[Chem. Pharm. Bull. 19(8)1696—1699(1971)]

UDC 547.551.51.07 : 615.243.6.011.5

An Improved Synthesis of Metoclopramide

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(Received March 4, 1971)

This report relates to a new industrial synthesis of metoclopramide (I). Methyl 4-amino-2-methoxybenzoate (V) was prepared by methylation of *p*-aminosalicylic acid (III) using dimethyl sulfate in the presence of potassium hydroxide in acetone. V and it's saponified product (VI) were chlorinated with iodobenzene dichloride to obtain methyl 4-amino-5-chloro-2-methoxybenzoate (VII) and 4-amino-5-chloro-2-methoxybenzoic acid (VIII) respectively. VIII was also prepared by saponification of VII. VIII was condensed direct with N,N-diethylethylenediamine (IV), of which amino group was activated by phosphorus trichloride, whereby I was obtained in high yields.

Metoclopramide (I) is a very important compound which is widely used as an antiemetic. Many different routes for the synthesis of I have been reported.[2-8] Representative methods among them are as follows[2,4]; 4-acetamido-5-chloro-2-methoxybenzoic acid (IIa) or it's alkyl ester (IIb) was first synthesized using 3-amino-4-chlorophenol[9] or *p*-aminosalicylic acid (III), and IIa was converted to it's acid chloride derivative (IIc). Then IIb or IIc was condensed with N,N-diethylethylenediamine (IV) to prepare N-acetyl derivative of I, which produces I by hydrolysis. However, many problems were involved in these methods. For example, not only many steps were required and the yield of each step was not so well, but also protection of the amino group during the synthesis and removal of the protecting group at the final stage were indispensable.

This report describes a new industrial method for the synthesis of I and some interesting knowledges which were found during the investigation. The synthetic scheme found in this study is shown in Chart 1.

Synthesis of methyl 4-amino-2-methoxybenzoate (V) had been reported by Grimme, *et al.*[10] and Clinton, *et al.*[11] However, they did not succeed to synthesize V by methylating *p*-aminosalicylic acid (III) with methyl iodide or dimethyl sulfate, because the free amino group of III was easily methylated by these reagents.[12] Recently, Morimoto, *et al.*[13] reported that methyl 4-amino-5-chloro-2-methoxybenzoate (VII) could be synthesized by methylation of 4-amino-5-chlorosalicylic acid.[9] We investigated how to synthesize V by the methylation of III without protecting the amino group. It was found that V could be easily synthesized

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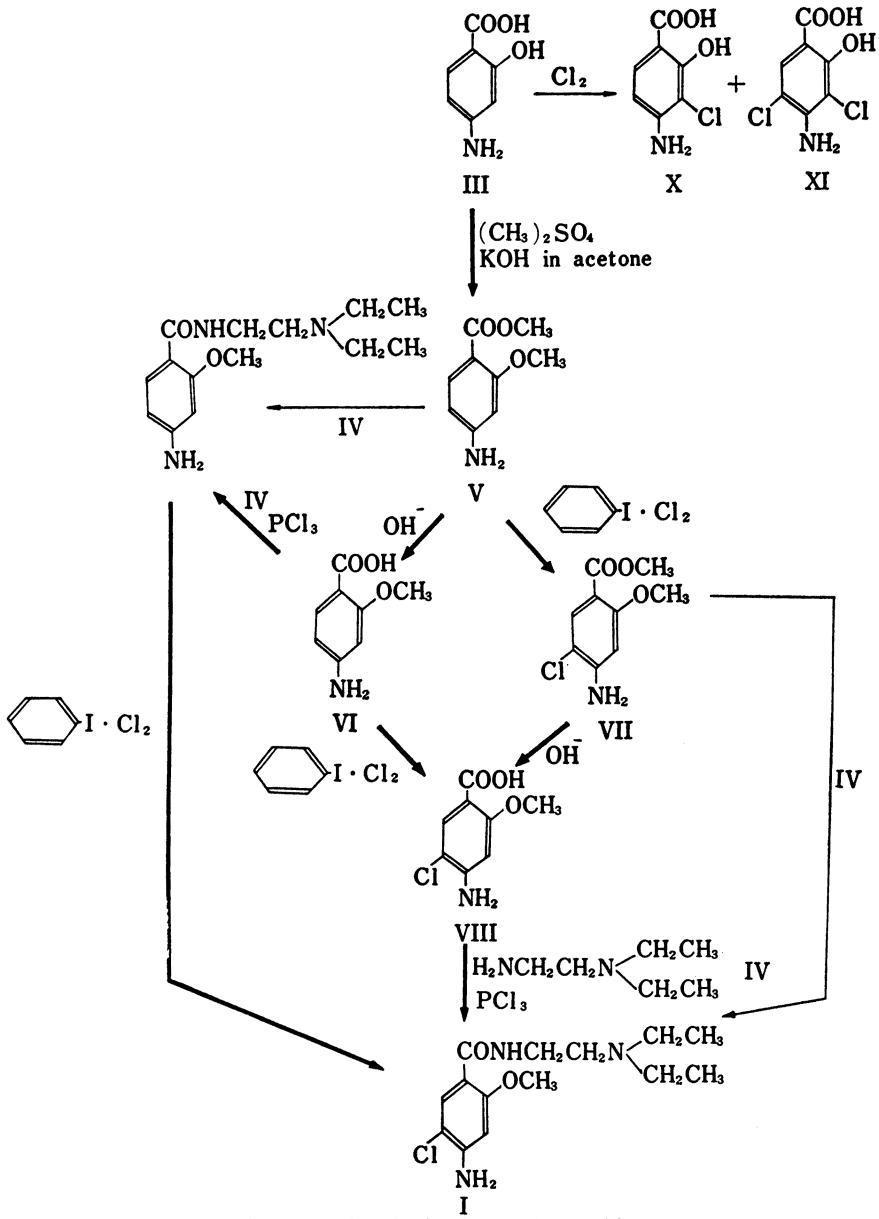

