# Determination of the Substitution Pattern of an Isoxazole by $^{13}C$ Nuclear Magnetic Resonance

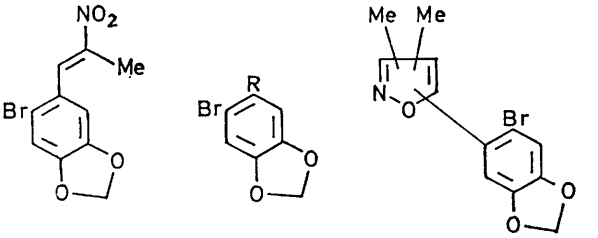
By **Gavin M. Buchan** and **Alan B. Turner,*** Chemistry Department, University of Aberdeen, Aberdeen AB9 2UE, Scotland

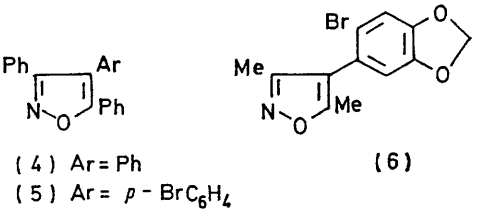
The isoxazole obtained by condensation of nitroethane and 6-bromopiperonal is shown to have the 3,5-dimethyl-4-aryl structure (6) by comparison of its $^{13}C$ n.m.r. spectrum with those of several model compounds.

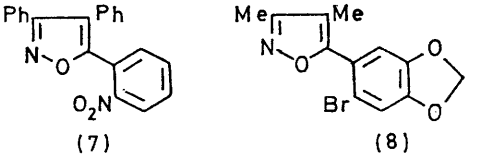
THE standard methods for determination of the substitution pattern of an isoxazole are hydrogenation and ozonolysis.[1] The former, carried out at room temperature and atmospheric pressure over Raney nickel, leads,[2] by rupture of the O–N bond, to a β-imino-ketone, which can be hydrolysed to a readily identified β-diketone. Ozone attacks the carbon–carbon double bond to give an acyl oxime, which can be hydrolysed to an α-diketone and a carboxylic acid.[3]

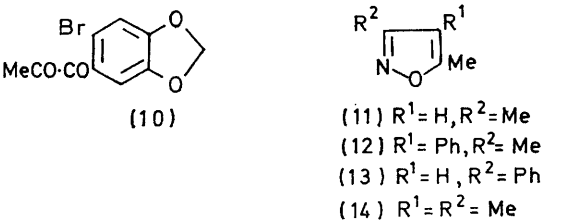
During attempts to prepare the β-nitrostyrene (1) by condensation of nitroethane with 6-bromopiperonal (2), we obtained instead in low yield a crystalline compound, $C_{12}H_{10}BrNO_3$. Its i.r., n.m.r., and u.v. spectra were consistent with the isoxazole structure (3), but the substitution pattern in the isoxazole nucleus could not be established from these spectral data.

One preparation of isoxazoles by base-catalysed condensation of aromatic aldehydes with nitroalkanes has been known since 1911, when Heim [4] obtained triphenylisoxazole (4) from benzaldehyde and α-nitrotoluene. Similar experiments with *para*-substituted benzaldehydes gave isoxazoles with the substituted aromatic ring in the 4-position; *e.g.* *p*-bromobenzaldehyde formed [5] the isoxazole (5) with α-nitrotoluene. This led to Scheme 1 being proposed for the mechanism of the condensation, and in the light of this mechanism structure (6) would be predicted for the isoxazole (3). However, Ruggli [6] obtained 5-(*o*-nitrophenyl)-3,4-diphenylisoxazole (7) by condensation of *o*-nitrobenzaldehyde with α-nitrotoluene. This shows that a second mechanism (Scheme 2) might operate to give the alternative substitution pattern [structure (8)] for the isoxazole (3), although the operation of this mechanism may depend upon the ability of the substituent (in this case the nitro-group) in the aromatic ring to promote Michael addition at the appropriate β-carbon atom of the intermediate styrene. Since



