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RESEARCHES ON SUBSTITUTED ARYLAMIDES OF THIOCARBOXYLIC ACIDS

VIII. Cyclizing Arylamide Derivatives of Monothio- and Dithio-Malonic Acids*

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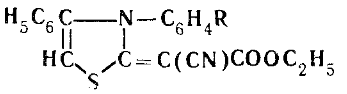
Heating monothio- and dithiomalonic acids with ω-bromoacetophenone in dry ethanol gives 2,3,4-substituted thiazole derivatives.

In the previous paper [1] it was shown that heating the arylamides of cyanoacetic acid with ω-bromoacetophenone in dry ethanol gives bromides of 2-cyanomethyl-3-aryl-4-phenylthiazoles. The latter readily split off hydrogen bromide to give the corresponding methylene bases.

Table 1



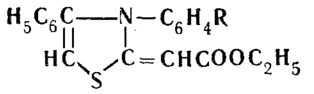
2-Carboethoxycyanomethylene-3-aryl-4-phenylthiazoles

No.	R	Mp, °C	Formula	Found, S, %	Calculated, S, %	Yield, %
1	H	>240	$C_{20}H_{16}O_2N_2S$	9.23; 9.28	9.19	94
2	p-CH_3	207	$C_{21}H_{18}O_2N_2S$	8.70; 8.65	8.86	90
3	p-CH_3O	188	$C_{21}H_{18}O_3N_2S$	8.79; 8.87	8.47	81
4	m-Cl	210	$C_{20}H_{15}O_2N_2SCl$	8.42; 8.44	8.36	85
5	p-NH_2SO_2	>240	$C_{20}H_{17}O_4N_3S_2$	14.86; 14.90	14.98	58
6	p-C_2H_5OOC	218	$C_{23}H_{20}O_4N_2S$	7.63; 7.51	7.62	91
7	p-NO_2*	180	$C_{20}H_{15}O_4N_3S$			82

* Found: N 11.17, 11.13%. Calculated: N 10.69%.

It is known that there are physiologically active compounds [2] among thiazole derivatives, and that some of them are used to synthesize cyanine dyes [3]. Hence it was of interest to use for synthesis with ω-bromoacetophenone previously described [4, 5] esters of monoaryl amides, of monothiomalonic, of monothiocyanomalonic, and monothiocarbomalonic acid, and diarylamides of dithiomalonic acid, to obtain the corresponding 2-substituted 3-aryl-4-phenylthiazole, and to investigate some of their properties.

Table 2



2-Carboethoxymethylene-3-aryl-4-phenylthiazoles

No.	R	Mp, °C	Formula	Found S, %	Calculated S, %	Yield, %
1	H	203	$C_{19}H_{17}O_2NS$	9.77; 9.62	9.90	94
2	p-C_2H_5O	144	$C_{21}H_{21}O_3NS$	8.54; 8.53	8.72	96
3	p-NO_2	162—163	$C_{19}H_{16}O_4N_2S$	8.59; 8.54	8.69	71
4	p-NH_2SO_2	No melting	$C_{19}H_{18}O_4N_2S_2$	16.29; 16.32	15.92	90

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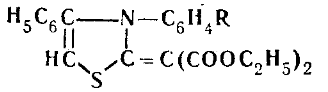
*For Part VI see [1].

Heating the ethyl esters of arylamides of monothiocyanomalonic acid with ω-bromoacetophenone in dry ethanol gives satisfactory yields of 2-carbomethoxymethylene-3-aryl-4-phenylthiazoles (Table 1). These are yellow compounds with comparatively high mp, insoluble in cold ether, water, and alkalies, soluble in dilute mineral acids, benzene, acetone, chloroform, and other organic solvents. They are purified by recrystallization from ethanol.

Table 3

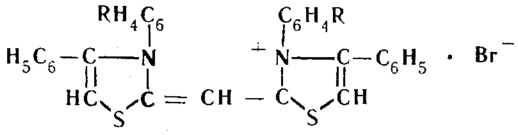


2-Dicarboethoxymethylene-3-aryl-4-phenylthiazoles

No.	R	Mp, °C	Formula	Found S, %	Calculated S, %	Yield, %
1	H	162	$C_{22}H_{21}O_4NS$	7.90; 7.97	8.10	88
2	p-CH_3	160	$C_{23}H_{23}O_4NS$	7.95; 8.02	7.82	66
3	p-C_2H_5O	118	$C_{24}H_{25}O_5NS$	7.52; 7.37	7.28	85
4	p-Br	168—169	$C_{22}H_{16}O_4NSBr$	6.44; 6.36	6.75	70
5	p-NO_2	205—206	$C_{22}H_{20}O_6N_2S$	7.39; 7.47	7.27	67

When the ethyl esters of the arylamides of monothiocyanomalonic acid are heated with 15% potassium hydroxide solution, they are comparatively easily hydrolyzed, with subsequent decarboxylation, on acidification, to give nitriles. It might be assumed that with the 2-carboethoxycyanomethylene derivatives of thiazole described, there was also ready saponification of the ester group, followed by decarboxylation. However, saponification did not take place with longer heating with aqueous or ethanolic potassium hydroxide, or on heating with 60% sulfuric acid, and in all those cases the starting esters were recovered.

