SYNTHESIS OF A CIMETIDINE ANALOGUE

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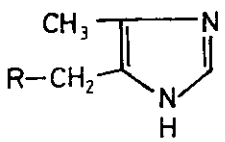
Abstract - 2-Hydroxymethyl-4-methylimidazole(2a) and 2,5-bis(hydroxymethyl)-4-methylimidazole(3a) have been synthesized and characterized. No reaction on the hydroxymethyl moieties in position 2 of these compounds could be observed with cysteamine under usual reaction conditions. The hydroxymethyl group in position 5 of compound 3a does react with cysteamine to give an intermediate leading to 3b and to cimetidine analogue 3c.

Cimetidine (1c), one of the best H_2-receptor antagonist for histamine has achieved an important position in the therapy of gastric ulcer[1]. Several processes are known for its preparation[2], but it is the procedure starting from 1a, which is the most useful[3] among them.

Aiming at the synthesis of this type of compounds for pharmacological testing we have attempted to build up the cimetidine regioisomer 2c and an analogue bearing two cimetidine side chains in the positions 2 and 5 of the imidazole ring starting from 2a and 3a, respectively. There are two short communications in the literature by Grimmet et al.[4] and by Komoto[5] for the synthesis of 2a from glycolic aldehyde, methylglyoxal in aqueous ammonium acetate[5] or aqueous ammonia solution[4], respectively, but neither of the procedures proved to be suitable for synthetic purposes, because of the very low yields (about 2%) and because both procedures supply the title compound only in mg scale and in the picrate form.

Data of the free base 2a have been missing until now.



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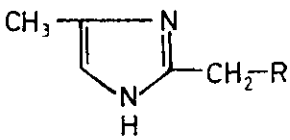

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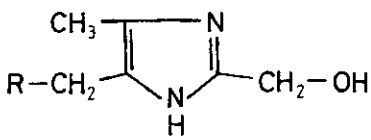

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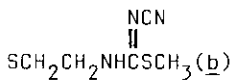
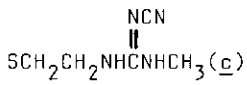
R=OH(a)



(b)



(c)

Starting from methylglyoxal, glycolic aldehyde and ammonia in dry ethanol we succeeded in working out a new method for the synthesis of 2a with satisfactory yield (35%). The compound is obtained by simple washing up procedures in analitically clean form as a base and characterized by analytical and spectroscopic methods. No problem of the scaling up of the procedure has arisen even into hundred gramm quantities.

Methylglyoxal and glycolic aldehyde required to the synthesis were made by using the method of Riley et al.[6] and Fischer et al[7]., respectively. To our big surprise however, reaction between 2-hydroxymethyl-4-methylimidazole(2a) and cysteamine hydrochloride could not be forced out under usual reaction conditions[8], so preparation of cimetidine regioisomer 2c has not been accomplished. For the synthesis of the other cimetidine analogue planned to synthetise, the bis(hydroxymethyl)-imidazole derivative 3a was required. Direct bis(hidroxymethylation) of 4-methylimidazole by paraformaldehyde could not be effected; the bis(hydroxymethyl) compound was observed to be formed only in a very low yield even after long reaction time and at higher temperature. Nor was succesful the reaction of 5-hydroxymethyl-4-methylimidazole with paraformaldehyde in aqueous alcoholic potassium hydroxide; the rate of the hydroxymethylation in position 2 of the imidazole ring was found to be very small, not satisfactory for preparative purposes. But bis(hydroxymethyl) derivative 3a has been obtained easily from 2a under the usual reaction conditions and characterized by elemental analysis, ^{1}H - and ^{13}C-n.m.r. spectra.

Compound 3a was refluxed with two moles of cysteamine hydrochloride in acetic acid, solution till 3a disappeared from the solution (15 h, TLC:Polygram^{R} Sil G/UV 254, diethyl ether: methyl alcohol = 1:1). The product was isolated after the evaporation and got rid of the traces of the solvent by azeotropic distillation with dioxane. The residue was dissolved in water, and after neutralization by sodium carbonate two moles of carbonimidothioic acid cyanodimethyl ester was added. The product was crystallized overnight at 0°C with excellent yield. The analytical, ^{1}H- and ^{13}C-n.m.r. data showed, that it was only the 5-hydroxymethly group which entered into reaction with cysteamine hydrochloride and subsequently with carbonic acid derivative to give compound 3b. Hydroxymethyl group in position 2 remained unchanged showing again, that not only imidazole nucleus, but also the reactive center of the substituent in that position are unreactive compared to position 5. Reaction of 3b with aqueous methylamine resulted in formation of 2-hydroxymethyl derivative of cimetidine 3c in 78% yield. Analytical and spectroscopic data are in good agreement with the proposed structure.

EXPERIMENTAL

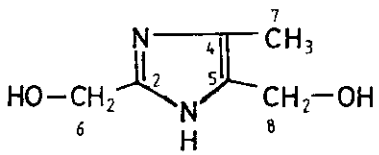
2-Hydroxymethyl-4-methylimidazole(2a)

Dry methylglyoxal 7.2g(100 mmol) and 6.0g(100 mmol) of dry glycolic aldehyde were dissolved in 50 ml of absolute ethanol at 40°C. Absolute ethanol (50 ml) saturated with ammonia was dropped into the above solution for 30 min and then ammonia was led into the mixture at 40°C for 5 h. The ammonia was absorbed fast at the beginning with slightly exothermic reaction. The mixture was stored in refrigerator for overnight, filtered, the filtrate evaporated in vacuo. The residue crystallized in deep-freezer. The crystals were slurried in dry acetone, filtered off, washed with cold acetone and diethyl ether, and dried. Yield: 3.9 g (35%); mp 120-122°C; Anal. calc. for $C_5H_8N_2O$: C,53.57;H,7.14;N,25.00. Found: C,53.72;H,6.85;N,24.92. ^{1}H-n.m.r. ($CDCl_3$-DMSO-d_6,δ): 2.13(s,3H,CH_3);4.46(s,2H, CH_2);6.53(s,1H,CH);5.95(br,NH and OH).

