EZ-Isomerism in Alkyl Phenyl Ketone Phenylhydrazones and Acetaldehyde Phenylhydrazone

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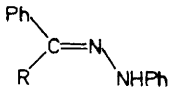
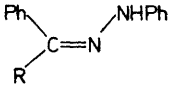
The *E*- and *Z*-isomers of the hydrazones PhRC=N·NHPh (R = Pr^i or Bu^t) exhibit anomalous n.m.r. spectra owing to the *C*-phenyl group being non-coplanar with the C=N bond. An improved procedure for the preparation of pure *Z*-acetaldehyde phenylhydrazone, the kinetically controlled product of the condensation, is described. Phenylhydrazine is shown to catalyse the interconversion of the *E*- and *Z*-isomers of phenylhydrazones by an addition–elimination mechanism.

Alkyl Phenyl Ketone Phenylhydrazones.—In their n.m.r. spectroscopic study of phenylhydrazones, Karabatsos and Taller [1] found that protons α and β to the C=N group are shielded more when *cis* to the NHPh group



(E)



(Z)

(I) a; R = Me
b; R = Et
c; R = Pr^i
d; R = Bu^t

than when they are *trans*. This observation enables the configuration of many phenylhydrazones to be determined. However we have found that this method gives incorrect assignments with sterically hindered alkyl phenyl ketone phenylhydrazones.

If the n.m.r. data for equilibrated isomer mixtures of alkyl phenyl ketone phenylhydrazones (see Table) are analysed on the basis that H_α and H_β absorb at higher field in the *E*-isomers, the major isomer appears to be *E* for (Ia), *Z* for (Ib), and, surprisingly, *E* for (Ic and d). Since the conclusion for the latter two compounds is at variance with that expected on the basis of steric arguments, we have used another spectroscopic method to locate the origin of this anomaly.

The u.v. spectra of compounds (Ia and b) were almost identical and differed markedly from those of (Ic and d) (see Table). Indeed the spectrum for (Id) was very similar to that of acetone phenylhydrazone [$\lambda_{max.}$(EtOH) 272 nm (ε 17 500)], suggesting that there is little conjugation between the *C*-phenyl group and C=N·NHPh in this case. In the case of the parent ketones, the u.v. spectrum of t-butyl phenyl ketone differs from those of the other three in having a considerably lower extinction coefficient, this being attributed to steric repulsion between the t-butyl group and the phenyl group resulting in the latter being non-coplanar with the carbonyl group.[2] A similar explanation would account

N.m.r. and u.v. data for the hydrazones PhRC=N·NHPh

			Chemical shift (δ) of alkyl protons					
			Major isomer		Minor isomer			
R	Solvent	Most abundant isomer (%)	H_α	H_β	H_α	H_β	$\lambda_{max.}$ (EtOH)/nm	ε
Me	CCl_4	96	2.18		2.26		233	12 000
							303	12 200
							331	17 000
Et	C_6H_6 *	51	2.56	1.18	2.19	0.84	235	13 300
							303	13 450
							334	19 800
Pr^i	CCl_4	82	2.77	1.13	3.14	1.30	260	10 500
							283	11 650
Bu^t	CCl_4	>99		1.20		1.27	267	15 600

* The two isomers have the same chemical shifts in CCl_4; the isomeric composition of phenylhydrazones in C_6H_6 is very similar to that in CCl_4.[1]

[1] G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, 1963, **85**, 3624.
[2] E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 1955, 3754.

for the differing u.v. spectra of the phenylhydrazones.[3] For both isomers of compounds (Ia and b), the *C*-phenyl group can be coplanar with C=N, but for compounds (Ic and d) steric repulsion between the alkyl group and the *C*-phenyl group does not allow this coplanarity. This effect will be more severe in (Id) than in (Ic), and is probably worse in the *Z*- than in the *E*-isomer since in the former the phenyl group will be ' sandwiched ' between the alkyl and the NHPh groups.

Loss of coplanarity between the *C*-phenyl group and C=N can also explain the anomalies in the n.m.r. spectra of the isomers of (Ic and d). As the angle between the plane of the phenyl group and the C=N plane increases, the alkyl group will move from the deshielding to the shielding region of the *C*-phenyl group, and since the angle will probably be larger for the *Z*- than for the *E*-isomer, the upfield shift of the signal due to the alkyl protons in the *Z*-isomer will be greater than that in the *E*-isomer. The spectra indicate that this effect is large enough to reverse the normal order of both H_α and H_β absorptions. We therefore conclude that the major isomer for (Ia) is *E*, but for (Ib—d), is *Z* as expected on the basis of steric arguments.

