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sym-TRIAZINE DERIVATIVES.

6.* CONVERSION OF 2,4,6-TRIETHOXYCARBONYL-1,3,5-TRIAZINE WITH ACYLHYDRAZINES INTO 3,5-DIETHOXYCARBONYL-1,2,4-TRIAZOLE

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The reaction of 2,4,6-triethoxycarbonyl-1,3,5-triazine with acylhydrazines leads to fragmentation with the formation of 3,5-diethoxycarbonyl-1,2,4-triazole, 1-acylethoxycarbonylformamidrazones N,N'-diacylhydrazines, and the amines of the corresponding carboxylic acids.

The interaction of 2,4,6-triethoxycarbonyl-1,3,5-triazine (I) with arylhydrazines (IIa-f), in contrast to the analogous reaction with ammonia, does not take place at the ester groups but at the C=N bonds of the heterocyclic system and is accompanied by a rearrangement with the formation of 2-methoxycarbonyl-4-arylhydrazino-5-oxoimidazoles (IIIa-f) [1, 2].

In order to evaluate the influence of the nature of the hydrazine component on the course of the reaction, we have used, in addition to the arylhydrazines, the acylhydrazines (IVa-c) in interaction with the ester (I). As in the case of the arylhydrazines [1], the process was performed at a ratio of the reactants (I) and (IV) of 1:4 by boiling for 2 h in ethanol, the course of the reaction being monitored by TLC.

In this case, together with the corresponding 5-oxoimidazole derivatives, from the products of the reaction of the ester (I) with all the acylhydrazines (IVa-c) we unexpectedly isolated, with yields of 60-75%, one and the same compound — the previously undescribed 3,5-diethoxycarbonyl-1,2,4-triazole (V). We also obtained the 1-acylethoxycarbonyl-formamidrazones (VIa-c) (yields 75-100%), the N,N'-diacylhydrazines (VIIa-c), and the amides of the

*For Communication 5, see [1].

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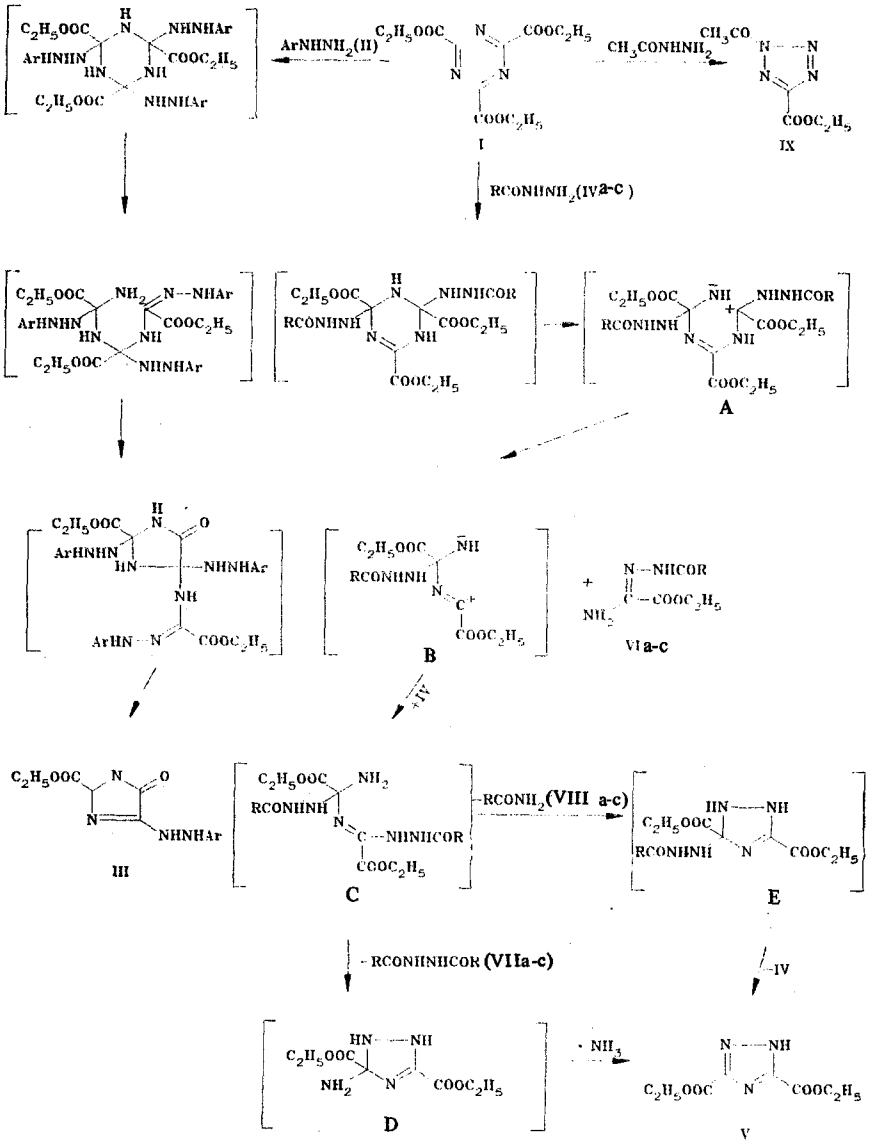
corresponding acids (VIIIa-c) (overall yields 33-58%), and in the case of acetylhydrazine, as by-product, also 12% of 2-acetyl-5-ethoxycarbonyltetrazole (IX).

