

Metabolites of the Pyridylallylamine Zimelidine

Syntheses *via* α,β -Unsaturated Aldehydes with Conservation of Stereochemistry

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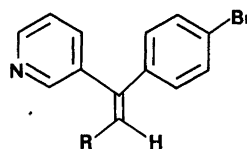
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Some tentative metabolites and metabolic intermediates of (*Z*)-3-(4-bromophenyl)-*N,N*-dimethyl-3-(3-pyridyl)allylamine (*1*, zimelidine) were synthesized. (*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propenal (*8*) and its *N*-oxide (*15*) were used in syntheses of *N*-methyl-hydroxylamines (*17*, *18*), the pyridyl *N*-oxide of zimelidine (*16*) and a nitron (*19*). The nitron was also formed by oxidation of the allylic carbon of the corresponding *N*-methylhydroxylamine *17* with silver oxide. The compounds were diastereomerically pure and shown to possess the *Z*-configuration by means of UV and ^1H NMR.

Recently, we described the identification and syntheses of the principal metabolites 2–10 of the antidepressant zimelidine (*1*) (see Table 1).¹ Some minor metabolites have not yet been identified and several possible intermediates may be postulated in the different metabolic pathways found.¹ Therefore, it was of interest to provide reference material for further metabolic investigations. This paper concerns the syntheses of such tentative metabolites and intermediates.

Both nitrogens in *1* form *N*-oxides *in vivo* and two metabolites (*4* and *5*) have been identified. Thus, it was of interest to synthesize the third possible *N*-oxide *16*, having only the pyridine nitrogen oxidized. Hydroxylamines and nitrones may be formed as metabolic intermediates in the dealkylation and deamination of alkylamines *in vivo*.^{2,3} The compounds *17*, *18* and *19* are examples of such compounds, which may be formed in the biodegradation of *1* (Table 1), or more specifically the secondary amine *2*.

Table 1.

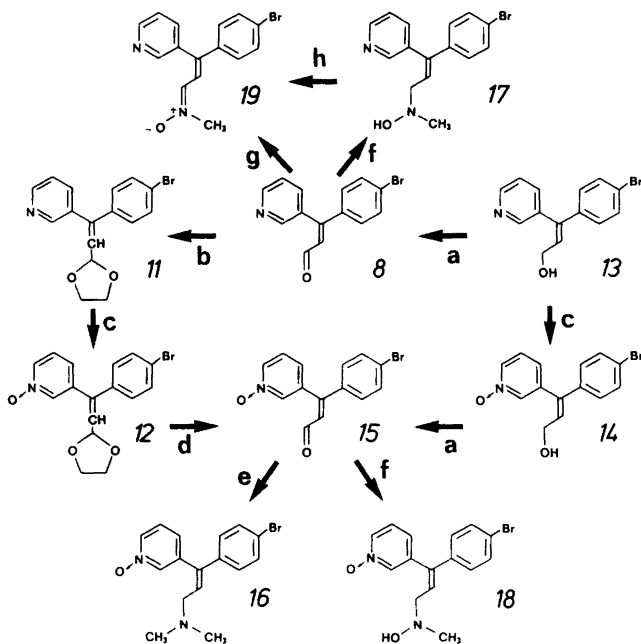


	R	Pyridine <i>N</i> -oxide
1	CH ₂ NMe ₂	16
2 ^a	CH ₂ NHMe	
3 ^a	CH ₂ NH ₂	
4 ^a	CH ₂ N(O)Me ₂	5 ^a
6 ^a	CH ₂ NHAc	7 ^a
8 ^a	CHO	15
9 ^a	COOH	10 ^a
11	CHOCH ₂ CH ₂ O	12
13	CH ₂ OH	14
17	CH ₂ N(OH)Me	18
19	CH=N(O)Me	

^aZimelidine metabolites.

Zimelidine (*1*) has the *Z*-configuration^{4,5} and the isolated metabolites 2–10 possessed this geometry.¹ However, both diastereomers of the acrylic acids 9 and 10, which can isomerize under the aqueous conditions,¹ were isolated. We expected difficulties in separating the relatively hydrophilic *Z*- and *E*-isomers of 16–19 and therefore stereospecific syntheses of the *Z*-forms were required.