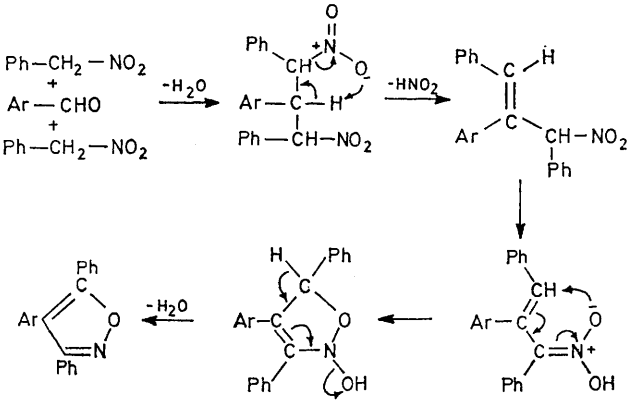




[1] A. Quilico, 'The Chemistry of Heterocyclic Compounds,' ed. R. H. Wiley, Interscience, 1962, vol. 17, pp. 24—27.
[2] G. S. d'Alcontres, *Gazzetta*, 1950, **80**, 441.
[3] E. P. Kohler and N. K. Richtmeyer, *J. Amer. Chem. Soc.*, 1928, **50**, 3092.
[4] F. Heim, *Ber.*, 1911, **44**, 2016.
[5] N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 1940, 446.
[6] P. Ruggli and B. Hegedus, *Helv. Chim. Acta*, 1939, **22**, 405.

routine spectral data could not be used to distinguish between the two isomers, the degradative methods referred to above were investigated.



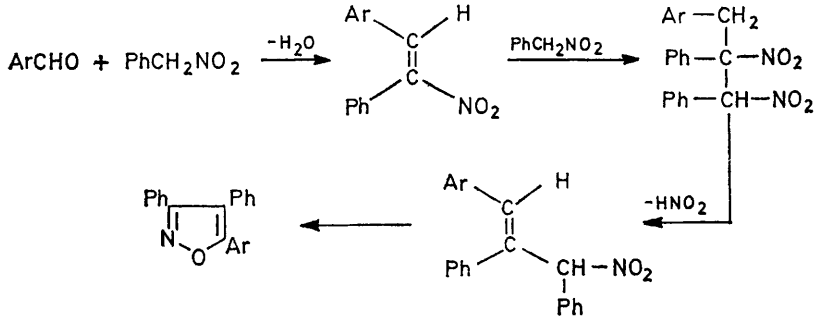
SCHEME 1

All attempts to carry out hydrogenation failed, both at 1 atm and at 4 atm. Ozonolysis of the isoxazole, followed by acidic hydrolysis, gave only a poor yield of a complex mixture of products, and although the failure to detect any 6-bromopiperonylic acid (9) was evidence against structure (8), the test was rendered inconclusive by the failure to detect or isolate any α-diketone (10) which should have arisen from (6).

Unambiguous synthesis of (8) appeared difficult, as the conventional routes involving 1,3-cycloaddition of acetonitrile oxide to an alkyne or diketone synthesis, followed by cyclisation of the mono-oxime, could give two possible products, or would be subject to steric hindrance by the *ortho*-bromo-substituent.

A much simpler solution to the problem was offered by $^{13}C$ n.m.r. spectroscopy,[7] as it seemed likely that the chemical shifts of the carbon atoms of the methyl groups and of the isoxazole ring would be markedly influenced by the substitution pattern. Although a number of five- and six-membered nitrogen heterocycles have been studied [8] by this technique, no reference could be found to its application to isoxazoles. It was therefore necessary to prepare some simple model compounds, whose spectra could be interpreted unambiguously.

