

Arsenic Containing Heterocycles. II (1).
Confirmation of the Structure of Benzo[*a*]-9-chlorophenarsazine
12-Chloride by ^{13}C -NMR Spectroscopy and Spin-lattice Relaxation
Time Studies: Possible Evidence for the Contribution of an ^{75}As - ^{13}C
Mechanism to the Relaxation of the Arsenic Bearing Quaternary
Carbons in the Phenarsazine Ring System

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The product of the reaction of (3-chlorophenyl)-2-naphthylamine with arsenic trichloride has been confirmed to be benzo[*a*]-9-chlorophenarsazine 12-chloride by ^{13}C -nmr spectroscopy and spin-lattice (T_1) relaxation time measurements. A considerable shortening of the spin-lattice relaxation times of the arsenic bearing quaternary carbons, relative to the calculated relaxation times, was observed. This discrepancy has been interpreted in terms of an ^{75}As - ^{13}C dipolar contribution to quaternary carbon relaxation.

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Total assignment of the ^{13}C -nmr spectra of phenarsazine 10-chloride and several substituted analogs have been reported (3). Syntheses of numerous other phenarsazine analogs have also been described (4,5), although there may remain some question with regard to the direction of cyclization in those cases where alternative pathways exist. This problem, coupled with the observation by Norton and Allerhand (6) that ^{14}N - ^{13}C dipolar mechanisms may be a significant contributor to the relaxation of quaternary carbons, has prompted us to extend our previous investigations (3) to include additional arsenic containing heterocycles. In particular, we were interested in the reaction of phenyl-2-naphthylamine (**1a**) with arsenic trichloride which was reported by Buu-Hoi and co-workers (4) to lead to the formation of benzo[*a*]phenarsazine 12-chloride (**2a**), rather than the benzo[*b*]phenarsazine (**3a**) ring system. Unfortunately, no spectroscopic evidence in support of this cyclization pathway was presented in these early reports (4,5). In addition to this mechanistic aspect of the synthesis, benzo[*a*]phenarsazine 12-chloride (**2a**) or a substituted analog would also provide a convenient means of probing potential contributions to quaternary carbon relaxation by an ^{75}As - ^{13}C mechanism, these problems forming the basis for the present report.

Since the benzo[*a*]phenarsazine 12-chloride ^{13}C -nmr spectrum has yet to be assigned, we elected to first prepare a 9-substituted analog of this system, **2b**, to insure the discrimination of the quaternary carbon resonances in the spectrum. Thus, (3-chlorophenyl)-2-naphthylamine (**1b**) was fused with arsenic trichloride at 150° for a period of six hours according to the general procedure of Buu-Hoi, Wei and Royer (4). Workup of the reaction mixture in the usual fashion (3) gave a single product which was isolated

in a 58% yield. On the basis of previous work (4,5), we anticipated this product to be the desired benzo[*a*]-9-chlorophenarsazine 12-chloride (**2b**).

The ^1H -decoupled ^{13}C -nmr spectrum of **2b** contained fifteen of the initially expected sixteen resonances, the resonance observed at $\delta = 123.99$ exhibiting considerably greater intensity, thus accounting for the missing resonance by accidental overlap of the two signals. Identification of the quaternary carbon resonances in the spectrum was conveniently accomplished by the use of an inversion-recovery pulse sequence (7), with the delay between the preparatory and observation pulses set to 700 msec. This delay gave a spectrum, Figure 1, in which all of the quaternary carbon resonances showed negative intensities

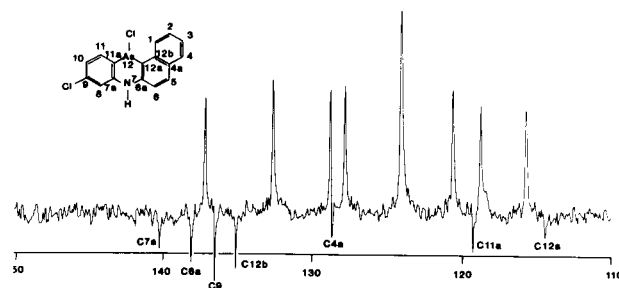


Figure 1. ^1H -Decoupled 25.158 MHz ^{13}C -nmr spectrum of benzo[*a*]-9-chlorophenarsazine 12-chloride (**2b**) in hexadeuteriodimethylsulfoxide. The spectrum was obtained using an inversion-recovery sequence for which the delay between the 180 and the 90 degree observation pulse was set to 700 msec giving quaternary carbons with negative intensities.

as a result of the long relaxation times (8). Calculated ^{13}C -nmr chemical shifts for **2b** were obtained by incrementing the observed chemical shifts for 3-chlorophenarsazine chloride (3) for the benzo[*a*] fusion, which gave the predicted chemical shifts shown in Figure 2. Among the quaternary carbons, the four observed furthest downfield at $\delta = 140.20, 138.06, 136.46$ and 135.05 were attributed to the resonances for C6a, C7a, C9 and C12b. The remaining quaternary carbons at $\delta = 128.58, 119.18$ and 114.37 were attributable to the C4a, C11a and C12a resonances. No assignments were made within these groups solely on the basis of chemical shift arguments.

