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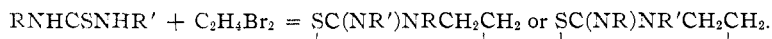
THE SUBSTITUTED THIO-UREAS. III. THE SYNTHESIS OF THIAZOLIDINE AND THIAZANE DERIVATIVES

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Thiazolidines of the type, $\text{SC}(\text{NR})\text{NRCH}_2\text{CH}_2$, have been prepared

by Will and others¹ by the action of ethylene bromide upon the di-substituted thio-ureas. They synthesized various derivatives, such as the di-phenyl, di-tolyl, di-naphthyl, etc., where only one thiazole was possible. When, however, the two groups of the α , β -di-substituted thio-urea were unlike, it was evident that two different thiazolidines might be formed.



Such a mixture was actually obtained by Foerster² on heating phenyl- α -naphthyl-thio-urea with ethylene dibromide. He succeeded in separating the two possible isomers, despite the difficulties in the way of their isolation and identification. If in the place of the simple ethylene dibromide, α , β -dibromo-propane is allowed to react with such thio-ureas, two additional isomeric thiazoles are possible, with the methyl group at Position 4 or 5.

The general investigation of which the present paper is a part, is the study of the action of alkylene bromides upon the thio-ureas, $\text{RNHCSNHR}'$, where the groups R,R' may be the same or different. The end in view was to ascertain what influence the nature of the groups in the thio-urea or the alkylene bromide would have upon the constitution of the resulting thiazole.

In solving this problem, it seemed advisable first to develop methods by which thiazolidines of known structure could be synthesized, since this would be of essential aid in the identification of the products that might be obtained by the action of the dibromides upon various thio-ureas. The paper which follows is devoted to this preliminary work.

Thiazolidines from α -Allyl- α , β -di-aryl Thio-ureas

It has been long known that allyl-thio-urea rearranged under the influence of acid reagents to a 5-methyl-thiazolidine, $\text{SC}(\text{NH})\text{NHCH}_2\text{CHCH}_3$,

¹ Will and others, (a) *Ber.*, **14**, 1490 (1881); (b) **15**, 1314 (1882); (c) **21**, 1864 (1888); **23**, 2195 (1890).

² Foerster, (a) *Ber.*, **21**, 1864 (1888); (b) *Monatsh.*, **35**, 157 (1914).

³ *Ber.*, **22**, 1146, 2988 (1889).

from which by the action of methyl iodide a 3-methylimino derivative could be obtained.³

On the other hand, α -allyl- β -phenyl-thio-urea gave a thiazole, which seemed to have the constitution, $\text{SC}(\text{NHPh})\text{NCH}_2\text{CHCH}_3$, since the

action of alkylating agents yielded only a secondary amine grouping, NRPh, at Position 2.⁴ The results would indicate that the 2,3-di-substituted thiazolidines could not be made by direct substitution of the simple thiazole. Our efforts to introduce a second phenyl group by boiling the 2-phenyl-thiazole in nitrobenzene solution with phenyl bromide and copper powder were fruitless.

The 2,3-di-substituted thiazolidines were prepared, however, by the addition of mustard oil to the aryl allylamines and the subsequent rearrangement of the thio-urea.



Allyl Aniline.—This was made from sodium formanilide and allyl bromide or iodide.⁵ While pure allylaniline could be distilled unchanged in a vacuum, at ordinary pressures it suffered some decomposition and the distillate always gave a test for aniline. The pure amine was heated in a sealed tube for 8 hours at 250°, to determine whether any rearrangement would occur, but the only products obtained were unsaturated gaseous hydrocarbons, aniline, allylaniline and a large amount of non-basic tarry material.

SALTS.—The hydrochloride formed white deliquescent crystals, which melted at 110°.

Analysis. Calc. for $\text{C}_{10}\text{H}_{11}\text{N}$. HCl: HCl, 21.77. Found: 21.39.

The acid oxalate melted at 120°.

***p*-Bromophenyl-allylamine.**—While the sodium salt of *p*-bromo-formanilide could be easily made, it gave with allyl bromide only decomposition products and no trace of the expected amine.

