(21) $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. The minimized function was $\Sigma w||F_o|^2 - |F_c|^2|$, where w is the reciprocal of the sum of the background and total integrated reflection counts. The latter were measured using the θ–2θ variable scan rate technique; background counts were measured for half the scan time at each end of the scan range. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography", Vol. 3, C. H. MacGillavry and G. D. Riech, Ed., Kynoch Press, Birmingham, England, 1962.

1,2,4-Triazolo- and 1,2,5-Triazino[4,3-*d*][1,4]benzodiazepinone Ring Systems: Synthesis and Barrier to Ring Inversion[1]

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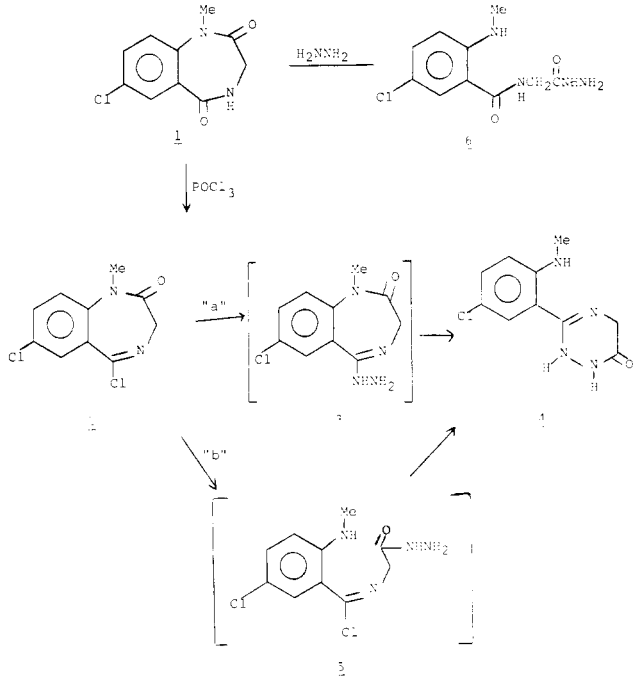
Reaction of the chloroimide 5,7-dichloro-1-methylbenzodiazepin-2-one with acylhydrazines produced annelated 3-substituted triazoles, and reaction with ethyl carbazate gave the analogous triazolone, which in turn could be alkylated on the 2 position via its thallous salt. Condensation of the chloroimide with 4-morpholineglyoxylic acid hydrazide gave the corresponding annelated triazinedione, which could also be alkylated via its thallous salt. The lactam moiety of the seven-membered ring proved labile to aminolysis by several cyclic secondary amines, yielding ring-opened amides. Temperature-dependent NMR studies revealed that the seven-membered rings of the triazolo derivatives were significantly less conformationally rigid (ΔF^* = 13.0–14.2 kcal/mol) than diazepam (ΔF^* = 18.1 kcal/mol), while the triazinedione derivatives were more rigid (ΔF^* = 19.9–20.7 kcal/mol). The solid state conformations (X-ray) of both annelated systems were distinctly nonplanar. Consistent with its higher ΔF^*, the triazinedione exhibited a greater degree of puckering than the triazolone.

The benzodiazepines have been known as therapeutically important compounds for many years.[2] More recently, derivatives with heterocyclic groups annelated to the "a" face of the molecule have become of interest for their physical,[3] chemical,[4] and biological[5] properties. Some derivatives with the heterocycle fused to the "d" face are also known.[3b,6] We have prepared a series of compounds related to diazepam, where the 5-phenyl group has been replaced by a five- or six-membered nitrogen heterocycle fused to the "d" face. The nature of the heterocycle has been found to exert a profound influence on the conformational properties of the seven-membered ring.

Synthesis. Amidrazones are useful synthetic intermediates[7] that are frequently used to prepare triazoles via their condensation with carboxylic acid derivatives.[8] Thus it was our intention to prepare a suitable amidrazone in the benzodiazepine series from which a variety of substituted triazoles could be synthesized. To this end, the dilactam 1[9] was converted to the chloroimide **2** with phosphorus oxychloride under established conditions. Treatment of **2** with hydrazine under conditions that would be expected to form the amidrazone[10] **3** gave instead a compound that was identified as the dihydro[*as*]triazinone **4.** This product could arise from one of two possible routes. Pathway "a" involves initial displacement of the 5-chloro substituent to form **3** and subsequent attack of the NH_2 function of the amidrazone on the lactam carbonyl. Pathway "b" involves the reverse sequence, initial hydrazinolysis of the lactam followed by cyclization at the chloroimide. This reaction was initially not investigated further since an alternate triazole synthesis became available. However, **3** was prepared later by reacting 2 equiv of hydrazine with **2** in ethanol at room temperature, and it was subsequently shown that extended heating of **3** in either benzene or butanol gave no detectable conversion to **4.** The **4** obtained in the initial reaction must therefore have arisen via pathway "b". The ring opening of the dilactam **1** with hydrazine in refluxing butanol to the hydrazide **6** lends further support to the initial attack at the lactam carbonyl shown in pathway "b".



Allowing **2** to stand in excess neat hydrazine at room temperature was found to be a convenient synthetic procedure for the preparation of **4.**

Since the initial attempts to prepare **3** were unsuccessful, an alternate method for the synthesis of the annelated tria-

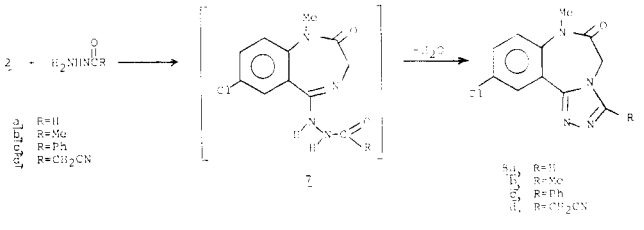


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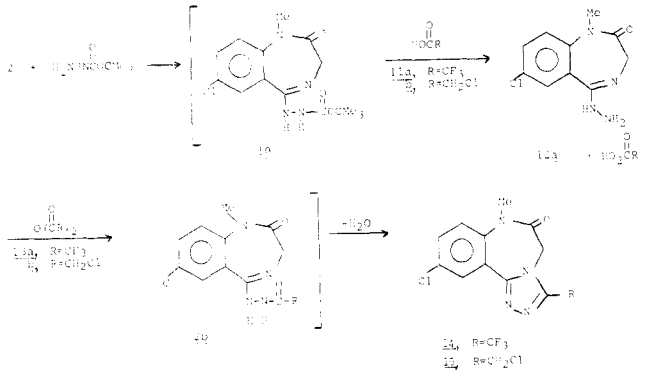
Table I. Ultraviolet Spectra

compd	registry no.	λ_{max},[a] nm	ϵ
17	56967-22-7	251	17 900
		300	3 680
20d	56967-23-8	253	18 200
		274 (sh)	8 780
		305	4 820
8a	60726-49-0	231	35 800
		250	12 600
		298	1 920

[a] In methanol.

zoles was investigated employing the condensation of **2** with acylhydrazines. The initial product of this reaction is presumably the acylamidrazone **7**, which undergoes a spontaneous cyclodehydration to give the triazole directly. This approach proved to be generally applicable within the scope of this investigation and was used to prepare the unsubstituted (**8a**), methyl- (**8b**), phenyl- (**8c**), and (cyanomethyl)-triazolo[1,4]benzodiazepinones (**8d**). The products were obtained in high yield under relatively mild conditions.

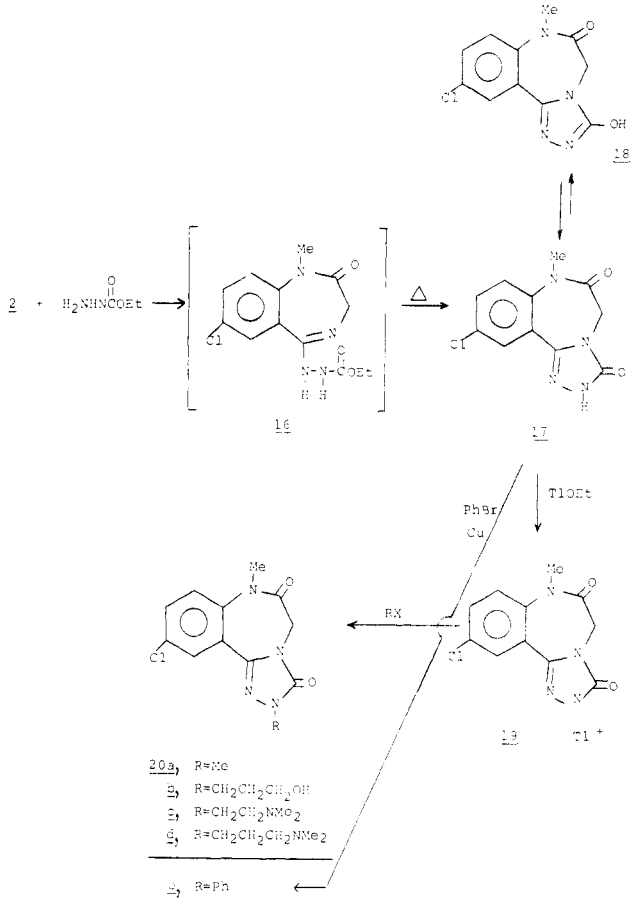
In order to expand the synthetic utility of this reaction to examples where the hydrazides were not readily available, an attempt was made to generate the elusive **3** under conditions where it would react preferentially with an acyl derivative to yield the triazole. The chloroimide **2** was condensed with *tert*-butyl carbazate to yield the presumed protected amidrazone **10**, which was not characterized. Subsequent deprotection of **10** with trifluoroacetic acid (**11a**) and treatment with trifluoroacetic anhydride (**13a**) gave the tricyclic (trifluoro-



methyl)triazole[11] **14**. Analogously, reaction of **10** with chloroacetic acid (**11b**) followed by chloroacetic anhydride (**13b**) produced the corresponding chloromethyl compound **15**.

In contrast to the thermally (80 °C) stable amidrazone **10** formed from **2** and *tert*-butyl carbazate, the amidrazone **16** (also not characterized), from **2** and ethyl carbazate, cyclized under the reaction conditions (100 °C) to give the triazolone **17**. The keto–enol equilibrium was found to lie heavily in favor of the keto form **17** both in the solid state and in solution. The IR spectrum (KBr) clearly showed two strong carbonyl bands, that of the seven-membered ring at 1676 cm^{-1} and that of the five-membered ring at 1706 cm^{-1}. In the NMR spectrum (Me_2SO-d_6), the C-11 proton at δ 7.70 was shifted upfield by 0.17 ppm from the C-11 proton at δ 7.87 in **8d**. This indicates that the ring current of the delocalized triazole (as seen in **8d**) has been disrupted and that the only deshielding influence affecting the C-11 proton in **17** other than the benzene ring is that of the isolated C=N double bond. In addition, the UV spectrum of **17** (cf. Table I) clearly resembled that of an N-alkylated triazolone (e.g., **20d**) rather than a typical triazole (e.g., **8a**).

It was found that **17** could be cleanly alkylated on the lac-

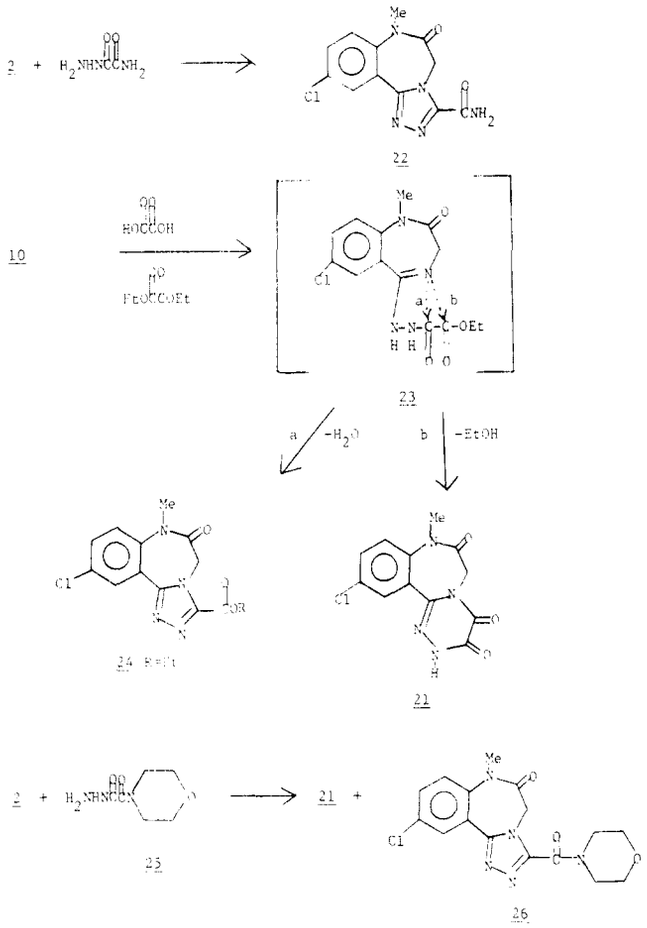


tam nitrogen with no indication of O-alkylation by employing the thallous salt[12] **19**. Satisfactory results were obtained whether **19** was generated from a suspension of **17** in THF or from a solution of **17** in DMF. Reaction of **19** in either neat methyl iodide or a toluene solution of the appropriate alkylating agent produced the *N*-methyl (**20a**), -hydroxypropyl (**20b**), -(dimethylamino)ethyl (**20c**), and -(dimethylamino)-propyl (**20d**) derivatives. Treatment of **17** with copper powder in bromobenzene[13] gave the *N*-phenyl derivative **20e**.

