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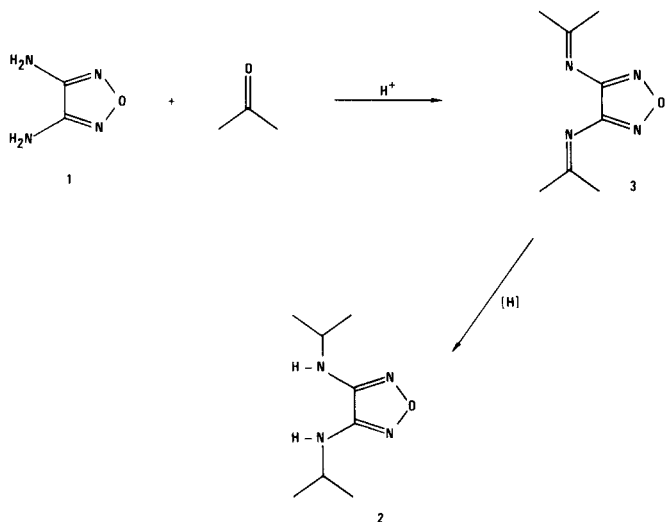
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A series of furazano-substituted 1,5-diazepines have been synthesized from the reaction of a methyl ketone and 3,4-diaminofurazan in the presence of a mild Lewis acid. The reaction was found to be regioselective. Other ketone substrates also yielded diazepines, however, these products were found to be unstable and decomposed upon contact with air.

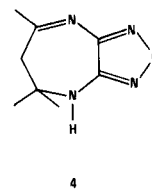
J. Heterocyclic Chem., **23**, 1519 (1986).

Our interest in synthetic routes to heterocycles high in nitrogen content prompted us to explore the utility of 3,4-diaminofurazan (**1**) as a potential precursor to ring systems of interest. During this investigation we found it necessary to adjust the reactivity of the amine nitrogens *via* appropriate substitution. Because of the strongly electron-withdrawing nature of the furazan group [2], the amino nitrogens are unreactive toward most electrophiles. In an attempt to increase the amine nucleophilic character, we chose to synthesize bis(isopropylamino)furazan (**2**) hoping the electron-donating isopropyl moieties would give the desired reactivity. This compound was anticipated to result from the reaction of 3,4-diaminofurazan and acetone in the presence of a mild acid to form the bis(isopropylimino)furazan (**3**), followed by reduction to yield **2**. Upon reacting 3,4-diaminofurazan with acetone in

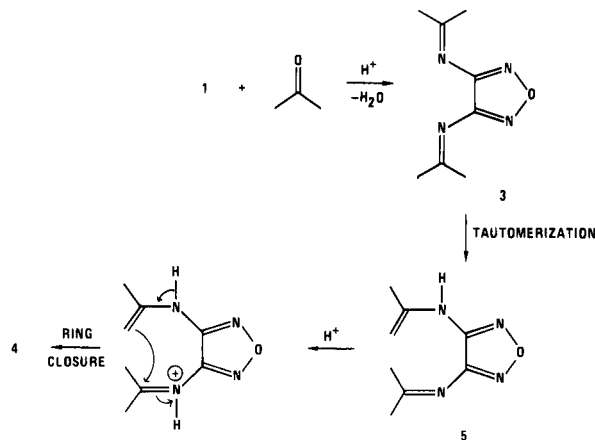


benzene at reflux in the presence of a catalytic amount of *p*-toluenesulphonic acid, a yellow crystalline solid (quantitative yield) was isolated. To our surprise, the product was not the expected bis(isopropylimino)furazan (**3**), but the furazano-substituted 2,4,4-trimethyl-3,4-dihydro-5H-furazano[3,4-*f*][1,5]diazepine (**4**). Similar diazepine formation has been observed for *o*-phenylenediamine [3], *cis*-

trans-*cis*-1,2,3,4-tetraaminocyclobutane [4], and 1,2-diaminoimidazole [5].



