

Copulation of Aryldiazonium Salts with 1,6-Diaryl-1,3,4,6-hexanetetrone. The Synthesis of 3-Aroyl Formazans and 5-Aroyl Tetrazolium Salts

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By the reaction of 1,6-bis(2-thienyl)-1,3,4,6-hexanetetrone and 1,6-diphenyl-1,3,4,6-hexanetetrone with different aryldiazonium salts, the corresponding 3-thenoyl and 3-benzoyl formazans (I) were obtained in good yields. Through oxidation with *N*-bromosuccinimide, 3-thenoyl and 3-benzoyl formazans (I) were converted into the corresponding 5-thenoyl and 5-benzoyl tetrazolium salts (II) respectively.

From the literature only three 3-aryol formazans¹ are known to be obtained through copulation of aryldiazonium salts with the corresponding phenylhydrazones and with benzoyl acetic acid or its ester.

First copulations of aryldiazonium salts with active methylene groups of polyoxo compounds of the type 1,6-diaryl-1,3,4,6-hexanetetrone were carried out in the Laboratory of Organic Chemistry and Technology². The copulations of such types had not been studied until then. This prompted us to synthesize 3-aryol formazans by the new method using compounds whose ability to react with aryldiazonium salts were not known.

Oxidation of 3-aryol formazans gave 5-aryol tetrazolium salts. The differences in colour of the obtained formazans and of the corresponding tetrazolium salts, as well as the difference in solubility in various solvents, make possible their use in biological research as oxidation-reduction indicators³.

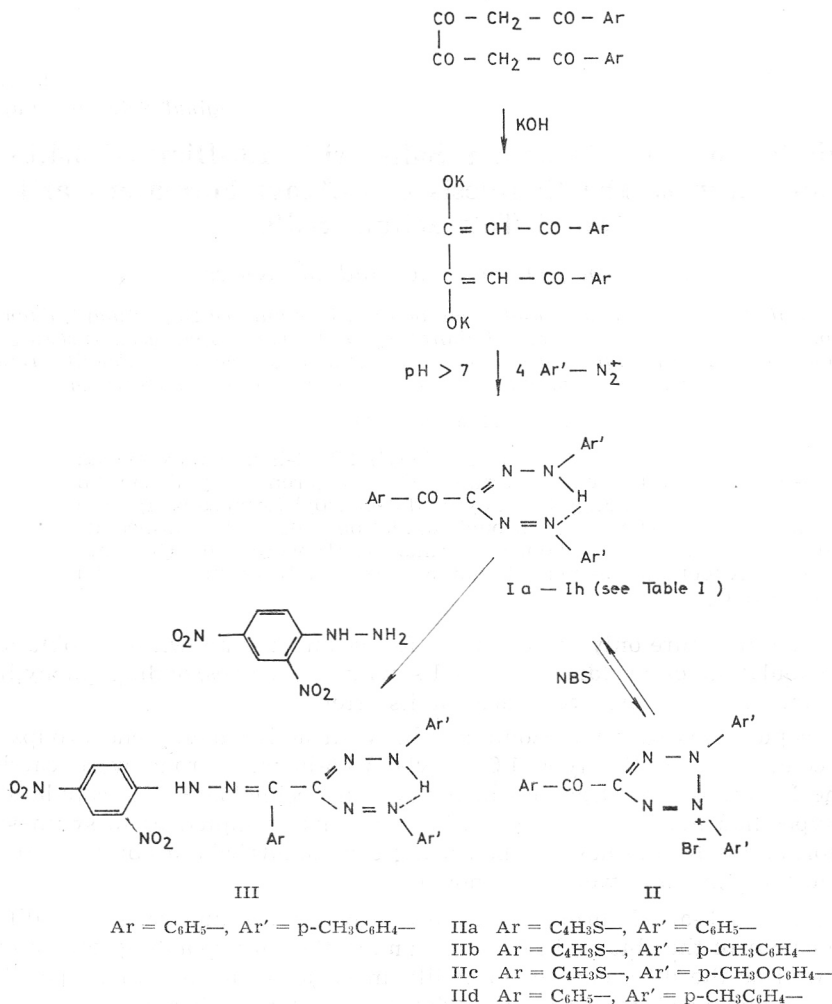
The synthesis of 3-aryol formazans was performed by copulation of different aryldiazonium salts with dipotassium enolates of tetraketones^{4,5}. The molar ratio of the compounds was 4 : 1 and the copulation was carried out in the presence of a 5% aqueous solution of potassium hydroxide (see Scheme 1). Only the copulation of 1,6-diphenyl-1,3,4,6-hexanetetrone with diazotised *p*-toluidine was performed in 50% ethanol.

