And for the lower group:

$$a_1 = 31.309 \times 10^{-4} \qquad \text{(Eq. 17}b\text{)}$$

The constant a_1, which is the coefficient of ΔE^e, might be related to an electronic factor associated with the change in the electronic energy. Hence, it is clear from the magnitude of a_1 (Eqs. 17*a* and 17*b*) or $-a_1\beta$ (Eqs. 16*a* and 16*b*) that both groups of compounds do not experience similar electronic interactions. Therefore, from this analysis, together with the apparent existence of two sterically different stable conformations, one can speculate that groups of compounds falling on the same line (upper or lower) might behave electronically and sterically similarly while acting on the same site.

The influence of electronic and hydrophobic interactions can be assessed by considering Eqs. 3–6. From the correlation coefficients of these equations, it is evident that the hydrophobic interactions are not significant in the upper group of compounds whereas they are important in the lower group. This difference can be explained in terms of the nature of the substituents. The lower group of compounds has one or two methoxy groups present on the ring portion (except Compounds 1, 16, and 22), and all of them (except Compound 10) carry a side-chain substituent. These groups (methyl, ethyl, and methoxy) present on the side chain as well as on the ring portion might engage in hydrophobic interactions.

On the other hand, the upper group of compounds carries hydroxyl and amino substituents (except Compound 29) on the ring portion, and only a few of them carry side-chain amino substituents. The hydroxyl and amino groups have much smaller hydrophobicity factors (8) compared to a methoxy group. Apart from that, the average lipophilicity of the upper and lower groups is 1.033 ± 0.756 and 2.292 ± 0.671, respectively. These values indicate that hydrophobicity does not play a large role in the upper group of compounds.

Figures 4 and 5 show the activity surface generated by Eqs. 7 and 8, respectively. For the upper group (Fig. 4), the influence of log P for a given total orbital energy is smaller, but it is larger for the lower group (Fig. 5).

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Carbon-13 Magnetic Resonance Spectroscopy of Drugs II: Antihistamines

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Abstract □ The natural abundance carbon-13 magnetic resonance spectra of a series of antihistamines (pheniramine, chlorpheniramine, methapyrilene, tripelennamine, pyrilamine, and thonzylamine) were determined using the pulse Fourier transform technique. The chemical shifts were assigned with the aid of long-range carbon-13–hydrogen coupling constants.

Keyphrases □ Magnetic resonance spectroscopy, carbon-13—various antihistamines, spectra determined using pulse Fourier transform technique □ Antihistamines—carbon-13 magnetic resonance spectra determined using pulse Fourier transform technique □ Fourier transform technique—carbon-13 magnetic resonance spectra of various antihistamines

Histamine has continuously received great attention from chemists and biologists (1). This interest is stimulated by the variety and potency of its biological effects, *e.g.*, activities in the cardiovascular system, smooth muscle contraction, and gastric acid and other exocrine gland secretions. Numerous drugs antagonize the action of histamine at its cellular site of action.

According to the classical receptor theory, the biological effect of histamine and antihistamines is the result of physicochemical interactions with the receptor sites. Any successful attempt to correlate these receptor interactions with the configuration and conformation of the drug must rely on detailed studies of the structural chemistry of antihistamines. Great effort has been made recently to characterize these compounds by various physical techniques (2–7).

The development of the Fourier transform technique has added a new tool for the study of the structure and conformation of organic molecules in solution and, potentially, when bound to receptors. Carbon-13 magnetic resonance (CMR) spectroscopy (8–11) increasingly is being directed to the study of drugs (12–20). A detailed

