

ELECTROCHEMICALLY INITIATED INTRAMOLECULAR CYCLIZATION OF 2-NITRO-2'-ISOTHIOCYANATOBIPHENYL

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ABSTRACT

2-Nitro-2'-isothiocyanatobiphenyl was prepared as a new substance, suitable for the investigation of an electrochemically initiated intramolecular cyclization. If it is reduced at a mercury cathode in acidic media an acid catalysed intramolecular follow-up reaction occurs which leads to the formation of 6-mercaptodibenzo (*d, f*)-(1,3)-diazepin-5-oxide. The rate of the follow-up reaction decreases in neutral or alkaline media and the reduction of the isothiocyanato group also takes place. The main product is here 5,6-dihydrobenzo(*c*)cinnoline.

INTRODUCTION

The electrolytically initiated intramolecular cyclization as a follow-up reaction has been intensively studied in recent years¹. It represents one of the synthetic routes for the preparation of more complicated organic structures. This, in essence electrochemical method, is based on the electrolytic transformation of the starting substance into a chemically reactive species.

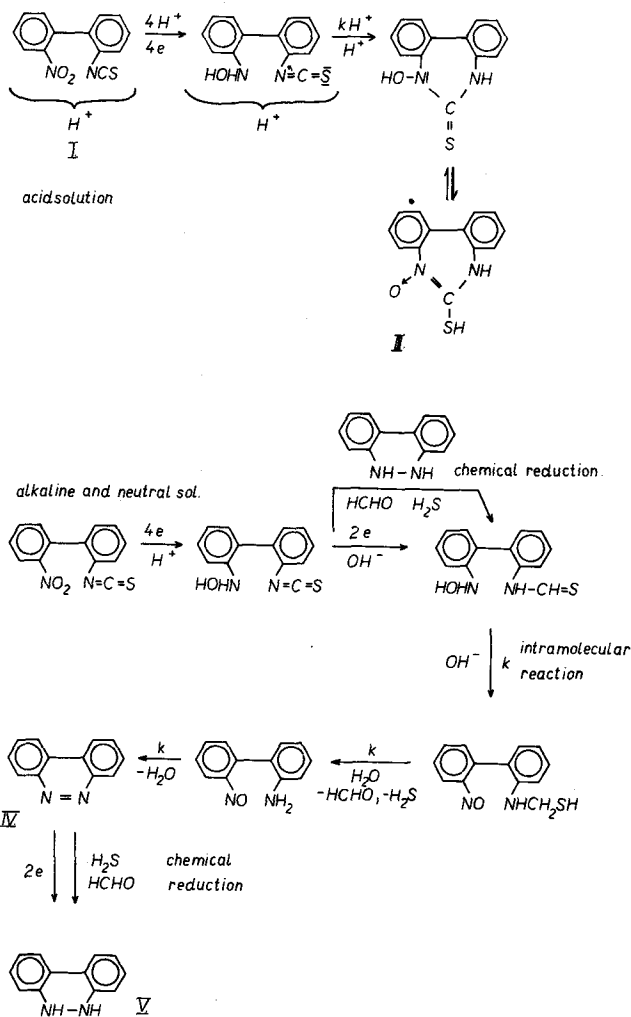
One of the combinations of substituents which can be used for the investigation of the above type of synthetic reactions, is a sterically suitably substituted substrate with a nitro and an isothiocyanato group. Lund and Feoktistov² carried out a preparative electrolytic reduction of *o*-nitroisothiocyanatobenzene in 0.1 *M* HCl with 40% ethanol and isolated 2-mercaptobenzimidazol-N-oxide in a 58% yield. This electropreparation of a isothiocyanato derivative represents an example of the preparation of heteroaromatic N-oxides which are otherwise not easily accessible.

In order to investigate the perspectives and the course of such a reaction path we prepared a new starting substance 2-nitro-2'-isothiocyanatobiphenyl (I). If the chemical follow-up reaction after the partial reduction of the nitro group is fast enough one can expect that a 7-membered heterocyclic ring should be formed with two fused benzene nuclei.

