Methylation of 3-Methyl- and 3-Phenyl-4-arylhydrazonoisoxazol-5-ones with Methyl Iodide and Dimethyl Sulfate

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Received August 22, 1984

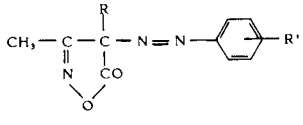
Methylation of 3-methyl-4-arylhydrazonoisoxazol-5-ones with methyl iodide affords both 2,3-dimethyl-4-arylazoisoxazol-5-ones and 3-methyl-4-(*N*-methylarylhydrazono)isoxazol-5-ones but with dimethyl sulfate only the former products are formed. 3-Phenyl-4-arylhydrazonoisoxazol-5-ones behave in a similar way on methylation with methyl iodide and dimethyl sulfate.

J. Heterocyclic Chem., **22**, 457 (1985).

4-Arylazo-3-methylisoxazol-5-ones [1] have been known for many years. Apart from synthetic methods [*eg* 2-4], hydrolysis studies [4] and reactions with nitric acid [4,5], hydrazines [1,6] and bromine [7] their chemistry was not well studied until about 1960 when it was discovered [8] that they were fungicides active against a number of plant pathogens. 4-Arylazo-3-methylisoxazol-5-ones are formally capable of existence in four tautomeric forms (I, R = H), (II, R = H), (III, R = H) and (IV, R = H). It was established [9,10] and subsequently confirmed [11] that they exist as the phenylhydrazono tautomer (IV, R = H) and this result is in accord with recent molecular orbital calculations [12]. Another view that they exist as tautomer (II, R = H) [13,14] was based on incorrect structural assignments [15]. Studies of the alkylation (9,10,16,17], acylation [18], chemical hydrolysis [19], sulfurization [10, 20-22], flash pyrolysis [23,24], solubility [25], ionization constants [11,25], chelating properties [11], mass spectra [26] and polarography [27-29] of 4-arylhydrazono-3-methylisoxazol-5-ones have been carried out as well as work on the relationship between chemical structure and fungicidal activity [19,30]. They are potent uncouplers of oxidative phosphorylation [31] and this property is responsible, at least in part, for their fungitoxic properties. Several papers reporting the fungicidal properties of 4-(*o*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = H, R′ = *o*-Cl), known as drazoxolon, [*eg* 32-45] and other 4-arylhydrazono-3-methylisoxazol-5-ones [*eg* 46-48] have appeared. Metabolic [49,50], toxicological [51], degradative [52] and analytical [53] studies with drazoxolon have also been reported as well as a method of manufacture [54].

4-Arylhydrazono-3-phenylisoxazol-5-ones (V, R = H) have also been prepared [*eg* 13,14, 55-59] and their behaviour on alkylation [13,17,55] and sulfurization [60] reported. Molecular orbital calculations are in accord with the phenylhydrazono tautomeric structure [12]. They have been patented as fungicides [59].

This paper is concerned with further work on the behaviour of 4-arylhydrazono-3-methylisoxazol-5-ones (IV, R = H) and 4-arylhydrazono-3-phenylisoxazol-5-ones (V, R = H) on alkylation and is specifically concerned with the products which are obtained when methyl iodide and dimethyl sulfate are used as alkylating agents. Very little has so far been reported on the use of methyl iodide as alkylating agent with these compounds. Working with 4-phenylhydrazono-3-methylisoxazol-5-one (IV, R = H, R′ = H), 4-(*o*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = H, R′ = *o*-Cl), 4-(*m*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = H, R′ = *m*-Cl) and 4-(*o*-methylphenylhydrazono)-3-methylisoxazol-5-one (IV, R = H, R′ = *o*-CH_3) the only products isolated from their reaction with



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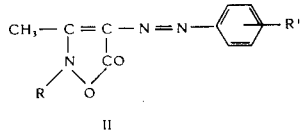

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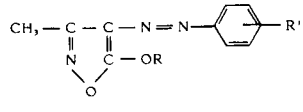