The isoxazoles (11)—(14) were readily prepared by literature methods; their $^{13}C$ n.m.r. spectra are collected in the Table. Assignments follow directly from multiplicities in the off-resonance decoupled spectra and/or chemical shift values,[7] although the assignments for C-3 and -5 are tentative, as are those for the methyl groups attached to these carbon atoms. The signal at 6.6 p.p.m. in the spectrum of (14) could be unambiguously ascribed to the 4-methyl group, since it appeared upfield by *ca.* 4 p.p.m. from all other 3- and 5-methyl signals in the model compounds, and these showed little variation with the presence or absence of a 4-substituent. Also the chemical shifts of C-3 and -5 remained virtually unchanged regardless of the substitution pattern, whereas C-4 showed a smooth progression from 100.1—102.3 (no substituent),



SCHEME 2

$^{13}C$ N.m.r. data for isoxazoles

| Compound | C-3 (s) | C-4 (d) | C-5 (s) | 3-$CH_3$ (q) | 4-$CH_3$ (q) | 5-$CH_3$ (q) | Aromatic |
|---|---|---|---|---|---|---|---|
| (11) | 169.0 | 102.3 | 159.9 | 12.1 | | 11.3 | |
| (12) | 165.1 | 116.7 | 158.6 | 11.4 | | 10.7 | 127.5, 128.4, 128.7, 129.1, 130.2, and 130.5 |
| (13) | 169.6 | 100.1 | 160.3 | | | 11.5 | 125.8, 127.6, 128.9, and 130.0 |
| (14) | 164.2 | 109.0 | 159.9 | 10.7 | 6.6 | 10.0 | |
| (6) | 166.1 | 115.9 or 116.4 | 158.5 | 11.6 | | 10.5 | 111.3 and 113.0 (2′ and 5′), 115.9 or 116.4 (6′), 124.0 (1′), and 147.5 and 148.0 (3′ and 4′) [102.1(t), $OCH_2O$] |

Unambiguous synthesis of (8) appeared difficult, as the conventional routes involving 1,3-cycloaddition of acetonitrile oxide to an alkyne or diketone synthesis, followed by cyclisation of the mono-oxime, could give through 109.0 (methyl substituent), to 116.7 (phenyl substituent).

The $^{13}C$ n.m.r. spectrum of the isoxazole (3), recorded under the same conditions (Table), allowed assignment of the signals of the methyl groups, the methylenedioxy group, and C-2′ and -5′ directly from their multiplicities in

[7] (*a*) J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972; (*b*) F. A. L. Anet and G. C. Levy, *Science*, 1973, **180**, 141; (*c*) J. A. Elvidge, 'Introduction to Spectroscopic Methods for the Identification of Organic Compounds,' vol. 2, ed. F. Scheinmann, Pergamon, Oxford, 1974, pp. 222—230.

[8] F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, 1968, **90**, 3543; F. J. Weigert, J. Husar, and J. D. Roberts, *J. Org. Chem.*, 1973, **38**, 1313.

the off-resonance decoupled spectrum, and the C-3 and -5 signals were identified by comparison with the data from the model compounds. The presence of various substituents in the aromatic ring made the assignments of C-1′, -3′, -4′, and -6′ more difficult, although tables of substituent effects in the benzene ring are available,[9] indicating the effects on the chemical shifts of the carbon atoms to which the substituents are attached and of the other carbon atoms in the ring. Although these changes in chemical shift are strictly additive only in those cases in which none of the substituents are *ortho* to one another (in which case steric effects cause deviations from predicted behaviour), the general trends allow certain assignments to be made. Thus a methoxy-group induces a shift of +30.2 p.p.m. in the δ value of the carbon atom to which it is attached (relative to the chemical shift of benzene itself, 128.7 p.p.m.), and a shift of −15.5 p.p.m. in the δ value of the *ortho*-carbon atom. This explains the low values (111—113 p.p.m.) observed for C-2′ and -5′, and allows assignment of the two signals at *ca.* 148 p.p.m. to C-3′ and -4′, because the shifts induced by a methoxy-group far outweigh those induced by a bromo-substituent, and similar properties would be expected for the methylenedioxy-group.

