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Studies on Electrolytic Substitution Reactions. XXI.* Anodic Oxidation of *N,N*-Dimethyl-ω-hydroxyamides

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Five *N,N*-dimethyl-ω-hydroxyamides were oxidized at a platinum anode in various solvents. No direct formation of the expected 1,3-oxazaheterocycles was observed but instead formation of *N*-methoxy-*N*-methyl-ω-hydroxyamides. The latter could in some cases (formation of 5-, 6- and 7-membered rings) easily be transformed to 1,3-oxaza-4-oxo heterocyclic systems by acid catalysis.

N-α-Alkoxylated amides are useful synthetic intermediates that are easily and inexpensively available *via* anodic alkoxylation of various types of amides.[1-5] The mechanism of anodic amide alkoxylation has so far been believed to be of the ECE type (eqns. (1) and (2)).

$$RCH_2N(R^1)CHO \xrightarrow{-e^-} [RCH_2N(R^1)CHO]^{\cdot +}$$
$$\xrightarrow{-H^+,\ -e^-} \overset{+}{R}CHN(R^1)CHO \qquad (1)$$

$$\overset{+}{R}CHN(R^1)CHO \xrightarrow{R^2OH} RCH(OR^2)N(R^1)CHO + H^+ \qquad (2)$$

With very few exceptions,[6,7] most studies have dealt with intermolecular alkoxylation, *i.e.* the alkoxy moiety has been derived from an external alcohol molecule. It thus seemed worthwhile to examine whether the intramolecular reaction, *i.e.* the formation of heterocycles, would proceed with the ease and smoothness earlier experienced with the intermolecular cases (Fig. 1).

We now report that five model amide derivatives (Fig. 1, n=0–4) *do not form cyclized products directly by anodic oxidation* in methanol but instead are *N*-α-methoxylated in the "normal" way. As expected these products can be cyclized in favorable cases (Fig. 1, n=0, 1, 2) *via* an acylimmonium ion by treatment with a catalytic amount of acid.[8] The intervention of such intermediates in the anodic process [according to eqns. (1) and (2)] thus seems rather unlikely, unless the intramolecular reaction is rendered impossible owing to the heterogeneous conditions.

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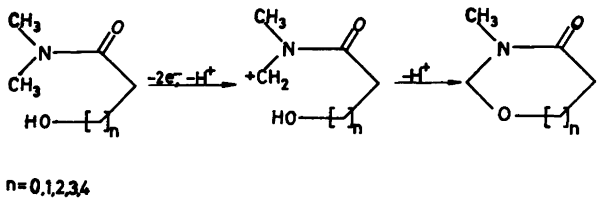

Fig. 1. Formation of heterocycles.

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RESULTS AND DISCUSSION

It would seem imperative that the formation of a cationic centre in a molecule possessing a fairly strong nucleophilic centre adequately located, ultimately would lead to ring formation (Fig. 1). Moreover the formation of a cyclized product from a properly designed starting material could indeed be taken as evidence for the presence of such a cationic centre somewhere in the reaction sequence. As the generally accepted mechanism [eqns. (1) and (2)] for anodic amide alkoxylation involves the formation and further reaction of an intermediate acylimmonium ion, the presence of an "internal" nucleophile should result in ring formation. Support for this assumption was found in the reports from Shono [6] and Ban [7] where formation of a 1,3-oxazolidine and various cyclic lactones, utilizing acyclic precursors, was achieved. As a model compound we chose 2-hydroxy-*N*,*N*-dimethylpropanamide capable of forming the six-membered ring *N*-methyl-4-oxotetrahydro-1,3-oxazine (Fig. 1, n=2). In order to circumvent competetive solvent interactions we initially tried to run the electrolysis in non-nucleophilic solvents. Surprisingly, anodic oxidation of the β-hydroxy compound in acetonitrile or dichloromethane solution failed to given even trace amounts of the desired cyclized product. GLC analysis showed complete consumption of starting material after ~2.2 F/mol and work-up demonstrated the formation of tars and resinous materials. This drawback led us to reconsider performing the electrolysis in methanol, hoping that the ring-forming reaction would be able to capitalize from the kinetic advantage of a monomolecular reaction. On anodic oxidation in methanol GLC analysis revealed the formation of a single product in high yield. Work-up and subsequent MS and ^{1}H NMR examination unambiguously demonstrated the formation of *N*-methoxymethylene-*N*-methyl-2-hydroxypropanamide. This remarkable finding was further emphasized by the demonstration of prompt cyclization of *N*-methoxymethylene-*N*-methyl-2-hydroxypropanamide to *N*-methyl-4-oxotetrahydro-1,3-oxazine in dichloromethane in the presence of either trifluoroacetic acid or Armberlyst 15 (eqns. (3) and (4), n=1).