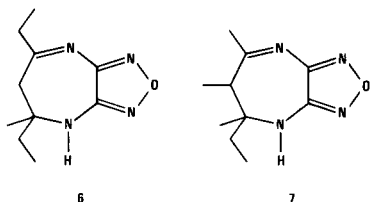
The formation of the diazepine ring most likely proceeds *via* the following mechanism (Scheme I). Reaction of



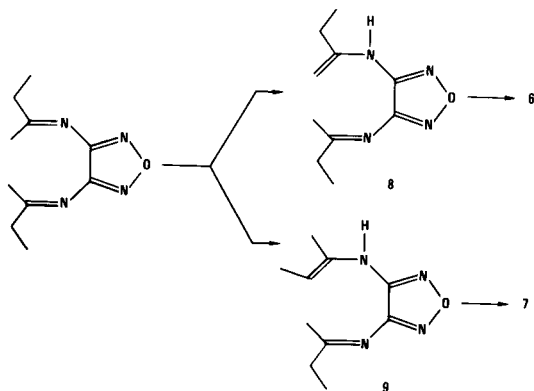
3,4-diaminofurazan with acetone would generate the expected bis(isopropylimino)furazan (**3**) which rapidly tautomerizes to *N*-isopropenybis(isopropylimino)furazan (**5**). Bis-imine formation followed by tautomerization is known to occur with 1,2-aromatic amines as seen by the reaction between *o*-phenylenediamine and acetyl acetone [6]. Subsequent ring closure *via* the enamine tautomer **5** produces diazepine **4**. Attempts to detect reaction intermediates by ¹H nmr revealed only reactants and product. This reaction is evidently extremely fast after formation of the bis-imine.

Reaction of 3,4-diaminofurazan with unsymmetrical ketones showed the process to be regioselective. With methyl ethyl ketone, products 2,4-diethyl-4-methyl-3,4-dihydro-5H-furazano[3,4-*f*][1,5]diazepine (**6**) and 2,3,4-trimethyl-4-

ethyl-3,4-dihydro-5*H*-furazano[3,4-*f*][1,5]diazepine (**7**) are possible. Only **6** was formed. No trace of regioisomer **7** could be detected by ¹H nmr analysis of the reaction product mixture. This result supports the proposed imine-enamine intermediate. Consider the two possible intermediates *N*-(1-ethylmethylene)methylethyliminofurazan (**8**)



and *N*-(1,2-dimethylethylene)methylethyliminofurazan (**9**). It is known that enamines will exclusively yield the less-hindered of two possible products [7]. This is due to the steric requirements of the intermediates where the carbon-carbon double bond π orbitals and the nitrogen lone pair



must achieve coplanarity. This favors imine-enamine **8**. Successful reactions were carried out between 3,4-diaminofurazan and the ketones shown in Table I. These results are all consistent with the proposed mechanism.

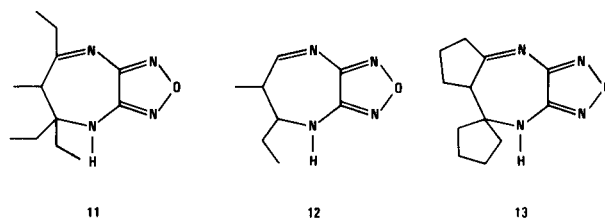
Table I

Yields of Isolated Diazepines

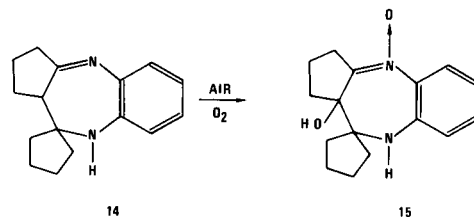
R Group	% Yield (Purified Yield)
methyl 4	100 (80)
ethyl 6	50 (21)
propyl 18	60 (34)
<i>n</i> -butyl 19	65 (40)
phenyl 10	75 (53)
benzyl 20	50 (36)

Since few examples of this ring system are known, we felt it appropriate to unequivocally establish the structure assignment. 2,4-Diphenyl-4-methyl-3,4-dihydro-5*H*-furazano[3,4-*f*][1,5]diazepine (**10**) formed suitable crystals for X-ray analysis. The X-ray-determined molecular structure is shown in Figure 1, and confirms the furazano fused-ring system.

Attempts to extend the reaction to substrates other than methyl carbonyls, *i.e.*, 3-pentanone, cyclopentanone, and propionaldehyde, gave the expected diazepines 2,4,4-triethyl-3-methyl-3,4-dihydro-5*H*-furazano[3,4-*f*][1,5]diazepine (**11**), 3-methyl-4-ethyl-3,4-dihydro-5*H*-furazano[3,4-*f*][1,5]diazepine (**12**), and 2,3-cyclopentane-4-spirocyclopentane-3,4-dihydro-5*H*-furazano[3,4-*f*][1,5]diazepine (**13**), respectively, although in low yields. Evidently, steric requirements play an important role in ring closure.



