

PREPARATION OF 3,5-DIMETHOXY-1,2,4-TRIAZINE AND ITS 6-METHYL DERIVATIVE*

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Methanolysis of 3,5-bis(methylthio)triazines *III* and *IV* with an equimolar amount of methanolic sodium methoxide at room temperature gives 5-methoxy derivatives *VII* and *IX* selectively. A substitution of the methylthio group in the position 3 requires higher temperatures. In the latter case aliphatic S_N2 demethylation of the methoxy groups in the position 5 with methanethiolate ions takes place already distinctly under formation of 3-methylthio- and 3-methoxytriazinones *VIII* and *X*, or *XII* and *XIII*. In the presence of methyl iodide or mercury ions the proportion of demethylation products decreases considerably and the yield of 3,5-dimethoxytriazines *I* and *II* increases appreciably.

3,5-Dimethoxy-1,2,4-triazine (*I*) and its 6-methyl derivative *II* may represent versatile intermediates in the synthesis of nucleosides and N-alkyl derivatives of 6-azapyrimidine nucleobases by the classical Hilbert-Johnson method. In our effort to carry out the indicated preparative study we looked for a suitable approach for the preparation of the mentioned compounds.

The preparation of dimethoxytriazine *I* could be carried out conventionally by methanolysis of 3,5-dichloro-1,2,4-triazine which was obtained¹ in a low yield (10%) on reaction of 1,2,4-triazine-3,5-dione with an "aged" phosphorus oxychloride. This approach failed, however, in the past due to the difficulties with the preparation of the mentioned dichlorotriazine². 6-Methyl derivative *II* was prepared recently³ by methanolysis of 3,5-dichloro-6-methyl-1,2,4-triazine which is accessible, however, in a low yield only during its time-consuming isolation. In view of the good results we obtained in the synthesis of methoxytriazinones by methanolysis of the corresponding methylthiotriazinones⁴, we tried to apply this method to the synthesis of dimethoxytriazines.

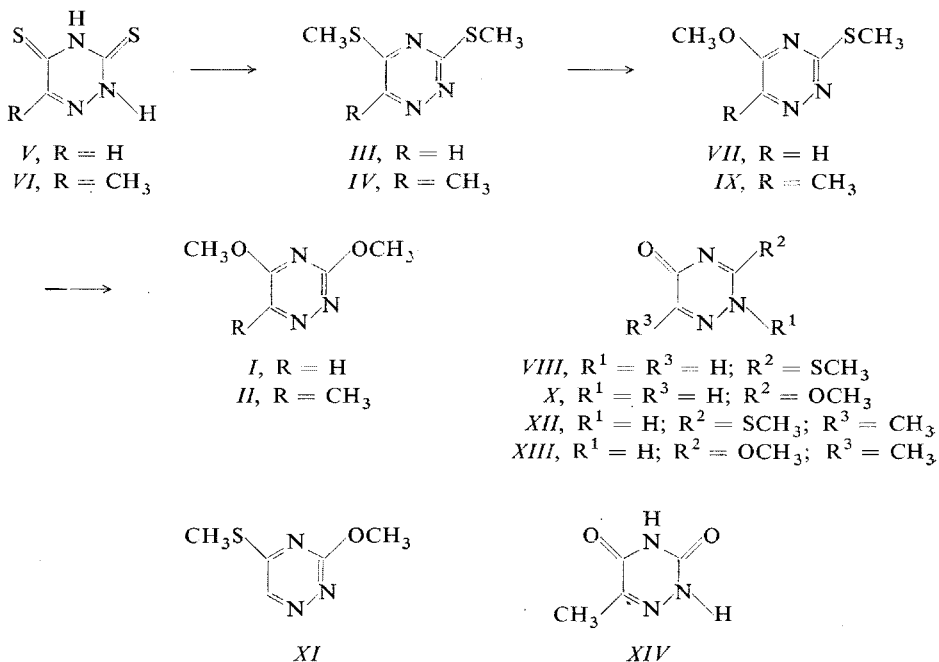
The starting 3,5-bis(methylthio)-1,2,4-triazine⁵ (*III*) or its 6-methyl derivative⁶ *IV* can be obtained by methylation of dithio derivatives of 1,2,4-triazine-3,5-dione and 6-methyl-1,2,4-triazine-3,5-dione, *V* or *VI*. The preparation of these compounds could be much improved by adjusting the reaction conditions and the isolation procedure.