Table I—Carbon-13 NMR Chemical Shifts in Aqueous Solution

Carbon	I	II	III	IV	V	VI
α	56.3	56.2	56.9	56.6	57.2	56.2
β	28.6	28.6	44.3	44.8	44.8	50.0
γ	49.7	49.1	47.9	52.6	52.1	55.4
N-Methyl	42.8	42.9	43.4	43.6	43.0	43.8
2	160.9	160.4	157.1	157.7	157.6	161.3
3	122.9[a]	123.0[a]	108.0	107.7	108.0	—
4	138.7	138.8	138.9	138.6	138.9	158.6
5	123.4[a]	123.5[a]	114.0	113.6	113.6	111.4
6	148.3	148.4	147.2	147.6	146.7	158.6
1′	141.4	140.1	—	137.8	129.4	130.2
2′	127.8	129.3	140.5	126.9	128.1	129.2
3′	129.2	129.0	126.4	128.9	114.3	114.3
4′	127.5	132.4	127.3	127.4	158.3	158.6
5′	129.2	129.0	125.2	128.9	114.3	114.3
6′	127.8	129.3	—	126.9	128.1	129.2
C-Methyl	—	—	—	—	55.2	56.2

[a] These assignments might be reversed.

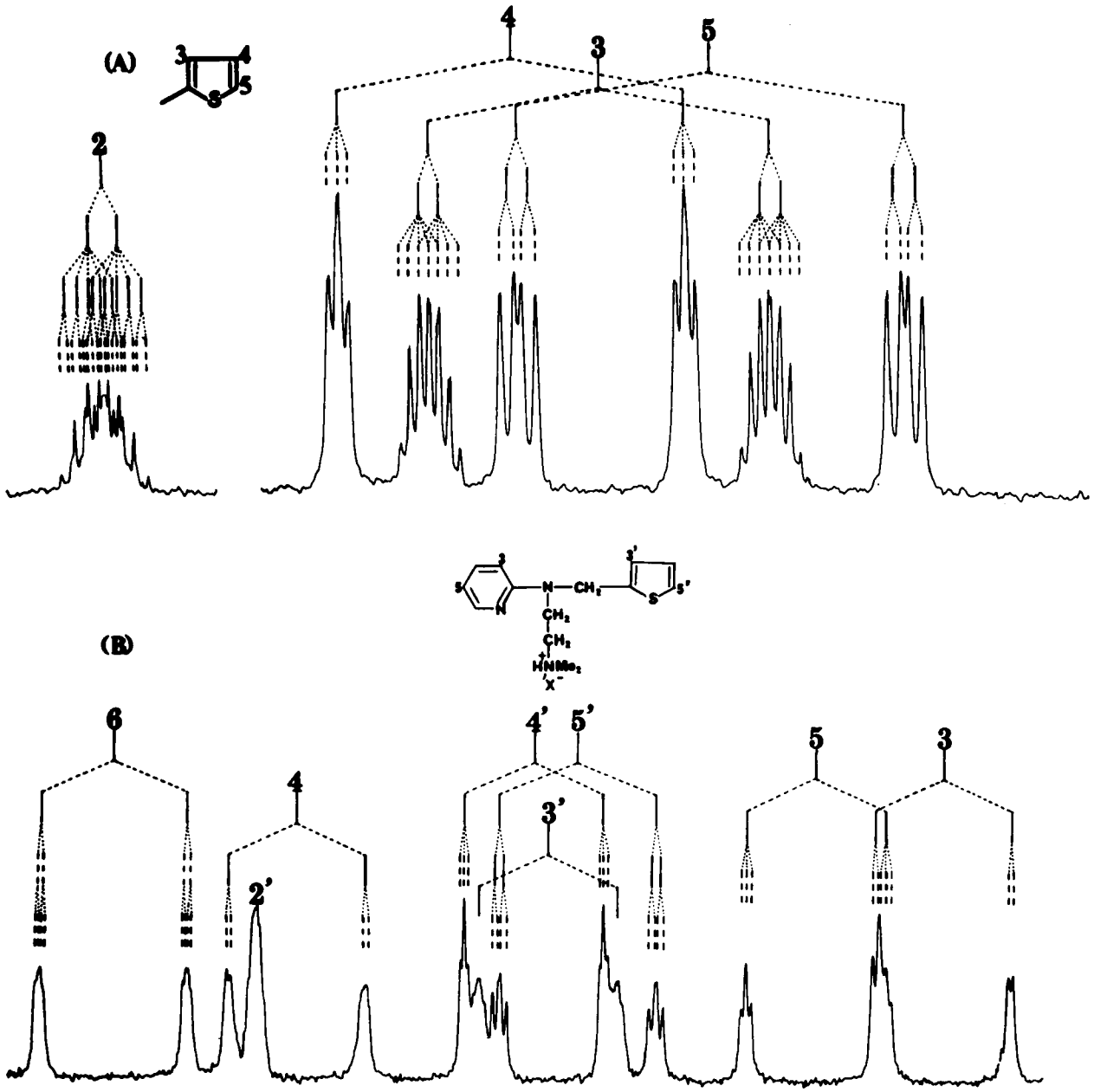


Figure 1—*High-resolution carbon-13 spectra of 2-methylthiophene (A) in deuterochloroform solution and methapyrilene hydrochloride (B). Only part of the aromatic carbon signals is shown.*

