

Electrochemical Behaviour of Heterocyclic Amidines I. Anodic Oxidation of 2-Amino-5-Ethoxycarbonyl-4-Methylthiazole

G. Cauquis*, H. M. Fahmy***, G. Pierre** and M. H. Elnagdi***

*Laboratoire d'électrochimie Organique et Analytique, ERA (CNRS) 675, Département de Recherche Fondamentale, Centre d'Etudes Nucléaires de Grenoble, 85X, 38031 Grenoble Cedex, France, **Laboratoire de Chimie Organique analytique, Département de Chimie, Université Scientifique et Médicale de Grenoble, BP 53, 38041 Grenoble Cedex, France, ***Department of Chemistry, Faculty of Science, Cairo University, Cairo, Egypt, A.R.E.

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The behaviour of 2-amino-5-ethoxycarbonyl-4-methylthiazole on oxidation at a rotating platinum disc electrode is reported. The mechanism of the formation of the azo and hydrazo dimeric compounds as main oxidation products is discussed.

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Sir:

The importance of heterocyclic amidines as precursors for the synthesis of biologically active compounds has drawn the attention of many investigators throughout the last decade (1). However, a literature survey revealed the absence of comprehensive electrochemical data concerning such a class of compounds. As part of a program dealing with the chemistry of cyclic amidines we discuss through this work the electrochemical oxidation of 2-amino-5-ethoxycarbonyl-4-methylthiazole I at the rotating platinum disc electrode (2). This compound was chosen on the basis of its ready availability (3) and the potential biological activity (4) of its oxidation products, which are difficult to be obtained by other synthetic routes. Moreover, inspection of literature data revealed that oxidation of unsubstituted amino thiazole may be complicated by the formation of a mixture of by-products resulting from the reaction of the initially formed charged free radical with the hetero ring giving head to tail coupling (5).

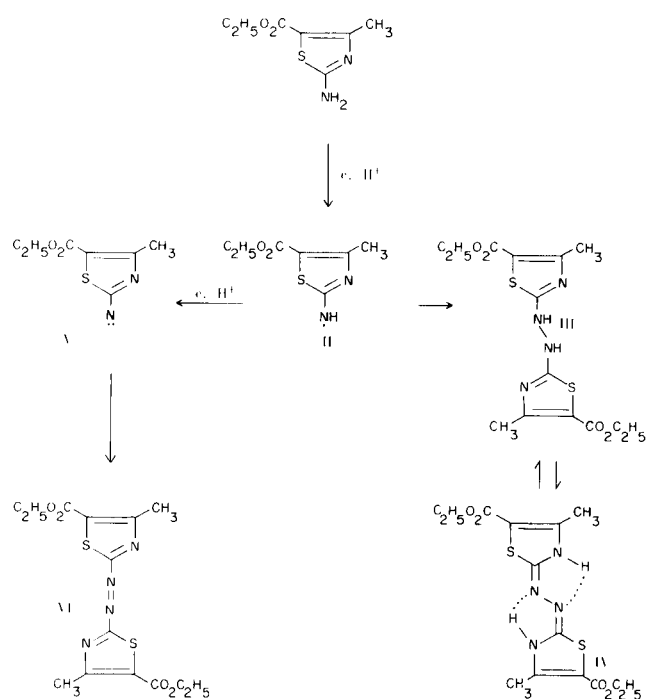
In acetonitrile containing $10^{-1}M$ lithium perchlorate (or tetraethylammonium perchlorate) as a supporting electrolyte, compound I was oxidized along a well defined anodic wave, $E_{1/2} = 1.0$ V vs. Ag/Ag^+ $10^{-2}M$, with a limiting current practically equal to a one electron transfer ($i_1 = 4.8$ μA mm^{-2}) for $10^{-3}M$ concentration. Logarithmic analysis ($dE/d\log \frac{i_1}{i_1 - i} = 0.171$) of this wave together with cyclic voltammetric curves indicate that the electrode process is irreversible. The effect of varying the concentration of i_1 reveals that the current is mainly controlled by diffusion within the concentration limits 10^{-4} – $3 \times 10^{-3}M$, above which it is practically constant and independent of any concentration variation. This effect is probably due to the adsorption of the compound on the surface of the electrode. In order to obtain the actual number of electrons transferred in the electrode reaction, controlled potential electrolysis was carried out at 1.15 V (*i.e.*, on the limiting current of the wave). The progress of electrolysis was followed by recording current-potential

