# 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 I 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[21,23-29,31,46-73], IV[31,66-68,74-77], VI[31,33,34,36,76,78-81], VIII[22], 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] and XIII[39,44,45]). 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-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 0.1 M NaOH is used as supporting electrolyte (Fig. 1a). The 4(or 5)-nitroimidazolium salt does not affect this

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 (Fig. 1b).

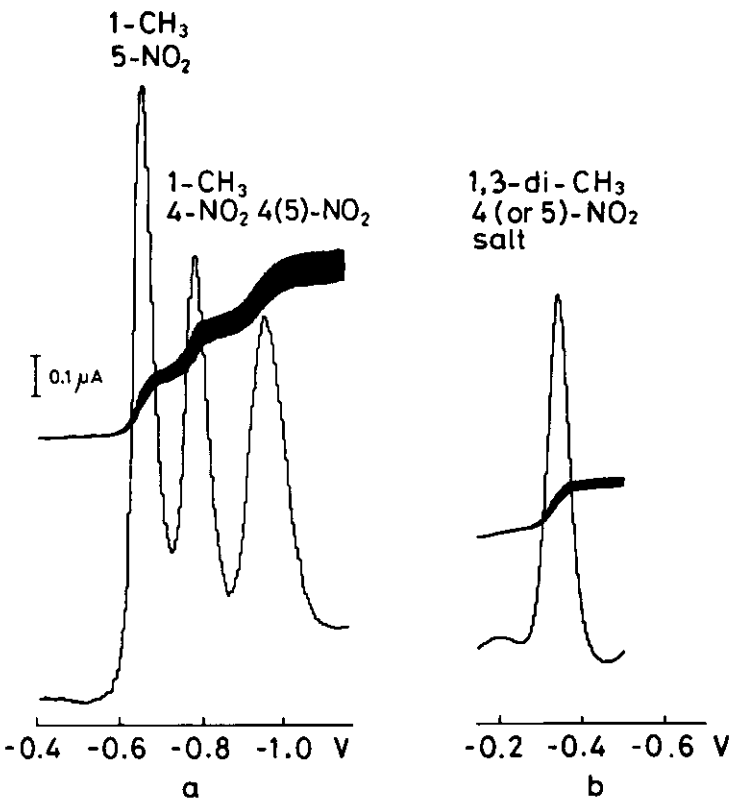


Figure 1. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 2-isopropyl-4(5)-nitroimidazole, 1-methyl-2-isopropyl-4-nitroimidazole, 1-methyl-2-isopropyl-5-nitroimidazole-ipronidazole, and 1,3-dimethyl-2-isopropyl-4(or 5)-nitroimidazolium iodide. Supporting electrolyte: (a) 0.1 M NaOH;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

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 (Fig. 2).

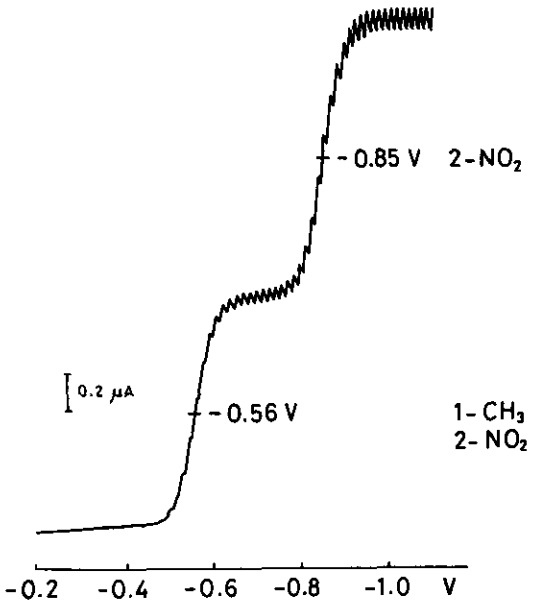


Figure 2. Polarogram by DCP of an equimolar ($10^{-4}$ M) mixture of N-unsubstituted 2-nitroimidazole (azomycin) and 1-methyl-2-nitroimidazole. Supporting electrolyte, 0.1 M NaOH.

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 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 (Fig. 3), in the rearrangement XIII 1-nitropyrazole and 3(5)-nitropyrazole (Fig. 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 to determine a trace of the starting 1-nitropyrazole in the final N-unsubstituted compounds.

