^{13}C Nuclear Magnetic Resonance Spectroscopy of Nitrogen Heterocycles. Part 4.[1] *intra-extra* Configuration of the *N*-Acetyl Group in Phenothiazine and Related Systems with a 'Butterfly' Shape

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Nitrogen lone-pair delocalization into aromatic rings has been studied for phenothiazine, *N*-acetylphenothiazine, and related tricyclic systems with a 'butterfly' conformation, by using ^{13}C n.m.r. spectroscopy. Pyridazo[4,5-*d*][1,4]benzothiazines, phenoxazines, acridane, and simple model compounds such as diphenylamine, 2-methylthioaniline, and their corresponding *N*-acetyl derivatives were examined. The preferred configuration of the *N*-acetyl group has been determined for $CDCl_3$ and Me_2SO solutions. Nitrogen lone-pair delocalization of the *N*-acetyl group into the aromatic system is strongly hindered for all tricyclic compounds, and greatly reduced for *N*-acetyldiphenylamine and also for 2-methylthioacetanilide in Me_2SO. For this last compound, the decrease of conjugation is due to a solvent-induced change of conformation; for tricyclic systems it is a consequence of the preferred *extra*-configuration of the *N*-acetyl group.

During a study of the dynamic aspects of the stereochemistry of phenothiazines in solution,[2,3] we have approached the problem of the *extra–intra* configuration at the thiazine nitrogen atom by n.m.r. techniques. The librational motion originating from N-inversion and ring-inversion processes ‡ in tricyclic molecules with a folded structure such as phenothiazine has been found to be fast at temperatures higher than −60 °C. Evidence has been given [3] that the population of the *extra*-isomer increases significantly when the ligand at the nitrogen is larger than a proton (*i.e.* methyl or an alkyl chain). We report here the capacity of the nitrogen lone pair to delocalize into tricyclic systems related to phenothiazine, *i.e.* acridane (8), phenothiazine (10), pyridazo[4,5-*d*][1,4]-benzothiazine (12), the lactams (13) and (15), phenoxazine (17), and their *N*-acetyl derivatives. A few model compounds were also considered, the simplest of which is aniline (1), then 2-methylthioaniline (3), diphenylamine (6), and the corresponding *N*-acetyl compounds.

Experimental

The n.m.r. spectra have been measured with a Varian XL-100-15 spectrometer operating at 35 °C with internal Me_4Si as standard. The concentrations and the solvents were 0.5M-$CDCl_3$ and -Me_2SO unless specified in the Tables. The dilution effect on ^{13}C shifts, measured for a few compounds from 0.5 to 0.2M, was within 0.2 p.p.m. The shift of benzene (0.5M) in both solvents is δ 128.2 p.p.m. The synthesis of the pyridazobenzothiazine derivatives has already been published.[4] Attempts to synthesize the 10-acetyl derivative of (12) were unsuccessful,[4] due to the formation of a tautomeric *N*-acetyl derivative.

Assignments of ^{13}C *Resonances.*—The assignments in Tables 1 and 2 have been performed by single-frequency selective decoupling (s.f.s.d.) of protons whenever the proton signals can be unequivocally attributed.[5] For the second-order ^1H spectra of (10), (12),[3] (13)—(18) LAOCN 3 analysis [5] was necessary; the detection of a long-range $^5J_{NH_{10}-H_6}$ coupling of 0.5 Hz allows the assignment of 6-H in preference to 9-H for the amines as already reported.[3,6] For the acetyl derivatives 9-H has been attributed by reason of the similarity with *N*-acetylacridane, where the most deshielded signal (δ 7.57 in $CDCl_3$, 7.67 in Me_2SO) has been assigned to 9-H by the use of $Eu(fod)_3$. Thus the assignments of C-9 *versus* C-7 and of C-6 *versus* C-8 for (8) and (9) have been performed by s.f.s.d. of 9-H and of the methylene protons 5- and 5'-H, respectively. The distinction between C-7 and C-8 for (9) was impossible as the signals for 7- and 8-H are too close to each other whereas C-13 can be distinguished from C-14 through the long-range interactions with 5- and 5'-H. These couplings have been determined for acridane (8), where C-14 and C-13 are assigned by taking into account the electron-donor effect of N-10 ($^2J_{C_{13}-H_5}$ 3, $^3J_{C_{14}-H_5}$ 2 Hz). Carbon atoms C-6—C-9 could not be assigned for acetylphenothiazine (11), because the proton signals are too close to each other but this does not affect the discussion of the results, as the carbon frequencies are also very similar. Finally the quaternary carbon atoms C-11 *versus* C-14 and C-12 *versus* C-13 in pyridazobenzothiazinones (13)—(16) have been attributed by s.f.s.d. of 2-H [(13) and (14)] and 3-H [(14) and (15)], respectively.