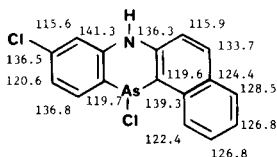
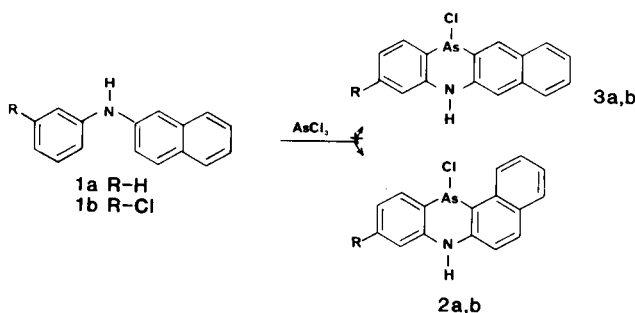


Figure 2. Calculated ^{13}C -nmr chemical shifts for benzo[*a*]-9-chlorophenarsazine 12-chloride (**2b**) obtained by incrementing the assigned ^{13}C -nmr chemical shifts of 3-chlorophenarsazine 10-chloride for benzo[*a*] fusion.

Condensation of (3-chlorophenyl)-2-naphthylamine (**1b**) with arsenic trichloride has the potential of leading to two completely different ring systems as a result of rotation about the N-C2 bond axis. Work by Buu-Hoi and co-workers (4,5) suggested that cyclization occurred at the 1-position of the naphthyl moiety, giving the benzo[*a*]phenarsazine 12-chloride (**2a** or **2b**) as the sole product of the reaction. The first problem to be dealt with was thus the identity of the product formed. This aspect of the problem, however, is most conveniently dealt with concurrent to the investigation of the quaternary carbon relaxation times. In particular, we would expect the C11a carbon, which has a proton at a distance of 2.0 \AA , to be relaxed considerably more efficiently than the C12a resonance whose nearest proton is at a distance of

Scheme 1



approximately 3.2 \AA . Thus, by measuring the quaternary carbon relaxation times, we may also unequivocally establish the structure of the molecule as the benzo[*a*] or

alternatively as the benzo[*b*] ring fusion product in the event that the relaxation times measured for C11a and C12a were of similar magnitude.

Relaxation time differences between C11a and C12a, in addition to providing a means of discriminating between the two possible products, are central to the issue of ^{75}As - ^{13}C relaxation mechanisms. As in the case of the ^{14}N - ^{13}C dipolar mechanism (6), contributions arising *via* this mechanism are expected to be greater than those of a proton located at a distance of 3.2 \AA from the quaternary carbon and somewhat smaller than those of a proton located 2.0 \AA from the quaternary carbon. Thus, a substantial shortening of the relaxation time of the C12a resonance (assuming **2b** is indeed the structure of the product formed in the reaction) relative to that predicted solely on the basis of proton contributions to relaxation should be observed, the deviation, if observed, providing preliminary evidence in support of the existence of a ^{75}As - ^{13}C dipolar relaxation mechanism.

Equipped with the basic tenants concerning the quaternary carbon relaxation which were presented above, the relaxation times for the quaternary carbons were measured using the progressive saturation method (9). Protonated carbon relaxation times were measured using the inversion-recovery method to allow the computation of the correlation time, τ_c , which was found to be 1.8×10^{-10} seconds (10). Calculated *vs.* observed T_1 relaxation times are shown in Table I for the quaternary carbons. From

Table I

Calculated *vs.* Observed Chemical Shift and Relaxation Times for the Quaternary Carbons of Benzo[*a*]-9-chlorophenarsazine 12-Chloride at 25.158 MHz in Hexadeuteriodimethylsulfoxide at 33°

