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NUCLEAR MAGNETIC RESONANCE SPECTRA OF TROPIC ACID AND SOME DERIVATIVES

V. S. DIMITROV, S. L. SPASSOV and T. Zh. RADEVA

Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia 13 (Bulgaria)

J. A. LADD

Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT (Gt. Britain)

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ABSTRACT

The NMR spectra of tropic acid, its methyl ester and acetyltropic acid methyl ester were measured at 100 and 220 MHz in various solvents. The spectra were analysed by means of an iterative computer procedure. The results indicate, for all the compounds studied, a predominance of the conformation where the phenyl and hydroxyl (or acetoxyl) groups are in anti-positions to each other. The solvent and concentration effects upon the vicinal coupling constants and hence upon the position of the conformational equilibria are rather weak.

INTRODUCTION

The application of NMR for conformational analysis of substituted ethanes has been the subject of a number of studies during the last two decades — for selected literature on the subject see ref. 1. In most of the investigations the vicinal coupling constant values were the principal source of information concerning the position of the conformational equilibria. In this respect, much more reliable results are obtained for 1,2-di- and 1,1,2-tri-substituted ethanes, for which, in favourable cases (non-degenerate spectra) it is possible to determine the values of the two vicinal constants. Usually the coupling constants are connected with the stereochemistry of the molecule via the Karplus relationship or one of its modifications.

The elucidation of the conformation of tropic acid is of interest mainly on account of its participation as an acidic component in the structure of some physiologically important natural alkaloids such as atropine, scopolamine, etc. The conformation of the aminoalcoholic part of these alkaloids has already been subject to NMR investigations [2], whereas no published results are available for the tropic acid residue.

In the present work, the rotational isomerism of tropic acid (1), its methyl ester (2), and acetyltropic acid methyl ester (3), with respect to the C_2—C_3

bond, has been investigated by means of proton NMR spectroscopy at 100 and 220 MHz.

$R^2O-CH_2-\underset{\underset{Ph}{|}}{CH}-COOR^1$

1 $R^1 = R^2 = H$
2 $R^1 = CH_3$; $R^2 = H$
3 $R^1 = CH_3$; $R^2 = CH_3CO$

EXPERIMENTAL

Tropic acid methyl ester (2)

This compound was prepared by reaction between methyl phenylacetate and paraformaldehyde in dimethylsulfoxide solution in the presence of sodium ethylate [3]. B.p. 125—128 °C/2 mm, $n_D^{25} = 1.5220$; literature values[3]: b.p. 120—125 °C/0.5 mm.

Tropic acid (1)

This acid was obtained by saponification of the ester (2) via boiling with alcoholic sodium hydroxide and subsequent treatment with sulphuric acid, ether extraction and recrystallization from benzene. M.p. 117.5—118 °C; literature values[4]: m.p. 117.5—118.5 °C.

Methyl-d_3 ester of tropic acid (2a)

Tropic acid (1.5 g) was refluxed with 2 ml of methanol-d_4 and one drop of concentrated sulphuric acid for 3 h. Vacuum-distillation yielded the deuterated ester (0.65 g), b.p. 125—128 °C/2 mm, $n_D^{25} = 1.5185$.

Methyl ester of acetyltropic acid (3)

1.8 g (0.01 mol) of tropic acid methyl ester (2) was refluxed with 5.1 g (0.05 mol) of purified acetic anhydride and 4.9 g (0.06 mol) of dried sodium acetate for 5 h. (oil bath temperature 110—125 °C). The mixture was left overnight at +5 °C, then poured into water, extracted with ether, dried over anhydrous magnesium sulphate and fractionated in vacuo. B.p. of the acetyl ester (3), 122.5—124 °C/1 mm, yield 1.4 g (63%).

The identity and purity of all compounds were confirmed by IR and NMR spectra.

Spectra

The NMR spectra of the compounds studied were measured on VARIAN spectrometers, models HA-100 and HR-220 at normal probe temperatures.

The IR spectra were taken on a C.Zeiss-Jena spectrometer, model UR-10.

