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Imidazoles I. *N*-Alkylation of 4(5)-Nitroimidazoles[1]

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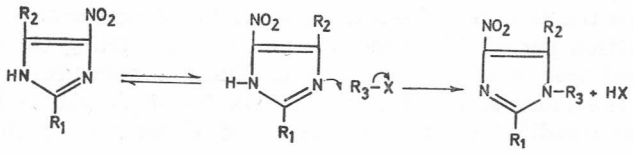
N-Alkylation of 4(5)-nitroimidazoles *1a—d* with 2-chloroethylacetamide in acetic acid was studied. Time dependent amounts of the starting compounds *1*, as well as of the two series of isomeric products *2a—d* and *3a—d* were monitored by preparative chromatography. While 5-nitro isomers *2* regularly accumulated faster in the reaction mixture, maximum concentrations were highest during the first 3—5 hrs, and then remained constant or slowly decreased. The amounts of 4-nitro isomers *3* increased steadily during the whole monitoring period (24 hrs). In the absence of alkylating agent no isomerization of the bases $2 \rightleftharpoons 3$ was observed. Since both the bases and conjugate acids of *2a—d* reacted with the second mole of the alkylating agents to produce *3a—d* at a much higher rate then *1a—d*, it is suggested that *3a—d* were formed via intermediary 1,3-dialkyl quaternary salts *4a—d*. The same isomerization was observed during the pyrolyses of the hydrochlorides of *2a—d*, while *3a—d* isomerized affording only traces of *2a—d*.

INTRODUCTION

Selective alkylation of 4(5)-nitroimidazoles, which exist in the solution as an unseparable mixture of tautomers, to obtain 5-nitro isomers exclusively has been repeatedly studied[2–5]. 5-Nitroimidazole derivatives are well known antiprotozoal agents[6,7], but sometimes they are only minor products of *N*-alkylation of 4-nitroimidazoles with alkylhalides in neutral and acidic media[2,4,5]. The formation of 5-nitro isomers is interpreted in view of a S_E2'-type mechanism in *N*-alkylation of the more stable, but less basic 4-nitro tautomers. Alkylation of these tautomers is further suppressed by the considerable steric hindrance caused by the vicinal position both of the C(2)-substituent and the 5-nitro group to the pyridine-like free-electron pair bearing nitrogen. Consequently, more basic 5-nitro tautomer could compete favourably for the electrophilic agent in a wide range of pH conditions, yielding 4-nitro isomers as the predominant products[4] (Scheme I).

Scheme I



There may be another mechanism contributing to the formation of 4-nitro isomers, which includes second alkylation of the 5-nitro isomers to yield 1,3-dialkyl quaternary salts, and their subsequent decomposition into the more stable 4-nitro isomers.

RESULTS AND DISCUSSION

All alkylations of *1a—d* were performed in glac. acetic acid, and the amounts of *2a—d* and *3a—d* were followed by quantitative determination of the separated compounds by preparative chromatography. Variation of the composition of the reaction mixture with time at diverse ratios of the reacting components and acetic acid is shown in Figure 1A—C (*a—d*).

