PAPER CHROMATOGRAPHY AND CHEMICAL STRUCTURE

VI. TAUTOMERISM AND INTRAMOLECULAR HYDROGEN BONDING IN THE SAME MOLECULE. o-NITROSOPHENOLS

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INTRODUCTION

In the preceding parts[1-5] it has been shown that MARTIN's equation is rigorously obeyed if molecular increments are free from constitutive effects. Several types of molecular interaction, which lead to constitutive effects on R_M, have already been discussed, and, in the two preceding papers[4,5], two of these, internal hydrogen bonding and tautomerism, have been studied in some detail. In this communication, we wish to present a study on a series of compounds in which both these phenomena can be expected to occur.

Such a group of compounds is the o-nitrosophenols. MARCINKIEWICZ AND GREEN[6] have already reported on the separation of the o-nitrosotocopherols by reversed phase chromatography, and GREEN, McHALE, MARCINKIEWICZ, MAMALIS AND WATT[7] prepared some nitroso derivatives of tocol and its higher homologues. In both these studies, a serious lack of obvious correlation with the requirements of MARTIN's equation was noted. We have now prepared and chromatographed the o-nitroso derivatives of some phenols, naphthols, phenanthrols, alkoxyphenols, coumaranols and chromanols. All these compounds can be regarded as tautomeric mixtures of nitroso (I) and oxime (II) forms.
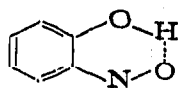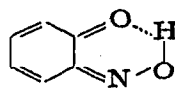
(I)   (II)

As already indicated[5], it is likely that two such different structures would always be found to exhibit a considerable difference in R_F if they could be isolated. In practice, however, the nitroso and oxime forms of compounds can only rarely be obtained as distinct compounds, and then only when there is a particular structural configuration present that effects a stabilisation of one or other form. Thus HENRICH[8] was able to isolate both forms of nitrosoresorcinol monomethyl ether. Usually, either one form exists to the exclusion of the other (as in 4-nitroso-1-naphthol, which exists exclusively as the oxime of 1,4-naphthaquinone), or the two forms have such a rapid rate of interconversion that neither form can be isolated singly. The latter appears to be

the case with p-nitrosophenol and its derivatives and also with 1-nitroso-2-naphthol[9].

o-Nitrosophenols, in contrast to the p-nitroso compounds, have received little study. In the simple mononuclear phenol series they are difficult to prepare, and CRONHEIM[10], who prepared most of the known ones by a modification of BAUDISCH's[11] reaction, obtained such minute yields that he was only able to identify them by their ultra-violet spectra. o-Nitroso derivatives of polynuclear phenols are obtained more readily, however, and alkoxyphenols, and cyclic mono-ethers such as coumaranols and chromanols, also yield o-nitroso derivatives. Pronounced hydrogen bonding can be expected to occur in both the nitroso and the oxime form (I and II) of all these compounds. Thus the two phenomena, tautomerism and chelation, will co-exist and they will affect each other in a complex fashion, for the degree of bonding will affect the position of the tautomeric equilibrium and *vice versa*. Furthermore, the two phenomena can be expected to be influenced both sterically and electronically by additional substitution in the aromatic ring, especially if this occurs *ortho* to either the nitroso or hydroxy group.

EXPERIMENTAL

Compounds

The nitrosonaphthols and 10-nitroso-9-phenanthrol are known compounds. *1-Nitroso-2-phenanthrol* is a new compound. It was made by the standard procedure for preparing nitroso-β-naphthol[12] and was obtained from aqueous ethanol or light petroleum–benzene as a dark brown micro-crystalline powder, m.p. 170°. It analysed correctly. The o-nitroso derivatives of the alkoxyphenols, coumaranols and chromanols are unknown, and compounds of this type have only been prepared in the analogous tocopherol series[6,7,13]. These compounds (which can all be regarded as substituted o-nitrosoquinols) are even less accessible than the o-nitrosophenols. Their preparation was desirable, however, for systematic correlation with the parent phenols and mono-ethers we have already studied[1-5]. They cannot be prepared by CRONHEIM's method, which is too drastic, but can be obtained on a submilligram scale by QUAIFE's original procedure for the nitrosotocopherols[13]. Accordingly, as we have described elsewhere[7], pure specimens of each nitroso derivative in amounts sufficient for chromatography were prepared and characterized by their infra-red (and where possible) their ultra-violet spectra. Table I records their ultra-violet maxima and minima.

