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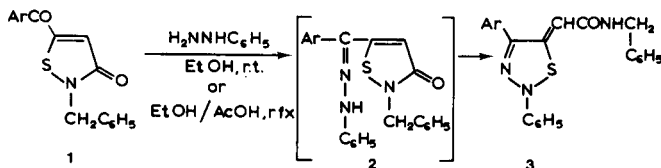
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Received March 13, 1985

Reaction of 2-substituted-5-aryloxy-3(2*H*)-isothiazolones **1** with phenylhydrazine in refluxing ethanol was found to give sulfur-free products, which were characterized as 3-phenylhydrazono-3-aryloxy-*N*-substituted-propionamides **4**. Acid hydrolysis of the 3-benzoyl compounds **4** was shown to yield 1-phenyl-3-benzoyl-2-pyrazolin-5-one (**7**), whose structure was confirmed by an independent synthesis starting with the chloride of 1-phenyl-5-methoxy-pyrazole-3-carboxylic acid (**10**).

J. Heterocyclic Chem., **22**, 1465 (1985).

We have recently reported [2] that reaction of 2-substituted-5-aryloxy-3(2*H*)-isothiazolones with phenylhydrazine results in the formation of (*N*-substituted-carboxamido)-methylene derivatives of 1,2,3-thiadiazole. The *N*-benzyl-5-aryloxyisothiazolones **1a** and **1b** were thus shown to give

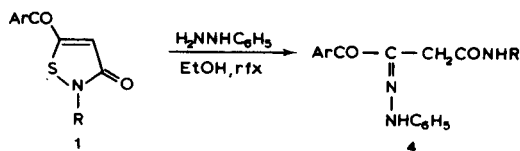


a, Ar = -C₆H₅

b, Ar = -C₆H₄-Cl-p

an excellent yield of the corresponding compounds **3** on reaction with phenylhydrazine *in ethanol at room temperature*. A considerably better yield of compounds **3** was obtained when the reaction was carried out *in refluxing ethanol containing acetic acid*. The overall reaction of **1** to **3** was ascribed to a mononuclear heterocyclic rearrangement of the initially formed phenylhydrazones **2**.

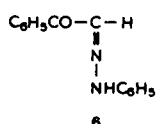
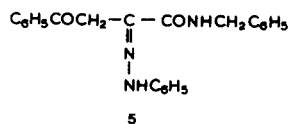
We now report an unexpected evolution of the reaction of isothiazolones **1** with phenylhydrazine *in ethanol at reflux*, which resulted in the isolation of new, sulfur-free, compounds. Chemical and spectroscopic evidence will be presented below to disclose structure **4** for these new compounds.



a, Ar = -C₆H₅, R = -CH₂C₆H₅

b, Ar = -C₆H₄-Cl-p, R = -CH₂C₆H₅

c, Ar = -C₆H₅, R = -C₆H₅



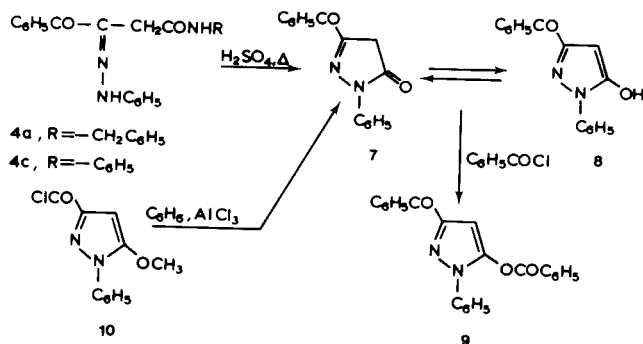
The new compound obtained from the isothiazolone **1a**, a yellow crystalline product, mp 150-151° dec, was assigned the molecular formula C₂₃H₂₁N₃O₂ on the basis of its elemental analysis. The proton nmr spectrum of the product revealed a methylene singlet, a methylene doublet, a multiplet of 15 aromatic protons and two broad signals assigned to N-H protons. The aromatic protons' multiplet includes a two protons signal, probably characteristic of the *ortho* protons in a benzoyl group. On the other hand, one of the N-H signals (in DMSO-d₆, δ 8.63 ppm, broad triplet J = 5.6 Hz) is coupled to the methylene doublet (δ 4.30 ppm, doublet J = 5.6 Hz), thus suggesting the presence of an *N*-benzylcarboxamido group, -CONHCH₂C₆H₅.

