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# The Novel Product of Cathodic Reduction of Phthalimide Anion.

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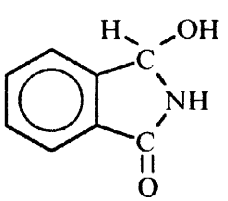
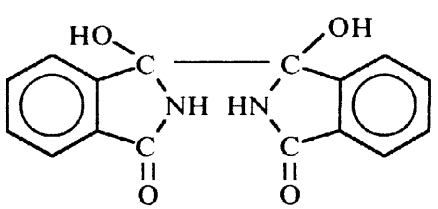
***Abstract.*** Cathodic reduction of phthalimide anion in methanol was studied. The novel product, N-hydroxymethyl-3-hydroxyphthalimidine, was found. Full characterization of this new compound was carried out by means of NMR, FT-IR, MS, and X-ray crystallography. The mechanism of electrolytic formation of N-hydroxymethyl-3-hydroxyphthalimidine is proposed. 

Electrolytic reduction of phthalimide and N-substituted phthalimides has been studied extensively, and the results were published in a number of papers.[1-8] Notably, the composition of the product mixture showed high variability depending on the experimental conditions. For instance, the main product formed in acidic aqueous solution was 3-hydroxyphthalimidine (**1**), whereas in moderately alkaline aqueous solution this compound dimerized to yield **2** among other products.[5] Electrochemical reduction of phthalimide as well as of its derivatives in nonaqueous aprotic solvent (DMF) was reported to give a variety of products the formation of which could be explained on the basis of imide ring opening.[6] These findings indicate that cathodic reduction of phthalimide yields similar products to those obtained by reduction with sodium borohydride.[8]




**1**




**2**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Imides and their derivatives are valuable substrates for the production of anti-seizure drugs. The N-hydroxymethyl (>N-$CH_2OH$) group is frequently found in a variety of compounds with anti-neoplastic activity.[9] Imides are also important monomers in the synthesis of thermostable polymers and copolymers.[10]

There are a number of reports on electrolytic imide reduction in aqueous solutions. In contrast, the electrochemical behavior of phthalimide in protic organic media remains practically unexplored, and we have tried to fill this gap in the present study. To our surprise, the main reaction product of phthalimide anion electrolysis in methanol in andivided cell, differed from previously described products of electrochemical conversion of phthalimide. Below we give a detailed report of our findings.

## Results and Discussion

Our choice of methanol as the reaction medium was based on its being the most commonly used protic solvent for electrolysis of organic compounds. The electrolysis of methanolic phthalimide solution was performed in the presence of either the organic base 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) or sodium methoxylate. TLC of the electrolysis mixture revealed one major spot and trace amounts of a number of byproducts. However, HPLC analysis of the same mixture showed that the major spot represented a 2 to 1 mixture of two compounds with similar retention times (8.64 and 9.25 min, respectively). The derivative of lower mobility (9.25 min) was identical to that obtained by either phthalimide reduction with sodium borohydride, or electrolytic reduction of phthalimide in acidic aqueous solution, and has been identified as 3-hydroxyphthalimidine (**1**).[7,8] Pre-electrolysis of methanolic solution of sodium methoxylate followed by the addition of either phthalimide or its DBU salt prior to the main electrolysis step resulted in a change of the above two main products ratio to 5:1. This shift enabled purification of the unknown product (i.e., the one showing higher HPLC mobility) by silica gel chromatography and crystallization from acetone/hexane mixture. Elemental analysis, UV, FT-IR, $^1H$ NMR and mass spectroscopy data indicated that this compound is the yet undescribed N-hydroxymethyl-3-hydroxyphthalimidine (**4**). The reaction mixture also contained a small amount of a phthalimide derivative **3** with the HPLC retention time of 23.88 min. UV absorption spectra of **1**, **3** and **4** demonstrated the similarity of the electronic structure of these compounds. However, the UV spectrum of **3** showed a band at 300 nm which was absent in the spectra of **1** and **4** (Fig. 1). This band is characteristic of authentic phthalimide and its N-substituted derivatives.

