85.8 mg of a clear, colorless oil, 3, 58%. Also obtained was 5.1 mg of recovered hydroxy acid 7. The product 3 had the following data: $[\alpha]^{25}_D$ 21.37° (c 1.17, $CHCl_3$); IR ($CHCl_3$) 3440, 1730, 1710, 1655, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (d of d, J = 8, 16 Hz, 1), 5.83 (d, J = 16 Hz, 1), 5.1–4.5 (NH), 4.85 (d of d, J = 5, 6 Hz, 1), 4.28 (q, J = 7 Hz, 2), 2.55–2.38 (m, 1), 2.05–1.78 (m, 1), 1.47 (s, 9), 1.31 (d, J = 5 Hz, 3), 1.24 (d, J = 7 Hz, 3), 1.02 (t, J = 7 Hz, 3), 0.93 (d, J = 6 Hz, 6); ^{13}C NMR δ 172.81, 165.86, 154.77, 149.16, 121.61, 60.19, 49.38, 38.41, 29.88, 19.49, 18.73, 16.57, 14.64, 14.18.

Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.43. Found: C, 63.04; H, 6.33.

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Registry No. 1, 58717-24-1; 3, 97522-37-7; 4, 77877-19-1; 5, 77877-21-5; 6, 97522-38-8; 7, 82290-72-0; 8, 97522-39-9; 10, 97522-40-2; isobutyraldehyde, 78-84-2; triethyl phosphonoacetate, 867-13-0; diethyl phosphonoacetamide, 5464-68-6; (S)-phenyl-2-methoxy-2-(trifluoromethyl)acetyl chloride, 20445-33-4; t-BOC-D-alanine, 7764-95-6.

N-Oxides of 2,2′:6′,2″-Terpyridine

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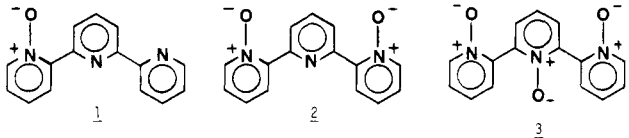
Whereas preparation of the tri-N-oxide of 2,2′:6′,2″-terpyridine (3) was described by Case in 1962,[1] the mono- and di-N-oxides (1 and 2) were previously unknown. We wish to report the preparation of these two systems and some conformational properties associated with this series of molecules.

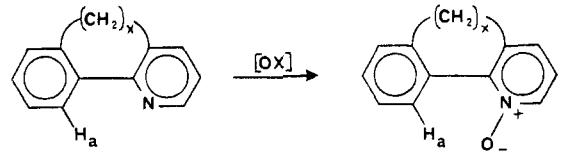


1 2 3

The tri-N-oxide 3 has been efficiently prepared (88%) by the reaction of 2,2′:6′2″-terpyridine with 30% hydrogen peroxide in acetic acid at 80 °C.[1] None of the lower N-oxides were observed in this reaction. On the other hand, the use of a stoichiometric amount of m-chloroperbenzoic acid as oxidant provides the mono-N-oxide 1 while excess of this reagent gives the di-N-oxide 2, both to the total exclusion of tri-N-oxide. Both 1 and 2 may be converted to 3 by treatment with 30% hydrogen peroxide. As expected, the increasing polarity of these substances leads to a monotonic increase in their melting points: 1 (134–135 °C), 2 (232–233 °C), and 3 (320–321 °C dec).

All three N-oxides showed a very intense and characteristic N–O stretching band at about 1250 cm^{-1} in their infrared spectra. Mass spectra were obtained by the thermospray ionization technique in which the positively charged protonated ions are observed. All three N-oxides showed a base peak equal to p + 1, giving values of m/z 250, 266, and 282 for the mono-, di-, and tri-N-oxides, respectively. Furthermore, the mono-N-oxide showed a significant peak at m/z 234, indicating the loss of one oxygen, the di-N-oxide showed peaks at m/z 250 and 234 indicating the successive loss of two oxygens, and the tri-N-oxide showed peaks at m/z 266, 250, and 234, indicating the successive loss of three oxygens. As the temperature of the thermospray nozzle was increased the proportion of deoxygenated species also increased.

