

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS.]

THE REACTIONS OF THE FORMAMIDINES. VIII. SOME THIAZOLIDONE DERIVATIVES.

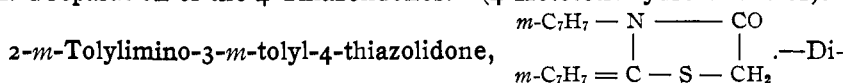
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In a previous paper¹ some preliminary experiments showed that the complex $-\text{CO}-\text{CH}_2-\text{S}$ in the 4-thiazolidones exhibited the general properties of an acid methylene grouping and combined with the formamidines yielding derivatives in which the methylene hydrogen was replaced by the aminomethylene complex, $>\text{CH}_2 + \text{RN}-\text{CHNHR} = >\text{C}=\text{CHNHR} + \text{RNH}_2$.

The experimental results which follow continue this investigation and describe the preparation of various 4-thiazolidones and show in somewhat greater detail that they are all characterized by the same reactivity of the methylene hydrogen toward benzaldehyde and the substituted formamidines.

I. Preparation of the 4-Thiazolidones. (4-Ketotetrahydro-thiazoles).



m-tolyl-thiourea (75 g.), chloro-acetic acid (30 g.) and alcohol (200 cc.) were boiled for several hours under a reflux condenser. Three compounds were obtained: *m*-toluidine hydrochloride, a small amount of 2-*m*-tollylimino-3-*m*-tolyl-4-thiazolidone and the diketo derivative, 3-*m*-tolyl-thiazoledione (m. p. 90°). This, which was the main product,² was formed by the hydrolysis in the acid solution of the 2-*m*-tolyl-imino compound. The same type of hydrolysis occurred to a large extent in other cases where the free chloro-acetic acid was used.

Good yields of the pure thiazolidones varying from 60 to 80% were obtained, however, by the addition of enough pyridine to combine with the free acid. The general procedure was to heat the substituted thio-urea in alcoholic solution for an hour with ethyl chloro-acetate and pyridine (one mol) or chloro-acetic acid and pyridine (2 mols). Under these conditions either none of the diketo-thiazole was obtained or the amount was very small.

2-*m*-Tolly-imino-3-*m*-tolyl-4-thiazolidone was moderately soluble in organic solvents and crystallized from alcohol in yellow prisms, which melted at 154-5°.

Calc. for $\text{C}_{17}\text{H}_{16}\text{ON}_2\text{S}$: N, 9.46. Found: 9.20, 9.54.

2-*p*-Tolly-imino-3-*p*-tolyl-4-thiazolidone crystallized from alcohol in

¹ Dains and Stevenson, *THIS JOURNAL*, **38**, 1841 (1916).

² Beckurts and Frerichs, *Arch. Pharm.*, **253**, 238 (1915).

flat, pale yellow prisms, which melted at 127°. ¹ This has previously been prepared from bromo-acetic acid and the thiourea, but the melting point given was 115°.

Calc. for C₁₇H₁₆ON₂S: N, 9.46. Found: 9.40.

Hydrochloride.—When the di-*p*-tolyl-4-thiazolidone was dissolved in benzene and dry hydrogen chloride passed into the solution, a gummy precipitate was formed, which, on standing, became crystalline. It then melted at 195–205° with decomposition.

Calc. for C₁₇H₁₆ON₂S.HCl: HCl, 10.97. Found: 11.45, 11.51.

The hydrochloride was readily hydrolyzed, when heated with *N* potassium hydroxide solution, with the formation of di-*p*-tolyl-urea (m. p. 264°).

Calc. for C₁₆H₁₆ON₂: N, 11.66. Found: 11.70, 11.80.

3-*p*-Tolyl-2,4-thiazolidone, which has been prepared by other methods, ² can be readily made by hydrolyzing the di-tolyl derivative in alcoholic hydrogen chloride solution. It is also the main product isolated in the synthesis of the di-*p*-tolyl-thiazolidone with chloro-acetic acid without the addition of pyridine. It crystallized from hot water in fine needles which melted at 162°.

Calc. for C₁₀H₉O₂NS: N, 6.76. Found: 6.68, 6.90.

