SYNTHESIS AND REARRANGEMENTS IN THE THIAZOLINE IMINE SERIES

V. Synthesis of 2-Imino-3-p-Ethoxyphenyl-4-Thiazolines and Their Rearrangement into 2-p-Ethoxyphenylaminothiazoles

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The reaction of 1-acyl-3-(p-ethoxyphenyl)thioureas with chloroacetone or α-bromoacetophenone has given 2-acylimino-3-(p-ethoxy-phenyl)-4-hydroxy-4-methylthiazolidines or the corresponding 4-phenyl compounds, which readily split out water and are converted into the corresponding acylated 4-thiazolines. The action of aqueous alcoholic hydrochloric acid leads to hydrolysis with the formation of the corresponding 2-imino-3-p-ethoxyphenylthiazolines. When the latter are boiled with 20% hydrochloric acid, they undergo rearrangement to 2-p-ethoxyphenylaminothiazoles.

In our previous investigations [1] it was shown that substituted thioureas react with α-halo ketones with the formation of 4-hydroxythiazolidines, which readily split out a molecule of water and are converted into 4-thiazolines. In the present work we have carried out the reaction of 1-benzoyl- [2], 1-(p-dimethylaminobenzoyl)- [2], and 1-isonicotinoyl-3-ethoxyphenylthioureas (Ia–c) with chloroacetone and α-bromoacetophenone. The corresponding thiazolidines, 2-acylamino-3-p-ethoxyphenyl-4-hydroxy-4-methylthiazolidines and the 4-phenyl derivatives, were obtained (table: IIa, IIc, IIIa–c). The presence of the hydroxy group in these compounds was confirmed by the presence in their IR spectra of absorption bands in the 3230–3360 cm^{-1} region and the absence of the absorption band of a carbonyl group in the 1690–1730 cm^{-1} region. In the case of 2-(p-dimethylaminobenzoyl)imino-3-(p-ethoxyphenyl)-4-methylthiazoline (IVb) it was impossible to isolate the intermediate 4-hydroxy compound in the pure state, since it lost water even during recrystallization. The splitting out of water from the 4-hydroxythiazolidines IIa, IIc, IIIa, and IIIb took place when they were treated with concentrated hydrochloric acid at room temperature with the formation in quantitative yields of the corresponding 2-acylimino-3-(p-ethoxyphenyl)-4-methyl-4-thiazolines or the corresponding 4-phenyl compounds (table: IVa, IVc, Va, Vb).

The acyl groups of these compounds were eliminated by boiling them with aqueous alcoholic hydrochloric acid, giving 2-imino-3-(p-ethoxy-phenyl)-4-methyl-4-thiazoline and the corresponding 4-phenyl compound (VI and VII). These iminothiazolines underwent a rearrangement on being boiled with 20% hydrochloric acid [3, 4] as a result of which the aryl residue migrated to the exocyclic nitrogen forming 2-(p-ethoxyphenylamino)-4-methyl-thiazole and the corresponding 4-phenyl compound (VIII and IX). The substances VIII and IX that we synthesized proved to be completely identical with those obtained by Bhargava's method [5] and also with those from p-ethoxyphenylthiourea and the appropriate α-halo ketones. However, IX had mp 142°–143° C, and not 102° C as given by the previous authors.

All the compounds obtained were studied in the chemotherapy division of the All-Union Chemical and Pharmaceutical Scientific Research Institute by G. N. Pershin and T. N. Zykova for tuberculostatic activity, which proved to be only very slight in the presence of serum.