Scheme I. Effect of N-Oxidation on the Bay-Region Proton of 2-Phenylpyridines



4a, X = 2; H_a = 8.28 ppm
b, X = 3; H_a = 7.71 ppm

5a, H_a = 9.38 ppm
b, H_a = 7.98 ppm

The aromatic proton resonances for terpyridine and its mono- and di-N-oxides are dispersed over almost 2 ppm making assignment of the 300-MHz NMR spectra fairly straightforward (Table I). This analysis was facilitated by comparison with the previously assigned NMR spectrum of 2,2′-bipyridine mono-N-oxide.[2] The tri-N-oxide 3 exhibits a coincidental overlap of four different resonances at about 7.85 ppm, so that complete assignment was not possible.

It is most likely that 1–3 all assume a somewhat transoid conformation such that the nitrogen lone pair electrons and the N–O moieties are oriented as far apart as possible. This geometry is substantiated by examination of the proton resonances on the central ring as one goes from terpyridine to 1 to 2 (Table I). The central $H_{4'}$ resonance is sterically and electronically unaffected by the addition of oxygen to the two neighboring pyridines and remains unchanged at 7.95–7.98 ppm. When N-1 is oxygenated, $H_{3'}$ becomes deshielded, and its resonance shifts about 0.54 ppm downfield, while $H_{5'}$ remains essentially unaffected. When N-1″ is oxygenated in 2, $H_{3'}$ is very little affected, while $H_{5'}$ moves downfield 0.47 ppm.

The degree of deshielding of $H_{3'}$ and $H_{5'}$ can also reveal information about the dihedral angle between the adjacent pyridine rings. To assist in examining this situation we considered the analogous change in chemical shift in the 3,2′-annelated 2-phenylpyridine system 4, where the dihedral angle between the two aromatic rings is controlled by the length of a polymethylene bridge (Scheme I). For system **5a**, where the bridge contains two methylene units, the dihedral angle between the phenyl and pyridyl rings as estimated from Dreiding models is about 20°. The change in chemical shift of the bay proton, H_a, upon N-oxidation is substantial (−1.1 ppm) due to its constrainment in the proximity of the deshielding N–O moiety. For **5b**, with a trimethylene bridge, the dihedral angle is estimated to be 55°, and the deshielding effect on H_a is only −0.27 ppm. Thus if we assume a proportional relationship between the changes in dihedral angle and chemical shift, for the terpyridine mono- and di-N-oxides 1 and 2, where the observed deshielding of $H_{3'}$ and $H_{5'}$ is about −0.5 ppm, we predict an intermediate dihedral angle of about 45°.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian Associates FT-80 or a Nicolet NT-300 WB spectrometer, and

(1) Case, F. H. *J. Org. Chem.* **1962**, *27*, 640.

(2) Wenkert, D.; Woodward, R. B. *J. Org. Chem.* **1983**, *48*, 283.

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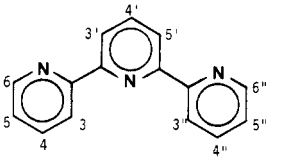
Table I. 300-MHz ^{1}H NMR Data for *N*-Oxides of 2,2′:6′,2″-Terpyridine



	3	4	5	6	3′	4′	5′	3″	4″	5″	6″
terpyridine	8.62	7.82	7.33	8.70	8.46	7.96	8.46	8.62	7.86	7.33	8.70
mono-*N*-oxide 1	8.34	~7.32	~7.32	8.34	9.00	7.95	8.47	8.47	7.81	~7.32	8.68
di-*N*-oxide 2	8.20	~7.35	~7.35	8.35	8.94	7.98	8.94	8.20	~7.35	7.35	8.35
tri-*N*-oxide 3	←	7.95–7.74	→	8.48	←		7.95–7.74	→			8.48

chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Perkin-Elmer 330 spectrometer. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933A GC–mass spectrometer or by introduction as a 0.1 M NH_4OAc solution into a Biospec LC–MS with a thermospray ionization interface. High-resolution mass spectral analyses were carried out on a Kratos MS-50TA Spectrometer at the Chemistry Department, Texas A&M University. All solvents were freshly distilled reagent grade.

