CYCLIZATION OF ARYLHYDRAZONES OF NITROFORMALDEHYDE AND ITS DERIVATIVES

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2,3,4,5-Tetrahydro-1,2,4-triazine derivatives are obtained when nitroformaldehyde arylhydrazones are heated with formaldehyde and aromatic amines. Bromonitroformaldehyde arylhydrazones react with thiourea to give substituted 5-inimo-4,5-dihydro-1,3,4-thiadiazoles and react with sodioacetoacetic ester to give 1-aryl-3-nitro-4-acetyl-5-pyrazolones. The action of chlorosulfonic acid on cyanonitroformaldehyde arylhydrazones leads to ring closing to the corresponding 1,3,5-triazines.

N-Hydroxymethylarylhydrazones of glycolaldehyde are formed in the reaction of nitroformaldehyde arylhydrazones (I) with benzylamine in alcohol or dimethylformamide (DMF). It is known that closing to a triazine ring occurs in the condensation of arylhydrazones of glyoxal, p-nitrobenzaldehyde [1, 2], and furfural [3] with formaldehyde and benzylamine in DMF.

We have found that triazine derivatives (IVa-m, Table 1) are also formed on prolonged heating of hydrazones I with formaldehyde and benzylamine or aromatic amines. The IR spectra of IV contain an intense C = N absorption band (1620 cm⁻¹) but do not contain an NH absorption band (3220 cm⁻¹).

Thiadiazole derivatives (V) are formed when II [4] are heated with thiourea. Pyrazolone derivatives (VII) are obtained when II react with sodioacetoacetic ester.

In analogy with [6], we obtained VI by reaction of hydrazones III [5] with chlorosulfonic acid. The reaction apparently proceeds through a step involving the formation of an intermediate that results from 2 mole of the nitrile and 1 mole of chlorosulfonic acid $[RC=NC(R)=NH]^+SO_3Cl^-$ [7], which forms the corresponding triazine with a third molecule of the nitrile. The IR spectra of VI contain an intense C=N absorption band (1620 cm⁻¹) but do not contain a $C \equiv N$ absorption band (2250 cm⁻¹).



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TABLE 1. Tetrahydrotriazines

Com- pound	R	R'	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
					N	Hal	N	Hal	i I
IVa* IVb† IVc IVd IVf IVf IVf IVf IVi IVi IVj IV k‡ IVI IVm	<i>p</i> -Cl <i>p</i> -Br <i>p</i> -NO ₂ H H <i>p</i> -Cl <i>p</i> -Cl <i>p</i> -Br <i>p</i> -Br <i>p</i> -NO ₂ 2,3-(CH ₃) ₂	$\begin{array}{c} CH_2C_6H_5\\ CH_2C_6H_5\\ CH_2C_6H_5\\ C_6H_5\\ p\text{-}CIC_6H_4\\ p\text{-}BrC_6H_4\\ p\text{-}BrC_6H_4\\ p\text{-}BrC_6H_4\\ p\text{-}BrC_6H_4\\ p\text{-}CIC_6H_4\\ p\text{-}CIC_6H_4\\ p\text{-}CIC_6H_4\\ p\text{-}BrC_6H_4\\ p\text{-}CIC_6H_4\\ p\text{-}CIC_6H_4\\ p\text{-}CIC_6H_4\\ \end{array}$	$\begin{array}{c} 125 & -126\\ 120 & -121\\ 150 & -151\\ 104 & -106\\ 147 & -149\\ 164 & -166\\ 135 & -137\\ 148 & -150\\ 130 & -132\\ 148 & -151\\ 184 & -185\\ 190 & -192\\ 98 & -100\\ \end{array}$	$\begin{array}{c} C_{16}H_{15}CIN_4O_2\\ C_{16}H_{15}BrN_4O_2\\ C_{16}H_{15}N_5O_4\\ C_{15}H_{14}N_4O_2\\ C_{15}H_{14}N_4O_2\\ C_{15}H_{13}BrN_4O_2\\ C_{15}H_{12}CIP_4O_2\\ C_{15}H_{12}BrN_4O_2\\ C_{15}H_{12}BrN_4O_2\\ C_{16}H_{12}BrN_4O_2\\ C_{16}H_{15}BrN_4O_2\\ C_{16}H_{15}BrN_4O_2\\ C_{15}H_{12}BrN_5O_4\\ C_{17}H_{17}CIN_4O_2\\ \end{array}$	16,9 14,4 20,8 19,9 17,2 	$ \begin{array}{c} 10.9\\ 21.5\\ -\\ 11.0\\ 22.0\\ -\\ 29.1\\ 36.3\\ 21.4\\ 9.7 \end{array} $	17,0 14,9 20,5 19,9 17,7 — — — 19,4 17,2 16,3	10,6 21,3 11,0 22,2 16,0 29,1 36,4 21,3 9,7	84 95 86 89 83 46 90 92 88 70 72 75

* Found: C 57.7; H 4.4%. Calculated: C 58.2; H 4.5%. † Found: C 51.0; H 3.9%. Calculated: C 51.2; H 3.7%. ‡ Found: C 49.9; H 3.4%. Calculated: C 49.8; H 3.3%.

