SYNTHESIS OF METRONIDAZOLE FROM ETHYLENEDIAMINE*

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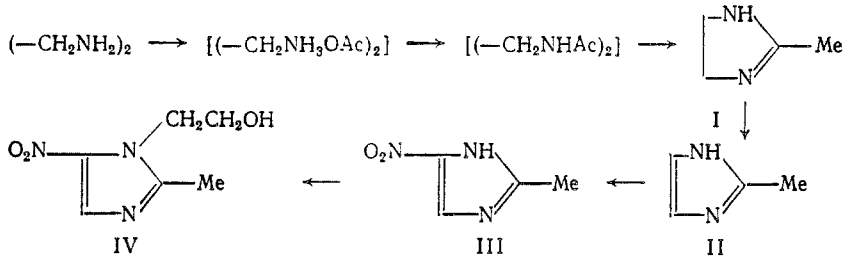
1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole (IV, metronidazole) has been widely accepted in medical practice for treating various diseases [8].

We have previously described the preparation of IV from tartaric acid and o-phenylenediamine, whereby the most important intermediate product of the synthesis of IV, 2-methylimidazole (II), was obtained by decarboxylation of 2-methylimidazol-4,5-dicarboxylic acid, the nitration of II was carried out using inorganic nitrates, and the hydroxyethylation of 2-methyl-4(5)-nitroimidazole (III) was effected by means of ethylene chlorohydrin [1, 7, 11].

The simplest single-stage method of preparation of II is synthesis from glyoxal, acetaldehyde, and ammonia [9, 15, 16]. However, because of the high cost of glyoxal and its scarcity, this method cannot be used for the time being for a large-scale production of IV.

To extend the raw material base, we carried out a simple synthesis of IV from the cheap and readily available ethylenediamine according to the scheme shown below [2-6].



To obtain 2-methylimidazoline (I), ethylenediamine and AcOH can be used in a ratio of 1 mole per 2 moles, at both high (70-97%) and low (10-40%) concentrations. On mixing the aqueous solutions of the above components, a diacetic acid salt of ethylenediamine is formed, which upon evaporation of water converts into N,N'-diacetylethylenediamine [3]. The latter, without isolation and purification, is treated with quick lime to give I. This compound is readily dehydrogenated in the presence of Raney nickel [2] or nonpyrophoric nickel [6] with the formation of II.

We have also greatly improved the stages of nitration of II to III and hydroxyethylation of III to IV. Thus, by carrying out the nitration of II using a mixture of HNO_3 and H_2SO_4 in the presence of Na_2SO_4 and $NaHSO_4$, we were able to increase the yield of III to 63-66% [5], as compared with 48-52% obtained in the nitration of II with inorganic nitrates [1].

The hydroxyethylation of III using ethylene oxide is conveniently carried out in a homogeneous medium consisting of H_3PO_4 and AcOH [4] instead of HCOOH or AcOH [10].

EXPERIMENTAL

2-Methyl-4,5-dihydroimidazole (2-Methylimidazoline, Lysidine, I). A 1- to 1.05-mole portion of AcOH (glacial or in the form of 20-85% aqueous solution) was added with water cooling and stirring to 0.5 mole of ethylenediamine (in the form of a 20-85% aqueous solution). The mixture was boiled with the simultaneous evaporation of water, while the temperature was increased to 220-240°C, and at the end was heated for 30-40 min at 240-250°C,

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until water ceased to separate out. The technical grade N,N'-diacetylethylenediamine obtained (mp in a sample 176-177°C) was cooled to 180-185°C, 43 g (0.75 mole) of 97.5% calcium oxide was added, and the downward condenser was replaced by an air-cooled reflux condenser. Heating of the hot mass was continued at 220-265°C, whereby I was soon formed and the whole mass began to boil (the bp of I is 197-200°C). The mixture was boiled for 2 h, cooled to 185-190°C, the reflux condenser was replaced by an air-cooled downward condenser, and I was distilled off at atmospheric or reduced pressure. Compound I can also be separated by dissolution of the mass in an anhydrous organic solvent (isopropanol, dichloroethane, diphenyl oxide, etc.). Yield 37-43 g (88-95%) of I, mp 101-104°C, which was suitable for the preparation of II without additional purification. According to the data in [14], the mp of I is 105°C.

2-Methylimidazole (II). a) A 16.8-g portion of I was added to 0.7-3.3 g of moist (or alcohol-washed) Raney nickel paste. The mixture was rapidly heated to 170-175°C under an air-cooled reflux condenser, whereby a rapid evolution of hydrogen began. Heating was continued with a gradual increase in the temperature of the mass to 220°C (up to the cessation of evolution of hydrogen). The reaction time was 60-90 min, depending on the amount of the catalyst used. The mass was then cooled to 40-50°C, 50-100 ml of ethanol and 0.5 g of activated charcoal were added, the mixture was boiled for 5-10 min, and filtered. The solvent was evaporated from the filtrate under vacuum to dryness, and the crystallized residue was dried at 40-50°C. Yield 13.9-14.7 g (85-90°C) of II, mp 139-142°C. According to the data in [7, 11, 13], the mp of II is 140-143°C. b) A mixture of 50 ml of diphenyl oxide and 7.5 g of nickel formate dihydrate was heated in a flask with a downward air-cooled condenser for 1 h at 190-250°C up to cessation of distillation of water. The suspension of nonpyrophoric nickel catalyst thus obtained was cooled to 20-30°C and 47 g of I in 180 ml of diphenyl oxide, preliminarily heated to 180°C, was added to the solution. The mixture was rapidly heated with stirring under an air-cooled reflux condenser to 220°C. At this temperature a vigorous evolution of hydrogen began. The heating was continued with stirring and with increase of the temperature to 230°C for 2.5-3 h up to the complete cessation of the evolution of hydrogen. The mixture was then cooled to 155-165°C, filtered, and the catalyst was washed on the filter with hot toluene (2 × 40 ml). The combined filtrate was cooled to 20°C, the precipitate of II that separated out was filtered off, washed on the filter with cold toluene, and dried at 40-50°C. Yield 41.3-41.8 g (90-91%) of II, mp 139-143°C. Compound II obtained by methods a or b was suitable, without additional purification, for use in the synthesis of III.