A well-known synthetic method to amines and hydroxylamines is reductive amination of the corresponding carbonyl compound with sodium cyano-



Scheme 1. a. MnO_2 , CHCl_3 ; b. $\text{HOCH}_2\text{CH}_2\text{OH}$, H_2SO_4 , C_6H_6 , Δ ; c. MCPBA, CHCl_3 ; d. aq HCl, EtOH; e. $\text{HNMe}_2 \cdot \text{HCl}$, NaBH_3CN , MeOH; f. HONHMe , NaBH_3CN , MeOH, H_2O , pH 5; g. HONHMe , Et₂O, CH_2Cl_2 ; h. Ag_2O , Et₂O.

borohydride in the presence of an amine.^{6,7} Accordingly, it was desirable to obtain the aldehydes 8 and 15 as the pure *Z*-forms, for subsequent transformations with conservation of the stereochemistry. Moreover, the *N*-oxide 15 is also a conceivable metabolite, since it may be formed in the metabolic route to 10.

Direct oxidation of 8¹ with *meta*-chloroperoxybenzoic acid (MCPBA) gave a mixture from which 15 was difficult to obtain in pure form. In another attempted synthesis of 15 from 8, the aldehyde function was protected as an acetal prior to oxidation. However, the isolated ethylene acetal 11 consisted of an isomeric mixture, which was converted to a *Z/E* mixture of 15 (Scheme 1). We have previously shown that the allylic alcohol 13 is easily oxidized with manganese dioxide to 8 with retained stereochemistry.¹ Thus the corresponding conversion of 14 to 15 is likely to take place. Direct oxidation of 13 with MCPBA gave 14 in *Z*-form after flash chromatography and recrystallization in 35% yield (*cf.* the direct *N*-oxidation of morphine⁸). Subsequent treatment of 14 with manganese dioxide gave isomerically pure 15 (Scheme 1).

Previous experiments on reductive amination of 8 with sodium cyanoborohydride in anhydrous methanol showed that a low pH was essential for conversion to 1, while minimizing isomerization.⁹ Thus, the corresponding reductive amination of 15 was carried out with dimethylamine hydrochloride in methanol without addition of base (*cf.* Ref. 10) and the *N*-oxide 16 was obtained with a purity of >97% *Z*-form (Scheme 1).

The reductive *N*-methylhydroxylaminations of the aldehydes 8 and 15, respectively, were performed with sodium cyanoborohydride in aqueous methanol at pH ≈ 5 in analogy with a procedure described by Morgan and Beckett.⁷ The reaction was rapid and produced 17 and 18, respectively, in high yields. The work-up of 17 was straightforward, but the more hydrophilic *N*-oxide 18 was isolated from the aqueous reaction mixture by absorption on an XAD-2 column.

The stereochemical assignments of the new compounds above were based on UV and NMR spectra as described previously.¹ It was found that the pyridine *N*-oxides of the allylic derivatives have a λ_{max} (UV in 0.1 M HCl) at 5–6 nm longer wavelength

than the corresponding nonoxidized derivatives (cf. 1–16, 4–5, 13–14 and 17–18). Furthermore, the 2,6-pyridyl protons are shifted upfield in the NMR spectra of the *N*-oxides 12, 14, 15, 16 and 18.

The oxidation of the hydroxylamine 17 to a nitrone can either involve the allylic position or the methyl group. The allylic carbon is likely to be more vulnerable to oxidation since we have shown that 1 is oxidized with manganese dioxide to the aldehyde 8.¹ Oxidation of 17 was accomplished with silver oxide¹¹ and as expected the α,β -unsaturated nitrone 19 was obtained. Alternatively, 19 was prepared by condensation of 8 with *N*-methylhydroxylamine in the presence of molecular sieves, a reaction which is identical to the first step in the reductive *N*-methylhydroxylation of 8 (Scheme 1). The conjugated nitrone 19 was unusually stable, since it was not hydrolyzed directly in aqueous hydrochloric acid (cf. UV spectra of 8 and 19). The shifts of the 2,6-pyridyl protons in the NMR spectrum of 19 indicated the *Z*-configuration of the olefinic bond (cf. Ref. 1). Besides, the nitrone could be in *syn* or *anti* form, but no conclusive evidence of this could be obtained by ¹H NMR (200 MHz). The mass spectrum of 19 has the abundant fragments *m/z* 161 (M – C₆H₄Br) and *m/z* 240/238 (M – pyridyl), which may be explained by formation of stabilized 1,2-oxazoles by elimination of the aryl radicals during ring closure (Fig. 1).

