The following paper was originally published in HETEROCYCLES, 1994, 37, 2009. Unfortunately, errors on the text were such as to render the paper unintelligible. We are therefore reproducing the whole paper with revised form.

OPTIMIZATION OF SYNTHESIS OF NITROIMIDAZOLES AND NITROPYRAZOLES BASED ON POLAROGRAPHIC INVESTIGATIONS

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Abstract - Direct, simple, fast and inexpensive polarographic method enables selective determinations of nitroimidazoles or nitropyrazoles (nitroazoles) in mixtures which can be used for monitoring synthetic processes and selecting optimal conditions for synthesis.

INTRODUCTION

Though the first nitroimidazole was synthesized as early as in 1892,[1] and the first nitropyrazole only one year later,[2] a more systematic work on the synthesis of nitroazoles, particularly for applications in human and veterinary medicine, was initiated after the introduction of the first antibiotic (azomycin) containing a 2-nitroimidazole grouping. This antibiotic was first isolated in 1953[3] from a *Streptomyces* sp., but synthesized much later.[4,5] In 1956, azomycin was found to have antitrichomonal in addition to antibiotic properties.[6] These findings initiated interest in syntheses of new nitroazoles, especially of nitroimidazoles, which were tested for antitrichomonal, antihistomonal and other activities. The 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole, flagyl, orvagil, clont, ...) synthesized in 1959 was found to be a significantly better trichomonacide than azomycin,[7] and was successfully clinically applied.[8] As a result of

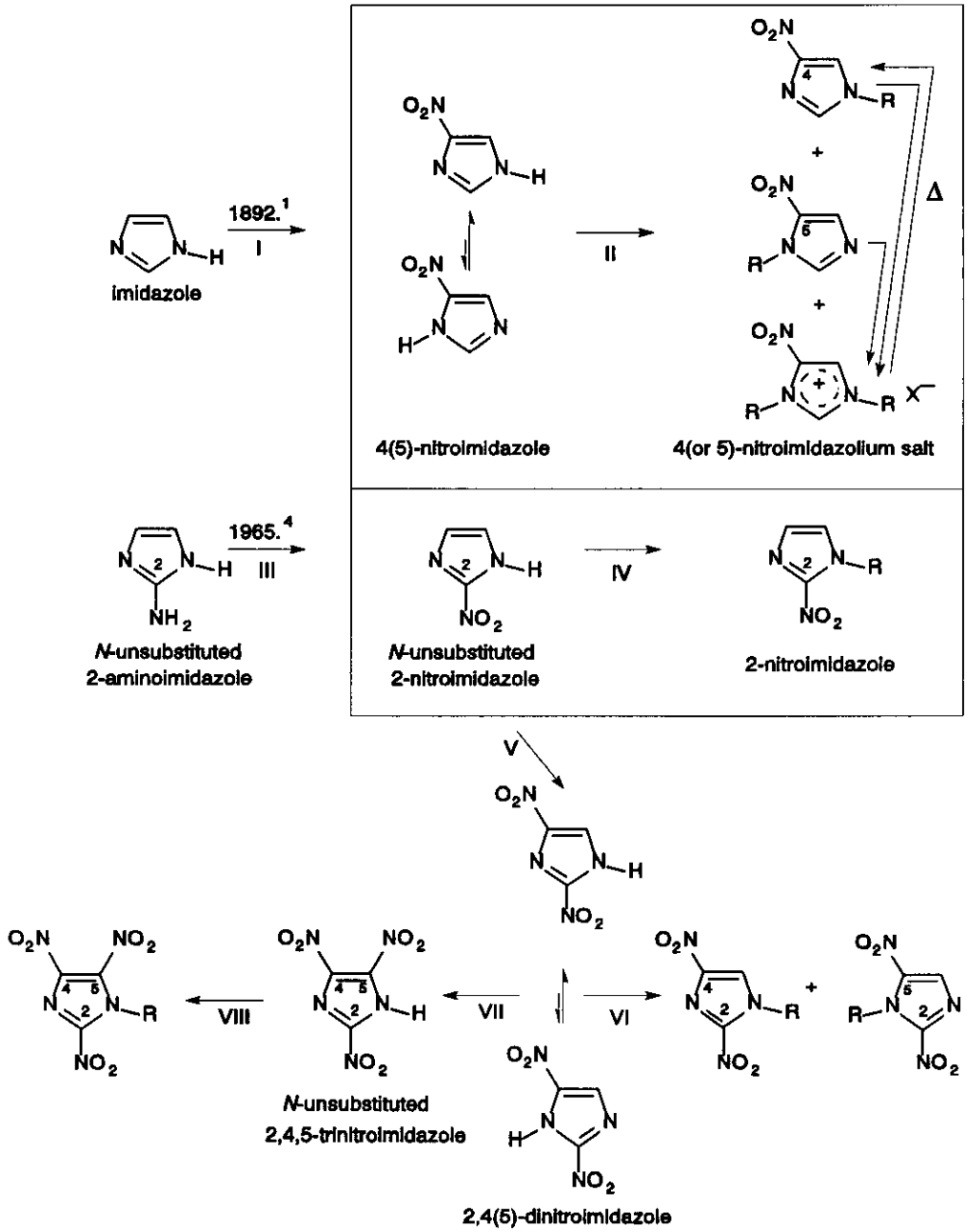
successful applications of metronidazole, several thousands of new nitroazoles were prepared in a search for more efficient chemotherapeutics, radiosensitizers, additives, explosives, energetic materials, *etc*. In preparation of these compounds different synthetic routes have been used. Some of these routes are presented in the Schemes 1 and 2 (reactions I - XVII), which involve *nitrations* (reactions I,[1,11-31] V,[32-36] VII,[22,31,35] IX,[2,30,37] XI[38-45] and XVI[45]), *N-substitutions* (reactions II,[21,23-29,31,36,46-73] IV,[31,66-68,74-77] VI,[33,34,76,78-81] VIII,[22,31] X,[37,82,83] XV[10,84-96] and XVII[35]), *oxidations* (reactions III[4,5,31,34-36,66,97-101] and XIV[9,94-96]) and *rearrangements* (reactions XII[38,44] and XIII[39,40,44,45]). The references given in the schemes indicate in each instance the first application of the given process, which span a period of eighty years.

