THE POSSIBILITIES OF POLAROGRAPHY IN THE CHEMISTRY OF NITROAZOLES

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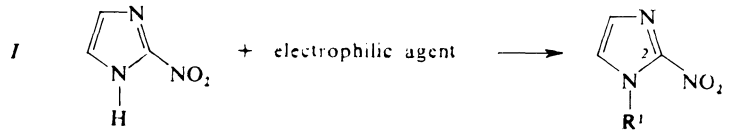
Based on systematic investigation of mononitroimidazoles, selective polarographic and spectrophotometric methods for determination of nitroazole compounds in reaction mixture are proposed. It was proved that the selectivity is based on the different properties of the nitro group due to the effects of the nitro group position in the ring, the type and the position of other substituents and on the fact whether the compound is N-substituted or not. The proposed methods can be successfully used for monitoring the synthetic procedures and decreasing the number of experiments for optimization. Based on the anticipated and proved behaviour of the nitro compounds of pyrazole, novel mononitropyrazole derivatives were synthetized in a new way and with high yields. Applying the polarographic method it was discovered that during N-substitution of tautomeric mononitroimidazole and mononitropyrazole substrates other byproducts were obtained besides the main products and undesired isomers. The products were identified and then a corrected and more complete N-substitution scheme could be given. Following quantitatively these N-substitution processes conclusions which directly concern the mechanism of reactions were drawn.

Several thousands novel mononitroimidazole compounds have been synthetized the last 20 years in order to discover more effective chemotherapeutics with antibacterial and antiprotozoal activity. Of all this enormous number of compounds, only a few dozens satisfy requirements for substances used in human and veterinary medicine. This shows that extensive and expensive research leading to the discovery of more effective chemotherapeutics or substances with other practical applications still lies ahead.

The main purpose of our study was to shorten this way and to make the task easier. This can be achieved if methods for direct determination of the mononitroimidazoles (substrate and products) in the reaction mixture were found. Such methods would greatly improve the moniroring and programming of synthetic procedures, decrease the number of experiments for optimization, enable determination of the reaction rate and mechanism, thus greatly facilitating the research and development efforts.

The greatest number of mononitroimidazoles can be obtained by N-substitution processes according to Scheme 1 or 2. The substrates are N-unsubstituted compounds, the starting materials for all N-substituted products: derivatives of 2-nitro-

imidazoles (Scheme 1), 4- and 5-nitroimidazoles (Scheme 2, X = H), as well as 5-halogeno-4- and 4-halogeno-5-nitroimidazoles (Scheme 2, X = halogen).



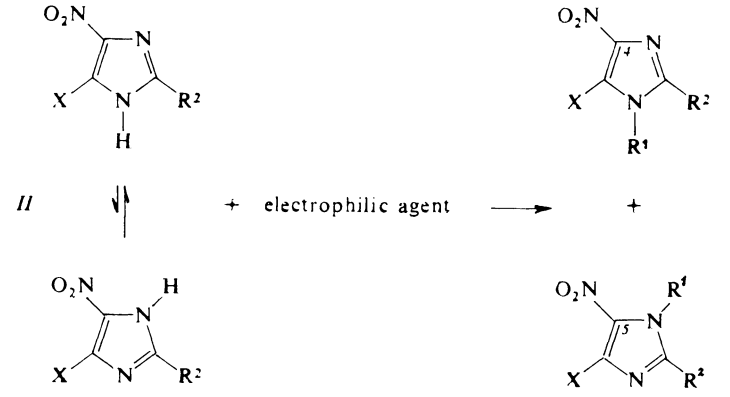
I: N-unsubstituted-2-nitroimidazole; R^1 = any substituent

SCHEME 1

Since all compounds in the syntheses contain a polarographically active nitro group and since no interference from the various solvents and agents used for the synthetic processes was expected, we decided to use polarography as analytical method in our studies.

RESULTS AND DISCUSSION

It was found that polarography enabled simultaneous determination of nitro compounds of almost any synthetic process using only one supporting electrolyte, 0·1M--NaOH (refs[1-4]). (see *e.g.* Scheme 1); even a simultaneous determination of all the three compounds according to Scheme 2 (X = H) is possible. Almost the same holds for halogenonitroimidazole derivatives.



