207. Circular Dichroism of Some Isomeric Alkyl Pyridines

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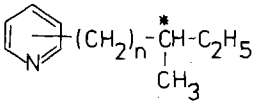
(28.VI.82)

Summary

The UV. and CD. spectra of the optically active 2-, 3- and 4-(1-methylpropyl)-pyridines (**1a, b, c**) and of the corresponding (2-methylbutyl)pyridines (**2a, b, c**) have been investigated in hexane at RT. and at −85°, in hexane/TFA and in aqueous HCl-solution. In **1c** and **2c** both the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ transitions are optically active, an $n \rightarrow \pi^*$ transition being located above 265 nm. The position and the sign of the CD. bands are greatly influenced by the position and the nature of the alkyl substituent.

In the course of our research on optically active stereoregular polyalkenes containing aromatic chromophores [1] [2], we needed more information about the chiroptical properties of the pyridine chromophore. Optically active pyridine derivatives with functional groups (*e.g.* OH or NH_2) have been investigated to some extent and their CD. spectra have been reported [3–8]. However, in such cases the position, the intensity, and the sign of the CD. bands can be influenced significantly by shifts in conformational equilibria connected with interactions between the functional group and the N-atom of the pyridine. The only reported data [9] about the chiroptical properties of a pyridine derivative without functional groups concern a 2,3-disubstituted conformationally rigid derivative, 5α-cholest-2-eno[3,2-*b*]pyridine, for which a negative CD. band between 280 and 290 nm disappears in the presence of glacial acetic acid; it was postulated that there is a $n \rightarrow \pi^*$ transition red-shifted with respect to the first $\pi \rightarrow \pi^*$ transition.

In order to obtain information about the chiroptical properties of monosubstituted alkyl pyridines in the absence of other functional groups, and particularly about the influence of the position of the substituent on the sign and ellipticity of the CD. bands, we investigated the UV. and CD. spectra of the 2-(**1a**), 3-(**1b**) and 4-(1-methylpropyl)pyridines (**1c**), and of the corresponding 2-methylbutyl derivatives **2a**, **2b** and **2c**.



1 n = 0
2 n = 1

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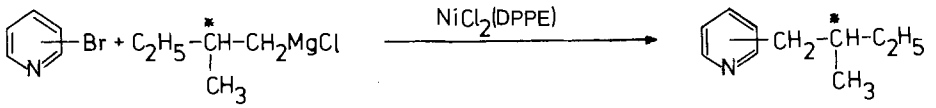
Results and discussion. – The preparation and the relationship between the sign of the optical rotation and the absolute configuration as well as that between optical purity and the value of the rotatory power of the isomeric (1-methylpropyl)-pyridines (**1a,b,c**) have been reported [10]. The 2-, 3- and 4-(2-methylbutyl)-pyridines (**2a,b,c**) were synthesized by nickel-catalyzed cross-coupling between (*S*)-2-methylbutylmagnesium chloride and 2-, 3- or 4-bromopyridine *(Scheme)* [11]. As the chiral center is probably little affected in this reaction [11], we assumed that **2a,b,c** have the same configuration and optical purity as those of the starting 2-methylbutyl chloride.



DPPE = 1,2-Bis(diphenylphosphino)ethane

Tables 1 and *2* give some data concerning the UV. and CD. spectra of the compounds investigated at RT. and at low temperature (−85°), in hexane with and without the addition of trifluoroacetic acid (TFA), and in 1 N HCl. *Figure 1* shows the UV. and CD. spectra of the alkylpyridines and TFA/alkylpyridines (10:1) between 220–290 nm. *Figure 2* reports the UV. and CD. spectra of 3-(2-methylbutyl)pyridine (**2c**) with different ratios of TFA/**2c**. The UV. spectra of the alkyl pyridines **1** and **2** show a broad band in the region investigated; the ε_{max} is larger for the 2-substituted derivatives and decreases as the substituent is moved to the positions 3 and 4. These results are similar to those obtained for the corresponding methyl derivatives [12]. Increasing the amount of TFA in the hexane solutions brings about a strong hyperchromic effect.

