s-TRIAZINE DERIVATIVES

2.* A STUDY OF THE REACTIONS OF SODIOMALONIC ESTER WITH 2,4-DICHLORO-6-METHOXY-s-TRIAZINE AND CYANURYL CHLORIDE

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2,4-Dichloro-6-methoxy-s-triazine reacts with sodiomalonic ester in dimethylformamide at room temperature to give 2,4-bis(diethoxycarbonylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine which forms a sodium salt with caustic soda. Under similar conditions cyanuryl chloride forms 2,4,6-tris(dimethoxycarbonylmethylene)-hexahydro-s-triazine and 2-chloro-4,6-bis(diethoxycarbonylmethylene)tetrahydro-s-triazine.

In a preceding communication [1] we described the synthesis of the first representatives of alkoxy-s-triazinylmalonic esters by reactions of monochloroalkoxy-s-triazines with sodiomalonic ester. It was shown that even in an aprotic medium these reactions take place ambiguously and, in addition to the main products, the yields of which amount to about 50%, by-products are formed, which were separated by preparative chromatography. It could be expected that the reaction of sodiomalonic ester with 2,4-dichloro-6-methoxy-s-triazine (I), where the number of reacting chlorine atoms has risen, the possibility of an ambiguous course of the process would be substantially increased. In view of this it was necessary to develop the optimum conditions for performing this reaction. As in the preceding investigation [1], it proved to be desirable to perform the process in anhydrous dimethylformamide in the absence of protonic solvents and to obtain the sodiomalonic ester with sodium hydride. To determine the end of the reaction we used the TLC method. Conditions for performing the process were selected under which the spot of the initial (I) disappeared. During these investigations it was established that the final product of the reaction — 2,4-bis(diethoxycarbonylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (II) — readily forms a monosodium derivative (III) which is highly soluble in dimethylformamide and sparingly soluble in diethyl ether. For the reaction to take place sufficiently completely a fivefold excess of sodiomalonic ester is required. Under these conditions the yield of compound (II) amounted to 75%, and its isolation in the form of the sodium derivative (III) caused no difficulties. A decrease in the amount of sodiomalonic ester to 3 mole per mole of substance (I) led to a fall in the yield to 44%. A further increase in the excess of sodiomalonic ester is undesirable, since it contaminates the compound (III) and after neutralization substance (II) is obtained in admixture with malonic ester and is partially lost through dissolution in it. The yield of compound (II) in the reaction of, for example, 6 moles of sodiomalonic ester with 1 mole of substance (I) amounted to 61%. A variation in the temperature (from 10 to 80°C) and in the time of the reaction (from 1 to 3 h) did not appreciably affect the yield of compound (II).

The methoxy group in compound (II) is almost completely saponified by concentrated hydrochloric acid at room temperature, forming 2,4-bis(diethoxycarbonylmethylene)-6-oxohexahydro-s-triazine (IV), identical with the product of the reaction of sodiomalonic ester with cyanuryl chloride described previously [2]. With an aqueous solution of caustic soda at room temperature, substance (II) is easily converted into the monosodium derivative (III).

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*For communication 1, see [1].

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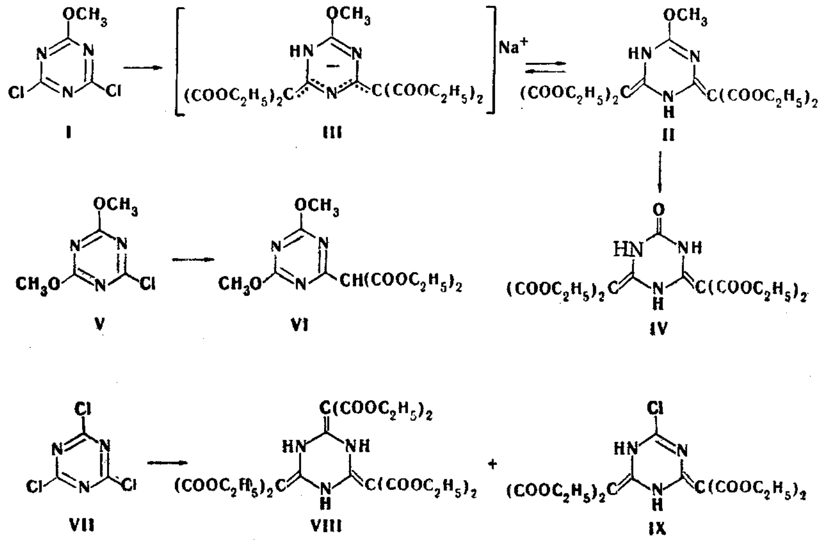

