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RAPID NITROSAMINE FORMATION FROM A TERTIARY AMINE: THE NITROSATION OF 2-(N,N-DIMETHYLAMINOMETHYL)PYRROLE

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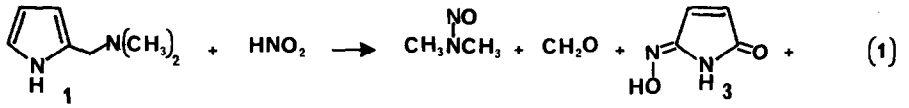
Abstract: 2-(N,N-Dimethylaminomethyl)pyrrole reacts instantaneously with nitrous acid at 25° to produce diemthylnitrosamine, maleimidemonooxine, formaldehyde and other products. The data implicate new mechanisms of tertiary amine nitrosation.

N-Alkyl tertiary amines react very slowly at 25° with nitrous acid but at higher temperatures they produce nitrosamines and an aldehyde or ketone in good yields. A mechanism for this reaction has been postulated[1] and is supported by various experiments[1] as well as recent rate data[2]. We report here that 2-(N,N-dimethylaminomethyl)pyrrole 1, a model for the malt containing alkaloid gramine 2, reacts rapidly with nitrous acid at 25° to produce dimethylnitrosamine (DMN) as the sole nitrosamine product. Evidence is presented that this transformation is occuring by a new mechanism of tertiary amine nitrosation. The potent animal carcinogenicty of numerous nitrosamines places an emphasis on a detailed understanding of their modes of formation and the prevention thereof.

The substrate 1 was prepared by a Mannich condensation of dimethylamine, formaldehyde and pyrrole[4]. This reaction does not reverse itself when 1 is placed in aqueous acetic acid (GC), the nitrosation solvent. The nitrosation of 1 with sodium nitrite in acetic acid ([1] = 0.22M, see Table) was followed by 300 MHz proton NMR, HPLC, and TLC. Dimethylnitrosamine is produced immediately upon the introduction of nitrite and is the sole nitrosamine product detected from this reaction (TLC, Griess reagent).



(1)

Data for the per cent consumption of 1 and yield of DMN as a function of $[NO_2]^-$ and time are given in the Table. The reaction is complex from several points of view. The nitrosation produces a dark brown-black mixture having many of the characteristics of "nitrosopyrrol-schwarz"[5], an amorphous dye produced from the nitrosation of pyrrole. The reaction mixture is sensitive to composition change during workup. Except for DMN, it is not easily separated into its constituents (the pyrrole ring derived products) by conventional chromatographic procedures. On the other hand NMR tracking of the reaction in D_4-HOAc has been very profitable and shown that several distinct pyrrole derived products are formed in significant amounts. Careful NMR monitoring combined with reversed phase HPLC has permitted the isolation and X-ray crystallographic characterization[6] of maleimidemonooxime 3 as a principal reaction product[7,8]. Moreover, DMN appears to be produced in two kinetic "stages", one rapid and the other proceeding more slowly after the complete consumption of the substrate.

The rapid rate of DMN production, the reaction's altered regiochemistry, the absence of expected products and the formation of unusual ones, as well as trapping and other experiments, all provide strong evidence that this nitrosation is proceeding by at least one new mechanism of tertiary amine nitrosation. We consider each of these points of evidence in turn.

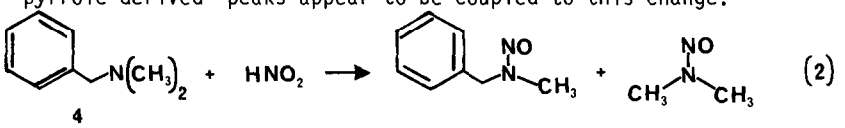
To our knowledge no other tertiary amine has been found to produce high yields of nitrosamines within 3 min. of the introduction of nitrite to an acidic solution of the amine at temperatures as low as 25°[3]. Treatment of 1 with 10 equivalents of nitrite in aqueous acetic acid at 25° results in the immediate (3 min.) production of a 95% yield of DMN. The data of the Table provide good evidence that DMN is being formed by at least two pathways. One of these is a very rapid process and is associated with the products derived from the pyrrole ring (including 3). The NMR data show that the second pathway occurs by the rapid formation of an intermediate which generates DMN more slowly. The only NMR line which we have been able to associate with this

TABLE

THE NITROSATION OF 1 IN D-4 HOAC

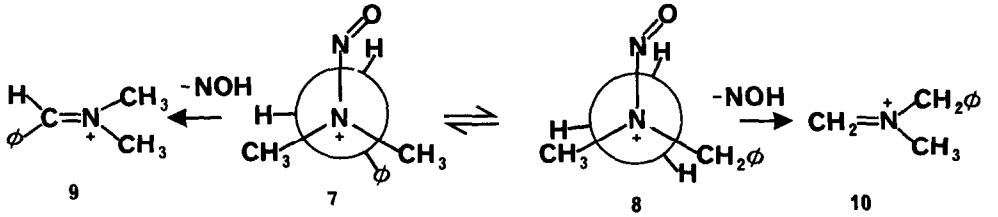
Entry	Run Time	2M Nitrite Equivalents	%DMN Formed	%1 Consumed
1	6 min	1.00	10.0	30.0
2	18 hr	1.00	12.0	35.0
3	3 min	2.00	22.0	65.0
4	20 hr	2.00	33.0	70.0
5	6 min	3.67	52.0	95.0
6	40 min	3.67	56.0	100.0
7	20 hr	3.67	80.0	100.0

intermediate is a"mystery methyl" peak (δ2.796) which disappears as DMN is formed in the slow stage. No "pyrrole derived" peaks appear to be coupled to this change.



