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Composition of Iodopropylideneglycerol: an Example of the Application of 2D NMR Spectroscopy to Structure Elucidation

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Using 1D and 2D NMR spectra, the compounds obtained, in a mixture, in the reaction of glycerol with iodine were identified as the two isomers (*cis* and *trans*) of 2-iodomethyl-5-hydroxymethyl-1,4-dioxane and the two isomers (*cis* and *trans*) of 2-iodomethyl-6-hydroxymethyl-1,4-dioxane. Thus, the composition of the pharmaceutical formulation named IPG has finally been established.

KEY WORDS ^{1}H NMR; ^{13}C NMR; gradient-enhanced 2D NMR; iodopropylideneglycerol; dioxanes

INTRODUCTION

The reaction of glycerol with iodine gives a complex mixture, known as iodopropylideneglycerol[1] (IPG) or iodinated glycerol[2] (CAS No. 5634-39-9), which is greatly appreciated for its expectorant properties. The world production is about 15 tons per year. The structures of the components of IPG are described in the patent[1] and in the literature as an isomeric mixture of 2-(1-iodoethyl)-4-hydroxymethyl-1,3-dioxolane and 2-(2-iodoethyl)-4-hydroxymethyl-1,3-dioxolane.

In 1989, a manufactured sample of IPG was studied[3] in an attempt to determine its toxicity. In contrast to the description given above, the sample was now described as a mixture containing 33% of 3-iodopropane-1,2-diol (named glyceryl iodide[4]) and 17% of glycerol as its two main components. Apart from polymers containing glycerol and iodine, numerous additional components were detected (e.g. hydroxymethyliodomethyl-1,4-dioxane and trioxobicyclononane).

In this study, we attempted to clarify the differences in the data and we elucidated the structure of the four principal components of the reaction mixture obtained under the same conditions as those described in original method.[1] These components were separated by medium-pressure liquid chromatography. The four compounds were studied in the same way using ^{1}H NMR, ^{13}C NMR, ^{1}H-COSY, HMQC and HMBC. In the last three experiments, the pulse field gradient technique was used.

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RESULTS AND DISCUSSION

IPG was prepared following the method described in the patent,[1] with 75% conversion. The composition of the reaction mixture was analysed by HPLC. It was virtually invariant during the time of reaction and depended only slightly on the reaction conditions. The major compounds are the two isomers of 2-iodomethyl-5-hydroxymethyl-1,4-dioxanes [*cis* (**1**) (15%) and *trans* (**2**) (31%)] and the two isomers of 2-iodomethyl-6-hydroxymethyl-1,4-dioxane (CAS No. 19589-33-4) [*cis* (**3**) (CAS No. 6963-00-4) (21%) and *trans* (**4**) (CAS No. 20454-42-6) (26%)] (Scheme 1). Another compound isolated and identified was trioxobicyclononane[6] (*endo*, *endo*-bicyclo[3.7.9]-3,3,1-trioxanonane (CAS No. 281-09-4) (**5**) among the minor compounds detected by GC and HPLC. In all cases, we assume an equatorial orientation of the hydroxymethyl substituent that stabilizes the conformation by the formation of a hydrogen bond with one of the oxygen atoms in the ring. All the compounds mentioned were isolated by preparative chromatography (medium pressure) and their structures were determined by a combination of 1D and 2D NMR methods.

Table 1 shows ^{13}C chemical shifts for compounds **1–4**. The assignment of the signals was possible after obtaining the $^{1}H/^{13}C$ correlation spectra (one-bond and long-range correlation). One of the crucial points in the identification of each isomer was the assignment of C-5 and C-6 and its character as CH_2 or CH. This was only possible once these ^{13}C signals had been located in the HMBC spectrum, through the occurrence of cross peaks of long-range coupling of H-3 with C-5 and (or) H-2 with H-6, and then identifying one or two protons