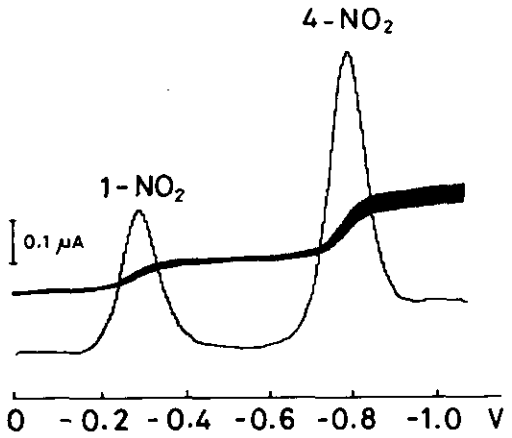


Figure 3. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 1-nitropyrazole and N-unsubstituted-4-nitropyrazole. Supporting electrolyte, Britton-Robinson buffer pH 9.4. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

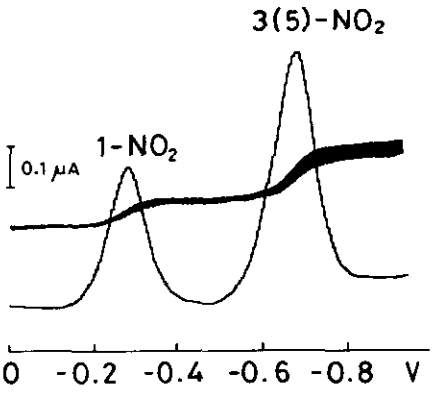


Figure 4. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 1-nitropyrazole and 3(5)-nitro-pyrazole. Supporting electrolyte, Britton-Robinson buffer pH 9.4. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

In 0.1 M NaOH it is possible to determine polarographically four mononitropyrazoles when present in comparable concentrations (Fig. 5).

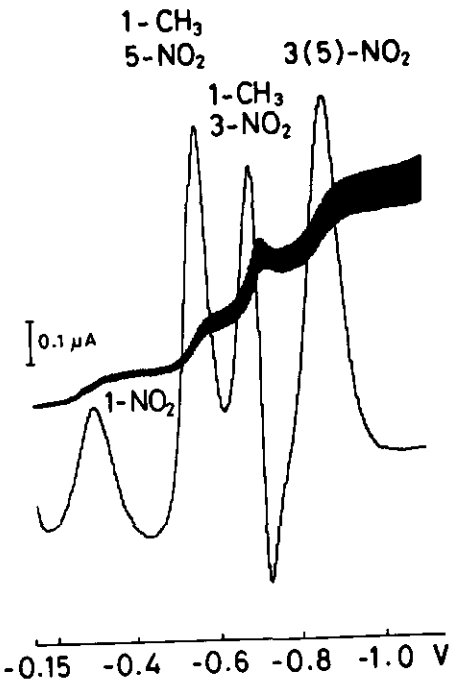


Figure 5. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 1-nitropyrazole, 1-methyl-3-nitropyrzole, 1-methyl-5-nitropyrzole, and 3(5)-nitropyrazole. Supporting electrolyte, 0.1 M NaOH. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

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 0.1 M NaOH (Fig. 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-alkylderivative and the unsubstituted parent compound is possible (Fig. 6b).

Similarly, the alkylation of 3(5)-nitropyrazole in reaction XV can be followed. Analysis using 0.1 M

NaOH enables determination of the unalkylated compound in the presence of 1-alkyl-3-nitro- and 1-alkyl-5-nitropyrazole (Fig. 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 (Fig. 7b).

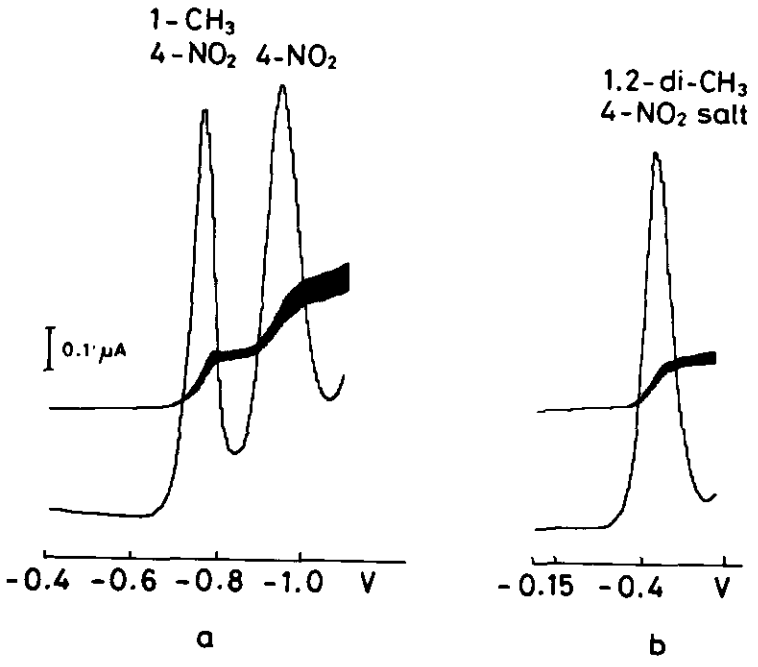


Figure 6. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of N-unsubstituted 4-nitropyrazole, 1-methyl-4-nitropyrazole and 1,2-dimethyl-4-nitropyrazolium methylsulfonate. Supporting electrolyte: (a) 0.1 M NaOH; (b) Britton-Robinson buffer pH 8.4. Scan rate, 5 mV/s. Pulse amplitude, 25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

