

James M. Hamby and Ludwig Bauer*

Department of Medicinal Chemistry and Pharmacognosy,
College of Pharmacy, University of Illinois at Chicago,
P. O. Box 6998, Chicago, IL 60680

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Reactions of 3-benzenesulfonyloxyalloxazine (**1a**) and its 1-methyl analog **1b** with a number of nucleophilic reagents are reported. Relatively small nucleophiles, such as hydroxide ion, methanol, ethanol, methylamine, hydrazine and hydroxylamine converted **1a** to 4-carboxy-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-ones and the corresponding esters or amides. As the size of the amine increased from methylamine to ethylamine, dimethylamine, propylamine and isopropylamine, there were obtained 4-(carboxamido)-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-ones, (1-carboxamido)imidazo[4,5-*b*]quinoxalines and 2,3-bis(ureido)quinoxalines. Sodium hydride or potassium cyanide in hot DMF degraded **1a** to imidazo[4,5-*b*]quinoxaline. However, methylmercaptide and benzylmercaptide ions attacked the sulfonate group of **1a** to form 3-hydroxyalloxazine.

1-Methyl-3-benzenesulfonyloxyalloxazine (**1b**) reacted with methanol, ethanol, 1-propanol, and to some degree 2-propanol, in the presence of triethylamine to furnish anhydro-1-hydroxy-3-methyl-4-(alkoxycarbonyl)-*s*-triazolo[4,3-*a*]quinoxalinium hydroxides. However, sodium methoxide in methanol converted this starting material to a mixture of anhydro-1-hydroxy-3-methyl-*s*-triazolo[4,3-*a*]quinoxalinium hydroxide and 1-methyl-3-hydroxyflavazole. A saturated aqueous solution of triethylamine transformed **1b** to anhydro-1-hydroxy-3-methyl-*s*-triazolo[4,3-*a*]quinoxalinium hydroxide, apparently *via* the corresponding unstable 4-carboxylic acid. The reactions of **1b** with a number of aliphatic amines yielded either amides based on the above mesoionic system or on the 3-carboxamido-2-quinoxalyl semicarbazide structure. The reaction of **1b** with potassium cyanide furnished 1-methylimidazo[4,5-*b*]quinoxaline. Mechanisms to explain all of the degradations are advanced.

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Introduction.

Preliminary studies reported some of the reactions of 3-benzenesulfonyloxyalloxazine (**1a**) with nucleophilic reagents [2]. It appears that the fused uracil ring of **1a** is opened under nucleophilic attack by two different degradations. There were obtained either derivatives of 2-hydrazino-3-quinoxalinecarboxylic acid, such as *s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-ones (**5**) or semicarbazides **7**. The other degradative ring-opening of **1a** led to derivatives of 2,3-diaminoquinoxaline, exemplified by imidazo[4,5-*b*]quinoxalines **12** or ureas **13**. For example, an attempt to hydrolyze **1a** by sodium hydroxide to form 3-hydroxyalloxazine, **17a**, yielded instead 4-carboxy-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one (**5a**). Similarly, methanol and methylamine converted **1a** to the cognate ester and amide of the *s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one system, **5b** and **5d**, respectively [2]. However, dibutylamine unexpectedly degraded **1a** to 1-(*N,N*-dibutylcarboxamido)imidazo[4,5-*b*]quinoxaline (**12g**) [2].

At first glance, it would appear that the size of the attacking nucleophile might control the degradation of **1a**. To substantiate such a thesis, a systematic investigation was launched to study these reactions as a function of the size of different amines, as well as some oxygen- and sulfur-bearing nucleophiles and cyanide ion.

Nucleophilic Reactions of **1a**.

The reaction of **1a** with hydroxide ion is improved con-

siderably by using an aqueous saturated triethylamine solution to provide the pure acid, **5a** (25°, 15 minutes, 94%). This reaction is quite remarkable since **1a** does not react when boiled in *anhydrous* triethylamine for 30 minutes. Even more interesting is the observation that triethylamine can be substituted for sodium methoxide in the quantitative degradation of **1a** to the methyl ester, **5b**. While ethanol containing triethylamine converts **1a** to the ethyl ester **5c**, quantitatively, reactions of **1a** with 1- and 2-propanol (and triethylamine) provide mixtures of products. When the corresponding alkoxide ion is substituted for triethylamine, 1- and 2-propanol still react with **1a** but still afford almost inseparable mixtures consisting of at least 3 components (tlc, ¹H nmr). The reactions of these alcohols with **1a** were not investigated further at this time.

Instead, we turned our attention to the investigation of **1a** with amines, which proved to be unexpectedly complex. While 40% aqueous methylamine transforms **1a** exclusively to the triazoloquinoxaline amide **5d** [2], few other amines underwent such a clean-cut degradation. Relatively small amines, like hydrazine and hydroxylamine, convert **1a** to **5e** and **5f**, predominantly. But even small structural changes from methylamine to ethylamine or dimethylamine causes **1a** to undergo more than one reaction. Therefore, we included also propylamine, isopropylamine, and several larger amines, like diethylamine and piperidine in this study. The overall yields of products from **1a** and amines were quite high (80-90%). However, the pro-

Table I
Distribution of Products from the Reaction of 3-Benzene-sulfonyloxyaloxazine (**1a**) with Amines

Amine, HN <u>Nu</u> (Nu is amino)	Solvent(s)	Temperature of Reaction °C (Time)	Conversion %	Molar Ratios				
				5, Nu = OH	5, Nu = amino	12, Nu = amino	13, Nu = amino	17a
CH ₃ NH ₂	40% in water	90 (5 minutes)	100	—	100	—	—	—
NH ₂ NH ₂	5% in methanol	25 (5 minutes)	61	—	100	—	—	—
NH ₂ OH	5% in methanol	60 (10 minutes)	79	—	100	—	—	—
CH ₃ CH ₂ NH ₂	40% in water	25 (5 minutes)	87	17	76	7	—	—
CH ₃ CH ₂ NH ₂	10% DMF in ethylamine	-78 (2 hours)	79	—	94	6	—	—
CH ₃ CH ₂ NH ₂	ethylamine	5 (5 minutes)	82	—	47	47	6	—
CH ₃ CH ₂ NH ₂	20% in dioxane	25 (5 minutes)	97	—	—	56	44	—
CH ₃ CH ₂ CH ₂ NH ₂	40% in water	5 (5 minutes)	93	40	47	—	—	13
CH ₃ CH ₂ CH ₂ NH ₂	propylamine	-78 (2 hours)	80	—	81	19	—	—
CH ₃ CH ₂ CH ₂ NH ₂	10% DMF in propylamine	-78 (2 hours)	80	—	81	19	—	—
CH ₃ CH ₂ CH ₂ NH ₂	propylamine	5 (5 minutes)	99	—	—	87	13	—
CH ₃ CH ₂ CH ₂ NH ₂	20% in dioxane	25 (5 minutes)	92	—	—	54	46	—
(CH ₃) ₂ CHNH ₂	40% in water	25 (15 minutes)	88	98	—	2	—	—
(CH ₃) ₂ CHNH ₂	10% DMF in isopropylamine	-78 (2 hours)	0	—	—	—	—	—
(CH ₃) ₂ CHNH ₂	isopropylamine	5 (5 minutes)	98	—	—	89	11	—
(CH ₃) ₂ CHNH ₂	20% in dioxane	25 (5 minutes)	91	—	—	52	48	—
(CH ₃) ₂ NH	40% in water	25 (15 minutes)	71	18	18	21	—	43
(CH ₃) ₂ NH	dimethylamine	5 (5 minutes)	97	—	43	57	—	—
(CH ₃) ₂ NH	20% in dioxane	25 (5 minutes)	84	—	—	100	—	—
(CH ₃ CH ₂) ₂ NH	diethylamine	25 (1.5 hours)	80	—	—	100	—	—
(CH ₂) ₅ NH	piperidine	25 (5 minutes)	94	—	—	100	—	—

portion of major products was greatly influenced by solvent and temperature (Table I).

Ideally, it would have been helpful to conduct this study if one could have added the amine to a solution of **1a** in various solvents. However, **1a** is virtually insoluble in most common solvents at room temperature. Methanol might have served as a solvent but could not be used since this alcohol reacts with **1a** in the presence of an amine. Although dimethylformamide or dimethyl sulfoxide might have been satisfactory solvents, they are difficult to remove entirely from crude reaction mixtures at low temperatures (25-50°). Furthermore, residual solvents of these kinds were found to interfere with some ¹H nmr analyses and in the separation and purification of components of these mixtures. Due to similar chemical and spectral properties of the highly polar type of compounds like **5**, **12**, **13** and **17**, formed from **1a**, their proportions were estimated (¹H nmr) at the end of each reaction (Table I).

To study as many of these reactions as possible in homogeneous solutions, reactions of **1a** were conducted essentially in three different solvent systems. The three solvent systems which were used were: an aqueous solution of the amine, a solution of the amine in dioxane and an excess of the amine as solvent. Solutions in these media were obtained quickly when finely powdered **1a** was added to a stirred solution of the solvent system. All reactions were followed by tlc until **1a** could no longer be detected.

Some definite patterns emerge from these studies. Methylamine in water, as well as the highly nucleophilic hydrazine and hydroxylamine in methanol convert **1a** primarily to amides **5d**, **5e** and **5f**, respectively. Although aqueous ethylamine (25°, 5 minutes) transforms **1a** predominantly to **5g** (76%), there are also isolated the acid **5a** (17%) and the imidazo compound, **12a** (7%). The acid **5a** could not have arisen from the amide **5g**, since an independent hydrolysis of **5g** to **5a** required much more stringent conditions (reflux, 20 minutes). It is surprising that hydroxide ion competes with the more nucleophilic (and relatively small) ethylamine. But this competition between the amine and hydroxide ion becomes more evident as the size of the amine increases from methylamine to ethylamine, dimethylamine, propylamine and isopropylamine. The percent of acid **5a** in the product increases from 17 to 98% as the amine increases from ethylamine to isopropylamine (Table I).

To avoid competition between hydroxide ion and the amine, reactions of **1a** were studied in an excess of anhydrous amines. We had expected that in pure amine solutions, the relatively small ethylamine and dimethylamine would degrade **1a** (0 to 25°) predominantly to amides of type **5**. Instead, **1a** is degraded in pure ethylamine and dimethylamine to a mixture consisting of almost equal parts of triazoloquinoxaline amides **5**, and 1-carboxamidoimidazoloquinoxalines **12**. With propylamine and isopropylamine at 5°, no amides of type **5** are

obtained and the major product consists of **12**, with **13** as the minor product.

