STUDIES OF THE IMIDAZOLE SERIES.

XLIII. SYNTHESIS OF 4(5)-NITRO-5(4)-BROMOIMIDAZOLES BY BROMINATION OF 4(5)-NITROIMIDAZOLES

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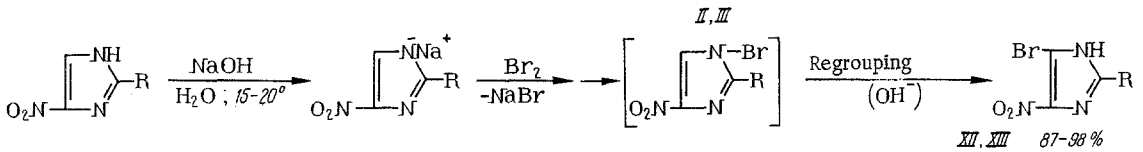
6-(1'-Methyl-4'-nitroimidazolyl-5')-mercaptopurine (azathioprine, imurane) synthesized previously [1-5] has been widely used in the transplantation of organs as an efficient preparation for the suppression of reactions of tissue incompatability [4, 6-8]. For the synthesis of new nitroimidazole derivatives of 6-mercaptopurine, potential immunosuppressive agents, besides 4(5)-nitro-5(4)-chloroimidazoles [1, 2, 4, 5], 4(5)-nitro-5(4)-bromoimidazoles can be used [1, 2, 5]. But obtaining these compounds by nitration of the scarce 4(5)-bromoimidazoles is complicated [9, 10]. Due to this fact we studied the bromination of the more easily available 2-alkyl-4(5)-nitro-, 1,2-dialkyl-4-nitro-, and 1,2-dialkyl-5-nitroimidazoles (II, III, VI-XI).

According to literature data, bromination of 4(5)-nitro-imidazole (I) by bromine in alkaline medium leads to the formation of 2,4(5)-dibromo-5(4)-nitroimidazole [11]. We found that the 2-alkyl-4(5)-nitro-imidazoles (II, III) in cold aqueous caustic soda solution are also very easily brominated by bromine. High yields (87-98%) at 2-alkyl-4(5)-nitro-5(4)-bromoimidazoles (XII, XIII) are obtained. This method of synthesizing nitrobromoimidazoles [12] one stage shorter than the known method of nitration of bromo-imidazoles [9, 10].

The easiness of the bromination of 2-alkyl-4(5)-nitroimidazoles is apparently explained by the fact that in this instance, consistent with the hypothesis of the transhalogenation of imidazoles [13, 15], the anion of nitroimidazole is subjected to bromination. The intermediate N-bromoderivative forming initially is regrouped under the effect of the alkali catalyst to the stable 4(5)-bromosubstituent of imidazole:



An indirect confirmation of this reaction mechanism is the fact that the N-alkylsubstituents of imidazole (IV-XI) are not brominated under analogous conditions, since they are not able to form anions. The brominating agent in the reaction studied is bromine and not the products of its interaction with NaOH (NaOBr, etc.), since with the change of the order of charging the components – by dissolution of bromine in NaOH solution and subsequent addition of (II) the reaction does not take place – the initial compound reforms.

The bromination of nitroimidazoles by bromine also proceeds without an alkaline agent. In this case, apparently, the usual reaction of electrophilic substitution takes place. Thus, the bromination of (II) in water occurs much more slowly than in alkaline solution and leads to a much lower yield (52%) of the compound (XII). The bromination of 1,2-dialkyl-4-nitroimidazoles (VI, X) takes place more easily owing to the presence of the electron-donor alkyl group at the nitrogen atom and leads to the formation of 1,2-dialkyl-4-nitro-5-bromoimidazoles (XIV-XVI) with a good yield (80-92%):

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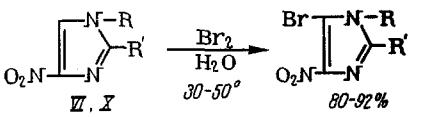
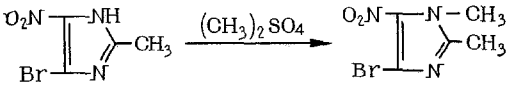