2-*p*-Bromo-phenyl-imino-3-*p*-bromophenyl-4-thiazolidone.—Fry's method ³ gave good results in the preparation of the needed di-*p*-bromodiphenyl-thiourea, which was also obtained in a 57.5% yield on boiling the ammonium salt of *p*-bromo-phenyl-dithiocarbamate (BrC₆H₄NHCSS-NH₄) with water. The gray powder which was deposited crystallized from alcohol in long, white needles, which melted at 188°. The melting point for the thiourea recorded in Richter is 180°.

Calc. for C₁₃H₁₀N₂Br₂S: N, 7.26. Found: 7.57.

The thiazolidone which melted at 183° was easily soluble in alcohol, more so in chloroform or carbon tetrachloride.

Calc. for C₁₅H₁₀ON₂Br₂S: N, 6.57. Found: 6.20.

2-*p*-Chloro-phenyl-imino-3-*p*-chlorophenyl-4-thiazolidone.—This was obtained in the usual manner from the thiourea. ⁴ It crystallized from alcohol in pale yellow crystals, which melted at 165°.

Calc. for C₁₅H₁₀ON₂Cl₂S: N, 8.32. Found: 8.48, 8.25.

Synthesis of 4-Thiazolidones from Mixed Thioureas.

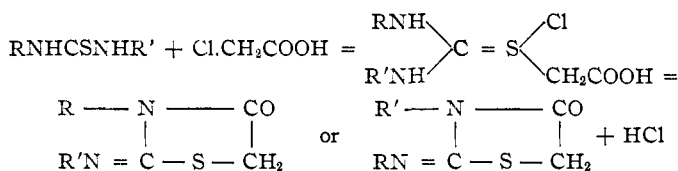
When a thiourea of the type RNHCSNHR' is heated with chloro-acetic acid, it is evident that 2 isomeric products may result.

¹ Pozzi-Escot, *Compt. rend.*, **139**, 1032 (1904).

² *Ber.*, **13**, 1579 (1880); **21**, 976 (1888).

³ Fry, *THIS JOURNAL*, **35**, 1539 (1913).

⁴ A 50% yield of the di-*p*-chloro-diphenyl-thiourea was obtained by simply boiling a water solution of the ammonium-*p*-chlorophenyl-dithiocarbamate.



That there seems to be a selective action is shown¹ by the fact that thus far only one of the possible isomers has been isolated. The conditions which control the choice are under investigation and it is hoped that enough definite experimental evidence can be obtained to throw light upon the reaction.

2-Phenylimino-3-*p*-bromophenyl-4-thiazolidone.—Crystallized from alcohol in thick, colorless prisms, which contained bromine and melted at 175–6°.

Calc. for C₁₈H₁₁ON₂BrS: N, 8.07. Found: 8.02, 8.28.

3-*p*-Bromophenyl-2,4-thiazolidone.—When the 2-phenylimino-3-*p*-bromophenyl-4-thiazolidone was hydrolyzed with hydrochloric acid, aniline and the diketo compound were obtained, thus proving the structure of the original compound. The white needles deposited from alcohol or hot water melted at 130°. The same thiazolidone together with *p*-bromo-aniline was formed by the hydrolysis of the 2-*p*-bromophenylimino-3-*p*-bromophenyl-4-thiazolidone.

Calc. for C₉H₆O₂NBrS: N, 5.15. Found: 5.12.

2-Phenylimino-3-*m*-bromophenyl-4-thiazolidone was readily soluble in alcohol and melted at 171°.

Calc. for C₁₈H₁₁ON₂BrS: N, 8.07. Found: 7.83, 8.08.

2-Phenylimino-3-*p*-chlorophenyl-4-thiazolidone was prepared in the usual manner from the thiourea, chloro-acetic acid, pyridine and alcohol. It was necessary to heat the mixture for a number of hours to bring about the reaction. The yield of purified material was only 21%. This was due partially to its further hydrolysis since there was also isolated di-*p*-chloro-diphenylurea.

Calc.: N, 9.97. Found: 9.80.

The thiazolidone crystallized from alcohol in which it was difficultly soluble in thick, colorless prisms, which melted at 184–5°.

Calc. for C₁₈H₁₁ON₂ClS: N, 9.26. Found: 9.36, 9.44.

3-*p*-Chlorophenyl-2,4-thiazolidone.—The structure of the original thiazolidone was shown by the fact that when hydrolyzed it gave aniline and a diketo compound with the *p*-chlorophenyl group in the 3 position, which crystallized from alcohol in colorless needles and melted at 136–7°.²

¹ Dains, THIS JOURNAL, 28, 1183 (1906); Dains, Roberts, Brewster, *ibid.*, 38, 137 (1916).

