DERIVATIVES OF s-TRIAZINE.

I. REACTION BETWEEN 2-CHLORO-4,6-DIMETHOXY-s-TRIAZINE AND SODIUM MALONATE

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Atoms of chlorine in chlorine-substituted s-triazine, as is well-known, exhibit a greater tendency toward reactions of nucleophilic substitution than α-atoms of chlorine in analogous pyridines and pyrimidines. Nevertheless, reactions of malonate synthesis, opening up the way to C—C-substituted compounds, have been very little investigated in a number of chlorotriazines.

In 1894, the publication [1] described a reaction between cyanuric chloride and sodium malonate in alcohol with the formation of 2,4-dihydroxy-s-triazinyl malonate, without specifying the yield of this reaction product. In 1972-1975 it was shown that [2-4] cyanuric chloride reacts with sodium malonate in dioxane and, after treatment with aqueous solutions, derivatives of hydroxy-s-triazine with residues of malonate are obtained in yields up to 10%. Alkoxy-s-triazinyl malonates are not described in the literature.

To the end of the synthesis of 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine, the present authors made a study of the reaction between 2-chloro-4,6-dimethoxy-s-triazine (I) and sodium malonate under different conditions. It was found optimal to conduct the process in dimethylformamide at 80°C with chromatographic separation of the products. The use in the synthesis of sodium malonate instead of the sodium hydride of metallic sodium worsens the results. The yields are also lowered if, in the state of obtaining or separating the reaction products, protic solvents are used; this is obviously connected with the ease of saponification of the methoxy group and the splitting of the triazine cycle. Thus, the use of water in separation of the reaction products leads to the formation, along with 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (II) (15.4%), of 2-(dicarboethoxymethylene)-4-oxo-6-methoxy-1,2,3,4-tetrahydro-s-triazine (III) (5%). Even under optimal conditions, the yield of the compound II is 53.5% and there are side reactions. Due to a reaction between chlorodimethoxytriazine I and the dimethylamine contained in dimethylformamide in an amount up to 0.15%, there is formed 2-dimethylamino-4,6-dimethoxy-s-triazine (IV) (yield 5%), which has also been synthesized by the present authors with a yield of 77% by the reaction between the chloride I and aqueous dimethylamine. The compound IV was obtained earlier by a more complex path [5].

Part of the compound II formed as a result of the reaction separates out in the form of a sodium derivative (V), only slightly soluble in ether and water, which was also obtained by the present authors with the treatment of the compound II with an aqueous solution of caustic soda. In this case, the sodium derivative 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (V) falls out into the residue from the aqueous solution.

From the reaction mixture there was also obtained 2-(4',6'-dimethoxy-s-triazinyloxy)-4,6-dimethoxytriazine (VI), in a small yield (around 1%). Another, minor product of this reaction is 2-(carboethoxymethyl)-4,6-dimethoxy-s-triazine (VII); this has not been separated out in pure form, and its structure is postulated on the basis of mass-spectroscopic data for a product containing an admixture of the substance VII.

The methoxy groups in the triazine ring of the compound II are more reactive than the ester groups of the residue of the malonate. Treatment of the substance II with concentrated hydrochloric acid at 20°C leads to 2-(dicarboethoxymethylene)-4,6-dioxohexahydro-s-triazine (VIII) with a yield of 58%, identical with the previously described product of the reaction between cyanuric chloride and sodium malonate [1, 2].

