s-TRIAZINE DERIVATIVES.

3.* INVESTIGATION OF THE REACTION OF CHLOROMETHOXY-s-TRIAZINES WITH CH ACIDS

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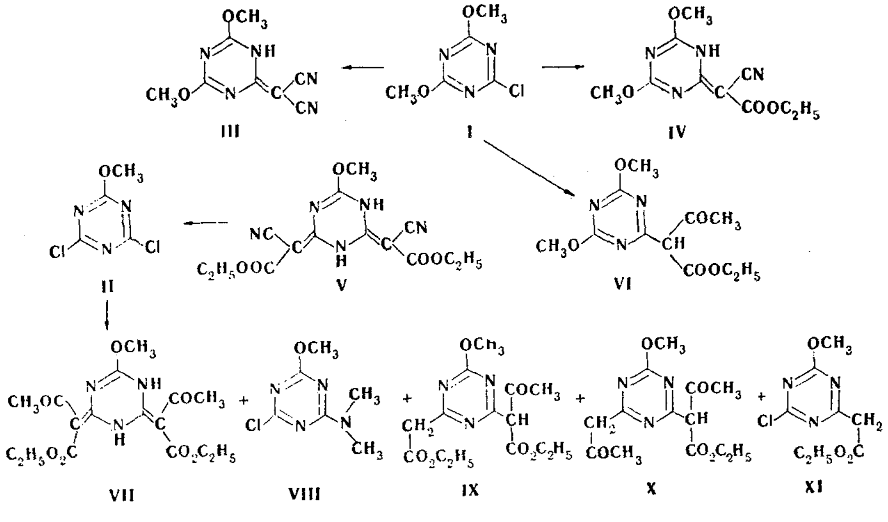
The condensation of 2-chloro-4,6-dimethoxy- and 2,4-dichloro-6-methoxy-s-triazines with sodium derivatives of ethyl esters of acetoacetic and cyanoacetic acids and malonodinitrile was investigated. 2-Dicyanomethylene-4,6-dimethoxy-1,2-dihydro-, 2-carbethoxycyanomethylene-4,6-dimethoxy-1,2-dihydro-, and 2,4-bis(carbethoxymethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazines were obtained in high yields.

In our preceding communications [1, 2] we described the products of the reaction of various chloro- and chloromethoxy-s-triazines with sodiomalonic ester. Continuing our investigation of the reactions of chlorotriazine compounds with salts of CH acids we have accomplished the condensation of 2-chloro-4,6-dimethoxy-s-triazine (I) and 2,4-dichloro-6-methoxy-s-triazine (II) with sodium derivatives of ethyl esters of acetoacetic and cyanoacetic acids and malonodinitrile.

The preparation of (4,6-dimethoxy-s-triazin-2-yl)malonodinitrile (III) in 82% yield by condensation of I with sodiomalonodinitrile in dimethoxyethane and similar reactions of I and II with methyl cyanoacetate have been reported [3].

The use of our previously employed [1, 2] method of condensation of chloromethoxy-s-triazines I and II with sodium salts of CH acids in anhydrous dimethylformamide (DMF) in the absence of protic solvents enabled us to raise the yield of III to 91%. The 2-dicyanomethylene-4,6-dimethoxy-1,2-dihydro-s-triazine structure was established for III by PMR spectroscopy. The reactions of I and II with the sodium derivative of ethyl cyanoacetate proceeded just as readily. 2-Carbethoxycyanomethylene-4,6-dimethoxy-1,2-dihydro-s-triazine (IV) and 2,4-bis(carbethoxycyanomethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (V) were obtained in 85 and 83% yields, respectively. The reaction proceeded ambiguously in the case of condensation of II with sodiomalonodinitrile, and we were unable to isolate individual products from the resulting complex mixture of substances.



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*See [1] for Communication 2.

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The reactions of I and II with the sodium derivative of ethyl acetoacetate proceeded ambiguously. 2-Carbethoxyacetylmethyl-4,6-dimethoxy-s-triazine (VI) was isolated in 41% yield from the products of the first reaction.

