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N-Quaternary Compounds

Part XXI.[1] Sulphoxidation

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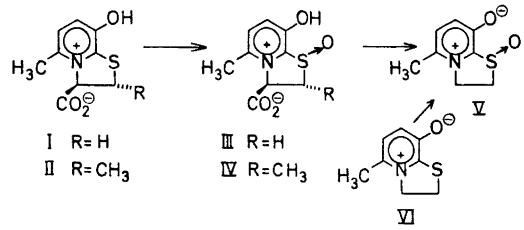
8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate under the influence of oxidative agents gave mainly the *cis* sulphoxide through carboxyl participation. Oxidation of the 2-carboxy derivative led to water elimination from the sulphoxide. The major product was the corresponding thiazole, while the minor products arose by opening of the ring and further oxidation of the sulphur to sulphonic acid. The 2,3-dicarboxy derivative was decarboxylated in the 3-position. Possible reaction mechanisms are discussed.

Peracid oxidation of I has been found to give a diastereomeric sulphoxide ratio 9 : 1.[2] A *trans* methyl group in the 2-position increases the stereoselectivity of the oxidation further.[2] The sulphinyl oxygen in the major isomer was by NMR evidence assigned [2] a *cis* configuration with respect to the carboxy group, and this assignment has been verified by X-ray analysis.[3]



About the same product ratio has now been found, using other oxidizing agents. Thus both dinitrogen tetroxide, ozone in formic acid, and D-(+)-monopercamphoric acid in DMF with perchloric or sulphuric acid gave mainly the *cis* isomer. Our explanation for *cis* oxidation is based on kinetic control, in that the carboxy group is either preferentially oxidized or forms a complex with the oxidizing agent, causing preferential intramolecular oxidation. Therefore, the participating carboxy group and the sulphinyl oxygen must be *cis*. We have now tested the postulated mechanism experimentally by

looking at other possible pathways. Firstly, the observed product ratio could be due to equilibration. Epimerization could occur both at the sulphinyl sulphur and at the chiral carbon.

In a sterically, non-selective oxidation, followed by epimerization at either the carbon or the sulphur, to give the major sulphoxide isomer, the decarboxylated sulphoxide would be largely racemized. The high optical purity of V, however, excludes any such epimerization. If the sulphur were selectively *trans* oxidized with respect to the carboxy group, followed by epimerization at carbon-3, deoxygenation should give the sulphide I with opposite configuration. The major sulphoxide diastereomer (III) was therefore catalytically reduced. The product was largely racemized during the reduction experiment, but the sign of the rotation was as in the original sulphide.

The minor *trans* diastereomer was not isolated pure, but was enriched to a 2 : 1 *trans/cis* ratio. This ratio did not appear to change during acid type epimerization experiments.[4] Therefore, no equilibration occurs during the oxidation. In neutral or near neutral solutions, decarboxylation is the most important reaction.

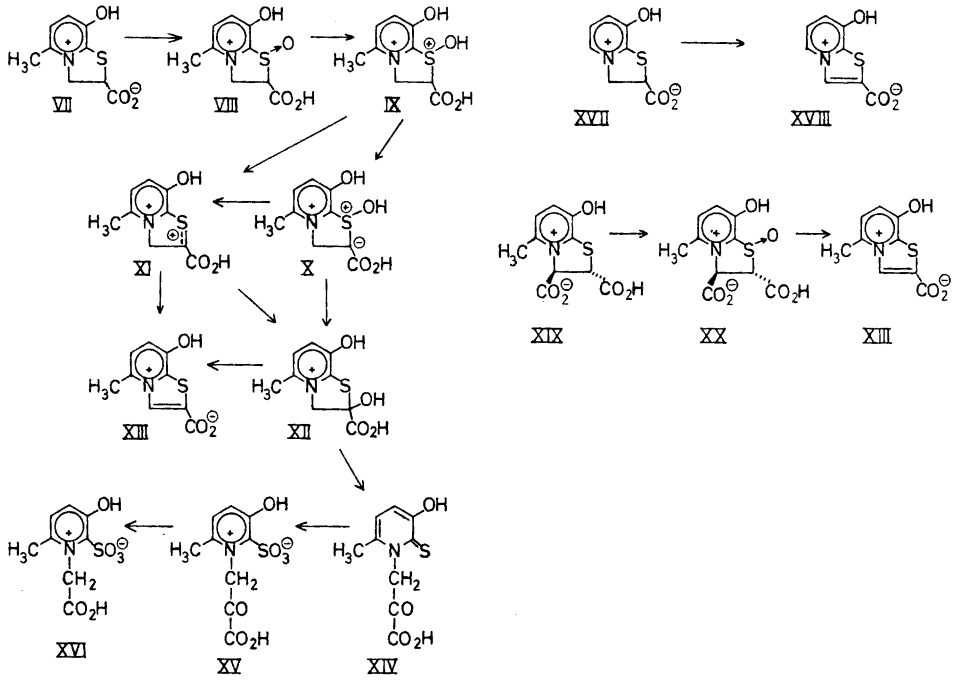
Configurational assignments based on the Cram-Prelog rule have been applied to sulphoxides, formed by the use of chiral peracids, but doubt has been cast on the validity of such interpretations.[5] Since we have as reference a sulphoxide with known absolute configuration, *e.g.* *S*-configuration [2] of (V) from the L-acid (I), we would have a means of assigning the stereochemistry in any selective oxidation. Our experiments with D-(+)-monopercamphoric acid oxidation of the decarboxy sulphide (VI), however, gave only optically inactive sulphoxide.