Since a similar effect was observed in the spectra of solutions in aqueous 1 N HCl, TFA must protonate the pyridines in hexane; the extent of the dissociation of the ion pair trifluoroacetate/substituted pyridinium is uncertain. When the spectra were measured using different TFA/pyridine ratios, there was a limiting value of the absorption which, for all the pyridines, was reached with ratios of about 10. We assumed that for ratios of 10 or greater, practically only the protonated form of the pyridine derivative was present in solution. The spectra for the different TFA/(substituted pyridine) ratios show that for the 4-substituted derivatives **1c** and **2c**, an almost complete protonation is reached at a lower TFA/pyridine ratio than for the other derivatives.

At least two transitions for the pyridine chromophore should be located in the region of the spectra between 220 and 290 nm; one corresponds to a $\pi \rightarrow \pi^*$ transition of the aromatic system and the other is connected with the $n \rightarrow \pi^*$ transition of the lone pair of the N-atom [3–9] [12]. It has been postulated [3] [4] [6] that there is a third electronic transition related to a second $n \rightarrow \pi^*$ transition; even if theoretical consideration [8] suggests that it should not contribute appreciably to the observed absorptions, the possibility of the existence of bands connected with that transition cannot be neglected also on the basis of recent experimental results[1]).

[1]) Private Communication of *P. Salvadori.*

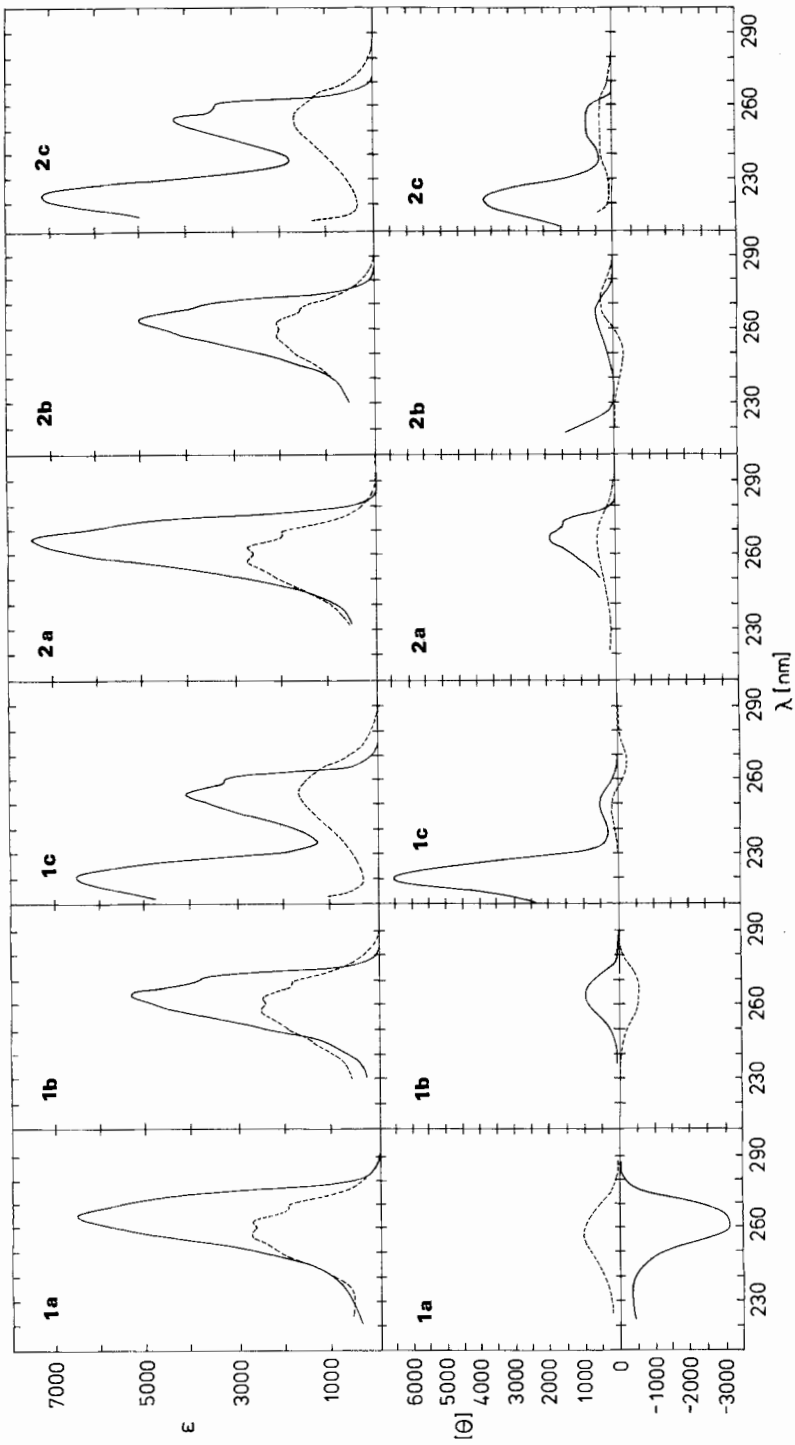


Fig. 1. *UV.* (top) *and CD.* (bottom) *spectra of the 2-, 3- and 4-(1-methylpropyl)-* (**1a,b,c**) *and of 2-, 3- and 4-(2-methylbutyl)pyridines* (**2a,b,c**): (- - - -) alkyl pyridine in hexane; (——) alkyl pyridine and TFA in hexane, molar ratio (TFA)/(alkyl pyridine) = 10

When the UV. and CD. spectra of the pyridines in aprotic solvents were compared with those obtained in glacial acetic acid and aqueous sulfuric acid, the larger absorptions in the longer wavelength regions (290 nm) for the aprotic solvents were attributed to the contribution of an $n \rightarrow \pi^*$ transition [9]. However, these results could also reflect solvent effects [14]. The 4-substituted derivatives **1c** and **2c** in hexane show a definite decrease of absorption in the UV. spectrum

