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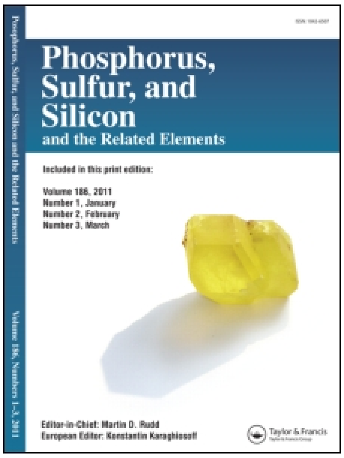

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STEREOCHEMISTRY OF SULPHUR ORGANIC COMPOUNDS. PART 23. DOUBLE GAUCHE EFFECT OXYGEN/SULPHUR IN 2-ALKYLTHIO-DERIVAHVES OF 1,1-DIMETHOXYETHANE

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STEREOCHEMISTRY OF SULPHUR ORGANIC COMPOUNDS. PART 23. DOUBLE GAUCHE EFFECT OXYGEN/SULPHUR IN 2-ALKYLTHIO-DERIVATIVES OF 1,1-DIMETHOXYETHANE

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The synthesis and conformational analysis, by ^{1}H-NMR in several solvents, of 2-X-1,1-dimethoxyethane (X: MeS, EtS, ^{i}PrS, ^{t}BuS, BnS, SOMe, SOEt, SO^{i}Pr, SO^{t}Bu, SOBn) are reported. The results are concordant with a high, unexpected, solvent independent preference (~30%) of the sterically most hindered conformation. A stereoelectronic interaction between orbitals has been invoked to explain the obtained results. MM2 method was used to calculate the energy of the conformations resulting from CH—CH$_2$ bond rotation.

Key words: Thioderivatives of acetals; preparation; conformational analysis; ^{1}H-nmr study; sulphur–oxygen interaction; stereoelectronic interaction.

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INTRODUCTION

The role played by the (Oxygen/Sulphur)$_{1,2\text{-}gauche}$ interaction, as opposed to the steric destabilization resulting from sizing up the present groups, has previously been studied by our group in β-methylthioderivatives of alcohols,[2] 1,3-dioxanes[3] and oxanes.[4]

The conformational analysis of 2-alkylsulphenyl and 2-alkylsulphinyl derivatives of 1,1-dimethoxyethane (scheme 1) which present a double (O/S)$_{1,2\text{-}gauche}$ interaction, is reported in the present paper.

The interest of these compounds resides in their structures that group together some interesting conformational effects (*anomeric* and *gauche* effect, attractive or repulsive electrostatic interactions between heteroatoms and donor-acceptor interactions between orbitals). Additionally, it is worth pointing out that in compounds with these connectivities, the reported vicinal coupling constant values for the acetalic proton are smaller than those expected by considering the substituent electronegativities.[5] A satisfactory explanation for this behaviour is lacking up to now. In this sense, as a result of sulphur chirality in sulphoxides, the β-alkylthio derivatives of acetals make the ^{1}H-NMR study particularly interesting due to the non equivalence of the methylene protons which could throw some light on the conformational behaviour of this kind of compounds.

Some X-ray diffraction and ^{1}H-NMR studies in dialkylacetals and thioacetals of aldohexoses[5c] suggest that the conformational equilibrium around the C$_1$—C$_2$

$X—CH_2—CH(OMe)_2$

Thioethers	X	Sulphoxides	X
1	MeS	**6**	MeSO
2	EtS	**7**	EtSO
3	^{i}PrS	**8**	^{i}PrSO
4	^{t}BuS	**9**	^{t}BuSO
5	BnS	**10**	BnSO

SCHEME 1 List of studied compounds.

bond is affected by other 1,3-parallel interactions in the molecule. On the contrary, compounds **1–10**, are simpler models for the conformational study of β-heterosubstituted acetals and the conclusions could be extrapolated to more complex systems.

RESULTS AND DISCUSSION

The synthesis of the 2-alkylsulphenyl-1,1-dimethoxyethanes (**2–5**) has been carried out by reaction of 2-chloroacetaldehyde dimethylacetal with the potassium or sodium salts of the corresponding thiols, according to the method described in the synthesis of other acetals.[6–8] The reaction of thioethers with 1 eq. of sodium metaperiodate yielded the alkylsulphinyl derivatives (**6–10**) as racemic mixtures.

