168. Circular Dichroism of Some 2-(Phenylmethyl)pyridine Derivatives

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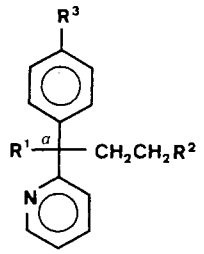
(20.VI.90)

The absolute configuration of the 2-(phenylmethyl)pyridine derivatives **1**–**9** had been established by X-ray diffraction and chemical correlation. Their CD spectra have been studied in different solvents for the free and protonated forms. It has now been found that, from the sign of the strong CD couplet between 270 and 220 nm, which was observable for all these compounds besides **7** and **9**, their absolute configuration can be determined much quicker.

1. Introduction. – Several 2-substituted pyridine derivatives show important pharmacological activities, and a few of them are used in human medicine. In Sofia, many compounds of this type have been synthesized [1] in enantiomerically pure form, but, of several, the absolute configuration could not be determined by chemical correlations alone. This could, however, be achieved by a combination of chemical correlation with the X-ray diffraction of two suitable derivatives [2]. Here, we report on the chiroptical properties of nine compounds related to each other, and compare the conformations in the crystal [2] and in solution.



	R^1	R^2	R^3
1	HO		Cl
2	HO		H
ent-**3**	H	H	H
ent-**4**	HO	H	H
5	H	NMe_2	Cl

Recently, we [3] described the chemical correlation between compounds **1**–**4**, including the catalytic replacement of an OH group by H. Although it is claimed [4] that this step can take place with retention, we nevertheless had to prove this independently for our compounds. For the sake of clarity, the same absolute configuration at the chiral centre has been assumed throughout, although in some cases actually the enantiomer had been investigated.

It is now proved unequivocally that the catalytic replacement of OH by H takes place with retention also in our case, as had been claimed for this reaction in general [4].

Table. *CD Data for* **1**–**9**

Compound[a])	Solvent[b])	CD [nm] ($\Delta\varepsilon$)[c])
1 [3]	H	262 (+10.16), 258 (+9.90, sh), 226 (−18.90)
	A	268 (+4.60, sh), 261 (+6.20, sh), 256 (+6.36), 224 (−14.27)
	A + H^+	265 (−7.67), 227 (+9.68), negative below 210
	E	270 (+3.53, sh), 262 (+4.28), 225 (−9.20)
	E + H^+	273 (−10.50), 267 (−10.32), 228 (+14.37)
1 (Hydrogen maleate)	W	267 (+2.47, sh), 255 (+3.03), 226 (−6.24)
2 [3]	H	265 (+5.87), 254 (+5.18, sh), 221 (−14.12), positive below 205
	A	269 (+2.68, sh), 265 (+2.76, sh), 258 (+3.60), 221 (−11.40)
	A + H^+	266 (−8.20), 232 (+4.27, sh), 208 (+5.38, sh)
	M	270 (+1.40), 265 (+1.29), 257 (+1.26, sh), 249 (+1.62), 221 (−5.46)
	M + H^+	273 (−10.14), 264 (−8.45, sh), 232 (+5.85, sh)
2 (Hydrogen maleate)	W	268 (+1.67, sh), 254 (+1.76, sh), 244 (+2.24), 218 (−5.12)
3 [3]	H	272 (−6.08), 266 (−5.88), 222 (+8.08), negative below 205
	A	270 (−2.94), 265 (−3.11), 260 (−2.57, sh), 219 (+5.69)
	A + H^+	273 (+3.91, sh), 262 (+4.90), 222 (−3.53)
	M	273 (−1.22), 265 (−0.71), 260 (+0.35), 254 (+0.73), 220 (−1.67)
	M + H^+	273 (+7.09, sh), 267 (+7.90), 262 (+7.95), 223 (−5.98)
4 [3]	H	283 (−0.03), 268 (+5.15, sh), 261 (+7.05), 257 (+6.10, sh), 222 (−7.86), 200 (−6.10), positive below 195
	A	280 (−0.08), 267 (+3.79, sh), 261 (+5.28), 257 (+4.42, sh), 221 (−4.53), 197 (−5.51), positive below 190
	A + H^+	270 (+11.13), 232 (−4.60, sh), 213 (−8.72)
	M	274 (−0.47), 267 (0.83), 261 (+1.41), 243 (−0.68), 224 (+0.92), 207 (+1.81)
	M + H^+	271 (+11.40), 232 (−5.11, sh), 214 (−9.80)
5 [10]	H	270 (+7.72, sh), 265 (+8.78), 226 (−13.89), 207 (−6.80)
	A	270 (+4.92, sh), 263 (+5.63), 243 (+1.04, sh), 223 (−7.82), 201 (−4.98), negative below 197
	A + H^+	264 (−7.47), 236 (+4.18, sh), 226 (+5.81), 204 (+2.10), positive below 197
	M	270 (+2.94), 264 (+3.11), 258 (+1.84, sh), 225 (−2.30), 207 (−3.01)
	M + H^+	265 (−9.06), 225 (+9.56)
6	H	263 (+17.38), 233 (−14.33)
	A	262 (+7.46), 231 (−6.41), 210 (+1.45)
	A + H^+	269 (+8.70), 234 (−8.00), 194 (−18.63)
	M	275 (−0.50), 266 (−0.45), 261 (+0.13), 257 (−0.17), 251 (−0.24), 233 (+0.48, sh), 202 (+5.21)
	M + H^+	290 (+6.26, sh), 271 (+8.67), 235 (−7.50)
7	H	266 (+9.63), 236 (−14.91)
	A	293 (+0.02), 287 (−0.06), 265 (+8.73), 260 (+7.56, sh), 233 (−13.40), 201 (−12.50)
	A + H^+	285 (−8.29, sh), 269 (−10.77), 234 (+16.88)
	M	292 (+0.02), 285 (−0.16), 265 (+5.03), 232 (−7.46)
	M + H^+	285 (−8.50, sh), 270 (−10.77), 245 (+7.98), 235 (+9.71)
8	A	300 (−0.62), 272 (−3.88), 241 (+1.15, sh), 228 (+4.30)
	M	273 (−4.48), 244 (+1.63, sh), 230 (+5.42)
9	A	284 (+7.40), 262 (−6.00), 220 (−46.67), 197 (+85.13)
	M	283 (+4.53), 262 (−4.11), 239 (+1.37), 219 (−32.71), 197 (+66.23)

