INVESTIGATIONS ON ARYLHYDRAZONES OF SUBSTITUTED GLYOXYLIC ACIDS

XII. Cyclization of the Arylhydrazone of Ethyl Cyanoglyoxylate*

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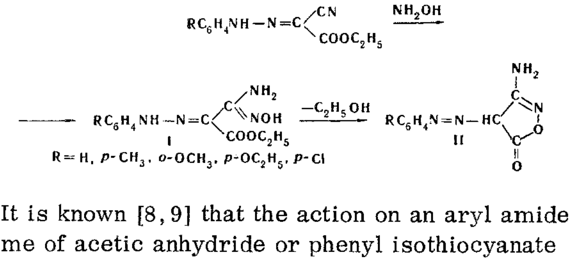
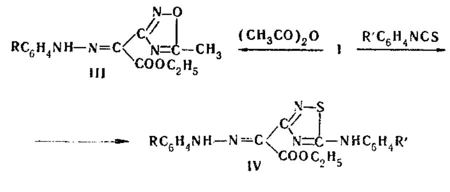
The reaction of arylhydrazones of ethyl cyanoglyoxylate with hydroxylamine hydrochloride in aqueous ethanolic solution in the presence of sodium acetate at the boil has given 3-amino-4-arylazoisoxazol-5-ones. The reaction of arylhydrazones of ethy cyanoglyoxylate with hydroxylamine in the presence of sodium ethoxide in the cold has given arylhydrazones of the amide-oxime of ethyl mesoxalate. The action of acetic anhydride or aryl isothiocyanates on arylhydrazones of the amide oxime of ethyl mesoxalate has given arylhydrazones of the ethyl esters of 5'-substituted 1',2',4'-oxadiazolyl- or 1',2',4'-thiadiazolylglyoxylic acids.

In previous papers [1–3] we have reported the synthesis of arylhydrazones of the ethyl esters and amides of cyanoglyoxylic and monothiomesoxalic acids, 3-amino-4-arylazo derivatives of pyrazol-5-one, and arylhydrazones of the ethyl ester and amide of 4'-phenylthiazolylglyoxylic acid.

In the present work we have studied the reaction of arylhydrazones of ethyl cyanoglyoxylate with hydroxylamine and the action on the compounds obtained of aryl isothiocyanates and acetic anhydride. It is known [4] that the action of hydroxylamine hydrochloride on the hydrazide of malononitrile forms the hydrazide of the amide oxime of malonic acid. If, however, the arylazoacetoacetic ester is treated with hydroxylamine in aqueous ethanolic solution in the presence of sodium acetate, 4-arylazo-3-methylisoxazol-5-ones are formed [5]. We have studied the reaction of arylhydrazones of ethyl cyanoglyoxylate with hydroxylamine in the presence of sodium alkoxide in the cold and in the presence of sodium acetate on heating [6, 7]. It was found that the reaction takes place predominantly with the formation of arylhydrazones of the amide oxime of ethyl mesoxalate [1]. In individual case, if the aromatic nucleus contains an electron-donating group, the reaction takes place both in the cold and on heating with splitting out of ethanol and the formation of 3-amino-4-arylazo derivatives of isoxazol-5-one (II).



It is known [8, 9] that the action on an aryl amide oxime of acetic anhydride or phenyl isothiocyanate forms the corresponding derivatives of oxadiazole or thiadiazole. The action of acetic anhydride and an aryl isothiocyanate on arylhydrazones of the ethyl ester of the amide oxime of mesoxalic acid gave us oxadiazole and thiadiazole derivatives III and IV.



Compounds I–IV are yellow or yellow-orange crystalline substances. They were crystallized from ethanol.

EXPERIMENTAL

3-Chloro-2-methylphenylhydrazone of the amide oxime of ethyl mesoxalate. Metallic sodium (0.12 g; 0.005 mole) was dissolved in 5 ml of absolute ethanol and 0.4 g (0.006 mole) of hydroxylamine was added. This solution was mixed with an ethanolic solution of 1.3 g (0.005 mole) of the 3-chloro-2-methylphenylhydrazone of ethyl cyanoglyoxyalate. After the mixture had stood at room temperature for 48 hr, yellow crystals deposited. They were filtered off and were washed with a small amount of 5% hydrochloric acid, then with water to neutrality (Congo Red), and with ethanol and ether, and were dried in vacuum. Yield 1.4 g (98%), mp 219–220° C.

