-81-4; **2e**, 108471-29-0; **2f**, 108471-30-3; **2g**, 108471-31-4; **2h**, 108471-32-5; **2i**, 108471-33-6; **2j**, 108471-34-7; **2k**, 108471-35-8; **2k′**, 108471-36-9; **2l**, 108471-37-0; **2m**, 108471-38-1; **2m′**, 108471-39-2; **2m″**, 108472-34-0; **2n**, 108471-40-5; **2n′**, 108472-35-1; **2o**, 108471-41-6; **2p**, 108471-42-7; **2q**, 108471-43-8; **2r**, 108471-44-9; **3s**, 5272-46-8; **3t**, 108471-45-0; **3u**, 108471-46-1; **4q**, 108471-47-2; **4r**, 108471-48-3; **4s**, 100230-70-4; **4t**, 108471-49-4; **4u**, 108510-34-5; **5q**, 108471-50-7; **5s**, 108510-35-6; **6r**, 108471-51-8; **7s**, 100230-72-6; **7t**, 108471-52-9; **7u**, 108471-53-0; **8a**, 106013-82-5; **8b**, 106224-37-7; **8c**, 106013-83-6; **8d**, 106013-84-7; **8e**, 108471-54-1; **8f**, 108471-55-2; **8g**, 108471-56-3; **8h**, 108471-57-4; **8i**, 108471-58-5; **8j**, 108471-59-6; **8k**, 108471-60-9; **8l**, 108471-61-0; **8m**, 108471-62-1; **8m′**, 108471-63-2; **8n**, 108471-64-3; **8o**, 108471-65-4; **8p**, 108471-66-5; **9a**, 108471-67-6; **9b**, 108471-68-7; **9c**, 108471-69-8; **9d**, 108471-70-1; **9e**, 108471-71-2; **9f**, 108471-72-3; **9g**, 108471-73-4; **9h**, 108471-74-5; **9i**, 108471-75-6; **9j**, 108471-76-7; **9k**, 108471-77-8; **9l**, 108510-36-7; **9m**, 108471-78-9; **9n**, 108471-79-0; **9o**, 108471-80-3; **9p**, 108471-81-4; **10a**, 64771-37-5; **10b**, 108471-82-5; **10c**, 83305-62-8; **10e**, 108471-83-6; **10h**, 108471-84-7; **10l**, 108471-85-8; **11a**, 108471-86-9; **11b**, 108471-87-0; **11c**, 108471-88-1; **11f**, 108471-89-2; **11h**, 108510-37-8; **11i**, 108471-90-5; **11j**, 108471-91-6; **11k**, 108471-92-7; **11k′**, 108471-93-8; **11l**, 108471-94-9; **11m**, 108471-95-0; **11m′**, 108471-96-1; **11n**, 108471-97-2; **11o**, 108471-98-3; **11p**, 108471-99-4; **11r**, 108472-00-0; **11s**, 108472-01-1; **11t**, 108472-02-2; **12**, 5031-83-4; **14a**, 106013-88-1; **14b**, 106013-89-2; **14c**, 106013-90-5; **14d**, 59416-53-4; **14e**, 108472-03-3; **14f**, 108472-04-4; **14h**, 108472-05-5; **14i**, 108472-06-6; **14j**, 108472-07-7; **14k**, 108472-08-8; **14l**, 108472-09-9; **15a**, 108472-10-2; **15c**, 108510-38-9; **15d**, 108472-11-3; **15h**, 108472-12-4; **15l**, 108472-13-5; **16m**, 108472-14-6; **16n**, 108472-15-7; **16o**, 108472-16-8; **16p**, 108472-19-1; **17**, 108472-19-1; (*E*)-**18g**, 108472-18-0; (*Z*)-**18g**, 108472-20-4; (*E*)-**18p**, 108472-21-5; (*Z*)-**18p**, 108472-22-6; (*E*)-**18r**, 108472-23-7; (*Z*)-**18r**, 108510-39-0; (*E*)-**18s**, 108472-24-8; (*Z*)-**18s**, 108472-25-9; (*E*)-**18t**, 108472-26-0; (*Z*)-**18t**, 108510-40-3; **19g**, 108472-27-1; **19r**, 108472-28-2; **19s**, 108472-29-3; **19t**, 108472-30-6; **20r**, 108472-31-7; **20s**, 18871-71-1; **20t**, 108472-32-8; **21**, 4737-20-6; **22**, 108472-33-9; **23**, 69193-53-9; phenylacetaldehyde, 122-78-1; carbamylmorpholine, 2158-02-3; 6-morpholino-5-phenyl-1,3-oxazin-2-one, 61744-62-5.

Supplementary Material Available: Table X, containing IR and ^1H NMR data for the 95 new compounds for which this data is not given in text (3 pages). Ordering information is given on any current masthead page.