RESULTS

The 100 MHz NMR spectra of the $-CH_2-\dot{C}H$ fragment of tropic acid and its methyl ester were of the ABC type (Fig. 1). The 220 MHz spectra (Fig. 2) however were suitable for an approximate ABX analysis and the resulting parameters were further refined by iterative least-squares adjustments using the programs LACX (computations carried out at Salford University) and LAOCOON 3 (computations carried out at Sofia) [5]. The values of the chemical shifts and coupling constants thus obtained were used for simulation and iteration of the 100 MHz spectra. The final results, shown in Table 1, are statistically weighted averages over at least four spectra, measured and analysed for each compound in the solvents specified. The error between the

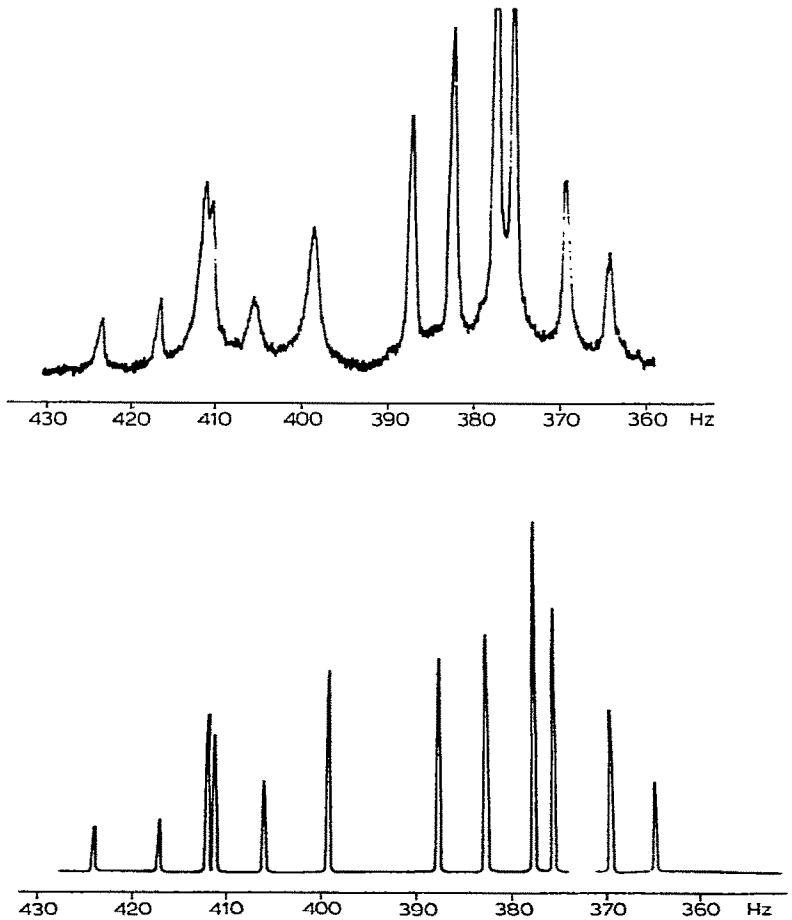

Fig. 1. Experimental (top) and calculated (bottom) 100 MHz NMR spectra of tropic acid methyl-d_3 ester (2a) in methanol-d_4.

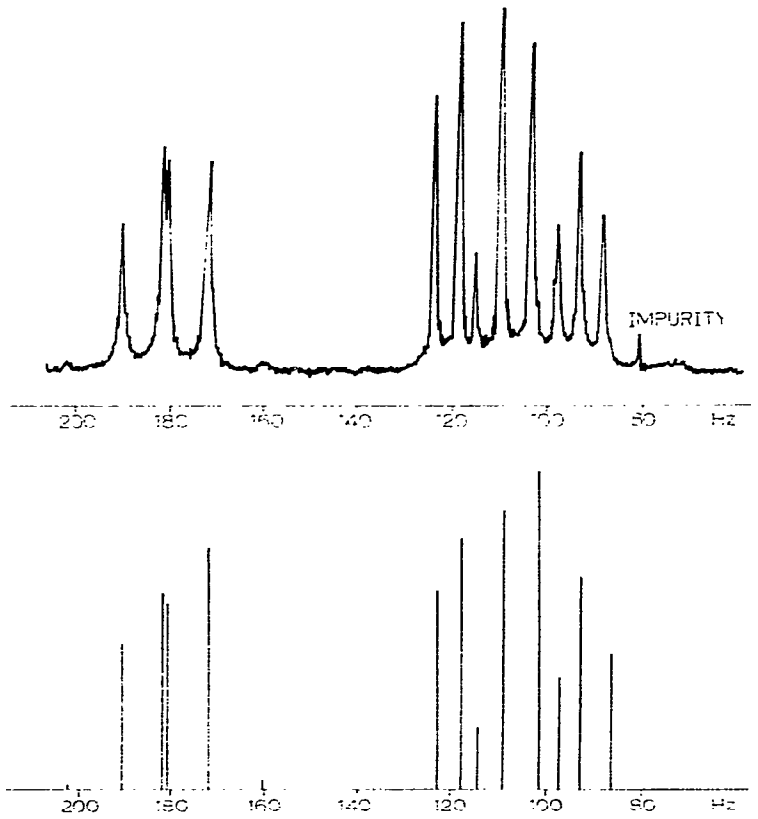

Fig. 2. Experimental (top) and calculated (bottom) 220 MHz NMR spectra of tropic acid methyl-d_3 ester (2a) in methanol-d_4.