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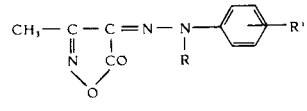

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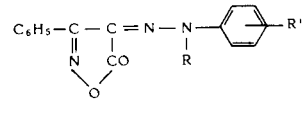

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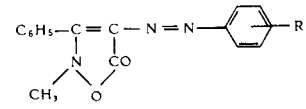

VI

methyl iodide in acetone in the presence of potassium carbonate were the corresponding 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) in about 35-40% yield [9,10,16]. The structure of the 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) was fully authenticated by unambiguous synthesis from the appropriate ethyl α-arylazoacetoacetate and *N*-methylhydroxylamine [9,10,16]. The 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) have characteristic ultraviolet spectra which contain three maxima at about λ 235, 280 and 350 nm (log ε ~3.90, 3.85 and 4.22) and characteristic chemical shifts in the proton nuclear magnetic resonance spectra for the methyl groups. The methyl group on the C-3 carbon gives a signal at δ ~ 2.65 ppm and the methyl group on the N-2 nitrogen at δ ~ 3.70 ppm. The behaviour of 4-arylhydrazono-3-phenylisoxazol-5-ones (V, R = H) towards methyl iodide has been studied only once [55] and no reaction was observed.

We have now undertaken a careful examination of the products obtained by reaction of seven 4-arylhydrazono-3-methylisoxazol-5-ones, (IV, R = H, R′ = H), (IV, R = H, R′ = *p*-Cl), (IV, R = H, R′ = *m*-Cl), (IV, R = H, R′ = *o*-Cl), (IV, R = H, R′ = *p*-CH_3), (IV, R = H, R′ = *m*-CH_3) and (IV, R = H, R′ = *o*-CH_3) and three 4-arylhydrazono-3-phenylisoxazol-5-ones, (V, R = H, R′ = H), (V, R = H, R′ = *p*-Cl) and (V, R = H, R′ = *p*-CH_3), with methyl iodide in acetone in presence of potassium carbonate. In all cases it has been found that two products are obtained. From the seven 4-arylhydrazono-3-methylisoxazol-5-ones as well as the expected 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3), methylation occurred on the phenylhydrazono nitrogen to afford 4-(*N*-methylarylhydrazono)-3-methylisoxazol-5-ones (IV, R = CH_3). The 4-(*N*-methylarylhydrazono)-3-methylisoxazol-5-ones (IV, R = CH_3) are fully authenticated since the compound (IV, R = CH_3, R′ = H) has previously been obtained unambiguously from the reaction of 3-methyl-4,4-dibromoisoxazol-5-one with *N*-methylphenylhydrazine (Ph-NMe-NH_2) [13]. The 4-(*N*-methylarylhydrazono)-3-methylisoxazol-5-ones (IV, R = CH_3) have characteristic ultraviolet spectra which contain two maxima at about λ 245 and 390 nm (log ε ~ 3.94 and 4.30) although those compounds which contain a bulky substituent in the *ortho* position of the aryl ring, as expected, show a pronounced hypsochromic shift with reduced intensities [10]. The 4-(*N*-methylarylhydrazono)-3-methylisoxazol-5-ones (IV, R = CH_3) have characteristic chemical shifts in the proton nuclear magnetic resonance spectra for the methyl groups. The methyl group on the C-3 carbon gives a signal at δ ~ 2.3 ppm and the methyl group on the hydrazono nitrogen at δ ~ 4.15 ppm [10]. The 4-(*N*-methylarylhydrazono)-3-methylisoxazol-5-ones (IV, R = CH_3) are thus readily distinguished from the 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) by comparison of their ultraviolet and nuclear magnetic resonance spectra. Likewise the three 4-arylhydrazono-3-phenylisoxazol-5-ones (V, R = H) afforded the analogous 2-methyl-3-phenyl-4-arylazoisoxazol-5-ones (VI) and 4-(*N*-methylarylhydrazono)-3-phenylisoxazol-5-ones (V, R = CH_3) on reaction with methyl iodide. Details of the yields of the two series of products are given in Table 1.