The obtained 3-thenoyl formazans (see Table I) Ia—Ie were isolated in good yield. They were crystalline products of an intensive metallic red colour.

3-Benzoyl formazans (see Table I) If—Ih were also red coloured crystalline products.

The presence of the keto group in the 3-benzoyl-1,5-diphenyl formazan (If) was proved by the formation of its 2,4-dinitrophenylhydrazone.

SCHEME 1



By heating Ia, Ib, Ic and If with *N*-bromosuccinimide⁶ in an inert solvent, the corresponding pure 5-thenoyl and 5-benzoyl tetrazolium salts (II) were obtained in 73, 49, 74, and 70% yields, respectively. The reduction of 5-aryoyl tetrazolium salts with ascorbic acid was performed at pH 7.5–8 and it proceeded quantitatively.

The products IIa, IIb, IIc, and IId were colourless or bright yellow crystalline substances.

Spectroscopic data obtained from NMR, IR, and UV spectra of the compounds I (a–h), and II (a–c, f) confirmed the structure of formazan and tetrazolium salts, respectively.

The NMR spectra of 3-thenoyl as well as of 3-benzoyl formazans (Ia–h) showed the characteristic chemical shift of the NH proton in the form of a

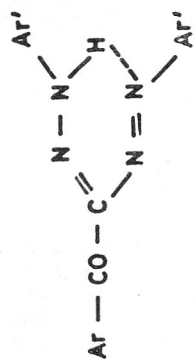


TABLE I
Preparation of 3-aryldiazoniium salts

Nc	Ar	Ar'	Method of isolation	Solvent	Yield %	M. p., °C	$\tilde{\nu}/\text{cm}^{-1}$				Formula	Analysis				calc'd.: found:					
							C=N	N=N	C=N	N-N		C	H	Cl	N	S	C	H	Cl	N	S
Ia	C ₄ H ₉ S—	C ₆ H ₅ —	C	A	76	172—4 ^a *	1510s	1370s	1280s	1048m	C ₁₈ H ₁₄ N ₄ O ₈ S	64.67	4.19	—	16.77	9.59	64.80	4.39	—	17.02	9.37
Ib	C ₄ H ₉ S—	<i>p</i> -CH ₃ C ₆ H ₄ —	C	A	74	180—2 ^a *	1520s	1375m	1275s	1050m	C ₂₀ H ₁₈ N ₄ O ₈ S	66.29	4.97	—	15.47	8.85	66.08	5.23	—	15.33	8.83
Ic	C ₄ H ₉ S—	<i>p</i> -CH ₃ OC ₆ H ₄ —	C	A	77	142—4 ^a *	1500s	1360w	1240s	1025s	C ₂₀ H ₁₈ N ₄ O ₈ S	60.89	4.60	—	14.21	8.13	61.13	4.88	—	14.40	8.03
Id	C ₄ H ₉ S—	<i>p</i> -ClC ₆ H ₄ —	C	A	68	207—9 ^a	1520s	1375s	1275s	1040m	C ₁₈ H ₁₂ Cl ₂ N ₄ O ₈ S	53.61	2.99	17.58	13.89	7.95	53.40	2.91	17.70	14.04	7.95
Ie	C ₄ H ₉ S—	<i>p</i> -NO ₂ C ₆ H ₄ —	E ₁	A	47	226—8 ^b	1520s	1375s	1240w	1040m	C ₁₈ H ₁₂ N ₆ O ₅ S	50.94	2.85	—	19.80	7.56	50.72	3.05	—	19.93	7.45
If	C ₆ H ₅ —	<i>p</i> -CH ₃ C ₆ H ₄ —	C	B	47	141—3 ^a *	1515s	1370m	1275s	1010w	C ₂₂ H ₂₀ N ₄ O	74.03	5.66	—	15.71	—	73.98	5.83	—	15.90	—
Ig	C ₆ H ₅ —	<i>p</i> -CH ₃ OC ₆ H ₄ —	E ₂	A	52	143—5 ^a	1520s	1350s	1250s	1025m	C ₂₂ H ₂₀ N ₄ O ₃	68.03	5.19	—	14.43	—	68.09	5.49	—	14.66	—
Ih	C ₆ H ₅ —	<i>m</i> -ClC ₆ H ₄ —	E ₃	A	81	140—2 ^a	1515s	1370m	1250m	1015w	C ₂₀ H ₁₄ Cl ₂ N ₄ O	60.45	3.55	17.86	14.11	—	60.66	3.84	18.11	14.28	—