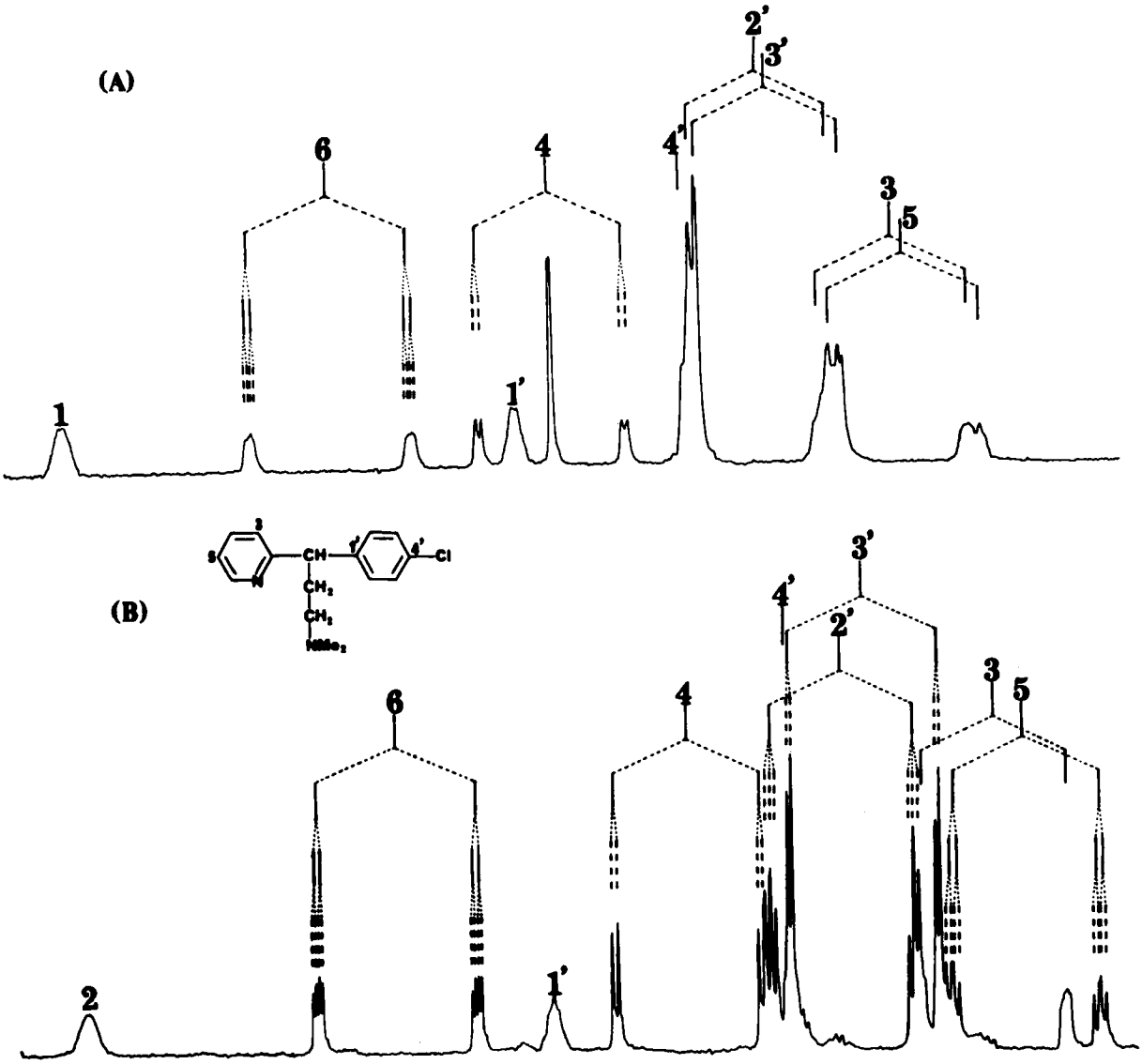


Figure 2—*High-resolution carbon-13 magnetic resonance spectra of chlorpheniramine maleate (A) and chlorpheniramine (B) in deuterochloroform solution. Only part of the aromatic carbon signals is shown.*

CMR spectral analysis of six antihistaminic drugs is reported here.

EXPERIMENTAL

The CMR spectra[1] of about 3 *M* solutions of the compounds in deuterium oxide and deuterochloroform solution were obtained in 10-mm spinning tubes. The carbon-13 resonances of methanol served as the internal reference, and chemical shift values were converted to the tetramethylsilane (I) scale using the following equation: δ (I) = δ (methanol) + 49.3 ppm.

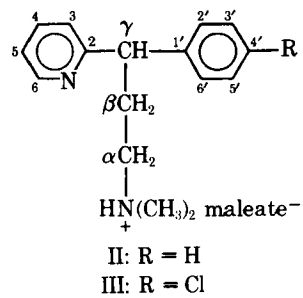
The spectra were recorded at ambient temperature using a deuterium lock. All proton lines were decoupled by a broad band (2.5 kHz) irradiation from an incoherent 99.99-MHz source. The chemical shifts were measured for a 5000-Hz sweepwidth. The carbon-13–hydrogen coupling constants were measured from proton-coupled spectra. The typical pulse width was 12.25 μsec, and the repetition time between pulses was 3.0 sec.

All antihistaminic drugs were USP grade materials and were used without further purification.