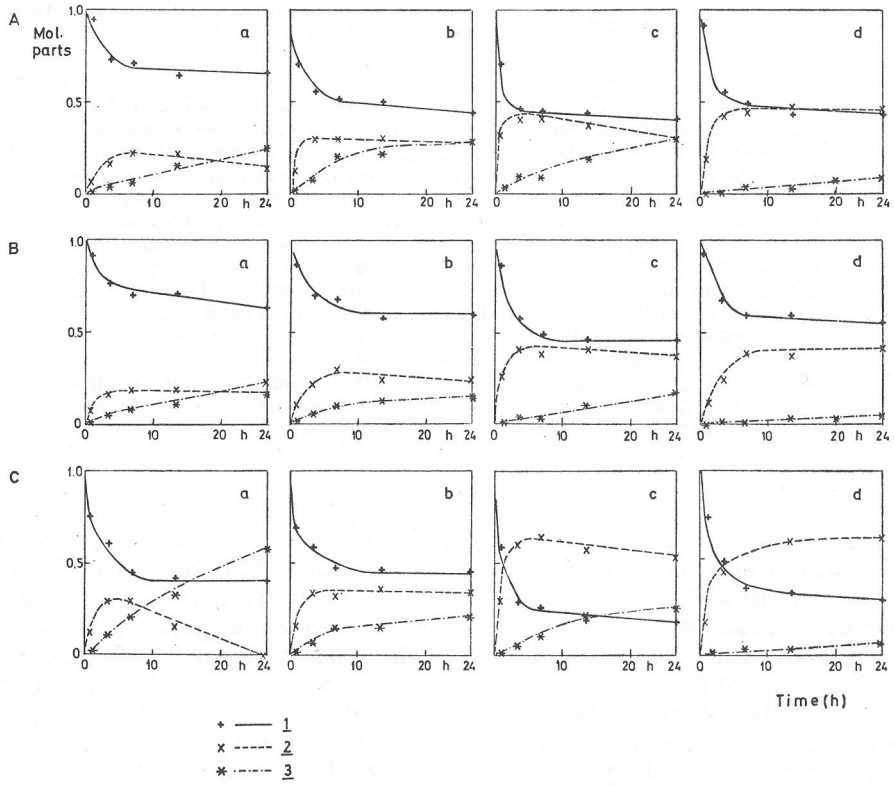


Figure 1. The plot of the molar parts of *1*, *2*, and *3* during the reaction of *1* and RCl for the various ratios of reacting components and acetic acid.
Mol. ratio of *1* : RCl : AcOH = (A) 1 : 1 : 18; (B) 1 : 1 : 36; (C) 1 : 3 : 36

In Figure 1 it can be seen that amounts of the 5-nitro products *2a—d* increased abruptly in the first 3—5 hrs, then remained constant or were diminished, while the amounts of 4-nitro isomers *3a—d* slowly augmented during the whole reaction period. The concentration of the starting compounds *1a—d* exhibited non-linear decrease with time. These results revealed that the formation of the more stable 4-nitro isomers *3a—d* should at least in part, proceed via intermediary 5-nitro isomers *2a—d*. Consequently, the latter must

undergo to the second *N*-alkylation yielding 1,3-quaternary compounds *4a—d*. We could not isolate, or otherwise identify these intermediates although similar 1,3-imidazolium salts were isolated in other instances[8–11,12].

To confirm this assumption we alkylated the isolated, less stable 5-nitro isomers *2a—d*, both as free bases or as hydrochlorides, with the same alkylating agent, i. e. 2-chloroethylacetamide [Figure 2A, B (*a—d*)]. Straightforward formation of the 4-nitro derivatives *3a—d* occurred, besides minor quantities of *N*-dealkylated 4-nitroimidazole derivatives *1a—d*. The same treatment was also applied to *3a—d*, and the formation of *1a—d* and *2a—d* in traces only was observed on TLC. Another test of the instability of the 4-nitro and 5-nitro isomers in the acidic medium in the absence of the alkylating agent was performed, and the results for the *2* · HCl are presented in Figure 2C (*a—d*).

Once again formation of the 4-nitro isomers *3a—d* and 4-nitroimidazoles *1a—d* was verified. The same isomerization process $2 \rightleftharpoons 3$ was not observed for the bases of *2a—d* and *3a—d*, but in the case of hydrochlorides of the 4-nitro isomers *3a—d* formation of *2a—d* was observed in traces only on TLC. Thus, the above series of experiments suggested the following mechanistic scheme for the interaction of 4-nitroimidazoles *1a—d* with 2-chloroethylacetamide in acetic acid as the reaction medium (Scheme II).

