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N^1-Substitution in 2-Methyl-4(5)-Nitroimidazole. II.*

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During the syntheses of some new derivatives of 2-methyl-4(5)-nitroimidazole with potential antitrichomonal activity, we have noticed that the substitution on N^1 did not always depend on the *p*H of the medium, as it has been stated by Pyman[1–4] and Grimison *et al.*[5–8]. Therefore, we have approached the systematic investigations of the influence of *p*H on the formation of the 4-nitro and 5-nitroisomers of N^1-substituted 2-methyl-4(5)-nitroimidazole. The results obtained indicate that the conclusion of Pyman[1–4] is valid only when strongly alkylated agents are applied, *e. g.* dialkylsulphates and alkyl tosylates[9], since, with other alkylated agents this conclusion could be applied only with restrictions. In addition, we have measured pK_a constants for some isomer pairs prepared, in order to apply the statement of Grimison *et al.*[6] that the tautomer ratio, calculated from pK_a values, determines the ratio of the isomers in the product mixture. In spite of the fact that the pK_a measurements were in good accordance with some earlier performed[6,10,15], N^1-substitution with a number of alkylating agents indicate that the statement of Grimison *et al.*[5–8] is of importance only for alkylation with dimethylsulphate under strictly determined conditions.

INTRODUCTION

N^1-Substitution in 2-methyl-4(5)-nitroimidazole, which exists as the tautomeric substrate, could give as the product the 4-nitro or-5-nitroisomer because tautomery, *i. e.* prototropy, disappears when the proton is replaced by a larger group, *R*. On the basis of the investigations of Grimison *et al.*[6,7], the isomers' ratio in the product mixture is determined by the reaction mechanism and should be dependent upon the *p*H of the medium, *i. e.* on the form in which the imidazolic substrate is present at a definite *p*H. On the other hand the same authors[6] calculated from the measured pK_a values, *i. e.* from the proton gained constants[11] of the isomeric compounds obtained, the tautomer ratio in the 4(5)-nitroimidazolic substrate in the *p*H range where it is present predominantly as the neutral molecule. On the basis of this calculation and the statement that the tautomer present in lower concentration will have a higher rate

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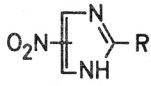
coefficient for S_E2' mechanism, they predicted the isomer ratio in the product mixture.This paper is an enlargment of these measurements, which were carried out on the series of the N^1-substituted 4-nitro and 5-nitroisomers. These measurements are an attempt to apply conclusions of Grimison *et al.*[5–8] on our reaction conditions where we have applied other N^1-alkylated agents.

RESULTS AND DISCUSSION

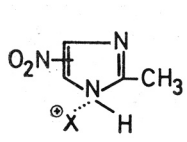
To obtain the *p*H value at which, according to Grimison *et al.*[5–8], the mechanism changes from S_E2cB to S_E2' in the case of 2-methyl-4(5)-nitroimidazole, we have measured *pK* values, *i. e.* proton lost constants[11], of this compound and, for comparison, of some related imidazole derivatives. The results obtained are presented in Table I.

TABLE I
The pK Values of Some Imidazole Derivatives

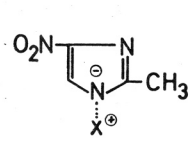
Compound	R	*pK*
	CH_3	10.10
	H	14.45*
	CH_3	9.51
	H	9.29**

* The p*K* of imidazole could not be determined spectrophotometrically because of its high value[12] — about 14. The obtained value was polarographically determined and it is in good agreement with the one reported in the literature — 14.50[13] — also obtained polarographically.
** The earlier reported value — 9.30[6].

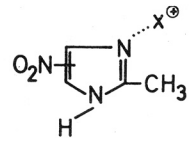
The compounds are listed according to the expected decreasing order of basicity, because the methyl group increases the basicity of imidazoles by its hyperconjugative effect[9], while the nitro group decreases the basicity by its electron attracting activity. Imidazole unexpectedly diverges from this series by its high *pK* value for the proton lost constant. For the N^1-substitution of 2-methyl-4(5)-nitroimidazole, the following transition states could be proposed:



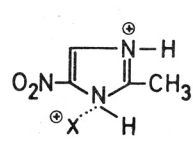
S_E2
I



S_E2cB
II



S_E2'
III



S_E2cA
IV

The four possible mechanisms[6] are characterized by these transition states. For mechanisms I and III the position of the nitro group could not be written

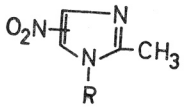
exactly[6]. For mechanisms II and IV it is more justifiable to write exactly the position of the nitro group, *i. e.* to expect that when mechanism II is operative the 4-nitroisomer is formed exclusively, and if the conjugate acid is involved in the reaction, according to mechanism IV, the 5-nitro isomer is predominantly formed.