The effect of a 2-carboxy group on the peracid oxidation of the sulphur was studied next. In performic acid, a major yellow product and two minor products, one blue fluorescent, the other absorbing in UV light, were formed. The major product and the minor absorbing component were isolated after crystallization from water and separated by preparative paper chromatography. The major product showed no sulphoxide absorption in IR (KBr), but had a carbonyl band at 1630 cm^{-1}. The NMR in TFA showed a third aromatic proton as a singlet at 0.8 τ. The long-wave UV absorption maxima were at 370 mμ (NaOH) and 345 mμ (HCl). The UV and NMR data are as previously reported for thiazolo[3,2-a]pyridinium-8-oxides.[6] The mass spectrum showed no molecular ion because of decarboxylation, but the $(M-CO_2)$ peak at *m/e* 165 was the base peak in the spectrum, and the fragmentation followed the established pattern.[7]

The minor component from chromatography showed carbonyl stretching at 1695 cm^{-1} (KBr) and a methylene singlet at 4.3 τ (TFA). The lack of fluorescense in UV light and the long-wave absorption maxima at 370 mμ (NaOH) and 347 mμ (HCl) would suggest the compound to be an *N*-alkylpyrid-2-thione.[8] This was readily verified by mass spectrometry, and structure XIV could be assigned to the product. Thus the molecular ion is at *m/e* 227 ($C_9H_9NO_4S$), which is 30 % of the base peak at *m/e* 182 ($M-CO_2H$). The other diagnostically important fragments in the higher mass region are at *m/e* 155 ($M-COCO_2$), at *m/e* 154 ($M-COCO_2H$), and at *m/e* 141 ($M-CH_2COCO_2$).

When the thiolactam (XIV) was further treated with performic acid, the third component was formed. This product has been identified as the sulphonic acid XVI. Strong sulphonyl absorption is present in the IR spectrum (KBr) at 1045 cm^{-1}, a weaker band at 1025 cm^{-1}, besides strong absorption at 1220 cm^{-1} and 1180 cm^{-1}. The methylene protons in NMR (TFA) are at 3.9 τ, and the compound undergoes a red shift in UV from 311 mμ in HCl to 356 mμ in NaOH. The mass spectrum is also in accordance with the assigned structure. The highest mass unit is at *m/e* 203 ($M-CO_2$), but the most significant peak is at *m/e* 183 ($M-SO_2$), due to pyrolytic SO_2 expulsion to give the corresponding 2-lactam ($C_8H_9NO_4$). The base peak is at *m/e* 139 ($M-SO_2-CO_2$). Other important fragments are at *m/e* 123 ($M-SO_3-CO_2$) and *m/e* 167 ($M-SO_2-H_2O$).