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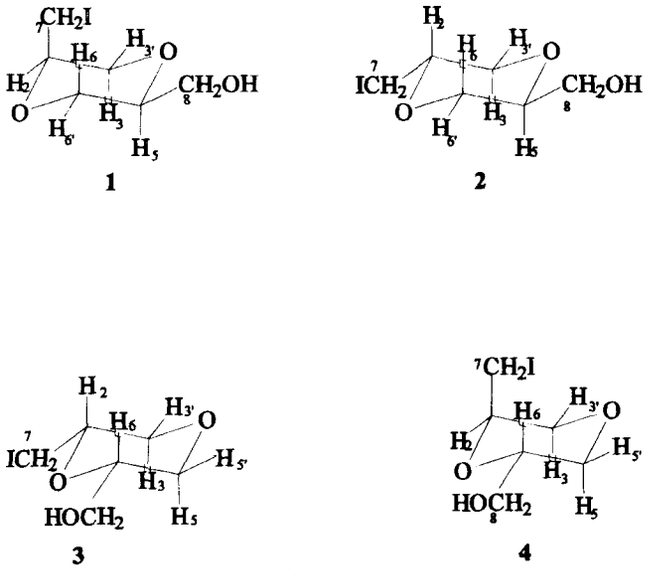

Scheme 1.

in the HMQC spectrum through cross peaks of one-bond coupling (see Figs. 1–6).

We should emphasize the high-field absorption of the iodomethyl substituent and the relative position of C-7, low field for the equatorial configuration (**2** and **3**) and high field for the compounds which adopt the axial configuration (**1** and **4**).

Table 1. ^{13}C chemical shifts (in ppm from TMS) of compounds 1–4

Compound	C-2	C-3	C-5	C-6	C-7	C-8
1	72.4	65.9	74.1	62.7	3.2	61.3
2	74.0	70.6	75.0	68.1	2.1	62.1
3	74.1	70.2	67.1	76.0	2.5	62.2
4	70.8	68.1	67.2	69.9	3.8	61.5

Figure 7 shows the ^1H NMR spectra of compounds **1–4** and Tables 2 and 3 give the chemical shifts and the coupling constants, respectively. In three of the four cases the assignment was aided by a spectral simulation and iteration process[7] (for **1** the description was not complete). The resonances of **2** and **4** appear in a window of 1 ppm (δ 3–4) and the signals of **1** and **3** appear in window of a 0.6 ppm (δ 3.25–3.85). The protons of the iodomethylene group present the absorption at higher field when that group is in an equatorial orientation and as a first-order doublet of doublets (**2** and **3**).

The similarity between $J_{3/2}$ and $J_{3'/2}$ in **1** and **4** implies a similarity between corresponding dihedral angles and confirms the axial configuration of the iodomethyl group (H-2 axial). On the other hand, the same couplings in **2** and **3** are very different, since $J_{3/2} \gg J_{3'/2}$ corresponding to an axial proton H-2, i.e. an equatorial position for the iodomethyl group. In contrast, for protons H-5 and H-6, the situation is the same in each pair of compounds, because the values of the coupling constants are different in all cases $J_{5/6} \gg J_{5/6'}$ for **1** and **2** (or $J_{5/6} \gg J_{5'/6}$ for **3** and **4**), indicating an equatorial configuration for the hydroxymethyl group in each isomer.

EXPERIMENTAL

Preparation of iodopropylideneglycerol (IPG)

A 2 ml volume of toluene, 1 g of *p*-toluenesulphonic acid and 17 g of iodiine were added to 43 ml of glycerol in a 250 ml three-necked flask equipped with an efficient stirrer, a Dean–Stark separator and a thermometer. The well stirred mixture was heated to 100–120 °C and the water formed was collected in the Dean–Stark separator. The crude mixture was cooled and then dissolved in

