# An NMR Study of Isomeric Benzoxazoles

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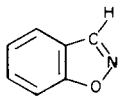
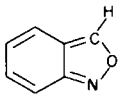
As an extension of our nmr studies of benzotriazoles (1) we turned to other bicyclic ring systems with two heteroatoms in the non-benzenoid ring. Many 6,5 heterocyclic compounds have been studied but very few have yielded complete spectral analyses. One reason for this is the complicated spectra generated by the benzenoid protons. Fusion of benzene rings to a heterocyclic ring results in complex ABCD type spectra similar to unsymmetrically 1,2-disubstituted benzenes. Also, long range inter-ring couplings add to the spectral complexity.

Benzoxazole and its isomers comprise a particularly interesting heterocyclic group. These compounds contain three different atoms in the 5-membered ring. The relative positions of these atoms should have a profound effect on the electronic configurations and on the spectral parameters. A few nmr studies have been reported on the parent compound and its derivatives (2-4) but only one gives a complete analysis (3). However, the two isoconjugate isomers of benzoxazole, namely benzisoxazole and anthranil, have never been studied. It is the purpose of this paper to report the high resolution spectral analyses of these two compounds and their 3-methyl derivatives.





## EXPERIMENTAL

Benzisoxazole was prepared from salicylaldehyde (5) and 3-methylbenzisoxazole from 2-bromoacetophenone (6). Anthranil and 3-methylanthranil were prepared by known procedures (7) from the corresponding 2-nitrobenzaldehyde and 2-nitroacetophenone.

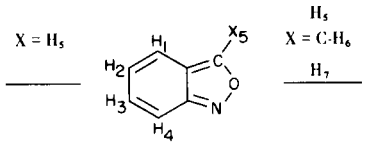
The nmr spectra were recorded on a Varian HA-60-IL high resolution spectrometer operating in the frequency sweep mode. Samples were neat liquids containing approximately 2% tetramethylsilane which served as a lock signal and reference peak. The liquids were degassed by repeated freeze-pump-thaw cycles, transferred under vacuum to a 5 mm sample tube and flame sealed while continually pumping (8).

To obtain the peak frequencies, five spectra were run in both sweep directions and the ten analog traces were simultaneously digitized and recorded on a seven-track magnetic tape. A computer program called EDREM (9) was then used to measure and average the positions of the voltage maxima (absorption peaks) stored on the tape. Thus, the speed and precision of a digital computer allowed the arbitrarily large number of sweeps (ten) to be included in the averaging.

The analyses were performed through the use of LOACN3 (10). As an aid in selecting the input parameters for the first phase of the analyses, LAOCNP (11) was used to graphically represent the spectra computed from the trial input parameters. The frequencies averaged by EDREM were then used as input in the second phase of the least-squares fitting program. All computations were done on an IBM 7090/7094 digital computer. The theoretical spectra shown below were computed with a 1000 point FREQINT IV program (12) and a CALCOMP plotter operating at a resolution of 5 mil.

TABLE I

Spectral Parameters of Anthranil and 3-Methylanthranil




| | X = $H_5$ | X = C-$H_6$ |
|---|---|---|
| | $\nu$ | $\nu$ |
| 1 | 454.417 ± .012 | 437.399 ± .005 |
| 2 | 417.658 ± .011 | 408.181 ± .003 |
| 3 | 436.662 ± .012 | 432.087 ± .004 |
| 4 | 461.742 ± .012 | 449.898 ± .003 |
| 5 | 529.983 ± .010 | 5 = 6 = 7 = 158.0 |
| | J | J |
| 1,2 | 8.833 ± .018 | 8.874 ± .005 |
| 1,3 | 0.953 ± .017 | 0.931 ± .006 |
| 1,4 | 1.215 ± .015 | 1.232 ± .007 |
| 1,5 | 0.188 ± .016 | 1,5 = 1,6 = 1,7 = 0.024 ± .005 |
| 2,3 | 6.340 ± .015 | 6.349 ± .005 |
| 2,4 | 0.824 ± .020 | 0.796 ± .004 |
| 2,5 | 0.432 ± .015 | 2,5 = 2,6 = 2,7 = 0.399 ± .004 |
| 3,4 | 9.013 ± .017 | 8.949 ± .004 |
| 3,5 | -0.020 ± .016 | 3,5 = 3,6 = 3,7 = -.013 ± .004 |
| 4,5 | 1.049 ± .016 | 4,5 = 4,6 = 4,7 = 0 |
| | | 5,6 = 5,7 = 6,7 = 0 |