experimental and calculated line frequencies was always less than 0.15 Hz. In some solvents the methoxyl signal of ester 2 overlapped the ABC spectrum of the $-CH_2-\underset{|}{C}H$ fragment. The analysis of the spectra was then facilitated by study of the analogous compound with a deuterated methyl group (2a).

An interesting and rather unusual feature of the ABC spectra of compounds 1 and 2 is the fact that the AB part (at higher field) was due to the methine and one of the methylene protons (J_{AB} is positive and hence vicinal), whereas the other methylene proton (C) resonated at lower field. This peculiarity may be explained on conformational grounds, as is discussed below. In the case of the acetylated ester (3) the stronger deshielding effect of the acetoxyl group causes a large downfield shift of the methylene signals, thus rendering the spectrum amenable to a preliminary ABX analysis even at 100 MHz.

DISCUSSION

In order to use the NMR data of tropic acid and its derivatives for con-

TABLE 1

NMR parameters of the $-CH_2-CH$ fragment of tropic acid (1), its methyl (2) and methyl-d_3 (2a) esters and acetyltropic acid methyl ester (3) in various solvents (concentrations 1.5—2 *M*)

Compound	Solvent	Dielectric constant of solvent	Chemical shifts[a,c]			Coupling constants[b,c]		
			ν_A	ν_B	ν_C	J_{AB}	J_{BC}	J_{AC}
1	CD_3OD	32.6	374.29 ± 0.08	377.19 ± 0.13	410.48 ± 0.10	5.55 ± 0.05	8.88 ± 0.05	−10.75 ± 0.06
2	CCl_4	2.2	364.67 ± 0.09	374.64 ± 0.10	403.11 ± 0.14	5.20 ± 0.02	9.13 ± 0.07	−10.61 ± 0.06
	C_6D_6	2.3	376.13 ± 0.20	387.53 ± 0.12	419.71 ± 0.12	5.23 ± 0.03	9.07 ± 0.17	−10.69 ± 0.20
	CS_2	2.6	356.62 ± 0.30	367.53 ± 0.22	395.46 ± 0.26	5.04 ± 0.03	8.21 ± 0.09	− 9.72 ± 0.09
	$CDCl_3$	4.8	376.83 ± 0.05	382.79 ± 0.11	410.66 ± 0.12	5.29 ± 0.01	8.99 ± 0.01	−11.07 ± 0.03
	CD_3OD	32.6	373.81 ± 0.14	381.92 ± 0.14	411.25 ± 0.17	5.54 ± 0.01	9.19 ± 0.03	−10.67 ± 0.01
	$C_6H_5NO_2$	34.8	398.21 ± 0.05	402.67 ± 0.13	430.91 ± 0.09	5.37 ± 0.01	8.71 ± 0.03	−10.88 ± 0.04
2a	CD_3OD	32.6	373.19 ± 0.10	381.08 ± 0.07	410.21 ± 0.07	5.37 ± 0.10	9.44 ± 0.15	−10.80 ± 0.16
3	$CDCl_3$	4.8	432.74 ± 0.14	394.75 ± 0.11	457.38 ± 0.16	5.74 ± 0.03	9.33 ± 0.01	−10.92 ± 0.01

[a]In Hz relative to internal TMS at 100 MHz. Other signals: 1 — 730 (Ph); 2 — (in $CDCl_3$, 0.5 *M*), 268 (OH), 366 (OCH_3), 720 (Ph); 3 — 197 (CCl_3), 365 (OCH_3), 730 (Ph).

[b]In Hz.

