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178. **Motohiro Nishio and Teiichiro Ito** : Nuclear Magnetic Resonance Studies of Sulfur Compounds. I. The Preparation of α-(Alkylsulfinyl)cinnamic Acid Derivatives and Their Nuclear Magnetic Resonance Spectra.

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In the previous papers,[1,2] we reported the preparation of α-methylthio-substituted cinnamic acids (I) and their geometrical isomerism. Synthetic penicillins derived from these acids exhibited interesting biological activities on the microorganisms which are resistant to the penicillin G.

To obtain more effective penicillins, the authors have undertaken to synthesize other derivatives whose structures are closely related to mother compounds. In this paper we wish to report the synthesis of the α-(alkylsulfinyl)cinnamic acids (II) which are easily derived from α-(alkylthio)cinnamic acids (I) by simple oxidation procedure (Chart 1), and an interesting observation obtained from an examination of nuclear magnetic resonance spectra of these compounds.

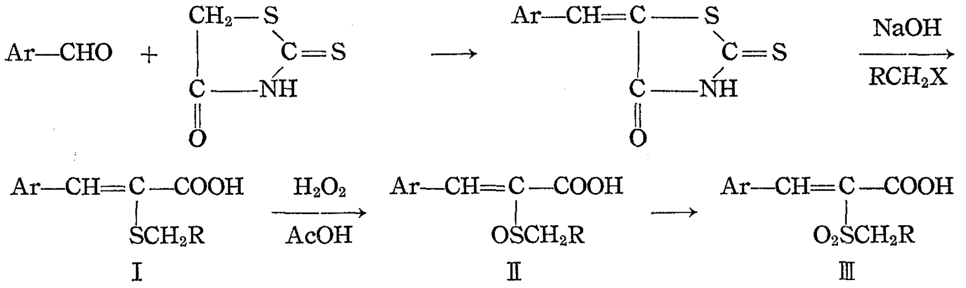

Chart 1.

We employed α-(alkylthio)cinnamic acids (I) as the starting materials, which were prepared by the hydrolysis of various derivatives of benzylidene rhodanine, followed by alkylation with alkylhalides.[1,2] Benzylindene rhodanines are obtained by the condensation of various aromatic aldehydes with rhodanine. α-(Alkylthio)cinnamic acids are dissolved in acetic acid and treated with 30% aqueous hydrogen peroxide to give corresponding sulfoxides. The reaction conditions should be strictly controled because of the fact that the corresponding sulfones (III) are obtained if the reaction time is too long or the reaction temperature is too high. The yields of sulfoxides, however, are excellent if appropriate reaction conditions are employed. Fortunately, the infrared absorption band in the range of 1000～1050 $\mathrm{cm^{-1}}$ attributed to S-O stretching mode makes it easy to distinguish sulfoxides from the corresponding sulfones (III) or sulfides (I).

The geometrical configurations of α-(alkylthio)cinnamic acids (I) are already established to be *trans* except that which corresponds to IId (*cis*) from various data including the nuclear magnetic resonance spectra.[2]

The nuclear magnetic resonance data of the sulfoxides (II) which we have synthesized are listed in Table I.

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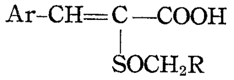
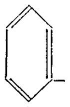
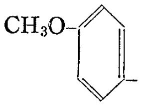
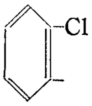
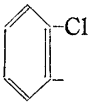
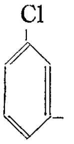
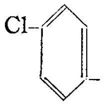
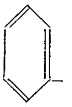
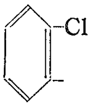
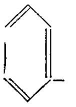
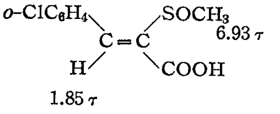
[1] T. Ito, T. Ishii, M. Nishio : Agr. Biol. Chem., **29**, 728 (1965).

