Effect of *N*-acylamino groups on the chemical shift of the *ortho* proton in biphenyls

F. K. Hess
Pharma-Research Canada Ltd., 250 Hymus Blvd., Pointe-Claire, Quebec

AND

K. H. Pook
C. H. Boehringer Sohn, Ingelheim a. Rhein, Germany

Received November 1, 1968

The proton magnetic resonance spectra of several acylamino biphenyls were determined. Evidence was obtained that the proton adjacent to the acylamino group was shifted to lower field relative to the remaining ring protons.

Canadian Journal of Chemistry, 47, 1151 (1969)

In a recent paper, Ribera and Rico (1) described the deshielding of the *ortho* proton in the nuclear magnetic resonance (n.m.r.) spectra of *N*-(2-substituted-phenyl)amides. A low-field shift of the signal corresponding to the *ortho* proton was observed only for those compounds which simultaneously had one free (H) and one occupied (F, Cl, Br, I) position. The magnitude of the chemical shift in this series varied from 0.86 to 1.04 p.p.m. relative to benzene.

The deshielding effect of a proton adjacent to an *N*-acetyl group had been described previously in a number of publications. For instance, it was shown by Carter (2) that the resonance for the *ortho* protons in the spectrum of acetanilide was shifted 0.89 p.p.m. downfield from the corresponding resonance in the spectrum of aniline, by determining the residual proton spectra of the partially deuterated compounds. The low-field shift was attributed primarily to the fact that the anisotropic carbonyl group in acetanilide points towards the aromatic ring, with the plane of the acetamido group and the benzene ring making an angle of approximately 38° (3). A lowering for the *ortho* proton signal was also reported for several *para*-substituted acetanilides (4).

A low-field shift arising from the anisotropic shielding of a neighboring *N*-acetyl group was observed in a number of pyridine derivatives. Brügel (5) showed that acetylation of 2-aminopyridine markedly influenced the resonance of the 3-proton. The chemical shift difference expressed as $\Delta\nu_3 - \nu_4$ relative to pyridine between 2-aminopyridine and 2-acetamidopyridine was approximately 1.1 p.p.m.

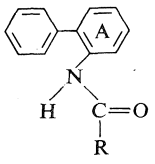
Similar effects have been observed for other heterocyclic acylamines in which the *N*-acylamino group is adjacent to a ring hydrogen atom. In the n.m.r. spectra of the *N*-acetyl derivatives of benzimidazoles and purines (6), a constant downfield shift of about 19 c.p.s. (40 Mc.p.s.) of the proton adjacent to the acetyl position had been noted. In 4-*N*-acetylpyrimidine all the remaining ring protons are shifted to lower field relative to the signals for the corresponding 4-amino derivative; however, by far the most striking effect was noticed for the adjacent proton (H-5), which was shifted by 1.5 p.p.m. to low-field (7).

The situation where one of the *ortho* positions is occupied exists also in *N*-acylindoline and compounds related to it. Some years ago it was shown by Anet (8) that the aromatic proton in strychnospermine nearest to the *N*-acyl grouping (H-12)[1] appeared as a doublet at 2.35 τ when the spectrum was taken at about −20°; this corresponded to that conformation in which the carbonyl group was preferentially oriented towards the phenyl ring. The band of the same proton in the opposite conformation was at about 3.25 τ. The low-field position was ascribed to the strong, magnetic anisotropy of the carbonyl group. A similar effect was observed in the n.m.r spectrum of fruticosin (9), and depended on the steric arrangement of the N_a-carbomethoxy group. At −30° two doublets of different intensity at 8.00 p.p.m. and 7.55 p.p.m. (100 Mc.p.s.) for H-17[1] were observed. In fruticosamin the *N*-$COOCH_3$ group is conformationally fixed through hydrogen

[1]This corresponds to H-7 in indoline.