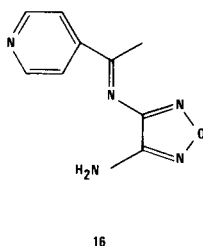
Known 2,3-cyclopentano-4-spirocyclopentano-3,4-dihydro-5*H*-1,5-benzodiazepine (**14**), available from *o*-phenylenediamine and cyclopentanone, is reported to undergo oxidation in air to 1-*N*-oxy-2,3-cyclopentano-3-hydroxy-4-spirocyclopentano-3,4-dihydro-5*H*-1,5-benzodiazepine (**15**) [8]. The allylic methine carbon and imine nitrogen are



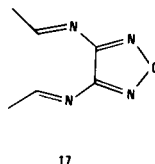
both readily oxidized. No mechanism for this reaction is given. In this example, **15** is a stable compound upon which further transformations can be made. A similar oxidation may be occurring with diazepines **11-13**. Each of these molecules proved to be sensitive to the atmosphere. In each case, a signal appeared in the ¹H nmr and ir spectra which corresponded to a hydroxyl proton. Unfortunately, the proposed oxidation products could not be isolated. The oxidations of **11-13** are fast. The hydroxyl proton could be detected in the nmr spectrum (δ 4.0-5.0) within 30 minutes of isolation of the pure diazepine.

Very electron-deficient carbonyls, *i.e.*, 4-acetylpyridine and *trans*-4-phenyl-3-buten-2-one, failed to react with 3,4-diaminofurazan. This is not surprising given the poor nucleophilic character of the amine nitrogens. Only a

small amount of 3-(methyl-4-pyridoinimino)-4-aminofurazan (**16**) was isolated from the 4-acetylpyridine attempt.



Acetaldehyde and 3,4-diaminofurazan did not yield the desired diazepine but rather the bis(ethylimino)furazan (**17**) which was liable and decomposed rapidly. Apparently, the necessary mono-substituted enamine intermediate required for diazepine formation is thermodynamically unstable.



In summary, 3,4-diaminofurazan was found to react with a number of ketones to form a new series of furazano-fused diazapines. The products were stable unless they possessed a tertiary carbon in an allylic position. These latter compounds rapidly air oxidized and decomposed. Further work is currently underway to investigate the mechanism of the reactions discussed and ways to extend this method to more substituted systems.

EXPERIMENTAL

Melting points were determined with a Buchi 510 Melting Point Apparatus. The nmr spectra were recorded on a Nicolet WB200 or IBM NR80 instrument using TMS as an internal reference in the solvents indicated. Splittings are apparent. Infrared spectra were recorded on a Perkin-Elmer 137 or Nicolet 7199 FT instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

A representative example of this technique is shown for the reaction of 3,4-diaminofurazan and acetone.

Preparation of 2,2,4-Trimethyl-3,4-dihydro-5H-furazano[3,4-f]-1,5-diazepine (**4**).

Acetone (3.2 ml, 44 mmoles), 3,4-diaminofurazan [9] (1 g, 10 mmoles), and *p*-toluenesulphonic acid (10 mg) were mixed in benzene (50 ml) and refluxed for 24 hours. The yellow solution was cooled and the solvent removed under reduced pressure to afford 1.8 g (100%) of **4** as a light-yellow solid. An analytical sample was prepared by flash chromatography on silica gel, eluting with ethyl acetate/hexane followed by recrystallization from ethyl acetate (mp 150-151 °C); ¹H nmr (deuteriochloroform): 200 MHz, δ 5.4 (br s, 1 H), 2.74 (s, 2 H), 2.36 (s, 3 H), 1.34 (s, 6H); ¹³C nmr (deuteriochloroform): δ 177.9, 151.4, 150.9, 52.7, 50.5, 31.5, 29.8; ir (chloroform): 3320, 2850, 1640, 1590, 1350, 990 cm⁻¹.

Anal. Calcd. for C₈H₁₂N₄O: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.30; H, 6.69; N, 30.87.

Diazepines **6**, **10**, and **18-20** were all purified by column chromatography on Florisil eluting with ethyl acetate/hexane followed by recrystallization from ethyl acetate/hexane (except **19** and **20** which remained oils).