Two probable structures, **4a** and **5**, can be derived from these data. Structure **4a** should, however, be favored on the basis of the resemblance of its uv spectrum [in ethanol, absorption maxima at 264 (ε 17900), 285 (shoulder, ε 6300), 295 (shoulder, ε 4700) and 361 nm (ε 23000)] with the spectrum of the ω-phenylhydrazone of phenylglyoxal (**6**) [in methanol, absorption maxima at 247 (ε 12000), 289 (shoulder, ε 5000) and 375 nm (ε 20000)] [3]. It should be noted, that the low-field N-H broad singlet (-NHC₆H₅) of the compound (δ 10.76 ppm in deuteriochloroform and 10.63 ppm in DMSO-d₆, respectively) can now be assigned to an intramolecular hydrogen bonding to the benzoyl carbonyl group in structure **4a**.

The analogous compounds **4b** and **4c** were also obtained, starting with the isothiazolones **1b** and **1c**, respectively.

Chemical evidence for structure **4** was obtained from a hydrolysis reaction. It was presumed that hydrolysis of the *N*-substituted amide moiety would afford a simpler, easily identified, product. Attempts of alkaline hydrolysis were unsuccessful, but treatment with sulfuric acid of either the *N*-benzylamide **4a** or the *N*-phenylamide **4c** resulted in the isolation of the same nitrogen containing compound, C₁₆H₁₂N₂O₂. Its proton nmr spectrum in deuteriochloroform revealed the characteristic signals of a benzoyl group besides a methylene singlet at δ 3.55 ppm. However, its

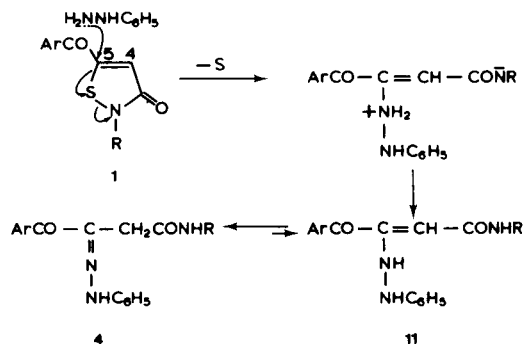
spectrum in DMSO- d_6 showed a vinylic proton at δ 6.10 ppm besides the benzoyl group signals. These spectral data indicated the possibility of a pyrazolinone-pyrazolol tautomerism [4] and structure **7** (in deuteriochloroform) or **8** (in DMSO- d_6) was thus considered as highly probable for the hydrolysis compound.



In agreement with this structure, a phenylhydrazone was easily prepared, while reaction with benzoyl chloride afforded an excellent yield of the benzoyloxy derivative **9**, whose structure is fully supported by spectral data (see Experimental). Finally, a conclusive evidence for the structure of the hydrolysis compound, **7** or **8**, was obtained from an independent synthesis starting with the known [5] acid chloride **10**. A Friedel-Crafts reaction of **10** with benzene resulted in a concomitant cleavage of the methoxy group and the benzoyl compound **7** (or **8**) was isolated in excellent yield. Structure **4** can thus be accepted as securely established.

The evolution of the reaction of the isothiazolones **1** with phenylhydrazine in ethanol is thus shown to depend on concrete reaction conditions. When the reaction of **1a** was carried out at room temperature [2] the thiadiazole derivative **3a** was found (see Experimental) to be the unique product formed, whereas at reflux the two compounds, **3a** and **4a**, were formed in a ratio of about 1:3. On the other hand, compound **3a** was unaffected under the reaction conditions which result in the formation of **4a** and thus compound **3a** is not an intermediate in the transformation of the isothiazolone **1a** to the open chain phenylhydrazone **4a**.

