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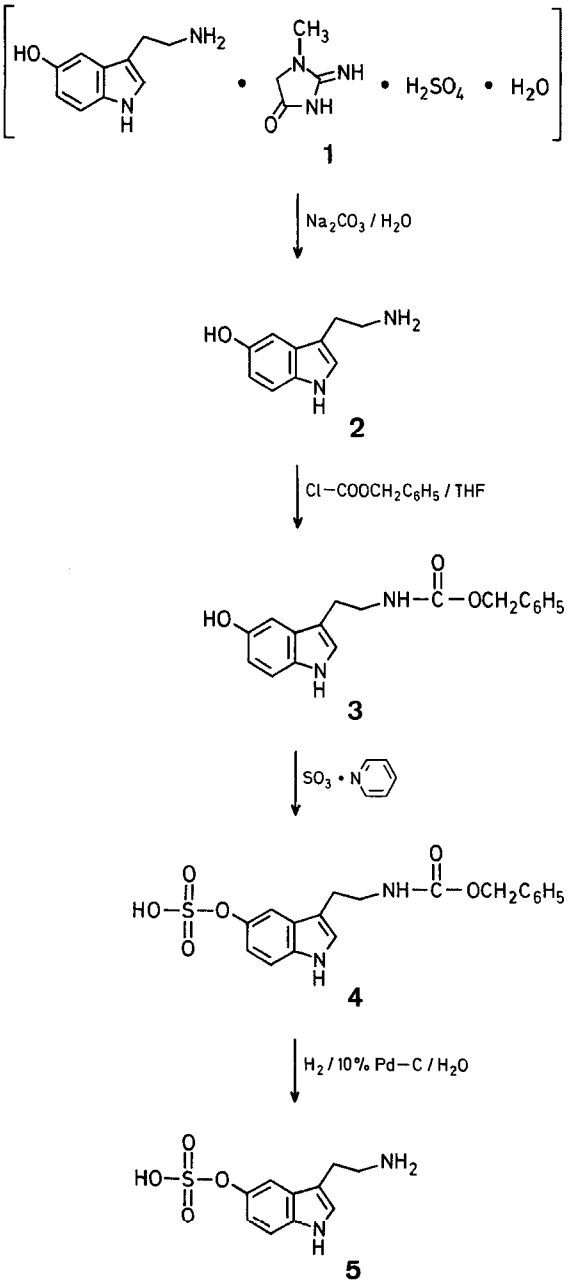
A Practicable Synthesis of 3-(2-Aminoethyl)-1*H*-indol-5-yl Hydrogen Sulfate (Serotonin *O*-Sulfate)

Janos BORGULYA, Karl BERNAUER*

Pharmaceutical Research Department, F. Hoffmann-La Roche & Co., Ltd., CH-4002 Basle, Switzerland

The title compound **5** is formed in the mammalian organism as a metabolite of serotonin **(2)**[1]. It is excreted in the urine. In the urine of carcinoid patients the level of **5** is significantly increased[2]. Enzyme preparations from e.g. brain[3], liver[4], and platelets[5] have been shown to catalyze the transformation **2**→**5**. In relevant biochemical studies, pure **5** is needed, e.g. as an analytical standard. A non-enzymatic synthesis of **5** by direct sulfation of serotonin **(2)** with chlorosulfonic acid/sulfuric acid was described in 1961[6], but no melting point is given for **5**, and the yield is low. Several studies published later in which **5** has been made use of, refer to that paper without giving additional data regarding to yield or physical properties of **5**.



For our own studies, we have developed a simple, three-step synthesis starting from **2**, making **5** easily available: the primary amino group of **2** is first blocked by benzyloxycarbonylation (**2**→**3**; 82%)[7]. Subsequently, the phenolic hydroxy group of **3** is sulfatized by sulfur trioxide/pyridine (**3**→**4**; 83%). Finally, the protecting group of **4** is removed by catalytic hydrogenation, affording the analytically pure hydrogen sulfate ester **5** as colourless crystals in 49% yield.

Benzyl [2-(5-Hydroxyindol-3-yl)-ethyl]carbamate (Z-Serotonin; 3)[7]**:**
To a vigorously stirred suspension of serotonin creatinine sulfate (**1**; 8.1 g, 20.0 mmol; obtained from Fluka AG) in tetrahydrofuran (50 ml) and water (100 ml) is added under a nitrogen atmosphere simultaneously dropwise over a period of 30 min at room temperature a solution of sodium carbonate (7.0 g, 66.0 mmol) in water (45 ml) and benzyl carbonochloridate (8.5 g, 50.0 mmol) in tetrahydrofuran (20 ml). After the addition, the suspension changes into a emulsion (pH ~9). The reaction mixture is stirred for 60 min and then extracted with ether (3 × 100 ml). The ether solution is washed with brine (3 × 100 ml), dried with sodium sulfate, and filtered; the filtrate is treated with speedex/charcoal, filtered again, and evaporated. The product is crystallized from ether/petroleum ether (30–60 °C) to give white crystals of **3**; yield: 3.9 g (63%); m.p. 100–102 °C.

$C_{18}H_{18}N_2O_3$	calc.	C 69.66	H 5.85	N 9.03
(310.3)	found	69.60	5.73	8.96

The yield of the product can be improved by renewed treatment of the combined water reaction mixture and brine with sodium carbonate (3.2 g, 30.0 mmol) and benzyl carbonochloridate (3.4 g, 20.0 mmol). The crude product obtained by ether extraction yielded upon crystallization as above an additional 1.2 g (19%) of pure **3**.

3-[2-(Benzyloxycarbonylamino)-ethyl]-1*H*-indol-5-yl Hydrogen Sulfate (Z-Serotonin *O*-Sulfate; 4):
To a stirred suspension of pyridine/sulfur trioxide complex (11.1 g, 69.7 mmol) in dry pyridine (70 ml) is added in portions under nitrogen benzyl [2-(5-hydroxyindol-3-yl)-ethyl]carbamate (**3**; 7.2 g, 23.2 mmol) over a 20 min period. Stirring is continued for 19 h at room temperature. After removal of the pyridine under reduced pressure, water (200 ml) is added, and the emulsion extracted with ether (3 × 50 ml). The ether extract is discarded and the emulsion layer is extracted further with chloroform (3 × 50 ml), whereby the partly soluble product separates as an oil in the chloroform layer. The combined chloroform extracts with the oily material are dissolved in acetonitrile (100 ml), the turbid solution is filtered, and the solvent distilled off in vacuo. After evaporation with toluene (2 × 50 ml), the crude product **4** is obtained as an oil, which is used without further purification in the next step; yield: 7.5 g (83%).

3-(2-Aminoethyl)-1*H*-indol-5-yl Hydrogen Sulfate (Serotonin *O*-Sulfate; 5):
The crude **4** (7.4 g, 18.95 mmol) is hydrogenated in water (75 ml) over 10% palladium-carbon (750 mg) as catalyst at room temperature for 20 h. The reaction mixture is filtered, the filtrate concentrated to a volume of 15 to 20 ml, and the product crystallized at 5 °C. After filtra-

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tion and drying over sodium hydroxide one obtains white crystals of **5**; yield: 2.4 g (49%); m.p. 192–194 °C.

$C_{10}H_{12}N_2O_4S$	calc.	C 46.87	H 4.72	N 10.93	S 12.51
(256.3)	found	46.56	4.57	10.68	12.41

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