Thio-ureas.—Allylaniline and allyl-*p*-toluidine formed with the phenyl-, *p*-bromophenyl- and *p*-tolylisothiocyanate the corresponding thio-ureas. These were white solids easily soluble in the ordinary organic solvents.

Thiazolidines.—By the action of acetyl chloride, or on heating with conc. hydrochloric acid, the thio-ureas were converted into the acid-soluble 5-methyl-thiazoles.

Derivatives of α -allyl- α , β -diaryl thio-urea		M. p. ° C.	Nitrogen	
			Calc.	Found
α, β -Diphenyl-, ^a $\text{C}_{16}\text{H}_{16}\text{N}_2\text{S}$	(1)	91		
α -Phenyl- β - <i>p</i> -bromo-phenyl-, $\text{C}_{16}\text{H}_{15}\text{N}_2\text{SBr}$	(2)	123	8.07	8.25
α -Phenyl- β - <i>p</i> -tolyl-, $\text{C}_{17}\text{H}_{18}\text{N}_2\text{S}$	(3)	107	9.93	9.85
α - <i>p</i> -Tolyl- β -phenyl-, $\text{C}_{17}\text{H}_{18}\text{N}_2\text{S}$	(4)	91.5	9.93	9.81
α - <i>p</i> -Tolyl- β - <i>p</i> -bromo-phenyl-, $\text{C}_{17}\text{H}_{17}\text{N}_2\text{SBr}$	(5)	121	7.75	7.64
α, β -Di- <i>p</i> -tolyl-, $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}$	(6)	113	9.46	9.26

⁴ Ref. 3, p. 2997; *Ber.*, **24**, 267 (1891); *J. Chem. Soc.*, **89**, 59 (1906).

⁵ *Ber.*, **36**, 3791 (1903).

Derivatives of 2-arylimino 3-aryl-5 methyl-thiazolidine					
2,3-Diphenyl-, C ₁₆ H ₁₆ N ₂ S ^b	(1')	98	10.44	10.19	Picrate, m. p. 168-9°
2- <i>p</i> -Bromophenyl-3-phenyl-, C ₁₆ H ₁₅ N ₂ SBr	(2')	106	8.07	8.23	
2- <i>p</i> -Tolyl-3-phenyl-, C ₁₇ H ₁₅ N ₂ S	(3')	oil	44.82	44.80°	Picrate, m. p. 188°
2-Phenyl-3- <i>p</i> -tolyl-, C ₁₇ H ₁₆ N ₂ S	(4')	72-3	9.93	9.62	Picrate, m. p. 164-6°
2- <i>p</i> -Bromophenyl-3- <i>p</i> -tolyl-, C ₁₇ H ₁₇ N ₂ SBr	(5')	81	7.75	7.73	
2,3-Di- <i>p</i> -tolyl-, C ₁₈ H ₂₀ N ₂ S	(6')	oil	43.6	44.4°	Picrate, m. p. 140°

^a The numbers 1, 1' indicate the thio-ureas and the corresponding thiazolidine.

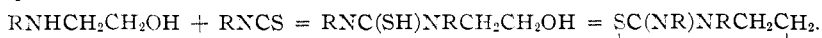
^b This was also obtained by the action of propylene dibromide upon thiocarbanilide.

^c Percentage of picric acid in the picrate.

Thiazolidines from Aryl-amino-ethanols, RNHCH₂CH₂OH

In the literature a few instances of thiazole synthesis from amino-ethanols have been noted. Thus Knorr and Rossler⁶ made the 2-thiocarbonyl compound from amino-ethanol, carbon disulfide and potassium hydroxide in alcohol solution, while Dersin⁷ found that amino-methyl-dimethyl-carbinol gave with phenyl-isothiocyanate a thio-urea, which on heating at 100° with hydrochloric acid suffered ring closure.

Our experiments have shown that the R-amino-ethanols united smoothly with mustard oils and gave thio-ureas. By heat alone or with halogen acids, such ureas reacted in the enol form with loss of water and the consequent formation of the thiazole ring.