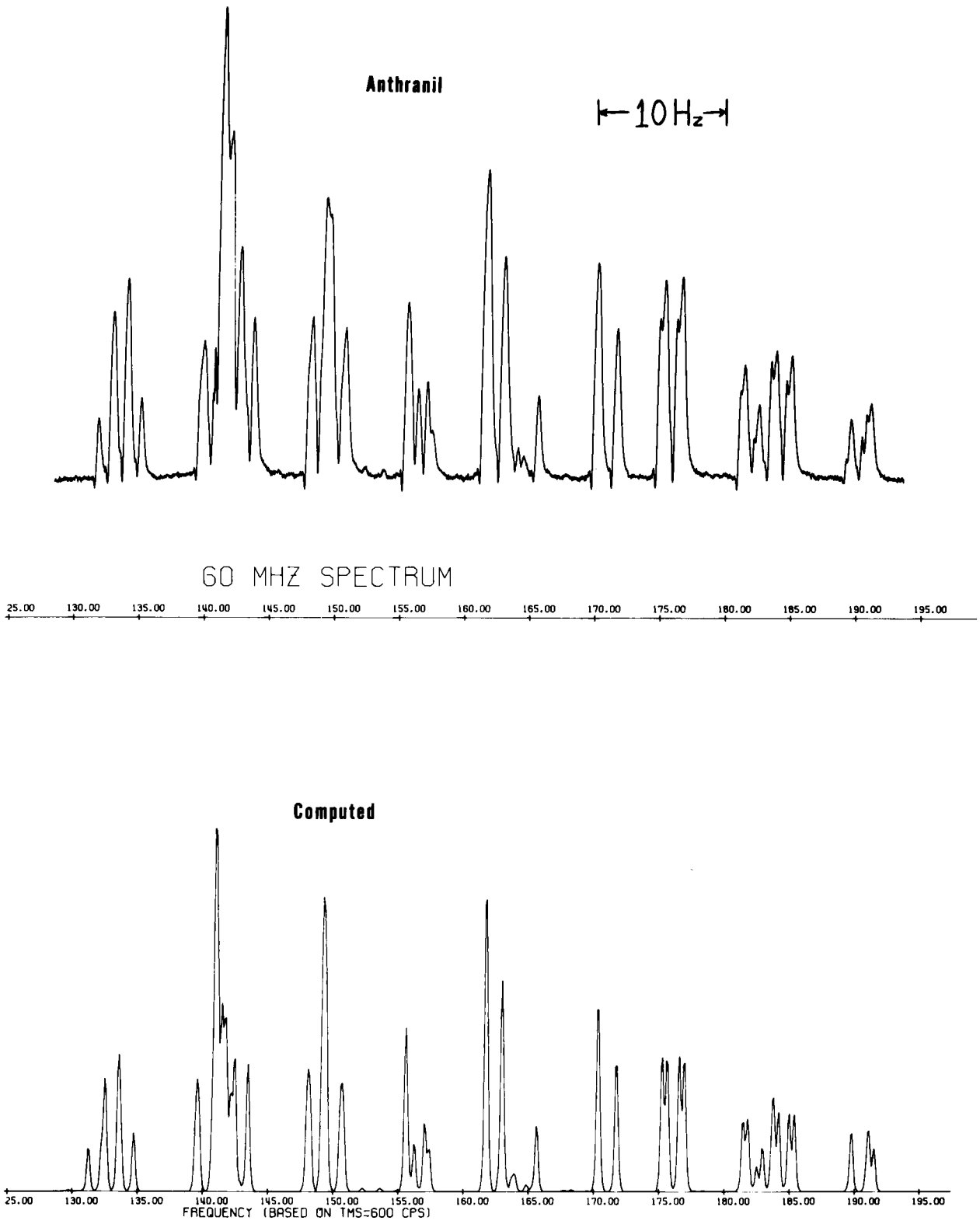



Figure 1. Comparison of experimental and computer simulated spectra of anthranil.