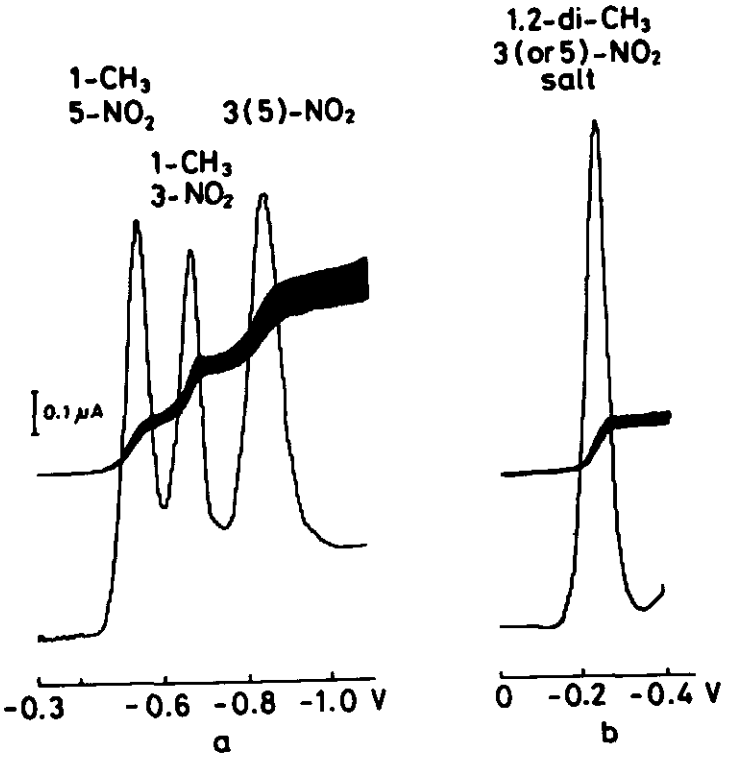


Figure 7. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 3(5)-nitropyrazole, 1-methyl-3-nitropyrazole, 1-methyl-5-nitropyrazole and 1,2-dimethyl-3(or 5)-nitropyrazolium methylsulfonate. Supporting electrolyte: (a) 0.1 M NaOH; (b) Britton-Robinson buffer pH 9.2. Scan rate, 5 mV/s. 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 (Fig. 8), the unreacted mononitro compound can be determined in the presence of the final dinitro product.

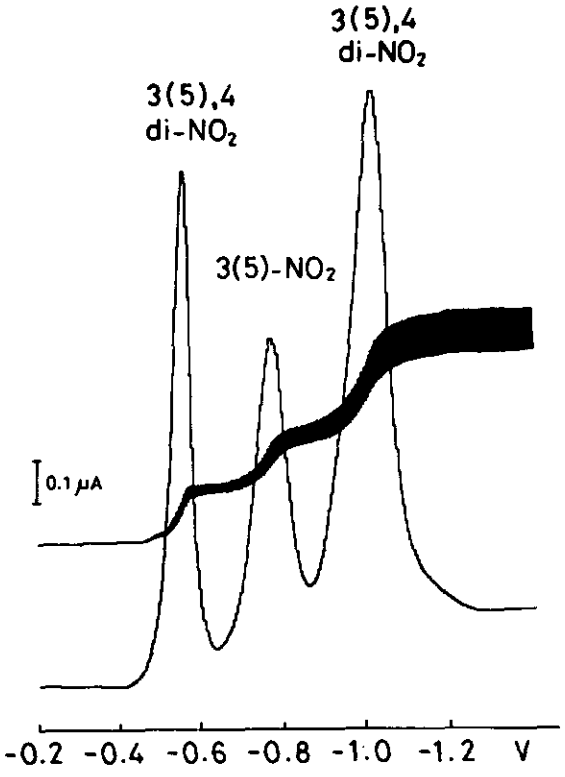


Figure 8. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 3(5)-nitropyrazole and 3(5),4-dinitropyrazole. Supporting electrolyte: Britton-Robinson buffer pH 11.6. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

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 (Fig. 9). Well separated d.c. polarographic waves seem particularly well suitable for analyses of such mixtures.