[2] M. Nishio, T. Ito : *Ibid.*, **29**, 732 (1965).

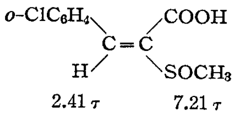
Table I. 
$Ar\text{-}CH{=}C(SOCH_2R)\text{-}COOH$
in $CDCl_3$, TMS as internal reference (τ-values)

	Ar	R	-CH=	$SOCH_2R$	Others	Geometrical configuration
a		H	1.71	7.01		*trans*
b		〃	1.81	7.01	OCH_3 6.12	〃
c		〃	1.59	7.07		〃
d		〃	insoluble in chloroform			*cis*
e		〃	1.81	7.01		*trans*
f		〃	1.80	7.03		〃
g		〃	1.63	7.02		〃
h		C_6H_5	1.75	5.64[b)]		〃
i		〃	1.67	5.72		〃
j		COC_6H_5	1.73	5.18[a)]		〃

a) AB-quartet, J=15.6 c.p.s., $\nu_A-\nu_B=23.8$ c.p.s.
b) singlet (in acetone, however, AB-quartet of J=15.9 c.p.s., $\nu_A-\nu_B=18.5$ c.p.s.)



IIc



IId

in $(CD_3)_2SO$

It will be safely assumed that the inversion of geometrical configuration was not occurred in this mild oxidative condition. On examining the nuclear magnetic resonance spectra, it is shown that all olefinic protons appear as 1-H singlets in the region of magnetic field of τ=1.59~1.81 (in $CDCl_3$), except that of IId which was insoluble in this solvent. From this fact, combined with the nuclear magnetic resonance data of corresponding sulfides (I)[2)] (olefinic protons of *trans*-I; 1.78~2.33 τ, *cis*-I; 3.06~3.32 τ), it is shown that the geometrical configurations of these compounds are *trans* except that of IId. In Table I are also included the nuclear magnetic resonance data obtained for IIc and IId in deuteriated dimethyl sulfoxide. The olefinic proton of IIc gives rise to a singlet of $\tau=1.85$, while that of IId appears as a singlet of $\tau=2.41$. From this, it is shown that the geometrical configuration of IId is *cis* and that the diamagnetic deshielding effect of sulfinylmethyl group is smaller, although more important than that of methylthio group, than that of carbonyl group.

Among these compounds, *trans*-α-(phenacylsulfinyl)cinnamic acid (IIj; Ar=C_6H_5, R=COC_6H_5) is distinguished from others in that the methylene proton signals are splitted to exhibit an AB-quartet. On the other hand, *trans*-α-(benzylsulfinyl) cinnamic acid (IIh; Ar=R=C_6H_5) gives rise to a singlet which is assigned to the methylene adjacent to sulfoxide group.

Furthermore, it is very interesting to note that the nuclear magnetic resonance spectrum of IIh exhibited an AB-type quartet in acetone solution (4.78 τ, J=15.9 c.p.s., $\nu_A-\nu_B=18.5$ c.p.s).

There seems to be an interesting relationship between the magnitude of magnetic nonequivalence and chemical structure. Unfortunately, however, *trans*-α-(phenacylsulfinyl) cinnamic acid (IIj) was insoluble in acetone and we could not examine this situation more extensively.

It is well known that two protons in the system $XYZCCH_2$-R are sometimes magnetically nonequivalent due to the absence of symmetric plane on the carbon atom adjacent to the methylene group.

It is a well known fact too, that sulfites, sulfoxides and sulfonium compounds have an asymmetric center on sulfur atom and are mixtures of optically active antipodes. Actually, Finegold[3] reported an "abnormal" splitting in the methylenic absorption region for diethyl sulfite. Kaplan and Roberts[4] analysed the nuclear magnetic resonance spectrum of diethyl sulfite and showed that the pattern obtained with this compound was well explained as ABC_3 spin system. Recently, Ōki and Iwamura[5] reported that the dibenzyl sulfites, which have no other magnetic nuclei to interact with methylene protons, gave rise to AB-type quartets and offered an experimental support for the computation result.

