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Sporidesmins. XIX†
The Diazotization and Coupling in Acid of *p*-Nitro- and 2,4-Dinitro-aniline to Veratrole or Guaiacol: ^{1}H N.M.R. of the Products in Deuterochloroform and Deuteroacetone

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Abstract

p-Nitrobenzenediazonium chloride in conc. HCl coupled to guaiacol (2-methoxyphenol) to give 4-hydroxy-3-methoxy-4′-nitroazobenzene, but did not couple to veratrole (1,2-dimethoxybenzene). 2,4-Dinitroaniline, diazotized in conc. HCl with no urea added, yielded 2-chloro-4,5-dimethoxy-2′,4′-dinitroazobenzene with neat veratrole. However, 2,4-dinitroaniline, diazotized in conc. HCl and then treated with urea, yielded 2-chloro-4-nitrobenzenediazonium chloride which again coupled in acid with guaiacol to give 2-chloro-4′-hydroxy-3′-methoxy-4-nitroazobenzene but not with veratrole in acetic acid. Veratrole added to 2,4-dinitrobenzenediazonium phosphate or trichloroacetate in acid media yielded 3′,4′-dimethoxy-2,4-dinitroazobenzene. These 2,4-dinitrobenzenediazonium salts coupled to guaiacol giving 4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene. *p*-Nitrobenzenediazonium and 2-chloro-4-nitrobenzenediazonium salts in acid gave the Gomberg reaction with veratrole forming the corresponding biphenyls. The ^{1}H n.m.r. spectra of all the products obtained in this investigation and the deshielding effect of deuteroacetone on four of the compounds are discussed. The deuterochloroform spectrum of 4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene at 60 MHz shows an anomalous set of 26 or more lines that are not attributable to a quinone hydrazone structure.

Introduction

The mycotoxin sporidesmin has a 5-chloro-6,7-dimethoxyindoline ring system. In order to form an antigen from sporidesmin without interfering with the toxic moiety, namely the epidithiodioxopiperazine ring system, it was proposed to form azo derivatives of sporidesmin at the remaining aromatic hydrogen at position 4 of the indoline system. Sporidesmin has no phenolic groups and is an unstable compound; therefore, the feasibility of diazonium coupling with veratrole as a model compound was investigated. The reaction conditions for, and the products obtained from, coupling to veratrole (1,2-dimethoxybenzene) were checked by comparison with those in coupling to guaiacol (2-methoxyphenol) and methylating.

Diazonium coupling to phenol is usually accomplished in an alkaline medium but, since sporidesmin is less stable in this medium than in acid, the diazotizations and couplings were investigated in acid media. Meyer *et al.*[1] have shown experimentally that 2,4-dinitrobenzenediazonium salts, precipitated from acetic acid solutions, couple to resorcinol dimethyl ether or phloroglucinol trimethyl ether in acetic acid. Therefore, couplings to veratrole should be possible and that in concentrated hydrochloric acid; sporidesmin is far less stable in sulfuric acid.

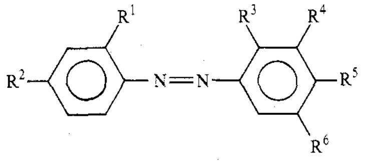
† Part XVIII, *Aust. J. Chem.*, 1981, **34**, 1215.

[1] Meyer, K. H., Irschick, A., and Schlösser, H., *Ber. Dtsch. Chem. Ges.*, 1914, **47**, 1741.

Discussion

p-*Nitrobenzenediazonium Chloride*

When guaiacol in methanol was added to *p*-nitrobenzenediazonium chloride solution (pH <1), prepared by the method of Nietzki,[2] 4-hydroxy-3-methoxy-4′-nitroazobenzene (2) was precipitated immediately. Raising the pH (5 M NaOH) increased the yield of (2) by about 10%. Thus neither the low pH nor the methanol was a hindrance to coupling. The melting point (171·5–173°) observed for compound (2) was at variance with that in the literature[3] (125–135°). Methylation with diazomethane gave 3,4-dimethoxy-4′-nitroazobenzene (3), the melting point of which agreed with that reported in the literature.[4] This derivative of veratrole was insoluble in the acidic coupling medium; hence, if a significant amount of it was formed it would precipitate in attempts to couple *p*-nitrobenzenediazonium chloride to veratrole. When veratrole in methanol was added to the Nietzki[2] solution, the expected dye, 3,4-dimethoxy-4′-nitroazobenzene (3), did not precipitate.



	R¹	R²	R³	R⁴	R⁵	R⁶
(1)	H	H	H	H	H	H
(2)	H	NO_2	H	OMe	OH	H
(3)	H	NO_2	H	OMe	OMe	H
(4)	Cl	NO_2	H	OMe	OH	H
(5)	Cl	NO_2	H	OMe	OMe	H
(6)	NO_2	NO_2	Cl	H	OMe	OMe
(7)	NO_2	NO_2	H	OMe	OH	H
(8)	NO_2	NO_2	H	OMe	OMe	H

When veratrole was added to *p*-nitrobenzenediazonium chloride at pH about 4·5, a precipitate was obtained. Chromatography (SiO_2 gel) and gradient sublimation yielded a yellow oil which crystallized slowly. The mass spectrum of this sublimate showed a series of peaks which suggested that *p*-nitrophenylveratrole and bis-, tris- and tetrakis-(*p*-nitrophenyl)veratroles were formed presumably by means of a Gomberg reaction.[5] Although the Gomberg reaction usually occurs in alkaline media, it has been recorded[6] as taking place in sulfuric acid/acetic acid/water between 2,4-dinitrobenzenediazonium ions and thiophen.

