Synthesis, Spectral and Structural Studies, and an Evaluation of the Hydrogen Bonding of Some Phenylhydrazones

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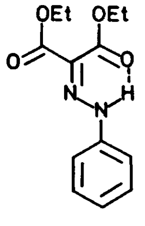
A series of 46 phenylhydrazones, some novel, containing a variety of structural types has been synthesised. These have been studied by ^1H n.m.r. and i.r. spectroscopy with respect to potential inter- and intra-molecular hydrogen bonding. *ortho*-Nitro or -carbonyl groups form strong hydrogen bonds to the imino-group which are readily observed by ^1H n.m.r. but not by i.r. spectroscopy. ' Terminal ' carbonyl groups also form strong hydrogen bonds to the imino-group and these can be detected by both i.r. and ^1H n.m.r. spectroscopy. When both *ortho*-nitro- or -carbonyl groups and ' terminal ' carbonyl groups are present the imino hydrogen atom is doubly hydrogen bonded and this is apparent in the ^1H n.m.r. spectrum. The formation of an intramolecular hydrogen bond in the phenylhydrazone prevents the formation of an intermolecular hydrogen bond between the phenylhydrazone and a polar solvent.

In the course of developing the use of sodium hypochlorite as a reagent in the synthesis of carbonyl compounds,[1] we have prepared a range of phenylhydrazones, some novel, whose spectroscopic properties reveal interesting and unusual features.

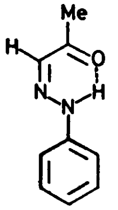


(1)

Structural aspects of phenylhydrazones as derived from ^1H n.m.r. and i.r. spectroscopy have been reviewed.[2] It has been found that aldehyde, ketone, and keto-ester derivatives reveal large δ(NH) values which are seen to reflect intramolecular hydrogen bonding[3] *e.g.* (1) which has δ(NH) 12.8. These pronounced chemical shifts in phenylhydrazones may vary quite markedly depending on the type of ring substituent and, often, on the choice of solvent[4-9] *viz.*, unsubstituted, δ(NH) 7.5—9.0 (CH_3OH), *ca.* 6.5 (C_6H_6); *o*-nitro, δ(NH) *ca.* 10.0, insensitive to concentration and very weakly solvent dependent; *m*-nitro, no values quoted, masking by solvent and/or benzenoid protons most likely; *p*-nitro, δ(NH) 7.0—8.0, usually independent of solvent; 2,4-dinitro, δ(NH) *ca.* 11.0.

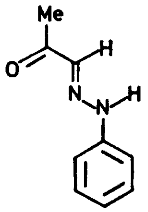
The ν(NH) stretching frequencies for these compounds appear in the range 3 150—3 350 cm^{-1}, and differentiation between ν(NH) hydrogen-bonded, and ν(NH) non-bonded modes is often possible, *e.g.* $MeCOCH{=}NNHC_6H_5$ exists as a mixture of *Z* [δ(NH) 13.8; ν(NH) hydrogen-bonded, 3 260 cm^{-1}] and *E* [δ(NH) 8.7; ν(NH) non-bonded, 3 326 cm^{-1}] forms [(2) and (3)] in $CDCl_3$ solution whereas the solid isolated from the reaction mixture is solely the *E*-isomer.[10]

In previous investigations[3-9] there has been no systematic choice of solvents for ^1H n.m.r. studies, which made it difficult to compare potential inter- and intra-molecular hydrogen bonding. Also earlier workers had studied either hydrogen bonding from the NH group to the carbonyl oxygen of a terminal CO_2Et group, as in (1), or hydrogen bonding from the NH to a ring o-nitro-group. No attempt had been made to study the effects of having both terminal carbonyl groups and *o*-nitro (or carbonyl) groups in the molecule. (Terminal groups are those attached to the imino-carbon atom.)



Z (*cis*)

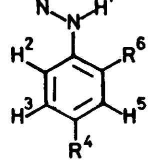
(2)



E (*trans*)

(3)

To examine further the variation of δ(NH) and ν(NH) values and the extent of hydrogen bonding (intra- *versus* inter-) we have synthesised the comprehensive range of phenylhydrazones (I)—(IV) (see Tables 1—4) for



(I)-(IV)

^1H n.m.r. and i.r. spectral analysis. For the n.m.r. studies, the spectra were determined in $CDCl_3$, which was not expected to form a hydrogen bond to N–H, and [$^2H_6$]DMSO which was.