EXPERIMENTAL

1-(p-Ethoxyphenyl)-3-isonicotinoylthiourea (Ic). A suspension of 45 g (0.366 mole) of isonicotinic acid in 150 ml (2.28 mole) of thionyl chloride was boiled for several days. The excess of thionyl chloride was eliminated in vacuum and the residue was boiled in 280 ml of benzene with 130 g (0.403 mole) of lead thiocyanate. The solution was evaporated in vacuum to give 32.6 g of isonicotinoyl isothiocyanate (X). 20.6 g (0.15 mole) of p-phenetidine in 90 ml of benzene was added in drops to 24.6 g (0.15 mole) of X in 10 ml of dry benzene. The mixture was boiled for 1 hr and the precipitate was filtered off and washed with benzene. This gave 36 g of Ic, mp 173.5°–174.5° C (yellow prisms from ethanol). Found, %: C 59.69; H 5.06; N 13.62; S 10.46. Calculated for $C_{15}H_{15}N_3O_2S$, %: C 59.78; H 5.02; N 13.94; S 10.64.

2-Benzoylimino-3-(p-ethoxyphenyl)-4-methyl-4-hydroxythiazoline (IIa). A solution of 3 g (0.01 mole) of Ia in 65 ml of CH_2Cl_2, 6.6 ml (0.091 mole) of triethylamine, and 2 ml (0.019 mole) of chloroacetone was left for 9 hr. Then the solution was evaporated in vacuum and the residue was triturated with water. This gave 3.56 g of IIa in the form of colorless crystals (table). Similarly, IIc was obtained from 4.52 g (0.015 mole) of Ic, 7 ml (0.0965 mole) of triethylamine, and 4 ml (0.038 mole) of chloroacetone; IIIb from 6.87 g (0.02 mole) of Ib, 3.5 ml (0.048 mole) of triethylamine, and 4.2 g (0.0211 mole) of α-bromoacetophenone; and IIIc from 6.03 g (0.02 mole) of Ic, 3.4 ml (0.0468 mole) of triethylamine, and 4.1 g (0.0206 mole) of α-bromoacetophenone.

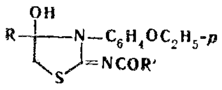
Compound IIIc was also obtained by boiling together 6.03 g of Ic (0.02 mole) in 30 ml of anhydrous ethanol, 5.8 ml (0.08 mole) of triethylamine, and 7.96 g (0.0398 mole) of α-bromoacetophenone in 70 ml of ethanol. Similarly, IIIa was obtained from 12 g (0.04 mole) of Ia in 60 ml of ethanol, 6.5 ml (0.0895 mole) of triethylamine, and 8.8 g (0.0441 mole) of α-bromoacetophenone is 50 ml of ethanol.

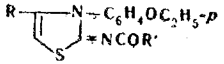
2-Benzoylimino-3-(p-ethoxyphenyl)-4-methyl-4-thiazoline (IVa) (table). A solution of 0.43 g (0.0012 mole) of IIa in 10 ml of concentrated HCl was made alkaline with ammonia. This gave 0.4 g of IVa. Similarly, IVc was obtained from IIc, Va from IIIa, and Vb from IIIb. Compound IVb was obtained in the same way as IIa; the residue was dissolved in hydrochloric acid and the IVb was precipitated with ammonia.

Compound Va was also obtained by boiling 12 g (0.04 mole) of Ia and 8.8 g (0.0441 mole) of α-bromoacetophenone in 110 ml of anhydrous ethanol. Similarly, Vb was obtained from 3.43 g (0.01 mole) of Ib and 2.2 g (0.011 mole) of α-bromoacetophenone in 40 ml of ethanol, and Vc from 6.03 g (0.02 mole) of Ic and 4.4 g (0.022 mole) of α-bromoacetophenone in 120 ml of ethanol via 4.18 g of Vc hydrobromide, mp 225°–226° C. Found, %: C 57.4; H 4.34; N 8.46; S 6.62.

Constants and Analytical Results for the Compounds Obtained

IIa, b; IIIa, b, c.