With the 4-arylhydrazono-3-methylisoxazol-5-ones yields of the products obtained by methylation of the hydrazono nitrogen were greater than the yields of compounds obtained by methylation of the isoxazolone nitrogen except in cases where the aromatic ring had an *ortho* substituent. Then the products of methylation on the isoxazolone nitrogen predominated. This result is almost certainly due to steric influences. With the three 4-arylhydrazono-3-phenylisoxazol-5-ones the yields of the products obtained by methylation of the hydrazono nitrogen were much greater than the yields of the products from methylation of the isoxazolone nitrogen.

In view of the interesting results obtained when methyl iodide was used as alkylating agent we investigated carefully the behaviour of the seven 4-arylhydrazono-3-methylisoxazol-5-ones, (IV, R = H, R′ = H), (IV, R = H, R′ = *p*-Cl), (IV, R = H, R′ = *m*-Cl), (IV, R = H, R′ = *o*-Cl), (IV, R = H, R′ = *p*-CH_3), (IV, R = H, R′ = *m*-CH_3) and (IV, R = H, R′ = *o*-CH_3) and the three 4-arylhydrazono-3-phenylisoxazol-5-ones, (V, R = H, R′ = H), (V, R = H, R′ = *p*-Cl) and (V, R = H, R′ = *p*-CH_3) on methylation with di-

Table 1

Products from the Reaction of 3-Methyl and 3-Phenyl-4-arylhydrazonoisoxazol-5-ones with Methyl Iodide

Starting Material	Yield of Products (%)			
	II, R = CH_3	IV, R = CH_3	VI	V, R = CH_3
IV, R = H, R′ = H	35	42	—	—
IV, R = H, R′ = *p*-Cl	11	25	—	—
IV, R = H, R′ = *m*-Cl	33	46	—	—
IV, R = H, R′ = *o*-Cl	26	23	—	—
IV, R = H, R′ = *p*-CH_3	19	44	—	—
IV, R = H, R′ = *m*-CH_3	18	29	—	—
IV, R = H, R′ = *o*-CH_3	31	23	—	—
V, R = H, R′ = H	—	—	15	54
V, R = H, R′ = *p*-Cl	—	—	13	32
V, R = H, R′ = *p*-CH_3	—	—	20	64

methyl sulfate. In previous work the only products obtained from methylation with this reagent of 4-arylhydrazono-3-methylisoxazol-5-ones were 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) [10,16,17]. With 4-arylhydrazono-3-phenylisoxazol-5-ones it has been reported that they do not react with dimethyl sulfate [55] but another report [17] showed that 2-methyl-3-phenyl-4-arylazoisoxazol-5-ones (VI) were formed with this reagent. In our present study we have confirmed that 4-arylhydrazono-3-methylisoxazol-5-ones give only 2,3-dimethyl-4-arylazoisoxazol-5-ones (II, R = CH_3) on reaction with dimethyl sulfate. 4-Arylhydrazono-3-phenylisoxazol-5-ones likewise give only 2-methyl-3-phenyl-4-arylazoisoxazol-5-ones (VI).

EXPERIMENTAL

The nmr spectra refer to proton nmr spectra (60 MHz) with tetramethylsilane as internal standard. Microanalyses were performed by the Australian Microanalytical Service.

3-Methyl-4-arylhydrazonoisoxazol-5-ones (IV, R = H).

The following seven compounds were prepared by literature methods [2,8,10]: 3-methyl-4-phenylhydrazonoisoxazol-5-one (IV, R = H, R′ = H), mp 200°; 3-methyl-4-(*p*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *p*-Cl), mp 194°; 3-methyl-4-(*m*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *m*-Cl), mp 162-164°; 3-methyl-4-(*o*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *o*-Cl), mp 168°; 3-methyl-4-(*p*-methylphenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *p*-CH_3), mp 208-210°; 3-methyl-4-(*m*-methylphenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *m*-CH_3), mp 170°; 3-methyl-4-(*o*-methylphenylhydrazono)isoxazol-5-one (IV; R = H, R′ = *o*-CH_3), mp 160°. The melting points are in good agreement with literature values.