2,4-Dinitroaniline

Since diazotized *p*-nitroaniline did not react with veratrole, the reaction of diazotized 2,4-dinitroaniline, a weaker base than *p*-nitroaniline, with veratrole was then investigated. In attempts at diazotization of 2,4-dinitroaniline in concentrated hydrochloric acid the *o*-nitro group was replaced by a chlorine atom and produced 2-chloro-4-nitrobenzenediazonium chloride. Proof of this came from treatment of this diazonium salt with potassium iodide which yielded 2-chloro-1-iodo-4-nitrobenzene. Meldola[7] similarly observed that an *o*-nitro group had been replaced by a

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[2] Nietzki, R., (1887) in 'Methoden der Organischen Chemie' (Ed. J. Houben-Weyl) Vol. 10/3, p. 266 (Verlag: Stuttgart 1965).

[3] Colombano, A., and Leonardi, B., *Atti Accad. Naz. Lincei*, 1908, **16**, [II], 639.

[4] Kokkinos, K., and Wizinger, R., *Helv. Chim. Acta*, 1971, **54**, 330.

[5] Saunders, K. H., 'The Aromatic Diazo-Compounds and their Technical Applications' 2nd Edn, pp. 308–23 (Arnold: London 1949).

[6] Bartle, M. G., Mackie, R. K., and Tedder, J. M., *J. Chem. Soc., Chem. Commun.*, 1974, 271.

[7] Meldola, R., and Eyre, J. V., *J. Chem. Soc.*, 1902, **81**, 988.

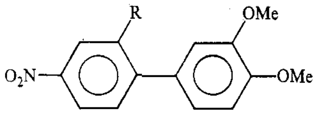
chlorine atom in the diazotization of 4-methoxy-2,3-dinitroaniline in concentrated hydrochloric acid to form 2-chloro-4-methoxy-3-nitrobenzenediazonium chloride. During the diazotization of the 2,4-dinitroaniline in acid, a pressure built up in the flask from the slow decomposition of excess nitrous acid to nitrogen dioxide, hence large amounts of urea were needed to discharge the excess of nitrous acid.

When neat veratrole was added to 2,4-dinitroaniline diazotized in concentrated hydrochloric acid from which the excess nitrous acid had not been discharged with urea, 2-chloro-4,5-dimethoxy-2′,4′-dinitroazobenzene (6) was formed. This structure was deduced from the mass spectrum and the ^{1}H n.m.r. spectrum. A metastable peak indicated the transition from the molecular ion to *m/e* 199 ($C_8H_8ClN_2O_2$), hence the chlorine atom was on the same ring as the two methoxy groups. In the ^{1}H n.m.r. spectrum the higher-field aromatic resonances consisted of two singlets at 7·03 and 7·33 ppm consistent with the 1,2,4,5-substitution pattern suggested for the methoxy-substituted moiety. It appeared that in the concentrated hydrochloric acid solution there was some 2,4-dinitrobenzenediazonium chloride or that there was an equilibrium. Therefore, when the veratrole was added, the dinitro compound reacted immediately with the veratrole and, at the same time, because of the reaction[8a]

$$2NO_2^- + 2Cl^- + 4H^+ \rightarrow 2NO + Cl_2 + 2H_2O$$

the veratrole moiety was chlorinated. The formation of this compound (6) was inhibited by adding the veratrole in acetic acid.

By adding veratrole in acetic acid to 2,4-dinitroaniline diazotized in concentrated hydrochloric acid and then treated with urea, a dark brown material was formed from which pale yellow 2-chloro-3′,4′-dimethoxy-4-nitrobiphenyl (9) was obtained by sublimation. The mass spectrum showed the presence of a chlorine atom, the molecular weight and analysis indicated the absence of the azo group, and the ^{1}H n.m.r. spectrum was consistent with the structure (9). The reaction is clearly a Gomberg reaction. When the reaction was performed without discharging excess nitrous acid, a dichloro substance was detected in the mass spectrum of the sublimate.



(9) R = Cl
(10) R = NO_2

Attempts to form 2-chloro-3′,4′-dimethoxy-4-nitroazobenzene (5) directly from the discharged diazonium salt solution and veratrole dissolved in acetic acid failed. It was formed indirectly. Guaiacol in acetic acid was added to 2,4-dinitroaniline diazotized in concentrated hydrochloric acid and discharged with urea. The reaction formed 2-chloro-4′-hydroxy-3′-methoxy-4-nitroazobenzene (4). This phenol was methylated with diazomethane to form compound (5). The presence of the chlorine atom in each of compounds (4) and (5) was confirmed by their mass spectra.

To retain the 2,4-dinitrophenyl moiety intact during diazotization of 2,4-dinitroaniline, orthophosphoric acid (pK_a 2·12) was tried. Reaction of this 2,4-dinitrobenzenediazonium phosphate with veratrole dissolved in orthophosphoric acid was immediate. The reaction product, isolated in low yield, was separated by means of

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[8] Zollinger, H., 'Diazo and Azo Chemistry' (*a*) p. 18; (*b*) p. 253 (Interscience: New York 1961).

gradient sublimation into two products, namely, 3′,4′-dimethoxy-2,4-dinitroazobenzene (8) and 3′,4′-dimethoxy-2,4-dinitrobiphenyl (10). When the stronger acid trichloroacetic acid (pK_a 0·70), as water saturated with trichloroacetic acid, was used, 3′,4′-dimethoxy-2,4-dinitroazobenzene (8) was obtained by chromatography, in 25% yield. This yield is comparable with that obtained by Bartle *et al.*[6] in the corresponding reaction with anisole.