At first, it was thought that the size of the attacking amine plays a crucial role. However, this assumption is invalid since both ethylamine and propylamine and **1a** at -78° (2 hours) produce primarily amides of type **5**, admixed with **12**. Apparently, a kinetic effect operates since raising the temperature from -78 to 5° sharply curtails the formation of **5**. It is interesting to note that when a concentrated solution of **1a** in DMF is added to an excess of propylamine at -78° there is still obtained **5h** and **12h** (4:1).

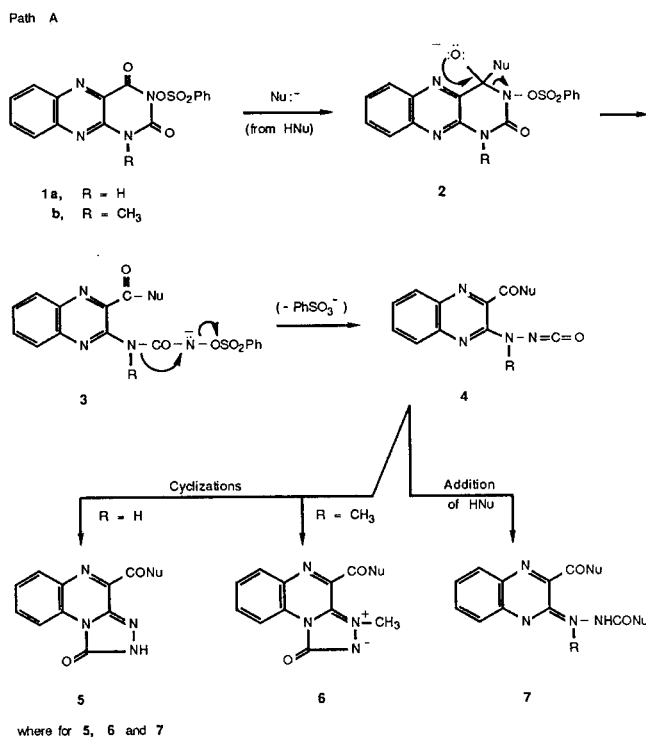
At -78° (2 hours), isopropylamine fails to react at all with **1a**. Originally, this lack of reactivity was thought to be due to the extreme insolubility of **1a** in the amine at that temperature. However, a solution of **1a** in a 10% DMF solution of isopropylamine still failed to react at -78° (2 hours). But, at 5° **1a** reacts with isopropylamine to form the imidazoloquinoxaline **12c** and bis-ureide **13c** in excellent overall yields (Table I). Apparently, isopropylamine exceeds the size of an amine which could attack **1a** at a critical juncture leading to **5**. It was therefore not surprising that amines larger than isopropylamine, like diethylamine and piperidine, react with **1a** to form only **12** and/or **13**.

We were interested in exploring alternate syntheses of amides of type **5**. The standard procedure *via* the acid halide **5** (Nu = Cl) was employed, with some modifications. Since the acid **5a** tended to decarboxylate above 80° , its conversion to the acid chloride was conducted at room temperature. Hence, the sequence of reactions of **5a** with thionyl chloride, followed by diethylamine furnishes **5k** in fair yield.

In searching for polar but non-reactive low-boiling solvents for the reactions of **1a** with amines, dioxane was chosen. Quite unexpectedly, the reactions of **1a** with even such small amines, as ethylamine, dimethylamine and propylamine at 25° , give only imidazoloquinoxalines **12** and bis-ureides **13** and no amides of type **5** (Table I). The presence of even small quantities of triazoloquinoxalines **5** in the crude reaction mixtures would have been detected readily in their ^1H nmr spectra since the signal for H-9 is usually set apart and considerably downfield from the other aromatic proton signals of the products. The chemical shift of that proton is highly deshielded due to the anisotropic effect of the neighboring C = O group [3].

General mechanistic pathways are advanced to account for the formation of the products reported in this study. It is suggested that triazoloquinoxalines of type **5** and the related semicarbazides, **7**, are formed *via* Path A. The electrophilic character of the carbonyl carbon at C-4 of **1a** is expected to be very high, being part of a *N*-sulfonyloxyimide system and being attached to the electron-attracting quinoxaline ring. Attack of a nucleophile (Nu: or Nu:⁻) at

the highly electrophilic C-4 of **1a** [4] generates the tetrahedral intermediate, **2**. Collapse of this intermediate forms an acid, or acid derivative, and the anion of an *O*-sulfonylhydroxamate ion, **3**. A spontaneous Lossen rearrangement of such a hydroxamate anion [7] affords the isocyanate, **4**. Spontaneous cyclization of the isocyanate of **4** with the neighboring quinoxaline nitrogen leads to **5**. Alternatively, HNu could add to **4** to form the semicarbazide. Apparently, the route to **5** predominates since in the series of reactions starting with **1a**, no semicarbazides to type **7** were isolated. The structure of the triazoloquinoxaline system **5** had been established previously [3].

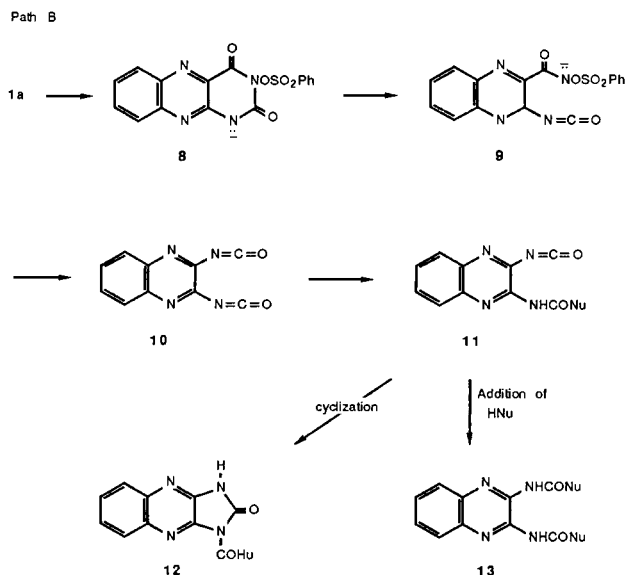


where for **5**, **6** and **7**

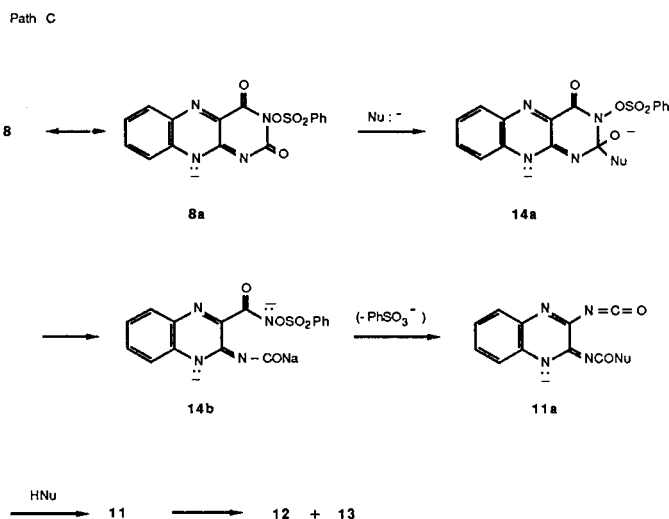
- | | |
|---|--|
| a, Nu = OH | l, Nu = NHC ₃ H ₇ - iso |
| b, Nu = OCH ₃ | l, Nu = N(CH ₃) ₂ |
| c, Nu = OC ₂ H ₅ | k, Nu = N(C ₂ H ₅) ₂ |
| d, Nu = NHCH ₃ | l, Nu = N(CH ₂) ₅ |
| e, Nu = NHNH ₂ | m, Nu = OC ₃ H ₇ - n |
| f, Nu = NHOH | n, Nu = OC ₃ H ₇ - iso |
| g, Nu = NHC ₂ H ₅ | o, Nu = O ⁻ N(C ₂ H ₅) ₃ H ⁺ |
| h, Nu = NHC ₃ H ₇ - n | p, Nu = O ⁻ Na ⁺ |

The formation of **12** and **13** is explained if the nucleophile attacks at a different site (than C-4) of **1a**, as is suggested by either Path B or C. These reactions represent degradations of **1a** to derivatives of 2,3-diaminoquinoxaline. From this point of view, the overall reaction is analogous to the conversion of 3-benzenesulfonyloxy-5,6-dihydrouracil by nucleophilic reagents to derivatives of ethylenediamine [5]. Path B is perhaps more logical in strongly basic media since it commences with the neutralization of the NH group of **1a** to form the anion, **8**. In the alloxazine system, such an anion is quite stable at low temperatures

and is alkylated readily by alkyl halides to form 1-alkyl derivatives of **1**. Upon heating, the anion, **8**, is prone to ring open to form an isocyanate and a Lossen precursor. Instant rearrangement of the hydroxamate anion in **9** generates the equivalent of the diisocyanate, **10**, which is not isolated. Addition of one equivalent of HNu to **10** provides **11**, which can either cyclize to **12** or add another equivalent to HNu to furnish **13**. No attempt was made to alter conditions to examine changes in the proportions of **12** and **13**. The thrust of the research concentrated on establishing conditions under which either **5** or **12** (and/or **13**) are formed. The experiments were designed to keep as many factors constant and varying primarily the size of the nucleophile.



Support for Path B is available from the following experiments. In utilizing the non-nucleophilic hydride ion of sodium hydride to generate **8** from **1a**, further reaction in hot DMF produces imidazolo[4,5-*b*]quinoxaline in 60% yield. Such a reaction is analogous to the conversion of 3-sulfonyloxy-2,4-quinoxalinedione to 2-benzimidazolone by sodium hydride in DMF [6]. The reaction of **1a** with potassium cyanide in hot dioxane also yields imidazolo[4,5-*b*]quinoxaline (91%). One could surmise that in this reaction, cyanide ion acts as a base and transforms **1a** first to **8** which degrades to the product, as discussed above.

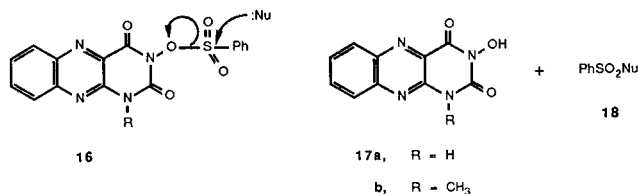


However, one cannot rule out that Path C for the reaction of **1a** with CN⁻, particularly as will be shown later that 1-methyl-3-benzenesulfonyloxyalloxazine (**1b**) reacts with cyanide ion to form 1-methylimidazolo[4,5-*b*]quinoxaline, **27**. Since **1b** cannot form an anionic intermediate like **8**, it is quite likely that cyanide ion attacks C-2 which leads to **27** (Path E).