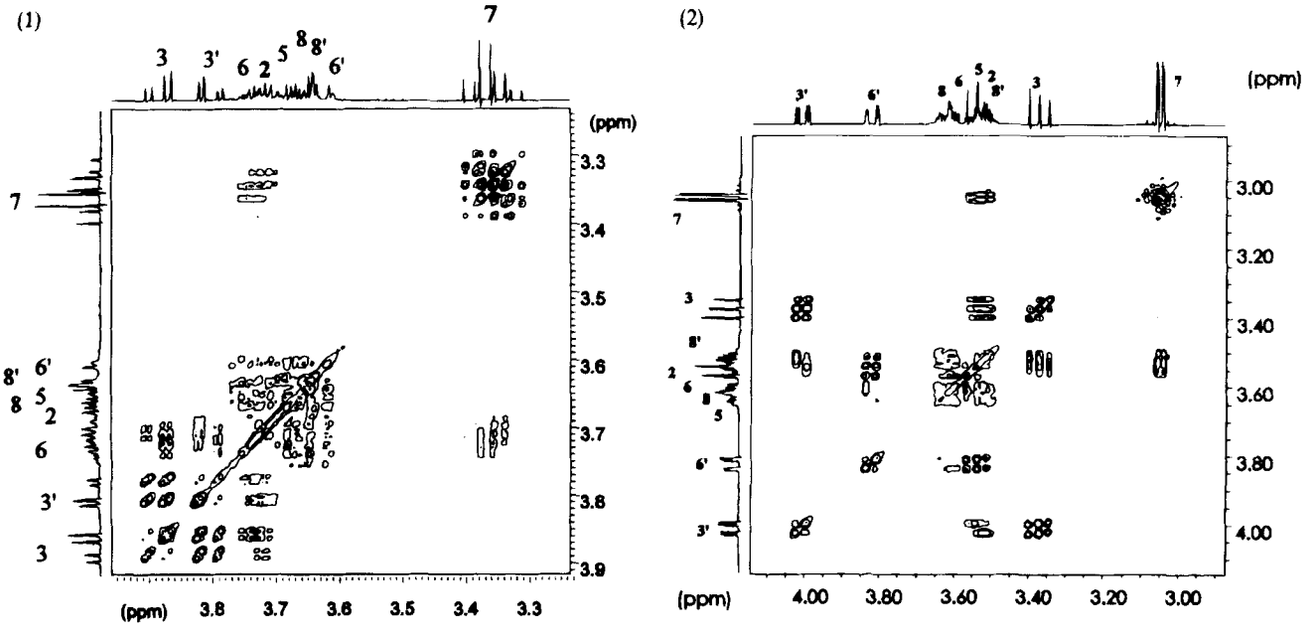

Figure 1. COSY spectra of compounds **1** and **2**.