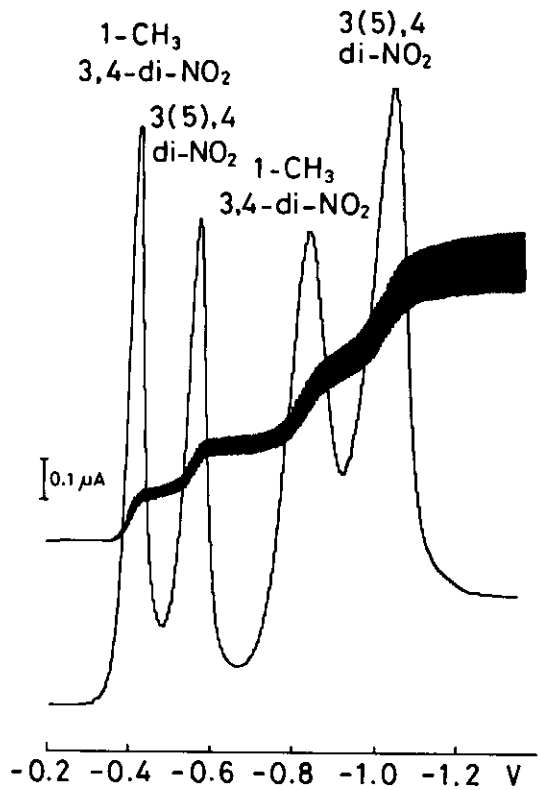


Figure 9. Polarograms by DCP and DPP of an equimolar ($10^{-4}$ M) mixture of 3(5),4-dinitropyrazole and 1-methyl-3,4-dinitropyrazole. Supporting electrolyte: Britton-Robinson buffer pH 11.6. Scan rate, 5 mV/s. Pulse amplitude, 25 mV.

## 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 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 0.1 M 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 (Figs. 10 and 11).

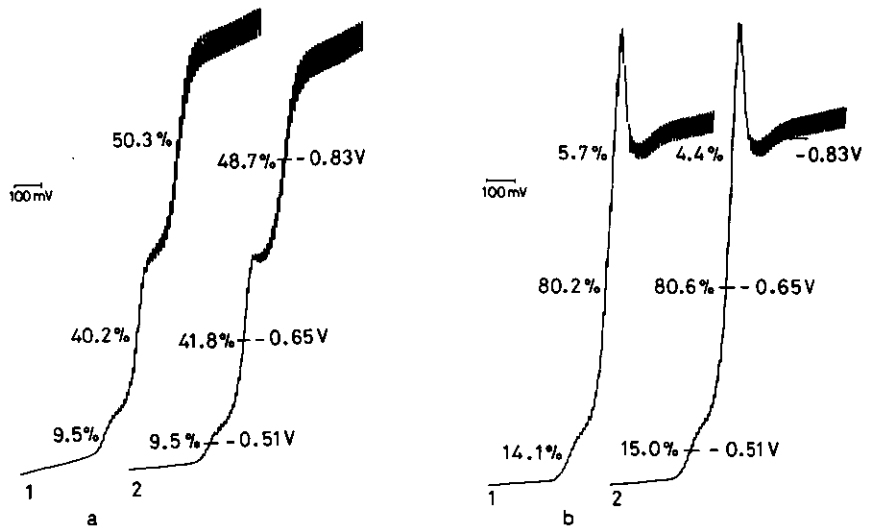


Figure 10. Polarograms by DCP of a reaction mixture during N-substitution of 3(5)-nitropyrazole ($E_{1/2}$ = -0.83 V) under different reaction conditions (a,b) as a function of time (curves 1a, 1b: 60'; curves 2a, 2b: 120').

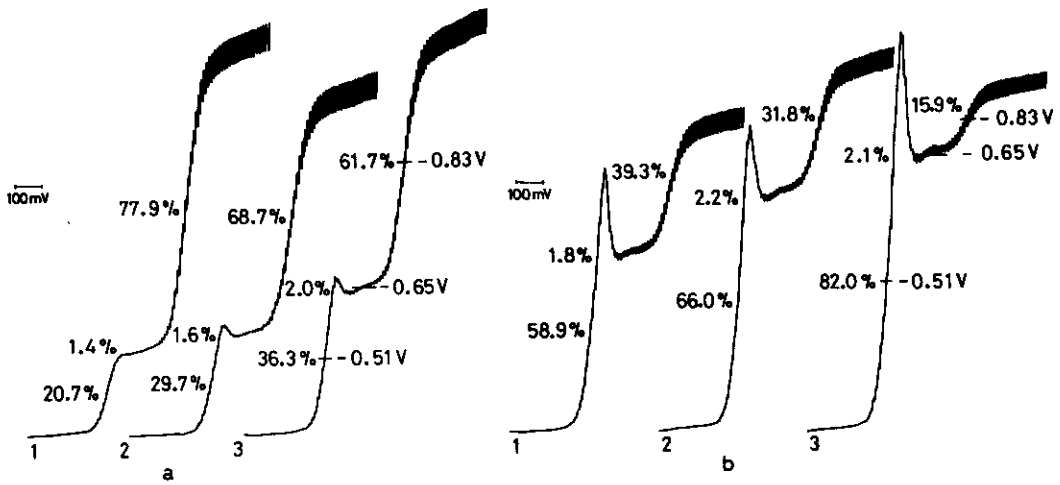


Figure 11. Polarograms by DCP of a reaction mixture during N-substitution of 3(5)-nitropyrazole ($E_{1/2}$ = -0.83 V) under different reaction conditions (a,b) as a function of time (curves 1a, 1b: 30'; curves 2a, 2b: 45'; curves 3a, 3b: 60').