The verification of this idea and the influence of external factors, in particular that of pH of the supporting electrolyte, is dealt with in this communication.

EXPERIMENTAL

The polarographic measurements were carried out with an LP 60 polarograph



in connection with a Kalousek cell and a saturated mercurous sulphate electrode as anode. The solutions of the substance studied contained 50% ethanol. The Britton–Robinson buffers used in some cases as supporting electrolyte were prepared from analytical grade chemicals. The pH values were measured with a glass electrode making use of a Radiometer PHM-4c pH-meter. The coulometric measurements at a large-area mercury electrode were performed making use of a micro cell with mercury on the bottom and a saturated mercurous sulphate reference electrode. The concentrations of (I) were in the range of polarographic concentrations. In this case the polarograph enabled a potentiostatic control of the electrode potential. The preparative experiments were carried out in a cell with platinum wire anodes and with a mercury pool on the bottom, as described in our recent communication³. A saturated mercurous sulphate electrode was again applied here as reference electrode. The anolyte was a saturated sodium sulphate solution. In 200 ml of the

catholyte the substance (I) was dissolved at a concentration level from 2.5 to $5.0 \times 10^{-3} M$ (i.e. 128–256 mg), either in hydrochloric acid or in the Britton–Robinson buffers (always with 50 vol.% of ethanol). The potentiostatic course of the reduction was ensured by a circuit, containing a variable voltage source (Tesla BM 208) and an electronic voltmeter (BM 289). The charge consumed was measured with an electronic integrator (Amel 558/RM, Milano). The changes in concentration of (I) during electrolysis were followed by recording d.c. polarograms with a DME placed in the electrolysis cell. After electrolysis the catholyte was neutralized with aqueous potassium hydroxide making use of a universal indicator paper and evaporated from a rotating vacuum evaporator at 40–50°C and at 14–20 mm Hg to dryness. The residue was then extracted with warm chloroform and ethanol. The extracts were analysed by thin-layer chromatography (Silufol, silica gel of the firm Kavalier) followed by detection with iodine vapour. The mixtures of organic products were then separated on poured chromatographic silica gel columns (Silpearl-Kavalier). The isolated pure substances were identified by elemental analysis and spectral methods. For elemental analysis the products were dried over phosphorus pentoxide. The i.r. spectra were measured with a Zeiss UR 10 apparatus, the electronic spectra with an Unicam SP 800. The mass spectra were obtained with a LKB 9000. The melting points given below have not been corrected. Ethanol used as a component of the solution to be electrolysed was treated with metallic calcium and rectified on a rectification column.

2-Nitro-2'-isothiocyanatobiphenyl (I) was prepared by treating, with thiophosgen, 2-nitro-2'-aminobiphenyl (II), obtained by combining published procedures^{4,5}. We dissolved 2.1 g of (II) in about 20 ml of chloroform and 0.5 g of pulverised CaO were added to the solution. 0.8 g of thiophosgen were introduced into the suspension. The reaction mixture was heated to 60–70°C and kept at this temperature for about 4 h. From the cooled suspension the excess CaO was filtered off and the filtrate was left to crystallize. 2 g of the slightly yellowish crystals (80% yield) were twice crystallised from ethanol. They melted at 76.0–76.5°C. Elemental analysis for $C_{13}H_8N_2SO_2$ (molecular weight 256.2):

<i>calculated</i>	<i>found</i>
60.92% C	61.04% C
3.14% H	3.24% H
10.93% N	10.89% N

In order to verify the structure an i.r. spectrum of (I) in chloroform was recorded. Bands at 2050 cm^{-1} (s), 1580 cm^{-1} (m), 1530 cm^{-1} (s), 1475 cm^{-1} (m), 1350 cm^{-1} (s) were found. In the electronic spectra of an ethanolic solution only a single clear-cut band appears ($A_{\text{max}} = 271\text{ nm}$, $\epsilon = 12300$).

