

XCIV.—*Reactions of Thiosemicarbazones. Part II.*
Action of Esters of α -Halogenated Acids.

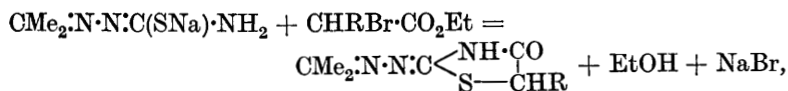
By FORSYTH JAMES WILSON and ROBERT BURNS.

IN Part I (T., 1922, **121**, 870), an account of the reactions between the sodium derivative of acetone-thiosemicarbazone and certain halogen compounds was communicated. Esters of chloroacetic acid yielded a ψ -thichydantoin derivative of a new type,

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$\text{CMe}_2\text{N}\cdot\text{N}\cdot\text{C} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ | \\ \text{S}-\text{CH}_2 \end{smallmatrix}$, 2:4-diketotetrahydrothiazole-2-isopropylidenehydrazone, hydrolysis of which with acid gave 2:4-diketotetrahydrothiazole by elimination of acetone and hydrazine. It was not found possible to remove acetone only and isolate the intermediate hydrazone; the cases reported in this communication have been more successful.

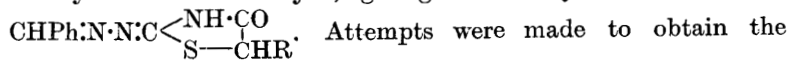
We have now investigated the reactions between the sodium derivative of acetone thiosemicarbazone and ethyl α -bromopropionate, ethyl α -bromo-*n*-butyrate, and ethyl phenylbromoacetate. With each of these esters the product was the 2-isopropylidenehydrazone derivative of a 2:4-diketotetrahydrothiazole, the reactions, which were carried out in boiling alcoholic solution, proceeding according to the scheme



the yields being from 70 to 75 per cent. of the theoretical.

Hydrolysis of these compounds by boiling with concentrated hydrochloric acid for several hours removed acetone and hydrazine and gave a 2:4-diketotetrahydrothiazole, $\text{CO} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ | \\ \text{S}-\text{CHR} \end{smallmatrix}$, in very satisfactory yield. If, however, the hydrolysis was effected by boiling with 2*N*-hydrochloric acid for about fifteen minutes, acetone only was removed and the intermediate hydrazone, $\text{NH}_2\cdot\text{N}\cdot\text{C} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ | \\ \text{S}-\text{CHR} \end{smallmatrix}$,

could be isolated as the hydrochloride. These two types of hydrolysis were quite sharply distinguished in the cases investigated. The hydrochlorides of these hydrazones, which, it is believed, represent a new type of ψ -thiohydantoin derivatives, can be obtained in good yield and are well-defined, crystalline salts which appear to be quite stable. In aqueous solution, they reacted readily with benzaldehyde, giving the benzylidene derivative,



free hydrazones from these hydrochlorides, but with unsatisfactory results owing to the unstable nature of the hydrazones. We succeeded, however, in preparing 2:4-diketo-5-ethyltetrahydrothiazole-2-hydrazone, $\text{NH}_2\cdot\text{N}\cdot\text{C} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ | \\ \text{S}-\text{CHEt} \end{smallmatrix}$, from its hydrochloride

by means of sodium carbonate as a crystalline powder which was moderately stable. All the compounds described were soluble in aqueous sodium hydroxide.

These hydrazones and the 2:4-diketotetrahydrothiazoles contain an asymmetric carbon atom, and it is hoped to effect a resolution and to bring about the synthesis of an optically active one. We also propose to investigate the interaction between thiosemicarbazones and esters of other classes of halogenated acids.

EXPERIMENTAL.

Reaction with Ethyl α -Bromopropionate. 2:4-Diketo-5-methyltetrahydrothiazole-2-isopropylidenehydrazone, $\text{CMe}_2\text{:N:N:C} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ \text{S} - \text{CHMe} \end{smallmatrix}$.

