SYNTHESIS AND PROPERTIES OF 1,3,4-THIADIAZINE DERIVATIVES.

1. INVESTIGATION OF THE CONDENSATION OF SUBSTITUTED PHENACYL BROMIDES AND BROMOACETYLPYRIDINES WITH THIOSEMICARBAZIDE

A. P. Novikova, N. M. Perova, L. G. Egorova, and E. I. Bragina

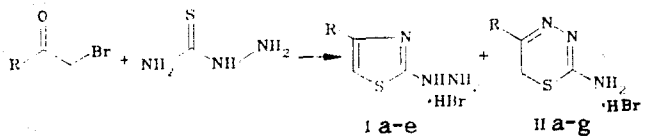
UDC 547.789.1.07

2-Amino-5-aryl(pyridyl)-6H-1,3,4-thiadiazines and isomeric 2-hydrazino-4-aryl(pyridyl)thiazoles, the ratio of which depends on the reaction conditions, were obtained by the reaction of substituted phenacyl bromides and bromoacetylpyridines with thiosemicarbazide.

One of the principal methods for obtaining 2-amino-5-aryl(alkyl)-substituted 1,3,4-thiadiazines is the condensation of thiosemicarbazide (TSC) with α-halo carbonyl compounds; three isomers, viz., 2-amino-6H-1,3,4-thiadiazines, 2-hydrazinothiazoles, and 3-amino-2-thiazolinimines, may be formed [1]. When the reaction is carried out in ethanol thiadiazines are formed in low yields as a consequence of the formation of a mixture of isomers. The available publications dealing with the study of the conditions for the formation of 1,3,4-thiadiazines [1-3] do not give a complete representation of the character and ratio of the isomers formed and their identification.

In the present research we studied the products of the condensation of TSC with 4-substituted derivatives of phenacyl bromide and 2-, 3-, and 4-bromoacetylpyridines in ethanol, ethanol with added acid, and in concentrated HBr and concentrated HCl. Aryl α-halo ketones react with TSC on refluxing in ethanol (pH 4-5) to give mixtures of 2-hydrazinothiazoles Ia-e (in 60-65% yields) and 2-amino-5-aryl-6H-1,3,4-thiadiazines IIa-e (in no higher than 30% yields).

3-Bromoacetylpyridine also reacts with TSC on refluxing in ethanol to give 2-hydrazino-4-(3′-pyridyl)thiazole (Ig) in 64% yield, and the presence of isomer IIf in the reaction mixture was detected by means of TLC and the UV spectra.



I a-e II a-g

I, II a R = C_6H_5, b R = $C_6H_5C_6H_4$-4, c R = C_6H_4Cl-4, d R = $C_6H_4NO_2$-4, e R = C_6H_4OH-4; If R = C_5H_4N-2; Ig, IIf R = C_5H_4N-3; IIg R = C_5H_4N-4

Isomeric compounds I and II differ with respect to their melting points, R_f and pK_a values, and PMR and UV spectra (see Table 1).

To identify the isomers we synthesized 2-hydrazino-4-arylthiazoles Ia-e from 1-acetylthiosemicarbazide and aryl halo ketones [4], which we found to be identical to the products that we obtained.

Thiazole ring 5-H signals at 6.7-7.3 ppm, as well as NH_2 signals at 4.65-4.85 ppm and NH signals at 8.5-8.7 ppm for the hydrazino group (in contrast to the possible 3-amino-2-thiazolinimine isomers, for which the thiazoline δ_{CH} value is 5.3 ppm, δ_{NH_2} is 4.2 ppm, and δ_{NH} is 5.9 ppm [3]) are observed in the PMR spectra of Ia-e in the aromatic-proton region. In the case of pyridyl analogs If, g the thiazole δ_{CH} signal is observed at 7.3-7.35 ppm.

In the case of thiadiazines IIa-g a singlet (2H) at 3.60-3.85 ppm, which corresponds to the CH_2 group of the thiadiazine ring, appears in the PMR spectra; this constitutes evidence for its 6H structure. Two absorption maxima (λ_{max} at 250-270 and 300-320 nm) are observed in the UV spectra of IIa-g. Three absorption maxima at 210-230, 240-260, and 270-290 nm are characteristic for thiazoles Ia-g. A long-wave absorption maximum at 300-320 nm is absent in the spectra of Ia-g.

Almost quantitative yields of thiadiazines IIa-e (70-90%) are obtained when the condensation is carried out in an acidic medium (pH 1-2). Thiadiazines IIa-e are obtained in the form of the hydrohalides, which were converted to the

S. M. Kirov Ural Polytechnical Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 843-846, June, 1991. Original article submitted February 2, 1990.

