N-Oxides and Related Compounds. Part XXXI.[1] The Nuclear Magnetic Resonance Spectra and Tautomerism of Some Substituted Benzofuroxans

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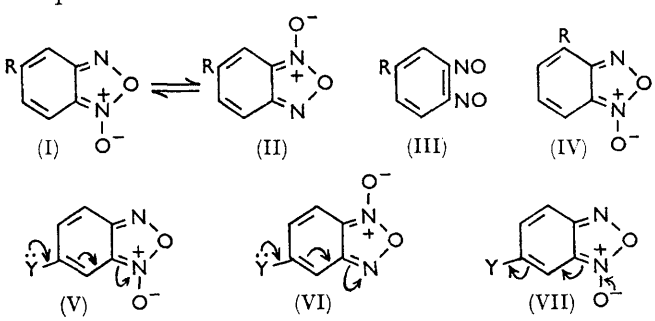
The tautomerism of eight benzofuroxans has been studied by proton magnetic resonance at low temperatures. The equilibrium constants implied small (0—500 cal./mole) energy differences, and indicated that electron-acceptor groups favoured the 6-position and electron-donor groups the 5-position. The activation energies for the equilibrations were in the region of 14 kcal./mole.

NUCLEAR MAGNETIC RESONANCE spectroscopy has established the structure of benzofuroxan as a rapidly-equilibrating system between benzofurazan 1- and 3-oxides (I ⇌ II; R = H), probably *via* the intermediate *o*-dinitrosobenzene (III).[2-6] The activation energy (estimated at *ca.* 15 kcal./mole [3]) for the equilibration is such that the aromatic protons show coalescence temperatures near 5°, averaging chemical shifts of *ca.* 8 c./sec.[3] 4-Nitrobenzofuroxan shows a single ABC spectrum at all temperatures, indicating that one form, presumably represented by formula (IV; R = NO_2), predominates to the extent that the alternative 3-oxide structure is undetectable at the low temperatures required to "freeze" the equilibrium on the n.m.r. time-scale. In the case of the corresponding 5-substituted derivative, however, both 5-nitro- (I) and 6-nitro- (II; R = NO_2) structures are present, the spectrum at −31° indicating that *ca.* 70% of (II) exists with *ca.* 30% of (I) in the equilibrium mixture.[3] Other benzofuroxans which have been studied by n.m.r. at low temperatures include the 5,6-dinitro-,[3,7,8] 5,6-dichloro-,[9] 4,7-dichloro-,[9] 4,7-dibromo-,[7,9] and 5-methyl-[7] compounds.



The equilibrium between (I) and (II) appears to provide a direct comparison between the electronic properties of the nitrogen atom (position 3) and the *N*-oxide group (position 1) of the benzofuroxan system. At first sight, it might be supposed that both electron-

[1] Part XXX, R. Eisenthal, A. R. Katritzky, and E. Lunt, *Tetrahedron*, 1967, **23**, 2775.
[2] A. R. Katritzky, S. Øksne, and R. K. Harris, *Chem. and Ind.*, 1961, 990.
[3] R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 1963, 197.
[4] F. B. Mallory and C. S. Wood, *Proc. Nat. Acad. Sci.*, 1961, **47**, 697.
[5] G. Englert, *Z. analyt. Chem.*, 1961, **181**, 447 (*Chem. Abs.*, 1962, **56**, 1082).
[6] P. Diehl, H. A. Christ, and F. B. Mallory, *Helv. Chim. Acta*, 1962, **45**, 504.
[7] G. Englert, *Z. Electrochem.*, 1961, **65**, 854 (*Chem. Abs.*, 1962, **57**, 6771).
[8] B. Dischler and G. Englert, *Z. Naturforsch.*, 1961, **16**a, 1180.
[9] F. B. Mallory, S. L. Manatt, and C. S. Wood, *J. Amer. Chem. Soc.*, 1965, **87**, 5433.

donor and electron-acceptor groups would show a preference for conjugation with the *N*-oxide group rather than with the nitrogen atom (cf. pyridine and pyridine *N*-oxide [10]). In the former case, conjugation to the oxide (as V) would be preferred to (VI), while in the latter, the *N*-oxide group can act as an electron-donor (VII); the latter type of interaction has already been invoked to explain the preference for form (II; R = NO_2) in 5-nitrobenzofuroxan.[3] The present results appear to indicate either that conjugative influences in the ground electronic states of these molecules are small, or that opposing influences are fairly evenly balanced.

