A Short Synthesis of 5-Methylhistamine (1)

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Received November 5, 1980

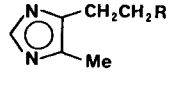
Methoxybromination of 4,5-dihydro-2-methylfuran (**4**), followed by treatment of the resulting bromoketal **5** with hot formamide, gave 4-(2-hydroxyethyl)-5-methyl-1*H*-imidazole (**3**) in 25% yield. This method provides easy access to the selective H_2-agonist 4-methylhistamine (**1**) *via* the chloromethyl intermediate **2**.

J. Heterocyclic Chem., **18**, 831 (1981).

In connection with pharmacological studies concerning the identification of gastric acid secretion inhibitors of the H_2-antagonist type, we were interested in synthesizing gram quantities of the selective H_2-agonist, 5-methylhistamine (**1**) (2a-c).

For this purpose, we wanted first to prepare the hydroxyethyl derivative **3**, and thence proceed to the corresponding chloride **2**, which would easily provide not only 5-methylhistamine (**1**) itself, but also a variety of other side-chain substituted analogs. However, our attempts to obtain **3** by the multi-step procedure of Fox, *et al.* (3), were continuously frustrated by low yields. Therefore, we have devised the following short and straightforward method of synthesis for this key intermediate. Enol ether methoxybromination (4) of the bulk chemical 4,5-dihydro-2-methylfuran (**4**) with bromine in methanol buffered with sodium acetate (5) provided the bromoketal **5**. It has already been demonstrated (6) that compounds of this type can serve as substrates for the Bredereck imidazole synthesis (7) which entails heating of the substrate in formamide. Under these conditions, crude **5** afforded the desired hydroxyethylimidazole **3** in yields of *ca.* 25% based on the dihydrofuran precursor **4**, after simple bulb-to-bulb distillation (Scheme I).

With intermediate **3** in hand, 5-methylhistamine (**1**) was obtained uneventfully *via* the chloride **2** essentially following published procedures (8).



1 R = NH_2

2 R = Cl

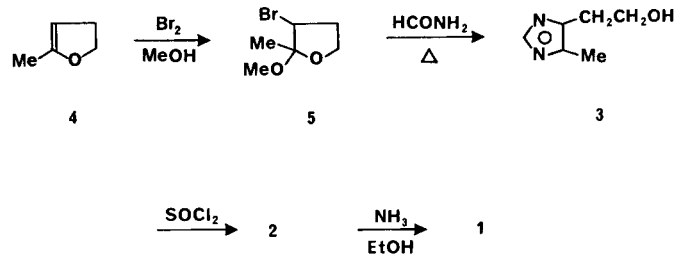
3 R = OH

EXPERIMENTAL

4-(2-Hydroxyethyl)-5-methyl-1*H*-imidazole (**3**).

To a solution of 17.5 g (0.21 mole) of 4.5-dihydro-2-methylfuran (**4**, Aldrich Chemical Co.) and 19.25 g (0.235 mole) of anhydrous sodium acetate in 10 ml of methanol cooled to −60° in a dry ice-acetone bath, was added dropwise during 3 hours a precooled solution of 11.0 ml (34.1 g, 0.123 mole) of bromine in 150 ml of methanol with vigorous overhead stirring. The reaction mixture was diluted with 750 ml of cold water and extracted with ether-pentane (1:1). The organic layer was washed successively with 1*N* sodium bicarbonate, 1*N* sodium sulfite and brine. After drying (magnesium sulfate) the solvent was removed on a rotary evaporator (bath temperature 40°) to afford 40 g of the bromoketal **5** as a colorless liquid which was immediately refluxed with 150 ml of freshly distilled formamide for 6 hours. After cooling, the reaction mixture was concentrated *in vacuo* (oil pump), the residue was diluted with 400 ml of water, and treated with 200 g of Dowex 50W-8X resin (acid form). The resin was washed successively with water and methanol and the crude base was eluted with 0.5*N* ammonia-methanol (15 ml of 58% aqueous ammonia per liter of methanol). Evaporation left 11.0 g of a brown oil which was distilled (bulb-to-bulb, 140-160°, 0.1 mm) to give 6.25 g (24% yield) of **3** as a slightly brownish oil which solidified on standing; glc purity 93.5% (6′ column, 10% OV 101). An analytical sample obtained by crystallization from ethyl acetate had mp 95-97° [lit. (3) mp 96.5°], hydrochloride (from ethanol-ether), mp 128-130° [lit. (8) mp 129-131°]. The oxalate (mp 168-169°, from isopropyl alcohol) had the following nmr (DMSO-d_6): δ 2.15 (s, 3H), 2.66 (t, J = 6 Hz, 2H), 3.56 (t, J = 6 Hz, 2H), and 8.12 (s, 1H). In a second run, 20 g of **4** afforded 7.8 g (26.2%) of **3**. Other brominating agents, such as NBS (9) and NBA, gave inferior results.

Scheme 1



4-(2-Chloroethyl)-5-methyl-1*H*-imidazole (**2**).

To 4.8 g (29.5 mmoles) of 4-(2-hydroxyethyl)-5-methyl-1*H*-imidazole (**3**) was added 50 ml of thionyl chloride dropwise with ice cooling. The reaction was allowed to proceed at room temperature for 20 hours and then under reflux for 1 hour (nitrogen blanket). After cooling, excess thionyl chloride was removed on a rotary evaporator, and the residue was evaporated three times with 30 ml each of toluene. Crystallization of the crude product from ethanol-ether (charcoal) afforded 4.8 g (90%) of the hydrochloride of **2**, mp 188-191° [lit. (8) mp 189-191°].

4-(2-Aminoethyl)-5-methyl-1*H*-imidazole (**1**).

A solution of 2.4 g (13.25 mmoles) of 4-(2-chloroethyl)-5-methyl-1*H*-imidazole hydrochloride (**2**) in 90 ml of ethanol saturated with ammonia

0022-152X/81/040831-02$02.25

was heated in a Parr stainless steel bomb at 100° for 18 hours. After cooling, the contents of the bomb were evaporated to dryness and the residue refluxed for 1 hour with 5.0 g of potassium carbonate in 35 ml of methanol containing 5 ml of water. After evaporation to dryness, 20 ml of ethanol were added to the semi-solid residue, and the mixture was filtered. The filtrate was evaporated and the oily residue subjected to bulb-to-bulb distillation at 140-180° (0.5 mm) to provide 1.28 g (77%) of **1** as a slightly yellow, viscous oil. The dihydrochloride (from ethanol-ether) had mp 236-238° [lit. (2b) mp 239-242°].

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