From these works, the origin of magnetic nonequivalence of methylene protons in sulfites is well established. In sulfoxides, however, although splittings on nuclear magnetic resonance spectra of methylene protons adjacent to sulfoxide group are reported by several workers,[6~8] convincing experiment to establish the origin of nonequivalence in these compounds have not yet been published.

To confirm the necessity of the existence of sulfoxide group for observable magnetic nonequivalence of methylene protons and to examine the dependence of magnitude of magnetic nonequivalence on solvent, we have synthesized the following compounds (Chart 2) and examined their nuclear magnetic resonance spectra, where $n=0$

$C_6H_5SO_nCH_2C_6H_5$
IV

$(C_6H_5SO_nCH_2)_2$
V

$C_6H_5SO_nCH_2COC_6H_5$
VI

$C_6H_5CH_2SO_nCH_2COC_6H_5$
VII

$C_6H_5SO_nCH_2CONHC_6H_4CH_3(p)$
VIII

Chart 2.

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3) H. Finegold: Proc. Chem. Soc., **1960**, 283.
4) F. Kaplan, J.D. Roberts: J. Am. Chem. Soc., **83**, 4668 (1961).
5) M. Ōki, H. Iwamura: Bull. Chem. Soc. Japan, **35**, 1428 (1962).
6) T.D. Coyle, F.G.A. Stone: J. Am. Chem. Soc., **83**, 4138 (1961).
7) J.S. Waugh, F.A. Cotton: J. Phys. Chem., **65**, 562 (1961).
8) K. Griesbaum, A.A. Oswald, B.E. Hudson: J. Am. Chem. Soc., **85**, 1969 (1963).

to 2 corresponding respectively to sulfides (a), sulfoxides (b) and sulfones. Sulfoxides and sulfones are easily distinguished by their infrared spectra (SO; near 1050 cm^{-1}, SO_2; near 1150 cm^{-1}).

The data obtained by examining their nuclear magnetic resonance spectra in deuterochloroform, carbon tetrachloride and in acetone are listed in Tables Ⅱ and Ⅲ.

In deuterochloroform or carbon tetrachloride, all these compounds except Ⅵb, Ⅶb, and Ⅷb exhibited "normal" patterns with singlets in methylene region. On the other hand, the nuclear magnetic resonance spectra of Ⅵb and Ⅷb displayed AB-type quartets, and in the nuclear magnetic resonance spectrum of Ⅶb, a singlet assigned to the AB-methylene and an AB-quartet assigned to the A′B′-methylene were observed (Fig. 1).

In acetone solution, however, the methylene proton spectra of Ⅵb and Ⅶb (A′B′-methylene) reduced to singlets. On the contrary, the two protons in Ⅳb and the AB-methylene of Ⅶb are nonequivalent in this solvent and displayed AB-type spectra (Fig. 2).

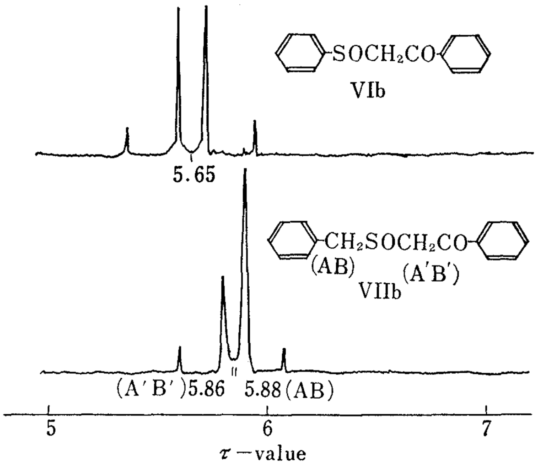


Fig. 1. Nuclear Magnetic Resonance Spectra of Phenyl Phenacyl Sulfoxide (Ⅵb) and Benzyl Phenacyl Sulfoxide (Ⅶb) in Deuterochloroform at 60 Mc.p.s.