[1] The instrument employed was a Jeol PFT-100 spectrometer, operating at 23.5 kG, interfaced with a Jeol EC-100 Fourier transform computer with 20 K memory (Jeol Inc., Cranford, NJ 07016).

RESULTS AND DISCUSSION

The spectral data of six antihistaminic drugs recorded in deuterium oxide solution are summarized in Table I. The carbon-13 resonances generally could be assigned through a combination of the following two methods: (*a*) use of chemical shift values expected for specific types of carbons from the carbon-13 chemical shift theory (8–11) and (*b*) determination of carbon-13–hydrogen coupling constants and the number of protons directly attached to each carbon atom from the proton-coupled spectrum. This system classifies all carbon atoms into four categories on the basis of the multiplicity. The γ-carbon atom and *N*-methyl carbons of pheniramine maleate (II) and chlorpheniramine maleate (III) can thus be designated directly. The α- and β-carbons can be distinguished since the α-carbon is directly attached to a nitrogen atom.



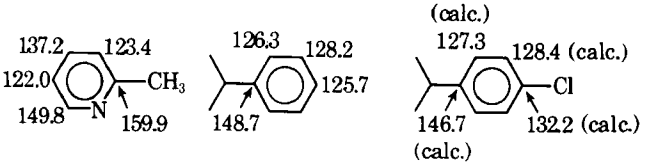
II: R = H
III: R = Cl

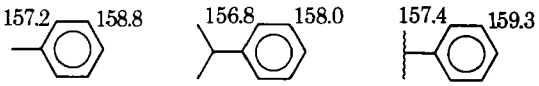
Table II—Carbon-13–Hydrogen Coupling Constants (Hertz)