3-Phenyl-4-arylhydrazonoisoxazol-5-ones (V, R = H).

The following three compounds were prepared by literature methods [59]: 3-phenyl-4-phenylhydrazonoisoxazol-5-one (V, R = H, R′ = H), mp 162-164°; 3-phenyl-4-(*p*-chlorophenylhydrazono)isoxazol-5-one (V; R = H, R′ = *p*-Cl), mp 220°; 3-phenyl-4-(*p*-methylphenylhydrazono)isoxazol-5-one (V, R = H, R′ = *p*-CH_3), mp 177-178°. The melting points are in good agreement with literature values.

Reaction with Methyl Iodide.

The 3-methyl or 3-phenyl-4-arylhydrazonoisoxazol-5-ones (2.4 g), potassium carbonate (1.4 g) and methyl iodide (1.5 g) in acetone (32 ml) were refluxed for 6 hours and the solution filtered. The following work up procedures were adopted:

(a) With 3-Methyl-4-phenylhydrazonoisoxazol-5-one (IV, R = H, R′ = H).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford 2,3-dimethyl-4-phenylazoisoxazol-5-one (II, R = CH_3, R′ = H), mp 200° (yield 35%). Literature melting points [10,16] range from 190-198°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.60 (C-CH_3), a singlet at 3.62 (N-CH_3) and a multiplet at 7.28-7.89 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 231, 275 and 344 nm (log ϵ 3.80, 3.79 and 4.21). The ir spectrum (potassium bromide) showed a CO group at 1730 cm^{-1}.

From the acetone mother liquors there was obtained after three recrystallizations from chloroform/ethanol 4-(*N*-methylphenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = H), mp 102° (yield 42%). Literature melting points [13,16] are 105° and 106°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.27 (C-CH_3), a singlet at 4.21 (N-CH_3) and a multiplet at 7.25-7.60 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 240 and 390 nm (log ϵ 3.92 and 4.19). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

(b) With 3-Methyl-4-(*p*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *p*-Cl).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized twice from chloroform/ethanol to afford 4-(*N*-methyl-*p*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *p*-Cl), mp 208° (yield 25%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.22 (C-CH_3), a singlet at 4.21 (N-CH_3) and a singlet at 7.45 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 242 and 391 nm (log ϵ 4.01 and 4.33). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_2$: C, 52.5; H, 4.0; N, 16.7. Found: C, 52.3; H, 3.7; N, 17.1.

The mother liquors from the above crystallizations were passed through a chromatographic column packed with alumina using chloroform/ethanol (3:1) as eluant. The compound which came off first consisted of 2,3-dimethyl-4-(*p*-chlorophenylazo)isoxazol-5-one (II, R = CH_3, R′ = *p*-Cl) which was recrystallized twice from chloroform/ethanol to afford yellow crystals, mp 202° (yield 11%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.60 (C-CH_3), a singlet at 3.62 (N-CH_3) and two doublets at 7.30-7.80 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 237, 275 and 351 nm (log ϵ 3.97, 3.88 and 4.36). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_2$: C, 52.5; H, 4.0; N, 16.7; OCH_3, 0.0. Found: C, 52.7; H, 4.2; N, 17.0; OCH_3, < 0.3.

A small quantity of 4-(*N*-methyl-*p*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *p*-Cl) came off the column later.

