Acyl Derivatives of Hydroxylamine. Part XVIII.[1] Configuration and Conformation of Benzamidoximes

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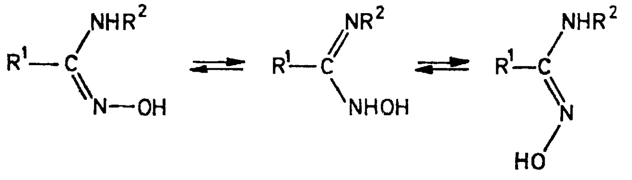
The configuration and conformation of some benzamidoximes have been established from electric dipole moments measured in benzene and from the n.m.r. spectra in [$^2H_6$]dimethyl sulphoxide. The results of the two experimental approaches are complementary and compatible with a hydroxyimino-tautomeric structure as well as with a *Z*-configuration for the C=N bond. Most of the compounds examined exist in a single, almost planar conformation (D); for *ortho*-phenyl substituted derivatives only the conformational equilibrium (D) $\rightleftharpoons$ (H) takes place.

N-SUBSTITUTED amidoximes can be prepared from amines and nitrile oxides or their precursors, *viz.* hydroxamoyl chlorides, probably *via* complex mechanisms.[2] Information on the stereochemistry of amidoximes may be of importance both in connection with mechanistic studies on these compounds and with configurational problems in related systems; we have recently assigned [1] the *E*-configuration to benzohydroxamoyl chlorides. The stereochemical problem of amidoximes is quite complex since in addition to the configuration of the C=N double bond [structure (A) or (C)], the conformations of the formally single bonds N–O and C–N also have to be considered [structures (D)—(L)]; finally, there is the possibility of tautomerism [(A) $\rightleftharpoons$ (B) or (B) $\rightleftharpoons$ (C)]. To overcome the problem we have employed two independent and complementary experimental approaches, namely the dipole moment method [3] which requires examination of the molecule as a whole and takes into consideration all the possible forms, and n.m.r. spectroscopy which gives information on the partial structure and population of individual forms.



(A) (B) (C)

RESULTS AND DISCUSSION

The electric dipole moments with related data in benzene and the n.m.r. spectral data † in [$^2H_6$]dimethyl sulphoxide ([$^2H_6$]DMSO) of benzamidoximes (1)—(9) are listed in Tables 1 and 2 respectively. Both sets of these results will be used at the same time throughout the discussion to clarify each point of the overall problem.

The problem of tautomerism in unsubstituted amidoximes has been solved in favour of the hydroxyimino-forms (A) or (C) in both the solid state and in solution.[5,6]

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† The spectra were recorded at room temperature in dilute solution of [$^2H_6$]DMSO since these conditions were shown to be the most suitable for stereochemical studies of hydroxyimino-compounds (ref. 4).

[1] Part XVII, A. Battaglia, A. Dondoni, and O. Exner, *J.C.S. Perkin II*, 1972, 1911.

[2] G. Barbaro, A. Battaglia, and A. Dondoni, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 149.

[3] O. Exner and V. Jehlička, *Coll. Czech. Chem. Comm.*, 1965, **30**, 639.

[4] G. G. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, 1967, **32**, 460.

[5] (*a*) O. Exner, *Coll. Czech. Chem. Comm.*, 1965, **30**, 652; (*b*) W. B. Jennings and D. R. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 7187.

[6] (*a*) D. Hall and F. J. Llewellyn, *Acta Cryst.*, 1956, **9**, 108; (*b*) W. J. Orville-Thomas and A. E. Parsons, *Trans. Faraday Soc.*, 1958, **54**, 460; (*c*) D. Prevoršek, *Compt. rend.*, 1958, **247**, 1333; (*d*) C. L. Bell, C. N. V. Naumburg, and L. Bauer, *J. Org. Chem.*, 1964, **29**, 2873.