IVa, b; Va, b, c.

a $R' = C_6H_5$; b $R' = C_6H_4N(CH_3)_2$-*p*; c $R' = \gamma$- Pyridyl

Substance	R	Reaction conditions			Mp, ° C (from ethanol)	Empirical formula	Found, %				Calculated, %				Yield, %
		medium	temperature, ° C	time, hr			C	H	N	S	C	H	N	S	
IIa	CH_3	CH_2Cl_2 TEA *	20	9	152—153.5	$C_{19}H_{20}N_2O_3S$	64.03	5.6	8.07	8.97	64.02	5.66	7.86	9.00	100
IIB	"	CH_2Cl_2 TEA	20	24	159.5—160.5	$C_{18}H_{19}N_3O_3S$	60.42	5.43	11.83	9.07	60.48	5.36	11.76	8.97	80
IIIa	C_6H_5	C_2H_5OH TEA	76	0.3	158—159	$C_{24}H_{22}N_2O_3S$	68.93	5.25	6.70	7.79	68.88	5.3	6.69	7.66	90
IIIb	"	CH_2Cl_2 TEA	20	24	145—147 from C_6H_6 and acetone	$C_{26}H_{27}N_3O_3S$	67.70	5.86	9.10	6.94	67.65	5.90	9.1	6.95	80
IIIc	"	C_2H_5OH TEA	76	0.4	159—160	$C_{23}H_{21}N_3O_3S$	65.67	5.10	9.63	7.67	65.85	5.05	10.02	7.64	32
		CH_2Cl_2 TEA	20	24											76
IVa	CH_3	HCl	20		147—148	$C_{19}H_{18}N_2O_2S$	67.72	5.27	8.64	9.72	67.43	5.36	8.28	9.48	Quant
IVb	"	CH_2Cl_2 TEA	20	24	152.5—153.5	$C_{21}H_{23}N_3O_2S$	65.90	6.06	11.09	8.37	66.11	6.08	11.02	8.41	90
		CH_2Cl_2 CH_3COONa	20	24											82
IVc	"	C_2H_5OH	76	2	178—179	$C_{18}H_{17}N_3O_2S$	63.56	4.93	12.38	9.33	63.70	5.05	12.38	9.45	50
Va	C_6H_5	C_2H_5OH	76	4.5	194.5—195.5	$C_{24}H_{20}N_2O_2S$	72.32	5.14	6.99	8.07	71.97	5.9	7.00	8.01	76
Vb	"	C_2H_5OH	76	2	202—203	$C_{26}H_{25}N_3O_2S$	70.31	5.70	9.23	7.26	70.40	5.68	9.47	7.23	85
Vc	"	C_2H_5OH	76	5	204—205	$C_{23}H_{19}N_3O_2S$	68.98	4.93	10.67	8.14	68.81	4.77	10.47	7.99	39

*TEA—triethylamine

Calculated for $C_{23}H_{19}N_3O_2S \cdot HBr$, %: C 57.26; H 4.18; N 8.71; S 6.65. After 6.02 g (0.0198 mole) of **Ic** and 3.4 ml (0.0316 mole) of chloroacetone had been boiled in 150 ml of ethanol, 3.28 g of unchanged **Ic** was recovered and 1.54 g of **IVc** was obtained from the mother liquor (table).

2-Imino-3-(p-ethoxyphenyl)-4-methyl-4-thiazoline (VI). A solution of 1.45 g (0.00408 mole) of **IIa** in 25 ml of aqueous ethanolic hydrochloric acid was boiled for 3 hr. After the solution had been cooled, the benzoic acid was filtered off and the filtrate was evaporated. The residue was dissolved in water, and the action of ammonia then yielded 0.47 g of VI, mp 79°–81° C (from aqueous ethanol). Found, %: C 60.90; H 6.13; N 12.08; 11.80; S 13.50; 13.71. Calculated for $C_{12}H_{14}N_2OS$, %: C 61.51; H 6.02; N 11.96; S 13.68. The benzoylation of VI by the Schotten-Bauman method gave **IVa**.

Action of hydrochloric acid on VI. A solution of 0.11 g (0.00047 mole) of VI in 10 ml of 20% hydrochloric acid was boiled for 14 hr and evaporated. The residue was dissolved in water, and sodium carbonate precipitated 0.1 g of a substance with mp 130°–132° C (from ethanol). A mixture with 2-(p-ethoxy-phenylamino)-1-methylthiazole (VIII) gave no depression of the melting point. Similarly, 1.46 g (0.00432 mole) of **IVc**, on being boiled fro 4 hr with 40 ml of 20% hydrochloric acid, gave 0.09 g of **VIII**. From the mother liquor ammonia precipitated 0.55 g of VI.