It has already been suggested [6], that the reaction of 5-benzoylisothiazolones with diethyl malonate in methanolic sodium methoxide can be initiated by the addition of the carbanion to the 4-position of the electron deficient 4,5-double bond. The transformation of the isothiazolones **1** to the phenylhydrazone-amides **4** could only be explained by a nucleophilic attack of phenylhydrazine at C-5, followed by ring opening and loss of sulfur. The enehydrazine **11** could not be detected, probably because of a greater stabilization of the phenylhydrazone tautomer **4** [7].



The experimental results obtained thus far do not allow for a thorough explanation of the direction of the reaction of the aroylisothiazolones **1** to either **3** or **4**. Nevertheless, the 5-arylisothiazolone system is thus shown to be a reactive species, whose ring fission through cleavage of the S-N bond can proceed with either preservation or loss of the sulfur atom.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The uv spectra were obtained with a Perkin Elmer 124 spectrophotometer. The ir spectra were obtained with a Perkin Elmer 267 spectrophotometer as nujol mulls and were calibrated against the polystyrene 1601 cm^{-1} band; absorption bands, in reciprocal centimeters, are characterized as of very strong (vs), strong (s), medium (m) or weak (w) intensity and as broad (br) or sharp (sh). The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and are accurate to ± 0.02 ppm. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

3-Phenylhydrazono-3-benzoyl-*N*-benzylpropionamide (**4a**).

A mixture of isothiazolone **1a** [8] (1 g, 3.3 mmoles) and phenylhydrazine (0.4 ml, 4 mmoles) in 20 ml of ethanol was refluxed for 30 minutes - a solution was obtained after 5 minutes of heating. After cooling, compound **4a** crystallized as a yellow product (0.9 g, 71%), mp $148\text{--}150^\circ$ dec. A recrystallization from ethanol gave an analytically pure product, mp $150\text{--}151^\circ$ dec; uv (ethanol): absorption maxima at 264 (ϵ 17900), 285 (shoulder, ϵ 6300), 295 (shoulder, ϵ 4700) and 361 nm (ϵ 23000); ir: bands at 3360 (br, m), 3260 (br, m), 1627 (sh, s), 1605 (sh, m) and 1550 (br, s); pmr (deuteriochloroform): 3.52 (s, 2H, $-\text{CH}_2\text{CO}-$), 4.38 (d, $J = 5.6$ Hz, 2H, $-\text{CH}_2\text{Ph}$), 6.70-7.70 (m, 14H, aromatic protons and $-\text{CONH}-$); the $-\text{CONH}-$ proton appears as a broad signal at 7.00 ppm, while the *N*-benzyl aromatic protons appear as a sharp singlet at 7.26 ppm), 7.86-8.16 (m, almost a dd, 2H, *ortho* protons of the benzoyl group) and 10.76 (br s, 1H, $-\text{NHPh}$); pmr (DMSO- d_6): 3.83 (s, 2H, $-\text{CH}_2\text{CO}-$), 4.30 (d, $J = 5.6$ Hz, 2H, $-\text{CH}_2\text{Ph}$), 6.80-7.66 (m, 13H, aromatic protons; the *N*-benzyl aromatic protons appear as a sharp singlet at 7.30 ppm), 7.70-8.00 (m, almost a dd, 2H, *ortho* protons of the benzoyl group), 8.63 (br t, $J = 5.6$ Hz, 1H, $-\text{CONH}-$) and 10.63 (br s, 1H, $-\text{NHPh}$).

Anal. Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2$: C, 74.37; H, 5.69; N, 11.31. Found: C, 74.32; H, 5.80; N, 11.46.

In a similar reaction as described above, the mixture was refluxed for 30 minutes and was then concentrated under vacuum. The pmr spectrum of the residue in deuteriochloroform revealed the presence of compounds **3a** [2] and **4a** in a ratio of about 1:3, as evidenced from the integration of the vinylic proton singlet of **3a** versus the methylene singlet of **4a**.

A similar mixture of isothiazolone **1a** and phenylhydrazine in ethanol was stirred at room temperature for four days and was then concentrated under vacuum. The residue was shown (pmr in deuteriochloroform) to be a pure sample of the thiadiazole **3a**.

3-Phenylhydrazono-3-(*p*-chlorobenzoyl)-*N*-benzylpropionamide (**4b**).

