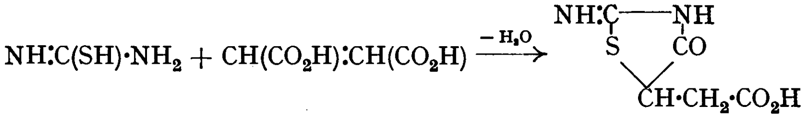
## 225. *The Reaction between Thiosemicarbazones and Maleic Anhydride.*

By John M'Lean and F. J. Wilson.

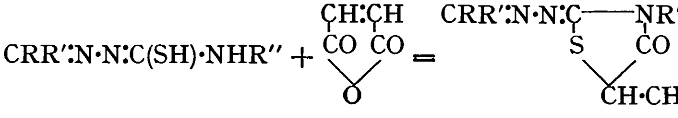
In continuation of previous work on thiosemicarbazones and thiazoles, the authors have shown that thiosemicarbazones and δ-substituted thiosemicarbazones combine with maleic anhydride to yield thiazole derivatives.

It was shown by Andreasch (*Monatsh.*, 1895, **16**, 789; 1897, **18**, 56) that thiourea reacted on heating with maleic or fumaric acid in aqueous solution, giving 2-imino-4-ketotetrahydrothiazole-5-acetic acid:



Diphenylthiourea reacted in a similar manner. Citraconic acid or its anhydride condensed similarly with thiourea or substituted thioureas.

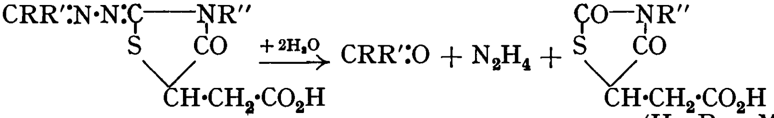
In continuation of previous work (J., 1922, **121**, 870; 1923, **123**, 799; 1926, 2531; 1937, 556) we have found that the thiosemicarbazones of acetone, acetophenone, 3-methyl*cyclo*hexanone and benzaldehyde condense with maleic anhydride on heating in benzene solution, yielding derivatives of 2 : 4-diketotctrahydrothiazole-5-acetic acid:



(I, R'' = H)

The δ-phenylthiosemicarbazones of acetone, acetophenone, *cyclo*hexanone, 3-methyl-*cyclo*hexanone and benzaldehyde reacted in a similar manner (R″ = Ph), as did the δ-methylthiosemicarbazones of acetophenone and benzaldehyde (R″ = Me).

We expected that hydrolysis of these compounds with dilute hydrochloric acid would give the hydrazone (I, CRR′ = $H_2$), but the results were indefinite (cf. Stephen and Wilson, J., 1928, 1415). On heating with concentrated hydrochloric acid, however, 2 : 4-*diketotetrahydrothiazole*-2-α-*phenylethylidenehydrazone*-5-*acetic acid* gave acetophenone, hydrazine dihydrochloride, and 2 : 4-diketotetrahydrothiazole-5-acetic acid :



(II; R = Me, R′ = Ph, R″ = H)

Some ammonium chloride and resin were formed also, apparently owing to further decomposition.

Hydrolysis with concentrated hydrochloric acid of compounds of type (I, R″ = Ph) produced resins and hydrazine dihydrochloride. However, 2 : 4-*diketo*-3-*methyltetrahydrothiazole*-2-α-*phenylethylidenehydrazone*-5-*acetic acid* (I; R = R″ = Me, R′ = Ph) with concentrated hydrochloric acid gave acetophenone, hydrazine dihydrochloride, and 2 : 4-diketo-3-methyltetrahydrothiazole-5-acetic acid (II, R″ = Me) together with some resin.

The results of these methods of hydrolysis with concentrated acid show that the compounds produced by the addition of maleic anhydride to thiosemicarbazones or δ-substituted thiosemicarbazones have the structure of type (I).