The compounds given in Table 1 were obtained under similar conditions.

3-Amino-4-phenylazoisoxazol-5-one. A solution of 0.4 g of hydroxylamine hydrochloride and 0.7 g of sodium acetate in 10 ml of water was added to a boiling solution of 1.1 g of the phenylhydrazone of ethyl cyanoglyoxylate in 10 ml of ethanol in such a way that the solution did not cease to boil. After 15–20 min, the color of the solution deepened and orange crystals began to separate out. The mixture was left for 24 hr and then the precipitate was filtered off, washed with ethanol, and dried in vacuum. Yield 0.6 g (64%), mp 230–231° C (from ethanol).

The compounds given in Table 2 were obtained under similar conditions.

2-Methoxy-5-nitrophenylhydrazone of ethyl 5'-phenylamino-1', 2', 4'-thiadiazol-3'-ylglyoxylate. A suspension of 1.3 g (0.004 mole) of the 2-methoxy-5-nitrophenylhydrazone of the amide oxime of ethyl mesoxalate in 50 ml of chloroform was treated with 1.1 g (0.008 mole) of phenyl isothiocyanate, and the mixture was boiled for 10 hr. After cooling, an orange crystalline precipitate deposited. Yield 1.3 g (76%), mp 212–213° C (from chloroform). Found, %: N 19.14, 19.15. Calculated for $C_{19}H_{18}N_6O_5S$, %: N 19.01.

The 2-methyl-5-nitrophenylhydrazone of ethyl 5'-phenylamino-1', 2', 4'-thiadiazol-3'-ylglyoxylate was obtained similarly from the appropriate hydrazone. Yield 73%. Yellow crystals, mp 160–161° C (from a mixture of ethanol and chloroform). Found, %: N 19.67, 19.77. Calculated for $C_{19}H_{18}N_6O_4S$, %: N 19.72.

The 2-methoxy-5-nitrophenylhydrazone of ethyl 5'-(p-bromophenylamino)-1', 2', 4'-thiadiazol-3'-ylglyoxylate. A suspension of 1.3 g (0.004 mole) of the 2-methoxy-5-nitrophenylhydrazone of the amide oxime of ethyl mesoxalate in 50 ml of ethanol was treated with 1.7 g (0.008 mole) of p-bromophenyl isothiocyanate, and the mixture was boiled for 4 hr. The yellow-orange precipitate that de-

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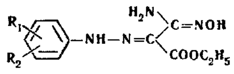
*For part XI, see [11].

Table 1

Arylhydrazones of the Amide Oxide of Ethyl Mesoxalate



R_1	R_2	Mp, °C	Empirical formula	N, % found	N, % calculated	Yield, %
4-CH_3O	H	153—154	$C_{12}H_{16}O_4N_4$	20.11; 20.22	20.00	57
2-C_2H_5O	H	234—236	$C_{13}H_{18}O_4N_4$	19.35; 19.48	19.05	63
2-Cl	H	125—126	$C_{11}H_{13}O_3N_4Cl$	19.33; 19.38	19.68	69
2-NO_2	H	242—243	$C_{11}H_{13}O_5N_5$	23.70; 23.79	23.73	42
4-NO_2	H	221—222	$C_{11}H_{13}O_5N_5$	23.26; 23.44	23.73	39
3-COOH	H	222—223	$C_{12}H_{14}O_5N_4$	18.82; 18.95	19.05	66
3,4-benzo		176—177	$C_{15}H_{16}O_3N_4$	18.35; 18.50	18.66	53
2-CH_3	3-Cl	219—220	$C_{12}H_{15}O_3N_4Cl$	18.92; 18.85	18.76	98
2-CH_3	4-NO_2	231—232	$C_{12}H_{15}O_5N_5$	22.42; 22.48	22.66	74
2-CH_3O	5-NO_2*	193—194	$C_{12}H_{15}O_6N_5$	21.22; 21.25	21.54	73
2-Br	5-NO_2**	>240	$C_{11}H_{12}O_5N_5Br$	18.63; 18.68	18.72	85
3-NO_2	4-CH_3	>240	$C_{12}H_{15}O_5N_5$	22.29; 22.41	22.66	58
2-NO_2	4-Cl	>240	$C_{11}H_{12}O_5N_5Cl$	20.91; 21.05	21.24	73

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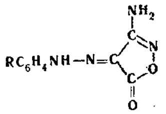
* Found, %: C 43.92; 43.95; H 4.32; 4.39. Calculated, %: C 44.3; H 4.61.