2,2′:6′,2″-Terpyridine Mono-*N*-oxide (1). To 0.47 g (2 mmol) of 2,2′:6′,2″-terpyridine in 20 mL of CH_2Cl_2 was added a solution of 0.40 g (2 mmol) of 85% *m*-chloroperbenzoic acid in 20 mL of CH_2Cl_2, and the mixture was allowed to stir at room temperature for 13 h.[3] After washing with 5% Na_2CO_3 solution and drying over anhydrous $MgSO_4$, the solvent was evaporated to give 0.38 g of solid, which was chromatographed on 15 g of alumina, eluting with CH_2Cl_2 followed by EtOAc. The early fractions of CH_2Cl_2 gave 0.04 g of unreacted terpyridine, while later fractions gave 0.20 g (40%) of mono-*N*-oxide 1, mp 134–135 °C. The early EtOAc fractions gave 0.11 g of 2,2′:6′,2″-terpyridine 1,1″-di-N-oxide (2), mp 230–231 °C. The mono-*N*-oxide was characterized by its spectral properties: IR (KBr) 1582, 1568, 1430, 1255, 1104, 905, 868, 763, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, $H_{3'}$, J = 8 Hz), 8.68 (d, $H_{6''}$, J = 4.8 Hz), 8.47 (overlapping d, $H_{5'}$ and $H_{3''}$, J = 8 Hz), 8.34 (overlapping d, H_3 and H_6), 7.95 (t, $H_{4'}$, J = 8 Hz), 7.81 (t, $H_{4''}$), 7.40–7.23 (m, H_4, H_5, and $H_{5''}$); UV λ_{max} (95% EtOH) (ϵ) 305 (10 100), 275 (13 900), 225 (26 100), 207 (24 600); mass spectrum, m/z (relative intensity) 250 (M + 1, 17), 249 (M, 82), 233 (M − 16, 18), 221 (58), 117 (100), 78 (86). Anal. Calcd for $C_{15}H_{11}N_3O$: m/z 249.0902. Found: m/z 249.0901.

2,2′:6′,2″-Terpyridine 1,1″-Di-*N*-oxide (2). The procedure described above for 1 was followed using 0.47 g (2 mmol) of 2,2′,2″-terpyridine and 1.30 g (7.5 mmol) of *m*-chloroperbenzoic acid to yield 0.44 g (83%) of 2,2′:6′,2″-terpyridine 1,1″-di-*N*-oxide, which was purified by washing with acetone, mp 232–233 °C: IR (KBr) 3070, 1560, 1486, 1453, 1425, 1261, 1102, 900, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, $H_{3'}$ and $H_{5'}$, J = 8 Hz), 8.35 (d, H_6 and $H_{6''}$, J = 6.2 Hz), 8.20 (d, H_3 and $H_{3''}$, J = 8.2 Hz), 7.98 (t, $H_{4'}$, J = 8 Hz), 7.41–7.27 (m, H_4, H_5, $H_{4''}$, and $H_{5''}$); UV λ_{max} (95% EtOH) (ϵ) 235 (13 000), 204 (36 100); mass spectrum, m/z (relative intensity) 266 (M + 1, 5), 265 (M, 28), 249 (M − 16, 15), 233 (M − 32, 16), 220 (21), 105 (45), 78 (100). Anal. Calcd for $C_{15}H_{11}N_3O_2$: m/z 265.0851. Found: m/z 265.0849.

