# Spectral analysis of amide conformers (*s-cis* and *s-trans*) of N-isopropylidenehydrazinocarbonyl derivatives

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New N-isopropylidenehydrazinocarbonyl derivatives and other, related compounds display in solution two sets of characteristic NMR signals which are attributable to the presence of *s-cis* and *s-trans* conformers; the conformations are established by extensive NMR experiments.

**Keywords:** amide conformers, N-isopropylidenehydrazinocarbonyl derivatives

A programme of synthesis aimed at the preparation of N-alkylidenehydrazinocarbonyl derivatives having potential anti-tuberculosis activity, affords products which in general display two sets of NMR signals. The components of each mixture are not separable by chromatography or by crystallisation.

The most probable explanation for this behaviour is the occurrence of pairs of amide conformers. The possibility of tautomerism is ruled out by the fact that any alternative tautomeric form which can be envisaged would necessarily involve an alkyl group instead of alkylidene, and there is no evidence for this in the spectra. Most of the compounds are symmetrical (isopropylidene) derivatives, so the possibility of *E*/*Z* geometrical isomerism is also ruled out in these cases.

The occurrence of two sets of NMR signals in solution due to the presence of *s-cis* and *s-trans* amide confomers (which exist because of hindered rotation about the C–N amide bond) is well documented. Much of the earlier work dealt with pairs of $^{1}$H NMR signals (see ref. 3). Full analysis of complex conformer mixtures has been less frequently reported. The advantages of using both $^{13}$C and $^{1}$H NMR (instead of $^{1}$H NMR alone) in studying barriers to internal rotation are clear, however, since the most useful information is frequently derived from non-protonated carbon signals.

N-Acylhydrazones of aromatic aldehydes have been identified as mixtures of *s-cis* and *s-trans* amide conformers.[4] The most marked spectral differences between the conformers occurred in the $^{13}$C NMR spectra, particularly in the signals of the C = O (carbonyl) and C = N carbons. In the spectra of the *s-cis* conformers, the carbonyl carbon signals appeared 5–6 ppm down field compared to those of the *s-trans* conformers, but the C = N carbon signals appeared 4–5 ppm up field.[6] Similar characteristic spectral differences have been recorded recently for more complex *s-cis* and *s-trans* amide conformers.[7]

The simplest of the compounds examined by us is the malonyl derivative **1**. Spectral analysis shows that the two amide conformers are present in 63:37 ratio. The significant difference in intensities between each set of proton signals makes it a simple matter to distinguish them, and then to assign the relevant protonated carbons by HMQC. The characteristic C-1 and C-2 signals appear at $\delta_C$ 150.6 and 167.6 respectively in the major component, which by analogy with the amide conformers described in the literature, is formulated as the *s-cis* conformer. The corresponding signals at $\delta_C$ 155.9 and 161.3 are those of C-1 and C-2 in the *s-trans* conformer.

Apart from the C-1 and C-2 signals, the most striking aspect of isopropylidene hydrazone derivatives such as **1** is the NMR methyl signals. The methyl groups are chemically identical, and so the possibility of geometrical *E/Z* isomerism is not present. Nevertheless, in each conformer striking differences are evident between the $^{13}$C NMR shifts of the two methyl groups. Characteristically, in each isopropylidene group the signal for one methyl carbon appears at $\delta_C$ 16–17, and the signal for the other at $\delta_C$ 24–25. This is not a new observation, but the signals were not correctly assigned in the past.[6] In the case of both *s-cis* and *s-trans* conformers of **1** (and in all other acetone hydrazone derivatives which we have studied), NOE experiments reveal the spatial proximity of the hydrazone NH proton to the protons of the up field methyl group ($CH_3^b$), but not to the protons of the down field methyl group ($CH_3^a$).

Variable temperature NMR has been widely employed in the study of activation parameters about the C(O)–N bond of simple amides.[9] The rotational barrier for **1** is calculated using the $^{1}$H NMR multicoalescence method. The $T_C$ values vary according to the site within each molecule and the limiting chemical shifts of the resonances being observed in each pair of conformers. The $\Delta G^‡$ value (calculated by the usual method and averaged within the molecule) is 89 kJ/mol, indicating the presence of significant steric hindrance.