From the measured *pK* value of 2-methyl-4(5)-nitroimidazole we concluded that the formation of the 5-nitro isomer could be expected at a *p*H below 6.5. This conclusion was based upon the proposal of Grimison *et al.*[7], that the transition from S_E2cB mechanism to S_E2' mechanism should occur at a *p*H which is about 3 *p*H units below the *pK* of the neutral molecule — see Table I. We attempted to utilize this conclusion carrying out N^1-substitution of 2-methyl--4(5)-nitroimidazole with electrophylic agents *i. e. N*-alkylated agents, other than dimethylsulphate. The substitution with agents of similar electrophylic power should have a similar dependence on the *p*H of the medium, *i. e.* on the form in which imidazole exists as the nucleophylic substrate. The results are set out in Table II. They refer to a series of condensations of 2-methyl--4(5)-nitroimidazole with some compounds containing α-activated or β-deactivated halogen. We shall compare our preparative results with some others obtained by earlier authors. Pyman noticed[14] that in the case of N^1-methylation of 2-methyl 4(5)-nitroimidazole with dimethylsulphate the ratio of the 5-nitro to the 4-nitro isomer in the product was 50 : 1. The same reagent gave as the product of the reaction with the series of 4(5)-nitroimidazoles a mixture of the 4-nitro and 5-nitro isomers in which the 5-nitro isomer predominated[8]. Cosar *et al.*[9] obtained a number of 5-nitro isomers using alkyl tosylates as alkylating agents. When they used alkyl halides very low yields of the 5-nitro isomers were recorded, but no data about the formation of the 4-nitro isomers are given *(loc. cit.)*.

In the series of alkylation that we have carried out — see Table II — ethylenechlorohydrine, (No. 6), appeared to be the only agent which gave predominatly the 5-nitro isomer. Repeating the procedure described[9,15], we were not able to isolate the 4-nitro isomer as the possible by-product. In all other examples *N*-substitution with alkyl halides, carrying other functional groups, gave rise to the 4-nitro isomers, the only exception being the agent No. 1. where we were able to isolate a minimum quantity of the 5-nitro isomer as the by-product. Summerising these experimental results it may be concluded that the esters of hydrohalide acids gave the 4-nitro isomers only (Nos. 4, 7—12), or predominatly (No. 1) — the only exception proved to be ethylenechlorohydrine. The presence of others functional groups, *i .e.* activation or deactivation of the halogen by the neighbouring group, seems to be of little importance. Tosylates and sulphates on the other hand, are agents which cause the formation of the 5-nitro isomers predominantly[5–9]. This fact could be hardly understood without further investigations. The reactions were regularly carried out by refluxing the mixture of 2-methyl-4(5)-nitroimidazole and alkylating agent in a large molar excess for several hours. Under these conditions, 1,2-dihaloethanes (Nos. 2 and 3) were the only unreactive species, even after prolonging the reaction time to 64 hrs., or carrying out the reaction under pressure and elevated temperature (seeled tube — 180°). It is important to emphasize that the *p*H of the reaction medium was extremely low in all cases and much lower than is needed for the transition value at which the change in the

TABLE II

N^1-*Substitution in 2-Methyl-4(5)-nitroimidazole*[a]



No.	*N*-Alkylating Agent	No Additives to the Reactants					Carboxylic Acid Medium					Na-Ethoxyde in Ethanol Medium				
		Yield (%) of the Isomers[b]				% Regen. MNI[c]	Yield (%) of the Isomers				% Regen. MNI	Yield (%) of the Isomers				% Regen. MNI
		4-nitro	m. p.	5-nitro	m. p.		4-nitro	m. p.	5-nitro	m. p.		4-nitro	m. p.	5-nitro	m. p.	
1.	$ClCH_2CH_2OCH_2CH_2Cl$	40	98—101[d]	0.8	77—80	—	—	—	55	76—79	72	70	98—101	—	—	—
2.	$BrCH_2CH_2Br$	no reaction				90—96	—	—	26	80—81	63	72	98—100	—	—	—
3.	$BrCH_2CH_2Cl$	no reaction				90—96	—	—	45	78—80[e]	64	68	97—99	—	—	—
4.	$BrCH_2CH_2OCH_2CH_3$	14	99—100	—	—	68	—	—	72	59—62	57	65—70	100—101	—	—	—
5.	$BrCH_2CH_2OC_6H_5$	16	104—137	—	—	76—80	—	—	39	105—106	65	65—70	136—137	—	—	—
6.	$ClCH_2CH_2OH$	—	—	41[f]	158—160	40	—	—	12	158—160	71	74[g]	129—131	—	—	—
7.	$ClCH_2CH_2COOH$	76	219—221	—	—	—	0—30	219—221	—	—	60—95	h	—	—	—	90—95
8.	$ClCH_2COOH$	25	242—247	—	—	20	no reaction		—	—	60—80	h	—	—	—	90—95
9.	$ClCH_2CN$	28	122—125	—	—	56	—	—	14	92—93[i]	81	36	123—126	—	—	70—75
10.	$ClCH_2COOC_2H_5$	73[e]	108—110	—	—	—	—	—	12	70—73	74	h	—	—	—	90—95
11.	$ClCH_2COCH_3$	16	211—213	—	—	72	no reaction		—	—	—	82	212—214	—	—	—
12.	$ClCH_2COC_6H_5$	18	208—210	—	—	60	no reaction		—	—	—	80—85	208—210	—	—	—

