

D. Robert Sliskovic*, Joseph Ashcroft, George O. Morton,

John C. James and Yang-i Lin

American Cyanamid Company, Medical Research Division, Lederle Laboratories,
Pearl River, NY 10965

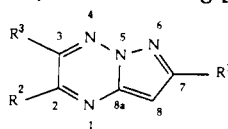
Received October 29, 1987

The ¹H and ¹³C nmr resonances of pyrazolo[1,5-*b*][1,2,4]triazine (**1**) were assigned and the structure of its 2,3-dimethyl derivative **2** was determined using X-ray crystallography.

J. Heterocyclic Chem., **26**, 1109 (1989).

Introduction.

We have synthesized in our laboratories several derivatives of the previously unknown pyrazolo[1,5-*b*][1,2,4]triazine ring system [1]. The ¹H and ¹³C nmr resonances of the parent compound **1** and several derivatives **2-4** were assigned employing 2D C-H chemical shift correlation experiments. The X-ray crystal structure of the 2,3-dimethyl derivative **2** was determined and compared to that reported for imidazo[1,2-*b*][1,2,4]triazine (**6**), a closely related analog [2] (Figure 1).



- 1** R¹ = R² = R³ = H
2 R¹ = H, R² = R³ = CH₃
3 R¹ = H, R² = R³ = Ph
4 R¹ = Ph, R² = R³ = CH₃

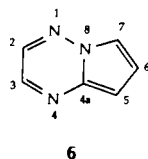
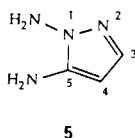


Figure 1. Compounds prepared and numbering system.

Results and Discussion. ¹H and ¹³C-NMR Studies.

The ¹H nmr spectrum of the parent compound **1** in deuteriochloroform at 80 MHz consists of four doublets resonating at δ 8.41 (J = 1.8 Hz), 8.31 (J = 1.8 Hz), 8.25 (J = 2.6 Hz) and 6.87 ppm (J = 2.6 Hz). Since the coupling constant (J) between the resonances H7 and H8 of **2** and **3** is 2.6 Hz (Table 1), we are able to assign the doublets at 8.25 ppm (J = 2.6 Hz) and 6.87 ppm (J = 2.6 Hz) to the H7 and H8 protons. By analogy with other 1-substituted pyrazole derivatives [3], the resonances at δ 8.25 and 6.87 ppm are assigned respectively to H7 (*alpha* to nitrogen) and H8 (*beta* to nitrogen). The two remaining doublets must be due to the H2 and H3 protons. Long range spin-spin coupling between protons separated by five or six bonds and situated on different rings of polynuclear systems have been reported [4,5]. A very small coupling (J < 1 Hz) was observed between H7 and the resonance at δ 8.31 ppm, however, assignment of the resonances at δ 8.31

ppm and δ 8.41 ppm was finally completed employing a direct 1H-13C COSY experiment optimized for multiple bond coupling constants (MB-HETCOR) [6]. Since the H2-13C8a spin system was likely to have a three bond coupling constant larger than the four bond coupling constant of the H3-13C8a spin system [7], the COSY experiment would exhibit crosspeaks between H2 and C8a but not between H3 and C8a. Figure 2 shows a portion of the 2D-spectrum obtained using the MB-HETCOR experiment. Not all 1 bond ¹H-¹³C correlations were suppressed, however, there is a cross peak present at the point 8.41 ppm, 141.7 ppm (C8a), indicating the 8.41 ppm proton resonance should be assigned to H2, thus assigning the 8.31 ppm resonance to H3. The ¹H nmr data of compounds **1-5** are summarized in Table 1.

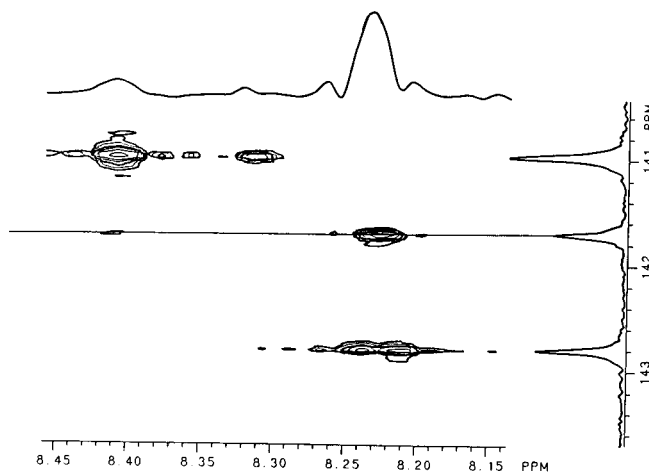


Figure 2. Shows a segment of the 2D MB-HETCOR spectrum of compound **1**. A one-dimensional slice of the F₁ dimension (¹H) through 141.7 ppm is shown above the 2D spectrum. A projection of the F₂ (¹³C) dimension is shown below.