The structure of this dimethoxy compound (8) followed from its ^{1}H n.m.r. spectrum and was confirmed by synthesis: the phenol (7), obtained by reaction of 2,4-dinitrobenzenediazonium phosphate with guaiacol, was methylated with diazomethane. This phenol, 4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene (7), appears to be the same as that obtained by Haginiwa *et al.*[9] from their reaction of 2,4-dinitrobenzenediazonium sulfate with veratrole in acetic acid. They assigned the structure 3-hydroxy-2-methoxy-2′,4′-dinitroazobenzene. Haginiwa *et al.*[9] also claimed that the dimethyl ether melted at 135°, whereas compound (8) melted at 151–152°.

^{1}*H N.M.R. Spectra*

The aromatic substitution patterns postulated for the azobenzenes and biphenyls isolated in the present investigation were deduced from their ^{1}H n.m.r. spectra in deuterochloroform and for compound (7) in deuteroacetone. In the deuterochloroform spectrum for the nitro-substituted moiety of the *p*-nitro compounds (2) and (3) there were first-order AX quartets where the protons *meta* to the azo group were deshielded by >1 ppm compared with azobenzene (1). The protons of the 2,4-dinitrophenyl and 2-chloro-4-nitrophenyl rings exhibited the familiar 1,2,4-trisubstituted ring pattern (H 3, d, *J* 2 Hz; H 5, dd, *J* 2 and 9 Hz; H 6, d, *J* 9 Hz). Protons at position 3 were deshielded by *c.* 1·4 ppm from that in azobenzene (1). It was conceivable that substitution on the methoxy-substituted ring could have occurred *ortho* to the hydroxy group but the splitting pattern indicated 1,2,4-substitution for all the pure compounds, azobenzenes and biphenyls, isolated; this confirmed Zollinger's claim[8b] that diazonium coupling occurred *para* to the hydroxy group.

Compound (7), 4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene, showed an anomalous spectrum in deuterochloroform, viz., a spectrum of apparently 26 lines (at 60 MHz), but in deuteroacetone there were the expected 16 lines. When phenols are dissolved in a large excess of acetone the phenolic hydroxy group is almost completely hydrogen-bonded to the acetone carbonyl and any intramolecular or intermolecular hydrogen bonding within or between solute molecules is suppressed. So then the spectrum of a phenol in acetone is that of one species, i.e. that of the phenol hydrogen-bonded to acetone.

By comparing the resonances of compound (7) observed in deuterochloroform with those observed for it in deuteroacetone it has been possible to select those lines which belong to this hydrogen-bonded phenol–deuteroacetone complex (compound (7a)). The correctness of this assignment of the lines was confirmed by the results of serial addition of deuteroacetone up to *c.* 50% to the deuterochloroform solution. Fig. 1 shows some of the spectra obtained, the shifts observed and the disappearance of a set of lines attributable to a second species (compound (7b)) present in the

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[9] Haginiwa, J., Murakoshi, I., Yokota, K., Takayama, H., and Tsuchiya, T., *Yakugaku Zasshi*, 1958, **78**, 232.

deuterochloroform solution but systematically suppressed by hydrogen bonding to the carbonyl of the added deuteroacetone. This new species (7b) which has no analogue when there is only a *p*-nitro group, compound (2), or a 4′-methoxy group, compound (8), has anomalous shifts: apparently the proton at position 3 is deshielded by 0·4 ppm from its position for the apparently non-bonded compound (7c) while the upfield resonances associated with the phenolic ring are shielded by >0·5 ppm.

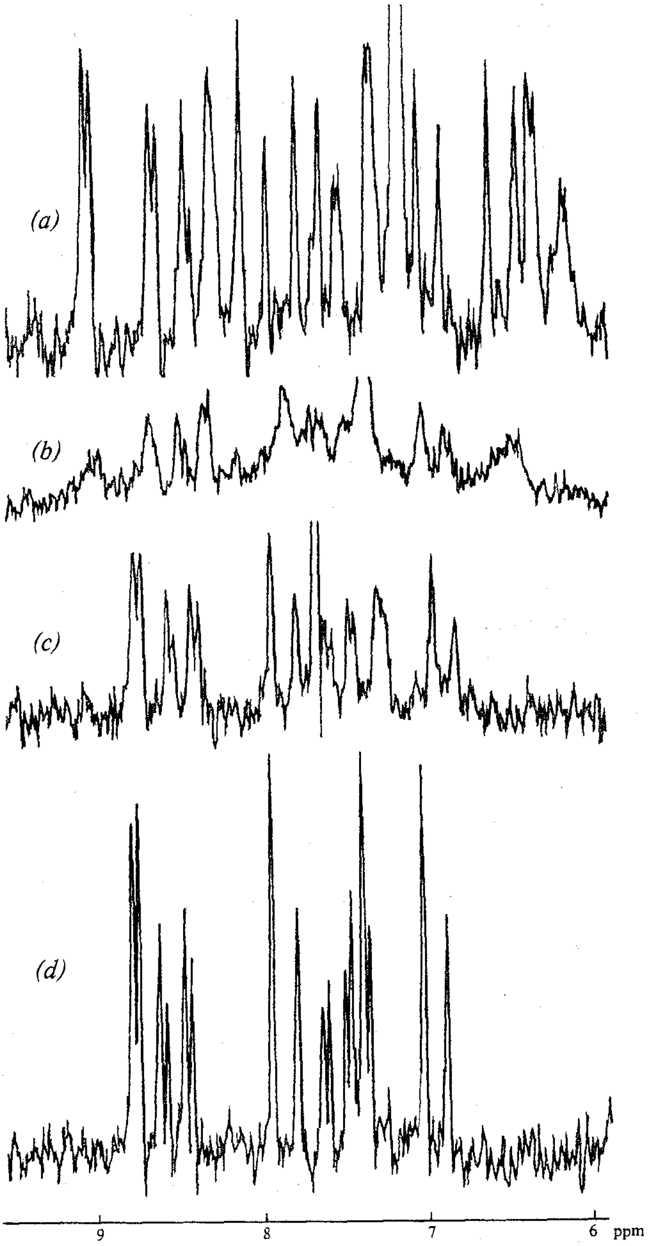
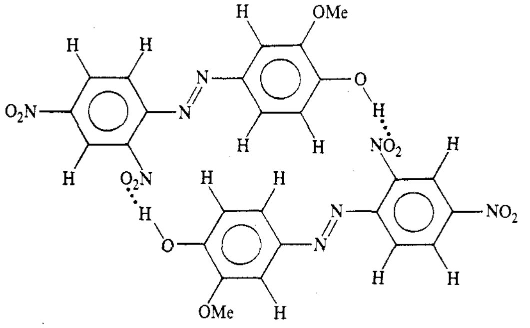


