[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF JOHNS HOPKINS UNIVERSITY]

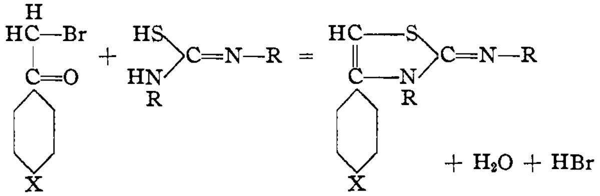
Isomeric 2-Iminotolyl-3-tolyl-4-*p*-chloro and *p*-Bromophenyl-Δ⁴-thiazolines

BY RAYMOND M. HANN AND E. EMMET REID

In continuation of a series of researches upon the relation between constitution and color absorption of certain heterocyclic compounds, advantage has been taken of the reactive nature of the ω-halogen acetophenones in condensation reactions with symmetrically disubstituted thioureas to prepare a series of iminoarylthiazolines.

Hantzsch[1] in 1888 published a paper which not only outlined the complete field of the azoles, but was a masterpiece of scientific recapitulation of the particular group in which he was then interested, namely, the thiazoles and their reduction products. This résumé in part reported the pioneer work of Traumann,[2] one of his pupils, who investigated the action of halogen ketones upon thiourea, monoalkyl thioureas and symmetrical dialkyl thioureas. The general utilization of aryl ketones and thioureas was introduced by von Walther,[3] who advanced a theory regarding the mechanism of the condensation reaction involved.

The present paper details the application of the *p*-halogen-phenyl ω-bromomethyl ketones as synthetic agents in the preparation of some isomeric 2-iminotolyl-3-tolyl-4-*p*-halogen-phenyl-Δ⁴-thiazolines. The general reaction is



Since the iminothiazolines are strong bases, the halogen acid released during the condensation is reabsorbed to yield the hydrobromide of the base. In the present study no effort was made to isolate the intermediate compounds, but the free base was obtained directly by alkalinization of the reaction mixture. The bases were characterized, however, by preparation of the addition compounds with picric acid.

Experimental

The ω-bromoacetophenone was prepared as described by Rather and Reid[4] and the para halogenated compounds according to the general procedure of Judefind and Reid.[5]

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(1) Hantzsch, *Ann.*, **249**, 1 (1888).

(2) Traumann, *ibid.*, **249**, 31 (1888).

(3) Von Walther, *J. prakt. Chem.*, [2] **75**, 187 (1907).

(4) Rather and Reid, THIS JOURNAL, **41**, 77 (1919).

(5) Judefind and Reid, *ibid.*, **42**, 1044 (1920).

The bromination of *p*-chloroacetophenone was conducted as indicated by Hann, Jamieson and Reid[6] in their study of the phenacyl esters of the fatty acids. The thioureas were obtained by the interaction of mustard oils with the required amine.

The condensation of the *p*-ω-dihalogen ketones with the thioureas was effected by heating molecular proportions of the constituents in absolute alcohol for a period of two hours. In certain cases separation of the thiazoline hydrobromide took place before the expiration of this time period, in which case solution was effected by addition of more alcohol. To the alcoholic solution, which in a majority of cases could be cooled without solid separating, was now added 100 cc. of normal sodium hydroxide and the free thiazoline base precipitated as a gum or crystalline solid. This was washed with water and recrystallized from alcohol or acetone until physical properties were constant. Analyses were conducted by the Kjeldahl–Gunning–Arnold procedure and melting points were obtained with Anschütz thermometers with stems totally immersed. The yields were 80 to 90%. The data are summarized in Table I.

TABLE I

ISOMERIC 2-IMINOTOLYL-3-TOLYL-4-*p*-HALOGEN-PHENYL-$\Delta^{4,5}$-THIAZOLINES

	Compound, phenyl-Δ^4-thiazoline	Appearance
1	2-Iminophenyl-3-phenyl-4-*p*-chloro-[a]	Colorless micro-crystalline needles
2	2-Iminophenyl-3-phenyl-4-*p*-bromo-	Colorless micro-crystalline needles
3	2-Imino-*o*-tolyl-3-*o*-tolyl-4-*p*-chloro-	Slightly yellow brilliant granules
4	2-Imino-*o*-tolyl-3-*o*-tolyl-4-*p*-bromo-	Slightly yellow brilliant crystalline aggregates
5	2-Imino-*p*-tolyl-3-*p*-tolyl-4-*p*-chloro-	Colorless opaque micro-crystalline groups
6	2-Imino-*p*-tolyl-3-*p*-tolyl-4-*p*-bromo-	Opaque colorless asbestos-like shreds

[a] The hydrochloride of this base separates in colorless acicular needles melting at 228–229 °C. (corr.)