A proton decoupled ¹³C nmr spectrum of compound **1** in deuteriochloroform shows five carbon resonances at δ 142.8, 141.7, 140.9, 136.5 and 97.8 ppm. The low intensity resonance at δ 141.7 ppm was assigned to the quaternary carbon, C8a [8]. Comparison with the spectra obtained for 1,5-diaminopyrazole (**5**) and three 2,3-disubstituted

Table 1

 ^1H and ^{13}C NMR Data for Compounds 1-5

Compound No.	^1H NMR (deuteriochloroform, TMS int) ppm	^{13}C NMR (deuteriochloroform) ppm [a]
1	6.87 (d, 1H, H8, $J_{8,7} = 2.6$ Hz), 8.25 (d, 1H, H7, $J_{7,8} = 2.6$ Hz), $J_{7,2} < 1$ Hz), 8.3 (d, 1H, H3, $J_{3,2} = 1.8$ Hz), 8.41 (d, 1H, H2, $J_{2,3} = 1.8$ Hz)	97.8 (C8, $^1J_{\text{CH}} = 183.2$ Hz, $^2J_{\text{CH}} = 9.2$ Hz), 140.9 (C2, $^1J_{\text{CH}} = 189.7$ Hz, $^2J_{\text{CH}} = 9.1$ Hz), 136.5 (C3, $^1J_{\text{CH}} = 189.4$ Hz, $^2J_{\text{CH}} = 12.6$ Hz), 142.8 (C7, $^1J_{\text{CH}} = 188.9$ Hz, $^2J_{\text{CH}} = 4.7$ Hz), 141.7 (C8a, Quat C)
2	2.60 (s, 3H, CH ₃), 2.61 (s, 3H, CH ₃), 6.63 (d, 1H, H8, $J_{8,7} = 2.6$ Hz), 8.05 (d, 1H, H7, $J_{7,8} = 2.6$ Hz)	19.75 (CH ₃), 22.53 (CH ₃), 95.79, 140.23, 141.23, 145.81 (Quat C), 151.45 (Quat C)
3	6.88 (d, 1H, H8, $J_{8,7} = 2.6$ Hz), 7.5 (m, 10H, benzene protons), 8.27 (d, 1H, H7, $J_{7,8} = 2.6$ Hz)	97.31, 128.20, 129.60, 134.71 (Quat C), 136.74 (Quat C), 140.36 (Quat C), 141.26, 146.96 (Quat C), 150.72 (Quat C)
4	2.5 (s, 6H, CH ₃), 7.0 (s, 1H, H7), 8.0-7.5 (m, 5H, benzene protons)	19.74 (CH ₃), 22.56 (CH ₃), 92.08, 126.28, 128.80, 132.40 (Quat C), 141.67 (Quat C), 145.48 (Quat C), 151.45 (Quat C), 152.53 (Quat C)
5	5.0 (br s, 2H, C-NH ₂), 5.8 (br s, 2H, N-NH ₂), 5.35 (d, 1H, H4, $J_{4,3} = 2.0$ Hz), 7.0 (d, 1H, H3, $J_{3,4} = 2.0$ Hz)	8.35 (C4), 133.99 (C5), 144.83 (C3) 9

[a] All proton decoupled except for compound 1.

pyrazolo[1,5-*b*][1,2,4]triazines **2-4** (Table 1) allowed the direct assignment of C7(δ 142.8 ppm) and C8(δ 97.8 ppm). No conclusive assignment of C2 and C3 could be obtained from the fully coupled spectra of the available pyrazolo-triazines **1-4**. Since the ^1H nmr resonances were fully assigned, 2D C-H chemical shift correlation spectroscopy [9,10] was employed to complete the ^{13}C assignments.

