COMMUNICATION 9. PRODUCTS OF THE CONDENSATION OF (ETHOXYMETHYLENE)MALONIC ESTER WITH 2-AMINOTHIAZOLES AND 2-AMINO-1,3,4-THIADIAZOLES

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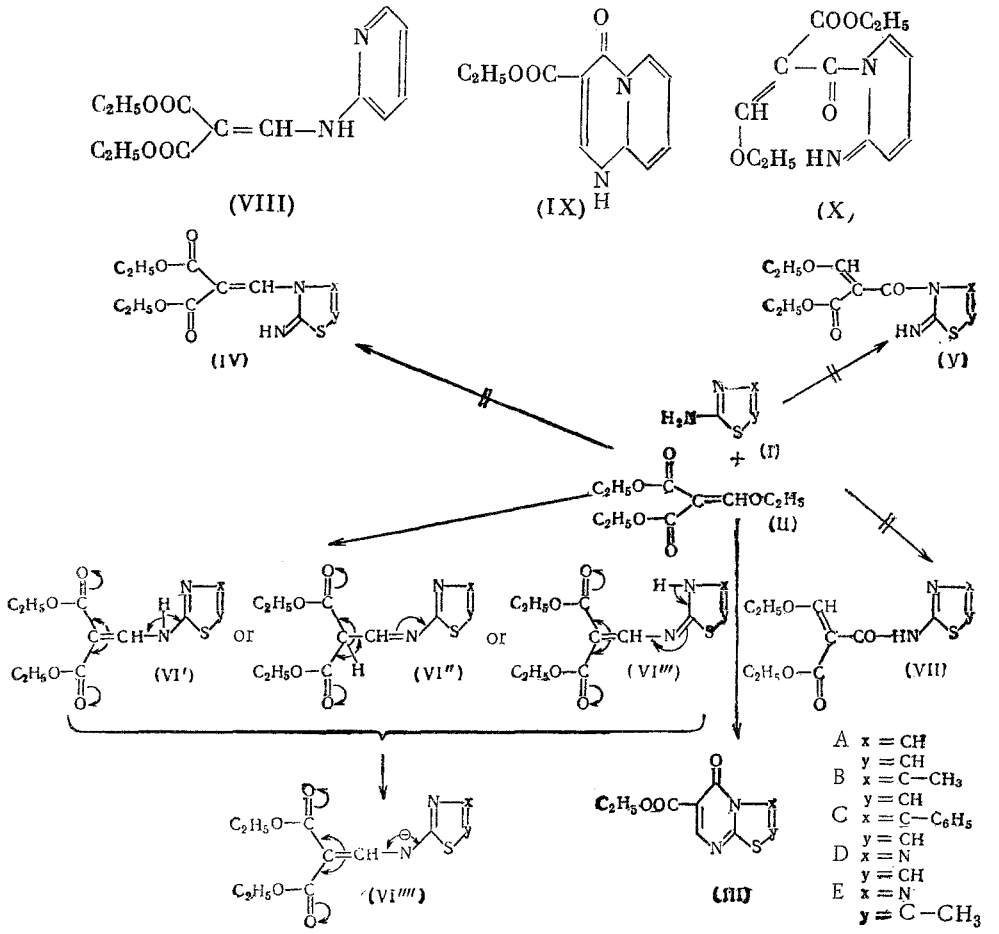
According to Allen, Beilfuss, and others [1], by the reaction of 2-aminothiazoles (I A, B, C) and 2-amino-1,3,4-thiadiazoles (I D, E) with (ethoxymethylene)malonic ester (II) the bicyclic compounds (III) are obtained (see scheme). The structures of these products were established by comparing their ultraviolet spectra with those of some heterobicycles of known structure prepared by carbon-nitrogen condensation.