Acetonethiosemicarbazone, dissolved in boiling alcohol, was treated with sodium ethoxide (1 mol.) in alcohol, and ethyl α -bromopropionate (slightly more than 1 mol.) was added to the cooled solution, which was kept at room temperature for one hour and then boiled for half an hour under reflux. Sodium bromide was removed by filtering the boiling solution which, on cooling, deposited the tetrahydrothiazole derivative. This was recrystallised from alcohol, from which it separated in fine, white needles melting at 150° . It was slightly soluble in benzene, sparingly soluble in ether or water. The above method may be varied by dissolving the previously prepared sodium derivative of acetonethiosemicarbazone in alcohol, adding the ester, and then proceeding as before (Found: $\text{N} = 22.66, 22.70$. $\text{C}_7\text{H}_{11}\text{ON}_3\text{S}$ requires $\text{N} = 22.70$ per cent.).

2:4-Diketo-5-methyltetrahydrothiazole, $\text{CO} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ \text{S} - \text{CHMe} \end{smallmatrix}$. — The

above isopropylidene derivative was boiled under reflux with concentrated hydrochloric acid for three hours and the solution then evaporated to dryness on the water-bath. The residue was extracted with hot benzene, and the undissolved solid identified as hydrazine hydrochloride by reduction of Fehling's solution and by conversion into benzalazine. The benzene solution on evaporation gave an oil which distilled at $165\text{--}168^\circ/20$ mm.; the distillate, on cooling with solid carbon dioxide and ether, solidified to a crystalline mass which melted at $46\text{--}47^\circ$. From its properties it is evidently the substance already described by Wheeler and Barnes (*Amer. Chem. J.*, 1900, **24**, 78), who prepared it by a different method (Found: $\text{N} = 10.64$. Calc., $\text{N} = 10.69$ per cent.).

2:4-Diketo-5-methyltetrahydrothiazole-2-hydrazone Hydrochloride, $\text{NH}_2\text{:N:C} \begin{smallmatrix} \text{NH}\cdot\text{CO} \\ \text{S} - \text{CHMe} \end{smallmatrix}$.HCl. — The isopropylidene derivative was boiled with 2*N*-hydrochloric acid under reflux for about fifteen minutes and the solution, after filtration from a small quantity of insoluble matter, was evaporated to dryness under reduced pressure at $40\text{--}50^\circ$. Acetone was recognised in the distillate by

its odour and by the iodoform reaction. The residue, consisting of the hydrochloride, was a white, granular, crystalline substance which was slightly hygroscopic, very soluble in water, slightly soluble in alcohol, and practically insoluble in ether. It decomposed above 220° . The aqueous solution gave a precipitate of silver chloride with silver nitrate and nitric acid and it appeared to give a silver salt due probably to the tetrahydrothiazole complex, but this was not investigated. The substance reduced Fehlings' solution on boiling (Found: N = 22.99, 23.15. $C_4H_7ON_3S \cdot HCl$ requires N = 23.14 per cent.). The *benzylidene* derivative was prepared by shaking an aqueous solution of the hydrochloride with benzaldehyde and recrystallising the product from alcohol, from which it was deposited as fine, white needles melting at 236° . It was slightly soluble in cold alcohol and in water (Found: N = 18.03. $C_{11}H_{11}ON_3S$ requires N = 18.03 per cent.).

It was not found possible to obtain the hydrazone itself in pure condition from its hydrochloride.

Reaction with Ethyl α -Bromo-n-butyrate. 2:4-Diketo-5-ethyltetrahydrothiazole-2-isopropylidenehydrazone, $CM_2 \cdot N \cdot N \cdot C \begin{smallmatrix} \text{NH} \cdot \text{CO} \\ \text{S} - \text{CHEt} \end{smallmatrix} -$

This reaction was carried out in the same way as with ethyl α -bromopropionate. The compound was recrystallised from alcohol, from which it separated in fine, white, glistening needles melting at 116° . It was only slightly soluble in benzene, ether, or water (Found: N = 20.99, 20.90. $C_8H_{13}ON_3S$ requires N = 21.11 per cent.).