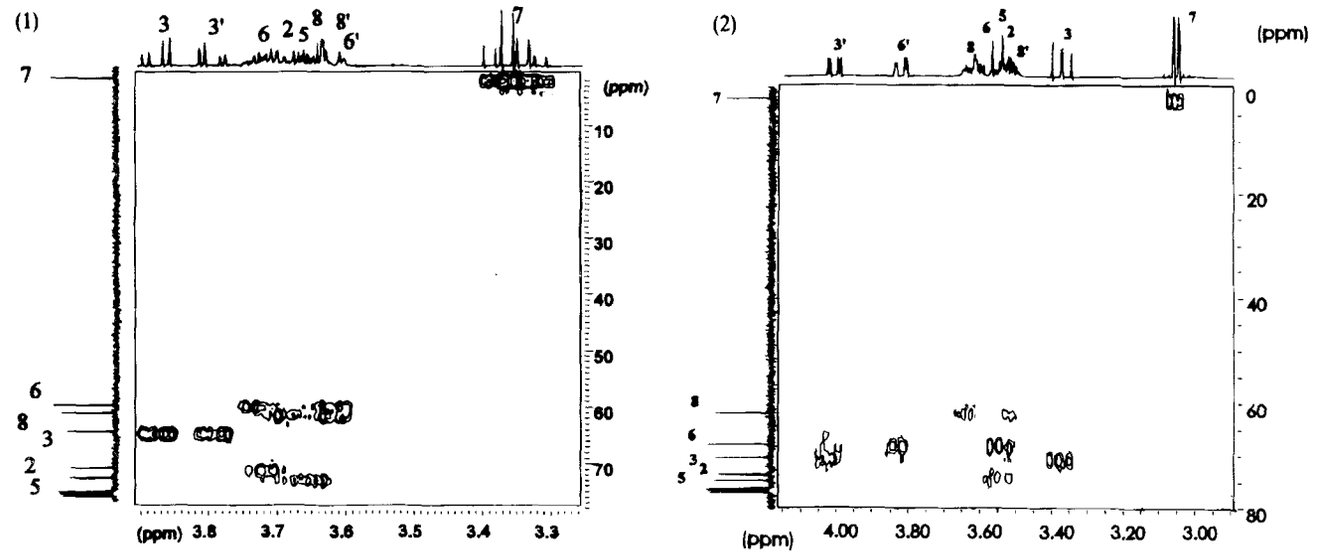

Figure 2. HMQC spectra of compounds **1** and **2**.

100 ml of water. The mixture was stirred with charcoal, filtered and the solution was made alkaline (pH 10) and extracted with methylene chloride (3 × 100 ml). IPG (10 g) was obtained after concentration *in vacuo*, as a viscous, yellow oil.

HPLC analysis

The IPG mixture was analysed on a 100RP-18 5 μm column (250 × 4 mm i.d.), using methanol–water (1:9) as the solvent system at a flow rate of 1.5 ml min^{-1}. The retention times of the major components were **1** 16.2 min, **2** 24.4 min, **3** 20.8 min and **4** 17.62 min.

Preparative chromatography

A column of LiChroprep RP-18 (40–63 μm) LOBAR-B (310–25) from Merck was used with methanol–water (1:9) as the mobile phase at flow rate of 2 ml min^{-1}. A