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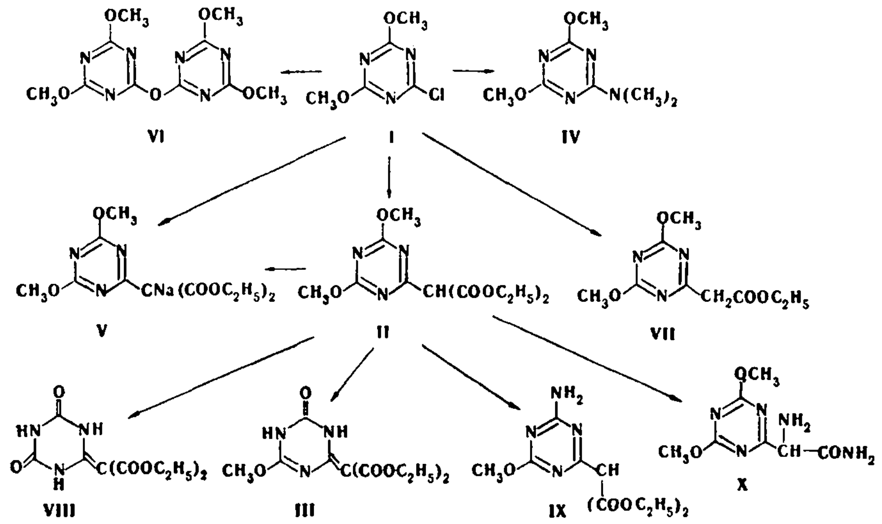

With an alcohol solution of ammonia at 20°C, the methoxy group is substituted by an amino group and there is formed 2-(dicarboethoxymethyl)-4-amino-6-methoxy-s-triazine (IX), and the side product of this reaction is 2-(carboxyamidoaminomethyl)-4,6-dimethoxy-s-triazine (X).

On the basis of the data of PMR spectroscopy, the compounds II, IX, and X are characterized by an ordinary bond between the aromatic s-triazine ring and the carbon-containing substituent in position 2. The compound VIII, in accordance with the literature data [4], has a dioxodicarboethoxymethylenehexahydro-s-triazine structure. An analogous transition to a dicarboethoxymethylene structure is observed also for the compound III, where there is only one oxo group in the ring.

EXPERIMENTAL

The IR spectra were recorded in a Perkin–Elmer-457 spectrometer in Vaseline oil, and the PMR spectra in a JNM-4H-100 spectrometer in $CDCl_3$ (internal standard TMS). The mass spectra were obtained in a Varian MAT-112 (direct introduction) at 70 eV. Thin-layer chromatography was carried out on Silufol UV-254 plates (R_f are given for the system benzene–ethyl acetate, 3:1, for an ascending chromatogram). The chromatography in the column (650 × 30 mm) was carried out on brand L 40/100 μ, or aluminum oxide of the II degree of activity.

Reaction between 2-Chloro-4,6-dimethoxy-s-triazine (I) and Sodium Malonate. 1) To a suspension of 1.23 g (51.3 mmole) of sodium hydride in 60 ml of anhydrous dimethylformamide 7.8 ml (51.3 mmole) of malonate is gradually added in a stream of argon at a temperature not above 40°C. After the end of the evolution of hydrogen, the mixture is held for 20 min and portions of 6 g (34.2 mmole) of 2-chloro-4,6-dimethoxy-s-triazine (I) are added. The reaction is monitored by the disappearance of the spot of I (R_f 0.67) on the thin-film chromatogram. The reaction mixture then evaporated in a vacuum. The residue is pulverized with 150 ml of anhydrous ether. The insoluble residue (4.72 g) is filtered, washed with 500 ml benzene, and extracted with sodium chloride (2.01 g) in 150 ml of hot anhydrous ethanol; this yields 2.24 g of 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine. The ether solution was evaporated in a vacuum. The residue was dissolved in a minimal amount of benzene and chromatographed in a column with 200 g of silica gel. With the elution of 500 ml of a mixture of benzene–ethyl acetate (17:3), there is obtained 3.22 g of 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (II). The total yield of substance II is 5.46 g (53.5%). Colorless crystals; mp 32-33°C (from heptane). The substance is readily soluble in the usual organic solvents and insoluble in water; R_f 0.52. IR spectrum: 1740 cm^{-1} ($COOC_2H_5$); PMR spectrum: 1.20 (6H, t, CH_3-CH_2); 3.95 (6H, s, OCH_3); 4.21 (4H, q, CH_2-CH_3); 4.73 ppm (1H, s, CH); mass spectrum: 299 ($M^{+\bullet}$); 269 [$(M - OCH_2)^{+\bullet}$]; 254 [$(M - OC_2H_5)^{+}$]; 227 [$(M - CO_2 - C_2H_4)^{+\bullet}$]; 182 [$(M - CO_2 - C_2H_4 - OC_2H_5)^{+}$]; 155 [$(M - 2CO_2 - 2C_2H_4)^{+\bullet}$]. Found: C 48.5; H 5.9; N 14.0%. $C_{12}H_{17}N_3O_6$. Calculated: C 48.2; H 5.7; N 14.0%.