For the preparative separation of compounds (V-IX) we used their solubilities in water and ethanol, and also chromatography on silica gel columns. The structures of compounds (V-IX) were established with the aid of IR, PMR, and mass spectroscopy. Compounds (VIIa-c) and (VIIIa-c) were identified by direct comparison, using mixed melting points and IR spectra, with the authentic sample obtained by independent synthesis.

The results obtained permit a possible scheme of transformations for the reactions of 2,4,6-triethoxycarbonyl-1,3,5-triazine (I) with the acylhydrazines (IV) which differs from the scheme of the interaction of the ester (I) with the arylhydrazines proposed previously [1].

Apparently, on the reaction of the ester (I) both with arylhydrazines (II) and with acylhydrazines (IV) the process begins with the addition of the hydrazine component to the C=N double bonds of the triazine ring with the subsequent opening of the heterocyclic system. However, although in all cases the best results were obtained by the use of 4 moles of the hydrazine component per mole of the ester (I), the order of interaction of the latter with the acylhydrazines was apparently different from that with the arylhydrazines. Halving the amounts of hydrazines lowered the yields of imidazole derivatives (III) with the recovery of unchanged ester (I) from the reaction mixture, which is evidence in favor of the direct



IV, VI—VIII a R=CH_3; b R=C_6H_5; c R=4-pyridyl

addition to the triazole ring of three molecules of the arylhydrazine. A similar halving of the amount of the acylhydrazines (IV) (as is shown in the Experimental part using the hydrazide (IVc) as example) correspondingly lowered the yield of the triazole (V) but the initial ester (I) was not detected in the reaction products by the TLC method, and the yields of the acylamidrazones (VI) formed in the first stages of the fragmentation of triazine compounds scarcely changed. This gives grounds for assuming a "stepwise" nature of the reaction of the ester (I) with the acylhydrazines (IV), in which only two molecules of (IV) add to a molecule of (I) initially, and only after fragmentation with the splitting out of the acylamidrazone (VI) does a third molecule of acylhydrazine participate in the reaction.

The opening of the cyclic triazine system, in the initial fragmentation of the molecules, in the reactions with acylhydrazines apparently leads to the formation of the intermediate bipolar ions A and B, which facilitates the subsequent addition of another molecule of acylhydrazine (IV) to the ion B. The resulting intermediate reaction product C undergoes further fragmentation with the formation of the intermediate triazoles D and E, apparently by two parallel schemes: with the splitting out of a molecule of a N,N'-diacylhydrazine (VII) and the splitting out of an acylamine (VIII). The intermediate D undergoes aromatization with the ejection of a molecule of ammonia, and the intermediate E with the loss of a molecule of the acylhydrazine (IV). In both cases the thermodynamically favorable triazole derivative (V) is formed.