EXPERIMENTAL

General procedures. Melting points were determined on a Mettler FP61 apparatus in open capillary tubes and are uncorrected. ¹H NMR spectra were recorded on a Varian T-60 or a Jeol FX-200 spectrometer. UV spectra were obtained on a Zeiss DMR 21 spectrophotometer. Mass spectra (70 eV) were recorded on an LKB 9000 instrument. GLC were run on an OV-17 column. TLC were run on precoated plates (Merck, Silica Gel F₂₅₄). Elemental analyses, performed by Analytische Laboratorien, Elbach, W. Germany, were within $\pm 0.4\%$ of the theoretical values unless otherwise noted. Amberlite XAD-2 was purchased from Rohm and Haas, Philadelphia. Molecular sieves were of 3 Å.

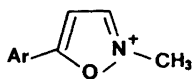


Fig. 1. Major fragments in the mass spectrum of the nitrone 19 (Ar = C₆H₄Br or C₅H₄N).

(*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propenal (8). Prepared according to Ref. 1. UV [0.1 M HCl (ε)]: λ_{\max} 312 (16400), λ_{\min} 273 (9500), λ_{\max} 236 (13000), λ_{\min} 218 (11200) nm; UV [EtOH (ε)]: λ_{\max} 302 (22000), λ_{\min} 253 (11500), λ_{\max} 230 (18100), λ_{\min} 221 (17700) nm; TLC (EtOAc/MeOH/H₂O 8:3:2) *R_F* = 0.75.

1-(4-Bromophenyl)-3-ethylenedioxy-1-(3-pyridyl) propene (11). Compound 8 (0.58 g, 2 mmol) was heated under reflux with 5 g ethylene glycol and 4 drops of conc. H₂SO₄ in 25 ml benzene for 2 days in a Dean-Stark apparatus. After cooling the mixture was diluted with ether and washed with saturated aqueous NaHCO₃ and NaCl solutions. Drying (MgSO₄) and evaporation gave 0.7 g of an oil, which on GLC was shown to be an isomeric mixture (2:3) of the acetals 11. MS [*m/z* (rel. int.)]: 333/331 (26/27, M), 261/259 (50/50), 260/258 (20/14), 180 (100), 179 (33), 152(24), 73 (36).

1-(4-Bromophenyl)-3-ethylenedioxy-1-(3-pyridyl) propene *N*-oxide (12). To the crude acetal mixture, 11 (2 mmol) dissolved in 12 ml chloroform 3-chloroperbenzoic acid (0.41 g, 2.1 mmol, 90%) was added with cooling in an ice-bath. The temperature was allowed to rise to ambient and the mixture was stirred for 4 h. Filtration through 40 g alumina, subsequent elution with chloroform and evaporation of the solvent gave 0.35 g (50%) of an oil. ¹H NMR (CDCl₃): δ 3.8–4.3 (m, 4, ethylene), 5.23 (d [overlapping], 1, OCHO), 6.20–6.23 (two d, 1, vinyl), 7.0–7.8 (m, 6, aromatic), 8.1–8.4 (m, 2, 2,6-pyridyl); MS [*m/z* (rel. int.)]: 349/347 (21/22, M), 333/331 (35/35, [M – O]), 261/259 (53/54, [M – O – CO₂ – CH₂CH₂]), 260/258 (30/23), 180 (100, [261/259 – Br]), 179 (46), 73 (48).

Hydrolysis in aqueous ethanol with HCl gave 0.26 g (43% overall yield from 8) of a *Z/E* (2:1) mixture of 15. ¹H NMR (CDCl₃): δ 6.65, 6.59 (two d, 1, vinyl), 7.1–7.8 (m, 6, aromatic), 8.1–8.4 (m, 2, 2,6-pyridyl), 9.54, 9.58 (two d, 1, CHO).

(*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propen-1-ol (13). Prepared according to Ref. 1. UV [0.1 M HCl (ε)]: λ_{\max} 248 (19700), λ_{\min} 224 (11600) nm.