With further elution of 400 ml of the same mixture of benzene and ethyl acetate, there is obtained a mixture of the substances IV and VII (according to mass-spectroscopic data, molecular peaks with m/e 184 and 227), in which the main compound is the substance IV (R_f

0.34). Yield of IV 0.33 g (5%). After recrystallization from alcohol, a substance is obtained with a melting point of 102-103°C, which, according to its IR spectrum, is identical with 2-dimethylamino-4,6-dimethoxy-s-triazine (IV), synthesized from I and dimethylamine (see below). PMR spectrum (in $CDCl_3$): 3.17 (6H, s, NCH_3); 3.95 ppm (6H, s, OCH_3); mass spectrum: 184 $[(M^{+\bullet})]$; 169 $[(M - CH_3)^+]$; 155 $[(M - NCH_3)^{+\bullet}]$; 154 $[(M - OCH_2)^{+\bullet}]$; 139 $[(M - OCH_2 - CH_3)^+]$.

With the further elution of 350 ml of the same mixture of benzene and ethyl acetate, there are taken from the column 0.14 g of a mixture of substances, from which, after recrystallization from benzene, there are obtained 0.07 g (0.7%) of 2-(4',6'-dimethoxy-s-triazinyloxy)-4,6-dimethoxy-s-triazine (VI). Colorless crystals, mp 164-165° (from benzene) [6]. The substance is readily soluble in alcohols and chloroform, and only slightly soluble in benzene in water. PMR spectrum: 4.00 ppm (12H, s, OCH_3); mass spectrum: 296 $[(M^{+\bullet})]$; 281 $[(M - CH_3)^+]$; 266 $\{[(M - 2CH_3)^+]$; $[(M - OCH_2)^{+\bullet}]\}$; 251 $[(M - 3CH_3)^+]$; 236 $[(M - 4CH_3)^+]$. Found: C 40.9; H 4.4; N 28.4%. $C_{10}H_{12}N_6O_5$. Calculated: C 40.9; H 4.0; N 28.4%.

2) To sodium malonate, prepared from 11.5 g (74 mmole) of malonate and 1.78 g (74 mmole) of sodium hydride in dimethylformamide in accordance with the above-described method, there is added 6.48 g (37 mmole) of chloride I, by small portions. The reaction mixture is heated for 1 h and 30 min at 80°C, cooled to 5°C, and 180 ml of water are added. It is extracted with ether (4 × 70 ml). The ether extract is dried with magnesium sulfate, and evaporated to dryness. The residue is distilled at 145-150° (1 mm). There are obtained 1.7 g (15.4%) of the substance II, identical to that described above.

After extraction with ether, the aqueous solution is acidified with hydrochloric acid to pH 6.5-7 and again extracted with ether (4 × 70 ml). The ether extract is dried with sodium sulfate and boiled until dessicated. There are obtained 3.58 g of a mixture of substances, from which, after pulverization with 5 ml ether, there are separated out 0.46 g (5%) of 2-(dicarboethoxymethylene-4-oxo-6-methoxy-1,2,3,4-tetrahydro-s-triazine (III), which, according to thin-layer chromatography, has one spot with Rf 0.70. Colorless crystals, mp 135-135.5°C (from petroleum ether). The substance is readily soluble in ordinary organic solvents, and only slightly soluble in water. IR spectrum: 1750 cm^{-1}:$(COOC_2H_5)$. PMR spectrum: 1.5 (6H, t, CH_3—CH_2), 3.51 (3H, s, OCH_3), 4.45 (4H, q, CH_2—CH_3), 12.35 ppm (broad signal of NH). Mass spectrum: 285 $[(M^{+\bullet})]$, 257 $[(M - C_2H_4)^{+\bullet}]$, 240 $[(M - OC_2H_5)^+]$, 213 $[(M - CO_2 - C_2H_4)^{+\bullet}]$, 184 $[(M - CO_2 - C_2H_4 - C_2H_5)^+]$, 168 $[(M - CO_2 - C_2H_4 - OC_2H_5)^+]$, 141 $[(M - 2CO_2 - 2C_2H_4)^{+\bullet}]$. Found: C 46.6; H 5.4; N 15.0%. $C_{11}H_{15}N_3O_6$. Calculated: C 46.4; H 5.3; N 14.8%.