bonding; this compound shows a normal doublet at 7.54 p.p.m. More recently a detailed study by Nagarajan *et al.* (10) on the configuration of the amide bond in *N*-acylindolines and *N*-acyltetrahydroindolines, clearly indicated that the carbonyl group was oriented towards the phenyl ring as in the case of the low temperature n.m.r. spectrum of strychnospermine; the proton at C-7 was seen as a broad doublet at 8.22 p.p.m. as compared to 6.45 p.p.m. in indoline ($\Delta\delta = 1.77$ p.p.m.!). In compounds in which the carbonyl group is rigidly held in the vicinity of a nearby proton, as in hexahydropyrrolo[1,2-*a*]quinoxaline (11, 12), a pronounced low-field shift was again observed.

In connection with some other studies we had prepared a number of acylamino biphenyl derivatives:



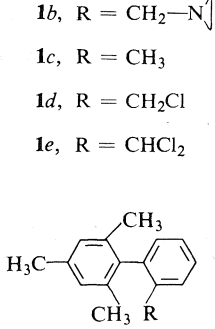
1*a*, R = CH_2—N⟨O⟩ **1***f*, R = CCl_3

1*b*, R = CH_2—N⟨ **1***g*, R = CH_2F

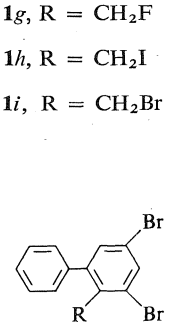
1*c*, R = CH_3 **1***h*, R = CH_2I

1*d*, R = CH_2Cl **1***i*, R = CH_2Br

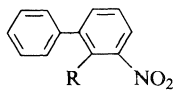
1*e*, R = $CHCl_2$



2, R = $NHCOCH_2Cl$



3, R = $NHCOCH_2Cl$



4, R = $NHCOCH_3$

The n.m.r. spectra of the various amides were determined at 60 Mc.p.s. in chloroform-*d* solution. It was found, that the resonance for one of the protons in compounds (**1***a–i*) was shifted downfield from the corresponding spectrum in 2-amino biphenyl, ranging from 1.40–1.95 p.p.m., (corrected for the diamagnetic anisotropy effect of the vicinal phenyl ring, see below), representing a downfield shift of 1.23–0.68 p.p.m. relative to benzene. Our results are summarized in Table I. The partial n.m.r. spectrum of compound **1***a* is shown in Fig. 1.

TABLE I

Nuclear magnetic resonance data for the *ortho* proton in *N*-acyl biphenyls*

Compound	τ_H†	τ'_H‡	Δ§
1*a*	1.28	1.40	1.23
1*b*	1.39	1.51	1.12
1*c*	1.45	1.57	1.06
1*d*	1.45	1.57	1.06
1*e*	1.56	1.68	0.95
1*f*	1.54	1.66	0.97
1*g*	1.70	1.82	0.81
1*h*	1.73	1.85	0.78
1*i*	1.83	1.95	0.68

*Spectra were determined at 60 M c.p.s., using 0.66 *M* solutions in $CDCl_3$.
†With reference to internal TMS, (τTMS 10 p.p.m.).
‡Adjusted for adjacent ring current effect: $\tau'_H = \tau_H + 0.12$.
§Shift to low field with reference to the chemical shift of benzene, (τ p.p.m. 2.63).

Except for compounds **3** and **4**, all derivatives have one free and one occupied *ortho* position. With regard to the orientation of the carbonyl group, it is clear from our results that this group is oriented towards the aromatic ring as in acetanilide (3), but not necessarily coincident with it and that the adjacent proton lies in the deshielding zone of this group. The *a priori* possibility that the *ortho* position in the neighboring ring might be deshielded because its proximity (cf. 13), was ruled out by the following facts:

a) The spectrum of the mesityl derivative (**2**) clearly showed that the position and the intensity of the low-field signal had not been altered.

b) In the spectrum of **3** the low-field C—H proton signal was absent.

c) In 2-nitro-1-acetamidobiphenyl (**4**) the *N*-acetyl carbonyl group is probably oriented towards the neighboring phenyl ring because of intramolecular hydrogen-bonding between the amido proton and the nitro group.[2] However, the characteristic low-field signal observed for com-

[2]The deshielding of aromatic protons in *ortho*-nitro substituted acetanilides was recently described in great detail (14, 15).