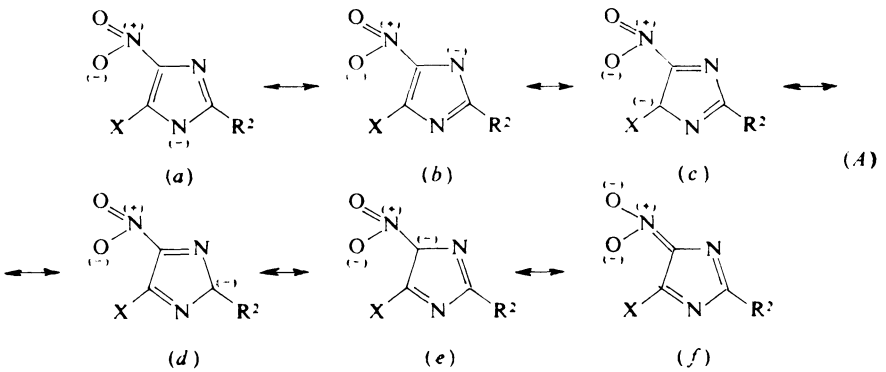
II: 4(5)-nitroimidazole or 5(4)-halogeno-4(5)-nitronimidazole X = H or halogen; R^1, R^2 = = any substituent

SCHEME 2

The conditions in which the compounds could simultaneously be identified and quantitatively determined from reaction mixtures were investigated and confirmed on 35 derivatives of nitroimidazoles and halogenonitroimidazoles[1-5].

For practical applications, it was necessary to find a complete explanation for the selective polarographic behaviour of the investigated compounds. To get additional information spectrophotometric characteristics of the compounds were considered and their polarographic and spectrophotometric behaviour compared[4]. As a result, two general conclusions were made which could substantially explain the phenomenon of selectivity.

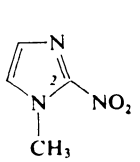
First, N-unsubstituted mononitroimidazoles are reduced at more negative potentials if an alkaline medium is used as the supporting electrolyte. At the same time, very negative half-wave potential values are accompanied by a marked shift of λ_{max} to longer wave-lengths. Such behaviour is the result of the chemical reaction of N-unsubstituted mononitroimidazoles with hydroxide and is influenced by the properties of the resulting dissociated ionic forms, *i.e.* the mononitroimidazole anions, where the remaining electron pair is in resonance interaction with the nitro group. These anions can be considered as resonance forms (*A*) where the contribution of the resonance structure (*f*) is quite important. It clearly explains the marked shift of half-wave potentials towards more negative values, and the marked shift of λ_{max} towards longer wave-lengths.



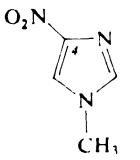
The corresponding N-substituted compounds have no imino hydrogen atom and do not react with hydroxide, thus lacking all the properties characteristic of anions.

The different behaviour of N-unsubstituted and corresponding N-substituted mononitroimidazole compounds in a suitable alkaline supporting electrolyte enables simultaneous polarographic or spectrophotometric determination of any such pair of compounds.

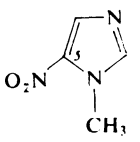
The second general conclusion refers to differences among N-substituted isomers themselves:



$pK_{BH^+} = -0{\cdot}48$
$E_{1/2} = -0{\cdot}38$ V



$pK_{BH^+} = -0{\cdot}58$
$E_{1/2} = -0{\cdot}56$ V



$pK_{BH^+} = 2{\cdot}12$
$E_{1/2} = -0{\cdot}48$ V

The half-wave potential values depend on the nitro group position in the imidazole ring.* The isomer with the nitro group in position 2 is the most positive one, and the one with the nitro group in position 4 the most negative one. However, although these two isomers are polarographically different to the greatest possible extent, they are very similar in their basic strength. So, it seemed, at first, that there is no correlation between their polarographic and spectrophotometric behaviour.

Observing the spectrophotometric characteristics of other isomer compounds[6-10], the differences in their basic strength were found to depend on the position of the nitro group in relation to the pyridinic nitrogen; if the nitro group is closer to the pyridinic nitrogen the compounds are weaker bases.

