

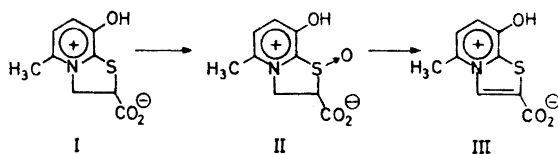
NMR Studies of Sulphoxidations in the Dihydrothiazolo- [3,2-a]pyridinium- and quinolinium System

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Sulphoxidation of dihydrothiazolo[3,2-a]pyridinium compounds with performic acid has been studied using NMR. Relative oxidation rates and diastereoisomer ratios of sulphoxides have been measured. Dihydrothiazolo[3,2-a]pyridinium sulphoxides with an electro-negative substituent in the 2-position in aqueous formic acid gave the corresponding thiazoles while the quinoline analogues were substituted at the α -quinolyl *S*-carbon. *S*-Carboxymethio α -pyridyl and α -quinolyl ethers behaved correspondingly.

Sulphoxides with activating α -substituents are rearranged by heating under acidic conditions.¹ Performic acid oxidation of 8-hydroxy-5-methyl-dihydrothiazolo[3,2-a]pyridinium-2-carboxylate (I) in the cold did not give the sulphoxide (II) but mainly the thiazole (III),² probably through rearrangement of the sulphoxide intermediate with water elimination.



This oxidation has now been conveniently studied by performing the reaction at 4.5°C in the NMR tube. Use of performic acid, generated from formic acid with 85 % hydrogen peroxide, gave the sulphoxide (II) in the diastereoisomer ratio 1:1. With 35 % H₂O₂ mainly the thiazole (III) was formed. This reaction also goes through the sulphoxide since addition of water to the sulphoxide in the stronger peroxide solution gave the thiazole. The above results appear to support the suggested mechanism of an intermediate nucleophilic attack of water at the 2-position in the sulphoxide.²

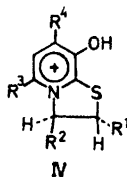
The *cis/trans* ratios in the diastereoisomer sulphoxides which previously was determined by paper-chromatography³ now has been confirmed by NMR.

The compounds I and IVc which both gave sulphoxides in a diastereoisomer ratio of about 1:1 showed a difference in the chemical shift of about 2 cps between the protons of the methyl groups in the sulphoxide diastereoisomer. The sulphoxide of the 2,3-dicarboxy derivative (IVa) showed only one signal for the methyl protons (11 cps downfield from the sulphide). The signals from the 2- and 3-methine protons also appeared as singlets, 14 cps and 12 cps downfield compared to the sulphide, which means that only one diastereomer was formed. Since the 2,3-carboxy groups are *trans* and the 3-carboxy derivative (IVb) gives mainly the *cis* sulphoxide this must be the 3-*cis* isomer with respect to the sulphinyl group.

Table 1. Reaction time for 80 % oxidation with 85 % H₂O₂ in formic acid at 4.5°C.

Compound	Time, min	Compound	Time, min
IVb	10	IVa	75
IVd	12	IVf	100
IVc	14	V	70
IVe	23	XI	6
I	30		