EXPERIMENTAL

The compounds were prepared by methods previously described, and had melting points corresponding to those in the literature: 5,6-dichloro-, 130—131° (lit.,[9] 130·8—131·2°), 5-chloro-, 47—48° (lit.,[11] 48°), 5-methyl-, 97° (lit.,[11] 97°), and 5-methoxy-benzofuroxan, 116—117° (lit.,[12] 118°). The preparations of 5-acetoxy-, 5-carboxy-, 5-acetamido-, and 5-ethoxycarbonylamino-benzofuroxan are described in ref. 13. 5-Methyl-6-nitrobenzofuroxan was supplied by Dr. A. S. Bailey.

Treatment of ethyl 4-chloro-3-nitrobenzoate with sodium azide in aqueous acetone (cf. the procedure for halide–azide exchange described by Bailey and Case [14]) gave the corresponding *azide* as pale yellow needles, m. p. 83—84° (decomp.), from hexane (Found: C, 46·1; H, 3·6; N, 23·6. $C_9H_8N_4O_4$ requires C, 45·8; H, 3·4; N, 23·7%). The azide decomposed at 110° in acetic acid to yield 5-*ethoxycarbonylbenzofuroxan* which crystallised from ethanol or hexane as needles, m. p. 66° (Found: C, 51·8; H, 4·1; N, 13·6. $C_9H_8N_2O_4$ requires C, 51·9; H, 3·9; N, 13·5%).

Some spectra were obtained on a Varian V4300B spectrometer, under the experimental conditions described earlier; [3] others were measured on a Varian HA 100 instrument, and room-temperatures spectra (*ca.* 34°) were taken on Perkin-Elmer 40 and 60 Mc./sec. instruments. Solutions were approximately 10% (w/v) in acetone for the room-temperature spectra. For low-temperature studies, saturated solutions were used at −60°. Tetramethylsilane was used as an internal standard in all cases. Temperatures quoted are accurate to ±2°. Free energies of activation, ΔG^*, were obtained as in previous work [3,15] from the coalescence temperature T_c and the chemical shift δ (in c./sec.) being averaged by application of the expression (see Note below):

$$\Delta G^* = 4{\cdot}59T_c[9{\cdot}97 + \log_{10}(T_c/\delta)] \qquad (1)$$

Uncertainties in the measurement of T_c and δ introduce errors into ΔG^* which may be as great as ±1 kcal./mole. ΔG ($= -RT \ln K$) values for the equilibria are susceptible to errors in K: figures quoted are probably correct to ±50 cal.

Chemical shifts for the ABC spectra were calculated following Hoffman and Gronowitz: [16] the spectra were analysed on the digital computer EDSAC 2, and the I.C.T. Atlas computer at the National Institute for Research in Nuclear Sciences, Chilton, Didcot, Berkshire.

Note.—Eyring's equation [17] relates to the first-order rate constant of a reaction with its free energy of activation as in (2).

$$k_r = (kT/h) \cdot \exp \cdot (-\Delta G^*/RT) \qquad (2)$$

The simplified form of Gutowsky and Holm's expression for the line shapes of exchanging species [18] gives $2\tau = \sqrt{2}/\pi\delta$ as the relation between the chemical shift, δ, and the lifetime of the state, 2τ, at the point where the signals coalesce. Substituting $k_r = 1/(2\tau) = \pi\delta/\sqrt{2}$ into the Eyring equation leads to equation (1).

RESULTS AND DISCUSSION

Chemical shifts and coupling constants are recorded in Tables 1 and 2, respectively. Assignments of chemi-

TABLE 1

Chemical shifts and free energy values for the tautomerism of substituted benzofuroxans

