

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.

Literatur

- 1 E. Akgün, U. Pindur und J. Müller, *J. Heterocyclic Chem.* **20**, 1303 (1983).
- 2 J. Müller und U. Pindur, *Arch. Pharm. (Weinheim)* **317**, 555 (1984).
- 3 U. Pindur und J. Müller, *Chimia* **39**, 141 (1985).
- 4 U. Pindur und J. Müller, *Chem.-Ztg.* **108**, 150 (1984).
- 5 Dissertation J. Müller, Würzburg 1986.
- 6 J. Bergmann, *J. Heterocyclic Chem.* **8**, 329 (1971).
- 7 R. Naef, *Dyes and Pigments* **2**, 57 (1981).
- 8 W. Massa, U. Pindur, J. Müller und T. Kämpchen, Publikation in Vorbereitung.
- 9 W.A. Remers, *Indoles, Part I*, Hergsb.: W.J. Houlihan, S. 41, Wiley-Interscience, New York 1971.
- 10 Q.N. Porter und J. Baldas, *Mass Spectrometry of Heterocyclic Compounds*, Wiley-Interscience, New York 1971.
- 11 U. Pindur, J. Müller und L. Pfeuffer, *Monatsh. Chem.* **116**, 365 (1985).

[Ph 135]

Kurzmitteilungen

Arch. Pharm. (Weinheim) **319**, 862–864 (1986)

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

Herstellung von 4-Methylaminbenzoesäure aus Anaesthesin® (4-Aminobenzoessäureethylester) durch Phasentransfer-Methylierung seiner Aminogruppe

Włodzimierz Skupiński, Lidia Pichnej, Ryszard Pakuła, Wanda Jahn-Andrychowska, Zofia Trojanowska, Karol Butkiewicz*

Institute of Pharmaceutical Industry, 8 Rydygiera St., 01-793 Warsaw, Poland
Eingegangen am 11. März 1986

4-Methylaminobenzoic acid (**1**) is a key substrate in the preparation methods of methotrexate. Several reports have appeared recently about the properties of **1**. Findlay¹⁾ found that **1** is a protector against sunburn with a photoprotective index 707. Cerrati²⁾ proved the protecting properties of **1** against the toxic effects of hyperbaric oxygen. According to Bertelli³⁾ **1** (500 mg/kg orally) provided 100 % protection against α -amanitin poisoning. Rimmer⁴⁾ found that radiopharmaceuticals can be stabilized by **1** or its salts. Finally, in 1980 Weissflog⁵⁾ 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-nitroization 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 laborious⁸⁾. Cosulich⁹⁾ N-formylated the amino group of p-aminobenzoic acid and reduced the formylamino moiety by zinc powder. Sekiya¹⁰⁾ 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 H₂ at 115–135°). Other productions of **1** use 4-bromo-N-methylaniline (Gilman¹¹⁾) or 4-chlorobenzoic acid (Emerson¹²⁾).

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-acetylnaesthesin is well known (Laakso¹³⁾), but N-acetyl-N-methylanaesthesin is – to our knowledge – unknown until now. In 1973 Benkovic¹⁴⁾ produced the analogous N-formyl derivative 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 Suster⁸⁾.

Experimental part

Apparatus and reagents: Mps: Büchi. – ¹H-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 J₂, bromocresol green.

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

To 21.5 g ethyl N-acetyl-4-aminobenzoate¹³⁾ (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°. C₁₂H₁₅NO₃ calc. C 65.1 H 6.8 N 6.3; found C 65.1 H 7.1 N 6.3. – TLC: R_f = 0.68. – ¹H-NMR: (CDCl₃-TMS): 1.33–1.48 (t, 3H, CH₃), 1.93 (s, 3H, COCH₃), 3.30 (s, 3H, NCH₃), 4.29–4.51 (q, 2H, CH₂), 7.23–8.14 (m, 4H, arom.). – IR: 870–890; 1670; 1725; 2900–3000 cm⁻¹. – UV (EtOH): λ_{\max} 256 nm, $a_{1\%}^{1\text{cm}}$ = 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 alkalinized 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: R_f = 0.75. – C₈H₉NO₂ calc. C 63.6 H 6.0 N 9.3; found: C 63.8 H 6.3 N 9.3. – ¹H-NMR/ (CDCl₃-TMS): 2.90 (s, 3H, NCH₃), 6.52–7.89 (m, 4H, arom.). – IR: 840; 1680; 2400–3200; 3390–3440 cm⁻¹. – UV (EtOH): λ_{max} 299 nm, a $\frac{1\%}{1\text{ cm}}$ = 1534.