Table 4



3, 3'-Diaryl-4, 4'-diphenyl-2-methine-dithiazoles

No.	R	Mp, °C	Formula	Found S, %	Calculated S, %	Yield, %
1	H	No melting	$C_{31}H_{26}N_2S_2Br$	10.83; 10.70	11.25	85
2	p-CH_3O	"	$C_{33}H_{29}O_2N_2S_2Br$	9.96; 10.02	10.17	83
3	o-C_2H_5O	"	$C_{35}H_{31}O_2N_2S_2Br$	9.94; 9.87	9.77	78
4	p-C_2H_5O	"	$C_{35}H_{31}O_2N_2S_2Br$	9.61; 9.46	9.77	86

Heating the ethyl ester of anilidomonothiomalonic acid with ω-bromoacetophenone in dry ethanol gave 2-carboethoxymethylene-3, 4-diphenylthiazole. A compound with identical physical and chemical properties was obtained by reacting diethyl anilidothiocarbomalonate with ω-bromoacetophenone. The 2-carboethoxymethylene-3-aryl-4-phenylthiazoles given in Table 2 were obtained from diethyl esters of arylamides of thiocarbomalonic acid. They were crystalline compounds varying in color from yellow to pale brown, insoluble in water, cold ether, and alkalies, soluble in benzene, chloroform, acetone, and other organic solvents, and also in mineral acids. They were purified by recrystallization from ethanol.

Investigation of the reaction of diethyl esters of arylamides of thiocarbomalonic acid with ω-bromoacetophenone established that brief heating of the reactants together on a water bath, or 24 hr standing leads to formation of 2-dicarboethoxymethylene-3-aryl-4-phenylthiazoles. Longer heating of the mixture (3–4 hr) results in splitting off of one carboethoxy group and formation of 2-carboethoxymethylene-3-aryl-4-phenylthiazoles.

Table 3 sets out the 2-dicarboethoxymethylene-3-aryl-4-phenylthiazoles prepared. These crystalline substances were pale brown and had relatively high melting points. They were insoluble in ether, water, and alkalies, soluble in mineral acids and many organic solvents. They were recrystallized from ethanol.

2-Dicarboethoxymethylene-3-aryl-4-phenylthiazoles-3-aryl-4-phenylthiazoles, isolated pure, were heated in ethanol, but this did not result in splitting off of the carboethoxy group, as obtains when preparing 2-carboethoxymethylene-3-aryl-4-phenylthiazoles, where splitting off of a carboethoxy group is evidently facilitated by hydrobromic acid, formed by the reaction with ω-bromoacetophenone. The ester groups are not hydrolyzed when monocarboethoxy- and dicarboethoxy-2-methylene-3-aryl-4-phenylthiazoles are heated with aqueous and ethanolic potassium hydroxide, or with 60% sulfuric acid.

Heating diarylamides of dithiomalonic acid with ω-bromoacetophenone gives only monobromides of 3, 3'-diaryl-4, 4'-diphenyl-2-methinedithiazoles, independent of the ratio of diarylamides to ω-bromoacetophenone used. The methylene bases could not be obtained from these quaternary salts, though it was possible for other 2, 3, 4-substituted thiazoles. Table 4 gives the bromides of 3, 3'-diaryl-4, 4'-diphenyl-2-methyldiathiazoles obtained. They were crystalline and pale brown, insoluble in benzene and ether, soluble in water, acetone, chloroform, and methanol, less soluble in alkali solutions.

Experimental

2-Carboethoxycyanomethylene-3, 4-diphenylthiazole. A mixture of 1 g ethyl anilidomonothiocyanomalonate and 0.8 g ω-bromoacetophenone in 5 ml dry EtOH was refluxed on a water bath for about an hour. At the start of heating everything went into solution, then a precipitate gradually formed. After cooling, the precipitate was filtered off with suction, washed on the funnel with a small amount of ethanol, and then dried in air. The compounds shown in Table 1 were prepared similarly.

2-Carboethoxymethylene-3-p-ethoxyphenyl-4-phenylthiazole. A mixture of 2 g diethyl p-phenetidothiocarbomalonate and 1.12 g ω-bromoacetophenone in 5 ml dry ethanol was refluxed on a water bath for about 3 hr. Then the ethanol was distilled off under reduced pressure, and a little water added. The resultant crystalline precipitate was filtered off and dried in air. The compounds given in Table 2 were prepared similarly.

2-Dicarboethoxymethylene-3-p-ethoxyphenyl-4-phenylthiazole. 1 g diethyl p-phenetididothiocarbomalonate and 0.58 g ω-bromoacetophenone in 4 ml dry ethanol was shaken until solution was complete, then left overnight, The solvent was removed under reduced pressure, and a little water added to the residue. The solid formed was filtered off, washed on the filter with water, and dried in air. The compounds of Table 3 were prepared similarly.

3, 3', 4, 4'-Tetraphenyl-2-methyldithiazole. A mixture of 0.7 g dianilidodithiomalonic acid and 0.5 g ω-bromoacetophenone in 3 ml dry EtOH was refluxed on a water bath for about an hour. The crystalline precipitate formed on cooling was filtered off, washed on the funnel, and dried in air.

The compounds of Table 4 were prepared similarly.

REFERENCES

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