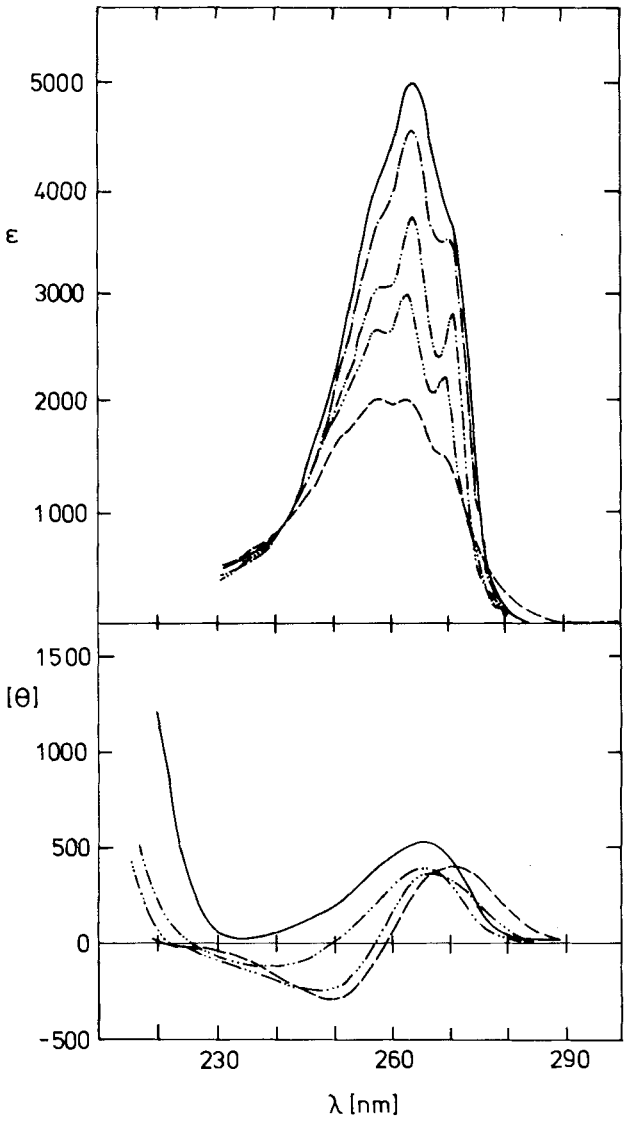


Fig. 2. *UV.* (top) *and CD.* (bottom) *spectra of 3-(2-methylbutyl)pyridine* (**2b**) *in hexane with different TFA/***2b** *ratios (r):* (-----) $r = 0$; (- · - · - · -) $r = 1$; (——) $r = 10$

above 265 nm *(Fig. 1)* in the presence of low concentrations of TFA. As a solvent effect can there be excluded, the results definitely indicate, at least for these two compounds, the presence in this region of an absorption connected with an $n \rightarrow \pi^*$ transition, in agreement with some reported data [3–9].

The band connected to the second $\pi \rightarrow \pi^*$ transition appears below 220 nm and, for all the derivatives investigated, the addition of TFA shifts it towards the red. As expected, the shift is particularly large for **1c** and **2c** *(Fig. 1)*, since protonation should affect the long axis polarized transition (the second $\pi \rightarrow \pi^*$ transition) [15] in all derivatives, but more strongly in the 4-substituted ones. The protonation which is likely to occur would not cause appreciable shifts of the short-axis polarized ($\pi \rightarrow \pi^*$)-transition band at longer wavelength [15] [16]. A similar phenomenon has been observed in aqueous 1 N HCl.

Table 1. *Low energy UV. bands of 2-, 3- and 4-(1-methylpropyl)-* (**1a,b,c**) *and of 2-, 3- and 4-(2-methylbutyl)pyridines* (**2a,b,c**)[a])

Compound	Solvent	mol TFA/ mol pyr	λ_{max}	$\varepsilon_{max} \times 10^{-3}$	Other bands and shoulders
1a	Hexane	0	261	2.8	251 *S*, 256, 268
	Hexane + TFA	10	264	6.6	256 *S*, 270 *S*
	1 N HCl	–	262	7.5	
1b	Hexane	0	261	2.5	252 *S*, 256, 268
	Hexane + TFA	10	264	5.4	258 *S*, 270
	1 N HCl	–	263	6.3	
1c	Hexane	0	255	1.6	251 *S*, 262 *S*
	Hexane + TFA	10	253	4.2	220 *S*, 259 *S*
	1 N HCl	–	251	4.8	220, 259 *S*
2a	Hexane	0	262	2.8	252 *S*, 257, 269
	Hexane + TFA	10	266	7.9	259 *S*, 271 *S*
	1 N HCl	–	265	5.6	
2b	Hexane	0	262	2.7	251 *S*, 257, 268
	Hexane + TFA	10	264	5.1	257 *S*, 269 *S*
	1 N HCl	–	263	5.2	
2c	Hexane	0	256	1.7	251 *S*, 263 *S*
	Hexane + TFA	10	254	4.1	222 *S*, 260
	1 N HCl	–	252	4.1	223

[a]) Solutions $1.0\text{–}4.3 \times 10^{-4}$ M, 2 mm–1 cm cells; [b]) pyr = **1a–2c**.

Despite the unfavourable dissymmetry factor, particularly in the case of **1c**, **2a** and **2b** *(Table 1)*, some interesting features of the CD. spectra could be ascertained. In hexane, in the absence of TFA, the CD. bands are positive for **1a**, **2a** and **2c**, and the sign did not change when the solutions were cooled from 25° to −85°. For **2b**, at RT. and at low temperature, both, negative and positive bands, were observed. For **1b**, a negative band was detected at RT., but both, a positive and a negative band, were observed at −85°. On the contrary, **1c** showed negative and positive bands at RT., but only a positive one at low temperature. For **1c** and