TABLE 1

Polarization data and dipole moments of amidoximes $R^1C(=NOH)NHR^2$ in benzene at 25°

Amidoxime R^1	R^2	R_D^{20}/ cm^3 [a]	$_\infty P_2$/ cm^3	μ(5%)/ D [b]	μ(15%)/ D [b]
(1) Ph	Me	44·5	111·8	1·78	1·72
(2) Ph	Ph	65·3	99·2	1·22	1·09
(3) Ph	4-MeC_6H_4	70·0	122·6	1·55	1·43
(4) Ph	4-ClC_6H_4	70·2	106·3	1·26	1·12
(5) 4-ClC_6H_4	Ph	70·2	143·6	1·84	1·75
(6) 2,4,6-$Me_3C_6H_2$	Ph	79·2	136·1	1·61	1·48
(7) 3,5-Cl_2-2,4,6-Me_3C_6	Ph	89·1	204·1	2·32	2·22
Methyl mesitoate		51·9	136·1	2·00	1·93

[a] Calculated from Vogel's increments (A. I. Vogel, *J. Chem. Soc.*, 1948, 1833) and the value of 9·91 cm^3 for the C=NOH group conjugated with an aromatic nucleus (ref. 5*a*). [b] Correction for the atomic polarization 5% or 15% of the R_D value, respectively. The difference of the two columns represents the experimental uncertainty, in addition to a common error of *ca.* 0·05 D.

Nevertheless, the tautomeric equilibrium (A) $\rightleftharpoons$ (B) $\rightleftharpoons$ (C) may exist and it was considered to be the reason[5] why the two stereoisomers (A) and (C) have not been isolated. The n.m.r. data (Table 2) also support the hydroxyimino-form for the *N*-substituted derivatives (1)—(9). The resonance at low field for the hydroxylic proton is in the range for oximes[4] or hydroximic acid derivatives,[7] whereas the resonances of the NHOH group (a sharp singlet for OH and a triplet for NH) observed in the spectrum of *N*-phenylhydroxylamine (Table 2), are absent. This indicates that the two signals observed for the hydroxylic, amide, and *ortho*-methyl protons in the spectra of compounds (6)—(9) do not result from the presence of tautomers but derive from hydroxyimino-isomers. Discussion on this point is postponed and the following treatment applies only to derivatives without *ortho*-substituents; these contain no more than 2—3%, the lowest amount detectable by n.m.r. spectroscopy, of another tautomer or rotamer.

The spatial arrangement of the C=NOH group is defined by the configuration of the C=N bond and by the conformation of the N–O bond; the latter has been attributed partial double bond character.[5a] For oximes in the gas phase[8] as well as in solution,[9] the whole $\rangle$C=NOH group is planar with O–H antiperiplanar (ap) to N=C. This conformation is consistent with dipole moment data of more complex compounds.[1,5a,10] The conformational problem of the C–N bond in the amidoximes (1)—(9) is similar to that in monosubstituted amides, where partial double character is highly developed. For these compounds the synperiplanar (sp) arrangement of the C=O and N–R bonds is preferred,[11] but the population of the ap-form increases with particular substituents[12] and even non-planar forms have been claimed.[12b] In the case of amidoximes the planarity of the NHR^2 group is supported particularly by the results on formamidoxime[5b] and amidines.[13] Hence we consider primarily the eight planar conformations (D)—(L), namely the sequence from the form* $_{ap}Z_{ap}$ to $_{sp}E_{sp}$. The (E), (G), (J), and (L) forms, however, appear to be of low probability because of the unusual[8,10] conformation of the NOH group and for steric reasons.

