Reactions of Some 1-(Carboxyalkyl)nitroimidazole Derivatives in Polyphosphoric Acid (1)

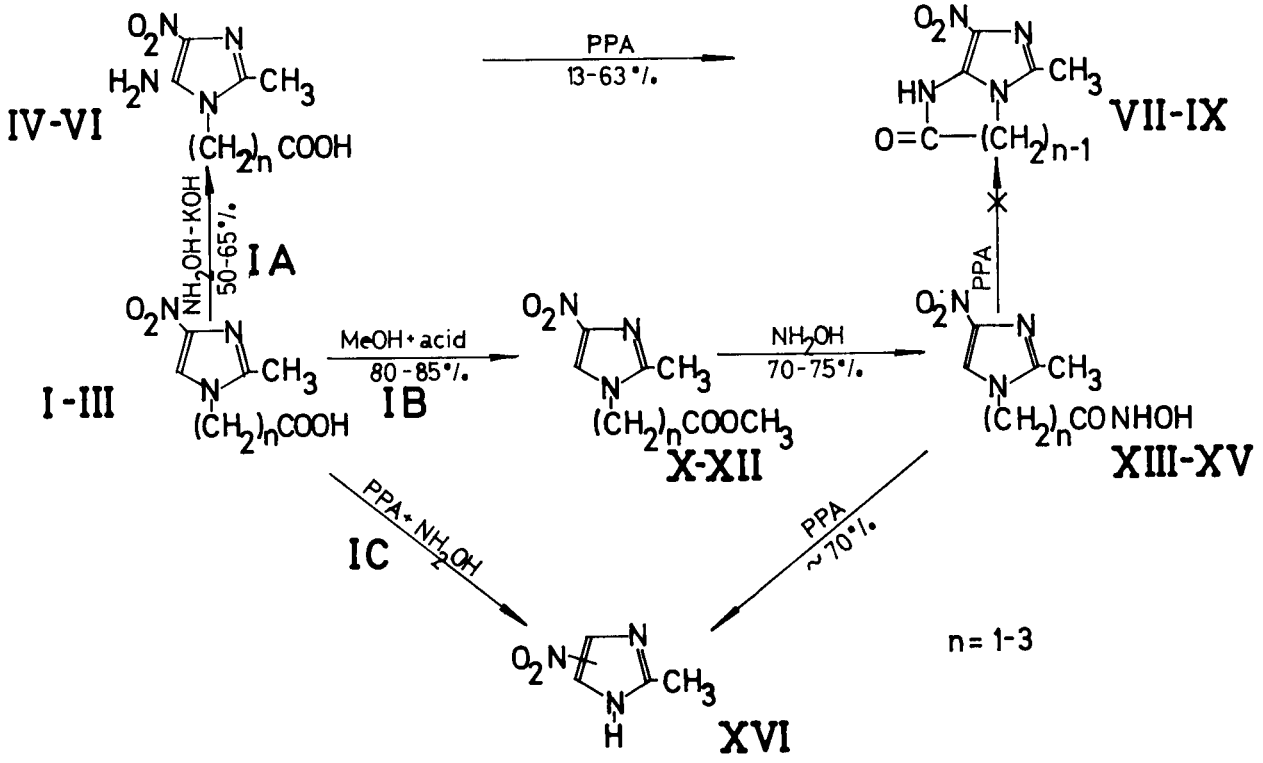
V. Šunjić (2), T. Fajdiga and M. Japelj

Research-Development Institute, KRKA Pharmaceutical and Chemical Works

Continuing the investigation on substitution reactions of nitroimidazoles (3,4) we have considered the possibilities for the preparation of 1,5-lactams of some 1-substituted 4-nitroimidazoles. These compounds should be of particular interest for studying the influence of the neighbouring groups in some 4- and 5-nitroimidazoles on their $E_{1/2}$ values as well as on their antitrichomonal activity (5). It was possible to prepare the lactams VII-IX *via* the 5-amino derivatives IV-VI obtained by amination with hydroxylamine according to a procedure recently described (4) (see Scheme IA). However, an alternative route of intramolecular amidation *via* hydroxamic acids XIII-XV, according to another briefly described procedure (6), furnished unexpectedly 2-methyl-4-(or 5)-nitroimidazole (XVI) as the only product. It could be proposed that the amidation mentioned is an electrophilic substitution where RCONH–OH group exhibits electrophilic properties. On the contrary, hydroxylamine (H–NHOH) could generate the nucleophilic agent $NHOH^-$ (7). Since position 5 in 4-nitroimidazoles is strongly affected by the electron-attracting action of both *vicinal* nitro and aza-groups (4), it is deactivated for the first type of reaction.