Chart 1. Synthesis of Metoclopramide

in high yields by methylation of III with dimethyl sulfate in acetone at room temperature in the presence of caustic alkali. During this reaction, N-methylation of V was scarecely observed. Saponification of V gave easily 4-amino-2-methoxybenzoic acid (VI).

Methyl 4-amino-5-chloro-2-methoxybenzoate (VII) had been prepared *via* chlorination of methyl 4-acetamido-2-methoxybenzoate with chlorine gas.[3] However, chlorination of V without protecting the amino group has not been reported yet. We studied the chlorination of V in detail under various conditions using various chlorinating reagents. It was consequently found that VII was easily obtained in satisfactory yields when V was treated with iodobenzene dichloride in an organic solvent, such as acetone, tetrahydrofuran, acetonitrile or chloroform, at temperatures below room temperature. On the other hand, when chlorine

gas was used for the same purpose, many side reactions occurred. Similarly, VI and 4-amino-2-methoxy-N-(2-diethylaminoethyl)-benzamide (XII) were chlorinated selectively at 5-position with iodobenzene dichloride, whereby VIII and I were obtained respectively in satisfactory yields. VIII was also prepared from VII by saponification. Such result of our investigation is particularly surprising in view of the fact that the mono-chlorination of benzene ring of aniline derivatives was difficult unless the amino group of them was protected on account of producing several unknown compounds.[14,15] Further, the selective chlorination at 5-position of V and VI using iodobenzene dichloride is very interesting in contrast with the following facts; when *p*-aminosalicylic acid (III) is chlorinated with chlorine gas, 4-amino-3-chlorosalicylic acid (X) and 4-amino-3,5-dichlorosalicylic acid (XI) are obtained in low yields and 4-amino-5-chlorosalicylic acid is scarcely obtained.[16]

Metoclopramide (I) has been prepared, as already described, *via* reacting an N-acetyl derivative of VIII, in which the carboxyl group is activated as acid chloride or alkyl ester, with IV. On the other hand, it is known that the condensation reaction of VII with IV gives I in a low yield.[17] Under such level of the art, if it is possible to prepare I by condensing VIII direct with IV, the method for the condensation would be the most useful one for the industrial synthesis of I. We studied to activate the amino group of IV in stead of activating the carboxyl group of VIII, and now it has been found that, when IV is first activated using phosphorus trichloride and the resultant phosphazo derivative is allowed to react with VIII, I is obtained easily in satisfactory yields (80—90%). Such techniques are well known as the phosphazo method in the peptide chemistry.[18] It has also been found that procainamide (*p*-amino-N-(2-diethylaminoethyl)-benzamide) can be prepared by reacting the phosphazo derivative of IV with *p*-aminobenzoic acid in the same way. By the way, the use of acid chloride of VIII is undesirable, because it is difficult to prepare the acid chloride in a pure form unless the amino group of VIII is protected beforehand.