² Beckurts and Frerichs, *Arch. Pharm.*, 253, 244 (1915), obtained this from the 2-imino-3-chlorophenyl-4-thiazolidone and record a melting point of 145°.

The same product was formed when the di-*p*-chlorophenyl-thiazolidone was hydrolyzed with alcoholic hydrochloric acid.

Calc. for $C_9H_8O_2NCIS$: N, 6.21. Found: 6.58.

2-*m*-Nitrophenyl-imino-3-phenyl-4-thiazolidone.—When the mono-*m*-nitro-diphenyl-thiourea¹ was treated with chloro-acetic acid or ethyl chloro-acetate under various conditions, it formed a gummy non-crystalline mass, which could not be purified sufficiently for analysis. That it consisted essentially of this thiazolidone was shown by its reactions. Thus, when heated with benzaldehyde a benzal derivative was formed and it gave on hydrolysis *m*-nitro-aniline and 3-phenyl-2,4-thiazoledione which melted at 148°.

Calc. for $C_9H_7O_2NS$: N, 7.26. Found: 7.21.

It is of interest to note that in this instance the substituted phenyl group is at position 2 and not at position 3, as in the case of the mono-chloro- or bromo-diphenyl-thiazolidones.

5-Benzal Derivatives of the Substituted Thiazolidones.

2-*m*-Tolylimino-3-*m*-tolyl-5-benzal-4-thiazolidone.—It has been shown in numerous instances that the methylene group of the 4-thiazolidones condensed with aldehydes in solution in the presence of piperidine, sodium ethylate, sulfuric acid, etc.² Experiment showed, however, that the use of a solvent or condensing agent was unnecessary. Thus, when the *m*-tolyl derivative was heated with benzaldehyde at 150° for 5 hours an 83% yield of the benzal compound was obtained. It was almost insoluble in hot alcohol and was best purified by solution in hot chloroform and cautious precipitation with alcohol. The pale yellow microscopic needles melted at 175–7°.

Calc. for $C_{24}H_{20}ON_2S$: N, 7.29. Found: 7.11, 7.16.

The following compounds were prepared in order to further characterize the new thiazolidones and to show the applicability of this method of synthesis.

2-*p*-Tolylimino-3-*p*-tolyl-5-benzal-4-thiazolidone formed yellow needles from alcohol which melted at 197° and which were readily soluble in carbon tetrachloride, chloroform and glacial acetic acid.

Calc. for $C_{24}H_{20}ON_2S$: N, 7.29. Found: 7.50, 7.61.

When the benzal derivative was boiled in alcoholic potassium hydroxide solution it gave di-*p*-tolyl urea and a small amount of a compound which melted at 208° and proved to be the 3-*p*-tolyl-5-benzal-2,4-thiazoledione. This was difficultly soluble in alcohol, from which it crystallized in short white needles, which melted at 210°.

Calc. for $C_{17}H_{13}O_2NS$: N, 4.75. Found: 4.60, 4.54.

¹ This melted at 160°. Richter gives 155°.

² Andreasch, *Monatsh.*, **24**, 516 (1903); **38**, 121 (1917); Kucera, *ibid.*, **35**, 144 (1914); Wheeler and Jamieson, *THIS JOURNAL*, **25**, 367 (1903).

The corresponding derivative, 3-*p*-tolyl-5-*m*-nitro-benzal-2-4-thiazolidone was almost insoluble in alcohol; the brownish-yellow crystals from chloroform melted at 230°.

Calc. for C₁₇H₁₂O₄N₂S: N, 8.24. Found: 8.45, 8.50.

2-*p*-Bromophenyl-imino-3-*p*-bromophenyl-5-benzal-4-thiazolidone formed light yellow crystals, which melted at 220°. It was very difficultly soluble in alcohol, but readily so in chloroform and glacial acetic acid.

Calc. for C₂₂H₁₄ON₂Br₂S: N, 5.45. Found: 5.50, 5.57.

2-*p*-Chlorophenyl-imino-3-chlorophenyl-5-benzal-4-thiazolidone crystallized from alcohol in greenish-yellow needles which melted at 213°.

Calc. for C₂₂H₁₄ON₂Cl₂S: N, 6.59. Found: 6.49, 6.60.