curves at several time intervals. The number of faradays was computed and found to be 1 F mole⁻¹ in neutral unbuffered medium. In the presence of solid sodium carbonate, a value of ~ 1.75 F mole⁻¹ was obtained. For large scale preparative electrolysis, an H-cell similar to that described by Lund (6) was used with a concentration varying from 20 to 50 mg. in 60 ml. After complete electrolysis, the resulting solution was evaporated *in vacuo* and extracted with dichloromethane which was in turn evaporated. The mixture thus obtained was then chromatographed on thin layer silica gel plates (Merck type 60) using the same solvent. The zone with R_f value 0.169 was scraped off the plate and the compound was extracted on a column by hot dichloromethane (yield 10%), m.p. 168°; ms: m/e 340, (M - 28) main fraction, 295, 198 and 170; nmr (reference TMS, deuteriochloroform): δ (t, 3H), 2.9 (s, 3H), 4.35 ppm (q, 2H); ir (potassium bromide): 1730 and 1260 (ester), 1340, 1050, 1020, 840 and 770 cm^{-1} (thiazole ring structure); uv (acetonitrile): λ max nm (ϵ) 443 (8400), 298 (3900) and 217 (6900).

Anal. Calcd. for $C_{14}H_{16}N_4O_4S_2$: C, 45.65; H, 4.3; O, 17.32; N, 15.21; S, 17.32. Found: C, 45.60; H, 4.40; O, 17.40; N, 15.20; S 17.40.

Based on these data, VI was assigned as the structure for this product. The product that did not migrate by the solvent used was scraped off and the mixture was extracted by hot ethanol and rechromatographed with a solvent mixture consisting of dichloromethane and ether in a ratio 6/1. Zones with R_f values 0.23, 0.66 and 0.92 were observed. The compound in the first zone (R_f 0.23) was extracted (yield 50%) and identified as III or its possible tautomeric azine form IV, m.p. 145° dec.; ms: m/e 370 (main fraction), 297, 197; nmr: same peaks as VI with an additional broad peak at δ 8.2 ppm; ir (potassium bromide): 3300 (NH), 1740 and 1265 cm^{-1} (ester).

Anal. Calcd. for $C_{14}H_{18}N_4O_4S_2$: C, 45.40; H, 4.90; O, 17.28; N, 15.13; S, 17.28. Found: C, 45.40; H, 4.90; O, 17.29; N, 15.10; S, 17.00.



It seems most probable that compounds VI and IV are formed *via* a common free radical II obtained by the oxidation of the amino group of I in a way similar to that well established for primary aromatic amines (5). This free radical can thus dimerize to the hydrazo III which can also be formulated as the azine IV, both structures being stabilized by hydrogen bonding. On the other hand, this free radical II may be further oxidized by the loss of one electron to afford the nitrene V (7), which then undergoes self condensation to afford VI. The latter was shown to be

reduced at the dropping mercury electrode in a two electron wave ($E_{1/2} = -0.13$ V, acetonitrile, $10^{-1}M$ perchloric acid) into the corresponding hydrazo III or azine IV derivative. Although at first glance it seems that III would be readily oxidized into the correspondant azo derivative, a well known reaction, the stabilization of the hdyrazo derivative through hydrogen bonding seems to deactivate the molecule toward further oxidation. Deactivation of similarly chelated hydrazo derivatives has been previously reported (8).

REFERENCES AND NOTES

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- (2) G. Cauquis and G. Pierre, *Tetrahedron*, in press.
- (3) Readily prepared from thiourea and ethyl α -chloroacetate, as has been described by H. Zurcher, *Ann. Chem.*, **250**, 281 (1888). *Anal. Calcd.* for $C_7H_{10}O_2N_2S$: C, 45.1; H, 5.4; N, 15.0; S, 17.2. *Found*: C, 45.3; H, 5.5; N, 15.0; S, 17.3. The product was found identical with an authentic sample.
- (4) *Cf.*, the pronounced antibiotal activity of thiazole containing compounds such as penicillines and also fungicides (Merck Index).
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- (8) *Cf.*, stabilization of similarly bonded hydrazo compounds, P. J. Krueger, in "The Chemistry of Hydrazo, Azo and Azoxy Compounds," S. Patai, Ed., John Wiley and Sons, New York, N. Y., 1975, pp. 180, 183 and 186.