Fig. 1. The ^{1}H n.m.r. spectra of 4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene in:
(*a*) $CDCl_3$ alone;
(*b*) $CDCl_3/(CD_3)_2CO$, 4 : 1 (v/v);
(*c*) $CDCl_3/(CD_3)_2CO$, 1 : 1 (v/v);
(*d*) $(CD_3)_2CO$ alone.
The truncated peaks are those of $CHCl_3$.

Therefore, structure (11) is proposed for (7b) where the methoxyphenyl rings are adjacent to each other and have a mutual aromatic shielding effect on their protons, and hence their resonances are upfield. At the same time there is an aromatic deshielding effect upon the resonance of H 3. In the deuterochloroform spectrum there were two hydroxy signals: one at 6·26 ppm ($W_{h/2}$ 5 Hz) assigned to the free OH of compound (7c) and the other at 12 ppm ($W_{h/2}$ 5 Hz) assigned to the hydrogen-bonded OH of compound (7b). Upon addition of *c.* 20% of deuteroacetone the upfield signal disappeared while the downfield one shifted to 11·8 ppm ($W_{h/2}$ 20 Hz) and then disappeared at 25% deuteroacetone.



(11)

When the ^{1}H n.m.r. spectra of compounds (2), (3), (7) and (8) were determined in deuteroacetone, the resonances for the nitrophenyl ring were observed to be 0·09–0·12 ppm downfield from those in $CDCl_3$; the shift was more marked (0·12–0·16 ppm) for the dimethoxy dinitro compound (8). A similar positive Δ_s† effect has been observed with substituted benzalmalonitrile[10] and was considered to be neither a van der Waals contribution nor a reaction field effect.[11]

The shifts, Δ_s, of the resonances in the methoxyphenyl moieties of the monomers showed anomalies:

(i) The H 2′ protons in the mononitro compounds (2) and (3) showed the deshielding as observed above for the nitrophenyl ring.

(ii) The H 2′ protons in the dinitro compounds (7) and (8) were shifted minimally (−0·03 and 0·03 ppm respectively).

(iii) The H 5′ proton, adjacent to the phenolic group, was shifted minimally (deshielded 0·02 ppm) in the mononitro compound (2) while in the dinitro compound (7) H 5′ was shielded by 0·08 ppm. This phenomenon is attributed to the adjacent intermolecular-hydrogen-bonding environment, between the phenolic hydrogen and the solvent carbonyl, since methylating these phenolic compounds (2) and (7), and thus removing the intermolecular-hydrogen-bonding environment, resulted in deshielding the H 5′ ring protons by 0·19 and 0·28 ppm (respectively, i.e. $\Delta_s^{OMe} - \Delta_s^{OH}$). The degree of deshielding of H 5′ is influenced by the degree of substitution in the nitrophenyl ring. Where there is a nitro group *ortho* to the azo group the deshielding is greater.

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† $\Delta_s = \delta(CD_3COCD_3) - \delta(CDCl_3)$.

[10] Weinberger, M. A., Heggie, R. M., and Holmes, H. L., *Can. J. Chem.*, 1965, **43**, 2585.

[11] Ronayne, J., and Williams, D. H., *Annu. Rev. NMR Spectrosc.*, 1969, **2**, 83.

(iv) Similarly, for the H 6′ protons: the greater deshielding occurs in the dinitro compound in going from the phenol to the methyl ether. Whereas this deshielding shift was only minimal (0·04 ppm) in the mononitro compound, it was 0·12 ppm in the dinitro compound.

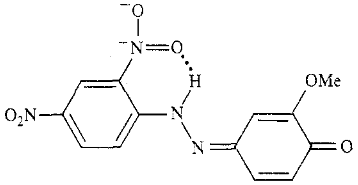
The protons in 2-chloro-3′,4′-dimethoxy-4-nitrobiphenyl (9) *ortho* to the electron-withdrawing nitro group are, as expected, downfield (*c.* 1 ppm) from those in biphenyl, while the one *meta* to the nitro group is deshielded minimally ($<0\cdot1$ ppm). Where a veratrole derivative has a π-bonded group in the *para* position the veratrole protons (positions 2, 5, 6) show the typical d, d, dd splitting pattern, but the singlet observed for these three protons in compound (9) is what would be expected if there were a methylene group in the *para* position on the veratrole ring. So, instead of the 2-chloro-4-nitrophenyl ring splitting these substituted-veratrole resonances it merely deshielded the singlet by *c.* 0·2 ppm or more from where 4-methyleneveratrole ring protons resonate.[12]

Now that it has been verified that 2,4-dinitrobenzenediazonium salts in strong acids can couple with veratrole, it is hoped that such coupling will be successful with sporidesmin which is stable in concentrated acids for short periods. The results of this coupling will be presented in another paper.