Preparation of the Aryl-amino-ethanols.—The following procedure gave the best results. The amine (2 mols.) was heated at 120-130° for several hours with the ethylene chlorohydrin (1 mol.). The mixture was then made alkaline with sodium hydroxide and distilled with steam to remove unchanged amine. The oily residue when distilled under reduced pressure gave the pure ethanol.

o-Tolyl-amino-ethanol, *o*-C₇H₇NHCH₂CH₂OH.—This was a viscid oil which boiled at 172° at 12 mm.

Analyses. Calc. for C₉H₁₀ON: N, 9.27. Found: 9.21, 9.31.

In one preparation, using *o*-toluidine, chlorohydrin and anhydrous sodium carbonate, the main product was di-*o*-tolyl-piperazine.⁸

2-Phenylimino-3-phenyl-thiazolidine.—Molar proportions of the anilino-ethanol and phenyl mustard oil combined on standing or warming gently, either alone or in alcohol solution, and gave the thio-urea which crystallized from alcohol in white flakes with a melting point of 108°. The urea was heated for a short time with conc. hydrochloric or hydrobromic acid. It dissolved completely and when the solution was neutralized, there was precipitated the base, which proved to be identical with the thiazole made by the action of ethylene dibromide upon thiocarbanilide, following the directions of Will.^{1a}

⁶ Knorr and Rossler, *Ber.*, **36**, 1281 (1903).

⁷ Dersin, *ibid.*, **54**, 3160 (1921).

⁸ THIS JOURNAL, **42**, 1724 (1920). *Ber.*, **22**, 781 (1889); **23**, 1982 (1900).

^a These ethanol di-aryl thio-ureas will be described in a later paper.

The use of acid was unnecessary in order to bring about ring closure. Thus when the amino-ethanol (1 mol.) was heated at 110° for several hours with the isothiocyanate (2 mols.), a good yield of the above thiazole was obtained.¹⁰

Derivatives of 2-arylimino-3-aryl thiazolidine	M. p. ° C.	Nitrogen		Source α -Ethanol- α,β -diaryl-thio-urea
		Calc.	Found	
2,3-Diphenyl, C ₁₆ H ₁₄ N ₂ S	136	11.02	11.16	α,β -Diphenyl
2- <i>o</i> -Tolyl-3-phenyl-, C ₁₆ H ₁₆ N ₂ S	94	10.45	10.08	α -Phenyl- β - <i>o</i> -tolyl
2- <i>p</i> -Tolyl-3-phenyl-, C ₁₆ H ₁₆ N ₂ S	113	10.45	10.48	α -Phenyl- β - <i>p</i> -tolyl
2,3-Di- <i>o</i> -tolyl-, C ₁₇ H ₁₈ N ₂ S ^a	105	α,β -Di- <i>o</i> -tolyl
2-Phenyl-3- <i>o</i> -tolyl-, C ₁₆ H ₁₆ N ₂ S	92	10.45	10.37	α - <i>o</i> -Tolyl- β -phenyl

^a Ref. 3 b, p. 1317.

2-Phenylimino-3-phenyl-oxazolidine, $\text{OC(NPh)CH}_2\text{CH}_2$.—From the ethanol-thio-ureas were obtained the corresponding ring oxygen derivatives. Ethanol-diphenyl-thio-urea was dissolved in benzene and then desulfurized by boiling with yellow mercuric oxide. The oxazole was isolated from the solution in the form of white crystals which melted at 124°.

Analyses. Calc. for C₁₆H₁₄ON₂: N, 11.77. Found: 11.71, 11.86.

The same product was obtained by another method. Gault¹¹ has shown that the anilino-ethanol united with phenylisocyanate (2 mols.) and formed a urea-urethane, PhNHCONPhCH₂CH₂OCONHPh (m. p., 136°). When this compound was boiled with conc. hydrobromic acid, the above oxazolidine and diphenylurea were formed.