TABLE 2

N.m.r. data [a] for $R^1C(=NOH)NHR^2$

Amidoxime	δ (p.p.m.) ±0·01 OH	NH	R^1	R^2	4-Me	2-Me	Isomer (%) [b]
(1)	9·80	5·82	7·50	2·60			
(2)	10·57	8·28	7·35	7·20—6·50			
(3)	10·50	8·15	7·35	6·90—6·50	2·13		
(4)	10·67	8·50	7·35	7·20—6·70			
(5)	10·65	8·35	7·40	7·20—6·70			
(6)	10·10	8·33	7·35	7·70—6·50	2·23	2·11	67
	9·10	8·08			2·28	2·17	33
(7)	10·35	8·60		7·70—6·50	*c*	2·18	54·5
	9·40	8·30				2·25	45·5
(8) R^1 = 2-MeC_6H_4, R^2 = Ph	10·35	8·35	7·45—7·20	7·80—6·60		2·10	83·5
	9·23	8·18				2·25	16·5
(9) R^1 = 2,6-$Cl_2C_6H_3$, R^2 = Ph	10·45	8·64	7·65—7·35	7·30—6·70			62
	9·50	8·51					38
N-Phenylhydroxylamine	8·20	8·00—8·30					

[a] Spectra were recorded in *ca.* 7% solution of $[^2H_6]$DMSO. [b] Percentages of forms (D) and (H). [c] Overlapped with CD_2HSOCD_3 (1%) in the solvent.

The expected dipole moments for conformations (D)—(L) were calculated by vector addition of bond moments, the same values being used as previously,[1,10] *viz.* H–C_{al}, 0·3; H–C_{ar}, 0·0; C–N, 0·45; C=N, 1·8; N–O, 0·3; H–N,

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* In this notation the conformation of C–N (with respect to N–R^2 and C=N), configuration of C=N, and conformation of N–O (with respect to N=C and O–H), are indicated successively.

[7] D. Šnobl and O. Exner, *Coll. Czech. Chem. Comm.*, 1969, **34**, 3325.

[8] I. N. Levine, *J. Mol. Spectroscopy*, 1962, **8**, 276; *J. Chem. Phys.*, 1963, **38**, 2326.

[9] K. E. Calderbank and R. J. W. LeFèvre, *J. Chem. Soc.*, 1949, 1462.

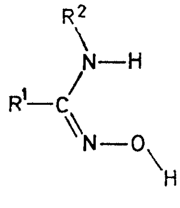
[10] (*a*) O. Exner, V. Jehlička, and A. Reiser, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3207; (*b*) O. Exner, M. H. Benn, and F. Willis, *Canad. J. Chem.*, 1968, **46**, 1873; (*c*) O. Exner and O. Schindler, *Helv. Chim. Acta*, 1969, **52**, 577.

[11] R. B. Corey and L. Pauling, *Proc. Roy. Soc.*, 1953, *B*, **141**, 10; Y. Koyama, T. Shimanouchi, and Y. Iitaka, *Acta Cryst.*, 1971, **27B**, 940; A. Kotera, S. Shibata, and K. Sone, *J. Amer. Chem. Soc.*, 1955, **77**, 6183.

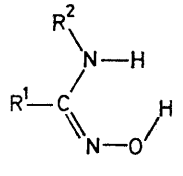
[12] (*a*) C. N. R. Rao, K. G. Rao, A. Goel, and D. Balasubramanian, *J. Chem. Soc.* (*A*), 1971, 3077; (*b*) H. E. Hallam and C. M. Jones, *J. Mol. Struct.*, 1970, **5**, 1.

[13] D. C. Prevoršek, *J. Phys. Chem.*, 1962, **66**, 769.

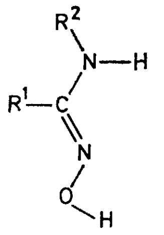
1·31; H–O, 1·51; and C_{ar}–Cl, 1·60 D. In addition, a mesomeric moment of 0·5 D, directed from nitrogen to R^2 (R^2 = phenyl) was applied to account for π-conjugation within the amide group.* The bond angles used were $N{-}\widehat{C}{=}N = C{-}\widehat{C}{=}N = 125°$, $C{=}\widehat{N}{-}O = 114$ or 118° for the *Z*- or *E*-configuration respectively,[10c] $N{-}\widehat{O}{-}H = 105°$; and angles around the amide nitrogen atom were 120°.