On the other hand, the polarographic distinction of N-substituted isomers, which occur in the entire pH range (Fig. 1), is the result of electron density distribution

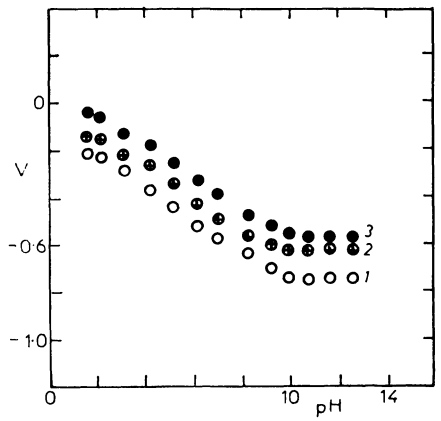
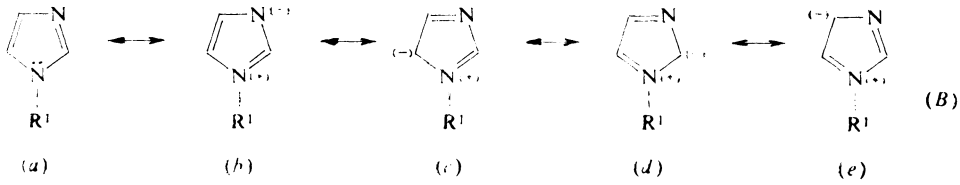


FIG. 1

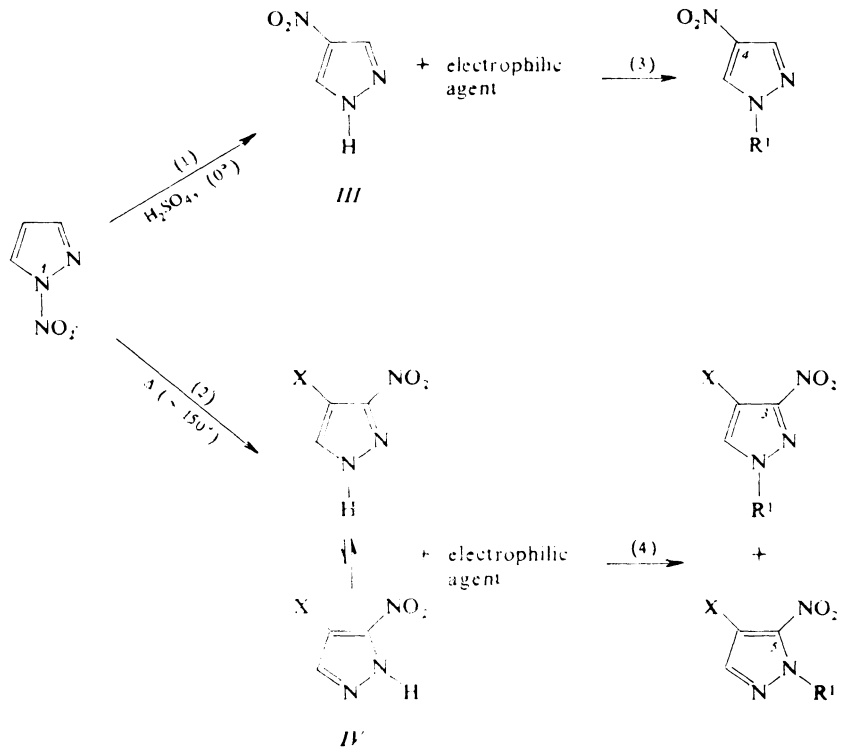
$E_{1/2}$-pH plot of *1* 1-methyl-4-nitroimidazole, *2* 1-methyl-5-nitroimidazole and *3* 1-methyl-2-nitroimidazole

* The values of $E_{1/2}$ given here are from Britton–Robinson buffer pH 7·04, but the effects are the same when $E_{1/2}$ from other pH are mutually compared.

within the imidazole ring which contains two types of nitrogen atom; *i.e.* pyrrolic – electron releasing and pyridinic – electron attracting type. Consequently, the remaining three carbon atoms exhibit different nucleophilicities (*B*). Slight differences in carbon atoms nucleophilicity produce significant changes in the electron density of the attached nitro group which can be detected polarographically (Fig. 1).