To optimize the synthesis of a given product, selective analytical methods are needed to enable simple and rapid determination of all compounds involved in the synthetic process. The lack of analytical methods in the nitroazole chemistry, especially of those to be used for simultaneous determination of several compounds during a given synthetic process, lead us to a development of polarographic methods.[102-108] Using in some cases d.c. (DCP), in others differential pulse polarography (DPP), enabled simultaneous, simple, accurate and rapid determination of nitro compounds present in reaction mixtures during syntheses. Such successful application will be demonstrated here for analyses of nitroimidazoles obtained according to reactions I - IV (Scheme 1) and nitropyrazoles obtained according to reactions IX - XVII (Scheme 2). Development of such procedures was based on studies of polarographic behavior and reduction mechanisms of nitroimidazoles and - pyrazoles.[109-113]

NITROIMIDAZOLES

The syntheses of the known active compounds - derivatives of 5-nitroimidazoles (metronidazole, tinidazole, flunidazole, ornidazole, secnidazole, nimorazole, dimetridazole, ipronidazole, ...) are carried out according to reaction II (Scheme 1). The substrate [4(5)-nitroimidazole] yields 1-alkyl-5-nitroimidazole in strongly acidic media, while under alkaline conditions it yields the 1-alkyl-4-

Nitroimidazole Syntheses

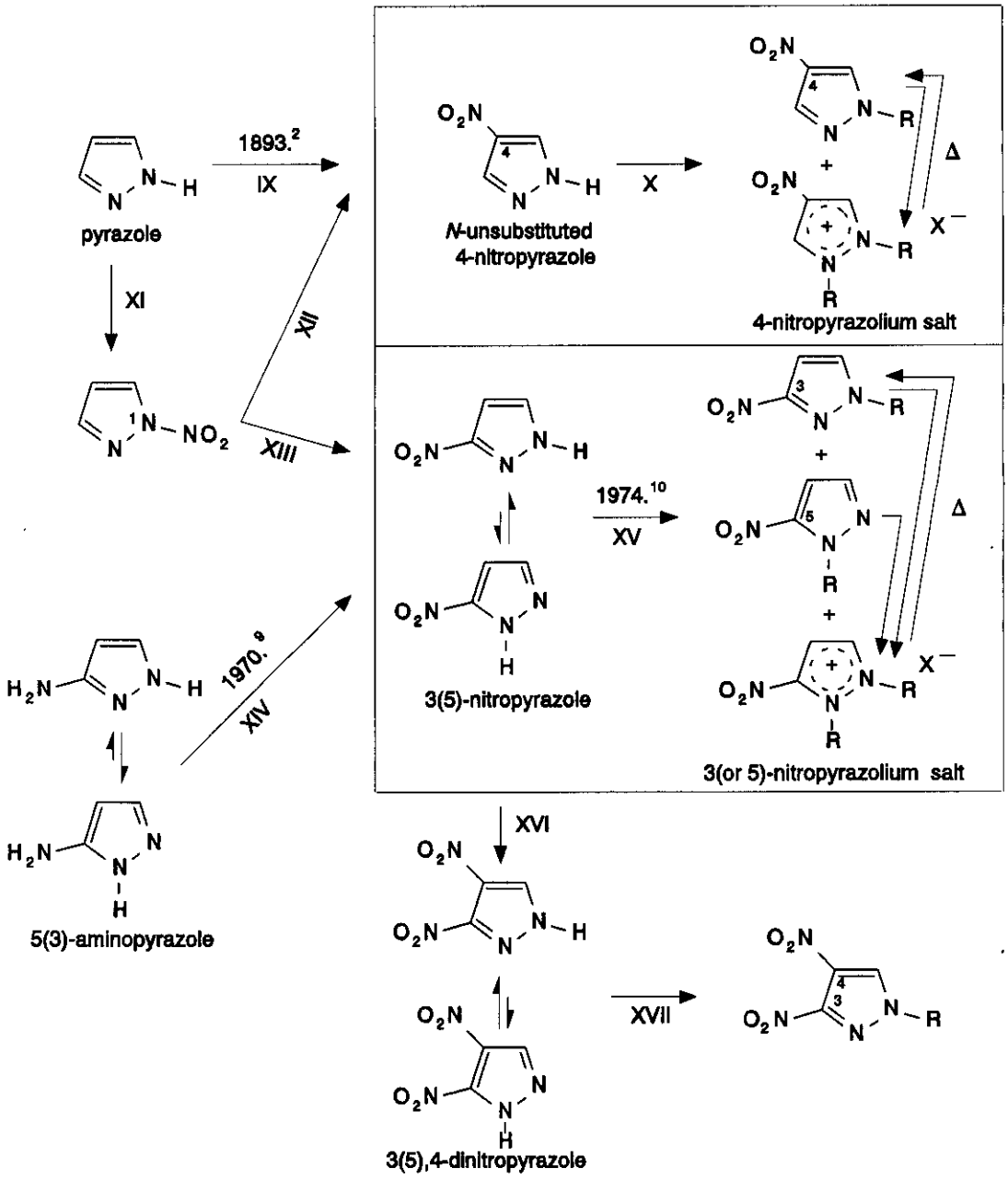


Scheme 1

Reactions: I, V, VII - nitration