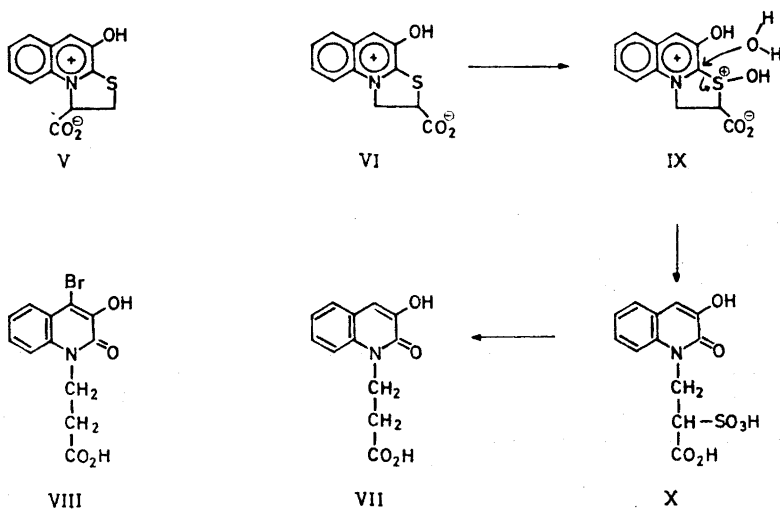
The rate of sulphoxide formation was only weakly influenced by the substituents in the 3-position (IV b,c,d); Table 1. A 3-carboxy group provided in addition to the stereospecific oxidation also the fastest reaction. This was previously suggested³ but never shown because of inadequate measuring methods. The reactions were all finished within less than 20 min. A carboxy group in the 2-position increased the reaction time (for 80 % oxidation) to 30 min (compared to 12 min with IVd). The 2,3-dicarboxy compound (IVa) increased this further to 75 min (Table 1). Substituents in the pyridine ring produced significant rate variations. Thus the desmethyl derivative (IV f) and the 7-bromo compound (IV e) both increased the oxidation time substantially.



- IV a R¹ = R² = CO₂H, R³ = CH₃, R⁴ = H
 b R¹ = H, R² = CO₂H, R³ = CH₃, R⁴ = H
 c R¹ = H, R² = CONH₂, R³ = CH₃, R⁴ = H
 d R¹ = R² = H, R³ = CH₃, R⁴ = H
 e R¹ = CH₃, R² = CO₂H, R³ = CH₃, R⁴ = Br
 f R¹ = CO₂H, R² = R³ = R⁴ = H

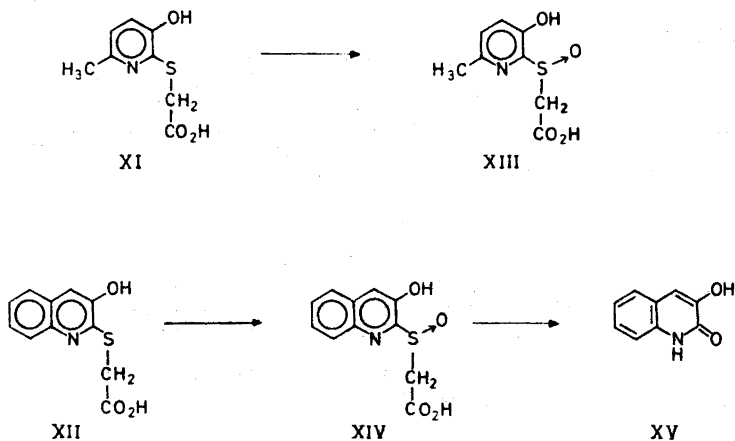
The benzene ring in the quinoline (V) increased the reaction time (70 min) relative to the pyridine (IVb) (10 min) and the oxidation also gave several

products. Oxidation of the 2-carboxy-quinoline derivative (VI) was difficult to follow in NMR because of overlap of signals, but isolation gave as the major product the ring opened quinoline (VII). The hydrobromide of VI gave the 4-bromo analogue (VIII). The structures were deduced from the mass spectra (M , $M - CO_2H$, $M - CO_2H - CHCH_2$) and from the NMR (two triplets of two protons each).



The initially formed sulphoxide (IX), protonized at the sulphanyl oxygen, evidently is attacked by water at the α -pyridyl carbon. The intermediate sulphenic acid then is oxidized to the activated sulphenic acid (X) which is easily hydrolyzed.⁴

In a further study of the difference in reactivity of the pyridine and the quinoline ring the *S*-carboxymethio compounds (XI and XII) were oxidized.



Both gave the sulphoxides XIII and XIV, in the NMR characterized by the AB-quartet of the methylene protons α to the sulphoxide group. The quinoline sulphoxide, however, was not stable and reacted further to the 2-quinolone (XV). The pyridine sulphoxide did not react under these conditions.

EXPERIMENTAL

The NMR spectra were recorded on a Varian A-100 instrument and the high resolution mass spectra on an AEI MS-902 double focusing mass spectrometer.