Table 2. *Low energy CD. bands of 2-, 3- and 4-(1-methylpropyl)-* (**1a,b,c**) *and of 2-, 3- and 4-(2-methylbutyl)pyridines* (**2a,b,c**)[a])

Compound	Solvent	mol TFA/mol pyr[b])	Molar ellipticity [θ] At 25° λ_{max}	$[\theta]\times 10^{-3}$	At −85° λ_{max}	$[\theta]\times 10^{-3}$	Dissymmetry factor at 25° $\frac{\Delta\varepsilon}{\varepsilon}\times 10^4$
1a	Hexane	0	257	+1.1	255	+1.2	1.2
	Hexane+TFA	10	261	−3.1			1.4
	HCl (1N)		262	−0.3			
			273	+0.1			
1b	Hexane	0	265	−0.6	252	−0.9	0.7
	Hexane+TFA	10	264	+1.0	278	+0.5	0.6
	HCl (1N)		267	+6.6			
1c	Hexane	0	248	+0.2	241	+0.8	0.6
			267	−0.2			0.7
	Hexane+TFA	10	220	+6.6			10.0
			250	+0.5			0.4
	HCl (1N)		284	+3.8			
			250	+0.8			
2a	Hexane	0	264	+0.5	265	+1.6	0.5
	Hexane+TFA	10	266	+1.9			0.7
	HCl (1N)		269	+0.6			
2b	Hexane	0	249	−0.3	251	−0.3	0.4
			270	+0.4	272	+0.6	0.4
	Hexane+TFA	10	265	+0.5			0.3
	HCl (1N)		262	+0.3			
2c	Hexane	0	252	+0.4	254	+0.5	0.7
	Hexane+TFA	10	222	+3.7			2.0
			255	+0.7			0.5
	HCl (1N)		227	+2.7			
			253	+0.7			

[a]) Solutions $1.0\text{–}4.3\times 10^{-4}$ M, 2 mm, 5 mm or 1 cm cells; [b]) pyr = **1a–2c**.

2a, decreasing the temperature brought about a very large increase in the CD. band *(Table 2)*.

For TFA/pyridine ratios of 10, the CD. band above 240 nm has a positive sign, except for **1a**, which has a negative band and the largest ellipticity observed.

In some cases two CD. maxima of opposite sign were observed above 240 nm, which would indicate that, even if in other cases only one CD. band appears, both the $\pi\rightarrow\pi^*$ and the $n\rightarrow\pi^*$ transitions in the series of compounds are optically active, in agreement with reported information [3–9]. For **1c** and **2c**, on the basis of the disappearance of a CD. band at higher wavelengths and the decrease in absorption in the UV. spectra in the same region due to protonation, the CD. band at longer wavelengths could be attributed to an $n\rightarrow\pi^*$ transition. However, protonation decreases the intensity of the CD. band connected with the $n\rightarrow\pi^*$ transitions as well as of the band connected with the $\pi\rightarrow\pi^*$ transition of the non-protonated species. Therefore the changes in the CD. spectra due to protonation in the absence of a detectable decrease of the UV. absorption in the same region cannot

be unequivocally attributed to the disappearance of bands connected with $n \rightarrow \pi^*$ transitions.

For **1c** and **2b** it is tempting to attribute the CD. band at longer wavelengths, accompanied by the decrease in the UV. intensity in the same region, to an $n \rightarrow \pi^*$ transition. Hence, it would seem that the band connected with an $n \rightarrow \pi^*$ for **2b**, and also that the band connected to the $\pi \rightarrow \pi^*$ transition for **2b** changes its sign upon protonation. Pursuing this line of reasoning, we could also attempt to interpret the cases in which only one CD. maximum appears at RT. However, since with other assumptions, other interpretations are possible, we prefer to avoid further speculation. To obtain reliable information about the sign of the CD. bands connected with the $\pi \rightarrow \pi^*$ and with the $n \rightarrow \pi^*$ transition of all the monosubstituted alkyl pyridines investigated, chiral pyridines having more favorable dissymmetry factors should be investigated.