II, IV, VI, VIII - *N*-substitution
III - oxidation

Any substituent may be in unsubstituted positions

Nitropyrazole Syntheses



Scheme 2

Reactions: IX, XI, XVI - nitration
X, XV, XVII - *N*-substitution
XIV - oxidation
XII, XIII - rearrangement

Any substituent may be in unsubstituted positions

nitro isomer as the major product. During the synthesis of the 5-nitroimidazole derivative, the 4-nitro isomer and 1,3-disubstituted-4(or 5)-nitroimidazolium salt appear as by-products. Due to the differences in their half-wave potentials the three compounds: the 5-nitro isomer, the 4-nitro isomer and the starting 4(5)-nitroimidazole compound can be determined in strongly alkaline media. Three separate waves (on DCP) or peaks (on DPP) are observed when 0.1M NaOH is used as supporting electrolyte (Figure 1a). The 4-(or 5)-nitroimidazolium salt does not affect this

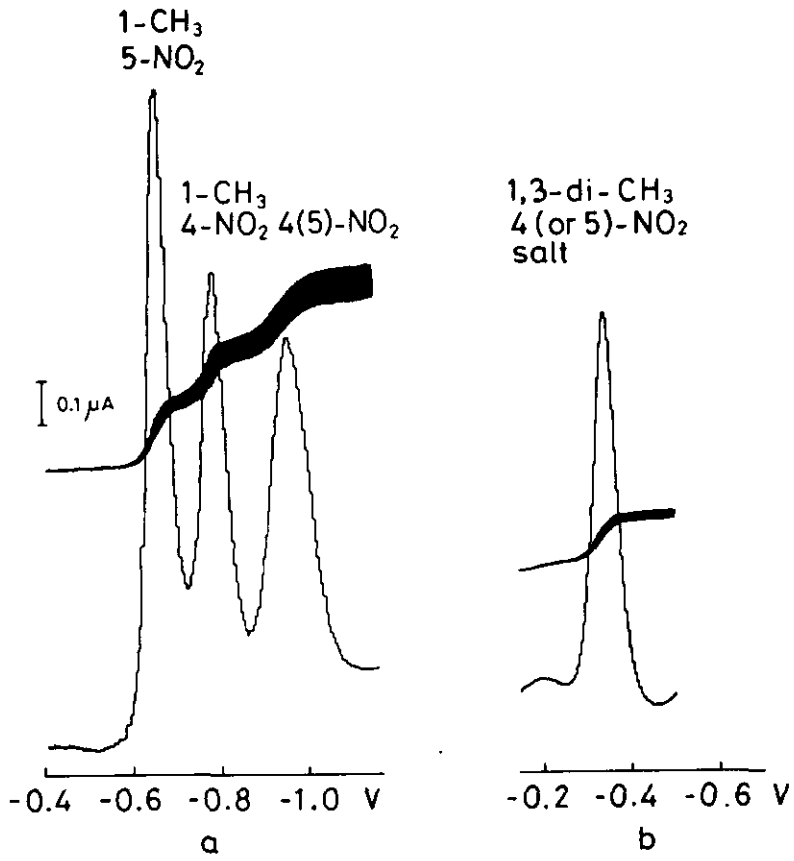


Figure 1. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 2-isopropyl-4(5)-nitroimidazole, 1-methyl-2-isopropyl-4-nitroimidazole, 1-methyl-2-isopropyl-5-nitroimidazole - ipronidazole and 1,3-dimethyl-2-isopropyl-4(or 5)-nitroimidazolium iodide. Supporting electrolyte: (a) 0.1M NaOH; (b) Britton-Robinson buffer pH 9.2. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

determination, because in strongly alkaline media the salt degradates immediately. Alternatively, the content of the 4(or 5)-nitroimidazolium salt can be determined by using a buffer pH 8 - 9.5 (Figure 1b).