TABLE 1

Compounds (I) having neither *ortho*-substituents nor carbonyl groups

					δ (NH^1)					ν(NH^1)/cm^{-1}		
	R^4	R^6	R^7	R^8	CDCl$_3$	[^{2}H$_6$]DMSO	MeOH	CH$_2$Br$_2$	Neat	Nujol	CHCl$_3$	DMSO
a	H	H	Me	Me	7.0	8.5						
b	H	H	Me	Et	*	8.4	7.7 ‡					
c	H	H	H	Ph	7.0	10.4				3 320	3 333	3 200
d	H	H	Ph	Ph	*	8.8				3 320		
e	H	H	H	Et			8.75 ‡					
f	H	H	H	Pr^i			8.4 ‡					
g	H	H	Me	Pr^i			7.7 ‡					
h	H	H	Me	Bu^t			7.6 ‡		6.5 ‡			
i	H	H	Me	Bu^i			7.8 ‡					
j	NO$_2$	H	Me	Me	†	9.8		7.5		3 305		
k	NO$_2$	H	Me	Et	7.7	9.8		7.6		3 310		
l	NO$_2$	H	Et	Et	7.7	9.9		7.8		3 340	3 372	
m	NO$_2$	H	H	Me	7.9	10.8				3 320		
n	NO$_2$	H	H	Et		10.8				3 260		
o	NO$_2$	H	H	Ph	7.5	11.3				3 285		

* Compound insoluble in this solvent. † Band obscured by aromatic proton resonance. ‡ Ref. 8.

TABLE 2

Compounds (II) having *o*-nitro or -carbonyl groups (including 2,4-dinitrophenylhydrazones), but no other carbonyl group

					δ (NH^1)			ν(NH^1)/cm^{-1}	
	R^4	R^6	R^7	R^8	CDCl$_3$	[^{2}H$_6$]DMSO	CH$_2$Br$_2$	Nujol	CHCl$_3$
a	H	NO$_2$	H	Me	10.8	10.8	10.7 †	3.310	
b	H	NO$_2$	H	Et	10.8	10.7		3 320	
c	H	NO$_2$	Me	Me		10.4	10.5 †	3 300	
d	H	NO$_2$	Me	Et	10.7	10.4	10.5 †	3 300	
e	H	NO$_2$	Et	Et	10.9	10.6	10.8 †	3 340	3 340
f	H	NO$_2$	H	Ph	11.1	11.2		3 385	
g	H	NO$_2$	Ph	Ph	10.9	10.8		3 290	
h	NO$_2$	NO$_2$	H	H	11.5	11.2		3 320	
i	NO$_2$	NO$_2$	H	Me	11.3	11.2		3 300	
j	NO$_2$	NO$_2$	H	Et	11.2	11.0		3 295	
k	NO$_2$	NO$_2$	Me	Me	11.0	10.8		3 300	
l	NO$_2$	NO$_2$	Me	Et	11.1	10.8		3 315	
m	NO$_2$	NO$_2$	Et	Et	11.0	11.2		3 310	3 326
n	NO$_2$	NO$_2$	H	Ph	*	11.6		3 300	
o	NO$_2$	NO$_2$	Ph	Ph	11.2	11.0		3 285	
p	H	CO$_2$H	Me	Me	10.4	10.7		3 305	3 319
q	H	CO$_2$Me	Me	Me		10.5		3 290	
r	H	CO$_2$H	Me	Et			11.4 †		

* Compound insoluble. † Ref. 9.

TABLE 3

Compounds (III) with no *o*-nitro or -carbonyl groups but having other carbonyl groups.

					δ(NH^1)		ν(NH^1)/cm^{-1}	
	R^4	R^6	R^7	R^8	CDCl$_3$	[^{2}H$_6$]DMSO	Nujol	CHCl$_3$
a	H	H	CO$_2$H	CO$_2$H	13.1	13.2	3 120	
b	H	H	CO$_2$Me	CO$_2$Me	12.9	12.1	3 130	3 170
c	H	H	CO$_2$Et	CO$_2$Et	12.8 *			
d	H	H	COCH$_3$	COCH$_3$	14.7 *			
e	NO$_2$	H	CO$_2$H	CO$_2$Me		12.5	†	
f	NO$_2$	H	CO$_2$Me	CO$_2$Me	12.8	12.0	3 150	3 205
g	CO$_2$Me	H	CO$_2$Me	CO$_2$Me		11.9	3 150	

* Ref. 3. † Band not detectable.