A water solution
 B 50% C₂H₅OH
 C crystallization
 E₁ extraction with THF and ethylacetate
 E₂ extraction with ethylacetate
 E₃ the gummy product was dissolved in acetone under mild heating and water was added to turbidity
^a ethanol
^b acetone
 * the corresponding tetrazolium salt was obtained

sharp singlet at 16 ppm. This is entirely missing in the NMR spectra of tetrazolium salts, thus confirming at the same time their structure. The chemical shift of the proton in the NH group of 3-thenoyl and 3-benzoyl formazan chain is similar to that of 1-phenyl-5 (*p*-methoxyphenyl)-3-phenyl formazan^{7,8}.

The infrared spectra of all synthesized 3-thenoyl and 3-benzoyl formazans show absorption bands from 1625 to 1670 cm^{-1} which are characteristic for the keto group, and characteristic bands for the formazan structure which are similar to the absorption bands of 1,3,5-triphenyl formazan⁹.

The infrared spectra of all synthesized 5-thenoyl and 5-benzoyl tetrazolium salts showed characteristic absorption bands for tetrazolium structure which are similar to the absorption bands of 2,3,5-triphenyl tetrazolium bromide⁹.

EXPERIMENTAL

All melting points are uncorrected. All IR spectra were recorded in KBr pellets with Perkin-Elmer Infracord Model 137 spectrometer.

The NMR spectra of saturated deuteriochloroform solutions of 3-thenoyl (Ia—d) and 3-benzoyl (If—h) formazans and deuterodimethylsulfoxide solution of 5-thenoyl and 5-benzoyl tetrazolium salts were determined on a Varian A-60 NMR spectrometer with tetramethylsilane as an internal standard.

UV spectra of 3-thenoyl and 3-benzoyl formazans and of 5-thenoyl and 5-benzoyl tetrazolium salts are similar to the spectra of 1,3,5-triphenyl formazan¹⁰ and 2,3,5-triphenyl tetrazolium bromide¹¹ respectively.

Preparation of 3-aryoyl-1,5-diaryl formazans Ia to Ih (see Table I)

General procedure: 1,6-diaryl-1,3,4,6-hexanetetrone (0.01 mol) was dissolved in Erlenmayer flask (200 ml) in 120 ml of water to which 4 ml of 30% potassium hydroxide (0.02 mol) was added. After 30 min the yellow solution of dipotassium enolate was filtered into a three-necked flask (750 ml) fitted with a stirrer, thermometer and dropping funnel. To this solution cooled with a mixture of ice and salt to 0–5 °C, a solution of corresponding aryldiazonium salt (0.04 mol) was added dropwise. Almost instantly upon addition the solution turned intensively red, the red precipitate deposited and the mixture started to foam. pH value was constantly controlled and adjusted when needed with diluted potassium hydroxide solution. After the completion of the reaction the mixture was diluted with an equal volume of water. The next day the product was filtered off, washed with water and dried in a desiccator over potassium hydroxide. The crude products were obtained in good yields. After several recrystallizations from corresponding solvent and active charcoal, pure products were obtained. The data for 3-aryoyl-1,5-diaryl formazans (Ia—Ih) are summarized in Table I.

2,4'-Dinitrophenylhydrazone (III), m. p. 216–218 °C, yield 50%, from xylene-ethanol (1:3). IR spectrum: 1510 s (C=N), 1430 w and 1340 s (N=N) cm^{-1} .

Anal. $\text{C}_{28}\text{H}_{24}\text{N}_8\text{O}_4$ (536.64) calc'd.: C 62.68; H 4.51; N 20.89%
found: C 62.76; H 4.67; N 21.03%

5-Thenoyl-2,3-diphenyl tetrazolium bromide (IIa)

Ia (3.34 g, 0.01 mol) was dissolved by heating in chloroform (35 ml) in a 250-ml flask equipped with reflux condenser and a calcium chloride tube. A solution of *N*-bromosuccinimide (1.78 g, 0.01 mol) in chloroform (150 ml) was added in several portions into the boiling reaction mixture. After short refluxing the dark-red solution of formazan became light yellow and a yellow precipitate was formed. After recrystallization from ethanol and several recrystallizations from an ethanol—petroleum—ether mixture (1 : 10) white needles were obtained in a yield of 73%, m. p. 251–4 °C (decomp.). IR spectrum: 1640 s (CO), 1520 m (C=N), 1420 m (N=N), 1175 m (C—N) and 1000 m (N—N) cm^{-1} .