Response to a Referee's Suggestion

A referee requested comments on the possibility of a species like (12) being involved.

In the above n.m.r. work with compound (7) no obvious colour change from deep orange-red was observed when going from chloroform to acetone solutions.



(12)

Kaul *et al.*[13] pointed out that the n.m.r. spectrum of 4′-hydroxy-3′-methyl-2,4-dinitroazobenzene in the polar solvent dimethylacetamide showed the azo phenol form but in deuterochloroform the same compound showed both the azo phenol and quinone hydrazone forms. They attributed to the quinone hydrazone form the appearance in the latter solvent of two doublets in the aromatic-methyl region. Unfortunately, Kaul *et al.* did not describe or publish the aromatic portion of the spectrum of 4′-hydroxy-3′-methyl-2,4-dinitroazobenzene, so we do not know if it has an analogous spectrum to (7).

The '*anti*' 2-methoxy-1,4-benzoquinone oxime[14] has a doublet (J 2·4 Hz) at 6·37 ppm comparable with the highest-field doublet (6·45 ppm) in compound (7). This and the apparent uniformity of intensities in Fig. 1*a* would suggest that compound (7) exists in solution as a mixture of the azo phenol and the '*syn*' and '*anti*' quinone hydrazones in *c.* 1 : 1 : 1 ratio. But this would require a doublet at *c.* 6·8 ppm

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[12] Pouchert, C. J., and Campbell, J. R., 'The Aldrich Library of N.M.R. Spectra' Vol. 5, pp. 16, 117, 118; Vol. 6, p. 130 (Aldrich Chemical Co.: Milwaukee 1974).

[13] Kaul, B. L., Nair, P., Rao, A. V. R., and Venkataraman, K., *Tetrahedron Lett.*, 1966, 3897.

[14] Norris, R. K., and Sternhell, S., *Aust. J. Chem.*, 1969, **22**, 935.

which is absent, a doublet for the *syn* isomer proton corresponding to the *anti* one at 6·4 ppm. Furthermore, would a structure such as (12) account for the deshielding (from 8·77 to 9·17 ppm) which has been observed for the postulated structure (11)? By comparison with compounds which are similarly hydrogen-bonded, e.g. 2,4-dinitroaniline or 2,4-dinitrophenylhydrazine (8·85 ppm, CD_3SOCD_3),[12] the hydrogen bonding in structure (12) would not account for the observed deshielding.

Experimental

Unless otherwise stated, the coupling reactions were performed in an ice bath. Silica gel G (for t.l.c.) was used for column chromatography. Melting points (Kofler block) were uncorrected. Microanalyses were determined by the Microanalytical Laboratory, University of Otago, New Zealand. Infrared spectra were measured with a Beckman IR8 (micro) instrument. Mass spectra were measured in a Varian MAT CH5 instrument by Dr P. T. Holland and ^{1}H n.m.r. spectra were recorded on a JEOL C-60HL spectrometer by Miss K. J. Ronaldson, by Dr S. Gumbley and by Mr F. Povel.

4-Hydroxy-3-methoxy-4′-nitroazobenzene (2)

A stirred suspension of *p*-nitroaniline (135 mg) in water (3 ml) and conc. HCl (0·26 ml) was cooled (ice bath) and a solution of sodium nitrite (76 mg) in water (0·75 ml) added rapidly. After 30 min, guaiacol (116 mg) in methanol/water (1 : 1, 2 ml) was added. A dark orange precipitate (140 mg) was formed. Since coupling to phenols is not normally performed in strong acid, the pH of the supernatant after 90 min was raised (5 M NaOH) to *c.* 5·5 whereupon the solution turned purple; acidification yielded more precipitate (30 mg) bringing the total yield to 64%. Sublimation of some of the precipitates gave *4-hydroxy-3-methoxy-4′-nitroazobenzene*, m.p. 171·5–173° (Found: M, 273; C, 57·4; H, 4·2; N, 15·3. $C_{13}H_{11}N_3O_4$ requires M, 273; C, 57·1; H, 4·1; N, 15·4%). ^{1}H n.m.r. δ ($CDCl_3$) 4·03, s, ArOMe; 6·13, s, OH; 7·09, d, $J_{5,6}$ 8·5 Hz, H5; 7·53, d, $J_{2,6}$ 2·5 Hz, H2; 7·71, dd, $J_{2,6}$ 2·5, $J_{5,6}$ 8·5 Hz, H6; 7·98, d, $J_{2',3';5',6'}$ 9·5 Hz, H2′, H6′; 8·41, d, $J_{2',3';5',6}$ 9·5 Hz, H3′, H5′; [$(CD_3)_2CO$] 4·02, s, ArOMe; 7·13, d, $J_{5,6}$ 9 Hz, H5; 7·65, s, H2; 7·71, dd, $J_{2,6}$ 2, $J_{5,6}$ 9 Hz, H6; 8·09, d, $J_{2',3';5',6'}$ 9·5 Hz, H2′, H6′; 8·51, d, $J_{2',3';5',6'}$ 9·5 Hz, H3′, H5′. ν_{max} (KBr) 1585s, 1515vs, 1510vs, 1340vs, 1270vs, 850s, 865s cm^{-1}.