This of course brings up the possibility that **12** and **13** can be arrived at *via* Path C. Attack at the C-2 carbonyl of **8a** generates a tetrahedral dianionic intermediate, **14a** which can open to **14b** and then rearrange to **11a**, which is the anion of **11**. Addition of HNu to **11a** (as shown for **11** in Path B) forms **12** or **13**. Since the anion **8** is stable enough to be alkylated quantitatively at 5°, the question arises on how can an amine like propylamine or isopropylamine, which are basic enough to form the anion from **1a**, effect its degradation of **1a** quantitatively at 5° to produce **12** and **13**. In a revealing experiment, **8** was preformed from **1a** with sodium hydride in DMF at 5°, and then treated with propylamine. The otherwise stable salt (shown by anion **8**), **8** reacts immediately upon addition of the amine and produces **12b** and **13b**. However, at this point, it is difficult to pinpoint if **1a** reacts with amines primarily *via* Path B or C. Some facts are certain. The anion **8** is stable at 0-25° and an amine must somehow attack sites other than C-4 or NH to form **12** and **13**.

The isolation of 3-hydroxyalloxazine (**17a**) from some of the reactions of **1a** with amines (Table 1) is not surprising since one would have anticipated nucleophilic displacement on the sulfonate *via* **16** (Path D). This process is one which has taken place in related systems and is the one involved for examples in the hydrolysis of the *N*-sulfonyloxy compounds [6,7].

Path D



The reactions of several mercaptide ions were included in this study. Their reactions with **1a** produces only 3-hydroxyalloxazine (**17a**) and this is consistent with reactions along *via* Path D. This is perhaps not surprising since their relatively large size and good nucleophilicity make them ideal candidates for displacement of the sulfonate group in **1a**, *via* **16** (R = H).

Thus, nucleophilic attack at C-4, C-2, the NH proton and the sulfonate are all possible. The products of attack on the sulfonate are clearly discernable, but the structures of the nucleophile which prefer to attack there are not. Apparently size is not critical in directing attack exclusively at C-4 since small amines like ethylamine already produce a mixture of products from **1a**. To eliminate one of the suggested pathways, A-C, particularly Path B, **1a** was methylated and reactions of the methyl analog (**1b**) were studied.

Reactions of 1-Methyl-3-benzenesulfonyloxyalloxazine (**1b**) with Nucleophiles.

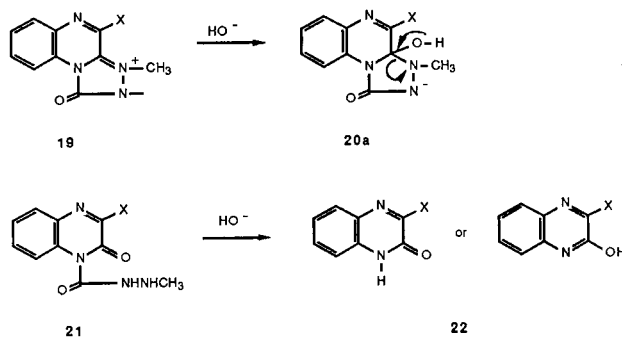
The cleanest reactions of **1b** were those with small alcohols and triethylamine. Methanol, ethanol, 1-propanol, and to some extent, 2-propanol, reacted with **1b** in the presence of triethylamine to form the mesoionic esters, **6b** (96%), **6c** (94%), **6m** (94%), and **6n** (50%), respectively. Steric effects should be more recognizable in this system and it was not unexpected to find that the reaction of **1b** with *t*-butyl alcohol (and triethylamine) failed to produce an ester of type **6**. The formation of esters of type **6** are explained by the mechanisms outlined in Path A. Nucleophilic attack of the alcohol at C-4 of **1b** leads to an intermediate **2**, which opens and rearranges to **4** (R = CH₃). Cyclization of **4** forms the mesoionic ester **6** (NU = OR).

Although the major product from the reactions of **1b** with 1- and 2-propanol are the corresponding esters, there was also formed some 1-methylalloxazine, (5% from 1-propanol, 50% from 2-propanol). This compound was identified by conversion to the known 1,3-dimethylalloxazine. No explanation is advanced at present to account for this apparent reduction of the *N*-sulfonyloxy group.

Amines seem to react with **1b** *via* Path A, also. The major differences from the reactions of amines with **1a** seems to be in the last step, namely in the cyclization of **4** to **6**, *vs* the addition of HNu to **4** to form **7**. Competition between cyclization and addition of HNu appears to be a function

of concentration of the amine used. In more dilute solutions, mesoionic amides **6** are formed instead of amide semicarbazides **7**. Thus, the reaction of 40% aqueous methylamine and hydrazine in methanol with **1b** furnish **6d** and **6e** (40% and 71%, respectively). Reactions conducted in pure isopropylamine or piperidine yield the amide semicarbazides **7i** (63%) and **7l** (78%), respectively. When the reaction of **1b** with piperidine is carried out in methylene chloride, there is isolated the semicarbazide, **7f** (8%), the mesoionic amide, **6l** (32%) and 1-methyl-3-hydroxyalloxazine **17b** (52%). The formation of **7f** and **6l** are expected, but the appearance of **17b** from the reaction in methylene chloride is new. Apparently, in a dilute solution, piperidine attacks the sulfonate group (Path D).

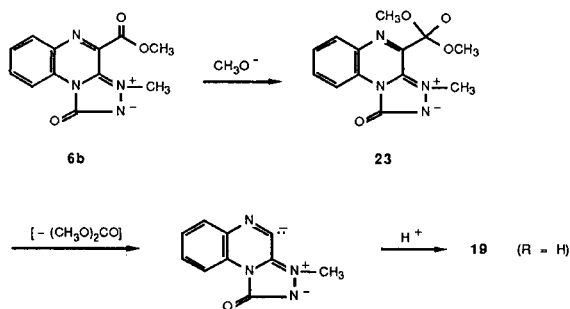
Reactions of **1b** with hydroxide and methoxide ions proved to be quite complicated. The reaction of **1b** with a hot aqueous triethylamine affords the known [8] mesoionic triazoloquinoxaline, **19** (R = H), quantitatively. It is suggested that hydroxide ion attacks C-4 of **1b** to initiate a reaction along Path A which would produce initially the triethylammonium salt of the acid, **6o**. This salt could decarboxylate in this weakly basic solution. Alternatively, during the acid workup the corresponding acid **6a** decarboxylates to **19**. Attempts to isolate **6a** have failed presumably due to this facile decarboxylation at room temperature to release **19** (X = H). This mesoionic system is very stable to acids as judged from a number of experiments. The best evidence is from the hydrolysis of hydrazide **6e** by boiling hydrochloric acid to afford the mesoionic parent (**19**, X = H), quantitatively.



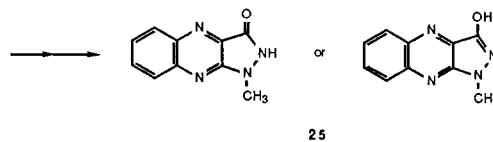
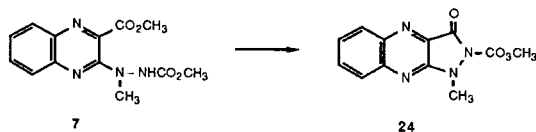
However, the mesoionic ring system of **6** (or **19**) is quite sensitive towards hydrolysis by strong bases. The reaction of **19** (X = H) to sodium hydroxide yields 2-hydroxyquinoxaline (**22**, X = H). This hydrolysis is not surprising. Attack of hydroxide ion at the highly electrophilic bridge carbon the mesoionic system of **19** generates the tetrahedral intermediate, **20**. Collapse of **20** leads to the semicarbazide, **21**, which is not isolated but apparently hydrolyzes quickly, releasing 2-hydroxyquinoxaline (**22**).

On this basis, the degradation of **1b** with dilute sodium hydroxide to 2-hydroxy-3-quinoxalinecarboxylic acid (**22**, X = CO₂H) is understandable. After nucleophilic attack of hydroxide ion at C-4 of **1b**, (Path A), the sodium salt of the mesoionic acid, **6p**, is formed. However, in such an alkaline solution, the mesoionic system of **6p** is hydrolyzed as explained above to form 2-hydroxy-3-quinoxalinecarboxylic acid (**22**, X = CO₂H). Apparently, the salt **6p** is not decarboxylated in the alkaline solution since the isolated product (**22**) still possesses the carboxylic acid.

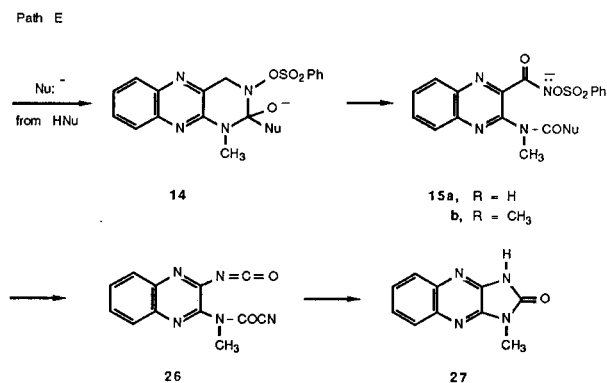
While the reaction of **1b** with methanol and triethylamine was clean-cut and produced only **6b**, degradation in methanol with sodium methoxide at 0° yielded three compounds: the ester, **6b** (21%), the urethane ester, **7** (R = CH₃, Nu = OCH₃), (11%), and the parent mesoionic, **19** (X = H), 17%. Of course, the ester **6b** had already been characterized and its mode of formation explained *via* Path A. The urethane ester also arises by means of Path A when methanol adds to the isocyanate of **4** (R = CH₃). To explain the presence of **19** (X = H) in this mixture presents a bit of a problem. One could argue that if water was present in the methanolic solution, any ensuing hydroxide ion would hydrolyze **6b** to **6p**, which would decarboxylate during an acid workup. Alternatively, the ester group could have hydrolyzed during the acid workup and the unstable acid decarboxylated to form **19** (X = H). This is less likely in view of the very short exposure to cold dilute acid. We prefer another explanation: **6b** undergoes methoxide-catalyzed methanolysis, *via* **23**, to form **19** (X = H) and methyl carbonate. This suggestion is supported by the



fact that at 25°, **1b** reacts with methanolic sodium methoxide to furnish only the parent mesoionic (**19**, X = H, 74%) together with a small amount of 1-methyl-3-hydroxyflavazole (**25**, 3%). This new by-product is the product of cyclization of **7** (R = CH₃, Nu = OCH₃) to the cyclic urethane, **24**, which is either methanolized or hydrolyzed during the workup to yield **25**. An authentic sample of **25** was prepared from 2-chloro-3-quinoxalinecarboxylic acid.