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Reaction of bismethylthiotriazine *III* with an equimolar amount of 0.33M-NaOCH₃ (room temperature, 45 minutes) gave 5-methoxy-3-methylthio-1,2,4-triazine (*VII*) in 87% yield. It was identified by comparison with an authentic sample^{7,8} prepared from 3-methylthio-1,2,4-triazin-5(2*H*)-one (*VIII*) by methylation with diazomethane. In the mother liquors the presence of dimethoxytriazine *I* in addition to starting triazine *III* could also be proved chromatographically. The formation of dimethoxy derivative *I* is evidently the reason why a quantitative substitution of the methylthio group in the position 5 of the triazine nucleus could not be carried out even when the reaction time was prolonged considerably.

We obtained 5-methoxy-6-methyl-3-methylthio-1,2,4-triazine (*IX*) in 82% yield by an analogous synthetic method. The compound was prepared recently in a different manner, but in a substantially lower yield⁹. In this case however, the reaction takes place under comparable conditions much more slowly.

The substitution of the methylthio group in the position 3 in methoxymethylthio-triazine *VII* could be achieved only under refluxing of the reaction mixture (0.5M-NaOCH₃, 2 hours). However, in this reaction aliphatic S_N2 demethylation of the methoxy group in the position 5 of the triazine nucleus by methanethiolate ions already takes place in addition to the aromatic S_NAr2 substitution. In consequence of this a mixture of 3,5-dimethoxy-1,2,4-triazine (*I*), 3-methylthio-1,2,4-triazin-5(2*H*)-



-one (*VIII*), and 3-methoxy-1,2,4-triazine-5(2*H*)-one (*X*) is formed in this reaction. Acidic demethylation products *VIII* and *X* prevail considerably in the mixture, but they can still be separated easily from the neutral dimethoxytriazine in the form of sodium salts. The mixture of triazinones *VIII* and *X* was liberated from the sodium salts on Amberlite IRC-50[H^+] and separated chromatographically on silica gel. The fact that triazinones *VIII* and *X* are indeed formed by $\text{S}_{\text{N}}2$ demethylation and not by $\text{S}_{\text{N}}\text{Ar}2$ hydrolysis was checked by a gas chromatographic determination of dimethyl sulfide in the mixture. The preparative yield of dimethoxytriazine *I* is somewhat lower than could be expected on the basis of the analytical determination of dimethyl sulfide. As we had worked in a strictly anhydrous medium we suppose that this discrepancy was caused by losses or by a partial hydrolysis during the working up of the reaction mixture and the isolation of the product.

A good preparative yield (57%) of the poorly accessible 3-methoxytriazinone *X* could be achieved by using two equivalents of sodium methoxide, prolongation of the reaction time (6 hours), and temperature increase (100°C, sealed tube). The proportion of the demethylation products in the mixture can be lowered considerably by methanolysis of triazine *VII* in the presence of methyl iodide or mercury ions. The effect of these reagents consists in the capturing of the methanethiolate ions from the reaction mixture. We suppose that dimethyl sulfide is formed with methyl iodide, while dimethyl disulfide is formed with mercury ions. When these reagents were used very good preparative yields (78%) of dimethoxytriazine were achieved. Dimethoxytriazine *I* is formed in 89% yield by methanolysis (0.33M- NaOCH_3) of 3-methoxy-5-methylthio-1,2,4-triazine (*XI*) at room temperature (45 min). However, this reaction is not preparatively important due to the difficult accessibility of the triazine⁸ *XI*.