The mass spectrometry yielded a molecular ion 256 m/e , an intense peak of a fragment 210 m/e corresponding to the loss of the nitro group and an intense peak of a fragment 198 m/e which corresponds to the loss of the isothiocyanato group. The less intense peaks of the fragments 166 m/e and 152 m/e also point to the validity of the assumed formula of (I).

RESULTS AND DISCUSSION

Polarography

The d.c. polarographic investigation of (I) revealed that this substance reacts with ethanol present in the solution, probably with the formation of a thiourethane. When the ethanolic solution stands for several days, the reduction wave of (I) decreases and a diffusion-controlled anodic wave appears. Its limiting current is pH-independent whereas the half-wave potential is shifted towards more negative potentials with increasing pH. The reaction of (I) was also proved by thin-layer chromatography. This finding made it necessary always to prepare fresh solutions of (I) before polarography or preparative electrolysis.

TABLE 1
HALF-WAVE POTENTIALS OF (I)

Solution 50% ethanol	
pH	$-E_{1/2}/V$
2.10	0.65
2.90	0.72
3.3	0.73
4.5	0.81
5.24	0.89
6.10	0.92
7.70	1.01
8.56	1.05
9.44	1.10
10.65	1.13
11.0	1.13

The half-wave potential $E_{1/2}$ of the cathodic wave of (I) is a linear function of pH (*cf.* Table 1) with a slope $E_{1/2}/\text{pH} = -0.060 \text{ V/pH}$. Within the normal range of polarographic concentrations this wave is diffusion-controlled, irreversible and is a linear function of the concentration of (I). It corresponds to the reduction of the nitro group in (I). The value of limiting current decreases to about 85% of its value in strongly acidic solutions. Above pH 6.0 its height remains constant.

At concentrations of (I) exceeding $7.5 \times 10^{-4} \text{ M}$ a new, clear-cut, more negative reduction wave appears in neutral and alkaline media. Its origin remains obscure, but it is most probably adsorption-controlled. The coulometric determination of the number of electrons n consumed in the electrolysis at a mercury pool electrode in the potential range corresponding to the limiting current of the main wave gave $n=5.8$ for 0.1 *M* HCl and $n=3.9$ in buffers pH 2.7, and $n=3.85$ at pH 3.9.

Preparative electrolysis

The yields of products after electrolysis, their quantitative composition, the conditions of electrolysis and the values of n from the simultaneous coulometric measurements are shown in Table 2.

TABLE 2

Solution	Applied potential /V (vs. SME)	Starting current /mA	Isolated products from a CHCl ₃ extract /mg	TLC of the mixture of products ^a	Coulometric values of n
2 M HCl 50% ethanol 5×10^{-3} M	-0.9	300	180	N-oxide III	4.57
0.1 M HCl 50% ethanol 5×10^{-3} M	-1.0	300	168	N-oxide III 57%	6.40
B.R. buffer pH 2.9 50% ethanol 5×10^{-3} M	-1.0	300	181	N-oxide III 74%	6.0
B.R. buffer pH 4.5 50% ethanol 5×10^{-3} M	-1.2	290	226	N-oxide III 93%	4.82
B.R. buffer pH 7.6 50% ethanol 5×10^{-3} M	-2.0	300	197	N-oxide III 81%	4.65
B.R. buffer pH 10.35 50% ethanol 5×10^{-3} M	-1.5	270	156	N-oxide III Benzo(c)cinnoline IV Benzo(c)cinnoline IV	4.47 4.52
	-1.9	250	200	Benzo(c)cinnoline IV 86% Benzo(c)cinnoline IV	4.37 4.45

^a Yields based on reactant consumed.

As the main product of preparative electrolysis in acid media white substance (III) was isolated. After recrystallization from ethanol-water a melting point of 150.5–151°C was found. Elemental analysis for 6-mercaptodibenzo (*d,f*)-(1,3)-diazepin-5-oxide: C₁₃H₁₀N₂SO, molecular weight 242.1:

<i>calculated</i>	<i>found</i>
64.47% C	64.69% C
4.15% H	4.53% H
11.56% N	11.37% N

In order to prove the assumed structure of the product its i.r. and mass spectra were measured.