The presence of chiral carbon atom C(3) in **4** makes the aliphatic protons of the -$CH_2$- ($H^aCH^b$) group, which is encompassed by a diastereotopic environment, chemically and magnetically dissimilar. The chemical shifts and coupling constants of these protons differ, respectively, by approximately 0.6 ppm and 1.5 Hz. Based on homodecoupling in **1** and **4**, the coupling pairs were identified as H(4)-H(5) and H(6)-H(7). The coupling constants of $^3J$(4-5,6-7) and $^3J$(5-6) in the symmetrical compound **3** are of similar magnitude (about 7.5 Hz),

which is somewhat higher than that in either **1** or **4**, and is the consequence of increased electron density of the aromatic system resulting from $sp^3$ hybridization of the C(3) carbon atom (see Table 1).

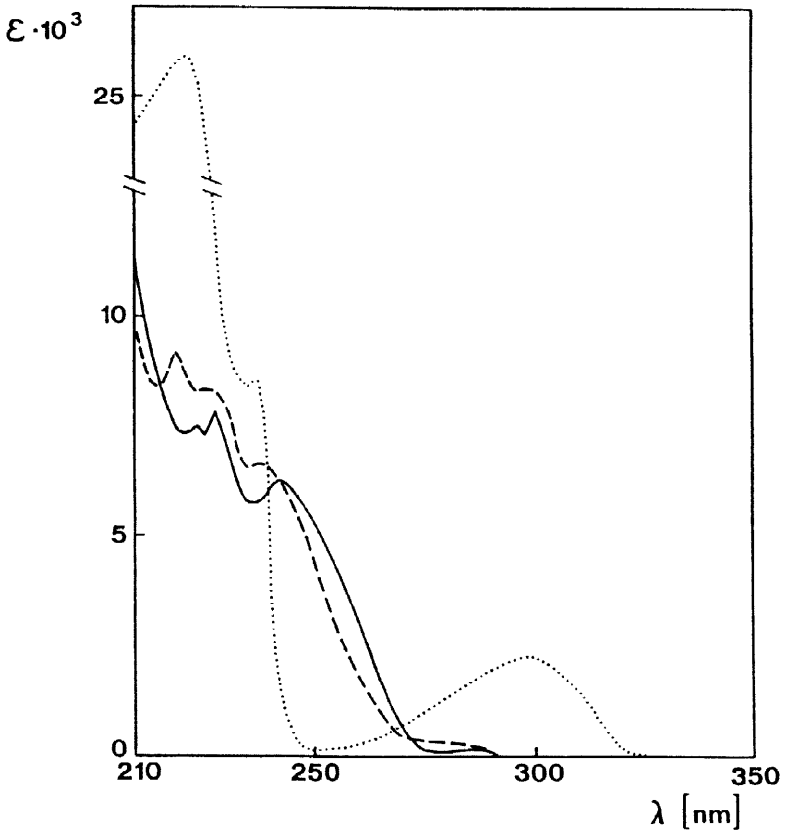


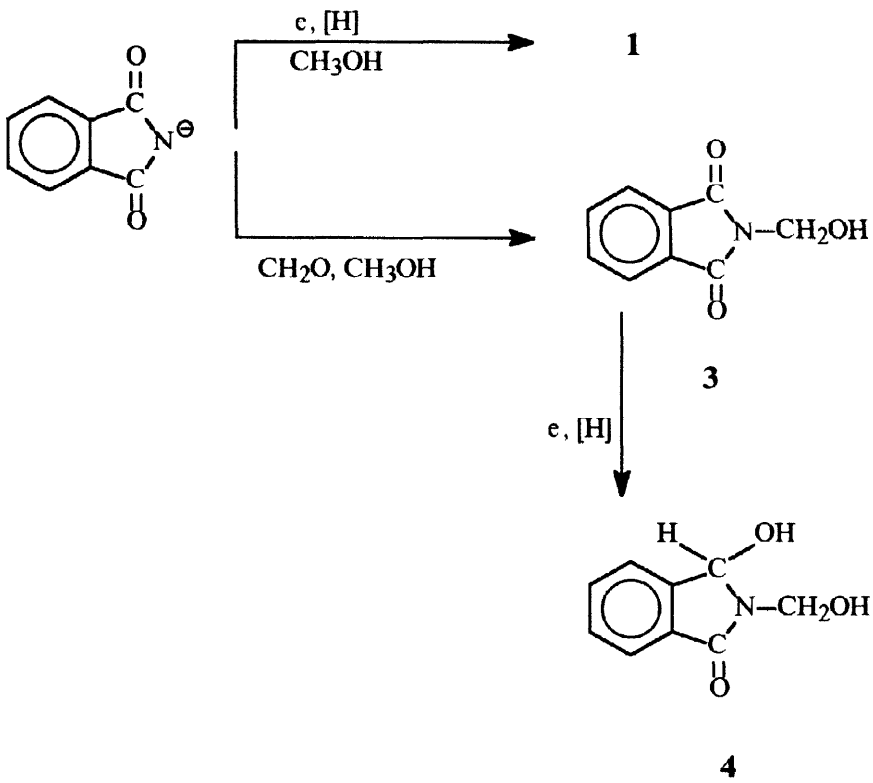

Fig. 1. UV spectra of **1** (dashed line), **3** (dotted line) and **4** (solid line) in aqueous solutions (pH 7.0).

**Table 1.** Chemical shifts (±0.005 ppm) and $^1H$-$^1H$ coupling constants (±0.1 Hz) in **1**,**3** and **4** as measured in [$^2H_6$]DMSO at 25°C.

| Proton | 1 | 3 | 4 | Coupling | 1 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| | | δ | | | | *J* | |
| (N)-H | 8.843 | - | - | $^2J(H^a\text{-}H^b)$ | - | - | 10.6 |
| | | | | $^3J(OH\text{-}H^a)$ | - | >5.5 | 6.2 |
