

Schwefligsäuredi-{6a-hydroxy-6H,7H,12aH-[1]-benzopyran[4,3-b]-[1]-benzopyran}ester (11)

2 g **10a** wurden in 40 ml absol. Pyridin gelöst und nach Zugabe von 5 ml SOCl_2 12 h bei 0° gerührt, das Reaktionsgemisch wurde in Eis gegossen, das abgeschiedene Produkt getrocknet und aus Benzol-Petrolether umkristallisiert. Man erhält 1 g farbloses kristallines Produkt mit Schmp. $173\text{--}174^\circ$. $\text{C}_{32}\text{H}_{26}\text{O}_7\text{S}$ (554.3). Ber.: C 67.3 H 4.69 S 5.8; Gef.: C 69.4 H 4.75 S 5.9.

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New Findings in the Synthesis of Metoclopramide

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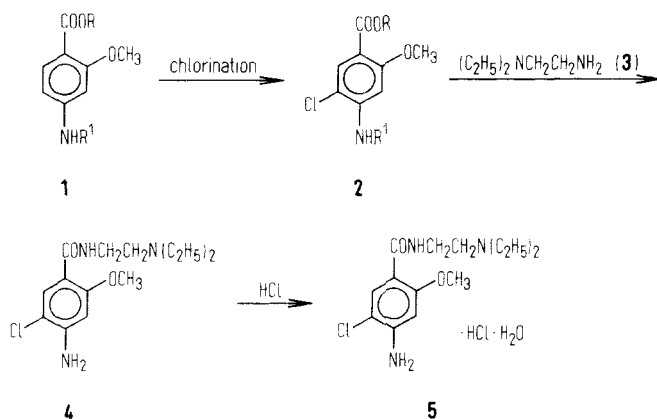
New technologically useful procedures for the chlorination and condensation processes in the synthesis of Metoclopramide are described. Sodium hypochlorite (or potassium perchlorate + HCl) in aq. acetic acid are used as agents for the chlorination of **1**. The condensation of **2** with **3** is carried out in the presence of acetic acid as a catalyst.

Neue Befunde zur Synthese von Metoclopramid

Neue technologisch nützliche Arbeitsverfahren für die Chlorierung und die Kondensation bei der Synthese von Metoclopramid werden beschrieben. Natriumhypochlorid (oder Kaliumperchlorat + HCl) werden als Chlorierungsmittel von **1** angewendet, und die Kondensation von **2** mit **3** wird in Essigsäure (als Katalysator) durchgeführt.

Metoclopramide (MCP) is widely used in therapy as an antiemetic. Many different routes for the synthesis of MCP have been described, almost exclusively in the patent literature; consequently, it is impossible to refer the methods exhaustively in this report. A review of the patent literature indicates, however, that substantial problems of the synthesis concern the chlorination and condensation processes (Scheme 1). This report describes new simple and technologically useful procedures for both of the processes.

Scheme 1



$\text{R} = \text{CH}_3$ (or H , another alkyl) ; $\text{R}^1 = \text{COCH}_3$ (or H , another acyl)

Although **2** may be synthesized either from starting materials containing chlorine in the benzene ring (e. g. 3-amino-4-chlorophenol)¹⁾ or by chlorination of a suitable amino-methoxy derivative of benzene (e. g. methyl 4-amino-2-methoxybenzoate (**1**)), the last procedure is much more frequently used in practice.

Many various media and chlorination agents have been proposed to obtain **2** from **1** in a good yield. However, a selective chlorination of **1** in position 5 makes the most important problem of the reaction. For example, when gaseous chlorine is used as a chlorination agent many side reactions occur. The selectivity of the chlorination of **1** in position 5 can be secured when having regard to steric effects the molecule of the chlorination agent is large enough. According to Murakami et al.²⁾ iodobenzene dichloride in various anhydrous organic solvents at temperatures below room temperature makes it possible to chlorinate **1** selectively in position 5 without a need of the protection of its amino group.

Similar steric effect can be achieved by protection of the amino-group of **1** (in position 4) with an acylating agent of a large molecule (e. g. phthalic acid derivative³⁾).

Kodama et al.⁴⁾ used a hypochlorite (i. e. tert-butyl hypochlorite) for the chlorination of **1** and then, they condensed **2** with **3** in the presence of $\text{Et}_2\text{P}(\text{O})\text{Cl}$. Unexpectedly, we have found that **2** can be easily obtained in a good yield by chlorination of **1** (in acetyl form) with

NaOCl (or $\text{KClO}_3 + \text{HCl}$) in aq. acetic acid at a temperature below 20°C . Glacial acetic acid was already proposed as a medium for the chlorination process⁵). The selective chlorination of **1** in position 5 using NaOCl is very interesting in view of the fact that when p-aminosalicylic acid is chlorinated with gaseous chlorine, 4-amino-3-chlorosalicylic acid and 4-amino-3,5-dichlorosalicylic acid are obtained in low yields and 4-amino-5-chlorosalicylic acid is scarcely obtained²). The use of NaOCl as a chlorination agent simplifies considerably the chlorination process (with regard to the fact that it is carried out in an aqueous medium) and consequently, makes the process more economic. The analytical control of the chlorination is also very simple when NMR spectrometry is used for this purpose (see experimental). These findings are very important from the technological point of view.