[a] The methods of preparation of all new compounds are described in Part I. For the reactions with agents 7, 11. and 12. see Experimental. [b] The yields are calculated on the crude products from 2-methyl-4(5)-nitroimidazole uncovered. [c] MNI = 2-methyl-4(5)-nitroimidazole. [d] All melting points refered to the crude product. [e] Firstly synthetized from $TsCH_2CH_2Cl$ and MNI by Cosar *et al.*[9], [f] Prepared according to the procedure given by Cosar *et al.*[9] and in ref. 15. [g] Prepared according to the procedure described by Kochergin *et al.*[16] [h] In these three exceptions it was not possible to carry out the reaction with Na-ethoxyde in ethanol because of the instability of β-chloropropionic acid[17], α-chloroacetic acid[18] and its esters in this medium. [i] Ref. 19.

mechanism from S_E2cB to S_E2' should take place. In examples 1, 4—6, and 9—12, the low *p*H was caused by the hydrogen halides which arised by the uncontroled decomposition of the individual halogen containing compounds under the reaction conditions. In examples 7 and 8 the low *p*H was caused by the alkylating agent — (No. 7 $pK_a = 4.1$, No. 8 $pK_a = 2.8$[20]).

We succeded to obtain alteration of substitution and formation of the 5-nitro isomers using the lower carboxylic acids as the reaction medium[21]. It was always necessary to apply a larger amount of carboxylic acid to obtain exclusively the 5-nitro isomers. A decrease in the amount of carboxylic acid resulted in an increase in the 4-nitro isomer in the product mixture. At some extremely low concentration of the carboxylic acid the latter became the only product. At the same time the yields, *i. e.* conversions of 2-methyl-4(5)-nitroimidazole, were considerably lower and a greater amount of the reactant could be recovered, which is evident from the data in Table II. Probably, this is a consequence of the formation of the markedly unreactive quarternary salts. The behaviour of β-chloropropionic acid was rather unexpected; it reacts comparatively easy but giving the 4-nitro isomer only. In the medium of the other carboxylic acids the reaction rate was lower and the yields were decreased to zero but even in this medium only the 4-nitro isomer could be isolated. When the most acidic reagent, α-chloroacetic acid was placed in the medium of the other carboxylic acids, no product formation at all was noticed. *N*-Substitution by α-chloroacetic acid was only achieved in nitrobenzene as an inert solvent which allowed a high reaction temperature, but only the 4-nitro isomer was formed even under these conditions. Formic, acetic, and propionic acid, which were used as the reaction medium, allowed the formation of the 5-nitro isomers only, when applied in sufficient quantity, which were determined empirically for each reaction. Working in the basic medium the 4-nitro isomers were formed in high yields, except in the examples 7—10 because of the great instability of the agents applied[17,18]. The reactions were carried out in ethanolic solutions of sodium ethoxyde[16]. The preferred position of N^1-substitution should be at the more nucleophylic nitrogen atom[6], and in accordance to this proposal only the 4-nitro isomers were formed. It can be stated that the behaviour of the agents investigated in the basic medium was in good accordance with the conclusions of the earlier authors[6].

To confirm the connection between the tautomer ratio and pK_a values of the *N*-substituted isomers[6], we have carried out spectrophotometric measurements on the proton gained constants of the conjugated acids of some synthetized isomer pairs. The pK_a values obtained and the ratios Ka_4/Ka_5 calculated are given in Table III.

