

THE OXIDATION OF THIOUREAS IN THE PRESENCE OF PYRROLES

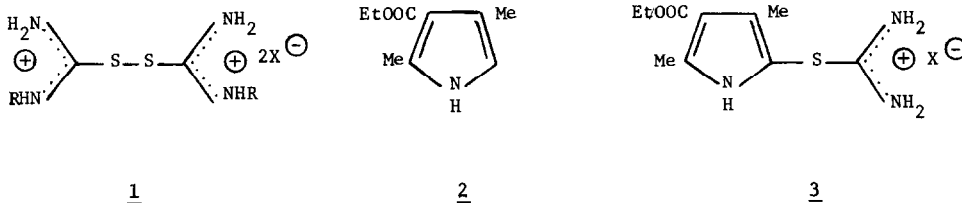
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(Received in UK 5 March 1968; accepted for publication 17 June 1968)

The oxidation of thiourea and its N-alkyl and N-aryl derivatives with halogens and other oxidising agents in acidic solution gives initially diformamidine disulphide salts 1, (R = H, alkyl or aryl; X = Cl, Br or I) (1-3). The N-alkyl- and N-aryl-substituted members of this class of compounds undergo a number of subsequent reactions on further oxidation leading to thiadiazolidines (4) and aminobenzothiazoles (5). It has now been shown that oxidation of thiourea itself with halogens in the presence of pyrroles (eg 2) gives S(pyrrolyl)isothiuronium salts (eg 3).

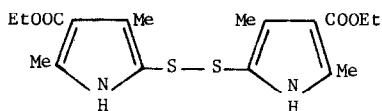
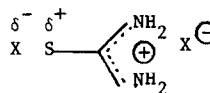


For example, addition of bromine to a solution of equivalent amounts of thiourea and the pyrrole 2 in acetic acid at <20°C gave the isothiuronium salt 3, (X = Br) (6) in 75-85% yield. The iodide 3, (X = I) was obtained in 85-95% yield by the addition of iodine-potassium iodide solution to a mixture of thiourea and the pyrrole 2 dissolved in aqueous ethanol. The structure of these salts was established by analysis and n.m.r. spectra (in DMSO-d₆) which showed signals at δ1.28 (triplet, 3 protons; CH₃ of ethyl ester), δ2.22 (singlet, 3 protons; β-CH₃ of pyrrole), δ2.43 (singlet, 3 protons; α-CH₃ of pyrrole), δ4.22 (quadruplet, 2 protons, CH₂ of ethyl ester), δ8.81 and δ11.95 (two broad signals, 5 exchangeable protons partly exchanged with traces of water in the solvent; isothiuronium NH and pyrrolic NH respectively). Further proof was

obtained by their hydrolysis with cold alkali and oxidation of the intermediate thiol (not isolated) by air or halogen to the dipyrrolyl disulphide 4, which proved to be identical (m.p., mixed m.p., mass spectrum) with an authentic sample prepared from 2 by the action of sulphur monochloride in ether (7).

The iodination procedure was found to be of general applicability and a number of S(pyrrolyl)isothiuronium iodides were prepared by this method. Some, including that from pyrrole itself, were isolated as the less soluble picrates.

The mechanism of the reaction is presumed to involve initially the oxidation of thiourea by halogen to the diformamidine disulphide salt 1, (R = H), which is then cleaved by more halogen to give a transient sulphenyl halide 5. Electrophilic attack of the sulphenyl cation of 5 on the reactive pyrrole nucleus would then give the S(pyrrolyl)isothiuronium salt 3.

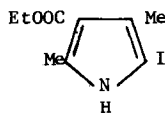
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The implication of the diformamidine salt 1, (R = H) in this sequence was demonstrated by carrying out the reaction using half the required amount of bromine, when the salt 1, (R = H, X = Br) was isolated from the reaction mixture. Furthermore, oxidation of 1 (R = H, X = Br or I) with halogen in the presence of 2 gave excellent yields of the S(pyrrolyl)isothiuronium salt 3.

This oxidative electrophilic substitution reaction may be related to the Hugerschoff reaction (8) in which N-aryl thioureas are oxidized by bromine to 2-aminobenzothiazoles. In a recent study of this reaction (5) diformamidine disulphide salts were isolated as intermediates and their oxidative cyclisation to 2-aminobenzothiazoles was considered to involve a sulphenyl halide similar to 5.

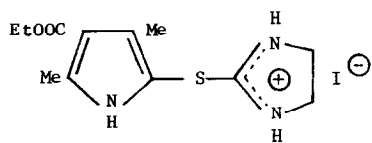
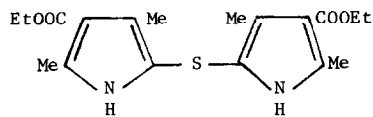
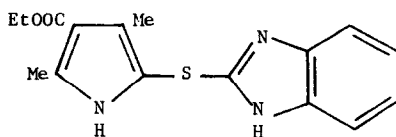
An alternative mechanism for the formation of the S(pyrrolyl)isothiuronium salts would involve halogenation of the pyrrole as an initial step followed by nucleophilic displacement of the halogen by thiourea (the normal mechanism for the formation of S-substituted isothiuronium salts from active halogen compounds). Such a mechanism was proposed by Woodbridge and Dougherty (9) as an intermediate stage in the reaction of certain pyrroles with thiourea,

iodine and alkali to give dipyrrolyl disulphides. In the present work it was shown conclusively that the iodopyrrole 6 did not react with thiourea under conditions in which the

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pyrrole 2, thiourea and iodine gave almost quantitative yields of the salt 3, (X = I). Under more vigorous conditions, however, displacement of iodide from 6 did take place to give the same salt 3, (X = I).

The extension of the oxidative substitution reaction to other thiourea derivatives has been undertaken. Whereas N,N'-ethylenethiourea and iodine reacted with the pyrrole 2 to give the expected thiuronium salt 7, N,N'-diphenylthiourea gave the dipyrrolyl sulphide 8. Oxidation of 2-mercaptobenzimidazole in the presence of 2 gave the pyrrolyl benzimidazolyl sulphide 9 in almost quantitative yield.

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The scope of this oxidative electrophilic substitution reaction is currently being investigated by the substitution of other thiol-thione tautomeric systems for thiourea and other reactive nucleophiles for pyrroles in the reaction sequence.

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