Substituted benzofuroxan	Time-averaging	Chemical shifts of proton at position [a,b] 4	5	6	7	ΔG^* or ΔG [a,c] (kcal./mole)
5,6-Dichloro-	No	1·88	—	—	2·12	(0)
5,6- ,, ...	Yes	2·00	—	—	(2·00)	13·3
5-Chloro-	No	2·21	—	2·72	2·47	0·20
6- ,, ...	No	2·22	2·55	—	2·46	—
5(6)- ,, ...	Yes	2·34	—	2·64	2·35	13·9
5-Methoxy-	No	3·16	—	3·03	2·63	0·40
6- ,, ...	No	2·38	2·85	—	3·49	—
5(6)- ,, ...	Yes	3·33	—	2·94	2·51	14·6
5-Acetoxy-	No	2·50	—	2·91	2·49	0·10
6- ,, ...	No	2·26	2·65	—	2·72	—
5(6)- ,, ...	Yes	2·61	—	2·78	2·37	13·8
5-Carboxy-	No	1·60	—	2·22	2·46	—
6- ,, ...	No	2·21	2·06	—	1·90	0·40
5(6)- ,, ...	Yes	1·75	—	2·14	2·33	14·0
5-Ethoxycarbonyl-	No	1·63	—	2·26	2·47	—
6- ,,	No	2·22	2·09	—	1·92	0·45
5(6)- ,,	Yes	1·78	—	2·17	2·35	14·0
5-Methyl-6-nitro-	No	2·20	—	—	1·75	—
6-Methyl-5- ,,	No	1·59	—	—	2·39	0·05
5(6)-Methyl-6(5)-nitro-	Yes	2·29	—	—	1·66	12·1
5-Acetamido-	No	1·76	—	2·76	2·61	0
6- ,, ...	No	2·37	2·63	—	1·98	—
5(6)- ,, ...	Yes	1·87	—	2·70	2·49	14·1
5(6)-Ethoxycarbonylamino-	Yes	2·18	—	2·59	2·47	— [d]

[a] Values which, owing to chemical equivalence, are zero or are identical with others listed earlier in the Table, are in parentheses. [b] Low-temperature chemical shifts are "corrected" to 28° by adjusting the centre of gravity of the spectrum to the value assumed at the higher temperature. [c] ΔG^* values (free energy of activation for equilibration between tautomers) are entered in the row applicable to the time-averaged spectra; ΔG values (free-energy differences between tautomers) are entered in the row applicable to the *more-favoured* tautomer. [d] Not determined.

[10] A. R. Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[11] A. G. Green and F. M. Rowe, *J. Chem. Soc.*, 1912, **101**, 2452; 1913, **103**, 897.
[12] G. Tappi and P. V. Forni, *Ann. Chim. appl.*, 1949, **39**, 338; R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Amer. Chem. Soc.*, 1954, **76**, 2233.
[13] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* (*C*), 1966, 971.
[14] A. S. Bailey and J. R. Case, *Tetrahedron*, 1958, **3**, 113.
[15] A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, *J. Chem. Soc.*, 1965, 5958.
[16] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, 1961, **16**, 515.
[17] S. Glasstone, "Textbook of Physical Chemistry," 2nd edn., Macmillan, London, 1956, p. 1104.
[18] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, pp. 222—224.

cal shifts to protons, and, with the low-temperature spectra, of the individual spectra to the correct tautomers, are in many cases ambiguous. Reasons for the assignments made and discussion of alternative possibilities will be presented in the course of consideration of the individual compounds.

5,6-*Dichlorobenzofuroxan*.—At room temperature the rapid equilibration of this compound gives rise to an A_2 singlet (τ 2·00) from the two aromatic protons. On cooling the solution, the singlet broadened, and then split into an AB pattern. At the same time the chemical shift moved down-field, and at −40° the spectrum appeared as two barely-split peaks at τ 1·71 and 1·95.

TABLE 2

Coupling constants (c./sec.) in substituted benzofuroxans

Substituted benzofuroxan	*ortho*, across 4,5 or 6,7	*meta*, across substituent	*para*, across 4,7
5,6-Dichloro-	—	—	0·8
5-Chloro-	9·4	1·6	0·8
6- ,,	9·2	1·4	0·7
5(6)- ,,	9·5	1·7	0·7
5-Methoxy-	9·0	1·8	1·0
6- ,,	9·9	2·2	0·4
5(6)- ,,	9·8	1·9	0·3
5-Acetoxy-	9·3	2·0	1·0
6- ,,	9·7	1·9	0·8
5(6)- ,,	9·5	1·9	0·7
5-Carboxy-	9·6	1·2	1·0
6- ,,	9·7	1·4	1·0
5(6)- ,,	9·2	1·2	0·8
5-Ethoxycarbonyl-	9·6	1·2	1·0
6- ,,	9·6	1·4	0·9
5(6)- ,,	9·7	1·2	1·0
5-Methyl-6-nitro-	—	—	—[b]
5-Acetamido-	9·6	1·6	0·9
6- ,,	9·9	1·8	0·9
5(6)- ,,	10·0	1·8	0·9
5(6)-Ethoxycarboxylamino-	9·5	1·5	0·9

[a] In $CHCl_3$ solution. [b] Not determined (<1 c./sec.).