4 (2)

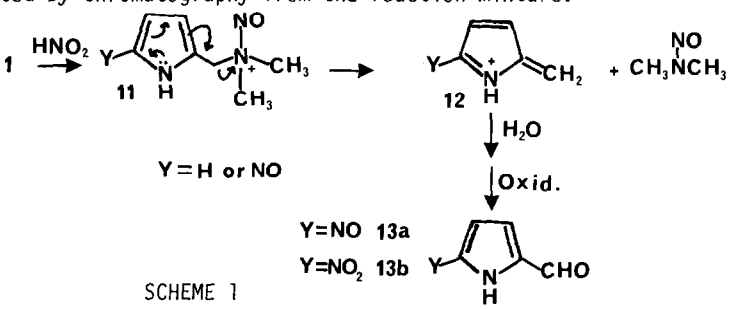
If the established mechanism of tertiary amine nitrosation were operative here (and in the case of gramine) we would expect preferential cleavage of the N-methyl group to give formaldehyde. Even though formaldehyde is a reaction product, the high yields of DMN show it not to be derived from the methyl group. To further examine the problem of the regiochemistry of the cleavage we nitrosated N,N-dimethylbenzylamine 4, 2-(N-methylaminomethyl)pyrrole 5, and pyrrole-2-carboxaldehyde 6 under the same and more vigouous conditions as 1. Unlike 1 the amine 4 does not react detectably with nitrous acid at 25°. At 65° the reaction proceeds (Eq. 2) to give a 76:24 ratio of benzylmethylnitrosamine and DMN. While the reaction of 1 is complete within five minutes at these conditions 4 is only 3% consumed. The data for 4 are in accord with previous



9 7 8 10

work because the product determining step involves the syn cyclic elimination of NOH and is strongly influenced by steric factors[1]. The nitrosammonium ion 7 undergoes elimination more slowly than 8 because of the unfavorable methyl-phenyl eclipsing in the former. The nitrosamines are formed from 9 and 10 by subsequent reactions[1,9]. The reaction of 1 by this mechanism would involve the formation of 5 and 6. The nitrosation of 5 produces a complex mixture of pyrrole derived products including 3 but the NMR exhibits no peaks in the δ 0-6 region coincident with those produced in the nitrosation of 1. Neither 5 nor its derived nitrosamine can, therefore, be an intermediate in the reaction of 1. The aldehyde 6 reacts slowly with nitrous acid to produce 3 among other products but its slow rate of disappearance precludes its intermediacy in the nitrosation of 1.

Although mechanistic details at this point are speculative the results suggest two possible hypotheses (Schemes 1 and 2). The formation of the nitrosammonium ion 11 (Scheme 1), either before or after ring nitrosation at C-5, is followed by ring nitrogen assisted ionization to give 12 and DMN. Subsequent nucleophilic attack of water or nitrite at the methylene of 12 followed by oxidation gives the aldehyde 13a or 13b. The NMR spectra of the nitrosation of 1 show a transient aldehyde peak at δ 9.715[10]. We believe that DMN production during stage one can partially be accounted for by this scheme. Nitrosamine formation occurs by a somewhat analogous pathway during the ring opening of 1-substituted aziridines[11]. Partial support for this pathway is provided by a trapping experiment and the well explored chemistry of certain heterobenzylic trialkylammonium compounds[15]. The substrate 1 was nitrosated with $NOBF_4$/pyridine in CH_2Cl_2 at -78°. After 45 min. an excess of KCN/18-crown-6 was added. 2-Pyrroleacetonitrile was isolated by chromatography from the reaction mixture.[16]

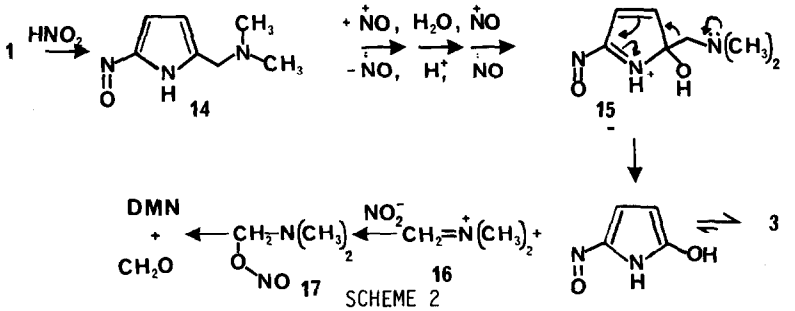


SCHEME 1

Scheme 2 displays a mechanistic hypothesis which not only accounts for the slower formation of DMN in stage two but shows how 1, 5, and 6 could all give 3 upon nitrosation. Ring nitrosation of 1 at C-5 to give 14 is followed by oxidation (NO+ → NO), addition of water at C-2, and another oxidation to give 15. A retro-Mannich type reaction of 15, which could also apply to intermediates derived from 5 and 6, results in the formation of 3 and the key intermediate 16. DMN formation from 16 either could occur through hydrolysis and nitrosation or by reaction with nitrite to give 17 (or the corresponding acetate), the possible source of "mystery methyl" which yields DMN more slowly. This argument is consistend with the NMR shift of "mystery methyl". Both rapid nitrous acid oxidation of electron rich C-nitroso aromatic compounds[12] and nitrosamine formation from 16[13] have precedent.

Mangino and Scanlan[14] have suggested that the indole alkaloid gramine 2 is the main progenitor of DMN in malted beverages. Because of the structural similarity between 1 and 2 the

pathways presented here could explain DMN's rapid formation during malting and why more complex nitrosamines derived from 2 are apparently absent from beer and other malted beverages. Our work



SCHEME 2

also suggests that other similar tertiary amines could rapidly produce nitrosamines under mild conditions. Research in this area continues in our laboratory.

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