[a]) Literature cited refers to the synthesis and determination of the absolute configuration.

[b]) The solvents are abbreviated as follows: A: MeCN, E: EtOH, H: cyclohexane, M: MeOH, W: H_2O.

[c]) CD: a *Dichrograph Mark III* (*ISA, Jobin-Yvon*), connected on-line to a *PDP-8/e*. Noise was eliminated by curve-smoothing according to the *Golay-Savitzki* algorithm (corrected data given in *D. Ziessow*, 'On-line Rechner in der Chemie', p. 345, *Walter de Gruyter*, Berlin, 1973).

2. CD of (+)-*ent*-3. – The CD spectrum of (+)-*ent*-**3** *(Table)* in cyclohexane shows a relatively strong positive *Cotton* effect (+6) at 269 nm, and a negative one (−8.1) at 222 nm. The first absorption corresponds to the first $\pi \rightarrow \pi^*$ transition of the pyridine chromophore, the second may arise from the second $\pi \rightarrow \pi^*$ transition of either the benzene or the pyridine ring. Since a change of solvent causes very similar changes (magnitudes and even signs) within both these *Cotton* effects, it is very probable that both these bands form an exciton couplet and, therefore, the 222-nm band has to be associated with a benzene transition.

MM-2 calculations for (+)-*ent*-**3** predict [5] that, at room temperature, *ca.* 80% of the molecules adopt a conformation in which the C(2)–N bond of the pyridine ring is synperiplanar to the C(α)–CH_2 bond at the bridge. The first pyridine $\pi \rightarrow \pi^*$ band is polarized perpendicularly to the C_2-axis of pyridine, α-substitution by alkyl introduces a deviation from this direction by *ca.* 10° [6]. The p band as well as one component of the β,β′-doublet of Ph is polarized along the C_2-axis of this chromophore, and if we assume a conformation as suggested by the MM2 calculation, then a positive CD couplet is predicted for (+)-*ent*-**3**, which is in agreement with the result of the measurement. MeCN should not change this conformational equilibrium too severely; indeed the CD bands in this solvent have same signs and similar shape, but the magnitude has dropped to *ca.* one half of that in cyclohexane.