Reaction of the malonyl hydrazide derivative **1** with salicylaldehyde affords the coumarin derivative **2**; only one conformer of this is present, and spectral data confirm that this is the less hindered *s-trans* conformer. Reaction of the coumarin derivative **2** with acetone and ammonium acetate, by a method previously described,[10] affords the bridged structure **3**, which in solution displays two sets of NMR signals; these are identifed as *s-cis* and *s-trans* conformers, present in 1:1 ratio.

A different series of hydrazone derivatives, with similar spectral characteristics, is obtained from the reactions of the dihydrazino derivative **4a**. With acetone this affords *s-cis* and *s-trans* conformers of **5**, present in solution in 1:1 ratio. Two sets of NMR signals are also present in the dipyrazole product **6** obtained from reaction of **4a** with pentan-2,4-dione, but in this case the features associated with *s-cis* and *s-trans* conformers are absent, and the occurrence of two sets of signals may be attributable to chirality at C-4 or C-14.

Less reactive ketones such as the β-ketone **7** react only with the hydrazine group of **4a** to afford the product **8** (with the azine **9** formed as a minor byproduct). The presence of the unreacted hydrazide grouping in **8** rules out the occurrence of amide conformers.

In the case of the product **10** (obtained from reaction of **4a** with methyl 3-oxobutanoate), two sets of signals are also present; the possibility of geometrical (*E*/*Z*) stereoisomerism is ruled out by NOE experiments, and the signals are assigned to amide conformers. Not surprisingly, the reaction of **4a** with the aldehydes benzaldehyde and *p*-tolualdehyde affords dihydrazone products **11**, each of which displays two sets of NMR signals in solution. The chemical shifts of the significant C-1 and C-2 signals are what would be expected of *s-cis* and *s-trans* conformers, present in 60–62: 40–38 ratio. The $\Delta G^‡$ value for the compound **11** (R = H) is 89.1 kJ/mol, identical with that obtained for compound **1**, and indicating the presence of similar hindrance.

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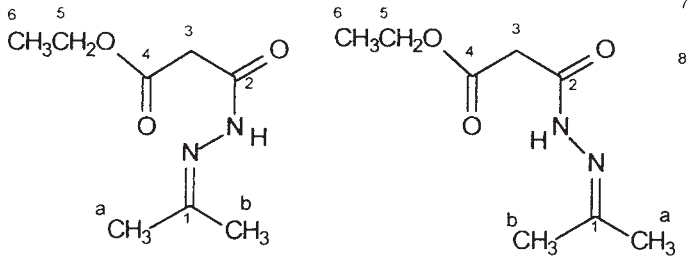
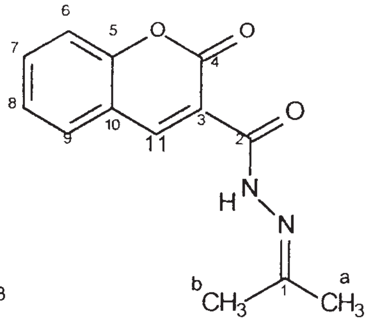


*s-cis* *s-trans*

1



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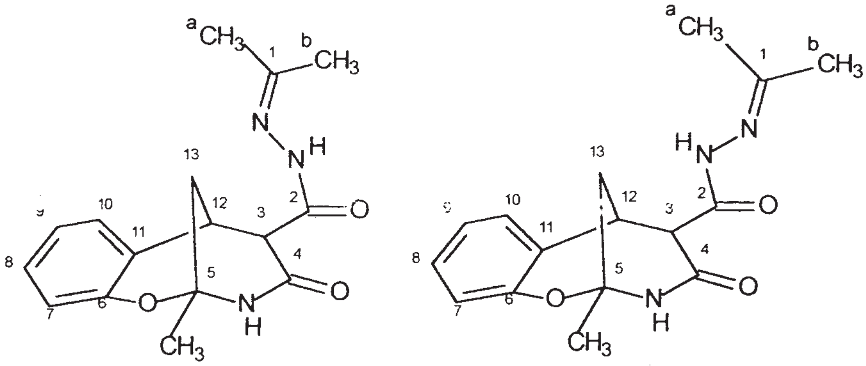
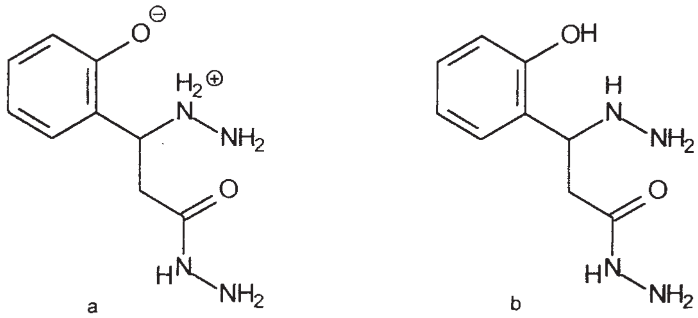


