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THE OXIDATION OF HYDROXYLAMINE BY FREMY'S SALT. PREPARATION OF N-NITROSAMINES AND TETRAZENES

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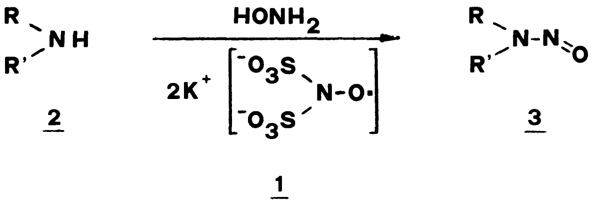
Treatment of secondary amines with Fremy's salt in aqueous sodium carbonate solution and in the presence of hydroxylamine gives a high yield of either N-nitrosamines or sym-tetrazenes. A mechanism for these conversions is proposed.

Interest in N-nitrosamines has considerably increased in the last few years with the discovery of their carcinogenic properties and their presence as pollutants in the atmosphere, food and beverages.[1)]

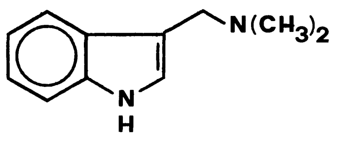
The nitrosation of amines by potassium nitrosodisulphonate 1 (Fremy's salt) in aqueous basic medium has recently been reported,[2)] and we wish now to publish our results on the mechanism and use of title oxidation, which can be optimized to produce a very high yield of either N-nitrosamines or sym-tetrazenes in just 5-15 minutes reaction time.

When an excess aqueous $HONH_2.HCl$ solution is added dropwise to a stirred 5% Na_2CO_3 solution containing a secondary amine 2 and excess F.S., immediate oxidation of $HONH_2$ takes place with the concomitant decoloration of the violet solution, after which extraction affords a very high yield of nitrosamines 3.[3)]



Amine 2	Yield of 3 / %
Dibutylamine	95
Piperidine	85
Morpholine	93
Piperazine	93
Cytisine[4)]	91
(-)-Ephedrine	85
3-Hydroxypiperidine	56
Proline methyl ester	55
Isopropylcyclohexylamine	40

Tertiary amines such as gramine 4, aminopyrine 5 and 2-(N,N-dimethylaminomethyl) pyrrole 6, also react with this nitrosating system affording the expected dimethylnitrosamine,5) while saturated tertiary amines gave the corresponding nitrosamines in about the same yield as reported for the reaction with F.S. alone.2)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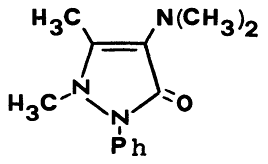
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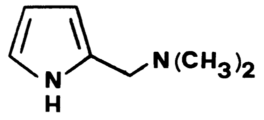
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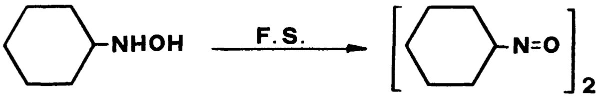
We interpret this result as clear indication that the N=O group of 3 has its origin in the $HONH_2$ added, thus suggesting that the nitrosations performed by F.S. alone are due to the oxidation of $HONH_2$ generated by slow hydrolysis of hydroxylamine disulphonate.6) The long time the secondary amine had to be in contact with the oxidant must therefore be responsable for the much lower yield of nitrosamine obtained in such conditions.

Our suggestion that F.S. oxidizes $HONH_2$ producing a species which nitrosates the amine and gives rise to the nitroso group is supported first, by the F.S. oxidation of hydroxylamine 7 and hydroxamic acid 9, to the corresponding nitroso compounds, which were isolated as the dimer 8, and the cyclohexadiene adduct 10,7) and secondly, by our finding that F.S. can replace pentaminoferrate in the Baudisch reaction giving o-nitrosophenol from benzene.8)



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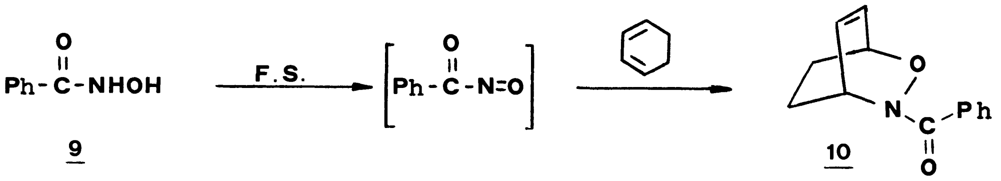