$$CH_3OCH_2N(CH_3)CO(CH_2)_nCH_2OH \xrightarrow[-CH_3OH]{H^+} {}^+CH_2N(CH_3CO(CH_2)_nCH_2OH \quad (3)$$

$${}^+CH_2N(CH_3)CO(CH_2)_nCH_2OH \xrightarrow[-H^+]{} \begin{matrix} CH_2N(CH_3)CO \\ | \quad\quad | \\ O—CH_2—(CH_2)_n \end{matrix} \quad (4)$$

n=0, 1, 2

Evidently the cation formed by acid catalysis [eqn. (3)] was immediately trapped by the β-hydroxy group [eqn. (4)] suggesting either that no cation is formed during electrolysis or that if the cation is formed it is effectively blocked by solvent molecules. Another plausible explanation as to why the β-hydroxy group fails to engage in the cyclization step during electrolysis is that it for some reason becomes nonreactive due to the electrolysis conditions. A possible rationalization of the above-mentioned results would then have to involve anode surface adsorption phenomena. If one assumes that the amide is adsorbed at the electrode by the amide oxygen and the β-hydroxy oxygen, the nitrogen-alkyl moiety reaching out into the solution, the *N*-α cation formed would be an easy prey to surrounding solvent molecules (Fig. 2a). Further support of this interpretation is provided by known cases of direct anodic cyclization of methyl *N*-(2-

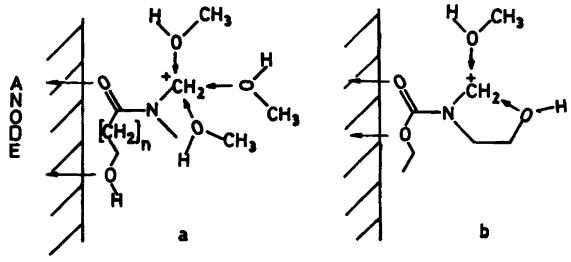

Fig. 2. Anode adsorption.

hydroxyethyl)-*N*-methylcarbamate[6] and 2-piperidone-5-acetic acid.[7] In both cases the internal nucleophile was located on the nitrogen side of the molecule. This would allow for successful competition for the cation formed (Fig. 2b).

The possibility of acid-catalyzed ring-opening/solvolysis caused by acidic species formed at the anode during electrolysis was recognized but seemed improbable. As no special precautions were taken to achieve dry reaction conditions the small concentration of water inevitably present would interfere in the solvolysis process and produce the demethylated analogue of the starting material.[9] Since secondary amides are known to be more oxidation resistant than tertiary ones,[10] the demethylated amide would accumulate and ultimately be detected at the end of the electrolysis. This was not the case. Moreover, the very high yields usually achieved in anodic alkoxylations contradict the involvement of solvolytic or/and hydrolytic processes.

In an effort to investigate whether the disinclination to cyclize was a structural feature of the chosen probe molecule we examined the behavior of the lower and some of the higher homologues. Thus, hydroxy-*N,N*-dimethylacetamide was electrolyzed according to the procedure adopted for 2-hydroxy-*N,N*-dimethylpropanamide. After 2.3 F/mol of substrate electrolysis was discontinued, and GLC analysis indicated the complete consumption of starting material and the formation of a single product. MS and NMR revealed its structure to be 2-hydroxy-*N*-methoxymethylene-*N*-methylacetamide. No trace of the cyclized *N*-methyl-4-oxo-1,3-oxazolidine could be detected in the reaction mixture. The homogeneous cyclization to the oxazolidine was not as easy an achievement as the formation of the above-mentioned oxazine. The oxazolidine, apparently being acid-sensitive, either failed to form or rapidly decomposed depending on the acid used. This obstacle was circumvented by the utilization of the Lewis acid boron trifluoride, promoting the formation of an oxazolidine $-BF_3$ complex in high yield [eqns. (3) and (4), n = 0].