The equilibrium isomer distribution in this series indicates that in this environment, the phenyl group is equal in ' size ' to the ethyl group, although steric interactions may not be the only factor governing the equilibrium; *e.g.* n–π repulsive interactions[4] may also be important. A recent study of the equilibrium distribution of *E*- and *Z*-isomers of *N*-α-alkylbenzylidenemethylamines[4] found that the phenyl group in that environment was intermediate in ' size ' between n-propyl and isopropyl.

Acetaldehyde Phenylhydrazone.—Details of an improved procedure for the preparation of pure *Z*-acetaldehyde phenylhydrazone are given in the Experimental section. This involves performing the condensation between acetaldehyde and phenylhydrazine in ethanol at as low a temperature as possible. Our previously published procedure[5] suffers from the disadvantage that the phenylhydrazone is often contaminated by another product, which has been characterised[6] as the condensation product of two molecules of the phenylhydrazone with a further molecule of acetaldehyde.

The isolation of pure *Z*-hydrazone from the *EZ*-mixture is possible because (i) the *E*-isomer is the more soluble in ethanol, and (ii) $E \longrightarrow Z$ isomerisation occurs during crystallisation. This isomerisation is much faster than that normally observed in solution at the same temperature; the energy released by a molecule when it passes from the solution to the solid state may be responsible for this increase.[7]

In an attempt to measure the kinetics of isomerisation of *Z*-acetaldehyde phenylhydrazone[5] in nitromethane solution at 28 °C, the n.m.r. spectrum was recorded at intervals until equilibration had been achieved. However, the rate constants obtained were widely inconsistent, varying by a factor of 4 around 1.2×10^{-4} s^{-1}.* As we suspected that traces of phenylhydrazine might catalyse the isomerisation by an addition–elimination mechanism, this possibility was investigated. The addition of 0.25 mol. equiv. of phenylhydrazine to a solution of *Z*-hydrazone in nitromethane at 28 °C produced complete equilibration in less than 5 min; 2—8 h was necessary to achieve equilibration in the absence of added phenylhydrazine. The actual exchange of phenylhydrazine groups during equilibration was demonstrated by observing the release of *o*-methylphenylhydrazine from acetaldehyde *o*-methylphenylhydrazone on addition of a small quantity of phenylhydrazine.

Since the above experiments demonstrate that any free phenylhydrazine which is present during the condensation of a carbonyl compound with phenylhydrazine must catalyse the equilibration of the isomeric mixture produced under kinetic control, it is difficult to measure the isomer distribution of the kinetically controlled product of the condensation. This effect can be reduced by using a large excess of the carbonyl compound. For example, when a solution of acetaldehyde in nitromethane was added to a slight excess of phenylhydrazine in nitromethane at −78 °C, and the temperature was raised to −20 °C, the n.m.r. spectrum, which was recorded immediately, showed that the phenylhydrazone was an equilibrated isomeric mixture (40% *Z*). However, when 0.05 mol. equiv. of phenylhydrazine in nitromethane was added to acetaldehyde in nitromethane at −78 °C and the temperature was raised to −40 °C, the initial isomeric mixture was found to contain 79% of the *Z*-isomer. The *Z*-isomer is therefore formed in preference to the *E*-isomer during the condensation, but the product of true kinetic control probably contains more than 79% *Z*-isomer.

A possible explanation for the preferential formation of the *Z*-hydrazone in an aprotic, non-basic solvent like nitromethane[8] is that the intermediate carbinolamine exists in a cyclic, intramolecularly hydrogen-bonded form [see (II)] prior to the elimination which generates the C=N system. In structure (II) the non-bonded interactions between $CH{\cdot}CH_3$ and NH are minimal when $C{-}CH_3$ and N–H are *trans*. If the hydroxy-group is then displaced by the β-nitrogen lone-pair electrons

* An n.m.r. study of the rate of geometrical isomerisation in acetone *N*-methylphenylhydrazone showed that this reaction is catalysed by solvents, or impurities therein, and acid (H.-O. Kalinowski, H. Kessler, D. Leibfritz, and A. Pfeffer, *Chem. Ber.*, 1973, **106**, 1023).

[3] Mme Ramart-Lucas and M. J. Hoch, *Bull. Soc. chim. France*, 1952, 220.

[4] J. Bjørgo, D. R. Boyd, C. G. Watson, and W. B. Jennings, *J.C.S. Perkin II*, 1974, 757.

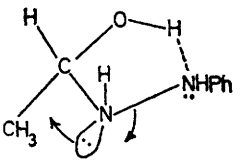
[5] A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1968, 2090.

[6] G. J. Karabatsos and R. A. Taller, *Tetrahedron*, 1968, **24**, 3557.

[7] D. Y. Curtin and J. H. Engelmann, *J. Org. Chem.*, 1972, **37**, 3439 (particularly ref. 22).