To test if any reaction could take place *via* nucleophilic attack at the C-2 carbonyl group, **1b** was treated with potassium cyanide. There was isolated the imidazolone, **27** (77%). The formation can be rationalized *via* Path E. Attack by cyanide ion on **1b** generates **14** (R = CH₃, Nu = CN) which opens to **15a** (R = CH₃, Nu = CN). Rearrangement of **15a** leads to **26** which cyclizes eventually to **27**.



The structure of **27** was established by synthesis. The starting material **12g** [2b] was alkylated by methyl sulfate in DMF to **28**, which was not isolated, but was hydrolyzed by aqueous base to give **27** (50% yield).

It was hereby demonstrated that **1b** is highly susceptible to nucleophilic attack by alcohols and amines at C-4, sometimes at the electrophilic sulfur of the sulfonate group. However, cyanide ion forms a product which can be explained if nucleophilic attack occurs at C-2.

EXPERIMENTAL

Melting points below 300° were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Melting points above 300° were determined on a Unimelt apparatus. Infrared (ir) spectra were recorded on a FT-IR spectrometer, Model MX-1, Nicolet Instrument Corporation. Mass spectra were obtained at 70 eV by Mr. Richard Dvorak using a Finnigan mass spectrometer, Model MAT 112 S. Usually, only the more intense ions (20% or more) are reported and relative intensities are shown in parentheses. The ¹H nmr spectra were recorded in DMSO-d₆ (unless specified otherwise) on a T60A Varian spectrometer fitted with a Nicolet TT-7 Fourier transform accessory or a Varian XL-300 spectrometer. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are denoted as singlets (s), doublets (d), triplets (t), quartets (q), and multiplets (m). Microanalyses were carried out by Micro-Tech Labs, Skokie, IL.

Flash column chromatography was carried out on a silica gel (Baker Chemical Co., 60-200 mesh) [9]. All reactions were followed, and all mixtures were examined by thin layer chromatography (tlc). Chromatograms were run on 8x4 cm (0.25 mm thick) strips of silica gel mixed with a uv indicator, Brinkmann Instruments, Inc., POLYGRAM Sil G/UV₂₅₄ or EM

Reagent No. 5539 Silica Gel 60 F-254 precoated tlc sheets. Spots were detected either by uv light or iodine stains.

Evaporation *in vacuo* implies that solvents were removed by means of a rotary flash evaporator at the water pump (20-30 Torr, unless specified otherwise). Petroleum ether refers to that hydrocarbon fraction, bp 30-60°. Brine refers to a saturated aqueous solution of salt.

3-Benzenesulfonyloxyalloxazine (1a).

This starting material was prepared essentially by the literature method [2b] except for one modification. Potassium hydroxide was used as the base instead of sodium ethoxide.

A solution of hydroxylammonium chloride (20.1 g, 0.29 mole) in methanol (200 ml) was neutralized at room temperature by a solution of potassium hydroxide (19.14 g, 0.29 mole, based on 85% purity) in methanol (150 ml). The mixture was filtered to remove potassium chloride. To this solution was added methyl quinoxalinedicarboxylate [10] (32.4 g, 0.13 mole) in several portions (20 minutes), and the reaction mixture was stirred at 25° (1 hour). An additional quantity of potassium hydroxide (19.14 g) in methanol (150 ml) was added and the suspension was stirred for another 2 hours at 25°. After cooling to 0-5°, the mixture was diluted with anhydrous ether (300 ml). The product was filtered, washed with ether, and dried *in vacuo* at 25° (18 hours) to give potassium quinoxaline dicarboxylate (67.2 g) which was used without further purification for the rearrangement. The purification of **1a** was carried out as described before [2b].

1-Methyl-3-benzenesulfonyloxyalloxazine (1b).

A solution of methyl sulfate (8.45 g, 67 mmoles) and **1a** (12.4 g, 33 mmoles) in dry DMF (400 ml) was stirred with sodium hydride (1.77 g, 36.8 mmoles, 50% suspension in mineral oil) first at 0-5° for 15 minutes and then for 1.5 hour at 25°. Solvents were distilled at 0.25 Torr and the residue was dissolved in boiling dioxane (400 ml). The hot solution was filtered and was diluted with boiling water (400 ml). After several hours, **1b** was collected as a yellow solid (12.08 g, 94%), mp 224-226°. The analytical sample was recrystallized from acetonitrile, mp 226-227°; ir (potassium bromide): ν max 1759, 1725 (C=O) cm^{-1} ; ^1H nmr δ 3.61 (s, 3H, CH_3), 8.33-7.70 (m, 4H, ArH); ms: m/z (relative intensity) 384 (M^+ , 16), 141 (83), 77 (100).

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_4\text{N}_4\text{S}$: C, 53.12; H, 3.15; N, 14.58; S, 8.34. Found: C, 53.16; H, 3.30; N, 14.58; S, 8.26.

A. Reactions of 3-Benzenesulfonyloxyalloxazine (1a).

1. With Sodium Hydride.

To a stirred solution of **1a** (0.1 g, 0.27 mmole) in DMF (3 ml) was added sodium hydride (0.026 g, 0.54 mmole, 50% suspension in mineral oil) at 25° and the mixture was then heated at 120° (1 hour). After cooling to 0-5° the mixture was poured into ice-cold aqueous 10% hydrochloric acid (20 ml), filtered and washed with petroleum ether (10 ml). The product (0.03 g, 60%) proved to be imidazolo[4,5-*b*]quinoxaline, identical to a literature sample [2b].

2. With Potassium cyanide.

To a suspension of potassium cyanide (1.41 g, 21.6 mmoles) and 18-crown-6 ether (5.7 g, 21.6 mmoles) in dioxane (40 ml) was added **1a** (1.0 g, 2.7 mmoles). After stirring 24 hours at 25°, tlc still showed the presence of starting material and hence, the reaction mixture was refluxed for 5 hours. Solvents were removed, *in vacuo*, the residue was dissolved in water (10 ml), acidified (pH 2) and diluted with brine (10 ml). The product (0.46 g, 91%) was identical to a sample of imidazolo[4,5-*b*]quinoxaline [2b].

3. With Hydroxide Ion.

A saturated solution of triethylamine in water was prepared by shaking water with triethylamine in a separatory funnel and separating the aqueous layer. To 15 ml of such a solution was added **1a** (2.0 g, 5.4 mmoles) and mixture stirred at 25° (15 minutes). The solution was cooled

(0-5°) and acidified to pH 2 with concentrated hydrochloric acid (pH 2). The solid was collected after 10 minutes at 0-5°, washed with ice-cold water (2 x 10 ml) to furnish of 4-carboxy-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one (**5a**, 1.16 g, 94%) mp > 360°, identical to a literature sample [2b].

4. With Alcohols.

a. Methanol and Triethylamine.

A solution of **1a** (0.5 g, 1.35 mmoles) in methanol (25 ml) and triethylamine (2.0 ml, 14.3 mmoles) was refluxed for 1 hour. Solvents were removed, *in vacuo*, the residue cooled, diluted with water (20 ml), and acidified (pH 2). After 30 minutes, 4-methoxycarbonyl-*s*-triazolo[4,3-*a*]quinoxaline-1(2*H*)-one (**5b**, 0.32 g, 97%) was collected and recrystallized from ethanol (70% recovery), mp 270-272°, lit [2b] mp 273-275°.

b. Ethanol and Triethylamine.

In an identical experiment but using ethanol (25 ml) and triethylamine (2.0 ml, 14.4 mmoles), **1a** was converted to **5c** (0.34 g, 98%), mp 249-250°. The mp was unchanged upon recrystallization from water (50% recovery); ir (Nujol): ν max 1728 (C=O) cm^{-1} ; ^1H nmr: δ 1.4 (t, 3H, J = 7.0 Hz, CH_3), 4.45 (q, 2H, J = 7.0 Hz, CH_2), 7.4-8.1 (m, 3H, ArH), 8.7-8.9 (m, 1H, ArH), 13.1 (s, 1H, NH, deuterium oxide exchangeable); ms: m/z (relative intensity): 258 (M^+ , 32), 186 (100), 142 (20), 130 (26), 90 (44).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_3$: C, 55.81; H, 3.90; N, 21.70. Found: C 55.42; H, 3.89; N, 21.98.

5. With Mercaptide Ions.

a. Sodium Methylmercaptide.

A suspension of sodium methylmercaptide (0.38 g, 5.4 mmoles) in DMF (10 ml) at 0-5° was added **1a** (0.5 g, 1.35 mmoles). After stirring for 5 minutes (0-5°), ice-cold water (30 ml) was added followed by hydrochloric acid (dropwise to pH 2). The yellow solid was collected and recrystallized from water to give 0.15 g, 45% yield, of 3-hydroxyalloxazine, (mp 348° dec), identical to a literature sample [2b].

b. Sodium Benzylmercaptide.

To benzyl mercaptan (0.67 g, 5.4 mmoles) in DMF (10 ml) was added sodium hydride (0.26 g, 0.54 mmole) and the suspension stirred at 80° for 15 minutes. To this warm suspension was added **1a** (0.2 g, 5.4 mmoles) and stirring continued at 80° for another 5 minutes. The mixture was cooled to 0-5° and poured into 25 ml of an ice-cold dilute hydrochloric acid solution. After 15 minutes, 3-hydroxyalloxazine (0.114 g, 92%) was isolated.

6. With Amines.

a. Hydrazine.

A solution of hydrazine (0.4 g, 12.6 mmoles) in methanol (20 ml) was stirred with **1a** (0.5 g, 1.35 mmoles) at room temperature for 5 minutes. The solution was evaporated to dryness *in vacuo*, the residue dissolved in water (10 ml, 0°) and acidified with concentrated hydrochloric acid to pH 8. 4-(*N*-Aminocarbonylamido)-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one, (**5e**, 0.2 g, 61%) was collected after 2 hours and was recrystallized from water, mp > 360°; ir (Nujol): 3303 (NH), 1725 (C=O), cm^{-1} ; ^1H nmr: δ 3.3 (br s, 2H), 4.7 (br s, 1H, exchangeable), 7.4-8.0 (m, 3H), 8.7-8.8 (m, 1H), 9.9 (br s, 1H, exchangeable); ms: m/z relative intensity) 244 (M^+ , 16), 216 (23), 187 (27), 186 (66), 174 (15), 142 (61), 131 (26), 102 (35), 90 (100), 75 (94), 64 (60).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_6\text{O}_2$: C, 49.18; H, 3.30; N, 34.41. Found: C, 48.87; H, 3.34; N, 34.10.

b. Hydroxylamine.