TABLE 4

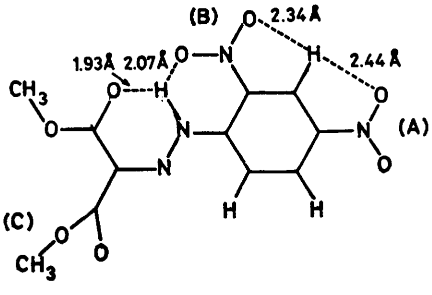
Compounds (IV) having *o*-nitro or -carbonyl groups plus other carbonyl groups

					δ(NH^1)		ν(NH^1)/cm^{-1}	
	R^4	R^6	R^7	R^8	CDCl$_3$	[^{2}H$_6$]DMSO	Nujol	CHCl$_3$
a	H	NO$_2$	CO$_2$H	CO$_2$H		14.1	3 380	
b	H	NO$_2$	CO$_2$Me	CO$_2$Me	14.2	13.8	3 195	3 205
c	H	NO$_2$	CO$_2$Et	CO$_2$Et		13.7	3 195	
d	NO$_2$	NO$_2$	CO$_2$H	CO$_2$H		14.2	3 240	
e	NO$_2$	NO$_2$	CO$_2$Me	CO$_2$Me	14.3	14.3	3 200	
f	NO$_2$	NO$_2$	CO$_2$H	H		14.2	3 300	

In general the phenylhydrazones were prepared from the carbonyl compound and the appropriate phenylhydrazine in dilute sulphuric acid solution, but in some instances the Japp–Klingemann reaction [11] was employed. Compounds (I)—(IV) were invariably isolated as the single isomer as confirmed by the spectral data.

In two instances, (IId) and (IIi), isomeric mixtures have been reported,[7] but unfortunately no preparative details were given. We observed no isomeric (*Z–E*) equilibria in solution ($CDCl_3$, [$^2H_6$]DMSO) for either series whether on standing for up to seven days, or upon the addition of a trace of acid.

Theoretical treatments of aniline and its *N*-substituted derivatives [12,13] assume sp^2 hybridised nitrogen with *p*-orbital (lone pair) conjugation with the aromatic π-system. In this approach the NR_2 groups and the benzene ring are considered coplanar. Such planarity has been established by *X*-ray crystallography for the *p*-bromophenylhydrazone of ribose [14] and also for methylglyoxal bis(guanyl)hydrazone.[15] With ring-substituted nitro-groups there is the added consideration as to their involvement in π-delocalisation, *e.g.* nitrobenzene is essentially planar [16] whereas *m*-dinitrobenzene has its nitro-groups inclined at 11° with respect to the ring plane.[17] In a recent study by *X*-ray crystallography we have determined the structure of compound (IVe).



(IVe)

Essentially planar molecule except that NO_2 groups (A) and (B) are twisted out of the plane by 14.6 and 11.6 °, respectively. The $COOCH_3$ group (C) is twisted out of the plane by 85°

The ring-NH–N=C–CO fragment is essentially planar implying that electron delocalisation persists throughout the molecule. Also, the *o*-nitro-group is twisted out of the plane of the benzene ring by 10.1° and the *p*-nitro-group by 14.6°. C=O $\cdots$ HN bonding is comparable in strength with $NO_2 \cdots$ H–N bonding as shown by the O $\cdots$ H internuclear separations which are 1.93 Å and 2.07 Å, respectively. Why, in the latter case, the bond should not be detected by i.r. spectroscopy when there is a substantial difference in the δ(NH) values for the non-substituted and *ortho*-substituted derivatives is not known. The non-planarity of nitro-groups in the present series of compounds, which is similar to that found in *m*-dinitrobenzene,[17] would lead to reduced overall conjugation.

Canonical form descriptions of phenylhydrazones indicate that a partial positive charge at the NH site is facilitated by the presence of *o*- and/or *p*-nitro group(s) and also by NH conjugation with terminal carbonyl groups. Any increase in cationic nature should be reflected by increased deshielding of the NH proton.