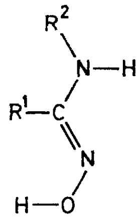
(D) ($_{ap}Z_{ap}$)



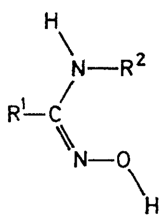
(E) ($_{ap}Z_{sp}$)



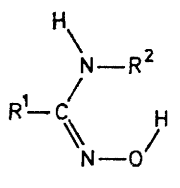
(F) ($_{ap}E_{ap}$)



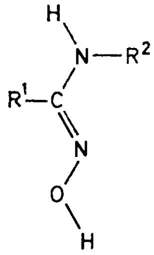
(G) ($_{ap}E_{sp}$)



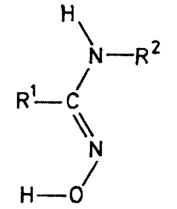
(H) ($_{sp}Z_{ap}$)



(J) ($_{sp}Z_{sp}$)



(K) ($_{sp}E_{ap}$)



(L) ($_{sp}E_{sp}$)

Comparison of the calculated and experimental dipole moments of the unsubstituted compound (2) with those of the *para*-chloro-derivative (5) are shown in Figure 1.[3] Each ' calculated ' conformation (D)—(L) is represented by a point and the hatched circle contains the experimental values. The broken lines correspond either to different mixtures, or to transitory conformations arising from rotation around the C–N bond; the two possibilities are indistinguishable by dipole moment data. The full lines indicate more complex mixtures having either the *E*- or *Z*-configuration with equal populations of C–N bond rotamers and different populations of the N–O rotamers. Taking into account the conclusions reached from the n.m.r. data, Figure 1 may be explained in terms of either the presence of only the $_{ap}Z_{ap}$ form (D), which may be somewhat distorted in the direction $_{sp}Z_{ap}$ (H), or the presence of the $_{sp}E_{ap}$ form (K). Comparison of the data for compounds (3) and (4) (Figure 2) removes this ambiguity and indicates that (D) is the only possible form. The agreement with experiment is not perfect in both diagrams although in Figure 2 this can be slightly

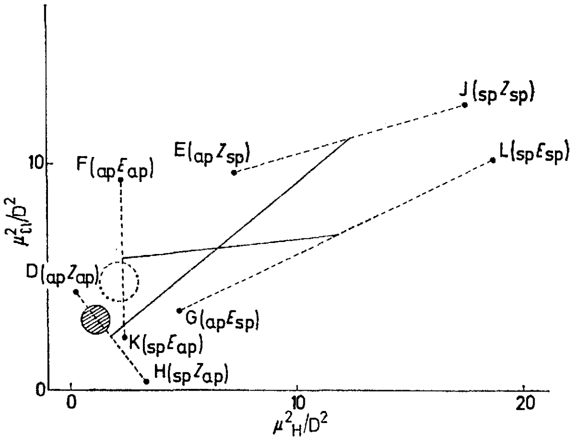


FIGURE 1 Graphical comparison of dipole moments (plotted as μ^2) of *N*-phenylbenzamidoxime (2) (*x*-axis) with its 4-chloro-derivative (5) (*y*-axis) and of *N*-phenylmesitylamidoxime (6) with its 3,5-dichloro-derivative (7). Experimental values [hatched circle for compounds (2) and (5) and dashed for (6) and (7)] and calculated values (full points) for various conformations are shown. The dashed lines represent rotamers of the C–N bond; the full lines represent mixtures of all forms with either the *E*- or *Z*-configuration