| (N)-$CH_2$ | - | 4.969 | $H^a$ 5.153 | $^3J(OH\text{-}H^b)$ | - | >5.5 | 7.7 |
| | | | $H^b$ 4.581 | | | | |
| ($CH_2$)-OH | - | 6.371 | 5.883 | $^3J$(OH-H) | 8.9 | - | 8.8 |
| (C3)-OH | 5.318 | | 6.575 | $^3J$(4-5) | 7.3 | 7.4 | 7.3 |
| H(3) | 5.8 | | 5.948 | $^3J$(5-6) | 6.5 | 7.5 | 7.0 |
| H(4) | 7 | 24 | 7.692 | $^3J$(6-7) | 7.7 | 7.4 | 7.3 |
| H(5) | | 878 | 7.548 | $^4J$(4-6) | 1.2 | 1.0 | 1.1 |
| H(6) | 7.( | 7.878 | 7.662 | $^4J$(5-7) | 1.6 | 1.0 | 1.8 |
| H(7) | 7.5( | 7.924 | 7.637 | $^5J$(4-7) | - | 0.6 | - |

The reaction pattern we propose here (see Scheme 1) assumes the presence of formaldehyde in the reaction medium. It has been conclusively shown in earlier reports that methanol easily oxidizes electrochemically to yield formaldehyde.[11] It is also well known that phthalimide anion reacts with formaldehyde under non-electrolytic conditions to yield **3**.[12] Most likely, the same reaction takes place in the anodic space during the electrolysis of phthalimide in methanolic solution. To verify the electrolytic mechanism of formation of **3** and **4**, electrolysis of the DBU phthalimide salt was performed in an electrolysis vessel equipped with a porous glass membrane separating the cathodic and anodic compartments. No formation of **3** and **4** was observed in the cathodic space under these conditions.

