CYCLIZATION OF N^1-(1-ANTHRAQUINONYL)-N^2-PHENYLTHIOUREA INTO THIAZOLE DERIVATIVES

V. A. Savel'ev and V. A. Loskutov

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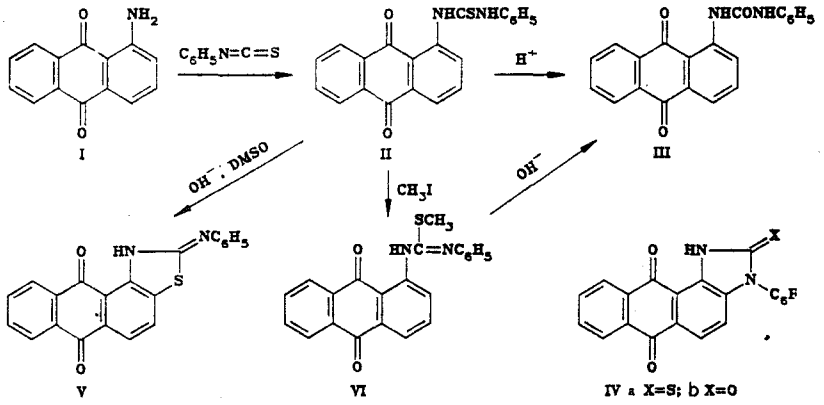
N^1-(1-Anthraquinonyl)-N^2-phenylthiourea, obtained from the reaction of 1-aminoanthraquinone with phenyl isothiocyanate, cyclizes in an alkaline medium into 2-3-dihydro-2-phenylimino-1H-anthra[1,2-d]thiazole-6,11-dione. Treatment of anthraquinonylthiourea with bromine in chloroform results in the formation of 1-(2-benzothiazolyl)aminoanthraquinone together with a small amount of anthrathiazole.

We have previously shown that anthraquinonylureas cyclize into derivatives of anthraimidazoline by the action of bases [1]. According to the literature data [2-5], aryl-substituted thioureas convert into the derivatives of benzothiazole under varied conditions. In the case of anthraquinonylthioureas, we can expect the formation of anthraimidazolethiones, although, because of the high nucleophilicity of the sulfur atom, cyclization into anthrathiazoles is more probable. The aim of the present work was to synthesize N^1-(1-anthraquinonyl)-N^2-phenylthioureas and to explore the possibility of their heterocyclization.

As expected, the isothiocyanates were found to be less active than isocyanates in the reaction with 1-aminoanthraquinone (I) [6]. Thus, in pyridine, at 90°C, amine I practically does not react with ethyl and allyl isothiocyanates, while with phenyl isothiocyanate, the reaction proceeds much more slowly than with phenyl isocyanate. The yield of anthraquinonylthiourea II does not exceed 40%. Increase of the temperature to 150...160°C on carrying out the reaction without a solvent (in an excess of phenyl isothiocyanate) was accompanied by resinification and several side-reactions, particularly the conversion of thiourea II into urea III. Desulfurization of thiourea II is also observed in DMSO or DMFA on heating (80...100°C), which in the presence of catalytic amounts of an acid, also occurs at room temperature (cf [7].



Treatment of thiourea II in a DMSO solution at room temperature with bases (5% aqueous solutions of alkalies, sodium alcoholate), as in the case of urea III [1], led to the formation of a cyclization product in high yield, the PMR spectrum of which indicates a 1,2-disubstitution in the anthraquinone molecule. The data obtained from physical methods of investigation do not permit an unequivocal choice between the isomeric structures IVa and V. A proof for the structure of imidazolinethione IVa can be obtained by an alternate synthesis of this compound from compound IVb with phosphorus pentasulfide, or by its desulfurization

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1273-1277, September, 1989. Original article submitted December 1, 1987; revision submitted February 13, 1989.

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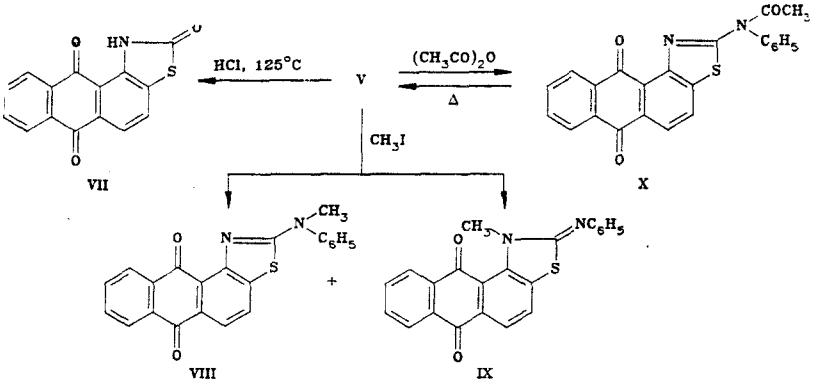
into imidazolinone IVb [1]. However, despite variation of the conditions, the reaction mixtures remained in both cases practically unchanged.