The three possible staggered conformations of compounds **1–10** around the C—C bond are given in Figure 1. The coupling constants of the CH_2—CH fragment in the ^{1}H-NMR spectra in several solvents were used for evaluating the conformational populations.

Because of the conformational mobility around the C—C bond, the observed values of the coupling constants in compounds **1–10** are weighted means between

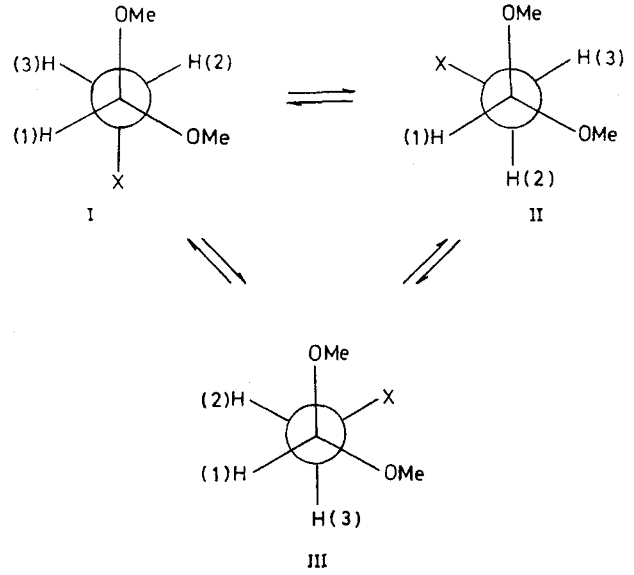

FIGURE 1 Staggered conformations of the compounds **1–10** around the C—C bond.

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the three different conformations (equation [1]).

$$J^{\text{obs}}_{1,2(3)} = X_I J^{I}_{1,2(3)} + X_{II} J^{II}_{1,2(3)} + X_{III} J^{III}_{1,2(3)} \quad [1]$$

In compounds **1–5**, owing to the protons H(2) and H(3) being enantiotopic there is only one experimental coupling constant value ($J^{\text{obs}}_{1,2} = J^{\text{obs}}_{1,3}$). However, in compounds **6–10** there are two different values for this parameter.

Theoretical $J^{I}_{1,2(3)} - J^{III}_{1,2(3)}$ values have been calculated by means of the Karplus equation modified by Altona[9] that, as previously indicated, is applicable to thioderivatives with sulphur in different oxidation states.[2d] From calculated and observed vicinal coupling constants, the molar fraction of each individual conformation was evaluated (equation [1]).

With regard to the acetalic function, if one takes into account the rotation around the C—OMe bonds, up to nine rotamers must be considered for each conformation I–III. Nevertheless, the more favourable dispositions between the methoxy groups are, those with two stereoelectronic interactions $n_0 \rightarrow \sigma^*_{C-O}$,[10] and having none 1,3-parallel (Me/Me) interaction.[11]

The *J* values deduced from computer analysis of the AX_2 systems in ^{1}H-NMR spectra recorded in $CDCl_3$ and DMSO-d_6, for compounds **1–5**, and conformational populations calculated from equation [1] are given in Table I. According to these data, the contribution of the three rotamers to the conformational equilibrium is very similar and remains nearly unchanged ($J = 5.5$–5.7 Hz) with the polarity of the solvent.

On steric and stereoelectronic grounds, the more stable rotamers for conformations I and III in these compounds are drawn in Figure 2 (conformation II is enantiomer of I and has therefore been excluded). In spite of the acetal function being flattened,[10,12] at first sight rotamers IIIa and IIIb could be considered as being less stable than Ia and Ib. In IIIa there is a steric $(Me/S)_{1,3\text{-p}}$ interaction far more destabilizing than the $(Me/H)_{1,3\text{-p}}$ one in Ia, Ib and IIIb. Rotamer IIIb is not specially destabilized by steric factors, but having only a $n_0 \rightarrow \sigma^*_{C-O}$ interaction and two repulsive *gauche* effect, it is not favoured on stereoelectronic grounds. From the solvent independence of *J* values in compounds **1–5**, can be inferred that dipole–dipole interactions in the different rotamers are not meaningful. The conformational behaviour of **1–5** as opposed to that of

