REACTION OF 3,5,6-TRICHLORO-1,2,4-TRIAZINE WITH DIMETHYLAMINE AND METHANOLYSIS OF 3,6-DICHLORO-5-DIMETHYLAMINO-1,2,4-TRIAZINE*

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Reaction of the trichlorotriazine *I* with two equivalents of dimethylamine in methanol affords 3,6-dichloro-5-dimethylaminotriazine (*II*). The acid-catalysed methanolysis of the triazine *II* gives the 6-chloro-3-methoxy derivative *V* as the predominant product while the isomer *VIII* is mainly obtained by reaction with one equivalent of sodium methoxide. Methanolysis of the triazine *II* with two equivalents of sodium methoxide or dimethylaminolysis of the trimethoxytriazine *XII* afford 3,6-dimethoxy-5-dimethyl-aminotriazine (*XI*). Reaction of the trichlorotriazine *I* with excess dimethylamine in methanol affords 6-chloro-3,5-bis(dimethylamino)triazine (*XIII*) from which the 6-methoxy derivative *XIV* is obtained on methanolysis. These results confirm the assumed decrease in positional reactivity towards neutral nucleophiles in the order $5 > 3 > 6$ and towards anionic nucleophiles in the order $5 > 6 > 3$.

In another paper of this series[1], ammonolysis and methanolysis of 3,5,6-trichloro-1,2,4-triazine (*I*) was examined. In this connection, we have now focussed our attention on the reaction of the trichlorotriazine *I* with dimethylamine and on the methanolysis of 3,6-dichloro-5-dimethylamino-1,2,4-triazine (*II*). The aim of the present work was to prepare suitable intermediates for investigations on reactions of chlorotriazines with organometallic compounds and to verify by additional examples the observed order of positional reactivities in 1,2,4-triazine towards simple nucleophilic agents.

Reaction of the trichlorotriazine *I* with two equivalents of dimethylamine in methanol afforded in 82% yield a dichlorodimethylaminotriazine. This compound was converted by acid-catalysed methanolysis into a chloromethoxydimethylaminotriazine, the acidic hydrolysis of which afforded the known[1,2] 6-chloro-1,2,4-triazine-3,5(2*H*,4*H*)-dione (5-chloro-6-azauracil; *III*) as the main product while the catalytic hydrogenolysis over a palladium catalyst on active charcoal in methanolic hydrogen chloride resulted in a smooth formation of 3-methoxy-5-dimethylamino-1,2,4-triazine (*IV*). The triazine *IV* was identified on comparison with an unambiguously prepared sample[3]. On the basis of the above transformations, the dichloro derivative was

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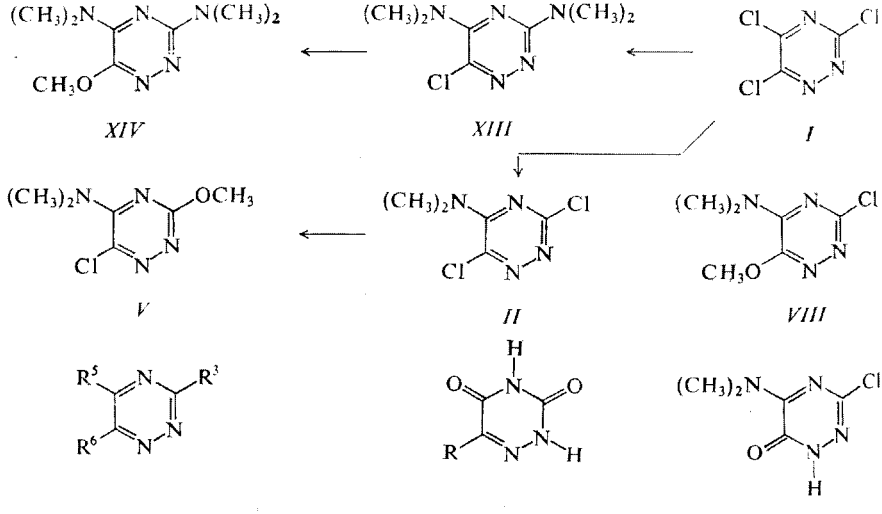
ascribed the structure of 3,6-dichloro-5-dimethylamino-1,2,4-triazine (*II*) and to its methanolytical product the structure of 6-chloro-3-methoxy-5-dimethylamino-1,2,4-triazine (*V*) was proposed.

