^{13}C NMR Relaxation Study and 2D Correlation Spectroscopic Investigation of some Quinazoline- and Pyrido[4,3-*d*]pyrimidine-2(1*H*)-ones and -thiones

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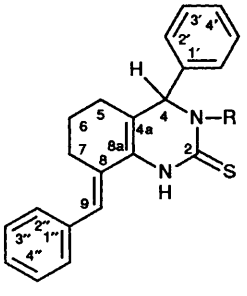
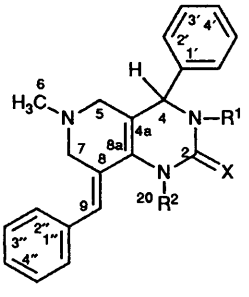
The conformation in solution and microdynamics of 8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thione (**1**) have been examined at high-field by two-dimensional NMR correlation spectroscopy and on the basis of T_1 relaxation times. To assist the interpretation theoretical energy calculations (MM2) were invoked. Earlier spectral assignments concerning **1** and related compounds have been corrected.

The syntheses of 4-aryl-8-arylidene-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thiones (including **1** and **2**) have been described.[1,2] A few of these compounds have antituberculotic activity[3] *in vitro*. The preparation and ^{13}C NMR spectra of some 8-benzylidene-6-methyl-4-phenyl-3,4,5,6,7,8-hexahydropyrido[4,3-*d*]pyrimidine-2(1*H*)-thiones (*e.g.* **3**) have already been published.[4] In the latter class of compound there are many biologically active substances, anticoagulants[5] and antihypoglycaemic agents[5] *etc.* 2-Amino derivatives of **3** showed antihypertensive and bactericide effects.[6]

The solution conformation of these compounds is of interest because of their structure–activity relationships. Moreover, some assignments of the ^{13}C NMR spectra of **1–3** were not unequivocal regarding the quaternary carbons and the resonances of the substituents. With the advent of high-field magnets and two-dimensional (2D) techniques,[7] however, many similar problems have been solved. In this paper the complete assignment of the ^1H and ^{13}C NMR spectra of **1**





R	
1	H
2	CH_3

	R^1	R^2	X
3	H	H	S
4	CH_3	H	S
5	CH_3	CH_3	O

is presented using 2D correlation spectroscopy. The value of heteronuclear long-range coupling information for unambiguous spectral assignments is illustrated. Knowledge of **1** helps in understanding the spectra of **2** and of the aza-analogues **4** and **5**.[4] Further, the solution conformation of **1** (as examined here) is compared with the X-ray structure of its 6-methyl derivative to demonstrate how information on the segmental motion of the molecule (*e.g.* substituents) correlates with the overall conformation.

Results and Discussion

High Resolution NMR Correlation Spectroscopy.—The 400 MHz ^1H spectrum of **1** could be assigned almost completely on the basis of chemical shifts and multiplicities (Table 1), the only ambiguity being the distinction between protons attached to C-5 and C-7, and between the NH protons (both having a half-width of 6 Hz). It is worth mentioning that during acylation or intramolecular alkylation, N-3 can be easily converted while N-1 is relatively unreactive[8,9] (partial enamine structure).

Table 1 ^1H NMR chemical shifts and spin-spin coupling constants of **1** ($CDCl_3$ solution, 40°, 400 MHz, TMS, internal reference). All multiplets were analysed by spin-simulation.[a]

	δ (ppm) M	$^3J_{HH}$/Hz
4-H	4.907s	
5a-H	1.970 ABt	−17.7, 6a,b-H: 5.8, 5.8
5b-H	1.878 ABt	6a,b-H: 6.5, 6.5
6a-H	1.651	−14.7, 7a,b-H: 5.3, 9.5
6b-H	1.650	7a,b-H: 6.1, 4.2
7a-H	2.697 ABddd	−14.7, 9-H: 1.9
7b-H	2.501 ABddd	9-H: 1.3
9-H	6.572s	
N–H	6.58s,br	
N–H	7.60s,br	
Aromatic	7.21–7.39	

[a] s, singlet; d, doublet; t, triplet; ABt, triplet of an AB pattern; br, broad; M, multiplet.