To a solution of hydroxylamine, prepared from the hydrochloride (2.0 g, 28.8 mmoles) and sodium bicarbonate (2.42 g, 28.8 mmoles) in methanol (20 ml) was added **1a** (0.5 g, 1.35 mmoles). The suspension was boiled for 10 minutes, solvents removed, *in vacuo*, and the residue acidified (pH 2). After 1 hour, 4-(*N*-hydroxycarbonylamido)-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one, **5f**, (0.26 g, 79%) was collected and recrystallized

from water (60% recovery), mp 250°; ir (Nujol): 3269 (NH, OH), 1666 (C=O) cm^{-1} ; ^1H nmr: δ 7.4-8.0 (m, 3H), 8.7-8.8 (m, 1H), 9.5 (br s, 1H, exchangeable), 11.4 (br s, 1H, exchangeable), 13.1 (br s, 1H); ms: m/z (relative intensity) 245 (M^+ , 8), 242 (25), 201 (70), 187 (33), 186 (47), 145 (27), 142 (24), 131 (21), 118 (34), 116 (25), 90 (60), 28 (100).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3 \cdot 0.5\text{H}_2\text{O}$: C, 47.83; H, 3.06; N, 27.82. Found: C, 47.25; H, 3.17; N, 27.54.

c. Ethylamine.

(i) In Water.

The sulfonate **1a** (0.3 g, 0.81 mmole), was added in one portion to 15 ml of a 40% (v/v) aqueous solution of ethylamine at 25°. After stirring for 5 minutes, the mixture was cooled to 0-5° and acidified to pH 2 by the dropwise addition of concentrated hydrochloric acid. After 2 hours, the precipitate was filtered and washed with ice-cold water (2 x 3 ml) to provide a yellow solid (0.184 g). This solid was triturated with 10 ml of ice-cold 0.24 M sodium bicarbonate solution, was filtered and washed with ice-cold water (2 x 2 ml) to give **5g** (0.077 g, 37%); tlc R_f = 0.37 (methanol/chloroform, 1:9). Recrystallization from ethanol (70% recovery) afforded the analytical sample, mp 322-323°; ir (Nujol) ν max 3297 (NH), 1722, 16786 (C=O) cm^{-1} ; ^1H nmr δ 1.18 (t, 3H, J = 7.0 Hz, CH_3), 3.33-3.40 (m, 2H, CH_2), 7.53-7.58 (m, 1H, H-7), 7.68-7.73 (m, 1H, H-8), 7.92 (dd, 1H, J = 8.1, 1.2 Hz, H-6), 8.74 (dd, 1H, J = 7.0, 1.2 Hz, H-9), 8.84 (t, 1H, J = 6 Hz, NHCH_2), 13.22 (s, 1H, aromatic NH) all NH groups were exchanged by deuterium oxide; ms, m/z (relative intensity) 257 (M^+ , 23), 186 (100), 158 (25), 143 (26), 116 (25).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.76; H, 4.33; N, 27.29.

The sodium bicarbonate solution from above was acidified at 0° to yield **5a** (0.094 g, 51%).

Since these experiments were carried out on a relatively small scale, components could not be separated quantitatively. Due to their inherently similar solubilities, a minor component **12a** formed in this experiment was missed. However, the ^1H nmr spectrum (at 300 MHz) of the initial product of this reaction (0.184 g) provided reliable estimates of the components of the mixture. Integration of the peaks at 8.84 (t, 1H, NHCH_2 of **5g**), 8.62 (t, 1H, NHCH_2 of **12a**) and 8.73-8.76 (m, 2H, H-9 of **5a** and H-9 of **5g**) ppm provided an estimate of the ratio of **5a**, **12a**, and **5g** (17:7:76).

(ii) In Dioxane.

To 10 ml of a 20% (v/v) solution of ethylamine in dioxane solution was added **1a** (0.5 g, 1.35 mmoles) in one portion. After stirring at 5° for 5 minutes, the reaction mixture was diluted with water (15 ml) and cooled to 0-5°. After 10 minutes, **13a** (0.126 g, 31%) was collected, washed with ice-water (2 x 3 ml), and was recrystallized from chloroform, mp > 360°, tlc R_f = 0.41 (ethyl acetate); ir (Nujol): ν max 1726, 1673 (C=O) cm^{-1} ; ^1H nmr: δ 1.89 (t, 6H, J = 7.2 Hz, CH_3), 3.28-3.36 (m, 4H, CH_2), 7.50-7.52 (m, 2H, ArH), 7.77-7.8 (m, 2H, ArH), 9.47 (br m, 2H, NHCH_2), 9.85 (br s, 2H, aromatic NH); ms: m/z (relative intensity) 302 (M^+ , 1), 186 (100), 158 (25), 71 (28), 55 (48).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_6\text{O}_2$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.39; H, 5.95; N, 27.66.

The basic filtrate from above was cooled to 0°, acidified (pH 2) and **12a** (0.2 g, 56%) collected after 10 minutes. Recrystallization from ethanol-1,2-dimethoxyethane (2:5) afforded the analytical sample, mp > 360°; ir (Nujol): ν max 1762, 1713 (C=O) cm^{-1} ; ^1H nmr: δ 1.19 (t, 3H, J = 7.2 Hz, CH_3), 3.28-3.39 (m, 2H, CH_2), 7.60-7.68 (m, 2H, ArH), 7.85-7.96 (m, 2H, ArH), 8.60 (br t, 1H, J = 5.5 Hz, NHCH_2), 12.58 (br s, 1H, aromatic NH); ms: m/z (relative intensity) 257 (M^+ , 1), 186 (100), 158 (28).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.94; H, 4.49; N, 27.27.

This experiment was repeated and the dioxane solution evaporated to dryness, *in vacuo*. The residue was diluted with ice-cold dilute hydrochloric acid. The solid which was isolated was analyzed by means of its ^1H nmr (300 MHz) spectrum. Integration of the triplets (NHCH_2) at 8.60 (**12a**, 1H) and 9.54 (**13a**, 2H) ppm indicated that **12a** and **13a** were formed in the ratio of 44:56.

(iii) In Excess Ethylamine.

Reactions in excess of this amine yielded products which had been described above, namely, **5g**, **12a**, and **13a**. Although their separation could be effected along the lines described above, their proportion in the product was determined by means of ^1H nmr spectra (300 MHz).

To anhydrous ethylamine (20 ml) at -78° was added a solution of **1a** (0.2 g, 0.54 mmole) in DMF (2 ml). The reaction mixture was stirred at this temperature for 2 hours and, then ethylamine was removed, *in vacuo*. The residue was suspended in 4 ml of a brine and acidified at 0° (pH 2) by concentrated hydrochloric acid. The colorless solid was collected, washed with ice-water (2 x 5 ml) to give 0.11 g of a mixture of **5g** and **12a**. Integration of the triplets (NHCH_2) at 8.63 (**12a**) and 8.81 (**5g**) ppm found the ratio of **12a** and **5g** to be 6:94.

Upon repeating this experiment at 0-5° for 5 minutes, a mixture of **5g**, **12a** and **13a** was isolated. From the integration of the triplets at 9.54 (NHCH_2 of **13a**) 8.85 (NHCH_2 of **5g**), 8.64 (NHCH_2 of **12a**) the ratio of **13a**, **12a** and **5g** was determined to be 7:47:47.

d. Propylamine.

(i) In Excess Propylamine.

To propylamine (20 ml) at 0-5° was added **1a** (1.0 g, 2.7 mmoles), in one portion. After stirring for 5 minutes the mixture was evaporated, *in vacuo*, and the residue dissolved in water (20 ml) and cooled to 0-5°. 2,3-Bis(3-propylureido)quinoxaline, **13b**, (0.095, 11%) tlc R_f = 0.51, (methanol-chloroform, 1:4) had precipitated and was recrystallized from ethanol (80% recovery), mp > 360°; ir (Nujol): ν max 3157 (NH), 1734, 1704 (C=O) cm^{-1} ; ^1H nmr: δ 0.97 (t, 6H, J = 7.3 Hz, CH_3), 1.55-1.63 (m, 4H, CH_2CH_2), 3.24-3.30 (m, 4H, NCH_2), 7.52-7.55 (m, 2H, ArH), 7.72-7.75 (m, 2H, ArH), 9.54 (t, 2H, J = 5.5 Hz, NHCH_2), 9.88 (br s, 2H, NHCO); ms: m/z (relative intensity) 330 (M^+ , 15), 187 (66), 186 (100), 160 (59), 159 (5), 158 (32), 144 (30), 56 (39).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_6\text{O}_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 57.95; H, 6.69; N, 25.59.

The basic filtrate from above was cooled to 0-5°, acidified to provide 1-(*N*-propylcarboxamido)imidazol[4,5-*b*]quinoxaline (**12b**, 0.5 g, 68%) which was recrystallized from ethanol, mp > 360°; ir (Nujol): ν max 3312 (NH), 1751, 1718 (C=O) cm^{-1} ; ^1H nmr: δ 0.98 (t, 3H, J = 7.3 Hz, CH_3), 1.58-1.65 (m, 2H, CH_2CH_2), 3.28-3.34 (m, 2H, NHCH_2), 7.60-7.93 (m, 4H, ArH), 8.61 (t, 1H, J = 5.8 Hz, NHCH_2), 11.94 (br s, 1H, ArNH); ms: m/z (relative intensity) 271 (M^+ , 2), 186 (100), 159 (25), 158 (39), 56 (26).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}_2$: C, 57.56; H, 4.83; N, 25.81. Found: C, 57.09; H, 4.89; N, 25.47.

A reaction carried out in stirred propylamine (10 ml) at -78° with **1a** (0.1 g, 0.27 mmole) for 2 hours and the mixture then evaporated to dryness, *in vacuo*. The residue was flash chromatographed on silica gel (65 g) when elution with ethanol-chloroform (2:98) furnished 4-(*N*-propylcarboxamido)-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one (**5h**) (0.056 g, 77% yield) which was recrystallized from ethanol, mp 288-289°; ir (Nujol): ν max 3327 (NH), 1722, 1662 (C=O) cm^{-1} ; ^1H nmr: δ 0.93 (t, 3H, J = 7.3 Hz, CH_3), 1.54-1.61 (m, 2H, CH_2CH_2), 3.25-3.31 (m, 2H, NHCH_2), 7.53-7.58 (m, 1H, H-7), 7.68-7.73 (m, 1H, H-8), 7.93 (dd, 1H, J = 7.8 and 1.5 Hz, H-6), 8.74 (dd, 1H, J = 8.3 and 1.5 Hz, H-9), 8.78 (t, 1H, J = 5.0 Hz, NHCH_2); ms: m/z (relative intensity) 271 (21), 186 (29), 185 (25), 142 (25), 90 (20), 58 (100).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.58; H, 4.96; N, 25.59.

