RESEARCH ON ARYLHYDRAZONES OF SUBSTITUTED GLYOXYLIC ACIDS

XXI.* NITROGEN-CONTAINING HETEROCYCLES WITH ARYLHYDRAZONE GROUPS

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3-Aryl-4-(arylhydrazonochloroformyl)-2-[(carbethoxy or carbamoyl)cyanomethylene]-4-thiazolines were obtained by condensation of arylhydrazones of chloromethylglyoxylic chloride with arylamides of cyanomonothiomalonic acid ethyl ester or amide. The chlorine atom in these compounds is readily exchanged by a hydrazino group to give 3-aryl-4-(arylhydrazonohydrazinoformyl)-2-[(carbethoxy or carbamoyl)cyanomethylene]-4-thiazolines. 2-(Arylhydrazonocarbethoxyformyl)-4-(arylhydrazonochloroformyl)thiazoles were obtained by reaction of arylhydrazones of chloromethylglyoxylic chlorides with arylhydrazones of monothiomesoxalic acid ethyl ester amide. Arylhydrazones of ethyl 1H-tetrazolyl-5-glyoxylate were synthesized by condensation of arylhydrazones of ethyl cyanoglyoxylate with ammonium azide in dimethylformamide.

Arylamides of cyanomonothiomalonic acid ethyl ester or amide [2-4], aryl hydrazones of ethyl cyanoglyoxylate, and arylhydrazones of monothiomesoxalic acid ethyl ester amide [5] are used for the synthesis of various nitrogen-containing heterocyclic compounds [6-8]. It seemed of interest to use the arylhydrazones of chloromethylglyoxylic chloride (I) [9] as the α-halocarbonyl component in reactions with these substances for the synthesis of substituted thiazoles and 4-thiazolines.

3-Aryl-4-(arylhydrazonochloroformyl)-2-[(carbethoxy or carbamoyl)cyanomethylene]-4-thiazolines (IIa-g, Table 1) were isolated from arylamides of cyanomonothiomalonic acid ethyl ester or amide in the condensation with I.

When thiazolines IIa, b, g are heated with hydrazine hydrate the chlorine atom is readily exchanged by a hydrazine residue to give 3-aryl-4-(arylhydrazonohydrazinoformyl)-2-[(carbethoxy or carbamoyl)-cyanomethylene]-4-thiazolines (IIh-j). On prolonged heating with excess hydrazine hydrate in the case of thiazoline IIb it was shown that in addition to exchange of a chlorine atom, the corresponding hydrazide rather than the 5-pyrazolone derivative, as in the case of arylhydrazones of ethyl cyanoglyoxylate or arylhydrazones of acetylhydrazides of cyanoglyoxylic acid [10, 11], is formed.

2-(Arylhydrazonocarbethoxyformyl)-4-(arylhydrazonochloroformyl) thiazoles (IIIa-c, Table 2) were synthesized in the reaction of I with arylhydrazones of monothiomesoxalic acid ethyl ester amide.

In order to obtain azoles with physiologically active properties [12-14] we obtained arylhydrazones of ethyl 1H-tetrazol-5-ylglyoxylate (Va-e, Table 3) by reaction of hydrazones IVa with ammonium azide. Arylhydrazones of hydrazido-1H-tetrazol-5-ylglyoxylic acid (VIa-d, Table 3) were synthesized by heating alcohol solutions of V with hydrazine hydrate. The corresponding benzalhydrazones (VIIa-b, Table 3) were isolated by the action of aromatic aldehydes on VIc.

*See [1] for communication XX.

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TABLE 1. 2,3,4-Substituted 4-Thiazolines (II)