0009-3122/91/2706-0666$12.50

TABLE 1. Characteristics of the 2-Hydrazino-4-aryl(pyridyl)thiazoles and 2-Amino-5-aryl(pyridyl)-6H-1,3,4-thiadiazines

Compound	mp, °C	R_f (system)	pK_a	PMR spectrum (d_6-DMSO), ppm (SSCC, J, Hz)	Yield, %
Ia	164...166	0,54 (I) 0,87 (II)	4,31±0,03	8,5 (1H, s, NH); 7,4...7,85 (5H, m, arom); 7,1 (1H, s, thiazole 5-H); 4,85 (2H, s NH_2)	65
Ib	178...179	0,78 (I) 0,88 (II)	—	7,3...8,0 (9H, m, arom.); 7,2 (1H, s, 5-H thiazole 5-H)	59
Ic	163...164	0,60 (I) 0,85 (II)	4,06±0,04	8,6 (1H, s, NH); 7,85 (2H, d, arom); 7,45 (2H, d, arom.; J=8,0); 7,15 (1H, s, 5-H thiazole); 4,65 (2H, s, NH_2)	63
Id	180...181	0,62 (I) 0,86 (II)	3,5±0,02	8,7 (1H, s, NH); 8,1 (4H, q, arom; J=9,19); 7,4 (1H, s, thiazole 5-H)	60
Ie	168...169	0,53 (I) 0,81 (II)	4,36±0,04	7,7** (2H, d, arom); 6,8 (2H, d, arom J=7,8); 6,72 (1H, q thiazole 5-H) 4,7 (1H, s, NH_2)	61
If	150...151	0,64 (II)	4,5±0,04 2,93±0,05	8,55 (1H, д, pyridine 6-H); 7,85 (2H, q, pyridine 4-H) 7,30 (1H, q, 4-H pyridine J_{34}=4,5; J_{35}=1,3); 7,35 (1H, s, thiazole 5-H)	(60) 90
Ig	146...148	0,61 (II)	—	9,05 (1H, d, 2-H pyridine); 8,5 (1H, dd, pyridine 6-H) 8,15 (1H, pyridine 4-H) ; J_{24}=1,6; J_{45}=7,2; J_{56}=5,3); 7,3 (1H, s, thiazole 5-H)	(64)
IIa	124...126	0,33 (I) 0,55 (II)	6,09±0,06	7,4...7,85 (5H, m, arom); 3,6 (2H, s, CH_2S)	10 (95)
IIb	157...158	0,44 (I) 0,55 (II)	5,76±0,08	7,3...8,1 (9H, m, arom); 3,8 (2H, s, CH_2S)	12 (79)
IIc	135...136	0,41 (I) 0,74 (II)	5,92±0,06	7,95 (2H, d, arom); ,5 (2H, d, arom J=8,0); 3,65 (2H, s, CH_2S)	15 (82)
IId	>250	0,45 (I) 0,75 (II)	5,59±0,04	8,25 (4H, q, arom J=9,19); 3,73 (2H, s, CH_2S)	10 (72)
IIe	154...156	0,47 (I)	6,18±0,04	7,75 (2H, d, arom); 6,8 (2H, d, arom J=7,8); 3,6 (2H, s, CH_2S)	28 (71)
IIf	171...172	0,33 (II)	5,73±0,06 2,50±0,04	9,1 (1H, d, 2-H pyridine); 8,63 (1H, dd, pyridine 6-H); 8,28 (1H, pyridine 4-H) q); 7,5 (1H, 3-H pyridine; J_{24}=1,6; J_{45}=7,2; J_{35}=3,2); 3,75 (2H, s, CH_2S)	(78)
IIg***	200...201	0,38 (II)	5,62±0,04 3,40±0,05	8,98 (2H, d, pyridine 2-H); 8,18 (2H, d, 3-H pyridine; J_{23}=6,65); 4,4 (2H, s, CH_2S)	(62)

*The yields of the compounds obtained in ethanol; the yields of the compounds obtained in concentrated HBr are indicated in parentheses, while the yield given for If is the amount of product obtained in 2 N HBr.

**The PMR spectrum was recorded in CD_3CD.

***The characteristics are presented for the dihydrobromide of IIg.

bases by the addition of ammonium hydroxide. Small amounts (4-10%) of thiazoles Ic, d are isolated in the synthesis of thiadiazines IIc, d; this is in agreement with the data in [3].

