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RESEARCHES ON IMIDAZOLES
XXII 1-(β-Hydroxyethyl)-2-Methyl-5-Nitroimidazole (Metronidazole) and Other Derivatives of 2-Methylimidazole

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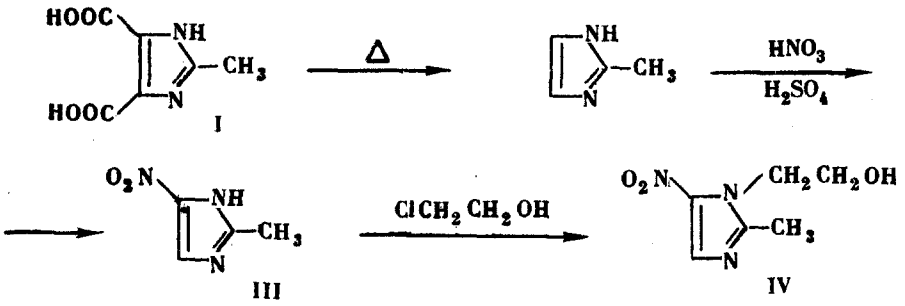
The effective anti-Trichomonas preparation 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) is synthesized, as well as its 4-nitro derivative, and a number of other 2-methylimidazole derivatives: 1-(β-hydroxyethyl)-2-methylimidazole, 1-(β, γ-dihydroxypropyl)-2-methyl-4-nitroimidazole, and nitric acid esters of 1-(β-hydroxyethyl)-2-methyl-4(& 5)-nitroimidazoles.

Since 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole (IV, metronidazole) [1-3] has such high anti-Trichomonas activity, it was of interest to prepare other 2-methylimidazole derivatives for biological testing. The patent literature states (4, 5) that the compound IV is obtained by heating 2-methyl-4(5)-nitroimidazole (III) with ethylene chlorohydrin (14% yield). In 1961 the present authors produced a metronidazole (IV) synthesis which was basically the same:



Synthesis of compounds I and II [6-12] has been somewhat improved. Nitration of II using a mixture of concentrated sulfuric acid and 66% nitric acid [8] at the boiling point of the reaction mixture gives a low yield of the methylnitroimidazole III. The best results (48-52% yield of III) are secured by nitrating II with sodium or potassium nitrate in concentrated sulfuric acid at 125-140° [6]. Depending on reaction conditions, alkylation of methylnitroimidazole III with ethylene chlorohydrin gave two compounds. Boiling compound III with ethylene chlorohydrin without neutralizing t the hydrogen chloride liberated by the reaction gave 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole (IV, metronidazole). Heating III with ethylene chlorohydrin in ethanol in the presence of sodium ethoxide gave 1-(β-hydroxyethyl)-2-methyl-4-nitroimidazole (V). To characterize the two isomers (IV and V) they were treated with nitric acid to give the corresponding nitrate esters. (VI and VII).

Reaction of the nitro compound III with glycerol monochlorohydrin in ethanol in the presence of sodium ethoxide apparently gave 1-(β, γ-dihydroxypropyl)-2-methyl-4-nitroimidazole (VIII), while reaction of II with ethylene chlorohydrin under the same conditions gave 1-(β-hydroxyethyl)-2-methylimidazole (IX).

The predominant formation of 1-alkyl-5-nitroimidazoles at pH < 7 and of 1-alkyl-4-nitroimidazoles at pH > 7 has been described in the literature [13], and evidently it is due to a varied alkylation mechanism for 4(5)-nitroimidazoles, in particular for 2-methyl-4(5)-nitroimidazole (III). In acid solution the ethylene chlorohydrin probably adds to the more basic tertiary nitrogen atom of the imidazole ring, in the way that quaternary salts are formed. Subsequent splitting out of the hydrogen chloride results in formation of the more basic 5-nitro isomer (IV, aqueous solution pH 6.32). In alkaline medium hydroxyethylation proceeds analogously to nucleophilic substitution, via the sodium salt of methylnitroimidazole III, and results in the formation of the less basic 4-nitro isomer (V, aqueous solution pH 6.23).