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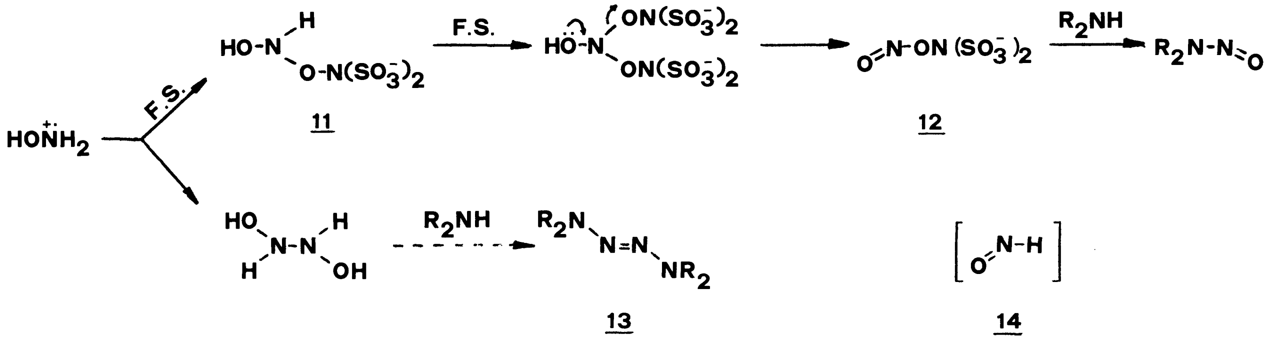
From a mechanistic point of view the conversion of hydroxylamine to the cation-radical $\overset{+\cdot}{HONH_2}$ by reaction with ferricyanide,9) cerium IV10) and photolysis11) is well documented. Accordingly we propose a mechanism in which F.S. oxidizes $HONH_2$ to this radical, which is trapped by F.S. and can still take another electron, as has been observed with ferricyanide,9) giving a species 12, which has the structure of a typical nitrosating agent X^-NO^+ with $(KSO_3)_2NO^-$ as nitroxyl carrier (scheme).

In this mechanism the role of F.S. is dual, acting not only as the oxidant but also trapping the hydroxylamine radical produced and preventing its coupling and subsequent transformation into N_2.12) In fact, typical oxidants of $HONH_2$ such as ferricyanide and MnO_4^- do not give nitrosamines when used in this reaction instead of F.S.

Scheme

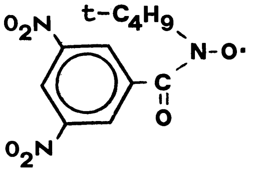


Further support for this hypothesis came, when the reaction was performed by inverse addition, i.e. by adding the F.S. to a solution containing the amine (e.g. piperidine or morpholine) and excess $HONH_2.HCl$. In this case no nitrosamine was formed and instead we isolated the corresponding sym-tetrazene 13 as the only reaction product, thus proving that when the hydroxylamine cation-radical is generated in the absence of F.S. it is not trapped but dimerizes.12) In accordance with this, other oxidants such as MnO_4^- and HgO can be used instead of F.S. in the preparation of tetrazenes.

An alternative mechanism based on the coupling of the amine and hydroxylamine cation radicals could also be considered, but we ruled it out because the reactivity of $HONH_2$ is much higher than that of the amine towards F.S., so that when F.S. and $HONH_2$ come in contact the reaction is so fast that no oxidant is left available for the amine.

Yet another mechanistic possibility exists involving the generation of nitroxyl 14 from intermediate 11 with $^-ON(SO_3^-)_2$ acting as leaving group (scheme). Nitroxyl 14 is a known decomposition product of Angeli's salt $N_2O_3Na_2$,13) and its ability to react as a nitrosating species has been suggested although it is not enterily proven. We ourselves have found that a sodium carbonate solution of Angeli's salt can replace $HONH_2$ in its reaction with F.S. giving a high yield of nitrosamine 3. Angeli's salt alone does not react in basic media with amines, and it might therefore be possible for a common nitrosating intermediate such as 14 to be formed by the action of F.S. on either $HONH_2$ or $N_2O_3Na_2$.

Finally, in a comparison of the reactivity of F.S. with that of other stable nitroxyl radicals14) we have found that 15 also oxidizes $HONH_2$, and that in the presence of secondary amines it produces nitrosamines, which confirms the analogy between the two reagents.



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As hydroxylamine has been identified as an intermediate in the nitrogen cycles in nature$^{15)}$ the incidence of this type of reaction in the formation of nitrosamines should now be considered.

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3) A typical experimental procedure was as follows: (-)-ephedrine (100 mg, 0.6 mmol) and 1 (2 g, 7.5 mmol) were dissolved in a 2% aqueous solution of sodium carbonate (40 ml) containing pyridine (3 ml). To this, an aqueous solution of $HONH_2.HCl$ (300 mg, 4.3 mmol) was added dropwise and with stirring over 15 min. A fast fading of the original colour was observed and the reaction mixture was extracted with Cl_2CH_2. The combined extracts were washed with 5% HCl solution, dried (Na_2SO_4) and concentrated to dryness in vacuo, yielding 100 mg of N-nitrosoephedrine (85%), identified by its spectral data (UV, ^1H NMR, MS) and direct comparison with an authenthic sample.$^{16)}$
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