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Electrochemical Transformation of N-Nitrosodialkylamines into N-Nitramines and β-Ketonitrosamines

Controlled potential electrolysis, based on the results of cyclic voltammetry, of simple dialkylnitrosamines such as N-nitrosodibutylamine and N-nitrosodicyclohexylamine in acetonitrile at a glassy carbon electrode resulted in the formation of the corresponding nitramines as the major products together with β-ketonitrosamines in which the carbonyl group is on the same side of the nitroso-oxygen atom. With N-nitrosopiperidine, one derived from a cyclic amine, N-nitropiperidine was formed similarly but the β-oxidized nitrosamine was not detected in the electrolysis solution. In deoxygenated acetonitrile, neither the nitramines nor the β-ketonitrosamines were obtained from the electrolysis.

Keywords——N-nitrosamines; N-nitramines; β-ketonitrosamines; anodic oxidation; cyclic voltammetry; controlled potential electrolysis

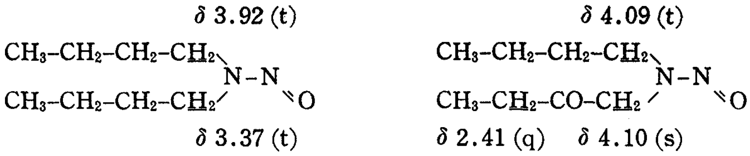
Although the chemistry of N-nitrosamines, including their oxidation with chemical oxidants, has been the subject of intensive studies,[1] little attention has been paid so far to the electrochemical oxidation of the compounds. We report here preliminary results on the anodic oxidation of some selected N-nitrosodialkylamines in acetonitrile at a glassy carbon electrode, where dissolved oxygen plays an important role in the follow-up chemical reactions.

TABLE I. Results of Cyclic Voltammetry of N-Nitrosamines[a]

No.	N-Nitrosamine (amine part)	E_{p1}[b,c]	i_p/C[d]	E_{p2}[b,e]	E_{p3}[b,f]
1	Dimethylamine	2.05	33.4	2.40	—
2	Diethylamine	1.95	29.7	2.28	2.63[g]
3	Dipropylamine	1.84	24.2	2.07	2.50[g]
4	Dibutylamine	1.83	28.8	2.03	2.45[h]
5	Diisopropylamine	1.80	25.5	2.00[g]	2.35
6	Dicyclohexylamine	1.72	21.9	2.00	2.27
7	Pyrrolidine	1.85	40.5	2.25	2.50
8	Piperidine	2.01	47.1	2.23[h]	2.50[h]
9	Morpholine	2.00	43.8	2.17	[i]

a) In a particular batch of distilled acetonitrile containing 0.1 M TEAP at a glassy carbon electrode (area, 0.071 cm^2) : voltage sweep rate, 50 mV/s. *b*) V *vs*. S.C.E. *c*) The peak potential of the first anodic peak. *d*) Peak current of the first anodic peak: μA/mM. *e*) The second anodic peak. *f*) The third anodic peak. *g*) Ill-defined peak. *h*) The peak potential coincided with that of the corresponding nitramine obtained in the controlled potential electrolysis. *i*) The position of the peak could not be defined precisely.

On cyclic voltammetry in acetonitrile[2] containing 0.1 M tetraethylammonium perchlorate (TEAP), the nitrosamines (**1**—**9**) showed two or three irreversible anodic peaks (Table I). When the dissolved oxygen in the medium was removed by bubbling argon gas through the solution, the peak current of the first anodic peak increased by a factor of 1.5—2 while the second and the third anodic peaks became obscure. Saturation of the deoxygenated solution with oxygen restored essentially the same voltammograms as those obtained originally in acetonitrile just distilled by the conventional method.[2] Small amount of added water ($\leq 1\%$) had no appreciable effect on the voltammetry of the nitrosamines (**1**—**6**) derived from simple dialkylamines, whereas the first anodic peaks of the nitrosamines (**7**—**9**) derived from cyclic amines increased with the water and a new peak appeared at the expence of the second and the



4 **11**

Fig. 1. PMR Spectra of N-Nitrosodibutylamine (**4**) and Its β-Keto Derivative (**11**)

In CCl_4 with TMS as the internal standard.

third anodic peaks. Thus, the enhanced i_p/C values (Table I) for the nitrosamines (**7**—**9**) can be ascribed to the effect of trace amount of water unavoidably contaminating the medium.