(c) With 3-Methyl-4-(*m*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *m*-Cl).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from acetone to afford 2,3-dimethyl-4-(*m*-chlorophenylazo)isoxazol-5-one (II, R = CH_3, R′ = *m*-Cl), mp 188-189° (yield 33%). Literature melting point [10,16] is 190°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.61 (C-CH_3), a singlet at 3.68 (N-CH_3) and a multiplet at 7.30-7.72 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 238, 274 and 349 nm (log ϵ 3.92, 3.83 and 4.28). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

From the acetone mother liquors there was obtained after two recrystallizations from chloroform/ethanol 4-(*N*-methyl-*m*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *m*-Cl), mp 180° (yield 46%). Literature melting point [10,16] is 181°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.26 (C-CH_3), a singlet at 4.20 (N-CH_3) and a multiplet at 7.25-7.60 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 244 and 389 nm (log ϵ 3.93 and 4.28). The ir spectrum (potassium bromide) showed a CO group at 1730 cm^{-1}.

(d) With 3-Methyl-4-(*o*-chlorophenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *o*-Cl).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford 2,3-dimethyl-4-(*o*-chlorophenylazo)-isoxazol-5-one (II, R = CH_3, R′ = *o*-Cl), mp 209-210° (yield 26%). Literature melting point [9,10,16] is 200°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.67 (C-CH_3), a singlet at 3.66 (N-CH_3) and a multiplet at 7.15-7.70 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 243, 274 and 361 nm (log ϵ 3.91, 3.82 and 4.14). The ir spectrum (potassium bromide) showed a CO group at 1730 cm^{-1}.

From the acetone mother liquors there was obtained after two recrystallizations from chloroform/ethanol 4-(*N*-methyl-*o*-chlorophenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *o*-Cl), mp 136-137° (yield 23%). Literature melting point [9,10,16] is 135-136°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.18 (C-CH_3), a singlet at 4.18 (N-CH_3) and a multiplet at 7.25-7.65 ppm (aromatic protons).

The uv spectrum (ethanol) showed λ max 238 and 358 nm (log ε 3.73 and 4.14). The ir spectrum (potassium bromide) showed a CO group at 1725 cm^{-1}.

(e) With 3-Methyl-4-(*p*-methylphenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *p*-Me).

On standing overnight a yellow precipitate was obtained. This was collecteced, washed with aqueous sodium hydroxide and water and crystallized from ethanol to afford 4-(*N*-methyl-*p*-methylphenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *p*-CH_3), mp 157° (yield 44%). Literature mp is 157° [17]. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.22 (C-CH_3), a singlet at 2.40 (aromatic CH_3), a singlet at 4.22 (N-CH_3) and a multiplet at 7.20-7.55 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 239 and 396 nm (log ε 3.91 and 4.29). The ir spectrum (potassium bromide) showed a CO group at 1715 cm^{-1}.

From the acetone mother liquors there was obtained after two crystallizations from acetone 2,3-dimethyl-4-(*p*-methylphenylazo)isoxazol-5-one (II, R = CH_3, R′ = *p*-CH_3), mp 196-198° (yield 19%). Literature mp is 185° [17]. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.40 (aromatic CH_3), a singlet at 2.60 (C-CH_3), a singlet at 3.60 (N-CH_3), and a multiplet at 7.20-7.80 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 237, 278 and 347 nm (log ε 3.85, 3.82 and 4.31). The ir spectrum (potassium bromide) showed a CO group at 1730 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.2. Found: C, 62.6; H, 5.65; N, 18.0.

(f) With 3-Methyl-4-(*m*-methylphenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *m*-Me).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford 2,3-dimethyl-4-(*m*-methylphenylazo)isoxazol-5-one (II, R = CH_3, R′ = *m*-CH_3), mp 188-189° (yield 18%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.40 (aromatic CH_3), a singlet at 2.60 (C-CH_3), a singlet at 3.60 (N-CH_3) and a multiplet at 7.25-7.70 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 236, 278 and 345 nm (log ε 3.89, 3.82 and 4.33). The ir spectrum (potassium bromide) showed a CO group at 1730 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.2. Found: C, 61.9; H, 5.5; N, 18.2.