In MeOH, on the other hand, H-bridge formation and solvation might drastically influence this conformational equilibrium and, accordingly, also the CD spectrum. This is nicely established by the experiment: no couplet-type CD is found in MeOH, but, in the range of the (weak) first band, pronounced fine structure develops. Protonation, both in MeCN and in MeOH, leads obviously to a preferred conformation of opposite helicity: more intense negative CD at 260 and positive one at 225–230 nm.

3. CD Spectra of (+)-1 and Its Dechloro Derivative (+)-2. – The IR spectrum of (+)-**1** indicates the presence of a very strong H-bridge formed between OH and the pyrrolidine-*N*-atom. The three most stable conformations of the pyridine ring should be those for which the C–N bond is approximately synperiplanar with one of the three bonds connected to the chiral centre. For steric reasons, it is improbable that this were the C–C(Ph) bond, and this conformation could even not give a CD couplet. Of the remaining two possibilities, in the synperiplanar arrangement of the C–N bond with the C–O bond, a negative couplet is predicted, but this would be positive, if the C–N bond is synperiplanar to the CH_2 group. This latter conformation seems to be preferred in order to avoid unfavourable dipole-dipole interactions, and both (+)-**1** and (+)-**2** give indeed positive couplets in cyclohexane and MeCN solution. Even in MeOH, a couplet is found, and in EtOH (measured only for (+)-**1**) the values are still larger, as expected. Addition of strong acid must, however, cleave this H-bond, and for both compounds in MeCN as well as in alcohols in presence of TFA, stronger CD couplets of opposite signs to those in neutral solutions are observed.

For **1**, **2**, and **3**, salt formation does, therefore, lead to a change of the sign of the torsional angle N(Py)–C(Py)–C–C(Ph), whereas for **4** this is not the case. However, no conclusion about the magnitude of these torsional angles can be derived from these facts. The presence of this H-bond is also supported by measurements of the CD spectra of **1** in EPA at different temperatures: down to −180°, the shape of the first CD band is not much

altered, although the fine structure becomes somewhat more pronounced than usual, and the relative change of $\Delta\lambda_{max}$ is only *ca.* 25%.

4. CD Spectra of (−)-*ent*-4. – The CD of **4** in presence of the complex $[Mo_2(OAc)_4]$ has already been discussed [7], and it could be shown that the replacement of the Et group of **4** by H-atom did not change the general features of the *Cotton* effects of these complexes. Here, we concentrated on the CD spectra of the compounds themselves and investigated also the influence of the medium and of salt formation.

Introduction of the OH group at the chiral centre allows strong H-bonding OH···N, which had been proved by IR measurements (*ca.* 80% intramolecular bridging in CCl_4 for **4** [5]). Such an H-bridge should also prevail in cyclohexane solution, and it is possible, only if the N-atom of the pyridine ring is synperiplanar to the OH. Accordingly, independent of the prefered torsional angle around the benzylic bond, a negative CD couplet is predicted for (−)-*ent*-**4**, and such is found not only in cyclohexane but also in MeCN solution. MeOH as solvent is expected to cleave this H-bridge, and, indeed, the CD curve has completely different shape for that solvent, and the $\Delta\varepsilon$ values are much smaller *(Fig. 1)*.

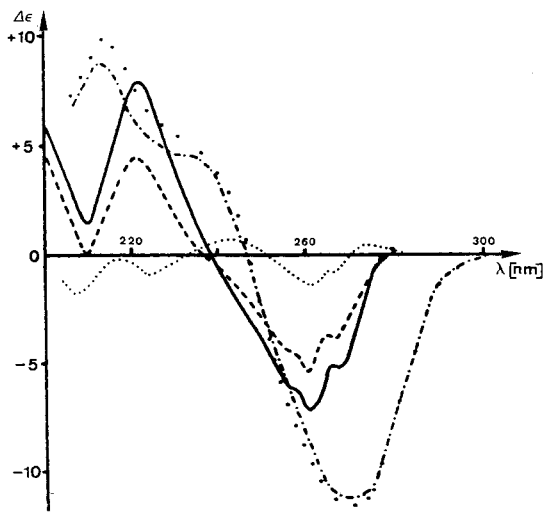


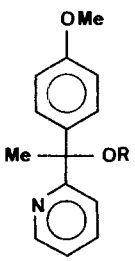
Fig. 1. *CD Spectrum of (−)-*ent-**4** *in cyclohexane* (——), *MeCN* (– – –), *MeCN + THF* (–·–·–·–), *MeOH* (·····), *and MeOH + HCl* (· · · · ·)

Protonation will inhibit such internal H-bridging, and it is interesting to note that the CD spectra for MeOH as well as for MeCN solution after addition of acid are nearly identical. They also have the couplet-type appearance with even much larger rotational strengths than for the neutral form. The protonated form can, therefore, adopt the same conformation in MeOH as the neutral one in unpolar solvents. Since there exist, however, several other different conformations, which are consistent with these data, we do not want to speculate about them.