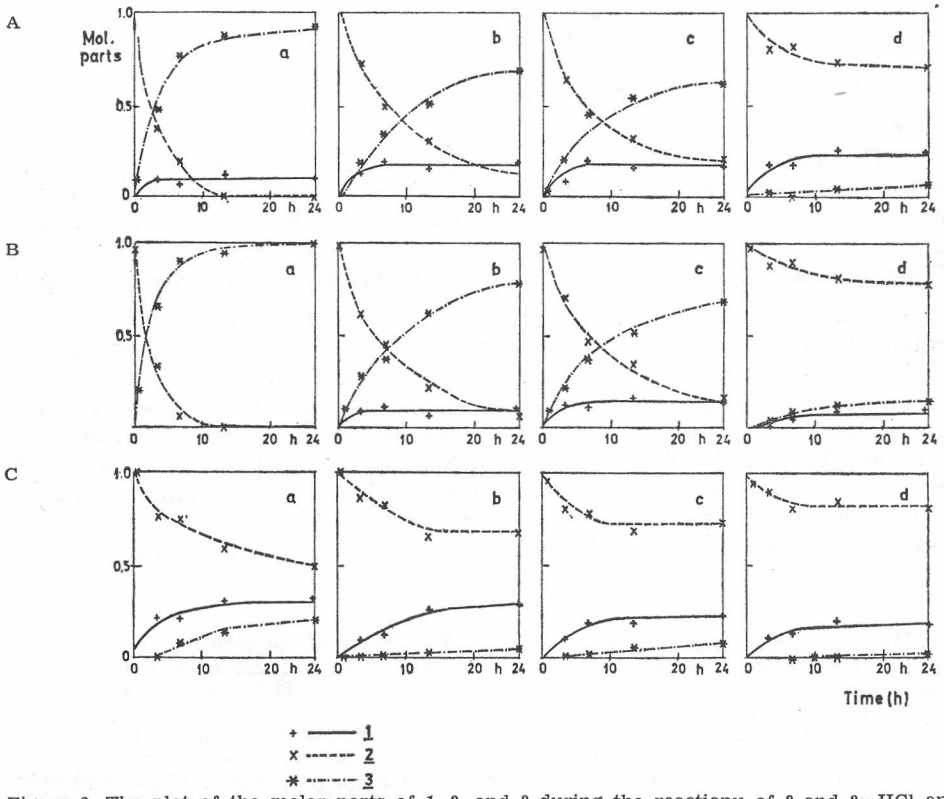
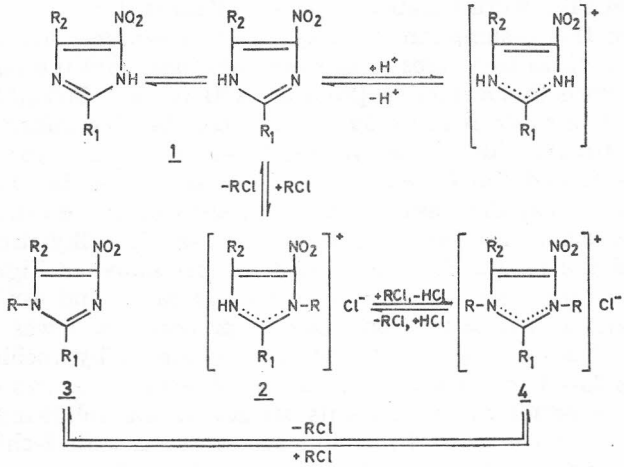


Figure 2. The plot of the molar parts of *1*, *2*, and *3* during the reactionu of *2* and *2* · HCl and RCl (A, B), and during the pyrolyses of *2* · HCl.

Molar ratio of (A) *2* · HCl : RCl : AcOH = 1 : 2 : 36, (B) *2* : RCl : AcOH = : 1 : 2 : 36, (C) *2* · HCl : : AcOH = 1 : 36

Scheme II



R = $CH_2CH_2NHCOCH_3$

1a, 2a, 3a; $R_1 = R_2 = H$

1b, 2b, 3b; $R_1 = CH_3$ $R_2 = H$

1c, 2c, 3c; $R_1 = H$, $R_2 = CH_3$

1d, 2d, 3d; $R_1 = R_2 = CH_3$

UV-spectra of all derivatives *1*—*3* remained unchanged on going from 96% ethanol to acetic acid as the solvent, with maxima between 284—316 nm and log ε_{max} 3.845—4.075, respectively. On addition of 0.1 M hydrochloric acid, however, they revealed a hypsochromic shift of ca 19—39 nm, revealing *N*(3)-protonation in the latter case. This is in accordance with earlier findings[3,4].

In conclusion it can be stated that alkylation of *1a*—*d* with 2-chloroethylacetamide, and consequently with a number of other alkylating agents as was tried earlier[3-5,9-11], consists of three reversible steps (Scheme II). Factors which can influence on the position of these equilibria are: substituents present within the imidazolic ring, type of alkylating agent, solvent, the reaction temperature and time. To optimize the yields in the preparation of the pharmacologically important 5-nitro isomers, a series of preliminary experiments should be performed similar to those described in Figures 1, 2. They should offer all necessary information required for the clean preparation of the 5-nitro isomers.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus, and are uncorrected. The IR-spectra were recorded with a Model 257 G Perkin-Elmer spectrometer. The UV-spectra were recorded with an SP 800 Unicam spectrometer in 96% ethanol (A), acetic acid (B), and in an acetic acid solution of 0,1 M hydrochloric acid (C). The ^{1}H-NMR measurements were performed with an A-60 Varian instrument in DMSO-d_6 or in $(CD_3)_2CO$, with TMS as internal standard. TLC was conducted on silica gel plates (Merck, Kieselgel HF_{254}), preparative chromatography on TLC-plates silica gel HF_{254} (Kemika), and column chromatography was performed using silica gel 0.063—0.200 mm (Kemika), with chloroform-methanol (9 : 1) as the eluent. All compounds were identified using an UV 254 nm lamp, or in iodine vapour.

