THIOUREA DERIVATIVES OF β-DICARBONYL COMPOUNDS

V. A New Method for the Synthesis of Imidazole-2-thione Derivatives*

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Under the action of sulfuric acid, N-(2-phenylindan-1,3-dion-2-yl)-thioureas (I) undergo hydrolytic cleavage of the five-membered ring with the subsequent cyclization of the intermediate products formed, thiocarbomido-o-carboxydeoxybenzoins, to give 4-(o-carboxyphenyl)-5-phenylimidazole-2-thiones (III). The structure of compounds III has been confirmed by their IR and UV spectra, and a mechanism for their formation has been proposed. A preparative method for the synthesis of 4-(o-carboxyphenyl)-5-phenylimidazole-2-thiones has been developed.

In a preceding investigation [1] we developed a method for the synthesis of N-2-arylindan-1, 3-dion-2-yl-thioureas (I), representatives of the 2-thiocarbamide-β-diketones. It is well known that N-subsituted thioureas are frequently used for the synthesis of imidazole-2-thiones or 2-mercaptoimidazoles. Thus, the fusion of thiourea [2] or ammonium thiocyanate [3–5] with α-hydroxy ketones has given imidazole-2-thione derivatives. The corresponding imidazole-2-thiones have also been obtained by the reaction of hydrogen halide salts of α-amino ketones with inorganic thiocyanates [6–13]. Markwald has developed a method for obtaining imidazole-2-thiones [14, 15] from amino acetals. Under the action of isothiocyanates, amino acetals give thiocarbamido acetals, which convert into imidazole-2-thione derivatives under hydrolysis with 30% sulfuric acid.

The thiocarbamidoarylindandiones that we have synthesized have been used successfully to obtain arylindandionylaminothiazoles [16]. In order to extend the range of application of compounds I for the synthesis of heterocyclic systems, we have studied more closely their transformations in concentrated sulfuric acid solutions. It was found that these lead to sulfur- and nitrogen-containing products of an acidic nature. This led to the assumption that under these conditions hydrolytic cleavage of the indandione ring takes place in a similar manner to that which has been described for 2-substituted 2-thiocyanato-1, 3-indandiones [17, 18].

The thiocarbamido derivatives of o-carboxydeoxybenzoin (II) so formed, which are difficult to obtain by other methods, cyclize to 4-(o-carboxyphenyl)-5-phenyl-2-imidazolethiones (III). The latter were isolated by diluting solutions of (I) in concentrated sulfuric acid with ice and neutralizing the acid with dilute alkali. The 2-imidazolethiones (III) form faintly yellow crystalline substances readily soluble in polar solvents and having the high melting points that are characteristic for imidazoles. The addition of triethylamine to solutions or suspensions of compounds III in ethanol gave the triethylamine salts of the 4-(o-carboxyphenyl)-5-phenyl-2-imidazolethiones (IV).

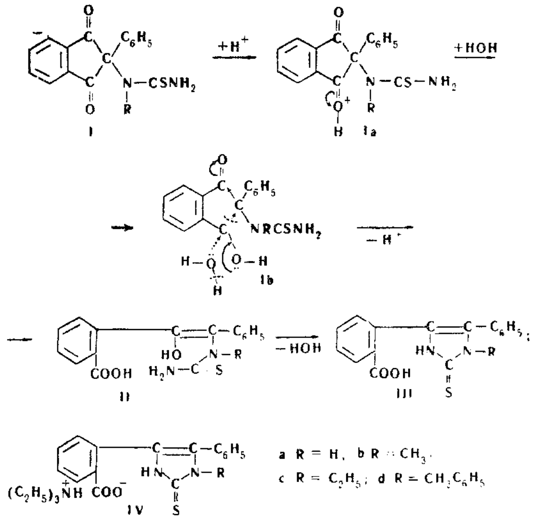
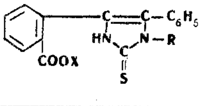


Table 1



4-(o-Carboxyphenyl)-5-phenyl-2-imidazolethiones and Their Triethylamine Salts

X	R	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
H	H	260–262	$C_{16}H_{12}N_2O_2S$	64.92	4.31	9.43	64.86	4.08	9.45	85.6
H	CH_3	263–265	$C_{17}H_{14}N_2O_2S$	66.06	4.54	9.35	65.80	4.54	9.02	90
H	C_2H_5	249–251	$C_{18}H_{16}N_2O_2S$	66.49	5.05	8.66	66.67	4.96	8.63	85
H	$CH_2—C_6H_5$	225–227	$C_{23}H_{18}N_2O_2S$	71.73	4.63	7.13	71.62	4.72	7.26	93
$\overset{+}{N}H(C_2H_5)_3$	H	213–215	$C_{22}H_{27}N_3O_2S$	66.46	7.11	10.64	66.46	6.84	10.57	82
$\overset{+}{N}H(C_2H_5)_3$	CH_3	263–265	$C_{23}H_{29}N_3O_2S$	67.01	7.01	10.13	67.11	7.10	10.21	75
$\overset{+}{N}H(C_2H_5)_3$	C_2H_5	195–197	$C_{24}H_{31}N_3O_2S$	67.67	7.27	9.50	67.72	7.34	9.87	91
$\overset{+}{N}H(C_2H_5)_3$	$CH_2—C_6H_5$	159–161	$C_{29}H_{33}N_3O_2S$	71.74	6.90	8.45	71.45	6.81	8.61	79

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*For communication IV, see [16].