A mixture of isothiazolone **1b** [2] (2 g, 6 mmoles) and phenylhydrazine (0.7 ml, 7 mmoles) in 25 ml of ethanol was refluxed for 30 minutes - a solution was obtained after 5 minutes of heating and finally a yellow mass was formed. After cooling and filtration, compound **4b** was obtained as a yellow solid (1.7 g, 69%), mp 163-165° dec. A recrystallization from ethanol gave an analytical sample, mp 169-170° dec; uv (ethanol): absorption maxima at 254 (ϵ 21800), 287 (shoulder, ϵ 9600), 296 (shoulder, ϵ 6000) and 365 nm (ϵ 25800); ir: bands at 3320 (sh, m), 3270 (sh, w), 1630 (sh, s), 1620 (sh, s), 1605 (sh, m), 1592 (sh, w) and 1555 (br, s); pmr (deuteriochloroform): 3.80 (s, 2H, -CH₂CO-), 4.43 (d, J = 5.6 Hz, 2H, -CH₂Ph), 7.00-8.13 (m, 15H, aromatic protons and -CONH-; the -CONH- proton appears as a broad signal at 7.10 ppm, the *N*-benzyl aromatic protons appear as a sharp singlet at 7.30 ppm and the *p*-chlorophenyl protons as a doublet, J = 8.5 Hz, at 7.46 and 8.00 ppm) and 10.75 (br s, 1H, -NHPh); pmr (DMSO-*d*₆): 3.85 (s, 2H, -CH₂CO-), 4.35 (d, J = 5.6 Hz, 2H, -CH₂Ph), 6.91-8.10 (m, 14H, aromatic protons; the *N*-benzyl aromatic protons appear as a sharp singlet at 7.36 ppm and the *p*-chlorophenyl protons as a doublet, J = 8.5 Hz, at 7.61 and 7.96 ppm), 8.70 (br t, J = 5.6 Hz, 1H, -CONH-) and 10.83 (br s, 1H, -NHPh).

Anal. Calcd. for C₂₃H₂₀ClN₃O₂: C, 68.06; H, 4.96; Cl, 8.73; N, 10.35. Found: C, 68.16; H, 4.93; Cl, 8.62; N, 10.43.

3-Phenylhydrazono-3-benzoyl-*N*-phenylpropionamide (**4c**).

A mixture of isothiazolone **1c** [8] (0.54 g, 1.9 mmoles) and phenylhydrazine (0.3 ml, 3 mmoles) in 10 ml of ethanol was refluxed for 30 minutes - a solution was obtained after 5 minutes of heating and finally a yellow solid mass was formed. Compound **4c** was obtained, after filtration, as a yellow solid (0.45 g, 66%), mp 185-186° dec. An analytical sample, obtained after recrystallization from ethanol, had the same mp; ir: sharp bands at 3330 (w), 3265 (w), 1665 (s), 1605 (s) and 1555 (s); pmr (DMSO-*d*₆): 3.99 (s, 2H, -CH₂CO-), 6.90-7.81 (m, 13H, aromatic protons), 7.81-8.08 (m, almost a dd, 2H, ortho protons of the benzoyl group), 10.36 (br s, 1H, -CONH-) and 10.76 (br s, 1H, -NHPh).

Anal. Calcd. for C₂₂H₁₆N₃O₂: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.68; H, 5.36; N, 11.49.

1-Phenyl-3-benzoyl-2-pyrazolin-5-one (7).

The *N*-benzylamide **4a** (2 g) was added in 70 ml of 50% sulfuric acid and the mixture was stirred and heated at a steam bath for 20 minutes. The resulting greenish suspension was poured in 200 ml of water containing ice and the precipitate was filtered and thoroughly washed with water to give 1.4 g (98%) of compound **7** as a gray solid, mp >260°. An intense blue colour was developed, when a 4% aqueous solution of ferric chloride was added in an acetone solution of the product. An analytical sample was obtained after crystallization from benzene; ir: sharp bands at 1645 (s), 1600 (m), 1570 (s) and 1510 (m); pmr (deuteriochloroform): 3.55 (s, 2H, ring methylene), 7.25-8.01 (m, 8H, aromatic protons) and 8.12-8.42 (m, almost a dd, 2H, ortho protons of the benzoyl group); pmr (DMSO-*d*₆): 6.10 (s, 1H, vinylic proton of the pyrazolol tautomer **8**), 7.29-7.95 (m, 8H, aromatic protons) and 8.08-8.38 (m, almost a dd, 2H, ortho protons of the benzoyl group).

