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RESEARCHES ON SUBSTITUTED ARYLAMIDES OF DITHIOCARBOXYLIC ACIDS

VII. Cyclization of Arylamides of Thiocarboxylic Acids to Thiazole Derivatives

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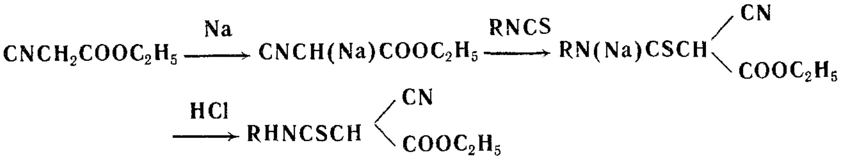
The following compounds hitherto undescribed in the literature, are prepared: ethyl esters of arylamides of cyanomonothiomalonic acid, with electronegative substituents in the phenyl groups, aryl amides of cyanoacetic acid, and nitriles of substituted anilides of arylazothiomalonic acid. Heating arylamides of cyanoacetic acid with ω-bromoacetophenone in absolute alcohol gives quaternary salts of 2-cyanomethyl-3-aryl-4-phenylthiazoles and their methylene bases. Reaction of the quarternary salts of 2-cyanomethyl-3-aryl-4-phenylthiazoles with substituted phenyldiazonium salts gives a number of 2-cyanoarylazomethylene-3-aryl-4-phenylthiazoles.

The present authors previously described the preparation of arylamides of cyanoacetic acid containing positive substituents by saponifying the ethyl esters of aryl amides of cyanomonothiomalonic acid [1]. It was of interest to synthesize a number of these compounds with electronegative substituents in the phenyl groups.

Ethyl esters of aryl amides of cyanomonothiomalonic acid are synthesized by reacting ethyl sodiocyanoacetate with arylisothiocyanates [1]



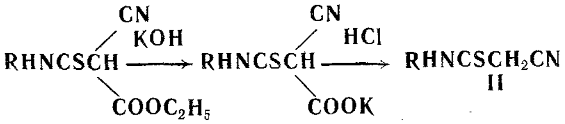
$$CNCH_2COOC_2H_5 \xrightarrow{Na} CNCH(Na)COOC_2H_5 \xrightarrow{RNCS} RN(Na)CSCH\begin{matrix}CN\\COOC_2H_5\end{matrix}$$

$$\xrightarrow{HCl} RHNCSCH\begin{matrix}CN\\COOC_2H_5\end{matrix}$$

I

Table 1 gives the compounds I. They are pale yellow crystalline substances. Mineral acids precipitate them from alkaline solutions. They are purified by recrystallizing from alcohol.

Heating compound I with 15% aqueous potassium hydroxide solution gives arylamides of cyanoacetic acid



$$RHNCSCH\begin{matrix}CN\\COOC_2H_5\end{matrix} \xrightarrow{KOH} RHNCSCH\begin{matrix}CN\\COOK\end{matrix} \xrightarrow{HCl} \underset{II}{RHNCSCH_2CN}$$

Table 2 gives the compounds II. They are pale brown crystalline substances, soluble in alkalies. They are purified by recrystallization from alcohol.

Table 1

Ethyl Esters of Arylamides of Cyanomonothiomalonic Acid

$RC_6N_4HCSCH(CN)COOC_2H_5$

Compound No.	R	Mp, °C	Formula	S, % Found	S, % Calculated	Yield, %
I	p-NO_2	154	$C_{12}H_{11}N_3O_4S$	10,92; 10,79	10,92	80
II	p-Cl	147	$C_{12}H_{11}N_2O_2SCl$	11,34; 11,32	11,32	65
III	m-Cl	105	$C_{12}H_{11}N_2O_2SCl$	11,36; 11,41	11,32	61
IV	p-C_2H_5OOC	93	$C_{15}H_{16}N_2O_4S$	10,00; 10,03	10,00	60
V	p-Br	144	$C_{12}H_{11}N_2O_2SBr$	9,98; 10,07	9,78	57
VI	p-NH_2*	161	$C_{12}H_{13}N_3O_2S$	12,31; 12,45	12,16	55
VII	p-NH_2SO_2**	144				50

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*Compound VI is prepared by treating an alcoholic-ammonia solution of I with H_2S.

**Found for VII: N 12.52, 12.34%. Calculated for $C_{12}H_{13}N_3O_4S_2$: N 12.84 %.

It was shown in a previous paper [2] that the methylene hydrogens in arylamides of cyanoacetic acid are labile, reacting with phenyldiazonium salts to give the corresponding phenylhydrazones. The nitriles of arylamides of arylazothiomalonic acid given in Table 3 are prepared by reacting II with aryldiazonium salts. They are crystalline brown compounds. They are soluble in alkalies, and are reprecipitated by acids. They are purified by recrystallizing from alcohol or dioxane.