$^4J_{HH}$ couplings are observed in the broadening of the multiplets of 5-H and in the doublet splitting of the resonances of 7a-,b-H. This suggests a distinction between 5-H and 7-H based on the usual values of allylic couplings. Later, however, we present stronger evidence for this.

Note that all protons attached to C-5 and C-7 have distinct chemical shift values. Computer analysis of the seven-spin system results in $^3J_{HH}$ values characteristic of motional averaging without magnetic equivalence.

^{13}C resonances were classified by multiplicities using DEPT editing.[10] ^{13}C–^1H correlation—taken with a delay optimized for one-bond coupling ($^1J_{CH}$ = 150 Hz)—was used to assign non-quaternary carbon resonances C-4, C-6 and C-11 using the known proton assignments.

Multiplicities caused by long-range carbon–proton couplings were observed in a fully proton-coupled 2D spectrum taken by a

Table 2 Long-range ^1H–^{13}C coupling information of the quaternary resonances of **1** obtained by 2D correlation and suppressing the resonances of all protonated carbons[a]

C	δ (ppm)	J_{CH}/Hz	H
2	174.2d	3.7	4
1′	141.3q	*ca.* 5	4, 3′, 5′
1″	136.4t	7.3	3″, 5″
8	129.9br	*ca.* 15	(9, 7, 6a)
8a	126.7q	*ca.* 7	4, 9, 7b
4a	113.5br	*ca.* 21	(4, 5, 6a)

[a] The multiplicities, from J_{CH} couplings, are given after the chemical shifts.

Table 3 ^{13}C chemical shifts (δ) of compounds **1**–**5** (in $CDCl_3$ solution at 25 °C and 50.3 MHz, TMS as internal standard)

C	1	2	3[a]	4	5
2	174.2	175.6	174.2	175.7	157.3
4	61.1	68.6	57.0	66.8	65.3
4a	113.5	113.4	112.0	110.8	116.6
5	26.1	26.1	54.0	54.3	55.4
6	22.4	22.6	—	—	—
7	26.7	26.7	53.9	54.2	54.4
8	129.9	129.8	126.5	127.6	127.3
8a	126.7	126.3	125.9	126.7	128.8
9	122.0	121.9	122.5	122.3	127.1
1′	141.3	140.0	142.6	139.7	139.5
2′	128.3	127.2	129.0	127.1	126.6
3′	127.3	127.2	128.2	127.1	126.6
4′	127.1	128.8	126.9	128.5	129.2
1″	136.4	136.6	136.3	135.8	136.7
2″	129.3	129.2	126.7	129.3	128.4
3″	129.1	129.4	128.6	129.3	128.4
4″	128.6	128.4	127.8	128.9	129.1
1-Me	—	—	—	—	35.8
3-Me	—	40.1	—	40.1	33.8
6-Me	—	—	44.5	44.9	44.8

[a] Data (taken from ref. 4) were determined in [$^2H_6$]DMSO.

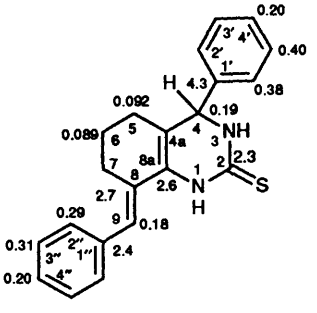


Fig. 1 ^{13}C NMR T_1 relaxation times/s of **1** measured in $CDCl_3$ solution at 25 °C and 25.2 MHz (concentration 50 mg cm^{-3}). The relative precision is ± 4%.

pulse sequence (QUAT in the Bruker library) which results in complete suppression of protonated ^{13}C resonances, thus avoiding the heavy overlapping of different lines in the aromatic region. This information is given in Table 2 in another heteronuclear correlation experiment (see below) for the complete assignment of all carbon resonances (Table 3).