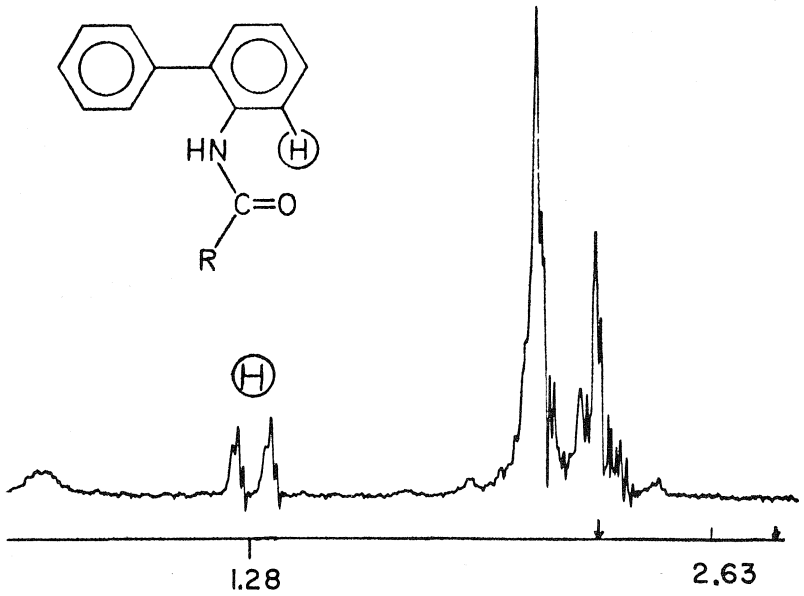


FIG. 1. Partial nuclear magnetic resonance spectrum of **1***a*, R = CH_2-N⟨ ⟩O, in $CDCl_3$ at 60 Mc.p.s. (numbers are in p.p.m. (τ)).

pounds (**1***a–i*) was absent in the n.m.r. spectrum ($CDCl_3$ and $(CD_3)_2SO$).

It may be concluded, therefore, that it is the proton next to the *N*-acetyl group which resonates at lower field.

In order to correct for the influence of the phenyl substituent on the chemical shift of the protons in ring A we have used the data given in the literature. A correction for the contribution of the halogen atoms to the chemical shift of the *ortho* proton was made by Ribera and Rico (1) using the ^{S}*meta* values given by Diehl (16). Mayo and Goldstein (17), who have carried out a detailed proton resonance investigation of biphenyl, showed that the anisotropic shielding of a given proton is a function of the dihedral angle between the two benzene rings. From their work as well as from a variety of independent evidence cited in their paper these authors suggested, that "the chemical shifts in biphenyl are most plausibly accounted for by a model involving free, or nearly free, rotation of the rings (in solution) and very weak interactions between the phenyl groups". The diamagnetic anisotropic shielding at each position was calculated as a function of the dihedral angle; the corrections were +19.1, +7.2, and +6.0 c.p.s. at 60 Mc.p.s. (determined in $CHCl_3$) for the *o-*, *m-*, and *p*-positions, respectively.[3]

The freely rotating model may not be strictly applicable in our series of biphenyl derivatives since one of the *ortho* positions is occupied by a relatively large group. However, since the shielding of the *meta* protons varies only slightly with the change in dihedral angle as shown by Mayo and Goldstein (17), we have taken the average values of 7.2 c.p.s. for our biphenyl derivatives (**1***a–i*). The correction was not applied for the mesityl compound (**2**), since the values for biphenyl are not necessarily applicable for this case. However, the general trend for the low-field shift was clearly observable (cf. Fig. 2).

