CYCLIZATION OF BENZOYLCYANOTHIOACETIC ACID ARYLAMIDES

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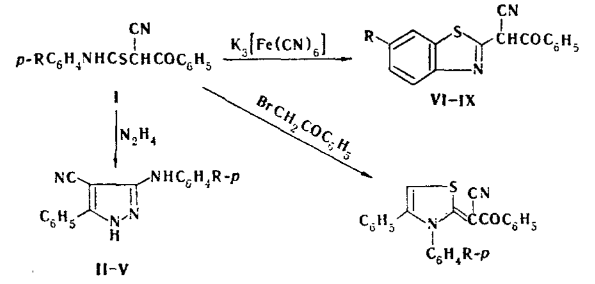
3-Arylamino-4-cyano-5-phenylpyrazoles and 3-aryl-4-phenyl-2-[(benzoyl)cyanomethylene]-4,5-thiazolines, respectively, were obtained by condensation of benzoylcyanothioacetic acid arylamides with hydrazine hydrate or with ω-bromoacetophenone. 2-[(Benzoyl)-cyanomethyl]benzothiazole derivatives were synthesized by oxidative cyclization of benzoylcyanothioacetic acid arylamides.

In order to obtain compounds with possible physiological activity, we investigated the cyclization of benzoylcyanothioacetic acid arylamides [1, 2].

Condensation of β-ketonitriles with hydrazine hydrate [3, 4] leads to amino- and iminopyrazoles. It might have been assumed that 3-amino-4-benzoyl-5-arylaminopyrazoles or 3-phenyl-4-arylthiocarbamoyl-5-aminopyrazoles would have been synthesized in the condensation of benzoylcyanothioacetic acid arylamides (I) with hydrazine hydrate. However, the previously undescribed 3-arylamino-4-cyano-5-phenylpyrazoles (II-V, Table 1) were isolated as a result of this reaction.

The presence of a nitrile group is confirmed by saponification of 3-(p-chlorophenylamino)-4-cyano-5-phenylpyrazole (V) to 3-(p-chlorophenylamino)-4-carbamoyl-5-phenylpyrazole (XII).



II, VI, X R = H; III, VII R = CH_3; IV R = NH_2; IX, XI R = NO_2; V, VIII R = Cl

The IR spectra of II-V contain a characteristic absorption band at 2220 cm^{-1} ($\nu_{C\equiv N}$) [5] and bands at 1610, 1575, and 1495 cm^{-1} (vibrations of the pyrazole ring [6, 7]). Absorption bands at 1650 cm^{-1} ($\nu_{C=O}$) and at 1500-1510 cm^{-1} which are characteristic for vibrations of the C−N bond in the thioamide group [5] are absent. In addition to absorption bands of the pyrazole ring, the IR spectrum of XII contains absorption bands at 1670 cm^{-1} ($\nu_{C=O}$) and at 3370 cm^{-1} (ν_{NH}) [5], which correspond to the stretching vibrations of a primary amide group; the characteristic absorption band for the nitrile group [5] is absent. It therefore follows that the products have structures II-V.

The reaction of benzoylcyanothioacetic acid arylamides with hydrazine hydrates probably commences with attack at the carbonyl group, as in the case of benzoylthioacetic [8] and monoacetylthioacetic acid [9] amides. However, we were unable to isolate the intermediate hydrazone. Simultaneous reduction of the nitro group to an amino group (IV, Table 1) occurs in the case of benzoylcyanothioacetic acid p-nitrophenylamide.