4-Hydroxy-*N,N*-dimethylbutanamide was electrolyzed according to the procedure stated above. The cyclized compound, *N*-methyl-4-oxohexahydro-1,3-oxazepine, could not be detected in the electrolyte. The only new compound present was the readily formed 4-hydroxy-*N*-methoxymethylene-*N*-methylbutanamide. This compound readily cyclized to the oxazepine when treated with trifluoroacetic acid or Amberlyst 15 [eqns. (3) and (4), n = 2].

5-Hydroxy-*N,N*-dimethylpentanamide and 6-hydroxy-*N,N*-dimethylhexanamide were treated in the manner described above. The formation of *N*-methyl-4-oxoperhydro-1,3-oxazocine and *N*-methyl-4-oxoperhydro-1,3-oxazonine was not observed but merely *N*-α methoxylation giving 5-hydroxy-*N*-methoxymethylene-*N*-methylpentanamide and 6-hydroxy-*N*-methoxymethylene-*N*-methylhexanamide, respectively. Taking into account the known resistance towards forming rings larger than seven-membered, this was not surprising. Treatment of the methoxy compounds with various Brönsted and Lewis acids in various solvents and applying the high dilution approach failed to give even trace amounts of the perhydrooxazocine or perhydrooxazonine derivative.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Jeol MH 100 instrument, using $CDCl_3$ as solvent. GLC–MS analyses were obtained on a Finnegan 4021 spectrometer operating at 70 eV. GLC analyses were performed on an HP-5830A gas chromatograph fitted with an HP-18850A recorder/integrator. Columns used were 3 m × 3 mm 5 % OV 17 on Chromosorb W or 2 m × 3 mm 5 % NPGS on Chromosorb W. Methanol was of AnalR quality and was used as received. Tetrabutylammonium tetrafluoborate was prepared according to the method of Nyberg.[11] Trifluoroacetic acid, Amberlyst 15 and boron trifluoride etherate were used as received.

3-Hydroxy-*N,N*-dimethylpropanamide,[12] 4-hydroxy-*N,N*dimethylbutanamide[13] and 6-hydroxy-*N,N*-dimethylhexanamide[14] were prepared according to published procedures.

Hydroxy-N,N-*dimethylacetamide* was prepared by refluxing butyl glycolate (66.0 g, 0.5 mol) with 45.0 g (1 mol) of dimethylamine in 250 ml of toluene overnight. After evaporation of the solvent the residue was distilled giving a colorless liquid, b.p. 79–81 °C/3 mmHg, which solidified in the receiver, colorless crystals m.p. 33–34 °C, yield 43.6 g, 83 %. MS *m/e* (% rel int): 104 (M + 1, 7), 103 (M, 21), 72 (100). ^{1}H NMR: 2.74 (3 H, s), 3.00 (3 H, s), 3.70 (1 H, br s), 4.10 (2 H, s).

5-Hydroxy-N,N-*dimethylpentanamide*. The method of Powers *et al.*[14] was adopted. Thus, 50.0 g (0.5 mol) of valerolactone was added to a cooled (ice) Parr bottle. Gaseous dimethylamine, 100 g (2.2 mol) was condensed into the bottle, which was stoppered and was allowed to reach room temperature. After one week the bottle was cooled to 0 °C,

the stopper removed and the excess amine was evaporated by means of a flow of nitrogen. The residue was distilled giving a colorless liquid, b.p. 132–133 °C/1 mmHg. Yield 65.1 g, 90 %. MS *m/e* (% rel int): 145 (M, 3), 127 (11), 100 (15), 87 (21), 72 (53), 55 (42), 45 (100). ^{1}H NMR: 1.40–1.85 (4 H, m), 2.35 (2 H, t), 2.92 (3 H, s), 3.03 (3 H, s), 3.59 (2 H, t), 4.16 (1 H, br s).