As the reasons for polarographic and spectrophotometric selectivity of mononitroimidazole compounds are explained, it can be concluded that the methods for



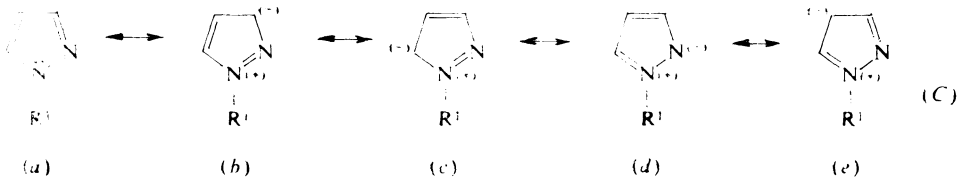
III: N-unsubstituted-4-nitropyrazole; *IV*: 3(5)-nitropyrazole or 4-cyano-3(5)-nitropyrazole; X = H or cyano, R^1 = any substituent

SCHEME 3

simultaneous determination of the compounds are based on general principles, and due to this, the proposed methods can be used to follow synthetic processes of thousands of already known or yet to be discovered derivatives of nitroimidazoles or halogenonitroimidazoles.

In order to make the results of this research even more effective and to confirm expected behaviour it was necessary to carry out similar investigations with other nitroazole compounds, such as mononitropyrazoles.

The nitro derivatives of pyrazole appropriate for this study were carefully selected in order to include compounds with the nitro group in any possible position of the pyrazole ring, and at the same time these compounds were introduced in the reactions for mononitropyrazole syntheses (Scheme 3, reactions (*1*)–(*4*)). We were able to forsee certain behaviour patterns for these compounds: *i*) differences (either polarographic or spectrophotometric) must occur between N-unsubstituted- and corresponding N-substituted mononitropyrazoles, but only from suitable media. *ii*) in all media differences among the N-substituted mononitropyrazole isomers themselves must exist.



From the resonance structure of pyrazole (*C*) we know that the isomer with the nitro group in position 5 (resonance structure (*c*)) must be less negative than the isomer with the nitro group in position 3 (r.s. (*b*)), while the isomer with the nitro group in position 4 (r.s. (*e*)) must be the most negative one – and that was what we actually proved[11,12] (Fig. 2).

The expected basicity of isomers was also confirmed[13] (1-methyl-4-nitropyrazole and 1-methyl-5-nitropyrazole with the nitro group and pyridinic nitrogen in *meta* position are significantly stronger bases (pK = −2·21 and −2·38, respectively) than 1-methyl-3-nitropyrazole (pK = −4·64), where the nitro group and pyridinic nitrogen are in *ortho* position).

At the time of our studies, N-methyl isomers with nitro group in position 3 and 5 did not exist, and the methods for their preparation were not known in literature either. We synthetized these compounds and determined their structures[11,12]. At the beginning the mentioned isomers and other newly synthetized compounds were obtained with rather low yields, because we only wanted to prove expected polarographic and spectrophotometric behaviour in order to develop new methods for the quantitative following of synthetic processes for these completely new classes of com-

pounds. Subsequently, knowing the properties of the new compounds and using the new methods[11-14], the desired compounds were obtained with high yields[11,15-18].

Thus, at the beginning, the confirmation of the assumed behaviour of mononitropyrazoles (Table I) was used to develop new methods[11-14] for the simultaneous determination of compounds present in reaction processes according to Scheme 3 (Figs 3–6).

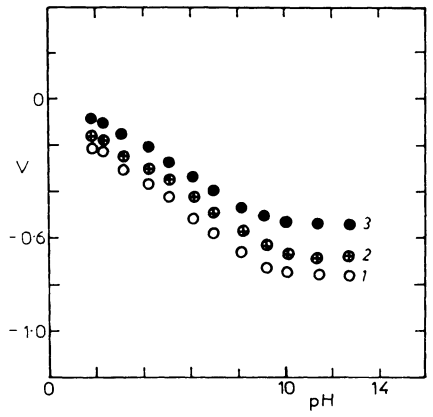


FIG. 2

$E_{1/2}$-pH plot of *1* 1-methyl-4-nitropyrazole, *2* 1-methyl-3-nitropyrazole and *3* 1-methyl-5-nitropyrazole