Table 2

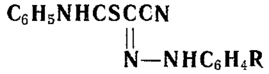
Arylamides of Cyanothioacetic Acid

$RC_6H_4NHCSCH_2CN$

Compound No.	R	Mp, °C	Formula	Found, %		Calculated,%		Yield, %
				S	Halogen	S	Halogen	
VIII	*p*-NO_2	171	$C_9H_7N_3O_2S$	14.13; 14.37		14.02		93
IX	*p*-Cl	151	$C_9H_7N_2SCl$	15.44; 15.33		15.20		90
X	*m*-Cl	107	$C_9H_7N_2SCl$		16.96; 16.97		16.86	83
XI	*p*-Br	152	$C_9H_7N_2SBr$		31.68; 31.84		31.37	80
XII	*p*-NH_2SO_2	180	$C_9H_9N_3O_2S_2$	24.67; 24.77		25.09		95

Table 3

Nitriles of Anilides of Arylazothiomalonic Acid



$$\begin{array}{l} C_6H_5NHCSCCN \\ \qquad\qquad\quad \| \\ \qquad\qquad\quad N{-}NHC_6H_4R \end{array}$$

Compound No.	R	Mp, °C	Formula	Found, %		Calculated,%		Yield, %
				N	S	N	S	
XIII	*p*-NO_2	227	$C_{15}H_{11}N_5O_2S$	21.52; 21.65	—	21.53	—	91
XIV	*p*-Br	228	$C_{15}H_{11}N_4SBr$	—	8.40; 8.48	—	8.91	95
XV	*p*-COOH	Does not melt up to 250	$C_{16}H_{12}N_4O_2S$	17.23; 17.06		17.28	—	90
XVI	*p*-NH_2SO_2	Does not melt up to 250	$C_{15}H_{13}N_5O_2S$	19.00; 18.97		19.49	—	85

Many compounds with thiazole systems in the molecules have interesting physiological activities, and have found application as medicinals [3, 4], as well as being used as starting materials for preparing cyanine dyes [5, 6]. Thiazole and its derivatives are usually prepared by reacting amides of thiocarboxylic acids with α-halogenoaldehydes or α-halogenoketones [7, 8]. It was of interest to prepare the corresponding thiazole derivatives starting with arylamides of cyanoacetic acid and ω-bromoacetophenone, and to investigate some of their properties.

The reaction can be represented by the following equation

III

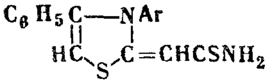
When equimolecular amounts of reactants are heated together for one hour in the presence of a small amount of absolute alcohol, a crystalline precipitate is formed. If a precipitate is not formed even after strong cooling, small amounts of water and ether are added, to help precipitate formation.

Under the action of bases the quarternary salts split off HBr, being converted to methylene bases. With some compounds the methylene bases are formed even by prolonged heating with alcohol.

Measurements of the IR spectra of the crystalline methylene bases disclose an absorption band in the 2200 cm^{-1} region, characteristic of the nitrile group.

The methylene hydrogens in bromides of 2-cyanomethyl-3-aryl-4-phenylthiazoles (III) are labile, as is confirmed by formation of 2-cyanoarylazomethylene-3-aryl-5-phenylthiazoles under the action of substituted phenyldiazonium salts. Table 4 gives the arylazo derivatives prepared.

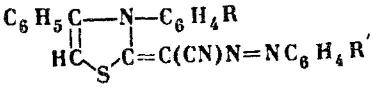
We were also interested in the possibility of adding hydrogen sulfide to the nitrile group in 2-cyanomethylene-3-aryl-4-phenylthiazoles to obtain amides of thiazolethioacetic acid, structure



However, addition of hydrogen sulfide in alcoholic ammonia, or in pyridine plus triethylamine, did not yield the desired products. In all cases the sulfur content was too high and variable. Purification by crystallization or reprecipitation for alkaline solution with acid only resulted in the sulfur content being raised.

Table 4

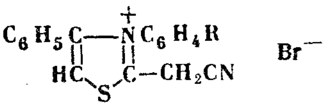
2-Cyanoarylazomethylene-3-aryl-4-phenylthiazoles



Compound No.	R	R¹	Mp, °C	Formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
XXVII	H	H	247	$C_{23}H_{16}N_4S$	14.55 14.46	—	14.73	—	92
XXVIII	*p*-CH_3	H	210	$C_{24}H_{18}N_4S$	14.61 14.70	—	14.21	—	90
XXIX	*o*-CH_3	H	190	$C_{24}H_{18}N_4S$	14.07 14.12	—	14.21	—	87
XXX	H	*p*-NO_2	Does not melt up to 240	$C_{23}H_{15}N_5O_2S$	16.14 16.12	—	16.47	—	90
XXXI	H	*p*-NH_2SO_2	Does not melt up to 240	$C_{23}H_{17}N_5O_2S_2$	—	14.24 14.20	—	13.94	80
XXXII	H	*p*-C_2H_5OOC	225	$C_{26}H_{20}N_4O_2S$	—	7.03 7.19	—	7.21	85
XXXIII	H	*p*-Br	242	$C_{23}H_{15}N_4SBr$	—	7.17 7.11	—	6.97	88