Optimizing the delays in the hetero-correlation experiment for typical $^2J_{CH}$ and $^3J_{CH}$ couplings (7 Hz) the new 2D spectrum gave direct evidence of the coupling between 4-H and C-4a, C-8a, C-1′, C-2 and C-5. Knowing the chemical shift of C-5 and the first hetero-correlation data associated with it, for 5-H, the distinction between the 5-H and 7-H protons could be achieved. At the same time it is possible to distinguish C-1′ from C-1″. Correlation between 4-H and C-2 explains the 3.7 Hz doublet of C-2.

Further cross-sections of this map (the row of 9-H) revealed the coupling between 9-H and C-8a, thus giving the assignment for C-8a.

The multiplicities of the *ortho*, *meta* and *para* carbons of the two phenyl groups—caused by $^3J_{CH}$ couplings inside the phenyl group—were observed in a separate ^{13}C experiment with full proton coupling. This resulted in the distinction between *ortho* and *meta* carbons, while intensity helped to distinguish *para* carbons from the former two. The only problem left was the assignment of these resonances to the substituents themselves. This was achieved by considering their relaxation behaviour.

Microdynamics.—^{13}C NMR relaxation times (T_1) were determined (Fig. 1) to obtain an insight into the relative flexibility[11] of the substituents of **1** and of the saturated bridge C-5 to C-7.

Monoprotonated carbon atoms C-4 and C-9 have very similar T_1 values (0.18 s), from which the correlation time of the overall tumbling motion of molecule **1** can be calculated giving $t_c = 2.5 \times 10^{-10}$ s (see below).

Carbon atoms in the bridge show T_1 values of 0.09 s. Interpreting the data according to the dipole–dipole relaxation mechanism and assuming isotropic tumbling motion, the equation[12] $t_c = a/T_1 n_H$, where a is a constant, connects the observed relaxation time and the number of protons (n_H) attached to a carbon to the local correlation time. The bridge methylene carbons have the same local correlation time as C-4 and C-9. The conclusion is that all these atoms move together as a rigid skeleton, without additional flexibility in the bridge. Relaxation times of quaternary carbons C-2, C-8, C-8a, C-4a and C-1″ are very similar, thus corroborating the above conclusion concerning a rigid bicyclic skeleton.

Relaxation times of aromatic carbon resonances are readily classified into two distinct sets (following the considerations below) and this gives the key for the missing assignment.

Phenyl groups (substituents at C-4 and C-9) may have some rotational freedom[11] along the symmetry axes (C-4–C-1′ and C-9–C-1″). Looking at the relaxation times of the *ortho* or *meta* carbons in each ring, and comparing these values to the respective relaxation time of the *para* carbon, we find ratios of *ca.* 1.5 and 2, figures that indicate[13] the rotation of the phenyl rings (gated rotation or libration). It is interesting to note that the phenyl ring substituted to the double bond (at C-9) shows a smaller $T_1^{ortho}:T_1^{para}$ ratio (*i.e.* has a more restricted motional frequency) than that at C-4 (on an sp^3 centre). Atom C-4″ does not participate in this process, because the C-4″/4″-H vector lies in the rotation axes. Therefore T_1^{para} is the same as for the other monoprotonated carbons and at C-1″ we find a similar value as in the case of the other quaternary carbons inside the rigid molecular framework.

The phenyl ring attached to C-4 shows proportionally longer T_1 values (at all carbon atoms) than that substituted to C-9, indicating an additional degree of motional freedom. Puckering of the heterocycle (N-3 is out of plane, forming a rather flat[14] envelope) may explain this.

UV Spectroscopy.—To obtain information about the extension of the conjugated electron system, we compared the UV spectra of **1** with those of compounds **6**–**11**.