A causal factor for the cleavage of N_1–C bond in the compounds XIII-XV had not been ascertained until the present. It is observed, however, that the free hydroxylamine in PPA under similar conditions caused the same cleavage of the compounds I-III (Scheme IC). Although it is cited in the literature (8) that these conditions are

SCHEME I



favourable for the Lossen degradation of hydroxamic acids, we were not able to isolate any of the corresponding alkylamino compounds.

EXPERIMENTAL

Melting points were determined on a Böetius-Microheiztisch apparatus and are uncorrected. Infrared spectra were run on the Perkin-Elmer N 137 Spectrophotometer, with samples in Nujol mull and hexachlorobutadiene, ultraviolet spectra were obtained on the Unicam SP 800 instrument in water or in dilute ethanol solutions. Microanalyses were performed in the Department of Organic Chemistry, University of Ljubljana, Ljubljana, Yugoslavia. Compounds I, II and X were described in refs. (10), (2) and (11).

1-(3-Carboxypropyl)-2-methyl-4-nitroimidazole (III).

Potassium hydroxide (3.08 g., 0.055 mole) was slurried in a mixture of 30 ml. of methanol, 40 ml. of DMF and 5 g. (0.03 mole) of 4-bromobutyric acid and these reagents were dissolved keeping the solution at 15-20°. Then 3.15 g. (0.025 mole) of 2-methyl-4(5)-nitroimidazole were added and the methanol evaporated until the temperature reached 140°. The reaction was continued for 20 hours, then the reaction mixture was cooled and the inorganic precipitate was removed by suction filtration. The filtrate was evaporated *in vacuo* and the oily residue was crystallized adding 10 ml. of ethanol. The crude product crystallized on cooling, m.p. 136-140°, and on recrystallization from water gave a pure substance (3.2 g., 59.5%), m.p. 143-144°; infrared cm^{-1}, ν (CO) 1710; ultraviolet, mμ (ϵ), λ max 316 (8,660).

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.02; H, 5.32; N, 19.81.

General Procedure for the Preparation of the Compounds IV-VI.

Compound I, II or III (0.015 mole) and 6.5 g. (0.0935 mole) of hydroxylamine hydrochloride in 120 ml. of ethanol were stirred and heated to 40-45° until all dissolved. Maintaining the same temperature, a solution of 13 g. (0.234 mole) of potassium hydroxide in 60 ml. of methanol was added dropwise during 1 hour and then heated for another hour. The reaction mixture was cooled, acidified to *p*H 5 with concentrated hydrochloric acid and then treated as described for the particular compound.

1-Carboxymethyl-2-methyl-4-nitro-5-aminoimidazole (IV).

The precipitate which separated on neutralization was removed by filtration, slurried in 50 ml. of water and the undissolved crude product removed by suction filtration. The second crop was obtained after evaporation of the methanolic mother liquors, slurrying the residue in 10 ml. of water and filtering the undissolved solids. Both fractions of the crude product were combined and crystallized from ethanol-water (2:1) giving 1.95 g. (65%) of the compound IV, m.p. 252-254°; infrared cm^{-1}, ν (NH_2) 3450, 3250, 1640; ν (CO) 1685; ultraviolet mμ (ϵ), λ max 375 (8,440).

Anal. Calcd. for $C_6H_8N_4O_4$: C, 36.00; H, 4.03; N, 28.00. Found: C, 36.12; H, 4.40; N, 28.32.

1-(2-Carboxyethyl)-2-methyl-4-nitro-5-aminoimidazole (V).

The same isolation procedure as described for IV furnished 2.2 g. of a crude product (m.p. 252-258°) which gave on recrystallization from ethanol-water (3:1) 1.9 g./59% of a pure V, m.p. 262-264°; infrared cm^{-1}, ν (NH_2) 3450, 3250, 1640; ν (CO) 1715; ultraviolet mμ (ϵ), λ max 372 (8,015).

Anal. Calcd. for $C_7H_{10}N_4O_4$: C, 39.25; H, 4.71; N, 26.16. Found: C, 39.46; H, 4.81; N, 26.35.