2-Methylthiophene									
C-3′–H-3	C-3′–H-4′	C-3′–H-5′	C-3′–H-γ	C-4′–H-4′	C-4′–H-3′	C-4′–H-5′	C-5′–H-5′	C-5′–H-4′	C-5′–H-3′
164.2	4.7	9.2	4.7	166.6	4.6	4.6	185.3	6.7	10.1
Methapyrilene Maleate									
C-3′–H-3′	C-3′–H-4′	C-3′–H-5′	C-3′–H-γ	C-4′–H-4′	C-4–H-3′	C-4–H-5′	C-5′–H-5′	C-5′–H-4′	C-5′–H-3′
165.7	—[a]	—[a]	—[a]	168.4	4.3	4.3	187.1	7.9	9.9
C-3–H-3	C-3–H-5	C-4–H-4	C-4–H-6	C-5–H-5	C-5–H-3	C-5–H-6	C-6–H-6	C-6–H-4	C-6–H-5
164.3	5.5	163.0	—[a]	167.3	7.0	7.0	177.7	6.3	3.9
Tripelennamine Hydrochloride									
C-2′–H-2′	C-2′–H-6′	C-3′–H-3′	C-3′–H-5′	C-4′–H-4′	C-4′–H-2′				
158.1	—[a]	159.3	—[a]	~161	—[a]				
C-3–H-3	C-3–H-5	C-4–H-4	C-4–H-6	C-5–H-5	C-5–H-3	C-5–H-6	C-6–H-6	C-6–H-4	C-6–H-5
164.7	5.5	161.8	5.5	167.2	6.1	6.1	177.7	7.0	3.2
Thonzylamine Hydrochloride									
C-2′–H-2′	C-2′–H-6′	C-3′–H-3′	C-3′–H-5′						
159.6	—[a]	160.9	4.0						
C-2–H-4	C-2–H-6	C-4–H-4	C-4–H-6	C-4–H-5	C-5–H-5	C-5–H-4	C-5–H-6		
11.9	11.9	179.4	—[a]	—[a]	172.2	6.7	6.7		
Chlorpheniramine									
C-2′–H-2′	C-2′–H-6′	C-2′–H-γ	C-3′–H-3′	C-3′–H-5′					
160.0	6.0	6.0	165.5	4.3					
C-3–H-3	C-3–H-5	C-3–H-γ	C-4–H-4	C-4–H-6	C-5–H-5	C-5–H-6	C-5–H-3	C-6–H-6	C-6–H-4	C-6–H-5
~165	—[a]	—[a]	163.0	6.8	164.2	8.1	6.3	177.4	6.8	3.5

[a] Small splittings which could not be measured due to unresolved multiplicity.

The effects of individual substituents (shielding constants) of aromatic molecules appear to be additive for polysubstituted compounds (8–11, 21–24), particularly for *para*-disubstituted compounds as illustrated in the CMR spectral analysis of sulfonamide drugs (12). The pyridyl carbon signals are assigned according to the model study of 2-methylpyridine by Lauterbur (25) and this laboratory. The 141.4- and 127.5-ppm peaks are the resonance signals of C-1′ and C-4′ of pheniramine maleate. The assignment of the 127.8- and 129.2-ppm signals to C-2′ and C-3′ is based on the model study of isopropylbenzene (10). In addition, these assignments were confirmed by comparison with their corresponding one-bond carbon-13–hydrogen coupling constants (Hz).

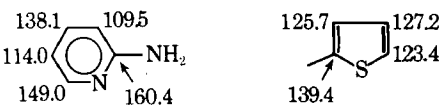


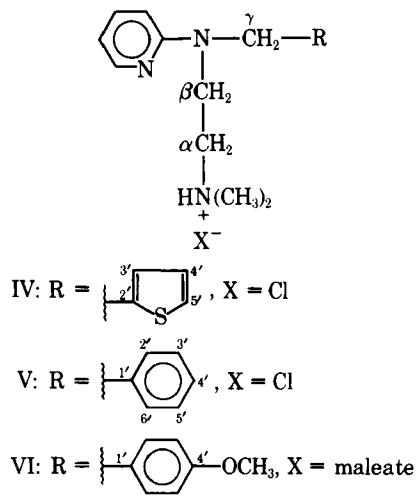


II

From the shielding constants of chloro and isopropyl groups, the chemical shifts of *p*-chloroisopropylbenzene can be calculated. Therefore, the observed signals at 140.1 and 132.4 ppm can be assigned to C-1′ and C-4′ of chlorpheniramine, respectively, and the signals at 129.3 and 129.0 ppm can be assigned to C-2′ and C-3′.