(*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propen-1-ol *N*-oxide (14). 3-Chloroperbenzoic acid (2.3 g, 12 mmol, 90%) was added to a solution of 13 (2.90 g, 10 mmol) in 15 ml chloroform with cooling in an ice-bath. After stirring for 0.5 h at 0°C and 2 h at room temperature the solution was filtered through 30 g alumina, which was washed with chloroform – methanol 3:1.

Evaporation of the solvent and recrystallization from chloroform – diisopropyl ether gave 1.7 g of crystals, mp 173–176°C. Flash chromatography of the product on a column of silica gel (40 g, 0.040–0.063 mm) with methanol – ethyl acetate 1:5 (250 ml) and 1:1 (200 ml) and subsequent recrystallization from chloroform – diisopropyl ether afforded 1.07

g (35 %) pure title compound, mp 182–184 °C.

¹H NMR (CDCl₃/CD₃OD): δ 4.13 (d, 2, allyl), 4.55 (s, 1, OH), 6.41 (t, 1, vinyl), 7.1–7.7 (m, 6, aromatic), 8.16 (m, 1, 2-pyridyl), 8.27 (dt, 1, 6-pyridyl); MS [*m/z* (rel. int.)]: 307/305 (24/27, M) 291/289 (19/37, [M–O]), 290/288 (42/51), 289/287 (37/18, [M–H₂O]), 278/276 (26/27), 262/260 (15/19), 248/246 (35/38), 210 (100, [M–O–Br]); UV [0.1 M HCl (ε)]: λ_{max} 253 (16400), λ_{min} 228 (10700) nm; Anal. C₁₄H₁₃BrNO₂: C, H, Br, N, O.

(*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propenal *N*-oxide (15). Compound 14 (0.15 g, 0.5 mmol) was dissolved in 6 ml chloroform and stirred with 1 g MnO₂ (Merck, gefällt) under a nitrogen atmosphere at ambient temperature overnight. TLC (EtOAc–MeOH–H₂O 8:3:2) showed that a complete conversion had taken place leading to a compound with R_F=0.54.

To the reaction mixture 10 ml chloroform and 10 ml methanol were added prior to filtration through Celite. The filter cake was washed with hot chloroform–methanol 1:1. Evaporation of the filtrate *in vacuo* gave 0.15 g (98 %) of an oil. ¹H NMR (CDCl₃): δ 6.65 (d, 1, vinyl) 7.1–7.8 (m, 6, aromatic), 8.18 (m, 1, 2-pyridyl), 8.31 (dt, 1, 6-pyridyl), 9.57 (d, 1, CHO); MS [*m/z* (rel. int.)] 305/303 (85/87, M), 289/287 (37/39, [M–O]), 288/286 (38/34, [M–OH]), 260/258 (19/17, [M–O–CHO]), 208 (100, [M–O–Br]), 180 (64), 179 (66), 165 (44), 155 (63), 153 (17), 152 (48); UV [0.1 M HCl (ε)]: λ_{max} 309 (14400), λ_{min} 280 (9300), λ_{max} 253 (14400), λ_{max} 241 (14800), λ_{min} 225 (13300)nm; UV [EtOH (ε)]: λ_{max} 299 (sh, 12000), λ_{max} 269 (16800), λ_{min} 246 (14400), λ_{max} 234 (sh, 15000)nm.

(*Z*)-3-(4-Bromophenyl)-*N,N*-dimethyl-3-(3-pyridyl *N'*-oxide)allylamine (16). Dimethylamine hydrochloride (0.41 g, 5 mmol) and 15 (0.15 g, 0.49 mmol) were dissolved in 5 ml methanol. After addition of NaBH₃CN (0.035 g, 0.5 mmol, 90 %) and 3 g molecular sieves the reaction mixture was stirred under nitrogen for 24 h. To the mixture was added 10 ml 6 M HCl and the methanol was removed under reduced pressure. The residue was made alkaline with 45 % NaOH and extracted twice with ether and once with dichloromethane. After drying (MgSO₄) the extracts were combined and evaporated to give 0.12 g (76 %) of colourless oil. ¹H NMR (CDCl₃, base): δ 2.31 (s, 6, CH₃), 3.07 (d, 2, allyl), 6.36 (t, 1, vinyl), 7.0–7.7 (m, 6, aromatic), 8.10 (m, 1, 2-pyridyl), 8.21 (dt, *J* = 6.2 and 1.5 Hz, 1, 6-pyridyl); MS [*m/z* (rel. int.)]: 334/332 (0.22/0.24, M), 333/331 (0.74/0.74), 318/316 (10/11, [M–O]), 317/315 (22/21), 303/301 (2.4/2.6), 275/273 (6.8/10), 274/272 (26/27), 240/238 (4.8/5.8), 193 (100, [M–O–NMe₂–Br]), 192 (16), 161 (4.8), 70 (13), 58 (41), 42 (23); UV [0.1 M HCl (ε)]: λ_{max} 256 (22900), λ_{min} 230 (15300).