The i.r. spectrum measured with a chloroform solution contains the following bands: 3400 cm⁻¹ (m), 3000 cm⁻¹ diffuse, 1490 cm⁻¹ (s), 1380 cm⁻¹ (m), 1290 cm⁻¹ (m). The characteristic bands of the nitro and isothiocyanato groups cannot be seen in the spectrum. The mass spectrum reveals the formation of a molecular ion 242 *m/e* which corresponds to the assumed molecular weight of substance (III). The first significant fragment has a mass of 255 *m/e* which most probably corresponds to splitting off of the N-oxide oxygen. In the fragment with 210 *m/e* the sulphur atom has been split off and points to the presence of a mercapto group in the original molecule. The next fragment with 192 *m/e* corresponds to the dibenzo-(*d, f*)-(1,3)-diazepine framework after the loss of both substituents. The fragments 181 *m/e*, 168 *m/e* and 167 *m/e* indicate already the fission of the seven-membered diazepine nucleus.

The electron spectra of (III) obtained with ethanolic solutions exhibit the following bands: $\lambda = 240$ nm, $\epsilon = 25100$; $\lambda = 275$ nm, $\epsilon = 19700$.

All these data confirm the structure of 6-mercapto-dibenzo-(*d, f*)-(1,3)-diazepin-5-oxide for the product (III). This substance is polarographically active because it gives a well-defined anodic wave at pH > 1.5. Its appearance is due to the reaction of the sulphhydryl group with mercury ions resulting by anodic dissolution from the DME.

TABLE 3

HALF-WAVE POTENTIALS OF THE ANODIC WAVE OF (III)

Solution 50% ethanol

<i>pH</i>	$-E_{1/2}/V$
2.8	0.24
4.5	0.31
5.8	0.42
7.8	0.56
11.8	0.68

In Table 3 the half-wave potentials $E_{\frac{1}{2}}$ of this anodic wave are listed for different pH-values. Substance (III) is stable towards atmospheric oxygen and it cannot be oxidized at a mercury anode since it forms a salt with mercury. In strong acid media one more white substance has been isolated, not melting up to 360°C; it is probably a high-molecular polymeric product.

In electrolyses in the neutral and alkaline region no mercaptan odour developed and the solution turned yellow. This colouration did not disappear during electrolysis, it resulted shortly after starting the electrolysis and was connected with the development of a new, rapidly increasing, anodic wave. This wave considerably differed both in its shape and in the values of $E_{\frac{1}{2}}$ from the anodic waves of the mercapto derivative (III). The t.l.c. analyses of the reaction mixtures from the preparative electrolyses are in accord with the decrease in the concentration of the mercapto derivative (III) formed with increasing pH values of the base solution. Another substance (IV) turns out to be the main product. It has been isolated as yellow crystals, with m.p. 156.5–157.0°C after recrystallization from chloroform. On the basis of the mechanisms of the electroreduction of aromatic isothiocyanato derivatives described in the literature^{6,7} and of the polarographic behaviour of substance (IV) one can assume that the product isolated is benzo(*c*)cinnoline. Elemental analysis for benzo(*c*)cinnoline, $C_{12}H_8N_2$, molecular weight 180.2:

<i>calculated</i>	<i>found</i>
79.98% C	79.91% C
4.47% H	4.62% H
15.52% N	15.43% N

The i.r. spectrum of substance (IV) recorded with a chloroform solution is composed of the following bands: 3000 cm^{-1} (m), 1610 cm^{-1} (w), 1580 cm^{-1} (w), 1455 cm^{-1} (m), 1435 cm^{-1} (m). The literature^{8,9} gives 158.5–160°C or 156°C as the melting points for benzo(*c*)cinnoline.