The methyl protons in compound **2** give rise to two signals at 2.35 p.p.m. (3 protons) and 2 p.p.m. (6 protons) respectively. The introduction of three large *ortho* substituents in **2** widens the dihedral angle to 70° or greater (18). The effect of twisting the two phenyl rings almost out of plane brings the protons of the *ortho* methyl groups under the influence of the induced field of the adjacent ring which accounts for the observed

[3]An ^{S}*m*-value of -11 ± 2 p.p.h.m. (40 Mc.p.s., CCl_4) was given by Smith (4).

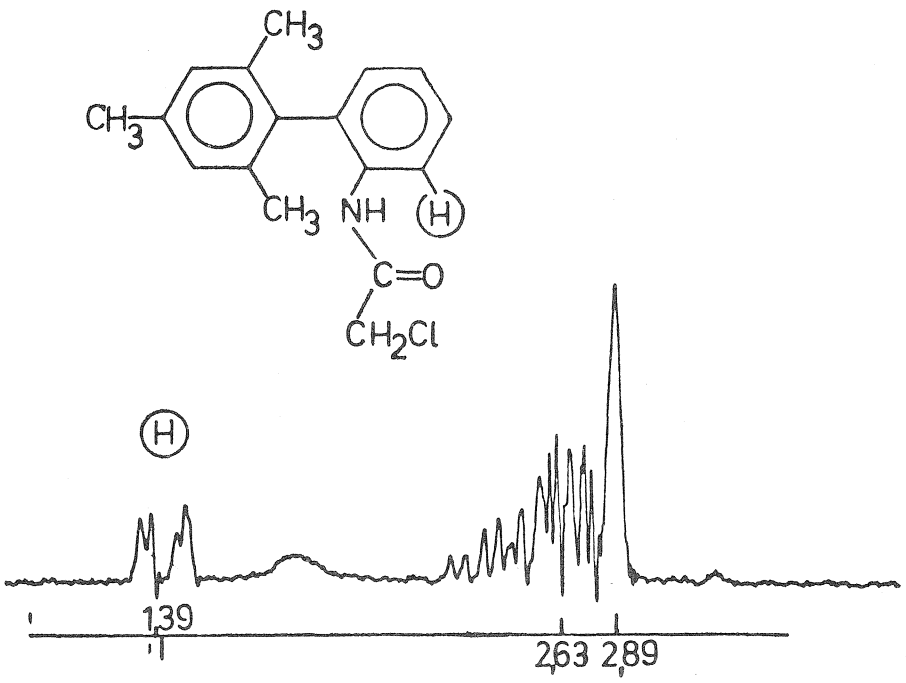
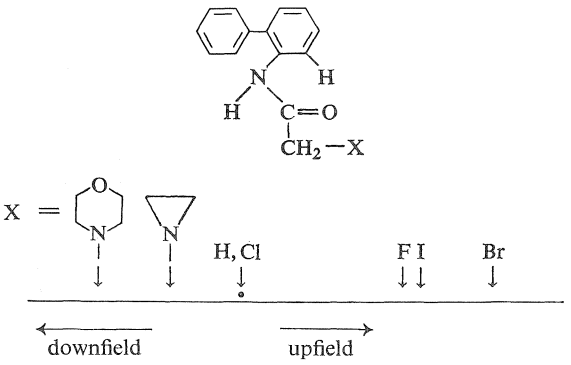


FIG. 2. Partial nuclear magnetic resonance spectrum of **2** in $CDCl_3$ at 60 Mc.p.s. (numbers are in p.p.m. (τ)).

upfield shift of approximately 0.3 p.p.m. For comparison, the signals for the methyl protons in 2,2′,4,4′-tetramethyl biphenyl, occur at 2.37 and 2.03 p.p.m., respectively (19). On the other hand, in 4,5-dimethyl-9,10-tetrahydrophenanthrene the methyl protons give rise to only one signal at 2.29 p.p.m. (20).