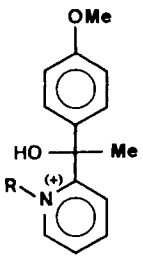
5. CD Spectrum of (+)-5. – The spectrum of (+)-**5** is very similar to that of (+)-*ent*-**3** of same absolute configuration, both for neutral and acidic solutions. The same conclusions

about the conformations can, thus, be drawn for both molecules. CD and ORD data of (+)-**5** and its dechloro derivative had already been described by *Testa* in 1974 [8], but, due to older instrumentation, he could record only the first *Cotton* effect. Although he could at that time not make more definitive suggestions for the preferred conformations, he already recognized that the high magnitude of the *Cotton* effects and their changes with pH should be explained by assuming an exciton-type interaction between the two aromatic systems.

6. CD Spectrum of (+)-6. – In cyclohexane, more than 80% of (+)-**6** are present in a conformation with internal H-bridge [5], arrangement giving rise to a positive CD couplet. Indeed, this is observed, and the same holds even for MeCN, although the magnitudes of the *Cotton* effects are somewhat smaller than those of *ent*-**7** (see later). In



6 R = H
ent-**7** R = Me



8 R = Me
9 R = O(-)

MeOH, however, the CD values are very small and show the usual fine structure found for such aromatic chromophores. This indicates the presence of a mixture of conformers of no great energy differences. In the protonated form, the CD couplet retains its sign and is nearly of the same shape and magnitude as for the neutral compound in both MeCN and even MeOH solution. This is, *e.g.*, consistent with a conformation in which the Me group is now synperiplanar with the CH of the pyridine ring, which is a reasonable one for the protonated form. To prove that the CD couplets obtained are indeed of intramolecular type, we have measured the CD data for (+)-**6** in a high concentration range and could not observe any significant dependance of the $\Delta\varepsilon$ values on concentration.

7. CD Spectrum of (+)-*ent*-7. – The conformation of lowest energy of (+)-*ent*-**7** is, according to calculations, the one in which the Me group is synperiplanar to the pyridine-N-atom [5]. For this, the two transition dipols involved in the exciton interaction lead to a negative CD couplet, which is, indeed, observed for (+)-*ent*-**7** in cyclohexane, MeCN, and even in MeOH solution, although in the last mentioned solvent the couplet is only half as large as for the other two. Protonation of the N-atom (MeCN or MeOH solution) inverts the signs of these couplets, and the values are even larger, reveiling, thus, that the afore mentioned preferred conformation has been changed by the protonation. Since again several geometries are consistent with such a CD, one can, therefore, not unequivocally deduce the conformation in the protonated form from these CD spectra alone *(Fig. 2)*.

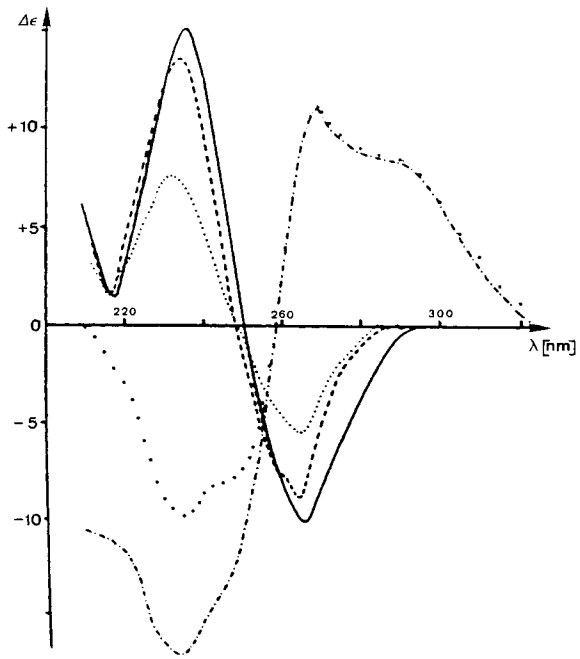


Fig. 2. *CD Spectrum of (+)-*ent-**7** *in cyclohexane* (——), *MeCN* (– – – –) *MeCN + TFA* (–·–·–·–), *MeOH* (·····), *and MeOH + HCl* (· · · · ·)