Compound	mp, °C	Empirical formula	Found, %	Calc., %	Yield, %
IIa	191—192	$C_{21}H_{17}ClN_4O_2S$	Cl 8.5 N 13,1	8,3 13,2	81
IIb	167—168	$C_{22}H_{19}ClN_4O_2S$	Cl 8.0 N 12,8	8,1 12,7	85
IIc	213—214	$C_{22}H_{19}ClN_4O_2S$	Cl 7.9 N 12.6	8,1 12.7	64
IId	199—200	$C_{23}H_{21}ClN_4O_2S$	Cl 8.0 N 12.3	7.8 12.4	69
IIe	219—220	$C_{19}H_{14}ClN_5OS$	Cl 8,7 S 7,9	9,0 8,1	80
IIf	231—232	$C_{20}H_{16}ClN_5OS$	Cl 8.5 N 16,8	8.7 17,1	60
IIg	218—219	$C_{21}H_{18}ClN_5OS$	Cl 8.2 S 7.2	8.4 7,5	72
IIh	131—132	$C_{21}H_{20}N_6O_2S$	C 59.8 H 4.5 N 19.7	60.8 4,8 20,0	75
IIi	137—138	$C_{22}H_{22}N_6O_2S$	C 60,8 H 4,9 N 19.2	61,0 5,1 19,4	68
IIj	Did not melt at 250	$C_{21}H_{21}N_7OS$	N 23.0 S 7.3	23,4 7.6	74

TABLE 2. 2,4-Disubstituted Thiazoles (III)

Compound	mp, °C	Empirical formula	Found, %	Calc., %	Yield, %
IIIa	122—124	$C_{21}H_{19}ClN_6O_4S$	Cl 7.2 S 6,4	7,3 6,6	63
IIIb	155—157	$C_{22}H_{21}ClN_6O_4S$	C 52,4 H 3,9 N 16.6	52,7 4,2 16,8	71
IIIc	133—135	$C_{22}H_{21}ClN_5O_3S$	N 13.6	13.8	75

TABLE 3. Arylhydrazones of Substituted 1H-Tetrazol-5-yl-glyoxylic Acids (V-VII)

Compound	mp, °C	Empirical formula	Found, %	Calc., %	Yield, %
Va	218—219	$C_{11}H_{12}N_6O_2$	C 50,7 H 4,2 N 32,0	50,8 4,6 32,3	61
Vb	219—230	$C_{13}H_{16}N_6O_3$	C 51,0 H 5,0 N 28,0	51,3 5,3 27,6	70
Vc	224—225	$C_{15}H_{20}N_6O_3$	C 54,0 H 6,2 N 25,4	54,2 6,0 25,3	57
Vd	241—242	$C_{11}H_{11}ClN_6O_2$	Cl 11,6 N 28,8	12,0 28,5	63
Ve	227—228	$C_{14}H_{16}N_6O_4$	C 50,8 H 4,5 N 25,5	50,8 4,8 25,4	54
VIa	172—173	$C_9H_{10}N_8O$	C 43,7 H 3,9 N 45,5	43,9 4,1 45,5	79
VIb	251—252	$C_9H_9ClN_8O$	Cl 12,4 N 39,7	12,7 39,9	85
VIc	236—236	$C_{12}H_{14}N_8O_3$	C 45,1 H 4,3 N 35,3	45,3 4,4 35,2	92
VId	Did not melt at 265	$C_9H_9N_9O_3$	C 36,8 H 2,8 N 43,6	37,1 3,1 43,3	87
VIIa	245—246	$C_{21}H_{22}N_9O_3$	C 55,8 H 4,9 N 27,9	56,1 5,1 28,1	95
VIIb	264—265	$C_{19}H_{17}N_9O_5$	C 50,4 H 3,5 N 27,7	50,6 3,8 27,9	91

The UV spectra of II contain one absorption maximum at 335-340 nm, which is close to the long-wave absorption maximum of the starting thioamides. The short-wave maximum at 220-240 nm vanishes [2, 3, 5]. Both of the absorption maxima characteristic for arylhydrazones of ethyl cyanoglyoxylate [4] at 240 nm ($\pi-\pi^*$ band of the carbonyl group) and 375 nm ($\pi-\pi^*$ band of the hydrazone grouping) are retained in the spectra of III. Compounds V-VII are characterized by bands close to the absorption maxima of II (240 and 370 nm) andthe starting hydrazones [4]. A bathochromic shift of the long-wave absorption maximum (390 nm) is observed for VIIa.