Carbon	$\delta^{13}\text{C}_{\text{calcd}}$	$\delta^{13}\text{C}_{\text{observed}}$	T_1 (seconds)	
			Calcd	Observed
C4a	124.4	128.58	4.59	3.65 ± 0.16 (a)
C6a	136.3	138.06	8.36	7.70 ± 0.44
C7a	141.3	140.20	8.36	7.32 ± 0.70
C9	136.5	136.46	4.85	4.10 ± 0.51
C11a	119.7	119.18	8.47 (b)	5.68 ± 0.21
C12a	119.6	114.37	55.56 (c)	22.83 ± 0.84
C12b	139.3	135.05	8.47	7.93 ± 0.34

(a) Relaxation time for this carbon may be somewhat longer than measured in this study since at 25.158 MHz this resonance is on the shoulder of a protonated carbon. (b) The relaxation time shown is computed ignoring any contribution for ^{75}As - ^{13}C dipolar mechanisms. When the ^{75}As contribution is computed in, the calculated relaxation time drops to 6.93 seconds. (c) The relaxation time shown is computed ignoring any contribution for ^{75}As - ^{13}C dipolar mechanisms. When the ^{75}As contribution is computed in, the calculated relaxation time drops to 25.58 seconds, which is in much better agreement with the observed relaxation time.

these data, it should be noted that the resonance observed at $\delta = 114.37$ exhibited a relaxation time of 22.83 ± 0.84 seconds, which is considerably longer than the relaxation times of any of the other upfield carbons. On this basis, that resonance is unequivocally assignable to C12a. Of the remaining two quaternary resonances in the upfield trio, which were observed at $\delta = 119.18$ and 128.58 , there was a reasonable correspondence between the calculated and observed chemical shifts, thereby permitting the assignment of the downfield resonance to C4a and the upfield resonance to C11a. These assignments are further corroborated by their respective relaxation times, C4a, with two protons at a distance of 2.0 \AA as opposed to the one at this distance for C11a, relaxing more efficiently. Assignments for the four quaternary carbons which resonated in the downfield group were straightforwardly made on the basis of chemical shift arguments, ^1H - ^{13}C spin-coupling constants and their relaxation times (see Table I).

Based on the relaxation times of the two arsenic bearing quaternary carbons, the structure of the isolated product of this reaction is unequivocally shown to be benzo[*a*]-9-chlorophenarsazine 12-chloride (**2b**), thus confirming the earlier work of Buu-Hoi and co-workers (4,5). Additionally, however, there was a substantial difference noted between the calculated and observed relaxation times of the C12a resonance, the observed relaxation time over thirty seconds shorter than predicted from the contributions of the protons to the relaxation of this carbon. This prompted us to consider further the possibility of ^{75}As - ^{13}C dipolar contributions to the relaxation of the arsenic bearing quaternary carbons.

Employing the generalized expressions of Norton and Allerhand (6) for the relaxation of nucleus *i* by nucleus *j*, which is given by the following expression (where $i = c$ for this study):

$$1/T_{1,cj} = (2/15)\hbar^2 \gamma_c^2 \gamma_j^2 S_j(S_j + 1) r_{cj}^{-6} \chi_j$$

where the term S_j is the spin quantum number of the nucleus *j*, γ_c and γ_j are the gyromagnetic ratios of ^{13}C and the nuclide *j*, the term r_{cj}^{-6} is the interatomic distance between ^{13}C and *j*, \hbar^2 is Planck's constant and the term χ_j is given by the expression:

$$\chi_j = \frac{\tau_R}{1 + (\omega_j - \omega_c)^2 \tau_R^2} + \frac{3\tau_R}{1 + \omega_c^2 \tau_R^2} + \frac{6\tau_R}{1 + (\omega_j + \omega_c)^2 \tau_R^2}$$

we may calculate ^{75}As - ^{13}C dipolar contributions to the relaxation of quaternary carbons. When this calculation is performed for a range of correlation times, the family of curves shown in Figure 3 is generated. From this data, it will be noted that the ^{75}As - ^{13}C dipolar contribution to relaxation (curve C) is somewhat more efficient than that for ^{14}N - ^{13}C (curve D) and considerably more efficient than that of a proton at 3.2 \AA (curve E). Curve A shows the con-

tribution to relaxation for a proton directly attached, which is considerably more efficient than the ^{75}As - ^{13}C dipolar mechanism. Curve B, which represents a proton at a distance of 2.0 \AA , presents a somewhat different picture. In the range of correlation times from 10^{-12} to 10^{-9} seconds, the curves for the proton at 2.0 \AA and the ^{75}As - ^{13}C mechanism are parallel. Above 10^{-9} seconds, curve C changes shape somewhat, eventually leading to a condition where the ^{75}As - ^{13}C mechanism is a more efficient contributor to relaxation than the proton at 2.0 \AA above 10^{-7} seconds. While this is not readily verified since small molecules generally have correlation times in the range of 10^{-12} to 10^{-10} seconds, it is interesting none-the-less, and would be significant if studies were ever performed on arsenic containing macromolecules. In addition to the presentation of relaxation shown in Figure 3, we have also computed relaxation contribution curves at constant correlation times in which the ^{75}As - ^{13}C bond distance is varied, these