The explanation for the observed products lies in the acidity of the C-2 proton in VIII. The acidity is due to the electronegative carboxy and sulphinyl groups. In acid solution, the sulphinyl oxygen will be protonated, whereby the acidity of the methine carbon is further increased. Therefore, it seems feasible that transient generation of an ylide (X) occurs with migration of the protonated sulphinyl oxygen to the C-2 carbon, giving a cyclic hemithioketal



(XII). Our experimental evidence, however, does not exclude a second intermolecular mechanism which goes through a stabilized carbonium ion (XI), as reported for the Pummerer reaction,[9] and favoured for the α-alkoxylation

of sulphides in alcoholic *t*-butyl hypochlorite.[10] Proton expulsion from the activated methylene carbon in XI gives the thiazole (XIII) directly. Alternatively, XI reacts with water to the hemithioketal (XII). If XI really is an intermediate stage, it must at least to some degree react with water, to explain the formation of the monocyclic thione (XIV). The hemithioketal can react further by two competing pathways; either water elimination with aromatization (XIII), which is strongly favoured, or by ring opening to the thiolactam (XIV), which is further oxidized to a sulphonic acid (XV) and oxidatively decarboxylated (XVI). The relative stereochemistry of the sulphoxide first formed should be of little importance for the reaction rate, if the further reaction goes through an ylide (X), where the original stereochemistry is lost. If XI is formed directly from IX by water elimination, however, the relative stereochemistry would be expected to be important. Since VIII was reacted further as formed in the oxidation, the relative stereochemistry of VIII is not known, and therefore no mechanistic decision can be made.

Relevant examples to the above reaction sequence can be found in the oxidation of phenyl thioacetic acid, followed by rearrangement of the sulphoxide in mineral acid, when thiophenol and glyoxylic acid were formed.[11] Later, this work was extended to include derivatives with other electron withdrawing substituents attached to the α-carbon of the sulphide.[12]

Two more available sulphoxides with an α-electron attracting group have been oxidized. The 5-desmethyl analogue (XVII) was oxidized at a slower rate than VII, but the major product was again a thiazole (XVIII). In the oxidation of the *trans*-2,6-dicarboxy derivative (XIX), the 2-carboxythiazole (XIII) was isolated. The experimental data do not tell at which stage the decarboxylation takes place, but in view of the very ready decarboxylation of the 3-carboxy sulphoxide (III), it seems most likely that the intermediate sulphoxide (XX) is decarboxylated before aromatization.

The 3-carboxy sulphoxide (III) is not readily dehydrated, since the C-2 carbon lacks a stabilizing group. No aromatization was seen chromatographically in the acid epimerization experiments, except after pertrifluoroacetic acid treatment, when some product with the thiazolo-pyridinium nucleus was formed.

EXPERIMENTAL

8-Hydroxy-5-methyl-1-oxo-dihydrothiazolo[3,2-a]pyridinium-3-carboxylate (III). The oxidation of the sulphide (I) with performic acid was carried out as previously described,[2] and the major *cis* isomer isolated by fractional crystallization from water. The minor *trans* isomer was enriched to a 2 : 1 *trans/cis* ratio in this way, and obtained by freeze-drying.

Epimerization experiments. The enriched *trans* sulphoxide isomer (III) was left in the cold in either formic acid, performic acid, trifluoroacetic acid, pertrifluoroacetic acid, trifluoroacetic acid to which was added KNO_3, the latter with added water, and finally in dinitrogen tetroxide at −10°. Chromatography [2] showed no change in the *trans/cis* ratio.

Catalytic reduction of the sulphoxide (III). 10 mg of the *cis* sulphoxide from L-(−)-8-hydroxy-5-methyldihydrothiothiazolo[3,2-a]pyridinium-3-carboxylate, $[\alpha]_D^{25} = +150°$ ($c = 0.75$ in H_2O), were dissolved in water (2 ml), ethanol (40 ml) was added, and the solution hydrogenated at 20° and atmospheric pressure over platinum oxide for 12 h. The catalyst was removed by filtration, and the filtrate evaporated to yield the chromatographically pure sulphoxide; $[\alpha]_D^{25} = -13°$ ($c = 0.33$ in H_2O), corresponding to 10 % optical purity of the L-enantiomer.[2]

