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Short Communications

Stereochemistry of the Oxidation of Nicotine to its 1′-*N*-Oxides. The Action of Tungstate(VI) and Molybdate(VI)

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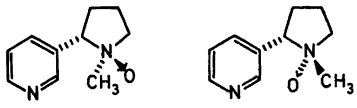
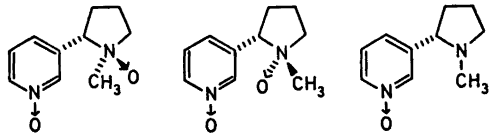
The stereochemistry of *N*-alkylation reactions in heterocyclic systems has been extensively investigated, but less interest has been paid to the corresponding oxidations to amine *N*-oxides.[1–9] Treatment of nicotine with 10 % aqueous hydrogen peroxide mainly brings about oxygenation at the aliphatic nitrogen atom, and a mixture of 1′*R*,2′*S* (*cis*) (*1*) and 1′*S*,2′*S* (*trans*) isomers (*2*) in the ratio 1:2.3 is obtained.[4] Oxidation with *m*-chloroperbenzoic acid gives the same compounds in the ratio 1:2.[5] The isomers *1* and *2* have been separated by preparative paper chromatography [5,6] and by fractional precipitation with ammonium reineckate, $NH_4[Cr(NH_3)_2(SCN)_4]$.[6]



1 *2*



3 *4* *5*

For a study of the stereospecificity of some *N*-oxide degradation reactions, *1* and *2* were needed in stereochemically pure forms. To facilitate the isolation of *1*, it was desirable to start with a mixture which contained a higher proportion of *1* than the preparations described above. Nicotine has been shown by NMR spectroscopy to consist of about 90 % of the *trans* form (with the methyl and pyridyl groups on different sides of the five-membered ring).[10] A ratio of the isomers *1*:*2* of 0.5 thus means that the *N*-oxidising reagent (hydrogen peroxide or *m*-chloroperbenzoic acid) reacts almost five times faster with the *cis* form than with the *trans* form. We anticipated that sterically more demanding reagents should be even more effective in discriminating between the *cis* and *trans* forms of nicotine. This proved to be the case; for instance, peroxotungstates [11] or peroxomolybdates,[11] obtained *in situ* from aqueous hydrogen peroxide and alkali tungstates(VI) or molybdates(VI), gave mixtures containing more *1* than *2* (Table 1). An analogous compound, MoO_5.HMPA.H_2O,* easily obtained in a crystalline state,[12] oxidised nicotine in dioxane solution (22 °C, 18 h) to a mixture of *1* and *2* in a ratio of 1.5. Peroxotungstates have previously been used for the oxidation of amines,[13,14] but the stereochemical characteristics of the reaction have never been exploited.

The addition of molybdate or, in particular, tungstate not only affected the stereochemistry of the *N*-oxidation reaction but also furnished a more reactive reagent. This is evident from the ^{1}H NMR [4] and HPLC * analyses of the products of the experiments referred to in

* HMPA hexamethylphosphoric amide. HPLC high performance liquid chromatography.

Table 1. Influence of molybdate(VI) and tungstate(VI) on the stereochemistry of oxidation of nicotine to its 1′-*N*-oxides *1* and *2*.[a]

Added salt	Mol equiv. added [b]	Ratio *1*:*2* [c]
K_2MoO_4	0	0.3
	0.05	1.1
	0.20	2.0
	0.80	2.2
Na_2WO_4	0	0.3
	0.05	1.8
	0.20	2.4
	0.80	2.7

[a] Reaction mixtures contained hydrogen peroxide (≈8 mol equivalents, 11 % solution). [b] Nicotine = 1. [c] Obtained by triangulation of HPLC peaks.