1-(3-Carboxypropyl)-2-methyl-4-nitro-5-aminoimidazole (VI).

The first fraction of the crude VI was obtained as described for IV. The main crop was obtained after evaporation of the methanolic mother liquors and crystallizing on ice as a yellow sirrupy mass by adding 10 ml. of ethanol-water (1:1). The combined fractions furnished on recrystallization from ethanol 1.1 g. (52%) of the compound VI, m.p. 194-196°. Sometimes VI crystallizes as a monohydrate which decomposes on heating above 105°. This compound gave satisfactory analysis for $C_8H_{12}N_4O_4 \cdot H_2O$; infrared cm^{-1}, ν (NH_2) 3450, 3250, 1640; ν (CO) 1720; ultraviolet mμ (ϵ), λ max 371 (7.910).

Anal. Calcd. for $C_8H_{12}N_4O_4$: C, 42.20; H, 5.30; N, 24.55. Found: C, 41.91; H, 5.44; N, 24.32.

General Proceudre for the Preparation of the Compounds VII-IX.

Compound IV, V or VI (1.0 g.) and 10 g. of PPA *ca.* 80% of phosphorus pentoxide, prepared according to the standard procedure (12), were sealed in a thick-wall glass tube. The tube was rotated and heated on 110° for 2 hours. After cooling the reaction mixture was poured on 50 g. of crushed ice and the *p*H adjusted to 6.5 with ammonia. The crude product separated on cooling. Additional quantities could be obtained by extraction with aniline (4 x 50 ml.). Both fractions were combined and recrystallized as follows.

Lactam of 1-Carboxymethyl-2-methyl-4-nitro-5-aminoimidazole (VII).

On recrystallization from ethanol-water (2:1), 0.12 g. (13.2%) of pure VII, m.p. 259-261°, was obtained; infrared cm^{-1}, ν (CO) 1780; ultraviolet mμ (ϵ), λ max 342 (6,280).

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.77. Found: C, 39.21; H, 3.13; N, 30.37.

Lactam of 1-(2-Carboxyethyl)-2-methyl-4-nitro-5-aminoimidazole (VIII).

On recrystallization from ethanol-water (3:1) 0.58 g. (63.5%) of the compound VIII, m.p. 259-260°, was obtained; infrared cm^{-1}, ν (CO) 1720; ultraviolet mμ (ϵ), λ max 339 (6,060).

Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.75; H, 4.50; N, 28.58.

Lactam of 1-(3-Carboxypropyl)-2-methyl-4-nitro-5-aminoimidazole (IX).

On recrystallization from ethanol 0.47 g. (52%) of the compound IX, m.p. 164-165°, was obtained; infrared cm^{-1}, ν (CO) 1690; ultraviolet mμ (ϵ), λ max 334 (5,670).

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 45.71; H, 4.80; N, 26.65. Found: C, 45.55; H, 4.69; N, 26.69.

Preparation of the Compounds XI-XII.

Compounds II and III were esterified in 5% sulfuric acid solution in methanol. The crude products were isolated after neutralization (sodium acetate) and evaporation of the methanol. The residue was dissolved in 100 ml. of water. The cooled solution was extracted with ethyl acetate (4 x 50 ml.) and the combined extracts were dried (calcium chloride and magnesium sulfate) whereupon evaporation gave an oily residue. The crude product was dried over phosphorus pentoxide in a stream of nitrogen, and dissolved in 50 ml. of dry ethyl acetate. After refluxing with charcoal, the product was filtered and the solvent evaporated. The oily residue was dried once more over phosphorus pentoxide *in vacuo* giving satisfactory pure ester in a 80-85% yield.

1-(2-Carbomethoxyethyl)-2-methyl-4-nitroimidazole (XI).

The yellow oily substnace decomposed above 250° at 0.01 mm. and solidified at −10°; infrared cm^{-1}, ν (CO) 1745; ultraviolet mμ (ϵ), λ max 316 (9,250).

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.21; N, 19.71. Found: C, 45.14; H, 5.34; N, 19.67.

1-(3-Carbomethoxypropyl)-2-methyl-4-nitroimidazole (XII).

The yellow oily substance decomposed above 250° at 0.01 mm. and solidified at about −10°–15°; infrared cm^{-1}, ν (CO) 1740; ultraviolet mμ (ϵ), λ max 316 (9,370).