TABLE I

^{1}H-NMR parameters and conformational populations of **1–5**

Compound	Solvent	J^{obs}	$X_I + X_{II}$	X_{III}
1	$CDCl_3$	5.48	67	33
	DMSO-d_6	5.52	68	32
2	$CDCl_3$	5.51	68	32
	DMSO-d_6	5.54	68	32
3	$CDCl_3$	5.57	69	31
	DMSO-d_6	5.56	69	31
4	$CDCl_3$	5.72	73	27
	DMSO-d_6	5.68	72	28
5	$CDCl_3$	5.53	68	32
	DMSO-d_6	5.54	68	32

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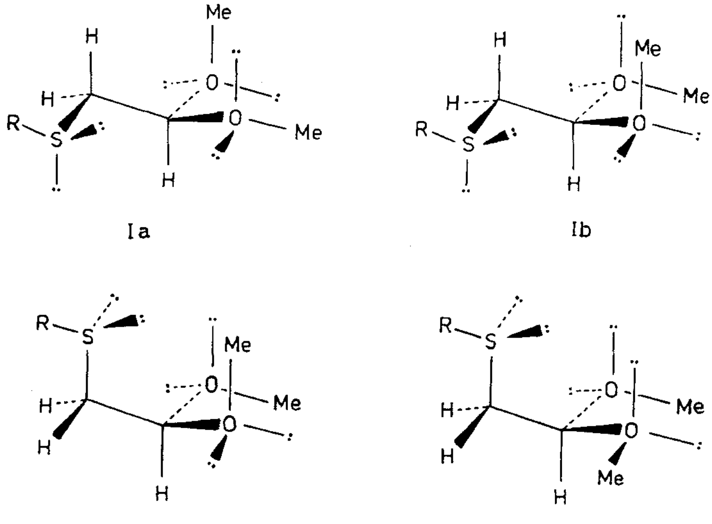

Ia Ib

IIIa IIIb

FIGURE 2 Favoured rotamers in thioethers **1–5**.

2-halo-1,1-dimethoxyethanes and 1,1,2-trihaloethanes, shown in Table II, reinforces this point. Thus, the variation of J values with solvent nature in haloderivatives can be explained taking into account that dipole–dipole interactions of like-III rotamers are less significant in solvents with higher dielectric constant (see below).

A reasonable explanation for the conformational behaviour of acetals, particularly of sulphur derivatives **1–5**, could be given invoking the generalized *gauche* effect.[10,12,14] First, the *anomeric* effect flattens the acetal function,[10,12] being III

TABLE II

Proton Coupling Constants and calculated conformer population[a] for several trisubstituted ethanes

R	X	X—CH$_2$—CHR$_2$ Solvent (ε)	J^{obs}	X_{III}
OMe	SMe[b]	CS$_2$(2.95)	5.54	32
		CDCl$_3$(4.90)	5.48	33
		DMSO-d$_6$(44.9)	5.52	32
OMe	Cl[b]	CS$_2$	5.52	29
		CDCl$_3$	5.41	31
		DMSO-d$_6$	5.28	34
OMe	Br[b]	CS$_2$	5.54	30
		CDCl$_3$	5.42	33
		DMSO-d$_6$	5.25	37
Cl	Cl[c]	CS$_2$	6.13	23
		CDCl$_3$	6.03	25
		DMSO-d$_6$	5.17	44

[a] Using Altona equation.
[b] This work.
[c] From reference 13.

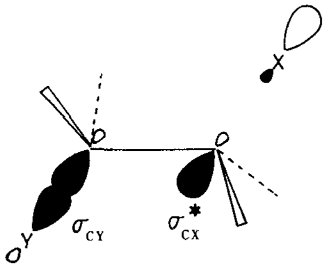

FIGURE 3 Interaction between σ_{CY} and σ^*_{CX} orbitals in the generalized *gauche* effect.

sterically less hindered. Secondly, in the derivatives with sulphur, the *gauche* effect that results from the stabilizing interaction between a doubly occupied bonding orbital (σ) and a vacant antibonding one (σ^*) in *antiperiplanar* arrangement (Figure 3) can explain the high proportion of III.[15] Thus, conformations Ia and Ib, with $\sigma_{CH} \rightarrow \sigma^*_{CO}$ and $\sigma_{CS} \rightarrow \sigma^*_{CO}$ interactions are, on stereoelectronic grounds, less stable than rotamers IIIa and IIIb where there are two $\sigma_{CH} \rightarrow \sigma^*_{CO}$ interactions and above all, another one $\sigma_{CS} \rightarrow \sigma^*_{CH}$ very stabilizing, because of the anomeric effect.[15d] Consequently, could be concluded that the steric and stereoelectronic destabilizations in IIIa and IIIb, respectively (see above) are compensated by the structural modifications and stabilizations brought about by the generalized *gauche* effect.