3,4-Dimethoxy-4′-nitroazobenzene (3)

The phenol (2) (83 mg), suspended in ether, was methylated with diazomethane. 3,4-Dimethoxy-4′-nitroazobenzene (71 mg, 81%), m.p. 157·5–180° (lit.[4] 158°), separated from the ether (Found: M, 287. Calc. for $C_{14}H_{13}N_3O_4$: M, 287). ^{1}H n.m.r. δ ($CDCl_3$) 4·05, s, 2ArOMe; 7·03, d, $J_{5,6}$ 8·5 Hz, H5; 7·53, d, $J_{2,6}$ 2 Hz, H2; 7·73, dd, $J_{2,6}$ 2, $J_{5,6}$ 8·5 Hz, H6; 7·99, d, $J_{2',3';5',6'}$ 9 Hz, H2′, H6′; 8·41, d, $J_{2',3';5',6'}$ 9 Hz, H3′, H5′; [$(CD_3)_2CO$] 3·97, s, ArOMe; 4·00, s, ArOMe; 7·24, d, $J_{5,6}$ 9 Hz, H5; 7·61, d, $J_{2,6}$ 2 Hz, H2; 7·77, dd, $J_{2,6}$ 2, $J_{5,6}$ 9 Hz, H6; 8·10, d, $J_{2',3';5',6'}$ 9·5 Hz, H2′, H6′; 8·50, d, $J_{2',3';5',6'}$ 9·5 Hz, H3′, H5′. ν_{max} (KBr) 1595s, 1525–1500vs, 1340vs, 1265vs, 860s, 805s cm^{-1}.

Reaction of p-*Nitrobenzenediazonium Chloride with Veratrole*

p-Nitroaniline (690 mg) in conc. HCl (10 ml) was diazotized with sodium nitrite (380 mg in H_2O, 10 ml). The aniline did not dissolve till the NO_2^- was added; a light amber solution was obtained.

(A) Veratrole (276 µl) in methanol/H_2O (6 ml, 1 : 1) was added to 2 mmol of the diazonium salt solution to yield a red colour but no precipitate.

(B) The pH of another 2 mmol of the solution was raised (5 M NaOH) to *c.* 4·5; there was a sudden colour change to brown. With veratrole (276 µl) this produced a brown precipitate (370 mg) which was extracted with ethyl acetate. The extract was chromatographed and some of the main leading fraction (93 mg) sublimed (gradient, 107°/0·001 mm). The yellow oil in the sublimate crystallized and its mass spectrum showed *m/e* 259, 380, 501 and 622.

2-Chloro-1-iodo-4-nitrobenzene

2,4-Dinitroaniline (368 mg) was diazotized by grinding with sodium nitrite (147 mg) and adding conc. HCl (4 ml). This solution (after 1 h) was added to a stirred solution (400 µl) of potassium iodide (420 mg): the mixture turned dark brown immediately. The extract ($CHCl_3$) was washed (aq. $Na_2S_2O_3$, aq. $NaHCO_3$, H_2O) and some of the dark orange oily residue (408 mg, 54%) sublimed (80°/0·3 mm). 2-Chloro-1-iodo-4-nitrobenzene (from MeOH) had m.p. 96–98·5° (lit.[15] 99°); *m/e* 285 and 283.

2-Chloro-4,5-dimethoxy-2′,4′-dinitroazobenzene (*6*)

While the 2,4-dinitroaniline (366 mg), ground with sodium nitrite (151 mg), was diazotizing (2 h at 18·5°) in conc. HCl (4 ml) the stopper blew out. Adding neat veratrole (255 μl), rapidly, immediately yielded a 'red tar' which collected around the stirring rod leaving an orange solution. *2-Chloro-4,5-dimethoxy-2′,4′-dinitroazobenzene* (54 mg), m.p. 222–224°, crystallized from AcMe/MeOH, after chromatography ($CHCl_3/C_6H_6$, 1 : 4) of the red tar (Found: M, 368, 366; C, 46·3; H, 3·1; N, 15·1. $C_{14}H_{11}ClN_4O_6$ requires M, 368, 366; C, 45·9; H, 3·0; N, 15·3%). ^{1}H n.m.r. δ ($CDCl_3$) 3·87, s, ArOMe; 3·96, s, ArOMe; 7·07, s, H3; 7·36, s, H6; 7·91, d, $J_{5',6'}$ 10 Hz, H6′; 8·52, dd, $J_{3',5'}$ 2, $J_{5',6'}$ 10 Hz, H5′; 8·81, d, $J_{3',5'}$ 2 Hz, H3′. ν_{max} (KBr) 1595s, 1530s, 1500s, 1335vs, 1270vs, 860s cm^{-1}. *m/e* 199, m* 108·3 [366 → 199 ($C_8H_8ClNO_2$)+167].

