

DRUG SYNTHESIS

A NEW METHOD FOR THE SYNTHESIS OF RANITIDINE

URSZULA LIPNICKA, RYSZARD JASZTOLD-HOWORKO,
KRYSTYNA WITKIEWICZ* and ZDZISŁAW MACHOŃDepartment of Organic Chemistry, Wrocław Medical University, 9 Grodzka Str., 50-137 Wrocław,
*Torf Corporation – Factory of Drugs, Kąty Wrocławskie**Abstract:** An improved synthesis of the antiulcer drug Ranitidine from an oxazolidine derivative is reported.**Keywords:** ranitidine, antiulcer drugs, oxazolidine derivatives.

Ranitidine hydrochloride is H₂ receptors antagonist. It decreases hydrochloric acid and pepsin excretion by stomach membrane cells. It acts four times stronger than Cimetidine. It does not inhibit microsomal enzymes in the liver and does not block histaminic receptors H₁ contrary to Cimetidine. It does not contain imidazole ring that is an essential fragment of Butyramide, Cimetidine and Metiamide and that seemed to be responsible for antisecretory activity (1–4). Chemically, Ranitidine is substituted with aminoalkilofurane. It inhibits secretive respond on peptone or simulated feeding, it makes concentration and volume of secretive acids get lower (3;5;6–9). Described properties of Ranitidine make it possible effective treatment of intestinal diseases, namely ulcer disease and Zollinger–Ellison (2;10–16). Ehsanullah (17) proved that addictive smokers and arthritis patients need higher doses of Ranitidine to cure ulcer disease (600 mg a day). It has been ascertained that the damage of patients digestive system, who have been treated non-steroid antiinflammatory drugs (Naproxen, Piroxicam, Diclofenac, Indometacine and such like) and Ranitidine parallely, decreases (17;18), although there are also information about intestine–stomach (gastric) disorders (19). Antagonists H₂, introduced to medicine, prevent so called Mendelson disease, it means, stomach contents sucking to lungs during medicinal operation. Andrews and collaborators (20) determined that treating of patients with Ranitidine before medicinal operation prevents stomach contents sucking. This research is still continuing (21).

Ranitidine allows curing orexia giving positive effect in 71% of patients (10;22;23). Ranitidine is used *per os* in the form of tablets, syrups, gels, effervescent agents and injections. It is well tolera-

ted and side effects are observed only in 2% of patients. In medicine, Ranitidine is used as Ranigast, Ranisan, Anzatac, Sostril, Zantic, Ranital.

There are many described synthetic methods of Ranitidine obtaining. In most cases there are the patents. The synthetic methods are mainly:

1. Obtaining of aminoalcohol **1**, aminothioli **2** or aminosulphide **3** (AS) and their further transformations (24–33).
2. Obtaining of thiazolidine **4** and its further transformations (33).

Lately, the synthesis of Ranitidine has been made from alcohol **5**, which has been converted into Ranitidine with good yield. An interesting method is the using of reductive amination (Figure 3) (34). Norwegian researchers oxidized alcohol **5** to aldehyde **6** with active MnO₂ with 94% yield.

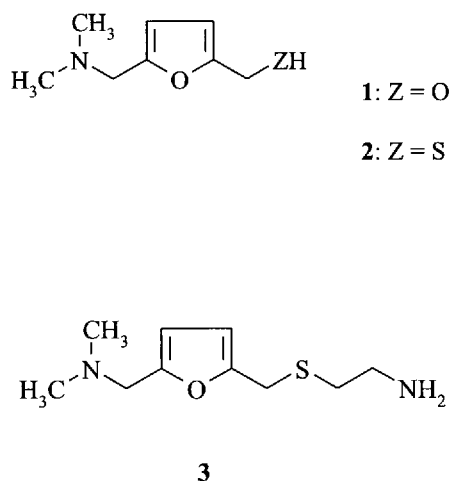


Figure 1.

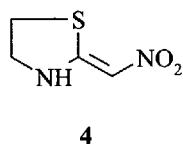


Figure 2.

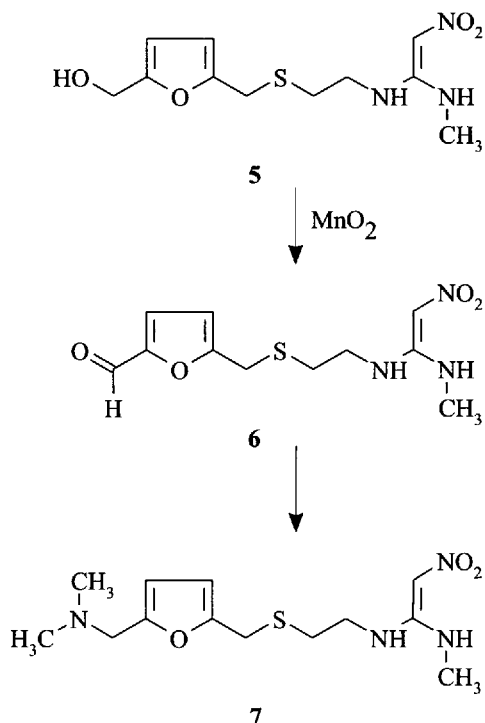


Figure 3.

Crude aldehyde **6** reacted with dimethylamine in the presence of NaBH₃CN giving Ranitidine **7** with 62% yielding.

The short review of synthetic methods presented above shows that the research of new ways of Ranitidine obtaining is still topical.