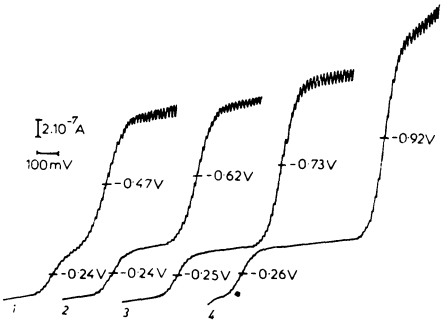


FIG. 3

Polarograms of equimolar mixture of 1-nitropyrazole and N-unsubstituted-4-nitropyrazole at different pH (these compounds appear together during the process of rearrangement — Scheme 3, Eq. (*1*). pH: *1* 5·03; *2* 7·04; *3* 9·30 (Britton–Robinson buffers); *4* 0·1M-NaOH. Concentration of each compound 10^{-4} mol/l Starting potential for curves *1*—*3* 0 V; *4* —0·1 V (S.C.E.)

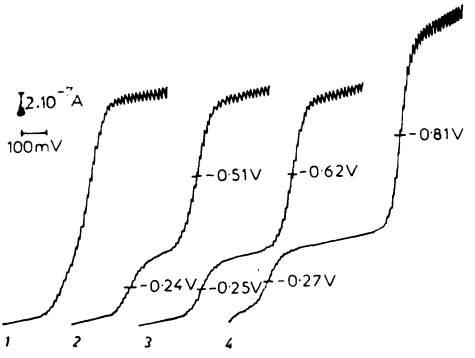


FIG. 4

Polarograms of equimolar mixture of 1-nitropyrazole and 3(5)-nitropyrazole at different pH (these compounds appear together during the thermal rearrangement (Scheme 3, Eq (*2*)). Conditions as for Fig. 3

TABLE I

$E_{1/2}$ as a function of pH

Nitropyrazole	$-E_{1/2}$, V (S.C.E.)											
	Britton–Robinson buffer											0·1M NaOH
	pH =	1·83	2·23	3·20	4·20	5·03	6·06	7·04	8·24	9·30	10·40	11·62	
1-		0·21	0·21	0·22	0·23	0·25	0·25	0·25	0·26	0·25	0·21	0·22	0·25
N-Unsubstituted-4-		0·24	0·25	0·33	0·40	0·47	0·56	0·63	0·70	0·73	0·82	0·85	0·92
1-Methyl-4-		0·21	0·22	0·29	0·35	0·42	0·53	0·57	0·65	0·69	0·72	0·72	0·72
1-Ethyl-4-		0·21	0·22	0·31	0·34	0·43	0·52	0·60	0·68	0·72	0·73	0·72	0·72
3(5)-		0·18	0·20	0·25	0·31	0·37	0·44	0·54	0·59	0·64	0·71	0·75	0·83
1-Methyl-3-		0·17	0·18	0·23	0·29	0·33	0·42	0·49	0·55	0·61	0·65	0·66	0·65
1-Ethyl-3-		0·17	0·19	0·23	0·29	0·35	0·41	0·48	0·59	0·64	0·65	0·66	0·65
1-Methyl-5-		0·09	0·11	0·15	0·20	0·26	0·31	0·39	0·47	0·49	0·51	0·51	0·51
1-Ethyl-5-		0·09	0·10	0·15	0·20	0·24	0·30	0·36	0·47	0·49	0·50	0·51	0·51
	pH =	1·98	2·35	3·46	4·41	5·30	6·35	7·19	8·18	9·04	10·40	11·62	
4-Cyano-3(5)-		0·08	0·09	0·12	0·16	0·21	0·26	0·34	0·46	0·56	0·63	0·68	0·70
1-Methyl-4-cyano-3-		0·05	0·08	0·12	0·16	0·19	0·24	0·28	0·37	0·43	0·47	0·47	0·46
1-(2-Hydroxyethyl)-4-Cyano-3-		0·05	0·07	0·12	0·16	0·19	0·24	0·29	0·37	0·41	0·44	0·46	0·45
1-Methyl-4-cyano-5-		+0·01	0·02	0·05	0·09	0·12	0·15	0·19	0·24	0·28	0·31	0·35	0·37
1-(2-Hydroxyethyl)-4-Cyano-5-		+0·01	0·02	0·05	0·07	0·10	0·15	0·17	0·21	0·24	0·28		