We have also used the optimum conditions for the condensation of sodiomalonic ester with the dichlorotriazine (I) found in the present work in the analogous reactions with the mono- and trichlorotriazines (V) and (VII). As in the case of compound (I), for the monochlorotriazine the optimum ratio proved to be 2.5 moles of sodiomalonic ester for each chlorine atom of the particular chlorotriazine taking part in the reaction. Under these conditions the yield of 2-(diethoxycarbonylmethyl)-4,6-dimethoxy-s-triazine (VI) increased from 53% when using 1.5 mole of sodiomalonic ester per mole of the chloride (V) to 78%. The isolation of the compound (VI) was simultaneously simplified. A further increase in the excess of sodiomalonic ester did not give satisfactory results in this case, either. As in the reaction of sodiomalonic ester with the dichlorotriazine (I), in the process under investigation a change in the temperature from 10 to 80°C and in the time of the reaction from 1 to 3 had no appreciable influence on the yield of substance (VI).

Somewhat different results were obtained in the reaction of sodiomalonic ester with cyanuryl chloride (VII). This reaction was first performed in 1894 in ethanol with no indication of the yield of 2-(diethoxycarbonylmethyl)-4,6-dihydroxy-s-triazine formed [3]. Subsequently, when the reaction was performed in dioxane followed by treatment with water [2, 4], s-triazine derivatives containing, depending on the ratio of substances used in the reaction, one, two, or three malonic ester residues and, as residual substituents on the carbon atom of the ring, hydroxy groups were obtained with yields of the order of 10%. We have shown that in dimethylformamide under conditions similar to those described above, a variation in the temperature from 10 to 80% and in the time from 1 to 3 h does not appreciably affect the results of the reaction. In all cases when using an excess of sodiomalonic ester, together with 2,4,6-tris(diethoxycarbonylmethylene)hexahydro-s-triazine (VIII) we also obtained 2-chloro-4,6-bis(diethoxycarbonylmethylene)tetrahydro-s-triazine (IX), and not its 6-hydroxy derivative as described in the literature [2, 4]. Apparently, the saponification of the chlorine atom in position 2 of compound (IX) is a secondary reaction determined by the nature of the working up of the reaction mixture. The magnitude of the excess of sodiomalonic ester has a substantial influence on the ratio of the amounts of substances (VIII) and (IX) formed: with a fourfold excess the yields of substances (VIII) and (IX) were 20 and 40%, respectively, and with an eightfold excess 71 and 2.5%. It must be mentioned that compound (VIII), unlike compound (II) and (VI), does not form a sparingly soluble sodium derivative during the reaction. No sodium derivative arises, either, when the isolated substance (VIII) is treated with an aqueous solution of caustic soda.

Compound (VI), having only one malonic ester residue, exists in the form of an aromatic s-triazine derivative bound with the malonic ester residue by an ordinary carbon bond. On passing to compound (II), (IV), (VIII), and (IX) where there are two and more malonic residues, the lateral carbon chains are bound to partially or completely reduced triazine rings by multiple bonds.

Questions of the tautomeric transitions in such a series of compounds require a special study.

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer 457 spectrometer in paraffin oil, and the PMR spectra on a JNM-4H-100 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained on a MAT-112 instrument (direct introduction) at 70 eV. TLC was performed on Silufol UV-254 plates (R_f values are given for the benzene—ethyl acetate (3 : 1) system).