In three compounds (Nos. 5, 10 and 11 in Table I) there are two non-equivalent *ortho*-positions available for nitrosation. Each of these compounds thus gave two isomeric o-nitroso derivatives, which could be separated by adsorption chromatography on $ZnCO_3$-impregnated paper[6], as they differ in the screening effect of the nitroso group on the phenolic OH (a similar phenomenon was observed in the nitrosation of δ-tocopherol[6]).

Chromatography

The tank descending method was used. Whatman No. 4 papers were impregnated with the stationary phase. The systems were (A) 50 % (v/v) aqueous ethanol against liquid paraffin (5 % v/v in light petroleum); (B) 40 % (v/v) aqueous ethanol against olive oil (5 % v/v in light petroleum); and (C) di-n-butyl ether against trigol (triethylene glycol, 10 % v/v in chloroform). The compounds were all visible on sodium fluorescein-treated paper under ultra-violet light. With systems (A) and (B) 4 h runs

were used and the front moved about 40 cm. With system (C), the same migration was achieved in $1\frac{1}{2}$–2 h.

RESULTS AND DISCUSSION

In Table I the R_F and R_M values are given for o-nitroso derivatives of alkoxyphenols, chromanols and coumaranols, chromatographed in the liquid paraffin/ethanol system. It is at once apparent that these values cannot be readily correlated with MARTIN's equation. Consider first the derivatives of p-methoxy-, p-ethoxy- and p-propoxy-phenol. $\Delta R_M(CH_2)$ in this system (determined from a homologous series not shown here) is about + 0.450. Since the nitroso derivatives of p-ethoxy- and p-propoxyphenol have almost the same R_M value, it is clear that even a minute structural change in the para-position is sufficient to influence the relationship of the two ortho-groups to each other and to produce a constitutive effect on R_M in cancellation of the molecular weight difference.

Compare now compounds 4 and 5 (Table I). 4-Methoxy-3-methylphenol yields two nitroso derivatives (III) and (IV), which are separable chromatographically in an

(III)   (IV)   (V)
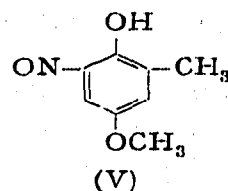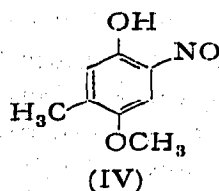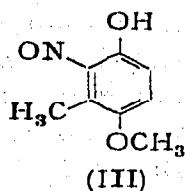
exactly analogous fashion to the separation of the nitroso derivatives of β- and γ-tocopherol[6], and they both have an R_F value different from that of the single nitroso derivative of 4-methoxy-2-methylphenol (V).
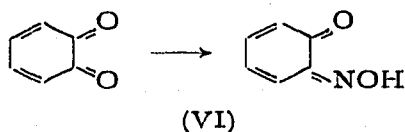
TABLE I

R_F AND R_M VALUES OF o-NITROSO DERIVATIVES OF ALKOXYPHENOLS, CHROMANOLS AND COUMARANOLS IN REVERSED PHASE SYSTEM A

| No.	Nitroso derivative of	λ_{max} (mμ)	λ_{min} (mμ)	R_F	R_M
1	p-Methoxyphenol	310	279; 390–395	0.81	—0.620
2	p-Ethoxyphenol	326	395	0.77	—0.523
3	p-Propoxyphenol	317	396	0.76	—0.500
4	4-Methoxy-2-methylphenol	323	400	0.65	—0.261
5	4-Methoxy-3-methylphenol (a)	350	399	0.75	—0.469
	4-Methoxy-3-methylphenol (b)	327	393	0.70	—0.366
6	2,3-Dimethyl-4-methoxyphenol	337	295; 401	0.52	—0.031
7	2,5-Dimethyl-4-methoxyphenol			0.92	—1.046
8	2-Propyl-4-methoxyphenol	322	286; 290	0.37	+0.279
9	4-Benzyloxy-2-methylphenol			0.28	+0.408
10	4-Benzyloxy-3-methylphenol (a)	333	399	0.42	+0.139
	4-Benzyloxy-3-methylphenol (b)	315–323	391	0.42	+0.139
11	2,2-Dimethyl-6-chromanol (a)	325	400–405	0.83	—0.678
	2,2-Dimethyl-6-chromanol (b)	335	400–405	0.67	—0.301
12	2,5,8-Trimethyl-6-chromanol	350–355	297; 407	0.69	—0.356
13	4-Methyl-5-coumaranol	331	294; 408	0.81	—0.620
14	6-Methyl-5-coumaranol			0.63	—0.222
15	2,4,7-Trimethyl-5-coumaranol	345	299; 415–203	0.68	—0.330