The contribution of each of the two parallel conversions (through the intermediate reaction products D and E) depends substantially on the nature of the acyl residues in the reactants. For the N-acetyl- and N-benzoyl-substituted compounds the process apparently takes place predominantly through the intermediate E, and for the N-isonicotinoyl derivatives with the predominant formation of the intermediate D. Supporting this hypothesis are the different ratios of the diacylhydrazines (VII) and amides (VIII) isolated from the reaction products: the yields of (VIIa, b) (20 and 26%) are greater than those of (VIIIa, b) (10 and 13%) and the yield of (VIIc) (17%) is less than that of (VIIIc) (42%). The formation of the tetrazole derivative (IX) is not included in the proposed scheme and, apparently, takes place by an independent mechanism.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer 457 spectrophotometer in paraffin oil; PMR spectra were taken on an XL-100 spectrophotometer with TMS as internal standard; and mass spectra on a MAT-112 instrument (with direct introduction) at 70 eV.* Column chromatography was performed with Chemapol 100/160μ silica gel.

Reaction of 2,4,6-Triethoxycarbonyl-1,3,5-triazine (I) with the Acetylhydrazine (IVa). A suspension of 1.2 g (4 mmole) of the triester (I) and 1.16 g (15.6 mmole) of the acylhydrazine [3] in 20 ml of absolute ethanol was boiled with stirring for 2 h. The precipitate that deposited on cooling was filtered off and washed with absolute ethanol. This gave 0.57 g (75%) of 1-acetylethoxycarbonylformamidrazone (VIa). Light-yellow crystals soluble on heating in water and alcohols, sparingly soluble in ether, benzene, chloroform, and other common organic solvents; mp 196-198°C (from absolute ethanol). IR spectrum (cm^{-1}): 1740 ($COOC_2H_5$); 1645, 1665 (CON, C=NH); 3210, 3330, 3370 (NH). PMR spectrum (in D_2O), δ, ppm: 1.10 (3, H, t), and 4.12 (2 H, q, CH_2CH_3); 1.83 (3 H, s, CH_3CO). Mass spectrum, m/z: 173 [M], 144 [$(M-C_2H_5)^+$], 128 [$(M-OC_2H_5)^+$], 100 [$(M-COOC_2H_5)^+$], 57 {$[M-NH_2C(=NH)COOC_2H_5]^+$}, 43 {$[M-NHNHC(=NH)COOC_2H_5]^+$}. Found: C 41.7; H 6.5; N 24.4%. $C_6H_{11}N_3O_3$: Calculated: C 41.6; H 6.4; N 24.2%.

The ethanolic solution, after the elimination of the amidrazone (VIa), was evaporated, and 0.15 g (13%) of acetamide (VIIIa), identical with the authentic substance according to its IR spectrum, was distilled off from the residue in vacuum (monitoring by TLC with the chlorine/toluidine revealing reagent).

The mixture of substances, after the removal of the acetamide, was deposited on a column of silica gel (35-fold amount in relation to the weight of the residue). Benzene–ethyl acetate (1:1) (a fivefold volume with respect to the volume of the silica gel) eluted

*The spectral investigations were performed by O. S. Anisimova, E. M. Peresleni, and K. F. Turchin in the laboratory of physicochemical methods of investigations of VNIKhFI directed by Yu. N. Sheinker.

3,5-diethoxycarbonyl-1,2,4-triazole (V). Yield 0.57 g (67%). Colorless crystals, readily soluble in alcohols, chloroform, and hot benzene; mp 112-113°C (from benzene). IR spectrum, cm^{-1}: 1740 ($COOC_2H_5$); 3100 (NH). PMR spectrum (in $CDCl_3$), δ, ppm: 1.28 (3 H, t) and 4.38 (2 H, q, CH_2CH_3); 13-15 ppm (1 H, very broad signal, NH). Mass spectrum, m/z: 213 $[M]^+$, 184 $[(M-C_2H_5)^+]$, 168 $[(M-OC_2H_5)^+]$, 140 $[(M-COOC_2H_5)^+]$, 113 $[(M-CNHCOOC_2H_5)^+]$. Found: C 44.9; H 4.9; H_{act} 0.5; N 20.1%. $C_8H_{11}N_3O_4$. Calculated: C 45.0; H 5.2; H_{act} 0.5; N 19.8%.

