SYNTHESIS OF SUBSTITUTED THIAZOLES AND OXAZOLES FROM 2-AMINO-1-(p-NITROPHENYL)ETHANOL

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New thiourea derivatives have been synthesized by the condensation of 2-amino-1-(p-nitrophenyl)ethanol with aryl and alkyl isothiocyanates. Their cyclization with ω-bromoacetophenone and methyl monochloroacetate and also their desulfurization with yellow lead oxide have been studied.

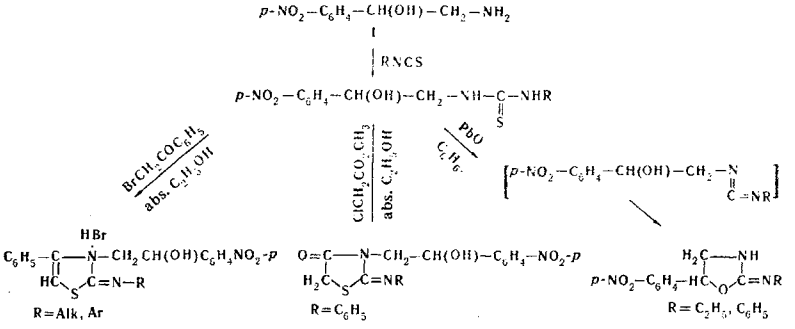
It is known that 2-amino-1-(p-nitrophenyl)ethanol (I) is an intermediate in the production of the synthetic antibiotic levomycetin (chloroamphenicol) [1]. The acylation [2] and the methylation [3] of I have been studied and from it valuable antiseptics [2] and substances reducing the blood pressure and promoting the respiratory functions have been obtained [3].

The reaction of I with alkyl and aryl isothiocyanates, leading to thiourea derivatives, has not been described in the literature. The thiourea derivatives are of interest, since among them are found substances with various physiological properties [4].

By the reaction of alkyl and aryl isothiocyanates with I we have synthesized N-aryl(alkyl)-N'-[β-hydroxy-β-(p-nitrophenyl)ethyl]thioureas in good yields (Table 1).

The cyclization of the latter with ω-bromoacetophenone in absolute ethanol gave the hydrobromides of 2-arylimino-3-[β-hydroxy-β-(p-nitrophenyl)ethyl]-4-phenyl-4-thiazolines which, on crystallization from a mixture of ethanol and pyridine, were converted into the corresponding bases. The cyclization of N-[β-hydroxy-β-(p-nitrophenyl)ethyl]-N'-phenylthiourea with methyl monochloroacetate in absolute ethanol in the presence of anhydrous sodium acetate [5] has given 3-[β-hydroxy-β-(p-nitrophenyl)ethyl]-2-phenyliminothiazolidin-4-one. N-[β-Hydroxy-β-(p-nitrophenyl)ethyl]-N'-phenylthiourea and the corresponding N'-ethyl compound are comparatively readily desulfated on being boiled with yellow lead oxide in benzene to form the corresponding oxazoline derivatives, probably through the intermediate formation of carbodiimides.

GENERAL SCHEME OF THE REACTIONS STUDIED



The structure of the oxazoline derivatives was confirmed by their IR spectra (absence of absorption bands of the carbodiimide grouping N=C=N at 2100–2130 cm^{-1} and of the OH group in the 3400–3500-cm^{-1} region). The absorption curves have intense bands of the stretching vibrations of C—O—C bonds (1215–1270 cm^{-1}), —C=N— bonds (1670–1695 cm^{-1}) and N—H bonds (3200–3240 cm^{-1}) [6].

Table 1

N-Aryl(alkyl)-N'-[β-hydroxy-β-(p-nitrophenyl)ethyl]thioureas

R	Mp, °C	Empirical formula	S, % found	S, % calculated	Yield, %
C_2H_5	112—113	$C_{11}H_{15}N_3O_3S$	11.92; 11.75	11.90	99
CH_2=CH—CH_2	78—80	$C_{12}H_{15}N_3O_3S$	10.88	11.39	93
C_6H_5	139—141	$C_{15}H_{15}N_3O_3S$*	10.00; 9.97	10.09	99
p-$CH_3C_6H_4$	157—159	$C_{16}H_{17}N_3O_3S$	9.89; 9.70	9.64	93
p-$C_2H_5OC_6H_4$	180	$C_{17}H_{19}N_3O_4S$**	8.81; 8.75	8.87	80
p-ClC_6H_4	146	$C_{15}H_{14}ClN_3O_3S$	9.14; 9.03	9.11	89
p-BrC_6H_4	162—163	$C_{15}H_{14}BrN_3O_3S$	7.81; 7.79	8.09	93
p-$C_2H_5OOCC_6H_4$	158	$C_{18}H_{19}N_3O_5S$	8.33; 8.16	8.16	Quantitative
p-$HOOCC_6H_4$	176—177	$C_{16}H_{15}O_5N_3S \cdot 1H_2O$	8.24	8.45	97

*Found, %: C 56.68, 56.67; H 4.76, 4.78; N 12.80, 12.93. Calculated, %: C 56.70; H 4.76; N 13.24.