Results and Discussion

The effect of nitrogen lone-pair delocalization on benzenoid carbons in tricyclic systems has been studied by the ^{13}C shifts of these carbons relative to that of benzene (Table 3). As the positions *ortho* and *para* to N-10 are the most affected, we will consider C-9 and C-7 in particular. Any effect induced by sulphur or methylene substituents, which are *meta* to C-9 and C-7, is neglected, since they are expected to be small (see benzene relative to thiophenol or toluene).[7]

The strong up-field shift of C-9 and C-7 (δ 14 and 10 p.p.m. respectively) for (1) and (3), in both $CDCl_3$ and Me_2SO, indicates the expected conjugative effect of the amino-group. This effect is considerably reduced, but still noticeable, when the amino-group is acetylated as in (2); for methylthioacetanilide (4) this effect still holds for $CDCl_3$ solution, but is absent in Me_2SO. For the acetyl derivative (4) there is a strong

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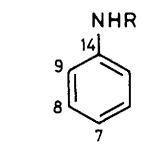
‡ For a definition of these processes see ref. 3.



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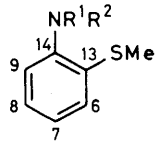
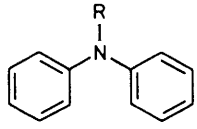


(3) $R^1 = R^2 = H$
(4) R^1 = H, R^2 = COMe
(5) $R^1 = R^2$ = COMe



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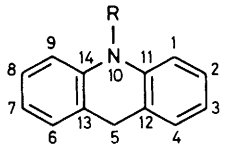

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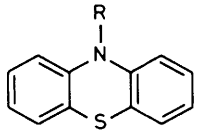

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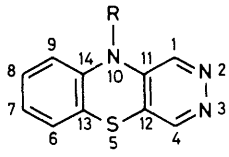

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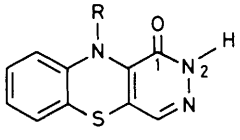

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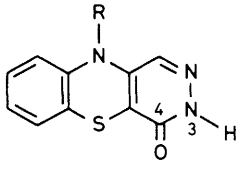
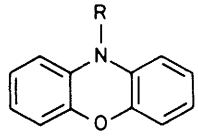


(15) R = H
(16) R = COMe



(17) R = H
(18) R = COMe

Table 1. ^{13}C Chemical shifts of aniline (1)—(5) and diphenylamine (6) and (7) derivatives [a]

Compd.		C-6	C-7	C-8	C-9	C-13	C-14	CO	Me	SMe
(1)	$CDCl_3$	129.2	118.4	129.2	115.0		146.3			
	Me_2SO	128.6	115.5	128.6	113.7		148.4			
(2)	$CDCl_3$	128.8	124.1	128.8	120.1		138.0	169.0	24.3	
	Me_2SO	128.5	122.8	128.5	118.9		139.2	168.1	23.9	
(3)	$CDCl_3$	133.3	118.6	128.8	114.8	120.1	147.0			17.7
	Me_2SO	131.6	116.6	127.9	114.1	118.4	147.7			16.4
(4)	$CDCl_3$	132.4	124.4	128.5	120.9	125.3	138.1	168.2	24.6	18.7
	Me_2SO	(126.6)	(125.9)	(125.9)	(125.1)	133.1	135.4	168.3	23.0	15.1
(5)	$CDCl_3$	125.7	129.5	125.7	129.3	138.1	136.6	172.5	26.3	14.5
	Me_2SO	125.5	129.5	125.5	129.3	137.7	136.3	171.6	26.0	13.7
(6)	$CDCl_3$	129.2	120.9	129.2	117.7		143.0			
	Me_2SO	128.9	119.5	128.9	116.6		143.0			
(7)	$CDCl_3$	129.2	126.9	129.2	127.3		142.9	170.3	23.8	
	Me_2SO	129.1	126.9	129.1	127.5		143.0	169.1	23.2	

[a] δ (p.p.m.) from $SiMe_4$ as internal reference. Similar values in parentheses may be interchanged.

