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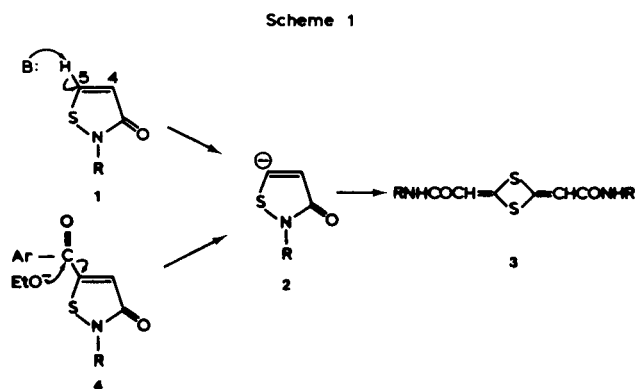
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2-Benzyl-5-mesityl-3(2*H*)-isothiazolone (**8**) has been prepared from 3-mesitylpropionic acid (**5**). Reaction of the isothiazolone **8** with sodium ethoxide in ethanol has been found to yield an isomeric rearranged compound, which was characterized as 2-phenyl-6-mesityl-3,4-dihydro-1,3-thiazin-4(2*H*)-one (**9**). This unexpected rearrangement is attributed to the abstraction of a benzylic hydrogen atom from the *N*-benzyl group, followed by ring enlargement through cleavage of the isothiazolone S-N bond.

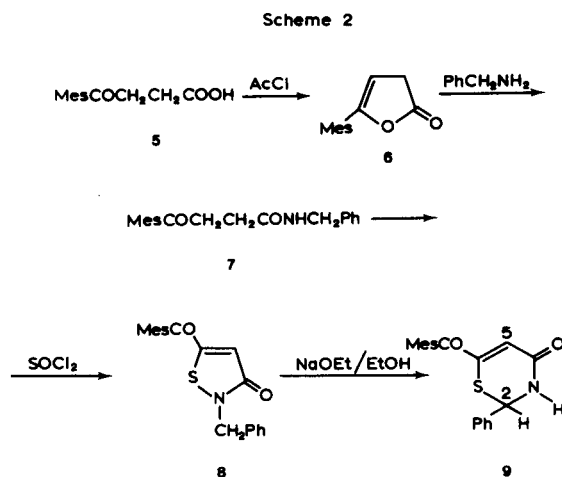
J. Heterocyclic Chem., **22**, 1635 (1985).

N-Substituted-3(2*H*)-isothiazolones bearing a free 5-position, of the general formula **1**, have been found [1] to dimerize readily by bases to 2,4-bismethylene-1,3-dithietanes **3** (Scheme 1). The dimerization was shown to proceed through attack of the initially formed 5-anion **2** on the S-N bond of a second isothiazolone molecule.



Dithietanes of the general formula **3** can also be obtained from *N*-substituted-5-aryloxy-3(2*H*)-isothiazolones **4**. For instance, reaction of the *N*-benzyl-5-benzoylisothiazolone **4** (Ar = -C₆H₅, R = -CH₂C₆H₅) with sodium ethoxide in ethanol has been found [2] to yield the corresponding dithietane **3** (R = -CH₂C₆H₅). In this case, the 5-anion **2** would result from a nucleophilic displacement on the 5-benzoyl group of compound **4**.

According to this mechanism, the transformation of 5-aryloxyisothiazolones **4** to dithietanes **3** would no more be possible, if the aroyl group of **4** is not accessible to nucleophilic attack by the ethoxide ion. Such would be the case with the sterically hindered carbonyl of a mesityl group (**4**, Ar = -C₆H₂Me₃, 2,4,6). An isothiazolone of this type, namely 2-benzyl-5-mesityl-3(2*H*)-isothiazolone (**8**) has been prepared (Scheme 2) and treated with an excess of sodium ethoxide in ethanol. As expected, no dithietane was formed, but, quite unexpectedly, a new compound was isolated, isomeric to the initial isothiazolone **8**, which will be shown to have the structure of a dihydrothiazinone **9**.

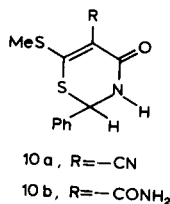


The mesitylisothiazolone **8** was prepared starting with 3-mesitylpropionic acid (**5**). The synthesis sequence reported in Scheme 2 is an application of a general procedure for the preparation of *N*-substituted-5-aryloxy-3(2*H*)-isothiazolones from 3-aryloxypropionic acids.