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) (Fig. 10) and of 1-methyl-5-nitropyrazole (with $E_{1/2}$ = -0.51 V) (Fig. 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 0.1 M 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.

## 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.

REFERENCES

1. F. Rung and M. Behrend, *Ann.*, 1892, **271**, 28.

2. E. Buchner and M. Fritsch, *Ann.*, 1893, **273**, 256.

3. K. Maeda, T. Osato, and H. Umezawa, *J. Antibiotics (Japan)*, Ser. A, 1953, **6**, 182; *Chem. Abstr.*, 1959, **53**, 7313e.

4. G.C. Lancini and E. Lazzari, *Experientia*, 1965, **21**, 83.

5. O.V. Lebedev, L.V. Epishina, V.V. Sevostyanova, T.S. Novikova, L.I. Khmelnitskii, S.S. Novikov, and A.S. Prikhodko, *U.S.S.R.* 177.897, 08 Jan 1966, Appl. 21 Oct 1964; *Chem. Abstr.*, 1966, **64**, 19630d.

6. H. Horie, *J. Antibiotics (Japan)*, Ser. A, 1956, **9**, 168.

7. C. Cosar and L. Julou, *Ann. Inst. Pasteur*, 1959, **96**, 238.

8. P. Durel, V. Roiron, H. Siboulet, and L.J. Borel, *Comptes Rendus de la Société Francaise de Gynecologie*, 1959, **29**, 36.

9. L.I. Bagal, M.S. Pevzner, A.N. Frolov, and N.I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 1970, (2), 259.

10. D. Dumanović, J. Ćirić, R. Maksimović, D. Jeremić, and A. Muk (Galenika), *YU* 36703, 18 Jun 1982, Appl. 11 Jul 1974.

11. A. Steimmig and H. Spänig (Badische Anilin- and Soda Fabrik A.G.), *Ger. Offen.* 1.808.104, 11 Jun 1970, Appl. 09 Nov 1968.

12. M.Ya. Kraft, P.M. Kochergin, A.M. Tsyganova, and V.S. Shlikhunova, *U.S.S.R.* 201.417, 08 Sep 1967, Appl. 22 Jul 1965.

13. R. Maksimović, S. Mikalački, and M. Savić (Galenika), *YU* 30481, 31 Dec 1971, Appl. 07 Sep 1965.

14. A. Zmojkzin, K. Urbanski, E. Utecht, and W. Stelmachowski, *U.S.* 4.209.631, 24 Jun 1980, Appl. 02 Jul 1973.

15. M. Wetzler and T. Dockner (BASF A.-G.), *Ger. Offen.* 2.645.172, 12 Apr 1978, App. 07 Oct 1976.

16. J. Kollonitsch and V.F. Verdi (Merck and Co., Inc.), *Fr.* 1.535.848, 09 Aug 1968, Appl. 12 Sep 1966; *Chem. Abstr.*, 1969, **71**, 70599s.

17. V. Aldea and E. Lefter, *Rom. RO* 84.119, 30 Jun 1984, Appl. 08 Jan 1982; *Chem. Abstr.*, 1985, **103**, 104970c.

18. T. Dockner, U. Kempe, and H. Kochler (BASF A.-G.), *Ger. Offen.* 3.641.514, 09 June 1988, Appl. 04 Dec 1986; *Chem. Abstr.*, 1988, **109**, 110436y.

19. W. Stelmachowski, K. Urbanski, E. Utecht, and A. Zmojdzin, *U.S.* 4.209.631, 24 Jun 1980, Appl. 02 Jul 1973; *Chem. Abstr.*, 1980, **93**, 186354s.

20. A. Zmojdzin, K. Urbanski, E. Utecht, and W. Stelmachowski, *Fr. Demande* 2.220.523, 04 Oct 1974, Appl. 06 Mar 1973; *Chem. Abstr.*, 1975, **82**, 156312g.

21. C. Cosar, C. Crisan, R. Horclois, R.M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupre, *Arzneim. Forsch.*, 1966, **16**, 23.

22. S.S. Novikov, L.I. Khmelnitskii, O.V. Sevastyanova, and L.V. Epishina, *Khim. Geterotsikl. Soedin.*, 1970, (4), 503.

23. G.N. Pershin, P.M. Kochergin, A.M. Tsyganova, N.A. Novitskaya, L.S. Blinova, and V.S. Shlikhunova, *Med. Prom.*, 1964, **18**, 12.