Some of these are readily soluble in water. The characteristics of the compounds **III** and **IV** synthesized are shown in Table 1.

To confirm the structure of the 2-imidazolethiones formed, we studied their UV spectra in comparison with the UV spectrum of a model substance, 4,5-diphenyl-2-imidazolethione. The latter was obtained by fusing benzoin with thiourea [2].

The question of the structure of the oxo- and thioderivatives of various tautomeric heterocyclic systems has been discussed repeatedly in the literature. A study of the UV and IR spectra of such compounds as 2-benzoxazolethione [19], 1-methyl-2-imidazolethione [20], 4,5-diphenyl-2-imidazolethione, 2-oxazolone, 2-oxazolethione [21], 2-thiazolone, triazolethione [23], and others, has shown that these compounds exist in the amide form.

On comparing the curves of the UV spectra (Fig. 1) of the model substance 4,5-diphenyl-2-imidazolethione and some of the imidazolethiones that we had synthesized, it can be seen that they are similar in nature, with two maxima: at 220–224 nm (log ε = 4.17–4.24) and at 273–289 nm (log ε = 4.17–4.27, Table 2) and agree with the literature data obtained for the model substance [21], the imidazolethione structure of which has been demonstrated. The UV spectra of the starting materials, N-ethyl-N-(2-aryl-1,3-indandion-2-yl)thioureas, do not differ fundamentally from the UV spectra of other 2,2-disubstituted 1,3-indandiones [24].

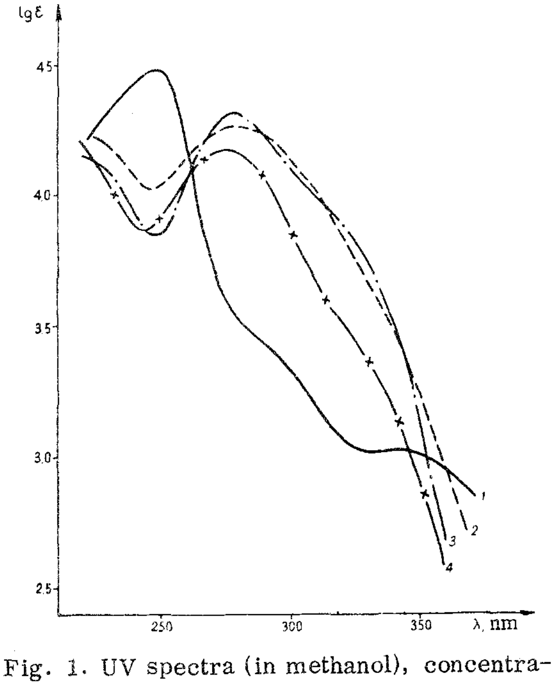

Fig. 1. UV spectra (in methanol), concentration 10^{-4} M: 1) N-ethyl-N-(2-phenyl-1,3-indandion-2-yl)thiourea; 2) 4-(o-carboxyphenyl)-5-2-imidazolethione; 3) 4,5-diphenyl-2-imidazolethione; 4) 1-benzyl-4-(o-carboxyphenyl)-5-phenyl-2-imidazolethione.

In the synthesis of the 2-imidazolethiones (III) it was important to find at what stage the cleavage of the indandione ring took place: on the dissolution of I in concentrated sulfuric acid or on the subsequent dilution of the solution. For this purpose, the UV spectra of solutions of N-ethyl-N-(2-phenyl-1,3-indandion-2-yl)thiourea in sulfuric acid of various concentrations (65–95%, Fig. 2) were recorded. The UV spectrum of the previously isolated analytically pure 4-(o-carboxyphenyl)-1-ethyl-5-phenyl-2-imidazolethione (IIIc) in concentrated sulfuric acid was also recorded. From the fact that the absorption curves of the latter compound and I in various concentrations of sulfuric acid do not differ, it may be concluded that the cleavage of the indandione ring and the cyclization of the intermediates so formed takes place as early as the dissolution of I in sulfuric acid. Since the formation of imidazolethione derivatives III from I is still observed at 65% sulfuric acid concentration, and this is the limiting concentration required for the protonation of the carbonyl group [25], it may be assumed that the first stage in the process of cleavage of the five-membered ring of the indandione system is the protonation of the carbonyl group (Ia), which favors the subsequent hydrolytic cleavage of the ring via the intermediate state Ib.