The assignment of the high-field absorption to H(7) is consistent with the assignments in benzofuroxan itself, in which H(4) is 0·24 p.p.m. to low-field of H(7).[3] (This earlier assignment was based[3] upon a comparison of the chemical shifts of the protons of benzofuroxan, benzofurazan, and their 4-nitro-derivatives, and the assumption that 4-nitrobenzofuroxan exists as such, and not as the 7-nitro-compound.) The coalescence temperature was 268°K, and δ was 24·8 c./sec., giving an estimate for ΔG^* of 13·3 kcal./mole (see Table 1, column vii).

During this research, Mallory, Manatt, and Wood[9] reported E_a as 15·0 kcal./mole for this molecule. ($E_a = \Delta G^* + T\Delta S^* + \boldsymbol{R}T$, from the equations of Arrhenius and of Eyring.) Their method is based on the matching of theoretical and observed line shapes, for the simple A_2 (fast equilibrium) ⟶ AB (slow equilibrium) spectra. Their chemical-shift difference at −40° (14·4 c./sec. at 60 Mc./sec.) is in agreement with the present measurement (24·8 c./sec. at 100 Mc./sec.), to within 0·8 c./sec. Although the above workers do not quote a value of ΔG^*, insertion of their values for T_c and δ into equation (1) gives a figure of 13·3 kcal./mole, which is identical with that obtained in the present work. The entropy of activation, ΔS^*, reported[9] (+6 e.u.) is small.

5-*Chlorobenzofuroxan* (I ⇌ II; R = Cl).—At 21°, 5-chlorobenzofuroxan gives a well-defined ABC spectrum, in which the isolated proton shows clearly at τ 2·34. On cooling, the spectrum first dissolved into a trace without fine structure and then re-sharpened until at −32° a complex series of bands, resolvable into two separate ABC spectra, was observed; the protons without an *ortho* coupling absorbed at τ 2·21 and 2·46. If the higher-field of these is assigned to H(7) of the 6-chloro-isomer, and the lower-field to H(4) of the 5-chloro-, the chemical shift of both are seen to be 0·08 p.p.m. to low-field of the corresponding protons of benzofuroxan. Thus, the chlorine atom has only a small effect on the chemical shift of this adjacent proton (cf. chlorobenzene), and the assumption that its effect is also small on the other side leads to the assignments in Table 1.

Because of overlapping, the relative intensities of the two components were compared by analysing the spectra of the mixture of the two isomers by an iterative procedure, and then the calculated spectra were combined in various intensity ratios and converted into Lorentzian plots, with half-band widths of 0·5 c./sec. The best fit was provided by a ratio of 5- to 6-chloro-isomers of 3 : 2 at −32·4°, corresponding to an energy difference of *ca.* 200 cal./mole in favour of the 5-substituted compound. This result is in agreement with an *X*-ray crystal structure determination by Britton and Noland,[19] who found that 5-chloro- and 5-bromo-benzofuroxan existed as such (I; R = Cl) in the solid phase.

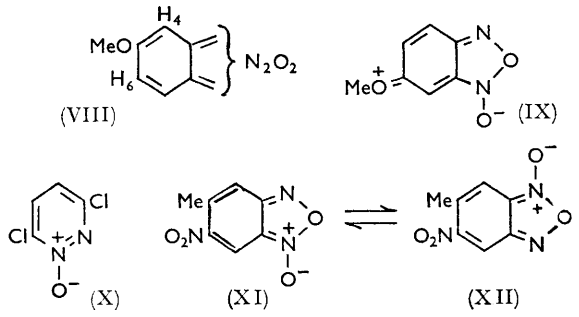
5-*Methylbenzofuroxan* (I ⇌ II; R = Me).—When this compound was studied (1963) the low-temperature spectra were available only at 40 Mc./sec. The separation of chemical shifts at this frequency was small, and both low- and room-temperature spectra gave poorly-defined traces. Much of the obscurity was due to coupling between the methyl group and the aromatic protons, as had been found earlier by Englert,[7] whose published spectrum at low temperatures (in CH_2Cl_2) showed two peaks at low-field and a group at *ca.* τ 3·0, in all probability assignable to the 4- and 7-protons, respectively, of the 6-methyl isomer. From a consideration of the areas of these bands and the area of the spectrum as a whole, it seems that the 5- and 6-methyl isomers are present in about equal proportions in the solution at −33°.