In order to investigate the effect of ring size on physical properties and biological (anxiolytic) activity, an effort was made to annelate a larger heterocycle onto the benzodiazepine nucleus. The initial attempt in this direction involved the condensation of the chloroimide **2** with a dicarbonylhydrazino compound such that ring closure to a six-membered ring would yield a triazinedione (**21**) that differed from **17** by the presence of an additional carbonyl group. Attempted reaction of **2** with oxamic hydrazide in either benzene or DME showed no indication of reaction. Reaction of **2** with oxamic hydrazide in DMF, however, proceeded smoothly but gave the triazole carboxamide **22** as the only product isolated.

Since condensation of an amidrazone with diethyl oxalate has been shown to yield triazinediones,[14] the analogous reaction was attempted with **3** (prepared in situ). The protected amidrazone (**10**) was generated from **2** as previously described and deprotected with oxalic acid in hot diethyl oxalate. This process presumably generated the intermediate oxalylamidrazone **23**, which could undergo further reaction by attack of the imino nitrogen on the amide carbonyl (path a) and subsequent dehydration to yield the triazole **24** or by attack on the ester carbonyl (path b) and expulsion of ethanol to yield the triazinedione **21**. In fact, both **21** and **24** were isolated in ca. 20% yield each, reflecting the difference in leaving ability of ethanol relative to that of ammonia as in the previous case.

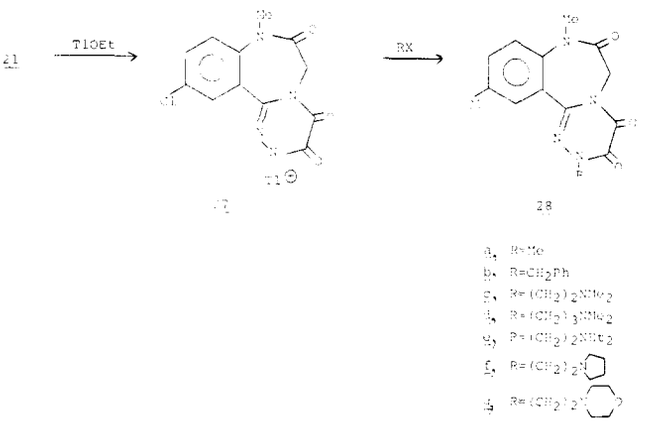
The triazinedione **21** was a high melting (ca. 365 °C) com-



pound of low solubility. While the IR and UV [215 nm (ε 26 800), 348 (16 400), 305 (8570); compare to Table I] spectra clearly resembled the triazolones, the methylene protons in the NMR spectrum appeared as an AB quartet rather than the singlet seen in all of the previous cases. This observation, indicating a frozen conformation of the diazepine ring, prompted the dynamic NMR work discussed in the next section.

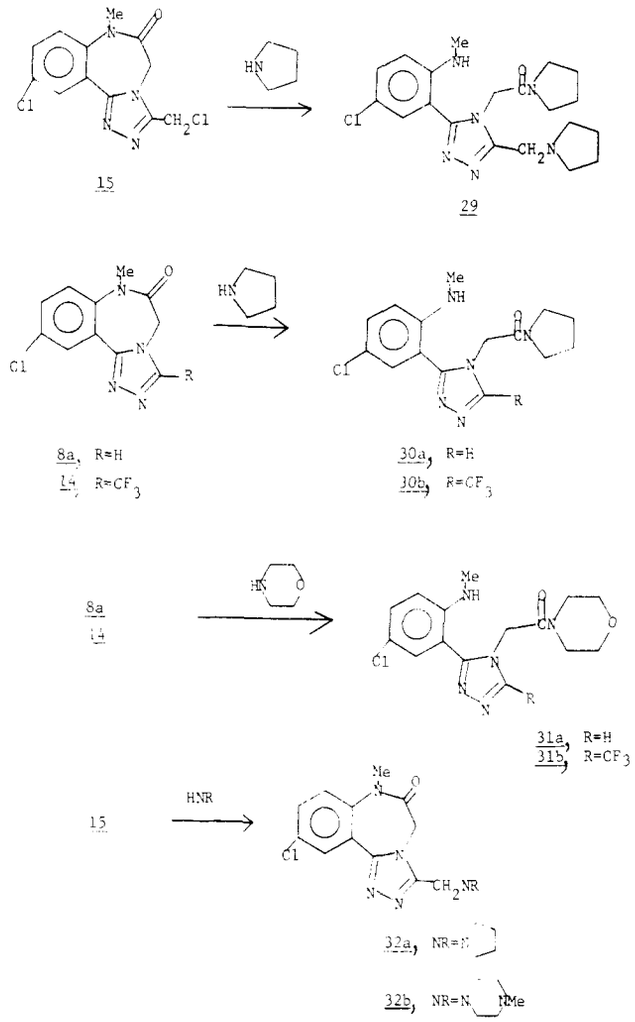
A substantial improvement in yield was achieved by condensing **2** with the morpholine analogue **25** of oxamic hydrazide. This modification produced **21** in 84% yield with a small amount (7%) of the triazole-3-carboxamide **26** as a byproduct.

N-Alkylation of **21** was accomplished in a manner similar to that of **17**. Conversion of **21** to its thallous salt (**27**) and



subsequent reaction with the appropriate halide produced the *N*-methyl- (**28a**), -benzyl- (**28b**), -(dimethylamino)ethyl- (**28c**), -(dimethylamino)propyl- (**28d**), -(diethylamino)ethyl- (**28e**), -(pyrrolidinyl)ethyl- (**28f**), and -(morpholinyl)ethyltriazinedione (**28g**) derivatives.

In an attempt to introduce basic substituents on the 3 position of the triazolobenzodiazepine, the (chloromethyl)triazole **15** was briefly heated in neat pyrrolidine. Somewhat surprisingly, the product was found to be aminoamide **29** re-



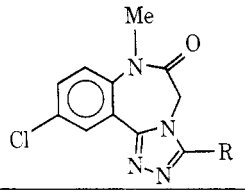
sulting from chloride displacement and aminolysis of the lactam. The aminolysis reaction was found to be unaffected by the substituent on the triazole moiety. The unsubstituted and CF_3-substituted triazoles **8a** and **14** were also cleaved by pyrrolidine to the corresponding ring-opened compounds **30a** and **30b**. Although only representative examples were fully characterized, these ring-opened compounds were readily detectable by NMR. When completely free of acid, the N–Me group appeared as a doublet at ca. δ 2.8 and the N–H proton as a quartet at ca. δ 5.75. Small amounts of acid impurities caused chemical exchange and eliminated this splitting.

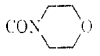
The aminolysis reaction was not limited to pyrrolidine, as was shown by the ring opening of **8a** and **14** to **31a** and **31b**, respectively, by neat morpholine. These reactions required considerably more time, presumably reflecting the difference in nucleophilicity of the two amines.[15]

Subsequently, it was found that **15** could indeed be cleanly converted to the desired intact amino derivatives by reacting it with, for example, only 3 equiv of pyrrolidine or *N*-methylpiperazine in DME to give the (pyrrolidinyl)methyl (**32a**) and *N*-(methylpiperazinyl)methyl (**32b**) derivatives, respectively. Under these conditions no evidence of ring opening was observed.

Variable Temperature NMR Analysis. Conformational interconversion is of particular importance in the context of

Table II. Chemical Shifts, Coupling Constants, Coalescence Temperatures, and ΔF^{*} [a]



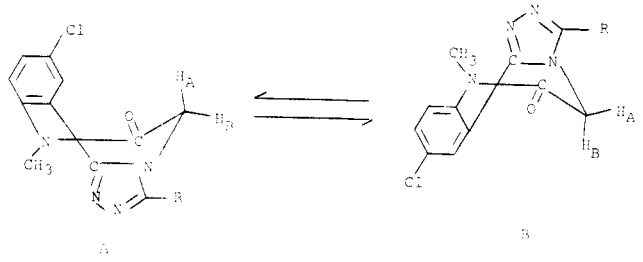
no.	R	registry no.	solvent	δ CH_2, Hz	$\Delta\nu$	J(H–H)	t_c, °C	ΔF^{*}, kcal/mol
8a	H		*b*	496, 448	48	14.0	−6.0	13.1
8b	Me	60726-47-8	*b*	477, 442	35	14.0	−9.0	13.0
8c	Ph	60726-48-9	*b*	499, 438	61	14.0	18.0	14.2
14	CF_3	60726-52-5	*b*	501, 452	49	14.0	−3.0	13.2
15	CH_2Cl	60726-55-8	*b*	501, 447	54	14.0	−3.0	13.2
24	CO_2Et	60726-53-6	*b*	616, 441	75	14.0	18.0	13.65
26		60726-54-7	*b*	480, 439	41	14.0	15.0	13.6

[a] The chemical shifts (internal reference Me_4Si) and the geminal coupling constants (hertz) are measured at the lowest temperatures possible. J_{gem} is arbitrarily chosen as positive. [b] $CDCl_3$.

structure–activity relationships, since the active conformation of a molecule at a biological receptor may in fact differ from that of the crystal state. Conformational considerations may also be important in the interpretation of the NMR spectra of certain compounds recorded at ambient temperature.

The conformational behavior of seven-membered heterocyclic rings,[16,17] including benzodiazepines,[2a,18,19] has received less attention than that of the more common six-membered ring systems. The benzodiazepine rings, observed in the four independent solid state molecular structures described in the following X-ray section, exist in boat conformations[20] having the methylene carbons as bow atoms.

In this section we present the results of dynamic nuclear magnetic resonance (DNMR) studies of benzodiazepinone nuclei bearing annelated triazole, triazolone, and triazinedione rings (compounds **8a**, **17**, **21**, and derivatives) as a measure of the interconversion of two boat conformations (A and B) in



solution. The conformational stability of the seven-membered ring is compared to that of the diazepine ring in diazepam and related compounds.

The NMR spectrum of **8b** at 36 °C in deuteriochloroform showed the presence of a sharp methylene proton resonance at δ 4.60 (2 H, NCH_2CO moiety). On cooling the solution, the CH_2 resonance broadened progressively, resulting in an AB quartet at δ 4.77 and 4.42 with a geminal coupling constant (J_{gem}) having an absolute value of 14.0 Hz at −40 °C. The coalescence point, indicating a slow rate of interconversion of the two "boat- or basket-like" conformations, was found to be between −8.0 and −10.0 °C (Figure 1). The NMR data of several 3-substituted triazolo[4,3-*d*][1,4]benzodiazepin-6-ones are presented in Table II.

The NMR spectrum of **20c** in deuteriochloroform exhibited, at 36 °C, a sharp methylene proton resonance at δ 4.45, which on cooling to −60 °C resulted in an AB quartet at δ 4.88 and 4.02 with J_{gem} = 14 Hz. On raising the temperature, the AB quartet coalesced at 12.0 °C (Figure 2). The NMR data for **17** (R = H) and **20c** are presented in Table III.

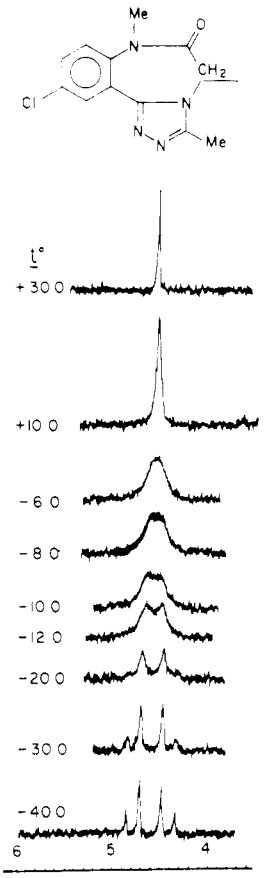
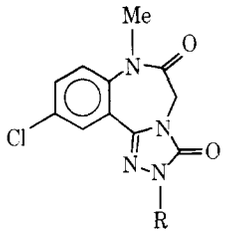


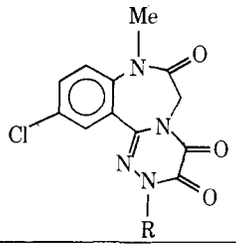
Figure 1. Variable temperature NMR spectra of the ring methylene protons of **8b** in $CDCl_3$.