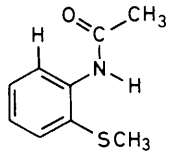
solvent effect in Me_2SO (see Table 1), whereas acetanilide (2) shows shifts of *ca.* 1 p.p.m. which represent the normal solvent effect found for most of these compounds and for the related tricyclic systems.[3] The magnitude of the solvent shifts found for (4) and their alternating direction in the ring carbon sequence indicate that conformational changes occur in Me_2SO which affect the delocalization of the nitrogen lone pair into the ring. For (4) the strong deshielding of 9-H in $CDCl_3$ (δ 8.2), compared with the normal shift in Me_2SO (δ 7.1—7.5) shows that a planar conformation is preferred in $CDCl_3$, with the carbonyl group opposite the *ortho* 9-position, such as to deshield 9-H by the magnetic anisotropy effect as in (4A). The factors which stabilize (4A) are both steric and electrostatic in nature. In Me_2SO, the formation of an intermolecular hydrogen-bond with the solvent should induce the NHAc group to rotate around the N–C-14 bond, in order to decrease the interactions with the *ortho* SMe group as in (4B). When the *N*-acetyl group is out of plane, the delocalization of the nitrogen lone pair into the benzene ring is no longer allowed. This explains the proton and carbon shifts, in particular for 9-H, C-9, and C-7. Conjugation with the ring in the diacetyl derivative (5) is even more reduced, almost non-existent, as shown by the values in both solvents.

Inspection of Table 3 shows the effect of the amino-group on the shift of benzenoid carbons for anilines and tricyclic amines. This effect is approximately constant for the *ortho*-

Table 2. ^{13}C Chemical shifts of tricyclic compounds (8)—(18) [a]

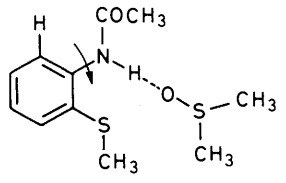
Compd.		C-1	C-4	C-6	C-7	C-8	C-9	C-11	C-12	C-13	C-14	CO	Me	Others
(8)	$CDCl_3$ [b]	115.4	128.5	128.5	120.5	126.9	113.4	140.0	119.9	119.9	140.0			31.4
	Me_2SO	113.2	128.1	128.1	119.4	126.6	113.2	140.5	118.9	118.9	140.5			30.6
(9)	$CDCl_3$	125.0	127.2	127.2	(125.9)	(126.1)	125.0	139.3	134.1	134.1	139.3	168.9	23.6	34.0
	Me_2SO	124.9	127.0	127.0	(125.6)	(125.8)	124.9	139.1	134.0	134.0	139.1	167.9	23.4	33.0
(10)	$CDCl_3$ [b]	114.5	126.5	126.5	122.2	127.2	114.5	141.8	117.8	117.8	141.8			
	Me_2SO	114.3	126.0	126.0	121.6	127.3	114.3	142.0	116.2	116.2	142.0			
(11)	$CDCl_3$	(126.7)	(127.1)	(127.1)	(126.9)	(126.7)	(126.7)	138.9	132.9	132.9	138.9	169.1	22.9	
	Me_2SO	(126.8)	(127.2)	(127.2)	(127.0)	(127.6)	(126.8)	138.5	131.8	131.8	138.5	168.2	22.5	
(12)	Me_2SO	137.4	146.2	126.6	123.5	128.0	115.6	139.5	117.0	114.1	138.4			
(13)	Me_2SO [b]	152.8	135.2	126.6	124.3	128.2	116.3	137.4	110.2	114.2	139.0			
(14)	Me_2SO [b]	155.8	135.8	127.8	127.0	127.8	127.4	134.7	138.2	128.6	136.6	167.9	21.9	
(15)	Me_2SO [b]	128.0	157.0	126.8	124.1	128.0	115.4	141.4	106.9	115.7	137.6			
(16)	Me_2SO [b]	135.5	158.3	128.1	127.5	128.0	127.1	139.2	132.0	129.2	135.9	169.0	22.6	
(17)	$CDCl_3$	113.3	115.7	115.7	121.4	123.5	113.3	131.6	143.5	143.5	131.6			
	Me_2SO	113.1	114.9	114.9	120.1	123.7	113.1	132.3	142.7	142.7	132.3			
(18)	$CDCl_3$	125.2	116.8	116.8	126.8	123.3	125.2	129.5	151.0	151.0	129.5	169.2	23.0	
	Me_2SO	125.1	116.4	116.4	126.8	123.4	125.1	129.2	150.2	150.2	129.2	168.6	22.7	

[a] δ (p.p.m.) from $SiMe_4$ as internal reference. Similar values in parentheses may be interchanged. [b] Concentration 0.2M.