EXPERIMENTAL

Materials and methods

The melting points of all new compounds have been measured on a Böethius hotstage apparatus and were uncorrected. IR spectra: Pye-Unicam SP-1000 apparatus in KBr. ¹H NMR spectra: Tesla BS 587 A, 80 MHz apparatus (HMDS as internal reference). TLC made with

„Silufol” plates, elution with chloroform/methanol (9:1) – detection of compounds on the chromatograms was made by treatment with iodine vapors.

1,1-bis(methylthio)-2-nitroethene (**8**) was obtained in accordance with (33).

2-nitromethylene-1,3-oxazolidine (**9**), 1,1-bis(β-hydroxyethylamino)-2-nitroethene (**10**).

To the boiling solution of 16.5 g (0.1 M) bis(methylthio) derivative **8** in 100 ml of ethanol, 0.5 g of TsOH was added. Next, 6.1 g of ethanoline in 50 ml of ethanol was slowly dropped into. The mixture was stirred and heated at reflux for 12 h. Evaporation to dryness under reduced pressure left a residue which was taken up in water (400 ml). The solid was collected and washed with water to provide 2.9 g of derivative **8**. The collected filtrations was again evaporated to dryness under reduced pressure. To the dry residue 100 ml of acetone was added and refluxed. After cooling, the precipitate was filtered off and crystallized from ethanol to yield 5.49 g (41.5%) of compound **9**, m.p. = 134–136°C. The filtrate was evaporated to dryness and the solid crystallized from ethanol yielding 3.5 g (26.5%) of 1,1-bis(β-hydroxyethylamino)-2-nitroethene (**10**) with m.p. = 147–149°C. Elementary analysis: C₄H₆N₂O₃, M.w. 130,0 (**9**); calculated %: C = 36.92; H = 4.61; N = 21.54; found %: C = 36.70; H = 4.60; N = 21.49.

IR **9** in KBr λ cm⁻¹: 3040 i 1380 (= CHNO₂); 1600 (C=C); 3400 i 1650 (NH).

¹H NMR **9** in DMSO-D₆: δ = 3.8 (2H, t) (-NHCH₂-); δ = 4.63 (2H, t)(J = 4 Hz)(-OCH₂-); δ = 6.53 (1H, s) (-CHNO₂); δ = 9.86 (1H, s)(-NH-). Elementary analysis: C₆H₁₃N₃O₄, M.w. 191 (**10**); calculated %: C = 37.69 ; H = 6.80 ; N = 21.98; found %: C = 37.85; H = 6.92; N = 22.01

IR **10** in KBr λ cm⁻¹: 3300 i 1100 (OH); 1650 (C=C); 3290 i 1595 (NH) oraz 1380 (= CHNO₂). ¹H NMR **10** in DMSO-D₆: δ = 3.23 (4H, m) (-NHCH₂-); δ = 3.46 (4H, m)(-CH₂OH); δ = 5.0 (2H, s) (-OH) oraz δ = 6.53 (1H, s)(-CHNO₂).

1-β-hydroxyethylamino-1-methylamino-2-nitroethene (**11**).

A mixture of 4.5 g oxazolidine **9** and 40 ml of 33% of ethanolic solution of methylamine was stirred at room temperature for 48 h. Next, the precipitated sediment was filtered off and crystallized from methanol to provide the pure expected compound **11** (5.1 g, 91.5%), m.p. = 166–167°C, according to reference (26).

Elementary analysis: C₃H₁₁N₃O₃, M.w. 161 (**11**); calculated %: N = 26.07; found %: N = 25.90

of NaOH and 3.3 g of NaCl was added and the resulting mixture was kept at 0°C. The mixture was extracted with ethyl acetate (3×25 ml). The extracts were washed with water and dried with MgSO₄. The dried solution was evaporated under reduced pressure at bath temperature that has been sustained below 40°C. 2.6 g of crude Ranitidine was obtained, which was purified by the chromatography method using a silica gel 0.05–0.2 mm column, eluting was performed with methanol. In this way 1 g (17.3%) of oil was obtained, which was transformed into oxalate of **7** with m.p. = 146–148°C according to (27).

a) Ranitidine hydrochloride (**7a**).

To the preceding compound **7** (0.5 g) dissolved in 2.5 ml of anhydrous ethanol, 38% ethanolic HCl was progressively added dropwise under stirring, until pH = 5 was reached. Next, ethyl acetate was added to light dim and the whole was left at 0°C for 12 h. Then, 0.39 g (70%) of white plate crystals of compound **7a** was collected. M.p. = 133–135°C is according to reference (36).

Elementary analysis, IR, ¹H NMR spectra of the compound **7a** were in accordance with reference obtained from Zantac drug (Glaxo).

RESULTS AND DISCUSSION

Chemical part

We conducted on original synthesis of Ranitidine according to Scheme 1.

The starting materials were 1-(β-hydroksyethylamino)-1-methylamino-2-nitroethene **11** and 5-(N,N-dimethylaminomethyl)-2-thiomethylfuran hydrobromide **12**. The compound **11** has been obtained from known 1,1-bis(methylthio)-2-nitroethene **8** that has been synthesized according to (35). 1,1-bis(methylthio)-2-nitroethene **8** and 2-aminoethanol in ethanolic solution in the presence of catalytic amount of p-toluenesulfonic acid gave a mixture of compounds **9** and **10**. Using acetonitrile as a solvent and acetic acid as a catalyst caused a yield decrease. The derivative of 1,3-oxazolidine **9** has been treated with ethanolic solution of methylamine. The result of reaction was the compound **11** that condensed with obtained by us, compound **12** (27). The product of condensation was a derivative **7** from which salt **7a** has been obtained. As a result of this study a new way was elaborated of the synthesis of the known antiulcer drug Ranitidine **7** from the yet unknown 2-nitromethylene-1,3-oxazolidine **9**.

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