[c]Everywhere in this Table root mean square errors of the parameters are given. The standard deviations obtained by the individual spectrum analysis were used to calculate the weighting factors in the averaging procedure: the smallest standard deviation corresponds to unity weighting factor.

formational purposes, it is first necessary to assign the calculated parameters to the respective protons of the $-CH_2-\dot{C}H$ fragment. It is well known from the literature that the vicinal couplings in similar systems are positive, whereas the geminal ones are negative. Thus from the data in Table 1 the assignment of the methine proton (B) follows directly. It is much more difficult to decide which of the methylene protons will correspond to A or C, respectively. For this purpose, consider two sets of staggered conformations of the compounds 1—3, corresponding to the two possible ways ((a) and (b)) of indexing the methylene protons (Fig. 3).

The observed vicinal constants J_{AB} and J_{BC} are of course, weighted averages of the corresponding constants in the individual conformers:

$$J_{AB} = N_I J^I_{AB} + N_{II} J^{II}_{AB} + N_{III} J^{III}_{AB} \quad (1)$$

$$J_{BC} = N_I J^I_{BC} + N_{II} J^{II}_{BC} + N_{III} J^{III}_{BC} \quad (2)$$

$$N_I + N_{II} + N_{III} = 1 \quad (3)$$

Here N_I, N_{II}, N_{III} are the mole fractions of the respective conformers. Conformer III can be disregarded on steric grounds (two gauche non-bonded group interactions versus one in the other conformers*). The experimental data (Table 1) also indicate that form III cannot be favoured since, in such a

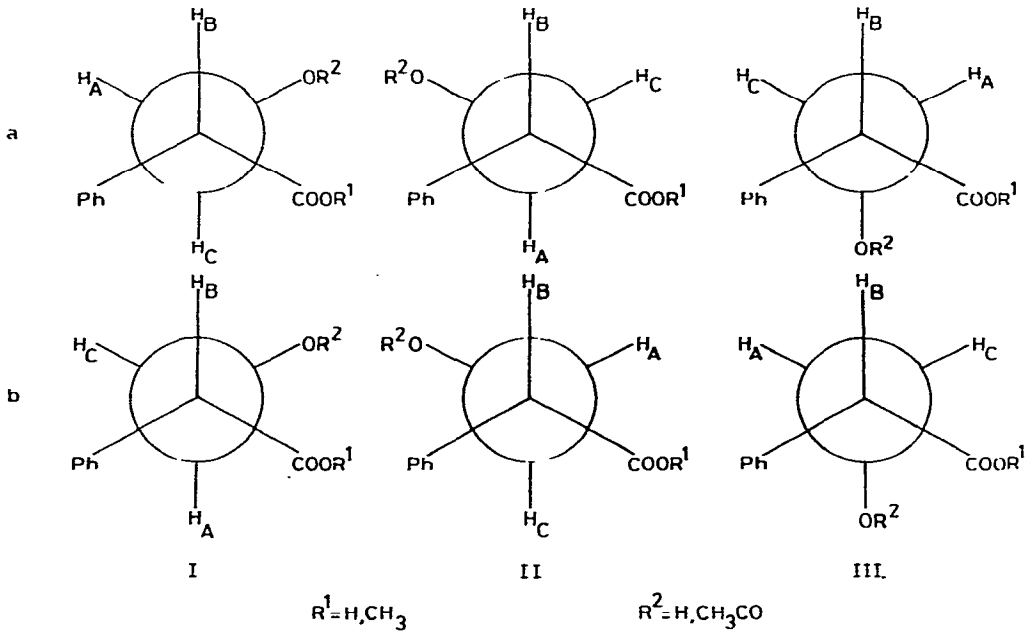

Fig. 3. Staggered conformations of tropic acid and its derivatives.

*For an alternative explanation of the instability of III, based on the gauche-hydrogen interactions, see ref. 6.

case, the values of both vicinal couplings J_{AB} and J_{BC} should be much lower ($\leqslant$ 4 Hz).

One may approximately assume equality of the anti-, and of the gauche-couplings in the different conformers:

$$J^{I}_{BC} = J^{II}_{AB}\,;\; J^{I}_{AB} = J^{II}_{BC}\,;\; J^{III}_{AB} = J^{III}_{BC} \qquad (4)$$

Subtracting eqn. (1) from eqn. (2), and taking into account eqns. (4), one obtains

$$J_{BC} - J_{AB} = (N_I - N_{II})\,(J^{I}_{BC} - J^{I}_{AB}) \qquad (5)$$

According to experiment (Table 1), in all cases $J_{BC} > J_{AB}$. On the other hand, it is always true that $J_{anti} > J_{gauche}$ (Karplus rule in qualitative form). In such a case, if the assignment of the methylene protons in set (a) is correct, then $J^{I}_{BC} > J^{I}_{AB}$, and hence $N_I > N_{II}$, i.e. conformer I(a) is the favoured one. In the alternative case (set (b)), $J^{I}_{BC} < J^{I}_{AB}$, and $N_I < N_{II}$, i.e. conformer IIb is preferred.