In order to gain a better understanding of the steric and polar factors involved in the interactions studied experimentally, MM2 calculations[16] were carried out for the compounds in Table II. The Molecular Mechanics Method does not consider stereoelectronic interactions which are responsible for the anomeric effect. Because of this, only the disposition with more $n_O \rightarrow \sigma^*_{CO}$ interactions for the acetal fragment of the molecule was taken into account in the calculations.[17]

The relative energies of the minima together with dipole moments, dihedral angles between protons, ϕ, and rotation angles θ derived from calculations for the considered compounds are shown in Table III. The results show that conformations of relative minima are not far from I–III rotamers. As seen in Table III the dipole moments are very similar in conformers I–III of acetals. This is in agreement with the results given for halogeneted derivatives in Table II, where the highest variation of J with solvent polarity corresponds to the trichloroderivative. On the contrary, the similar rotamer population, in different solvents, of sulphur compounds (Tables I and II) can only be explained by invoking stereoelectronic factors (see above).

FIGURE 4 Nomenclature system in Table III.

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TABLE III

Structural data obtained from MM2 calculations (see Figure 4)

X	R	E(Kcal/mol)	μ(D)	ϕ		θ
				1,2	1,3	
SMe	OMe	0.104	1.52	−170.00	70.95	68.72
		0.000	1.56	−57.22	−173.31	179.05
		1.762	1.60	80.77	−35.05	322.87
Cl	OMe	0.000	1.87	−168.03	69.00	68.69
		0.216	1.91	−57.03	−177.25	177.03
		1.915	1.94	77.35	−42.54	315.43
Br	OMe	0.000	1.71	−166.77	69.70	70.20
		0.401	1.77	−58.20	−178.80	175.02
		2.216	1.79	80.54	−39.72	319.06
Cl	Cl	0.000	1.72	−176.35	61.95	63.35
		0.000	1.72	−61.96	176.35	173.14
		1.429	3.45	60.00	−59.88	296.64

Table IV shows the *J* values obtained from computer analysis of the ABX systems in ^{1}H-NMR spectra for sulphoxides **6–10**, recorded in DMSO-d$_6$.

The more stable rotamers, on steric grounds, obtained from conformers I–III by rotation around the C—S bond are shown in Figure 5 for the *R* enantiomer. The acetalic fragment has been set out so that the interactions were the smallest. Those rotamers where an 1,3-parallel interaction is present between atoms of the second row (or the third) of the periodic table, have been excluded, except for conformers III.

Data from Table IV show that the rotamer I or II prevails largely in the conformational equilibria. Comparison between these rotamers (Figure 5) shows that Ia is the one with the greatest stability because it has a stabilizing $(0/H)_{1,3\text{-p}}$ interaction, besides a $(H/Me(O))_{1,3\text{-p}}$ destabilizing one, that is present in all rotamers. On the other hand, IIa has a $(R/H)_{1,3\text{-p}}$ interaction as a differentiation fact. However, according to the results obtained in β-methylthioderivatives of alcohols[2] and oxanes,[4] an (O/H) vs a (R/H) 1,3-parallel interaction is not sufficient to explain the conformational preference in diastereomeric sulphoxides, at least in **6, 7** and **10**, where R is not very large.