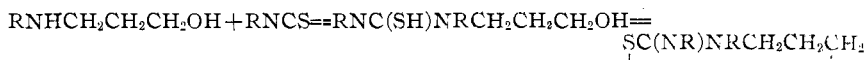
Analysis. Calc. for C₁₆H₁₄ON₂: N, 11.77. Found: 11.85.

The Synthesis of Meta-thiazanes



Ring compounds of this type have been made by the action of trimethylene dibromide or chlorobromide on thio-amides or thio-ureas and from γ -halogen propylamines with carbon disulfide, potassium thiocyanate or phenyl mustard oil with subsequent ring closure.¹²

In accordance with the preceding thiazole synthesis, it has been found that *m*-thiazanes of known structure can be readily prepared from aryl- γ -hydroxy-propylamines. Such amines add with ease aryl isothiocyanates and the resulting thio-ureas, under the influence of halogen acids, form a 6-membered ring.



Preparation of the aryl-amino-propanols.—Satisfactory yields were obtained when the trimethylene chlorohydrin (1 mol.) was heated with the amine (2 mols.)

¹⁰ Mr. I. Malm in some work now in progress has found that when a molar mixture of *p*-tolyl-isothiocyanate and *p*-tolyl-amino-ethanol was heated at 110° for 7 hours, the reaction product contained di-*p*-tolyl-thiazolidine, di-*p*-tolyl-thio-urea and di-*p*-tolyl-urea.

¹¹ Gault, *Bull. soc. chim.*, [4] 3, 366 (1908). *Ber.*, 33, 659 (1900).

¹² *Ber.*, 23, 157 (1890); 24, 783, 1123, 3848 (1891); 26, 1077 (1893); 29, 1029 (1896).

for several hours at 130°. The product was made alkaline and distilled with steam to remove unchanged amine. The residual oil was purified by vacuum distillation.¹³

γ -Hydroxy-propyl-*p*-tolylamine, *p*-C₇H₇NHCH₂CH₂CH₂OH.—This was a thick oil which boiled at 185–190° at 12 mm. and at 200–205° at 30 mm.

Analysis. Calc. for C₁₀H₁₃ON: N, 8.49. Found: 8.37.

α -Propanol- α,β -diphenyl-thio-urea, PhNHCSNPhCH₂CH₂CH₂OH.—Anilino-propanol and phenyl mustard oil reacted easily on standing and the thio-urea crystallized from alcohol in needles, which melted at 130°.

2-Phenylimino-3-phenyl-thiazane.—The thio-urea was soluble in conc. hydrochloric acid in the cold and was precipitated unchanged on dilution with water. On long standing in the cold or quickly by heating, the ring closed. Alkalies then precipitated the base, which crystallized from alcohol in needles and melted at 139°.

Foerster, who had made this same thiazane by heating thio-carbanilide with trimethylene dibromide, reported a melting point of 123°. Repetition of his work, however, gave a product identical with the above.

Derivatives of α -propanol- α,β -diaryl-thio-urea	M. p. ° C.	Nitrogen		Source
		Calc.	Found	
α,β -Diphenyl-, C ₁₈ H ₁₉ ON ₂ S (1)	130	9.86	9.71	Anilino-propanol and phenyl-isothiocyanate
α,β -Di- <i>p</i> -tolyl-, C ₁₅ H ₂₂ ON ₂ S (2)	142	8.92	8.72	Tolyl-N-propanol and tolyl-isothiocyanate
α - <i>p</i> -Tolyl- β -phenyl-, C ₁₇ H ₂₀ ON ₂ S (3)	146	9.34	9.36	Tolyl-N-propanol and phenyl-isocyanate
α -Phenyl- β - <i>p</i> -tolyl-, C ₁₇ H ₂₀ ON ₂ S (4)	127	9.34	9.27	Anilino-propanol and tolyl-isothiocyanate
Derivatives of 2-arylimino-3-aryl-thiazane				
2,3-Diphenyl-, C ₁₆ H ₁₆ N ₂ S	139	10.46	10.45	Thio-urea 1
2,3-Di- <i>p</i> -tolyl-, C ₁₃ H ₂₀ N ₂ S ¹⁴	111	9.46	9.44	Thio-urea 2
2-Phenyl-3- <i>p</i> -tolyl-, C ₁₇ H ₁₈ N ₂ S	139	9.93	10.12	Thio-urea 3
2- <i>p</i> -Tolyl-3-phenyl-, C ₁₇ H ₁₈ N ₂ S	94	9.93	9.96	Thio-urea 4