Experimental Part

Boiling points (b.p.) are uncorrected. GC. analyses were performed on a *Perkin-Elmer 990* gas chromatograph, using 2 m × 2.5 mm SP 1000 2.5% on *Chromosorb G* column at 100–130°. Preparative GC. purification was carried out on a *Perkin-Elmer F 21* gas chromatograph using 5 m × 8 mm SP 1000 15% on *Chromosorb G* column at 180°. Optical rotations were measured on a *Perkin-Elmer 141* polarimeter. UV. spectra were measured on a *Cary 14* spectrophotometer. CD. spectra were measured on a *Jasco J-40 AS* spectropolarimeter. Low temperature CD. spectra were measured using a *Beckman* variable temperature cell holder adapted to hold the strain-free *Hellma* cylindrical cells. The values given in the tables and figures have been corrected for the optical purity of the samples. NMR. spectra were recorded on a *Bruker WH90* spectrometer in $CDCl_3$ with TMS as internal standard.

Materials. Hexane (*Fluka*, UV. spectroscopic grade) and trifluoroacetic acid (*Merck, Uvasol®*) were used without further purification. (+)-(*S*)-2-Methylbutyl chloride, $d_4^{25} = 0.8837$, $[\alpha]_D^{25} = +1.61$ (neat) (o.p. 99%) was prepared by a known method [17]. 2- and 3-Bromopyridines *(Fluka)* were distilled; 4-bromopyridine, recovered from the hydrochloride adduct *(Fluka)* in ether, was used without further purification. $NiCl_2$ (DPPE) was prepared by the method described in [18].

(+)-(S)-2-(1-methylpropyl)pyridine (**1a**) was prepared according to [10]. B.p. 73°/15 Torr, $d_4^{25} = 0.904$, $[\alpha]_D^{25} = +32.41$ (neat; optical purity 81%) [8].

(+)-(S)-3-(1-methylpropyl)pyridine (**1b**) was prepared according to [10]. B.p. 74°/15 Torr, $d_4^{25} = 0.914$, $[\alpha]_D^{25} = +27.13$ (neat; optical purity 61%) [8].

(+)-(S)-4-(1-methylpropyl)pyridine (**1c**) was prepared according to [10]. After preparative GC. purification, b.p. 128°/100 Torr, $[\alpha]_D^{25} = +19.20°$ ($c = 1.634$, heptane; optical purity 84%) [8].

Preparation of (+)-(S)-2-(2-methylbutyl)pyridine (**2a**). A solution of 0.13 mol of 2-methylbutylmagnesium chloride, prepared from the corresponding (+)-(*S*)-2-methylbutyl chloride (o.p. 99%) in 150 ml ether was added in 2 h to an ice-cooled suspension of 0.1 mol of 2-bromopyridine and 0.5 mmol $NiCl_2$ (DPPE) in 50 ml of ether. The mixture was allowed to reflux overnight. After addition of ice-water, the ether phase was separated and the aqueous phase was extracted with ether. The ether was evaporated, the residue was dissolved in dilute HCl-solution and the impurities were removed by extraction with ether. The aqueous phase was neutralized with NaOH and **2a** extracted with ether and purified by distillation over KOH; 10 g (67%); b.p. 85–86°/10 Torr), $[\alpha]_D^{25} = +1.41°$ (neat, $l = 0.1$. – NMR.: 8.52 (*d*, 1 H); 7.53 (*m*, 1 H); 7.01 (*m*, 2 H); 2.68 (*m*, 2 H); 1.90 (*m*, 1 H); 1.31 (*m*, 2 H); 0.90 (*t*, 3 H) overlapped with 0.86 (*d*, 3 H).