A substantial difference was observed in the case of the annelated six-membered triazinedione. In this instance, the NMR spectrum of **28c** in deuteriobromobenzene (C_6D_5Br) at 36 °C exhibited an AB quartet at δ 5.24 and 3.33 with J_{gem} = 14.0 Hz for the methylene protons. As the temperature of the solution was increased, the resonances first broadened and then coalesced at 145 °C. The variable temperature NMR spectra of **21** (R = H) in dimethyl-d_6 sulfoxide are shown in Figure 3, and the data for triazinediones **28c** and **21** are presented in Table III. For comparison, variable temperature NMR data for diazepam (**33**), for a triazole isomeric with **8a** (**34**[21]), and for a triazole annelated to the "a" face of diazepam

Table III. Chemical Shifts, Coupling Constants, Coalescence Temperatures, and ΔF^{*} [a]



no.	registry no.	R	solvent	δ CH_2, Hz	$\Delta\nu$	J(H–H)	t_c, °C	ΔF^{*}, kcal/mol
17		H	*b*	496, 412	84	14.0	−13.5	12.5
20c	68013-38-7	$CH_2CH_2NMe_2$	*b*	488, 402	86	14.0	−12.0	12.5



no.	registry no.	R	solvent	δ CH_2, Hz	$\Delta\nu$	J(H–H)	t_c, °C	ΔF^{*}, kcal/mol
28c	56969-34-7	$CH_2CH_2NMe_2$	*c*	524, 333	191	14.0	145.0	19.9
21	57254-29-2	H	*d*	508, 408	100	14.0	152.0	20.7

[a] Same as in Table II. [b] $CDCl_3$. [c] C_6D_5Br. [d] Me_2SO-d_6.

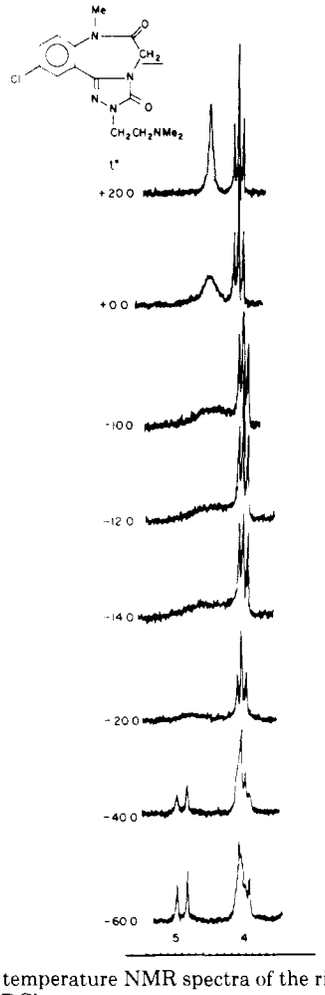


Figure 2. Variable temperature NMR spectra of the ring methylene protons of **20c** in $CDCl_3$.

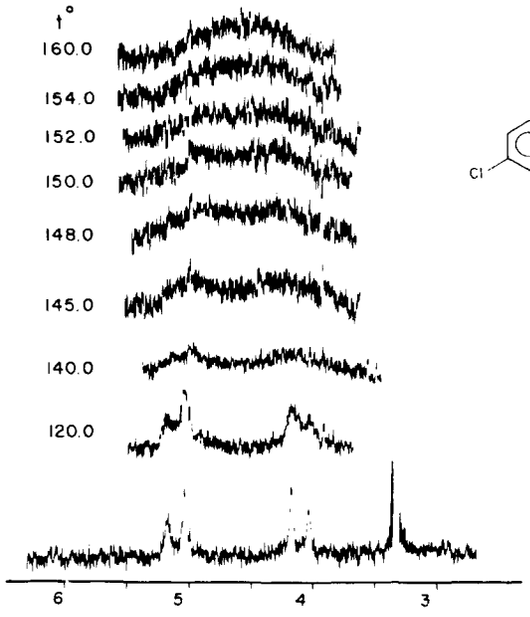
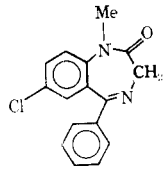
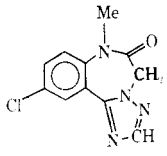
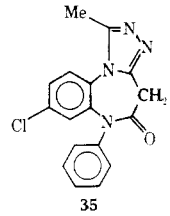
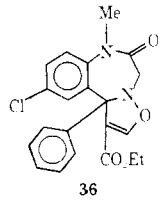


Figure 3. Variable temperature NMR spectra of the ring methylene protons of **21** in Me_2SO-d_6.

(**35**[22]) are presented in Table IV.

The main factors which influence the conformational barriers to ring inversion (ΔF^{*}) in these systems are anisotropic effects of the carbonyl groups and the collapse temperatures (t_c) of the nonequivalent methylene protons. Not only the carbonyl function of the seven-membered ring but also the additional carbonyl groups in the annelated triazolone or triazinedione rings exert considerable anisotropic effects on the methylene protons of the benzodiazepinone ring, thereby inducing the large chemical shift differences observed between the nonequivalent protons (Table III). In the triazole series,

Table IV. Chemical Shifts, Coupling Constants, Coalescence Temperatures, and ΔF^* [a]

compd	registry no.	solvent	δ CH_2, Hz	$\Delta\nu$	J(H–H)	t_c, °C	ΔF^*, kcal/mol
 33	439-14-5	*d*	459, 379	80	11.0	97.0	18.1 (17.7)[c]
 34	55511-01-8	*b*	529, 461	68	15.0	−25.0	12.0
 35	54748-06-0	*e*	419, 374	45	14.0	160.0	21.6
 36							(17.7)[c]

[a] Same as in Table I. [b] $CDCl_3$. [c] Literature[3b] value. [d] Me_2SO-d_6. [e] Me_2SO-d_6–C_6D_5Br.

the alkyl or aryl substituents have less influence than the carbonyl of the annelated ring. The additional carbonyl of the CO_2Et moiety (in **24**) shifts the nonequivalent CH_2 protons furthest apart ($\Delta\nu$ is large) of all the 3-substituted triazoles (Table II).

The average barrier (ΔF^*) to inversion of the seven-membered benzodiazepinone ring bearing a fused 1,2,4-triazole (Table II) was 13.4 kcal/mol.[24] Except for the steric bulk of the phenyl group (in **8c**), the ΔF^* was not substantially affected by the substituents at the 3 position (Table II). ΔF^* was slightly lower (12.5 kcal/mol) for compounds **17** and **20c** with a fused triazolone ring (Table III). The small difference in the ring inversion barrier between the "3-oxo" triazolone compounds, **17** and **20c**, and the triazoles in Table II is ascribed to the presence of an exocyclic oxo double bond in the former compared to the somewhat more restraining 2,3-endocyclic double bond in the latter.

The annelation of the triazinedione ring to the benzodiazepinone nucleus resulted in a significant increase in the conformational rigidity. The ΔF^* values were of the order of 20 kcal/mol for **28c** and **21** (Table III) for the ring inversion and were considerably higher than those observed in the analogously fused triazole and triazolone systems, except for **35** which, like diazepam, retains a phenyl group.

Higher values of ΔF^* for the ring inversion process in **21** and **28c** suggest not only a higher energy transition state but also lower potential energy in the ground state.[23] Increased resonance delocalization of the π system in the bridgehead lactam in **28c** relative to **20c** is expected to impart a greater degree of coplanarity to the three groups attached to the bridgehead nitrogen. This lowers the potential energy in the ground state and increases the rigidity of **28c** relative to **20c** by several kcal/mol. In addition, the increased rigidity of **28c** presumably also stems from the repulsive dipole–dipole interactions, in the transition state, of the adjacent carbonyl groups. ΔF^* values (in **28c** and **21**) significantly larger than that of diazepam and related compounds reflect extreme stability, almost approaching the enantiomeric separability stage.

X-ray Results. The three-dimensional monoclinic crystal structures of the methiodide of **20c**, the hydrobromide of **28c**, and triazolo[5,1-*a*][2,4]benzodiazepine (X)[25] (Table V) were determined through Patterson and Fourier methods and refined through least-squares analyses using diffractometer data sets (Cu Kα; λ = 1.542 Å) which had been corrected for absorption. The heavy atoms (four per asymmetric unit in the case of **20c**·CH_3I) have limited the accuracy of the analyses. While not providing an independent definitive proof of chemical structure, the results adequately characterize the conformational aspects of these compounds. The methiodide crystallized as a hemihydrate with two methiodides per asymmetric unit ($C_{32}H_{42}I_2Cl_2N_{10}O_4·H_2O$), and the analysis thus has provided two independent measures of its solid state conformation. The hydrobromide of **28c** crystallized with one molecule of acetonitrile per asymmetric unit ($C_{16}H_{18}ClN_5O_3·HBr·CH_3CN$). Compound X, which contains Cl as the only halogen, is the most precisely determined structure.

The solid state conformation of these diazepine rings can be described in terms of the dihedral angles between three least-squares planes: plane 1, the five (six in the case of the HBr salt of **28c**) cyclic atoms of the fused triazole ring, and the attached phenyl carbon atom; plane 2, the four atom group –CH_2**CON**– of the seven-membered ring (three atoms in X: –CH_2**N**=**C**Ph); plane 3, nine atoms (the fused phenyl ring and its three substituents). The dihedral angles between these planes are given in Table VI.

Table V. Crystal Data

structure	registy no.	a, Å	b, Å	c, Å	β, deg	d_m, g cm^{-3}	space group	Z	no. of obsd intensities[c]	final R factor[d]
20c·CH_3I	68013-39-8	11.121 (3)	14.885 (5)	23.34 (1)	91.52 (2)	1.693	$P2_1/n$	8	1446	0.08[a]
28c·HBr	56969-34-7	19.328 (7)	11.536 (5)	16.063 (6)	144.2 (1)	1.590	Cc	4	1144	0.10[b]
X	66492-65-7	15.958 (3)	7.064 (2)	13.637 (4)	103.12 (2)	1.38	$P2_1/c$	4	1038	0.10[a]

[a] All nonhydrogen atoms were refined anisotropically. [b] Halogens were refined anisotropically; all other nonhydrogen atoms were refined isotropically. [c] Reflections having $I \geq 3\sigma$. [d] $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$. The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|$, where w is the reciprocal of the sum of the background and total integrated reflection counts. The latter were measured using the θ–2θ variable scan rate technique; background counts were measured for half the scan time at each end of the scan range. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography", Vol. 3, C. H. MacGillavry and G. D. Riech, Ed., Kynoch Press, Birmingham, England, 1962.

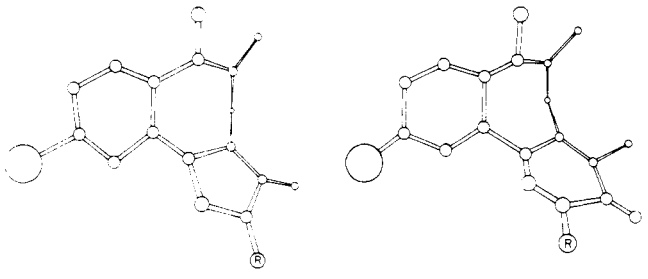


Figure 4. Perspective drawings of the observed solid state molecular conformation of **20c**·CH_3I (left) and **28c**·HBr (right). In each case, the plane of the drawing is parallel to the least-squares plane (plane 3) of the phenyl ring and its three substituent atoms. In both molecules the side chain has been omitted for clarity.

Table VI. Dihedral Angles between Least-Squares Planes

A. Dihedral Angles

structure	$\phi_{1,2}$	$\phi_{1,3}$	$\phi_{2,3}$
(**20c**·CH_3I)$_1$[a]	65°	37°	45°
(**20c**·CH_3I)$_2$	53°	37°	45°
28c·HBr	68°	46°	50°
X	62°	34°	39°

B. Average Deviation from Least-Squares Planes 1, 2, and 3

structure	average deviation (Å) from least-squares plane 1	2	3
(**20c**·CH_3I)$_1$	0.05	0.03	0.04
(**20c**·CH_3I)$_2$	0.04	0.04	0.02
28c·HBr	0.02	0.03	0.08
X	0.005		0.006

[a] Subscripts refer to the two independent molecules in the asymmetric unit.

The dipole–dipole repulsion between the adjacent carbonyl groups in the triazinedione ring of **28c** is alleviated through a 15° twist about the bond between the carbonyl carbon atoms. This effect and to some extent relief of the nonbonded peri interaction of the hydrogen ortho to Cl and the N-1 of the triazinedione ring apparently are responsible for the somewhat more puckered conformation of **28c**·HBr and contribute to the observed increase in the barrier to conformational interconversion (Figure 4).

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Routine ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Varian T-60 or Perkin-Elmer R12B spectrometer, and chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (Me_4Si) as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 621 as KBr pellets. Ultraviolet spectra were obtained on a Cary 15 in methanol. All characterized compounds were dried at 1 torr in a vacuum oven at a temperature between 25 and 90 °C unless otherwise indicated. Temperatures are on the centigrade scale.

Variable temperature NMR spectra were recorded on a Varian XL-100-15 NMR spectrometer internally locked to deuterium frequency (15.4 MHz) of the solvent and equipped with a variable temperature probe. The sample temperature was controlled to ±1.0 °C with the V-6040 temperature controller and was calibrated by use of a methanol or ethylene glycol sample provided by Varian Associates. The concentration of the solutions was approximately 10% (w/v) in deuterated solvents with tetramethylsilane (Me_4Si) as an internal reference.