The C-4, -1′, and -6′ signals could not be identified with the same certainty, owing to lack of information on the effects of isoxazoles or comparable ring systems as substituents. However, C-1′ and -6′ would be equally affected by the methylenedioxy-group, and since bromine is one of the few recorded substituents (I and CN are the only others [7]) to induce a negative shift on the attached carbon atom, it seemed likely that of the remaining three signals, that 124 p.p.m. corresponded to C-1′ and those near 116 p.p.m. arose from C-4 and C-6′. Despite the uncertainty in the assignments of the last three carbon atoms, there was sufficient information to allow identification of the isoxazole as (6). The methyl signals at 10.5 and 11.6 p.p.m. clearly fitted the 3,5-dimethyl pattern shown by (11), (12), and (14), and particularly striking was the similarity to (12) (10.7 and 11.4 p.p.m.), the closest analogue of (6). The δ value for C-4 (116 or, possibly, 124 p.p.m.) was far enough removed from that of C-4 in (14) (109 p.p.m.) to rule out structure (8), and once again a value of 116 p.p.m. is in very good agreement with the data obtained for the 4-phenylisoxazole (12). This establishes that the isoxazole (6) is formed by a mechanism analogous to that in Scheme 1 (for Ph read Me).

Thus $^{13}C$ n.m.r. proved to be a convenient means of distinguishing structures (6) and (8), and the technique could find general use for the solution of this type of problem. In particular, the orientation of the 1,3-cycloaddition of nitrile oxides to unsaturated systems is the subject of a great deal of effort,[10] and $^{13}C$ n.m.r. should become of considerable value in elucidation of the structures of the product isoxazoles and isoxazolines.

## EXPERIMENTAL

$^{13}C$ n.m.r. spectra were recorded for solutions in deuteriochloroform solution with tetramethylsilane as internal standard by the Physico-Chemical Measurements Unit, Aldermaston, on a Bruker HX 90E spectrometer operating at 22.63 MHz.

*Model Isoxazoles.*—3,5-Dimethylisoxazole (11) was prepared by reaction of acetylacetone with hydroxylamine,[11] 3,5-dimethyl-4-phenylisoxazole (12) by reaction of 3-phenylpentane-2,5-dione [12] with hydroxylamine,[13] 5-methyl-3-phenylisoxazole (13) by reaction of benzoylacetone with hydroxylamine,[14] and trimethylisoxazole (14) by treatment of nitroethane with aqueous sodium hydroxide.[15]

*4-(6-Bromo-3,4-methylenedioxyphenyl)-3,5-dimethylisoxazole* (6).—A mixture of 6-bromopiperonal (26.5 g), nitroethane (21.0 ml), butylamine (2.0 ml), anhydrous sodium carbonate (1.12 g), and ethanol (130 ml) was heated under reflux for 3 h, and allowed to cool overnight. Concentration of the mixture *in vacuo*, followed by cooling in ice failed to elicit any precipitate of the expected nitrostyrene, and after almost all the solvent had been removed the dark oily residue was left at ambient temperature for 1 week. The resulting prisms were recrystallised from aqueous methanol to give the *isoxazole* (6) as needles (1.05 g, 3%), m.p. 109—110° (Found: C, 48.6; H, 3.5; Br, 27.1; N, 4.5%; $M^+$, 294.985 4. $C_{12}H_{10}BrNO_3$ requires C, 48.6; H, 3.4; Br, 27.0; N, 4.7%; $M^+$ for $^{79}Br$, 294.984 5), $\lambda_{max.}$ (MeOH) 219, 250sh, and 298 nm (ε 13 900, 6 000, and 4 200), $\nu_{max.}$ (KBr) 1 640 and 1 620 $cm^{-1}$, δ ($CDCl_3$) 2.15 (s, 5-Me) 2.30 (s, 3-Me), 6.05 (s, $OCH_2O$), 6.65 (s, 2′-H), and 7.14 (s, 5′-H), *m/e* 297/295 ($M^+$, 100%), 254(20), 252(20), 228(28), 226(28), 215(13), and 147(67).

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[9] Ref. 7*a*, p. 196.
[10] *Cf. e.g.* G. Bianchi, C. D. Micheli, R. Gandolf, P. Grünanger, P. V. Finzi, and O. V. de Pava, *J.C.S. Perkin I*, 1973, 1148, and refs. therein.
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[13] B. Bobranski and R. Woztowski, Pol. P. 50,520/1966 (*Chem. Abs.*, 1967, **66**, 55,480z).
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[15] W. R. Dunstan and T. S. Dymond, *J. Chem. Soc.*, 1891, 410.