Anal. $\text{C}_{18}\text{H}_{13}\text{BrN}_4\text{OS}$ (413.32) calc'd.: C 52.30; H 3.18; Br 19.34; N 13.56; S 7.76%
found: C 52.40; H 3.45; Br 19.17; N 13.79; S 7.65%

5-Thenoyl-2,3-di(p-ethylphenyl) tetrazolium bromide (Iib)

Ib (1g, 2.76 mmol) was dissolved by heating in ethylacetate (50 ml) and a solution of *N*-bromosuccinimide (0.65 g, 3.66 mmol) in ethylacetate (50 ml) was added. After short refluxing, the red solution of formazan turned yellow and a yellow precipitate separated. After recrystallization from ethanol—water mixture (1 : 10) bright yellow needles were obtained in the yield of 49%, m. p. 257—260 °C(decomp.). IR spectrum: 1650 s (CO), 1500 s (C=N), 1415 s (N=N), 1175 m (C—N) and 1000 m (N—N) cm⁻¹.

Anal. C₂₀H₁₇BrN₄OS (441) calc'd.: C 54.42; H 3.88; Br 18.11; N 12.7; S 7.27%
found: C 54.12; H 4.10; Br 18.36; N 13.09; S 7.22%

5-Thenoyl-2,3-di(p-methoxyphenyl) tetrazolium bromide (Iic)

Ic (1.2 g, 3.4 mmol) was dissolved by heating in ethylacetate (50 ml) and a solution of *N*-bromosuccinimide (0.54 g, 3.4 mmol) in 50 ml of cold ethylacetate was added in several portions. After a short refluxing the reaction mixture became yellow and a precipitate separated. After several recrystallizations from absolute ethanol and decolorization with charcoal, needles of an intensive yellow colour were obtained, in the yield of 74%, m. p. 226—228 °C. IR spectrum: 1640 s (CO), 1505 s (C=N), 1415 s (N=N), 1170 s (C—N) and 992 w (N—N) cm⁻¹.

Anal. C₂₀H₁₇BrN₄S (473.35) calc'd.: C 50.74; H 11.84; Br 16.89; N 11.84; S 6.77%
found: C 50.50; H 12.26; Br 17.19; N 12.26; S 6.77%

*5-Benzoyl-2,3-di(p-methylphenyl) tetrazolium bromide (Iif)**

In a 100 ml flask equipped with reflux condenser, 1 g (2.8 mmol) of If was dissolved in chloroform (15 ml), heated to 180 °C, and a solution of *N*-bromosuccinimide (2 g, 11.2 mmol) in cold chloroform (60 ml) was added. After 15 min the reaction mixture became colourless, this being the sign that the reaction is completed. Chloroform was evaporated *in vacuo* and the residue was dissolved in 60 ml of hot 80% ethanol. After evaporation the formed yellow crystals were filtered off and dried in a desiccator. After several successive recrystallizations from ethanol—petrolether mixture (1 : 10), a crystalline product of yellow colour had m. p. 256—9 °C (decomp.). Yield 70%. IR spectrum: 1670 s (CO), 1500 s (C=N), 1460 m (N=N), 1170 m (C—N), and 1000 m (N—N) cm⁻¹.

Anal. C₂₂H₁₉BrN₄O (435.32) calc'd.: C 60.64; H 4.39; Br 18.34; N 12.86%
found: C 60.87; H 4.59; Br 18.23; N 12.86%

Compound Iif (0.03 g; 0.068 mmol) dissolved in 30 ml 80% ethanol, was reduced with aqueous solution of ascorbic acid (0.03 g; 0.17 mmol). By addition of NH₄OH or NaOH to a pH of 7.5—8, after few minutes the white coloured solution turned into red with precipitation of the red formazan. The yield was 98%.

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* The oxidation was also performed in ethylacetate instead of chloroform. The same product was obtained in less than 20% yield.

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IZVOD

Kopulacija arildiazonijevih soli s 1,6-diaril-1,3,4,6-heksantetronima. Sinteza 3-aroil formazana i 5-aroil tetrazolijevih soli

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Reakcijom 1,6-ditienil-1,3,4,6-heksantetrona, kao i 1,6-difenil-1,3,4,6-heksantetrona s različitim arildiazonijevim solima dobiveni su 3-tienoil i 3-benzoil formazani (I) u dobrim iskorištenjima. Oksidacijom *N*-bromosukcinimidom prevedeni su 3-tienoil i 3-benzoil formazani (I) u odgovarajuće 5-tienoil odnosno 5-benzoiltetrazolijeve soli (II).

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