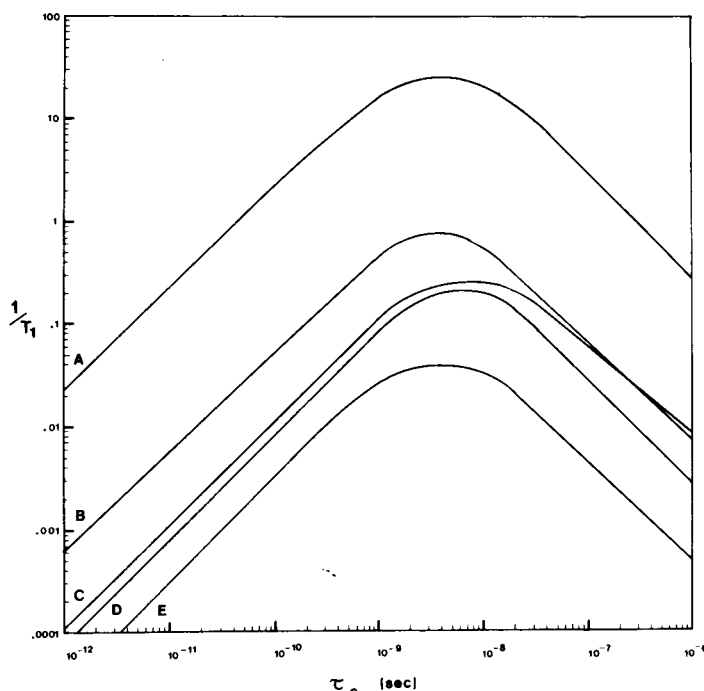


Figure 3. Relaxation contribution curves for ^1H - ^{13}C , ^{14}N - ^{13}C , ^{75}As - ^{13}C dipolar relaxation as a function of the correlation time, τ_c : A) calculated for a proton at 1.09 \AA ; B) calculated for a proton at 2.0 \AA ; C) calculated for ^{75}As at 1.91 \AA (A. Camerman and J. Trotter, *J. Chem. Soc.*, 730 (1965)); D) calculated for ^{14}N at 1.4 \AA ; E) calculated for a proton at 3.2 \AA .

shown in Figure 4. We anticipate that these curves should prove useful in estimating contributions to relaxation for varied arsenic-carbon bond distances over ranges of correlation times which would be helpful in establishing spectral acquisition parameters in studies dealing with other arsenic containing heterocycles.

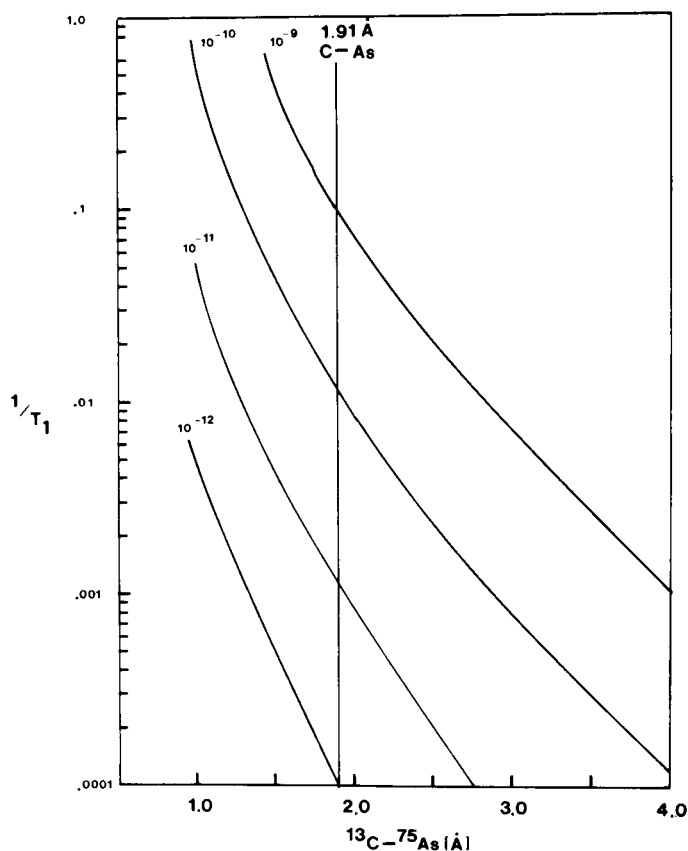


Figure 4. Relaxation contributions for ^{75}As at constant correlation times as a function of the ^{75}As - ^{13}C bond distance.

