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Synthesis of Some Thiazolidino Pyrimidines

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Diphenyl thiourea was first reacted with chloroacetic acid to yield substituted thiazolidinone(III), which on treatment with aromatic aldehydes (*viz.* benzaldehyde, *p*-methoxybenzaldehyde and 3-methoxy-4-hydroxybenzaldehyde to yield corresponding benzylidine derivatives (IV, V, VI). These derivatives were condensed with urea and thiourea to yield substituted thiazolidino pyrimidines (VII, VIII, IX, X, XI, XII) (Scheme II).

INTRODUCTION

We observed from literature that most of the compounds having pyrimidine or thiazolidinone nucleus possess pharmacological action. For example they are sedatives, antiubercular, antiinflammatory or anaesthetic etc.

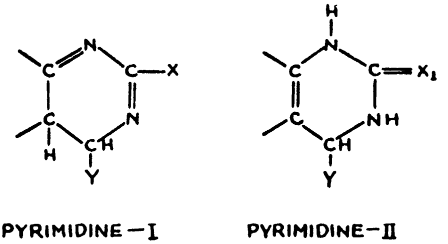
Thiazolidinones are also used as sedatives[1, 2], local anaesthetics[3, 4], hypnotics[5–7], analgesics[6] or antitubercular and antispasmodic[9] or anticonvulsants[8] etc. Thiazolidinones are employed in the synthesis of merocyamine dyes, which are used in photographic film industry. The compounds such as 5-arylidin 3-phenyl 2-phenylimino, thiazolidin-4-one are reported to give fast colour when dyed on wool.

Pyrimidine derivatives play a vital role in many biological processes, this ring system being present in nucleic acids, several vitamins, coenzymes, uric acid and other purines. Synthetic members of the group are also important as synthetic drugs (*i.e.* barbituric acid derivatives) and chemotherapeutic agents (*i.e.* sulphadiazine). Although the pyrimidine nucleus occurs in a considerable number of natural products of vital importance living organisms as uridine, cytidine, thymidine, deoxycytidine, 5-methoxy deoxycytidine and 5-hydroxy methyldeoxycytidine, pyrimidine rings condensed with other heterocyclic systems are also found useful. Most of them are reported for their pharmacological action. Sengupta *et al.* and others[9–16] synthesised thiazolidinones condensed with other heterocyclic rings having pharmacological action. In view of the rare availability and importance of condensed ring compounds of thiazolidinone and pyrimidine ring system it is desirable to synthesise the thiazolidino pyrimidines.

RESULTS AND DISCUSSION

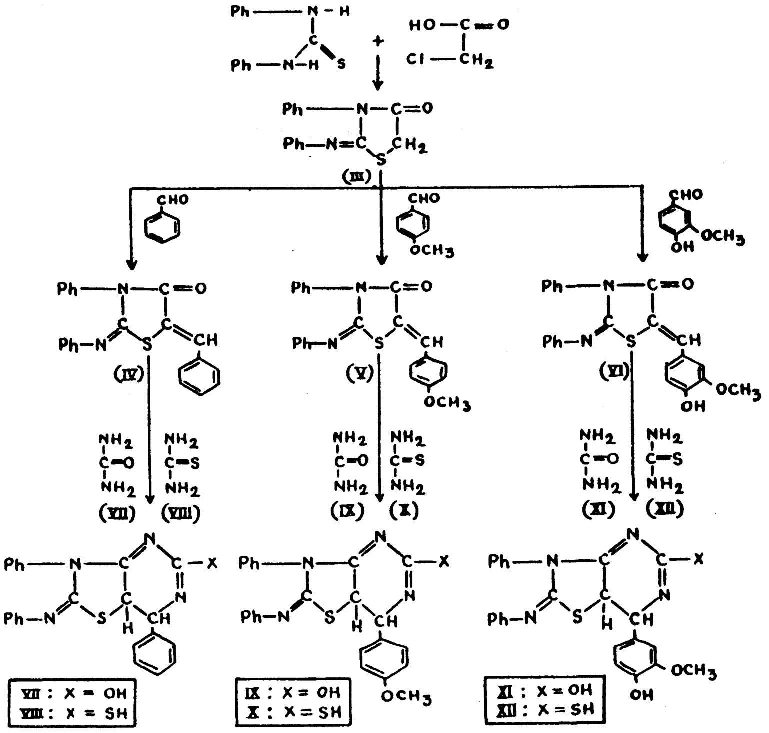
The mechanism of thiazolidinone ring formation is well known but the mechanism of pyrimidine ring system is not very clear and thus it opens a scope for the study of the mechanism.