	Formula	M. p., °C. (corr.)	Analyses, Kjeldahl-Gunning Arnold Method			
			Weight, g.	Cc. of 1 *N* HCl consumed	Nitrogen, %	
					Found	Calcd.
1	$C_{21}H_{15}N_2SCl$	204	0.1347	7.3	7.59	7.72
2	$C_{21}H_{15}N_2SBr$	206	.1015	5.0	6.90	6.88
3	$C_{23}H_{19}N_2SCl$	132	.1255	6.3	7.03	7.17
4	$C_{23}H_{19}N_2SBr$	123	.1058	4.9	6.49	6.44
5	$C_{23}H_{19}N_2SCl$	227	.1038	5.2	7.02	7.17
6	$C_{23}H_{19}N_2SBr$	239	.1367	6.0	6.15	6.44

The basic character of the thiazolines is emphasized by the ease of reaction with picric acid to form beautifully crystalline picrates. One gram of base was dissolved in a minimum amount of alcohol and 10 cc. of alcoholic 10% picric acid added. An immediate separation of the picrate usually occurred and in a number of instances the solution set to a solid mass due to the interwoven structure of the picrate crystals. The picrates were filtered by suction, washed with 95% alcohol and recrystallized from alcohol. Analyses were conducted in this case by the salicyl-sulfonic acid method in order to avoid loss of nitro nitrogen. The description and physical properties of the compounds prepared are included in Table II.

(6) Hann, Jamieson and Reid, THIS JOURNAL, **52**, 818 (1930).

TABLE II

PICRATES OF ISOMERIC 2-IMINOTOLYL-3-TOLYL-4-*p*-HALOGEN-PHENYL-$\Delta^{4,5}$-THIAZOLINES

	Picrates of Δ^4-thiazoline	Appearance
1	2-Iminophenyl-3-phenyl-4-*p*-chlorophenyl-	Golden shimmering platelets
2	2-Iminophenyl-3-phenyl-4-*p*-bromophenyl-	Golden shimmering platelets
3	2-Imino-*o*-tolyl-3-*o*-tolyl-4-*p*-chlorophenyl-	Yellow cleavage-like crystals
4	2-Imino-*o*-tolyl-3-*o*-tolyl-4-*p*-bromophenyl-	Yellow brilliant aggregates
5	2-Imino-*p*-tolyl-3-*p*-tolyl-4-*p*-chlorophenyl-	Yellow brilliant needles
6	2-Imino-*p*-tolyl-3-*p*-tolyl-4-*p*-bromophenyl-	Yellow lustrous granules

			Analyses, salicyl sulfonic acid method			
	Formula	M. p., °C. (corr.)	Weight, g.	Cc. of 1 *N* HCl consumed	Nitrogen, % Found	Calcd.
1	$C_{27}H_{18}O_7N_5SCl$	206	0.1331	11.0	11.58	11.84
2	$C_{27}H_{18}O_7N_5SBr$	203	.1209	9.4	10.89	11.01
3	$C_{29}H_{22}O_7N_5SCl$	187	.1237	9.7	10.98	11.30
4	$C_{29}H_{22}O_7N_5SBr$	196	.1145	8.5	10.40	10.54
5	$C_{29}H_{22}O_7N_5SCl$	183	.1115	9.0	11.31	11.30
6	$C_{29}H_{22}O_7N_5SBr$	193	.1713	12.6	10.30	10.54

Summary

p-Chloro and *p*-bromo-ω-acetophenones have been condensed with diphenyl, di-*o*-tolyl and di-*p*-tolyl thioureas to yield 2-imino aryl-3-aryl-4-*p*-halogen-phenyl-Δ^4-thiazolines. The corresponding picrates have also been isolated and described.

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The Influence of a Quaternary Ammonium Group on the Hydrogen Atoms of an Adjacent Methylene Group

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It is a well-known fact that when two groups, such as carbonyl, cyano, sulfono, nitro and others of this type which are meta-directing in the benzene nucleus, are attached to a methylene group, the methylene group can be alkylated by the action of sodium ethylate and an alkyl halide. The quaternary ammonium salt group $-NR_3^+$ is also a meta-directing group in benzene and it seemed logical to expect that a molecule of the type represented in formula I would be easily alkylated. Such a reaction would be exceedingly useful in the synthesis of complex betaines.

$$\begin{array}{cc} [(CH_3)_3NCH_2COOC_2H_5]^+Cl^- & [(CH_3)_3NCH_2COOC_2H_5]^+Br^- \\ \text{I} & \text{II} \\ [(CH_3)_3NCH_2CONH_2]^+Br^- & [(CH_3)_3NCHCNCONH_2]^+Br^- \\ \text{III} & \text{IV} \end{array}$$

Treatment of carbethoxymethyltrimethylammonium chloride (I) with sodium ethylate and ethyl bromide under the conditions usually used for