The substitution in position 8 of **6** with a benzylidene group causes a bathochromic effect (from 258 to 276 nm and from 279 to 315 nm). In the case of **8** the introduction of the same group causes the appearance of a new maximum (298 nm in **7**). The other maximum does not change. The λ_{max} value of **11** (298 nm, a phenylbutadiene derivative)[15] suggests that the chromophore

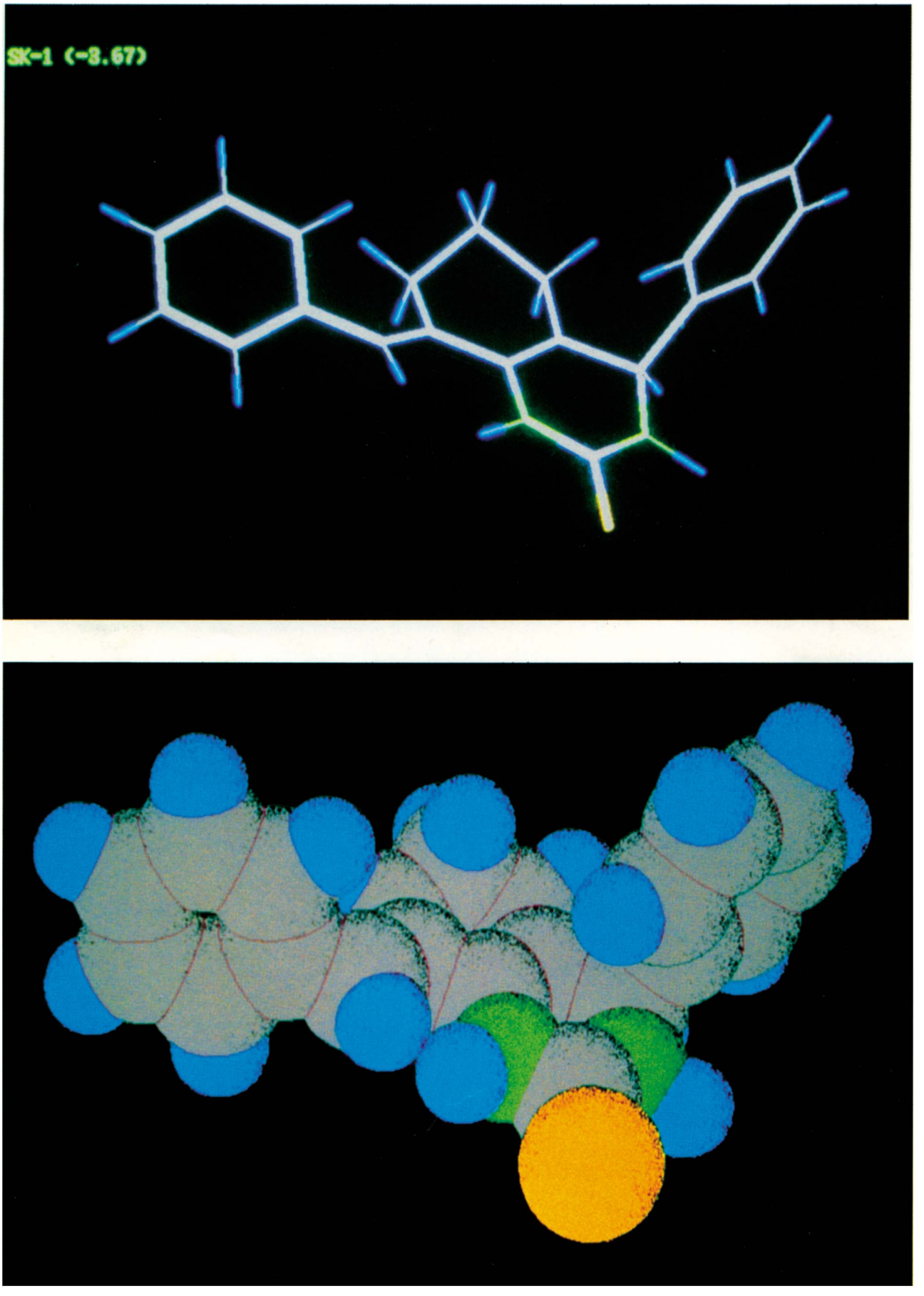


Fig. 2 Perspective model of compound **1** represented in the minimum energy conformation (see text)