Catalytical hydrogenolysis of the dichloro derivative *II* over a palladium catalyst on active charcoal in ether and in the presence of two equivalents of N-ethylpiperidine yielded 16% of 3-chloro-5-dimethylamino-1,2,4-triazine (*VI*), the structure of which was inferred from the acidic hydrolysis to the known[4] 1,2,4-triazin-3,5(2*H*,4*H*)-dione (6-azauracil; *VII*).

Methanolysis of the dichloro derivative *II* with one equivalent of sodium methoxide at room temperature afforded 3-chloro-6-methoxy-5-dimethylamino-1,2,4-triazine (*VIII*). The structure *VIII* is based on the acidic hydrolysis which afforded as the main product the known 6-methoxy-1,2,4-triazine-3,5(2*H*,4*H*)-dione[1] (5-methoxy-6-azauracil; *IX*) along with 3-chloro-5-dimethylamino-1,2,4-triazin-6(1*H*)-one (*X*). As shown by chromatography, the by-product of the base-catalysed methanolysis of the dichlorotriazine *II* is the 6-chloro derivative *V* while the acid-catalysed methanolysis of compound *II* afforded the 3-chloro derivative *VIII* as a by-product.

Owing to the resonance deactivation of the triazine ring by the methoxyl and dimethylamino group, a further methanolysis of the chlorotriazines *V* and *VIII* is very difficult. Thus, a prolonged reflux of the dichloro derivative *II* with methanolic sodium methoxide (two equivalents) was necessary to obtain a fair yield of 3,6-di-



XIV *XIII* *I*

V *II* *VIII*

IV, $R^3 = OCH_3$; $R^5 = N(CH_3)_2$; $R^6 = H$
VI, $R^3 = Cl$; $R^5 = N(CH_3)_2$; $R^6 = H$
XI, $R^3 = R^6 = OCH_3$; $R^5 = N(CH_3)_2$
XII, $R^3 = R^5 = R^6 = OCH_3$

III, R = Cl
VII, R = H
IX, R = OCH_3

X

methoxy-5-dimethylamino-1,2,4-triazine (*XI*). The dimethoxytriazine *XI* may be more advantageously prepared by reaction of 3,5,6-trimethoxy-1,2,4-triazine (*XII*) with excess dimethylamine in methanol at room temperature.

Reaction of the trichlorotriazine *I* with excess dimethylamine in methanol afforded hygroscopic 6-chloro-3,5-bis(dimethylamino)-1,2,4-triazine (*XIII*) in fair yield. The structure of this compound was confirmed by methanolysis into 6-methoxy-3,5-bis(dimethylamino)-1,2,4-triazine (*XIV*). The authentic specimen of compound *XIV* was unambiguously obtained by reaction of the 6-methoxy derivative *VIII* with dimethylamine in methanol. Owing to the resonance deactivation of the triazine ring, vigorous reaction conditions (100°C, sealed tube) are required both in the methanolysis of the triazine *XIII* and in the dimethylaminolysis of the triazine *VIII*. Since solvolysis or demethylation interfere with the main reaction, the yield of the methoxy derivative *XIV* is low in both cases.

The above results are in accordance with the earlier observed decrease of positional reactivities[1] of 1,2,4-triazine in the order $5 > 3 > 6$ towards neutral nucleophiles and in the order $5 > 6 > 3$ in the case of anionic nucleophiles. A higher reactivity of position 5 when compared with position 3 of the triazine ring was also inferred from investigations on 3,5-disubstituted 1,2,4-triazines[5–7]. Only the paper of Grundmann and coworkers[8] is at variance with these conclusions since 3,5-dichloro-1,2,4-triazine is assumed[8] to display a higher reactivity at position 3 than at position 5; on the basis of this assumption and without any further proofs, positions are ascribed to substituents in triazine derivatives[8]. As suggested by several authors[1,6,9], the conclusions of Grundmann and coworkers[8] are probably incorrect. The virtual structure of the compounds in question has not been so far established because of the difficult accessibility of 3,5-dichloro-1,2,4-triazine. The melting point value (119°C) of a product (claimed[8] as 5-chloro-3-dimethylamino-1,2,4-triazine) of the selective dimethylaminolysis of 3,5-dichloro-1,2,4-triazine is strikingly similar to that one (117–118°C) of the present authentic 3-chloro-5-dimethylamino-1,2,4-triazine (*VI*) obtained by partial hydrogenolysis of the dichloro derivative *II*; it is thus highly probable that the correct structure of the product of Grundmann and coworkers[8] is *VI*. It also should be mentioned in this connection that 5-amino-3-chloro-1,2,4-triazine reported in our earlier paper[1] is obviously identical with the product (erroneously claimed by Grundmann and coworkers[8] as 3-amino-5-chloro-1,2,4-triazine) of the selective ammonolysis of 3,5-dichloro-1,2,4-triazine

