New Aspects of the Chemistry of 5-Thiazolones

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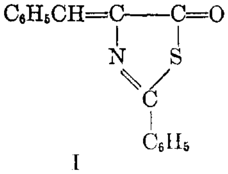
Highly conjugated γ-thiolactones, such as 2-phenyl-4-benzylidene-5(4*H*)-thiazolone (I), have been described previously in connection with structural studies on penicillin.[1b] These compounds are prepared by condensation of aromatic aldehydes with thiohippuric acid[2,3] or by the action of thio acids on 4-benzylidene-5(4*H*)-oxazolones.[4-6] However, little is known about the chemistry of these compounds, other than their behavior under hydrolysis and aminolysis conditions.

It was therefore of interest to study the reactions of such thiazolones under Friedel-Crafts conditions and with organometallic reagents, as we have done in detail for the structurally related 5(4*H*)-oxazolones.[7-10]

When compound I was treated with benzene in the presence of anhydrous aluminum chloride in an atmosphere of dry nitrogen, the only product isolated was 2-phenyl-4-benzhydryl-5-thiazolone (II), in 68% yield. This 1,4-addition of the elements of benzene to the α,β-unsaturated carbonyl system, without attack of the thiolactone ring, closely paralleled the behavior of 2-mercaptothiazolones under these conditions,[11] and differed from the results observed with the oxazolones only in the absence of any benzylidene cleavage product.[7]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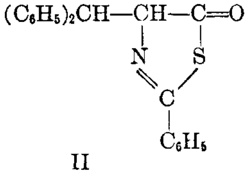
II

The structure of II was established by analytical and spectral data, by hydrolysis and aminolysis, and by independent synthesis.

Compound I exhibited strong carbonyl absorption at 1684 cm.$^{-1}$, typical of unsaturated γ-thiolactones[12,13] and >C=N absorption at 1645 cm.$^{-1}$.[14] This marked difference in the position of carbonyl absorption relative to that observed in the corresponding oxazolones (1780 cm.$^{-1}$) may be due to the greater relative polarizability of sulfur than of oxygen.[15] This point merits further investigation. Compound II possessed an intense band at 1705 cm.$^{-1}$. This shift in carbonyl absorption is consistent with removal of the exocyclic double bond in the 4-position. The >C=N band was unaffected.

Compound II gave 2-thiobenzamido-3,3-diphenylpropionanilide on treatment with aniline and the corresponding acid with alkali. This acid was converted to 3,3-diphenylalanine hydrobromide[16] by hydrolytic cleavage with hydrobromic acid and acetic acid.

Final confirmation of the structure of II was accomplished by its preparation from 2-phenyl-4-benzhydryl-5-oxazolone[16] and thioacetic acid.

Compound I reacted with excess phenylmagnesium bromide to give II in 70% yield. No tertiary alcohol (or the corresponding thiazoline), which would have formed by 1,2-addition, could be detected. This result is in direct contrast to the behavior of the analogous oxazolones under the same conditions.[8] However, with phenyllithium, I gave 2,5,5-triphenyl-4-benzylidene-2-thiazoline and an oil, whose infrared spectrum indicated the probable presence of 1,1-diphenyl-2-thiobenzamidocinnamyl alcohol.[17]

The geometric isomer of I was prepared by reaction of the labile isomer of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone[9] with thioacetic acid or alternatively, by isomerization of I in saturated hydrobromic acid.[9,18] This isomer was isomerized to I by pyridine.

Experimental[19]

2-Phenyl-4-benzylidene-5(4*H*)-oxazolone.—The azlactone was obtained in 90-97% yield by a previously described method.[20]

Preparation of Compound I.—In a 500-ml. round-bottomed flask, fitted with a condenser, 25 g. of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone, 20 g. of thioacetic acid, and 1 ml. of triethylamine were mixed and heated on a steam bath for 18 hr. The flask was cooled and the contents

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[1a] Abstracted from the Ph.D. thesis of Y. S. Rao to be submitted to the Graduate School, Illinois Institute of Technology.

[1b] "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, ed., Princeton University Press, Princeton, New Jersey, 1949, pp. 773, 848.

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(11) A. Mustafa and M. M. M. Sallam, *ibid.*, **26**, 1782 (1961), and references therein.

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(17) The corresponding oxazolone is also converted to the tertiary alcohol and the oxazoline with phenyllithium; unpublished results.

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(19) All melting points were determined on a Fisher-Johns block and are uncorrected.

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triturated with absolute ethanol and filtered. The crude thiazolone was crystallized from a mixture of absolute ethanol and benzene to give 15.4 g. (58% yield) of I, m.p. 130°, lit.,[3-5] 129.5–130°, 132–133°.[6]

Reaction of I with Benzene under Friedel–Crafts Conditions.—In a 500-ml. round-bottomed flask, fitted with a mechanical stirrer, dropping funnel, and reflux condenser, was placed 6.4 g. (0.048 mole) of anhydrous aluminum chloride in 65 ml. of dry thiophene-free benzene. The mixture was cooled to 10° and stirred for 1 hr. in a nitrogen atmosphere. To this solution was added 3.18 g. (0.012 mole) of 2-phenyl-4-benzylidene-5(4*H*)-thiazolone (I) in 60 ml. of dry benzene and the temperature maintained at 10–20° during the addition. The mixture turned deep red. When all of the thiazolone had been added, the mixture was stirred for an additional 3 hr. at room temperature. The complex was decomposed with 125 ml. of dilute (1:15) hydrochloric acid to form two clear layers. The benzene layer was separated, the aqueous layer extracted with benzene and the combined benzene layers washed with dilute hydrochloric acid and then with water until neutral to litmus. Benzene was removed under reduced pressure to give an oil which was triturated with absolute ethanol. The product was crystallized from an ethanol–benzene mixture to give 3.02 g. of pale yellow crystals (II), m.p. 109–110°.