We were able to show that, when the above-described reactions are carried out under milder conditions, only one molecule of alcohol is eliminated with formation of monocyclic products. In view of the dual reactivity of



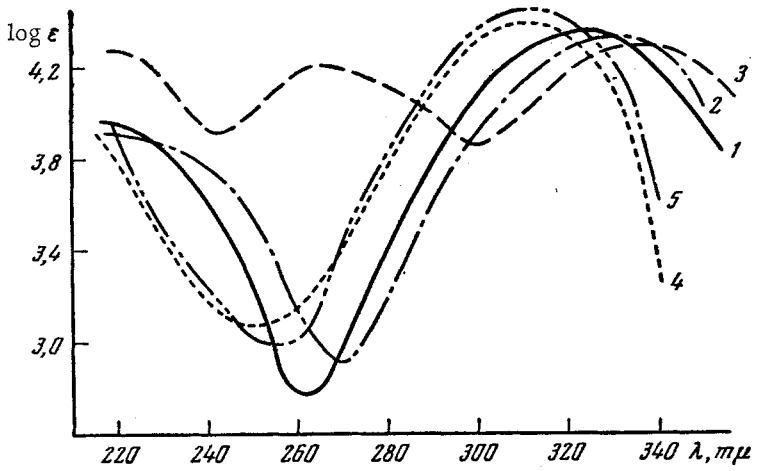


Fig. 1. Ultraviolet absorption spectra in ethanol: 1) (VI A); 2) (VI B); 3) (VI C); 4) (VI D); 5) (VI E).

α-aminoazoles and the presence of two types of the reactive groups in (ethoxymethylene)malonic ester, these products can have the structures represented by the four isomeric formulas (IV)-(VII). For the isomer (VI) three tautomeric forms (VI'), (VI"), and (VI"') are possible. An analogous monocyclic product is known for 2-aminopyridine [2], and to this the formula (VIII) is attributed.

This formula is based on the cyclization of the monocyclic product into the pyridopyrimidine derivative (IX) of known structure. The possibility of rearrangement in the course of the cyclization, similar to the rearrangement described for acetoacetamidopyridine [3], was not considered. The formula (X), which well explains the result of the cyclization, was not examined, probably in view of the generally accepted postulate of the higher reactivity of the β-ethoxyl in the ester (II) as compared with the ethoxycarbonyl groups [4]. We also succeeded in eliminating a molecule of alcohol from the monocyclic products (VI B) and (VI E) and obtained the corresponding bicyclic substances (III), identical to those synthesized by the direct action of (ethoxymethylene)malonic ester on the amines. This transformation is possible only for the structures (V) and (VI), but only if the formula (III) is correct and no rearrangement occurs in the cyclization process. If rearrangement does not occur, then the formation of the bicyclic compounds (III) probably proceeds through the stage of the formation of the monocyclic compounds that we obtained. We were able to obtain further support for the formula (VI). For this purpose we investigated the behavior of the above-described monocyclic products toward cold neutral dilute permanganate solution and toward alkali. It was found that these products do not decolorize permanganate, whereas (ethoxymethylene)malonic ester decolorizes it instantly. The only explanation of this can be that the products studied do not contain the $>C=CH-OC_2H_5$ grouping, but the carbon-carbon bond is deactivated by the adjacent nitrogen atom or is altogether absent, as in the tautomer (VI"). The formulas (V) and (VII) must therefore be rejected.

It is known that 2-(acylamino)thiazoles show acidic properties [5]. It may be supposed also that (VI) will also be capable of dissociation as an acid, for in each of its tautomeric forms the proton is activated by two electronegative ethoxycarbonyl groups and by an electronegative heterocyclic residue; in any case, the anion (VI"") will be stabilized. Hence, only from the compound (VI) and (VII) can the occurrence of acidic properties be expected. The investigated thiadiazole derivatives can indeed be titrated to phenolphthalein with alkali, so that the formulas (IV) and (V) for them must be rejected. Hence, an examination of their behavior toward alkali and permanganate confirms the formula (VI) for the thiadiazole derivatives. The thiazole derivatives cannot be titrated to phenolphthalein with alkali, but a comparison of their ultraviolet spectra with those of the thiadiazole derivatives enables us to assert that these also have the formula (VI) (Fig. 1). The cause of the lower acidity of the thiazole derivatives must be sought in the lower electronegativity of the thiazole ring in comparison with the thiadiazole ring. The accumulation of hetero atoms in the ring always leads to an increase in its electronegativity and therefore in its power to form acidic derivatives [6].