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are corrected. Unless stated otherwise, analytical samples were dried at 22°C/0·1 Torr for 10 h. Solutions were taken down on a rotatory evaporator at 15 Torr and bath temperature of 35–40°C. Paper chromatography was performed by the descending technique on paper Whatman No 1 (without any previous

saturation) in the solvent systems S_1, 1-butanol–acetic acid-water (4 : 1 : 1), and S_2, ethyl acetate saturated with 3% aqueous acetic acid. Spots were detected by viewing in ultraviolet light (Chromatolite). Thin-layer chromatography was performed on loose neutral alumina (Brockmann activity, II—III) in the solvent S_3, ether. Column chromatography was carried out on the macroporous Pitra[10] silica gel (produced by Service laboratories of this Institute) previously partially deactivated by the addition of water (10%).

3,6-Dichloro-5-dimethylamino-1,2,4-triazine (*II*)

To a solution of the trichlorotriazine *I* (1·84 g; 0·01 mol) in ether (30 ml) there was rapidly added at −78°C under vigorous magnetic stirring and exclusion of atmospheric moisture a 7·2% solution (13·5 ml) of dimethylamine in methanol. The resulting solution was evaporated, the residue triturated with water (10 ml), and the mixture cooled down in ice (10 min). The crystalline dichloro derivative was collected with suction, washed with a little ice-water, and dried under diminished pressure over conc. sulfuric acid and potassium hydroxide pellets. Yield, 1·58 g (82%) of the triazine *II*, m.p. 74—75°C; after recrystallisation from tetrachloromethane–light petroleum, m.p. 76°C. R_F values: 0·94 (in S_2) and 0·61 (in S_3). For $C_5H_6Cl_2N_4$ (193·0) calculated: 31·11% C, 3·13% H, 29·03% N, 36·74% Cl; found: 31·21% C, 3·06% H, 28·93% N, 36·97% Cl.

6-Chloro-3-methoxy-5-dimethylamino-1,2,4-triazine (*V*)

A solution of the triazine *II* (0·386 g; 0·002 mol) in 2% methanolic hydrogen chloride (10 ml) was refluxed for 30 min, cooled down, passed through a column (packed in methanol) of Amberlite IR-45 (OH^-) ion exchange resin (10 ml), and then the column washed with methanol (50 ml). The effluents were taken down and the residue triturated with ethyl acetate (30 ml). The insoluble portion was filtered off and the filtrate evaporated. Crystallisation of the residue from cyclohexane and work-up of mother liquors yielded total 0·305 g (81%) of the triazine *V*, m.p. 68—69°C; after recrystallisation from cyclohexane, m.p. 74—75°C. R_F values: 0·83 (in S_1), 0·89 (in S_2), and 0·34 (in S_3). For $C_6H_9ClN_4O$ (188·6) calculated: 38·21% C, 4·81% H, 29·71% N, 18·80% Cl; found: 38·46% C, 4·94% H, 29·67% N, 19·10% Cl. As shown by thin-layer chromatography, the mother liquors also contained the isomer *VIII*, R_F 0·42 (in S_3).

Hydrolysis. A solution of the triazine *V* (0·019 g; 0·1 mmol) in 1M-HCl (1 ml) was heated under reflux condenser for 12 h at 100°C and evaporated. The residue was triturated with ethanol (1 ml), the insoluble portion filtered off, and the filtrate evaporated. The residue was crystallised from water to afford 0·007 g (47%) of 6-chlorotriazine *III*, m.p. 232—233°C, undepressed on admixture with an authentic specimen[2]; R_F value 0·76 (in S_2).