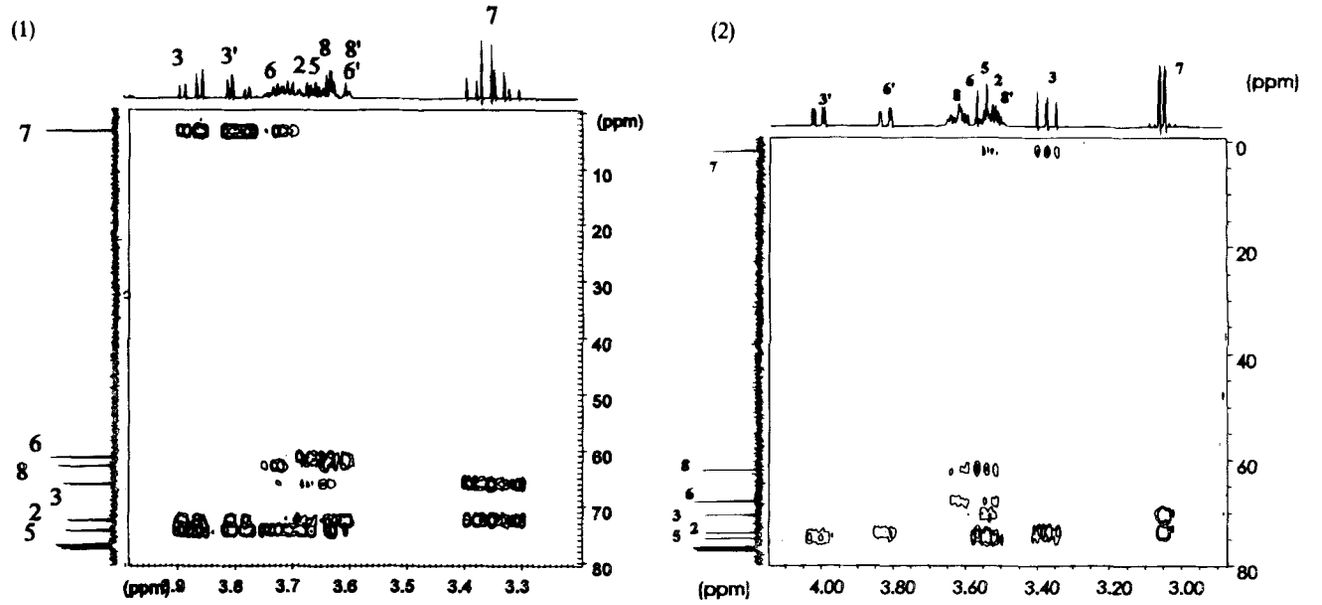

Figure 3. HMBC spectra of compounds **1** and **2**.

Table 2. ^{1}H chemical shifts (in ppm from TMS) of compounds 1–4

Compound	H-2	H-3	H-3′	H-5	H-5′	H-6	H-6′	H-7	H-7′	H-8	H-8′
1	3.73	3.87	3.80	3.66	—	3.72	3.61	3.37	3.33	3.67	3.62
2	3.53	3.37	4.01	3.52	—	3.54	3.82	3.04	3.06	3.61	3.51
3	3.66	3.18	3.91	3.41	3.67	3.76	—	3.06	3.07	3.63	3.53
4	3.90	3.70	3.77	3.50	3.73	3.84	—	3.38	3.36	3.71	3.62

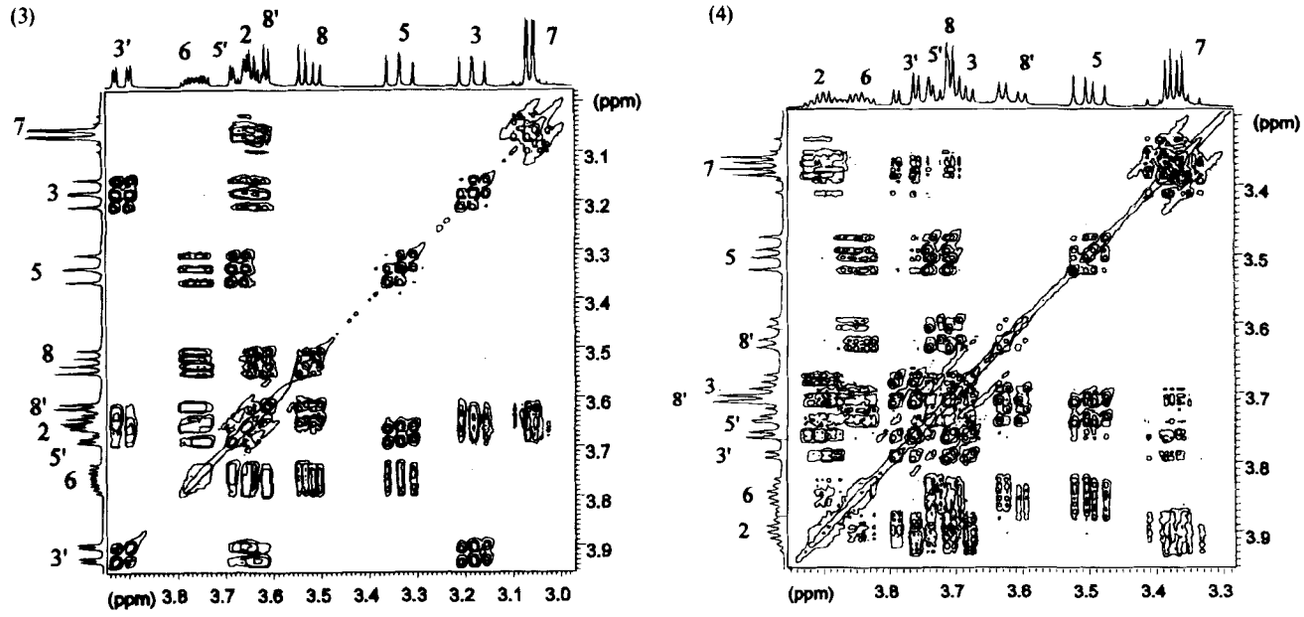

Figure 4. COSY spectra of compounds **3** and **4**.