While quantitatively following the amount of components during synthetic processes with a tautomeric mononitroimidazole or mononitropyrazole as the substrates (Schemes 2, 3, Eq. (*4*)) we found that, even under the reaction conditions for the desired product, its isomer is also obtained in varying quantities. Following a great number of such processes we were able to draw conclusions which directly lead to the evaluation of reaction mechanisms. We concluded that the presence of undesired isomers is particularly high under conditions for the synthesis of imidazoles with the nitro group in position 4 and pyrazoles with the nitro group in position 3. Alternatively, under conditions for the preparation of imidazoles and pyrazoles with the nitro group in position 5, a substantial amount of salts with 1,3-disubstituted -4 (or 5)--nitroimidazolium- or 1,2-disubstituted- 3(or 5)-nitropyrazolium cation may be present. We first faced the problem of salts while choosing optimal conditions for higher yields of 1-methyl-5-nitropyrazole by N-substitution[15] (yields over 80%) when we found that the reaction mixture contains not only three compounds but

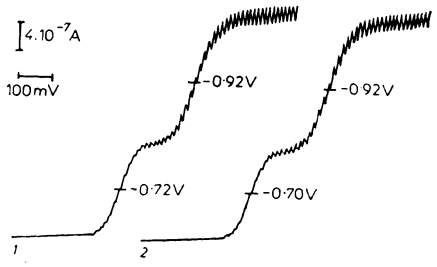


FIG. 5

Polarograms of equimolar mixture of compounds appearing together during N-substitution processes (Scheme 3, Eq. (*3*)). *1* N-unsubstituted-4-nitropyrazole and 1-methyl--4-nitropyrazole; *2* N-unsubstituted-4-nitropyrazole and 1-ethyl-4-nitropyrazole. 0·1M--NaOH, concentration of each compound 10^{-4} mol/l. From −0·40 V *vs* S.C.E.

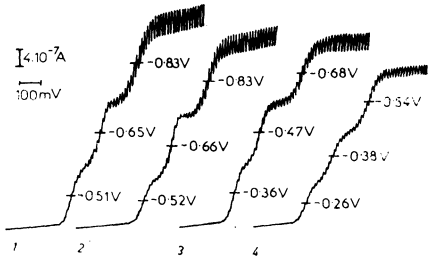
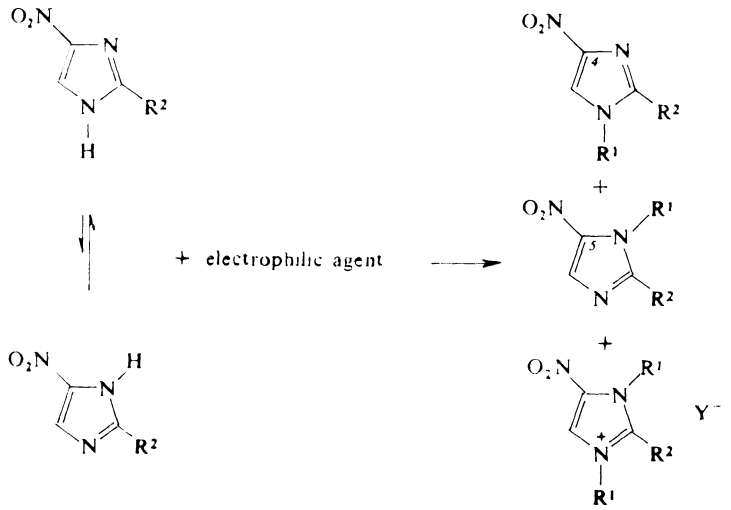