Methanolysis of 6-methyl derivative *IX* with two equivalents of methanolic 0.5M- NaOCH_3 (8 hours, reflux) leads, analogously as in the reaction of triazine *VII*, to a mixture of dimethoxytriazine *II*, methylthiotriazinone *XII*, and methoxytriazinone *XIII*. Triazinones *XII* and *XIII* were demonstrated in this case chromatographically, by comparison with authentic samples. The as yet undescribed methoxytriazinone *XIII* was prepared for comparison by an unambiguous methanolysis of 3-methylthiotriazinone *XII*. In view of the anionization of the substrate this reaction takes place similarly as in the case of triazinone⁴ *VIII* with difficulty and affords 6-methyl-1,2,4-triazine-3,5-dione (*XIV*) in addition to methoxy derivative *XIII*.

We succeeded, similarly as in the synthesis of dimethoxytriazine *I*, in increasing the yield of 6-methyl derivative *II* substantially by using methyl iodide or mercuric ions for the elimination of sodium methanethiolate from the mixture. The substitution of the methylthio group in 6-methyl derivative *IX* requires a much longer time than in the lower homologue *VII*. A distinct decrease in the rate of methanolysis in 6-methyltriazines *IV* and *IX* in comparison with triazines *II*, and *VII* can be explained by the effect of the inductive donor effect of the methyl group.

The observed higher reactivity of the position 5, in comparison with the position 3 of the triazine nucleus, towards nucleophilic reagents was also observed in a series of further cases¹⁰⁻¹² and it is in agreement with the theoretical supposition following from considerations on the

stabilitation of the negative charge in the transition state by sp^2 hybridized nitrogen atoms of the triazine nucleus¹¹. In this connection it should be mentioned that Grundmann¹ and coworkers obtained on reaction of 3,5-dichloro-1,2,4-triazine with sodium methanethiolate in a mixture of ethanol and methanethiol ethoxy-methylthio-1,2,4-triazine to which they assigned the structure of 3-ethoxy-5-methylthio-1,2,4-triazine without conclusive proof. The improbability of this structure was already pointed out by Shepherd and Fedrick¹¹ who suppose a primary formation of 3,5-bis(methylthio)-1,2,4-triazine and a subsequent selective alcoholysis at the position 5 under formation of 5-ethoxy-3-methylthio-1,2,4-triazine. This theoretical assumption is in agreement with our results. The spectral data of 3,5-dimethoxy-1,2,4-triazine were published in the preceding paper of this series⁴.

EXPERIMENTAL

The melting points were determined on a Kofler block. The analytical samples were dried at 22°C/0.1 Torr for 8 hours. The solvents were evaporated on a rotatory evaporator at 35–40°C (bath temperature) and 15 Torr. Thin-layer chromatography on bound silica gel with fluorescent indicator (Service laboratories of this Institute, Lysolaje near Prague) was carried out in the systems S_1 , benzene–ethyl acetate (8 : 2), and S_2 , ethyl acetate. Detection of the spots was carried out visually under UV light (Chromatolite). Column chromatography was carried out on silica gel of Woelm, Eschwege, GFR.

3,5-Bis(methylthio)-1,2,4-triazine (*III*)

Methyl iodide (36 ml) was added at once under stirring to a solution of dithione⁵ *V* (42.1 g; 0.29 mol) in methanolic 1M- NaOCH_3 (580 ml) and the exothermic reaction was allowed to subside. The temperature rose of itself to 47°C, and the solution was allowed to stand at room temperature for 1.5 hours. After filtration with active charcoal (5 g) the solution was evaporated until the residue was of a pasty consistence. Water was added in several portions (totally 250 ml) to the paste under stirring and cooling with icy water. The suspension was cooled for 2 hours in ice-cold water. The product was filtered off under suction, washed with icy water and dried in a vacuum; yield 43.5 g (87%) of compound *III*, m.p. 53–54°C, undepressed on admixture with an authentic sample⁵; R_F 0.74 (S_1).