The calculations of the rate constants, k_c, at the coalescence temperatures, t_c, for the coupled system, i.e., NCH_2CO methylene protons AB quartet of the benzodiazepine ring, were carried out by using eq 1. The free energies of activation, ΔF^* (kcal/mol), were calculated from eq 2[26] using the coalescence temperature, t_c.

$$k_c = \pi[\Delta\nu^2 + 6J(\text{H–H})^2]^{1/2}/1.4142 \quad (1)$$

$$\Delta F^* = (2.303)RT(10.319 + \log T - \log k_c) \quad (2)$$

Low-resolution mass spectra were obtained on an Associated Electrical Industries Model MS-902 double-focusing mass spectrometer. The source, maintained at 170 °C, had an electron energy of 70 eV. Samples were introduced via the direct insertion probe. All spectra were recorded on frequency modulated analog magnetic tapes, which were subsequently processed on a PDP-11 computer using Squibb programs.

5,7-Dichloro-1-methyl-1,4-benzodiazepin-2-one (2). To a mixture of 44.8 g (0.2 mol) of 7-chloro-1-methyl-1,4-benzodiazepine-2,5-dione[9] (1), 400 mL of benzene, and 48.4 g (0.4 mol) of dimethylaniline in a 1-L three-neck flask fitted with a reflux condenser ($CaCl_2$ drying tube), thermometer, dropping funnel, mechanical stirrer, and heating mantle was added 20.4 g (0.132 mol) of phosphorus oxychloride. There was no rise in temperature during the phosphorus oxychloride addition. The mixture was refluxed for 7 h (becomes homogenous after a few minutes) and allowed to stand at room temperature overnight. After cooling to 7 °C, 200 mL of cold water was added and the mixture stirred for 15 min. The organic layer was separated, washed with an additional 200 mL of cold water, and dried over $MgSO_4$. The benzene solution was concentrated under vacuum (maximum bath temperature 50 °C) to a solid residue (40.4 g) which contained some dimethylaniline. This solid was stirred with 100 mL of CCl_4 for 2 h at room temperature, filtered, washed with CCl_4, and dried over P_2O_5 at 25 °C (10 torr) to yield 27 g (55%) of **2**: mp 133–135 °C; IR (mineral oil) ν 1670 (C=O), 1630 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 3.43 (s, 3 H, CH_3), 4.16 (broad s, 2 H, CH_2), 7.30 (d, J = 9 Hz, 1 H, 9-H), 7.59 (q, J = 9, 2.5 Hz, 1 H, 8-H), 7.83 (d, J = 2.5 Hz, 1 H, 6-H); mass spectrum, m/e (% total ionization) 242 (4.8, M^+), 213 (2.8), 207 (9.1, base), 179 (5.2).

Initial Attempt to Prepare 3. A mixture of 1.2 g (0.005 mol) of **2** and 0.32 g (0.01 mol) of anhydrous hydrazine (97%) in 25 mL of benzene was refluxed for 20 h. Although TLC (silica gel; choroform–ethyl acetate, 3:2) still showed unreacted starting material and no major new spots, the mixture was cooled to room temperature. The precipitate that formed on standing was filtered off and recrystallized once from benzene and once from absolute ethanol to yield 90 mg of material, mp 165–168 °C. Structure **4** was assigned from IR, NMR, and mass spectra (see preparation of **4** for spectral data).

7-Chloro-5-hydrazino-1-methyl-1,4-benzodiazepin-2-one (3). To a solution of 1.2 g (0.005 mol) of **2** in 5 mL of absolute ethanol was

added 0.32 g (0.01 mol) of anhydrous hydrazine; a precipitate formed immediately. The mixture was stirred for 2 days at room temperature until TLC (silica gel; chloroform–ethyl acetate, 3:2) showed the disappearance of starting material. The mixture was filtered and the solvent removed from the filtrate under vacuum. The residue was taken up in chloroform and extracted with 10% HCl. The acid solution was backwashed with chloroform, cooled, and basified with 10% NaOH to pH 9; the mixture was immediately extracted with chloroform. The chloroform solution was dried (Na_2SO_4), concentrated, and applied to seven preparative silica gel plates (Quantum PQF 1000); after developing with chloroform–ethyl acetate (3:2), the large band just above the spotting line was collected and extracted with chloroform. The chloroform was removed under vacuum to yield 0.4 g (32%) of **3**. The product was difficult to crystallize from the usual polar solvents. Crystals were obtained, however, by dissolving the crude material in a small volume of toluene, diluting to a little past the cloud point with methylcyclohexane, and allowing the mixture to stand overnight at room temperature. The resulting crystals were filtered off to yield 0.26 g of pure **3**: mp 139–140.5 °C; IR (KBr) ν 3300 (NH), 1662 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.33 (s, 3 H, CH_3), 3.77 (s, 2 H, CH_2), 4.80 (broad s, 3 H, N–H), 7.12 (d, J = 9 Hz, 1 H, 9-H), 7.35 (q, J = 9, 2.5 Hz, 1 H, 8-H), 7.65 (d, J = 2.5 Hz, 1 H, 6-H).

Anal. Calcd for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; N, 23.48; Cl, 14.85. Found: C, 50.15; H, 4.56; N, 23.52; Cl, 14.90.

3-[5-Chloro-2-(methylamino)phenyl]-2,5-dihydro-1,2,4-triazin-6(1*H*)-one (4). A 6-g (0.025-mol) amount of **2** was stirred in 100 mL of anhydrous hydrazine at 25 °C for 2 days under nitrogen. The resulting precipitate was filtered off and recrystallized once from methanol and once from chloroform to give, after drying (80 °C, 1 torr), 4 g (67%) of **4** as slightly yellow plates: mp 166–167.5 °C; IR (KBr) ν 3380, 3310 (NH), 1660 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 2.81 (d, J = 5 Hz, 3 H $NHCH_3$), 3.80 (d, J = 0.5 Hz 2 H, ring CH_2), 6.65 (d, J = 9 Hz, 1 H, aromatic 3-H), 7.15–7.65 (m, 4 H, 2 aromatic and 2NH), 10.40 (s, 1 H, NH); UV (MeOH) λ_{max} (ϵ) 265 (14 400), 300 (5100), 357 (6320) nm; mass spectrum, m/e (% total ionization) 238 (13.9, M^+), 179 (16.1, base).

Anal. Calcd for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; N, 23.47; Cl, 14.85. Found: C, 50.20; H, 4.54; N, 23.67; Cl, 14.72.

[5-Chloro-2-(methylamino)benzamido]acetic Acid Hydrazide (6). A mixture of 10.0 g (0.0446 mol) of **1**, 25 g of hydrazine hydrate (85%), and 25 mL of 1-butanol was refluxed for 90 min. The mixture was cooled to room temperature, and the resulting cotton-like crystals were filtered off and recrystallized from absolute ethanol to give 9.7 g (85%) of **6**: mp 197–197.5 °C; IR (KBr) ν 3425 (NH), 3355 (NH), 3330 (NH), 1614 (C=O), 1632 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 4.19 (s, 2 H, NH_2), 6.62 (d, J = 9 Hz, 1 H, Ph 3-H), 7.28 (q, J = 9, 3 Hz, 1 H, Ph 4-H), 7.62 (m, 2 H, Ph 6-H and NHMe), 8.60, (t, J = 6 Hz, 1 H, amide NH), 9.06 (s, 1 H, hydrazide NH); UV (MeOH) λ_{max} (ϵ) 263 (18 200), 360 (6030) nm; mass spectrum, m/e (% total ionization) 256 (5, M^+), 168 (27, base peak).

Anal. Calcd for $C_{10}H_{13}ClN_4O_2$: C, 46.79; H, 5.10; N, 21.82; Cl, 13.81. Found: C, 46.52; H, 5.23; N, 22.10; Cl, 13.57.

10-Chloro-7-methyl-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (8a). A mixture of 14.6 g (0.06 mol) of **2** and 12.0 g (0.2 mol) of formylhydrazine (Eastman) in 300 mL of benzene was refluxed for 12 h. The solvent was removed under vacuum, and the residue recrystallized twice from 95% ethanol to yield 12.5 g (84%) of **8a** as a white powder: mp 272–274 °C; IR (KBr) ν 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.36 (s, 3 H, NCH_3), 4.65 (s, 2 H, CH_2), 7.34 (d, J = 9 Hz, 1 H, 8-H), 7.60 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.08 (d, J = 2.5 Hz, 1 H, 11-H), 8.35 (s, 1 H, 3-H); UV (MeOH) λ_{max} (ϵ) 231 (35 800), 250 (12 600), 298 (1920) nm; mass spectrum, m/e (% total ionization) 248 (6.2, M^+), 220 (15.9, base).

Anal. Calcd for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53; Cl, 14.26. Found: C, 53.23; H, 3.57; N, 22.82; Cl, 14.05.

10-Chloro-3,7-dimethyl-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (8b). A mixture of 4.86 g (0.02 mol) of **2** and 5.02 g (0.067 mol) of acetohydrazide (Aldrich) was refluxed in 300 mL of benzene for 14 h. The solvent was removed under vacuum and the residue recrystallized from water. The product was obtained as a hydrate (needles) and was recrystallized again from a methanol–water (1:3) mixture to yield 4.2 g (74%) of **8b**. Drying the product at 150 °C (1 torr) for 12 h reduced the needles to a powder: mp 228.5–229.5 °C; IR (KBr) ν 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.54 (s, 3 H, 3-CH_3), 3.34 (s, 3 H, NCH_3), 4.51 (s, 2 H, CH_2), 7.34 (d, J = 9 Hz, 1 H, 8-H), 7.55 (q, J = 9, 2.5 Hz, 1 H, 9-H), 7.96 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 234 (34 400), 255 (12 500), 298 (1980) nm; mass spectrum, m/e (% total ionization) 262 (18.2, M^+, base), 233 (3.0), 220 (8.0).

Anal. Calcd for $C_{12}H_{11}ClN_4O$: C, 54.86; H, 4.42; N, 21.37; Cl, 13.50. Found: C, 54.68; H, 4.18; N, 21.29; Cl, 13.35.

10-Chloro-7-methyl-3-phenyl-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (8c). A mixture of 2.79 g (0.0115 mol) of **2** and 2.86 g (0.021 mol) of benzoylhydrazine (Aldrich) was refluxed in 150 mL of benzene for 3 h. Some insoluble material was filtered from the hot reaction mixture, and the solvent was removed from the filtrate under vacuum. The residue was recrystallized twice from methanol and dried at 125 °C (1 torr) to yield 2.9 g (82%) of white crystals: mp 204.5–205.5 °C; IR (KBr) ν 1662 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.46 (s, 3 H, NCH_3), 4.66 (broad s, 2 H, CH_2), 7.43 (d, J = 9 Hz, 1 H, 8-H), 7.5–8.0 (m, 6 H, 9-H and Ph), 8.14 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 244 (39 700), 298 (3860) nm; mass spectrum, m/e (% total ionization) 324 (35.8, M^+, base), 295 (3), 267 (2.5), 220 (3.0).

Anal. Calcd for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; N, 17.26; Cl, 10.92. Found: C, 62.58; H, 3.95; N, 17.16; Cl, 10.93.

10-Chloro-6,7-dihydro-7-methyl-6-oxo-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3-acetonitrile (8d). A mixture of 5.0 g (0.02 mol) of **2** and 3.0 g (0.03 mol) of cyanoacetohydrazide (Aldrich) in 150 mL of 1,2-dimethoxyethane (DME) was refluxed for 5 h. The solvent was removed under vacuum and the residue stirred with 50 mL of 95% ethanol. The ethanol was decanted, and the residue (4.79 g, 70%) was recrystallized from a large volume of methanol to yield, after drying at 100 °C (1 torr), the nitrile: mp 252–253.5 °C; IR (KBr) ν 2253 (weak, C≡N), 1665 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.25 (s, 3 H, NCH_3), 4.55 (s, 2 H, CH_2CN), 4.79 (s, 2 H, ring CH_2), 7.5–7.9 (m, 3 H, aromatic); UV (MeOH) λ_{max} (ϵ) 233 (36 400), 256 (11 900), 300 (1930) nm; mass spectrum, m/e (% total ionization) 287 (9.1, M^+, base), 258 (1.7), 220 (2.7).

Anal. Calcd for $C_{13}H_{10}ClN_5O$: C, 54.27; H, 3.51; N, 24.34; Cl, 12.32. Found: C, 54.11; H, 3.61; N, 24.55; Cl, 12.42.

10-Chloro-7-methyl-3-(trifluoromethyl)-5*H*-1,2,4-triazolo-[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (14). A mixture of 7.5 g (0.03 mol) of **2** and 7.9 g (0.06 mol) of *tert*-butyl carbazate (Aldrich) was refluxed in 300 mL of benzene for 90 min. The solvent was removed under vacuum, and 20 mL of trifluoroacetic acid was added. The resulting mixture was stirred for 30 min at 25 °C and the volatile material removed under vacuum. Trifluoroacetic anhydride (30 mL) was added, and the resulting solution refluxed for 2 h. Again the volatile material was removed under vacuum, and the residue was triturated with 250 mL of ether. The resulting white powder (6.9 g, 70%) was filtered off, recrystallized from methanol and dried at 130 °C (1 torr): mp 186–187 °C; IR (KBr) ν 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.36 (s, 3 H, NCH_3), 4.71 (s, 2 H, CH_2), 7.40 (d, J = 9 Hz, 1 H, 8-H), 7.60 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.02 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 230 (39 200), 252 (11 900), 300 (2240) nm.