EXPERIMENTAL

2-(p-Nitrophenyl)-4-benzyl-6-nitro-2,3,4,5-tetrahydro-1,2,4-triazine (IVc). A 1 g (4 mmole) sample of nitroformaldehyde p-nitrophenylhydrazone was dissolved in 10 ml of ethanol, and 1 g of 36% formalin (1 mmole of formaldehyde) and 0.6 g (6 mmole) of benzylamine were added. The mixture was heated on a boiling-water bath for 25 h, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol. The yield of yellow crystals (from alcohol) was 1.4 g (86%). Compounds IVa,b were similarly obtained.

 $\frac{2-(p-Nitrophenyl)-4-(p-chlorophenyl)-6-nitro-2,3,4,5-tetrahydro-1,2,4-triazine (IVk). A 1.0 g (4 mmole) sample of nitroformaldehyde p-nitrophenylhydrazone was dissolved in 20 ml of DMF, and 1.0 g of 36% formalin and 0.6 g (4 mmole) of p-chloroaniline were added. The mixture was heated on a water bath for 3 h, after which it was allowed to stand at room temperature for 14 h and then poured into ice water. The precipitate was removed by filtration and washed with water. The yield of orange crystals (from dioxane) was 1.2 g (70%). Compounds IVd-m were obtained under similar conditions.$

2-Nitro-4-(p-carboxyphenyl)-5-imino-4,5-dihydro-1,3,4-thiadiazole (Va). A 1.44 g (5 mmole) sample of bromonitroformaldehyde p-carboxyphenylhydrazone was dissolved in 20 ml of ethanol, and equimo-lecular amounts of thiourea (0.38 g) and sodium hydroxide (0.2 g) in 3 ml of water were added. The mixture was heated on a water bath for 5-6 h. The product was isolated from the alcohol solution by acidification with 5% hydrochloric acid. Workup gave 0.26 g (20%) of dark-orange crystals with mp 163-165° (from alcohol). Found: N 17.7%. $C_9H_9N_4O_4S \cdot C_2H_5OH$. Calculated: N 17.9%.

 $\frac{2-\text{Nitro-4-}(p-\text{nitrophenyl})-5-\text{imino-4,5-dihydro-1,3,4-thiadiazole (Vb).}{\text{This compound was similarly obtained in 22\% yield. The orange crystals had mp 137-138° (from alcohol).}{\text{Found: S 11.8\%. C}_8H_5N_5O_4S.}$ Calculated: S 12.0%.

<u>1-(p-Nitrophenyl)-3-nitro-4-acetyl-5-pyrazolone (VIIa)</u>. A 1 g (3.5 mmole) sample of bromonitroformaldehyde p-nitrophenylhydrazone was dissolved in absolute ethanol (20 ml), and 3.5 mmole of the sodium salt of acetoacetic ester in 7 ml of ether was added to the alcohol solution. The mixture was then heated on a water bath for 10 h. The solvent was partially evaporated, and the resulting precipitate was removed by filtration and washed with alcohol to give 0.26 g (26%) of brown crystals with mp 202-203° (dec., from alcohol). Found: N 19.9%. $C_{11}H_8N_4O_6$. Calculated: N 19.2%.

 $\frac{1-(p-Amidosulfonylphenyl)-3-nitro-4-acetyl-5-pyrazolone (VIIb). This compound was similarly obtained. The brown crystals had mp 250° (dec., from alcohol). The yield was 44%. Found: N 17.3%. C₁₁H₁₀N₄O₆S. Calculated: N 17.2%.$

2,4,6-Tri(p-bromophenylhydrazononitroformyl)-1,3,5-triazine (VIa). A 0.54 g (2 mmole) sample of cyanonitroformaldehyde p-bromophenylhydrazine was dissolved in 40 ml of chloroform, after which the solution was cooled with ice and 10 ml of chlorosulfonic acid was added slowly. The mixture was poured into ice water after 3 h, and the resulting dark-orange precipitate was removed by filtration and washed with water until it was neutral. The yield of product with mp 145-147° (from alcohol) was 0.42 g (80%). Found: N 20.4%. $C_{24}H_{15}Br_3N_{12}O_6$. Calculated: N 20.8%.

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