Peracid oxidation of 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-2-carboxylate (VII). Formation of XIII, XIV, and XVI. To 8-hydroxy-5-methyldihydrothiazolo[3,2-a]-pyridinium-2-carboxylate (1.6 g, 0.008 mol) in formic acid (100 ml) was added 30% hydrogen peroxide (2.0 ml, 0.025 mol). The solution was left in the cold for 12 h, evaporated at reduced pressure, water (50 ml) was added, and the solution left in the cold overnight. The precipitated solid (1.1 g) was shown by NMR to consist of 80 % of the thiazole (XIII) and 20 % of the thione (XIV). Chromatography also showed small amounts of the sulphonic acid (XVI). The two major products were separated by preparative paper chromatography on Whatman No. 4 paper, using the system BuOH : EtOH : NH_3 : H_2O (4 : 1: 2 : 1). The thiazole (XIII) has the higher R_F value. The separated products were eluated with formic acid, the eluates freeze-dried, and the residue crystallized from water. The yellow *8-hydroxy-5-methylthiazolo[3,2-a]pyridinium-2-carboxylate (XIII)* thus obtained had m.p. 172 – 174°. (Found: C 47.83; H 3.78; N 6.13. Calc. for $C_9H_7NO_3S.H_2O$: C 47.57; H 3.96; N 6.17.) NMR in TFA: AB quartet at 2.12 – 2.23 τ with $J = 9.0$ cps (pyridine protons); singlet at 0.80 τ, due to thiazole proton, and a methyl group singlet at 6.95 τ. UV maxima in N HCl at 347 mμ (3.97), 275 mμ (2.88), and 245 mμ (4.10); in N NaOH at 370 mμ (3.97), 306 mμ (2.75), 251 mμ (4.14), and 240 mμ (4.15).

The other product, *3-hydroxy-6-methyl-N-β-oxalylmethylpyrid-2-thione* (XIV), had m.p. 258 – 260°. (Found: C 47.60; H 3.64; N 6.20. Calc. for $C_9H_9NO_4S$: C 47.57; H 3.96; N 6.17.) NMR in TFA: AB quartet at 2.20 – 2.53 τ, with $J = 8.0$ cps (pyridine protons); methylene singlet at 4.35 τ, and methyl singlet at 7.17 τ. UV maxima in N HCl at 337 mμ (4.02) and 241 mμ (3.73); in N NaOH at 370 mμ (3.97) and 263 mμ (3.85).

The aqueous filtrate after removal of the above products was concentrated to about 5 ml, and left in the cold when 0.15 g of a solid was precipitated, which was found to be a mixture of all three components. The filtrate was then concentrated to 1 ml and left at 5° for 1 week, when the third component (0.10 g) was precipitated in pure state. *N-Carboxymethyl-3-hydroxy-6-methylpyridinium-2-sulphonate (XVI)* thus obtained had m.p. 183 – 185°. (Found: C 38.70; H 3.78; N 5.82. Calc. for $C_8H_9NO_6S$: C 38.90; H 3.65; N 5.67.) NMR in TFA: AB quartet 1.92 – 2.05 τ, with $J = 9.0$ cps (pyridine protons); methylene protons at 3.90 τ, and methyl protons at 7.08 τ. UV maxima in N HCl at 310 mμ (3.91 and 230 mμ (3.70); in N NaOH at 354 mμ (3.82) and 255 mμ (3.82).

Peracid oxidation of the trans *2,3-dicarboxy derivative (XIX). Formation of XIII.* The dicarboxy derivative (XIX) (0.16 g, 0.006 mol) was dissolved in formic acid (10 ml), and 30 % hydrogen peroxide (0.25 ml, 0.003 mol) in formic acid (10 ml) was added. The solution was left for 2 days in the cold, when chromatography showed the reaction product to be nearly homogeneous. The solution was then freeze-dried, and the residue crystallized from water. The yellow crystalline material obtained (0.12 g, 91 %) was found to be identical with 8-hydroxy-5-methylthiazolo[3,2-a]pyridinium-2-carboxylate (XIII), as obtained above.

8-Hydroxythiazolo[3,2-a]pyridinium-2-carboxylate (XVIII). 8-Hydroxydihydrothiazolo [3,2-a]pyridinium-2-carboxylate (1.0 g, 0.005 mol) was dissolved in formic acid (100 ml), containing 30 % H_2O_2 (0.8 ml, 0.01 mol). The solution was left at 5° for 2 days, freeze-dried, and the solid residue triturated with water (2 ml). The insoluble yellow product was dissolved in a little N NaOH and reprecipitated at pH about 3 by N HCl addition; yield 0.7 g (65 %), m.p. 190 – 192°. (Found: C 45.13; H 3.11; N 6.36. Calc. for $C_8H_5NO_3S.H_2O$: C 45.10; H 3.28; N 6.57.) NMR in TFA showed three pyridine protons in an ABX pattern at 1.10 τ, and at 2.0 – 3.0 τ, and a thiazole proton at 0.80 τ. UV maxima in N HCl at 332 mμ (4.01) and 234 mμ (4.03); in N NaOH at 361 mμ (4.00), 255 mμ (4.02), and at 237 mμ (4.03). The carbonyl absorption was at 1605 cm^{-1} (KBr).

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