2:4-Diketo-5-ethyltetrahydrothiazole was prepared from the above isopropylidene derivative by boiling with concentrated hydrochloric acid as in the previous case. After recrystallisation from a mixture of benzene and light petroleum, it melted at $63-64^{\circ}$ and was easily soluble in alcohol or benzene, less soluble in light petroleum. It agreed in melting point and properties with the substance previously prepared by Wheeler and Barnes (*loc. cit.*, p. 76) by another method.

2:4-Diketo-5-ethyltetrahydrothiazole-2-hydrazone hydrochloride was prepared by boiling the isopropylidene derivative with 2N-hydrochloric acid as with the corresponding 5-methyl compound. It was a white, granular, crystalline solid, soluble in water, slightly soluble in alcohol, and practically insoluble in ether, and decomposed on heating at $215-220^{\circ}$ (Found: N = 21.44, 21.39. $C_5H_9ON_3S \cdot HCl$ requires N = 21.49 per cent.). The *benzylidene* derivative was prepared in the usual way. After recrystallisation from alcohol, it was obtained as white, microscopic needles melting at 206° and was practically insoluble in ether,

water, or cold alcohol (Found : N = 16.90. $C_{12}H_{13}ON_3S$ requires N = 17.00 per cent.).

2 : 4-Diketo-5-ethyltetrahydrothiazole-2-hydrazone was prepared from equivalent quantities of the hydrochloride and sodium carbonate in aqueous solution. After the effervescence had ceased, the solution was evaporated to dryness at room temperature in a vacuum over sulphuric acid, the residue was washed with a small quantity of cold water to remove sodium chloride, and analysed after drying in a vacuum (Found : N = 26.23. $C_5H_9ON_3S$ requires N = 26.41 per cent.). It was a white, crystalline powder, soluble in hot alcohol, slightly soluble in benzene, ether, or water. It melted at 139° and appeared to be moderately stable, becoming slightly yellow on keeping.

Reaction with Ethyl Phenylbromoacetate. 2 : 4-Diketo-5-phenyltetrahydrothiazole-2-isopropylidenehydrazone, $CM_e_2N:N:C \begin{smallmatrix} \text{NH} \cdot \text{CO} \\ \text{S} - \text{CHPh} \end{smallmatrix}$,

was prepared by the usual method from this ester and the sodium derivative of acetonethiosemicarbazone. Recrystallisation from alcohol gave fine, white needles melting at 198–199° which were not appreciably soluble in benzene, ether, or water (Found : N = 16.89, 16.96. $C_{12}H_{13}ON_3S$ requires N = 17.00 per cent.).

2 : 4-Diketo-5-phenyltetrahydrothiazole was obtained by hydrolysis of the previous compound by means of concentrated hydrochloric acid in the usual way. After recrystallisation from alcohol, it melted at 125–126° and corresponded in its properties with the compound prepared according to another method by Wheeler (*Amer. Chem. J.*, 1901, 26, 352).

2 : 4-Diketo-5-phenyltetrahydrothiazole-2-hydrazone hydrochloride, prepared from the isopropylidene-hydrazone by hydrolysis with dilute hydrochloric acid in the usual way, was a white, microcrystalline powder which decomposed above 240°; it was rather sparingly soluble in cold water, soluble with difficulty in alcohol, and practically insoluble in ether (Found : N = 17.20, 17.15. $C_9H_9ON_3S.HCl$ requires N = 17.25 per cent.). The benzylidene derivative, prepared in the usual way and recrystallised from alcohol, formed microscopic, white, hair-like crystals melting at 257°; it was only slightly soluble in cold alcohol, benzene, ether, or water (Found : N = 14.15. $C_{16}H_{13}ON_3S$ requires N = 14.23 per cent.).

Attempts were made by various methods to liberate the free hydrazone from its hydrochloride, but a pure specimen could not be obtained.

In conclusion, we wish to thank the Governors of this College for a scholarship which has enabled one of us (R. B.) to participate in

this investigation. We desire also to thank the Carnegie Trust for the Universities of Scotland for a grant which has partly defrayed the expenses of the work.

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