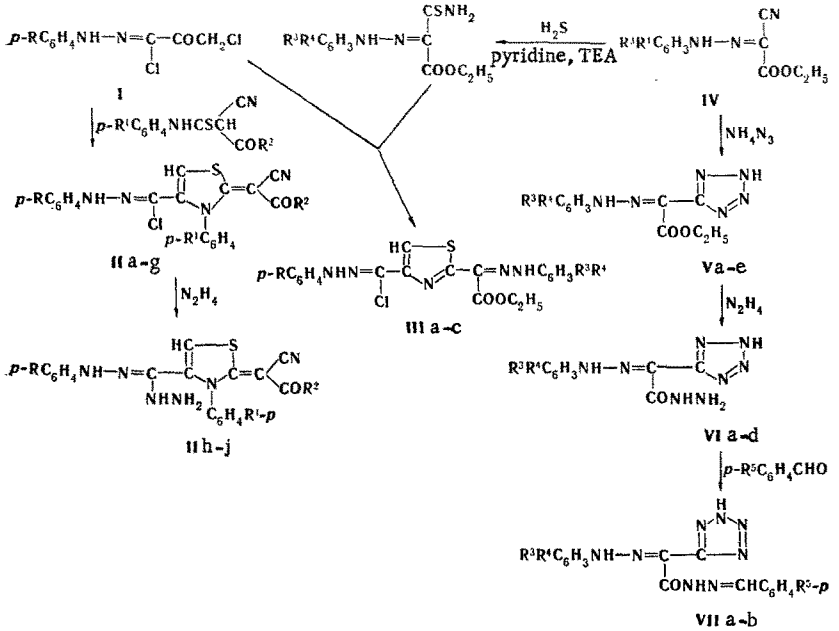
EXPERIMENTAL METHOD

The UV spectra of alcohol solutions of the compounds ($5 \cdot 10^{-5}$ M) were recorded with an SF-4A spectrophotometer. The purity and homogeneity of the synthesized compounds were monitored by column chromotography with activity II aluminum oxide and elution with benzene–chloroform (3:1).

3-Phenyl-4-(phenylhydrazonochloroformyl)-2-[carbethoxycyanomethylene]-4-thiazoline (IIa). A 1.24-g (5 mmole) sample of the phenylamide of ethyl cyanomonothiomalonate was added to 1.16 g (5 mmole) of the phenylhydrazone of chloromethylglyoxylic anhydride in 10 ml of absolute alcohol, after which the mixture was refluxed for 4-5 h. It was then cooled, and the resulting light-yellow crystals were removed by filtration, washed with alcohol and ether, and dried to give 1.72 g of product. The solid was dissolved in benzene and chromatographed with a column filled with aluminum oxide and elution by benzene–chloroform (3:1). The solvent was removed from the eluate, and the product was crystallized from alcohol. All of the compounds presented in Tables 1-3 were similarly purified, and IIa-g were obtained under the same conditions.

3-Phenyl-4-(phenylhydrazonohydrazinoformyl)-2-[(carbethoxy)cyanomethylene]-4-thiazoline (IIh). A 0.07-g sample of 99% hydrazine was added to 0.85 g (2 mmole) of I in 3 ml of alcohol, and the mixture was heated on a water bath for 10 min; all of the solid dissolved. The solution was then cooled to precipitate 0.63 g of a yellow crystalline product. Compounds IIi, j were similarly obtained.

3-Phenyl-4-(p-tolylhydrazonohydrazinoformyl)-2-[(hydrazido)cyanomethylene]-4-thiazoline. A 1.4-g sample of 99% hydrazine was added to 0.9 g (2 mmole) of 3-phenyl-4-(p-tolylhydrazonochloroformyl)-2-[(carbethoxy)cyanomethylene]-4-thiazoline (IIb) in 5 ml of alcohol, and the mixture was refluxed for 4 h. It was then cooled to give 0.7 g (83%) of a yellow crystalline precipitate. Found: N 26.3%. $C_{20}H_{20}N_8OS$. Calculated: N 26.7%. mp 122-123°C