This 2DFT experiment provides a means of correlating the chemical shifts of C-nuclei with the chemical shifts of the directly attached protons. From the matrix we were able to correlate the ^1H nmr resonance at δ 8.41 ppm (H2) to the carbon resonance at δ 140.9 ppm, and the ^1H nmr resonance at δ 8.31 ppm (H3) to the carbon resonance at δ 136.5 ppm, thus assigning both the C2 and C3 ^{13}C resonances. The assignment of C7 was confirmed by correlation of the ^1H nmr resonance at δ 8.25 ppm (H7) with the carbon resonance at δ 142.8 ppm. See Table 1 for complete ^{13}C chemical shift and coupling constant data for compounds **1-4**.

X-Ray Crystallographic Studies [11].

The crystals of 2,3-dimethylpyrazolo[1,5-*b*][1,2,4]triazine **2**, are monoclinic with space group $P2_1/c$. Details of the X-ray crystallographic analysis and unit cell are given in the Experimental Section and in Table 2.

Table 2

Crystallographic Data

Molecular formula	$\text{C}_7\text{H}_8\text{N}_4$
Molecular Weight	148.2
Space group	Monoclinic $P2_1/c$
Calculated density (ρ)	1.32 g/cm ³
Cell dimensions	$a = 7.362(2)\text{\AA}$ $b = 6.944(1)\text{\AA}$ $c = 14.615(1)\text{\AA}$ $\beta = 91.52(1)\text{ deg.}$ $Z = 4$ $V = 746.9\text{\AA}^3$
Unweighted agreement factor (R_1)	0.046
Weighted agreement factor (R_2)	0.060
Factor including unobs. data	0.089
Esd of obs. of unit weight	1.52
Convergence, largest shift	0.06 σ
High peak in final diff. map	0.21 (5) $e/\text{\AA}^3$

An Ortep plot of the X-ray crystallographic structure of a typical molecule in a unit cell of **2** is shown in Figure 3.

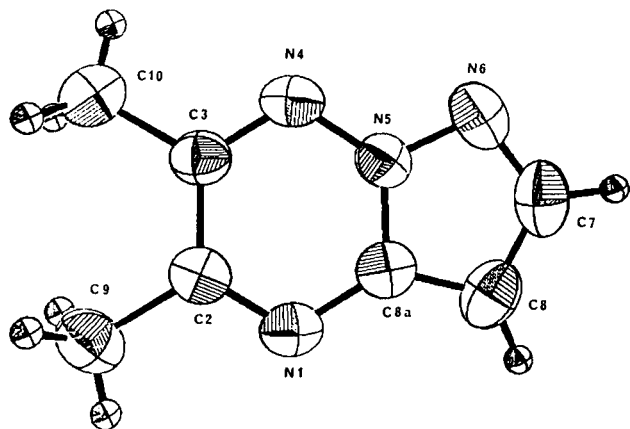


Figure 3. An Ortep plot of compound **2** shown with 50% probability ellipsoids.

The bond distances and angles are indicated in Figure 4. In Table 3 the bond lengths are compared with the corresponding values in imidazo[1,2-*b*][1,2,4]triazine (**6**) [2].

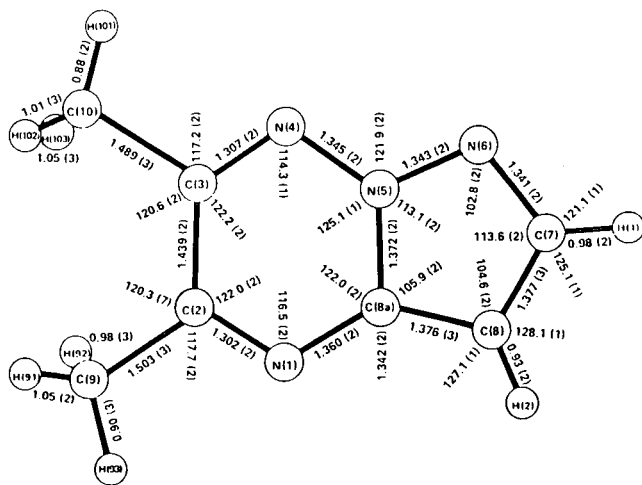


Figure 4. The bond lengths and bond angles of compound **2**. Numbers in parentheses are estimated standard deviations in the least significant digits.

