Conformational Studies on Some 5,6,11,12-Tetrahydrodibenzo[*b,f*][1,4]-diazocine and 11,12-Dihydro-6*H*-dibenzo[*b,f*][1,4]thiazocine Derivatives

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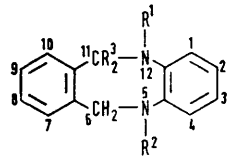
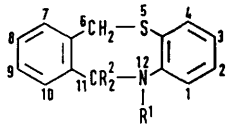
On the basis of spectroscopic evidence, the favoured conformations of 5,6,11,12-tetrahydrodibenzo[*b,f*][1,4]diazocine (1a) and its *NN'*-diacetyl derivative (1b) have been deduced. For the diacetyldibenzodiazocine (1b), interchange between the conformations (II) and (III) [and the equivalent interchange between (I) and (IV)] takes place more readily than that between (I) and (II) [or (III) and (IV)]. The stable conformations of the 5-acetyl-12-methyldibenzodiazocine (1e) have also been deduced; those for *N*-acetyl-11,12-dihydro-6*H*-dibenzo[*b,f*][1,4]thiazocine (2a) are analogous.

We have previously dealt with the synthesis of derivatives of 5,6,11,12-tetrahydrodibenzo[*b,f*][1,4]diazocine (1a).[1] We now discuss the conformation of certain dibenzodiazocine and 11,12-dihydro-6*H*-dibenzo[*b,f*][1,4]-thiazocine derivatives.



(1)

	R^1	R^2	R^3
a;	H	H	H
b;	Ac	Ac	H
c;	H	H	D
d;	Ac	Ac	D
e;	Me	Ac	H
f;	Me	H	D
g;	Me	Ac	D



(2)

	R^1	R^2
a;	Ac	H
b;	H	D
c;	Ac	D

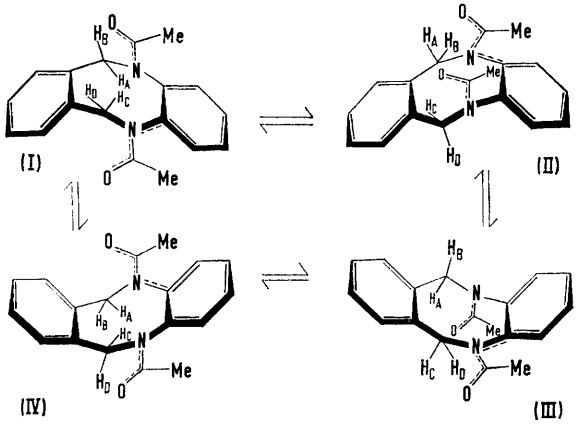
The u.v. absorption spectrum [1a] of 5,6,11,12-tetrahydrodibenzo[*b,f*][1,4]diazocine (1a) is similar to that of *o*-phenylenediamine,[2] although it shows a bathochromic shift due to the *N*-alkylation. The absorption at longer wavelengths indicates that the lone pair of electrons on one of the nitrogen atoms is conjugated with the adjacent aromatic π-electron system. A model shows that it is impossible for both nitrogen atoms to be conjugated with the π-system simultaneously, and that there are four possible conformations in which one or other nitrogen atom is in conjugation. These are shown in Scheme 1 for the diacetyldibenzodiazocine (1b).[1a] In each of compounds (1a) and (1b), both the *N*-substituents are the same, with the result that conformations (II) and (III) are superimposable, as are (I) and (IV), and (I) is the mirror image of (II). [In the more general case, where the nitrogen atoms carry different substituents, (I) and (III) are mirror images, as are (II) and (IV).] Whereas in the diacetyl compound illustrated both nitrogen atoms will be sp^2 hybridised, it seems likely that in the free base (1a) the nitrogen atom which is not conjugated will be sp^3 hybridised. This, however, does not affect the subsequent argument.

In each of the conformations (I)—(IV) the four

[1] (*a*) N. J. Harper and J. M. Sprake, *J. Chem. Soc.* (*C*), 1969, 882; (*b*) A. Saunders and J. M. Sprake, *ibid.*, 1970, 1161; (*c*) A. Saunders and J. M. Sprake, *J.C.S. Perkin I*, 1972, 1964.