Table 1. Only 3 % of the nicotine was oxidised when hydrogen peroxide was the sole reagent. Addition of 0.05 mol equivalents of sodium tungstate raised this figure to 40 %. At the same time, however, oxidation at the less reactive pyridyl nitrogen atom became more important. Only traces of the di-*N*-oxides *3* and *4* were formed in the absence of salts, but with 0.80 mol equivalents of sodium tungstate present, *3* and *4* together amounted to approximately one fourth of the oxidised material. The *N*-oxide *5* could also be detected. In all experiments, the ratio of *3:4* was lower than the ratio of *1:2*. A similar result was obtained in the essentially quantitative oxidation[15] of a mixture of mono-*N*-oxides (*1:2* = 1.5) with *m*-chloroperbenzoic acid into di-*N*-oxides (*3:4* = 0.8).

It is reasonable to assume that *3* is thermodynamically less stable than *4*, and the most likely explanation of the low ratios of *3:4* in the above and previous[4] reactions is that a decomposition of *3* takes place in the presence of peracid, possibly followed by reoxidation to *4*. Support for this view comes from an experiment in which a solution of *3*, *4* and *m*-chloroperbenzoic acid (0.5 mol equiv.) in chloroform was left at 22 °C. After 20 h, the ratio of *3:4* had decreased from 11.6 to 6.7, and after five days to 2.8, as found by HPLC. No similar effects could be observed when nicotine or benzoic acid were used instead of the peracid, either alone or in combination. The latter experiments rule out a transoxygenation reaction in which the unshared electron pair of the amine attacks the oxygen atom of a protonated *N*-oxide to give a new N – O bond and a simultaneous rupture of the old one. An analogous reaction probably occurs in the deoxygenation of amine oxides with triphenylphosphine.[16] In the reaction of this phosphine with a mixture of *1* and *2*, a high preference (87 %) for reaction with *1* was observed.

The *N*-oxidation method using *tert*-butyl hydroperoxide and bis(2,4-pentanedionato)-vanadium(IV) oxide in refluxing *tert*-butyl alcohol (40 min)[17] gave a ratio of *1:2* = 1.1.

In the large-scale preparation of *1*, the oxidation was carried out using 0.05 mol equivalents of sodium tungstate (0 °C, 2 h) and the products were then separated by chromatography on alumina. For the preparation of *2*, it proved advantageous to oxidise with *m*-chloroperbenzoic acid according to the literature conditions[15] to obtain a ratio of *1:2* = 0.18.

Experimental. HPLC was performed on a LiChrosorb ALOX T column (10 μ, 10 × 250 mm, Altex) mounted to an LDC pump and UV monitor (254 nm). Solvent: diethyl ether – methanol – water (10:10:1); flow rate: 2.5 ml/min. The retention times were: nicotine, 5.6 min; *5*, 6.2; *2*, 7.3; *1*, 8.8; *4*, 21.5; *3*, 50 min. Column chromatography (≈1 g) was carried out on basic alumina (Merck) (4 × 40 cm) with diethyl ether – methanol – conc. aqueous ammonia (100:25:2) as solvent. NMR spectra were recorded on a JEOL JNM-FX 100 instrument. The samples were dissolved in D_2O and sodium 3-(trimethylsilyl)propanesulfonate was used as reference. The *cis:trans* ratios were determined by integration over the N-CH_3 signals; the separation of these signals from others was best for acidic solutions. Similar ratios were obtained from HPLC assuming equal responses of stereoisomers *1* and *2* (or *3* and *4*) to the UV detector. On the other hand, *3* and *4* (and presumably *5* as well) gave much better responses than did *1* and *2*. This is to be expected since the extinction coefficient of pyridine-*N*-oxide at 255 nm is approximately 3.4 times that of pyridine.[18]

Oxidation with peroxomolybdates or peroxotungstates. To an ice-cooled and stirred solution of nicotine (0.20 g, 1.23 mmol) and the tungstate or molybdate in water (2.5 g), ice-cooled aqueous hydrogen peroxide (1.0 g, 35 %, 10.3 mmol) was added. After 1 h, an aliquot (0.5 – 1 ml) was taken out and rapidly subjected to ion exchange on a Dowex 1X4 column (chloride form, 5 × 0.5 cm) to remove the W and Mo-containing anions. The yellow (tungstate) or brown (molybdate) colours were thus removed. The eluate was then treated with an excess of manganese dioxide (0 °C) to destroy excess hydrogen peroxide. When the evolution of O_2 had ceased (≈5 min), the solution was filtered. For the HPLC examination, the solution was diluted with the solvent system used, and for the NMR investigation, the solution was acidified (pH ≈ 4) and the water evaporated below 30 °C. The residue was then dissolved in D_2O with or without added NaOD.