From the acetone mother liquors there was obtained after two recrystallizations from chloroform/ethanol 4-(*N*-methyl-*m*-methylphenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *m*-CH_3), mp 126° (yield 29%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.22 (C-CH_3), a singlet at 2.42 (aromatic CH_3), a singlet at 4.22 (N-CH_3) and a multiplet at 7.20-7.50 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 240 and 391 nm (log ε 3.82 and 4.26). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.2; OCH_3, 0.0. Found: C, 62.3; H, 5.4; N, 18.4; OCH_3, < 0.3.

(g) With 3-Methyl-4-(*o*-methylphenylhydrazono)isoxazol-5-one (IV, R = H, R′ = *o*-Me).

On standing overnight a yellow precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford 2,3-dimethyl-4-(*o*-methylphenylazo)-isoxazol-5-one (II, R = CH_3, R′ = *o*-CH_3), mp 196° (yield 31%). Literature melting point [10,16] is 192°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.60 (6H, C-CH_3 and aromatic CH_3 substituent), a singlet at 3.60 (N-CH_3) and a multiplet at 7.15-7.65 ppm (aromatic protons). The uv specrum (ethanol) showed λ max 238, 275 and 350 nm (log ε 3.84, 3.87 and 4.28). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

From the acetone mother liquors there was obtained after two recrystallizations from chloroform/ethanol 4-(*N*-methyl-*o*-methylphenylhydrazono)-3-methylisoxazol-5-one (IV, R = CH_3, R′ = *o*-CH_3), mp 162-164° (yield 23%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.15 (C-CH_3), a singlet at 2.35 (aromatic CH_3), a singlet at 4.20 (N-CH_3) and a multiplet at 7.20-7.65 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 237 and 363 nm (log ε 3.54 and 4.13). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.6; N, 18.2. Found: C, 62.4; H, 5.7; N, 18.4.

(h) With 3-Phenyl-4-phenylhydrazonoisoxazol-5-one (V, R = H, R′ = H).

On standing overnight an orange precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from ethanol/chloroform to afford 4-(*N*-methylphenylhydrazono)-3-phenylisoxazol-5-one (V, R = CH_3, R′ = H) mp 148° (yield 54%). Literature melting point is 148° [13,17,55]. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 4.24 (N-CH_3) and a multiplet at 7.25-7.96 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 228 and 399 nm (log ε 4.25 and 4.21). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

From the acetone mother liquors there was obtained after two recrystallizations from acetone 2-methyl-3-phenyl-4-(phenylazo)isoxazol-5-one (VI, R′ = H), mp 218-220° (yield 15%). Literature melting point is 221° [17]. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 3.56 (N-CH_3) and a multiplet at 7.25-7.90 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 220 sh, 268 and 351 nm (log ε 4.11, 3.95 and 4.37). The ir spectrum (potassium bromide) showed a CO group at 1740 cm^{-1}.

(i) With 3-Phenyl-4-(*p*-chlorophenylhydrazono)isoxazol-5-one (V, R = H, R′ = *p*-Cl).

On standing overnight an orange precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from acetone to afford 4-(*N*-methyl-*p*-chlorophenylhydrazono)-3-phenylisoxazol-5-one (V, R = CH_3, R′ = *p*-Cl), mp 140-142° (yield 32%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 4.22 (N-CH_3) and a multiplet at 7.25-7.95 ppm (aromatic protons). The uv spectrum (ethanol) showed λ 229 and 405 nm (log ε 4.17 and 4.20). The ir spectrum (potassium bromide) showed a CO group at 1710 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.2; H, 3.8; N, 13.4; OCH_3, 0.0. Found: C, 61.4; H, 3.8; N, 13.6; OCH_3, < 0.3.

From the acetone mother liquors there was obtained after two recrystallizations from acetone 2-methyl-3-phenyl-4-(*p*-chlorophenylazo)isoxazol-5-one (VI, R′ = *p*-Cl), mp 192-193° (yield 13%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 3.60 (N-CH_3) and a multiplet at 7.25-7.75 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 231, 274 and 357 nm (log ε 4.12, 3.95 and 4.35). The ir spectrum (potassium bromide) showed a CO group at 1740 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.2; H, 3.8; N, 13.4; OCH_3, 0.0. Found: C, 61.0; H, 3.5; N 13.5; OCH_3, < 0.3.