Electrolyses were conducted in a 250 ml water-jacketed cell and stirred magnetically. Electrolytes were 1.0 M in substrate and 0.1 M in supporting electrolyte. Platinum was used as anode material and stainless steel as cathode. Current was passed by means of an Amel 552 potentiostat/galvanostat, operated in the galvanostatic mode and the amount of charge was monitored by an electronic integrator. The current density was maintained at 50 mA/cm^2.

Typical oxidation procedure: 3-Hydroxy-*N,N*-dimethylpropanamide (23.4 g, 0.2 mol) was dissolved in 200 ml of methanol. Bu_4NBF_4 (6.58 g, 0.02 mol) was added and the resulting solution was transferred to the electrolysis cell. A platinum foil anode and a a stainless steel rod cathode were immersed. Current was passed and the current density was adjusted to a constant 50 mA/cm^2. The consumption starting material was monitored by GLC. When the starting material was totally consumed equalling 2.4 F/mol of substrate, electrolysis was stopped. Methanol was evaporated and the residue transferred to a Claisen apparatus and distilled *in vacuo*. Yield 25.6 g, 87 %, b.p. 99–100 °C/1 mmHg of 3-hydroxy-*N*-methoxymethylene-*N*-methylpropanamide. MS *m/e* (% rel int): 148 (M+1, 2), 147 (M, 1), 132 (9), 79 (19), 60 (56), 45 (100). ^{1}H NMR: 2.29–2.42 (2 H, br t, $-COCH_2-$), 3.04 (3 H, 2 s, CH_3-N), 3.22, 3.29 (3 H, 2 s, CH_3-O), 3.42–3.78 (2 H, m, $-CH_2-OH$), 3.80 (1 H, br s, HO–), 4.71, 4.76 (2 H, 2 s, NCH_2O).

Hydroxy-N-methoxymethylene-N-methylacetamide. Yield 73 %, b.p. 92–94 °C/2.5 mmHg. MS *m/e* (% rel int): 134 (M+1, 2), 133 (M, 2), 131 (11), 118 (21), 100 (27), 45 (100). ^{1}H NMR: 2.92, 3.05 (3 H, 2 s, CH_3-N), 3.30 (3 H, s, CH_3-O), 3.80 (1 H, br s, HO–), 4.18, 4.27 (2 H, 2 s, $-COCH_2-$), 4.58, 4.83 (2 H, s, NCH_2O).

4-Hydroxy-N-methoxymethylene-N-methylbutanamide. Yield 78 %, b.p. 114–116 °C/0.3 mmHg, MS *m/e* (% rel int): 162 (M+1, 2), 161 (M, 1), 146 (7), 87 (21), 60 (78), 45 (100). ^{1}H NMR: 1.53–2.03 (2 H, m, $-CH_2-$), 2.39–2.66 (2 H, m, $-COCH_2-$), 2.99, 3.06 (3 H, 2 s, CH_3-N), 3.24, 3.30 (3 H, 2 s, CH_3-O), 3.39–3.75 (2 H, 2 t, $-CH_2OH$), 3.90 (1 H, br s, HO–), 4.72, 4.78 (2 H, 2 s, NCH_2O).

5-Hydroxy-N-methoxymethylene-N-methylpentaamide. Yield 69 %, b.p. 115–117 °C/0.1 mmHg. MS *m/e* (% rel int): 176 (M+1, 2), 160 (2), 144 (5), 101 (23), 83 (10), 74 (10), 60 (61), 55 (52), 45 (100). ^{1}H NMR: 1.39–1.93 (4 H, m, $-CH_2CH_2-$), 2.26–2.62 (2 H, m, $-COCH_2-$), 2.95, 2.98 (3 H, 2 s, CH_3N), 3.22, 3.28 (3 H, 2 s, CH_3-O), 3.49–3.91 (2 H, br t, $-CH_2-OH$), 3.70 (1 H, br s, HO–), 4.66, 4.75 (2 H, 2 s, NCH_2O).