Anal. Calcd for $C_{12}H_8ClF_3N_4O$: C, 45.51; H, 2.55; N, 17.69; Cl, 11.20; F, 18.00. Found: C, 45.38; H, 2.78; N, 17.92; Cl, 11.26; F, 18.23.

10-Chloro-3-(chloromethyl)-7-methyl-5*H*,1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (15). A mixture of 2.43 g (0.01 mol) of **2** and 1.68 g (0.012 mol) of *tert*-butyl carbazate (Aldrich) was refluxed in 125 mL of benzene for 12 h. The volatile material was removed under vacuum, and 6.0 g (0.063 mol) of chloroacetic acid was added. After the mixture was stirred at 80–90 °C for 2 h, 4.0 g (0.023 mol) of chloroacetic anhydride was added and the resulting mixture was stirred at 90 °C for another 2 h. The reaction was cooled, and 100 mL of ether was added, producing an insoluble gum. The ether was decanted, and the residue was warmed and stirred with a small volume of methanol. After standing at 25 °C for several hours, the resulting white powder (1.2 g) was filtered off. Diluting the filtrate with water gave a further 0.3 g (total 1.5 g, 52%) of **15**. Both crops were combined and recrystallized from 95% ethanol: mp 193–194.5 °C; IR (KBr) ν 1664 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.34 (s, 3 H, NCH_3), 4.65 (s, 2 H, ring CH_2), 4.82 (s, 2 H, CH_2Cl), 7.38 (d, J = 9 Hz, 1 H, 8-H), 7.55 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.02 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 233 (38 300), 256 (12 500), 300 (3020) nm.

Anal. Calcd for $C_{12}H_{10}Cl_2N_4O$: C, 48.51; H, 3.40; N, 18.85; Cl, 23.86. Found: C, 48.32; H, 3.64; N, 19.03; Cl, 23.96.

10-Chloro-7-methyl-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3,6(2*H*,7*H*)-dione (17). A mixture of 50 g (0.203 mol) of **2** and 43 g (0.57 mol) of ethyl carbazate (Aldrich) was refluxed in 2 L of toluene for 4 h. The toluene layer was decanted from the resulting insoluble gum, and the solvent was removed under vacuum to yield 11 g of **17**. The insoluble gum was then refluxed for 2 h in 500 mL of dioxane. The dioxane was removed under vacuum, and the residue was triturated with acetonitrile to yield, on filtration, 34 g of **17**. Another 5.5 g of **17** was later obtained from the acetonitrile filtrate, total yield 50.5 g (94%). Recrystallization of some crude material from a methanol–dioxane (1:1) mixture gave a pure sample: mp 268–269 °C; IR (KBr) ν 1706 (triazole C=O), 1676 (azepine C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.28 (s, 3 H, NCH_3), 4.32 (s, 2 H, CH_2), 7.68 (m, 3 H, aromatic), 12.25 (broad s, 1 H, NH); UV (MeOH) λ_{max} (ϵ) 251 (17 900),

300 (3680) nm; mass spectrum, *m/e* (% total ionization) 264 (17.3, M^+, base), 235 (5.5), 222 (3), 221 (3).

Anal. Calcd for $C_{11}H_9ClN_4O_2$: C, 49.92; H, 3.42; N, 21.17; Cl, 13.40. Found: C, 49.85; H, 3.44; N, 21.20; Cl, 13.32.

Thallium Salt (19) of 17. To a solution of 6.0 g (0.023 mol) of **17** in 90 mL of DMF at 45 °C was added 5.72 g (0.023 mol) of thallous ethoxide. The solution was stirred for 1 h at 25 °C and diluted with 300 mL of ether. The resulting precipitate was filtered off, washed with ether, and dried at 50 °C (1 torr) for 2 h to give 9.5 g (86%) of **19** which was stored under anhydrous conditions and used without further purification.

10-Chloro-2,7-dihydro-2,7-dimethyl-3*H*-1,2,4-triazolo[4,3-*d*]-[1,4]benzodiazepine-3,6(5*H*)-dione (20a). A mixture of 9.5 g (0.02 mol) of the thallium salt **19** and 100 mL of methyl iodide was refluxed for 18 h. The reaction mixture was filtered, and the volatiles were removed under vacuum to yield 3.7 g of powder. The powder was taken up in chloroform and chromatographed on a dry column of 75 g of silica gel (Baker, grade III). Elution with 600 mL of chloroform–ethyl acetate (3:2) gave, after removal of the solvents and recrystallization from chloroform–methanol (1:1), 1.0 g (17%) of **20a:** mp 292–294 °C; IR (KBr) ν 1685 (triazole C=O), 1665 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 3 H, azepine NCH_3), 3.54 (s, 3 H, triazole NCH_3), 4.38 (s, 2 H, CH_2), 7.30 (d, J = 9 Hz, 1 H, 8-H), 7.55 (q, J = 9, 2.5 Hz, 1 H, 9-H), 7.83 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 252 (17 800), 279 sh (7720), 300 sh (3900) nm.

Anal. Calcd for $C_{12}H_{11}ClN_4O_2$: C, 51.72; H, 3.97; N, 20.10; Cl, 12.72. Found: C, 51.85; H, 3.92; N, 20.16; Cl, 12.79.

10-Chloro-2-[2-(dimethylamino)ethyl]-2,7-dihydro-7-methyl-3*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3,6(5*H*)-dione (20c) and Its Hydrochloride Salt. To a stirred suspension of 13.5 g (0.029 mol) of the thallium salt **19** in refluxing toluene was added a toluene solution of (dimethylamino)ethyl chloride [obtained by treating 6 g (0.042 mol) of the HCl salt (Michigan Chemical) with excess 10% NaOH and immediately extracting with 150 mL of toluene]. After 2 h, an equal amount of the chloride was added and reflux was continued for 5 h. The reaction mixture was cooled to 25 °C, filtered through Celite, and concentrated under vacuum. The residue was passed through a 12 × 4.5 cm column of Florisil with 3 L of ethyl acetate, and the solvent was removed under vacuum to yield 7.5 g (71%) of the free base as a white powder. This material was washed as a slurry with hexane to remove some yellow color and recrystallized from ethyl acetate: mp 160.5–162 °C; IR (KBr) ν 1690 (triazole C=O), 1675 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.34 (s, 6 H, $N(CH_3)_2$), 2.74 (t, J = 7 Hz, 2 H, $CH_2CH_2N(CH_3)_2$), 3.37 (s, 3 H, lactam CH_3), 4.00 (t, J = 7 Hz, 2 H, $CH_2CH_2N(CH_3)_2$), 4.40 (s, 2 H, ring CH_2), 7.34 (d, J = 9 Hz, 1 H, 8-H), 7.55 (q, J = 9, 2.5 Hz, 1 H, 9-H), 7.80 (d, J = 2.5 Hz, 1 H, 11-H).

The HCl salt was prepared by dissolving 3.5 g of the free base in ether containing enough methanol to achieve complete solution, adding 1.1 equiv of ethereal HCl, and filtering off the resulting precipitate. The crude salt was taken up in hot methanol, precipitated by the addition of ether, filtered off, and dried at 140 °C (1 torr): mp 284–285.5 °C; UV (MeOH) λ_{max} (ϵ) 253 (17 600), 275 sh (8220), 302 sh (4310) nm.

Anal. Calcd for $C_{15}H_{19}Cl_2N_5O_2$: C, 48.40; H, 5.15; N, 18.81; Cl, 19.05. Found: C, 48.14; H, 5.42; N, 18.60; Cl, 18.78.

Methiodide Derivative for Single-Crystal X-ray Analysis. The free base (ca. 0.1 g) was dissolved in hot absolute ethanol and treated with excess methyl iodide. The resulting crystals were filtered off, washed with a small amount of ethanol, and dissolved in acetonitrile. The acetonitrile was allowed to slowly evaporate to dryness over several days, resulting in compact crystals containing 0.5 mol of H_2O, mp 249–250 °C.

Anal. Calcd for $C_{16}H_{22}ClIN_5O_{2.5}$: C, 39.48; H, 4.56; N, 14.39; Cl, 7.28; I, 26.07. Found: C, 39.61; H, 4.31; N, 14.49; Cl, 7.20; I, 25.87.

10-Chloro-2,7-dihydro-2-(3-hydroxypropyl)-7-methyl-3*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3,6(5*H*)-dione (20b). Using the procedure for **20c,** 3.0 g (0.0064 mol) of the thallium salt **19** was reacted with a total of 6.0 g (0.064 mol) of 3-chloropropanol (MCB) to give 1.3 g (63%) of **20b:** mp 171–172 °C; IR (KBr) ν 3410 (OH), 1695 (triazole C=O), 1662 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.0 (m, J = 6 Hz, 2 H, $CH_2CH_2CH_2OH$), 2.52 (broad s, 1 H, OH), 3.41 (s, 3 H, NCH_3), 3.70 (t, J = 6 Hz, 2 H, CH_2OH), 4.10 (t, J = 6 Hz, 2 H, $CH_2CH_2CH_2OH$), 4.43 (s, 2 H, ring CH_2), 7.25 (d, J = 9 Hz, 1 H, 8-H), 7.56 (q, J = 9, 2.5 Hz, 1 H, 9-H), 7.80 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 252 (18 100), 277 sh (8160), 303 sh (4670) nm.

Anal. Calcd for $C_{14}H_{15}ClN_4O_3$: C, 52.10; H, 4.68; N, 17.36; Cl, 10.99. Found: C, 51.88; H, 4.75; N, 17.38; Cl, 11.10.

10-Chloro-2-[3-(dimethylamino)propyl]-2,7-dihydro-7-methyl-3*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3,6(5*H*)-dione (20d). Using the procedure for **20c,** 4.5 g (0.01 mol) of the thallium salt **19** was reacted with a total of 3 equiv of (dimethylamino)propyl chloride (Michigan Chemical) to yield 2.6 g (75%) of **20d:** mp 178–179 °C; IR (KBr) ν 1690 (triazole C=O), 1670 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 6 H, $N(CH_3)_2$), 1.7–2.5 (m, 4 H, $CH_2CH_2N(CH_3)_2$), 3.35 (s, 3 H, NCH_3), 3.91 (t, J = 7 Hz, 2 H, $CH_2CH_2CH_2N(CH_3)_2$), 4.37 (s, 2 H, ring CH_2), 7.35 (d, J = 9.0 Hz, 2 H, 8-H), 7.54 (q, J = 9, 2.5 Hz, 1 H, 9-H), 7.81 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 253 (18 200), 274 sh (8780), 305 sh (4820) nm; mass spectrum, *m/e* (% total ionization) 349 (6, M^+), 291 (1), 277 (1), 265 (0.5), 58 (25.8, base).

Anal. Calcd for $C_{16}H_{20}ClN_5O_2$: C, 54.95; H, 5.76; N, 20.02; Cl, 10.14. Found: C, 54.72; H, 6.00; N, 20.02; Cl, 10.06.

10-Chloro-7-methyl-2-phenyl-5*H*-1,2,4-triazolo[4,3-*d*][1,4]-benzodiazepine-3,6(2*H*,7*H*)-dione (20e). A mixture of 1.0 g (0.0038 mol) of **17,** 0.95 g (0.015 g-atom) of copper powder (MCB), 0.66 g of potassium acetate, and 18 mL of bromobenzene was refluxed for 6 h. The mixture was cooled to 25 °C, diluted with 20 mL of dichloromethane, and filtered thru Celite. The filter cake was washed with 200 mL of hot chloroform, the combined filtrates were washed with 40 mL of 1 N ammonium hydroxide and dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was chromatographed on silica gel plates (quantum PQF-1000) with chloroform–ethyl acetate (3:1), and the second band (the first is bromobenzene) was extracted with dichloromethane–ethyl acetate (1:1). The solvents were removed under vacuum and the residue recrystallized from aqueous methanol to yield 94 mg of **20e:** mp 174–175 °C; NMR ($CDCl_3$) δ 3.38 (s, 3 H, NCH_3), 4.48 (s, 2 H, CH_2), 7.20–8.20 (m, 8 H, aromatic).

Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44; Cl, 10.40. Found: C, 60.04; H, 4.13; N, 16.22; Cl, 10.12.

10-Chloro-6,7-dihydro-7-methyl-6-oxo-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3-carboxamide (22). A mixture of 10.0 g (0.04 mol) of **2** and 4.12 g (0.04 mol) of oxamic hydrazide (Aldrich) was refluxed for 50 min in 300 mL of DMF. The resulting purple solution was concentrated to ca. 50 mL and allowed to stand overnight at 25 °C. The resulting precipitate was filtered off and recrystallized from DMF to give 2.7 g of **22:** mp 303–304 °C; IR (KBr) ν 3455, 3405 (NH_2), 1670 (both C=O's) cm^{-1}; NMR (Me_2SO-d_6) δ 3.30 (s, 3 H, NCH_3), 5.31 (s, 2 H, CH_2), 7.5–8.5 (m, 5 H, NH_2 and aromatic); UV (MeOH) λ_{max} (ϵ) 236 (35 500), 300 (2510) nm; mass spectrum, *m/e* (% total ionization) 291 (15.9, M^+), 247 (0.5), 234 (18.1, base).

Anal. Calcd for $C_{12}H_{10}ClN_5O_2$: C, 49.41; H, 3.46; N, 24.00; Cl, 12.15. Found: C, 49.14; H, 3.43; N, 24.00; Cl, 11.91.

