Experimenteller Teil

MS: LKB Producter 2091 bei 20 und 70 eV. Probeneinlaßtemp.: 80–200°, Ionenquellentemp.: konstant 260°.

Die Darstellungen und die Stabilitäten bzw. Reaktivitäten der vermessenen Verbindungen **3** und **5** sind von uns in Lit.[1,2,5] beschrieben.

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Kurzmitteilungen

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Preparation of 4-Methylaminobenzoic acid from Anaesthesin® (4-aminobenzoic acid ethyl ester) via Phase-Transfer Methylation of its Amino group

Herstellung von 4-Methylaminobenzoesäure aus Anaesthesin® (4-Aminobenzoesäureethylester) durch Phasentransfer-Methylierung seiner Aminogruppe

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4-Methylaminobenzoic acid **(1)** is a key substrate in the preparation methods of methotrexate. Several reports have appeared recently about the properties of **1**. *Findlay*[1] found that **1** is a protector against sunburn with a photoprotective index 707. *Cerrati*[2] proved the protecting properties of **1** against the toxic effects of hyperbaric oxygen. According to *Bertelli*[3] **1** (500 mg/kg orally) provided 100 % protection against α-amanitin poisoning. *Rimmer*[4] found that radiopharmaceuticals can be stabilized by **1** or its salts. Finally, in 1980 *Weissflog*[5] observed liquid-crystalline properties of **1**.

1 is known for dozens of years. The preparation procedure of **1** is based on nonselective N-methylation of 4-aminobenzoic acid (which is therefore contaminated with the N,N-dimethyl derivative) and separation of the mixture obtained by e.g. N-nitrozation of the monomethyl derivative[6][7]. In 1977 *Suster* applied that method for preparation of **1** from anaesthesin® but the procedure seemed to be rather laborious[8]. *Cosulich*[9] N-formylated the amino group of p-aminobenzoic acid and reduced the formylamino moiety by zinc powder. *Sekiya*[10] found that catalytic hydrogenation of N-amidomethyl derivatives resulted in cleavage of the binding between the methylene C-atom and the amide-N. **1** was produced by that way in 84–97 % yield. A disadvantage of that method is the high pressure (80 atm H_2 at 115–135°). Other productions of **1** use 4-bromo-N-methylaniline (*Gilman*[11]) or 4-chlorobenzoic acid (*Emerson*[12]).

We intended to use phase-transfer methylation of anaesthesin® after foregoing acetyl protection of its amino group. This method seemed to be suitable for a large scale production. N-acetylanaesthesin is well known (*Laakso*[13]), but N-acetyl-N-methylanaesthesin is – to our knowledge – unknown until now. In 1973 *Benkovic*[14] produced the analogous N-formylderivative by N-formylation of N-methylanaesthesin. The protective acetyl group can easily be removed during hydrolysis of the ester group. The total yield of our procedure is about the same as given by *Suster*[8].

Experimental part

Apparatus and reagents: Mps: Büchi. – ^{1}H-NMR: Bruker WP 100 SY. – IR: Zeiss-UR-20 (values for solid state). – UV: Pay-Unicam SP-8000. – Elemental analysis: *Heraeus-Mikro*. – TLC: solvent benzene-dioxane-acetic acid (90 : 25 : 4), layer silica gel GF-254 Merck, spray reagent I_2, bromocresol green.

Ethyl N-acetyl-N-methyl-4-aminobenzoate

To 21.5 g ethyl N-acetyl-4-aminobenzoate[13] (0.1 mole), 10.2 g 60 % aqueous NaOH, 4.7 g benzyltriethylammonium chloride (TEBA) and 150 ml benzene 14.6 ml dimethyl sulphate were dropped within 1 h. The temp. spontaneously raised to 40° and stirring was continued at this temp. for 4 h. Then 100 ml water was added and the mixture was separated. The organic layer was washed 4 × with dil. HCl and then with water, 2 g charcoal was added, the mixture stirred for 15 min and filtered. The organic layer was concentrated to remove the benzene. The remaining oil crystallized: pink-yellow solid (21.5 g, 85 % yield). Purification by tripled recrystallization from petroleum ether, m.p. 55–56°. $C_{12}H_{15}NO_3$ calc. C 65.1 H 6.8 N 6.3; found C 65.1 H 7.1 N 6.3. – TLC: Rf = 0.68. – ^{1}H-NMR: ($CDCl_3$-TMS): 1.33–1.48 (t, 3H, CH_3), 1.93 (s, 3H, $COCH_3$), 3.30 (s, 3H, NCH_3), 4.29–4.51 (q, 2H, CH_2), 7.23–8.14 (m, 4H, aromat.). – IR: 870–890; 1670; 1725; 2900–3000 cm^{-1}. – UV (EtOH): λmax 256 nm, $a\ ^{1\,\%}_{1\,cm}$ = 415.

4-Methylaminobenzoic acid **(1)**

22.8 g (0.1 mole) crude ethyl N-acetyl-N-methyl-4-aminobenzoate and 50 ml HCl (1 : 1) were heated to 90–92° for 4 h, 7 ml ethanol was removed. 2 g charcoal was added, the heating continued for 30 min,

and the hot mixture was filtered. After cooling to 0–10° a yellow precipitate of 4-methylaminobenzoic acid-HCl was obtained. The precipitate was suspended in 40 ml water, cooled below 10° and alkalized with 32.8 g 25 % aq. NaOH. 0.8 g charcoal was added and the mixture stirred for 30 min below 10° and filtered. Then 5.6 ml glacial acetic acid was added and the mixture stirred for 1.5 h at 10°. The precipitate was twice washed with 10 ml water and dried to give 10.0 g white crystals (64.2 % yield). This crude product (m.p. 160–162°) was twice recrystallized from benzene. M.p. 158.5–160.5° (lit.[5] 160–162°). – TLC: Rf = 0.75. – $C_8H_9NO_2$ calc. C 63.6 H 6.0 N 9.3; found: C 63.8 H 6.3 N 9.3. – ^{1}H-NMR/ ($CDCl_3$-TMS): 2.90 (s, 3H, NCH_3), 6.52–7.89 (m, 4H, aromat.). – IR: 840; 1680; 2400–3200; 3390–3440 cm^{-1}. – UV (EtOH): λmax 299 nm, a $^{1\,\%}_{1\,cm}$ = 1534.

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