2-(p-Ethoxyphenylamino)-4-methylthiazole (VIII). A mixture of 0.96 g (0.005 mole) of p-ethoxyphenylthiourea (XI) and 1.5 ml (0.0141 mole) of chloroacetone in 30 ml of ethanol was boiled for 1 hr and evaporated. The residue was dissolved in water, and ammonia precipitated 1.14 g of VIII, mp 132°–133° C (literature data [5]: 132° C).

2-Imino-3-(p-ethoxyphenyl)-4-phenyl-4-thiazoline (VII). A solution of 7.65 g of **Va** (0.0191 mole) is 25 ml of aqueous ethanolic HCl was boiled for 2 hr and cooled, and the hydrochloride was filtered off. The latter was dissolved in water, made alkaline with ammonia, and extracted with ether. This gave 3.71 g of VII, mp 95°–96° C. Found, %: C 68.70; 68.31; H 5.15; 5.47; N 9.19; S 10.81. Calculated for $C_{17}H_{16}N_2OS$, %: C 68.89; H 5.44; N 9.45; S 10.82. **Hydrochloride:** colorless crystals (from absolute ethanol) mp 249°–251° C (decomp). Found, %: Cl 10.84. Calculated for $C_{17}H_{16}N_2OS \cdot HCl$, %: Cl 10.65. **Picrate:** yellow needles (from ethanol), mp 213°–214.5° C. Found, %: N 13.65; S 6.06, calculated for $C_{23}H_{19}N_2OS \cdot C_6H_3N_3O_7$, %: N 13.32; S 6.10.

Action of hydrochloric acid on Va. A solution of 6.14 g (0.0153 mole) of **Va** in 45 ml of 20% hydrochloric acid was boiled for 17 hr and evaporated. The residue was triturated with water, filtered off, and washed with water. This gave 1.8 g of 2-(p-ethoxyphenylamino)-4-phenylthiazole (IX), mp 142°–143° C (from ethanol). Found, %: C 68.76; H 5.36; N 9.35; S 10.65. Calculated for $C_{17}H_{16}N_2OS$, %: C 68.66; H 5.42; N 9.42; S 10.78. **Hydrochloride:** colorless crystals (from ethanol), mp 182°–183.5° C. Calculated, %: Cl 10.70; 10.81. Calculated for $C_{17}H_{16}N_2OS \cdot HCl$, %: Cl 10.65. **Picrate:** mp 167.5°–169° C (from ethanol). Found, %: N 13.66. Calculated for $C_{17}H_{16}N_2OS \cdot C_6H_3N_3O_7$, % : N 13.32. The mother liquor was made alkaline with bicarbonate and extracted with ether. This gave another 2.1 g of **IX**. Then the solution was made alkaline with ammonia, and 0.54 g of VII was isolated.

2-(p-Ethoxyphenylamino)-4-phenylthiazoline (IX).

a) A mixture of 0.62 g (0.00323 mole) of **XI**, 0.08 g (0.00665 mole) of acetophenone, and 1.68 g (0.00665 mole) of iodine was heated in the water bath for 16 hr. The melt was treated by the method indicated in [5]. This gave 1.39 g of **IX**, mp 141°–142° C (from ethanol). A mixture with **IX** obtained by method (b) gave no depression of the melting point.

b) A mixture of 1.96 g (0.01027 mole) of **XI** and 2.2 g (0.011 mole) of α-bromoacetophenone in 50 ml of ethanol was boiled for 1 hr and cooled. The precipitate of the hydrobromide of **IX** was filtered off, mixed with water, and made alkaline with ammonia, and ether extracted 1.7 g of **IX** with mp 142°–143° C. A further 1.02 g of **IX** was isolated from the mother solution. **Picrate:** mp 169.5°–171° C.

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