8. CD Spectra of (+)-8 and (+)-9. – The CD spectra of (+)-**8** in MeOH as well as in MeCN are very similar to each other and the *Cotton* effects around 272 and 229 nm have opposite signs, being characteristic for a CD couplet. Since, however, the $\Delta\varepsilon$ values are relatively small, they may be due to two individual *Cotton* effects which by chance have opposite signs and similar absolute magnitudes for the rotational strengths.

The most characteristic feature in the CD spectra of the *N*-oxide (+)-**9** is a very pronounced couplet-type CD at 220/197 nm, (MeOH or MeCN solution) with $\Delta\varepsilon$ values up to 74. In this wavelength range, several transitions may give rise to absorption bands, and we can, therefore, at present not discuss these CDs in another than purely empirical way. Since also other *N*-oxides of this type show this very intense CD couplet, we are now investigating such compounds in more detail.

9. Conclusions. – In the crystals of **1** [2], the torsional angle around the pivot bond to the pyridine is arranged in such a way, that the N-atom is synperiplanar to the substituted Et group. This is the same overall conformation as observed in solutions in unpolar solvents, as it could be deduced from the sign of the CD couplet. Its IR spectrum in very dilute solution in CCl_4 indicated, furthermore, an internal H-bridge between the OH group and the pyrrolidine-N-atom, which, on the basis of the models, seems easily possible for the discussed conformation of the pyridine ring. This synperiplanar conformation is retained even in more polar solvents like MeOH or EtOH, since a similar CD couplet is also found under these conditions.

After protonation, again a CD couplet can be found, but this time of opposite sign to the first mentioned one. This would not be expected, if the more basic pyrrolidine-N-atom were protonated. Accordingly, we can conclude that also the pyridine-N-atom is protonated under these conditions. Since the HN^+ moiety is larger than the free pyridine-N-atom alone, obviously the synperiplanar arrangement of the pyridine-N-atom and CH_2 is no more preferred, and the pyridine ring is rotated into another conformation. Molecular models show that several 'reasonable' conformations would be consistent with the CD, and, therefore, we are not able to deduce the new torsional angle from this CD.

Compound **2** differs from **1** only by the lack of the *p*-Cl substituent on the benzene chromophore. As we had proved in our CD studies of chiral 1,2-diphenylethanes, such a substituent has no essential influence upon the *p*- and *β,β'-Cotton* effects [9]; we expect, therefore, the CD behaviour of **2** to be very similar to that of **1**, which was indeed established. Furthermore, the absolute configuration of **2** is, thus, also determined by this comparison.

Like **1** and **2**, also *ent*-**4** contains an OH group at the chiral centre, but no other, more basic N-atom is present, which could act as a better acceptor for an H-bond than the pyridine-N-atom. One can, therefore, predict, that an internal H-bridge is now formed between OH and the pyridine-N-atom, and as already discussed, CD data support this view.

Compound **3** contains only one N-atom and no OH group. Since we observed a similar CD couplet in unpolar solvents for *ent*-**3** as for **1** and **2**, the arrangement of both rings of *ent*-**3** must also be similar to those of **1** and **2**. This conclusion from the CD data is supported by the MM-2 calculation [5]. Solvation by MeOH destabilizes this conformation, since in MeOH the CD couplet disappears, and one observes the usual small CD (with fine structure) within the α band.

For **6**, with Me instead of a bulkier substituent at the chiral centre, we also found great similarity between the crystal and the solution conformation. In unpolar solvents, most of the molecules have an internal H-bridge, being in accordance with the synperiplanar arrangement of the N–C–C–O moiety found in the crystal, even though there are several intermolecular H-bridges present to the tartrate unit. As a consequence of this preferred conformation in solution, the sign of the observed CD couplet in unpolar solvents is correctly predicted for **6**.

In view of the fact that, for other members of this series, an even more remote substitution may, however, cause changes of the conformation and, therefore, also of the CD, we still strongly advice, in any new set of even related compounds, to determine the absolute configuration for at least one member in an independent way.

