

CHEMISTRY OF THE THIAZOLES

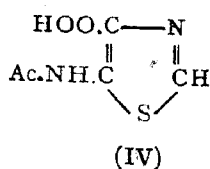
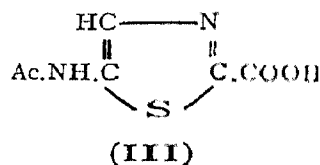
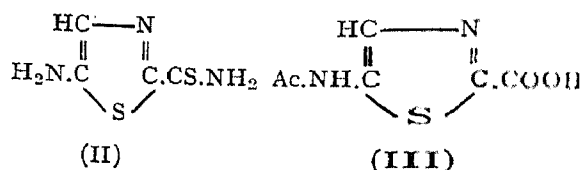
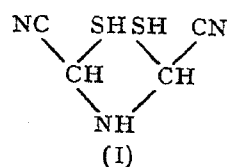
Part VI. Chrysean and Some of Its Derivatives

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WHAT appears to be the first thiazole compound appears to have been prepared inadvertently by Wallach¹ in 1874 by the extremely simple operation of passing hydrogen sulphide into a concentrated solution of sodium cyanide expecting to get thioformamide. Instead, he got a golden yellow compound which he called 'chrysean' invoking its brilliant golden colour. Twenty-five years later, Helsing² studied this compound. He first assigned this compound the structure (I) which, some time later, he revised to 2-thioamido-5-aminothiazole (II). As the final degradation product he obtained a

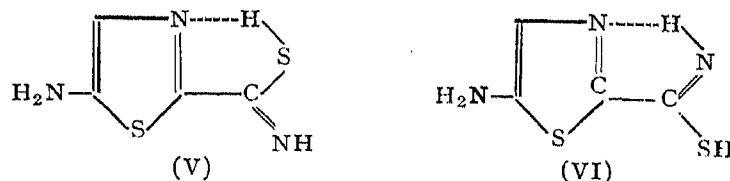


acetamido compound which he reasoned out should be 5-acetamidothiazole. This has been confirmed by the synthesis of 5-acetamidothiazole by Erlenmeyer *et al.*,³ starting from ethyl thiazole-5-carboxylate according to the method developed by Ganapathi and Venkataraman.⁴ That chrysean cannot be 5-amino-4-thioamidothiazole has been proved by the fact that 5-acetamido-4-carbomethoxythiazole synthesised by Cook *et al.*⁵ is not identical with the acetamidothiazolecarboxylic acid obtained from chrysean, which should therefore be 5-acetamidothiazole-2-carboxylic acid. While the structure (II) of chrysean is undoubtedly correct, it has not yet been synthesised. A number of attempts made by Ganapathi and Venkataraman to synthesise chrysean or 5-acetamido-2-cyanothiazole were not successful.

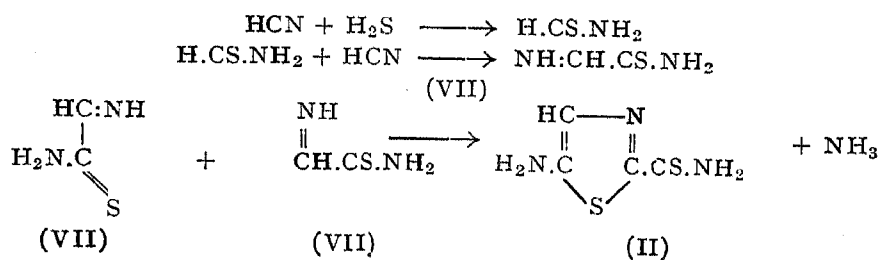
We present here our work on chrysean, its probable mode of formation and the compounds we have prepared making use of the two reactive groups in the compound.

It has been reported by previous workers, as also by Arnold and Scaife,⁶ that chrysean has the m.p. 204°. But by repeated crystallisation of the product we have been able to obtain two compounds, one separating in golden yellow plates, m.p. 222°, and the other, more soluble and obtainable in only small quantities, separating in needles, m.p. 146–46.5°. The mixed melting point of the two is anywhere between the two figures. They give the same acetyl compound and yield on degradation 5-acetamidothiazole. Existence of two compounds in the thiazoles has been reported in the case of sulphathiazole, which can be isolated in two forms, m.p. 176° and 202° and in the case of thiamine chloride which is known to exist in two forms, m.p. 232.4° and 249–50°. As regards the last, William and Cline⁷ think that the two forms are stereoisomers, while Todd and Bergel⁸ consider them to be due to dimorphism, because both are interconvertible.

Now the question arises whether the two forms of chrysean isolated are stereoisomers or dimorphs. While this could be settled only by physical measurements, we wish to discuss the theoretical possibilities. Because of the presence of the double bond between the carbon atoms 4 and 5 of the thiazole nucleus, these two carbon atoms, their fourth valencies, the nitrogen and sulphur atoms should all lie in the same plane. As regards the carbon atom 2, there are two possibilities: either it can lie in the same plane as the others or can be slightly out of plane. Since this carbon has only one valency free, the possibility of stereoisomerism is not there in the second case, unless there is restricted rotation of the group attached to the carbon atom 2. But there is a distinct possibility of two isomers in the case of chrysean if we take into account the possibility of hydrogen bond formation between the ring nitrogen with the hydrogen attached to the mercapto or the imino group, as shown in (V) and (VI). We hope to decide this question soon.