5-Methoxy-3-methylthio-1,2,4-triazine (*VII*)

A solution of bis(methylthio)triazine *III* (17.1 g; 0.1 mol) in methanolic 0.33M- NaOCH_3 (300 ml) was allowed to stand at room temperature for 45 minutes. After neutralization with solid carbon dioxide the mixture was evaporated and the residue partitioned between chloroform (100 ml) and water (200 ml). The organic phase was dried over sodium sulfate and evaporated. Crystallization of the residue from a benzene–light petroleum mixture (1 : 5) gave compound *VII* (13.6; 87%) in two portions, m.p. 66–68°C, undepressed on admixture of an authentic sample⁷; R_F 0.64 (S_1). The last mother liquors contained according to thin-layer chromatography, in addition to the title compound, the starting bis(methylthio)triazine *III* and dimethoxytriazine *I*.

3,5-Dimethoxy-1,2,4-triazine (*I*)

A) A solution of methoxymethylthiotriazine *VII* (1.57 g; 0.01 mol) in a mixture of methanolic 0.5M- NaOCH_3 (20 ml) and 0.6 ml of methyl iodide was refluxed for 4.5 hours. The mixture

was added during the heating at 90 minutes' intervals first with 10 ml methanolic 1M-NaOCH₃ and 0.6 ml of methyl iodide, and then with 5 ml methanolic 1M-NaOCH₃. After cooling the solution was neutralized with solid CO₂ and evaporated. The residue after addition of 0.1 g of sodium hydrogen sulfite was dissolved in 10 ml of icy water and the solution was extracted with two 10 ml portions of chloroform. The organic layer was filtered with active charcoal (0.2 g), dried over sodium sulfate, and evaporated. After drying in a vacuum (water pump) for 20 min the yield of dimethoxytriazine *I* was 1.10 g (78%); m.p. 58–61°C; *R_F* 0.60 (S₂). The sample for analysis was recrystallized from light petroleum (m.p. 61–63°C). For C₅H₇N₃O₂ (141.1) calculated: 42.55% C, 5.00% H, 29.77% N, 43.99% OCH₃; found: 42.82% C, 5.26% H, 29.48% N, 43.70% OCH₃. In longer contact with air humidity the compound undergoes decomposition.

B) A mixture of methoxy(methylthio)triazine *VII* (1.57 g; 0.01 mol), methanolic 0.66M-NaOCH₃ (30 ml) and mercuric acetate (1.6 g; 0.005 mol) was refluxed for 2 hours under stirring. After cooling the mixture was saturated with dry hydrogen sulfide (15 min) and the brick-red precipitate formed was filtered through a layer of celite. The material on the filter was washed with methanol and the filtrate evaporated. The residue was dissolved in 10 ml of ice cold water and the solution extracted with chloroform (twice with 10 ml). The organic layer afforded after drying over sodium sulfate, evaporation, and drying in a vacuum 1.10 g (78%) of compound *I*; m.p. 58–61°C, undepressed in admixture with the sample obtained under *A*).

C) A solution of methoxy(methylthio)triazine *VII* (1.57 g; 0.01 mol) in methanolic 0.33M-NaOCH₃ (30 ml) was refluxed for 15 minutes, cooled and neutralized with solid carbon dioxide and evaporated. The residue was triturated with benzene (20 ml) and the insoluble fraction filtered off under suction and the filtrate evaporated. A solution of the residue in 15 ml of methanolic 0.33M-NaOCH₃ was refluxed for 2 hours, cooled, neutralized with solid carbon dioxide, and evaporated. The residue was worked up as under *A*) to give 0.80 g (57%) of compound *I*; m.p. 58–61°C, undepressed on admixture of a sample prepared as under *A*).