An additional 5.0 g of less pure product was obtained by diluting the various filtrates with water (total yield 65%).

10-Chloro-6,7-dihydro-7-methyl-6-oxo-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepine-3-carboxylic Acid Ethyl Ester (24) and 11-Chloro-2,8-dihydro-8-methyl-1,2,5-triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (21). A mixture of 10 g (0.04 mol) of **2** and 5.8 g (0.044 mol) of *tert*-butyl carbazate (Aldrich) was refluxed for 5 h in 300 mL of benzene. The volatiles were removed under vacuum, and a mixture of 5 g (0.055 mol) of oxalic acid and 30 mL of diethyl oxalate was added. The resulting solution was heated on a steam bath for 3 h, cooled to 25 °C, and poured into 400 mL of ether, immediately precipitating a gum. The supernatant was decanted, and the ether and excess diethyl oxalate were removed under vacuum. The residue was poured into water, and the slow-forming precipitate was filtered off after an hour to give, after recrystallization from absolute ethanol, 2.5 g (20%) of **24:** mp 201–202 °C; IR (KBr) ν 1740 (ester C=O), 1690 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.48 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.35 (s, 3 H, NCH_3), 4.54 (q, J = 7 Hz, 2 H, CH_2CH_3), 5.20 (broad s, 2 H, ring CH_2), 7.38 (d, J = 9 Hz, 1 H, 8-H), 7.60 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.06 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 237 (36 300), 303 (2830) nm.

Anal. Calcd for $C_{14}H_{13}ClN_4O_3$: C, 52.43; H, 4.08; N, 17.47; Cl, 11.05. Found: C, 52.20; H, 3.99; N, 17.57; Cl, 11.03.

Triturating the gum (obtained above) with ethanol gave 2.5 g (21%) of **21,** which was identical with the material obtained from reaction of **2** with 4-morpholineglyoxylic acid hydrazide.

11-Chloro-2,8-dihydro-8-methyl-1,2,5-triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (21) and 10-Chloro-7-methyl-3-(morpholinocarbonyl)-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (26). A mixture of 20 g (0.08 mol) of **2** and 15 g (0.088 mol) of 4-morpholineglyoxylic acid hydrazide[27] (**25**) was heated at 100 °C for 30 min in 300 mL of DMF. The solvent was removed under vacuum and the residue triturated with 400 mL of absolute ethanol. After stirring overnight, the precipitate was filtered off, washed as a slurry with water, and then digested in refluxing absolute ethanol for 2 h. The mixture was filtered hot (saving the filtrate), and the filter cake was dried at 120 °C (1 torr) to yield 19 g (84%) of **21:** mp indistinct (contraction, partial melting, and decomposition) 342–365 °C (complete melting at 365 °C); IR (KBr) ν 3240 (NH), 1690 (broad,

C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.25 (s, 3 H, NCH_3), 4.15 (d, J = 14 Hz, 1 H, CH_2), 5.03 (d, J = 14 Hz, 1 H, CH_2), 7.65 (m, 3 H, aromatic), 12.65 (s, 1 H, NH); UV (MeOH) λ_{max} (ε) 254 (15 300), 272 (13 000), 310 (9590) nm; mass spectrum, *m/e* (% total ionization) 292 (22.1, M^+, base), 249 (2), 235 (4), 221 (2), 220 (2).

Anal. Calcd for $C_{12}H_9ClN_4O_3$: C, 49.25; H, 3.11; N, 19.14; Cl, 12.11. Found: C, 49.14; H, 3.41; N, 19.41; Cl, 11.90.

The ethanol from the filtrate (above) was removed under vacuum, the residue leached with hot $CHCl_3$, and the mixture filtered. The $CHCl_3$ was removed from the filtrate under vacuum, and the residue recrystallized from absolute ethanol to yield 1.4 g (7%) of **26:** mp 200–200.5 °C; IR (KBr) ν 1670 (lactam C=O), 1628 (amide C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.42 (s, 3 H, NCH_3), 3.85 and 4.33 (multiplets, 6 H and 2 H, morpholine CH_2), 5.13 (broad s, 2 H, azepine CH_2), 7.42 (d, J = 9 Hz, 1 H, 8-H), 7.66 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.12 (d, J = 2.5 Hz, 1 H, 11-H); UV (MeOH) λ_{max} (ε) 235 (36 500), 298 (2740) nm; mass spectrum, *m/e* (% total ionization) 361 (1, M^+), 275 (2), 247 (2), 86 (23.7, base).

Anal. Calcd for $C_{16}H_{16}ClN_5O_3$: C, 53.11; H, 4.46; N, 19.36; Cl, 9.79. Found: C, 53.04; H, 4.72; N, 19.48; Cl, 9.71.

11-Chloro-2-[2-(dimethylamino)ethyl]-2,8-dihydro-8-methyl[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28c) and Its Hydrochloride and Hydrobromide (1:1) Salts. A solution of 5.0 g (0.017 mol) of **21** in 50 mL of DMF was treated with 4.25 g (0.017 mol) of thallous ethoxide (Aldrich) at room temperature. After 2 h, 150 mL of ether was added and the precipitate was filtered off and dried at room temperature (1 torr). The resulting salt (8 g, 0.016 mol) was suspended in 200 mL of toluene and treated with a toluene solution of (dimethylamino)ethyl chloride [prepared by treating 4 g (0.027 mol) of the hydrochloride (Michigan Chemical) with excess 10% NaOH and immediately extracting with 150 mL of toluene]. The reaction mixture was refluxed for 2 h, after which another equal amount of the chloride was added and refluxing continued overnight. The insoluble material was filtered off, and the filtrate was evaporated to a solid (4.3 g). This was dissolved in chloroform and applied to a 125 g neutral alumina (Woelm, activity grade I) column. Elution with 200 mL of chloroform–ethyl acetate–ethanol (5:4:1) and removal of the solvents under vacuum gave 3.7 g of slightly impure solid. This was recrystallized twice from methanol to give 2.3 g (27%) of **28c:** mp 227–229 °C; IR (KBr) ν 1705 (triazine C=O's), 1670 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.33 (s, 6 H, $N(CH_3)_2$), 2.73 (t, J = 7 Hz, 2 H, $CH_2N(CH_3)_2$), 3.34 (s, 3 H, NCH_3), 3.90 (d, J = 14 Hz, 1 H, ring CH_2), 4.11 (t, J = 7 Hz, 2 H, $CH_2CH_2N(CH_3)_2$), 5.40 (d, J = 14 Hz, 1 H, ring CH_2), 7.25 (d, J = 9 Hz, 1 H, 9-H), 7.50 (q, J = 9, 2.5 Hz, 1 H, 10-H), 7.71 (d, J = 2.5 Hz, 1 H, 12-H); UV (MeOH) λ_{max} (ε) 256 (15 800), 277 (13 400), 307 (10 300) nm; mass spectrum, *m/e* (% total ionization) 363 (1, M^+), 319 (0.5), 58 (31.7, base).

Anal. Calcd for $C_{16}H_{18}ClN_5O_3$: C, 52.82; H, 4.98; N, 19.25; Cl, 9.75. Found: C, 52.81; H, 5.20; N, 19.26; Cl, 9.78.

Hydrochloride Salt. To a suspension of 1.7 g (0.0047 mol) of the free base in 20 mL of water was added 0.8 mL of concentrated hydrochloric acid. Complete solution resulted followed by a rapid formation of crystals, which were filtered off and recrystallized from hot water to yield 1.6 g of the salt, mp 296–299 °C dec.

Anal. Calcd for $C_{16}H_{19}Cl_2N_5O_3$: C, 48.01; H, 4.79; N, 17.50; Cl, 17.72. Found: C, 47.87; H, 4.65; N, 17.30; Cl, 17.86.

Hydrobromide Salt for Single-Crystal X-ray Analysis. The free base (ca. 0.1 g) was dissolved in hot absolute ethanol and treated with excess HBr (48% in HOAc). The resulting precipitate was filtered off, washed with ethanol, and dissolved in hot acetonitrile. Slow cooling and standing overnight gave needles that contained 1 mol of solvent, mp 297–298 °C. The crystals stored at room temperature were stable; those stored at 5 °C deteriorated to a powder, losing the acetonitrile.

Anal. Calcd for $C_{18}H_{22}N_6BrClO_3$: C, 44.51; H, 4.56; N, 17.30; Br, 16.45; Cl, 7.30. Found: C, 44.64; H, 4.74; N, 17.53; Br, 16.45; Cl, 7.27.

11-Chloro-2,8-dihydro-2,8-dimethyl[1,2,4]triazino[4,3-*d*]-[1,4]benzodiazepine-3,4,7(6*H*)-trione (28a). The thallous salt obtained from 3.54 g (0.012 mol) of **21** (as in the procedure for **28c**) was refluxed in 50 mL of methyl iodide for 6 h. The excess methyl iodide was removed in an air stream, and the residue was extracted in a Soxhlet with chloroform. The resulting solution (ca. 400 mL) was washed thru a column of 60 g of Florisil with 2 L of chloroform. The solvent was removed under vacuum to yield 1.0 g (27%) of **28a:** mp 350–353 °C; IR (KBr) ν 1710 (triazine C=O's), 1670 (azepine C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.25 (s, 3 H, triazine NCH_3), 3.48 (s, 3 H, azepine NCH_3), 4.15 (d, J = 14 Hz, 1 H, ring CH_2), 4.95 (d, J = 14 Hz, 1 H, ring CH_2), 7.45–7.80 (m, 3 H, aromatic); UV (MeOH) λ_{max} (ε) 255 (15 000), 278 (12 600), 308 sh (9840) nm.

Anal. Calcd for $C_{13}H_{11}ClN_4O_3$: C, 50.90; H, 3.61; N, 18.27; Cl, 11.56. Found: C, 50.76; H, 3.85; N, 18.07; Cl, 11.28.

Further elution of the column with ethanol gave an additional 1.5 g (total yield 68%) of **28a,** although less pure.

11-Chloro-2,8-dihydro-8-methyl-2-(phenylmethyl)[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28b). Using the procedure of **28c,** 2.93 g (0.01 mol) of **21** was reacted with a total of 3 equiv of benzyl bromide to yield 2.2 g (75%) of **28b:** mp 241–243 °C; IR (KBr) ν 1710 (triazine C=O's), 1676 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 3 H, NCH_3), 3.90 (d, J = 14 Hz, 1 H, ring CH_2), 5.14 (s, 2 H, CH_2Ph), 5.40 (d, J = 14 Hz, 1 H, ring CH_2), 7.20–7.75 (m, 8 H, aromatic); UV (MeOH) λ_{max} (ε) 257 (15 600), 279 (13 300), 300 sh (10 000) nm.

Anal. Calcd for $C_{19}H_{15}ClN_4O_3$: C, 59.61; H, 3.95; N, 14.64; Cl, 9.26. Found: C, 59.62; H, 3.86; N, 14.90; Cl, 9.21.

11-Chloro-2-[3-(dimethylamino)propyl]-2,8-dihydro-8-methyl[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28d) and Its Hydrochloride (1:1) Salt. Using the procedure of **28c,** 5.0 g (0.017 mol) of **21** was reacted with a total of 3 equiv of (dimethylamino)propyl chloride (Michigan Chemical) to give 4.8 g (75%) of the free base, which was in turn dissolved in hot absolute ethanol and treated with 1.1 equiv of ethanolic HCl. The solution was cooled, and the resulting precipitate was filtered off and dried at 100 °C (1 torr) to yield 4.6 g of the salt of **28d:** mp 233–238 °C; IR (KBr) ν 1702 (triazine C=O's), 1667 (azepine C=O) cm^{-1}; UV (MeOH) λ_{max} (ε) 257 (14 500), 278 (12 300), 310 sh (9230) nm.

Anal. Calcd for $C_{17}H_{21}Cl_2N_5O_3$: C, 49.28; H, 5.11; N, 16.91; Cl, 17.12. Found: C, 49.13; H, 5.10; N, 16.85; Cl, 16.87.

A sample of the free base, **28d,** prepared by neutralizing the salt had the following NMR data: ($CDCl_3$) δ 1.75–2.95 (m, 4 H, $CH_2CH_2N(CH_3)_2$), 2.26 (s, 6 H, $N(CH_3)_2$), 3.45 (s, 3 H, NCH_3), 4.0 (d, J = 14 Hz, 1 H, ring CH_2), 4.13 (t, J = 7 Hz, 2 H, $CH_2CH_2CH_2N(CH_3)_2$), 5.46 (d, J = 14 Hz, 1 H, ring CH_2), 7.36 (d, J = 9 Hz, 1 H, 9-H), 7.56 (q, J = 9, 2.5 Hz, 1 H, 10-H), 7.77 (m, 1 H, 12-H).