Preparation of 1. The oxidation was performed as described above using 0.05 mol equivalent of sodium tungstate, but the reaction time was extended to 2 h. Starting with 1 g of nicotine, 0.1 g of *1* (containing less than 2 % of *2*) was obtained after the column chromatography described above.

Preparation of 2. Nicotine (1.60 g) was oxidized as described.[15] The *N*-oxides were extracted with 1 M hydrochloric acid (2 × 10 ml) and the water was then evaporated under reduced pressure (25 °C). The residue was subjected to ion exchange on a Dowex 1X4 (OH^-) column with methanol as solvent. ^1H NMR and HPLC of the product showed a ratio of *1:2* = 0.18. After the column chromatography described above, 0.2 g of *2* (containing less than 2 % of *1*) was obtained.

Reactions with triphenylphosphine. The starting solutions contained *1* (0.084 mmol) and *2* (0.046 mmol) in acetic acid (1 ml). Different amounts of triphenylphosphine (0, 0.024, 0.045, and 0.062 mmol) were added and the four reaction mixtures were then heated (60 °C, 18 h). Aliquots (≈0.5 ml) were taken out, cooled and neutralised with conc. aqueous ammonia. After filtration through a column of basic alumina (0.5 × 1.5 cm), each sample was

examined by HPLC as described above. Peak areas were determined by triangulation. Results (mmol PPh_3, ratio of *1:2*): 0, 1.76 (2 % of nicotine was formed); 0.024, 1.34; 0.045, 0.96; 0.062, 0.69. These values correspond to an 87 % preference for reaction with *1*.

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Homogeneous Electron Transfer Reactions. Increased Selectivity in Reduction of Some Disulfones Using Indirect Electrolysis

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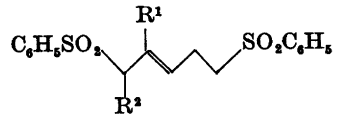
Electrocatalytic reductions in organic electrochemistry have recently been the subject of several papers.[1–11] Anion radicals or dianions are generated electrochemically, and these species transfer electrons to the substrate. Quite frequently such a homogeneous electron transfer occurs without consumption of the catalyst, whereas in other cases, especially when the substrate is an aliphatic halide,[1] the catalyst concentration decreases due to a coupling reaction.

Indirect electrolysis has certain advantages and disadvantages compared to direct electrolysis. Among the advantages of indirect electrolysis is the relative independence of cell-design. In an ordinary laboratory cell the current distribution at the working electrodes is not uniform and the effective potential is therefore not the same over the whole electrode. It is thus difficult to reduce selectively one of two electroactive groups when the difference in reduction potential between the groups is less than 0.15 V. Other advantages are that complications with inhibitions occurring during macroelectrolysis may be overcome, lower electrode potentials may be employed, and higher current densities may be used especially towards the end of the experiment, compared to direct electrolysis.

In the present investigation a comparison is made with regard to the selectivity of direct and indirect electrochemical reduction of some compounds XRY where the difference in peak potential between the groups X and Y is 0.1 – 0.15 V; X and Y are here both benzenesulfonyl groups, X being allylic, whereas Y is not activated. The following compounds were included: 2-Methyl-1,5-bis(benzenesulfonyl) pent-2-ene(*1*), 2-ethyl-1,5-bis(benzenesulfonyl)-pent-2-ene (*2*), and 2,6-dimethyl-5,9-bis(benzenesulfonyl)-nona-2,6-diene (*3*).



1, $R^1 = CH_3$, $R^2 = H$; *2*, $R^1 = C_2H_5$, $R^2 = H$; *3*, $R^1 = CH_3$, $R^2 = CH_2CH=C(CH_3)_2$.