**Found, %: C 56.76, 56.80; H 4.80, 4.95. Calculated, %: C 56.62; H 5.30.

Table 2

2-Arylimino-3-[β-hydroxy-β-(p-nitrophenyl)ethyl]-4-phenyl-4-thiazolines

R′	Mp, °C	Empirical formula	S, % found	S, % calculated	Yield, %
C_6H_5	230 (decomp.)	$C_{23}H_{19}N_3O_3S$*	7.60; 7.61	7.68	82
p-$CH_3C_6H_4$**	148	$C_{24}H_{21}N_3O_3S$	7.35; 7.24	7.43	89
p-$C_2H_5OC_6H_4$**	210 (decomp.)	$C_{25}H_{23}N_3O_4S$	6.80	6.94	90
p-ClC_6H_4	135	$C_{23}H_{18}ClN_3O_3S$	7.07; 7.03	7.32	80
p-$C_2H_5CO_2C_6H_4$	170 (decomp.)	$C_{25}H_{23}N_3O_5S$	6.46; 6.27	6.54	71

*Found, %: C 65.90, 65.91; H 4.16, 4.30. Calculated, %: C 66.16; H 4.58.

**Obtained by evaporating the mother liquor to dryness with subsequent washing with water and recrystallization from a mixture of ethanol and pyridine (10 : 1).

The compositions of the products were confirmed by the results of analysis and molecular weight determinations.

EXPERIMENTAL

N-[β-Hydroxy-β-(p-nitrophenyl)ethyl]-N′-phenylthiourea. A solution of 1.82 g (0.01 mole) of 2-amino-1-(p-nitrophenyl)ethanol in 10 ml of acetone was treated with 1.35 g (0.01 mole) of phenyl isothiocyanate. The mixture was heated in the water bath under reflux for 5 hr. The solvent was evaporated off to dryness, and the resulting residue was washed with dilute hydrochloric acid and then with water to neutrality and dried over phosphorus pentoxide. After recrystallization from a mixture of benzene and ethanol, 2.75 g (87%) of reaction product was obtained. Pale yellow crystals, mp 139–141° C.

The substituted thioureas given in Table 1 were obtained under similar conditions. They consist of faintly colored or colorless crystalline products moderately soluble in pyridine, dioxane, acetone, and acetic acid, sparingly soluble in benzene, and insoluble in water, ether, and carbon tetrachloride. In the IR spectra, absorption maxima at 240 and 270 nm are characteristic for A (sic).

3-[β-Hydroxy-β-(p-nitrophenyl)ethyl]-4-phenyl-2-phenylimino-4-thiazoline. A solution of 0.63 g (2 mM) of N-[β-hydroxy-β-(p-nitrophenyl)ethyl]-N′-phenylthiourea in 8–10 ml of absolute ethanol was treated with 0.4 g (2 mM) of ω-bromoacetophenone. After 10 minutes' boiling, a white precipitate began to deposit. The mixture was boiled for 5 hr, and then the precipitate was filtered off and dried. After recrystallization from a mixture of aqueous ethanol and pyridine (10 : 1), pale yellow crystals were obtained. The other thiazoline derivatives, which were obtained with yields of 71–90% (Table 2) consisted of colorless or pale yellow crystalline substances readily soluble in pyridine and less readily in acetone, dioxane, and ethanol. They are insoluble in water, carbon tetrachloride, and benzene.

3-[β-Hydroxy-β-(p-nitrophenyl)ethyl]-2-phenyliminothiazolidin-4-one. A solution of 0.6 g (1 mM) of N-[β-hydroxy-β-(p-nitrophenyl)-ethyl]-N′-phenylthiourea in 10 ml of absolute ethanol was treated with 0.2 g (1 mM) of methyl monochloroacetate and 3.22 g (4 mm) of anhydrous sodium acetate. The mixture was boiled in the water bath under reflux for 10 hr and was evaporated to dryness. The residue obtained was crystallized from anhydrous benzene, giving 0.2 g (28%) of pale yellow needles with mp 103–104° C. Found, %: S 8.71, 8.56. Calculated for $C_{17}H_{15}N_3O_4S$, %: S 8.69.

5-(p-Nitrophenyl)-2-phenylimino-1,3-oxazoline. A solution of 1.1 g (3.15 mM) of N-[β-hydroxy-β-(p-nitrophenyl)ethyl]-N′-phenylthiourea in 40 ml of anhydrous thiophene-free benzene was treated with 2.2 g of finely ground yellow lead oxide, and the mixture was boiled in the water bath under reflux. After 1 hr, the precipitate was filtered off, a new portion of lead oxide (2.2 g) was added to the filtrate, and it was boiled for another 4 hr. The precipitate of lead sulfide was filtered off, and the filtrate was boiled until another new portion of lead oxide did not darken (12–16 hr). The solid matter was filtered off, the filtrate was concentrated, and the gray-green precipitate that deposited was crystallized from anhydrous benzene. Yield 0.27 g (86%), mp 172–173° C. Found, %: N 14.66, 14.63; mol. wt. 305, 302. Calculated for $C_{15}H_{14}N_3O_3$, %: N 14.81; mol. wt. 283.3.

1-Ethylimino-5-(p-nitrophenyl)-1,3-oxazoline was obtained similarly. Yield 84%, mp 130–132° C. Found, %: N 17.67, 17.58. Calculated for $C_{11}H_{13}N_3O_3$, %: N 17.86.

The IR spectra of the samples in tablets with KBr were taken on a UR-10 spectrometer. The UV spectra were measured on an SF-4 spectrophotometer.

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