2-Dimethylamino-4,6-dimethoxy-s-triazine (IV). A suspension of 2 g (11.4 mmole) of chloride I in 25 ml of a 33% aqueous solution of dimethylamine (164 mmole) is mixed for 2 h at 20°C, 30 ml of water are added, and the solution is extracted with ethyl acetate (3 × 50 ml). The ethyl acetate extracts are dried with magnesium sulfate and evaporated in a vacuum. There are obtained 1.61 g (77%) of 2-dimethylamino-4,6-dimethoxy-s-triazine (IV). Colorless crystals, mp 102-103°C (from ethyl alcohol) [5]. Found: C 45.4; H 6.5; N 30.4%. $C_7H_{12}N_4O_2$. Calculated: C 45.6; H 6.6; N 30.4%.

2-(Dicarboethoxymethylene)-4,6-dioxohexahydro-s-triazine (VIII). A solution of 1 g (3.35 mmole) of 2-(dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (II) in 12 ml concentrated hydrochloric acid is left to stand for 3 days at 20°C. The residue of compound VIII separating out is filtered and washed with water to a neutral reaction. There are obtained 0.52 g (58%) of compound VIII. Colorless crystals, mp 185-186°C (from water) [2]. The substance is readily soluble in acetone, benzene, chloroform, alcohols, and dimethylformamide, and only slightly soluble in water; it is insoluble in petroleum ether. IR spectrum: 1715, 1860 cm^{-1} $(COOC_2H_5)$. PMR spectrum: 1.23 (6H, t, CH_3—CH_2), 4.20 (4H, q, CH_2—CH_3), 12.35 ppm (broad signal of NH). Mass spectrum: 271 $[(M^{+\bullet})]$, 243 $[(M - C_2H_4)^{+\bullet}]$, 226 $[(M - C_2H_5O)^+]$, 199 $[(M - CO_2 - C_2H_4)^{+\bullet}]$, 154 $[(M - CO_2 - C_2H_4 - OC_2H_5)^+]$, 127 $[(M - 2CO_2 - 2C_2H_4)^{+\bullet}]$. Found: C 44.9; H 5.0; N 15.7%. $C_{10}H_{19}N_3O_6$. Calculated: C 44.4; H 4.9; N 15.5%.

Sodium Derivative of 2-(Dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (V). A solution of 0.26 g (0.87 mmole) of a suspension of compound II in 3 ml of a 10% aqueous solution of caustic soda is left to stand for 1 day at 20°C. The residue falling out is filtered and washed with a minimal amount of water. There are obtained 0.04 g (14%) of the sodium derivative V. Colorless crystals, mp 159-160°C (decomp.). Found: C 45.1; H 5.1; N 13.1; Na 7.2%. $C_{12}H_{16}N_3NaO_6$. Calculated: C 44.9; H 5.0; N 13.1; Na 7.2%.