500 mg amount of sample was injected and compounds **1**–**5** were isolated. The characteristics of the minor component **5** were as follows: ^{1}H NMR (400 MHz) ($CDCl_3$), δ = 3.23 (^{1}H, t, J = 2.1 Hz), 3.67, 3.69, 3.80 (d, J = 3.0 Hz), 3.82 (d, J = 3.0 Hz), AB system (2H); ^{13}C NMR (100 MHz) ($CDCl_3$), δ = 68.0 (CH), 69.3 (CH_2); MS, m/z 57 (20%), 71 (44%), 87 (11%), 103 (4%), 130 (100%).

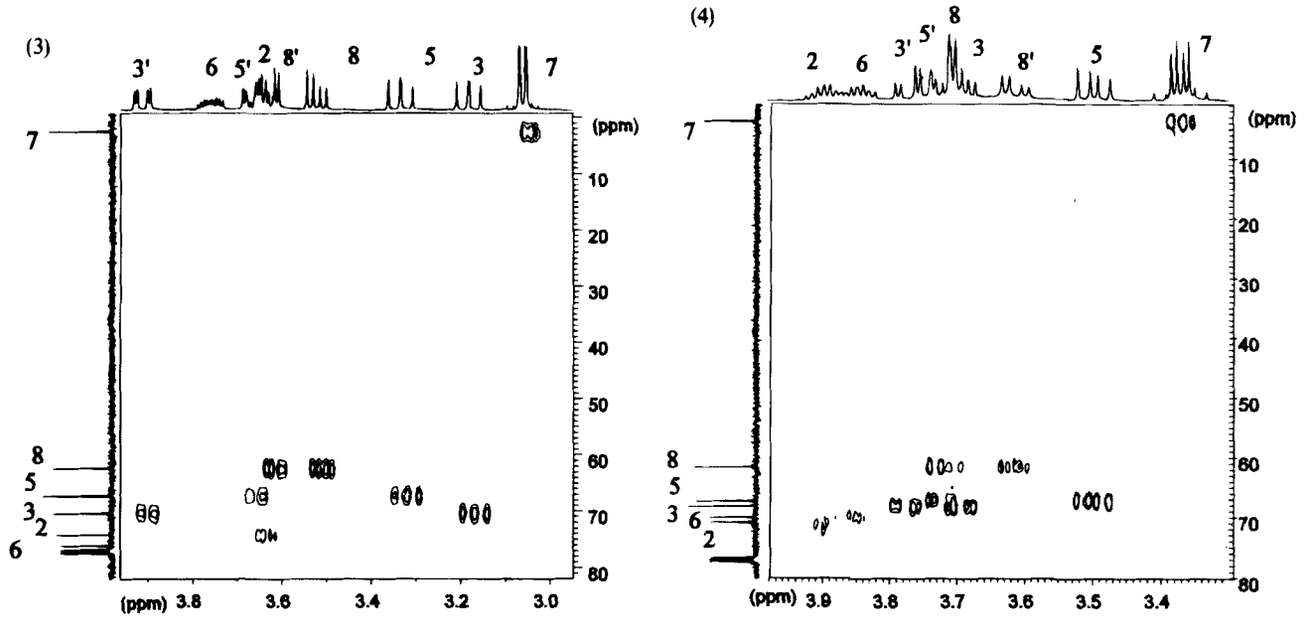

Figure 5. HMQC spectra of compounds **3** and **4**.

Table 3. Coupling constants (in Hz) of protons of compounds 1–4

Compound	J(H-2, H-3)	J(H-2, H-3')	J(H-3, H-3')	J(H-5, H-5')	J(H-5, H-6)	J(H-5', H-6)	J(H-6, H-6')	J(H-5, H-6')
1	4.2	3.4	12.1	—	n.d.	—	n.d.	n.d.
2	10	2.4	11.3	—	10.0	—	10.0	1.9
3	10.2	2.4	11.3	10.5	11.4	2.7	—	—
4	4.0	3.3	11.7	11.9	7.3	0	—	—

[a] n.d. = Not determined.