In accord with these views are the chiroptical properties of *ent*-**7**. No internal H-bridge is possible, and its CD is in agreement with the one predicted for the preferred conformation (see above). Since no H-bridges are involved for this compound, MeOH weakens but does not completely eliminate the CD couplet.

In conclusion, we would like to emphasize that, for the determination of the absolute configuration of such conformationally mobile compounds of pharmacological importance, the quickly performed CD method, which, furthermore, does not destroy any material, can successfully be applied, provided a correct model compound of known configuration is available.

Whe thank *KFA Jülich, Deutsche Forschungsgemeinschaft, Fonds der Chemie,* and *Hoechst AG* for financial support.

Experimental Part

General. M.p.: *Kofler* hot-stage apparatus, uncorrected. Optical rotations: *Perkin-Elmer 241* instrument in $CHCl_3$ soln. if not otherwise stated.

1. *(+)-(S)-1-(4-Methoxyphenyl)-1-(2-pyridyl)ethanol* ((+)-(*S*)-**6**). Compound (+)-(*S*)-**6** was prepared according to the general procedure given in [7] from 4-methoxyacetophenone and 2-pyridyllithium in dry Et_2O at −78°. After the diastereoisomeric mixture of equimolar quantities of *rac*-**6** and (+)-(2*R*,3*R*)-tartaric acid (24.85 g) was recrystallized from i-PrOH (110 ml), 20.1 g of salt with m.p. 104–129° was isolated. Five more recrystallizations from i-PrOH afforded an optically pure crystalline salt (8.14 g). M.p. 153–155°. $[\alpha]_D = +31.5$ ($c = 0.9$, MeOH). From this salt, the corresponding free base (4.89 g, 65%) was isolated with $[\alpha]_D = +84.1$ ($c = 0.8$). When (−)-(2*S*,3*S*)-tartaric acid was used as resolving agent, a pure laevorotatory free base *ent*-**6** was obtained.

2. *Conversion of* ent-**6** *into (−)-(R)-2-[1-Methoxy-1-(4-methoxyphenyl)ethyl]pyridine* ((−)-(*R*)-**7**). A mixture of NaH suspension (370 mg) in dry benzene (6 ml) and a soln. of *ent*-**6** (1.15 g) in 4 ml dry benzene was refluxed for 3 h, then, at r.t., 0.35 ml of MeI dissolved in 2 ml of benzene was added, *cf.* [11]. After stirring for 1 h at r.t. and another 1 h at 60°, the mixture was hydrolyzed, extracted with Et_2O und purified over silica gel (hexane/Et_2O 6:1). The resulting pure (−)-**7** was an oil (0.58 g, 48%). $[\alpha]_D = -23.6$ ($c = 0.5$). CI-MS: 244 (100, MH^+), 228 (8), 212 (47), 165 (9). Anal. calc. for $C_{15}H_{17}NO_2$: C 74.05, H 7.04; found: C 74.09, H 7.11.

3. *Conversion of* ent-**6** *into* (+)-(R)*-2-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]pyridinium Iodide* ((+)-(*R*)-**8**). To a soln. of *ent*-**6** (0.57 g) in 2 ml of aceton, MeI (2 ml) was added, and the mixture was allowed to stand at r.t. for 7 d. After evaporation to dryness and recrystallization from EtOH/Et_2O, crystalline (+)-**8** (0.46, 50%) was obtained. M.p. 176–177°. $[\alpha]_D = +102.2$ ($c = 0.5$). Anal. calc. for $C_{15}H_{18}INO_2$: C 48.53, H 4.89, N 3.77; found: C 48.38, H 4.95, N 3.94.

4. *Conversion of* ent-**6** *into (+)-(R)-2-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]pyridinium Oxide* ((+)-(*R*)-**9**). H_2O_2 (30%, 3 ml) was mixed with glacial AcOH (5 ml) at 0°, and this mixture was stirred for 1 h at the same temp. Then a soln. of *ent*-**6** (450 mg) in 1 ml of glacial AcOH was added, and this was stirred for another 5 h at 70° according to [12]. The mixture was worked up with 25% NH_4OH and $CHCl_3$. The crude product was purified by TLC (silica gel, hexane/$CHCl_3$ 3:7) and recrystallized from AcOEt/Et_2O to give 17 mg (3%) of (+)-**9**. M.p. 127–129°. $[\alpha]_{546} = +182.2$ ($c = 0.3$). CI-MS: 247 (88, M^+), 246, 231, 228, 212.

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