Anal. Calcd. for C₁₆H₁₂N₂O₂: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.91; H, 4.47; N, 10.47.

The *N*-benzylamide **4a** was also hydrolyzed on heating with either 20% sulfuric acid in methanol or 5% sulfuric acid in ethanol-water, and compound **7** was isolated in 85-90% yields.

A similar hydrolysis reaction of the *N*-phenylamide **4c** with 50% sulfuric acid, as described above, resulted in the isolation of compound **7** in 83% yield.

Friedel-Crafts Reaction with Acid Chloride **10**.

Anhydrous aluminum trichloride (1.61 g, 12 mmoles) was added in a solution of the acid chloride **10** [5] (0.97 g, 4 mmoles) in 15 ml of benzene, which was kept at 20°. The mixture was stirred at room temperature for one hour and was then refluxed for another hour. The resulting greenish mixture was cooled with ice-water and was hydrolyzed by successive additions of 20 ml of cold water and 10 ml of 10% hydrochloric acid. The gray precipitate was filtered and thoroughly washed with water to give 0.9 g (83%) of a solid, mp >260°. This product proved to be identical (ir and pmr spectra) to compound **7**, which has been obtained from the acid hydrolysis of compounds **4a** and **4c**.

Phenylhydrazone of Compound 7.

In a suspension of the pyrazolone **7** (0.3 g, 1.1 mmoles) in 5 ml of ethanol, phenylhydrazine (0.14 ml, 1.4 mmoles) was added and the mixture was stirred at room temperature for two days. The precipitate formed was filtered and washed with ethanol to give 0.28 g (70%) of the phenylhydrazone of compound **7** as a light brown product, mp 214-215°. An analytical sample, obtained after recrystallization from ethanol, had the same mp; ir: sharp bands at 3290 (m), 1700 (vs), 1610 (s), 1580 (w) and 1553 (m); pmr (deuteriochloroform): 4.00 (s, 2H, ring methylene), 6.90-7.95 (m, 15H, aromatic protons) and 8.10 (br s, 1H, -NH-, exchangeable with deuterium oxide).

Anal. Calcd. for C₂₂H₁₆N₄O: C, 74.55; H, 5.12; N, 15.81. Found: C, 74.43; H, 5.15; N, 15.74.

1-Phenyl-3-benzoyl-5-benzoyloxy-pyrazole (9).

In a solution of the pyrazolone **7** (0.5 g, 1.9 mmoles) in 5 ml of pyridine, benzoyl chloride (0.35 ml, 3 mmoles) was added dropwise. The mixture was stirred at room temperature for 1.5 hour and was then heated at 60° for 10 minutes. The reaction mixture was poured in 70 ml of cold water and the precipitate formed was filtered and thoroughly washed with water to give compound **9** (0.6 g, 87%) as a gray solid, mp 118-120°. A recrystallization from ethanol gave an analytically pure product, mp 127-128°; ir: sharp bands at 1766 (vs), 1637 (m), 1600 (w) and 1550 (m); pmr (deuteriochloroform): 7.13 (s, 1H, =C-H), 7.30-7.88 (m, 11H, aromatic protons), 7.97-8.23 (m, almost a dd, 2H, ortho protons of the benzoyl group) and 8.23-8.51 (m, almost a dd, 2H, ortho protons of the benzoyloxy group).

Anal. Calcd. for C₂₃H₁₆N₂O₃: C, 74.99; H, 4.38; N, 7.61. Found: C, 75.08; H, 4.30; N, 7.67.

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- [4] See for example the related tautomerism of 1-phenyl-3-carbethoxy-2-pyrazolin-5-one: G. A. Newman and P. J. S. Pauwels, *Tetrahedron*, **26**, 1571 (1970).
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