Throughout the series δ(NH) shows a discernible low field shift for incipient increase in nitro-group ring substitution in accord with inductive–mesomeric effects, *i.e.*, (Ia) (unsubstituted) δ 8.5; (Ij) (*para*) δ 9.8; (IIc) (*ortho*) δ 10.4; (IIk) (2,4-substituted) δ 10.8 ([$^2H_6$]DMSO). The extent of this deshielding, cannot, however, be reconciled to a purely mesomeric argument, *e.g.*, (Ia) δ 7.0 $\longrightarrow$ (IIk) δ 11.0 in $CDCl_3$ solution. There must be considerable intramolecular hydrogen bonding associated with *o*-nitro- substituents; similarly for ring *o*-carboxy-groups as in (IIp), δ 10.4. It appears also that the formation of intramolecular hydrogen bonds prevents the formation of DMSO $\cdots$ H–N bonds since chemical shifts are essentially the same in $CDCl_3$ and in [$^2H_6$]DMSO (Table 2).

In a parallel *X*-ray crystallographic study [18] we have determined the structures of a selection of these phenylhydrazones. Only in the case of compound (IIb) is there any evidence for the formation of intermolecular hydrogen bonds, but dilution studies on this compound and on a selection of other compounds in series (I)—(IV), by both ^{1}H n.m.r. and i.r. spectroscopy, have produced no evidence for the presence of intermolecular hydrogen bonding in solution.

Carbonyl groups in a terminal position give an emphatic low field shift *e.g.* (Ia) δ 7.0 compared with (IIId) δ 14.7 ($CDCl_3$), signifying extensive intramolecular hydrogen-bonding. Moreover the direct comparison (IIp) δ 10.4 *versus* (IIIa—d) δ 12.9—14.7 implies a much greater contribution to such bonding from terminal rather than ring-substituted carbonyl groups. When both ring nitro or carbonyl groups and terminal carbonyl groups are present [compounds (IV)] there is a further downfield shift, and the mean δ(NH) is *ca.* 14. This suggests simultaneous $NO_2 \cdots$ H–N and C=O $\cdots$ H–N bonding. Thus the N–H hydrogen atom is triply bonded, one bond being covalent, the other two being hydrogen bonds.

Evidence from electronic spectroscopy that these terminal carbonyl groups are in conjugation with the π-ring system is not clearcut. While it is often assumed that increasing conjugation results in a red shift for $\lambda_{max.}$ there is no such trend in this series of compounds. Thus phenylhydrazine and its *o*-nitro-, *p*-nitro-, and 2,4-dinitro-derivatives show $\lambda_{max.}$ 283, 430, 384, and 349 nm respectively; the phenylhydrazone, *o*-nitro-, *p*-nitro-, and 2,4-dinitro-phenylhydrazones of acetone show $\lambda_{max.}$ 276, 435, 396, and 362 nm respectively. In terms of conjugation we might expect $\lambda_{max.}$ for *o*-nitro- and *p*-nitro-compounds to be somewhat similar but less than that for 2,4-dinitro-derivatives; this expectation is evidently unfilled. The (mono)phenylhydrazones of acetone and of pentane-2,3,4-trione show $\lambda_{max.}$ 276 and 380 nm, respectively, whereas the corresponding *p*-nitro-derivatives show $\lambda_{max.}$ 393 and 379 nm, respectively. Significantly, we have observed that compounds which have one or more ring nitro-groups (***ortho*** and/or ***para***) ***and*** also terminal $COCH_3$ or CO_2CH_3 groups form vivid red molecular complexes ($\lambda_{max.}$ *ca.* 540 nm) with, *e.g.*, hydroxide ion in DMSO solution. If either structural feature is absent, no compound is formed. Presumably either nitro-group(s), or electron-withdrawing terminal carbonyl groups, alone, are insufficient to render the ring susceptible to attack by hydroxide ion (or other nucleophile). The implication is, therefore, that the nitro-group(s) and the terminal carbonyl groups are in conjugation with each other.

Variations in the intensity and position of ν(NH) stretching frequencies (see Tables 1—4) correlate with chemical shift [δ(NH)] variations but qualitative differentiation between the series as to the degree of hydrogen-bonding involved has been based principally on the latter. Other correlations from i.r. spectroscopy are as follows: ring vibrations appear at *ca.* 1 600 cm^{-1}, and ν(CO) bands show a doublet profile due to in-phase and out-of-phase vibrational modes (1 650—1 750 cm^{-1}). The ring ν(CH) bending vibrations fall into the general classification: unsubstituted, one band at 690—700 cm^{-1}, and one (or two) band(s) between 740—780 cm^{-1}; *o*-nitro derivatives, one doublet at 730—740 and 750—780 cm^{-1}; *p*-nitro derivatives, three bands at 690—700, 740—770, and 835—860 cm^{-1}; 2,4-dinitro derivatives, four bands at 720—740, 740—775, 830—860 (often a doublet), and 920—945 cm^{-1} respectively. The ν(CN) stretching mode appears in the region 1 525—1 575 cm^{-1}.[19]