A representative preparation method of MCP is the condensation of **2** with an excess of N,N-diethylethylenediamine (**3**). However, according to Clinton et al.⁶) the condensation gives MCP in a low yield. Thus, other authors use catalysts of the reaction (e. g. Lewis acids: SiCl_4 , GeCl_4 , SnCl_4 etc. ⁷) or activate the amino-group of **3** (e. g. using phosphorus compounds^{2,4}) to obtain MCP in a good yield.

We have found that the use of acetic acid as a catalyst of the condensation improves the reaction conditions and makes it possible to obtain a high-purity product in a good yield. When using acetic acid as a catalyst it is possible to reduce the condensation time and the excess of **3** as well to lower the temperature of the reaction.

MCP is precipitated from the reaction mixture in the form of the free base **4** and then, it is transformed into the hydrochloride **5**. Usually, the transformation is carried out in an anhydrous medium by the use of gaseous HCl; thus, this procedure is rather complicated. We have established that hydrochloride of MCP can be simply obtained when MCP-base is treated with hydrochloric acid in water-containing acetone. The use of hydrochloric acid for the preparation of MCP hydrochloride eliminates the necessity of the work in anhydrous solvents and consequently, simplifies the process and makes it more economic.

Experimental

Melting points: apparatus Tottoli (uncorr.); *NMR spectra:* Jeol (Japan) JNM-C-60HL spectrometer; *elemental analysis:* $\text{C}_9\text{H}_9\text{N} + \text{O}$ automatic analyzer, model 1102, Carlo Erba (Italy)..

Methyl 4-acetamino-5-chloro-2-methoxybenzoate (**2**)

a. 36.2 g (0.2 mole) of methyl 2-methoxy-4-aminobenzoate²) were suspended in 100 ml H_2O , 32 ml (about 0.3 mole) of acetic anhydride were added, and the mixture was stirred for 30 min at room temp. and then, at $60\text{--}70^\circ\text{C}$ for 1 h to give methyl 2-methoxy-4-acetaminobenzoate. The solution of the benzoate was cooled and 180 ml of aq. solution of sodium hypochlorite (containing 0.22 mole of NaOCl) were added dropwise at a temp. below 20°C . Next, the mixture was stirred for 1 h, the precipitate was washed with water, and dried to give a crude product (41.5 g) in a yield of 80 %. The product was recrystallized from methanol to give **2**, m. p. $153\text{--}155^\circ\text{C}$.

$C_{11}H_{12}NO_4Cl$ Calcd.: C 63.0 H 5.77 N 6.7 Cl 16.9; Found: C 63.1 H 5.92 N 6.9 Cl 17.0. NMR (10 % solution in CD_3SOCD_3 , TMS) δ (ppm) = 2.18 (s, 3H), 3.82 and 3.84 (2s, $2 \times 3H$), 7.89 (s, 1H), 8.03 (s, 1H), and 9.62 (s, 1H).

b. 36.2 g (0.2 mole) of methyl 2-methoxy-4-aminobenzoate, 32 ml (0.3 mole) of acetic anhydride, and 100 ml of glacial acetic acid were heated at 55–60°C for 1 h to give a solution of methyl 2-methoxy-4-acetaminobenzoate. The solution was cooled to room temp., 27 ml (0.3 mole) of concentrated hydrochloric acid were added, and then, a solution containing 7.2 g (0.07 mole) of potassium chlorate in 30 ml H_2O was added dropwise at such a rate as to keep temp. of the reaction mixture below 30°C. The whole was stirred for 15 min, 0.5 l of H_2O were added, and the precipitated **2** was washed with water, and dried to give a crude **2** (about 70 g), m. p. 152–155°C, in a yield of 70 %. Found: C 62.9 H 5.87 N 6.8 Cl 17.1.

Metoclopramide (**4**)

51.5 g (0.2 mole) of **2**, 69 g (0.6 mole) of N,N-diethylethylenediamine (**3**), and 6 g of glacial acetic acid were heated under stirring at 90–95°C for 4 h and then, 400 ml of H_2O and 40 g of NaOH were added. The mixture was steam distilled to separate the excess of **3** and to deacetylate the amino-group. Next, the mixture was cooled to room temp. and the precipitate was washed with H_2O to give crude **4** (48 g), m. p. 146.5–148°C, in a yield of 86 %.

$C_{14}H_{22}N_3O_2Cl$ Calcd.: C 56.1 H 7.40 N 14.0 Cl 11.8; Found: C 56.3 H 7.56 N 14.0 Cl 11.6.

Metoclopramide hydrochloride (**5**)

60 g of **4** were suspended in a mixture containing 12 ml of H_2O and 22.5 ml of acetone and the suspension was treated with 15 ml of concentrated hydrochloric acid until the precipitate dissolved (pH 5.5–5.9). Then, 300 ml of acetone were added and the precipitate was washed with acetone to give monohydrate of MCP hydrochloride (54 g), m. p. 182.5–184°C, in a yield of 76 %. The filtrate was neutralized and 16 % of **4** was recovered and recycled.

$C_{14}H_{25}N_3O_3Cl_2$ Calcd.: C 47.4 H 7.12 N 11.9 Cl 20.0; content of H_2O 5.1. Found: C 47.6 H 7.36 N 12.0 Cl 19.9 content of H_2O determined by K. Fischer method 4.96.

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