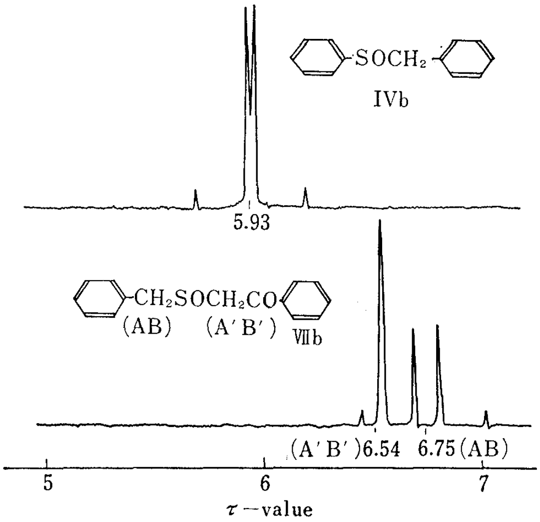


Fig. 2. Nuclear Magnetic Resonance Spectra of Phenyl Benzyl Sulfoxide (Ⅳb) and Benzyl Phenacyl Sulfoxide (Ⅶb) in Acetone at 60 Mc.p.s.

Table Ⅱ. Chemical Shifts of Methylene Protons in Deuterochloroform (or Carbon Tetrachloride)

	$n=0$ (a)	$n=1$ (b)	$n=2$ (c)
$C_6H_5SO_nCH_2C_6H_5$ (Ⅳ)		6.09	5.88$^{d)}$
$(C_6H_5SO_nCH_2)_2$ (Ⅴ)	6.98$^{d)}$	7.02	6.53
$C_6H_5SO_nCH_2COC_6H_5$ (Ⅵ)		5.65 (AB-quartet)$^{a)}$	5.35$^{d)}$
$C_6H_5CH_2SO_nCH_2COC_6H_5$ (Ⅶ) (AB) (A′B′)			
CH_AH_B	6.32	5.88	5.87$^{d)}$
$CH_{A'}H_{B'}$	6.22	5.86 (AB-quartet)$^{b)}$	5.69
$C_6H_5SO_nCH_2CONHC_6H_4CH_3(p)$ (Ⅷ)			
CH_3 (aromatic)	7.70	7.76	7.68
CH_2	6.26	6.33 (AB-quartet)$^{c)}$	5.84

a) J=14.1 c.p.s., $\nu_A-\nu_B$=14.7 c.p.s.
b) J=14.0 c.p.s., $\nu_A-\nu_B$=7.8 c.p.s.
c) J=13.9 c.p.s., $\nu_A-\nu_B$=15.2 c.p.s.
d) In CCl_4, all values but otherwise noted are single peaks. Chemical shifts are reported in τ-values.

TABLE Ⅲ. Chemical Shifts of Methylene Protons in Acetone

	$n=0$ (a)	$n=1$ (b)	$n=2$ (c)
$C_6H_5SO_nCH_2C_6H_5$ (Ⅳ)		5.93 (AB-quartet)a)	5.50
$(C_6H_5SO_nCH_2)_2$ (Ⅴ)			6.45
$C_6H_5SO_nCH_2COC_6H_5$ (Ⅵ)	5.50	6.01	4.94
$C_6H_5CH_AH_BSO_nCH_{A'}H_{B'}COC_6H_5$ (Ⅶ)			
CH_AH_B	6.22	6.75 (AB-quartet)b)	5.35
$CH_{A'}H_{B'}$	6.17	6.54	5.24

All data but otherwise noted are single peaks. Chemical shifts are reported in τ-values.

a) J=12.9 c.p.s., $\nu_A-\nu_B$=5.4 c.p.s.

b) J=13.0 c.p.s., $\nu_A-\nu_B$=12.2 c.p.s.