Experimental[19]

Methyl 4-Amino-2-methoxybenzoate (V)——To a mixture of *p*-aminosalicylic acid (III) (10 g, 0.065 mole) and potassium hydroxide (9.2 g, 0.164 mole) in dry acetone (200 ml), dimethyl sulfate (14.6 ml, 0.155 mole) was added dropwise with vigorous stirring at room temperature. After the mixture was further stirred for 3 hr, the solvent was evaporated off under reduced pressure to obtain solid residues. Water (150 ml) was added to the solid residues and an insoluble material was collected by filtration. The material was dissolved in ethyl acetate and the solution was washed successively with 5% sodium bicarbonate and water, and dried over anhydrous sodium sulfate. The evaporation of the solvent left a crystal, which was recrystallized from ethyl acetate and petroleum ether; wt. 10.5 g (89%), mp 155—156° (lit., 159°,[10] 157.3—158.1°[11]). *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.59; H, 6.19; N, 7.88.

4-Amino-2-methoxybenzoic Acid (VI)——Compound V (15.1 g, 0.0835 mole) was suspended to a solution of potassium hydroxide (10 g, 0.18 mole) in methanol (100 ml) and water (40 ml), and the suspension was refluxed for 2 hr. V was almost dissolved in about 5 minutes after the starting of reflux. After the end of the reaction, a small amount of insoluble materials was filtered off, and the filtrate was concentrated.

14) H.J. Lucas and E.R. Kennedy, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 482.
15) R. Neu, *Chem. Ber.*, **72**, 1505 (1939); A. Pieroni, "Beilsteins Handbuch der Organischen Chemie," ed. by Deutschen Chemischen Gesellschaft, Band V-2, 1944, p. 167.
16) Compound X: mp 179—181° (decomp.), nuclear magnetic resonance (NMR) (10% solution in Na_2CO_3 (D_2O)) τ: 2.4 (1H, doublet, J=8.8 cps), 3.6 (1H, doublet, J=8.8 cps). *Anal.* Calcd. for $C_7H_6O_3NCl$: C, 44.82; H, 3.22; N, 7.47; Cl, 18.90. Found: C, 44.84; H, 3.08; N, 7.47; Cl, 18.55. [*cf.* 4-Amino-5-chlorosalicylic acid; NMR (10% solution in $Na_2CO_3(D_2O)$) τ: 2.33 (1H, singlet), 3.65 (1H, singlet)]. Compound XI: mp 213—215°. *Anal.* Calcd. for $C_7H_5O_3NCl_2$: C, 37.87; H, 2.27; N, 6.31; Cl, 31.94. Found: C, 37.93; H, 2.33; N, 6.28; Cl, 31.74.
17) R.O. Clinton, S.C. Laskowski, U.J. Salvador, H.G. Bates and P.M. Carroll, *J. Am. Chem. Soc.*, **79**, 2285 (1957).
18) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York–London, 1961, p. 999.
19) All melting points are not corrected.

The residues were dissolved in water (50 ml) and, when the aqueous solution was neutralized to pH 5 using 3 N aqueous hydrogen chloride, white crystals were immediately precipitated. The crystals were collected by filtration and recrystallized from methanol; wt. 13 g (93%), mp 149—150°. (lit.,[11] 150.5—151.4°). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.37. Found: C, 57.08; H, 5.19; N, 8.37.

Methyl 4-Amino-5-chloro-2-methoxybenzoate (VII)——(a) To a mixture of compound V (3.62 g, 0.02 mole) and dry pyridine (1.62 g, 0.0205 mole) in dry tetrahydrofuran (100 ml), iodobenzene dichloride (5.5 g, 0.02 mole) was gradually added over a period of about 4 hrs at 0° with stirring. After stirring was continued for further 2 hrs at 0°, the mixture was allowed to stand overnight in an ice bath. The solution was concentrated under reduced pressure. Ethyl acetate (150 ml) and water (50 ml) was added to the residue and the solution was shaken well. The ethyl acetate layer was separated and washed successively with 1 N aqueous hydrogen chloride (50 ml), 5% aqueous sodium bicarbonate (50 ml) and water (50 ml × 2), and then dried over anhydrous sodium sulfate. The evaporation of the solvent left a crude crystal. After the crystal was triturated in petroleum ether, it was collected by filtration and washed with petroleum ether, and then recrystallized from methanol; wt. 3.3 g (77%), mp 135° (lit.,[13] mp 135—137°). NMR[20] (20% solution in $CDCl_3$) τ: 2.09 (1H, singlet), 3.63 (1H, singlet), 6.20 (3H, $COOCH_3$), 6.25 (3H, OCH_3). *Anal.* Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.18; H, 4.55; N, 6.32 (From the petroleum ether solution, iodobenzene (3.5 g) was recovered.)