5-*Methoxybenzofuroxan* (I ⇌ II; R = OMe).—At 21° the aromatic protons of the rapidly-equilibrating 5-methoxybenzofuroxan give a well-defined ABC pattern in which the isolated proton absorbs at highest field, at τ 3·33. This considerable up-field shift of the proton at position 4 (VIII) due to the methoxy-group indicates that H(6) should absorb well up-field of H(7), as in the assignments of Table 1.

[19] D. Britton and W. E. Noland, *Chem. and Ind.*, 1962, 563; *J. Org. Chem.*, 1962, **27**, 3218.

On cooling, the spectrum coalesced, then sharpened into a complex trace analysed as for the 5-chloro-analogue into two ABC spectra in a ratio of approximately 2 : 1, at −16°. The minor component had its isolated proton at the highest field (τ 3·49), so is the 6-methoxy-tautomer (II; R = OMe). Other assignments follow as outlined above.

The preponderance of the 5-methoxy-tautomer ($\Delta G \sim$ 400 cal./mole) is somewhat surprising, as it might be supposed that conjugation with the *N*-oxide group (as V) would be preferred over that with the nitrogen atom (VI). It is hardly likely that entropy factors are obscuring a real enthalpy preference (ΔH) for the 6-methoxy-compound. A possible explanation is that canonical form (IX), with its accumulation of electron lone-pairs in the region of N(1) is very unfavoured and so unimportant. Nucleophilic substitution in 3,6-dichloropyridazine 1-oxide (X) has been shown to involve preferential displacement of the 3-chlorine atom:[20] activation of the 6-chlorine by the *N*-oxide group would require a similar accumulation of electron pairs in the σ-complex intermediate. Dipolar repulsion between the *N*-oxide and the methoxy-groups may also play a part, and this effect may predominate in deciding the preferred structure of 5-chloro-compound.



5-Acetoxybenzofuroxan (I ⇌ II; R = OAc).—The ABC spectrum of the aromatic protons (Figure 1) shows the isolated (C) proton at intermediate chemical shift between the A and B protons (as with the 5-chloro-compound). On cooling, coalescence occurs (Figure 2) and then the spectrum sharpens again (Figure 3). The coalescence temperature was 273°K, and the chemical shift averaged was 24 c./sec. giving $\Delta G^* = 13{\cdot}8$ kcal./mole. The 5-acetoxy-tautomer appears to predominate in the mixture, although not to the same extent as the 5-methoxy- does over the 6-tautomer. From Figure 3, an estimate of 5 : 4 for the ratio can be made, corresponding to $\Delta G = 100$ cal.

5-Carboxybenzofuroxan (*Benzofuroxan-5-carboxylic Acid*) (I ⇌ II; R = CO_2H).—Figures 4 and 5 illustrate the room- and low-temperature spectra, respectively. The isolated aromatic proton absorbs well to low-field of the two others; observing the coalescence is thus relatively simple. From $T_c = 278$°K, and $\delta = 29{\cdot}5$ c./sec., ΔG^* was estimated as $14{\cdot}0 \pm 1$ kcal./mole. Assignment follows the usual criteria, and leads to the conclusion that the 6-carboxylic acid predominates over the 5-,

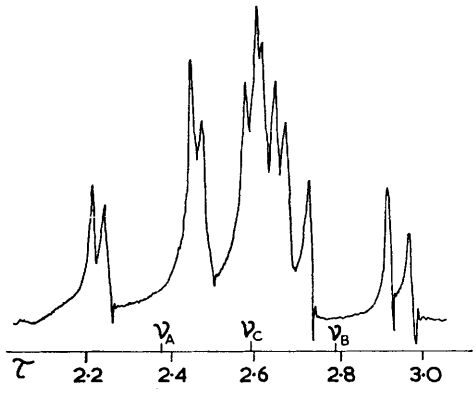
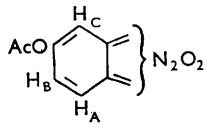