The choice between the sets (a) and (b) can be made by considering the chemical shifts of the methylene protons. An inspection of the conformational structures (Fig. 3) reveals that the difference in shielding of the methylene protons should be determined by the orientation of the phenyl and COOR-substituents (R = H,CH_3). It is known that in similar systems [1, 7] the gauche-protons are shielded by the phenyl and deshielded by the COOR groups.

Then, if set (a) is the correctly assigned one, the relationship $\nu_C > \nu_A$ should hold, since H_C will be deshielded with respect to H_A in the favoured conformation I(a), and also in II(a). Otherwise, if set (b) is the correctly chosen one, the relationship will be $\nu_C < \nu_A$. Since the experimental data (Table 1) are compatible with the first case, it can finally be concluded that assignment (a) is correct and the favoured conformer is I(a), i.e. with anti-located phenyl and hydroxyl (or acetoxyl) groups.

The investigation of the solvent effect on the NMR spectral parameters of the tropic acid ester (2) showed that the vicinal coupling constants are only slightly influenced by this factor (Table 1). There is no clear dependence between the polarity of the solvent and coupling constants values. On the basis of these results it can be concluded that the solvent effect on the conformational equilibrium of the ester (2) is rather weak.

The influence of concentration on the spectral parameters was studied in the case of the deuterated ester (2a). The results for the coupling constants are presented in Table 2. By comparison of these data with Table 1, it is seen that the changes in the vicinal coupling values are rather small. For the solutions in chloroform-d, the tendency, if any, is towards an increase of the amount of conformer I at lower concentrations.

In order to estimate the conformer populations from eqns. (1)—(3), one must know the values of the anti- and gauche-couplings in the individual conformers. In our opinion, there is no reliable way at present for calcula-

TABLE 2

Coupling constants (Hz) obtained from the analysis of 100 MHz NMR spectra of tropic acid methyl-d_3 ester taken at various concentrations

Solvent	Concentration (M)	J_{AB}	J_{BC}	J_{AC}
$CDCl_3$	0.5	5.38 ± 0.12	9.05 ± 0.11	−11.24 ± 0.13
$CDCl_3$	0.05	5.05 ± 0.18	9.17 ± 0.24	−11.39 ± 0.22
C_6D_6	0.5	5.17 ± 0.85	8.95 ± 0.13	−10.65 ± 0.92

tion of these values*. The principal difficulties lie in the complicated effect of substituent electronegativities and the uncertain dihedral angles.

On the basis of a number of published data for structurally similar compounds [1, 9—12], we feel that the values J_{anti} = 11—12 Hz and J_{gauche} = 3—4 Hz are good approximations for the trans- and gauche-couplings in the compounds 1—3. The values of the gauche-couplings in conformer III will probably be lower than those in conformers I and II, owing to the oriented effect of electronegative substituents [13]. Taking all these considerations into account, eqns. (1)—(3) were used to calculate the conformational distribution of tropic acid and its derivatives for various combinations of the coupling constants values within the above mentioned limits. The results are summarized in Table 3.

The conformational populations found for tropic acid (1) and its ester (2) are very similar and, in view of the approximations involved, the small differences cannot be unequivocally interpreted. Although the results for the acetylated ester (3) are not very different, there is nevertheless a marked

TABLE 3

Conformational population of tropic acid (1), its methyl ester (2), and acetyltropic acid methyl ester (3)

Combination number	Individual couplings (Hz)[a]			1 in CD_3OD J_{AB} = 5.55 Hz J_{BC} = 8.88 Hz			2 in $CDCl_3$ J_{AB} = 5.30 Hz J_{BC} = 9.00 Hz			3 in $CDCl_3$ J_{AB} = 5.74 Hz J_{BC} = 9.33 Hz		
	a	b	c	N_I	N_{II}	N_{III}	N_I	N_{II}	N_{III}	N_I	N_{II}	N_{III}
C1	4	12	3	0.63	0.21	0.16	0.65	0.18	0.17	0.68	0.23	0.09
C2	4	12	4	0.61	0.19	0.20	0.63	0.16	0.21	0.66	0.22	0.12
C3	3	12	3	0.65	0.28	0.06	0.66	0.26	0.08	0.70	0.30	−0.01
C4	4	11	3	0.71	0.23	0.06	0.72	0.20	0.08	0.76	0.25	−0.01
C5	4	11	4	0.70	0.22	0.08	0.71	0.19	0.10	0.76	0.25	−0.01
C6	3	11	3	0.73	0.32	−0.05	0.75	0.29	−0.04	0.79	0.34	−0.13
Average (C6 rejected)				0.66	0.23	0.11	0.67	0.20	0.13	0.71	0.25	0.04