D) A solution of methoxy(methylthio)triazine *VII* (1.57 g; 0.01 mol) in methanolic 0.5M-NaOCH₃ (20 ml) was refluxed for 2 hours. Before further working up the mixture was analysed by gas chromatography (Carbowax, 3.2 m, 70°C) and dimethyl sulfide was determined in it (55% yield) by comparison with a standard. After cooling and neutralization with solid carbon dioxide the mixture was evaporated. The residue was dissolved in water (10 ml) and the solution extracted with two 10 ml portions of chloroform. The organic layer afforded 0.34 g (24%) of dimethoxytriazine *I* after conventional working up; m.p. 58–61°C, undepressed with a sample prepared by procedure *A*). The aqueous layer was acidified with glacial acetic acid (1 ml) and decationized on an Amberlite IRC-50 [H⁺] column (50 ml). The column was washed with water (200 ml) and the eluate evaporated. The residue was dissolved in methanol (20 ml), added with 10 g of silica gel and evaporated again. The residue was dried *in vacuo* until the silica gel was free-flowing and could be suspended in ethyl acetate and put onto a column of 90 g of silica gel also packed in ethyl acetate. The column was eluted with ethyl acetate (900 ml; fractions 1–45). Evaporation of fractions 12–18 gave 0.42 g (29%) of methylthiotriazinone *VIII*; m.p. 221–222°C (ethanol) undepressed on admixture of an authentic sample⁵; *R_F* 0.37 (S₂). Working up of fractions 19–45 gave 0.46 g (36%) of methoxytriazinone *X*; m.p. 167–169°C (ethanol) undepressed with an authentic sample⁴; *R_F* 0.23 (S₂).

E) A solution of methoxy(methylthio)triazine⁸ *XI* (1.57 g; 0.01 mol) in methanolic 0.33M-NaOCH₃ (30 ml) was allowed to stand at room temperature for 45 minutes. According to thin-layer chromatography methanolysis is over within 5 minutes. The mixture was neutralized with solid carbon dioxide and further worked up analogously as under *A*). Yield 1.26 g (89%) of dimethoxytriazine *I*, m.p. 58–61°C, undepressed on admixture with a product prepared as under *A*).

3-Methoxy-1,2,4-triazin-5(2*H*)-one (*X*)

A solution of methoxy(methylthio)triazine *VII* (1.57 g; 0.01 mol) in methanolic 0.5*M*-NaOCH₃ (40 ml) was heated in a sealed tube at 100°C for 6 hours. After cooling the solution was decationized on an Amberlite IRC-50 [H⁺] column (80 ml), prepared in methanol. The column was eluted with methanol (300 ml) and the eluate evaporated. The residue was crystallized by fractional crystallization from ethyl acetate and ethanol to give totally 0.66 g (57%) of methoxytriazinone *X*, m.p. 167–169°C, undepressed with an authentic specimen⁴; *R_F* 0.23 (S₂). The mother liquors contained according to thin-layer chromatography in addition to compound *X* also methylthio-triazinone *VIII* and dimethoxytriazine *I*.

6-Methyl-3,5-bis(methylthio)-1,2,4-triazine (*IV*)

Dithione⁵ *VI* (23.9 g; 0.15 mol) afforded by a procedure analogous to that for the preparation of compound *III* 26.7 g (95%) of compound *IV*, m.p. 76–78°C, undepressed with an authentic sample⁶; *R_F* 0.65 (S₁).

5-Methoxy-6-methyl-3-methylthio-1,2,4-triazine (*IX*)

Bis(methyl)thiotriazine *IV* (3.76 g; 0.02 mol) was reacted and further worked up as in the case of the preparation of triazine *VII*, but the reaction time was prolonged to 5 hours. Crystallization of the crude product from benzene–light petroleum (1 : 4) gave 2.8 g (82%) of compound *IX* in two fractions; m.p. 82–83°C (lit.⁹ gives 79–80°C); *R_F* 0.54 (S₁). The last mother liquors contain according to thin-layer chromatography in addition to the title compound *IX* also bis(methylthio)triazine *IV*.