FIG. 6

Polarograms of equimolar mixture of compounds appearing together during N-substitution processes according to Scheme 3, Eq. (*4*) (*1*, *2* X = H; *3*, *4* X = CN). *1* 3(5)--nitropyrazole, 1-methyl-3-nitropyrazole and 1-methyl-5-nitropyrazole; *2* 3(5)-nitropyrazole, 1-ethyl-3-nitropyrazole and 1-ethyl--5-nitropyrazole; *3* 4-cyano-3(5)-nitropyrazole, 1-methyl-4-cyano-3-nitropyrazole and 1-methyl-4-cyano-5-nitropyrazole; *4* 4-cyano-3(5)-nitropyrazole, 1-(2-hydroxyethyl)-4--cyano-3-nitropyrazole and 1-(2-hydroxyethyl)-4-cyano-5-nitropyrazole. *1*, *2* 0·1M NaOH; *3* pH 11·62; *4* pH 9·04 (Britton-Robinson buffers). Concentration of each compound 10^{-4} mol/l. From *1*, *2* −0·20 V; *3* −0·10 V; *4* 0 V (S.C.E.)

that another compound is formed which we first mistakenly identified as 1-nitropyrazole[12]. Later we identified it as a salt with 1,2-dimethyl-3 (or 5)-nitropyrazolium cation. A similar discovery was made during the syntheses of 5-nitroimidazoles[19]. Therefore, we suggest that reaction schemes for N-substitutions should be presented in such a way that they show, in addition to the substrate and the main product, every byproduct regardless of the isomer we wish to obtain as the main product (Schemes 4, 5).

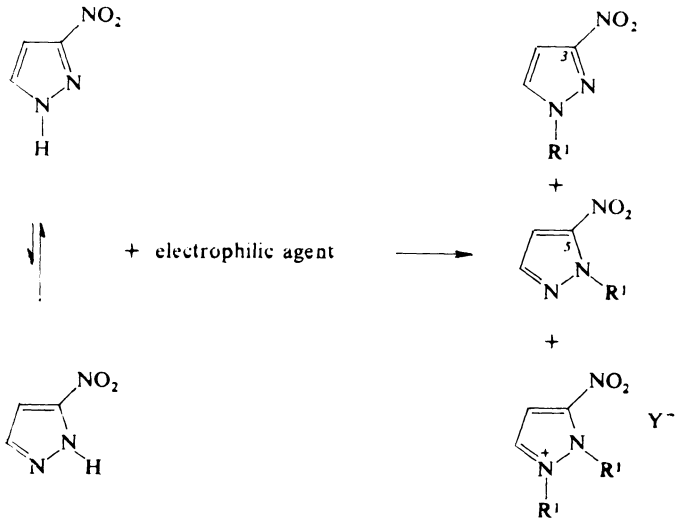


4(5)-nitroimidazole; 4(or 5)-nitroimidazolium salt; R^1, R^2 = any one substituent

SCHEME 4

From these reaction mixtures all four compounds can be quantitatively determined due to the different nitro group properties[20]. Only 10–15 minutes and a few drops of the reaction mixture are needed to obtain complete information on the content of all nitro compounds in the reaction mixture.

The results of the new methods indicate that such selective, simple, accurate and rapid methods enable very easy monitoring of synthetic processes and determining the completion of a process under given experimental conditions. Besides, these methods make separation or isolation of closely related substances in the reaction mixtures unnecessary until the optimal conditions for the obtaining of the desired compound are reached. Thus, it is possible to carry out multiple and quick changes of reaction conditions in order to reduce experimental time and consumption of raw materials.



3(5)-nitropyrazole; 3(or 5)-nitropyrazolium salt; R^1 = any one substituent

SCHEME 5

After establishing the basic principles of the selective behaviour of nitro compounds in the mixture during 2-, 4- and 5-nitroimidazoles, 5-halogeno-4- and 4-halogeno-5-nitroimidazoles syntheses, we were able to anticipate and confirm polarographic and spectrophotometric behaviour of mononitropyrazoles. Knowing the properties and discovering the methods for following the processes of synthesis, novel mononitropyrazole compounds are synthetized in a new way and with high yields. Following quantitatively the N-substitution processes conclusions were drawn which directly concern the evaluation of the reaction mechanisms. A more complete presentation of reaction schemes for the synthesis of mononitroimidazoles or mononitropyrazoles from the tautomeric substrates were suggested.

The anticipated behaviour of mononitropyrazole compounds was confirmed and new insight into this field was gained and we hope that many other nitroazole compounds will behave as expected and that the results of the present study offer unlimited possibilities. Synthetic and analytical procedures, the research and development of new pharmaceutical and other useful compounds can be made easier and quicker, which was substantially the objective of our work.

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