The higher nucleophilicity of the sulfur atom in thiourea II, and consequently, the preference for the heterocyclization into thiazole V, is indicated by the result of the alkylation of thiourea by methyliodide in the presence of an alkali. When the reaction is carried out in dioxane, the only alkylation product was found to be S-methylisothiourea VI, the structure of which is confirmed by the presence in the IR spectrum not only of the vibration band of the C=N bond (1620 cm^{-1}), but also of two absorption bands of the C=N groups (1650 and 1670 cm^{-1}) and a band of the NH group at 3180 cm^{-1}. In the mass spectrum of compound VI the most intense is the peak of the $[M-47]^+$ ion, corresponding to the loss of the SCH_3 fragment. Urea III is a by-product in the alkylation reaction as a result of the desulfurization of isothiourea. We showed by a special experiment that when an aqueous solution of an alkali is added, isothiourea VI in DMSO converts almost instantly into urea III.

In the IR spectrum of the heterocyclization product of thiourea II, there are two absorption bands, one very strong (1645 cm^{-1}) and one a strong band (1670 cm^{-1}). Such a nontypical distribution of the band intensities for anthraquinones in this region may indicate the presence of an exocyclic C=N bond in thioazoline V*. This is confirmed by the hydrolytic transformation of compound V into thiazolinone VII, occuring on heating in DMSO in the presence of hydrochloric acid, similarly as described in [3]. As in the case of imidazolinone IVb [1], in the IR spectrum of thiazolinone VII, a single band at 1670 cm^{-1} corresponds to the carbonyl groups of quinone, and the band at 1725 cm^{-1} corresponds to the vibrations of the C=O bond in the heterocyclic ring. A similarity between these compounds is also observed in the character of the absorption bands in the electronic spectra.

Theoretically, iminothiazoline V may also exist in the aminothiazole form, but this could not be detected by means of the spectral methods. To synthesize the aminothiazole derivatives, we examined the methylation and acetylation reactions of thiazoline V. The reaction with methyl iodide in DMSO or DMFA takes 1 h at room temperature, whereby the product is anthrathiazole VIII (yield 72%), in the IR spectrum of which there is only one absorption band of the quinone carbonyl groups in the 1600...1700 cm^{-1} region. Thiazoline IX is obtained in a lower yield (16%), and its IR spectrum, similarly to that of the initial thiazoline V, is characterized by the presence of vibration bands of the C=N (1640 cm^{-1}) and C=O bonds (1675 cm^{-1}). In the ^{13}C NMR spectra of compounds VIII and IX, the position of the carbon atom signals of the C=N fragment, differs by 7 ppm, whereby in the case of compound VIII, this signal is present in a weaker field, which agrees with the literature data [9]. Boiling of thiazoline V in acetic anhydride results in the acetyl derivative X, which is very unstable, and is readily deacetylated on heating without a solvent, or in organic solvents, as well as during chromatography on silica gel.



A method is known for the preparation of benzothiazole derivatives by cyclization of aryl-substituted thioureas in the presence of bromine (the Hugershoff synthesis) [2]. The asymmetric N,N'-di-aryl-substituted thioureas can thus give two reaction products. By the treatment of thiourea II with bromine in chloroform, we obtained urea III (yield 44%), as a result of desulfurization of thiourea II, and thiazoline V (yield 7%). The third reaction product was identified on the basis of spectral data as 1-(2-benzo-thiazolylamino)anthraquinone (XI). In the PMR spectrum of this compound, as in the spectra of the thiourea derivatives II and VI,

*For thiazoles containing a C=N bond in the ring, frequency values lower than 1600 cm^{-1} are characteristic [8].