11-Chloro-2-[2-(diethylamino)ethyl]-2,8-dihydro-8-methyl[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28e) and Its Hydrochloride (1:1) Salt. Using the procedure of **28c,** 10 g (0.034 mol) of **21** was reacted with a total of 3 equiv of (diethylamino)ethyl chloride to give 9.6 g (71%) of **28e:** mp 260–262 °C; IR (KBr) ν 1703 (triazine C=O's), 1665 (azepine C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 6 H, CH_2CH_3), 2.52 (q, J = 7 Hz, 4 H, CH_2CH_3), 2.78 (t, J = 7 Hz, 2 H, $CH_2CH_2NEt_2$), 3.28 (s, 3 H, NCH_3), 3.80 (d, J = 14 Hz, 1 H, ring CH_2), 4.02 (t, J = 7 Hz, 2 H, $CH_2CH_2NEt_2$), 5.39 (d, J = 14 Hz, 1 H, ring CH_2), 7.18 (d, J = 9 Hz, 1 H, 9-H), 7.50 (q, J = 9, 2.5 Hz, 1 H, 10-H), 7.68 (d, J = 2.5 Hz, 1 H, 12-H).

Hydrochloride Salt. The free base (9.6 g) was suspended in water and dissolved by the addition of dilute hydrochloric acid. The resulting solution was extracted with chloroform, and the aqueous phase was evaporated under vacuum to a white solid. It was crystallized from 95% ethanol to yield 10.7 g of the salt: mp 265–266 °C dec; UV (H_2O) λ_{max} (ε) 252 (15 100), 270 (12 600), 303 sh (8970) nm.

Anal. Calcd for $C_{18}H_{23}Cl_2N_5O_3$: C, 50.48; H, 5.42; N, 16.35; Cl, 16.52. Found: C, 50.76; H, 5.53; N, 16.37; Cl, 16.51.

11-Chloro-2,8-dihydro-8-methyl-2-[2-(1-pyrrolidinyl)ethyl]-[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28f) as Its Hydrochloride (1:1) Salt. Using the procedure of **28c** without the chromatography, 10 g (0.034 mol) of **21** was reacted with a total of 3 equiv of *N*-(2-chloroethyl)pyrrolidine (Aldrich) to give 11 g of crude free base. The free base was dissolved in 2 N hydrochloric acid and washed with dichloromethane. The aqueous solution was evaporated under vacuum to give a solid residue. This material was recrystallized from absolute ethanol to yield 8.0 g (85%) of the salt of **28f:** mp 300–303 °C; IR (KBr) ν 1715 (triazine C=O's), 1675 (azepine C=O) cm^{-1}; NMR (D_2O) δ 2.10 (m, 4 H, pyrrolidine β-H), 3.38 (s, 3 H, NCH_3), 3.50 (m, 4 H, pyrrolidine α-H), 3.72 (t, J = 6 Hz, 2 H, CH_2CH_2-pyrrolidine), 4.30 (d, J = 14 Hz, 1 H, azepine CH_2), 4.48 (t, J = 6 Hz, 2 H, CH_2CH_2-pyrrolidine), 5.20 (d, J = 14 Hz, 1 H, azepine CH_2), 7.55 (d, J = 9 Hz, 1 H, 9-H), 7.76 (q, J = 9, 2.5 Hz, 1 H, 10-H), 7.94 (m, 1 H, 12-H); UV (H_2O) λ_{max} (ε) 253 (15 000), 273 (12 400), 305 (9040) nm.

Anal. Calcd for $C_{18}H_{21}Cl_2N_5O_3$: C, 50.72; H, 4.97; N, 16.43; Cl, 16.63. Found: C, 50.86; H, 5.27; N, 16.57; Cl, 16.52.

11-Chloro-2,8-dihydro-8-methyl-2-[2-(1-morpholinyl)ethyl]-[1,2,4]triazino[4,3-*d*][1,4]benzodiazepine-3,4,7(6*H*)-trione (28g) as Its Hydrochloride (1:1) Salt. Following the procedure of **28c,** 10 g (0.034 mol) of **21** was reacted with a total of 3 equiv of *N*-(2-chloroethyl)morpholine (Aldrich) to yield 11 g (80%) of the free base. The 11 g of free base was dissolved in 3 N hydrochloric acid and washed with dichloromethane. The aqueous solution was evaporated to a solid under vacuum and recrystallized two times from 95% ethanol to yield

7.5 g of the salt of **28g**: mp 287–290 °C; IR (KBr) ν 1710 (triazine C=O's), 1675 (azepine C=O) cm^{-1}; NMR (D_2O) δ 3.38 (s, 3 H, NCH_3), 3.38–4.60 (m, 13 H), 5.20 (d, J = 14 Hz, 1 H, azepine CH_2), 7.55 (d, J = 9 Hz, 1 H, 9-H), 7.76 (q, J = 9, 2.5 Hz, 1 H, 10-H), 7.90 (m, 1 H, 12-H).

Anal. Calcd for $C_{18}H_{21}Cl_2N_5O_4$: C, 48.88; H, 4.79; N, 15.83; Cl, 16.02. Found: C, 48.64; H, 5.05; N, 15.68; Cl, 16.13.

3-[5-Chloro-2-(methylamino)phenyl]-4-[(1-pyrrolidinylcarbonyl)methyl]-5-(1-pyrrolidinylmethyl)-1,2,4-triazole (29) and Its Hydrochloride (1:1) Salt. A mixture of 5.0 g (0.0168 mol) of **15** in 40 mL of pyrrolidine was refluxed for an hour and allowed to stand overnight at 25 °C. The resulting precipitate was filtered off and recrystallized from absolute ethanol to yield 3.1 g of **29**. The volatiles were removed from the filtrate under vacuum, and the residue was partitioned between 3 N aqueous sodium hydroxide and benzene. The aqueous layer was washed (3×) with benzene, and the combined organic layers were dried (Na_2SO_4). Removal of the solvent under vacuum gave an additional 3.2 g (total 94%) of **29**. Both crops of **29** were combined and recrystallized from absolute ethanol: mp 160–161 °C; IR (KBr) ν 3305 (NH), 1648 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.8 (m, 8 H, pyrrolidine β-H), 2.50 (m, 4 H, basic pyrrolidine α-H), 2.76 (d, J = 5 Hz; 3 H, NCH_3), 3.44 (m, 4 H, amide pyrrolidine α-H), 3.87 (s, 2 H, 5-CH_2N), 4.80 (s, 2 H, 4-CH_2C=O), 5.75 (q, J = 5 Hz, 1 H, N**H**CH_3), 6.62 (d, J = 9 Hz, 1 H, phenyl 3-H), 7.2 (m, 2 H, phenyl 4- and 6-H); mass spectrum, m/e (% total ionization) 402 (0.3 M^+), 333 (1), 290 (0.6), 235 (0.6), 222 (6.5, base).

Hydrochloride Salt. The free base (3 g) in methanol–ethanol (1:1) was neutralized with 1 equiv of ethereal HCl. The addition of more ether produced a precipitate which was filtered off to yield 2.8 g (86%) of the salt: mp 247–248 °C; UV (MeOH) λ_{max} (ϵ) 259 (12 600), 330 (3820) nm.

Anal. Calcd for $C_{20}H_{28}Cl_2N_6O$: C, 54.68; H, 6.43; N, 19.13; Cl, 16.14. Found: C, 54.44; H, 6.33; N, 18.89; Cl, 15.87.

3-[5-Chloro-2-(methylamino)phenyl]-4-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2,4-triazole (30a). A solution of 0.1 g of **8a** in 3 mL of pyrrolidine was heated in an oil bath at 80 °C for 5 days. The solution was evaporated to dryness under vacuum (1 torr), and the residue was taken up in chloroform. The chloroform solution was then extracted with 10% HCl. The HCl solution was made basic with 10% NaOH and extracted with chloroform. The solution was dried (Na_2SO_4), evaporated to dryness, and taken up in deuteriochloroform. The NMR data were as expected: δ 1.86 (m, 4 H, pyrrolidine β-H), 2.82 (d, J = 5 Hz, 3 H, CH_3), 3.46 (m, 4 H, pyrrolidine α-H), 4.73 (s, 2 H, CH_2), 5.77 (q, J = 5 Hz, 1 H, NH), 6.72 (d, J = 9 Hz, 1 H, 3-H), 7.12 (d, J = 2.5 Hz, 1 H, 6-H), 7.33 (q, J = 9, 2.5 Hz, 1 H, 4-H), 8.43 (s, 1 H, triazole H). The compound was not characterized further.

3-[5-Chloro-2-(methylamino)phenyl]-4-[2-oxo-2-(1-pyrrolidinyl)ethyl]-5-(trifluoromethyl)-1,2,4-triazole (30b) and Its Hydrochloride (1:1) Salt. A solution of 4.8 g (0.0152 mol) of **14** in 40 mL of pyrrolidine was refluxed for 1 h. The volatiles were removed under vacuum, and the residue was partitioned between benzene and 3 N aqueous sodium hydroxide. The aqueous solution was extracted (3×) with benzene, and the benzene layers were combined. The solution was dried (Na_2SO_4), and the volatiles were removed under vacuum to yield 5.64 g of an orange-red gum. The gum was taken up in ether and treated with 1 equiv of ethereal HCl. The resulting precipitate was filtered off, dissolved in absolute ethanol, and reprecipitated by the addition of ether. The precipitate was filtered off and dried at 80 °C (1 torr) to yield 4.4 g (72%) of **30b**: mp 161–162.5 °C; IR (KBr) ν 1658 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.98 (m, 4 H, pyrrolidine β-H), 3.14 (s, 3 H, NCH_3), 3.48 (m, 4 H, pyrrolidine α-H), 4.72 (s, 2 H, CH_2CON), 7.72 (m, 3 H aromatic), 9.09 (broad s, 2 H, $H_2^+NCH_3$); UV (MeOH) λ_{max} (ϵ) 257 (12 000), 333 (3500) nm.

Anal. Calcd for $C_{16}H_{18}Cl_2F_3N_5O$: C, 45.30; H, 4.28; N, 16.51; Cl, 16.71; F, 13.43. Found: C, 45.45; H, 4.42; N, 16.77; Cl, 16.97; F, 13.20.

A sample of the free base **30b**, isolated by neutralization of the salt, had the following NMR data: ($CDCl_3$) δ 1.98 (m, 4 H, pyrrolidine β-H), 2.75 (d, J = 5 Hz, 3 H, NHC**H**$_3$), 3.40 (m, 4 H, pyrrolidine α-H), 4.75 (s, 2 H, azepine CH_2), 5.40 (q, J = 5 Hz, 1 H, N**H**CH_3), 6.70 (d, J = 9 Hz, 1 H, 3-H), 7.3 (m, 2 H, 4-H and 5-H); mass spectrum, m/e (% total ionization) 387 (3.5, M^+), 113 (6), 84 (15.9, base).

3-[5-Chloro-2-(methylamino)phenyl]-4-[2-oxo-2-(1-morpholinyl)ethyl]-1,2,4-triazole (31a). A solution of 50 mg of **8a** in 2 mL of morpholine was refluxed for 4 days. Even though the starting material was not completely consumed, the reaction mixture was evaporated to dryness, taken up in chloroform, and extracted with 10% HCl. The acid solution was made basic with 10% NaOH and extracted with chloroform. The chloroform solution was concentrated and applied to a silica gel preparative TLC plate (Quantum PQF 1000) which was developed with chloroform–ethyl acetate–ethanol (5:4:1). The large blue fluorescent band (R_f 0.2) was collected and recrystallized from ethanol to yield 20 mg of **31a**: mp 151–152 °C; IR ($CDCl_3$) ν 3400 (NH), 1675 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.79 (d, J = 5 Hz, 3 H, CH_3), 3.53 (m, 8 H, morpholine H), 4.86 (s, 2 H, CH_2), 5.80 (q, J = 5 Hz, 1 H, NH), 6.68 (d, J = 9 Hz, 1 H, 3-H), 7.05 (d, J = 2.5 Hz, 1 H, 6-H), 7.30 (q, J = 9, 2.5 Hz, 1 H, 4-H), 8.35 (s, triazole H). The compound was not characterized further.

3-[5-Chloro-2-(methylamino)phenyl]-4-[2-oxo-2-(1-morpholinyl)ethyl]-5-(trifluoromethyl)-1,2,4-triazole (31b). A solution of 0.1 g of **14** in 2 mL of morpholine was allowed to stand in an oil bath at 100 °C for 10 days. Even though all of the starting material was not consumed, the mixture was evaporated to dryness, taken up in chloroform, and extracted with 10% HCl. The acid solution was made basic and extracted with chloroform. The chloroform solution was dried (Na_2SO_4), concentrated, applied to a silica gel preparative TLC plate (Quantum PQF 1000), and developed with chloroform–ethyl acetate–ethanol (5:4:1). The large blue fluorescent band (R_f 0.2) was collected. The NMR ($CDCl_3$) data clearly showed the characteristics of a ring-opened compound: δ 2.60 (d, J = 5 Hz, 3 H, N–CH_3), 3.60 (m, 8 H, morpholine H), 4.80 (s, 2 H, CH_2), 5.50 (unresolved q, 1 H, NH), 6.70 (d, J = 9 Hz, 1 H, 3-H), 7.10 (d, J = 2.5 Hz, 1 H, 6-H), 7.35 (q, J = 9, 2.5 Hz, 1 H, 4-H). The compound was not characterized further.