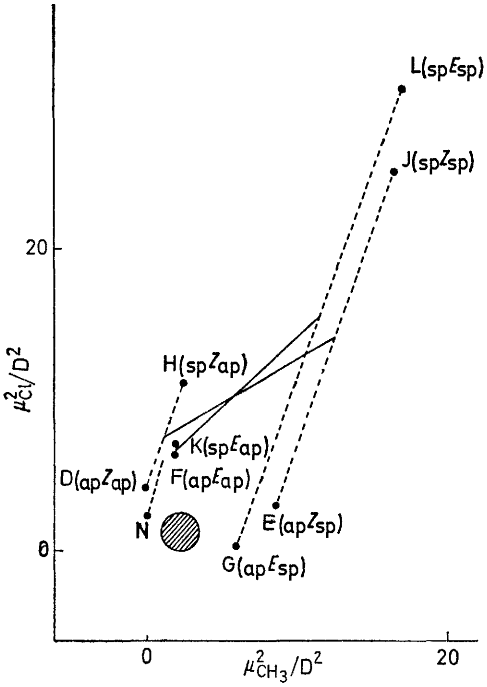


FIGURE 2 Graphical comparison of dipole moments of benzamidoximes (3) and (4) with the same symbols as in Figure 1

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* These values of bond moments are certainly not universal but apply to many derivatives of hydroxylamine.[5a,9,10] The moments of the C=N and N–O bonds have been recently re-examined[14] with respect to possible conjugations within the Ph–C=N or C=N–O groups. The N–O value is somewhat less certain than the others but as it is relatively small it cannot substantially affect the results.

[14] H. Lumbroso and G. Pifferi, *Bull. Soc. chim. France*, 1969, 3401; H. Lumbroso, D. M. Bertin, and G. P. Cum, *Compt. rend.*, 1969, **269**, 5; A. Dondoni and O. Exner, *J.C.S. Perkin II*, 1972, 1908.

improved by ignoring the mesomeric moment of 0·5 D (point N); in Figure 1 the same correction is immaterial.

The above conclusions appear to be supported by independent reasoning based on the n.m.r. data (Table 2). Compounds (6)—(9) clearly exist in two forms which *a priori* may result from: (i) a configurational change of C=N, *e.g.* (D) $\rightleftharpoons$ (F); (ii) hindered rotation around the N–O bond, *e.g.* (D) $\rightleftharpoons$ (E); (iii) hindered rotation around the C–N bond, *e.g.* (D) $\rightleftharpoons$ (H). The first two possibilities seem unlikely for several reasons but mainly because the second form is observable only in *ortho*-phenyl-substituted derivatives and its population depends mainly on the magnitude of the steric hindrance of the substituent * (last column of Table 2). Moreover, the differences in chemical shifts of the OH proton are much larger than those reported in the case of *Z*- and *E*-isomers [4,7] and the two *meta*-protons in R^1 of (6) are equivalent since only one sharp signal is observed. Consequently, the two forms observed represent rotamers of the C–N bond having a rather high energy barrier as indicated by the coalescence temperature [15] of *ca.* 120° for the two *ortho*-methyl signals in (7). The less abundant conformation is the (sp), where the OH proton experiences the greatest shielding by the *N*-phenyl ring lying perpendicular † to the NCN plane. The differences of the amide hydrogen resonances in compounds (6)—(9), although smaller than those of the hydroxylic protons, are also consistent with the above conclusions owing to the deshielding effect [17] of the NOH group.

The equilibrium under consideration is thus represented by one of four possibilities, (D) $\rightleftharpoons$ (H), (E) $\leftrightarrows$ (J), (F) $\rightleftharpoons$ (K), and (G) $\rightleftharpoons$ (L), but the first two are more likely since these produce the larger effect on the OH proton. With this conclusion in mind, the dipole moment and n.m.r. data are complementary and indicate (D) as the preferred form for all the compounds examined. Only in the case of *ortho*-phenyl-substituted derivatives (6)—(9) can the less abundant form ‡ (H) be observed. The presence of this conformation as well as of others derived from rotation about the C–N and N–O bonds cannot be strictly excluded even for compounds (1)—(5). However, under the experimental conditions adopted, it is unlikely that rotations about the C–N and N–O bonds is so fast [when compared with (6)—(9)] to prevent completely the observation of other forms.