A mixture containing, according to data from thin-layer chromatography (TLC), no less than five different products was formed in the second reaction. 2,4-Bis(carbethoxyacetylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (VII) and 2-dimethylamino-4-chloro-6-methoxy-s-triazine (VIII) were isolated preparatively from this mixture in 21% and ∿3% yields, respectively. The formation of VIII is evidently due to the reaction of dichloromethoxytriazine II with the dimethylamine that is present in the DMF in up to 0.15% amounts. We have previously described a similar reaction of chlorodimethoxytriazine I [2]. Substance VIII was identical to the compound obtained by the method in [4]. Preparative chromatographic separation of the residual mixture with a column filled with silica gel enabled us to isolate in ∿0.6% yield the product of deacetylation of VII, viz., 2-carbethoxyacetylmethyl-4-carbethoxymethyl-6-methoxy-s-triazine (IX), and a mass-chromatographic study of the remaining substances made it possible to identify 2-carbethoxyacetylmethyl-4-acetylmethyl-6-methoxy-s-triazine (X) with m/e 295 and 2-carbethoxymethyl-4-chloro-6-methoxy-s-triazine (XI) with m/e 231 in the reaction products.

It is interesting that cleavage of the introduced carbethoxyacetylmethyl residues both at the acetyl and carbethoxy groups occurs in the reaction of II with sodioacetoacetic ester.

The structures of III-VIII are in good agreement with the data from the IR, PMR, and mass spectra and the results of elementary analysis. In particualr, the PMR spectra of VI and IX contain singlets of protons at 3.5-6.0 ppm that are characteristic for CH groups, while such signals are absent in the spectra of IV, V, and VII, but broad signals of NH protons appear at 12-14 ppm.

EXPERIMENTAL

The IR spectra of Vaseline oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra were recorded with a Varian XL-100A spectrometer on the δ scale with tetramethylsilane as the internal standard. The chromatographic mass spectra were obtained with a Varian MAT-112 spectrometer at 70 eV; the ionization chamber temperature was 180°C, the Varian 1440 chromatograph was equipped with a column filled with 3% SE-30 on Varaport 30, the column was 180 cm × 2 mm, the helium flow rate was 20 ml/min, the vaporization temperature was 250°C, the column temperature was 150-250°C, the heating rate was 15 deg/min, and the separator temperature was 260°C. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates [the R_f values are presented for the benzene—ethyl acetate system (3:1)]. Column chromatography (650 × 30 mm) was accomplished on L 40/100 μ silica gel.

Reaction of 2-Chloro-4,6-dimethoxy-s-triazine (I) with Malonodinitrile. A solution of 1.65 g (25 mmole) of malonodinitrile in 5 ml of DMF was added gradually with vigorous stirring at no higher than 40°C in a stream of nitrogen to a suspension of 0.6 g (25 mmole) of sodium hydride in 20 ml of anhydrous DMF. When hydrogen evolution was complete (after 20 min), 1.75 g (10 mmole) of I was added in portions, and the mixture was stirred at 20°C for 1 h. It was then evaporated *in vacuo*, and 30 ml of dilute hydrochloric acid was added. The precipitate was removed by filtration and washed with water to neutrality and with methylene chloride to remove the malonodinitrile to give 1.87 g (91%) of 2-dicyanomethylene-4,6-dimethoxy-1,2-dihydro-s-triazine (III) as colorless crystals with mp 195.5-196°C (dec.) [3] (from ethanol). The product was insoluble in ether, benzene, chloroform, and water but soluble in acetone and DMF. IR spectrum: 2216 cm^{-1} (CN). PMR spectrum (in d_6-DMSO): 3.95 ppm (6H, s, OCH_3). Mass spectrum: 205 $[(M)^+]$, 190 $[(M-CH_3)^+]$, 175 $[(M-OCH_2)^+]$, 160 $[(M-OCH_2-CH_3)^+]$, 145 $[(M-2OCH_2)^+]$. Found: C 46.8; H 3.5; N 34.5%. $C_8H_7N_5O_2$. Calculated: C 46.8; H 3.4; N 34.1%.