Table 5

Bromides of 2-Cyanomethyl-3-aryl-4-phenylthiazoles



Compound No.	R	Mp, °C	Formula	Br, %		Yield, %
				Found	Calculated	
XVII	H*	237	$C_{17}H_{13}N_2SBr$	22.24; 22.15	22.40	71
XVIII	*p*-CH_3	231	$C_{18}H_{15}N_2SBr$	21.38; 21.53	21.56	61
XIX	*o*-CH_3	235	$C_{18}H_{15}N_2SBr$	21.53; 21.57	21.56	65
XX	*p*-CH_3O	212	$C_{18}H_{15}N_2OSBr$	20.55; 20.44	20.67	60
XXI	*o*-CH_3O	220	$C_{18}H_{15}N_2OSBr$	20.45; 20.47	20.67	50
XXII	*p*-Cl	198	$C_{17}H_{12}N_2SBrCl$	30.30; 30.39	29.50 (Br+Cl)	55

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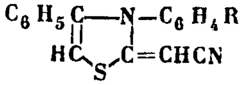
*Compound XVII was prepared along with E. D. Sych.

Experimental

2-Cyanomethyl-3, 4-diphenylthiazole bromide. A mixture of 1.8 g(~ 0.1 mole) cyanoacetanilide, 2 g(~ 0.1 mole) ω-bromoacetophenone, and 2 ml absolute alcohol was refluxed on a water bath for 40-60 min. At the start of heating the components dissolved in the alcohol, then a crystalline precipitate was formed, and that considerably increased on cooling. The precipitate was filtered off, washed with ether, and dried in air. Yield 2.5 g (71% of theoretical), mp 237° (from alcohol).

Table 6

2-Cyanomethylene-3-aryl-4-phenylthiazoles



Compound No.	R	Mp, °C	Formula	Found, %		Calculated,%		Yield, %
				N	S	N	S	
XXIII	H	160—161	$C_{17}H_{12}N_2S$	9.89; 9.86	—	10.14	—	70
XXIV	o-CH_3	125	$C_{18}H_{14}N_2S$	—	10.71; 10.70	—	11.03	80
XXV	p-CH_3	150	$C_{18}H_{14}N_2S$	—	10.78; 10.64	—	11.03	83
XXVI	o-CH_3O	160	$C_{18}H_{14}N_2OS$	—	10.53; 10.60	—	10.45	65

The quaternary salts of 2-cyanomethyl-3-aryl-4-phenylthiazoles listed in Table 5 were prepared similarly. They were pale brown, insoluble in ether, very slightly soluble in water. Except in the cases of XX and XXII, they were recrystallized from alcohol.

2-Cyanomethylene-3-p-methyl-4-phenylthiazole. 0.5 g(1.3 mmole) 2-cyanomethyl-3-p-methoxy-4-phenylthiazole bromide was dissolved, with slight heating, in 4 ml 5% alcoholic sodium hydroxide, the solution filtered, diluted with an equal volume of water, made acid with hydrochloric acid, and excess acid neutralized with aqueous ammonia, when a yellow precipitate separated. It was filtered off, washed with water, and dried in air. Yield 0.3 g (75% of theoretical), mp 150° (from alcohol).

The methylene bases of Table 6 were prepared similarly. They were pale yellow crystalline compounds, insoluble in water, soluble in concentrated hydrochloric acid, soluble with more difficulty in the dilute acid. They were purified by recrystallization from alcohol.

2-Cyanophenylazomethylene-3, 4-diphenylthiazole. An aqueous solution of the diazonium salt was prepared in the usual way from 0.13 g(1.4 mmole) aniline and sodium nitrite, cooled, and 2 g(24 mmole) sodium acetate added, and a solution of 0.5 g(1.4 mmole) 2-cyanomethyl-3, 4-diphenylthiazole bromide in 7 ml alcohol added dropwise with vigorous stirring.

A pale orange precipitate separated immediately when the quaternary salt was added, but to complete reaction, stirring was continued for about an hour. The products were poured onto 50 g of finely crushed ice, the precipitate filtered off, washed with water, and dried in air, yield 0.53 g, mp 247° (from alcohol).

The 2-cyanophenylazomethylene-3-aryl-4-phenylthiazoles listed in Table 6 were prepared similarly. They were pale orange crystalline substances, which were purified by recrystallizing from alcohol.

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