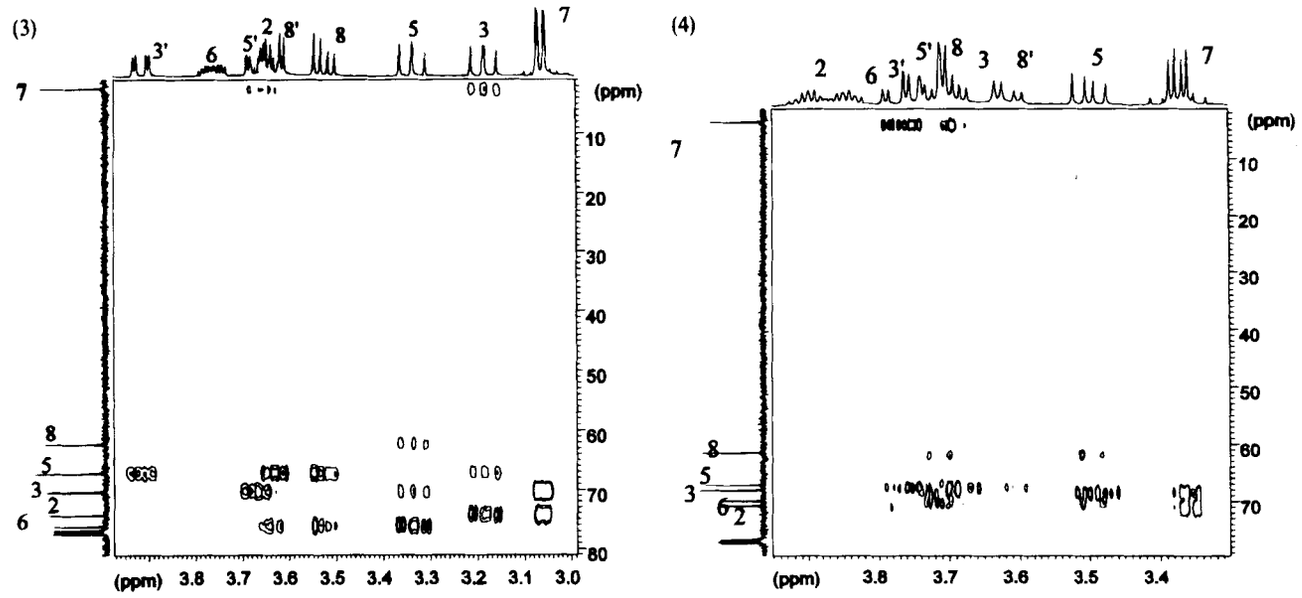

Figure 6. HMBC spectra of compounds **3** and **4**.