VII, X

XII-XVI

R=CH_3, CH_2CH_2OH, $CH_2CH(OH)CH_2OH$;
R'=CH_3

Bromination by bromine of 1,2-dialkyl-5-nitroimidazoles (VII, X) in water, aqueous caustic soda solution and organic solvents (i.e., in boiling dichloroethane) does not work; this is presumably due to the lower electron charge density at position 4 of the imidazole ring of these compounds than at position 5 of 1,2-dialkyl-4-nitroimidazoles. However, one compound of this series, namely 1,2-dimethyl-4-bromo-5-nitroimidazole (XVII), was synthesized by the methylation of (XII) with dimethyl sulfate in the absence of a solvent. This method had earlier been used in the preparation of (V, VII) [16-18]:



XII XVII

It should be noted that in the literature no representative of 1,2-dialkyl-4-nitro-5-bromo- or 1,2-dialkyl-4-bromo-5-nitroimidazoles is described. Only 1-methyl-4-nitro-5-bromoimidazole is known. This was obtained by nitration of 1-methyl-5-bromoimidazole [19, 20] and methylation of 4(5)-nitro-5(4)-bromoimidazole [19].

An investigation of the activity of the initial 4(5)-nitroimidazoles (I-IX, XI) as well as the synthesized nitrobromoimidazoles (XII-XVIII) against trichomas was of interest in connection with the high antitrichomonas activity of 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole (X, metronidazole) [21, 22], 1-methyl-4-chloro-5-nitroimidazole (chlomizole) [22] and several other derivatives of 4(5)-nitroimidazole [23]. The results of the studies carried out in our institute by G. N. Pershin and N. A. Novitskaya have shown that among these groups of compounds no preparations more active than metronidazole exist.

EXPERIMENTAL

4(5)-Nitroimidazole (I), 2-Methyl-4(5)-nitroimidazole (II) and 2-Ethyl-4(5)-nitroimidazole (III) are obtained by nitration of imidazole and its 2-alkylsubstituents by sodium nitrate in 75-80% H_2SO_4 solution or in a mixture of concentrated HNO_3, 75-80% solution of H_2SO_4 and Na_2SO_4 according to methods developed by us [21, 24, 25]; yield 72-73%.

1-Methyl-4-nitro-, 1-Methyl-5-nitro-, 1,2-Dimethyl-4-nitro-, and 1,2-dimethyl-5-nitroimidazoles (IV-VII) are prepared according to [16-18].

1-(β-Hydroxyethyl)-2-methyl-4-nitro-, 1-(β-Hydroxyethyl)-2-methyl-5-nitro-, and 1-(β,γ-Dihydroxypropyl)-2-methyl-4-nitroimidazoles (IX-XI) are obtained according to [21, 25].

2-Methyl-4(5)-nitro-5(4)-bromoimidazole (XII). A. To 63.5 g (II) dissolved in 500 ml 1N NaOH solution under cooling and stirring within 35-40 min 85 g bromine is added, maintaining a temperature of 20-25°. Bromine is decolorized almost instantly, at the same time the precipitate (XII) separates. After completion of the admixture of bromine the mixture is stirred for 20 min, the precipitate is filtered off, washed with water and dried at 80-100°. Yield 89.7-91.2 g (87-88.6%), mp 267-268° (decomp.). According to the data of [9, 10]: mp 267-269°.

B. To the warm (30-35°) solution of 3.2 g (II) in 1.5 liter water 4.4 g bromine is added, the reaction mixture is stirred for 4 h at 30-35° and let stand overnight; the precipitate is filtered off and washed with water. 2.25 g (XII) with mp 260-261° is obtained. By evaporation of the mother liquor to a small volume 0.65 g XII with mp 255-260° is additionally separated. Total yield 2.9 g (52%).