Direct comparison between bonds of similar character shows that the only considerable difference involves the C(2)-C(3) bond (1.439 Å) in compound **2**, which is longer than the corresponding C(3)-C(2) bond (1.408 Å) in compound **6**, the difference between N5-C8a (1.372 Å) in **2** and N8-C4a (1.404 Å) in (**6**) is also noteworthy.

Compound **2** is a planar molecule and its plane is described by the following equation:

Plane 1: $0.9488X + 0.0995Y - 0.3122Z = -0.7517\text{Å}$. The largest deviation from the plane is -0.011Å for C(8). There are no abnormally short contacts between molecules in the unit cell.

Table 3

Comparison of Bond Lengths Between Pyrazolo[1,5-*b*][1,2,4]triazine **2** and Imidazo[1,2-*b*][1,2,4]triazine **6**

Pyrazolo[1,5- <i>b</i>][1,2,4]triazine (2)	Bond Length (Å)	Imidazo[1,2- <i>b</i>][1,2,4]triazine (6)	Bond Length (Å)
N(1)-C(2)	1.302(2)	N(4)-C(3)	1.313(6)
C(2)-C(3)	1.439(2)	C(3)-C(2)	1.408(11)
C(3)-N(4)	1.307(2)	C(2)-N(1)	1.312(7)
N(4)-N(5)	1.345(2)	N(1)-N(8)	1.350(5)
N(5)-C(8a)	1.372(2)	N(8)-C(4a)	1.404(10)
C(8a)-C(8)	1.376(3)	C(4a)-N(5)	1.320(6)
C(8)-C(7)	1.377(3)	N(5)-C(6)	1.370(7)
C(7)-N(6)	1.341(2)	C(6)-C(7)	1.364(8)
N(6)-N(5)	1.343(2)	C(7)-N(8)	1.375(7)
N(1)-C(8a)	1.360(2)	N(4)-C(4a)	1.341(6)

Numbers in parentheses are estimated standard deviations in the least significant digits.

EXPERIMENTAL

The pyrazolotriazines were prepared as previously described [1]. Routine nmr spectroscopy was performed on a Varian FT 80 nmr spectrometer. High field ^1H and ^{13}C nmr spectra were recorded with a Nicolet NT 300 WB spectrometer.

X-Ray Crystallographic Analysis.

A pale yellow needle-like crystal of compound **2** having the approximate dimensions of 0.10 x 0.15 x 0.40 mm was analyzed. X-Ray intensities were measured on an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. Using $\text{CuK}\alpha$ radiation ($\lambda = 1.54184\text{Å}$), cell constants and an orientation matrix were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $9 < \theta < 21^\circ$, measured by the computer controlled diagonal slit method of centering. As a check on crystal quality, omega scans of several intense reflections were measured; the width at half-height was 0.20° with a take-off angle of 2.8° , indicating good crystal quality. The data was collected at a temperature of $23 \pm 1^\circ$ using the ω - θ technique. The scan rate varied from 2 to $20^\circ/\text{min}$ (in omega). Data were collected to a maximum 2θ of 150.0° . The scan range (in degrees) was determined as a function of θ to correct for separation of the $\text{K}\alpha$ doublet, the scan width was calculated as follows: θ scan width = $0.7 + 0.300 \tan \theta$.

A total of 1730 reflections were collected, of which 1534 were unique and not systematically absent. As a check on crystal and electronic stability, 3 representative reflections were measured every 41 minutes. A systemic drop in the intensities of these reflections was noted with a total loss of intensity of 11.9%. A linear decay correction was applied. The correction factors on I ranged from 1.00 to 1.14 with an average value of 1.06. Lorentz and polarisation corrections were applied to the data. The linear

absorption coefficient is 7.2 cm^{-1} for $\text{CuK}\alpha$ radiation. No absorption correction was made. A secondary extinction correction was applied [12]. The final coefficient, refined in least-squares, was 3.5×10^{-6} (in absolute units). A summary of the crystal data is given in Table 2.