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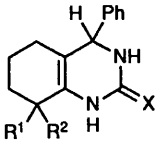
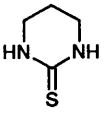
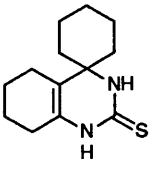
Table 4 UV absorption of some quinazoline derivatives in ethanol

Compound	λ_{max}/nm	log ε	λ_{max}/nm	log ε	Ref.
1	276	4.43	315	4.14	1
6	258	4.26	279	4.14	1
7	256	4.14	298	41.9	1
8	257	3.29	—	—	1
9	245	—	—	—	16
10	256	3.95	278	3.92	17
11	298	4.36	—	—	15

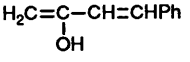






	R^1	R^2	X
6	H	H	S
7	Ph—CH=		O
8	H	H	O

9 **10**



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(C-4a/C-9) of **1** is connected with the higher absorption maximum. It is also noteworthy that the absorption maximum of **9** (cyclic thiourea) is at 245 nm. We conclude that (i) the presence of the phenyl group attached to C-4 of **6** does not influence the absorption maxima (as compared with the spectrum of **10**) and (ii) the lower maximum in **1** belongs to the thiourea residue (see also Table 4).

Molecular Modelling.—Computer-aided molecular modelling[18] was used to calculate the conformation energy of **1**. Starting coordinates were chosen from X-ray data.[14] In the carbocycle of the quinazoline skeleton two nearly equal minima were found due to the flexible bridge (C-5, C-6 and C-7 are sp^3 hybrids, C-6 is either up or down, having high out-of-plane displacement). With C-6 up, the minimum-energy conformation of **1** is represented in Fig. 2

It is worth noting that while the X-ray structure of the 6-methyl derivative of **1** corresponds only to one of the two theoretical minima (the 6-methyl being in the plane and C-6 up), in solution molecule **1** is less rigid, up and down transitions between the two minima being compatible with the longer relaxation times observed for C-6 and C-5 with respect to the values found for the monoprotonated carbon atoms (C-4, C-7 and C-9) of the skeleton.

Calculating the conformational energy with respect to the rotation of the phenyl substituents, a one-minimum curve was found in both cases (the minima are located at dihedral angles C-4a–C-4–C-1′–C-2′ 80° and C-8–C-9–C-1″–C-2″ 77°). In each case deviations (libration) of ±45° are within 2 kcal, after which the energy rises rapidly toward 80 kcal (maximum). The gated rotation was corroborated by the observation of increased relaxation times at *ortho* and *meta* positions of both phenyl substitutents.

Puckering motion in the heterocycle (involving the planar thiourea group) is always associated with slight deviations from the plane (7°). This additional flexibility is reflected in the increased set of T_1 values found for C-1′, C-2′, *etc.*, resulting in a handy method of assignment for these resonances.

Experimental

NMR Spectra.—Varian XL-400, Bruker SY-200 and Varian XL-100-FT spectrometers were used together with their standard microprogram libraries. All spectra were measured in $CDCl_3$ with TMS as internal reference.

^{13}C spectra: 50.3 MHz, 25° flip-angle. Multiplicities were determined by the DEPT method[10] (using JMODXH). 2D-Proton-carbon correlations were determined by different microprograms (*e.g.* XHCORRD, QUAT, RELAY2).

^{13}C longitudinal relaxation times (T_1) were measured at 25.1 MHz by the inversion–recovery method[19] and evaluated by a three-parameter fit.[20] The statistical error was less than 4%.

^1H spectra: 400 MHz, 40° flip-angle. 5a,b-H; 6a,b-H; 7a,b-H and 9-H form a seven-spin system, analysed by simulation using the LAOCOON program.[21]

UV spectra. Perkin-Elmer 402, in ethanol.

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