From an inspection of Table I, it can be seen that there is a noticeable change in chemical shift values within this series of compounds. This is diagrammatically shown below:



The observed downfield shift of the *ortho* proton is due to a combination of the anisotropic deshielding by the *N*-acetyl carbonyl group as well as to electric and field effects of the amide group, in accord with the general observations cited in this text. This effect is then further modified as shown above. Although there is no observable change for the mono-chloro derivative (**1***d*), additional α-halogenation causes an upfield shift. However, a direct correlation between this upfield shift and the size or the number of the halogen atoms does not exist as shown in Table I; substitution by fluorine, bromine, or iodine results in a noticeable shift to higher frequencies. On the other hand, a shift to lower fields was observed for the two compounds with nitrogen-containing substituents, (**1***a*) and (**1***b*).[4] This variation in chemical shift is rather difficult to assess. Transmission solely through bonds cannot alone account for it; both inductive effects and changes in the magnetic anisotropy of the C—X bond as well as steric differences and

[4]Zanger and co-workers, in a recent publication on the nuclear magnetic resonance spectra of *N*-acylanilines, (21 and cf. ref. 1) also found no change for the monochloroacetyl derivative, and concluded that the nature of the group attached to the acyl carbon atom has relatively little effect on the chemical shift of the aromatic protons.

TABLE II

Characterization of *N*-acylamino biphenyls

Compound	Melting point* °C	Analysis calculated							Analysis found						
		C	H	N	F	Cl	Br	I	C	H	N	F	Cl	Br	I
1*a*	148–149	72.95	6.80	9.45	—	—	—	—	72.90	6.93	9.39	—	—	—	—
1*b*	96–98	76.16	6.39	11.11	—	—	—	—	75.91	6.59	11.02	—	—	—	—
1*c*	120–122	79.59	6.20	6.63	—	—	—	—	79.81	6.32	6.76	—	—	—	—
1*d*	98–100	68.43	4.93	5.70	—	14.43	—	—	68.26	5.04	5.69	—	14.46	—	—
1*e*	106–107	60.02	3.96	5.00	—	25.31	—	—	60.09	3.77	5.11	—	25.38	—	—
1*f*	95–96	53.45	3.20	4.45	—	33.81	—	—	53.65	3.28	4.59	—	33.76	—	—
1*g*	91–93	73.35	5.27	6.11	8.29	—	—	—	73.35	5.46	6.20	8.44	—	—	—
1*h*	122–123	49.87	3.59	4.16	—	—	—	37.64	49.98	3.49	4.15	—	—	—	37.64
1*i*	96–98	57.95	4.15	4.83	—	—	27.54	—	57.92	4.45	4.88	—	—	27.45	—
2	95–96	70.95	6.29	4.87	—	12.32	—	—	70.21	6.25	4.91	—	12.46	—	—
3	196	41.67	2.50	3.47	—	8.79	39.61	—	41.56	2.10	3.45	—	8.94	39.82	—
4	184–186†	—	—	—	—	—	—	—	—	—	—	—	—	—	—

*Melting points (in °C) are uncorrected.
†Lit., 185–187 °C (25).

changes in bond angles are likely contributing factors and are probably interdependent.[5]

Experimental

Elemental microanalyses were provided by Dr. C. Daesslé, Montreal, Quebec, and Dr. A. B. Gygli, Toronto, Ontario. The nuclear magnetic resonance (n.m.r.) spectra were determined as 0.66 *M* solutions in $CDCl_3$ using a Varian Associates model A60-A.

