AZOLIDINE-4-THIONES, THEIR DERIVATIVES AND ANALOGS

VI. Condensation of Isorhodanine with Amino Compounds*

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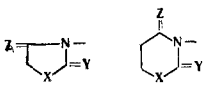
4-Thioxothiazolid-2-one (isorhodanine) is distinguished from the initial thiazolidine-2,4-dione, and also from rhodanine and other azolid-4-ones, by the highly active C=S group in position 4. When isorhodanine is heated in methanol with various amino compounds, condensation products—substituted 4-iminothiazolid-2-ones—are obtained.

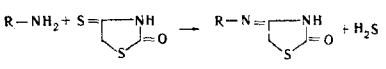
Among the various derivatives of the azolid-4-ones of structure A (X, Y = O, NH, S; Z = O), the most studied are the numerous 5-substituted derivatives and the least studied, the 4-substituted derivatives. This is due primarily to the different degrees of accessibility of these compounds, the synthesis of which is easily effected in the one case because of the high reactivity of the methylene group in position 5 and is made difficult in the second case by the inertness of the oxo group in position 4. The latter, as part of an amide group, does not exhibit ketonic properties [1] and only in the molecules of certain 3- and 5-substituted derivatives is it capable of condensing with amines [2].

We have shown that in the azolid-4-ones (A) and their six-membered analogs **B** (X = S; Y = O; Z = O), the oxo group can easily be converted into a thioxo group [3] and thereby position 4 can be strongly activated in respect of nucleophilic substitution reactions [4, 5]. The high



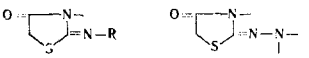
A B

is due to introduction of the less electronegative sulfur atom and, consequently, to the considerably greater polarizability of the C=S group than the C=O group. In the 4-thioxo compounds obtained, the C=S group has a typical thioketonic nature, readily reacting with amines with the liberation of hydrogen sulfide. We have used it to obtain 4-substituted thiazolidine-2,4-diones, employing as the initial compound the highly active isorhodanine that we synthesized previously [6], which readily condenses with aromatic and aliphatic amines and hydrazine derivatives on heating in methanol, forming substituted 4-iminothiazolid-2-ones of structure C in the following way:



C

The condensation takes place at various rates, which vary within wide limits, being maximal for the more basic amines (see table). The above-mentioned reaction actually opens up a new route for the synthesis of the previously difficultly accessible compounds of type C, which are isomers of 2-arylaminothiazolid-4-ones (D) and of thiazolidine-2,4-dione 2-hydrazones (E), which is of undoubted interest, since many compounds of types D and E possess antitubercular [7], fungicidal [8], and antithyroid [9] properties.



D E

Both in isorhodanine and in the other compounds of types A and B (Z = S) the thioxo group in position 4 has a greater reactivity than a thioxo group in position 2 (Y = S), because of the nonequivalence of these positions. The propinquity of the two heteroatoms in positions 1 and 3 with unshared electron pairs depolarizes the C=S group in position 2, lowering its ketonic nature, in consequence of which it undergoes condensation reactions only with difficulty.

EXPERIMENTAL

Thiazolidine-2,4-dione 4-oxime (I). A flask was charged with 3 ml of methanol and 0.01 mole each of hydroxylamine hydrochloride, isorhodanine, and pyridine. Even in the cold the evolution of hydrogen sulfide and the formation of a precipitate began. After an additional 30 minutes' boiling on the water bath and cooling, colorless needles of I were obtained. A further small amount of I was filtered off after two days. The total yield was 0.63 g (48%). Mp 152–153° C (from methanol). Soluble on heating in water and alcohols; sparingly soluble in other solvents. Found, %: N 21.04; S 24.19. Calculated for $C_3H_4N_2O_2S$, %: N 21.20; S 24.26.

Thiazolidine-2,4-dione 4-isonicotinoylhydrazone (II). A mixture of 0.01 mole of isonicotinic acid hydrazide (tubazid), 0.01 mole of isorhodanine, and 6 ml of methanol was heated in the water bath for 45 min and was left overnight. The precipitate that had deposited was filtered off and washed with methanol. Yield 1.18 g (50%). From ethanol or butanol it formed colorless crystals with mp 171–174° C. Soluble in water and alcohols on heating. Found, %: N 23.45; S 13.52. Calculated for $C_9H_8N_4O_2S$, %: N 23.72; S 13.57.

The other amino compounds were condensed with isorhodanine similarly. The majority of the condensation products readily separated out in the crystalline state during the reaction. They were filtered off after cooling and were washed with cold methanol. Products IX and XI were precipitated with water in the form oily liquids which gradually crystallized. VIII deposited in the course of 36 hr. XVIII deposited partially and required additional precipitation with water. Purification for analysis was carried out by crystallization: III, IV, VI, and VIII from water, VII from aqueous propanol; V, X, and XV from ethanol; XI and XIV from methanol; IX from propanol; XII from a mixture of butanol and acetic acid; and XIII, XVI, XVII, and XVIII from butanol.

All the substances synthesized were colorless (XI and XIII bright yellow) substances readily soluble in pyridine and aqueous alkalis and somewhat in hot alcohols, and insoluble in the majority of organic solvents.

*For part V, see [10].

Products of the Condensation of Isorhodanine with Amines

Compound	Initial amine	Mp, °C	Time of condensation, min	Empirical formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
III	Aminoethanol	156	20	$C_5H_8N_2O_2S$	17.35	19.94	17.49	20.01	40
IV	Thiosemicarbazide	193	180	$C_4H_6N_4OS_2$	29.25	33.79	29.45	33.71	53
V	Phenylhydrazine	149	3	$C_9H_9N_3OS$	20.04	15.08	20.28	15.46	41
VI	o-Aminophenol	178	40	$C_9H_8N_2O_2S$	13.20	15.28	13.45	15.40	44
VII	m-Aminophenol	236	45	„	13.37	15.15	„	„	55
VIII	p-Aminophenol	213	60	„	13.30	15.21	„	„	30
IX	o-Toluidine	150	50	$C_{10}H_{10}N_2OS$	13.58	15.53	13.86	15.55	53
X	p-Toluidine	234	10	„	13.82	15.71	„	„	59
XI	o-Anisidine	163	30	$C_{10}H_{10}N_2O_2S$	12.83	14.52	12.60	14.43	50
XII	p-Anisidine	232	10	„	12.85	14.58	„	„	55
XIII	p-Phenetidine	222	2	$C_{11}H_{12}N_2O_2S$	11.95	13.66	11.85	13.57	52
XIV	m-Bromoaniline	189	15	$C_9H_7N_2OSBr$	10.12	11.66	10.33	11.89	43
XV	Anthranilic acid	190	240	$C_{10}H_8N_2O_3S$	11.76	13.63	11.85	13.57	18
XVI	p-Aminobenzoic acid	200	60	„	11.78	13.59	„	„	26
XVII	m-Aminobenzoic acid	243	60	„	11.62	13.31	„	„	38
XVIII	β-Naphthylamine	252	30	$C_{13}H_{10}N_2OS$	11.56	13.58	11.48	13.23	70

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