Performic acid solution for NMR use. Cold 85 % H_2O_2 (1 ml) was added to formic acid (9 ml). The solution was kept at 0° for 1 h. 0.2 ml of this solution contained 4×10^{-4} mol peroxide.

Oxidation in the NMR tube. The sulphides were synthesized as previously^{3,5} described. To a solution of a sulphide (10^{-4} mol) in formic acid (0.3 ml) at 0° was added 0.25 ml of the performic acid solution. The tube was shaken and spectra recorded at 4.5°C with intervals. In the sulphoxides the 5-methyl singlet was shifted 10–15 cps downfield compared to the sulphides. The methyl signals was split into a doublet in the diastereoisomeric sulphoxides. The desmethyl derivative and the quinoline compounds were studied at the dihydrothiazolo ring protons, which gave less accurate measurements.

4-Bromo-1-(β -carboxyethyl)-3-hydroxy-2-quinolone (VIII). To a solution of 10-hydroxy-2-carboxy-dihydrothiazolo[3,2-a]-quinolinium bromide⁵ (0.66 g, 0.02 mol) in formic acid (50 ml) was added 35 % H_2O_2 (0.8 ml, 0.01 mol). After two days at 4–5° the solution was evaporated, the residue treated with hot acetone (10 ml), the solution filtered and water (30 ml) added to the filtrate. The precipitate after 3 days (0.45 g, 73 %) was dissolved in N NaOH and reprecipitated with N HCl, m.p. 225–228°. (Found: C 45.83; H 3.23; N 4.43; Br 25.35. Calc. for $\text{C}_{12}\text{H}_{10}\text{BrNO}_4$: C 46.10; H 3.21; N 4.48; Br 25.60.) MS fragmentations: M (m/e 313, 311), M– CO_2H , M– CO_2H –CHCH₂. NMR in TFA showed two triplets at 5.0 and 6.9 τ ($J = 7.0$ cps), each containing 2 protons in addition to the 4 aromatic protons at 1.7–2.4 τ . UV. λ_{max} (log ϵ) N NaOH: 342 (4.15), 330 (4.13), 305 sh (3.76), 295 sh (3.71), 253 (4.27); N HCl: 333 (3.79), 320 (3.92), 292 (3.84), 283 (3.83), 250 sh (3.99), 240 sh (4.16).

The zwitterion was oxidized in the same way for comparative purposes. The product (VII) showed the corresponding MS fragments M (m/e 234, M–45, M–72) and the similar triplets in NMR.

Oxidation of 2-carboxymethio-3-hydroxy-6-methyl-pyridine. To the sulphide³ (3.0 g, 0.015 mol) dissolved in formic acid (100 ml) was added 35 % H_2O_2 (2.3 ml, 0.023 mol). After 24 h at 4–5°C the solution was evaporated and water (30 ml) added. The precipitated sulphoxide (XIII) was filtered off after 2 days, 2.7 g (85 %), m.p. 154–157°C. (Found: C 44.51; H 4.25; N 6.30. Calc. for $\text{C}_7\text{H}_9\text{NO}_2\text{S}$: C 44.65; H 4.19; N 6.51.) IR_{KBr}. Sulphoxide band at 1040 cm^{-1} . UV. N NaOH: 325 (3.82), 245 (3.87). N HCl: 310 (4.15), 230 sh (3.80). NMR in TFA: Aromatic AB quartet at 1.78 τ and 2.05 τ ($J = 9.0$ cps), methyl singlet at 7.0 τ and methylene AB quartet at 5.28 τ and 5.50 τ ($J = 16.0$ cps).

Oxidation of 2-carboxymethio-3-hydroxy-quinoline. To the sulphide⁶ (0.235 g, 0.001 mol) in formic acid (10 ml) was added 35 % H_2O_2 (0.4 ml, 0.004 mol) at 0°. The solution was evaporated after 24 h at 4–5°C and water (25 ml) added. The precipitate after 2 days was filtered off and dried, 0.15 g. Paper chromatography, m.p., MS and NMR showed 3-hydroxy-2-quinolone in about 85 % yield.

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