An explanation for this behaviour could be based on the fact that conformation Ia has the appropriate arrangement for an effective overlap between a lone pair of the acetalic oxygen, which is *gauche* to the sulphur, and a d orbital of the sulphinylic sulphur.[18] This stabilizing interaction has previously been invoked to

TABLE IV

^{1}H-NMR parameters and conformational populations of **6–10**

Compound	$J^{obs}_{1,2}$	$J^{obs}_{1,3}$	X_I	X_{II}	X_{III}
6	7.37	3.98	0.61	0.13	0.26
7	7.48	3.78	0.62	0.10	0.28
8	7.81	3.52	0.67	0.06	0.27
9	8.33	3.04	0.74	0.00	0.26
10	7.69	3.72	0.65	0.09	0.26

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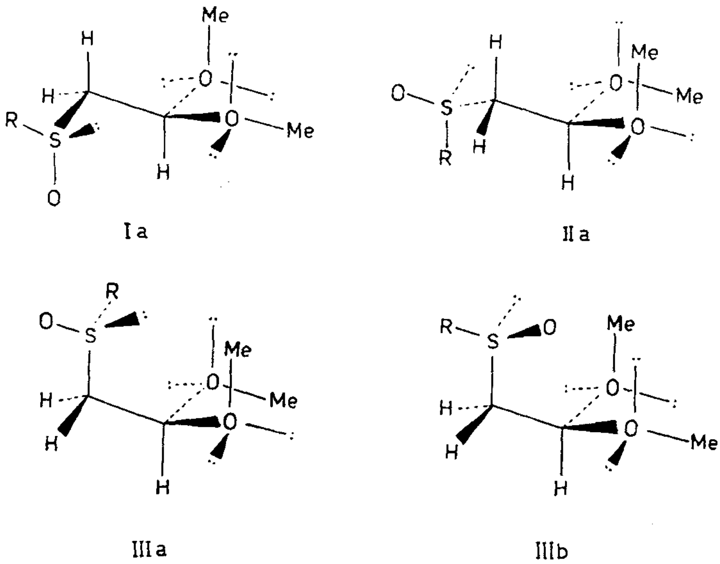

FIGURE 5 Favoured rotamers in sulphoxides **6–10**.

explain the differences in the conformational behaviour of diastereisomeric sulphoxides,[2,4] where other configurational factors could interfere the conformational equilibrium of each estereoisomer. In sulphoxides **6–10** these factors are present in the same molecula, which gives proof of the importance of $n_{(\text{oxygen})} \rightarrow d_{(\text{sulphinylic sulphur})}$ interaction.

To explain the high proportion of conformer III in sulphoxides it could be suggested that in this rotamer there are two electrostatic $(S^{\delta+}/O^{\delta-})_{1,2\text{-g}}$ interactions.[3]

EXPERIMENTAL

I.R. spectra were obtained using a Perkin Elmer model 1310 spectrometer. Mass spectra were recorded on an AEI model MS-30 spectrometer at 70 ev. Proton N.M.R. spectra were recorded on a Bruker WP-80-SY instrument. Shifts are reported in ppm downfield from internal TMS. The silica-gel used in chromatography was Merck F-254 (TLC) or 60 (70–230 mesh column).

2-Alkylsulphenyl-1,1-dimethoxyethane (**2–5**)

General Procedure. A mixture of 0.28 mol of KOH in 10 mL of ethanol, 0.11 mol of alkylthiol and 0.11 mol of chloroacetaldehyde dimethylacetal was refluxed and stirred for 2 days. The solution was distilled to remove the solvent and treated with 50 mL of water. The thioether was extracted into Cl_3CH, the organic layer dried and distilled.

2. b.p. 70–1°C (15 mm Hg).[19] Yield 85%. IR (film) ν_{max}: 2955, 2920, 2825, 1450, 1370, 1120 and 1060 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.49 (t, 1H, $J = 5.50$ Hz); 3.37 (s, 6H); 2.70 (d, 2H, $J = 5.50$ Hz); 2.60 (c, 2H, $J = 7.30$ Hz); 1.25 (t, 3H, $J = 7.30$ Hz).

3. b.p. 138–140°C (160 mm Hg). Yield 87%. I.R. (film) ν_{max}: 2965, 2940, 2840, 1460, 1370, 1130 and 1065 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.49 (t, 1H, $J = 5.57$ Hz), 3.37 (s, 6H); 2.90 (m, 1H, $J = 6.60$ Hz); 2.70 (d, 2H, $J = 5.57$ Hz) and 1.27 (d, 6H, $J = 6.6$ Hz); M.E. m/z (%): 166 (0.2, $M^+ + 2$); 165 (0.5, $M^+ + 1$); 164 (3.5, M^+); 133 (10); 101 (3); 91 (11); 90 (3); 75 (100); 59 (16); 47 (13) and 45 (5).