Like aryl halo ketones, 3- and 4-bromoacetylpyridines react with thiosemicarbazide (TSC) in concentrated HBr to give 2-amino-5-(3′- or 4′-pyridyl)-6H-1,3,4-thiadiazines and dihydrobromides IIf, g. 2-Bromoacetylpyridine, which in concentrated HBr and 2 N HBr gives 2-hydrazino-4-(2′-pyridyl)thiazole (If) in the form of the dihydrobromide in 60% and 90% yields, respectively, constitutes an exception. The PMR spectrum of If does not contain δ_{CH_2} signals of a thiadiazine ring, and a thiazole δ_{CH} signal is observed at 7.35 ppm.

In the preparation of thiadiazines in an acidic medium there is a probability of the formation of pyrazoles because of the possible transformation of the thiadiazine ring; however, they were not detected. The formation of 3-amino-2-thiazolinimines also is not observed.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with Perkin—Elmer 12-B (60 MHz) and Bruker WH-90 (80 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The pK_a values were calculated by the method in [5]. The progress of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in butanol—acetic acid—water (4:1:5) (R_{f_1}) and ethyl acetate—pyridine—ethanol (6:1:3) (R_{f_2}) systems with detection in UV light or by development with iodine vapors.

The results of elementary analysis for C, H, N, and S were in agreement with the calculated values.

The starting aryl α-halo ketones were obtained by bromination of the corresponding acetophenones in acetic acid at 50-60°C or without heating by the method in [6], with the exception of 4-hydroxyphenacyl bromide, which was synthesized by the selective bromination of 4-hydroxyacetophenone with $CuBr_2$ in chloroform—ethyl acetate [7]. The synthesis of the 2-, 3-, and 4-bromoacetylpyridines was carried out by the method in [8].

Condensation of Aryl α-Halo Ketones with TSC in Ethanol. A solution of 20 ml of the aryl α-halo ketone in 70 ml of ethanol was added to a suspension of 20 mmole of TSC in 50 ml of ethanol, and the mixture was refluxed for 1 h. It was then cooled, and the resulting precipitate was dissolved in water or aqueous ethanol. The solution was neutralized to pH 7 with 7% NH_3 solution or a saturated solution of sodium acetate, and the resulting precipitate was removed by filtration and crystallized from ethanol. Thiazoles Ia-e, g were obtained in 60-65% yields. Upon subsequent addition of the ammonia solution thiadiazines IIa-e (~30% yields) precipitated after a certain period of time..

Thiadiazines IIa-g. A 20-mmole sample of the aryl α-halo ketone or bromoacetylpyridine was added to a solution of 20 mmole of TSC in 60 ml of concentrated HCl or HBr (or 100 ml of absolute ethanol acidified to pH 1), after which the mixture was refluxed for 1 h and cooled. The precipitated hydrohalide II was dissolved in water or aqueous ethanol, the pH of the solution was adjusted to pH 8 (for IIa-d) and to 5 (for IIf, g) by the addition of a 7% solution of NH_3 with cooling, and the thiadiazine was isolated in the form of the base. The products were purified by crystallization from ethanol or aqueous ethanol.

2-Hydrazino-4-(2′-pyridyl)thiazole Hydrobromide (If). A solution of 1.4 g (5 mmole) of 2-bromoacetylpyridine hydrobromide in 7 ml of acid was added to a hot solution of 0.5 g (5 mmole) of TSC in 7 ml of concentrated HBr (or 2 N HBr), after which the mixture was refluxed for 1 h. It was then cooled, and the precipitated yellow crystals of dihydrobromide If, with mp 232-233°C [ethanol—2 N HBr—ethyl acetate (15:2:35)] were removed by filtration. The yields were 1.15 g (65%) and 1.6 g (90%), respectively. The base was obtained by neutralization of dihydrobromide If to pH 7 with a solution of ammonia.

LITERATURE CITED

1. H. Beyer, *Z. Chem.*, **9**, 361 (1969).
2. I. Ya. Postovskii, A. P. Novikova, L. A. Chechulina, and L. P. Sidorova, *Khim. Geterotsikl. Soedin.*, No. 8, 1051 (1976).
3. R. E. Busby and F. W. Dominey, *Chem. Soc., Perkin 2*, No. 6, 890 (1980).
4. H. Beyer, H. Höhn, and W. Lässig, *Ber.*, **85**, 1122 (1952).
5. A. Albert and E. Sergeant, *Ionization Constants of Acids and Bases* [Russian translation], Khimiya, Moscow—Leningrad (1964), p. 64.
6. K. Shvetlik (ed.), *Organicum* [Russian translation], Vol. 2, Mir, Moscow (1979), p. 173.
7. L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).
8. R. Menasse, G. Klein, and H. Erlenmeyer, *Helv. Chim. Acta*, **38**, 1289 (1955).