2-Ethyl-4(5)-nitro-5(4)-bromoimidazole (XIII). It is obtained analogously to XII (method A). Yield 94-98%, mp 176-177°, after recrystallization from water mp 180-181° (decomp.). According to the data of [10]: mp 180-181°.

1,2-Dimethyl-4-nitro-5-bromoimidazole (XIV). To the hot (45-55°) solution of 28 g (VI) in 3 liters water 31.4 g bromine is added within 10-15 min, the solution is stirred for 2 h at 50-60°, 400 ml saturated aqueous solution of sodium acetate is added, the mixture is cooled to 10-15°, the precipitate is filtered off and washed with water. Yield 22-30 g substance with mp 156-160°.

By evaporation of the mother liquor to a small volume 6-13 g of this substance with mp 132-156° is additionally separated. The total yield of technical (XIV) is 35-36 g (79.5-81.9%). Colorless crystals with mp 161-161.5° (from water), difficultly soluble in the cold in water and ethanol. Found, %: C 27.61; H 2.80; Br 36.16; N 18.72. $C_5H_6BrN_3O_2$. Calculated, %: C 27.29; H 2.85; Br 36.32; N 19.10.

1-(β-Hydroxyethyl)-2-methyl-4-nitro-5-bromoimidazole (XV). To the hot (50-55°) solution of 19.7 g (IX) in 600 ml water 6.4 g bromine is added within 5-7 min. The reaction mixture is heated and treated as in the preparation of (XIV). Yield 26.9 g (92.1%), mp 141-143°. Colorless crystals with mp 145-146° (from water), difficultly soluble in the cold in water and ethanol. Found, %: C 28.71; H 2.96; Br 32.30; N 17.02. $C_6H_8BrN_3O_3$. Calculated, %: C 28.82; H 3.22; Br 31.96; N 16.80.

1-(β,γ-Dihydroxypropyl)-2-methyl-4-nitro-5-bromoimidazole (XVI). To 4 g (XI) dissolved in 40 ml water 4.4 g bromine is added. The reaction mixture is stirred for 2 h at room temperature, the water is distilled off in vacuo, the residue is dissolved in 5 ml hot water, 5 ml saturated sodium acetate solution is added, the mixture is cooled, the precipitate is filtered off and washed with water. Yield 4 g (71.7%), mp 158-159°. Colorless crystals with mp 160-161° (decomp., from water), soluble in organic solvents, difficultly soluble in cold water. Found, %: C 30.19; H 3.66; Br 28.16; N 14.98. $C_7H_{10}BrN_3O_4$. Calculated, %: C 30.34; H 3.64; Br 27.76; N 15.16.

1,2-Dimethyl-4-bromo-5-nitroimidazole (XVII). To 10 ml dimethyl sulfate 10.3 g (XII). To 10 ml dimethyl sulfate 10.3 g (XII) is added, the mixture is heated to 70° under stirring and cooled, 15 ml water is added, the mixture is neutralized with 25% aqueous solution of ammonia to pH 8.0-9.0 and cooled, the residue is filtered off and washed with water. Pale yellow crystals with mp 101-102° (from aqueous methanol), soluble in most organic solvents, difficultly soluble in water. The substance causes a depression of the melting temperature after mixing with XIV. Found, %: C 27.43, H 2.79; Br 36.58; N 18.82. $C_5H_6BrN_3O_2$. Calculated, %: C 27.29; H 2.75; Br 36.32; N 19.10.

CONCLUSIONS

The bromination of 2-alkyl-4(5)-nitro-, 1,2-dialkyl-4-nitro-, and 1,2-dialkyl-5-nitroimidazoles was studied and at the same time a simple method was devised for obtaining 2-alkyl-4(5)-nitro-5(4)-bromo- and 1,2-dialkyl-4-nitro-5-bromoimidazoles. 1,2-Dialkyl-5-nitroimidazoles cannot be brominated. 1,2-Dialkyl-4-bromo-5-nitroimidazoles can be obtained by alkylation of 2-alkyl-4(5)-nitro-5(4)-bromoimidazoles by dialkyl sulfates.

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