Reaction of 2,4-Dichloro-6-methoxy-s-triazine (I) with Sodiomalonic Ester. In a current of nitrogen with stirring, 7.6 ml (0.05 mole) of malonic ester was gradually added to a suspension of 1.2 g (0.05 mole) of sodium hydride, a temperature not exceeding 40°C being maintained. After 20 min from the end of the evolution of hydrogen, 1.8 g (0.01 mole) of compound (I) [5] was added in portions. The mixture was stirred at room temperature for 1 h, the completion of the reaction being checked by the TLC method (from the disappearance of the spot of compound (I) with R_f 0.85). Then the reaction mixture was evaporated in vacuum. The residue was triturated with 150 ml of anhydrous ether. The insoluble precipitate (5.52 g) was filtered off and dissolved in 500 ml of water. The aqueous solution was neutralized with concentrated HCl to pH 7. The precipitate that deposited was filtered off and washed with 50 ml of water to give 2.33 g of compound (II) with R_f 0.54. The aqueous mother solution was extracted with ethyl acetate (3 × 50 ml), and the extract was dried with magnesium sulfate and evaporated. This gave an additional 0.04 g of substance (II), the total yield being 2.37 g (75%); colorless crystals with mp 149-150°C (from ethanol), readily soluble in chloroform, benzene, acetone, and ethyl acetate, and insoluble in water and petroleum ether. IR spectrum, cm^{-1}: 1720 ($COOC_2H_5$); PMR spectrum (ppm): 1.10-1.45 (overlapping t, $\underline{CH_3}{-}CH_2$); 3.95 (3 H, s, OCH_3); 4.10-4.45 (overlapping q, $\underline{CH_2}{-}CH_3$). A singlet in the 3.50-6.00 region characteristic for $\underline{CH}(COOC_2H_5)_2$ was absent. Mass spectrum, m/e: 427 ($M^{+\cdot}$), 397 $[M - OCH_2)^+]$, 382 $[(M - OC_2H_5)^+]$, 355 $[(M - CO_2 - C_2H_4)^{+\cdot}]$, 310 $[(M - CO_2 - C_2H_4 - OC_2H_5)^+]$, 283 $[(M - 2CO_2 - 2C_2H_4)^{+\cdot}]$, 282 $[(M - C_2H_5COO - CO_2 - C_2H_4)^+]$, 237 $[(M - 2CO_2 - 2C_2H_4 - OC_2H_5)^+]$, 236 $[(M - CO_2 - C_2H_4 - C_2H_5COO - C_2H_5OH)^+]$, 192 $[(M - 2CO_2 - 2C_2H_4 - 2OC_2H_5)^+]$. Found: C 50.5; H 6.0; N 9.7%. $C_{18}H_{25}N_3O_9$. Calculated: C 50.6; H 5.9; N 9.9%.

Sodium Derivative of 2,4-Bis(diethoxycarbonylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (III). A mixture of 0.5 g (1.17 mmole) of compound (II) and 15 ml of 10% aqueous caustic soda solution was stirred at room temperature for 1 h and 30 min, and the precipitate was filtered off and washed with 2 ml of water. This gave 0.4 g (77%) of the sodium derivative (III) in the form of colorless crystals with mp >270°C. Found: C 47.9; H 5.1; N 9.4; Na 4.9%. $C_{18}H_{24}N_3NaO_9$. Calculated: C 48.1; H 5.4; N 9.4; Na 5.1%.

2,4-Bis(diethoxycarbonylmethylene)-6-oxohexahydro-s-triazine (IV). A mixture of 0.5 g (1.1 mmole) of compound (II) in 10 ml of concentrated HCl was stirred at room temperature for 2 h and was left overnight. The precipitate was filtered off, washed with water to neutrality, and recrystallized from 20 ml of ethanol. This gave 0.4 g (83%) of compound (IV) in the form of colorless crystals with mp 177.5-178°C. The IR spectrum of the substance was identical with that described in the literature [2].