On further elution with ethyl acetate, 0.09 g (12%) of 2-acetyl-5-ethoxycarbonyltetrazole (IX) was obtained. Colorless crystals readily soluble in ethanol and chloroform, sparingly soluble in ether, benzene, isopropanol, and water; mp 267-268°C (from isopropanol). IR spectrum, cm^{-1}: 1740 ($COOC_2H_5$); 1640 and 1690 (CON=); 3450 (NH). Mass spectrum, m/z: 184 $[M]^+$, 112 $[(M-COOC_2H_4)^+]$, 69 $[(M-CH_3CO-COOC_2H_4)^+]$, 43 $[(M-NHCOCH_3-COOC_2H_4)^+]$. Found: C 39.0; H 4.3; N 30.5%. $C_6H_8N_4O_3$. Calculated: C 39.1; H 4.3; N 30.5%.

After the elimination of the tetrazole derivative (IX), elution of the column was continued with ethyl acetate, giving 0.14 g (20%) of N,N'-diacetylhydrazine (VIIa) with mp 137-138°C, identical according to a mixed melting point and its IR spectrum with an authentic sample [4].

Reaction of 2,4,6-Triethoxycarbonyl-1,3,5-triazine (I) with Benzoylhydrazine (IV). A mixture of 1.2 g (4 mmole) of the triester (I), 2.12 g (15.6 mmole) of benzoylhydrazine, and 20 ml of absolute ethanol was boiled with stirring for 2 h. After cooling, the precipitate was filtered off and washed with absolute ethanol. This gave 1 g (100%) of the 1-benzoylethoxycarbonylformamidrazone (VIb). Colorless crystalline powder, soluble in DMSO and DMFA, insoluble in other common organic solvents and in water; mp 224-225°C (from absolute ethanol). IR spectrum, cm^{-1}: 1710 ($COOC_2H_5$); 1635, 1665 (CON, C=NH); 3200, 3420 (NH). PMR spectrum (in DMSO), δ, ppm: 1.29 (3 H, t) and 4.28 (2 H, q, CH_2CH_3); 6.79 (2 H, s, NH_2); 7.53-7.83 (5 H, m, arom. protons); 10.07 (1 H, broad signal, NH); Mass spectrum m/z: 235 $[M]^+$, 204 $[(M-OC_2H_5)^+]$, 162 $[(M-COOC_2H_5)^+]$, 145 $[(M-COOC_2H_5-NH_3)^+]$, 119 $\{[M-NH_2C(=NH)COOC_2H_5]^+\}$, 105 $\{[M-NHNHC(=NH)COOC_2H_5]^+\}$, 77 $\{[M-CONHNHC(=NH)COOC_2H_5]^+\}$. Found: C 56.1; H 5.5; N 17.9%. $C_{11}H_{13}N_3O_3$. Calculated: C 56.1; H 5.6; N 17.8%.

The ethanolic solution, after the removal of the amidrazone (VIb), was evaporated, and since the further separation of the reaction products immediately on the chromatographic column with silica gel proved to be difficult, the mixture obtained was dissolved in boiling water. When the aqueous solution was cooled, 0.35 g of N,N'-dibenzoylhydrazine (VIIb) deposited with mp 235-236°C, identical according to a mixed melting point and its IR spectrum with an authentic sample [5].