[2] L. Doub and J. M. Vandenbelt, *J. Amer. Chem. Soc.*, 1949, **71**, 2414.

methylene protons are all in different environments, and so the methylene groups would be expected to give rise to two AB quartets in the n.m.r. spectrum under conditions of slow conformational change. If one specific methylene proton is traced through the four conformations, it is seen to experience each of the four



SCHEME 1 Favoured conformations of 5,12-diacetyl-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,4]diazocine (1b); the broken lines indicate conjugation

different environments in turn. Thus, under conditions of fast interchange between the conformations, the signals of the methylene protons will be time-averaged, and will appear as a singlet.

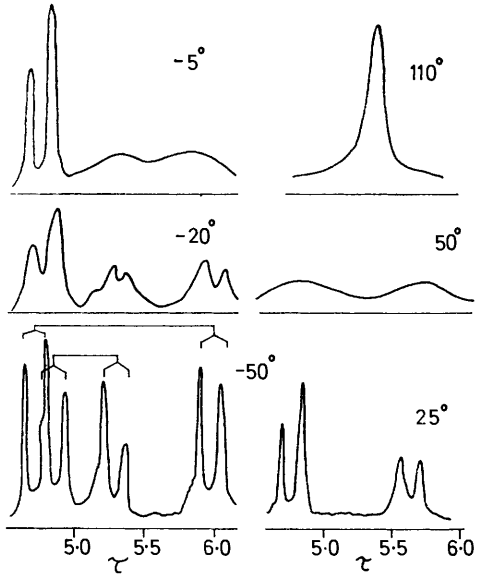


FIGURE 1 N.m.r. signals of the methylene protons of 5,12-diacetyl-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,4]diazocine (1b) (in deuteriochloroform at −50 to 50°, and in pyridine at 110°)

In the n.m.r. spectrum of the free base (1a), the methylene groups give rise to a singlet at ambient temperature, and no splitting occurs as the temperature is lowered to −70°. However, in the spectrum of the diacetyl derivative (1b) at −50°, the methylene signals do appear as AB quartets (Figure 1). As the temperature is raised, the signals from the two downfield protons become time-averaged, giving a broad doublet at −20° which then becomes sharper, whereas the two upfield doublets collapse, and a new doublet forms in the mean position. Thus at 25° the spectrum is beginning to resemble one AB quartet. Furthermore, the methyl protons of the acetyl groups give two singlets at −50° (not illustrated) (τ 8·02 and 8·20), but only one at 25° (τ 8·10). As the temperature is raised further, the AB quartet which was forming at 25° collapses to a singlet.

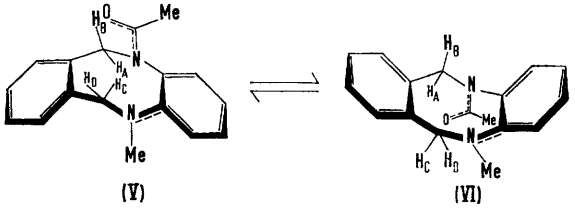
To account for the manner in which the spectrum changes with temperature, it is necessary to examine the conformations shown in Scheme 1. In structure (II), H_A and H_C are almost in the plane of the adjacent carbonyl groups, and close to the carbonyl oxygen atoms, and so their signals would be expected to occur downfield with respect to H_B and H_D. Thus in the low temperature spectrum (−50°) the two downfield halves of the AB quartets can be attributed to H_A and H_C. In structure (III), H_A and H_C are still in the planes of the adjacent carbonyl groups, but in the transition from (II) to (III) these protons have interchanged their environments. The protons H_B and H_D, which give rise to the upfield doublets, similarly exchange environments, as do the methyl protons of the two acetyl groups. Now if the interchange between (II) and (III) [and that between (I) and (IV)] is fast compared to that between (I) and (II) [or between (III) and (IV)], this would account for the time-averaging of the two downfield and two upfield protons observed at 25°. A relatively fast interchange between (I) and (II), in comparison to (II) and (III), would not account for the observed changes in the spectrum, since this would require time-averaging of each of the downfield proton signals with that of one of the upfield protons. Finally, as the interconversion of (I) and (II) becomes faster with increasing temperature, a complete time-averaging of the signals of the methylene protons results. In the conformations shown in Scheme 1 the amide carbonyl groups are drawn *cis*, rather than *trans*, to the adjacent methylene groups, for reasons given in the discussion of the monoacetyldibenzodiazocine (1e).