Reaction between 2-(Dicarboethoxymethyl)-4,6-dimethoxy-s-triazine (II) and Ammonia. To a solution of 2.38 g (8 mmole) of compound II in 5 ml anhydrous alcohol there are added 25 ml of alcohol saturated with ammonia (~10%); the mixture is left to stand for 2 days at 20°C. The reaction mixture is then evaporated to dryness in a vacuum. To the residue there are added 5 ml of ether. The residue separating out (0.3 g) is filtered and recrystallized from 6 ml of water. There are obtained 0.14 g (8%) of 2-(carboxyamidoaminomethyl)-4,6-dimethoxy-s-triazine (X). Colorless crystals, mp 186-187°C (decomp.). The substance is readily soluble in acetone and chloroform, and only slightly soluble in ether and water. IR spectrum: 1650 ($CONH_2$), 3140, 3330 cm^{-1} (NH_2). PMR spectrum (in DMSO): 3.82 (6H, s, OCH_3), 7.16 and 7.24 ppm (broad signals of NH). Mass spectrum: 213 [$(M^{+\bullet})$], 183 [$(M - OCH_2)^{+\bullet}$]. Found: C 39.7; H 5.2; N 32.6%. $C_7H_{11}N_5O_3$. Calculated: C 39.4; N 5.2; N 32.8%.

After separation of X, the ether filtrate is evaporated in a vacuum. To the residue there are added 10 ml of water. The crystalline substance which is insoluble in water is filtered and washed with water. There are obtained 0.47 g (21%) of 2-(dicarboethoxymethyl)-4-amino-6-methoxy-s-triazine (IX). Colorless crystals, mp 109-110°C (from water). The substance is readily soluble in acetone, alcohols, chloroform, benzene and ethyl acetate, and only slightly soluble in water. IR spectrum: 1745 ($COOC_2H_5$), 3320 and 3370 cm^{-1} (NH_2). PMR spectrum (in DMSO): 1.20 (6H, t, $CH_3{-}CH_2$), 3.83 (3H, s, OCH_3), 4.15 (4H, q, $CH_2{-}CH_3$), 4.65 ppm (1H, s, CH). Mass spectrum: 284 [$(M^{+\bullet})$], 254 [$(M - OCH_2)^{+\bullet}$], 239 [$(M - OC_2H_5)^{+}$], 212 [$(M - CO_2 - C_2H_4)^{+\bullet}$], 168 [$(M - CO_2 - C_2H_4 - OC_2H_5)^{+}$], 140 [$(M - 2CO_2 - 2C_2H_4)^{+\bullet}$]. Found: C 46.5; H 5.7; N 20.0%. $C_{11}H_{16}N_4O_5$. Calculated: C 46.5; H 5.6; N 19.8.

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SYNTHESIS AND SOME CONVERSIONS OF 2,3-DIHYDRO-2-CARBALKOXYMETHYL-3-IMINO-5,6-DIPHENYL-1,2,4-TRIAZINE

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Continuing investigations of the alkylation of substituted 3-amino-1,2,4-triazine (I) by α-halocarbonyl compounds [1], with the aim of obtaining new representations of the series imidazo[1,2-b]-1,2,4-triazine, we made a study of the action of the esters of α-haloacetic acids on I, and some of the conversions of the 2,3-dihydro-2-carbalkoxymethyl-3-imino-5,6-diphenyl-1,2,4-triazines formed in this case (IIa-c). With the heating of I with the bromium (iodine) esters of acetic acids in low-boiling solvents (lower alcohols, acetone) the hydrohalide salts IIa, b are formed. An analogous product (IIc) is formed when the process is conducted without a solvent, for example, in a medium of the methyl ester of chloroacetic acid.

In the IR spectra of IIa-c there are observed two characteristic absorption bands of an ester grouping in the region 1740-1760 and 1230-1245 cm^{-1} due to the group C=O and the ordinary bond C—O. The absorption bands for the imino group appear at 3280-3310 cm^{-1}.

The compounds IIa-c are easily saponified in concentrated hydrochloric acid to the hydrochloride of 2,3-dihydro-3-imino-5,6-diphenyl-1,2,4-triazinyl-2-acetic acid (III), which is confirmed by the appearance of bands of the OH group in the IR spectrum.

Alkaline hydrolysis of the esters (IIa-c) leads to the formation of a dicyclic product, i.e., 2,3-diphenyl-6-oxo-6,7-dihydroimidazo[1,2-b]-1,2,4-triazine (IV). The process obviously takes place through a stage of the formation of a unstable acid (III), which in an

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