References

- 1 G. Findlay, Br. J. Dermatol. Suppl. 1971, 7, 44 (1971); C.A. 76, 121420q (1972).
- 2 A. Cerrati, Minerva Med. 67, 2449 (1976); C.A. 85, 172511p (1976).
- 3 A. Bertelli, Curr. Probl. Clin. Biochem. 1977, VII Clin. Exp. Aspects Fungal Poisoning, Int. Symp. 75; C.A. 88, 84314h (1978).
- 4 J. Rimmer, Eur. Pat. Appl. EP 78642 (11.05.1983); C.A. 99, P. 76871z (1983).
- 5 W. Weissflog, Z. Chem. 20, 259 (1980).
- 6 J. Houben, Ber. Dtsch. Chem. Ges. 42, 3739 (1909).
- 7 A. R. Surey, J. Am. Chem. Soc. 66, 2127 (1944).
- 8 D. C. Suster, Rev. Roum. de Chimie 22, 1195 (1977).
- 9 D. B. Cosulich, J. Am. Chem. Soc. 70, 1922 (1948).
- 10 M. Sekiya, Chem. Pharm. Bull. 14, 1007 (1966).
- 11 H. Gilman, J. Am. Chem. Soc. 71, 2933 (1949).
- 12 W. S. Emerson, J. Am. Chem. Soc. 73, 1299 (1951).
- 13 P. V. Laakso, Tetrahedron 1, 103 (1957).
- 14 B. J. Benkovic, J. Am. Chem. Soc. 95, 8414 (1973).

[KPh 398]

© VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1986 – Printed in the Federal Republic of Germany
Verantwortlich für die Redaktion: Prof. Dr. W. Wiegrebe, Pharmazeutisches Institut der Universität Regensburg, Universitätsstr. 31, Postfach 397, D-8400 Regensburg – Anzeigenleitung: R. J. Roth, D-6940 Weinheim – VCH Verlagsgesellschaft mbH (Geschäftsführer: Prof. Dr. Helmut Grünwald und Hans Dirk Köhler), Postfach 1260/1280, D-6940 Weinheim – Alle Rechte, insbesondere die der Übersetzung in fremde Sprachen, vorbehalten. Kein Teil dieser Zeitschrift darf ohne schriftliche Genehmigung des Verlages in irgendeiner Form – durch Photokopie, Mikrofilm oder irgendein anderes Verfahren – reproduziert oder in eine von Maschinen, insbesondere von Datenverarbeitungsmaschinen verwendbare Sprache übertragen oder übersetzt werden. – All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers. – Von einzelnen Beiträgen oder Teilen von ihnen dürfen nur einzelne Vervielfältigungsstücke für den persönlichen und sonstigen eigenen Gebrauch hergestellt werden. Die Weitergabe von Vervielfältigungen, gleichgültig zu welchem Zweck sie hergestellt werden, ist eine Urheberrechtsverletzung. – Die Wiedergabe von Gebrauchsnamen, Handelsnamen, Warenbezeichnungen u. dgl. in dieser Zeitschrift berechtigt nicht zu der Annahme, daß solche Namen ohne weiteres von jedermann benutzt werden dürfen. Es handelt sich häufig um gesetzlich eingetragene Warenzeichen, auch wenn sie in dieser Zeitschrift nicht als solche gekennzeichnet sind. – Satz: Hans Richarz, Publikationsservice, Sankt Augustin. – Unverlangt zur Rezension eingehende Bücher werden nicht zurückgesandt.

Valid for users in the USA: The appearance of the code at the bottom of the first page of an article in this journal (serial) indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that copier pay the stated percopy fee through the Copyright Clearance Center, Inc., for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective work, or for resale. For copying from back volumes of this journal see »Permissions to Photo-Copy: Publisher's fee List« of the CCC.