2-Carbethoxycyanomethylene-4,6-dimethoxy-1,2-dihydro-s-triazine (IV). A 2.7-ml (25 mmole) sample of ethyl cyanoacetate was added gradually with vigorous stirring in a stream of nitrogen to a suspension of 0.6 g (25 mmole) of sodium hydride in 25 ml of anhydrous DMF while maintaining the temperature of the reaction mixture at no higher than 40°C. When hydrogen evolution was complete (after 20 min), 1.75 g (10 mmole) of I was added in portions, and the mixture was stirred at 20°C for 1 h with monitoring of the end of the reaction by TLC (from the disappearance of the spot of I with R_f 0.67). It was then evaporated *in vacuo*, and the residue was triturated with 100 ml of anhydrous ether. The undissolved substance (3.6 g) was removed by filtration and dissolved in 200 ml of water, and the solution was neutralized to pH 7 with HCl. The precipitate was extracted with three 150-ml portions of ethyl acetate, and the extract was dried with magnesium sulfate and evaporated to give 2.13 g (84.5%) of IV with R_f 0.30 as colorless crystals with mp 195-195.5°C. The product was insoluble in petroleum ether and ether but soluble in chloroform, DMF, DMSO, and hot benzene, alcohols, acetone, ethyl acetate, water, and carbon tetrachloride. IR spectrum: 1630 ($COOC_2H_5$), 2215 cm^{-1} (CN). PMR spectrum (in $CDCl_3$): 1.35 (3H, t, CH_3CH_2); 4.11, 4.12 (6H, s, OCH_3); 4.27 (2H, q, CH_2CH_3); 12.8 ppm (broad NH signal). Mass spectrum: 252 $[(M)^+]$, 222 $[(M-OCH_2)^+]$, 207 $[(M-OC_2H_5)^+]$, 196 $[(M\ OCH_2-CN)^+]$, 193 $[(M-OCH_2-C_2H_5)^+]$, 180 $[(M-CO_2-C_2H_4)^+]$. Found: C 47.6; H 4.8; N 22.1%. $C_{10}H_{12}N_4O_4$. Calculated: C 47.6; H 4.8; N 22.2%.

2,4-Bis(carbethoxycyanomethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (V). A 1.8-g (10 mmole) sample of 2,4-dichloro-6-methoxy-s-triazine (II) was added in portions at no higher than 40°C to sodiocyanoacetic ester prepared as described in the preceding experiment from 1.2 g (50 mmole) of sodium hydride and 5.4 ml (50 mmole) of ethyl cyanoacetate in 25 ml of anhydrous DMF, and the reaction mixture was stirred at 20°C for 1 h with monitoring of the end of the reaction from the disappearance of the starting II with R_f 0.85. It was then evaporated *in vacuo*, and 50 ml of dilute hydrochloric acid was added. The precipitate was removed by filtration and washed to neutrality with water to give 2.77 g (83%) of V as colorless crystals with mp 203-204°C (dec., from acetonitrile). The product was insoluble in ether, benzene, ethyl acetate, chloroform, and water but soluble in acetone, DMF, DMSO, and hot alcohol. IR spectrum: 1680 ($COOC_2H_5$) and 2210 cm^{-1} (CN). PMR spectrum (in d_6-DMSO): 1.22 (6H, t, CH_3CH_2), 3.85 (3H, s, OCH_3), 4.12 (4H, q, CH_2CH_3), and 13.76 ppm (broad NH signal). Mass spectrum: 333 $[(M)^+]$, 287 $[(M-C_2H_5OH)^+]$, 259 $[(M-C_2H_5OH-C_2H_4)^+]$, 242 $[(M-C_2H_5OH-C_2H_5O)^+]$, 215 $[(M-C_2H_5OH-CO_2-C_2H_4)^+]$. Found: C 50.6; H 4.6; N 21.1%. $C_{14}H_{15}N_5O_5$. Calculated: C 50.5; H 4.6; N 21.0%.