[a] $a = J^{I}_{AB} = J^{II}_{BC}$; $b = J^{I}_{BC} = J^{II}_{AB}$; $c = J^{III}_{AB} = J^{III}_{BC}$.

*For some recent attempts, whose general applicability has not yet been proven, see ref. 8 and references therein.

increase in the amounts of conformers I and II at the expense of III. This fact is already reflected in the higher values found for the averaged vicinal coupling constants J_{AB} and J_{BC}.

In order to estimate the relative energies of the individual conformers, it is necessary to consider not only the steric and polar group interactions involved, but also the possibilities for hydrogen bond formation with participation of the hydroxyl group.

For this purpose, the IR spectrum of tropic acid ester (2) was studied. The compound gave a very broad band in the region 3250—3650 cm^{-1} (bonded OH). In a 1% solution in chloroform, besides the broad band for bonded OH (centred at 3450 cm^{-1}), there was also an intense band at 3615 cm^{-1} (free OH). The latter maximum was prominent also in the spectrum taken at low concentration ($3 \cdot 10^{-3}$ *M*) in carbon tetrachloride. This spectrum however revealed also a broader band at ca. 3570 cm^{-1} (Fig. 4) which can be attributed to an intramolecular hydrogen bond between the hydroxyl and carbonyl groups. Very similar spectra were observed earlier in the case of the diastereomeric esters of 3-hydroxy-2,3-diphenylpropionic acids [14].

Inspection of the conformational structures (Fig. 3) reveals that formation of an intramolecular hydroxyl—carbonyl bond is possible in conformations I and III. Here the question that arises is to what degree does the hydrogen-bond stabilization contribute to the predominance of I in the equilibrium. In our opinion, the preference for conformation I is based mainly on other factors (more favourable steric and/or polar group interactions), whereas the hydrogen-bond formation plays a secondary role. The reasons for this assumption are the following. First, the intensity ratio between the intramolecularly bonded OH (3570 cm^{-1}) and the free OH (3615 cm^{-1}), although not precisely measurable from the spectrum, is clearly in favour of the latter (Fig. 4). Second, the results for the acetylated ester (3) (no hydrogen bonding) indicate an even higher amount of form I.

Apparently the intramolecular hydrogen bonding is, to a certain extent, important for the stabilization of conformer III, since in the absence of the former its amount becomes negligible (Table 3).

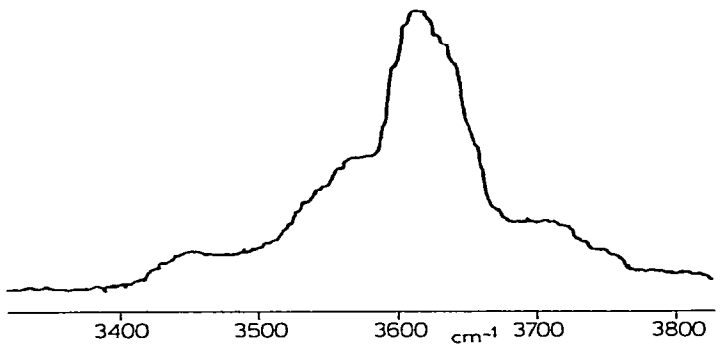

Fig. 4. Infrared spectrum (hydroxyl stretching band) of tropic acid methyl ester (2). Concentration $3 \cdot 10^{-3}$ *M* in carbon tetrachloride.

It might be argued that the comparison between NMR and IR data could not be straightforward because of the large differences in concentration. While this is principally true, in view of the relatively small concentration effect on the vicinal coupling constants in the NMR spectra of tropic acid ester (2), we tend to believe that such a comparison might be justified in that particular case.

Finally, the results from the present NMR study of tropic acid, its methyl ester, and the acetyltropic acid methyl ester lead to the conclusion that, for all these compounds, the conformer with anti-located phenyl and hydroxyl (or acetoxyl) groups dominates (65—70%) in solutions of both polar and non-polar solvents.

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