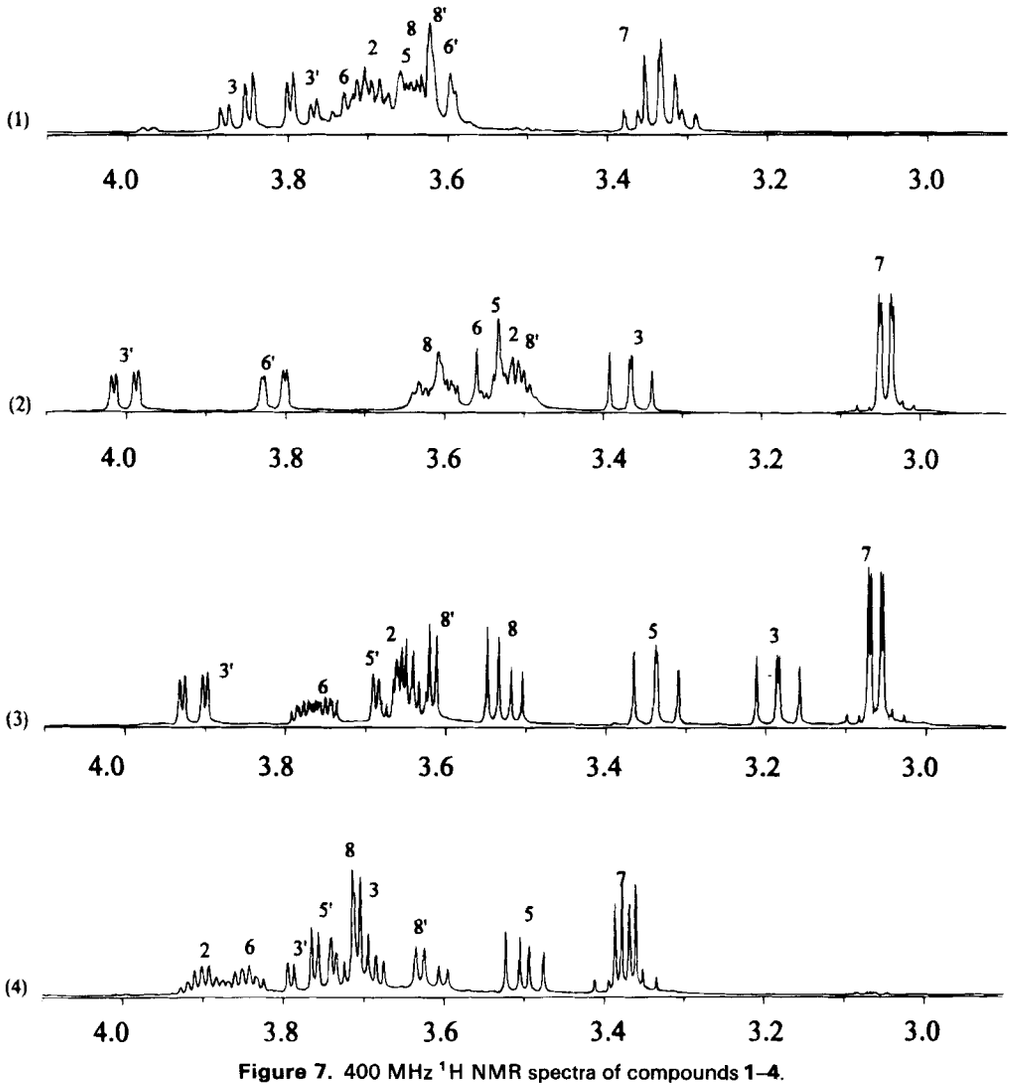

Figure 7. 400 MHz ^{1}H NMR spectra of compounds **1–4**.

NMR experiments

Structural studies were performed on a Bruker ARX400 NMR spectrometer equipped with an inverse broadband probe head incorporating a shielded Z-gradient coil. Proton and ^{13}C chemical shifts were referred to the solvent signals ($CDCl_3$) at 7.24 and 77 ppm, respectively.

Magnitude-mode gradient enhanced COSY spectra[8] resulted from 512 × 1024 data matrix size with two scans per t_1 value. The recycle time was 1 s and a 1:1 gradient combination was used. Magnitude-mode gradient-enhanced one-bond ^1H–^{13}C correlation (HMQC) spectra[9] resulted from[a] 128 × 1024 data matrix size with 2 scans per t_1 value. The delay was 3.5 ms and the recycle time was 1 s. A 2:2:1 gradient combination was used. Broadband ^{13}C decoupling with GARP-1[10] was applied during the acquisition. Magnitude-mode gradient-enhanced long-range ^1H–^{13}C shift correlation (HMBC) spectra[9] resulted from 128 × 1024 data matrix size with 2 scans per t_1 value and a recycle time of 1 s. The low-pass J-filter delay was set to 50 ms. A gradient combination of 2:2:1 was used to select the desired coherence. In all 2D spectra, before Fourier transformation, the data were zero-filled in the t_1 dimension and a sine-bell filter was applied before Fourier transformation in both dimensions.

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