6-Hydroxy-N-methoxymethylene-N-methylhexanamide. Yield 81 %, b.p. 137–139 °C/0.2 mmHg. MS *m/e* (% rel int): 190 (M+1, 2), 189 (M, 1), 174 (8), 115 (17), 69 (43), 60 (63), 55 (43), 45 (100). ^{1}H NMR: 1.39–2.05 (6 H, m, $-CH_2CH_2CH_2-$), 2.41–2.74 (2 H, m, $-COCH_2-$), 3.14, 3.17 (3 H, 2 s, CH_3-N), 3.41, 3.47 (3 H, 2 s, CH_3-O), 3.65–4.01 (3 H, m, $-CH_2-OH$), 4.68, 4.77 (2 H, 2 s, NCH_2O).

General procedure for the preparation/attempted preparation of cyclic derivatives of the methoxylated ω-hydroxyamides illustrated by the synthesis of *N-methyl-4-oxotetrahydro-1,3-oxazine:* (a) 3-Hydroxy-*N*-methoxymethylene-*N*-methylpropanamide (I) (25 g, 0.17 mol) was added to a solution of dichloromethane–trifluoroacetic acid, 200 ml (95:5, w/w). The resulting solution was stirred for 15 min and was then treated with saturated $NaHCO_3$ until neutral. The organic layer was separated and dried over $MgSO_4$. After removal of the solvent the residue was distilled through an efficient column giving 18.8 g of a colorless liquid, b.p. 67–68 °C/1 mmHg, yield 96 %. (b) 1.47 g (10 mmol) of (I) was added to a stirred suspension of 0.2 g Amberlyst 15 in 25 ml dichloromethane. After 15 min the solution was filtered and then evaporated. The crude oil was pure by NMR, yield 1.12 g, 98 %. MS *m/e* (% rel int): 115 (M, 47), 114 (50), 55 (100). ^{1}H NMR: 2.51–2.64 (2 H, t, $-COCH_2-$), 2.90 (3 H, s, CH_3-N), 3.93–4.05 (2 H, t, $-OCH_2-$), 4.73 (2 H, s, NCH_2O).

N-Methyl-4-oxohexahydro-1,3-oxazepine. Attempted distillation led to decomposition. The crude oil received after removal of the solvent was better than 95 % pure as demonstrated by GLC and NMR, yield 94 %. MS *m/e* (% rel int): 129 (M, 100), 114 (31), 98 (47), 87 (50), 55 (56). ^{1}H NMR: 1.78–2.09 (2 H, m, $-CH_2-$), 2.84–3.10 (2 H, t, $-COCH_2-$), 3.18 (3 H, s, CH_3-N), 4.08–4.22 (2 H, t, $-OCH_2-$), 5.09 (2 H, s, $-NCH_2O-$).

N-Methyl-4-oxo-1,3-oxazolidine. This compound could not be prepared by the above- mentioned general procedure but instead by treatment of hydroxy-*N*-methoxymethylene-*N*-methylacetamide (0.332 g, 0.0025 mol) with 0.355 g (0.0025 mol) of boron trifluoride etherate in 5 ml of dichloromethane. After stirring for 15 min at room temperature the solvent was removed and the semisolid residue was transferred to a sublimation apparatus. After treatment at 40–50 °C (care must be taken not to let the temperature exceed 50 °C whereupon excessive degradation sets in) and 0.05 mmHg colorless crystals (m.p. 132 °C dec.) could be collected. The yield was 0.296 g representing more

than 100 % of the theoretical and thus indicative of the formation of a BF_3 complex. This was confirmed by dissolution in water and titration of the resulting acidic solution with aqueous sodium hydroxide. Any attempt to isolate the oxazolidine in the pure state resulted in total decomposition of the organic moiety. On GLC–MS and ^{1}H NMR analysis the BF_3 was removed by vaporization and complexation with the solvent (DMSO-d_6), respectively, and thus behaved as the free oxazolidine. MS *m/e* (% rel int): 101 (M, 53), 100 (100). ^{1}H NMR (DMSO-d_6): 2.73 (3 H, s, CH_3-N), 4.10 (2 H, m, $-COCH_2-$),[15] 4.97 (2 H, br t, NCH_2O).[15]

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