## 102. *Thiopyrimidazine Derivatives.*

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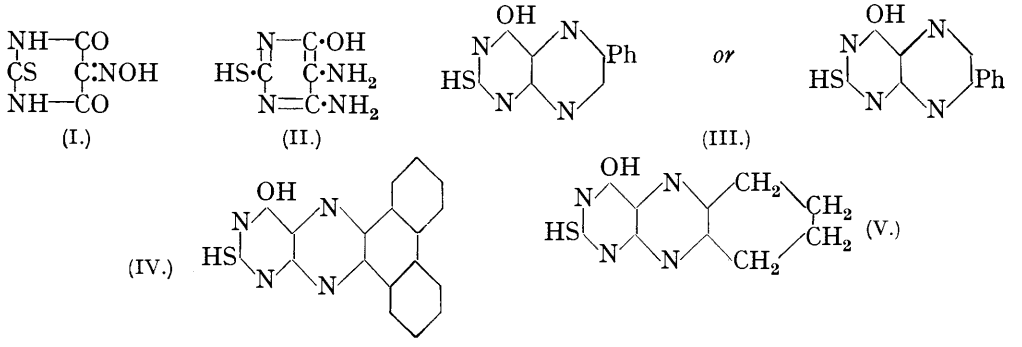
The substances herein described have been prepared in connection with Professor R. A. Peters' researches on vitamin-$B_1$, and in the hope of making a contribution to that investigation by orienting studies of synthetic compounds whose composition is comparable with that of the vitamin. The striking developments in the chemistry of the flavins, due to the pioneering work of Kuhn and others, have naturally directed attention to the chemistry of the fused nuclei comprising pyrimidine and azine units. But until quite recently there was no reason to suppose that vitamin-$B_1$ had any connexion with this group. Peters has, however, pointed out (*Nature*, 1935, **135**, 107) that vitamin-$B_1$ not only has the composition of a thiohexahydrolumichrome, but can actually be converted

by simple oxidation processes into substances which exhibit the characteristic fluorescent properties of known members of the alloxazine series. We directed our attention, therefore, to the synthesis of substances which might serve as models for the exhibition of the various characteristics of the vitamin. We have been successful in so far as the fluorescence properties are concerned. The introduction of the thiol group appears to inhibit the exhibition of fluorescence, which, however, appears after oxidation. (These facts are private communications from Professor Peters.)

In order to effect the desired syntheses, we attempted at first the preparation of thioalloxan; but although thiobarbituric acid (Michael, *J. pr. Chem.*, 1887, **35**, 456) could be readily nitrosated, the *thiovioluric acid* (I) produced could not be hydrolysed. We then condensed 4 : 5-diamino-2-thiouracil (II) (Traube, *Annalen*, 1903, **331**, 71) with phenylglyoxal (to III), with phenanthraquinone (to IV), and with *cyclo*hexane-1 : 2-dione (Riley, Morley, and Friend, J., 1932, 1878; compare Clemo and McIlwain, J., 1934, 1991, whose work appeared whilst ours was in progress). The product in the last case is considered to have the constitution (V), and on oxidation in aqueous solution the appearance of fluorescence corresponds rather closely with the behaviour of vitamin-$B_1$ under similar conditions. These substances are of course very different from the vitamin in other respects; they are, for example, very feebly basic, and attempts are now being made to reduce them in the hope of obtaining water-soluble bases.

Also it appears, from the available evidence, that the sulphur in the vitamin is otherwise disposed in the molecule.*

The thiopyrimidazines are infusible substances which darken from about 300° to 350°, the behaviour depending so much on the rate of heating that it was not deemed worthy of record; they all gave considerable difficulty in the analyses, leaving behind a nitrogenous residue under the usual conditions of combustion.




## Experimental.

*Thiovioluric Acid* (I).—An aqueous solution of sodium nitrite (2·5 g.) was slowly added to a well-stirred suspension of thiobarbituric acid (5 g.) in dilute hydrochloric acid; the colourless precipitate gave place to a yellow one. This crystallised from methyl alcohol in pale yellow prisms, which fell to a deeper yellow powder as the result of loss of methyl alcohol when dried at 100° (yield, 80%; no definite m. p.) (Found: C, 28·9; H, 1·8; N, 24·6. $C_4H_3O_3N_3S$ requires C, 27·8; H, 1·7; N, 24·3%). The substance was readily soluble in aqueous alkali and showed a pronounced tendency to become green on exposure to the air, especially in contact with filter-paper and other organic matter. On reduction with a boiling aqueous solution of ammonium sulphide, 2-thiouramil was undoubtedly obtained, but it could not be isolated in a sufficiently pure state for analysis. The base separated when its solution in dilute aqueous

* The important work of Williams and his colleagues was reported in an issue of the *J. Amer. Chem. Soc.* (**1935, 57, 229**; cf. Williams *et al.*, *ibid.*, p. 536) which reached us a few days after our MS. had been submitted to the Society. Evidently the vitamin does not contain a pyrimidazine ring, but the formation of such a system on oxidation is not excluded by the new information and is even rendered more probable. The constitution proposed by the American authors is that of a derivative of an *o*-diaminopyrimidine.

ammonia was evaporated, and it exhibited a marked tendency to become deep purple in the air.