**Scheme 1**




Derivative **4** contains a chiral center formed by the reduction of any of the two carbonyl groups of phthalimide. The presence of this center, and strong intermolecular interaction (hydrogen bonding) made the X-ray structural analysis of **4** interesting. While a racemic mixture was expected, the crystal of **4** appeared noncentrosymmetric, and consisted of two independent molecules in the asymmetric unit (see Fig. 2). The individual components of the stereo pair differed only slightly in their respective geometry, and torsion angles

also showed almost perfect centrosymmetry. The only exceptions were C(1)-N(2)-C(10)-O(3) and C(3)-N(2)-C(10)-O(3) torsion angles which indicated that 'non-primed' and 'primed' molecules were identical instead of being exact opposite numbers for the centrosymmetric case. The ring systems of both molecules were almost perfectly planar in their six-membered part (the rms deviations of the defining atoms were 0.003 and 0.003 Å, respectively), while the five-member fragments were less planar (the rms deviation of defining atoms were 0.011 and 0.013 Å, respectively). All in all, the condensed (six- and five-membered rings combined) ring system of either molecule might be considered planar (the rms deviations of defining atoms are 0.017 and 0.015 Å for 'primed' and 'non-primed' molecule, respectively). The non-hydrogen atoms bonded to the rings deviated from the condensed ring system planes with the O(2) and O(2') atoms being strongly out of plane [1.218(8) and 1.138(7) Å, respectively], whereas O(1) [O(1')] and C(10) [C(10')] atoms show lesser deviations [0.070(7) and 0.213(8) for 'non-primed', and 0.080(8) and 0.165(8) Å for 'primed' molecule, respectively].