For successful synthesis the content of the nitroimidazolium salt must be kept as low as possible, as its formation results in an irreversible loss of the starting material. Furthermore, its presence in a large scale production is particularly unwanted, as compounds containing a *nitroimidazolium* cation are potentially explosive.

Figure 1 shows the possibility for monitoring the synthesis of ipronidazole and/or its 4-nitro isomer. The synthesis of other 5- and 4-nitroimidazoles: metronidazole, iso-metronidazole, tinidazole, ornidazole, dimetridazole, *etc.*, can be monitored in the same manner.

Therapeutically active 2-nitroimidazoles are prepared according to reaction IV. In this reaction a determination of 2-nitroimidazole in the presence of an *N*-unsubstituted parent compound can be carried out using any buffer in the pH range 11-13 (Figure 2).

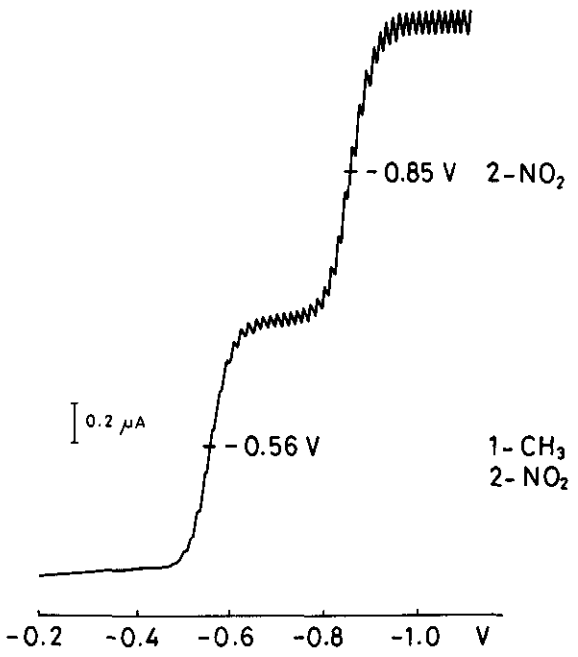


Figure 2. Polarogram by DCP of an equimolar (10^{-4} M) mixture of *N*-unsubstituted-2-nitroimidazole (azomycin) and 1-methyl-2-nitroimidazole. Supporting electrolyte, 0.1M NaOH.

For reactions I and III it is possible to monitor only the final nitro product, because the substrate is a polarographically inactive compound.

NITROPYRAZOLES

Similarly as for nitroimidazoles, the reactions involving nitropyrazoles (IX - XVII) following the Scheme 2 can be monitored polarographically.[104,105,107,108]

For reactions IX, XI and XIV it is possible to monitor only the final nitro product.

In the rearrangement XII it is possible to monitor simultaneously 1-nitropyrazole and 4-nitropyrazole (Figure 3), in the rearrangement XIII 1-nitropyrazole and 3(5)-nitropyrazole (Figure 4). In both cases a Britton-Robinson buffer pH 9.4 was used as a supporting electrolyte. Reduction of the 1-nitro compound occurs at more positive potentials, offering also a possibility

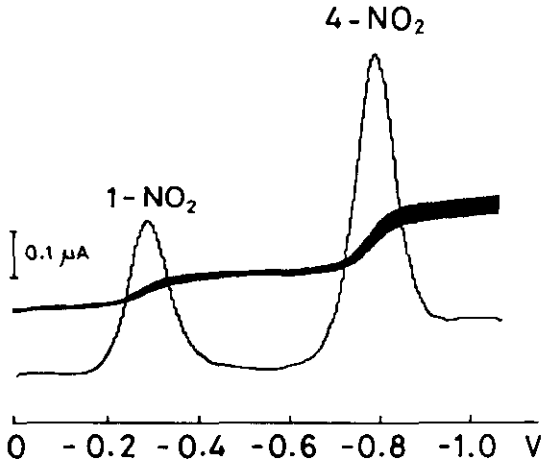


Figure 3. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 1-nitropyrazole and *N*-unsubstituted-4-nitropyrazole. Supporting electrolyte, Britton-Robinson buffer pH 9.4. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