The aqueous solution, after the elimination of the hydrazide (VIIb), was evaporated and the residue was deposited on a column of silica gel (50-fold amount in relation to the weight of the residue). Elution was performed with benzene–ethyl acetate, at first in a ratio of 97:3 and then with a gradual increase in the polarity of the eluant by the addition of more ethyl acetate. Benzene–ethyl acetate (19:2) (tenfold amount in relation to the volume of the silica gel) eluted an additional 0.1 g of the hydrazide (VIIb) from the column. The total yield of (VIIb) was 0.45 g (24%). Then benzene–ethyl acetate (19:3) (sevenfold volume in relation to the silica gel) eluted 0.19 g (10%) of benzamide (VIIIb) with mp 128-129°C, identical according to a mixed melting point and its IR spectrum with an authentic sample [6]. After this, benzene–ethyl acetate (19:4) (tenfold volume in relation to the volume of silica gel) eluted 0.52 g (60%) of compound (V), identical according to a mixed melting point and IR spectra with a sample obtained by the reaction of the ester (I) and acetylhydrazine (IVa).

On further elution of the silica gel column with benzene–ethyl acetate (13:6), byproducts from the reaction and also 0.16 g (7%) of benzoylhydrazine (IVb) were eluted.

Reaction of 2,4,6-Triethoxycarbonyl-1,3,5-triazine (I) with Isonicotinoylhydrazine (IVc). A. A mixture of 1.2 g (4 mmole) of the ester (I), 2.16 g (15.6 mmole) of isonicotinoylhydrazine (IVc), and 20 ml of absolute ethanol were boiled with stirring for 2 h, with monitoring by TLC. The precipitate of 0.88 g (94%) of the 1-isonicotinoylethoxycarbonylformamidrazone (VIc) that deposited when the reaction mixture was cooled was filtered off. Bright-yellow crystals soluble in DMFA and DMSO, sparingly soluble in other common organic solvents and in water; mp 205-206°C (from a mixture of equal amounts of methanol and ethanol). IR spectrum, cm^{-1}: 1740 ($COOC_2H_5$); 1645, 1605 (CON, C=NH); 3190, 3300, 3380 (NH). PMR spectrum (in DMSO), δ, ppm: 1.29 (3 H, t) and 4.28 (2 H, q, CH_2CH_3); 6.68 (1 H, broad signal, NH); 6.92 (1 H,

broad signal, NH); 7.92-8.76 (4 H, m, aromatic protons of the pyridine nucleus); 10.34 (1 H, broad signal, NH). Mass spectrum, m/z: 236 $[M]^+$, 163 $[(M-COOC_2H_5)^+]$, 146 $[(M-NH_3-COOC_2H_5)^+]$, 106 $\{[M-NHNHC(=NH)COOC_2H_5]^+\}$, 73 $\{[M-CONHNHC(=NH)COOC_2H_5]^+\}$. Found C 50.5; H 5.1; N 24.0%. $C_{10}H_{12}N_4O_3$. Calculated: C 50.8; H 5.1; N 23.7%.

The ethanolic solution, after the elimination of the amidrazone (IVc), was evaporated. The residue was dissolved in boiling water. When the aqueous solution was cooled, 0.32 g (17%) of N,N-diisonicotinoylhydrazine (VIIc) deposited; it had mp 258-259°C and was identical, according to a mixed melting point and its IR spectrum, with an authentic sample [6]. The aqueous solution after the separation of the hydrazide (VIIc) was evaporated and the residue was deposited on a column of silica gel. Ethyl acetate eluted 3,5-diethoxycarbonyl-1,2,4-triazole (V). The yield was 0.66 g (75%). The substance was identical, according to a mixed melting point and its IR spectrum, with the sample of (V) obtained by the reaction of the ester (I) with acetylhydrazine. On further elution with chloroform–methanol (10:1) 0.8 g (42%) of nicotinamide (VIIIc) was obtained with mp 155-156°C, identical according to a mixed melting point and its IR spectrum with an authentic sample [8].

B. In an analogous experiment, 1.2 g (4 mmole) of the ester (I) and 0.96 g (7 mmole) of the hydrazide (IVc) in 20 ml of absolute ethanol yielded 0.84 g (88%) of the amidrazone (IVc), 0.2 g (22%) of the diacylhydrazine (VIIc), 0.34 g (38%) of the triazole (V), and 0.19 g (22%) of the amide (VIIIc). The initial ester (I) was not detected in the reaction products by the TLC method.

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