TABLE 1. Characteristics of Synthesized Compounds

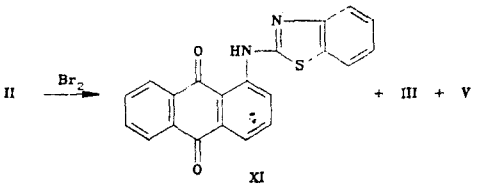
Compound	Empirical formula	M^+_{exp} m/z	M^+_{calc} m/z	T_{mp} °C*	UV spectrum, nm (lg ε)	IR spectrum, ν, cm^{-1} C=N	C=O	N—H	PMR spectrum, δ, ppm	Yield, %
II	$C_{21}H_{14}N_2O_2S$	—	—	198...201	307 (4,24), 450 (3,80)	—	1640, 1680	3180	7,18...8,23** (11H, m, C_6H_5 and 6H of anthraquinone); 9,00 (1H, d.d, 2-H; J=7 Hz and J=1,5 Hz); 10,92 (1H, s, N^2—H); 11,77 (1H, s, N^1—H)	40
V	$C_{21}H_{12}N_2O_2S$	356,0604	356,0620	206...208	322 (4,01), 475 (4,07)	1645	1670	3360	7,17...7,39 (5H, m, C_6H_5); 7,59 (1H, d, 4-H, J=8 Hz); 7,71 (2H, m, 8-H and 9-H); 7,95 (1H, d, 5-H, J=8 Hz,; 8,27 (2H, m, 7-H and 10-H); 10,49 (1H, br.s, NH)	88
VI	$C_{22}H_{16}N_2O_2S$	372,0924	372,0933	219...222	314 (4,01), 458 (3,83)	1620	1650, 1670	3180	2,64 (3H, s, CH_3); 6,96 (2H, d, o-C_6H_5, J=8 Hz); 7,09 (1H, t, p-C_6H_5, J=8 Hz); 7,33 (2H, t, m-C_6H_5, J=8 Hz); 7,67...7,84 (3H, m, 3-H, 6-H and 7-H); 7,97 (1H, d.d, 4-H, J=8 Hz and J=1,5 Hz); 8,29 (2H, m, 5-H and 8-H); 9,33 (1H, br.d, 2-H, J=8 Hz); 12,08 (1H, s, NH)	30
VII	$C_{15}H_7NO_3S$	281,0151	281,0146	268...272	339 (3,56), 411 (3,83)	—	1670, 1725	3320	7,80 (3H, m, 4-H, 8-H and 9-H); 8,11 (1H, d, 5-H, J=8 Hz); 8,30 (2H, m, 7-H and 10-H); 11,01 (1H, br.s, NH)	45
VIII	$C_{22}H_{14}N_2O_2S$	—	—	244...246	316 (4,13), 452 (4,01)	1525	1670	—	3,82 (3H, s, CH_3); 7,42 (5H, m, C_6H_5); 7,74 (3H, m, 4-H, 8-H and 9-H); 8,02 (1H, d, 5-H, J=8 Hz); 8,28 (2H, m, 7-H and 10-H)	72
IX	$C_{22}H_{14}N_2O_2S$	370,0752	370,0776	235...238	322 (3,78), 473 (4,00)	1640	1675	—	3,60 (3H, s, CH_3); 7,10 (3H, m-, o- and p-C_6H_5); 7,35 (2H, t, m-C_6H_5, J=8 Hz, 7,53 (1H, d, 4-H, J=8 Hz); 7,77 (2H, m, 8-H and 9-H); 8,02 (1H, d, 5-H, J=8 Hz); 8,20 (2H, m, 7-H and 10-H)	16
X	$C_{23}H_{14}N_2O_3S$	—	—	>240***		1490	1680	—		72
XI	$C_{21}H_{12}N_2O_2S$	356,0619	356,0620	225...226	331 (4,34), 479 (3,94)	1550	1650, 1680	3110	7,18...7,90 (7H, m, C_6H_4 and 3-H, 6-H and 7-H); 7,98 (1H, d.d, 4-H, J=8 Hz and 1 Hz); 8,29 (2H, m, 5-H and 8-H); 9,41 (1H, d.d, 2-H, J=8 Hz and J=1 Hz); 12,86 (1H, s, NH)	30

* Compound II was crystallized from dioxane, V from aqueous DMFA, VI from acetonitrile, VII from DMFA, VIII, IX, and XI from a 1:2 dioxane-ethanol mixture, X — from acetic anhydride,

** The spectrum was recorded on a Varian A-56/60 A spectrometer (60 MHz) in $(CD_3)_2SO$, using HMDS as internal standard.

*** Decomposition temperature.

and also of anthraquinonylureas [6], the signal of the proton at the $C_{(2)}$ atom in the form of a doublet of doublets is characteristic. This indicates cyclization at the phenyl and not the anthraquinone fragment of the molecule.



The formation of thiazole V from thiourea II under basic conditions and of two heterocyclization products, thiazoles V and XI, in chloroform in the presence of bromine, clearly can be explained by the different mechanisms of these reactions: a nucleophilic mechanism in the first case (cf [1]) and possibly, an electrophilic mechanism in the second (cf [10]).