Planar conformation ($CDCl_3$)

(4A)



Out of plane conformation (Me_2SO)

(4B)

carbon (C-9) * whereas for the *para*-position (C-7) Δδ values decrease gradually from aniline (−12.7 p.p.m. in Me_2SO) to diphenylamine and acridane (−9 p.p.m.) to phenothiazines (−6 to −4 p.p.m.). The presence of two benzene rings explains the reduced charge density in each of them; the further decrease of shielding for C-7 in the phenothiazines, compared with (6) and (8), must be attributed to a change of the folding of the molecule and of the pyramidality of the nitrogen atom, because the electronic effects of sulphur on the *meta*-carbons are known to be negligible.[7] As a decrease of flattening leads to a decrease of charge delocalization *via* the π bond, the *para* 7-position should be most affected. This is also shown by CNDO calculations of charge density for some phenothiazines.[3]

The chemical shifts of phenoxazine (17) (Table 2) indicate a generalized shielding as the oxygen atom is also a strong donor. The shifts of C-9 and C-7 are very similar to those of acridane.

The acetyl derivatives of diphenylamine and the tricyclic compounds (7), (9), (11), (14), and (16) show in both solvents the same results as methylthioacetanilide (4) in Me_2SO. Values of C-7 and C-9 (Table 3) indicate a net decrease of shielding, which is particularly remarkable in the case of the phenothiazine derivatives (11), (14), and (16). Here the lack of selectivity between the *ortho*-, *para*-, and *meta*-positions is apparent from the shift values (δ 127—128 p.p.m.), all very close to benzene. This means that nitrogen lone-pair delocalization into the aromatic rings is strongly hindered. In order to evaluate the effects of this decrease in charge delocalization at the other *ortho*-position, C-13, we have calculated the shift difference $\Delta\delta_{ac.} = \delta_{acetyl} - \delta_{amine}$ (Table 4). Among the benzenoid carbons, C-13 shows the largest shift (14—15 p.p.m.,† while C-9 gives 11—12 p.p.m.and C-7 varies from *ca.* 9 to *ca.* 3 p.p.m. The variation of C-7 actually reflects the decrease of conjugation in the amines series, from (4) to (12), as described before. The larger value of C-13 than for C-9 is in agreement with the absence of the upfield γ-effect of the acetyl group, which acts instead on C-9. The same trend but with enhanced Δδ values (25—28 p.p.m.) is observed for the other quaternary *ortho*-carbon, C-12, in pyridazobenzothiazinones (14)—(16). These results indicate that the *ortho*-positions C-13 and C-12 are the most sensitive to the substituent at N-10, as already observed for *N*-methylphenothiazines,[3] although in this case the decrease of conjugation is much less pronounced. The i.r. stretching frequencies of the carbonyl group in *N*-acetylamines (7), (9), and (11) $\nu_{C=O}$ 1 660, 1 660, and 1 670 cm^{-1}, respectively) are also in agreement with a decrease in conjugation in the aromatic part of the molecule compared with acetanilide ($\nu_{C=O}$ 1 680 cm^{-1}).

We can thus conclude that for tricyclic systems, the nitrogen lone-pair delocalization of the *N*-acetyl group into the aromatic rings appears to be almost nil. The break in conjugation for acetyldiphenylamine (7), as for methylthioacetanilide (4), is a consequence of rotation around the C-14–N-10 bond, whereas for ' butterfly ' shaped molecules, where rotation is impossible, the same result is obtained through nitrogen and/or ring inversion processes. This implies a certain degree of pyramidality for the amide nitrogen. With a planar configuration for the nitrogen atom, the angle between the direction of nitrogen lone pair and aromatic π orbitals is *ca.* 20° (from Dreiding models), which still allows overlap. With a pyramidal nitrogen atom and an *extra*-geometry, the lone pair and π orbitals are orthogonal and thus overlapping cannot occur. The dynamic process may still induce a certain degree of delocalization, but ^{13}C results indicate that it is poor; thus the population of the *extra* isomer must be high. A low-field δ effect of 2.6 p.p.m. experienced on acetylation by the CH_2 carbon atom of

* Except for diphenylamine, where γ and δ steric interactions might be reciprocally induced on the *ortho*-positions by the two phenyl groups, thus masking the shielding due to conjugation.