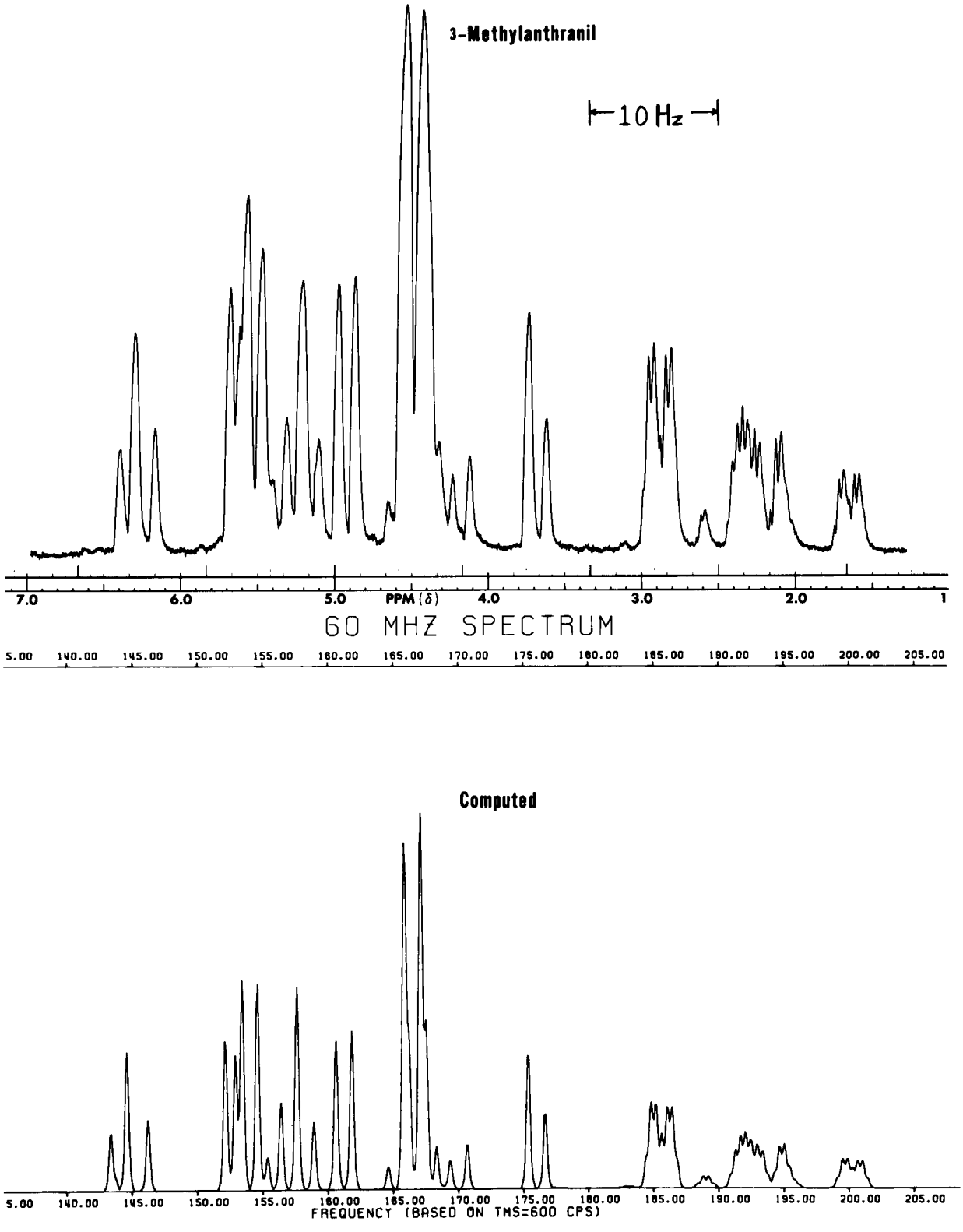



Figure 2. Comparison of experimental and computer simulated spectra of 3-methylanthranil.