The *Z*-configuration for the *N*-substituted benzamidoximes (1)—(9) is in agreement with their chemical behaviour, such as the cyclizations in the presence of phosgene [19] and thionyl chloride.§ The same configuration has also been proved for other benzamidoximes [5a] and formamidoxime [6a,b] and seems thus to be a general feature for these derivatives of hydroxylamine. The conformation of the C=NOH group is as observed in related systems [1,4a,8-10] whereas the prevailing conformation of C–N is reversed relative to that in *N*-monosubstituted amides.[11] The analogy between hydroxyimino and carbonyl compounds thus appears not to be very close. In fact it has been already pointed out [5a,10b] that in compounds of the type C(=NOH)X (X = OR or SR), the =NOH group exerts less influence on the conformation on the neighbouring C–X bond than the carbonyl group in related systems, such as in CO·OR and CO·SR.

EXPERIMENTAL

Materials.—Distilled samples of commercial anilines were used. *N*-Phenylhydroxylamine [21] and methyl mesitoate [22] were prepared according to literature procedures. Nitrile oxides were obtained by standard methods [23] and were recrystallized [24] before use, with the exception of *o*-toluonitrile *N*-oxide, and benzonitrile *N*-oxide which were prepared and used *in situ*. ***o*-Toluonitrile** N-***oxide***, not previously reported, was obtained by chlorination of *o*-tolualdehyde oxime with nitrosyl chloride in ethyl ether as described,[1] and subsequent treatment of the ice-cooled solution of the hydroxamoyl chloride with triethylamine; filtration of triethylammonium hydrochloride gave an ether solution of the nitrile oxide which showed an intense i.r. band at *ca.* 2290 cm^{-1} characteristic of the CNO group.[23] The nitrile oxide could be isolated by evaporation of the ether solution under reduced pressure to give an oil which crystallized from ether–light petroleum (1 : 2) (acetone–solid carbon dioxide bath); m.p. 29—31° (Found: C, 71·8; H, 5·4; N, 10·1. C_8H_7NO requires C, 72·2; H, 5·3; N, 10·5%), $\nu_{max.}$ (CCl_4) 2290s and 1320vs cm^{-1}. Occasionally, before the crystallization, the product was

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* This appears particularly evident for compounds (6) and (9) which have *ortho*-substituents of similar steric hindrance but opposite electronic effects.

† The average perpendicular position of the phenyl rings with respect to the NCN plane follows from their spectral patterns, *e.g.* A_2B_2 in (3)—(5), A_2B in (9), A_2 in (6), and from the equivalence of the two methyl groups in (6) and (7). This arrangement is in accord with that observed for similar compounds.[16]

‡ The presence of the form (H) could not be confirmed by the dipole moment data. In fact, in Figure 1 the dashed circle corresponding to compounds (6) and (7), deviates from (D) but not in the expected direction, *viz.* toward (H). Although the moments of the three methyl groups should cancel according to simple vector addition, the actual moments are too high. This effect is also observed in the case of methyl mesitoate (Table 1) whose dipole moment is significantly higher than those of alkyl benzoates.[18] Hence a detailed conformational study of the problem would require proper models of these overcrowded compounds, but this was not considered urgent in the present case since the n.m.r. data were convincing on just this point. Also the moment of the aliphatic derivative (1) is somewhat enhanced but the presence of form (H) was not demonstrated by the n.m.r. spectra.

§ Preliminary experiments have shown that *N*-aryl- and *N*-alkyl-benzamidoximes react readily with thionyl chloride to give 1-oxo-1,2,3,5-thiaoxadiazoles.[20]

[15] C. A. Boicelli and A. Dondoni, unpublished data.

[16] H. Hjeds, K. P. Hansen, and B. Jerslev, *Acta Chem. Scand.*, 1965, **19**, 2166; P. C. Cherry, W. R. T. Cottrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc.* (*C*), 1968, 459.