The structure was solved by direct methods. A total of 10 atoms were located from the first E-map. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full matrix least-squares where the function minimized was $\Sigma w(|F_o| - |F_c|)^2$ and the weight w is defined as $4F_o^2/\sigma^2(F_o^2)$. The standard deviation on intensities, $\sigma(F_o^2)$, is defined as follows: $\sigma^2(F_o^2) = [S^2(C + R^2B) + (pF_o^2)^2]/Lp^2$ where S is the scan rate, C is the total integrated peak count, R is the ratio of scan time to background counting time, B is the total background count, Lp is the Lorentz-polarisation factor, and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.050. Scattering factors were taken from Cromer and Weber [13]. Anomalous dispersion effects were included in F_c [14], the values of $\Delta F'$ and $\Delta F''$ were those of Cromer [15]. Only the 959 reflections having intensities greater than 3.0 times their standard deviations were used in the refinements. The final cycle of refinement included 133 variable parameters and converged (largest parameter shift was 0.06 times its esd) with unweighted and weighed agreement factors of $R_1 = \Sigma |F_o| - |F_c| / \Sigma |F_o| = 0.046$ and $R_2 = \text{SQRT}(\Sigma w(|F_o| - |F_c|)^2 / \Sigma w F_o^2) = 0.060$.

The standard deviation of an observation of unit weight was 1.52. The highest peak in the final differences Fourier had a height of $0.21 \text{ e}/\text{\AA}^3$, with an estimated error based on ΔF [16] of 0.05. Plots of $\Sigma w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, scan θ/λ and various classes of indices showed no unusual trends.

All calculations were performed on a PDP-11/60 based TEXRAY [17] system which includes the Enraf-Nonius SDP and proprietary crystallographic software of Molecular Structure Corporation.

Supplementary Material Available.

Complete X-ray data on compound (2) are available upon request from the author (DRS) including tables of fractional atomic coordinates for non-hydrogen atoms, thermal parameters, bond lengths, bond angles, intermolecular contacts, mean planes and torsion angles.

Acknowledgments.

We would like to thank Dr. Fredrick M. Lovell of American Cyanamid Company for helpful discussions concerning the X-ray work. We would also like to thank the reviewer who suggested the ^1H - ^{13}C COSY experiment.

REFERENCES AND NOTES

- * Author to whom correspondence should be addressed; present address: Warner Lambert-Parke Davis Co., 2800 Plymouth Road, Ann Arbor, MI, 48105.
- [1] D. R. Sliskovic, M. Siegel and Y.-i. Lin, *Synthesis*, 71 (1986).
 - [2] A. Rykowski, H. C. Van der Plas and C. H. Stam, *Acta Cryst.*, **B33**, 274 (1977).
 - [3] A. R. Katritzky and C. W. Rees, eds "Comprehensive Heterocyclic Chemistry", Vol. 5, Pergamon, 1984, p 186.
 - [4] M. Martin-Smith, S. T. Reid and S. Sternhell, *Tetrahedron Letters*, 2393 (1965).
 - [5] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).
 - [6] G. E. Martin and A. S. Zektzer, *Magn. Reson. Chem.*, **26**, 631 (1988).
 - [7] A. J. L. Marshall, "Carbon-Carbon and Carbon-Proton NMR Couplings: Applications of Organic Stereochemistry and Conformational Analysis", Verlag Chemie, 1983, p 46.
 - [8] R. J. Abrahams and P. Loftus, "Proton and Carbon-13 NMR Spectroscopy", Heyden, 1978, p 117.
 - [9] R. Benn and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **22**, 350 (1983).
 - [10] G. E. Martin, S. L. Smith, W. L. Layton, M. R. Wilcott, III, M. Iwao, M. L. Lee and R. N. Castle, *J. Heterocyclic Chem.*, **20**, 1367 (1983).
 - [11] The X-ray crystal data collection, structure solution and refinement were carried out by the staff of Molecular Structure Corporation, Texas.
 - [12] W. H. Zacharaisen, *Acta Cryst.*, **16**, 1139 (1963).
 - [13] D. T. Cromer and J. T. Weber, "International Tables for X-Ray Crystallography", Vol IV, The Kynoch Press, Birmingham, England, 1974, Table 2.2b.
 - [14] J. A. Ibers and W. C. Hamilton, *Acta Cryst.*, **17**, 781 (1964).
 - [15] D. T. Cromer, "International Tables for X-Ray Crystallography", Vol IV, The Kynoch Press, Birmingham, England, 1974, Table 2.3.1.
 - [16] D. W. J. Cruickshank, *Acta Cryst.*, **2**, 154 (1949).
 - [17] TEXRAY is a trademark of Molecular Structure Corporation (1982).