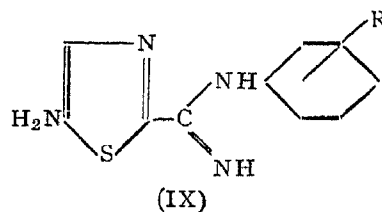
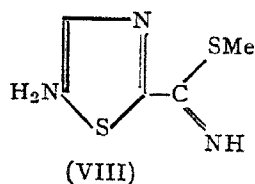


As regards the formation of chrysean by the simple process, the most plausible mechanism appears to us to be as follows:

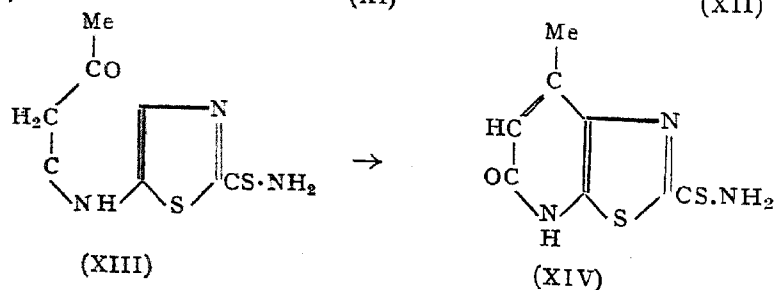
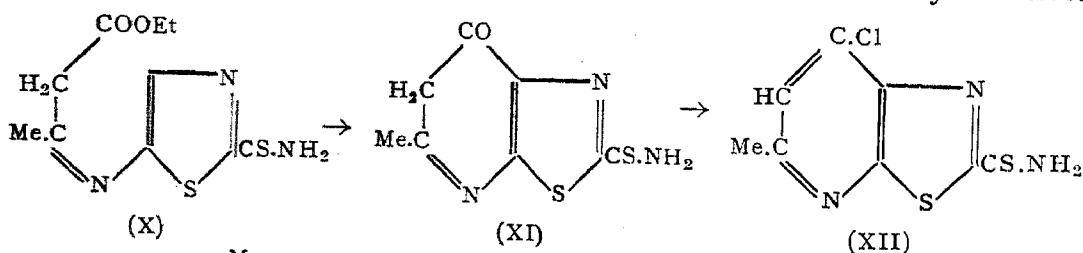


That thioformamide is an intermediate is certain because it itself with hydrogen cyanide furnishes chrysean. Since the compound (VII) should be very reactive it can not only condense with itself in which case chrysean is formed but can also polymerise. We do get, along with chrysean, a lot of tarry product, probably the polymerised product of (VII). This mechanism gives us a clue to devise new methods of synthesis of 5-aminothiazoles, which we are attempting.

On treatment with methyl iodide, chrysean easily furnishes the S-methyl derivative (VIII); under these conditions, the quaternary salt is not formed. The S-methyl derivative easily reacts with aromatic amines (aniline, *p*-chloraniline and *m*-aminophenol) to furnish the amidino derivatives (IX) which were prepared for testing their antimalarial properties.



The amino group of chrysean behaves as that of a typical aromatic amine. With the use of acetoacetic ester under the conditions of the Knorr-Conrad-Limpach synthesis, we could obtain a new type of pyridinothiazole. Chrysean with acetoacetic ester furnishes the acrylidene derivative (X) which on heating in Dowtherm for a short while easily cyclises to the pyridinothiazole compound (XI); this with phosphorus oxychloride is converted into the chloro derivative (XII) wherein the chlorine atom is very reactive.



On the other hand, the acetoacetyl derivative of chrysean (XIII) obtained by heating chrysean with acetoacetic ester at 145–50° C., does not cyclise on

heating with Dowtherm to the pyridinothiazole derivative (XIV). Attempts to effect the cyclisation with sulphuric acid caused decomposition. The properties of the pyridinothiazoles obtained are being studied.

EXPERIMENTAL

Chrysean.—A rapid stream of hydrogen sulphide was passed into a concentrated solution of sodium cyanide (200 g.) containing a little ammonia. Soon a golden yellow crystalline product separated. When there was no further increase in the separation of the crystalline product, it was filtered and washed (18 g.); m.p. 202–4°. In spite of numerous experiments we could not obtain a better yield of the product; this might be because the quality of the sodium cyanide we used was not quite good.

The above crystalline product was dissolved in boiling water and filtered. The crystals that separated on cooling were filtered off and a second crop was obtained by cooling the filtrate in ice-cold water. These were collected (m.p. 216–8°) and on crystallising once more from water, it separated in shining golden yellow plates (10–12 g.); m.p. 222° C. (Found: N, 26.02; $C_4H_5N_3S_2$ requires N, 26.4 per cent).