Since benzylidine derivatives of substituted thiazolidinones were allowed to condense with urea and thiourea under suitable conditions, the benzylidine derivatives having α-β-unsaturated carbonyl moiety is expected to form the pyrimidine ring after condensation by way of attack on electrophilic carbonyl carbon followed by elimination of water. The thiourea and urea undergo intramolecular rearrangement to yield pyrimidine-I (Scheme-I).



$X = OH, SH$
$X_1 = O, S$
$Y = C_6H_5, C_6H_4(OCH_3), C_6H_3(OCH_3)(OH)$

Scheme-I



Scheme-II

The other possible alternative arising by 1,4 addition of urea and thiourea results in the formation of pyrimidine-II (Scheme-I). But in literature it is reported that pyrimidine-I structure is more stable and more likely to be formed than pyrimidine-II and most of the pyrimidines are formed by the reaction of α-β unsaturated carbonyl compounds.

It is thus taken for granted that pyrimidine-II is formed during the reaction. The adjoining thiazolidine ring is converted into thiazoline ring system which can easily produce thiazole ring by possible tautomerisation. Thus the resulting compound may be thiazole ring condensed pyrimidines. If pyrimidine-II is formed then >C═N frequencies should disappear from the infrared spectra. But contrary to this expectation >C═N absorption peaks are distinctly observed in all the pyrimidines. Therefore the formation of pyrimidine-II ruled out.

The structures of synthesised substituted thiazolidino pyrimidines are based on Scheme-II. The structures of these thiazolidino pyrimidines have been established on the basis of analytical and spectral studies.

The structure of the substituted thiazolidino pyrimidine derivatives is synthesised on the basis of Scheme-II. The structures have also been established on the basis of analytical and spectral studies. Thus the above synthesis opens a new knowledge in this particular field.

EXPERIMENTAL

The substituted thiazolidinone and its benzylidine derivatives were prepared by known methods and thiazolidinone pyrimidines were synthesised on the basis of given method. The melting points were determined by Toshniwal melting point apparatus and are uncorrected. The purity of the compounds was monitored on silcagel G plates. These are soluble in hot acetic acid and sparingly soluble in ethanol and acetone and insoluble in nonpolar solvents such as benzene, ether, etc. Physical and spectral data of the compounds are given in Table-1.

2-Phenyl imino 3-phenyl thiazolidine Δ^2-hydroxy-6-phenyl (4,5-d)-pyrimidine (VII): 2-Phenyl imino 3-phenyl 5-benzylidine thiazolidin-4-one (1 g), urea (1 g), glacial acetic acid (10 mL) and fused sodium acetate (0.5 g) were refluxed for 6 h on water-bath. After 1 h of refluxing all the contents dissolved and after a few minutes light yellow crystals started appearing gradually. After cooling these were filtered, washed with alcohol and crystallised from glacial acetic acid. Yield obtained 1.95 g, having m.p. = 299°C (Lit. 298°C). Found C = 69.90, H = 4.15, N = 13.65%. $C_{23}H_{18}N_4OS$ requires C = 69.34, H = 4.52, N = 14.07%.

2-Phenyl imino 3-phenyl thiazolidine Δ^2-2-thio-6-phenyl (4,5-d)-pyrimidine (VIII): This was prepared in the same manner as VII, only by changing urea through thiourea. Yield obtained 2.1 g, having m.p. = 298°C (Lit. 299°C). Found: C = 66.21, H = 4.0, N = 13.12%. $C_{23}H_{18}N_4S_2$ requires C = 66.66, H = 4.34, N =13.52%.