3-Methoxy-5-dimethylamino-1,2,4-triazine (*IV*)

The chlorotriazine *V* (0·189 g; 0·001 mol) was hydrogenated in methanol (25 ml) and 2% methanolic hydrogen chloride (1·8 ml) over 10% palladium on active charcoal (0·1 g) as catalyst under atmospheric pressure and at room temperature for 10 min. The catalyst was filtered off and the filtrate applied to a column (packed in methanol) of Amberlite IR-45 (OH^-) ion exchange resin (15 ml). The column was eluted with methanol (50 ml) and the effluent evaporated. The residue (0·147 g) was crystallised from cyclohexane to afford (after work-up of mother liquors) total 0·115 g (75%) of the triazine *IV*, m.p. 98—101°C; after additional recrystallisation from cyclohexane, m.p. 101—102°C. R_F value: 0·60 (in S_1). For $C_6H_{10}N_4O$ (154·2) calculated: 46·74% C, 6·54% H, 36·34% N, 20·12% OCH_3; found: 46·82% C, 6·60% H, 36·20% N, 19·88% OCH_3.

3-Chloro-5-dimethylamino-1,2,4-triazine (*VI*)

The dichlorotriazine *II* (0·386 g; 0·002 mol) was hydrogenated in ether (100 ml) under atmospheric pressure and at room temperature in the presence of N-ethylpiperidine (0·452 g; 0·004 mol) over 10% palladium on active charcoal (2 g) as catalyst for 10 h. The catalyst was then filtered off, the filtrate evaporated, and the residue chromatographed on eight 10 × 20 cm layers of loose alumina in ether. Work-up of faster bands (R_F 0·61) yielded 0·307 g (79% recovered) of the starting compound *II*, m.p. 76°C (tetrachloromethane–light petroleum), undepressed on admixture with an authentic sample. Work-up of less mobile bands (R_F 0·08) afforded 0·051 g (16%) of the chlorodimethylamino derivative *VI*, m.p. 117–118° (decomposition; from light petroleum) (rapid heating). When heated slowly, the substance only sinters at the temperature stated and resolidifies instantaneously without melting up to 300°C. For $C_5H_7ClN_4$ (158·6) calculated: 37·87% C, 4·45% H, 35·33% N; found: 38·00% C, 4·62% H, 35·48% N.

Hydrolysis. A solution of the chlorodimethylaminotriazine *VI* (15·9 mg; 0·1 mmol) in 1M-HCl (2 ml) was heated under reflux condenser in a boiling water bath for 10 h and evaporated. The residue was triturated with ethanol (0·5 ml), the insoluble portion collected with suction, and crystallised from water to afford 0·007 g (62%) of the dione *VII*, m.p. 280–281°C, undepressed on admixture with an authentic specimen[4]; R_F values: 0·47 (in S_1) and 0·43 (in S_2).

3-Chloro-6-methoxy-5-dimethylamino-1,2,4-triazine (*VIII*)

A solution of the dichloro derivative *II* (0·580 g; 0·003 mol) in 0·33M methanolic sodium methoxide (9 ml) was kept at room temperature for 1 h, the mixture evaporated, and the residue triturated with ether (100 ml). The insoluble portion was filtered off, the filtrate evaporated, and the residue crystallised from tetrachloromethane to afford 0·42 g (74%) of compound *VIII*, m.p. 143°C; R_F values: 0·87 (in S_1), 0·90 (in S_2), and 0·42 (in S_3). For $C_6H_9ClN_4O$ (188·6) calculated: 38·21% C, 4·81% H, 29·71% N, 18·80% Cl; found: 38·40% C, 4·95% H, 29·42% N, 18·81% Cl. As shown by thin-layer chromatography, the mother liquors also contained the isomer *V*, R_F 0·34 (in S_3).

Hydrolysis. A solution of the triazine *VIII* (0·095 g; 0·5 mmol) in 1M-HCl (2 ml) was refluxed for 4 h and then cooled down to deposit 0·016 g (18%) of the triazine *X*, m.p. 223–224°C (sealed capillary); R_F values: 0·80 (in S_1) and 0·86 (in S_2). The analytical sample was obtained by sublimation at 160°C and 0·1 Torr. For $C_5H_7ClN_4O$ (174·6) calculated: 34·39% C, 4·04% H, 32·09% N, 20·31% Cl; found: 34·62% C, 3·99% H, 32·21% N, 20·15% Cl. The remaining mother liquors were then refluxed for additional 2 h, evaporated, and the residue triturated with ethanol (1 ml). The insoluble portion was recrystallised from a mixture of water–ethanol to afford 0·030 g (42%) of the methoxytriazine *IX*, m.p. 285–286°C (sealed capillary), undepressed on admixture with an authentic sample[1]; R_F value: 0·42 (in S_2).