2-Chloro-3′,4′-dimethoxy-4-nitrobiphenyl (*9*)

2,4-Dinitroaniline (367 mg) was diazotized with sodium nitrite (145 mg) in conc. HCl (4 ml) and acetic acid (3 ml), and excess nitrous acid discharged with urea (1 g). Veratrole (255 μl) in acetic acid (1 ml) reacted immediately to give a dark brown suspension which was poured into H_2O (100 ml) after 24 h (5°). From some of the extract ($CHCl_3$, 411 mg, 70%) was sublimed a yellow oil crystallizing to *2-chloro-3′,4′-dimethoxy-4-nitrobiphenyl* (AcMe), m.p. 126·5–127° (Found: M, 293, 295; C, 56·9; H, 4·0; N, 4·6. $C_{14}H_{12}ClNO_4$ requires M, 293, 295; C, 57·3; H, 4·1; N, 4·8%). ^{1}H n.m.r. δ ($CDCl_3$) 3·93, s, 2ArOMe; 7·02, s, H2′, H5′, H6′; 7·53, d, $J_{5,6}$ 8 Hz, H6; 8·18, dd, $J_{3,5}$ 2·5, $J_{5,6}$ 8 Hz, H5; 8·36, d, $J_{3,5}$ 2·5 Hz, H3. ν_{max} 1580s, 1515vs, 1505vs, 1335vs(br), 1250s, 860s, 800s cm^{-1}.

This experiment was repeated without discharging the nitrous acid with urea; the product was poured into water (100 ml). Some (40 mg) of the product (390 mg) obtained from a chloroform extraction was sublimed (200°/0·04 mm) to give a crystalline yellow zone, m.p. 120–126°. This product appeared (mass spectrum) to consist of 2-chloro-3′,4′-dimethoxy-4-nitrobiphenyl and a dichloro compound (possibly 2,2′-dichloro-4,5-dimethoxy-4′-nitrobiphenyl).

2-Chloro-4′-hydroxy-3′-methoxy-4-nitroazobenzene (*4*)

To an intimate mixture of 2,4-dinitroaniline (365 mg) and sodium nitrite (151 mg) was added cold conc. HCl (4 ml) and acetic acid (3 ml). After 1 h, urea (*c.* 1 g) was added till there was no smell of nitrogen dioxide; guaiacol (247 mg) in acetic acid (1 ml) was then added and the mixture left overnight (5°). Fine red needles (MeOH, 288 mg, 47%) of *2-chloro-4′-hydroxy-3′-methoxy-4-nitroazobenzene*, m.p. 150·5–152°, were obtained from the precipitate (500 mg) filtered from the reaction mixture (Found: M, 309, 307; C, 50·5; H, 3·4; Cl, 11·8; N, 13·2. $C_{13}H_{10}ClN_3O_4$ requires M, 309, 307; C, 50·8; H, 3·3; Cl, 11·5; N, 13·7%). ^{1}H n.m.r. δ ($CDCl_3$) 4·00, s, ArOMe; 6·17, s, OH; 7·08, d, $J_{5',6'}$ 8·5 Hz, H5′; 7·55, d, $J_{2',6'}$ 2 Hz, H2′; 7·72, dd, $J_{2',6'}$ 2, $J_{5',6'}$ 8·5 Hz, H6′; 7·75, d, $J_{5,6}$ 8·5 Hz; 8·18, dd, $J_{3,5}$ 2, $J_{5,6}$ 8·5 Hz, H5; 8·42, d, $J_{3,5}$ 2 Hz, H3. ν_{max} (KBr) 1590s, 1500vs, 1340vs, 1270vs, 865s cm^{-1}.

2-Chloro-3′,4′-dimethoxy-4-nitroazobenzene (*5*)

The methoxyphenol (4) was methylated with diazomethane. The residue after evaporation of the ether/methanol gave crystals (AcMe, 76%) of *2-chloro-3′,4′-dimethoxy-4-nitroazobenzene*, m.p. 157–158° (Found: M, 323, 321; C, 52·1; H, 3·9; Cl, 11·2; N, 12·9. $C_{14}H_{12}ClN_3O_4$ requires M, 323, 321; C, 52·3; H, 3·8; Cl, 11·0; N, 13·1%). ^{1}H n.m.r. δ ($CDCl_3$) 3·98, s, ArOMe; 4·00, s, ArOMe; 7·02, d, $J_{5',6'}$ 8·5 Hz, H5′; 7·53, d, $J_{2',6'}$ 2 Hz, H2′; 7·73, d, $J_{5,6}$ 8·5 Hz, H6; 7·74, dd, $J_{2',6'}$ 2, $J_{5',6'}$ 8·5 Hz, H6′; 8·17, dd, $J_{3,5}$ 2, $J_{5,6}$ 8·5 Hz, H5; 8·38, d, $J_{3,5}$ 2 Hz, H3. ν_{max} (KBr) 1510vs, 1340vs, 1270vs cm^{-1}.

4′-Hydroxy-3′-methoxy-2,4-dinitroazobenzene (*7*)

Ground sodium nitrite (166 mg) was added dry to a suspension of ground 2,4-dinitroaniline (370 mg) in orthophosphoric acid (8 ml). The 2,4-dinitroaniline did not dissolve in the acid but its

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[15] Wallagh, G., and Wibaut, J. P., *Recl Trav. Chim. Pays-Bas*, 1936, **55**, 1071, 1074.