On the other hand, all sulfides (Ⅳa～Ⅷa) and sulfones (Ⅳc～Ⅷc) exhibited "normal" patterns in methylene region in all conditions examined (see Tables Ⅱ and Ⅲ).

From these observations, it is concluded that the nuclear magnetic resonance spectra of the methylene of Ⅳb and the AB-methylene of Ⅷb in carbon tetrachloride, and those of Ⅵb and the A′B′-methylene of Ⅷb in acetone are not real singlets. According to the small chemical shift difference between methylene protons, they are observed as apparent singlets.

As far as the above data are concerned, it is concluded that the magnitude of magnetic nonequivalence of methylene protons adjacent to a carbonyl group is large in chloroform and small in acetone, and the reverse is true for the magnitude of magnetic nonequivalence of methylene protons which are bonded directly to a phenyl group.

These results indicate also that, the existence of an asymmetric sulfur atom is not the sufficient condition but is a prerequisite for observable nonequivalence of methylene protons. We are not certain why the magnitude of magnetic nonequivalence is suffered from such a drastic dependence on the solvent employed.

Sulfoxides as obtained above, which have no magnetic nuclei to interact with methylene protons, may provide a sensitive method of examining problems such as the substituent effect or solvent effect of the geminal coupling constants and on the magnetic nonequivalence, because this system contains only two coupling protons facilitating to obtain the desired spectral parameters by extremely simple AB-analysis. Moreover, there is another advantage that the systematic synthesis of sulfoxides $RSOCH_2$-R′, is extremely easier than the synthesis of corresponding carbon system $XYZCCH_2$-R′. By introducing various substituents R′ and employing various solvents, it will be possible to examine the influences reflected in spectral parameters.

Substituent effect and solvent effect on geminal coupling constants and on magnetic nonequivalence, employing sulfoxides as models, will be reported elsewhere.

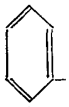
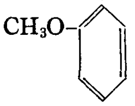
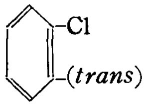
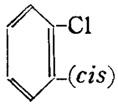
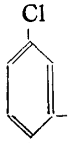
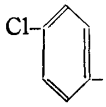
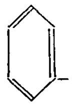
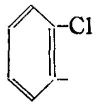
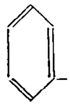
Experimental

The nuclear magnetic resonance spectra were obtained with a Japan Electron Optics Laboratory C-60 high resolution NMR spectrometer (60 Mc.). Measurements were made on 5% or saturated solutions with tetramethylsilane as internal reference at the operating temperature of the instrument. Chemical shifts are reported in τ-values and coupling constants in c.p.s.

Melting points are uncorrected.

α-(Alkylsulfinyl)cinnamic Acid Derivatives (IIa～j)——All these compounds were prepared by treating the corresponding sulfides (Ia～j) with equimolecular amount of 30% H_2O_2 in AcOH at room temperature. After standing for 2～3 hr., the reaction mixture was poured into H_2O and the resulting precipitate was filtered, washed with H_2O and dried. Recrystallization from EtOH afforded pure samples. Their melting points and analytical data were summarized in Table Ⅳ.

Table IV.

	Ar	R	m.p.	Analysis (%)					
				Calcd.			Obs.		
			(°C)	C	H	S	C	H	S
a		H	143	57.2	4.76	15.2	57.28	4.57	15.18
b		〃	147	55.0	5.00	13.3	54.70	5.34	13.59
c		〃	174	49.0	3.68		49.55	3.64	
d		〃	165	49.0	3.68		49.18	3.52	
e		〃	130	49.0	3.68		49.20	3.95	
f		〃	136	49.0	3.68		48.69	3.95	
g		〃	117	44.4	3.70	29.6	43.79	3.23	29.79
h		C_6H_5	179	67.2	4.90	11.2	66.25	5.19	11.13
i		〃	160	60.6	4.06		59.63	4.31	
j		COC_6H_5	121	65.0	4.46	10.2	65.38	4.79	10.44