Controlled potential electrolysis of the nitrosamine **4** in acetonitrile containing 0.1 M TEAP at the potential of the first anodic peak (1.80 V) in an H-type divided cell gave N-nitrodibutylamine (**10**) (~40%), N-butyl-N-nitroso-2-oxobutylamine (**11**) (~15%), and a trace amount of N-butylacetamide.[3] Formation of the β-ketonitrosamine **11** is interesting because β-oxidized nitrosamines are postulated to be the primary intermediates in the enzymatic degradation of N-nitrosamines with alkyl side chains larger than ethyl group.[4] Configurational isomers (*E* and *Z*) are known for N-nitrosodialkylamines.[5] Proton magnetic resonance (PMR) spectra of the nitrosamine **4** and the β-keto derivative **11** (Fig. 1) suggest that **11** is the *Z*-isomer. When the electrolysis was performed with oxygen bubbled through the solution, the yield of the nitramine **10** increased (~50%). The coulometric *n*-value in the electrolyses varied between 1.3—2, but a tendency was recognized that the value approaches unity as the yield of the nitramine **10** increases. Similar results were obtained with the nitrosamine **6**. N-Nitrodicyclohexylamine (**12**) (~60%) and N-cyclohexyl-N-nitroso-2-oxocyclohexylamine (**13**) (~13%) were formed with coulometric *n*-value of <1.5. N-Nitrosopiperidine (**8**), similarly gave N-nitropiperidine (**14**) (~50%; *n*-value, *ca.* 2), but formation of the corresponding β-ketonitrosamine was not detected in the electrolyzed solution.

On electrolysis of the nitrosamines **4**, **6**, and **8** in deoxygenated acetonitrile, neither the nitramines nor the β-ketonitrosamines were formed and the *n*-value increased (2—3 for **4** and **6** and >4 for **8**). The products of the electrolyses are still uncertain.

Electrolysis of **4** and **6** in the presence of 1% water (not deoxygenated) gave essentially the same results as those in the absence of water. However, N-nitropiperidine (**14**) was not formed on electrolysis of **8** in acetonitrile with added water. Electrolysis of **4** was also carried out in acetonitrile containing 1% of ^{18}O enriched water (50 atom %), but the resulting nitramine **10** and the β-ketonitrosamine **11** did not contain the labeled oxygen atom.

Although the present results are incomplete to propose any mechanism of the anodic oxidation of N-nitrosamines, the following statements seem reasonable. The cation radical (**15**) will be formed by the initial one-electron transfer from the substrate: $>N-N=O \leftrightarrow >N^+=N-O^- \xrightarrow{-e} >N^+=N-\dot{O}$ (**15**). Direct reaction of **15** with oxygen will lead to the formation of a nitramine. Intramolecular abstraction of a hydrogen on the β-carbon atom through six-membered-ring transition state, as suggested in the anodic oxidation of ketones,[6] followed by the reaction with oxygen will give a β-ketonitrosamine. In the case of N-nitrosopiperidine (**8**), such a transition state is highly unfavorable. Other reactions of the cation radical **15**, which must prevail in the absence of dissolved oxygen, would be degradations and/or reactions with water to give electroactive species responsible for the increase in the voltammetric i_p/C values and the coulometric *n*-values. Detailed studies on the nature of these species and the final products of the reactions are in progress.

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References and Notes

1) For a review, see "N-Nitrosamines," ed. by J.P. Anselme, ACS Symposium series **101**, American Chemical Society, Washington D.C., 1979.
2) Acetonitrile obtained commercially was distilled first from calcium hydride and then from phosphorus pentoxide after the treatment by the method reported [J.F. O'Donnell, J.T. Ayres, and C.K. Mann, *Anal. Chem.*, 37, 1161 (1965)]. The acetonitrile thus purified seems to contain oxygen enough for the electrolysis of at least 50 mM of a particular N-nitrosamine to give the products in the yields described in the text.
3) In the present study, 0.5—5 mmol of the nitrosamines were subjected to electrolysis in 10, 50, or 100 ml of anolyte. No fundamental difference in the results was observed with the changes in the substrate concentration and in the volume of the electrolysis solution. The yields of the products were determined by GLC.
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A Ring Transformation of Uracil into the Pyrazole Ring System. Reinvestigation of the Reaction of 5-Formyluracils with Hydrazines

Cheng *et al.* reported that the reaction of 5-formyluracil (**1a**) with hydrazine hydrate in the presence of acetic acid gave 4-ureidomethylene-1*H*-5-pyrazolone (3). However, results of our reinvestigation revealed that the Cheng's compound (3) should be 4-ureidocarbonylpyrazole (**4a**). Application of this ring transformation to preparation of several 4-ureidocarbonylpyrazoles (**4b**—**f**) was also described.

Keywords——ring transformation; 5-formyluracil; 4-ureidocarbonylpyrazoles; ambident nucleophile; hydrazinolysis

Although hydrazinolysis of uracil derivatives into pyrazolones has been already known,[1] further studies on its application in synthesis have been little done and the reaction has been investigated only in particular areas such as the chemical modification of nucleic acids.[2]

Recently, we found a novel ring transformation of uracil into a benzene ring system.[3] Thus, treatment of 5-formyl-1,3-dimethyluracil (**1b**) with α-substituted acetone derivatives (C–C–C type of ambident nucleophile; X=$COCH_3$, $CONH_2$, C_6H_5, $CO_2C_2H_5$) in ethanolic sodium ethoxide afforded the corresponding ethyl 4-hydroxybenzoates (**2**). In this reaction, an intermediate A was first produced by a condensation of C_5-formyl group with acetone derivatives and then it gave **2** by an intramolecular nucleophilic attack at the 6-carbon. On the other hand, Cheng *et al.* reported[4] that the reaction of 5-formyluracil (**1a**) with hydrazine hydrate (N–N type of ambident nucleophile) gave 4-ureidomethylene-1*H*-5-pyrazolone (**3**)