General Procedure for the Preparation of 1-(2-Acetylaminoethyl)-5-nitro-(2a—d) *and 4-nitroimidazoles* (3a—d)

A solution of the corresponding 4-nitroimidazole (*1a—d;* 0.04 mol) and 2-chloroethylacetamide (14.6 g; 0.12 mol) in acetic acid (82 ml) was heated under reflux for six hours. The solvent was evaporated, the oily residue dissolved in water (15 ml), and pH was adjusted to 2—2.5 with 1 M NaOH. Unreacted *1a—d* were separated, the filtrate was neutralized with sodium hydroxide, evaporated to oiliness, and the oily residue was extracted with chloroform. Separation on a column in the usual way gave *2a—d* and *3a—d,* which were subsequently crystallized from the mixture ethanol-benzene (1 : 2).

1-(2-Acetylaminoethyl)-5-nitro- (2a) *and 4-nitroimidazole* (3a)

According to the above procedure from 4-nitroimidazole (*1a*; 4.52 g), *2a* (2.15 g; 42.2%; m. p. 100—102 °C; $R_f = 0.61$) and *3a* (1.58 g; 31.0%; m. p. 144—146 °C; $R_f = 0.48$) were obtained.

2a Anal. $C_7H_{10}N_4O_3$ (198.18) calc'd: C 42.42; H 5.09; N 28.27%
found: C 42.18; H 5.27; N 28.34%

IR (KBr): λ_{max} = 3330(s), 3100(vs), 3060(s), 1660(vs), 1555(s), 1355(vs), 740(m) cm^{-1}.
UV: λ_{max} = 296 (log ε 3.945; A), 294 (log ε 3.920; B), 265 (log ε 3.828; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$), 3.34—3.36 (m, J = 6 Hz, β-CH_2), 4.42 (t, J = 6 Hz, α-CH_2), 7.88—8.15 (m, C-2 H, C-4 H, CONH).

3a: Anal. $C_7H_{10}N_4O_3$ (198.18) calc'd: C 42.42; H 5.09; N 28.27%
found: C 42.56; H 5.22; N 28.20%

IR (KBr): λ_{max} = 3280(vs), 3060(vs), 1660(vs), 1555(s), 1355(vs), 752(m) cm^{-1}.
UV: λ_{max} = 284 (log ε 3.920; A), 284 (log ε 3.894; B), 265 (log ε 3.899; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$), 3.34—3.60 (m, J = 6 Hz, β-CH_2), 4.18 (t, J = 6 Hz, α-CH_2), 7.83—8.18 (m, C-2 H, CONH), 8.48 (s, C-5 H).

1-(2-Acetylaminoethyl)-2-methyl-5-nitro- (2b) *and 4-nitroimidazole* (3b)

According to the general procedure from 2-methyl-4(5)-nitroimidazole (*1b*; 5.08 g), *2b* (2.55 g; 45.1%; m. p. 157—159 °C; $R_f = 0.58$) and *3b* (1.15 g; 20.7%; m. p. 141—142 °C; $R_f = 0.45$) were obtained.

2b: Anal. $C_8H_{12}N_4O_3$ (212.21) calc'd: C 45.28; H 5.70; N 26.40%
found: C 45.48; H 5.46; N 26.52%

IR (KBr): λ_{max} = 3320(vs), 3280(vs), 1660(vs), 1555(s), 1355(vs), 748(m) cm^{-1}.
UV: λ_{max} = 312 (log ε 3.999; A), 307 (log ε 3.994; B), 273 (log ε 3.804; C) nm.
^{1}H-NMR [$(CD_3)_2CO$]: δ = 1.90 (s, $COCH_3$), 2.38 (s, C-2 CH_3), 3.55—3.80 (m, J = 6 Hz, β-CH_2), 4.54 (t, J = 6 Hz, α-CH_2), 8.17—8.51 (m, C-4, CONH).