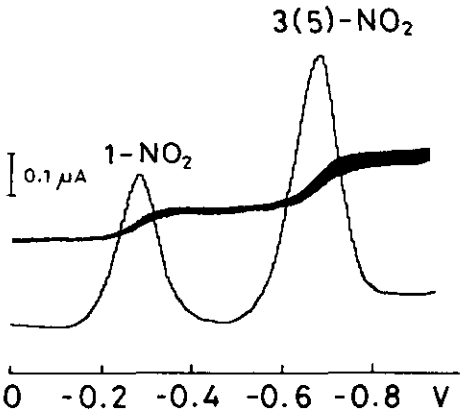


Figure 4. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 1-nitropyrazole and 3(5)-nitropyrazole. Supporting electrolyte, Britton-Robinson buffer pH 9.4. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

to determine a trace of the starting 1-nitropyrazole in the final *N*-unsubstituted compounds. In 0.1M NaOH it is possible to determine polarographically four mononitropyrazoles when present in comparable concentrations (Figure 5).

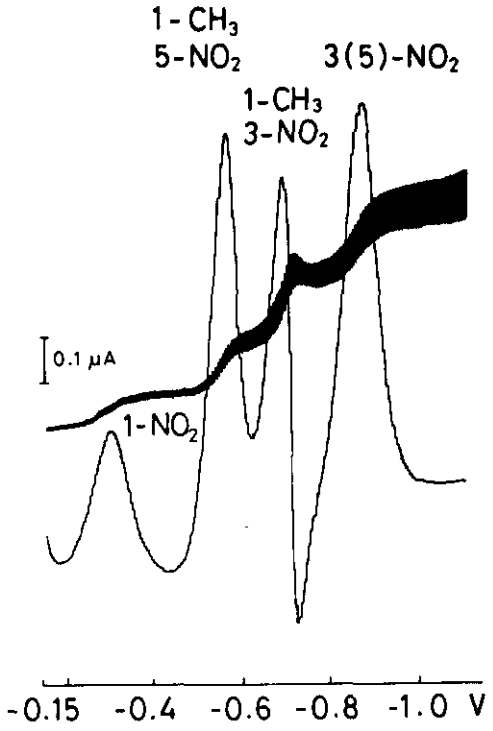


Figure 5. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 1-nitropyrazole, 1-methyl-3-nitropyrazole, 1-methyl-5-nitropyrazole and 3(5)-nitropyrazole. Supporting electrolyte, 0.1M NaOH. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

N-Alkylation (X) can yield monoalkylated and dialkylated products. In the presence of a dialkylated compound, determination of 1-alkyl-4-nitropyrazole and *N*-unsubstituted parent compound can be carried out using 0.1M NaOH (Figure 6a). Reduction of the 1,2-dialkyl-4-nitropyrazolium ion occurs in a Britton-Robinson buffer pH 8.4 at such positive potentials, that the determination of

even a trace of this product in the presence of an excess of the 1-alkyl derivative and the unsubstituted parent compound is possible (Figure 6b).

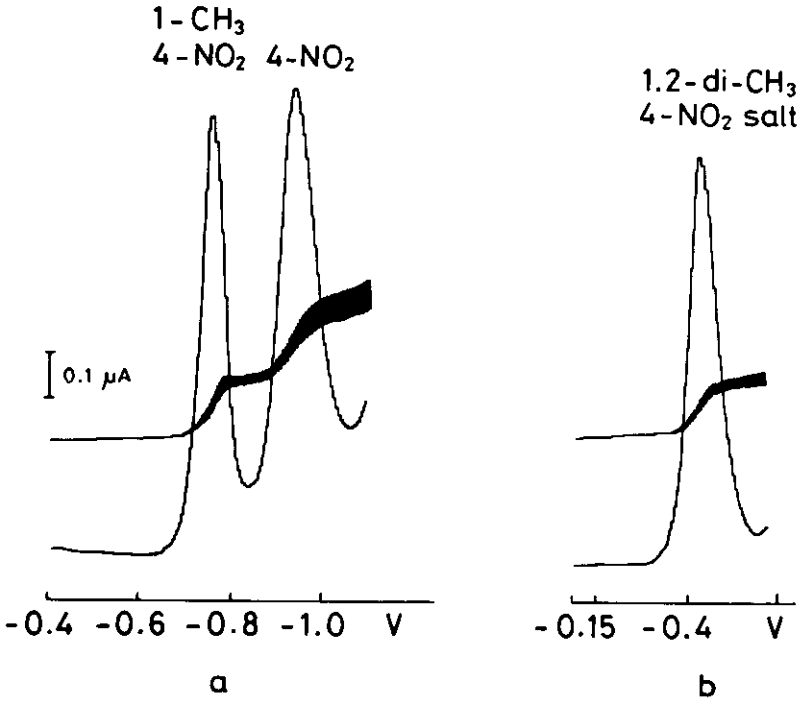


Figure 6. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of *N*-unsubstituted-4-nitropyrazole, 1-methyl-4-nitropyrazole and 1,2-dimethyl-4-nitropyrazolium methylsulfonate. Supporting electrolyte: (a) 0.1M NaOH; (b) Britton-Robinson buffer pH 8.4. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

Similarly, the alkylation of 3(5)-nitropyrazole in reaction XV can be followed. Analysis using 0.1M NaOH enables determination of the unalkylated compound in the presence of 1-alkyl-3-nitro- and

1-alkyl-5-nitropyrazole (Figure 7a). For determination of the 1,2-dialkyl-3(or 5)-nitropyrazolium ion the Britton-Robinson buffer pH 9.2 proved to be most suitable (Figure 7b).