FIGURE 1 The spectrum of 5-acetoxybenzofuroxan at 40 Mc./sec. and 28°



which is present to the extent of *ca.* 30% at −40°: $\Delta G = ca.$ 320 cal./mole. This compares with a value of *ca.* 360 cal./mole for 5-nitrobenzofuroxan;[3] the difference is probably not outside experimental error.

5-Ethoxycarbonylbenzofuroxan (*Ethyl Benzofuroxan-5-carboxylate*) (I ⇌ II; R = CO_2Et).—In the aromatic region, the spectrum was very similar to that for the

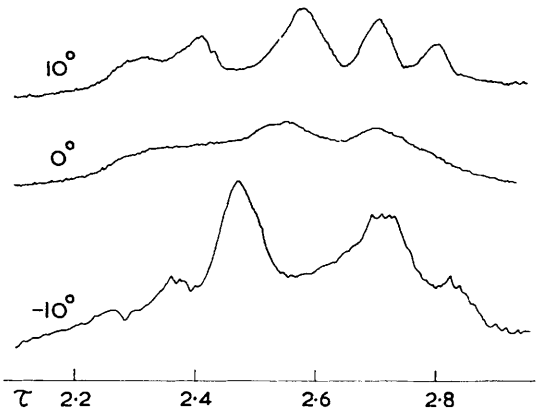


FIGURE 2 The spectra of 5-acetoxybenzofuroxan at 100 Mc./sec. at intermediate temperatures

carboxylic acid: parameters are in Table 1. The coalescence temperature was 278° ± 10°K and $\delta = 29{\cdot}0$ c./sec.; $\Delta G^* = 14{\cdot}0 \pm 1$ kcal./mole. Integration of the spectrum at low temperature showed the presence of *ca.* 27% of the 5-isomer at −40°; $\Delta G = 450$ cal./mole. The predominance of the 6-tautomer over the 5- is considered to be evidence for the importance of mesomerism of type (VII) in the ester and the acid, as reported earlier [3] for the nitro-compound.

[20] F. Yoneda and Y. Nitta, *Chem. Pharm. Bull.* (*Tokyo*), 1963, **11**, 269.

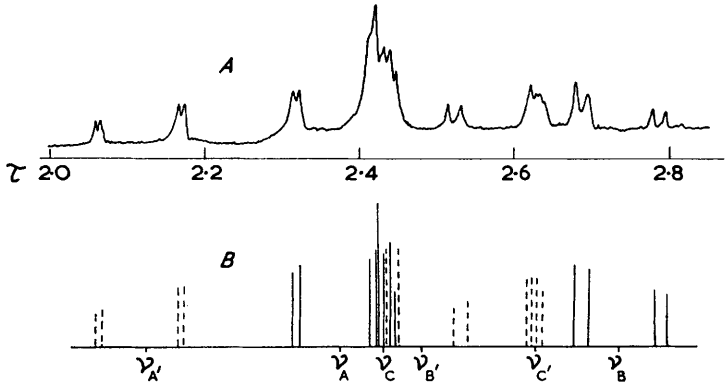
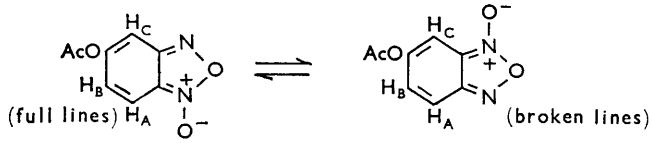


FIGURE 3 The spectra of 5- and 6-acetoxybenzofuroxan at 100 Mc./sec. and −40°: (*A*) observed, (*B*) calculated