Thiobarbituric acid condensed readily in alcoholic solution with *p*-nitrosodimethylaniline. The deep green precipitate obtained was freely soluble in water, but very sparingly soluble in organic solvents. It could not be hydrolysed with the formation of thioalloxan.

p-*Tolueneazothiobarbituric acid* was obtained in almost quantitative yield when a cold diazo-solution prepared from *p*-toluidine (1·1 g.), hydrochloric acid (3 c.c. of 33%), water (10 c.c.), and sodium nitrite (0·7 g.) was added to a solution of thiobarbituric acid (1·4 g.) in aqueous sodium hydroxide (3 g. in 20 c.c.). After acidification the orange-yellow mass was collected and recrystallised from much alcohol, forming orange-yellow prisms (Found : C, 50·1; H, 4·1. $C_{11}H_{10}O_2N_4S$ requires C, 50·4; H, 3·8%).

4 : 5-*Diamino*-2-*thiouracil* (II).—(A) This substance has been prepared by Traube (*loc. cit.*), but it does not appear to have been previously analysed (Found : C, 30·3; H, 3·8. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8%).

(B) A solution of *p*-toluidine (5·3 g.) in hydrochloric acid (15 c.c., *d* 1·16) and water (50 c.c.) was diazotised by the addition of a solution of sodium nitrite (3·5 g.), and then added to a cold solution of 4-amino-2-thiouracil (8 g.) in aqueous sodium hydroxide (15 g. in 160 c.c.). The mixture was acidified and the red infusible precipitate was collected (1 part) and eventually reduced by gradual addition to a hot solution of stannous chloride (3 parts) in concentrated hydrochloric acid. The liquid was brought to ebullition and cooled; the stannichloride that separated was collected and decomposed by trituration with concentrated aqueous ammonia, and on concentration of the filtered solution a crystalline precipitate was produced. The substance obtained appeared to be identical with Traube's diamine in respect of its solubility in aqueous ammonia and precipitation in a crystalline form on boiling; on examination of the crystals through crossed Nicols, the extinction values of the specimens were found to be identical. The base is also characterised by the formation of a sparingly soluble hydrochloride, and by its power of reducing alkaline solutions of silver, lead salts, and Fehling's solution.

7-*Thiol*-9-*hydroxy*-2 (or 3)-*phenylpyrimidazine* (III).—Equivalent quantities of phenylglyoxal and diaminothiouracil were condensed together in boiling acetic acid solution during 30 minutes. The precipitate was collected after cooling and recrystallised from acetic acid; the yellow needles obtained (yield, 50%) lost solvent of crystallisation at 100° and fell to a yellow powder (Found : C, 56·7; H, 3·2; S, 12·0. $C_{12}H_8ON_4S$ requires C, 56·3; H, 3·1; S, 12·5%). The substance is soluble in aqueous alkalis, but its basic properties are very feebly developed.

*Thiolhydroxyphenanthrapyrimidazine* (IV).—This substance was prepared in a like manner from phenanthraquinone, the reaction being complete in 15 minutes (yield, 30%). The slender yellow needles that separated from hot pyridine were soluble in aqueous sodium hydroxide but insoluble in most organic solvents and in aqueous acids (Found : C, 65·1; H, 3·2; N, 16·4. $C_{18}H_{10}ON_4S$ requires C, 65·4; H, 3·0; N, 16·9%).

11-*Thiol*-13-*hydroxy*-3 : 4 : 5 : 6-*tetrahydrobenzpyrimidazine* (V).—The substance usually termed *cyclo*hexanedione must be almost pure *cyclo*hexenonol, for it has none of the properties associated with the true α-diketones. It is colourless, devoid of sharp odour (the odour is more phenolic in character and resembles that of hydroxymethylene*cyclo*hexanone, or even that of salicylaldehyde), immediately soluble in alkalis, and gives an intense brownish-green ferric reaction. It was originally described as a crystalline solid, m. p. 38—40°, by Wallach (*Annalen*, 1924, **437**, 174), but Riley, Morley, and Friend (*loc. cit.*) obtained it only as an oil. It is therefore of interest that the product which we employed, and which was prepared by the method of the latter authors, crystallised completely and had m. p. 38—40°.

The condensation with an equivalent of diaminothiouracil in boiling acetic acid solution occupied 1 hour and the solid material that separated on cooling was recrystallised from acetic acid (yield, 25%), forming pale yellow needles. A better method consisted in heating the mixed reactants without solvent (oil-bath at 130—140°) for 15 minutes; the mass effervesced and then solidified. On trituration with aqueous ammonia a salt was obtained, and this crystallised from water in fine yellowish needles which lost solvent of crystallisation on drying at 100°. After decomposition by means of dilute hydrochloric acid, the *substance* crystallised from much hot water or from acetic acid in slender yellow needles (yield, 55%); the product from water was anhydrous (Found : C, 50·8; H, 4·4; S, 12·8. $C_{10}H_{10}ON_4S$ requires C, 51·3; H, 4·3; S, 13·7%). A further examination is being made by Professor Peters.

*Thioltrihydroxybispyrimidazine.*—Condensation of diaminothiouracil and alloxan was effected in the usual manner in acetic acid solution; the product was very sparingly soluble in organic solvents, but could be purified by crystallisation of its pyridine salt from aqueous pyridine.

The yellow plates were decomposed by means of dilute hydrochloric acid, and the resulting yellow powder analysed (Found : C, 32·2; H, 2·8. $C_8H_4O_3N_6S,2H_2O$ requires C, 32·0; H, 2·7%). This material was readily soluble in aqueous ammonia and other alkaline solutions.

Condensation of diaminothiouracil with isatin affords a deep red, insoluble substance which has not been purified. It dissolves in alkalis to deep red solutions, but no crystalline derivative has so far been encountered.

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