We regard it as unlikely that these pronounced differences are purely spatial in origin: the *ortho*-effect of a CH_3 group vicinal to OH is negligible in this system (*cf.* System 5 described previously[3]). They must be considered as being produced by the total electronic configuration of the molecule, which must affect the tautomeric equilibrium and chelation of the *ortho*-groups. Such an effect is even more clearly discerned in compounds 6 and 7, which exhibit a remarkable R_F difference (although here steric forces may reinforce the polar interactions, because in 6-nitroso-2,5-dimethyl-4-methoxyphenol, the nitroso–hydroxy chelate ring is under steric compression from a number of substituent groups). A similar phenomenon is observed with compounds 9 and 10. The two nitroso derivatives of 4-benzyloxy-3-methyl-phenol have the same R_F value in the partition system. Compound 11 also yields two nitroso derivatives, as there are two non-identical *ortho*-positions in this molecule. Compounds 12 and 15 have virtually the same R_M value, although one is a chromanol and the other a coumaranol, (the parent phenols, it should be noted, are easily separable[2]: in the nitroso derivatives, the slight difference in the electronic effect of the fused 5- and 6-membered rings is apparently sufficient to affect the equilibrium in the chelated ring and cancel out the molecular weight difference). Finally, compounds 13 and 14 illustrate in the coumaranol series exactly the same phenomenon as we have described in the separation of the tocopherols[6].

In order to pursue the investigation further, the relation between the R_M values of some *o*-nitrosophenols and the relevant bond order of the double bond (in the parent hydrocarbon) bearing the nitroso and hydroxy groups was studied. The oxime form of an *o*-nitrosophenol is formally derived from an *o*-quinone (VI) and the stability of *o*-quinones is related to the relevant bond order (hence the stability of *o*-naphthaquinones compared to *o*-benzoquinones).

By analogy, the stability of quinone oximes might also be expected to depend on relevant bond order, and we have already shown[4] that the degree of intramolecular hydrogen bonding is so related. Since the phenomena of tautomerism and chelation are intimately connected in *o*-nitrosophenols, it was thought possible that a relation between R_M and bond order might be discerned in these compounds. In order to test this hypothesis, several *o*-nitrosophenols were prepared and chromatographed in

(VI)

reversed phase system B and in the trigol/ether system C, in both of which the parent phenols could also be run. Table II gives their R_F and R_M values and also the relevant bond orders in the parent hydrocarbons (calculated by the L.C.A.O. approximation method[14]). The compound described as α-hydroxystilbene (VII) is of special

(VII)
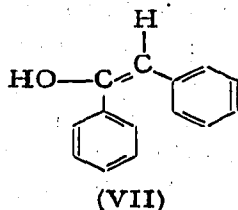
interest; this substance is, in fact, unknown; but its hypothetical R_F values in the two systems could be expected not to be too dissimilar from those of 9-phenanthrol, and these are the figures shown in parentheses in Table II.

TABLE II

R_F AND R_M VALUES OF PHENOLS AND THEIR NITROSO DERIVATIVES IN SYSTEMS B AND C.
ΔR_M(NO) VALUES AND RELEVANT BOND ORDER IN CORRESPONDING HYDROCARBONS

| Compound	System B			System C			Relevant bond order
	R_F	R_M	ΔR_M(NO)	R_F	R_M	ΔR_M(NO)	
Phenol	0.83	—0.70			—0.27		
o-Nitrosophenol	0.45	+0.08	+0.78	0.53	—0.06	+0.21	0.67[a]
1-Naphthol	0.45	+0.08			—0.25		
2-Nitroso-1-naphthol	0.73	—0.45	—0.53	0.37	+0.23	+0.48	0.73[b]
2-Naphthol	0.55	—0.08			+0.00		
1-Nitroso-2-naphthol	0.59	—0.17	—0.09	0.58	—0.14	—0.14	0.73[b]
2-Phenanthrol	0.22	+0.54			+0.03		
1-Nitroso-2-phenanthrol	0.10	+0.95	+0.41	0.74	—0.44	—0.47	0.70[c]
9-Phenanthrol	0.15	+0.76			—0.22		
10-Nitroso-9-phenanthrol	0.22	+0.55	—0.21	0.69	—0.34	—0.12	0.78[d]
(α-Hydroxy-stilbene)	(0.15)	(0.76)			(—0.22)		
α-Benzil monoxime	0.64	0.25	—1.01	0.66	—0.27		0.88[e]
β-Benzil monoxime	0.69	0.35	—1.11	0.66	—0.27	—0.05	0.88[e]