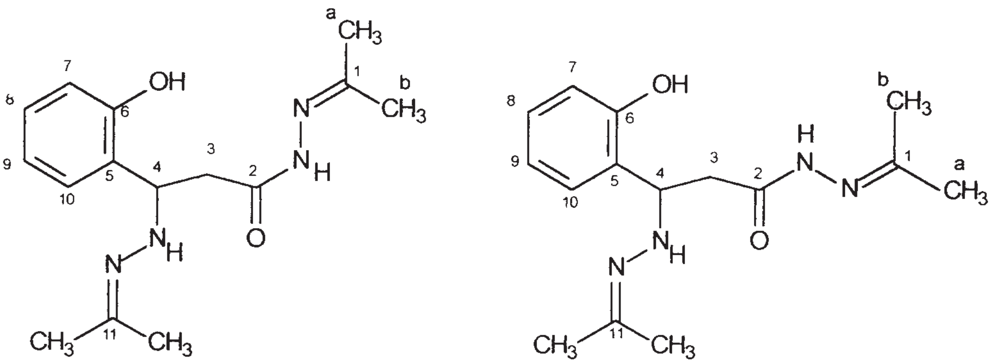
*s-cis* *s-trans*

3



a b

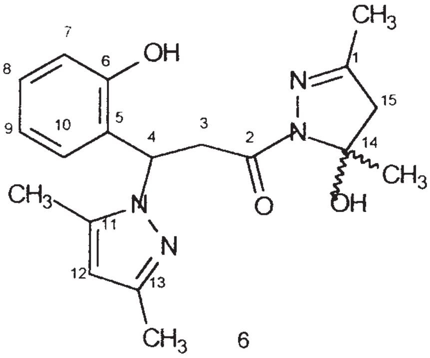
4



*s-cis* *s-trans*

5

The numbering systems used on these formulae are designed to facilitate comparison of $^{13}$C NMR spectra; they are not in accord with systematic IUPAC nomenclature (which is used in naming the compounds in the Experimental section of miniprint version)



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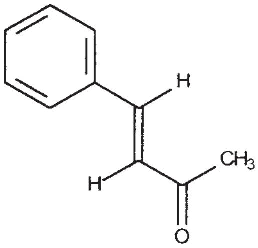

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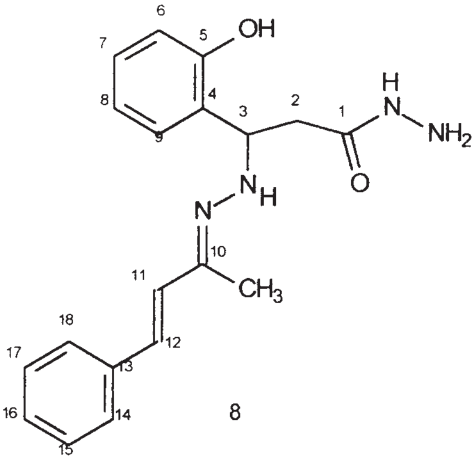