** Found, %: Br 23.56, 23.46. Calculated, %: Br 23.46.

Table 2

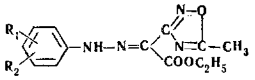
4-Arylazo Derivatives of 3-Aminooxazol-5-ones



R	Mp, °C	Empirical formula	N, % found	N, % calculated	Yield, %
H	230—232	$C_9H_8O_2N_4$	27.31; 27.37	27.46	64
p-CH_3	230—231	$C_{10}H_{10}O_2N_4$	25.87; 25.99	25.68	61
o-CH_3O	196—197	$C_{10}H_{10}O_3N_4$	23.78; 23.86	23.93	60
p-C_2H_5O	205—206	$C_{11}H_{12}O_3N_4$	22.22; 22.28	22.58	67
p-Cl	210—212	$C_9H_7O_2N_4Cl$	23.16; 23.32	23.48	88

Table 3

Arylhydrazones of Ethyl 5'-Methyl-1', 2', 4'-oxadiazol-3'-ylglyoxylate



R_1	R_2	Mp, °C	Empirical formula	N, % found	N, % calculated	Yield %
4-Br	H	142—143	$C_{13}H_{13}O_3N_4Br$	15.46; 15.39	15.86	65
2-NO_2	H	150—151	$C_{13}H_{13}O_5N_5$	21.46; 21.65	21.94	71
4-NO_2	H	199—200	$C_{13}H_{13}O_5N_5$	21.60; 21.70	21.94	63
2-COOH	H	>230	$C_{14}H_{14}O_5N_4$	17.33; 17.41	17.61	33
2-CH_3	4-Cl*	207—208	$C_{14}H_{15}O_3N_4Cl$	—	—	63
2-CH_3	4-NO_2	200—201	$C_{14}H_{15}O_5N_5$	21.00; 21.02	21.02	93
2-CH_3O	5-NO_2	241—242	$C_{14}H_{15}O_6N_5$	19.81; 19.95	20.06	95
2-NO_2	4-CH_3	177—178	$C_{14}H_{15}O_5N_5$	20.94; 20.89	21.02	67
2-Br	5-NO_2**	171—172	$C_{13}H_{12}O_5N_5Br$	—	—	95

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* Found, %: cl 10.87, 10.95. Calculated, %: Cl 11.01.

** Found, %: Br 19.83, 19.68. Calculated, %: Br 20.10.

posited on cooling was filtered off, washed with ethanol and ether, and dried in vacuum. Yield 1.85 g (86%), mp 213–214° C (from ethanol). Found, %: N 15.93; 15.94; S 6.05; 6.07. Calculated for $C_{19}H_{19}BrN_6O_6S$, %: N 16.16; S 6.14.

5-Bromo-5-nitrophenylhydrazone of ethyl 5'-methyl-1', 2', 4'-oxadiazol-3'-ylglyoxylate. A mixture of 1.1 g (0.003 mole) of the 2-bromo-5-nitrophenylhydrazone of the amide oxime of ethyl mesoxalate and 1.2 g (0.012 mole) of acetic anhydride was boiled for 5 min, after which all the solid matter had gone into solution. After cooling, a yellow crystalline precipitate deposited. Yield 1.1 g (95%), mp 171–172° C (from ethanol). Found, %: Br 19.82, 19.68. Calculated for $C_{19}H_{12}BrN_5O_5$, %: Br 20.10.

All the arylhydrazone derivatives of ethyl 5'-methyl-1', 2', 4'-oxadiazol-3'-ylglyoxylate given in Table 3 were obtained under similar conditions.

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