2,4-Diethyl-4-methyl-3,4-dihydro-5H-furazano[3,4-f][1,5]diazepine (**6**).

The spectral characteristics of this compound are; ¹H nmr (deuteriochloroform): δ 5.45 (br s, 1 H), 2.69 (s, 2 H), 2.58 (q, J = 7.3 Hz, 2 H), 1.60 (q, J = 7.6 Hz, 2 H), 1.25 (s, 3 H), 1.23 (t, J = 7.3 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H); ¹³C nmr: δ 181.25, 151.48, 150.85, 53.12, 47.87, 37.24, 34.73, 26.83, 10.15, 7.78; ir (chloroform): 3300, 2900, 1675, 1570, 1500, 1400, 1050, cm⁻¹; mp 93-95°.

Anal. Calcd. for C₁₀H₁₆N₄O: C, 57.67; H, 7.74; N, 26.91. Found: C, 57.73; H, 7.86; N, 26.68.

2,4-Di-*n*-propyl-4-methyl-3,4-dihydro-5H-furazano[3,4-f][1,5]diazepine (**18**).

The spectra characteristics of this compound are; ¹H nmr (deuteriochloroform): 200 MHz, δ 4.98 (br s, 1 H), 2.66 (s, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 1.55 (m, 6 H), 1.24 (s, 3 H), 1.0 (m, 6 H); ¹³C nmr: δ 179.92, 151.41, 150.76, 55.14, 48.30, 46.19, 44.66, 27.47, 19.37, 16.85, 14.16, 13.68; ir (potassium bromide): 3300, 2950, 1650, 1610, 1500, 1020 cm⁻¹; mp 103-105°.

Anal. Calcd. for C₁₂H₂₀N₄O: C, 60.98; H, 8.53; N, 23.71. Found: C, 61.11; H, 8.71; N, 23.62.

2,4-*n*-Butyl-4-methyl-3,4-dihydro-5H-furazano[3,4-f][1,5]diazepine (**19**).

The spectral characteristics of this compound are; ¹H nmr (deuteriochloroform): 200 MHz, δ 5.38 (br s, 1 H), 2.68 (s, 2 H), 2.54 (t, J = 7.5 Hz, 2 H), 1.55 (m, 10 H), 1.25 (s, 3 H), 0.92 (m, 6 H); ¹³C nmr: δ 180.54, 151.67, 151.05, 55.27, 48.51, 44.05, 42.24, 28.21, 27.54, 25.79, 22.92, 22.44, 13.85 (represents 2 carbons); ir (sodium chloride): 3250, 2900, 1650, 1600, 1500, 1475, 1375, 1025 cm⁻¹.

Anal. Calcd. for C₁₄H₂₄N₄O: C, 63.60; H, 9.15; N, 21.20. Found: C, 63.49; H, 8.88; N, 21.43.

2,4-Diphenyl-4-methyl-3,4-dihydro-5H-furazano[3,4-f][1,5]diazepine (**10**).

The spectral characteristics of this compound are; ¹H nmr (acetone-*d*₆): δ 7.5 (m, 10 H), 5.2 (br s, 1 H), 4.31 (d, J = 15.4 Hz, 1 H), 3.26 (d, J = 15.4 Hz, 1 H), 1.85 (s, 3H); ¹³C nmr: δ 172.95, 153.06, 152.03, 146.30, 139.93,

X-Ray.

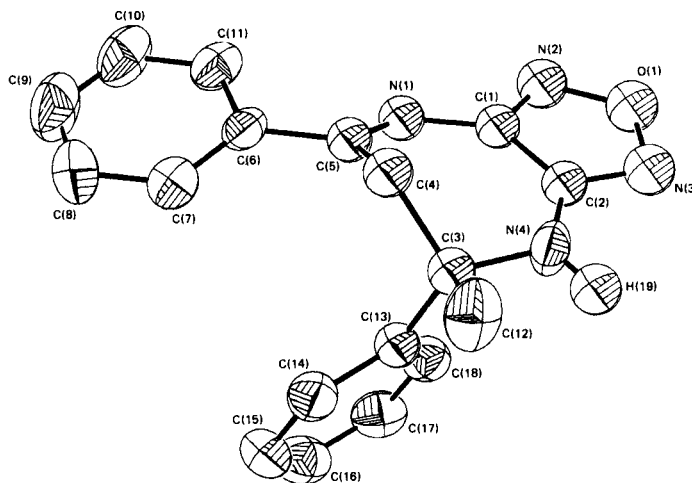


Figure 1. Diazepine **10** plotted with 50% probability thermal ellipsoids. Atoms shown are atoms that were refined. Hydrogen atoms that during refinement were defined as "riding" with fixed geometries have not been plotted.