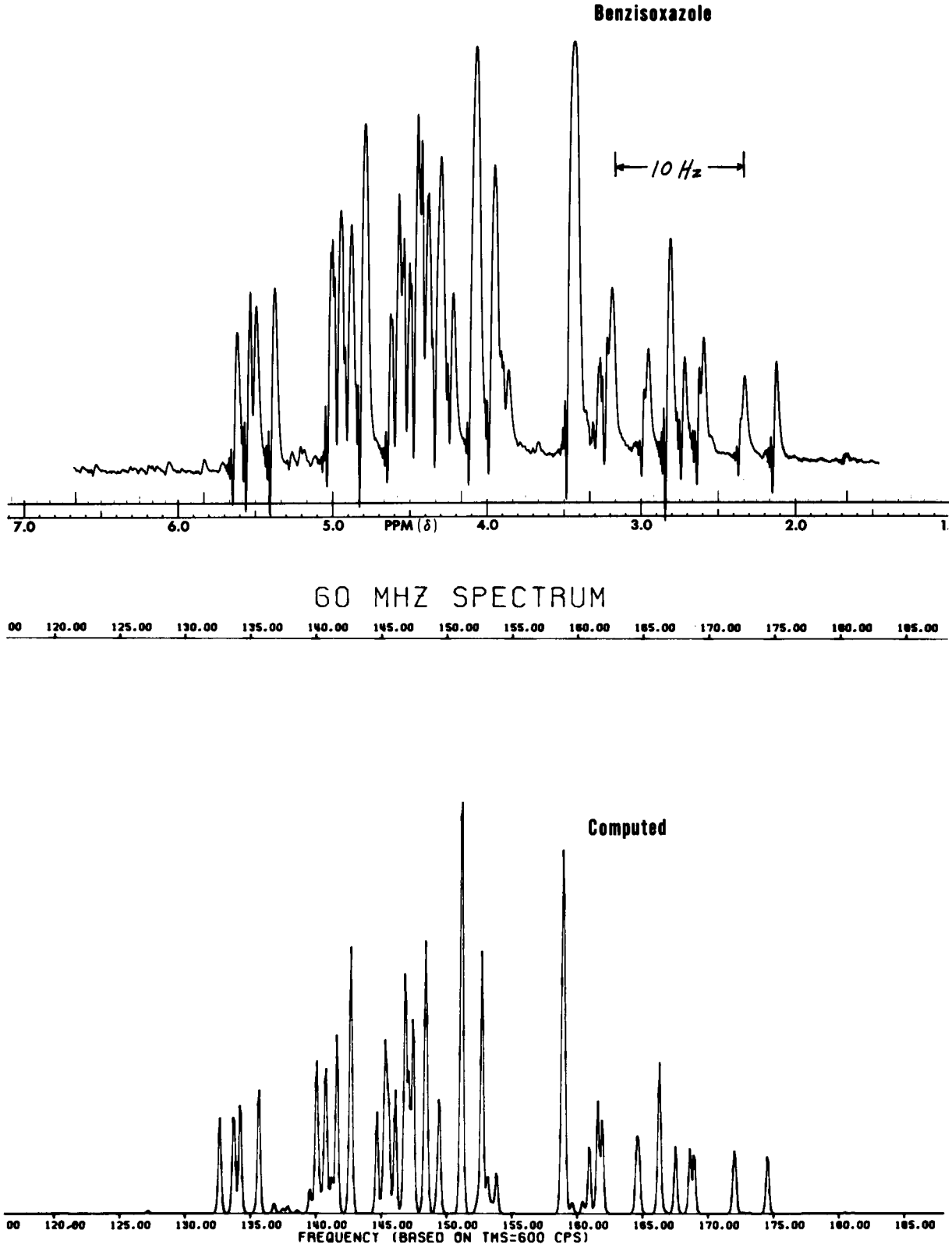



Figure 3. Comparison of experimental and computer simulated spectra of benzisoxazole.