3,5-Dimethoxy-6-methyl-1,2,4-triazine (*II*)

A) A solution of methoxy(methylthio)triazine *IX* (1.71 g; 0.01 mol) in a mixture of methanolic 0.5*M*-NaOCH₃ (20 ml) and 0.6 ml of methyl iodide was refluxed for 10 hours, while the mixture was added twice, at one hour intervals, with 10 ml methanolic 1*M*-NaOCH₃ and 0.6 ml of methyl iodide and eventually with 10 ml of methanolic 1*M*-NaOCH₃. The mixture was further worked up by a procedure analogous to that applied in the preparation of triazine *I* (procedure *A*). Yield 0.90 g (58%) of dimethoxytriazine *II*, m.p. 98–100°C; *R_F* 0.27 (S₁). A sample for analysis was recrystallized from light petroleum; m.p. 102–103°C (lit.³ 107–108°C).

B) A mixture of methoxy(methylthio)triazine *IX* (1.71 g; 0.01 mol) methanolic 0.66*M*-NaOCH₃ (30 ml) and mercuric acetate (1.6 g; 0.005 mol) was refluxed under stirring for 8 hours. Further working up as in the case of the preparation of triazine *I* (procedure *B*) gave 1.19 g (77%) of dimethoxytriazine *II*, m.p. 98–100°C, undepressed on admixture with a sample prepared as under *A*).

C) A solution of methoxy(methylthio)triazine *IX* (1.71 g; 0.01 mol) in methanolic 0.5*M*-NaOCH₃ (40 ml) was refluxed for 8 hours. Further working up as under *D* in the preparation of dimethoxytriazine *I* gave 0.40 g (26%) of compound *II*; m.p. 98–100°C, undepressed on admixture of the sample obtained by procedure *A*. According to thin-layer chromatography the decationized aqueous layer contained the demethylated product *XII* and *XIII*.

3-Methoxy-6-methyl-1,2,4-triazin-5(2*H*)-one (*XIII*)

A solution of methylthiotriazinone⁵ *XII* (0.63 g; 0.004 mol) in methanolic 1*M*-NaOCH₃ (8 ml) was refluxed for 240 hours. After cooling the mixture was diluted with methanol (20 ml) and

water was added dropwise to it until dissolution was complete. The solution was decationized on an Amberlite IRC-50 [H⁺] column (30 ml). The column was washed with methanol (150 ml) and the eluate evaporated. The residue was dissolved in methanol (20 ml), mixed with 10 g of silica gel, and the mixture evaporated. The residue was dried *in vacuo* until it was free-flowing, then suspended in ethyl acetate and applied onto a silica gel column (70 g) packed in ethyl acetate. The column was eluted with ethyl acetate (800 ml; fractions 1–40). Evaporation of fractions 4–8 gave 0.15 g (30%) of dione XIV; m.p. 214°C (water), undepressed on admixture with an authentic sample¹³; R_F 0.68 (S₂). Fractions 9–14 afforded after conventional work-up 0.25 g (40% of regeneration) of compound XII; m.p. 227–228°C (ethanol), underperped on admixture of an authentic sample⁵; R_F 0.42 (S₂). Working up of fractions 17–40 gave 0.17 g (30%) of compound XIII; m.p. 182–183°C; R_F 0.27 (S₂). For C₅H₇N₃O₂ (141.1) calculated: 42.55% C, 5.00% H, 29.78% N, 21.99% OCH₃; found: 42.39% C, 4.76% H, 30.06% N, 22.04% OCH₃. At elevated temperature (110–120°C bath temperature, sealed tube; 88 hours) 0.50 g (85%) of the sodium salt of dione XIV separated.

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