II a $R=R^1=H$, $R^2=OC_2H_5$; b $R=CH_3$, $R^1=H$, $R^2=OC_2H_5$; c $R=H$, $R^1=CH_3$, $R^2=OC_2H_5$; d $R=R^1=CH_3$, $R^2=OC_2H_5$; e $R=R^1=H$, $R^2=NH_2$; f $R=H$, $R^1=CH_3$, $R^2=NH_2$; g $R=R^1=CH_3$, $R^2=NH_2$; h $R=R^1=H$, $R^2=OC_2H_5$; i $R=CH_3$, $R^1=H$, $R^2=OC_2H_5$; j $R=R^1=CH_3$, $R^2=NH_2$; III a $R=H$, $R^3=2\text{-}CH_3$, $R^4=4\text{-}NO_2$; b $R=CH_3$, $R^3=2\text{-}CH_3$, $R^4=4\text{-}NO_2$; c $R=CH_3$, $R^3=2\text{-}CH_3O$, $R^4=5\text{-}Cl$; V a $R^3=H$, $R^4=H$; b $R^3=o\text{-}C_2H_5O$, $R^4=H$; c $R^3=o\text{-}n\text{-}C_4H_9O$, $R^4=H$; d $R^3=p\text{-}Cl$, $R^4=H$; e $R^3=p\text{-}C_2H_5OCO$; $R^4=H$; VI a $R^3=H$, $R^4=H$; b $R^3=p\text{-}Cl$, $R^4=H$; c $R^3=p\text{-}C_2H_5OCO$, $R^4=H$; d $R^3=p\text{-}NO_2$, $R^4=H$; VII a $R^3=p\text{-}C_2H_5OCO$, $R^4=H$, $R^5=(CH_3)_2N$; b $R^3=p\text{-}C_2H_5OCO$, $R^4=H$, $R^5=NO_2$.

2-(2'-Methyl-4'-nitrophenylhydrazonocarbethoxyformyl)-4-(phenylhydrazonochloroformyl)thiazole (IIIa). A 1.55-g (5 mmole) sample of the 2-methyl-4-nitrophenylhydrazone of monothiomesoxalic acid ethyl ester amide was added to 1.15 g (5 mmole) of the phenylhydrazone of chloromethylglyoxylic chloride in 10 ml of absolute alcohol, after which the mixture was refluxed for 10 h. It was then cooled, and the resulting red crystalline precipitate was removed by filtration, washed with alcohol and ether, and dried to give 1.53 g of IIIa. Compounds IIIb, c were similarly obtained.

Ethyl 1H-Tetrazol-5-ylglyoxylate Phenylhydrazone (Va). A 1.1-g (5 mmole) sample of ethyl cyanoglyoxylate phenylhydrazone was added to a mixture of 1.3 g (20 mmole) of sodium azide and 0.27 g (5 mmole) of ammonium chloride in 20 ml of dimethylformamide (DMF), and the mixture was heated at 120-135° for 5 h. It was then cooled and poured into 50 ml of ice water, and the aqueous mixture was acidified carefully to pH 2 with concentrated hydrochloric acid. The resulting yellow precipitate was removed by filtration, washed to neutrality with water, and dried to give 0.8 g of product. After column chromatography, it was crystallized from alcohol–benzene (1:1). Compounds Vb-e were synthesized under similar conditions.

1H-Tetrazol-5-ylglyoxylic Acid Hydrazide Phenylhydrazone (VIa). A 1.3-g (5 mmole) sample of ethyl 1H-tetrazol-5-ylglyoxylate phenylhydrazone was suspended in 5 ml of alcohol, 0.32 g (10 mmole) of 99% hydrazine was added, and the mixture was refluxed for 10 min. It was then cooled, and the resulting yellow crystalline product was removed by filtration, washed with alcohol and ether, and dried to give 1 g of VIa. Compounds VIb-d were synthesized under similar conditions.

1H-Tetrazol-5-ylglyoxylic Acid p-Dimethylaminobenzalhydrazide p-Carbethoxyphenylhydrazone (VIIa). A 0.8-g (2.5 mmole) sample of 1H-tetrazol-5-ylglyoxylic acid hydrazide p-carbethoxyphenylhydrazone (VIc) was suspended in 5 ml of alcohol, and 0.4 g (2.5 mmole) of p-dimethylaminobenzaldehyde was added. The mixture was then refluxed for 10 min, after which it was cooled, and the resulting orange precipitate was removed by filtration, washed with alcohol and ether, and dried to give 1.1 g of VIIa. The product was crystallized from acetic acid. Compound VIIb was similarly synthesized.

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