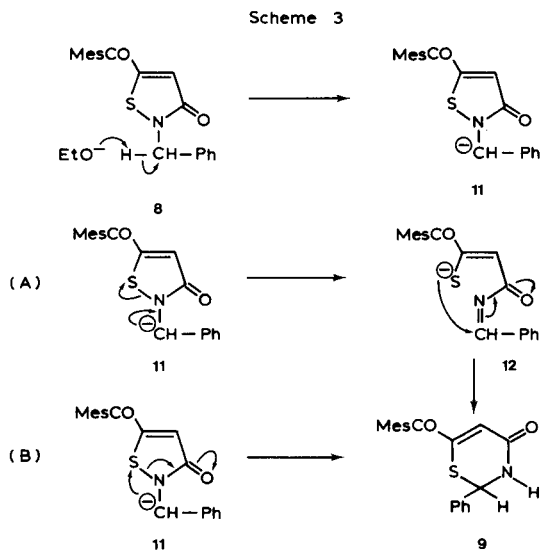
The acid **5** was treated at room temperature with an excess of acetyl chloride, which has been found [3] to be an effective lactonization reagent of 3-aryloxypropionic acids, to give an excellent yield of the mesityl butenolide **6**. It has been reported [4], that refluxing a mixture of the acid **5** with acetyl chloride results in the formation of a "Pechmann dye" and a second compound, which was formulated as the enol acetate of acid **5**. However, even under these conditions, the reaction was found to give again the butenolide **6**. Reaction of the butenolide with benzylamine afforded the corresponding γ -ketoamide **7**, whose open chain structure is supported by spectral data (see Experimental). Finally, the mesitylisothiazolone **8** was obtained from the reaction of the amide **7** with an excess of thionyl chloride at room temperature, a reaction which has been shown [2,5] to be a general method of synthesis of 2-substituted-5-aryloxy-3(2*H*)-isothiazolones from open chain *N*-substituted-3-aryloxypropionamides.

When the isothiazolone **8** was refluxed with an excess of

sodium ethoxide in ethanol, an isomeric compound was isolated, after acidification of the reaction mixture, in 55% yield. Structure **9** was assigned to this new compound on the basis of its pmr spectrum: besides the mesityl and phenyl protons' signals, two low-field one-proton's signals were found to be coupled to an exchangeable N-H proton. In deuteriochloroform solution, a doublet at δ 5.85 ppm, $J = 2$ Hz, was assigned to the C2 benzylic proton, while a doublet at δ 6.34 ppm, $J = 1.2$ Hz, was assigned to the C5 vinylic proton. The coupling between the C5-H and the N-H protons would be a typical case of long range coupling, as encountered in unsaturated systems incorporating a planar W-path [6]. On the other hand, the chemical shift and coupling of the C2 benzylic proton, in DMSO- d_6 δ 6.20 ppm a doublet $J = 4$ Hz, can be compared to the analogous signals reported [7] for the related compounds **10a** and **10b**: in DMSO- d_6 δ 6.30 ppm a doublet $J = 4$ Hz and 6.10 ppm a doublet $J = 4$ Hz, respectively.

