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Two Alternate Routes for the Preparation of N^1-(2,6-Dimethoxy-4-pyrimidinyl)-sulphanilamide*

S. Kukolja and Z. Cvetnić

Research Department, »Pliva« Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

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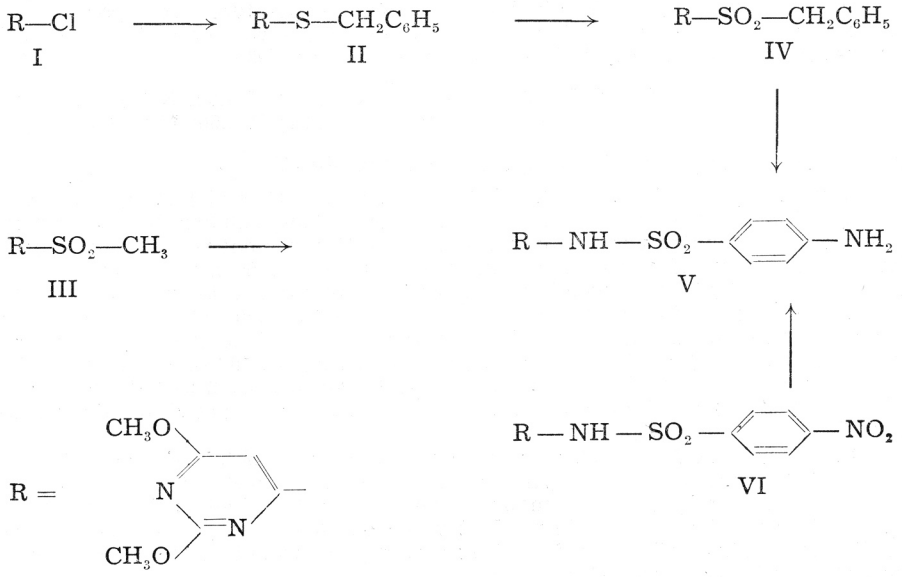
It is well known that N^1-(2,6-dimethoxy-4-pyrimidinyl)-sulphanilamide (V) is a valuable long-acting sulpha drug. This compound was first synthesized by the interaction of sodium sulphanilamide and (2,6-dimethoxy-4-pyrimidinyl) trimethylammonium chloride in molten acetamide by Klötzer and Bretschneider[1]. Later, Bretschneider *et al.*[2] synthesized the same compound by condensation of 4-carbethoxyaminobenzensulphonyl chloride with 2,6-dimethoxy-4-aminopyrimidine in pyridine followed by alkaline hydrolysis of the resulting N^4-carbethoxy derivative. During the work on the present paper Klötzer[3] reported a new route for the preparation of V by displacement of the ethyl- resp. phenylsulphonyl group in the appropriate pyrimidine derivatives by sulphanilamide anion.

In the present paper the preparation of V by two alternate routes according to the reaction scheme I—VI is described. The key intermediates in



* S. Kukolja and Z. Cvetnić, *Yugoslav Patent Application* P 1719, December 1, 1961.

the first synthesis of V were 2,6-dimethoxy-4-methlylsulphonylpyrimidine[4] (III) and 2,6-dimethoxy-4-benzylsulphonylpyrimidine (IV). The latter compound was prepared by treatment of 2,6-dimethoxy-4-chloropyrimidine[5] with sodium benzylmercaptide followed by oxydation of the resulting 4-benzylthiopyrimidine II with performic acid. The methylsulphonyl and benzylsulphonyl groups in III and IV were displaced by interaction with sulphanilamide anion in dimethylformamide similarly as described by Shepherd *et al.*[6] for the preparation of N^1-(6-methoxy-4-pyrimidinyl)sulphanilamide. The second route for the preparation of V was accomplished by condensing 2,6-dimethoxy-4-aminopyrimidine[2] with *p*-nitrobenzensulphonyl chloride in the presence of pyridine. The resulting nitro compound VI was then reduced with iron fillings and hydrochloric acid to the amino compound V.

EXPERIMENTAL

2,6-Dimethoxy-4-benzylthiopyrimidine (II)

To a solution of sodium methoxide, prepared from 2.3 g. (0.1 mole) of sodium and 50 ml. of absolute methanol, 12.4 g. (0.1 mole) of benzylmercaptan was added. After evaporation of the methanol under reduced pressure a solution of 17 g. (0.1 mole) of 2,6-dimethoxy-4-chloropyrimidine[5] in 160 ml. of dry toluene was added to the solid residue. The mixture was refluxed 4 hrs., cooled and filtered. The solvent was removed by evaporation and the crude pale yellow oily product (22.2 g. 84%) purified by distillation at 141°/0.1 mm.