Continued elution with ethanol/chloroform gave **12b** (0.004 g, 5%).

The molar ratios (Table I) were estimated from these reactions at 0° and at -78° from the ^1H nmr spectra using the following integration of these signals: the triplets (NHCH_2) at 9.60 (**13b**, 1H) and 8.64 (**12b**, 2H), and at 8.77 (**5h**, 1H) ppm.

(ii) In Water.

To 10 ml of a 40% (v/v) aqueous propylamine solution at 0-5° was added **1a** (0.5 g, 1.35 mmoles). After stirring at 0-5° for 5 minutes, the mixture was acidified and the precipitate (0.335 g) collected after 30 minutes.

This solid was extracted with boiling ethanol (20 ml) and 3-hydroxyalloxazine (**2b**) (0.023 g) was filtered from the hot alcohol. The ethanolic solution was evaporated, *in vacuo*, and the residue triturated with 10% sodium bicarbonate solution. The insoluble material was **5h** (0.09 g). When the basic solution was acidified, **5a** (0.023 g) was isolated.

(iii) In Dioxane.

To 20 ml of a 20% solution of propylamine in dioxane was added **1a** (0.5 g, 1.35 mmoles) at 25°. After 5 minutes, solvents were removed, *in vacuo*. After the usual work up, the components of the product was estimated by ¹H nmr (experiment f, above) and the results incorporated into Table I.

e. Isopropylamine.

After the reaction of **1a** (1.0 g, 2.7 mmoles) was carried out in stirred isopropylamine (10 ml) at 0-5° for 7 minutes and worked up, as usual. ¹H nmr analysis indicated the mixture to be one of **12c** and **13c** (Table I).

The mixture of **12c** and **13c** was separated by washing it with ice-cold 5% potassium hydroxide (pH 10) which dissolved most of **12c** and **13c** was filtered off. The process had to be repeated several times. The basic solution of **13c** was acidified at 0° quickly to prevent hydrolysis. The separation was conveniently followed by tlc and ¹H nmr. 2,3-Bis(3-isopropylureido)quinoxaline (**13c**, 0.055 g, 6%) was recrystallized from 1,2-dimethoxyethane, mp, gradually darkens above 350°, but did not melt by 500°; tlc, R_f = 0.4 (ethanol-chloroform, 5:95); ir (Nujol): ν max 3307 (NH), 1759, 1714 (C=O) cm⁻¹; ¹H nmr: δ 1.25 (d, 12H, J = 6.4 Hz, 4 CH₃'s), 3.87-3.96 (m, 2H, 2 CH₂'s), 7.50-7.8 (m, AA'BB', 4H, ArH), 9.57 (d, 2H, J = 7.1 Hz, NHCH), 9.87 (br s, 2H, ArNHCO); ms: m/z (relative intensity) 330 (M⁺, 6), 187 (21), 186 (100), 160 (36).

Anal. Calcd. for C₁₆H₂₂N₆O₂: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.02; H, 6.98; N, 25.24.

1-(*N*-Isopropylcarboxamido)imidazo[4,5-*b*]quinoxaline (**12c**, 0.60 g, 82%) was recrystallized from ethanol, mp, gradually darkens above 380°; tlc R_f = 0.29 (ethanol-chloroform, 5:95); ir (Nujol): ν max 3309 (NH), 1759, 1712 (C=O) cm⁻¹; ¹H nmr: δ 1.26 (d, 6H, J = 6.8 Hz, CH₃), 3.96-4.02 (m, 1H, CH), 7.6-7.9 (m, 4H, ArH), 8.49 (d, 1H, J = 7.3 Hz, NHCH), 12.6 (s, 1H, ArNH); ms: m/z (relative intensity) 271 (M⁺, 2), 187 (49), 186 (100), 159 (22), 158 (35), 70 (33).

Anal. Calcd. for C₁₃H₁₃N₅O₂: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.42; H, 5.06; N, 25.73.

The results of the reactions of isopropylamine with **1a** in 20% solution of isopropylamine in dioxane and in 40% solution in water, are listed in Table I. To estimate the proportions of the components, integration of the doublets (NHCH) of **12c** (8.51 ppm, 1H) and of **13c** (9.57 ppm, 2H) were used. For **5a** (which was formed in water), the signal at δ 8.72-8.75 (for H-9 of **5a**) was utilized.

f. Dimethylamine.

To stirred anhydrous dimethylamine (20 ml) at 0-5° **1a** (1.0 g, 2.7 mmoles), was added, at once. After stirring the reaction mixture at this temperature for 5 minutes, volatile solvents were removed, *in vacuo*. The residue was dissolved in methylene chloride (20 ml) and acidified by adding a methylene chloride solution saturated by hydrogen chloride (pH 2). Silica gel (2.0 g) was added to this solution and the solvents were removed, *in vacuo*. The residue was flash chromatographed on silica gel (65 g) eluting with ethyl acetate to give 1-(*N,N*-dimethylcarboxamido)imidazo[4,5-*b*]quinoxaline (**12d**) 0.38 g (55%) which was recrystallized from water, mp 260-261°; tlc R_f = 0.45 (methanol-chloroform, 1:9); ir (Nujol): ν max 1757, 1714 (C=O) cm⁻¹; ¹H nmr (300 MHz, DMSO-*d*₆): δ 3.08, 3.13 (two s, 6H, NCH₃'s), 7.58-8.00 (m, AA'BB', 4H, ArH), 12.44 (br s, 1H, NH); ms: m/z (relative intensity) 257 (M⁺, 21), 72 (100).

Anal. Calcd. for C₁₂H₁₁N₅O₂: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.65; H, 4.41; N, 27.09.

Continued elution with ethyl acetate gave 4-(*N,N*-dimethylcarboxamido)-*s*-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one (**5j**) 0.29 g (42%), mp 249-250° (from water); tlc R_f = 0.46 (methanol-chloroform, 1:9); ir (Nujol): ν max 1735, 1626 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.98, 3.06 (two s,

6H, NCH₃), 7.52-7.58 (m, 1H, H-7), 7.68-7.73 (m, 1H, H-8), 7.86-7.89 (m, 1H, H-6), 8.71-8.73 (m, 1H, H-9), 13.10 (br s, 1H, NH); ms: m/z (relative intensity) 257 (M⁺, 15), 186 (22), 72 (36), 44 (100).

Anal. Calcd. for C₁₂H₁₁N₅O₂: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.81; H, 4.35; N, 27.40.

The reaction in dioxane gave only **12j** which was identified by tlc and nmr (Table I).

The degradation of **1a** (0.1 g) by a 40% aqueous solution (2 ml; 15 minutes at 25°) was carried out as usual. The crude mixture was analyzed by ¹H nmr. Integration of the signals at δ 3.02, 3.08 (2 CH₃'s of **5j**), 3.09, 3.15 (2 CH₃'s of **12d**), 8.76-8.73 (H-9 of **5a** and H-9 of **5j**), and 12.42 (OH of 3-hydroxyalloxazine) gave a ratio of 43:18:18:21 for **17a:5j:5a:12d**.

In addition, there was a signal at δ 2.61 attributable to the 2 CH₃ groups of *N,N*-dimethylbenzenesulfonamide (compared to an authentic sample). It was estimated that 18% of this sulfonamide is also present.

g. Piperidine.

An exothermic reaction took place when **1a** (1.0 g, 2.7 mmoles) was added to stirred piperidine (20 ml) at 25°. After 5 minutes the solution was poured into a mixture of ice (40 g) and concentrated hydrochloric acid (10 ml). The product was collected after 20 minutes at 0° and was recrystallized from 2-propanol to give 1-(*N,N*-pentamethylenecarboxamido)imidazo[4,5-*b*]quinoxaline (0.75 g, 94%), mp 245-246°; ir (Nujol): ν max 1797, 1777, 1702, (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.56-1.89 (m, 6H, -(CH₂)₂-), 3.38-4.02 (m, 4H, N(CH₂)₂), 7.55-8.22 (m, 4H, ArH); ms: m/z (relative intensity) 297 (M⁺, 25), 187 (24), 186 (21), 112 (100), 84 (38), 69 (76), 56 (25), 41 (60), 28 (25).

Anal. Calcd. for C₁₅H₁₅N₅O₂: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.44; H, 5.18; N, 23.33.

h. Diethylamine.

After **1a** (0.5 g) was allowed to react in a stirred solution of diethylamine (15 ml), at 250 for 1.5 hours, solvents were removed, *in vacuo*. The residue was dissolved in water (10 ml), at 0°, and acidified. The colorless solid (**12e**, 0.308 g, 80%) melted at 235-237° and was recrystallized from aqueous ethanol, mp 238-239°; ir (Nujol): ν max 1704, 1734 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.01-1.38 (m, 6H, CH₃), 3.37-3.61 (m, 4H, CH₂), 7.53-8.00 (m, 4H, ArH), 12.50 (br s, 1H, NH); ms: m/z (relative intensity) 285 (M⁺, 4), 100 (100), 72 (90), 44 (42), 29 (48).

Anal. Calcd. for C₁₄H₁₅N₅O₂: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.86; H, 5.37; N, 24.52.

B. Reactions of 1-methyl-3-benzenesulfonyloxyalloxazine (**1b**).

1. With Alcohols.

a. Methanol and Sodium Methoxide.

To a stirred ice-cold solution of sodium methoxide in methanol, (from sodium, 0.24 g, 20 ml) was added **1b** (1.0 g, 2.6 mmoles) at once. After 5 minutes the reaction mixture was quenched by hydrogen chloride in methanol (pH 2). Solvents were removed, *in vacuo*. The residue was diluted with ice-water (20 ml), and a solid (0.3 g) was filtered off immediately, and was washed with water (2 x 3 ml). The residue was diluted with ice-water (20 ml), and a solid filtered and washed with ice-water (2 x 3 ml).

From the combined acidic mother liquor, there was isolated a colorless solid after 2 hours at 0°. Recrystallization from water gave methyl 3-[*N'*-methyl-*N*'-(methoxycarbonyl)hydrazino]-2-quinoxalinecarboxylate (**7b**, 0.08 g, 11%), mp 158-159°; tlc R_f = 0.50 (methanol-chloroform, 1:20); ir (Nujol): ν max 3305 (NH), 1750, 1710 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.30 (s, 3H, NCH₃), 4.09 (s, 3H, ester CH₃), 4.23 (s, 3H, urethane CH₃), 7.5-8.0 (m, 4H, ArH); ms: m/z (relative intensity) 291 (16), 290 (M⁺, 100), 259 (36), 258 (84), 216 (51), 200 (23), 199 (20), 184 (31), 130 (36), 129 (45), 102 (35).