## EXPERIMENTAL.

*General Procedure.*—The thiosemicarbazone or δ-substituted thiosemicarbazone and maleic anhydride (equimolecular quantities) were heated in benzene or toluene, with in some cases addition of a little acetone to promote solution, under reflux for a certain time as indicated in each case. The products which separated on cooling were recrystallised; they were all microcrystalline powders.

2 : 4-*Diketotetrahydrothiazole*-2-iso*propylidenehydrazone*-5-*acetic acid* (I; R = R′ = Me, R″ = H) (from acetonethiosemicarbazone in benzene–acetone, 15 minutes), m. p. 223° after recrystallisation from acetone–light petroleum (Found: C, 42·5; H, 4·9; N, 18·1. $C_8H_{11}O_3N_3S$ requires C, 41·9; H, 4·8; N, 18·3%).

2 : 4-*Diketotetrahydrothiazole*-2-α-*phenylethylidenehydrazone*-5-*acetic acid* (I; R = Me, R′ = Ph, R″ = H) (from acetophenonethiosemicarbazone in benzene, 1 hour), m. p. 244°, from alcohol (Found: C, 54·2; H, 4·5; N, 14·4. $C_{13}H_{13}O_3N_3S$ requires C, 53·7; H, 4·5; N, 14·4%).

2 : 4-*Diketotetrahydrothiazole*-2-3′-*methyl*cyclo*hexylidenehydrazone*-5-*acetic acid* (I; RR′ = $C_6H_9Me$, R″ = H) (from 3-methyl*cyclo*hexanonethiosemicarbazone in benzene, 20 minutes), m. p. 209°, from alcohol–benzene (Found: N, 14·9. $C_{12}H_{17}ON_3S$ requires N, 14·8%).

2 : 4-*Diketotetrahydrothiazole*-2-*benzylidenehydrazone*-5-*acetic acid* (I; R = R″ = H, R′ = Ph) (from benzaldehydethiosemicarbazone in benzene–acetone, 20 minutes), m. p. 255°, from acetone (Found: N, 15·1, 15·3. $C_{12}H_{11}O_3N_3S$ requires N, 15·2%).

2 : 4-*Diketo*-3-*phenyltetrahydrothiazole*-2-iso*propylidenehydrazone*-5-*acetic acid* (I; R = R′ = Me, R″ = Ph) (from acetone-δ-phenylthiosemicarbazone in benzene–acetone, 4 hours), m. p. 175—180°, from benzene–acetone (Found: N, 13·7. $C_{14}H_{15}O_3N_3S$ requires N, 13·8%).

2 : 4-*Diketo*-3-*phenyltetrahydrothiazole*-2-α-*phenylethylidenehydrazone*-5-*acetic acid* (I; R = Me, R′ = R″ = Ph) (from acetophenone-δ-phenylthiosemicarbazone in toluene, 1¼ hours), m. p. 185°, from toluene (Found: N, 11·5. $C_{19}H_{17}O_3N_3S$ requires N, 11·4%).

2 : 4-*Diketo*-3-*phenyltetrahydrothiazole*-2-cyclo*hexylidenehydrazone*-5-*acetic Acid* (I; RR′ = $C_6H_{10}$, R″ = Ph).—cyclo*Hexanone*-δ-*phenylthiosemicarbazone* was prepared by refluxing the ketone and δ-phenylthiosemicarbazide in absolute alcohol on the water-bath for 2 hours; on cooling, the solution deposited the compound in needles, m. p. 114° after recrystallisation from light petroleum (Found: N, 17·1. $C_{13}H_{17}N_3S$ requires N, 17·0%). The *thiazole*, prepared from this phenylthiosemicarbazone in benzene (1 hour), was recrystallised from alcohol–benzene and melted at 218° (decomp.) (Found: N, 12·1. $C_{17}H_{19}O_3N_3S$ requires N, 12·2%).

2 : 4-*Diketo*-3-*phenyltetrahydrothiazole*-2-3′-*methyl*cyclo*hexylidenehydrazone*-5-*acetic Acid* (I; RR′ = $C_6H_9Me$, R″ = Ph).—3-*Methyl*cyclo*hexanone*-δ-*phenylthiosemicarbazone* was prepared by refluxing equimolecular amounts of the ketone and δ-phenylthiosemicarbazide in absolute alcohol on the water-bath for 1 hour. On cooling and addition of a little water the compound separated, m. p. 139° after recrystallisation from benzene–light petroleum (Found : N, 15·9, 16·0. $C_{14}H_{19}N_3S$ requires N, 16·0%). The *thiazole* was prepared from this δ-phenylthiosemicarbazone in benzene (1 hour), and purified by addition of light petroleum to an alcoholic solution; it melted at 192° (Found : N, 11·7. $C_{18}H_{21}O_3N_3S$ requires N, 11·7%).

2 : 4-*Diketo*-3-*phenyltetrahydrothiazole*-2-*benzylidenehydrazone*-5-*acetic acid* (I; R = H, R′ = R″ = Ph) (from benzaldehyde-δ-phenylthiosemicarbazone in benzene, 1½ hours) melted at 215° after recrystallisation from alcohol (Found : N, 11·7. $C_{18}H_{17}O_3N_3S$ requires N, 11·9%).

2 : 4-*Diketo*-3-*methyltetrahydrothiazole*-2-α-*phenylethylidenehydrazone*-5-*acetic Acid* (I; R = R″ = Me, R′ = Ph).—*Acetophenone*-δ-*methylthiosemicarbazone* was obtained by refluxing acetophenone with δ-methylthiosemicarbazide in absolute alcohol for ¾ hour. The compound separated on cooling and after recrystallisation from alcohol melted at 135° (Found : N, 20·2. $C_{10}H_{13}N_3S$ requires N, 20·3%). The *thiazole* was prepared from this substance in benzene (5 hours); some resinous matter separated during the reaction. It was recrystallised from aqueous alcohol and melted at 154° (Found : N, 13·7. $C_{14}H_{17}O_3N_3S$ requires N, 13·7%).

2 : 4-*Diketo*-3-*methyltetrahydrothiazole*-2-*benzylidenehydrazone*-5-*acetic acid* (I; R = H, R′ = Ph, R″ = Me) (from benzaldehyde-δ-methylthiosemicarbazone in benzene, 4 hours) was recrystallised from acetone containing a little water and melted at 188° (Found : N, 14·7. $C_{13}H_{13}O_3N_3S$ requires N, 14·5%).

*Hydrolysis Experiments.*—2 : 4-Diketotetrahydrothiazole-2-α-phenylethylidenehydrazone-5-acetic acid was heated with concentrated hydrochloric acid for 30 minutes and then steam-distilled till no more acetophenone passed over. The cold solution was extracted ten times with ether; the extract on evaporation gave 2 : 4-diketotetrahydrothiazole-5-acetic acid, m. p. 170° after recrystallisation from acetone–petrol (Tambach, *Annalen*, 1894, **280**, 241) (Found : C, 34·5; H, 2·9; S, 18·6. Calc. : C, 34·3; H, 2·9; S, 18·4%). The aqueous portion on evaporation deposited hydrazine dihydrochloride, ammonium chloride, and a small quantity of resin.

2 : 4-Diketo-3-methyltetrahydrothiazole-2-α-phenylethylidenehydrazone-5-acetic acid was hydrolysed as above. The ethereal extract on evaporation left a syrup, which on scratching and standing solidified and after recrystallisation from benzene was identified as 2 : 4-diketo-3-methyltetrahydrothiazole-5-acetic acid in poor yield; it melted at 99° (Kallenberg, *Ber.*, 1923, **56**, 316) (Found : N, 7·5. Calc. : N, 7·4%). The aqueous portion on evaporation gave hydrazine dihydrochloride and a small amount of resinous matter.

We thank Imperial Chemical Industries, Ltd., for a research grant.

" Freeland " Chemical Laboratories,
The Royal Technical College, Glasgow.

[*Received, May* 10*th*, 1939.]