Anal. $C_{13}H_{14}N_2O_2S$ (262.26) calc'd.: C 59.53; H 5.38; N 10.68%
found : C 59.67; H 5.63; N 10.92%

2,6-Dimethoxy-4-benzylsulphonylpyrimidine (IV)

A mixture of 7 g. (0.027 mole) of 2,6-dimethoxy-4-benzylthiopyrimidine, 135 ml. of 88% formic acid and 13.5 ml. of 30% hydrogen peroxide was kept at room temperature for 3 hours. The clear solution was diluted with 150 ml. of water. After standing for several hours at room temperature, the separated colourless needles were filtered off. A crop of 5.8 g. (73%) was obtained, m.p. 98°. For analysis a sample was crystallized from ethanol, m. p. 98°.

Anal. $C_{13}H_{14}N_2O_4S$ (294.26) calc'd.: C 53.06; H 4.80; N 9.52%
found : C 53.21; H 4.50; N 9.49%

N^1-*(2,6-Dimethoxy-4-pyrimidinyl)-sulphanilamide* (V)

Procedure (A). From IV. A mixture of 2.94 g. (0.1 mole) of 2,6-dimethoxy-4--benzylsulphonylpyrimidine, 4 g. (0.02 mole) of sodium sulphanylamide and 20 ml. of dimethylformamide was refluxed for 4 hours. The solvent was removed by distillation under reduced pressure, the residue dissolved in 60 ml. of water and 6 ml. of 2 *N* sodium hydroxide. The suspension was kept for one hour at 0° and filtered. The filtrate was adjusted to *p*H 8 with dilute hydrochloric acid, left at 0° for one hour and the unchanged sulphanilamide removed. Acidification of the filtrate to *p*H 5 afforded 1.2 g. (39%) of a crude product melting at 188—190°. Recrystallization from dilute ethanol yielded colourless crystals melting at 200—201°. This product gave no melting point depression with the substance prepared by the procedure described by Bretschneider *et al*[2].

Procedure (B). From III. The same compound was obtained from 0.85 g. (0.004 mole) of 2,6-dimethoxy-4-methylsulphonylpyrimidine[4], 1.6 g. (0.008 mole) of sodium sulphanilamide and 10 ml. of dimethylformamide as described in the previous experiment. The yield of the crude product was 0.6 g. (50%), m. p. 193—195°. Recrystallization from dilute ethanol raised the melting point to 201—203° and no depression was observed with a mixed specimen.

Procedure (C). From VI. A mixture of 2.9 g. (0.0085 mole) of 2,6-dimethoxy-4-*p*--nitrobenzensulphonylpyrimidine, 4 g. of iron fllings, 0.5 ml. of concentrated hydro-

chloric acid and 60 ml. of 50% ethanol was refluxed with stirring during 2 hours. After evaporation of the solvent, the residue was alkalized with sodium hydroxide solution, treated with charcoal and filtered. Acidification of the filtrate to *pH* 6 yielded 1.4 g. of the product, m. p. 198°. Recrystallization from dilute ethanol gave colourless crystals, m. p. 202°. It gave no depression of m. p. when mixed with a specimen prepared as described under (A) and (B).

2,6-Dimethoxy-4-p-nitrobenzensulphonylaminopyrimidine (VI)

2.2 g. (0.014 mole) of 2,6-dimethoxy-4-aminopyrimidine[2] was added to 5 ml. of dry pyridine followed by 4.4 g. (0.02 mole) of *p*-nitrobenzensulphonyl chloride[7]. After heating at 50—60° for 30 minutes, the mixture was cooled and 140 ml. of water added. After keeping overnight in a refrigerator the yellow precipitate was filtered off and purified by dissolution in a dilute sodium hydroxide solution, treatment with charcoal and filtration. Acidification of the filtrate to *pH* 4.5 yielded 2.9 g. (60%) of yellow crystals melting at 155°. Recrystallization from ethanol gave colourless needles, m. p. 162°.

Anal. $C_{12}H_{12}N_4O_6S$ (340.25) calc'd.: C 42.36; H 3.50; N 16.47%
found: C 42.63; H 3.77; N 16.27%

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IZVOD

Dvije sinteze N^1-(2,6-dimetoksi-4-pirimidinil)-sulfanilamida

S. Kukolja i Z. Cvetnić

N^1-(2,6-Dimetoksi-4-pirimidinil)-sulfanilamid (V) pripravljen je redukcijom 2,6-dimetoksi-4-*p*-nitrobenzensulfonamidopirimidina (VI), a također i supstitucijom 4-alkilsulfonil grupa sa sulfanilamidnim anionom u odgovarajućim pirimidinskim derivatima III i IV.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH
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