[17] A. C. Huitric, D. B. Roll, and J. R. De Boer, *J. Org. Chem.*, 1967, **32**, 1661; A. Daniel and A. A. Pavia, *Tetrahedron Letters*, 1967, 1145.

[18] A. L. McClellan, 'Tables of Experimental Dipole Moments,' Freeman, San Francisco, 1963.

[19] C. Grundmann, H.-D. Frommeld, K. Flory, and S. K. Datta, *J. Org. Chem.*, 1968, **33**, 1464.

[20] A. Battaglia and A. Dondoni, unpublished data.

[21] O. Kamm, *Org. Synth.*, Coll. Vol. I, 1941, p. 445.

[22] M. S. Newman, *J. Amer. Chem. Soc.*, 1941, **63**, 2431.

[23] C. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, Heidelberg–New York, 1971.

[24] G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc.* (*B*), 1970, 558.

separated from red tars by rapid elution with methylene chloride through a short column of silica.

Benzamidoximes.—In the case of *N*-arylbenzamidoximes (2)—(9), a 10-fold excess of the stoicheiometric amount of the required aniline was added dropwise to the solution of the nitrile oxide (1 g) in carbon tetrachloride or ethyl ether (*ca.* 100 ml). The reactants were mixed at 0° or at room temperature depending on the stability of the nitrile oxide. To obtain *N*-methylbenzamidoxime (1), a slow stream of methylamine (Union Carbide) was bubbled for 2 h through a solution of benzonitrile oxide in carbon tetrachloride at 5°. In every case the mixture was left for at least 24 h at room temperature and then the solvent and the excess of amine were removed *in vacuo*. In the case of compounds (2), (5), (6), and (8) the oily residue was treated with light petroleum (b.p. 30—50°) to induce crystallization and in other cases the solid residue was chromatographed on silica to give the amine (eluant, benzene) and then the product [eluant, benzene–ethyl ether (8 : 2)] in *ca.* 70% yield. After recrystallization from benzene in the case of (1) and from benzene–light petroleum in other cases, the products were analytically pure (Table 3); the i.r. spectra (CCl_4–C_2Cl_4–CS_2) showed bands at 3600 (NH), 3400 (partially overlapping with a broad absorption having the maximum at *ca.* 3250; OH), and *ca.* 1630 (C=N) cm^{-1}.

TABLE 3
Properties of amidoximes (1)—(9)

			Found (%)			Required (%)		
	M.p. (°C)	Formula	C	H	N	C	H	N
(1)	157—159	$C_8H_{10}N_2O$	63·9	6·68	18·8	64·0	6·71	18·7
(2)	137—138	$C_{13}H_{12}N_2O$	73·4	5·66	13·0	73·6	5·70	13·2
(3)	159—160	$C_{14}H_{14}N_2O$	74·3	6·32	12·3	74·3	6·24	12·4
(4)	177—179	$C_{13}H_{11}ClN_2O$	63·2	4·36	11·4	63·3	4·50	11·4
(5)	130—132 [a]	$C_{13}H_{11}ClN_2O$	63·6	4·47	11·3	63·3	4·50	11·4
(6)	144—145 [b]							
(7)	161—162 [a]	$C_{16}H_{16}Cl_2N_2O$	60·0	4·80	8·57	59·5	4·99	8·67
(8)	93—94 [c]							
(9)	208—209	$C_{13}H_{10}Cl_2N_2O$	55·8	3·67	9·95	55·5	3·58	9·97

[a] Previously described in ref. 2. [b] Lit. m.p. 146° (C. Grundmann and J. M. Dean, *J. Org. Chem.*, 1965, **30**, 2809. [c] Despite several attempts on samples prepared independently, this compound gave unsatisfactory elemental analyses.

Physical Measurements.—The n.m.r. spectra were recorded at room temperature on a JEOL JNM-PS-100 Spectrometer with tetramethylsilane as internal standard. Determination of dipole moments was as described.[5a, 10]

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