crystals disappeared on diazotization, without the evolution of gas. Guaiacol (253 mg) in orthophosphoric acid (1·5 ml) was added (dropwise, after 50 min). The reaction mixture was poured (after 40 min) into ice-water (100 ml), and after separation from the aqueous phase the amorphous layer was dissolved in $CHCl_3$ leaving a solid phase. Crystals (344 mg, 54%) of *4′-hydroxy-3′-methoxy-2,4-dinitroazobenzene*, m.p. 174·5–176·5° (sublimed), were deposited on evaporation of an AcMe/MeOH solution of the $CHCl_3$ residue (Found: M, 318; C, 49·3; H, 3·1; N, 17·3. $C_{13}H_{10}N_4O_6$ requires M, 318; C, 49·1; H, 3·2; N, 17·6%). ^{1}H n.m.r. δ ($CDCl_3$) 4·00, s, ArOMe; 6·26, br, OH; 7·08, d, $J_{5',6'}$ 8 Hz, H5′; 7·43, d, $J_{2',6'}$ 2 Hz, H2′; 7·72, dd, $J_{2',6'}$ 2, $J_{5',6'}$ 8 Hz, H6′; 7·82, d, $J_{5,6}$ 8·5 Hz, H5; 8·47, dd, $J_{3,5}$ 2, $J_{5,6}$ 8·5 Hz, H5; 8·77, d, $J_{3,5}$ 2·5 Hz, H3; 12·0, br, OH (as well as these resonances there are the following lines: 386, 388·5, 393, 403, 444, 474·5, 485, 494·5, 505 b, 514·5, 549, 551 Hz); [$(CD_3)_2CO$] 3·91, s, ArOMe; 7·00, d, $J_{5',6'}$ 9 Hz, H5′; 7·40, d, $J_{2',6'}$ 2 Hz, H2′; 7·60, dd, $J_{2',6'}$ 2, $J_{5',6'}$ 9 Hz, H6′; 7·92, d, $J_{5,6}$ 9 Hz, H6; 8·57, dd, $J_{3,5}$ 2, $J_{5,6}$ 9 Hz, H5; 8·82, d, $J_{3,5}$ 2 Hz, H3. ν_{max} (KBr) 1610s, 1595s, 1580s, 1500s, 1340vs cm^{-1}.

3′,4′-Dimethoxy-2,4-dinitroazobenzene (8)

The methoxyphenol (7) (20 mg) was dispersed as an amorphous film on the wall of the flask. Some of the film dissolved in the methylating agent, diazomethane/ether, and reacted; the rest crystallized and was stable to the diazomethane/ether. Red crystals (AcMe/EtOEt) of *3′,4′-dimethoxy-2,4-dinitroazobenzene*, m.p. 151–152°, were obtained from chromatography and sublimation (Found: M^+, 332·077. $C_{14}H_{12}N_4O_6$ requires M^+, 332·076). ^{1}H n.m.r. δ ($CDCl_3$) 3·96, s, ArOMe; 4·02, s, ArOMe; 7·03, d, $J_{5',6'}$ 8·5 Hz, H5′; 7·45, d, $J_{2',6'}$ 2 Hz, H2′; 7·76, dd, $J_{2',6'}$ 2, $J_{5',6'}$ 8·5 Hz, H6′; 7·84, d, $J_{5,6}$ 9 Hz, H6; 8·56, dd, $J_{3,5}$ 2·5, $J_{5,6}$ 9 Hz, H5; 8·81, d, $J_{3,5}$ 2·5 Hz, H3; [$(CD_3)_2CO$] 3·96, s, ArOMe; 4·04, s, ArOMe; 7·23, d, $J_{5',6'}$ 9 Hz, H5′; 7·48, d, $J_{2',6'}$ 2·5 Hz, H2′; 7·75, dd, $J_{2',6'}$ 2·5, $J_{5',6'}$ 9 Hz, H6′; 7·97, d, $J_{5,6}$ 9 Hz, H6; 8·72, dd, $J_{3,5}$ 2·5, $J_{5,6}$ 9 Hz, H5; 8·93, d, $J_{3,5}$ 2·5 Hz, H3. ν_{max} (KBr) 1590s, 1530s, 1505s, 1340vs, 1270vs, 860s cm^{-1}.

By recycling the above crystallized phenol (7) with diazomethane/ether more dimethyl ether (8) was obtained. The amorphous film was formed by rapidly evaporating an acetone solution of the phenol. This acetone solution readily turned blue but the orange colour of the phenol was restored by adding HCl vapour. The total yield of dimethyl ether (8) was 10 mg (48%).

Reaction of 2,4-Dinitrobenzenediazonium Phosphate with Veratrole

To finely ground 2,4-dinitroaniline (370 mg) suspended in orthophosphoric acid (8 ml) was added ground sodium nitrite (160 mg). On stirring (1 h, magnetic), the dinitroaniline crystals disappeared in 45 min. When veratrole (250 μl) in orthophosphoric acid (2 ml) was added rapidly, there was immediate formation of a deep red colour. The non-volatile material (50 mg) in the extract ($CHCl_3$) was chromatographed then sublimed (gradient) to give dark red crystals (proximally; 12 mg, 5%), m.p. 150–151·5°, mixed m.p., with 3′,4′-dimethoxy-2,4-dinitroazobenzene above, 150–151·5°, and yellow crystals (distally from the heat source; 2 mg, <1%) of possibly 3′,4′-dimethoxy-2,4-dinitrobiphenyl, m.p. 177–178° (Found: M, 304. Calc. for $C_{14}H_{12}N_2O_6$: M, 304).

Reaction of 2,4-Dinitrobenzenediazonium Trichloroacetate with Veratrole

Ground 2,4-dinitroaniline (368 mg) in water (8 ml) saturated with trichloroacetic acid was diazotized with ground sodium nitrite (144 mg). After stirring (magnetic) for 15 min, veratrole (256 mg) in trichloroacetic acid (4 ml) was added dropwise. A dark red-brown mixture resulted immediately which was poured into water (100 ml) and extracted ($CHCl_3$; 216 mg). Chromatography gave red-orange crystals (160 mg, 25%) of 3′,4′-dimethoxy-2,4-dinitroazobenzene (AcMe/EtOEt), m.p. 150–151°, mixed m.p. 150–151·5°.

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