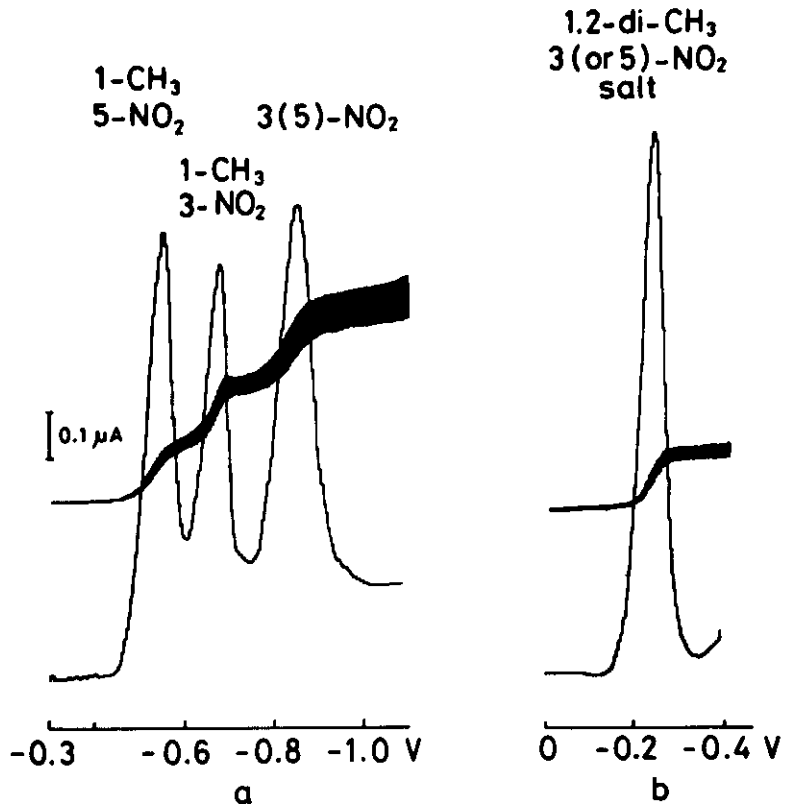


Figure 7. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 3(5)-nitropyrazole, 1-methyl-3-nitropyrazole, 1-methyl-5-nitropyrazole and 1,2-dimethyl-3 (or 5) - nitropyrazolium methylsulfonate. Supporting electrolyte: (a) 0.1M NaOH; (b) Britton-Robinson buffer pH 9.2. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

Further nitration of 3(5)-nitropyrazole yields a dinitropyrazole following reaction XVI. As the reduction peak of the mononitro compound occurs in Britton-Robinson buffer at pH 11.6 between the two reduction peaks of consecutive reductions of the first and second nitro group in the

dinitro derivative (Figure 8), the unreacted mononitro compound can be determined in the presence of the final dinitro product.

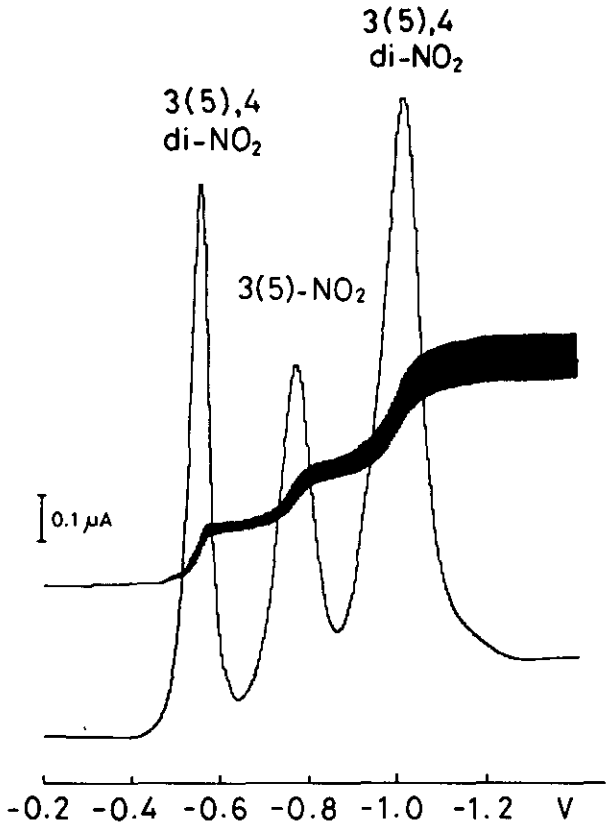


Figure 8. Polarograms by DCP and DPP of an equimolar (10^{-4}-M) mixture of 3(5)-nitropyrazole and 3(5),4-dinitropyrazole. Supporting electrolyte: Britton-Robinson buffer pH 11.6. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