3,6-Dimethoxy-5-dimethylamino-1,2,4-triazine (*XI*)

A. A solution of the trimethoxytriazine[1] *XII* (0·17 g; 0·001 mol) in 7·2% methanolic dimethylamine (1 ml) was kept at room temperature for 12 h and evaporated. The residue was crystallised from cyclohexane to afford 0·141 g (76%) of the triazine *XI*, m.p. 76°C; R_F 0·20 (in S_3). For $C_7H_{12}N_4O_2$ (184·2) calculated: 45·64% C, 6·55% H, 30·42% N; found: 45·46% C, 6·57% H, 30·45% N.

B. A solution of the triazine *II* (0·193 g; 0·001 mol) in 0·33M methanolic sodium methoxide (6 ml) was refluxed for 24 h, evaporated, the residue extracted with refluxing ethyl acetate (20 ml),

and the insoluble portion filtered off. The filtrate was evaporated and the residue crystallised from cyclohexane to afford 0·115 g (63%) of the triazine *XI*, m.p. 76°C, undepressed on admixture with the specimen obtained by procedure *A*.

6-Chloro-3,5-bis(dimethylamino)-1,2,4-triazine (*XIII*)

A solution of the trichlorotriazine[1] *I* (1·84 g; 0·01 mol) in ether (20 ml) was added at −78°C to magnetically stirred 7·2% methanolic dimethylamine (25 ml). The resulting solution was kept at room temperature for 30 min and evaporated. The residue was taken up into benzene (50 ml), the insoluble dimethylamine hydrochloride filtered off, and washed with benzene. The benzene filtrate and washings were passed through a layer of alumina (100 g) and the column washed with ether (300 ml). The effluents were combined, evaporated, and the residual oil dissolved in boiling tetrachloromethane (3 ml). The solution was cooled down (Dry Ice-ethanol) to the temperature of −78°C to deposit the substance *XIII* which was rapidly collected with suction, inserted into a vacuum desiccator, and kept there under diminished pressure over conc. sulfuric acid and potassium hydroxide pellets. Compound *XIII* is hygroscopic and liquefies on air. A damp sample melts unsharply at 40−50°C; R_F 0·28 (in S_2). The product was analysed in the form of a picrate which was obtained in an almost quantitative yield by precipitating a 10% ethereal solution of the base with a small excess of saturated ethereal picric acid. M.p. of the picrate, 174−175°C (ethanol). For $C_{13}H_{15}ClN_8O_7$ (431·0) calculated: 36·23% C, 3·51% H, 26·00% N, 8·23% Cl; found: 36·53% C, 3·80% H, 26·01% N, 8·57% Cl.

6-Methoxy-3,5-bis(dimethylamino)-1,2,4-triazine (*XIV*)

A. A solution of the triazine *XIII* (0·605 g; 0·003 mol) in 0·5M methanolic sodium methoxide (6 ml) was heated in a sealed tube for 6 h at the bath temperature of 100°C. The content of the tube was cooled down, the precipitate filtered off, and the filtrate evaporated. The residual oil was thoroughly triturated with ether (50 ml), the insoluble solid filtered off, and the filtrate evaporated. The residue (0·151 g) was crystallised from light petroleum to afford 0·112 g (19%) of the triazine *XIV*, m.p. 93−94°C; R_F 0·10 (in S_3). For $C_8H_{15}N_5O$ (197·2) calculated: 48·71% C, 7·67% H, 35·51% N, 15·73% OCH_3; found: 48·91% C, 7·52% H, 35·80% N, 16·05% OCH_3.

B. A solution of the triazine *VIII* (0·094 g; 0·5 mmol) in 7·2% methanolic dimethylamine (5 ml) was heated in a sealed tube for 15 h at 100°C (bath temperature). The methanol was evaporated and the residue triturated with ethyl acetate (20 ml). The insoluble portion was filtered off, the filtrate concentrated to half of the original volume, and the concentrate applied to a column of silica gel (10 g). Ethyl acetate (180 ml) was used as eluant (fractions 1−90). Fractions 40−56 were evaporated and the residue refluxed with light petroleum (2 ml). The mixture was cooled down, a small amount of the insoluble portion filtered off, and the filtrate evaporated. The residue was crystallised from light petroleum to afford 0·016 g (16%) of the triazine *XIV*, m.p. 93−94°C, undepressed on admixture with the product of procedure *A*.

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