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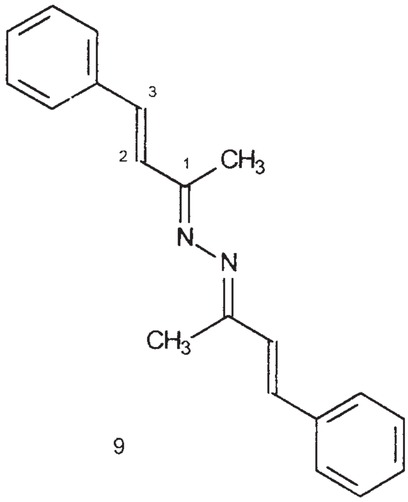

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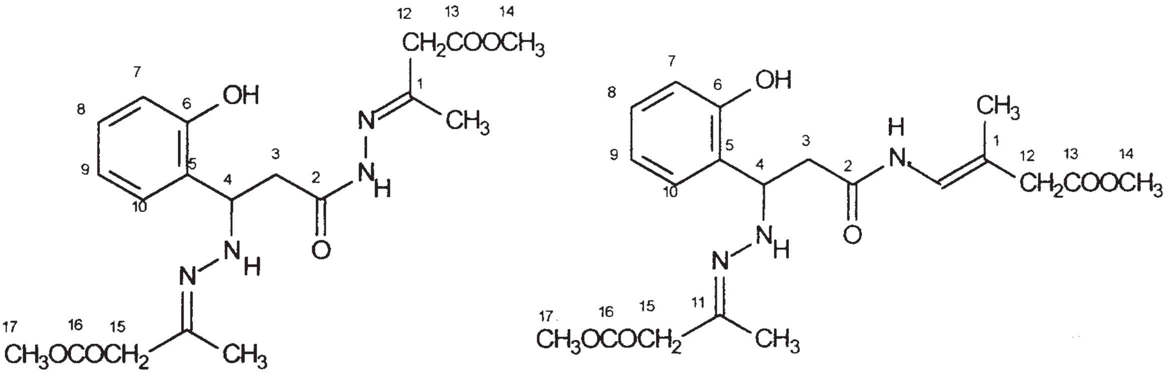
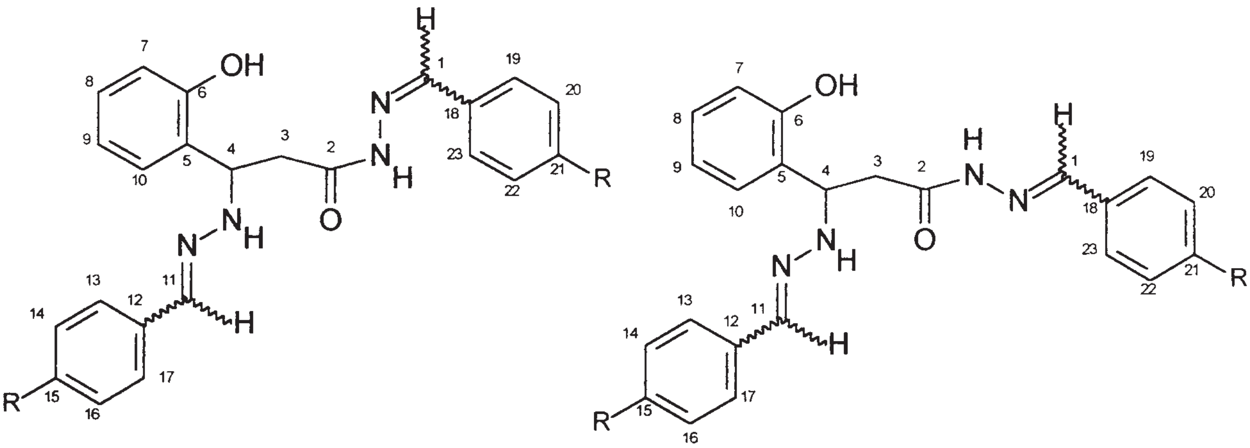


s - cis

s trans

10



s-cis

s-trans

11

It appears that the occurrence of *s-cis* and *s-trans* conformers may be a relatively common characteristic of ketone and aldehyde derivatives of hydrazides.

Techniques used: IR, $^{1}$H NMR, $^{13}$C NMR, CH COSY, HMBC, HMQC, TOCSY, NOE, variable temperature NMR.

References: 13

Fig. 1: Table of Tc values.

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