24. P.M. Kochergin, A.M. Tsyganova, L.S. Blinova, and V.S. Shlikhunova, *Khim. Geterotsikl. Soedin.*, 1965, (6), 875.

25. M.W. Miller, H.L. Howes, R.V. Kasubick, and A.R. English, *J. Med. Chem.*, 1970, **13**, 849.

26. Merck and Co., Inc., *Neth.* 6.605.106, 17 Oct 1966, Appl. 16 Apr 1965; *Chem. Abstr.*, 1967, **66**, 37928x.

27. S.P. Bhatnar, B.B. Singh, J. Biswas, D.C. Holia, and D.N. Kulkarni, *Indian IN* 1.559.428, 16 May 1987, Appl. 18 Nov 1983.

28. A. Shafiee, A. Ghanbarpour, and F. Ghasemian, *Synthesis*, 1987, (4), 385.

29. K. Hofmann, "Imidazole and its Derivatives", Part I, Interscience Publishers, Inc., New York, 1953, pp. 127-135.

30. K. Schofield, M.R. Grimmett, and B.R.T. Keene, "Heteroaromatic Nitrogen Compounds - The Azoles", Cambridge University Press, Cambridge, 1976, pp. 60-68.

31. M.D. Nair and K. Nagarajan, *Prog. Drug Res.*, 183, **27**, 163.

32. G.C. Lancini, N. Maggi, and P. Sensi, *Farmaco Ed. Sci.*, 1963, **18**, 390.

33. J. Suwinski, E. Salwinska, J. Watras, and M. Widel, *Pol. J. Chem.*, 1982, **56**, 1261.

34. K.G. Agrawal, K.B. Bears, R.K. Sehgal, J.N. Brown, P.E. Rist, and W.D. Rupp, *J. Med. Chem.*, 1979, **22**, 583.

35. R.J. Spear and W.S. Wilson, *J. Energ. Mater.*, 1984, **2**, 61.

36. H. Monney, J. Parrick, and R.G. Wallace, *Pharmacol. Ther.*, 1981, **14**, 197.

37. R. Huttel, F. Buchele, and P. Jochum, *Chem. Ber.*, 1955, **88**, 1577.

38. R. Huttel and F. Buchele, *Chem. Ber.*, 1955, **88**, 1577.

39. J.W.A.M. Janssen and C.L. Habraken, *J. Org. Chem.*, 1971, **36**, 3081.

40. K.J. Klebe and C.L. Habraken, *Synthesis*, 1973, (5), 294.

41. G.A. Olah, S.C. Narang, and A.P. Fung, *J. Org. Chem.*, 1981, **46**, 2706.

42. C.L. Habraken and E.K. Poels, *J. Org. Chem.*, 1977, **42**, 2893.

43. P. Cohen-Fernandes and C.L. Habraken, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 1185.

44. J.W.A.M. Janssen, *Thesis*, University of Leiden, 1975.

45. J.W.A.M. Janssen, H.J. Koeners, C.G. Kruse, and C.L. Habraken, *J. Org. Chem.*, 1973, **38**, 1777.

46. C.E. Hazeldine, F.L. Pyman, and J. Winchester, *J. Chem. Soc.*, 1924, **125**, 1431.

47. V.K. Bhagwat and F.L Pyman, *J. Chem. Soc.*, 1925, **127**, 1832.

48. W.G. Forsyth and F.L. Pyman, *J. Chem. Soc.*, 1925, **127**, 573.

49. R.M. Jacob and C. Crisan (Rhone-Poulenc), *Fr.* 1.216.238, 22 Apr 1960, Appl. 14 Sep 1957.

50. M.Ya. Kraft, P.M. Kochergin, A.M. Tsyganova, and V.S. Shlikhunova, *U.S.S.R.* 201.416, 08 Sep 1967, Appl. 14 Jan 1966.

51. R. Maksimović, S. Mikalački, and S. Perkučin (Galenika), *YU* 30355, 31 Aug 1971, Appl. 04 June 1964.

52. M.N. Messer and J.G. Robert (Rhone-Poulenc), *Fr.* 1.379.787, 27 Nov 1964, Appl. 18 Oct 1963; *Chem. Abstr.*, 1965, **62**, 7768e.

53. F. Kajfež, V. Sunjić, D. Kolbah, T. Fajdiga, and M. Oklobdžija, *J. Med. Chem.*, 1968, **11**, 167.

54. N.M. Scollick and E.F.J. Thorpe (Pfizer Corp.), *Ger. Offen.* 2.062.040, 24 Jun 1971, Appl. 17 Dec 1969; *Chem. Abstr.*, 1971, **75**, 63787f.