It follows from the literature⁹ that both 2,2'-dinitrobiphenyl and the N-oxides resulting in the course of its reduction are electrolytically reduced to 5,6-dihydrobenzo(*c*)cinnoline (V). This compound, however, very easily oxidizes *e.g.* by atmospheric oxygen under formation of benzo(*c*)cinnoline (IV). A 2-electron anodic wave of the dihydro derivative (V) has been described⁸; the electrode process leads to the formation of benzo(*c*)cinnoline. The data^{8,9} concerning the half-wave potentials of the cathodic waves of benzo(*c*)cinnoline also agree with our values of $E_{\frac{1}{2}}$ (*cf.* Table 4). Consequently, 5,6-dihydrobenzo(*c*)cinnoline is the main product of the electrolytical reduction of (I) in neutral and alkaline solutions. During isolation this primary product oxidizes to benzo(*c*)cinnoline (IV).

It follows from our results that the intramolecular chemical cyclization following the electrode process proper is so fast that in acid solutions it prevents a further reduction of the nitro group to an amine. Moreover it does not allow the electrolytical reduction of the isothiocyanato group. Only when passing to neutral and alkaline solutions where the follow-up reaction between $-NHOH$ and $-NCS$

TABLE 4
HALF-WAVE POTENTIALS OF BENZO(*c*)CINNOLINE

Solution 50% ethanol

<i>pH</i>	$-E_{1/2}/V$	
2.10	0.62	1.15
2.9	0.70	1.23
3.3	0.73	1.24
4.5	0.80	1.38
5.24	0.87	1.45
6.1	0.91	
7.7	1.01	
8.56	1.05	
9.44	1.12	
10.65	1.19	
11.0	1.23	

becomes slower the electrolytic reduction of the thiocyanato group becomes evident. Its course is in agreement with the results of other authors^{6,7}. The product is an amine which gives benzo(*c*)cinnoline by a follow-up intramolecular chemical reaction. The coulometric results in acid and neutral solutions do not present a full and convincing support for this mechanism; this is probably caused by chemical side reactions of the products which also cause a reduction of benzo(*c*)cinnoline to the dihydro derivative (V). Thus the reduction occurs in part on account of the oxidation of the products (*cf.* Scheme 1).

According to the data in the literature⁷ the aromatic isothiocyanates are reduced under consumption of 2 electrons in alkaline solutions and yield the corresponding thioformamide. On the basis of the structure of the main product of the electrolytical reduction of (I) in neutral and alkaline solutions, the assumed reduction of $-NCS$ to the amine more probably occurs by an intramolecular redox interaction of the thioformamide with the hydroxylamine. The $-NHOH$ group is oxidized to $-NO$ and from the thioformamide a mercaptomethylamine is formed which hydrolyses in water and gives an amine, formaldehyde and H_2S . 2-Nitroso-2'-aminobiphenyl results which gives rise to benzo(*c*)cinnoline. This probably causes the yellow colour of the solution during electrolysis.

The low electron consumption, the chemical activity of the intermediates and the final products in alkaline and neutral media support the mechanism according to Scheme 1 in which the intermediates function as reductants.

REFERENCES

- 1 M. J. Fioshin, P. A. Tomilov and L. G. Feoktistov, *Elektrosyntezy i mekhanizm organicheskikh reakcij*, Nauka, Moscow, 1973, pp. 58-62.
- 2 H. Lund and G. L. Feoktistov, *Acta Chem. Scand.*, 23 (1969) 3482.

- 3 O. Manoušek, *Z. Chem.*, 11 (1971) 18.
- 4 D. Purdie, *J. Amer. Chem. Soc.*, 63 (1941) 2276.
- 5 L. Mascarelli and M. Gatti, *Gaz. Chim. Ital.*, 59 (1929) 861; 61 (1931) 786.
- 6 A. M. Kardoš, J. Volke and P. Kristián, *Collect. Czech. Chem. Commun.*, 30 (1965) 931.
- 7 H. Lund, *Studier over elektode reaktioner, Organisk polarografi og voltametri*, Aarhus, 1961, p. 112.
- 8 T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 35 (1962) 1923.
- 9 S. D. Ross, G. I. Kahan and A. Leach, *J. Amer. Chem. Soc.*, 74 (1952) 4122.