Our observations of the spin-lattice relaxation behavior of the benzo[*a*]-9-chlorophenarsazine 12-chloride (**2b**) quaternary carbons suggests that there is a significant ^{75}As - ^{13}C dipolar contribution to relaxation in the absence of more efficient proton mediated relaxation mechanisms. We are continuing these studies with additional arsenic containing heterocycles in an effort to obtain further support for this observation. The results of these studies will be forthcoming.

EXPERIMENTAL

Melting points were obtained using a Thomas-Hoover melting point apparatus in open capillaries and are reported uncorrected. Infrared spectra were obtained (potassium bromide pellet) on a Model 567 Perkin-Elmer spectrophotometer. ^{13}C -nmr studies were conducted on a Varian XL-100-15 spectrometer operating at 25.158 MHz in the Fourier transform mode and equipped with a Nicolet 1180 computer interfaced to the spectrometer through a Model 293A pulse programmer. The spectrometer was also equipped with a TT-760 ^1H -decoupler, with the decoupler centered in the aromatic region of the proton spectral window with sufficient power such that $\gamma\text{H}_2/2\pi = 2.9$ KHz. Normal spectra were acquired using 8K data points, with a pulse width of 15 μs (90° pulse width = 22 μs); an interpulse delay of 2.0 seconds; sweep width = 5 KHz with an acquisition time = 0.8192 seconds. ^1H -Coupled ^{13}C -nmr

spectra were obtained using the same parameters as the normal spectra with the exception that the spectrum was digitized with 16K data points and the decoupler operated in the gated mode to retain the nuclear Overhauser enhancements. Protonated carbon relaxation times were measured using the inversion-recovery procedure with a set of fifteen tau values which ranged from 250 μs to 4.0 seconds with an interpulse delay of 20 seconds. The tau values were not randomized during data acquisition, but the list of values was repetitively cycled, with a portion of the total number of acquisitions collected during each cycle to minimize any inhomogeneity. Data reduction was accomplished using the three parameter fitting program (11), which ultimately gave a correlation time, τ_c , of 1.8×10^{-10} seconds. Quaternary carbon relaxation times were measured using the progressive saturation technique with delays which ranged from 1.0 to 128 seconds. Acquisition cycling was also used for this experiment to minimize inhomogeneities, as in the inversion-recovery data. Overhauser enhancements were measured for all quaternary carbons and, within experimental error, were found to be $\cong 3.0 (1.0 + \eta)$, where η has a theoretical maximum of 1.988 (12).

Synthesis of Benzo[*a*]-9-chlorophenarsazine 12-Chloride (**2b**).

A modification of the procedure of Buu-Hoi and co-workers (4) was used for the synthesis of **2b**. To 2.16 g (0.012 mole) of arsenic trichloride was added 3.30 g (0.013 mole) of (3-chlorophenyl)-2-naphthylamine, the resultant mixture fused at 150° for six hours. Hot xylene was added to the reaction mixture immediately upon completion of the fusing period and, after cooling, the product was filtered and washed with carbon tetrachloride. After two recrystallizations from xylene, the product was dried and weighed to provide 2.54 g (58% yield) of **2b** as glistening crystals which melted at 263-264° (lit mp 265° (4)).

Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{AsCl}_2\text{N}$: C, 53.07; H, 2.78; As, 20.69; Cl, 19.58; N, 3.87. Found: C, 52.76; H, 2.84; As, 21.01; Cl, 19.86; N, 3.57.

Calculated ^{13}C -nmr chemical shifts are shown in Figure 2. Assignments for the protonated carbon resonances were: C1, 123.99*; C2, 123.99*; C3, 127.72*; C4, 132.61; C5, 118.66; C7, 115.62; C9, 120.52; C10, 137.15; C12, 128.71* (those resonances labeled with a star represent permutable assignments).

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(10) As in the case of the previously examined phenarsazine chloride systems (see reference 3), **2b** undergoes significant anisotropic reorientation. However, to establish a point of departure for the examination of the quaternary carbon relaxation times, we elected to utilize the average correlation time (τ_c) as a basis for the computation of the quaternary carbon relaxation times.

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