55. V. Čaplar, V. Šunjić, F. Kajfež, and T. Kovač, *Acta Pharm. Jugoslav.*, 1975, **25**, 71.

56. K. Butler (Pfizer, Chas., and Co., Inc.), *Ger. Offen.* 1.620.117, 14 May 1970, Appl. 26 Oct 1964.

57. J. Heeres, J.H. Mostmans, B. Maes, and L.J.J. Backx, *Eur. J. Med. Chem. - Chim. Ther.*, 1976, **11**, 237.

58. M. Hoffer, M. Mitrović, A. Beaman, and A. Brossi, *J. Med. Chem.*, 1971, **14**, 993.

59. A. Grimison, J.H. Ridd, and B.V. Smith, *J. Chem. Soc.*, 1960, 1357.

60. J.H. Ridd and B.V. Smith, *J. Chem. Soc.*, 1960, 1363.

61. F. Kajfež, D. Kolbah, M. Oklabdžija, M. Slamnik, T. Fajdiga, M. Slamnik, and V. Šunjić, *Croat. Chem. Acta*, 1967, **39**, 199.

62. J. Suwinski, A. Rajca, J. Watras, and M. Widel, *Acta Polon. Pharm.*, 1980, **37**, 59.

63. Z. Crnić and B. Gluncić, *Croat. Chem. Acta*, 1981, **54**, 217.

64. J. Suwinsky, E. Salwinska, J. Watras, and M. Widel, *Acta Pol. Pharm.*, 1978, **35**, 529.

65. R. Klink, K.G.R. Packler, and R. Gottschlich, *Arzneim. Forsch.*, 1985, **35**, 1220.

66. B. Cavalleri, *NATO Adv. Study Inst. Ser.*, Ser. A, 1982, **42**, 9.

67. A.T.M.O. Adebayo, W.R. Bowman, and W.G. Salt, *J. Chem. Soc. Perkin Trans. I*, 1987, 2819.

68. A.T.M.O. Adebayo, W.R. Bowman, and W.G. Salt, *Tetrahedron Lett.*, 1986, **27**, 1943.

69. A. Frankowski, A. Kurnatowska, G. Kuswik, C. Seliga, and A. Szadowska, *Wiad. Parazytol.*, 1983, **29**, 167.

70. K.C. Reddy, K.A. Kumar, and G. Srimannarayana, *Indian J. Pharm. Sci.*, 1982, **44**, 6; *Chem. Abstr.*, 1982, **97**, 127564v.

71. T. Dockner, A. Frank, and H. Karn (BASF A.-G.), *Ger. Offen. DE* 3.400.531, 18 Jul 1985, Appl. 10 Jan 1984; *Chem. Abstr.*, 1986, **104**, 195806.

72. M. Šimko, F. Bachraty, E. Zlatinsky, L. David, and A. Rybar, *Czech CS* 237.849, 15 Mar 1987, Appl. 09 Jan 1984; *Chem. Abstr.*, 1988, **109**, 6511h.

73. J. Tulecki and L. Zaprutko, *Acta Polon. Pharm.*, 1984, **41**, 281.

74. A.G. Beaman, R. Duscinsky, and W.P. Tautz (to Hoffmann-La Roche, Inc.), *U.S.* 3.391.156, 02 Jul 1968, Appl. 09 Apr 1965; *Chem. Abstr.*, 1968, **69**, 96718p.

75. A.G. Beaman, W. Tautz, and R. Duschinsky, *Antimicrob. Agents Chemother.*, 1967, 520; *Chem. Abstr.*, 1969, **71**, 22065t.

76. G.C. Gallo, C.R. Pasqualucci, P. Radaelli, and G.C. Lancini, *J. Org. Chem.*, 1964, **29**, 862.

77. Kayaku Antibiotics Research Co., *JP* 59.139.363, 10 Aug 1984, Appl. 31 Jan 1983; *Chem. Abstr.*, 1985, **102**, 6491g.

78. R.K. Sehgal and K.C. Agrawal, *J. Heterocycl. Chem.*, 1979, **16**, 1499.

79. V. Sudarsanam, K. Nagarajan, T. George, S.J. Shenoy, V.V. Iyer, and A.P. Kaulgud, *Indian J. Chem.*, 1982, **21B**, 1022.

80. G.I. Migachev and V.A. Danilenko, *Khim. Geterotsikl. Soedin.*, 1982, (7), 867.

81. K.C. Agrawal, B.C. Millar, and P. Neta, *Radiation Research*, 1979, **78**, 532.

82. D.E. Derek (May Baker, Ltd.), *Brit.* 938.726, 02 Oct 1963, Appl. 26 Oct 1959; *Chem. Abstr.*, 1964, **60**, 2944d.

83. L. Domaschke (Kade Pharmazeutische Fabrik G.m.b.H.), *Ger. Offen.* 1.950.329, 08 Apr 1971, Appl. 01 Oct 1969; *Chem. Abstr.*, 1971, **75**, 20395j.