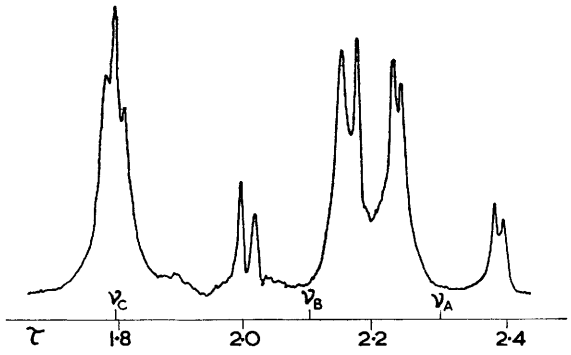
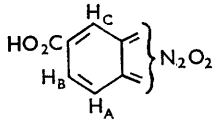


FIGURE 4 The spectrum of 5-carboxybenzofuroxan at 40 Mc./sec. and 28°



5-Methyl-6-nitrobenzofuroxan (XI ⇌ XII).—The spectrum in the region τ 1—3 at 21° showed two peaks: no *para* coupling was resolved. On cooling, coalescence (at −10°) was followed by the appearance of four singlets. A mean δ for the chemical shift of 7·6 c./sec. gives $\Delta G^* = 12{\cdot}1$ kcal./mole.

As with the 5-methyl compound, the 4-proton showed evidence of coupling with the methyl group, although the splitting was not resolved. The 7-proton adjacent to the nitro-group appeared at lower-field, but significantly higher (0·2—0·3 p.p.m.) than the corresponding proton in 5(6)-nitrobenzofuroxan. This suggests that the nitro-group is sterically hindered from attaining coplanarity with the ring, with consequent reduction in the importance of the canonical form derived from the electron-shift (VII), and further evidence for this is provided by the equilibrium constants. Unlike the case of the simple nitro-derivatives, (ΔG = *ca.* 360 cal.

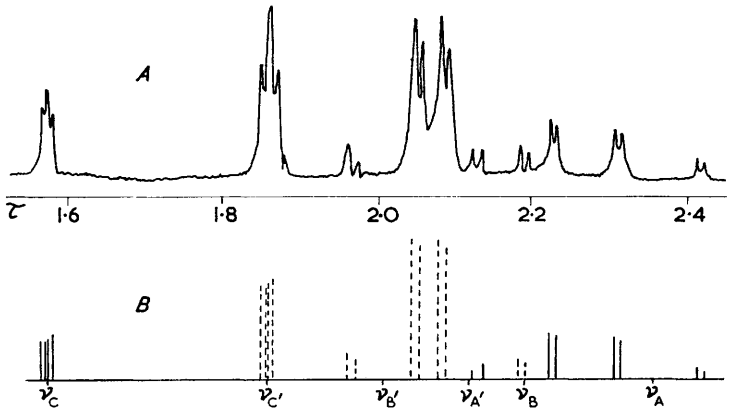
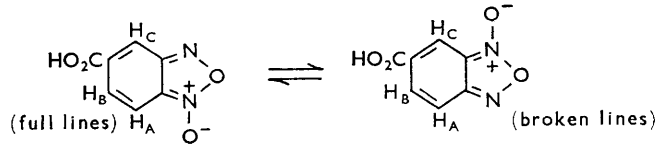


FIGURE 5 The spectra of 5- and 6-carboxybenzofuroxan at 100 Mc./sec. and −40°: (*A*) observed, (*B*) calculated



in favour of the 6-nitro-compound [3]) the two tautomers are of almost equal weight at −32°, with perhaps a 5% preponderance of the 5-methyl-6-nitro-tautomer (ΔG = *ca.* 50 cal./mole).

5-Acetamidobenzofuroxan (I ⇌ II; R = $NHCOCH_3$).—Widely separated chemical shifts gave well-resolved room- and low-temperature spectra, with the isolated protons to low-field of the others: aromatic protons *ortho* to the acetamido-groups of acetanilide and acet-*p*-toluidide in acetone are similarly situated with respect to the rest. Coalescence of this signal was observed at 277°K; the separation of the two components at low temperature was 21·9 c./sec., giving ΔG^* = 14·1 kcal./mole. Integration of these signals at −40° showed them to be of equal areas: ΔG is *ca.* zero between the isomers in this system.

5-Ethoxycarbonylaminobenzofuroxan (I ⇌ II; R = $NHCO_2C_2H_5$).—The aromatic region gave a room-temperature spectrum very similar to that of the 5-acetonitro-compound, but owing to poor solubility in acetone at low temperatures it proved impossible, with the equipment available, to obtain spectra of the fixed forms.

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