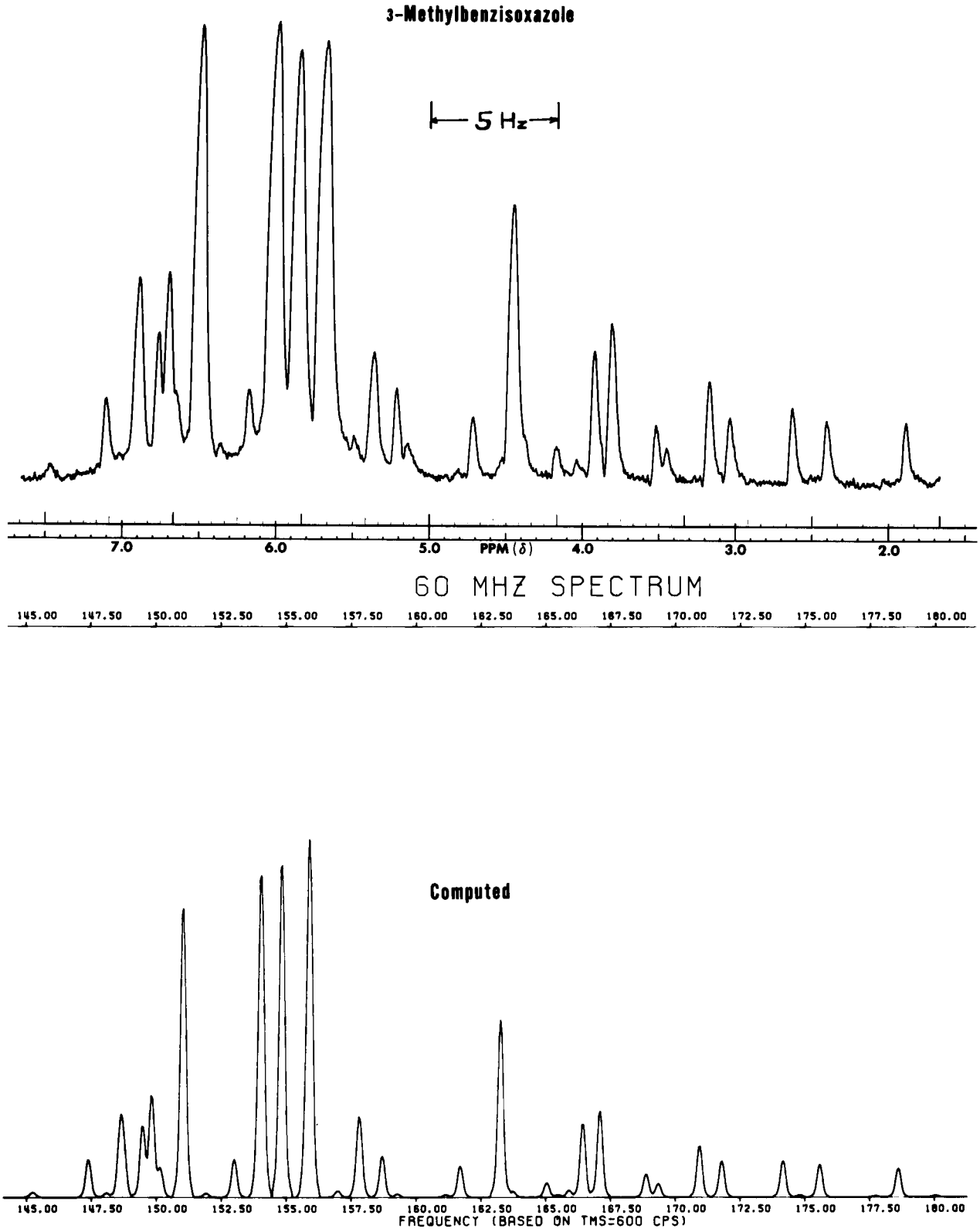
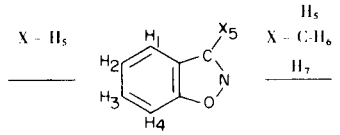



Figure 4. Comparison of experimental and computer simulated spectra of 3-methylbenzisoxazole.

TABLE II

Spectral Parameters of Benzisoxazole and 3-Methylbenzisoxazole




| | $\nu$ | $\nu$ |
|---|---|---|
| 1 | 461.675 ± .016 | 446.531 ± .024 |
| 2 | 434.732 ± .025 | 430.764 ± .026 |
| 3 | 448.437 ± .029 | 446.712 ± .061 |
| 4 | 454.536 ± .036 | 447.945 ± .044 |
| 5 | 531.196 ± .015 | 6 = 7 = 146.0 |
| | J | J |
| 1,2 | 7.884 ± .025 | 7.956 ± .031 |
| 1,3 | 1.367 ± .036 | 1.327 ± .056 |
| 1,4 | 0.775 ± .030 | 0.671 ± .069 |
| 1,5 | 0.035 ± .022 | 1,6 = 1,7 = 0 |
| 2,3 | 7.014 ± .065 | 6.923 ± .083 |
| 2,4 | 1.013 ± .084 | 0.960 ± .087 |
| 2,5 | 0.103 ± .023 | 2,6 = 2,7 = 0 |
| 3,4 | 8.439 ± .035 | 8.328 ± .021 |
| 3,5 | -0.178 ± .035 | 3,6 = 3,7 = 0 |
| 4,5 | 1.160 ± .034 | 4,6 = 4,7 = 0 |
| | | 5,6 = 5,7 = 6,7 = 0 |

Results and Discussion.