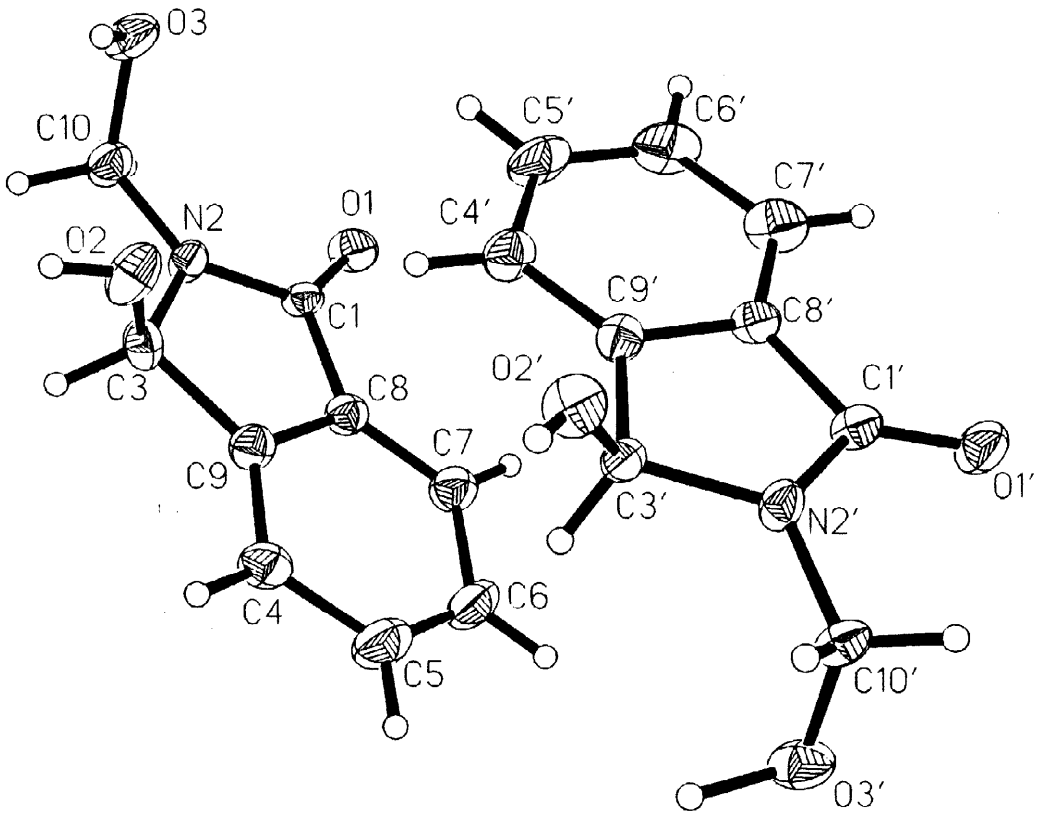



Figure 2. Atom numbering and molecular conformation of **4**.

The O(3) and O(3') atoms lie in the planes which are almost perpendicular to the respective ring planes, the dihedral angles defined by N(2), C(10) and O(3) atoms and the ring plane are 86.5(5)° and 81.9(3)° for primed molecule, respectively. The structure is held together by the series of hydrogen bonds shown as dashed lines in Fig. 3. The difference in conformation of the $CH_2OH$ group between the two stereoisomers resulted in different hydrogen bonding of both molecules and further inclination of both ring systems [the dihedral angle between both planes is 22.5(2)°]. Different conformations of substituents and the inclination of molecules lead to the noncentrosymmetry of the structure. This made this structure different from the known centrosymmetric structure of similar compound **1**,[13] where both planes were parallel, and the only type of hydrogen bond observed was $O–H\cdots O_{carbonyl}$.