[a] 1,2 bond in benzene.
[b] 1,2 bond in naphthalene.
[c] 1,2 bond in phenanthrene.
[d] 9,10 bond in phenanthrene.
[e] α, β-bond in stilbene.

Its value for the present purposes lies in the fact that the bond order of the α,β-bond in stilbene (the corresponding parent hydrocarbon) is exceptionally high and, although (VII) is hypothetical, its nitroso derivative, which is formally derived from it does exist in pure oxime form. This compound, benzil monoxime, exists in two stereochemical modifications, the α-oxime (VIII) and the β-oxime (IX), which are cis-trans isomers.

(VIII)   (IX)
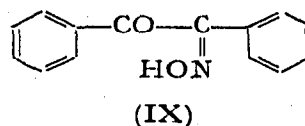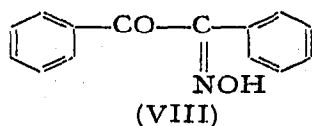
The results in Table II confirm the indications of Table I, that ΔR_M(NO) is exceedingly variable, there being no clear relation between structure and chromatography. Although in System B there seems to be a general trend for ΔR_M(NO) to decrease as the bond order increases, this is not confirmed in System C. Indeed, there is no correlation between the values of ΔR_M(NO) in the two systems. It is noteworthy that the stereochemical difference between benzil α-oxime and the β-oxime has a relatively insignificant effect on R_M or on ΔR_M(NO), compared to the major effects of hydrogen bonding and tautomerism. These results show most clearly how complex is the combined effect of tautomerism and internal hydrogen bonding. Not only is a mathematical correlation difficult even in one system, but it is likely that every system will produce

somewhat different results, since the ratio of nitroso–oxime forms probably differs in different solvents.

SUMMARY

A series of o-nitroso derivatives of phenols, alkoxyphenols, coumaranols and chromanols have been chromatographed. Two reversed phase and one direct phase system have been used. The correlation of the R_M values of these compounds with their structure is at present impossible, being complicated by the combined occurrence of tautomerism and internal hydrogen bonding. Since these factors are interdependent and since they also depend on the nature of the solvents, the chromatography of o-nitrosophenols cannot be satisfactorily interpreted in terms of the electronic structure of the parent phenols or the relevant bond orders in the parent hydrocarbons.

REFERENCES

1 J. GREEN AND S. MARCINKIEWICZ, *J. Chromatog.*, 10 (1963) 35.
2 S. MARCINKIEWICZ, J. GREEN AND D. McHALE, *J. Chromatog.*, 10 (1963) 42.
3 J. GREEN, S. MARCINKIEWICZ AND D. McHALE, *J. Chromatog.*, 10 (1963) 158.
4 S. MARCINKIEWICZ AND J. GREEN, *J. Chromatog.*, 10 (1963) 184.
5 J. GREEN AND S. MARCINKIEWICZ, *J. Chromatog.*, 10 (1963) 354.
6 S. MARCINKIEWICZ AND J. GREEN, *Analyst*, 84 (1959) 304.
7 J. GREEN, D. McHALE, S. MARCINKIEWICZ, P. MAMALIS AND P. R. WATT, *J. Chem. Soc.*, (1959) 3362.
8 F. HENRICH, *J. Prakt. Chem.*, 70 (1904) 313.
9 N. V. SIDGWICK, *Organic Chemistry of Nitrogen* (edited by T. W. J. TAYLOR AND W. BAKER), Oxford, 1942, p. 221.
10 G. CRONHEIM, *J. Org. Chem.*, 12 (1947) 7.
11 O. BAUDISH, *Naturwiss.*, 27 (1939) 768.
12 A. T. VOGEL, *Practical Organic Chemistry*, London, 1954, p. 958.
13 M. L. QUAIFE, *J. Biol. Chem.*, 175 (1948) 605.
14 C. A. COULSON, *Valence*, Oxford, 1954.