Benzyl Phenyl Sulfoxide (IVb)——To a solution of 1 g. of benzyl phenyl sulfide (IVa) in 5 ml. of AcOH, 1.2 ml. of 30% aqueous H_2O_2 was added dropwise with stirring at room temperature. After standing for 1 hr., it was diluted with 10 ml. of H_2O. The precipitated crystals were filtered, washed with H_2O and dried. Yield, 750 mg. Recrystallization from EtOH gave white needles, m.p. 127°.

Benzyl Phenyl Sulfone (IVc)——To a solution of 1 g. of IVa in 7 ml. of AcOH, 2.5 ml. of 30% aqueous H_2O_2 was added and heated with stirring at 80° for 3 hr. On adding H_2O, the benzylphenylsulfone precipitated immediately. It was filtered off and recrystallized from EtOH to give white needles, 800 mg., m.p. 147°.

1,2-Bis(phenylthio)ethane (Va)——To a solution of 2.2 g. of thiophenol in 20 ml. of aqueous alkali (NaOH 1 g. in H_2O), 1.90 g. of 1,2-dibromoethane was added dropwise with stirring at room temperature. A little of EtOH was added, and it was heated at 90° for 1 hr. After standing for 1 hr., it was diluted with 20 ml. of H_2O. The precipitate was filtered, washed with H_2O and dried. Yield, 2.0 g. Recrystallization from AcOH gave white needles, m.p. 75°. *Anal.* Calcd. for $C_{14}H_{14}S_2$: C, 68.3; H, 5.69; S, 26.0. Found : C, 68.07; H, 5.78; S, 25.36.

1,2-Bis(phenylsulfinyl)ethane (Vb)——To a solution of 500 mg. of Va in 3 ml. of AcOH, 1 ml. of 30% aqueous H_2O_2 was added dropwise with stirring at room temperature. After standing for 2 hr. at room temperature, it was diluted with H_2O. The precipitated crystals were filtered, washed with H_2O and dried. Recrystallization from AcOH gave white crystals, 230 mg., m.p. 160°. *Anal.* Calcd. for $C_{14}H_{14}$-

O_2S_2 : C, 60.4; H, 5.04; S, 23.0. Found : C, 59.92; H, 5.02; S, 23.06

1,2-Bis(phenylsulfonyl)ethane (Vc)——To a solution of 500 mg. of Va in 3 ml. of AcOH, 2 ml. of 30% aqueous H_2O_2 was added. It was heated at 75° for 1 hr. On cooling, white crystalline product precipitated. It was filtered off and recrystallized from AcOH to give white prisms, 130 mg., m.p. 169°. *Anal.* Calcd. for $C_{14}H_{14}O_4S_2$: C, 54.2; H, 4.52; S, 20.6. Found : C, 54.82; H, 4.76; S, 21.02.

2-(Phenylsulfinyl)acetophenone (VIb)——To a solution of 1 g. of 2-(phenylthio)acetophenone (VIa, m.p. 58°) in 5 ml. of AcOH, 1.2 ml. of 30% aqueous H_2O_2 was added with stirring at room temperature. After standing for 3 hr., it was diluted with 10 ml. of H_2O. On cooling, the precipitated oily product solidified slowly. It was recrystallized from EtOH-H_2O to give white needles, 800 mg., m.p. 81°. *Anal.* Calcd. for $C_{14}H_{12}O_2S$: C, 69.0; H, 4.92; S, 13.1. Found : C, 68.81; H, 5.09; S, 13.24.