2-Phenylimino-3-*p*-bromophenyl-5-benzal-4-thiazolidone formed light yellow plates with a melting point of 197-9°.

Calc. for C₂₂H₁₄ON₂BrS: N, 6.44. Found: 6.43, 6.14.

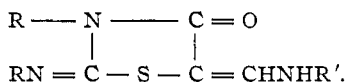
2-Phenylimino-3-*m*-bromophenyl-5-benzal-4-thiazolidone was almost insoluble in alcohol and sparingly so in glacial acetic acid. The pale yellow needles melted at 200-1°.

Calc. for C₂₂H₁₄ON₂ClS: N, 7.16. Found: 7.30.

2-*m*-Nitrophenyl-imino-3-phenyl-5-benzal-4-thiazolidone was a yellow crystalline compound which melted at 193°.

Calc. for C₂₂H₁₄O₃N₃S: N, 10.48. Found: 10.69.

II. Condensation Reactions with the Substituted Formamidines; Synthesis of Derivatives of the General Type,



These compounds were formed by simply heating the components in an oil-bath. In general the yields were from 50-60%; too prolonged heating gave rise to tarry decomposition products which lowered the yield and rendered more difficult the purification of the products.

2-*p*-Tolylimino-3-*p*-tolyl-5-anilino-methylene-4-thiazolidone. — A molar mixture of the thiazolidone and diphenyl formamidine was heated for 3 hours between 140° and 160°. From this melt were separated aniline and the new compound which crystallized from alcohol in bright yellow needles which melted at 168°. It was fairly soluble in alcohol and readily so in chloroform, carbon tetrachloride and in acetic acid. When boiled with alcoholic potassium hydroxide it gave di-*p*-tolylurea.

Calc. for C₂₄H₂₁ON₂S: N, 10.53. Found: 10.74, 10.90.

2-*p*-Tolylimino-3-*p*-tolyl-5-β-naphthyl-aminomethylene-4-thiazolidone and β-naphthylamine are the resulting products when di-β-naphthyl-

formamidine and the thiazole were heated for one hour between 200° and 230°. The new thiazolidone formed yellow crystals which melted at 215°.

Calc. for $C_{28}H_{23}ON_3S$: N, 9.36. Found: 9.45, 9.52.

3-*m*-Tolyl-5-anilino-methylene-2,4-thiazolidone.—When diphenyl-formamidine and the di-*m*-tolyl-thiazolidone were heated under various conditions a yellow product melting between 130° and 165° was obtained, but not in sufficient purity for analysis. When this was boiled with an alcoholic solution of potassium hydroxide, *m*-toluidine and the diketo compound were obtained. This formed colorless needles from alcohol and melted at 211°.

Calc. for $C_{17}H_{14}O_2N_2S$: N, 9.04. Found: 9.28, 8.88.

That the substitution of halogen in the phenyl groups does not effect the ease of condensation with the formamidines is shown by the following instances.

2-*p*-Bromophenyl-imino-3-*p*-bromophenyl-5- β -naphthylamino-methylene-4-thiazolidone.—This crystallized from a mixture of alcohol and chloroform in fine yellow needles which melted at 190°.

Calc. for $C_{26}H_{17}ON_3Br_2S$: N, 7.26. Found: 7.35, 7.40.

2-*p*-Chlorophenyl-imino-3-*p*-chlorophenyl-5- β -naphthylamino-methylene-4-thiazolidone.—This formed greenish-yellow crystals from alcohol which melted at 204°. It was readily soluble in chloroform, carbon tetrachloride and in glacial acetic acid.

Calc. for $C_{26}H_{17}ON_3Cl_2S$: N, 8.58. Found: 8.50, 8.70.

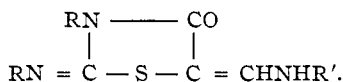
2-Phenylimino-3-*p*-chlorophenyl-5-anilino-methylene-4-thiazolidone is easily soluble in alcohol, from which it crystallized in yellow needles, with a melting point of 180°.

Calc. for $C_{22}H_{16}ON_4Cl$: N, 10.36. Found: 10.64.

Summary.

A number of new disubstituted 4-thiazolidones and their benzal derivatives have been prepared, containing either the same or different groups at Positions 2 and 3.

The methylene group in these 4-thiazolidones has been found to react with the substituted formamidines giving derivatives of the type



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