These measurements indicate that the 4-nitro tautomer of 2-methyl-4(5)-nitroimidazole is present in about 120 fold exces over the 5-nitro tautomer. This result is generally in accordance with that obtained by Grimison *et al.*[6] for 1-methyl 4-nitro and 5-nitro imidazole, and that obtained by Laviron[10] and Hoffer *et al.*[22] Laviron demonstrated by polarographic measurements that the other 4(5)-electrophylic substituents increased the ratio of the 4-substituted tautomer in the prototropic equilibrium. Hoffer *et al.*[22] have performed spectroscopic measurements in order to distinguish between the 4- and 5-nitroimidazole derivatives. With the substituents they have in position 2 the isomeric compounds exhibited rather different maxima in the region 300—360 mμ.

TABLE III

*p*K*a* *Values and* Ka_4/Ka_5 *Ratios of some Isomer Pairs of* N^1*-Substituted 2-Methyl-4(5)-nitroimidazole*

Isomer	*R*	pK_a	Ka_4/Ka_5
5-nitro	$-CH_2CH_2OCH_2CH_2Cl$	2.49 ± 0.06	150
4-nitro		0.31 ± 0.06	
5-nitro	$-CH_2CH_2Br$	2.19 ± 0.06	90
4-nitro		0.23 ± 0.06	
5-nitro	$-CH_2CH_2OH$	2.50 ± 0.06	140
4-nitro		0.35 ± 0.06	

Grimison *et al.*[6] reported the following values of pK_a: 2.13 for 1-methyl-5-nitroimidazole, 8.53 for 1-methyl-4-nitroimidazole, and $K_{a4}/K_{a5} = 455$.

When -H[6], or $-CH_3$ group, as in our example, is to be found in this position this difference is in the region of 3—6 mμ. (See Table IV).

On the basis of the above measurements the 4-nitro tautomer predominates in the *p*H range where the neutral molecule exists, *i. e.* in the *p*H range between 2.5—7.5, but the expected formation of the 5-nitro isomers could not be realised in this *p*H range, contrary to the assumption of Grimison *et al.*[5–8]. These authors stated that discrepancies in some results they obtained suggest »that steric factors and the heterogenity of the preparative conditions

TABLE IV

The Characteristic Maximums and Extinctions of UV-Spectra for some Derivatives of 2-Methyl-4(5)-nitro Imidazole

	Compound	Medium	Form	max/mμ		ε max.	
1.	2-methyl-4(5)-nitro imidazole	H_2O	N	196	311	11160	6870
		5 *M* HCl	I	208	279	4650	7270
2.	1-(2′-hydroxyethyl)-2-methyl-5 nitro imidazole	H_2O	N	200	320	4900	7920
		2 *M* HCl	I	212	279	4620	5580
3.	1-(2′-hydroxyethyl)-2-methyl-4-nitro imidazole	0.001 *M* HCl	N	200	314	9150	6570
		7 *M* HCl	I	212	279	4500	6700
4.	1-β-chloroethoxyethyl-2-methyl-5-nitroimidazole	H_2O	N	230	320	3290	9020
		2 *M* HCl	I	207	278	4900	6240
5.	1-β-chloroethoxyethyl-2-methyl-4-nitroimidazole	0.001 *M* HCl	N	230	315	3050	6180
		7 *M* HCl	I	210	280	4270	6250
6.	1-(2′-bromoethyl)-2-methyl-5-nitro imidazole	H_2O	N	197	318	7150	9240
		2 *M* HCl	I	208	277	5380	6520
7.	1-(2′-bromoethyl)-2-methyl-4-nitro-imidazole	0.001 *M* HCl	N	201	312	8980	6370
		7 *M* HCl	I	210	279	3980	6480

N = neutral molecule; I = ionized from of molecule.

may influence the orientation«; which is confirmed by our results. It is our opinion that these factors, especially the changes in the pK_a values of imidazoles with temperature and solvent, have to be studied in order to explain some of the results described in this paper.

In some specific instances (carboxylic acid medium) it was possible to obtain by alkylation N^1-substituted derivatives of 2-methyl-5-nitroimidazole. However, the conclusions of earlier authors, who exclusively used dimethylsulphate as alkylating agent, could not be confirmed.

On the other hand, the ratio of tautomers in the *p*H range where the neutral molecule exists should be indicative of the relative amounts in which *N*-substitution will give 4- and 5-nitro isomers. This regularity could not be confirmed, probably because of the rather more complex relation between the mechanism of N^1-substitution and the reactivity of quarternary salts formed in the acidic reaction solutions at elevated temperatures.

EXPERIMENTAL

All melting points are determined using Boetius — Mikroheiztisch apparatus, firm F. Küstner/Dresden and are corrected.