131.71, 128.84, 128.80, 128.38, 127.53, 127.72, 60.21, 46.20, 31.99; ir (potassium bromide): 3220, 3120, 2930, 2850, 1600, 1475, 1430, 1320, 1210, 1020, 900, 755 cm^{-1} ; mp 142-144°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}$: C, 71.03; H, 5.30; N, 18.41. Found: C, 71.13; H, 5.25; N, 18.42.

2,4-Dibenzyl-4-methyl-3,4-dihydro-5H-furazano[3,4-f][1,5]diazepine (20).

The spectral characteristics for this compound are: ^1H nmr (deuteriochloroform): 200 MHz, δ 7.15 (m, 10 H), 4.75 (br s, 1 H), 3.85 (s, 2 H), 2.75 (s, 2 H), 2.65 (d, $J = 13.2$ Hz, 1 H), 2.36 (d, $J = 13.2$ Hz, 1 H), 0.95 (s, 3 H); ^{13}C nmr: δ 177.75, 151.35, 150.67, 134.97, 134.91, 130.40, 129.55, 128.95, 128.59, 127.49, 127.32, 54.10, 48.01, 47.12, 26.72; ir (sodium chloride): 3250, 3050, 2950, 1640, 1600, 1500, 1450, 1050 cm^{-1} . A satisfactory elemental analysis could not be obtained for this compound.

Crystals of diazepine 10 suitable for an X-ray crystal structure analysis were grown from ethyl acetate/hexane. Crystals were generally rod shaped with well-defined faces and terminations. Preliminary oscillation and Weissenberg photographs indicated monoclinic symmetry with systematic absences $0k0$, $k = 2n + 1$; 00ℓ , $\ell = 2n + 1$ (needle axis of crystals = a). A crystal of size $0.26 \times 0.28 \times 0.42$ mm was used for data collection. Given in Table II are the relevant unit cell, data collection,

Table II

Unit Cell Parameters and Experimental Conditions

Space Group: $P2_1/n$, $Z = 4$

Unit Cell: $a = 9.635(2)$, $b = 15.665(4)$, $c = 10.900(3)$ Å, $\beta = 103.34(2)^\circ$,
 $V = 1600.9(7)$ Å³

$D = 1.26$ g/cm³

Data Collection: $2\theta/\theta$ scans, $\text{MoK}\alpha$

Scan Speed: variable, $4-12^\circ/\text{min}$.

Scan Range: $1^\circ < K\alpha_1$ ($2\theta_{\text{hkl}}$) to $1^\circ > K\alpha_2$ ($2\theta_{\text{hkl}}$)

Background/Scan Ratio: 1.0

2θ Range for Data Collection: $4-50^\circ$

Octants: $hk\ell$, hkl (partial $hk\ell$, hkl)

No. observations: 5349

No. Unique Data: 2830

Data Used for Refinement: $1862 |F_o| > 4\sigma(F_o)$

No. Refinement Parameters: 177

$R = 0.070$

$R_w = 0.072$

and refinement parameters. The unit cell parameters were determined by a symmetry-constrained least-squared fit of 25 computer-centered reflections with 2θ values ranging from 8 to 27 degrees. Intensity data were collected on a Nicolet R3 diffractometer with graphite-monochromated $\text{Mo K}\alpha$ radiation. Two check reflections (062) and (381) were monitored every 46 reflections and remained stable throughout the data collection. Systematic absences from photographs and intensity data indicated the space group $P2_1/n$ ($h0\ell$, $h + \ell = 2n + 1$; $0k0$, $k = 2n + 1$) [10]. Therefore, the crystal contained a racemic mixture of enantiomers as expected from the synthetic procedure. Intensity data were corrected for Lorentz and polarization effects but not for absorption ($\mu = 0.76$ cm^{-1}) [11].