Anal. Calcd. for $C_{22}H_{17}NOS$: C, 73.96; H, 4.95. Found: C, 73.91; H, 5.06.

Reaction of I with Phenylmagnesium Bromide.—To 0.45 g. (0.019 g.-atom) of magnesium turnings in 30 ml. of anhydrous ether in a nitrogen atmosphere was added dropwise 2 ml. of bromobenzene (.019 mole) dissolved in 25 ml. of ether. After the reaction had subsided, the mixture was heated under reflux for 0.5 hr. I (1.59 g.) suspended in 65 ml. of ether was added over a 1-hr. period. The mixture was heated under reflux for an additional 2 hr. and then decomposed with a saturated solution of ammonium chloride. The ether layer was removed, repeatedly washed with water, and dried over anhydrous magnesium sulfate. Ether was removed by evaporation on a water bath. The residual oil was triturated with absolute ethanol when a pale yellow solid separated. It was recrystallized from an ethanol–benzene mixture to give 3.3 g. (70% yield) of a pale yellow solid, m.p. 109°, mixture m.p., no depression.

2-Phenyl-4-benzhydryl-5-thiazolone (II).—A mixture of 2.5 g. of 2-phenyl-4-benzhydryl-5-oxazolone, 2 g. of thioacetic acid, and 1 drop of triethylamine was heated at 100° for 18 hr. After cooling, the residue was triturated with absolute ethanol, filtered, and crystallized from an ethanol-benzene mixture to give 1.5 g. of compound II. The melting point and infrared spectrum of this material were identical with those of compound II described previously.

Reaction of II with Aniline.—2-Phenyl-4-benzhydryl-5-thiazolone (0.69 g.), 0.28 ml. of aniline and a crystal of aniline hydrochloride were heated under reflux for 3 hr. in 20 ml. of dry benzene. The mixture was cooled and the anilide which separated was crystallized from absolute ethanol, m.p. 244°.

Anal. Calcd. for $C_{28}H_{24}N_2OS$: C, 74.33; H, 5.30. Found: C, 74.22; H, 5.47.

Alkaline Hydrolysis of II.—Two grams of thiazolone was heated under reflux in 100 ml. of 2 *N* ethanolic sodium hydroxide for 12 hr. The mixture was cooled and acidified with dilute hydrochloric acid. 2-Thiobenzamido-3,3-diphenylpropionic acid separated and was crystallized from benzene, m.p. 186°.

Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 73.13; H, 5.26. Found: C, 73.20; H, 5.16.

Acid Hydrolysis.—2-Thiobenzamido-3,3-diphenylpropionic acid (0.5 g.) was heated under reflux with 15 ml. of a 2:1 mixture of acetic acid and 48% hydrobromic acid. Excess acid was distilled and the residue dissolved in water and extracted with ether. The aqueous layer was concentrated to give 3,3-diphenylalanine hydrobromide, m.p. 204°.[16]

Reaction of I with Phenyllithium.—To 0.27 g. (0.0375 g.-atom) of lithium, suspended in 50 ml. of dry ether was added several milliliters of a solution of 2 ml. (0.019 mole) of bromobenzene in 10 ml. of ether.

The mixture was heated under reflux until reaction began and then the remainder of the bromobenzene solution was added at intervals so as to ensure gentle reflux. I (1.59 g.), in 60 ml. of ether, was added in portions during a 15-min. period and the mixture was heated under reflux for 0.5 hr. The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride, the ether layer was separated and dried over anhydrous magnesium sulfate. Evaporation of ether on a water bath gave an oil which was triturated with absolute ethanol to give 0.5 g. of a deep yellow compound melting at 183°.

Anal. Calcd. for $C_{23}H_{21}NS$: C, 83.37; H, 5.23. Found: C, 82.90; H, 5.31.

The infrared spectrum of this compound exhibited a band at 1610 cm.$^{-1}$ (>C=N in thiazolines[21,22]) but no absorption in the carbonyl region. The spectrum of the mother liquor showed absorption at 3570–3350 cm.$^{-1}$ (s): (—OH and —NH stretching); 1485 cm.$^{-1}$ (m) and 1450 cm.$^{-1}$ (s): $(-\mathrm{NH}-\overset{|}{\mathrm{C}}=\mathrm{S})$.[22]

Geometric Isomer of I. Method A.—To 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (m.p. 149°, 5 g.), 4 g. of thioacetic acid was added and the mixture heated at 100° for 18 hr. The residue was treated with absolute ethanol, filtered, and crystallized from a mixture of absolute ethanol and benzene, m.p. 139°. The melting point was depressed when mixed with I.

Method B.—I (1 g.) was suspended in 20 ml. of 48% hydrobromic acid and cooled in an ice bath. The suspension was saturated for 45 min. with anhydrous hydrogen bromide. The mixture was left overnight in a refrigerator, poured onto ice, filtered, and washed repeatedly until free of acid. The product was crystallized from a mixture of ethanol–benzene, m.p. 139°, mixture m.p., no depression.

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.45; H, 4.15. Found: C, 72.50; H, 4.19.

Isomerization to I.—The isomer of I, m.p. 139° (0.5 g.) was heated with a mixture of 5 ml. of ethanol and 2 drops of pyridine for 5 min. The mixture was poured into water and filtered. The solid was crystallized from an ethanol-benzene mixture, m.p. 130°; mixture m.p. with I showed no depression.

Spectral Measurements and Analyses.—Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer using chloroform as solvent. Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Illinois.

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Reductions with Quaternary Ammonium Borohydrides

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The ability of borohydrides to reduce certain organic functional groups is well documented in