2-(Diethoxycarbonylmethyl)-4,6-dimethoxy-s-triazine (VI). In a current of nitrogen with vigorous stirring, 3.8 ml (0.025 mole) of malonic ester was gradually added to a suspension of 0.6g (0.025 mole) of sodium hydride in 25 ml of anhydrous dimethylformamide, a temperature not higher than 40°C being maintained, and 20 min after the evolution of hydrogen had ceased 1.75 g (0.01 mole) of 2-chloro-4,6-dimethoxy-s-triazine (V) [5] was added in portions. The reaction mixture was stirred at room temperature for 1 h, the completion of the reaction being checked by the TLC method (from the disappearance of the spot of compound (V) with R_f 0.67). Then the reaction mixture was evaporated in vacuum. The residue was triturated with 150 ml of anhydrous ether. The insoluble residue (3.38 g) was filtered off and dissolved in 300 ml of water. The aqueous solution was neutralized with concentrated HCl to pH 7, and the reaction product was extracted with ethyl acetate (3 × 100 ml). The extract was dried with magnesium sulfate and evaporated. This gave 2.33 g (78%) of compound (VI) giving on TLC a single spot with R_f 0.52. The IR and PMR spectra of the substance were identical with those described previously [1]; mp 32-33°C (from heptane).

Reaction of Cyanuryl Chloride (VII) with Sodiomalonic Ester. At 10°C, and with the temperature not being allowed above 13°C, 3.7 g (0.02 mole) of cyanuryl chloride (VII) was added in portions to the sodiomalonic ester obtained by the method described above from 3.84 g (0.16 mole) of sodium hydride and 24.3 ml (0.16 mole) of malonic ester in 40 ml of anhydrous dimethyl formamide. The mixture was stirred at the same temperature for 1 h, the end of the reaction being checked by the TLC method (from the disappearance of the spot of substance (VII) with R_f 0.96). Then it was evaporated in vacuum and the residue was stirred with 350 ml of chloroform and 200 ml of water. The chloroform layer was separated off, dried with magnesium sulfate, and evaporated, to yield 7.91 g (71%) of 2,4,6-tris(diethoxycarbonylmethylene)hexahydro-s-triazine (VIII) giving a single spot on TLC with R_f 0.57. Colorless crystals with mp 190.5-191.5°C (from ethanol) [2]. The IR, PMR, and mass spectra of compound (VIII) were identical with those described in the literature [2, 4, 6].

The aqueous solution was neutralized with concentrated HCl, and the precipitate of 2-chloro-4,6-bis(diethoxycarbonylmethylene)tetrahydro-s-triazine (IX) that had deposited was extracted with chloroform (3 × 100 ml), and the extract was dried with magnesium sulfate and evaporated. This gave 0.21 g (2.4%) of compound (IX) (R_f 0.68) in the form of light yellow crystals with mp 142.5-143°C (from ethanol).* The substance was soluble in petroleum ether and water. IR spectrum, cm^{-1}: 1725 ($COOC_2H_5$); PMR spectrum, ppm: 1.15-1.45 (overlapping t, $\underline{CH_3}-CH_2$), 4.15-4.45 ppm (overlapping q, $\underline{CH_2}-CH_3$); there was no singlet in the 3.5-6.00 region that is characteristic for the $CH(COOC_2H_5)_2$ group. Mass spectrum, m/e: 431 $[(M^{+\cdot})]$, 386 $[(M - OC_2H_5)^+]$, 385 $[(M - C_2H_5OH)^+]$, 359 $[(M - CO_2 - C_2H_4)^{+\cdot}]$, 340 $[(M - C_2H_5OH - C_2H_5O)^+]$, 314 $[(M - CO_2 - C_2H_4 - OC_2H_5)^+]$, 313 $[(M - CO_2 - C_2H_4 - C_2H_5OH)^{+\cdot}]$, 287 $[(M - 2CO_2 - 2C_2H_4)^{+\cdot}]$, 241 $[(M - 2CO_2 - 2C_2H_4 - C_2H_5OH)^{+\cdot}]$, 215 $[(M - 3CO_2 - 3C_2H_4)^{+\cdot}]$, 196 $[(M - 2CO_2 - 2C_2H_4 - C_2H_5OH - OC_2H_5)^+]$, 195 $[(M - 2CO_2 - 2C_2H_4 - 2C_2H_5OH)^{+\cdot}]$, 169 $[(M - 3CO_2 - 3C_2H_4 - C_2H_5OH)^+]$. Found: C 47.1; H 5.3; Cl 8.2; N 9.7%. $C_{17}H_{22}ClN_3O_8$. Calculated: C 47.3; H 5.1; Cl 8.2; N 9.7%.

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*In a patent [7], compound (V) is described as an oil.