[8] G. J. Martin and M. L. Martin, *J. Chim. phys.*, 1964, **61**, 1222; G. R. Wiley and S. I. Miller, *J. Amer. Chem. Soc.*, 1972, **94**, 3287.

rotation as shown would lead to a *trans*-antiperiplanar arrangement of the lone-pair orbital on nitrogen and the



(II)

C–O bond, and would bring the CH_3 and NHPh into a *cis* arrangement, leading to the least stable geometrical isomer of the phenylhydrazone. In support of this explanation, when an excess of acetaldehyde in methanol was treated with phenylhydrazine in methanol between −78 and −40 °C, in a similar manner to the experiment with nitromethane, the n.m.r. spectrum cf the initial product showed the presence of an almost equilibrated mixture of phenylhydrazone isomers. In this case, methanol, being a protic and a basic solvent, would hydrogen bond intermolecularly with the carbinolamine, holding the latter in an open-chain conformation where normal steric effects in a *trans*-antiperiplanar elimination would favour formation of the *E*-isomer.

EXPERIMENTAL

All phenylhydrazones except *Z*-acetaldehyde phenylhydrazone were prepared by standard procedures. ^1H N.m.r. spectra were recorded with a Varian HA100 spectrometer at 28 °C except where other temperatures are indicated; relative intensities of absorptions were calculated from an average of 3—5 electronic integrals. U.v. spectra were recorded with a Unicam SP 800A spectrophotometer.

Determination of the Isomer Composition of Equilibrated Solutions of Alkyl Phenyl Ketone Phenylhydrazones.—The n.m.r. spectra of 5—10% molar solutions in CCl_4 or C_6H_6 under nitrogen were recorded at intervals until there was no further change in composition (*i.e.* up to 7 days). Isomer ratios were determined from integrals on 100 Hz sweep width expansions of the appropriate absorptions; for results see Table.

Preparation of Z-Acetaldehyde Phenylhydrazone.—Phenylhydrazine (9.83 g, 0.091 mol) in ethanol (20 ml) and acetaldehyde (4.0 g, 0.091 mol) in ethanol (20 m.) were separately cooled in liquid nitrogen; both solutions solidified. The acetaldehyde solution was allowed to warm until it was just liquid, and then poured onto the solid phenylhydrazine solution. The mixture was allowed to warm, with shaking, until it formed a homogeneous solution still well below room temperature. It was then placed in ice and allowed to warm slowly to 0 °C. The product separated as colourless crystals. The ethanol was evaporated off *in vacuo* at 20 °C to leave the crude product (10.4 g, 85%), m.p. 89—94 °C. N.m.r. (solvent benzene) indicated that the isomeric composition was 93% *Z* and 7% *E*. The crude product was purified by crushing twice in ethanol at 0 °C, and filtering off the solid. The purified product (6.58 g, 54%), m.p. 93—97 °C (lit.,[5] 91—94 °C), was shown by n.m.r. to contain less than 2% *E*-isomer. The *Z*-isomer was found to equilibrate with the *E*-isomer in the solid state within about 1 month at 20 °C; it remained stable for longer periods at −15 °C.

Application of the same procedure to the preparation of propionaldehyde phenylhydrazone gave an equilibrated isomeric mixture as the crude product, *i.e.* 80—90% *E*-isomer.

Isomerisation of Acetaldehyde Phenylhydrazone during Crystallisation.—A solution of acetaldehyde phenylhydrazone in benzene which was obtained at an intermediate stage in a former procedure [5] was shown by n.m.r. to contain 35% *Z*- and 65% *E*-isomer. Evaporation *in vacuo* at 20 °C gave a solid (87%) which on re-analysis in solution by n.m.r. was found to contain 87% *Z*- and 13% *E*-isomer.

Reaction of Phenylhydrazine with Acetaldehyde o-*Methylphenylhydrazone.*—The n.m.r. spectrum of acetaldehyde *o*-methylphenylhydrazone in benzene showed two methyl doublets, at δ 1.16 (37%; *Z*-isomer) and 1.65 (63%; *E*-isomer), and one singlet (1.84) for the *ortho*-methyl group. After adding phenylhydrazine (1 drop) to the solution, the spectrum showed two overlapping methyl doublets for the *Z*-isomers of the phenylhydrazone and the *o*-methylphenylhydrazone at δ 1.16, and two methyl doublets for the corresponding *E*-isomers at 1.63 and 1.65, together with a singlet for the *ortho*-methyl group in the *o*-methylphenylhydrazone at 1.84 (60%) and a singlet for the *ortho*-methyl group in free *o*-methylphenylhydrazine at 1.74 (40%). The combined isomeric composition of the substituted and unsubstituted phenylhydrazones was 35% *Z*, and 65% *E*.

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