The nitro derivatives of imidazole, III-VIII, were investigated by G. N. Pershinvyi and N. A. Novitska of the chemotherapy division of the Institute. Metronidazole has high anti-Trichomonas activity, but the activities of the other compounds are low.

Experimental

2-Methylimidazole-4, 5-dicarboxylic acid (I).

a) This compound was prepared similarly to imidazole-4, 5-dicarboxylic acid [14] from tartaric acid, using

acetaldehyde instead of formaldehyde, and with changes in the procedure for isolating the acid I. After adding the aldehyde ammonia solution to the reaction solution of the ammonium salt of dihydroxysuccinic acid, it was left for 14-16 hr (finally at 15-20°), the precipitate of monoammonium salt of acid I which separated was filtered off, dissolved in boiling water, and neutralized with hydrochloric acid. After cooling the precipitate was filtered off, washed with water, and dried at 50-60°. The yield of acid I hydrate was 65-68%, mp 263-267 (with decarboxylation). The literature gives [12] mp 273° (decomp). The monoammonium salt of acid I [7] forms colorless crystals mp 274-277° (decomp, ex water), sparingly soluble in cold water. Found: C 38.31; H 4.73; N 21.74%. Calculated for $C_6H_6N_2O_4 \cdot NH_3$: C 38.50; H 4.85; N 22.45%.

b) A mixture of 1 mole o-phenylenediamine and 1.5 mole glacial acetic acid was refluxed for 2 hr, and the solution obtained, without isolating and purifying the 2-methylbenzimidazole (the yield of technical product was almost quantitative), was poured into 70% sulfuric acid, the solution heated to 75-80° and then oxidized with potassium dichromate in the way described in the literature [12]. The yield of acid I hydrate, mp 263-265° (with decarboxylation) was 33-40% based on the o-phenylenediamine.

2-Methylimidazole (II). Prepared by decarboxylating technical hydrated acid I. The reaction can conveniently be run in a Wurtz flask with a sword-shaped outlet tube. The material was rapidly heated to 230°, and the temperature of the mass gradually raised to 265-270°. The residue in the flask and the small distillate in the sword-shaped outlet tube were dissolved in ethanol, heated with active carbon, filtered, and the solvent evaporated under reduced pressure. The residue was then recrystallized from benzene, to give colorless prisms, mp 140-143° [9], yield 95-99%.

2-Methyl-4(5)-nitroimidazole (III). 32 g II was added to 64 ml 94-96% sulfuric acid, the solution heated to 135°, and 84 g sodium nitrate added over 2 hr 30 min, the rate of addition being such that the temperature remained at 135-140°. The reaction mixture was stirred for 2 hr 30 min at 125-140°, cooled, and decomposed with warm (40-50°) water. A saturated sodium carbonate solution was used to neutralize the mixture, and to bring it to pH 3, the precipitate formed was filtered off, washed with cold water, and dried. Yield of III 25.2-25.7 g (50.9-51.9%), mp 259-263° (decomp). The literature [8] gives mp 254°. Colorless crystals mp 261-263° (decomp, ex water), soluble on heating in water, ethanol, aqueous solutions of mineral acids, and alkalies.

1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole IV). A mixture of 38.1 g III and 190 ml ethylene chlorohydrin was refluxed for 18-20 hr, the ethylene chlorohydrin evaporated under reduced pressure, the brown residue dissolved in boiling water (90 ml), the solution heated with active carbon, filtered, and cooled. The precipitate was filtered off and dried, to give 15.8 g (41.5%) of the starting material III mp 254-256°. About 30 ml 30% aqueous sodium hydroxide was added to bring the solution to pH 10 (universal indicator), the solution cooled to 2-5°, the precipitate filtered off, washed with water, and dried, to give 12.1-14.9 g (40.3-49.7% allowing for the recovered III) mp 156-160°. Recrystallization from ethyl acetate (25 ml per 1 g compound) gave 10.5-11.1 g pure IV mp 158-161 [4, 5], as colorless or pale yellow crystals soluble in hot water or hot ethanol. Found: C 41.76; H 5.39; N 24.34%. Calculated for $C_6H_9N_3O_3$: C 42.10; H 5.30; N 24.55%.