The ultraviolet spectrum of the substance obtained from 2-amino-4-phenylthiazole (I C) differed appreciably from the others. It is probable, however, that this product also has the structure (VI). The alternative structure (IV)

[(Thiazol-2-ylamino)methylene]malonic Esters and [(1,3,4-Thiadiazol-2-ylamino)methylene]malonic Esters

Cpd.	X	Y	Method of prepn.	Yield, %	M.p., °C (solvent for crystln.)	Found, %		Molecular formula	Calculated, %	
						N	S		N	S
VIA	CH	CH	b	48	57—59 (Decane)	—	12,35 12,40	$C_{11}H_{14}N_2O_4S$	—	11,86
VIB	C—CH_3	CH	c	56,5	62—63	10,32 10,28	11,55 11,84	$C_{12}H_{16}N_2O_4S$	9,85	11,28
VIC	C—C_6H_5	CH	a	72	100—102 (Alcohol)	8,04 7,82	9,02 9,17	$C_{17}H_{18}N_2O_4S$	8,09	9,26
VID	N	CH	a	83,5	111—112,5 (Alcohol)	15,97 15,91	—	$C_{10}H_{13}N_3O_4S$	15,48	—
VIE	N	C—CH_3	a	88,5	127—128,5 (Alcohol)	14,32 14,02	11,92 11,80	$C_{11}H_{15}N_3O_4S$	14,73	11,23

must be rejected in view of the ability of the phenyl compound, as incidently also (VI A) and (VI B), to form a dye by coupling with diazotized sulfanilic acid; according to [7] this ability is possessed only by aminothiazoles, and not by iminothiazolines. The peculiarities of the ultraviolet spectrum of (VI C) are probably to be explained by the influence of the phenyl group.

EXPERIMENTAL

[(Thiazol-2-ylamino)methylene]malonic Esters (VI A, B, C) and [(1,3,4-Thiadiazol-2-ylamino)methylene]malonic Esters (VI D, E). These substances were prepared as follows: Method (a). A mixture of 0.01 mole of the amine and 0.012 mole of (ethoxymethylene)malonic ester was heated in a distillation apparatus in a bath of Wood's metal at 140-160° until practically no more alcohol came over (15-30 min). The mixture solidified on cooling, and it was washed with alcohol and crystallized from a suitable solvent. Method (b) differed from Method (a) in that the reaction product was washed with petroleum ether. Method (c) differed from Method (a) in that, for purification, the reaction product was dissolved in chloroform, the solution was passed through a column of chromatographic alumina, and solvent was evaporated. Constants and analyses are given in the table.

Ethyl 3-Methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (III B). 1.89 g of (VI B) was heated in the vacuum of a water pump at 150-165°. After 20 h the weight loss was 96% of the theoretical value. The crystalline mass that formed on cooling was found to be the desired product; yield 1.53 g (99%); colorless starlike crystals, m.p. 189-191° (from alcohol). The literature [1] gives m.p. 192°. The ultraviolet spectrum corresponds to that given in the literature [1].

Ethyl 3-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidine-6-carboxylate (III E). This was prepared in a similar way to (III B) by heating 3.93 g of (VI E) in a vacuum for 11 h at 150-160°. By crystallizing the product from chlorobenzene we obtained 1.85 g (58%) of (III E) as colorless gleaming leaves, m.p. 135-136°. The literature [1] gives m.p. 192°. The ultraviolet spectrum corresponds to that given in the literature [1]. Found: N 12.94; 13.08%. $C_9H_9N_3O_3S$. Calculated: N 13.39%.

Ultraviolet spectra were determined on $5 \cdot 10^{-5}$ M alcoholic solutions with an SF-4 instrument.

SUMMARY

1. By the reaction of 2-aminothiazoles and of 2-amino-1,3,4-thiadiazoles with (ethoxymethylene)malonic ester [(thiazol-2-ylamino)methylene]malonic and [(1,3,4-thiadiazol-2-ylamino)methylene]malonic esters were obtained.

2. [(5-Methylthiazol-2-ylamino)methylene]- and [(5-methyl-1,3,5-thiadiazol-2-ylamino)methylene]-malonic esters were cyclized into ethyl 3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidene-6-carboxylate and ethyl 3-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidine-6-carboxylate.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