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TABLE 1. 3-Arylamino-4-cyano-5-phenylpyrazoles (II-V) and 2-[(Benzoyl)cyanomethyl]benzothiazoles (VI-IX)

Compound	mp, ℃	Empirical formula	N, %		Yield, %
			found	calc.	
II	257—258	$C_{16}H_{12}N_4$	21,1	21.5	56
III	193—194	$C_{17}H_{14}N_4$	20,4	20,4	57
IV	160—161	$C_{16}H_{13}N_5$	25,1	25,4	58
V	236—237	$C_{16}H_{11}ClN_4$*	18,9	19,0	60
VI	234—235	$C_{16}H_{10}N_2OS$	10,0	10.1	57
VII	241—242	$C_{17}H_{12}N_2OS$	9,8	9.6	56
VIII	264—265	$C_{16}H_9ClN_2OS$	9,3	9,0	53
IX	254—255	$C_{16}H_9N_3O_3S$†	12,8	13,0	51

*Found: C 65.1; H 3.8%. Calculated: C 65.4; H 3.7%.
†Found: C 59.0; H 2.8%. Calculated: C 59.5; H 2.8%.

The benzoylcyanothioacetic acid arylamides undergo oxidative cyclization with potassium ferricyanide in aqueous alkali to give 2-[(benzoyl)cyanomethyl]-6-benzothiazole derivatives (VI-IX). Compound I is not brominated at the methylidyne group by the action of bromine in acetic acid [10], but oxidative cyclization products identical to the compounds obtained in the oxidation with potassium ferricyanide (VI-IX) are formed.

3-Aryl-4-phenyl-2-[(benzoyl)cyanomethylene]-4,5-thiazolines (X, XI) were isolated when benzoylcyanothioacetic acid arylamides (I) were heated with ω-bromoacetophenone in alcohol.

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EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrophotometer.

3-(p-Chlorophenylamino)-4-cyano-5-phenylpyrazole (V). A 1.2-ml sample of hydrazine hydrate was added dropwise to 0.6 g (2 mmole) of benzoylcyanothioacetic acid p-chlorophenylamide, and the mixture was refluxed until hydrogen sulfide evolution ceased (~10-12 h). The mixture was cooled, and the resulting yellow-orange crystalline precipitate was removed by filtration, washed with alcohol, and crystallized from alcohol to give 0.34 g of product.

Compounds II, III, and IV were synthesized similarly (Table 1).

2-[(Benzoyl)cyanomethyl]-6-nitrobenzothiazole (IX). A solution of 0.32 g (1 mmole) of benzoylcyanothioacetic acid p-nitrophenylamide and 2.2 g of sodium hydroxide in a mixture of 10 ml of water and 5 ml of alcohol was added with stirring to a solution of 0.8 g of potassium ferricyanide in 20 ml of water containing 30 g of ice. The mixture was stirred for 6 h and then allowed to stand overnight at room temperature. The resulting precipitate was removed by filtration and washed with water to give 0.32 g of product. The product was crystallized from acetic acid.

Compounds VI-VIII were similarly obtained (Table 1), but the products precipitated only after acidification to pH 1-2 with concentrated hydrochloric acid.

3,4-Diphenyl-2-[(benzoyl)cyanomethylene]-4,5-thiazoline (X). A 0.8-g (2.8 mmole) sample of benzoylcyanothioacetic acid phenylamide and 0.5 g (2.8 mmole) of ω-bromoacetophenone were dissolved in 5 ml of alcohol, and the solution was refluxed for 5 h. It was then cooled, and the resulting light-yellow crystals were removed by filtration, washed with cold alcohol, and dried to give 0.45 g (45%) of a product with mp 184-185° (from alcohol). Found: N 7.7%. $C_{24}H_{16}N_2OS$. Calculated: N 7.4%.

3-(p-Nitrophenyl)-4-phenyl-2-[(benzoyl)cyanomethylene]-4,5-thiazoline (XI). This compound was similarly obtained in 47% yield and had mp 247-248° (from alcohol). Found: N 7.4%. $C_{24}H_{15}N_3O_3S$. Calculated: N 7.5%.

3-(p-Chlorophenylamino)-4-carbamoyl-5-phenylpyrazole (XII). This compound was obtained by saponification of 3-(p-chlorophenylamino)-4-cyano-5-phenylpyrazole (V) with concentrated sulfuric acid; the mixture of reagents (1 : 10) was allowed to stand in the cold for 36 h. Workup gave 60% of a product with mp 227-228° (from alcohol). Found: N 17.86%. $C_{16}H_{13}ClN_4O$. Calculated: N 17.98%.

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