2-Phenyl imino 3-phenyl thiazolidine Δ^2-2-hydroxy-6-(p-methoxyphenyl)-(4,5-d)-pyrimidine (IX): 2-Phenyl imino 3-phenyl 5-*p*-methoxy benzylidine thiazolidin-4-one (1 g), urea (1 g), glacial acetic acid (10 mL) and fused sodium acetate (0.5 g) were refluxed for 6 h on a water-bath. After 1 h of refluxing all the contents were dissolved and after few minutes deep yellow crystals started appearing gradually. The crystals were filtered, washed with alcohol and crystallised from glacial acetic acid. The yield obtained 2.2 g, having m.p. = 232°C (Lit. 230°C). Found: C = 67.0, H = 4.25, N = 12.75%. $C_{24}H_{20}N_4O_2S$ requires C = 67.28, H = 4.67, N = 13.08%.

TABLE-1

Compound No.	m.p. (°C)	λ_{max} IR (cm^{-1})	UV bands (nm)
VII	299	1580 ν(C—N) 1270 ν(C—S—C) 1460–1440 ν(C—OH) 750 (Substituted benzene)	265, 294, 362
VIII	298	1570 ν(C—N) 1280 ν(C—S—C) 1480–1450 ν(C—OH) 760 (Substituted benzene)	267, 295, 360
IX	232	1585 ν(C—N) 1484–1450 ν(C—OH) 1260 ν(C—S—C) 750 (Substituted benzene)	264,297,362
X	230	1590 ν(C—N) 1480–1455 ν(C—SH) 1270 ν(C—S—C) 770 (Substituted benzene)	265, 293, 365
XI	245	1575 ν(C—N) 1280 ν(C—S–C) 1465–1445 ν(C—OH) 765 (Substituted benzene)	267, 290, 350
XII	243	1580 ν(C—N) 1270 ν(C—S—C) 1460–1440 ν(C—SH) 760 (Substituted benzene)	263, 292, 340

2-Phenyl imino 3-phenyl thiazolidine Δ^2-2-thio-6-(p-methoxy phenyl)-(4,5-d)-pyrimidine (X): It was synthesised as compounds (XI) only by changing urea by thiourea. Yield obtained 2.3 g, having m.p. = 230°C. Found: C = 63.65, H = 4.32, N = 12.20%. $C_{24}H_{20}N_4S_2O$ requires C = 63.96, H = 4.95, N = 12.61%.

2-Phenyl imino 3-phenyl thiazolidine Δ^2-2-hydroxy-6-(3′-methoxy-4-hydroxy phenyl)-(4,5-d)-pyrimidine (XI): 2-Phenyl imino 3-phenyl 5-(3′-methoxy) 5′-hydroxy benzylidine thiazolidin-4-one (1 g), urea (1 g), glacial acetic acid (10 mL) and fused sodium acetate (1.5 g) were refluxed for 6 h on a water-bath. After 1 h of refluxing all the contents were dissolved and after few minutes deep red crystals started appearing gradually. The crystals were filtered, washed with alcohol and crystallised from glacial acetic acid. Yield obtained 1.98 g, having m.p. = 245°C (Lit. 243.5°C). Found: C = 64.51, H = 4.20, N = 12.50%. $C_{24}H_{20}N_4O_3S$ requires C = 64.86, H = 4.50, N = 12.70%.

2-Phenyl imino 3-phenyl thiazolidine Δ^2*-2-thio-6-(3'methoxy 4-hydroxy phenyl)-4,5-d)-pyrimidine* (XII): It was synthesised as compound (XI) only by changing urea by thiourea. Yield obtained 2.2 g, m.p. = 243°C (Lit. 245°C). Found: C = 62.30, H = 4.10, N = 11.90%. $C_{24}H_{20}N_4S_2O_2$ requires C = 62.60, H = 4.34, N = 12.17%.

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