The mother liquor yielded a crop in needles (2–3 g.); m.p. 150–80°. On repeated crystallisation this was separated into the plates, m.p. 216–18° and the other fraction crystallising in needles, m.p. 146–46.5° (Found: N, 26.0; $C_4H_5N_3S_2$ requires N, 26.4 per cent.). On admixture of the two, the melting point was 170–80°.

The same type of fractionation could be carried out by using alcohol instead of water.

Both the forms yield the same acetamino compound, softening at 214° and melting with decomposition at 236–7° (Found: N, 20.61; $C_6H_7ON_3S_2$ requires N, 20.89 per cent.).

Both these forms on degradation according to the method of Hellsing furnished 5-acetamidothiazole.

S-Methylchrysean hydroiodide (VIII).—Chrysean (2 g.) was suspended in alcohol (10 c.c.), methyl iodide (2.5 g.) added and the reaction mixture refluxed on the steam-bath for 10–15 minutes. The solution which was clear threw down immediately the hydroiodide of the S-methyl derivative. After cooling the crystalline mass was filtered (3.2 g.) and recrystallised from alcohol; m.p. 180° C. (Found: N, 13.6; $C_5H_7N_3S_2$, HI requires N, 13.9 per cent.).

5-Amino-2-(N-phenylamidino)-thiazole.—A mixture of the above described hydroiodide (2.2 g.), aniline (0.7 g.), and water (20 c.c.) was refluxed

for 10 hours when the smell of the evolving mercaptan ceased. The reaction mixture was cooled, filtered from the tarry mass and the filtrate made alkaline when a pasty mass separated. It became granular after two days (1.1 g.). It was filtered and on crystallisation from benzene, it separated in beautiful golden yellow needles, m.p. 148° C. (Found: N, 25.2; $C_{10}H_{10}N_4S$ requires N, 25.6 per cent.).

5-Amino-2-(N-p-chlorophenyl)-amidinothiazole.—This was prepared as above by using *p*-chloraniline in the place of aniline. The compound crystallised from benzene and had m.p. 144–5° (Found: N, 21.62; $C_{10}H_9N_4S$ requires N, 22.17 per cent.).

5-Amino-2-(N-metahydroxyphenyl)-amidinothiazole.—Prepared as above described by using *m*-aminophenol in the place of aniline. It crystallised from alcohol in golden yellow needles; m.p. 215–6° (Found: N, 23.80; $C_{10}H_{10}ON_4S$ requires N, 23.93 per cent.).

Acrylidene derivative (X).—A mixture of chrysean (4.0 g.), acetoacetic ester (3.5 g.) and alcohol (20 c.c.) was refluxed on the steam-bath for 6 hours, the alcohol removed by distillation under reduced pressure and the residue crystallised from alcohol whereby the condensation product separated in needles; m.p. 149° (yield, 3.0 g.) (Found: N, 15.2; $C_{10}H_{13}O_2N_3S_2$ requires N, 15.5 per cent.).

2-Thioamido-4-hydroxy-6-methylpyridinothiazole (XI).—The above condensation product (3.0 g.) in Dowtherm (15 c.c.) was heated to 250° C. and maintained there for 15 minutes when a dark brown solid was thrown out. It was cooled, filtered and washed (1.0 g.); being insoluble in all organic solvents it could not be crystallised.

2-Thioamido-4-chloro-6-methylpyridinothiazole (XII).—The foregoing compound (1.0 g.) was treated with phosphorus oxychloride (2.0 c.c.) with cooling. After the vigorous reaction subsided, the mixture was refluxed on the steam-bath for 15 minutes and then poured on ice. The solid that separated was collected and crystallised from alcohol (yield, 0.8 g.); m.p. 178–9° (Found: N, 17.3; $C_8H_6N_3S_2Cl$ requires N, 17.24 per cent.). This compound is easily desulphurised indicating the presence of the thioamide group. It also reacts with amines indicating that the chlorine atom is reactive.

Acetoacetylchrysean (XIII).—A mixture of chrysean (4.5 g.) and acetoacetic ester (20 c.c.) was heated in an oil-bath at 145–50° C. for 2 hours. The reaction mixture was cooled, the solid that had separated was filtered off (2.0 g.) and crystallised from alcohol; m.p. 208–10° (Found: N, 17.0; $C_8H_9O_2N_3S_2$ requires N, 17.2 per cent.).

We thank Mr. M. H. Shah, Microanalyst, for carrying out the analyses reported.

SUMMARY

Chrysean has been isolated in two forms; whether they are stereoisomers or only dimorphic forms is discussed. A mechanism of formation of chrysean is suggested. With methyl iodide it gives readily the S-methyl derivative which reacts easily with aniline, *p*-chloraniline and *m*-aminophenol to furnish the amidino derivatives of formula (IX). Chrysean on being refluxed with ethyl acetoacetate in alcohol gave the acrylidene derivative (X) which cyclises on heating to the pyridinothiazole derivative (XI). Ethyl acetoacetate and chrysean at higher temperature condensed to yield the acetoacetyl derivative (XIII) which however did not cyclise to furnish (XIV).

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