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Received May 2, 1980

Reaction of *N*-substituted-3-arylopropionamides with excess thionyl chloride was found to give sulfur-nitrogen heterocyclic compounds, which were characterized as 2-substituted-5-aryloxy-3-(2*H*)isothiazolones.

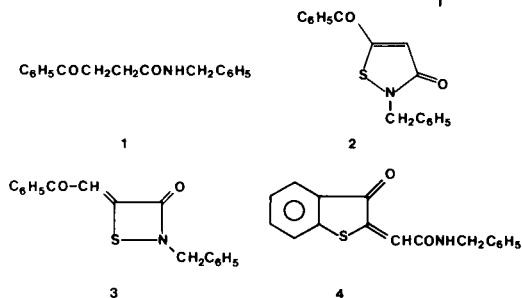
J. Heterocyclic Chem., **17**, 1645 (1980).

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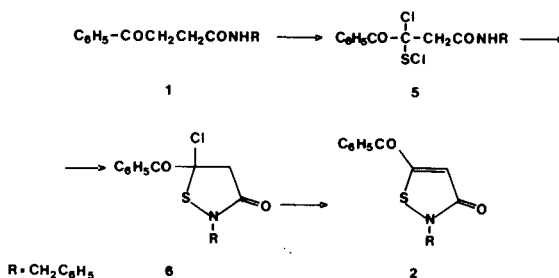
In connection with other work, we encountered an unexpected facile reaction of *N*-substituted-3-arylopropionamides with excess thionyl chloride leading to the formation of heterocyclic compounds. We wish to present evidence herein which establishes the structure of these compounds as 2-substituted-5-aryloxy-3-(2*H*)isothiazolones.

A mixture of *N*-benzyl-3-benzoylpropionamide (**1**) (**2**) and a great excess (20 fold) of thionyl chloride was stirred at room temperature for *ca.* 1 hour, when a dark yellow solution was obtained. The excess thionyl chloride was then removed *in vacuo* and the solid residue was recrystallized from ethanol to give a yellow product, m.p. 129-131°, in 70% yield. The product was assigned the molecular formula $C_{17}H_{13}NO_2S$ on the basis of elemental analysis and ms evidence (molecular peak at 295, relative intensity 14%). Other major peaks at *m/e* 105 ($C_6H_5CO^+$, 10%), 91 ($C_6H_5CH_2^+$, 100%) and 77 ($C_6H_5^+$, 10%) indicated the presence of $C_6H_5CO^-$ and $C_6H_5CH_2^-$ groups. The proton nmr spectrum of the product in deuteriochloroform revealed a multiplet of 10 aromatic protons (δ 7.20-7.95 ppm, with a 2H signal at 7.70-7.95 ppm, characteristic of the *ortho* protons in the benzoyl group), a singlet at 4.97 ppm (2H, could be assigned to a *N*-benzyl amide group, $C_6H_5CH_2-N-CO-$) and one more singlet in the vinyl proton region (6.72 ppm, 1H).

Reduction of the product with Raney nickel in ethanol for 1 hour at room temperature led to the isolation of the starting γ -keto amide **1** and when an excess of Raney nickel in refluxing ethanol for 10 hours was used the corresponding *N*-benzyl-4-phenylbutyramide, m.p. 77-79°, was isolated and characterized. These facts suggest again the presence of the $C_6H_5CO^-$ and $C_6H_5CH_2-N-CO-$ groups.



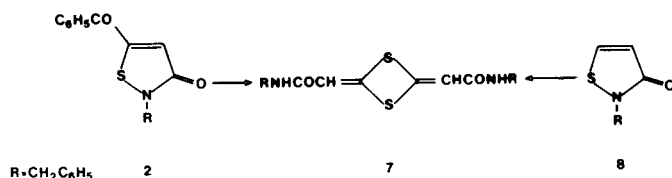
Two heterocyclic structures, **2** and **3**, are consistent with the above spectral and chemical data for compound $C_{17}H_{13}NO_2S$. It should be noted that the uv [in ethanol, absorption maxima at 244 nm (ϵ 8850), 269 nm (ϵ 9750) and 346 nm (ϵ 450)] and ir (in Nujol, a strong and sharp band at 1629 cm^{-1} and a weak band at 1595 cm^{-1}) data could not be clearly related to either structure **2** or structure **3**. The 3-(2*H*)isothiazolone structure **2** is favored on the basis of the abnormal reactions of thionyl chloride with carboxylic acids (**3**) and ketones (**4,5**) reported by Krubsack, *et al.* On the assumption that, in an analogous manner, oxidation of the methylene group adjacent to the carbonyl function of **1** is involved, the sulfonyl chloride **5** would be initially formed. A nucleophilic displacement reaction of the amide nitrogen on the sulfonyl chloride group of **5** would proceed to closure of the heterocyclic ring **6** and elimination of hydrogen chloride would then yield the 3-(2*H*)isothiazolone **2**. An alternative



benzothiophenone structure **4**, which would result through cyclization onto the aromatic ring of **5** (**5**), can be eliminated on the basis of the spectroscopic data of the product.