2-(Phenylsulfonyl)acetophenone (VIc)——To a solution of 3 g. of VIa in 10 ml. of AcOH, 4 ml. of 30% aqueous H_2O_2 was added. The mixture was heated at 70° for 2 hr. On adding H_2O, the 2-(phenylsulfonyl)acetophenone (VIc) precipitated. It was filtered off and recrystallized to give white needles, 2.5 g., m.p. 97°. *Anal.* Calcd. for $C_{14}H_{12}O_3S$: C, 64.7; H, 4.62; S, 12.3. Found : C, 63.89; H, 4.90; S, 12.14.

2-(Benzylthio)acetophenone (VIIa)——To a solution of 1.24 g. of benzylmercaptan in aqueous alkali (NaOH 500 mg. in 5 ml. of H_2O), 2.0 g. of 2-bromoacetophenone was added. A little of EtOH was added, and the mixture was heated at 95° for 1 hr. On cooling, pale yellow crystalline product precipitated. It was filtered, washed with H_2O and recrystallized from AcOH to give 1.95 g. of VIIa, m.p. 94°. *Anal.* Calcd. for $C_{15}H_{14}OS$: C, 74.4; H, 5.79; S, 13.2. Found : C, 73.91; H, 5.49; S, 13.11.

2-(Benzylsulfinyl)acetophenone (VIIb)——To a solution of 500 mg. of VIIa in 3 ml. AcOH, 0.5 ml. of 30% aqueous H_2O_2 was added dropwise with stirring at room temperature. After standing for 3 hr., it was diluted with 5 ml. of H_2O. White crystalline product formed was filtered off and recrystallized from AcOH-H_2O to give white needles, 450 mg., m.p. 131°. *Anal.* Calcd. for $C_{15}H_{14}O_2S$: C, 69.8; H, 5.43; S, 12.4. Found : C, 68.67; H, 5.79; S, 12.75.

2-(Benzylsulfonyl)acetophenone (VIIc)——To a solution of 500 mg. of VIIa in 5 ml. of AcOH, 1 ml. of 30% aqueous H_2O_2 was added. It was heated at 75° for 1 hr. On cooling, white crystalline product was separated. It was filtered off and recrystallized from AcOH to give white prisms, 550 mg., m.p. 107°. *Anal.* Calcd. for $C_{15}H_{14}O_3S$: C, 65.7; H, 5.12; S, 11.7. Found : C, 65.55; H, 5.20; S, 11.65.

2-(Phenylthio)-*p*-acetotoluide (VIIIa)——To a solution of 2 g. of *p*-toluidine in 15 ml. of ether, 1.5 ml. of phenylthioacetic acid chloride was added. Pale yellow crystalline product formed was filtered, washed with a small amount of ether and dried. Yield, 2.5 g., m.p. 124°.

2-(Phenylsulfinyl)-*p*-acetotoluide (VIIIb)——To a solution of 1 g. of VIIIa in 7.5 ml. of AcOH, 1.2 ml. of 30% aqueous H_2O_2 was added at room temperature. After standing for 0.5 hr., it was diluted with H_2O. White crystalline product was filtered, washed with H_2O and recrystallized from EtOH-H_2O. Yield, 400 mg., m.p. 122°.

2-(Phenylsulfonyl)-*p*-acetotoluide (VIIIc)——To a solution of 200 mg. of VIIIa in 2 ml. of AcOH, 1 ml. of 30% aqueous H_2O_2 was added. The mixture was heated at 70° for 3 hr. On adding H_2O, pale yellow crystalline product was precipitated. It was filtered, washed with H_2O and recrystallized from EtOH-H_2O to give pale yellow needles, 120 mg., m.p. 148° (decomp.).

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Summary

The synthesis of α-(alkylsulfinyl)cinnamic acid derivatives and the determination of their geometrical configuration by nuclear magnetic resonance method were described. In this connection, the nuclear magnetic resonance spectra of typical sulfides, sulfoxides and sulfones were measured in deuterochloroform, carbon tetrachloride and in acetone. It was shown that the methylene protons adjacent to the sulfinyl group are magnetically nonequivalent and the magnetic nonequivalence of these protons depends markedly on the nature of solvent.

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