1-(β-Hydroxyethyl)-2-methyl-4-nitroimidazole (V). A solution of sodium ethoxide was prepared from 2.3 g sodium metal and 100 ml absolute ethanol, 12.7 g III added, and the mixture heated until the precipitate dissolved completely. The solution was cooled to 18-20°, 10.4 g ethylene chlorohydrin added, and the whole refluxed for 20 hr, when a precipitate of sodium chloride was formed. Active carbon was added to the reaction products, the solution filtered, cooled to 10°, the precipitate formed filtered off, washed with ethanol, and dried, to give 10.4 g compound V mp 127-129°. The mother liquor was evaporated to dryness, and three recrystallizations of the residue from ethyl acetate gave a further 2.2 g of the same compound mp 127-129°. Total yield 74%, colorless crystals mp 129.5-130.5° (evaporated, ex ethyl acetate), soluble in water and most organic solvents. Mixed mp with IV 110-114°*. Found: C 42.07; H 5.29; N 24.58%. Calculated for $C_6H_9N_3O_3$: C 42.10; H 5.30; N 24.55%.

1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole nitrate ester (VI). 1 g IV was added over 5 min to 10 ml nitric acid (d 1.5) which had been freed from nitrogen oxides by treatment with urea (0.45 g) at 45-50°, and which was kept at −10° during the addition. The mixture was stirred for one hour at −10° to 0°, poured into 30 ml water, the solution neutralized and brought to pH 7 with a sodium carbonate solution, the precipitate formed filtered off, washed with water, and recrystallized from 80 ml water, to give 0.6 g (47.5%) nitro ester VI mp 71.5-72°, forming colorless crystals soluble in most organic solvents, but sparingly soluble in cold water. Found: C 33.65; H 3.77; N 26.04%. Calculated for $C_6H_8N_4O_5$: C 33.34; H 3.73; N 25.92%.

1-(β-Hydroxyethyl)-2-methyl-4-nitroimidazole nitrate ester (VII). Prepared by nitrating V in the way described above, yield 87.1%, colorless crystals mp 99-100.5° (ex water). Found: C 33.41; H 3.82; N 25.94%. Calculated for $C_6H_8N_4O_5$: C 33.34; H 3.73; N 25.92%.

*The melting point of V is given as 140° in a recently published abstract of a British patent [15].

1-(β-γ-Dihydroxypropyl)-2-methyl-4-nitroimidazole (VIII). Prepared similarly to compound V, save that freshly distilled glycerol monochlorohydrin was used instead of ethylene chlorohydrin. Yield 60%, mp 125-126.5° (ex ethanol), colorless crystals, soluble in hot water and most organic solvents. Found: C 41.47; H 5.37; N 20.68%. Calculated for $C_7H_{11}N_3O_4$: C 41.79; H 5.51; N 20.89%.

1-(β-Hydroxyethyl)-2-methylimidazole (IX). Prepared by ethylene chlorohydrin alkylation of compound II as described for V. After heating the solution was filtered to remove sodium chloride, the ethanol was distilled off under reduced pressure, and the viscous residue vacuum-distilled, to give a viscous liquid bp 160-166° (1.5-2.5 mm), soluble in water and organic solvents. The picrate formed yellow crystals mp 152.5-153° (ex ethanol). Found: C 40.58; H 3.80; N 19.80%. Calculated for $C_6H_{10}N_2O \cdot C_6H_3N_3O_7$: C 40.57; H 3.69; N 19.71%. The literature gives [15] bp 130-133° (0.15-0.25 mm).

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