Synthesis of 2-aryl-imino-3-aryl-5-hydroxy-thiazanes

Cohn and Friedlander¹⁵ have shown that epichlorohydrin added to *p*-toluidine in alcohol solution¹⁶ and gave α -*p*-tolylamino- β -hydroxy- γ -chloropropane (m. p. 81–2°), which when heated with *p*-toluidine formed α,γ -ditolylamino- β -hydroxy-propane (m. p. 113°). This work was repeated and it was found that the mono-tolylamino compound melted at 85° and the ditolyl at 116°. They assumed the above structure for these derivatives but it was proved directly as follows:

α,γ -Dichlorohydrin (1 mol.) was heated with *p*-toluidine (4 mols.) for 5 hours at

¹³ Ref. 2a, p. 1872.

¹⁴ This was also made from di-*p*-tolyl-thio-urea and trimethylene dibromide.

¹⁵ Cohn and Friedlander, *Ber.*, **37**, 3035 (1804).

¹⁶ We found that practically no addition occurred in benzene solution.

The arylamino-ethanols have been found to unite with the aryl-isothiocyanates and isocyanates and from the ureas thus obtained have been synthesized thiazolidines and oxazolidines of known structure.

In like manner the aryl-amino-propanols gave thio-ureas, which under the influence of acids, condensed to a 6-membered thiazane ring.

The α -arylamino- β -hydroxy- γ -chloropropanes combined with mustard oils and formed the 5-hydroxy-thiazanes.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

THE ESTIMATION OF ALIPHATIC NITRATE ESTERS IN THE PRESENCE OF CERTAIN NITRO-AROMATIC COMPOUNDS¹

BY WILBERT J. HUFF² AND RICHARD D. LEITCH³

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Storm,⁴ in a paper from this Laboratory, has shown that glycerine trinitrate in the presence of mononitro compounds cannot be estimated by means of the nitrometer, since the mononitro aromatic substance is converted into the dinitro compound, and the reading is correspondingly low.

To overcome this difficulty, Hyde,⁵ in another paper from this Laboratory, proposed the separation of the glycerine trinitrate from the nitro derivative by treatment with immiscible solvents, one phase of which was carbon disulfide, while the second phase was a mixture of 75 parts of acetic acid and 25 parts of water. The technique involved in this method is so exacting, however, that it has apparently never been widely used and in this Laboratory is at present practically abandoned.

We have made preliminary experiments which appear to promise a convenient solution for this problem. Since it now appears that neither of us will have an opportunity to complete the study in the near future, we are reporting the results as they stand, with suggestions for further experiments.

Essentially, the method is that developed at the Kent Chemical Laboratory of Yale University by I. K. Phelps⁶ for the estimation of inorganic nitrates.

The apparatus employed consisted of a 250 cc. Kjeldahl flask carrying a tight 2-holed rubber stopper in which was inserted a long-stemmed separatory funnel whose tip was drawn to a capillary so that it always stood full of liquid. An 8 mm. tube carrying a bulb to prevent splashing was also inserted in this stopper. This tube was bent twice at right angles and

¹ Published by permission of the Director, U. S. Bureau of Mines.

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³ Junior Chemist, U. S. Bureau of Mines.

⁴ Storm, *Eighth Inter. Cong. Appl. Chem.*, **4**, 117 (1912).

⁵ Hyde, *THIS JOURNAL*, **35**, 1173 (1913).

⁶ Phelps, *Am. J. Sci.*, [4] **14**, 440 (1902). Gooch, "Methods of Chemical Analysis," John Wiley and Sons Co., 1912, p. 259.