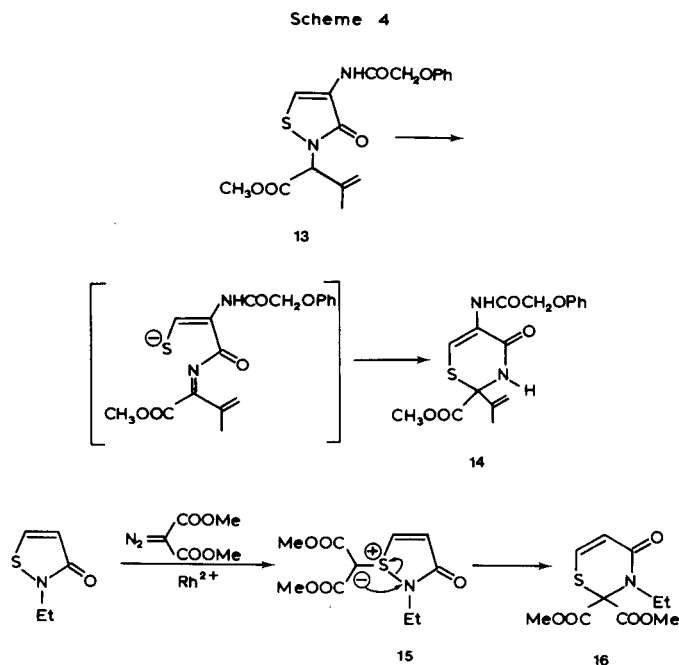


Under the conditions used for the transformation of the mesitylisothiazolone **8** to the dihydrothiazinone **9**, the benzoylisothiazolone **4** (Scheme 1, Ar = -C₆H₅, R = -CH₂-C₆H₅) was found to give the corresponding dithietane **3** (R = -CH₂-C₆H₅) in ~90% yield (see Experimental). Consequently, the possibility of a nucleophilic displacement of the 5-mesityl group in **8** should be excluded, as anticipated, and the ring enlargement of **8** into **9** can only be explained by the abstraction of a benzylic hydrogen atom



from the benzyl group to form the anion **11** (Scheme 3). This anion can then be assumed to give compound **9** either through the acylimine intermediate **12** (route A) or through a 1,2-shift (route B). Both routes involve cleavage of the labile S-N bond [8] of the isothiazolone ring system.

Route A closely follows the explanation, suggested by Morin *et al.* [9], for the analogous rearrangement of the isothiazolone **13** to the dihydrothiazinone **14** (Scheme 4). However, route B cannot be excluded, since the ring expansion of the sulfonium ylide **15** to the dihydrothiazinone **16**, recently reported by Crow *et al.* [10], has been explained by a most likely 1,2-shift mechanism.



Anyhow, the related rearrangements of the isothiazolones **8** and **13** into the dihydrothiazinones **9** and **14**, respectively, clearly show the general character of this ring expansion reaction, provided that a stabilized anion, such as **11**, can be generated prior to the cleavage of the S-N bond of the isothiazolone ring system.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. 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 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).

5-Mesitylfuran-2(3*H*)-one (**6**).

A mixture of 0.5 g of 3-mesitylpropionic acid (**5**) [11] and 10 ml of ace-

tyl chloride was stirred at room temperature for 30 minutes and the solution was then concentrated under vacuum. The colorless oily residue obtained was shown (pmr) to be an almost pure sample of the butenolide **6** and could be used as such for further reactions. The oily residue was dissolved in hexane and crystallized by cooling to give 0.35 g (77%) of compound **6**, mp 43-45°; ir: sharp bands at 1823 (vs), 1795 (s), 1671 (s) and 1620 (m); pmr (deuteriochloroform): 2.31 (s, 9H, mesityl methyls), 3.41 (d, J = 2.4 Hz, 2H, ring methylene), 5.31 (t, J = 2.4 Hz, 1H, vinylic proton) and 6.88 (s, 2H, aromatic protons).

Anal. Calcd. for C₁₃H₁₄O₂: C, 77.20; H, 6.98. Found: C, 77.15; H, 7.16.

N-Benzyl-3-mesitylpropionamide (**7**).

The oily residue of butenolide **6**, obtained from the reaction of 4 g of the acid **5** with acetyl chloride, was dissolved in 15 ml of ether. The ethereal solution was cooled in ice-water, 2 ml of benzylamine were added and the mixture was stirred at room temperature for 30 minutes. After cooling, the precipitated product was filtered to give 4.1 g (73% overall yield from the acid **5**) of compound **7**, mp 70-72°. A recrystallization from ether gave an analytically pure product, mp 72-73°; ir: sharp bands at 3380 (m), 3310 (m), 1705 (s) and 1650 (s); pmr (deuteriochloroform): 2.18 (s, 6H, mesityl *ortho*-methyls), 2.28 (s, 3H, mesityl *para*-methyl), 2.58 and 3.08 (two t, J = 6 Hz, 4H, -CH₂CH₂), 4.41 (d, J = 5.6 Hz, 2H, *N*-benzyl methylene), 6.30 (br t, J = 5.6 Hz, 1H, -NH-), 6.81 (s, 2H, mesityl aromatic protons), and 7.28 (s, 5H, phenyl aromatic protons).

Anal. Calcd. for C₂₀H₂₃NO₂: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.50; H, 7.92; N, 4.60.

2-Benzyl-5-mesityl-3(2*H*)-isothiazolone (**8**).