3b: Anal. $C_8H_{12}N_4O_3$ (212.21) calc'd.: C 45.28; H 5.70; N 26.40%
found: C 45.23; H 5.45; N 26.48%

IR (KBr): λ_{max} = 3280(s), 3100(vs), 1660(vs), 1550-1570sh(s), 1355(vs), 760(m) cm^{-1}.
UV: λ_{max} = 299 (log ε 3.912; A), 295 (log ε 3.843; B), 273 (log ε 3.939; C) nm.
^{1}H-NMR [$(CD_3)_2CO$]: δ = 1.90 (s, $COCH_3$), 2.38 (s, C-2 CH_3), 3.50—3.80 (m, J = 6 Hz, β-CH_2), 4.26 (t, J = 6 Hz, α-CH_2), 8.05—8.20 (m, C-5 H, CONH).

1-(2-Acetylaminoethyl)-4-methyl-5-nitroimidazole (2c) *and 1-(2-Acetylaminoethyl)-5-methyl-4-nitroimidazole* (3c)

According to the above procedure from 4(5)-methyl-5(4)-nitroimidazole (*1c*; 5.08 g), *2c* (4.51 g; 64.6%; m. p. 102—103 °C, $R_f = 0.64$) and *3c* (0.76 g; 10.9%; m. p. 143—145 °C; $R_f = 0.52$) were obtained.

2c: Anal. $C_8H_{12}N_4O_3$ (212.21) calc'd: C 45.28; H 5.70; N 26.40%
found: C 45.05; H 5.70; N 26.45%

IR (KBr): λ_{max} = 3330(s) 3280(s), 3100(s), 1660(vs), 1555(vs), 1355(vs) cm^{-1}.
UV: λ_{max} = 304 (log ε 3.965; A), 302 (log ε 3.975; B), 273 (log ε 3.716; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$), 2.46 (s, C-4 CH_3), 3.30—3.55 (m, J = 6 Hz, β-CH_2), 4.38 (t, J = 6 Hz, α-CH_2), 7.85—8.10 (m, C-2 H, CONH).

3c: *Anal.* $C_8H_{12}N_4O_3$ (212.21) calc'd: C 45.28; H 5.70; N 26.40%
found: C 45.45; H 5.42; N 26.29%

IR (KBr): λ_{max} = 3280(s), 3100(s), 1660(vs), 1550(vs), 1355(vs) cm^{-1}.
UV: λ_{max} = 297 (log ε 3.955; A), 295 (log ε 3.939; B), 273 (log ε 3.923; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$), 2.53 (s, C-5 CH_3), 3.30—3.55 (m, J = 6 Hz, β-CH_2), 4.16 (t, J = 6 Hz, α-CH_2), 7.78 (s, C-2 H), 8.10 (t, J = 6 Hz, CONH).

1-(2-Acetylaminoethyl)-2,4-dimethyl-5-nitroimidazole (2d) *and* *1-(2-Acetylaminoethyl)-2,5-dimethyl-4-nitroimidazole* (3d)

According to the general procedure from 2,4(5)-dimethyl-5(4)-nitroimidazole (*1d*; 5.65 g), *2d* (3.12 g; 52.9%; m. p. 136—138 °C; R_f = 0.73) and *3d* (0.17 g; 2.9%; m. p. 168—169 °C; R_f = 0.59) were obtained.

2d: *Anal.* $C_9H_{14}N_4O_3$ (226.23) calc'd: C 47.78; H 6.24; N 24.77%
found: C 47.97; H 5.96; N 24.86%

IR (KBr): λ_{max} = 3280(vs), 3100(s), 1660(vs), 1545(vs), 1345(vs) cm^{-1}.
UV: λ_{max} = 316 (log ε 4.075; A), 314 (log ε 3.967; B), 283 (log ε 3.859; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$), 2.38 (s, C-2 CH_3), 2.46 (s, C-4 CH_3), 3.22—3.58 (m, J = 6 Hz, β-CH_2), 4.30 (t, J = 6 Hz, α-CH_2), 8.12 (t, J = 6 Hz, CONH).

3d: *Anal.* $C_9H_{14}N_4O_3$ (226.23) calc'd: C 47.78; H 6.24; N 24.77%
found: C 47.65; H 5.95; N 24.69%

IR (KBr): λ_{max} = 3280(s), 3100(s), 1660(vs), 1545(vs), 1345(vs) cm^{-1}.
UV: λ_{max} = 309 (log ε 3.993; A), 307 (log ε 3.899; B), 283 (log ε 3.957; C) nm.
^{1}H-NMR (DMSO-d_6): δ = 1.78 (s, $COCH_3$, 2.38 (s, C-2 CH_3), 2.53 (s, C-5 CH_3), 3.20—3.48 (m, J = 6 Hz, β-CH_2), 4.00 (t, J = 6 Hz, α-CH_2), 8.10 (t, J = 6 Hz, CONH).