10-Chloro-7-methyl-3-(1-pyrrolidinylmethyl)-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (32a) as Its Hydrochloride (1:1) Salt. To a stirring suspension of 5.0 g (0.017 mol) of **15** in 150 mL of DME at 25 °C was added 3.6 g (0.051 mol) of pyrrolidine, and the resulting mixture was then refluxed for 3 h. The volatiles were removed under vacuum, and the residue was partitioned between 3 N aqueous sodium hydroxide and benzene. The aqueous layer was extracted (3×) with benzene, and the combined organic layers were dried (Na_2SO_4). The benzene was removed under vacuum to yield 4.4 g of a gum. The gum was taken up in a small amount of benzene and chromatographed on a 4 × 8 cm column of neutral alumina (Woelm, activity grade I). The first 700 mL of benzene eluate contained only byproducts (TLC) and was discarded. Elution with 600 mL of chloroform–ethyl acetate (3:2) then gave, after removal of solvent, 3.4 g of **32a** as an oil. The oil was taken up in a small amount of methanol and neutralized with 1 equiv of ethereal HCl, and the salt was precipitated by the addition of ether. The precipitate was filtered off and dried at 50 °C (25 torr) to yield 3.6 g (58%) of the HCl salt: mp 238–240 °C (rapid heating); IR (KBr) ν 1675 cm^{-1} (C=O); NMR (D_2O) δ 2.25 (m, 4 H, pyrrolidine β-H), 3.40 (s, 3 H, NCH_3), 3.68 (m, 4 H, pyrrolidine α-H), 4.97 (overlapping singlets, 4 H, ring CH_2 and 3-CH_2), 7.72 (m, 2 H, 8- and 9-H), 7.90 (m, 1 H, 11-H); UV (MeOH) λ_{max} (ϵ) 233 (36 300), 253 sh (13 000), 299 (2060) nm; mass spectrum, m/e (% total ionization) 331 (0.1, M^+), 262 (28, base).

Anal. Calcd for $C_{16}H_{19}Cl_2N_5O$: C, 52.18; H, 5.20; N, 19.02; Cl, 19.26. Found: C, 52.42; H, 5.06; N, 18.95; Cl, 19.46.

10-Chloro-7-methyl-3-[(4-methyl-1-piperazinyl)methyl]-5*H*-1,2,4-triazolo[4,3-*d*][1,4]benzodiazepin-6(7*H*)-one (32b) and Its Hydrochloride (1:2) Salt. Following the procedure of **32a**, 5 g (0.017 mol of **15** and 5.4 g (0.051 mol) of *N*-methylpiperazine (Aldrich) were reacted to yield 4.0 g (66%) of **32b** as the free base: mp 228.5–230.5 °C; NMR ($CDCl_3$) δ 2.30 (s, 3 H, piperazine NCH_3), 2.53 (m, 8 H, piperazine CH_2), 3.40 (s, 3 H, lactam NCH_3), 4.87 (s, 2 H, azepine CH_2), 7.40 (d, J = 9 Hz, 1 H, 8-H), 7.57 (q, J = 9, 2.5 Hz, 1 H, 9-H), 8.05 (d, J = 2.5 Hz, 1 H, 11-H); mass spectrum, m/e (% total ionization) 360 (2, M^+), 304 (1), 303 (2), 290 (3), 262 (3), 261 (2.5), 83 (8.2, base).

Hydrochloride Salt. A sample of the free base in methanol was neutralized with 2 equiv of ethereal HCl, and the salt was precipitated by the addition of ether. After recrystallization from absolute ethanol, the salt was ground in a mortar and allowed to stand open to the atmosphere for several days to yield the dihydrochloride salt as a sesquihydrate: mp 235–237 °C; IR (KBr) ν 1670 cm^{-1} (C=O); UV (MeOH) λ_{max} (ϵ) 253 (37 500), 255 sh (12 700), 300 (2100) nm.

Anal. Calcd for $C_{17}H_{26}Cl_3N_6O_{2.5}$: C, 44.31; H, 5.69; N, 18.24; Cl, 23.08. Found: C, 44.34; H, 5.65; N, 18.39; Cl, 23.21.

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Registry No.—**1,** 5973-28-4; **2,** 56967-27-2; **3,** 68013-40-1; **4,** 59742-85-7; **6,** 68013-41-2; **8d,** 60726-50-3; **19,** 61119-30-0; **20a,** 61119-25-3; **20b,** 56967-24-9; **20c** hydrochloride, 56967-21-6; **20e,** 61119-26-4; **22,** 60726-51-4; **25,** 19356-08-2; **28a,** 57632-91-4; **28b,**

57632-90-3; **28c** hydrochloride, 56969-35-8; **28d,** 68013-42-3; **28d** hydrochloride, 56969-36-9; **28e,** 68013-43-4; **28e** hydrochloride, 56969-37-0; **28f,** 68013-44-5; **28f** hydrochloride, 56969-38-1; **28g,** 68013-45-6; **28g** hydrochloride, 56969-39-2; **29,** 63354-18-7; **29** hydrochloride, 60929-11-5; **30a,** 68024-69-1; **30b,** 68013-46-7; **30b** hydrochloride, 60929-09-1; **31a,** 68013-47-8; **31b,** 60929-10-4; **32a,** 68013-48-9; **32a** hydrochloride, 60726-56-9; **32b,** 60726-57-0; **32b** dihydrochloride, 68013-49-0; *tert*-butyl carbazate, 870-46-2; trifluoroacetic anhydride, 407-25-0; chloroacetic anhydride, 541-88-8; ethyl carbazate, 4114-31-2; thallous ethoxide, 20398-06-5; (dimethylamino)ethyl chloride, 107-99-3; 3-chloropropanol, 627-30-5; (dimethylamino)propyl chloride, 109-54-6; bromobenzene, 108-86-1; oxamic hydrazide, 515-96-8; diethyloxalate, 95-92-1; benzyl bromide, 28807-97-8; (diethylamino)ethyl chloride, 100-35-6; *N*-(2-chloroethyl)pyrrolidine, 5050-41-9; *N*-(2-chloroethyl)morpholine, 3240-94-6; pyrrolidine, 123-75-1; morpholine, 110-91-8; *N*-methylpiperazine, 109-01-3.

Supplementary Material Available: X-ray data for the methiodide of **20c** (both molecules) and the hydrobromide salt of **28c** (Figure 4) consisting of fractional atomic coordinates, temperature factors, bond distances, and bond angles (11 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Preliminary results have appeared as (a) B. R. Vogt, P. C. Wade, and M. S. Puar, *Tetrahedron Lett.*, 1931 (1976), and (b) P. C. Wade, B. R. Vogt, and M. S. Puar, *ibid.*, 1699 (1977).

(2) (a) S. Garattini, E. Mussini, and L. O. Randel, Eds., "The Benzodiazepines", Raven Press, New York, 1973; (b) D. J. Greenblatt, "Benzodiazepines in Clinical Practice", Raven Press, New York, 1974, and references therein; (c) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning in "Psychopharmacological Agents", Vol. 3, M. Gordon, Ed., Academic Press, New York, 1974, Chapter 6.

(3) (a) K. Kamiya, Y. Wada, and M. Nishikawa, *Chem. Pharm. Bull.*, **21,** 1520 (1973); (b) M. Raban, E. H. Carlson, J. Szmuszkovicz, G. Slomp, C. G. Chidester, and D. J. Duchamp, *Tetrahedron Lett.*, 139 (1975).

(4) (a) R. V. Stevens, R. M. Cory, and S. Rosen, *J. Chem. Soc., Chem. Commun.*, 742 (1975); (b) D. L. Coffen, R. I. Fryer, D. A. Katonak, and F. Wong, *J. Org. Chem.*, **40,** 894 (1975), and references cited therein.

(5) (a) R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui, and Y. Nagawa, *Jpn. J. Pharmacol.*, **21,** 497 (1971); (b) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971); (c) B. Matta, A. E. Franco, L. A. LeZotte, A. D. Rudzik, and W. Veldkamp, *Curr. Ther. Res. Clin. Exp.*, **16,** 958 (1974); (d) J. Schwartz, M. Kramer, and T. Roth, *ibid.*, **16,** 964 (1974); (e) L. F. Fabre, Jr., and R. T. Harris, *ibid.*, **16,** 1010 (1974).

(6) (a) N. P. Peet and S. Sunder, *J. Heterocycl. Chem.*, **14,** 561 (1977); (b) A. Walser, W. J. Zally, and R. I. Fryer, *J. Heterocycl. Chem.*, **11,** 863 (1974).

(7) K. M. Doyle and F. Kurzer, *Tetrahedron*, **32,** 2347 (1976), and references therein.

(8) J. P. Maffrand, D. Frehel, F. Eloy, D. Aubert, and J. C. Ferrand, *Eur. J. Med. Chem. Chim. Ther.*, **10,** 528 (1975).

(9) R. G. Griot, U.S. Patent 3 414 563; *Chem. Abstr.*, **70,** 47512d (1969).

(10) H. Reimlinger, J. J. M. Vandewalle, and W. R. F. Lingier, *Chem. Ber.*, **103,** 1960 (1970).

(11) According to ref 6, the acid alone may have been sufficient to effect ring closure.

(12) (a) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 2, Wiley-Interscience, New York, 1969, p 410; (b) E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3,** 338 (1970).

(13) K. Weber, A. Bauer, and K. Hauptmann, *Justus Liebigs Ann. Chem.*, **756,** 128 (1972).

(14) H. Zimmer, J. M. Kokosa, and K. J. Shah, *J. Org. Chem.*, **40,** 2901 (1975).

(15) P. A. S. Smith, "Open-Chain Nitrogen Compounds", Vol. 1, W. A. Benjamin, New York, 1965, p 315.

(16) M. S. Puar, H. L. Yale, and A. I. Cohen, *Org. Magn. Reson.*, **6,** 106 (1974).

(17) C. R. Ellefson, L. Sweton, R. H. Bible, Jr., and P. M. Green, *Tetrahedron*, **32,** 1081 (1976).

(18) W. Sadee, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **302,** 769 (1969).

(19) M. Sarrazin, M. Bourdeaux-Pontier, C. Briand, and E. J. Vincent, *Org. Magn. Reson.*, **7,** 89 (1975).

(20) G. Bandoli and D. A. Clemente, *J. Chem. Soc., Perkin Trans. 2,* 413 (1976).

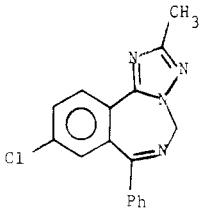
(21) H. Breuer, *Tetrahedron Lett.*, 1935 (1976).

(22) The synthesis of **35** has recently been disclosed through independent studies: R. B. Moffett, B. V. Kamdar, and P. F. Von Voigtlander, *J. Med. Chem.*, **19,** 192 (1976).

(23) M. Oki, *Angew. Chem., Int. Ed. Engl.*, **15,** 87 (1976).

(24) The $\Delta F^{\ddagger}$ for the isomeric triazole **34** was even lower (Table IV).

(25) X is triazolo[5,1-*a*][2,4]benzodiazepine. An account of the synthesis and X-ray structure determination appears in a companion paper, this issue.



(26) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, p 190.

(27) Von L. Heinisch, Chr. Küchler, and W. Küchler *Arzneim. Forsch.*, **18,** 1324 (1968).

Reactions of Azoles with Isocyanates at Elevated Temperature

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1*H*-1,2,4-Triazole, 1-methyl-1*H*-1,2,4-triazole, 4-methyl-4*H*-1,2,4-triazole, and benzothiazole react with aryl isocyanates in boiling nitrobenzene to form *N*-aryl heterocyclic *C*-carboxamides. Under the same conditions, pyrazole and benzotriazole yield their 1-carboxanilides, whereas benzoxazole is inert. Treatment of *N*-phenylimidazole-2-carboxamide (**6**), *N*-phenylimidazole-4(5)-carboxamide (**11**), and *N*-phenyl-1*H*-1,2,4-triazole-5-carboxamide (**1a**) with phenyl isocyanate leads to *N,N'*-diphenyl heterocyclic *C,N*-dicarboxamides. The *N*-carboxanilide group of these compounds is particularly reactive, and heat or reaction with nucleophilic reagents causes removal of the corresponding isocyanate unit.

Depending upon the conditions, imidazole reacts with isocyanates at either a nitrogen or a carbon atom of its ring. Thus, in the absence of solvent at 80 °C,[1] in tetrahydrofuran at the boiling point,[2] and in dichloromethane at room temperature[3] the products are N-substituted imidazole-1-carboxamides. In contrast, the reaction leads to N-substituted imidazole-2-carboxamides when run in boiling nitrobenzene or phenyl ether.[3] This temperature-controlled regiospecificity of the reaction is interesting and potentially useful, especially with regard to preparation of carbon-substituted imidazoles since very few acylation reactions are known to occur at ring carbon atoms of imidazole and other similar heterocycles.[4]

In this paper we wish to report on an extension of our earlier investigation[3] to other azole systems. Like imidazole, 1*H*-1,2,4-triazole and pyrazole have been known to react readily with isocyanates, under mild conditions to form N-substituted heterocyclic 1-carboxamides.[1,2] Our present results show that the reaction of 1*H*-1,2,4-triazole with an aryl isocyanate in boiling nitrobenzene leads to the corresponding *N*-aryl-1*H*-1,2,4-triazole-5-carboxamide (**1a–d**)[5] in analogy with the case of imidazole. In contrast, pyrazole still yields *N*-arylpyrazole-1-carboxamides when its reaction is run in boiling ni-

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