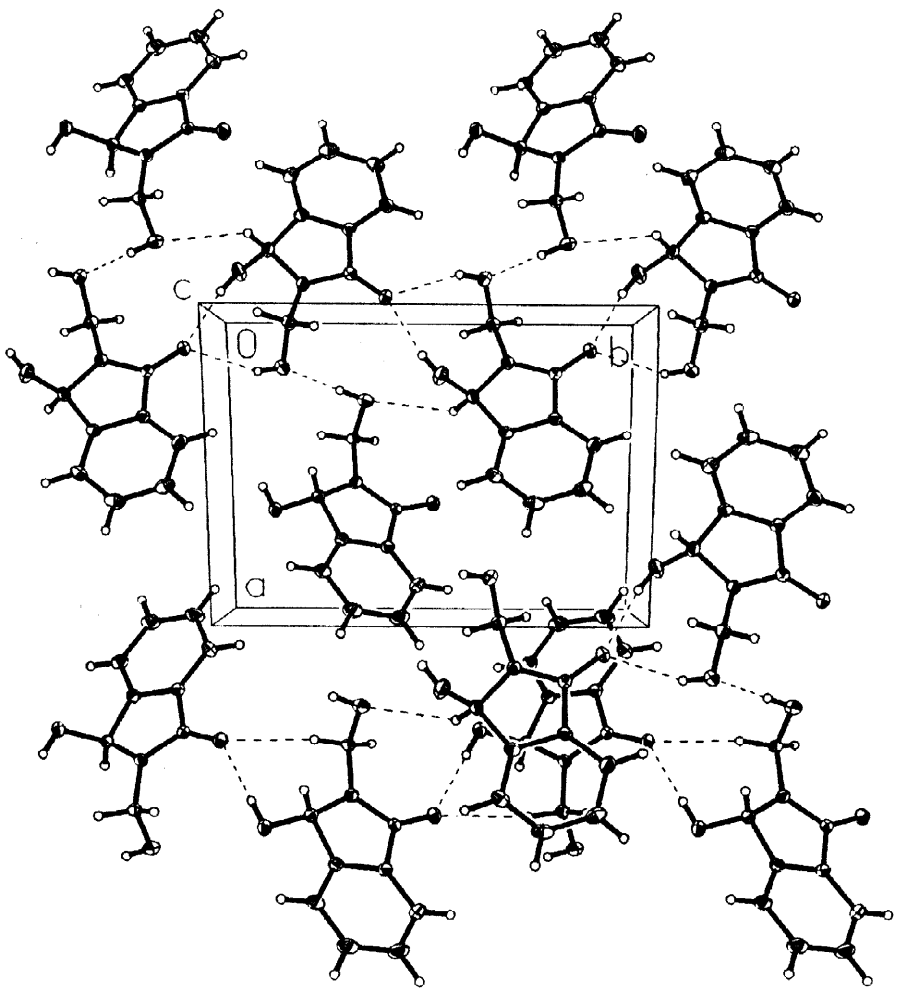



Figure 3. Crystal packing. The hydrogen bonds are shown as dashed lines.

## Materials and methods

Phthalimide, N-hydroxymethylphthalimide and phthalimide DBU salt were purchased from Aldrich. Electrolysis was performed in a water-cooled undivided cell equipped with two 3 $cm^2$ platinum electrodes spaced 5 mm apart. Analytical TLC was performed on precoated silica gel 60 $F_{254}$ (Merck). Melting points (uncorr.) were measured on a Boetius microscope hot stage. HPLC was performed using a model LC 6A Shimadzu instrument (UV detector, $\lambda$ = 254 nm) with a $C_{18}$ column (4.6 X 25 mm) (Beckmann) (water-MeOH, 87:13 v/v). Mass spectrum (70 eV) was obtained with a model AMD-604 Intectra spectrometer. UV spectra were recorded with a model Kontron Uvikon 940 spectrophotometer. NMR spectra were measured with a Varian UNITYplus 500 MHz spectrometer. FTIR spectra were recorded with Perkin Elmer 2000 spectrometer (KBr disc method). X-ray measurements were performed using a Kuma KM-4 $\kappa$-axis four-circle diffractometer. Graphite monochromatized MoK$\alpha$ radiation was used to collect the data. The unit cell parameters were obtained by the least-square treatment of 25 reflection with $19 \leq 2\theta \leq 25.3°$. 1669 reflections were collected using $\omega$–$\theta$ scan mode. Structure was solved in $P2_1$ noncentrosymmetric monoclinic space group using direct methods from SHELXS-86 program,[14] and refined using SHELXL-93 software.[15]

## Experimental

**N-hydroxymethyl-3-hydroxyphthalimidine (4)**. A solution of sodium methoxylate (6 mmoles) in methanol (30 ml) was pre-electrolyzed at current density of 0.05 A/$cm^2$ for 2 hours. Then phthalimide (882 mg, 6 mmoles) was added, and the solution was stirred for 15 min with no current flow. Next, the mixture was electrolyzed for 5 hours using current density of 0.02 A/$cm^2$. The reaction mixture was neutralized with acetic acid and evaporated to dryness, and the residue was adsorbed onto silica gel and chromatographed on a silica gel column (2.5x20 cm) with $CHCl_3$ (300 ml) and then with $CHCl_3$/MeOH (19:1). The product-containing fractions were evaporated to dryness, and the residue was crystallized from acetone/hexane to give white crystals (420 mg, 39%). Mp. 148-9°C. TLC ($CHCl_3$ - MeOH): Rf 0.15. MS: 179 (3), 161 (24), 131 (100). FTIR spectra: 3447, 3275, 1678, 1619, 1474, 1305, 1058 (in $cm^{-1}$). Analysis for $C_9H_9NO_3$ (179.18): calcd.: C 60.33; H 5.06; N 7.82; found: C 60.15; H 5.06; N 7.76.

In another experiment, the solvent (2 mmoles of MeONa in 30 ml MeOH) was pre-electrolyzed using the current density of 0.05 A/$cm^2$ for 1.5 hr. Next, the phthalimide DBU salt (6 mmoles) was added, and the mixture was stirred for 15 min with no current flow followed by 5 h electrolysis using the current density of 0.02 A/$cm^2$. The product distribution and yields did not significantly differ from those for the alternative procedure described above. However, the contents of byproducts was clearly reduced.

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