General Procedure for the Determination of the Molar Parts of 1, 2, *and* 3 *in the Reactions of 4-Nitroimidazoles* 1 *and 2-Chloroethylacetamide, 5-Nitro Isomers* 2 *and 2-Chloroethylacetamide, and for the Pyrolyses of Hydrochlorides of* 2 *and* 3

1. *Reaction of 4-Nitroimidazoles* 1a—d *and 2-Chloroethylacetamide*

a) A solution of 4-nitroimidazoles (1.13 g of *1a*; 1.27 g of *1b,c*; 1.41 g of *1d*; 0.01 mol) and 2-chloroethylacetamide (1.21 g; 0.01 mol) in acetic acid (20.6 ml; 0.36 mol) was heated under reflux for twenty four hours. At regular time intervals samples of the acetic acid solution (1 ml) were evaporated to oiliness. Separation of the oily residue by preparative chromatography in the usual way gave unreacted *1a—d* and products *2a—d* and *3a—d*. The results are presented in Figure 1A(a—d) as molar parts of *1a—d*, *2a—d*, and *3a—d*, plotted against the reaction time.

b) The same treatment, using a smaller quantity of acetic acid (10.3 ml; 0.18 mol), was applied to *1a—d* [Figure 1B(a—d)], and using a greater quantity of 2-chloroethylacetamide (3.63 g; 0.03 mol) in acetic acid (20.6 ml; 0.36 mol), was also applied to *1a—d* [Figure 1C(a—d)].

2. *Reaction of 1-(2-Acetylaminoethyl)-5-nitro-* (2a—d) *and 4-nitroimidazole Derivatives* (3a—d) *and 2-Chloroethylacetamide*

a) A solution of *2a—d* (1.98 g of *2a*; 2.12 g of *2b,c*; 2.26 g of *2d;* 0.01 mol) and 2-chloroethylacetamide (2.42 g; 0.02 mol), with and without the use of HCl(g) (0.365 g; 0.01 mol) in acetic acid (20.6 ml; 0.36 mol) was treated as above to give *1a—d* and *3a—d* [Figures 2A(a—d) and 2B(a—d)].

b) The same treatment was applied to *3a—d* and the formation of *1a—d* and *2a—d* in traces only was observed on TLC plates.

3. *The Pyrolyses of 1-(2-Acetylaminoethyl)-5-nitro-* (2a—d) *and 4-nitroimidazole Derivatives* (3a—d)

a) A solution of *2a—d* (1.98 g of *2a*; 2.12 g of *2b,c*; 2.26 g of *2d*; 0.01 mol) and HCl(g) (0.365 g; 0.01 mol) in acetic acid (20.6 ml; 0.36 mol) was treated as described under 1a to give *1a—d* and *3a—d* [Figure 2C(a—d)].

b) The same treatment as above, without the use of HCl(g) was applied to *2a—d* and to *3a—d*, and the isomerization $2 \rightleftharpoons 3$ was not observed.

c) The same treatment as above, with the use of HCl(g) was also applied to *3a—d*, where the isomerization $3 \rightleftharpoons 2$ gave traces of *2*, identified on TLC.

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SAŽETAK

Imidazoli I. *N*-alkiliranje 4(5)-nitroimidazola

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Studirana je *N*(1)-alkilacija 4(5)-nitroimidazola *1a—d* s 2-kloretilacetamidom u octenoj kiselini. Nastajanje izomernih spojeva *2a—d* i *3a—d* u ovisnosti o molarnom odnosu reakcijskih komponenata i octene kiseline, praćena je preparativnom kromatografijom. Nađeno je da se količina 5-nitro izomera *2a—d* u reakcijskoj smjesi povećava najviše za prvih 3—5 sati reakcije, a zatim ostaje konstantna ili se smanjuje, dok se količina odgovarajućih 4-nitro izomera *3a—d* povećava tokom cijelog reakcijskog perioda (24 sata). Primijećeno je da su baze *2* i *3* u istim reakcijskim uvjetima stabilni, dok odgovarajući hidrokloridi podliježu djelomičnoj izomerizaciji $2 \rightleftharpoons 3$. Na osnovi ovih rezultata, te činjenice da u reakciji baza i hidroklorida *2* s 2-kloretilacetamidom nastaju *3* mnogo brže nego u studiranoj reakciji, pretpostavlja se da u navedenoj reakciji nastaju *3* preko intermedijarnih 1,3-dialkil kvarternih soli *4*.

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