Anal. Calcd. for C₁₃H₁₄N₄O₄·¼ H₂O: C, 52.97; H, 4.96; N, 19.01. Found: C, 53.08; H, 4.73; N, 18.96.

Flash chromatography of the 0.3 g isolated originally (silica gel, methanol-chloroform, 1:20) furnished anhydro-1-hydroxy-3-methyl-4-

(methoxycarbonyl)-s-triazolo[4,3-*a*]quinoxalinium hydroxide (**6b**) (0.139 g, 21%) which was recrystallized from 2-propanol, mp 217-218°; tlc R_f = 0.34 (methanol-chloroform, 1:20); ir (Nujol): ν max 1735, 1682 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 4.15 (s, 6H, NCH_3 and OCH_3), 7.48-8.17 (m, 3H, ArH), 9.38-9.54 (m, 1H, ArH); ms: m/z (relative intensity) 259 (12), 258 (M^+ , 100), 129 (49), 102 (35), 43 (42).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.44; H, 3.87; N, 21.44.

Continued elution provided anhydro-1-hydroxy-3-methyl-s-triazolo[4,3-*a*]quinoxalinium hydroxide (**19**, X = H) (0.086 g, 17%) which was recrystallized from water, mp 315-316° (lit [8] mp 312-313°) identical to a sample made by the literature method [8]; tlc R_f = 0.13 (methanol-chloroform, 1:20); ir (Nujol): ν max 1668 (C=O) cm^{-1} ; ^1H nmr: δ 4.01 (s, 3H, CH_3), 7.63-8.10 (m, 3H, ArH), 9.02-9.17 (m, 1H, ArH); ms: m/z (relative intensity) 200 (M^+ , 100), 158 (36), 129 (63), 102 (51), 76 (24), 75 (27).

When this experiment was repeated at 25° for 0.5 hour, and basic solution evaporated, *in vacuo*, slightly different products were isolated. The residue was dissolved in cold water (10 ml) and then acidified (pH 2) by concentrated hydrochloric acid. The yellow solid was collected after 10 minutes at 0°, washed with cold water (2 x 10 ml) and after recrystallization (water) proved to be **19** (X = H, 0.385 g, 74%) mp 315-316° identical to the sample above.

From the combined acidic mother liquor, there was deposited an orange solid after 18 hours at 25°. Recrystallization from chloroform furnished 1-methyl-3-hydroxyflavazole (**25**) (0.014 g, 3%), mp 238-239°, identical to a sample which was prepared by an independent method, described below. The literature [11] mentions this compound, but provides no physical data; ir (Nujol): ν max 1579 (C=N) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.90 (s, 3H, CH_3), 7.62-8.34 (m, ArH); ms: m/z (relative intensity) 201 (13), 200 (M^+ , 100), 129 (48), 102 (51), 43 (24).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}$: C, 60.00; H, 4.03; N, 27.99. Found: C, 60.00; H, 3.94; N, 27.85.

b. With Methanol and Triethylamine.

A suspension of **1b** (0.5 g, 1.3 mmoles) in methanol (8 ml) containing triethylamine (4 ml, 28.7 mmoles) was refluxed for 20 minutes. After cooling to 25°, silica gel (1.0 g) was added to the dark solution and solvents were removed, *in vacuo*. Flash chromatography (silica gel 65 g, methanol-chloroform, 1:20) provided **6b** (0.322 g, 96%), mp 217-218°, identical to the sample prepared above.

c. With Ethanol.

A suspension of **1b** (0.5 g, 1.3 mmoles) was refluxed in ethanol (6 ml) containing triethylamine (4 ml, 28.7 mmoles) for 20 minutes. Silica gel (1.0 g) was added, solvents were removed, *in vacuo*. The residue was flash chromatographed (silica gel 65 g, methanol-chloroform, 1:20) yielding primarily **6c** (0.332 g, 94%) mp 173-176°. Recrystallization from 2-propanol furnished a yellow-orange solid, mp 177-178° ir (Nujol): ν max 1727, 1678 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.52 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 4.12 (s, 3H, NCH_3), 4.61 (q, 2H, J = 7.1, OCH_2CH_3), 7.47-8.16 (m, 3H, ArH), 9.36-9.52 (m, 1H, ArH); ms: m/z (relative intensity) 272 (M^+ , 100), 200 (22), 184 (23), 130 (28), 129 (90), 102 (50), 43 (64).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.21; H, 4.55; N, 20.55.

Using the same solvent system, (methanol-chloroform, 1:20) there was eluted eventually **19** (X = H, 0.006 g, 2%) mp 315-316°, lit [8] mp 312-313°.

d. With 1-Propanol.

To a suspension of **1b** (0.5 g, 1.3 mmoles) in 1-propanol (12 ml) containing triethylamine (8 ml, 57.4 mmoles) was refluxed (15 minutes) and was worked up as in the last experiment. Flash chromatography (silica gel 65 g, ethyl acetate) produced 1-methylalloxazine (0.014 g, 5%) as a yellow solid, mp 366-368° lit [12] mp 356-358°; ir (Nujol): ν max 1709 (C=O) cm^{-1} ; ^1H nmr: δ 3.55 (s, 3H, CH_3), 7.71-8.25 (m, 4H, ArH), 12.02 (br s, 1H, NH); ms: m/z (relative intensity) 228 (M^+ , 82), 157 (43), 130 (100),

129 (60), 103 (43), 102 (39).

Continued elution (ethyl acetate) afforded anhydro-1-hydroxy-3-methyl-4-*n*-propoxycarbonyl-s-triazolo[4,3-*a*]quinoxalinium hydroxide (**6m**), 0.348 g, (94%) as a yellow-orange solid (mp 173-175°). The analytical sample was obtained by recrystallization from 2-propanol, mp 176-177°; ir (Nujol): ν max 1725, 1680 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.09 (t, 3H, J = 6.84 Hz, CH_3), 1.85 (m, 2H, CH_2CH_3), 4.11 (s, 3H, NCH_3), 4.51 (t, 2H, J = 6.6 Hz, OCH_2), 7.51-8.16 (m, 3H, ArH), 9.40-9.54 (m, 1H, H-9); ms: m/z (relative intensity) 286 (M^+ , 55), 200 (100), 130 (27), 129 (74), 102 (46).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.65; H, 4.90; N, 19.44.

e. With 2-Propanol.

To a solution of triethylamine (8 ml, 57.4 mmoles) in 2-propanol (12 ml) and **1b** (0.5 g, 1.3 mmoles) was refluxed for 1.5 hours. The reaction mixture was cooled to 0°, and yellow crystals of 1-methylalloxazine (0.155 g) were filtered, mp 364-366° (from acetic acid). The propanol solution was worked up as in the experiment using ethanol. Flash chromatography yielded first more 1-methylalloxazine (0.043 g), then **6n** (0.106 g, 37%) as an orange solid, mp 183-184° (from 2-propanol); ir (Nujol): ν max 1723, 1682 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.52 [d, 6H, J = 6.3 Hz, $\text{OCH}(\text{CH}_3)_2$], 4.11 (s, 3H, NCH_3), 5.44 [sep, 1H, J = 6.3 Hz, $\text{OCH}(\text{CH}_3)_2$], 7.48-8.13 (m, 4H, ArH), 9.37-9.53 (m, 1H, ArH); ms: m/z (relative intensity) 286 (M^+ , 45), 200 (100), 158 (55), 130 (26), 129 (56), 103 (22), 102 (42).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.34; H, 4.78; N, 19.33.

2. With Hydroxide Ion.

A stirred suspension of **1b** (1.0 g, 2.6 mmoles) was heated in 5% aqueous sodium hydroxide solution (20 ml) at 90° for 5 minutes. The reaction mixture was cooled to 0°, filtered, and acidified to pH 2. After 30 minutes at 0°, 3-hydroxy-2-quinoxalinecarboxylic acid, **22** (X = CO_2H), (0.2 g, 40%) mp 266-268° was collected. The sample was identical (mp, ir, ^1H nmr) to one obtained commercially [13].

3. With Amines.

a. Hydrazine.

To a solution of hydrazine (0.33 g, 2.6 mmoles) in methanol (20 ml) was added **1b** (1.0 g, 2.6 mmoles) in one portion. The reaction mixture was refluxed for 15 minutes and then cooled to 0°. The solid was collected after 2 hours, washed with cold methanol (2 x 3 ml), and recrystallized from water to give 0.48 g (71% yield) of pure **6e** as a yellow-orange solid, mp 237-238°; ir (potassium bromide): ν max 3301 (NH), 1671 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.27 (s, 3H, CH_3), 7.47-8.11 (m, 3H, H-6, H-7, and H-8), 8.48 (br s, 2H, NH_2), 9.15-9.31 (m, 1H, H-9), 9.57 (br s, 1H, NH); ms: m/z (relative intensity) 258 (M^+ , 100), 217 (63), 200 (20), 199 (40), 130 (23), 129 (67), 102 (40).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_6\text{O}_2 \cdot \frac{1}{2} \text{H}_2\text{O}$: C, 49.44; H, 4.15; N, 31.45. Found: C, 49.47; H, 4.28; N, 31.68.

b. Methylamine.

To a 40 wt% aqueous solution of methylamine was added **1b** (1.0 g, 2.6 mmoles) in one portion. The reaction mixture was stirred at 25° for 1 hour, cooled to 0-5°, and filtered, washed with ice-water to give 0.53 g of a yellow solid (mp 220-222°). The solid was recrystallized twice from water to give 0.27 g (40% yield) of **6d**, mp 237-238°; ir (Nujol): ν max 1669 (C=O) cm^{-1} ; ^1H nmr: δ 3.30 (s, 3H, NCH_3), 3.99 (s, 3H, OCH_3), 7.54-8.12 (m, 3H, H-6, H-7, and H-8), 9.17-9.32 (m, 1H, H-9); ms: m/z (relative intensity) 257 (M^+ , 36), 215 (53), 156 (26), 130 (28), 129 (100), 102 (51).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_5\text{O}_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.77; H, 4.39; N, 27.25.

c. Isopropylamine.