The n.m.r. spectrum of the labelled diacetyldibenzodiazocine (1d) was identical in appearance, at all temperatures, with that of the unlabelled compound (1b), except that the intensity of the signals due to the methylene protons was halved.

The u.v. spectrum of the 5-acetyl-12-methyldibenzodiazocine [1a] (1e) shows bands at 260 and 307 nm which decrease markedly in intensity on the addition of hydrochloric acid. Thus in the favoured conformations of the molecule it is the amine nitrogen atom which is conjugated with the π-system. In the i.r. spectrum the carbonyl absorption occurs at 1650 cm^{-1}, which confirms that there is no conjugation between the lone pair of electrons of the amide nitrogen atom and the π-system.[3]

[3] L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1964, p. 213.

There are two possible conformations of the molecule in which the lone pair on the amine nitrogen atom is conjugated with the π-system, and these are mirror images of one another (Scheme 2).



SCHEME 2 Favoured conformations of 5-acetyl-5,6,11,12-tetrahydro-12-methyldibenzo[*b*,*f*][1,4]diazocine (1e); the broken lines indicate conjugation

In the n.m.r. spectrum of the acetylmethyldibenzodiazocine (1e), the methylene signals appear as AB quartets at ambient temperature, and these begin to collapse to singlets at higher temperature (Figure 2).

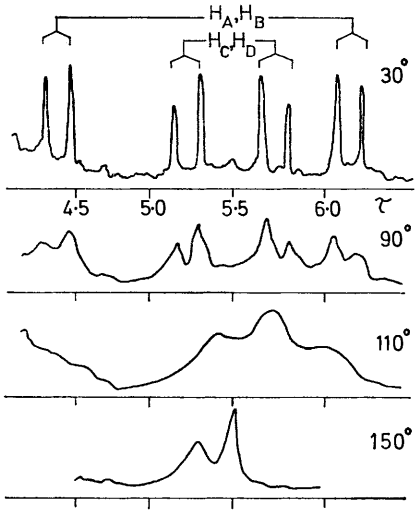


FIGURE 2 N.m.r. signals of the methylene protons of 5-acetyl-5,6,11,12-tetrahydro-12-methyldibenzo [*b*,*f*][1,4]diazocine (1e) (in diphenyl ether)

In the spectrum of the labelled compound (1g), the signals at τ 5·2 and 5·75 are absent; these therefore arise from the protons H_C and H_D. The signal at τ 4·4 can be assigned to H_B in structure (V) (Scheme 2), since this is deshielded by the adjacent carbonyl group. The signal at τ 6·15 is therefore due to H_A.

In the structures in Scheme 2 it is possible to draw the amide carbonyl group either *cis* or *trans* to the adjacent methylene group. It is represented as *cis* in order to account for the large difference in chemical shift between H_A and H_B. The group appears to exist entirely in this conformation, since if the *trans*-conformation were appreciably populated, the adjacent methylene group would give rise to two AB quartets under conditions of slow rotation about the amide C–N bond. Only one quartet is observed from this methylene group, even at −70°.

Meikle [4] has observed that the methylene protons of the acetyldibenzothiazocine (2a) give rise to two AB quartets at ambient temperature. One of the four protons is again markedly deshielded. It appears, therefore, that the most stable conformations of this molecule correspond to those shown in Scheme 2 for the analogous dibenzodiazocine. The quartets begin to collapse to singlets at 100°.

The labelled acetyl compounds (1g) and (2c) were used to study the collapse of a single AB quartet with temperature. The rate constants were obtained by matching the experimental curves to computer-calculated plots of line shapes. For the acetyldibenzodiazocine (1g) in diphenyl ether, the activation energy, E_a, for the process was found to be 12·5 kcal mol^{-1}, with log A = 9·2; the acetyldibenzothiazocine (2c) gave values of 18·6 and 11·7 for E_a and log A, respectively.

The labelled dibenzodiazocines (1c, d, f, and g) were prepared by the extension of syntheses previously described.[1c] The labelled dibenzothiazocine (2b) was prepared by reducing the corresponding amide [5] with lithium aluminium deuteride. Acetylation of the compound (2b) gave the desired derivative (2c).