Materials

Compounds (**1***c–f*) and (**1***i*) were obtained by reacting 2-aminobiphenyl (Aldrich Chemical Company) with the corresponding acetyl halides in DMF at 5–10 °C in the presence of K_2CO_3. The mono-iodo compound, (**1***h*), was prepared from the mono-chloro derivative, (**1***d*), by halogen exchange (NaI–acetone).

Monofluoroacetyl chloride was prepared by the method of Truce (22). The fluoroacetyl compound (**1***g*), was then prepared by the method indicated above.

We used the method of Smolinsky (23) for the preparation of 2,4,6-trimethyl-2′-aminobiphenyl; the latter was converted into the monochloroacetyl derivative (**2**) by the previous procedure.

According to the procedure of Scarborough and Waters (24) we obtained 3,5-dibromo-2-aminobiphenyl, which was subsequently converted into the monochloroacetyl compound (**3**) in the usual manner.

For the preparation of 2-nitro-1-acetamidobiphenyl we employed the procedure given by Stepan and Hamilton (25).

The morpholino- and aziridino-compounds (**1***a*) and (**1***b*) were prepared by reacting the monochloroacetyl derivative (**1***d*) with the respective amines.

Characterization data for all compounds are given in Table II.

[5]A correlation with other substituent parameters was not established, because the data are too limited to evaluate the relative importance of these factors accurately.

1. A. Ribera and M. Rico. Tetrahedron Letters, 535 (1968).
2. R. E. Carter. Acta Chem. Scand. **21**, 75 (1967).
3. C. J. Brown and D. E. C. Corbridge. Acta Cryst. **7**, 711 (1954).
4. G. W. Smith. J. Mol. Spectry. **12**, 146 (1964).
5. W. Brügel. Z. Elektrochem. **66**, 159 (1962).
6. G. S. Reddy, L. Mandell, and J. H. Goldstein. J. Chem. Soc. 1414 (1963).
7. S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson, and R. A. Hoffman. Arkiv Kemi, **22**, 65 (1963).
8. F. A. L. Anet. Can. J. Chem. **41**, 883 (1963).
9. A. Guggisberg, M. Hesse, W. von Philipsborn, K. Nagarajan, and H. Schmid. Helv. Chim. Acta, **49**, 2321 (1966).
10. K. Nagarajan, M. D. Nair, and P. M. Pillai. Tetrahedron, **23**, 1683 (1967).
11. E. C. Taylor and A. McKillop. J. Am. Chem. Soc. **87**, 1968 (1965).
12. S. C. Bell and G. Conklin. J. Heterocyclic Chem. **5**, 179 (1968).
13. S. Brownstein. J. Am. Chem. Soc. **80**, 2300 (1958).
14. R. F. C. Brown, L. Random, S. Sternhell, and I. D. Rae. Can. J. Chem. **46**, 2577 (1968).
15. J. R. Bartels-Keith and R. F. W. Cieciuch. Can. J. Chem. **46**, 2593 (1968).
16. P. Diehl. Helv. Chim. Acta, **44**, 829 (1961).
17. R. E. Mayo and J. H. Goldstein. Mol. Phys. **10**, 301 (1965).
18. M. S. Newman. Steric effects in organic chemistry. John Wiley and Sons, Inc., New York. 1956. p. 511.
19. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery. NMR Spectra Catalog. Varian Associates, Palo Alto. 1962. Spectrum No. 659.
20. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery. NMR Spectra Catalog. Varian Associates, Palo Alto. 1962. Spectrum No. 654.
21. M. Zanger, W. W. Simmons, and A. R. Gennaro. J. Org. Chem. **33**, 3673 (1968).
22. W. E. Truce. J. Am. Chem. Soc. **70**, 2828 (1948).
23. G. Smolinsky. J. Am. Chem. Soc. **82**, 4717 (1960).
24. H. A. Scarborough and W. A. Waters. J. Chem. Soc. 89 (1927).
25. A. H. Stepan and C. S. Hamilton. J. Am. Chem. Soc. **71**, 2438 (1949).