The iteratively refined spectral parameters are listed in Tables I and II. Unsubstituted benzisoxazole was treated as a five spin system which generates 210 theoretical lines. Most of these lines, however, arise from low probability multiplet spin flips and result in zero or low intensity transitions. Of the observable lines, 72 were assigned and the largest deviation between any observed and calculated line was .075 Hz. The iterative refinement was stopped at a root mean square error of .073 Hz. As an aid in making line assignments, energy level and transition diagrams were constructed. Assigned transitions were drawn between the appropriate energy levels to determine the self-consistency of these assignments and to insure that each energy level was involved in the computation.

Substituting a methyl group for the hydrogen in the heterocyclic ring removed some of the fine structure and allowed the benzenoid protons to be treated as an ABCD spin system. Of the 56 allowable transitions, 32 were assigned with the largest line error being 0.116 Hz. The rms error was .056 Hz.

Anthranil was also treated as a five spin system because of inter-ring coupling. The number of assigned lines was 75. The greatest line error and rms error were .131 and .053 Hz, respectively. As in the case of the methylbenzisoxazole, however, methyl substitution in this compound failed to simplify the spectrum because of some additional inter-ring couplings. In fact, the spectrum had to be treated as a seven spin system which produces 3003 theoretical transitions. In extracting the parameters from this spectrum, 256 lines were assigned. The largest error in any one line was .090 Hz and the rms error was .035 Hz.

In all four cases the iteratively refined chemical shifts and coupling constants were used to generate a theoretical spectrum. The agreement between these spectra and the experimental traces is illustrated in Figures 1-4.

Examination of the coupling constants listed in Tables I and II reveals some interesting comparisons among the intra-ring couplings and the long range inter-ring interactions. First, the intra-ring coupling constants in the benzisoxazoles reflect "normal" aromaticity; *i.e.* $J_{ortho} > J_{meta} > J_{para}$.

On the other hand, the ordering for the anthranil J's is $J_{ortho} > J_{para} > J_{meta}$. Also, in the latter compound, $J_{1,2}$ and $J_{3,4}$ are much larger than the other *ortho* coupling $J_{2,3}$. These facts point to a diene-type system with the size of the *ortho* couplings coinciding with the bond order. The much larger *para* coupling in anthranil further suggests a butadiene structure (13). Substitution of a methyl group in the smaller ring has little effect on the intra-ring coupling constants.

As expected, long ring inter-ring couplings occurred only along well defined paths. For example, the spin interactions between protons 4 and 8 in benzisoxazole and anthranil follow the well known straight zig-zag route (14) across five bonds and result in appreciable coupling. These *epi*-coupled protons are arranged in a planar trans-trans configuration and the interaction is believed to be dominated by the $\sigma$ framework (15). In both cases, substitution of a methyl group at the 5 position extends the path by one more bond and the attendent departure from coplanarity is apparently sufficient to reduce this coupling to zero. For benzisoxazole, this is the only observable inter-ring interaction and its elimination results in a substantially simplified spectrum. One other significant long range interaction was found in anthranil, namely that between protons 2 and 5. Although these connecting bonds also form a straight zig-zag path, the coupling interaction is not drastically reduced despite extending the path by one more bond with a methyl group. This again suggests the butadiene-type bond fixation of a quinoid structure with significant $\sigma$-$\pi$ interaction. Normally, $\sigma$-coupling decreases rapidly with increasing separation between coupled protons while $\pi$ coupling is not rapidly attenuated as the number of intervening bonds is increased (16).

A small coupling of approximately 0.2 Hz is also noted for $J_{1,5}$ in the spectrum of unsubstituted anthranil. Despite having the shortest inter-ring path between them, these two *peri* protons are not appreciably coupled, presumably since they are not part of the preferred zig-zag structure. Several other small couplings are listed in the tables; however, none is believed meaningful.

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