2,2′:6′,2″-Terpyridine Tri-*N*-oxide (3). A solution of 0.4 g (1.7 mmol) of 2,2′,2″-terpyridine in 2.0 mL of glacial acetic acid and 1.5 mL of 30% hydrogen peroxide was heated for 2 h at 80 °C. After addition of a further 1.5 mL of 30% hydrogen peroxide, the temperature was raised to 90 °C and maintained there for 18 h. The mixture was poured into 20 mL of acetone, and after standing for several hours, the precipitate was collected and washed with acetone to give 0.35 g (73%) of tri-*N*-oxide 3, mp 320 °C dec (lit.[1] mp 321–322 °C); IR (KBr) 1470, 1424, 1390, 1245, 1110, 905, 863, 790, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, H_6 and $H_{6''}$, J = 6.5 Hz), 7.95–7.74 (overlapping m, 9 H); mass spectrum, m/z (relative intensity) 282 (M + 1, 3), 281 (M, 10), 264 (M − 16, 6), 249 (M − 32, 2), 233 (M − 48, 5), 220 (4), 150 (20), 104 (33), 78 (100).

(3) Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721.

5,6-Dihydro-7,8-benzoquinoline *N*-Oxide (5a). The procedure described above for 1 was followed using 0.20 g (1.1 mmol) of 5,6-dihydro-7,8-benzoquinoline (**4a**)[4] and 0.21 g (1.2 mmol) of *m*-chloroperbenzoic acid to yield 0.12 g (55%) of **5a** as a white solid, mp 42–43 °C: IR (thin film) 2940, 2840, 1680, 1472, 1445, 1420, 1300, 1250, 1227, 1008, 790 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 9.38 (dd, H_{10}, J = 3.9, 5.0 Hz), 8.21 (dd, H_2, J = 2.4, 5.4 Hz), 7.41–7.20 (m, 3 H, Ar H), 7.09–7.02 (m, 2 H, Ar H), 2.84 (s, 4 H, CH_2CH_2). Anal. Calcd for $C_{13}H_{11}NO$: m/z 197.0841. Found: m/z 197.0854.

3,2′-Trimethylene-2-phenylpyridine *N*-Oxide (5b). The procedure described above for 1 was followed using 0.25 g (1.28 mmol) of 3,2′-trimethylene-2-phenylpyridine (**4b**)[5] and 0.40 g (2.32 mmol) of *m*-chloroperbenzoic acid to yield 0.14 g (35%) of **5b** as a semisolid: IR (KBr) 1580, 1530, 1420, 1390, 1192, 1069, 895, 753, 738 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.38 (dd, H_2, J = 3.0, 4.8 Hz), 7.98 (m, 1 H), 7.42–7.16 (m, 5 H, Ar H), 2.69–2.13 (m, 4 H, CH_2CH_2); ^{13}NMR (20 MHz, $CDCl_3$) δ 139.6, 139.2, 138.3, 131.8, 129.9, 129.6, 129.1, 128.1, 127.5, 125.4, 123.6, 32.0, 30.0 (2 overlapping peaks). Anal. Calcd for $C_{14}H_{13}NO$: m/z 211.0997. Found: m/z 211.1015.

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Registry No. 1, 97721-16-9; **2**, 97721-17-0; **3**, 78017-86-4; **4a**, 56568-10-6; **4b**, 97721-20-5; **5a**, 97721-18-1; **5b**, 97721-19-2; 2,2′:6′,2″-terpyridine, 1148-79-4.

(4) Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601.

(5) This material was prepared in the same manner as **4a**.[4] Complete details will be furnished in a future publication.

Synthesis of 2-*S*-Cysteinylhistidine and 2-Mercaptohistidine via Bromo Lactone Derivative of Histidine

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Aromatic amino acids may be found in nature combined covalently with cysteine through a thioether bond. 2-*S*-Cysteinyltryptophan (tryptathionine) and its derivatives are constituents of toxic peptides from fungus *Amanita phalloides*.[1] Savige and Fontana[2] have reported a syn-

(1) Whieland, Th. In "Progress in the Chemistry of Organic Natural Compounds"; Zechmeister, L. Z., Ed.; Springer-Verlag: New York, 1967; Vol. 25, pp 214–250.

0022-3263/85/1950-3636$01.50/0