2-Carbethoxyacetylmethyl-4,6-dimethoxy-s-triazine (VI). A 3.2-ml (25 mmole) sample of ethyl acetoacetate was added gradually with vigorous stirring in a stream of argon at no higher than 40°C to a suspension of 0.6 g (25 mmole) of sodium hydride in 25 ml of anhydrous DMF. When hydrogen evolution was complete (after 20 min), 1.75 g (10 mmole) of I was added in portions, and the mixture was stirred at 20°C for 1 h with monitoring of the end of the reaction from the disappearance of the spot of starting I with R_f 0.67. It was then evaporated *in vacuo*, and 80 ml of water was added. The aqueous mixture was extracted with ether (three 70-ml portions), and the ether extract was washed with water (three 30-ml portions), dried with magnesium sulfate, and evaporated to dryness. Water (30 ml) was added, and the precipitate was removed by filtration and washed with 20 ml of water to give 1.1 g (41%) of VI as colorless crystals with mp 94-95.5°C (from heptane). The product was quite soluble in ordinary organic solvents and hot water and had R_f 0.45. IR spectrum: 1717 ($COOC_2H_5$) and 1675 cm^{-1} ($COCH_3$). PMR spectrum (in $CDCl_3$): 1.29 (3H, t, CH_3CH_2), 2.47 (3H, s, $COCH_3$), 4.04 (3H, s, OCH_3), 4.2 (2H, q, CH_2CH_3), and 5.77 ppm (1H, s, CH). Mass spectrum: 269 $[(M)^+]$, 254 $[(M-CH_3)^+]$, 240 $[(M-C_2H_5)^+]$, 224 $[(M-C_2H_5O)^+]$, 196 $[(M-C_2H_5COO)^+]$, 182 $[M-C_2H_4-CO_2-CH_3)^+]$, 165 $[(M-C_2H_5COO-OCH_3)^+]$. Found: C 49.1; H 5.6; N 15.6%. $C_{11}H_{15}N_3O_5$. Calculated: C 49.4; H 5.5; N 15.3%.

Reaction of 2,4-Dichloro-6-methoxy-s-triazine (II) with Ethyl Acetoacetate. A 5-g (27.8 mmole) sample of triazine II was added in portions at no higher than 50°C to sodioacetoacetic ester prepared as described in the preceding experiment from 3.3 g (138 mmole) of sodium hydride and 17.5 ml (138 mmole) of ethyl acetoacetate in 85 ml of anhydrous DMF, and the reaction mixture was stirred at 20°C for 1 h with monitoring of the end of the reaction from the disappearance of the spot of starting II with R_f 0.85. It was then evaporated *in vacuo*, and 400 ml of water was added. The aqueous solution was extracted with ethyl acetate (three 70-ml portions), and the extract was washed with water, dried with magnesium sulfate, and evaporated to dryness. Ether (5 ml) was added, and the precipitate was removed by filtration to give 0.14 g (2.7%) of VIII as colorless crystals with mp 159.5-160°C [4]. Found: C 38.2; H 4.8; Cl 18.7; N 29.9%. $C_6H_9ClN_4O$. Calculated: C 38.2; H 4.8; Cl 18.8; N 29.7%.

The aqueous layer was neutralized to pH 7 with 17% hydrochloric acid and extracted with ethyl acetate (three 150-ml portions). The extract was dried with magnesium sulfate and evaporated, and 20 ml of ether was added. The precipitate was removed by filtration and washed with 10 ml of ether to give 1.93 g of 2,4-bis(carbethoxyacetylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine (VII) with R_f 0.30. The ether mother liquor was evaporated, and the residue was dissolved in the minimum amount of benzene and chromatographed with a column filled with 200 g of silica gel. Elution with benzene—ethyl acetate (9:1) gave 0.93 g of a light yellow oily product with R_f 0.56, which, according to the results of chromatographic mass spectrometry, was a mixture of 2-carbethoxymethyl-4-chloro-6-methoxy-s-triazine (XI) with m/e 231 [retention time 2 min 53 sec; mass spectrum: 231 $[(M^+)]$, 213 $[(M-H_2O)^+]$, 201 $[(M-OCH_2)^+]$, 196 $[(M-Cl)^+]$, 186 $[(M-OC_2H_5)^+]$, 185 $[(M-C_2H_5OH)^+]$, 159 $[(M-CO_2-C_2H_4)^+]$. The mass numbers are presented for ions that contain the ^{35}Cl isotope and 2-carbethoxyacetylmethyl-4-acetylmethyl-6-methoxy-s-triazine (X) with m/e 295 [retention time 6 min 33 sec; mass spectrum: 295 $[(M^+)]$, 280 $[(M-CH_3)^+]$, 266 $[(M-C_2H_5)^+]$, 250 $[(M-OC_2H_5)^+]$, 234 $[(M-C_2H_5OH-CH_3)^+]$, 222 $[(M-COOC_2H_5)^+]$, 208 $[(M-OC_2H_5-COCH_2)^+]$, 180 $[(M-COOC_2H_5-COCH_2)^+]$].