$C_{10}H_{15}N$ Calc. C 80.48 H 10.13 N 9.39% Found C 80.54 H 10.04 N 9.18%

Preparation of (+)-(S)-3-(2-methylbutyl)pyridine (**2b**). As described for **2a**, starting with 0.125 mol of the same *Grignard* reagent and 0.1 mol of 3-bromopyridine. After purification, 10.7 g of **2b** (72%)

were obtained, b.p. 92°/11 Torr, $[\alpha]_D^{25} = +1.18°$ (neat, $l = 0.1$). – NMR.: 8.43 (*m*, 2 H); 7.44 (*m*, 1 H); 7.16 (*m*, 1 H); 2.49 (*m*, 2 H); 1.35 (*m*, 3 H); 0.88 (*t*, 3 H) overlapped with 0.84 (*d*, 3 H).

$C_{10}H_{15}N$ Calc. C 80.48 H 10.13 N 9.39% Found C 80.62 H 10.04 N 9.42%

Preparation of (+)-(S)-4-(2-methylbutyl)pyridine (**2c**). As described for **2a**, starting with 0.15 mol of the same *Grignard* reagent and 0.1 mol of 4-bromopyridine. After purification 8.0 g of **2c** (53%) were obtained, b.p. 84°/10 Torr, $[\alpha]_D^{25} = +1.23°$ (neat, $l = 0.1$). – NMR.: 8.48 (*d*, 2 H); 7.06 (*d*, 2 H); 2.48 (*m*, 2 H); 1.65 (*m*, 1 H); 1.28 (*m*, 2 H); 0.88 (*t*, 3 H) overlapped with 0.84 (*d*, 3 H).

$C_{10}H_{15}N$ Calc. C 80.48 H 10.13 N 9.39% Found C 80.58 H 10.01 N 9.27%

The authors thank *D. Tatone* for his collaboration in the *Exper. Part.*

REFERENCES

[1] *P. Pino, C. Carlini, E. Chiellini, F. Ciardelli & P. Salvadori*, J. Am. Chem. Soc. *90*, 5025 (1968).
[2] *E. Spitzer-Wien & P. Pino*, in preparation.
[3] *G. Gottarelli & B. Samorì*, Tetrahedron Lett. *1970*, 2055.
[4] *G. Gottarelli & B. Samorì*, J. Chem. Soc., Perkin Trans II *1974*, 1462.
[5] *O. Cervinka & P. Malon*, Collect. Czech. Chem. Commun. *43*, 278 (1978).
[6] *H. E. Smith, L. J. Schaad, R. B. Banks, C. J. Wiant & C. F. Jordan*, J. Am. Chem. Soc. *95*, 811 (1973).
[7] *G. Gottarelli & B. Samorì*, J. Chem. Soc., Perkin Trans. II *1972*, 1998.
[8] *C.-Y. Yeh & F. S. Richardson*, J. Chem. Soc., Faraday Trans. II *1976*, 331.
[9] *S. Gladiali, G. Gottarelli, B. Samorì & P. Palmieri*, J. Chem. Soc., Perkin Trans. II *1980*, 598.
[10] *D. Tatone, D. C. Tran, R. Nacco & C. Botteghi*, J. Org. Chem. *40*, 2987 (1975).
[11] *K. Tamao, Y. Kiso, K. Sumitani & M. Kumada*, J. Am. Chem. Soc. *94*, 9268 (1972).
[12] *H. P. Stephenson*, J. Chem. Phys. *22*, 1077 (1954).
[13] *K. K. Innes, J. P. Byrne & I. G. Ross*, J. Mol. Spectrosc. *22*, 125 (1967).
[14] *G. Coppens, C. Gillet, J. Nasielski & E. Vander Dockt*, Spectrochim. Acta *18*, 1441 (1962).
[15] *R. Peacock & B. Samorì*, J. Chem. Soc., Faraday Trans. II *1975*, 1909.
[16] *G. Gottarelli, B. Samorì & R. Peacock*, J. Chem. Soc., Perkin Trans. II *1977*, 1208.
[17] *A. McKenzie & G. W. Clough*, J. Chem. Soc. *103*, 687 (1913).
[18] *M. J. Hudson, R. S. Nyholm & M. H. B. Stiddard*, J. Chem. Soc. (A) *1968*, 40.