(j) With 3-Phenyl-4-(*p*-methylphenylhydrazono)isoxazol-5-one (V, R = H, R′ = *p*-CH_3).

On standing overnight an orange precipitate was obtained. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford 4-(*N*-methyl-*p*-methylphenylhydrazono)-3-phenylisoxazol-5-one (V, R = CH_3, R′ = *p*-CH_3), mp 125-126° (yield 64%). Literature melting point [17] is 126°. The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.35 (aromatic CH_3), a singlet at 4.20 (N-CH_3) and a multiplet at 7.10-7.95 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 229, 255 sh and 407 nm (log ε 4.25, 3.84 and 4.24). The ir spectrum (potassium bromide) showed a CO group at 1720 cm^{-1}.

From the acetone mother liquors there was obtained after two recrystallizations from chloroform/ethanol 2-methyl-3-phenyl-4-(*p*-methylphenylazo)isoxazol-5-one (VI; R′ = *p*-CH_3), mp 138° (yield 20%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.35 (aromatic CH_3), a singlet at 3.50 (N-CH_3) and a multiplet at 7.05-7.75 ppm (aromatic protons). The uv spectrum (ethanol) showed λ max 225, 253 sh, 268 and 355 nm (log ε 4.13, 4.00, 3.95 and 4.40). The ir spectrum (potassium

bromide) showed a CO group at 1740 cm^{-1}.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.6; H, 5.1; N, 14.3; OCH_3, 0.0. Found: C, 69.7; H, 4.8; N, 14.15; OCH_3, < 0.3.

Reaction with Dimethyl Sulfate.

The 3-methyl or 3-phenyl-4-arylhydrazonoisoxazol-5-one (1.5 g) was heated in dimethyl sulfate (15 ml) to 140° for 5 minutes. The mixture was cooled and poured into ice and made alkaline with aqueous sodium hydroxide. The oil which formed was treated with a small quantity of ethanol whereupon a yellow solid formed. This was collected, washed with aqueous sodium hydroxide and water and crystallized from chloroform/ethanol to afford the corresponding 2,3-dimethyl or 2-methyl-3-phenyl-4-arylazoisoxazol-5-one respectively. The products were identical to the analogous compounds obtained from the methyl iodide experiments. The yields were as follows: 2,3-dimethyl-4-phenylazoisoxazol-5-one (II, R = CH_3, R' = H), 46%; 2,3-dimethyl-4-(*p*-chlorophenylazo)-isoxazol-5-one (II, R = CH_3, R' = *p*-Cl), 43%; 2,3-dimethyl-4-(*m*-chlorophenylazo)isoxazol-5-one (II, R = CH_3, R' = *m*-Cl), 50%; 2,3-dimethyl-4-(*o*-chlorophenylazo)isoxazol-5-one (II, R = CH_3, R' = *o*-Cl), 60%; 2,3-dimethyl-4-(*p*-methylphenylazo)isoxazol-5-one (II, R = CH_3 R' = *p*-CH_3), 47%; 2,3-dimethyl-4-(*m*-methylphenylazo)isoxazol-5-one (II, R = CH_3, R' = *m*-CH_3), 44%; 2,3-dimethyl-4-(*o*-methylphenylazo)isoxazol-5-one (II, R = CH_3, R' = *o*-CH_3), 81%; 2-methyl-3-phenyl-4-(phenylazo)isoxazol-5-one (VI, R' = H), 51%; 2-methyl-3-phenyl-4-(*p*-chlorophenylazo)isoxazol-5-one (VI, R' = *p*-Cl), 64%; 2-methyl-3-phenyl-4-(*p*-methylphenylazo)isoxazol-5-one (VI, R' = *p*-CH_3), 43%.

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