EXPERIMENTAL

The n.m.r. spectra were recorded for solutions in deuteriochloroform at low temperature, and in pyridine [for the diacetyl compounds (1b and d)] or diphenyl ether [for the monoacetyl compounds (1e and g) and (2a and c)] at high temperature, with a Bruker–Spectrospin HFX instrument. The experimental curves obtained from the labelled acetyldibenzodiazocine (1g) and acetyldibenzothiazocine (2c) in diphenyl ether were matched to computer-calculated plots of line-shapes. For both compounds, when the upper temperature limit of the instrument was reached the singlet due to the methylene group was still broadened by exchange; consequently it was only possible to determine an ' apparent ' T_2 value from the line-widths in the region of slow exchange. This value was used throughout in calculating the theoretical line-shapes, and it is not, therefore, possible to determine the degree of error.

6,6-Dideuterio-5,6,11,12-tetrahydro-12-*p*-tolylsulphonyldibenzo[*b*,*f*][1,4]diazocine was prepared by reduction of 11,12-dihydro-12-*p*-tolylsulphonyldibenzo[*b*,*f*][1,4]diazocin-6(5*H*)-one with lithium aluminium deuteride under the conditions used for the synthesis of the unlabelled compound.[1c]

6,6-Dideuterio-5,6,11,12-tetrahydro-5-methyl-12-*p*-tolylsulphonyldibenzo[*b*,*f*][1,4]diazocine was prepared similarly from 11,12-dihydro-5-methyl-12-*p*-tolylsulphonyldibenzo-[*b*,*f*][1,4]diazocin-6(5*H*)-one.[1c]

6,6-Dideuterio-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,4]diazocine (1c) was made by hydrolysing 6,6-dideuterio-5,6,11,12-tetrahydro-12-*p*-tolylsulphonyldibenzo[*b*,*f*][1,4]-diazocine with 90% (v/v) sulphuric acid, as described for the unlabelled compound.[1c]

The diacetyl derivative (1d) was prepared by heating the dibenzodiazocine (1c) under reflux in acetic anhydride.

[4] T. Meikle, B.Sc. Hons. Pharmacy (C.N.A.A.) Project, Sunderland Polytechnic, 1970.

[5] G. Seidl, Ger. Pat. 1,545,801/1965.

6,6-Dideuterio-5,6,11,12-tetrahydro-5-methyldibenzo-[*b*,*f*][1,4]diazocine (1f) was prepared by hydrolysis of 6,6-dideuterio-5,6,11,12-tetrahydro-5-methyl-12-*p*-tolylsulphonyldibenzo[*b*,*f*][1,4]diazocine with 90% (v/v) sulphuric acid.[1c]

The acetyl derivative (1g) was prepared by heating the dibenzodiazocine (1f) in acetic anhydride.

11,12-*Dihydro*-6H-*dibenzo*[b,f][1,4]*thiazocine*.—(*a*) This compound, synthesised [6] from αα′-dibromo-*o*-xylene and *o*-aminobenzenethiol, had m.p. 104°.

(*b*) The compound was also obtained by reducing 6*H*-dibenzo[*b*,*f*][1,4]thiazocin-11(12*H*)-one [5] with lithium aluminium hydride, as for the corresponding dibenzodiazocine.

The acetyl derivative (2a), prepared by heating the dibenzothiazocine under reflux with acetic anhydride,[4] had m.p. 119—120°, τ 2·70—3·15 (8H, m, aromatic), 3·79 and 5·94 (2H, ABq, *J* 15 Hz, N·CH_2), 5·49 and 6·30 (2H, ABq, *J* 12 Hz, S·CH_2), and 8·11 (3H, s, Me).

11,11-Dideuterio-11,12-dihydro-6*H*-dibenzo[*b*,*f*][1,4]-thiazocine (2b) was prepared by reducing 6*H*-dibenzo-[*b*,*f*][1,4]thiazocin-11(12*H*)-one [5] with lithium aluminium deuteride.

The acetyl derivative (2c) was prepared by heating the dibenzothiazocine (2b) under reflux in acetic anhydride.

All labelled compounds were compared with the unlabelled compounds by m.p. and i.r. spectroscopy.

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[2/619 *Received*, 16*th March*, 1972]

[6] H. L. Yale and F. A. Sowinski, U.S.P. 3,079,393/1963 (*Chem. Abs.*, 1963, **59** 8767).