1-(2′-(Carboxyethyl)-2-methyl-4-nitroimidazole (I)

6.3 g. (0.05 mole) of 2-methyl-5-nitroimidazole and 26.5 g. of β-chloropropionic acid were stirred and heated at 120° for 20 hr. The stirring was discontinued and the excess of β-chloropropionic acid evaporated *in vacuo* (0.5 mm.). The residue was recrystallized from water to give 7.5 g. (76%) of I, m. p. 219—221°. NMR spectrum; N-CH_2 triplet centered at 4.55 ppm[22], $E_{½}$ = — 0.41 (V) *vs.* SCE: these constants are characteristic for 4-nitro isomers. Methyl ester ($C_8H_{11}N_3O_4$), an oily substance which decomposes at 160° and 0.1 mm. gives no stable picrate or hydrochloride, a characteristic chemical behaviour of 4-nitroisomers[4].

Anal. $C_7H_9N_3O_4$ (199.2) calc'd.: C 42.20; H 4.56; N 21.10%
found: C 42.14; H 4.59; N 21.18%

1-(2′-Methyl-4′-nitroimidazolyl-1′)-acetone (II)

12.7 g. (0.10 mole) of 2-methyl 4(5)-nitroimidazole were dissolved under heating in the solution of Na-ethoxide obtained from 2.3 g. (0.1 mole) Na and 150 ml. of aps. ethanol. To the stirred solution 9.30 g. (0.11 mole) of monochloroacetone was added dropwise and refluxed on a steam bath for 6 hr., during which time NaCl precipitated. The hot solution was filtered with charcoal, the filtrate evaporated to dryness and the residue recrystallised from ethanol/water (2 : 1) which afforded 14.9 g. (82%) of II, m. p. 212—214°. NMR spectrum; N-CH_2 singlet peak at 4.65 ppm, $E_{½}$ = — 0.42 (V) *vs.* SCE, analytically pure sample gives no picrate or hydrochloride.

Anal. $C_7H_9N_3O_3$ (183.17) calc'd.: C 45.90; H 4.90; N 22.94%
found: C 45.93; H 4.79; N 22.70%

2-(2′-Methyl-4′-nitroimidazolyl-1′)-benzophenone (III)

According to the procedure described for compound II, from 12.7 g. (0.10 mole) of 2-methyl-4(5)-nitroimidazole and 17.10 g. (0.11 mole) of 2-chloroacetophenone, 20.2 g. (84%) of III, m. p. 208—210°, was obtained.

NMR spectrum; N-CH_2 singlet peak at 4.66 ppm., $E_{½}$ = — 0.42 (V) *vs.* SCE, gives no picrate or hydrochloride.

Anal. $C_{12}H_{11}N_3O_3$ (245.2) calc'd.: C 58.77; H 4.53; N 17.14%
found: C 58.93; H 4.39; N 17.12%

Spectrophotometric Measurements

All the pK and pK_a values in Table I and III were determined spectrophotometrically. The potentiometric method was used for control where it was possible. The accuracy of the measurements was ± 0.06 pK units. The experimental conditions

for the spectrophotometric measurements were identical with the ones described by Grimison *et al.*[5] The measurements were carried out on a Hitachi Perkin-Elmer UV-VIS Spectrophotometer M. 129.

The results were interpreted according to the methods of Albert and Serjaent[12], and Walba and Isensee[13]. The constants were calculated according to Grimison et *al.*[5] The measurements were carried out at 25.0 ± 0.2° — the other data are given in Table IV.

As is evident from Table IV, the spectra of all isomer pairs and those of 2-methyl-4(5)-nitroimidazole are similar: the maxima belonging to the neutral molecules lie in the ranges 196—201 mμ and 311—320 mμ. The only exceptions are compounds with the etheric chain (Nos. 4 and 5) which have the first maximum at 230 mμ.

The protonized forms of the listed compounds absorb in the ranges: 208—212 mμ and 277—280 mμ.

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N¹-Supstitucija u 2-metil-4(5)-nitroimidazolu. II.

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Provedena su mjerenja konstanti prototropskih ravnoteža u redu imidazola i u redu konjugiranih kiselina N^1-supstituiranog 2-metil-4(5)-nitroimidazola. Na bazi dobivenih rezultata i radova Pyman-a, Grimison-a i dr., pokušalo se odabrati onaj *p*H u kojem će doći N^1-supstitucijom do nastajanja 5-nitro izomera. Rezultati većeg broja kondenzacija na N^1- s različitim elektrofilnim agensima pokazali su da se ne može primjeniti na različite reakcione uvjete jednostavan odnos između *p*H i mehanizma reakcije koji su spomenuti autori prostudirali samo na primjeru metiliranja 4(5)-nitroimidazola.

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