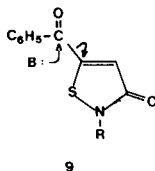
Conclusive evidence for the 3-(2*H*)isothiazolone structure **2** was obtained from its transformation to a known 1,3-dithietane derivative. The compound $C_{17}H_{13}NO_2S$ is fairly stable in acidic media; however, it was found to react easily with a solution of sodium ethoxide in ethanol. The reaction resulted in the isolation of ethyl benzoate and a new product, m.p. 305° (recrystallized from DMF or DMSO), in 65% yield. This was assigned, on the basis of elemental analysis and ms spectrum, the molecular formula $C_{20}H_{18}N_2O_2S_2$. A literature search revealed that the

spectral data (uv, ir, nmr and ms) of the new compound were identical with those reported by Crow, *et al.* (6), for the 2,4-bismethylene-1,3-dithietane derivative **7**, which they obtained by alkaline dimerization of 2-benzyl-3-(2*H*)-



isothiazolone (**8**). Dimerization products of 2-substituted-3-(2*H*)isothiazolones were obtained (6) by treatment with bases such as 5*N* sodium hydroxide, potassium *t*-butoxide/*t*-butyl alcohol and sodium ethoxide/ethanol; these bases were found to bring about the transformation **2** to **7** equally well.

The dimerization mechanism involves, according to Crow, *et al.* (6), attack by the 5-anion of **8** on the S-N bond of a second molecule. Accordingly, the transformation **2** to **7** would proceed, as shown in **9**, through a nucleophilic



displacement of the 5-anion of **8** from the corresponding 5-benzoyl derivative **2**, with simultaneous formation of ethyl benzoate when sodium ethoxide was used as the base.

This simple reaction of the γ -keto amide **1** with excess thionyl chloride was found to be of a rather general nature. Starting with different open chain γ -keto amides of the general formula ArCOCH₂CH₂CONHR, prepared according to standard methods (2,7), the corresponding *N*-substituted-5-aryloxy-3-(2*H*)isothiazolones **10** (Table 1) could be easily isolated in better than 50% yields.

Table 1
2-Substituted-5-aryloxy-3-(2*H*)isothiazolones (a)

Structure **10** is a 2-substituted-5-aryloxy-3-(2*H*)isothiazolone. It consists of a five-membered isothiazolone ring with a carbonyl group at the 3-position, an oxygen atom at the 5-position, and an R group at the 2-position. The 5-position is also substituted with an ArCO group.

Ar	R	M.p. (b)	Nmr in Deuteriochloroform (c) (δ , ppm)
C ₆ H ₅ -	-C ₆ H ₅	143-145°	6.81, s, =C-H
C ₆ H ₅ -	-C ₆ H ₄ Cl- <i>p</i>	189-190°	6.95, s, =C-H
C ₆ H ₅ -	-C ₆ H ₄ -CH ₃ - <i>p</i>	154-156°	2.47, s, -CH ₃ 6.96, s, =C-H
C ₆ H ₅ -	-C ₆ H ₄ -OH- <i>p</i>	213-216°	6.98, s, =C-H (d) 9.71, s, -OH
C ₆ H ₅ -	-C ₆ H ₄ -OCH ₃ - <i>p</i>	145-146°	3.92, s, -OCH ₃ 6.95, s, =C-H
C ₆ H ₅ -	-C ₆ H ₄ -NO ₂ - <i>m</i>	220-222°	7.29, s, =C-H (e)
<i>p</i> -CH ₃ O-C ₆ H ₄ -	-CH ₃	145-146°	3.43, s, -NCH ₃ 3.91, s, -OCH ₃ 6.70, s, =C-H

(a) All compounds gave satisfactory analytical results (C, H, N, S). (b) Recrystallized from methanol or ethanol. (c) Aromatic proton absorptions are not reported. (d) In deuteriochloroform/DMSO-*d*₆. (e) In deuteriochloroform/trifluoroacetic acid.

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