To isopropylamine (20 ml) was added **1b** (0.5 g, 1.30 mmoles) in one

portion. The reaction mixture stirred at 25° for 0.5 hour and the solvents removed under reduced pressure. The residue was dissolved in brine, cooled to 0-5°, and acidified to pH 2 by the dropwise addition of concentrated hydrochloric acid. The precipitate was collected, washed with ice-water (2 x 2 ml) to give 0.28 g (63% yield) of **7i** (mp 187-189°). The analytical sample was recrystallized from acetonitrile (82% recovery), mp 195-197°; ir (Nujol): ν max 1662, 1641 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.19 (d, 6H, J = 6.84 Hz, ester CH_3 's), 1.32 (d, 6H, J = 6.35 Hz, urea CH_3 's), 3.26 (s, 3H, NCH_3), 3.89-3.96 (m, 1H, ester CH), 4.18-4.29 (m, 1H, urea CH), 6.06 (d, 1H, J = 7.32 Hz, ester NH), 6.82 (d, 1H, J = 6.84 Hz, urea NH), 7.51-7.6 (m, 1H, H-8), 7.62-7.73 (m, 1H, H-7), 7.79-7.87 (m, 1H, H-6), 7.9-7.98 (m, 1H, H-9); ms: m/z (relative intensity) 344 (M^+ , 18), 259 (42), 243 (80), 201 (24), 200 (100), 129 (32).

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_6\text{O}_2$: C, 59.29; H, 7.02; N, 24.40. Found: C, 58.97; H, 7.02; N, 24.42.

d. Piperidine.

(i) In Piperidine.

To piperidine (10 ml) at 25° was added **12** (1.0 g, 2.6 mmoles) in one portion. After stirring for 1 hour at 25°, the reaction was quenched by pouring into ice (40 g) and concentrated hydrochloric acid (15 ml). The pH of the solution was adjusted to 6 by adding sodium acetate. A solid was collected after 20 minutes at 0-5° to give 0.8 g (78% yield) of **7i** (mp 208-211°). The analytical sample was recrystallized from acetonitrile, mp 214-215°; ir (Nujol) ν max 3306 (NH), 1646, 1623 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform) δ 1.48-1.78 (m, 12H, 2 x 3 CH_2 's), 3.05-3.38 [m, 8H, 2 x $\text{N}(\text{CH}_2)_2$], 3.38 (s, 3H, CH_3), 7.28-7.52 (m, 4H, ArH); ms: m/z (relative intensity) 396 (M^+ , 10), 269 (30), 129 (23), 112 (80), 84 (100), 69 (60).

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_6\text{O}_2$: C, 63.62; H, 7.12; N, 21.20. Found: C, 63.80; H, 7.19; N, 21.08.

(ii) In Methylene Chloride.

To a solution of **1b** (0.5 g, 1.3 mmoles) in methylene chloride (20 ml) containing piperidine (0.22 g, 2.6 mmoles) was refluxed for 1.5 hours. Solvents were removed, *in vacuo*, and the residue flash chromatographed on silica gel (65 g). Eluting with a gradient of ethanolic-chloroform (pure to 1:9) afforded first an off-white solid, **7i** (0.041 g, 8%) mp 214-215°. Anhydro-1-hydroxy-3-methyl-4-(*N,N*-pentamethylenecarboxamido)-s-triazolo[4,3-*a*]quinoxalinium hydroxide (**6i**) (0.129 g, 32%) was eluted next as a yellow-green solid which was recrystallized from water, mp 244-245°; ir (Nujol): ν max 1727, 1678 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform) δ 1.53-1.79 (m, 6H, 3 CH_2 's), 3.51-3.84 [m, 4H, $\text{N}(\text{CH}_2)_2$], 4.12 (s, 3H, NCH_3), 7.47-8.16 (m, 3H, H-6, H-7 and H-8), 9.36-9.52 (m, 1H, H-9); ms: m/z (relative intensity) 311 (M^+ , 67), 269 (73), 158 (20), 129 (75), 102 (25), 84 (100), 55 (21), 41 (37).

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.49; H, 5.47; N, 22.38.

1-Methyl-3-hydroxyaloxazine (**17b**) (0.166 g, 52%) was obtained last as a yellow solid. The analytical sample was recrystallized from DMF, mp 319-320°; ir (Nujol) ν max 1727, 1678 (C=O) cm^{-1} ; ^1H nmr: δ 3.65 (s, 3H, CH_3), 7.76-8.30 (m, 4H, ArH), 11.06 (br s, 1H, NH); ms: m/z (relative intensity) 244 (M^+ , 100), 214 (22), 130 (30), 129 (61), 103 (22), 102 (45), 70 (24). *Anal.* Calcd. for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 53.91; H, 3.20; N, 22.63.

4. With Potassium Cyanide.

To a suspension of **1b** (1.0 g, 2.6 mmoles), potassium cyanide (1.36 g, 20.8 mmoles) and 18-crown-6 ether (5.5 g, 20.8 mmoles) in dioxane (40 ml) was stirred at 25° for 18 hours. Solvents were removed, *in vacuo*, and the residue dissolved in water (10 ml) at 0°. The cold solution was acidified (pH 2) and was diluted with 10 ml of brine. 1-Methylimidazolo[4,5-*b*]quinoxaline (**27**, 0.4 g, 77%) was filtered off, mp 326-327°, identical to the sample prepared below.

C. Hydrolyses of Mesoionic Compounds.

A suspension of the mesoionic parent (**19**, X = H, 0.037 g, 0.18 mmole) was refluxed in 5% sodium hydroxide (3 ml) for 5 minutes. After cooling

to 0° and adjusting the pH to 2, 2-hydroxyquinoxaline (**22**, X = H, 0.017 g, 63%) was collected, mp 264-266°, identical (ir) to a commercial sample [**13**] (whose mp was 271-272°).

A suspension of **6b** (0.050 g, 0.25 mmoles) dissolved when heated in 5% sodium hydroxide (1 ml) at 90° (5 minutes). Upon acidification, 2-hydroxy-3-quinoxalinium carboxylic acid (**22**, X = CO_2H , 0.02 g, 54%) precipitated, mp 265-266°, identical to a commercial example (mp, ir).

A similar hydrolysis of **6e** (0.13 g, 0.5 mmole) with 10% boiling sodium hydroxide (5 ml) for 5 minutes provided a solution. Acidification at 0° (pH 2), furnished **22** (X = CO_2H , 0.057 g, 59% yield) which was collected after 20 minutes and was recrystallized from water (72% recovery), mp 266-267°.

Acid-catalyzed hydrolysis of **6e** (0.03 g, 0.12 mmole) in refluxing 1:1 hydrochloric acid (4 ml) was carried out for 2 hours. After evaporation to dryness, *in vacuo*, the residue was triturated with ice-water (2 ml) and pure **19** (X = H) was collected (0.023 g, quantitative), mp 315-316°, identical to the literature sample [**8**].

D. Synthesis of Reference Compounds.

1. 4-(*N,N*-Diethylcarboxamido)-s-triazolo[4,3-*a*]quinoxalin-1(2*H*)-one (**5k**).

A solution of **5a** (1.1 g, 4.8 mmoles) and thionyl chloride (1.7 g, 14.3 mmoles) in DMF (30 ml) was stirred for 18 hours at 25°. Solvents were removed at 0.25 Torr. The residue was treated with ice-cold diethylamine (30 ml). The reaction mixture was stirred at 0° (10 minutes) then at 25° (30 minutes). Solvents were removed, *in vacuo*, the residue diluted with ice-cold acetic acid (5 ml) and water (10 ml). Upon recrystallization from methanol **5k** (0.5 g, 36%) was obtained, mp 244-245°; ir (Nujol): ν max 1734, 1619 (C=O) cm^{-1} ; ^1H nmr (DMSO- d_6) δ 0.98-1.32 (m, 6H, CH_3), 3.16-3.57 (m, 4H, CH_2), 7.48-7.95 (m, 3H, ArH), 8.65-8.87 (m, 1H, ArH), 13.05 (s, 1H, NH); ms: m/z (relative intensity) 285 (M^+ , 5), 72 (100).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.89; H, 5.35; N, 24.64.

2. 1-Methyl-3-hydroxyflavazole (**25**):

Ethyl 2-chloroquinoxaline-3-carboxylate was prepared by a modified literature method. A mixture of ethyl 2-hydroxyquinoxaline-3-carboxylate [**14**] (5.0 g, 22.9 mmoles) and phosphorous oxychloride (25 ml) was refluxed for 10 minutes. Excess phosphorous oxychloride was distilled, *in vacuo*, and the dark green viscous residue poured onto crushed ice (300 g). The mixture was neutralized by adding a saturated sodium bicarbonate solution and extracting with chloroform (3 x 100 ml). The organic layer was dried (sodium sulfate) and solvents removed under reduced pressure. The residue was flash chromatographed (silica gel 65, chloroform) to give a colorless oil which solidified on standing overnight at 0° (4.75 g, 88%), mp 40° (lit [**14**] mp 42°).

A solution of methylhydrazine (0.55 g, 11.84 mmoles) and ethyl 2-chloroquinoxaline-3-carboxylate (1.4 g, 5.92 mmoles) in ethanol (10 ml) was refluxed for 10 minutes. Solvents were removed, *in vacuo*, to give 1.3 g of a bright red solid which was recrystallized from chloroform, to furnish **25** (1.04 g, 86%) as a yellow-orange solid, mp 237-238°. A pure sample of **25** was obtained by sublimation, at 240° (0.1 Torr), mp 238-239°; ir (Nujol): ν max 1579 (C=N) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.90 (s, 3H, CH_3), 7.62-8.34 (m, ArH); ms: m/z (relative intensity) 200 (M^+ , 100), 129 (48), 102 (51), 43 (24).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}$: C, 60.00; H, 4.03; N, 27.99. Found: C, 60.00; H, 3.94; N, 27.85.

3. 1-Methylimidazolo[4,5-*b*]quinoxaline (**27**).

To a solution of **12j** [**2b**] (1.13 g, 3.3 mmoles) and methyl sulfate (0.46 g, 3.62 mmoles) in DMF (30 ml) was added a 50% suspension of sodium hydride in mineral oil (0.17 g, 3.6 mmoles). After stirring for 1.5 hours at 25°, solvents were removed, *in vacuo* (0.1 Torr). The residue was refluxed with 25 ml of 10% sodium hydroxide, for 4 hours, cooled to 25° and was extracted with petroleum ether (25 ml). The aqueous layer was cooled to 0°, acidified and the precipitate collected and washed with water (2 x 5 ml) to give **27** (0.33 g, 50%), mp 326-327°. Recrystallization from glacial acetic acid (81% recovery) afforded the analytical sample, mp 328-329°.

ir (Nujol): ν max 1760, 1742 (C=O) cm^{-1} ; ^1H nmr: δ 3.36 (s, 3H, CH_3), 7.42-7.97 (m, 4H, ArH); ms: m/z (relative intensity) 200 (M^+ , 100), 171 (23).
Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.71; H, 3.88; N, 27.79.

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