A mixture of the amide **7** (3.5 g) and thionyl chloride (35 ml) was stirred at room temperature for 24 hours. The dark brown solution was concentrated under vacuum at room temperature and the solid residue was recrystallized from ethanol to give 2.3 g (60%) of a yellow crystalline product, mp 114-116°. A further recrystallization from ethanol gave an analytically pure sample of compound **8**, mp 117.5-118.5°; ir: sharp bands at 1673 (s), 1652 (s), 1615 (m) and 1550 (m); pmr (deuteriochloroform): 2.18 (s, 6H, mesityl *ortho*-methyls), 2.33 (s, 3H, mesityl *para*-methyl), 4.98 (s, 2H, *N*-benzyl methylene), 6.40 (s, 1H, vinylic proton), 6.90 (s, 2H, mesityl aromatic protons) and 7.40 (s, 5H, phenyl aromatic protons).

Anal. Calcd. for C₂₀H₁₉NO₂S: C, 71.19; H, 5.68; N, 4.15; S, 9.50. Found: C, 71.39; H, 5.66; N, 4.13; S, 9.45.

2-Phenyl-6-mesityl-3,4-dihydro-1,3-thiazin-4(2*H*)-one (**9**).

Isothiazolone **8** (1 g, 3 mmoles) was added in a solution of sodium ethoxide in ethanol (prepared from 0.5 g or 0.022 g-atom of sodium in 25 ml of absolute ethanol) and the mixture was refluxed for 30 minutes. The solution was cooled, poured in 10 ml of water and acidified with 10% hydrochloric acid. The resinous material which separated was crystallized from ethanol to give 0.55 g (55%) of a colorless crystalline product, mp 166-167°, which was shown (pmr) to be an almost pure sample of the dihydrothiazinone **9**. A recrystallization from ethanol gave an analytically pure product, mp 173-174°; ir: bands at 3270 (br, m), 1667 (sh, s), 1627

(sh, s) and 1565 (sh, m); pmr (deuteriochloroform): 2.10 (s, 6H, mesityl *ortho*-methyls), 2.29 (s, 3H, mesityl *para*-methyl), 5.85 (d, J = 2 Hz, 1H, C2-H), 6.34 (almost a d, J = 1.2 Hz, 1H, C5-H), 6.70 (br m, 1H, -NH-), 6.80 (s, 2H, mesityl aromatic protons), and 7.23-7.59 (m, 5H, phenyl aromatic protons); the -NH- signal disappears on addition of deuterium oxide and the two doublets become singlets; pmr (deuteriochloroform/DMSO-d₆): 2.06 (s, 6H), 2.28 (s, 3H), 5.85 (d, J = 2.8 Hz, 1H), 6.31 (almost a d, J = 1.2 Hz, 1H), 6.80 (s, 2H), 7.18-7.60 (m, 5H) and 7.88 (br m, 1H); when irradiating the -NH- signal at 7.88 ppm, the two doublets become singlets; pmr (DMSO-d₆): 1.95 (s, 6H), 2.28 (s, 3H), 6.13 (almost a d, J = 1 Hz, 1H, C5-H), 6.20 (d, J = 4 Hz, 1H, C2-H), 6.95 (s, 2H), 7.46 (s, 5H) and 9.02 (apparent br d, J = 4 Hz, 1H, -NH-); when irradiating the -NH-signal at 9.02 ppm, the two doublets become singlets.

Anal. Calcd. for C₂₀H₁₉NO₂S: C, 71.19; H, 5.68; N, 4.15; S, 9.50. Found: C, 71.01; H, 5.65; N, 4.11; S, 9.41.

2,4-Bis(*N*-benzylcarboxamido)methylene-1,3-dithietane (**3**, R = -CH₂-C₆H₅).

Isothiazolone **4**, Ar = -C₆H₅, R = -CH₂C₆H₅ (0.35 g, 1.2 mmoles) was added in a solution of sodium ethoxide in ethanol (prepared from 0.2 g or 0.008 g-atom of sodium in 10 ml of absolute ethanol) and the mixture was refluxed for thirty minutes. The resulting thick suspension was diluted with 20 ml of water and the precipitate was filtered and washed with water and ether, to give 0.2 g (88%) of an almost colorless product, mp > 250°. This was shown (pmr spectrum) to be identical to the dithietane **3**, R = -CH₂C₆H₅ [1].

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