Subsequent elution with a mixture of benzene and ethyl acetate gave 0.93 g of a mixture of substances, from which after the addition of 3 ml of ether we isolated 0.05 g (0.6%) of 2-carbethoxyacetylmethyl-4-carbethoxymethyl-6-methoxy-s-triazine (IX) with R_f 0.38 as colorless crystals with mp 159-159.5°C (from ethanol). The product was quite soluble in chloroform, acetone, ethyl acetate, DMF, hot alcohols, and benzene but insoluble in ether and water. Mass spectrum: 325 $[(M)^+]$, 310 $[(M-CH_3)^+]$, 283 $[(M-COCH_2)^+]$, 280 $[(M-OC_2H_5)^+]$, 279 $[(M-HOC_2H_5)^+]$, 264 $[(M-C_2H_5OH-CH_3)^+]$, 253 $[(M-CO_2-C_2H_4)^+]$, 238 $[(M-CO_2-C_2H_4-CH_3)^+]$, 234 $[(M-OC_2H_5-HOC_2H_5)^+]$, 211 $[(M-COCH_2-CO_2-C_2H_4)^+]$, 207 $[(M-CO_2-C_2H_4-C_2H_5OH)^+]$, 192 $[(M-OC_2H_5-C_2H_5OH-COCH_2)^+]$, 165 $[(M-CO_2-C_2H_4-C_2H_5OH-COCH_2)^+]$. Found: C 51.6; H 5.7; N 12.9%. $C_{14}H_{19}N_3O_6$. Calculated: C 51.7; H 5.9; N 12.9%.

Subsequent elution with ethyl acetate gave an additional 0.26 g of VII. The overall yield of 2,4-bis(carbethoxyacetylmethylene)-6-methoxy-1,2,3,4-tetrahydro-s-triazine was 2.19 g (21.5%). The colorless crystals had mp 160-160.5°C (from ethanol). The product was insoluble in water, slightly soluble in alcohols and ether, and quite soluble in benzene, acetone, chloroform, carbon tetrachloride, DMF, and DMSO. IR spectrum: 1720 ($COOC_2H_5$) and 1670 cm^{-1} ($COCH_3$). PMR spectrum (CD_2Cl_2): 1.37 (6H, t, CH_2CH_3), 2.39 (6H, broad s, $COCH_3$), 3.99 (3H, s, OCH_3), 4.35 (4H, m, CH_2CH_3), and 13.5 ppm (broad s, NH). Mass spectrum: 367 $[(M^+)]$, 352 $[(M-CH_3)^+]$, 325 $[(M-COCH_2)^+]$, 322 $[(M-OC_2H_5)^+]$, 321 $[(M-C_2H_5OH)^+]$, 306 $[(M-C_2H_5OH-CH_3)^+]$, 295 $[(M-CO_2-C_2H_4)^+]$, 276 $[(M-OC_2H_5-HOC_2H_5)^+]$, 264 $[(M-C_2H_5OH-CH_3-COCH_2)^+]$, 260 $[(M-C_2H_5OH-CH_3-C_2H_5O)^+]$, 249 $[(M-CO_2-C_2H_4-C_2H_5OH)^+]$, 234 $[(M-OC_2H_5-C_2H_5OH-COCH_2)^+]$. Found: C 52.5; H 5.9; N 11.6%. $C_{16}H_{21}N_3O_7$. Calculated: C 52.3; H 5.8; N 11.4%.

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