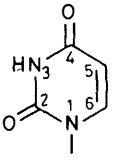
Synthesis of Heterocyclic Compounds *via* