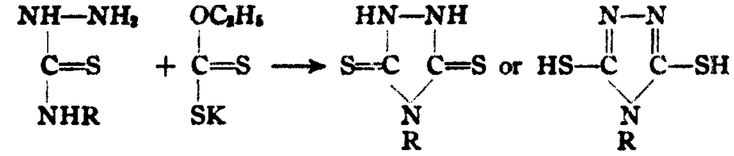
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DACCA UNIVERSITY, BENGAL, INDIA]

CONSTITUTION OF THE SO-CALLED DITHIO-URAZOLE OF MARTIN FREUND. III. SYNTHESIS OF SOME MONO-SUBSTITUTED THIODIAZOLES

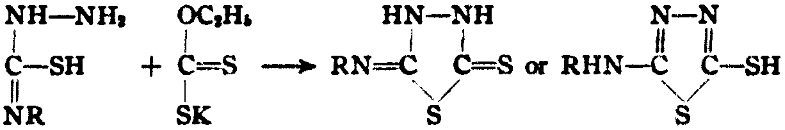
BY PRAPHULLA CHANDRA GUHA AND HARI PRASANNA RAY

RECEIVED FEBRUARY 23, 1924 PUBLISHED FEBRUARY 5, 1925

In a previous paper[1] it was shown that 2-imino-5-thio-tetrahydro-1,3,4-thiodiazole can be prepared from thiosemicarbazide by the direct action of carbon disulfide, and also that carbon disulfide in the presence of alcoholic potassium hydroxide reacts with various 1,4-disubstituted thiosemicarbazides to give disubstituted thiodiazoles. We have now studied the action of carbon disulfide on various 4-substituted (*p*-tolyl-, -xylyl-, *α*-naphthyl-, *m*-chlorophenyl- and *p*-bromophenyl-) thiosemicarbazides and obtained in each case the corresponding 5-R-imino-2-thio-tetrahydrothiodiazole. We have also investigated the action of carbon disulfide in the presence of alcoholic potassium hydroxide on several 4-substituted thiosemicarbazides which are capable of assuming either the thio-imino or thiol-amino form, according to the conditions of the experiment, and thus giving rise to either of two types of product, I or II.

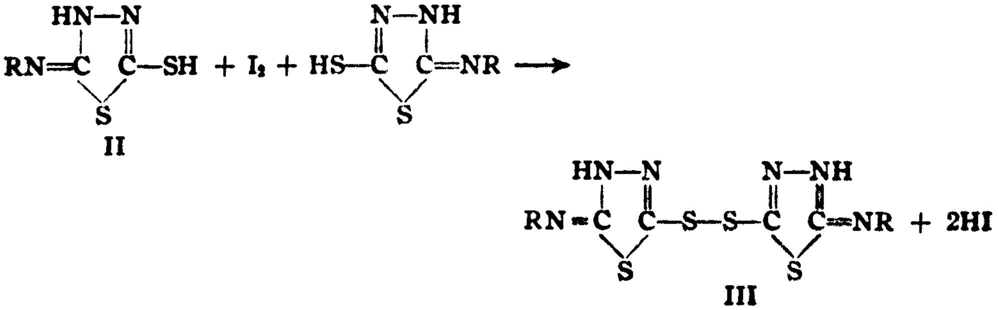


I (Triazole)



II (Thiodiazole)

The nature of the resulting product[2] has been demonstrated (whether represented by Formula I or II) by the action of iodine, acetic anhydride and alkyl iodides upon the thiodiazoles. Iodine yields a disulfide (III).



II

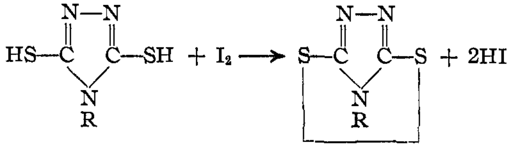
III

---

[1] Guha, THIS JOURNAL, **44**, 1516 (1922).

[2] Ref. 1, p. 1502.

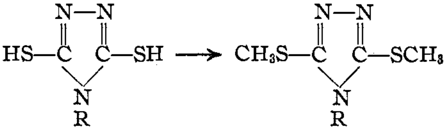
Were Formula I correct, then each molecule would require one molecule of iodine for the formation of a disulfide (IV).



I IV

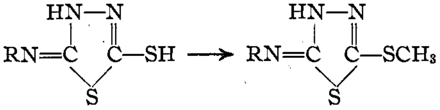
Formulas III and, therefore, II are supported by the fact that the disulfide forms a di-acetyl derivative, since the substance represented by III has two imino hydrogens, whereas that represented by IV has none.

According to I, methyl iodide should yield a dimethyl-dithiol compound (V),



I V

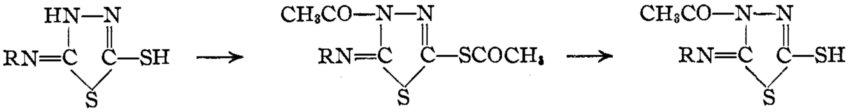
whereas from II a monomethyl-thiol derivative (VI) should result.



II VI

Actually, there has been obtained a monomethyl derivative into which one acetyl group can be introduced but not a second methyl group. This shows that the original thiodiazole compound contains only one thiol group.

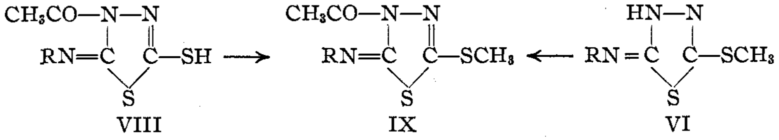
Acetic anhydride gives rise to a diacetyl derivative (VII) which very readily (heating with dil. hydrochloric acid) loses one of its acetyl groups. This mono-acetyl derivative forms insoluble mercury and lead salts, a monomethyl derivative and a disulfide. Thus, the thiodiazole (II) first forms a diacetyl derivative (VII),



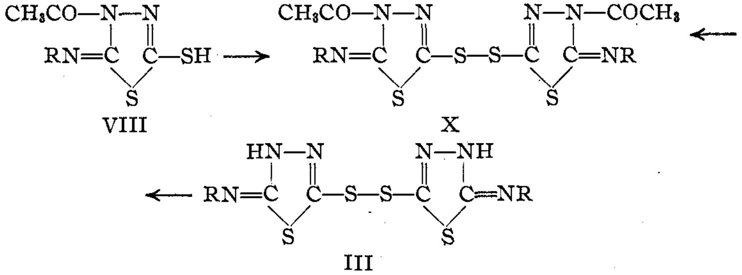
II VII VIII

which easily loses the acetyl group attached to thiol sulfur but not that attached to nitrogen and the result is an N-acetyl compound (VIII).

This N-acetyl-thiol (VIII) gives a methyl derivative (IX) identical with the product obtained by acetylating the monomethyl compound (VI),



and the same disulfide (X) which is obtained by acetylating the disulfide (III) of the original thiodiazole (II).



Thus, it is proved beyond all doubt that the products obtained by the action of carbon disulfide and alcoholic potassium hydroxide on 4-substituted thiosemicarbazides are 5-R-imino-2-thio-2,3,4,5-tetrahydro-1,3,4-thiodiazoles.

The authors wish to express their sincere appreciation to Sir P. C. Rây and to Dr. J. C. Ghosh for the kind interest they have taken in this work.

Experimental Part

Preparation of 4-Substituted Thiosemicarbazides.—4-Substituted alkyl-thiosemicarbazides have been prepared by the action of alkyl-thiocarbimides on hydrazine hydrate in cold alcoholic solution.[3] This same method was employed in preparing aryl-thiosemicarbazides, the 4-phenyl derivative having already been obtained.

4-*p*-Tolyl-thiosemicarbazide.[4]—A mixture of 1.3 g. of hydrazine hydrate and 12 cc. of an alcoholic solution of 3.9 g. of *p*-tolyl mustard oil was cooled and shaken constantly for a few minutes. The crystalline precipitate was crystallized from alcohol; yield, 4.1 g.; m. p., 177°.

Anal. Calcd. for $C_8H_{11}N_3S$: N, 23.2; S, 17.7. Found: N, 23.1; S, 17.9.

4-α-Naphthyl-thiosemicarbazide.[4]—Two g. of α-naphthyl mustard oil yielded 2.2 g. of the thiosemicarbazide; m. p., 137°.

4-*m*-Xylyl-thiosemicarbazide.—From 7.2 g. of *m*-xylyl mustard oil and 2.2 g. of hydrazine hydrate was obtained 6.5 g. of the thiosemicarbazide; m. p., 184°.

Anal. Calcd. for $C_9H_{13}N_3S$: N, 21.5; S, 16.4. Found: N, 21.6; S, 16.4.

4-*p*-Bromo-phenyl-thiosemicarbazide.[5]—A mixture of 2.2 g. of *p*-bromophenyl

---

[3] Pulvermacher, *Ber.*, **26**, 2812 (1893).

[4] Busch and Ulmer, *Ber.*, **35**, 1714 (1902).

[5] An isomeric thiosemicarbazide, m. p., 110°, was obtained by adding hydrazine hydrate to a very dilute alcoholic solution of *p*-bromophenyl mustard oil. It is soluble in alcohol but insoluble in cold dil. alkali, whereas the isomer mentioned above is very

mustard oil and 2.5 g. of hydrazine hydrate yielded 8.8 g. of thiosemicarbazide; m. p., 189°.

Anal. Calcd. for $C_7H_8N_3BrS$: Br, 32.5; S, 13.0. Found: Br, 32.4; S, 13.3.

4-*m*-Chlorophenyl-thiosemicarbazide.—Six and four-tenths g., m. p., 130°, was obtained from 6.5 g. of the corresponding mustard oil and 2 g. of hydrazine hydrate.

Anal. Calcd. for $C_7H_8N_3ClS$: Cl, 17.6; S, 15.9. Found: Cl, 17.4; S, 16.3.

Preparation of 5-R-Imino-2-thio-2,3,4,5-tetrahydro-1,3,4-thiodiazoles.—The general procedure was to heat 1 molecular proportion of thiosemicarbazide in a sealed tube at 100° for 4–5 hours with carbon di-sulfide (1 equivalent) and alcoholic potassium hydroxide (1 equivalent). The tube was then opened, the contents were transferred to a beaker, diluted with water and acidified with dil. hydrochloric acid. The white (sometimes yellowish) precipitate was then purified by crystallization from alcohol.

5-Tolylimino-2-thio-2,3,4,5-tetrahydro-1,3,4-thiodiazole.—Four g. of 4-tolyl thiosemicarbazide yielded 2.5 g. of thiodiazole; m. p., 219°.

Anal. Calcd. for $C_9H_9N_3S_2$: N, 18.8; S, 28.7. Found: N, 19.2; S, 28.7.

NITROSO DERIVATIVE.—By adding a solution of sodium nitrite to an acetic acid solution of 0.5 g. of tolylimino-thiodiazole, a bright yellow precipitate was obtained. It was crystallized from acetic acid; m. p., 228°. It was moderately soluble in alcohol but did not crystallize well from this solvent.

Anal. Calcd. for $C_9H_8ON_4S_2$: S, 25.4. Found: 25.4.

METHYL DERIVATIVE.—One g. of the thiodiazole in methyl alcoholic solution was refluxed for about 15 minutes with 2 cc. of methyl iodide. The excess of methyl iodide was then removed by warming on a water-bath. On the addition of water a yellowish solid separated which after crystallization from alcohol melted at 134°.

Anal. Calcd. for $C_{10}H_{11}N_3S_2$: N, 17.7. Found: 18.2.

DIACETYL DERIVATIVE.—A mixture of 0.5 g. of the thiodiazole with 5 cc. of acetic anhydride and 0.5 g. of finely ground, fused sodium acetate was warmed on a water-bath until a clear solution was obtained. When this was poured into water a heavy oil separated which solidified after 24 hours. Purified by crystallization from alcohol, it contracted at 200° and melted at 234–236°. Analysis showed that it was a mixture of the mono- and diacetyl derivatives.

Anal. Calcd. for $C_{13}H_{13}O_2N_3S_2$: S, 20.8. Found: 23.1, 23.3.

MONO-ACETYL DERIVATIVE.—A mixture of 0.6 g. of the impure diacetyl compound with dil. hydrochloric acid was heated on a water-bath for one-half hour, and then filtered and the residue after having been washed with water, crystallized from alcohol. Pale yellow, square crystals were obtained; m. p., 252°.

Anal. Calcd. for $C_{11}H_{11}ON_3S_2$: S, 24.2. Found: 23.7, 24.0.

ISOMERIC MONO-ACETYL DERIVATIVE.—One g. of 5-tolylimino-thiodiazole was dissolved in 10 cc. of acetic anhydride and the solution heated with 1 g. of sodium acetate for one-half hour on a sand-bath. When the solution was poured into water a heavy oil separated which solidified on cooling. Crystallization from alcohol yielded light yellow plates; m. p., 198–200°.

---

sparingly soluble in alcohol but readily soluble in cold dil. alkali. It does not yield any thiodiazole when treated with carbon disulfide and alcoholic potassium hydroxide.

Anal. Calcd. for $C_7H_8N_3BrS$; Br, 32.5; S, 13.0. Found: Br, 32.1; S, 12.9.

Anal. Calcd. for $C_{11}H_{11}ON_3S_2$: S, 24.2. Found: 24.4.

Formation of 5-Tolylimino-4-acetyl-2-methyl-thiolthiodiazole. (1) From the Mono-acetyl Derivative (m. p., 252°) and Methyl Iodide.—The mono-acetyl compound (0.5 g.) was refluxed with methyl iodide (2 cc.), the excess of methyl iodide removed by warming, the solution poured into water and the white precipitate crystallized from alcohol. The product was obtained as long, colorless needles; m. p., 89–90°.

Anal. Calcd. for $C_{12}H_{13}ON_3S_2$: N, 15.1. Found: 15.3.

(2) From the Isomeric Mono-acetyl Derivative (m. p., 198–200°) and Methyl Iodide.

Anal. Found: N, 14.9.

(3) From the Monomethyl Compound and Acetic Anhydride.

Anal. Found: N, 14.8.

Disulfide of Tolylimino-thiodiazole Compound.—One g. of the thiodiazole and 1 g. of iodine[6] were heated in alcoholic solution on a water-bath for one hour. The yellow precipitate obtained on the addition of water was purified by being washed with water and then shaken repeatedly with alcohol. The product is insoluble in alcohol and in cold, dil. alkali; m. p., 232°.

Anal. Calcd. for $C_{18}H_{16}N_6S_4$: S, 28.8. Found: 29.2.

Acetyl Derivative of Disulfide.—Heating the disulfide with acetic anhydride and sodium acetate at 100° for one-half hour and then pouring the product into water yielded an oil. By the use of alcohol as solvent, crystals were obtained; m. p., 245°.

Anal. Calcd. for $C_{22}H_{20}O_2N_6S_4$: S, 24.2. Found: 23.8.

Disulfide of Mono-acetyl Compound.—To a solution of 0.3 g. of the mono-acetyl compound (m. p., 254°) in dil. alkali was added iodine solution. The pale yellow precipitate thus obtained was crystallized from alcohol; m. p., 245°.

5-Xylylimino-2-thio-2,3,4,5-tetrahydro-1,3,4-thiodiazole.—From 4 g. of xylyl thiosemicarbazide 2 g. of thiodiazole was obtained. It was soluble in benzene, pyridine, and cold, dil. alkali; m. p., 230° (decomp.).

Anal. Calcd. for $C_{10}H_{11}N_3S_2$: N, 17.7; S, 27.0. Found: N, 18.2; S, 27.1.

Disulfide of Xylyl-thiodiazole.—Refluxing 1 g. of xylyl-thiodiazole in alcoholic solution with 0.8 g. of iodine for three hours yielded 1 g. of disulfide. It was insoluble in cold, dil. alkali; m. p., 114° (decomp.).

Anal. Calcd. for $C_{20}H_{20}N_6S_4$: S, 27.1. Found: 27.0.

Acetyl Derivative of Xylylimino-thiodiazole Disulfide.—On pouring the acetylation mixture into water an oily substance separated which solidified on standing. Crystallization from alcohol yielded a product melting at 130° with decomposition.

Anal. Calcd. for $C_{24}H_{24}O_2N_6S_4$: S, 23.0. Found: 22.9.

Bromophenylimino-thio-tetrahydro-thiodiazole.—Three g. of 4-*p*-bromophenylthiosemicarbazide yielded 2.8 g. of the thiodiazole; m. p., 220°.

Anal. Calcd. for $C_8H_6N_3BrS_2$: Br, 27.8; S, 22.2. Found: Br, 27.7; S, 22.6.

Disulfide of Bromophenylimino-thiodiazole.—The action of iodine on a solution of the thiodiazole in sodium hydroxide yielded a brownish-yellow precipitate. Since it

---

[6] To 0.2186 g. of thiodiazole in water-alcohol solution was added 15 cc. of 0.1 *N* iodine solution; the excess of iodine required 5.05 cc. of 0.1 *N* thiosulfate solution. Therefore the weight of iodine used was 0.1264 g., the amount theoretically necessary for the formation of $(C_9H_8N_3S)$—S—S—$(SN_3H_8C_9)$ being 0.1246 g.

could not be crystallized from any organic solvent it was purified by washing first with potassium iodide solution and then with water. It melts sharply at 216°.

Anal. Calcd. for $C_{16}H_{10}N_6Br_2S_4$: Br, 27.9; S, 22.3. Found: Br, 28.1; S, 22.7.

Diacetyl Derivative of Bromophenylimino-thiodiazole.—Seven-tenths g. of thiodiazole yielded 0.5 g. of product which, after crystallization from alcohol melted at 161°.

Anal. Calcd. for $C_{12}H_{10}O_2N_3BrS_2$: Br, 21.5; S, 17.2. Found: Br, 22.0; S, 16.0.

Hydrolysis of the Diacetyl to the Mono-acetyl Derivative.—A mixture of 0.6 g. of diacetyl derivative with dil. hydrochloric acid was heated on a water-bath for one hour, then filtered and the residue washed with water and crystallized from alcohol; m. p., 205°.

Anal. Calcd. for $C_{10}H_8ON_3BrS_2$: Br, 24.2; S, 19.4. Found: Br, 24.5; S, 19.1.

METHYL DERIVATIVE.—5-Bromophenylimino-2-thiol-1,3,4-thiodiazole, on treatment with methyl iodide, yielded a methyl derivative that was crystallized from alcohol; m. p., 212°.

Anal. Calcd. for $C_9H_8N_3BrS_2$: N, 13.9. Found: 14.2.

METHYL-ACETYL DERIVATIVE.—Five-tenths g. of the methyl compound yielded 0.4 g. of acetyl derivative. Crystallized from dil. acetic acid, it melted at 91°.

Anal. Calcd. for $C_{11}H_{10}ON_3BrS_2$: N, 12.2. Found: 12.1.

5-α-Naphthylimino-thiodiazole.—A mixture of 2 g. of α-naphthyl-thiosemicarbazide, 1 cc. of carbon disulfide and 3.2 cc. of alcoholic potassium hydroxide solution (1 cc. = 0.16 g.) was heated at 100° for four hours in a sealed tube. The white precipitate obtained when this was poured into water and the mixture acidified with dil. hydrochloric acid was crystallized from alcohol. It is soluble in alkali; m. p., 225°.

Anal. Calcd. for $C_{12}H_9N_3S_2$: N, 16.2; S, 24.7. Found: N, 16.5; S, 25.1.

5-*m*-Chlorophenylimino-thiodiazole.—Two g. of the corresponding thiosemicarbazide yielded 1.2 g. of thiodiazole. After crystallization from alcohol it melted at 240°.

Anal. Calcd. for $C_8H_6N_3ClS_2$: Cl, 14.6; S, 26.3. Found: Cl, 14.9; S, 25.9.

DISULFIDE.—A solution of 0.7 g. of thiodiazole in sodium hydroxide solution, acted on by an excess of iodine solution, yielded a light brown precipitate; m. p., 156°.

Anal. Calcd. for $C_{16}H_{10}N_6Cl_2S_4$: Cl, 14.6; S, 26.4. Found: Cl, 14.8; S, 26.2.

Summary

The authors have prepared a number of 2-R-imino-5-thio-2,3,4,5-tetrahydro-1,3,4-thiodiazoles by the direct action of carbon disulfide and also by the action of carbon disulfide and alcoholic potassium hydroxide upon 4-R-substituted-thiosemicarbazides (R = *p*-tolyl-, xylyl-, α-naphthyl-, *m*-chlorophenyl-, *p*-bromophenyl-). The structures of the compounds so formed have been established from the facts that (1) they form diacetyl derivatives on acetylation which yield mono-acetyl derivatives when one of the two acetyl groups (*thiol-acetyl*) is removed by hydrolysis, (2) monomethyl derivatives on methylation, (3) identical acetyl-methyl derivatives by methylating the monoacetyl derivatives, or (4) acetylating the monomethyl derivatives, (5) disulfides on oxidation with iodine or ferric chloride, (6) identical diacetyl-disulfides when the disulfide is acetylated and when the monoacetyl derivative is acted upon by iodine.

BENGAL, INDIA