TABLE 5

Compound	M.p. (°C)	Empirical formula	Found (%)			Required (%)		
			C	H	N	C	H	N
Propanone *o*-carboxymethylphenylhydrazone (IIq)	50—52	$C_{11}H_{14}N_2O_2$	64.0	6.70	13.4	64.1	6.79	13.6
Dimethyl 2-(phenylhydrazono)propanedioate (IIIb)	80	$C_{11}H_{12}N_2O_4$	56.0	5.15	11.9	55.9	5.08	11.9
Dimethyl 2-(p-nitrophenylhydrazono)propanodioate (IIIf)	160	$C_{11}H_{11}N_3O_6$	47.6	4.10	15.1	47.0	3.91	15.0
Dimethyl 2-(*p*-carboxymethylphenylhydrazono)propanedioate (IIIg)	135	$C_{13}H_{14}N_2O_6$	53.1	4.76	9.49	53.1	4.76	9.50
Dimethyl 2-(*o*-nitrophenylhydrazono)propanedioate (IVb)	138	$C_{11}H_{11}N_3O_6$	46.9	3.99	15.0	47.0	3.91	15.0

TABLE 6

Compound	M.p. (°C)	Empirical formula	Found (%)			Required (%)		
			C	H	N	C	H	N
Propanone *o*-carboxyphenylhydrazone (IIp)	172	$C_{10}H_{12}N_2O_2$	62.5	6.15	14.8	62.5	6.25	14.6
2-(2,4-Dinitrophenylhydrazono)propanedioic acid (IVd)	198	$C_9H_6N_4O_8$	36.9	2.07	19.3	36.2	2.01	18.8
2-(0-Nitrophenylhydrazono)propandioic acid (IVa)	139	$C_9H_7N_3O_6$	42.8	2.97	16.8	42.7	2.77	16.0

Tables of chemical shifts and coupling constants for protons other than N–H are given in Supplementary Publication No. SUP 22871 (15 pp.).*

EXPERIMENTAL

U.v.–visible and i.r. spectra were obtained using Pye-Unicam SP 8 000 and Perkin-Elmer 457 spectrophotometers, respectively. The n.m.r. spectra were recorded on a Brüker WH 90 spectrometer operating at 90 MHz, and using tetramethylsilane as external standard. For n.m.r. and i.r. studies in solution concentrations were *ca.* 0.5M if solubility permitted, otherwise the solution was saturated at 25°.

The data for compounds (Ie—i), and for (IIj) were taken from the work of Karabatsos *et al.*[8] The data for (IIIc and d) were obtained from Elguero *et al.*[3] Compounds (Ia—d), (Ij—o), (IIa—o), (IIIa and e), and (IVe and f) were all synthesised by adding the carbonyl compounds to an excess of a solution of the appropriate phenylhydrazine in 2M-H_2SO_4. Recrystallisation was from methanol or methanol–chloroform. The physical properties of the phenylhydrazones were all in accord with those published,[20] and the structures are confirmed by spectroscopic data.

The novel compounds listed in Table 5 were synthesised from the corresponding carboxylic acid using ethereal diazomethane. The compounds in Table 6 were prepared from the carbonyl compound and the appropriate phenylhydrazone in aqueous sulphuric acid solution.

Diethyl 2-(o-*Nitrophenylhydrazono*)*propanedioate* (IVc).—*o*-Nitroaniline (10 g) was added to a mixture of concentrated hydrochloric acid (23 ml) and water (23 ml). The solution was heated until all the amine was in solution and then cooled and stored in a freezer at −10°. To this cold solution was added with stirring a solution of sodium nitrite (6 g) in water (12 ml) which had also been cooled to −10°. The solution of the diazonium salt formed was rapidly filtered and added to a solution in methanol (100 ml) of diethyl malonate (10 g) and sodium acetate (20 g) held at 0° and stirred mechanically. The ***product*** separated as a red-brown solid which was twice recrystallised from methanol (charcoal) as yellow-brown plates, m.p. 68° (Found: C, 50.3; H, 5.05; N, 13.6. $C_{13}H_{15}N_3O_6$ requires C, 50.5; H, 4.85; N, 13.6%).

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