† For phenoxazine system (17) and (18), C-13 is not a reliable probe, as it is directly bonded to the strong electronegative oxygen atom but $\Delta\delta_{ac}$ for C-7 and C-9 are in line with that for phenothiazine.

Table 3. Substituent effect of N-10 $\Delta\delta = \delta X - \delta$ benzene [a]

	Amines					*N*-Acetylamines						
$CDCl_3$	(1)	(3)	(6)	(8)	(10)	(2)	(4)	(7)	(9)	(11)		
C-9	−13.2	−13.4	−10.5	−15.0	−13.7	−8.1	−7.3	−0.9	−3.2	−1.1 [b]		
C-8	0.0	0.6	1.0	−1.3	−1.0	0.5	0.3	1.0	−2.2 [b]	−1.1 [b]		
C-7	−9.8	−9.6	−7.3	−7.8	−5.5	−4.1	−3.8	−1.3	−2.2 [b]	−1.1 [b]		
C-6	0.0	5.1	1.0	0.3	−1.7	0.5	0.3	1.0	−1.0	−1.1 [b]		
Me_2SO	(1)	(3)	(6)	(8)	(10)	(12)	(13)	(15)	(2)	(4)	(7)	(9)	(11)	(14)	(16)
C-9	−14.5	−14.1	−11.6	−15.0	−13.9	−12.6	−11.9	−12.8	−9.3	−2.3 [b]	−0.7	−3.3	−1.0 [b]	−0.8	−1.1
C-8	0.4	−0.3	0.7	−1.6	−0.9	−0.2	0.0	−0.2	0.3	−2.3 [b]	0.9	−2.5 [b]	−1.0 [b]	−0.4	−0.2
C-7	−12.7	−11.6	−8.7	−8.8	−6.6	−4.7	−3.9	−4.1	−5.4	−2.3 [b]	−1.3	−2.5 [b]	−1.0 [b]	−1.2	−0.7
C-6	0.4	3.4	0.7	−0.1	−2.2	−1.6	−1.6	−1.4	0.3	−2.3 [b]	0.9	−1.2	−1.0 [b]	−0.4	−0.1

[a] δ benzene 128.2 p.p.m. in both solvents. [b] As these frequencies could not be assigned, Δδ values are obtained from averaged values from Tables 1 and 2. They are for (4), 125.9 (±0.6); for (9), $CDCl_3$ 126.0 (±0.1), Me_2SO 125.7 (±0.1); for (11), $CDCl_3$ 127.1 (±0.5), Me_2SO 127.2 (±0.3). Values in parentheses are the corresponding errors.

Table 4. Chemical shift differences between amines and *N*-acetylamines, $\Delta\delta_{ac} = \delta$ acetyl − δ amine [a]

	C-1	C-4	C-6	C-7	C-8	C-9	C-11	C-12	C-13	C-14
(2) − (1)			−0.1	7.3	−0.1	5.2				−9.2
(4) − (3)			−5.7 [b]	9.3 [b]	−2.0 [b]	11.8 [b]			14.7	−12.3
(7) − (6)			0.2	7.4	0.2	10.9				0.3
(9) − (8)	11.7	−1.1	−1.1	6.3 [b]	−0.9 [b]	11.7	−1.4	15.1	15.1	−1.4
(11) − (10)	12.8	1.1	1.2 [b]	5.6 [b]	−0.1 [b]	12.9 [b]	−3.5	15.6	15.6	−3.5
(14) − (13)	3.0	0.6	1.2	2.7	−0.4	11.1	−2.7	28.0	14.3	−2.4
(16) − (15)	7.5	1.3	1.3	3.3	0.0	11.7	−2.2	25.1	13.5	−1.7
(18) − (17)	12.0	1.5	1.5	6.7	−0.3	12.0	−3.1	7.5	7.5	−3.1

[a] δ (p.p.m.), solvent Me_2SO. [b] See footnote *b* to Table 3.

acridane is further evidence for the preferred *extra*-configuration of the acetyl group, which must be relatively close to the methylene group. This orientation allows a decrease in the steric interactions with the *peri*-positions, but requires the loss of delocalization energy, the most stable structure being the result of a balance between these two main forces.

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