(b) Iodobenzene dichloride (138 mg, 0.0005 mole) was carefully added to a solution of V (181 mg, 0.001 mole) in dry acetone (5 ml) at 0° with stirring at about 4 hr. The mixture was allowed to react for further 2 hr at 0° with stirring and to stand overnight in a refrigerator. A precipitated crystal, V·HCl (82 mg), was filtered off and the filtrate was treated as described above; wt. 77.5 mg (72%), mp 134—135°.

4-Amino-5-chloro-2-methoxybenzoic Acid (VIII)——(a) A mixture of VI (167 mg, 0.001 mole) and pyridine (79 mg, 0.001 mole) in dry acetone (5 ml) was allowed to react with iodobenzene dichloride (275 mg, 0.001 mole) in a similar method as described above. After the end of the reaction, the solution was concentrated. Ethyl acetate (50 ml) and water (10 ml) were added to the residue and the solution was shaken well. The ethyl acetate layer was separated and washed twice with 1 N aqueous hydrogen chloride (10 ml) and with water (10 ml), and then dried over anhydrous sodium sulfate. The solvent was evaporated off and the residual crystal was triturated with petroleum ether and then collected by filtration. The crystal was recrystallized from methanol; wt. 149 mg (72%), mp 208—209°. NMR[20] (5% solution in NaOD (D_2O)) τ: 2.43 (1H, singlet), 3.35 (1H, singlet), 6.13 (3H, singlet, OCH_3). *Anal.* Calcd. for $C_8H_8O_3NCl$: C, 47.66; H, 4.00; N, 6.95. Found: C, 47.50; H, 3.85; N, 6.78.

(b) To a mixture of V (21.7 g, 0.12 mole) and pyridine (9.5 g, 0.12 mole) in dry tetrahydrofuran (600 ml), a suspension of iodobenzene dichloride (37.5 g, 0.135 mole) in dry tetrahydrofuran (87 ml) was added dropwise at −20° with stirring. The temperature of the mixture was slowly raised to room temperature and the mixture was allowed to stand overnight. After the solvent was evaporated off, sodium hydroxide (12 g, 0.3 mole) and water (300 ml) was added to the residue. The mixture was then steam distilled until no iodobenzene could be detected in a sample of the aqueous distillate (26 g (93%) of iodobenzene was recovered.). The residual solution was neutralized with aqueous hydrogen chloride. The crystal precipitated was collected by filtration and washed with water and dried; wt. 24 g. The crystal was recrystallized from methanol. mp 208—209°.

Metoclopramide (I)——(a) A solution of phosphorus trichloride (0.7 g, 0.0051 mole) in pyridine (4 ml) was added dropwise to a solution of N,N-diethylethylenediamine (IV) (1.2 g, 0.0103 mole) in pyridine (20 ml) with stirring at 0—5° over 30 min. The stirring was continued for 30 min at 0—5° and for further 1 hr at room temperature. 4-Amino-5-chloro-2-methoxybenzoic acid (VIII) (1.0 g, 0.005 mole) was added to the solution and the mixture was heated for 3 hr at 90—100° with stirring. After the solution had been concentrated to a residue, the residue was dissolved in chloroform (110 ml), and an insoluble oily material was removed by decantation. The chloroform solution was washed with 10% aqueous sodium carbonate and with water, and then dried over anhydrous magnesium sulfate. The dried solution was concentrated to a crystal under reduced pressure and the crystal was recrystallized from benzene; wt. 1.3 g (85%), mp 143—144.5° (lit.,[2] 145°). *Anal.* Calcd. for $C_{14}H_{22}O_2N_3Cl$: C, 56.09; H, 7.40; N, 14.02. Found: C, 56.11; H, 7.32; N, 13.88.

(b) A solution of 4-amino-2-methoxy-N-(2-diethylaminoethyl)-benzamide (XII) (0.77 g, 0.0029 mole) in chloroform (20 ml) was treated with iodobenzene dichloride (0.8 g, 0.00295 mole) in a similar manner as already described. The reaction mixture was washed successibly with 5% aqueous sodium bicarbonate (5 ml) and with water (5 ml) and dried over anhydrous magnesium sulfate. The dried solution was concentrated and the crystalline residue was recrystallized from ethyl acetate; wt. 0.65 g (75%), mp 143—144.5°.

Acknowledgement The authors wish to express their thanks to Chief of First Research Division, Dr. Shigemi Kawahara for his encouragement and helpful advice. Thanks are also due to Measurement Division of this Central Research Laboratory for NMR measurements and for elemental micro-analyses.

20) The standard sample is trimethylsilane.