Alkylation of the 3(5),4-dinitropyrazole in reaction XVII can be followed using any of the four waves, obtained for a mixture of the alkylated species and parent dinitro compound in a Britton-Robinson buffer at pH 11.6 (Figure 9). Well separated d.c. polarographic waves seem particularly well suitable for analyses of such mixtures.

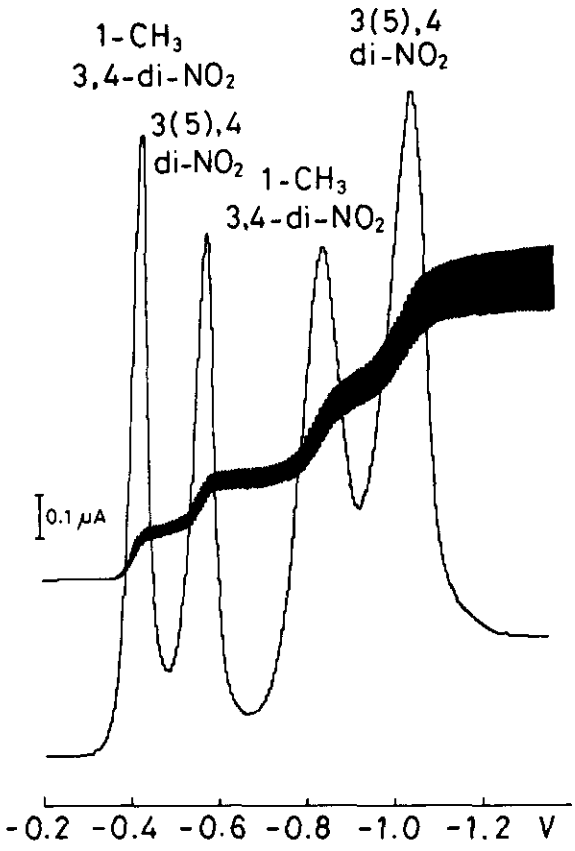


Figure 9. Polarograms by DCP and DPP of an equimolar (10^{-4} M) mixture of 3(5),4-dinitropyrazole and 1-methyl-3,4-dinitropyrazole. *Supporting electrolyte:* Britton-Robinson buffer pH 11.6. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

PROCEDURE FOR MONITORING THE NITROAZOLE SYNTHESES

An example of how to use the selective polarographic method in the control of a synthetic procedure is the *N*-substitution of 3(5)-nitropyrazole (reaction XV) under conditions when it yields[10] 1-methyl-3- or 1-methyl-5-nitropyrazole as the major product. In our patent[10] we *reported conditions for synthesis* of 1-methyl-5-nitropyrazole with 80 - 90% yield, while the

attempts of others,[88-90] some years later, were not equally successful (with a yield < 20%). To find optimum conditions for such syntheses, the samples (0.1 to 0.2 ml) were withdrawn from the reaction mixture at various times following the start of the reaction, diluted in water and 0.1 or 0.2 ml of the diluted solution were added to 10 ml of 0.1M NaOH. After deareation polarographic curves were recorded to determine percent conversion, amount of the desired final product, by-products and the starting compound as a function of time, temperature, medium, concentration, and/or other variable (Figures 10,11).