2-Methyl-4(5)-nitroimidazole (III). A mixture of 276 ml of water, 352 ml of a 93% H_2SO_4, 576 g of anhydrous Na_2SO_4 and 164 g (2 moles) of II was stirred under a reflux condenser, while heating the mass to 130°C. A 252-ml portion of 99% HNO_3 (5.2 moles) was then added gradually to the hot solution from a dropping funnel with stirring and heating. A vigorous evolution of nitrogen oxides thus took place. The mixture was boiled for 4 h at 130-132°C, whereby the evolution of nitrogen oxides ceased at the end of the heating. The solution was cooled to 60-70°C, poured with cooling and stirring into 1200 ml of water and neutralized with 25% aqueous ammonia to pH 4-5, while maintaining the mass at a temperature in the range of 30-40°C. The mixture was then stirred for 30 min at the same temperature, and the precipitate that separated out was filtered off, washed with water, and dried at 60-70°C. Yield 160-168 g (63-66%) of III, mp 252-254°C (decomp.). According to the data in [12], the mp is 254°C, and according to the data in [7], the mp of the chemically pure compound is 261-263°C. Compound III is suitable for the synthesis of IV without additional purification.

1-β-Hydroxyethyl-2-methyl-5-nitroimidazole (IV, Metronidazole). A 100-ml portion of Ac_2O was added, with water cooling and stirring, to 76 ml of 85% H_3PO_4 at such a rate that the temperature of the mixture did not rise above 70-90°C. A 63.5-g portion (0.5 mole) of III was added to the mixture of H_3PO_4 and AcOH obtained. The mass was stirred to the complete dissolution of III, then cooled to 25°C, and at this temperature, 120 ml (2.5 moles) of ethylene oxide, preliminarily cooled to 0-5°C, was added in the course of 1-1.5 h, with vigorous stirring and ice cooling. The reaction mixture was stirred for 2.5 h at 25-30°C, and then was diluted with 800 ml of water, cooled to 2-5°C, and held at this temperature for 4-5 h. The precipitate of unreacted III that separated out was filtered off, washed with water, and dried at 60-70°C. Thus, 5.5-10 g (8.7-15.7%) of III was recovered, which was subsequently used in the next batch in the preparation of IV. The acid filtrate was made alkaline with 25% aqueous ammonia to pH 10 (about 200-230 ml), an additional 50 ml of 25% aqueous ammonia was added, and the mixture was allowed to stand for 10-14 h at 10°C.

The precipitate that separated out was filtered off, washed with water, and crystallized from 500-530 ml of distilled water with addition of 2 g of activated charcoal. The hot filtrate was cooled to 2-5°C, held at this temperature for 10-12 h, the precipitate was filtered off, washed with distilled water, and dried at 70-80°C. Yield 45 g (63.7%, based on reacted III) of IV, mp 160-161.5°C. According to the data in [7, 10, 11], mp 158-161°C.

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SYNTHESIS AND MICROBIOLOGICAL HYDROXYLATION OF 16α,17α-DIHYDROXY-SUBSTITUTED 20-OXO-5α-PREGNANES

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At the present time, production of steroids, integrated microbiological hydroxylation, hydrolysis and dehydrogenation processes are being successfully used to provide a convenient path for the synthesis of corticosteroid preparations [1, 5].

In the preceding publications [7, 8] we reported studies of the influence of substituents at C(16), C(17) of the steroid on the transformation activity of the hydroxylating cultures of the microorganisms Curvalaria lunata, Tieghemella orchidis, Cunninghamella blakesleeana, Trichothecium roseum, and others. The dependence of the direction of the hydroxylation on the structure of the substrate was studied on 16,17-substituted derivatives of the Δ^4-pregnene series.

To study the possibilities of using the 5α-pregnane derivatives for the synthesis of corticosteroids, we examined the microbiological transformation of 20-oxo-5α-pregnanes (I), containing substituents – the hydroxyl groups and the isopropylidenedioxy group – at C(16) and C(17).

Data in the literature on the microbiological transformation of 5α-pregnane derivatives are sparse, and no data are available on the selective 11-β-hydroxylation. Derivatives of 3,20-dioxo-5α-pregnane – 11β,17α,21-trihydroxy-5α-pregnane-3,20-dione and its 17-acetate are steroid metabolites; the latter has anti-inflammatory and progestagenic activity. These compounds were obtained previously by hydrogenation of hydrocortisone and its acetate with hydrogen in the presence of a palladium catalyst at room temperature [6, 9].

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