2,5-Bis(hydroxymethyl)-4-methylimidazole(3a)

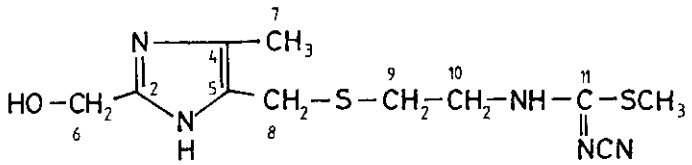
2-Hydroxymethyl-4-methylimidazole(11.2g, 100 mmol) was added to 2.8g (50 mmol) of potassium hydroxide in 100 ml of water under stirring. A brown solution was obtained in 30 min. Paraformaldehyde(3.3g, 100 mmol) was then added in small portions at ambient temperature, stirred for 5 h and stored in refrigerator for overnight. The solution was made acidic (pH=3) by means of hydrochloric acid

and evaporated in vacuo. The residue was extracted with boiling absolute ethanol (3x50 ml), the ethanol removed in vacuo. The residue was dissolved in 50 ml of water and the pH adjusted to 8 by means of saturated sodium carbonate. The solution evaporated in vacuo, the residue extracted with boiling absolute ethanol (3x50 ml) in the presence of charcoal, the mixture filtered and the alcohol removed in vacuo till the beginning of crystallization. The mixture was stored in refrigerator overnight. The crystallized product was filtered off, washed with cold ethanol and dried in desicator in vacuo over dried calcium chloride. Yield: 8.5(60%); mp 148-150°C; Anal. calc. for $C_6H_{10}N_2O_2$: C,50.10;H,7.00;N,19.70. Found: C,49.81; H,7.10;N,19.53. ^{1}H-n.m.r.(DMSO-d_6,δ): 2.08(s,3H,CH_3);4.25(s,2H,CH_2O);4.32(s,2H, CH_2O);4.8(br,1H,OH); 5.3(br,1H,OH);11.7(br,1H,NH) ppm. ^{13}C-n.m.r.(DMSO-d_6): 146.1(C2);126.9(C4);131.4 (C5);56.9(C6);10.7(C7);54.7(C8) ppm.



N-Cyano-S-methyl-N(2((2-hydroxymethyl-4 -(methyl-1H-imidazole-5-yl)methyl)thio) ethyl)thiourea(3b)

2,5-Bis(hydroxymethyl)-4-methylimidazole(7.1g, 50 mmol) and cysteamine hydrochloride(11.36g, 100 mmol) were refluxed in 25 ml of acetic acid for 15 h. After evaporation in vacuo by azeotropic distillation with dioxane, the remaining solid was treated with 15 ml of water and charchoal, and the mixture was stirred for 15 min and filtered. Sodium carbonate(8g) was added. The reaction mixture was added to carbonimidothioic acid cyanodimethyl ester(14.6g, 100 mmol) in 50 ml of absolute ethanol and stirred for 2 h at 30→80°C. The reaction mixture was allowed to stand overnight at 0°C. The precipitated product was filtered off, washed with cold water and dried. Yield: 12.5g(79%); mp 168°C. Anal. calc. for $C_{11}H_{17}N_5OS_2.H_2O$: C,40.00;H,5.48;N,23.60. Found: C,40.26;H,5.65;N,23.48. ^{1}H-n.m.r. (DMSO-d_6 ,δ):2.09(s,3H,CH_3);2.58(s,3H,SCH_3);4.34(s,2H,OCH_2);3.62(s,2H,SCH_2);2.61 and 3.48(t,2-2H,SCH_2-CH_2N);5.38 and 10.08(br,2H, 2xNH) ppm. ^{13}C-n.m.r.(DMSO-d_6): 145.7(C2);125.2(C4);129.5(C5);56.7(C6);9.6(C7);26.5(C8);29.4(C9);42.8(C10);169.8(C11) 115.0(CN);13.9(S-Me) ppm.



2-Hydroxymethyl-cimetidine(3c)

Compound 3b 3.2g(100 mmol) and 40% methylamine(3.6 ml) in 10 ml of water was stirred for 3 h at 60°C, the pH adjusted to 6-6,5 by acetic acid at 35°C, the mixture was treated with charchoal and filtered. The solution was made alkaline (pH=10) by concentrated ammonia solution, cooled and stirred for 1 h at 0°C. The precipitated product was filtered off, washed with cold water and dried. Yield: 2.2g(78%);mp 150°C(from propanol-2). Anal. calc. for $C_{11}H_{16}N_5OS$: C,46.80;H,6.38; N,29.78. Found: C,46.78;H,7.01;N,29.78. ^{1}H-n.m.r.($CDCl_3$+DMSO-d_6,δ):$NHCH_2CH_2S$,6.8 (br,1H,NH);3.33(q,2H,CH_2);2.60(t,2H,CH_2);$NHCH_3$,3.74(d,3H,CH_3);7.0(br,1H,NH); $ArCH_2S$,3.61(s,2H,CH_2);CH_2O,4.41(s,2H);$ArCH_3$,2.12(s,3H,CH_3);OH,5.1-6.4(br,1H) ppm.

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