EXPERIMENTAL*

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets, the UV spectra on a Specord UV-vis spectrometer for solutions in chloroform, and the PMR (200.13 MHz) and ^{13}C NMR spectra (50.32 MHz) on a Bruker WP-200 SY spectrometer for solutions in deuterochloroform. The mass spectra were obtained on a Finnigan MAT-8200 spectrometer. The course of the reactions was controlled on Silufol UV-254 plates, using chloroform as eluent. The characteristics of the synthesized compounds are given in Table 1. The data of the elemental analysis of the compound obtained for C, H, N, S correspond to the calculated values.

N^1-(1-Anthraquinonyl)-N^2-phenylthiourea (II). A mixture of 3.3 g (14.8 mmoles) of 1-aminoanthraquinone, 7.5 ml (45.8 mmoles) of phenyl isothiocyanate, and 45 ml of pyridine was stirred for 15 h at 90°C. After cooling, the precipitate was separated, washed with ether, and recrystallized. Yield, 2.1 g.

Desulfurization of Thiourea II. A. A mixture of 2 g (0.6 mmole) of thiourea II, 0.04 ml of concentrated H_2SO_4 and 10 ml of DMSO was allowed to stand for 7 days at room temperature with intermittent stirring. The mixture was then poured into water, the precipitate was separated and recrystallized from dioxane. Yield, 0.13 g (68%) of urea III, the mp and IR spectrum of which were identical with those described in [6].

B. A solution of 0.2 g (0.6 mmole) of thiourea II in 30 ml of DMFA was heated for 2 h 30 min at 100°C, and then was cooled and diluted with water. The precipitate was separated and chromatographed on silica gel, using chloroform as eluent. Yield, 0.085 g 45% of urea III and 0.06 g (48%) of 1-aminoanthraquinone.

2,3-Dihydro-2-phenylimino-1H-anthra[1,2-d]thiazole-6,11-dione (V). A mixture of 2.03 g (5.7 mmoles) of thiourea II and 29 ml (27 mmoles) of a 5% aqueous KOH solution and 250 ml of DMSO, was allowed to stand for 3 days at 20°C with intermittent stirring, and was then poured into water. The precipitate was separated and recrystallized. Yield, 1.78 g.

1-(1-Anthraquinonyl)-2-methyl-3-phenylisothiourea (VI). A mixture of 1 g (2.8 mmoles) of thiourea II, 0.33 g of pulverized KOH and 5 ml of methyl iodide in 100 ml of dioxine was stirred for 4 days at 20°C. The precipitate was filtered and washed with dioxane. The filtrate was evaporated to dryness, and the precipitate was twice recrystallized. Yield, 0.3 g.

2,3-Dihydro-1H-anthra[1,2-d]thiazole-2,6,11-trione (VII). A suspension of 0.84 g (2.35 mmoles) of thiazole V, 12 ml of concentrated HCl and 50 ml of DMSO was heated for 10 h at 125°C. After cooling, the precipitate was separated and recrystallized. Yield, 0.3 g.

2-(N,N-Methyl,phenyl)aminoanthra[1,2-d]thiazole-6,11-dione (VIII) and 2,3-dihydro-1-methyl-2-phenyliminoanthra[1,2-d]thiazole-6,11-dione (IX). A mixture of 0.6 g (1.7 mmole) of thiazole V, 7 ml (6.5 mmoles) of a 5% aqueous solution of KOH and 10 ml of methyl iodide in 75 ml of DMSO was stirred for 1 h at 20°C, The mixture was then diluted with water and extracted with chloroform (3 × 250 ml). The organic layer was dried over magnesium sulfate, evaporated and chromatographed on silica gel, using a 10:1 benzene-acetone mixture as eluent. Yield, 0.45 g of compound VIII and 0.10 g of compound IX.

*With the participation of O. V. Komissaruk.

2-(N,N-Acetyl,phenyl)aminoanthra[1,2-d]thiazole-6,11-dione (X). A suspension of 0.1 g (0.3 mmole) of thiazole V in 10 ml of acetic anhydride was boiled for 3 h. After cooling, the precipitate was separated, and recrystallized. Yield, 0.08 g.

1-(2-Benzothiazolyamino)anthraquinone (XI). A solution of 0.26 g (1.7 mmole) of bromine in 8 ml of chloroform was added dropwise at 20°C to a suspension of 0.54 g (1.5 mmole) of thiourea II in 40 ml of chloroform. The mixture was stirred for 5 h, washed with a 5% aqueous KOH solution and water. The organic layer was dried over magnesium sulfate, evaporated, and the residue chromatographed on silica gel. Elution with benzene gave 0.16 g of quinone XI. The elution was continued with chloroform to yield 0.04 g (7%) of anthrathiazoline V annd 0.23 g (44%) of urea III.

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