The aliphatic carbon resonance signals of diaminoethylene antihistamines are assigned by comparisons among them and with aminopropyl antihistamines, II and III. The interpretation of the aromatic carbon resonance signals of methapyrilene hydrochloride (IV) is based on the known chemical shift assignments of 2-aminopyridine (26) and 2-methylthiophene (27).

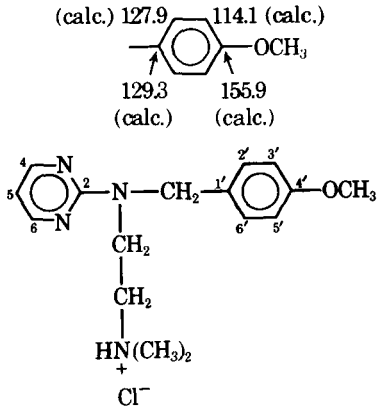




This interpretation was unambiguously confirmed by extensive analysis of the proton-coupled spectrum (Fig. 1). The carbon-13–hydrogen coupling constants of 2-methylthiophene and methapyrilene hydrochloride are summarized in Table II. The interpretation lies in the previous observations on aromatic compounds (28–33):

1. The ^3J (^{13}C-^1H) is normally in the range of 4–8 Hz.
2. The ^2J (^{13}C-^1H) is less than 4 Hz. The coupling between carbon-13 and the hydrogen adjacent to nitrogen is enhanced (14, 32–39). The ^2J (^{13}C-^1H) and ^3J (^{13}C-^1H) of five-membered heterocyclic compounds are almost the same (34–39).
3. The ^4J (^{13}C-^1H) is not larger than 2 Hz.

The chemical shifts of tripelennamine hydrochloride (V) can be assigned by analogy to methapyrilene hydochloride (IV) and pheniramine maleate (II). The intensive analysis of carbon-13–hydrogen coupling patterns of the aromatic carbon resonances further substantiates this conclusion (Table II). These results can then be applied to the spectral analysis of pyrilamine maleate (VI). The chemical shift assignments of the *p*-alkylanisole portion are made by the additivity rule of the shielding constants of aromatic substituents (21–24). Therefore, one can assign the corresponding moiety of thonzylamine hydrochloride (VII).



VII

The resonance signals of the pyrimidyl unit can be determined from their relative intensity and multiplicity. The C-3′ resonance signal appears as a doublet of doublets due to the ^1J (C-3′—H-3′) and ^3J (C-3′—H-5′), while the C-2′ signal appears as an unresolved multiple doublet. The unresolved multiplicity is due to the extra three-bond coupling between C-2′ and H-γ. This observation may be useful in distinguishing C-3′ from C-2′ of chlorpheniramine maleate. Unfortunately, these signals are not well resolved enough to yield unequivocal differentiation. The line-broadening effect is shown in all proton-coupled spectra of antihistaminic salts, which may be the result of intramolecular and/or intermolecular proton exchange among the nitrogen atoms. Thus, the spectrum of free chlorpheniramine in deuterochloroform solution was measured (Fig. 2) and clearly indicates that the more upfield peak at 127.7 ppm, doublet of doublets [^1J (C-3′—H-3′): 165.5 Hz, ^3J (C-3′—H-5′): 4.3 Hz], is the C-3′ resonance signal and that the peak at 128.7 ppm, triplet of doublets [^1J (C-2′—H-2′): 160.0 Hz, ^3J (C-2′—H-4′) = ^3J (C-2′—H-γ): 6.0 Hz], is the C-2′ signal.

The assignment of the carbon-13 resonance signals of substituted aromatic molecules usually has been accomplished on the basis of the additivity principle as already described. However, this approach often leaves some uncertainty in the assignment when the estimated chemical shifts are close. In fact, in the case of C-2′ and C-3′ of chlorpheniramine, the predicted values even provide incorrect relative chemical shifts. The assignment based on the long-range carbon-13–hydrogen coupling constants is unequivocal. We, therefore, believe that long-range carbon-13–hydrogen coupling constants can be a very valuable aid for structure determinations and spectral interpretations.

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