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.47; H, 5.77; N, 18.49 Found: C, 47.58; H, 5.89; N, 18.12.

General Procedure for the Preparation of the Compounds XIII-XV.

A solution of 0.05 mole of the free hydroxylamine in methanol (80 ml.) and 0.05 mole of sodium in 25 ml. of ethanol was added dropwise to the stirred and cooled (15°) solution of 0.05 mole of ester X, XI or XII in methanol (50 ml.) and sodium in ethanol. After chilling on ice the sodium salt of the hydroxamic acids XIII-XV separated, the salt was filtered off, dissolved in water (50 ml.) and the solution acidified to *p*H 2 with concentrated hydrochloric acid. The crude product which separated was removed by filtration and combined with the second crop obtained after evaporation of the methanol, dissolving the residue in water (20 ml.) and acidifying the solution to *p*H 2. Recrystallization from water after adding 2-3% of sodium acetate to dissolve free carboxylic acids furnished the pure compounds XIII-XV.

2-(2-Methyl-4-nitro)imidazol-1-ylacetohydroxamic Acid (XIII).

Yield, 7.5 g. (76%), m.p. 199-200°; infrared cm^{-1}, ν (OH) 3140; ν (NH) 3090; ν (CO) 1690.

Anal. Calcd. for $C_6H_8N_4O_4$: C, 36.00; H, 4.03; N, 28.00. Found: C, 36.30; H, 4.25; N, 28.23.

3-(2-Methyl-4-nitro)imidazol-1-ylpropionohydroxamic Acid (XIV).

Yield 7.7 g. (72%), m.p. 184-186°; infrared cm^{-1}, ν (OH) 3160; ν (NH) 3040; ν (CO) 1685.

Anal. Calcd. for $C_7H_{10}N_4O_4$: C, 39.25; H, 4.71; N, 26.16. Found: C, 39.57; H, 4.77; N, 26.05.

4-(2-Methyl-4-nitro)imidazol-1-ylbutyrohydroxamic Acid (XV).

Yield 7.75 g. (69%), m.p. 204-206°; infrared cm^{-1}, ν (OH) 3160; ν (NH) 3040; ν (CO) 1680.

Anal. Calcd. for $C_8H_{12}N_4O_4$: C, 42.20; H, 5.30; N, 24.55. Found: C, 42.38; H, 5.27; N, 24.28.

Attempted Cyclization of Hydroxamic Acids XII-XV).

One g. of the compound XIII, XIV or XV and 15 g. of PPA were heated in a sealed glass tube for 2 hours at 160°. The cooled reaction mixture was poured on 50 g. of crushed ice and the *p*H adjusted to 6.5 with ammonia. The crude substance which separated was filtered off; 0.5-0.6 g. was obtained, m.p. 250-254°, which on crystallization from water melted at 254-256°. A mixed melting point with an authentic sample of 2-methyl-4(5)-nitroimidazole (XVI) showed no depression. The infrared spectra were identical.

REFERENCES

(1) Presented in part at the Second International Congress of Heterocyclic Chemistry, Montpellier, 7-11 July 1969.

(2) Correspondence should be addressed to this author.

(3) F. Kajfež, D. Kolbah, T. Fajdiga, M. Oklobdžija, M. Slamnik and V. Šunjić, *Croat. Chem. Acta*, **39**, 199 (1967).

(4) V. Šunjić, T. Fajdiga, M. Japelj and P. Rems, *J. Heterocyclic Chem.*, **6**, 53 (1969).

(5) The results of these investigations will be published elsewhere.

(6) F. W. Wassmundt and S. J. Padegimas, *J. Am. Chem. Soc.*, 89, 7131 (1967).

(7) S. S. Gitis, N. N. Pankova, A. J. Kaminskii and E. G. Kaminskaya, *Zh. Org. Khim.*, **5**, 65 (1969).

(8) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958).

(9) K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers, Inc., New York, 1953, p. 53.

(10) F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga and M. Oklobdžija, *J. Med. Chem.*, 11, 167 (1968).

(11) V. Šunjić, F. Kajfež, and P. Mildner, *Croat. Chem. Acta.* **41**, 107 (1969).

(12) R. Sauer, *Angew. Chem.*, 67, 409 (1955).

Received August 22, 1969 Novo Mesto, Yugoslavia