With default parameters for the direct methods phase determination in SHELXTL [11], all of the non-hydrogen atoms were observed on the E-map with the lowest NQUEST figure of merit. The structure was refined with 177 least-squares parameters using the blocked-cascade least-squares refinement of SHELXTL. The diazepine and furazano ring atoms, except for the secondary amine N(4), were refined isotropically. The methyl carbon, phenyl carbons, and N(4) were refined anisotropically. All hydrogen atoms were refined as "riding" on the adjacent carbon with fixed distances of 0.96 Å but without constraints on their thermal parameters. H(19), the amine hydrogen attached to N(4), was refined without any constraints. The largest deviations on the last two refinement cycles were less than 0.1 esd. The final difference map had peaks

Atom	x	y	z	U
C(1)	8614(3)	9317(2)	420(3)	42(1)
C(2)	7129(3)	9531(2)	13(3)	42(1)
C(3)	6286(3)	8410(2)	-1619(3)	42(1)
C(4)	7757(3)	8471(2)	-1951(3)	44(1)
C(5)	9043(3)	8249(2)	-919(3)	40(1)
C(6)	9992(3)	7542(2)	-1132(3)	43(1) [a]
C(7)	9495(4)	6856(2)	-1911(4)	61(2) [a]
C(8)	10406(5)	6194(3)	-2064(4)	78(2) [a]
C(9)	11813(5)	6233(3)	-1465(4)	83(2) [a]
C(10)	12337(4)	6911(3)	-700(4)	73(2) [a]
C(11)	11430(4)	7564(3)	-523(4)	55(1) [a]
C(12)	5113(4)	8482(3)	-2828(3)	62(2) [a]
C(13)	6186(3)	7573(2)	-922(3)	40(1)
C(14)	5995(4)	6800(2)	-1565(4)	53(1) [a]
C(15)	5980(4)	6038(2)	-923(5)	65(2) [a]
C(16)	6129(4)	6030(3)	355(4)	67(2) [a]
C(17)	6293(4)	6788(3)	993(4)	59(2) [a]
C(18)	6327(4)	7546(2)	367(3)	50(1) [a]
N(1)	9432(3)	8651(2)	122(2)	45(1)
N(2)	9217(3)	9845(2)	1309(3)	57(1)
N(3)	6855(3)	10201(2)	645(3)	55(1)
N(4)	6095(3)	9153(2)	-861(3)	51(1) [a]
O(1)	8174(3)	10401(2)	1464(2)	62(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

and troughs ranging from $+0.36$ $e/\text{\AA}^3$ to -0.46 $e/\text{\AA}^3$. Two of the largest difference peaks were both associated with the furazano oxygen O(1) suggesting the O(1) might have been better modelled if refined anisotropically. Final atomic coordinates and temperature factors are given in Table III.

Acknowledgement.

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REFERENCES AND NOTES

- [1] Presented at the 190th meeting of the American Chemical Society, Chicago, IL, September 9-13, 1985.
- [2] M. A. Shokhen, V. G. Andrianov and A. V. Eremeev, *Khim. Geterotsykl. Soedin.*, 1355 (1979).
- [3a] D. Q. Quan, R. Caiyolle and T. B. T. Dang, *Comp. Rend.*, 1518 (1971); [b] J. A. L. Herbert and H. Suschitzky, *J. Chem. Soc., Perkin Trans. I*, 2657 (1974); [c] P. S. Reddi, C. V. Ratnam and N. V. S. Rao, *Indian J. Chem.*, 10, 982 (1972).
- [4] H. Scharf and W. Thunker, *Ann. Chem.*, 605 (1979).
- [5] V. D. Orlov, I. Z. Papiashvili, M. V. Povstyanoi, and V. P. Kruglenko, *Chem. Heterocyclic Compd. (USSR)*, 1152 (1985).
- [6] J. O. Halford and R. M. Fitch, *J. Amer. Chem. Soc.*, 85, 3354 (1963).
- [7] F. A. Carey and R. J. Sundberg in "Advanced Organic Chemistry", Vol 2, Plenum, New York, 1977, p 22.
- [8] J. W. H. Watthey, J. Stanton and N. P. Peet in "Heterocyclic Compounds, Azepines", Vol 43, Part 2, A. Rosowsky, ed, John Wiley and Sons, New York, 1984, p 652.
- [9] M. D. Coburn, *J. Heterocyclic Chem.*, 5, 86 (1968).
- [10] "International Tables for Crystallography", Vol A "Space Group Symmetry", T. Hahn, ed, D. Reidel, Boston, 1984.
- [11] SHELXTL, version 4.1, Nicolet XRD (1984).