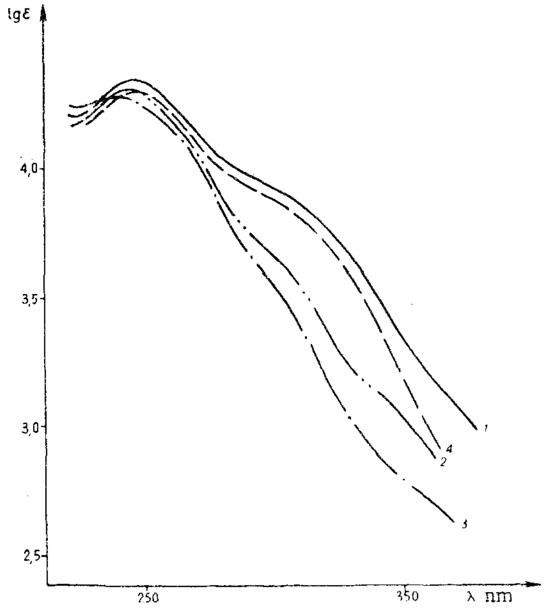

Fig. 2. A study of the cleavage of the indandione ring by UV spectra (concentration 10^{-4} M): 1) N-ethyl-N-(2-phenyl-1,3-indandion-2-yl)thiourea in concentrated H_2SO_4; 2) the same in 85% H_2SO_4; 3) the same in 65% H_2SO_4; 4) 4-(o-carboxyphenyl)-1-ethyl-5-phenyl-2-imidazolethione in concentrated H_2SO_4.

In the double-bond region of the IR spectra of the 2-imidazolethiones intense maxima are found at 1674–1694 cm^{-1}, which agree well with data for the vibrations of the carboxy groups of aromatic acids [26]. In the corresponding salts, this frequency disappears and a frequency appears in the range from 1529 to 1558 cm^{-1} which characterizes the asymmetrical vibrations of a COO^- group. In some compounds III and IV, $\nu_{C=C}$ of a five-membered ring can be distinguished clearly in the 1631–1643 cm^{-1} range, but sometimes this frequency is masked by the frequencies of the vibrations of the aromatic rings. For 4,5-

Table 2

UV and IR Spectra of 4-(o-Carboxyphenyl)-5-phenyl-2-imidazolethiones and Their Salts

Compound	1750–1590 region, cm^{-1}/absorption, %			λ_{max}, nm (log ε)
	ν_{COOH} or ν_{COO^-}, a sym	$\nu_{C=C}$	$\nu_{C=C}$ arom	
IIIa	$\frac{1688}{74}$	$\frac{1631}{50}$	$\frac{1604}{51}$	224 (4.23), 281 (4.27)
IIIb	$\frac{1674}{55}$	$\frac{1620}{30}$	$\frac{1594}{34}$	224 (4.17), 276 (4.26)
IIIc	$\frac{1691}{76}$	—	$\frac{1599}{32}$	222 (4.17), 273 (4.22)
IIId	$\frac{1690}{77}$	$\frac{1643}{41}$	$\frac{1592}{43}$	220 (4.24), 276 (4.17)
IVa	$\frac{1529}{72}$	$\frac{1635}{52}$	$\frac{1611}{54}$	—
IVb	$\frac{1548}{44}$	—	$\frac{1591}{37}$	—
IVc	$\frac{1558}{38}$	—	$\frac{1596}{51}$	—
IVd	$\frac{1551-1545}{40}$	—	$\frac{1600}{40}$	—

diphenyl-2-imidazolethione in KBr, this frequency is given at 1622 cm^{-1} [21]. The stretching vibrations of the aromatic rings in compounds **III** and **IV** are found in the 1611–1591 cm^{-1} region. The characteristics of the UV and IR spectra are given in Table 2.

EXPERIMENTAL

4-(o-Carboxyphenyl)-1-methyl-5-phenyl-2-imidazolethione (IIIb). A solution of 1.5 g of N-methyl-N-(phenyl-1,3-indandion-2-yl)thiourea in 10 ml of concentrated sulfuric acid was kept for half an hour and was then, with cooling, diluted with ice and neutralized with 10% alkali solution. The precipitate that deposited was dissolved in a small excess of alkali and then the solution was acidified. The precipitate that deposited was filtered off and washed with water. This gave 1.35 g (90%) of **IIIb** in the form of a faintly yellow substance with mp 263–265° C (from ethanol). The other imidazolethiones **III** were obtained similarly.

Triethylamine salt of 4-(o-carboxyphenyl)-1-methyl-5-phenyl-2-imidazolethione (IVb). A suspension of 0.20 g of **IIIc** in ethanol was treated with 0.06 ml of triethylamine. On heating, the suspended matter rapidly went into solution. The addition of ether yielded 0.20 g (75%) of IVb. Mp 263°–265° C (from ethanol with the addition of ether).

The other compounds of type IV were obtained similarly.

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