(*Z*)-3-(4-Bromophenyl)-*N*-hydroxy-*N*-methyl-3-

(3-pyridyl)allylamine (17). *N*-Methylhydroxylamine hydrochloride (0.67 g, 8 mmol) and 8 (2.0 g, 6.9 mmol) were dissolved in 3 ml water and 12 ml methanol with addition of a few drops of conc. HCl. Immediately after the dissolution the pH was adjusted to 5 with 45 % NaOH. NaBH₃CN (0.50 g, 7 mmol, 90 %) was added in one portion and during the reaction at room temperature the pH was kept at 4.7–5.3 by incremental addition of 2 M HCl. After 0.5 h no further increase in pH occurred and after 1.5 h TLC (EtOAc–MeOH–H₂O 8:3:2, title compound 17 R_F= 0.61) showed no trace of the aldehyde 8. After 4 h the excess of hydride was destroyed with conc. HCl and the solution was diluted with saturated aqueous NaCl, made alkaline and extracted twice with ether. The combined ether extracts were dried (MgSO₄) and evaporated to give 1.9 g (86 %) of crude product. The amine was converted to its oxalate salt and recrystallized twice from ethanol to give 1.85 g (56 %) of the pure oxalate of 17, mp 149–150 °C (dec.). ¹H NMR (CDCl₃, base): δ 2.59 (s, 3, CH₃), 3.35 (d, 2, allyl), 6.37 (t, 1, vinyl), 7.0–7.7 (m, 6, aromatic), 8.47 (m, 1, 2-pyridyl), 8.59 (dd, 1, 6-pyridyl); MS [*m/z* (rel. int.)]: 320/318 (3.4/3.6, M), 304(11), 303 (7.0), 302 (21), 301/299 (50/46), 275/273 (36/41, [M–ONMe]), 274/272 (24/21, [M–HONMe]), 193 (100, [M–HONMe–Br]), 192 (22), 46(25, [HONMe]), 45 (43), 44(38); TMS-derivative: 392/390 (5.2/5.0, M), 274/272(32/33, [M–TMSONMe]), 193 (100, [M–TMSONMe–Br]); UV [0.1 M HCl (ε)]: λ_{max} 250 (16300), λ_{min} 226 (11100). Anal. C₁₅H₁₅BrN₂O · 1.75 C₂H₂O₄: C (calc. 46.60, found 47.07), H, N, O, Br.

(*Z*)-3-(4-Bromophenyl)-*N*-hydroxy-*N*-methyl-3-(3-pyridyl)allylamine *N*-oxide (18). *N*-Methylhydroxylamine hydrochloride (0.13 g, 1.5 mmol) and 15 (0.26 g, 0.85 mmol) were dissolved in 0.6 ml water and 2.5 ml methanol. The pH was adjusted to 5 with 45 % NaOH and NaBH₃CN (0.09 g, 1.3 mmol, 90 %) was added. The pH was maintained at about 5 by addition of 2 M HCl at room temperature. TLC after 3 h showed no aldehyde 15. The solution was allowed to stand overnight before work-up. The reaction mixture was acidified and after the evolution of gas bubbles had ceased the mixture was made alkaline. The aqueous solution was allowed to pass through an XAD-2 column (20 g, prewashed with methanol and water). The eluent was passed through the column once more and then the column was washed with distilled water. The adsorbed product was eluted with methanol and TLC (EtOAc–MeOH–H₂O 8:3:2) revealed only traces of impurities in the product with R_F=0.44. Chloroform was added to the methanolic solution and the solvent was evaporated *in vacuo* to leave 0.27 g (95 %) of an oil. An oxalate was prepared and recrystallized from ethanol–diisopropyl ether