84. D. Dumanović, R. Maksimović, J. Ćirić, D. Jeremić, and A. Muk, *Fifth International Congress of Heterocyc. Chem.*, Ljubljana, 1975, 232.

85. H. Berger, R. Gall, K. Stach, M. Thiel, and W. Vomel, *Ger. Offen.* 2.558.117, 07 Jul 1977, Appl. 23 Dec 1975.

86. H. Berger, R. Gall, K. Stach, W. Vomel, and J. Veser, *Ger. Offen.* 2.522.082, 25 Nov 1976, Appl. 17 May 1975.

87. R.T. Mulcahy, D.J. Wustrow, R.R. Hark, and A.S. Kende, *Radiation Research*, 1986, **105**, 296.

88. C. Oldenhof and J. Cornelisse, *Rec. Trav. Chim. J. Roy Neth. Chem.*, 1978, **97**, 35.

89. I.J. Ferguson, K. Schofield, J.W. Barnett, and M.R. Grimmett, *J. Chem. Soc. Perkin Trans. I*, 1977, (6), 672.

90. M.R. Grimmett and K.H.R. Lim, *Aust. J. Chem.*, 1978, **31**, 689.

91. M.R. Grimmett, K.H.R. Lim, and R.T. Weavers, *Aust. J. Chem.*, 1979, **32**, 2203.

92. N.J. Hales and D.M. Mant (Imperial Chemical Industries PLC), *Eur. Pat. Appl. EP* 105.590, 18 Apr 1984, Appl. 07 Sept 1982; *Chem. Abstr.*, 1984, **101**, 110910h.

93. C.G. Newton and W.D. Ollis, *J. Chem. Soc. Perkin Trans. I*, 1984, (1), 63.

94. R.G. Jones and N.H. Terando (Eli Lilly and Co.), *U.S.* 4.066.776, 03 Jan 1978, Appl. 18 Jun 1976.

95. R.G. Jones and N.H. Terando (Eli Lilly and Co.), *U.S.* 4.145.554, 20 Mar 1979, Appl. 13 Oct 1977.

96. R.G. Jones and N.H. Terando (Eli Lilly and Co.), *Ger. Offen.* 2.212.080, 12 Oct 1972, Appl. 15 Mar 1971.

97. G. Lancini and E. Lazzari (Lepetit S.p.A.), *Brit.* 1.114.154, 14 Jan 1970, Appl. 12 Aug 1964; *Chem. Abstr.*, 1971, **75**, 140848f.

98. F. Hoffmann-La Roche and Co. A.-G., *Neth.* 6.514.946, 18 May 1966, Appl. 17 Nov 1964; *Chem. Abstr.*, 1966, **65**, 13725b.

99. A.G. Beaman, W. Tauty, T. Gabriel, and R. Duschinsky, *J. Amer. Chem. Soc.*, 1965, **87**, 389.

100. G.C. Lancini, E. Lazzari, and K. Pallanza, *Farmaco (Pavia), Ed. Sci.*, 1966, **21**, 278.

101. G.C. Lancini, E. Lazzari, V. Arioli, and P. Bellani, *J. Med. Chem.*, 1969, **12**, 775.

102. D. Dumanović, J. Volke, and V. Vajgand, *J. Pharm. Pharmac.*, 1966, **18**, 507.

103. D. Dumanović, S. Perkučin, and J. Volke, *Talanta*, 1971, **18**, 675.

104. D. Dumanović and J. Ćirić, *Talanta*, 1973, **20**, 525.

105. D. Dumanović, R. Maksimović, J. Ćirić, and D. Jeremić, *Talanta*, 1974, **21**, 455.

106. D. Dumanović, R. Maksimović, J. Ćirić, and D. Jeremić, *Talanta*, 1975, **22**, 811.

107. D. Dumanović, *Thesis*, University of Belgrade, 1979.

108. D. Dumanović, J. Ćirić, Dj. Kosanović, and D. Jeremić, *Coll. Czech. Chem. Commun.*, 1984, **49**, 1342.

109. P. Zuman, Z. Fijalek, D. Dumanović, and D. Sužnjević, *Electroanalysis*, 1992, **4**, 783.

110. D. Dumanović, J. Jovanović, D. Sužnjević, M. Erceg, and P. Zuman, *Electroanalysis*, 1992, **4**, 795.

111. D. Dumanović, J. Jovanović, D. Sužnjević, M. Erceg, and P. Zuman, *Electroanalysis*, 1992, **4**, 871.

112. D. Dumanović, J. Jovanović, D. Sužnjević, M. Erceg, and P. Zuman, *Electroanalysis*, 1992, **4**, 889.

113. D. Dumanović, J. Jovanović, B. Marjanović, and P. Zuman, *Electroanalysis*, 1993, **5**, 47.

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