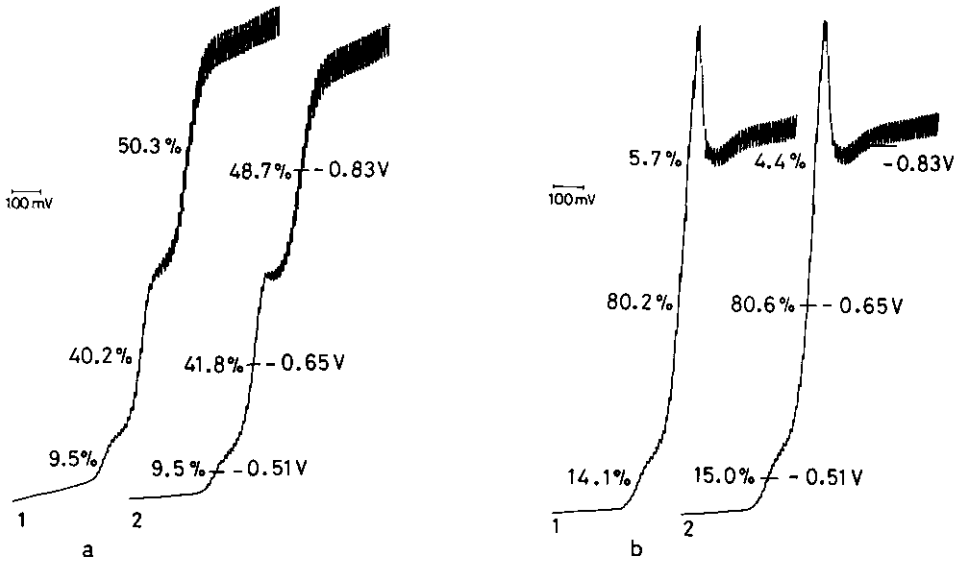


Figure 10. Polarograms by DCP of a reaction mixture during N-substitution of 3(5)-nitropyrazole ($E_{1/2}$ = -0.83 V) under different reaction conditions (a,b) as a function of time (curves 1a, 1b: 60′ ; curves 2a, 2b : 120′).

Relative heights of individual waves indicate relative content of individual compounds. Such procedures for choosing optimum reaction conditions are demonstrated for the synthesis of 1-methyl-3-nitropyrazole (with $E_{1/2}$ = - 0.65 V) (Figure 10) and of 1-methyl-5-nitropyrazole (with

$E_{1/2}$ = - 0.51 V) (Figure 11). In each case the set of curves (a) corresponds to unsatisfactory reaction conditions and the set (b) to satisfactory ones. When favorable conditions for the content of the desired 3- or 5-nitropyrazole are found in this way, then the actual content of the 3(5)-, 3- and 5-nitropyrazole can be determined by the method of standard addition, using 0.1M NaOH as a supporting electrolyte. To determine the content of the 1,2-dimethyl-3 (or 5)-nitropyrazolium salt, if present, a similar procedure can be used, employing buffer pH 8 - 9.5 as supporting electrolyte.

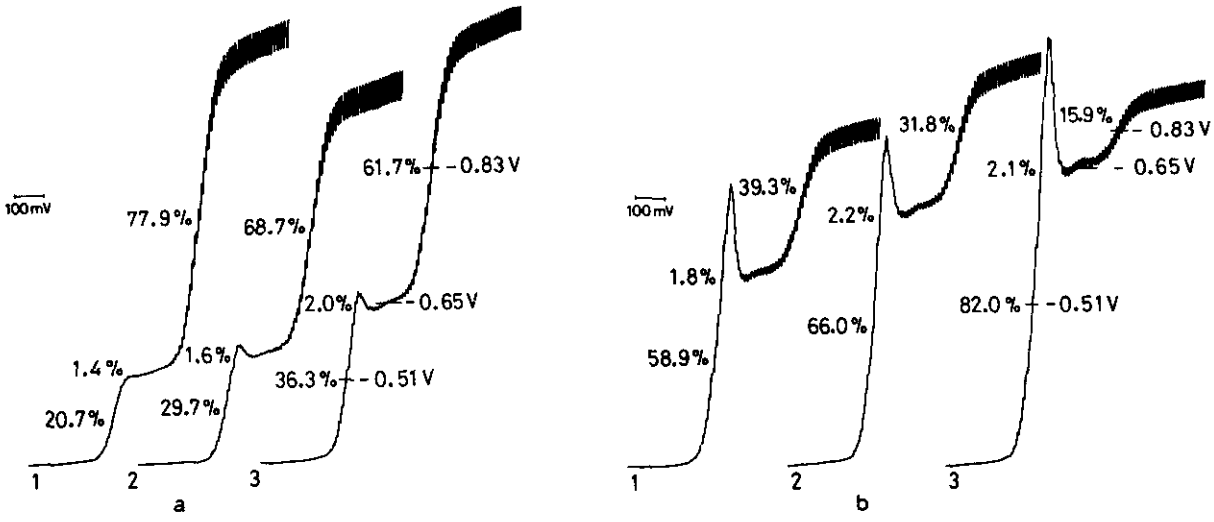


Figure 11. Polarograms by DCP of a reaction mixture during N-substitution of 3(5)-nitropyrazole ($E_{1/2}$ = -0.83 V) under different reaction conditions (a,b) as a function of time (curves 1a, 1b: 30′ ; curves 2a, 2b : 45′ ; curves 3a, 3b : 60′).

CONCLUSIONS

Polarography represents a very useful analytical method in the synthesis of nitroimidazoles and nitropyrazoles. This method enables simultaneous determination of several nitro compounds in reaction mixtures during the synthesis and therefore can be used for a choice of optimal conditions to obtain the highest yield of the desired product and the lowest amount of by-products. Similar behavior can be expected for other *nitro* derivatives of *azoles* (oxazole, thiazole, isoxazole, isothiazole), *diazoles* (oxadiazole, thiodiazole), *triazoles* and *tetrazoles* and analogous approaches could be developed for these classes of compounds.

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