4. b.p. 90–1°C (15 mm Hg). Yield 95%. IR (film) ν_{max}: 2960, 2385, 1465, 1365, 1120, 1115 and 1060 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.49 (t, 1H, $J = 5.72$ Hz); 3.36 (s, 6H); 2.75 (d, 2H, $J = 5.72$ Hz) and 1.32 (s, 9H). E.M. m/z (%): 180 (0.2, $M^+ + 2$); 179 (0.5, $M^+ + 1$); 178 (3, M^+); 147 (4); 91 (18); 90 (5); 88 (1.5); 75 (100); 59 (8); 57 (26); 47 (9) and 45 (3).

5. b.p. 76–8°C (0.05 mm Hg)[20]. Yield: 68%. I.R. (film) ν_{max}: 3080, 3060, 3035, 2930, 2840, 1600, 1495, 1455, 1365, 1120, 1075, 1060, 760 and 710 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 7.28 (m, 5H); 4.40 (t, 1H, $J = 5.52$ Hz); 3.76 (s, 2H); 3.32 (s, 6H); 2.58 (d, 2H, $J = 5.52$ Hz).

2-Alkylsulphinyl-1,1-dimethoxyethane (**6–10**)

General Procedure. 10 mml of the corresponding thioether in 20 mL of water were stirred with an aqueous solution of 10 mmol of $NaIO_4$ at 0°C for 15 hours. The solvent was removed and the sulphoxides extracted into $CHCl_3$. The dried organic layer was evaporated to dryness: Quantitative Yield.

6. IR (film) ν_{max}; 2940, 2830, 1450, 1360, 1120 and 1040 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.8 (t, 1H); 3.44 (s, 3H); 3.39 (s, 3H); 3.0 (d, 2H) and 2.6 (s, 3H). M.E. m/z (%): 152 (0.2, M^+); 137 (1.5); 135 (1.5); 121 (22.7); 105 (5); 88 (54.5); 75 (100) and 45 (13.5).

7. IR (film) ν_{max}: 2960, 2940, 2830, 1455, 1370, 1120, 1060 and 1040 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.8 (t, 1H); 3.45 (s, 3H); 3.39 (s, 3H); 2.95 (d, 2H); 2.70 (c, 2H); 1.32 (t, 3H). M.E. m/z (%): 166 (0.1, M^+); 149 (1.2); 137 (1.8); 135 (10); 88 (33), 77 (16) and 75 (100).

8. IR (film) ν_{max}: 2960, 2940, 2840, 1460, 1370, 1120, 1055 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.80 (part X of an ABX system, 1H, $J = 8.9$ and 2.2 Hz); 3.46 (s, 3H); 3.40 (s, 3H); 2.85 (m, 1H, $J = 6.9$ Hz); 2.85 (part AB of an ABX system, 2H, $J = 8.9$ and 2.2 Hz) and 1.25 (dd, 6H, $J = 6.9$ Hz). M.E. m/z (%): 180 (0.2, M^+); 149 (10); 138 (7), 106 (66.5); 91 (11), 88 (6); 75 (100) and 43 (33).

9. IR (film) ν_{max}: 2960, 2830, 1455, 1370, 1130 and 1065 cm^{-1}. ^1H-NMR ($CDCl_3$) δ_{ppm}: 4.85 (part X of an ABX system, 1H, $J = 8.5$ and 2.8 Hz); 3.48 (s, 3H); 3.30 (s, 3H); 2.71 (part AB of an ABX system, 2H, $J = 8.5$ and 2.8 Hz), and 1.25 (s, 9H). M.E. m/z (%): 194 (0.1, M^+); 163 (3); 138 (10); 106 (83); 75 (62.5) and 57 (100).

10. p.f. 50–1°C ($CHCl_3$). IR (KBr) ν_{max}: 3040, 3000, 2950, 2900, 2820, 1600, 1500, 1460, 1370, 1120, 1060 and 1040. ^1H-NMR ($CDCl_3$) δ_{ppm}: 7.30 (m, 5H); 4.81 (part X of an ABX system, 1H, $J = 7.4$ and 3.8 Hz); 4.04 (s, 2H); 3.40 (s, 3H); 3.37 (s, 3H); 2.80 (part AB of an ABX system, 2H, $J = 7.4$ and 3.8 Hz). M.E. *m/z* (%): 228 (0.1, M^+); 106 (22), 91 (100); 75 (14); 58 (5.5).

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