giving a hygroscopic product, which was deliquescent but resolidified on standing, mp 99–102 °C (dec.). ¹H NMR (CD₃OD, oxalate): δ 2.98 (s, 3, CH₃), 3.53 (d, 2, allyl), 6.49 (t, 1, vinyl), 7.1–7.8 (m, 6, aromatic), 8.27 (m, 1, 2-pyridyl), 8.36 (dt (partly concealed), 1, 6-pyridyl); MS [*m/z* (rel. int.)]: 336/334 (1.0/1.0, M), 320/318 (1.5/2.2, [M–O]), 304 (2.1), 303 (1.9), 302 (5.1), 301 299 (13/12), 275/273 (9.0/11, [M–O–ONMe]), 274/272 (9.6/9.3, [M–O–HONMe]), 193 (37, [M–O–HONMe–Br]), 192 (9.2), 46 (58, [HONMe]) 45 (100), 44 (50); UV [0.1 M HCl (ε)]: λ_{max} 256 (22500), λ_{min} 229 (15900); Anal. C₁₅H₁₅BrN₂O₂·C₂H₂O₄: C, H, Br, N, O.

N-[(2*Z*)-3-(4-Bromophenyl)-3-(3-pyridyl)-2-propenylidene]methylamine N-oxide (19). A. Oxidation of 17. The base of 17 (extracted from 0.5 mmol oxalate) was dissolved in 30 ml anhydrous ether under a nitrogen atmosphere at room temperature. Molecular sieves (4 g) and Ag₂O (0.70 g, 3 mmol, Fluka AG) were added and the mixture was stirred for 16 h. TLC showed an incomplete conversion and additional Ag₂O (0.46 g, 2 mmol) was added and the mixture was stirred overnight (total 40 h). TLC (EtOAc–MeOH–H₂O 8:3:2) showed a single compound having R_F=0.41 and no starting material 17. Ether (20 ml) and acetone (20 ml) were added to the reaction mixture. After stirring and filtration through Celite the solvent was evaporated *in vacuo*. Dichloromethane was added to the residue and evaporation gave 81 mg (51 %) of a crystalline product 19, mp 173–176 °C. ¹H NMR (200 MHz, CDCl₃): δ 3.69 (s, CH₃), 7.01 and 7.49 (two d, *J*=10.3 Hz, HC=CH), 7.10 and 7.46 (AA'BB', *J*=8.8 Hz, phenyl), 7.40 (ddd, *J*=7.8, 4.9 and 0.9 Hz, 5-pyridyl), 7.53 (dt, *J*=7.8 and 1.9 Hz, 4-pyridyl), 8.51 (narrow m, 2-pyridyl), 8.69 (dd, *J*=4.9 and 1.9 Hz, 6-pyridyl); MS [*m/z* (rel. int.)]: 319 (5.3), 318/316 (32/33, M), 301/299 (77/78, [M–OH]), 274 (13), 273/271 (39/39), 272/270 (37/24), 240/238 (86/86, [M–C₅H₄N]), 192 (32), 191 (36), 161 (100, [M–C₆H₄Br]), 131 (36), 42 (57); UV [0.1 M HCl (ε)]: λ_{max} 337 (21000), λ_{min} 273 (9200), λ_{max} 250 (15400), λ_{min} 222 (10500); UV [EtOH(ε)]: λ_{max} 341 (16000), λ_{min} 276 (6300), λ_{max} 249 (11400), λ_{min} 220 (6600).

B. Condensation of 8 with *N*-methylhydroxylamine. *N*-Methylhydroxylamine hydrochloride (42 mg, 0.5 mmol), NaOH (20 mg, 0.5 mmol) and 8 (144 mg, 0.5 mmol) were dissolved in 5 ml ether and 3 ml dichloromethane at room temperature. Molecular sieves (3 g) were added and the mixture was stirred under nitrogen overnight. TLC showed that most of 8 had been converted to 19. Another 0.1 mmol (8.4 mg) of *N*-methylhydroxylamine hydrochloride was added and the mixture was stirred for a further 6 h. TLC showed only traces of 8 and 10 ml dichloromethane and 10 ml ether were added and the mixture was stirred. Filtration through Celite and evapo-

ration of the solvent gave 50 mg (32 %) of the title compound 19 as a crystalline product, mp 174–176 °C. The product was chromatographically and spectroscopically identical with 19 obtained by oxidation of 17.

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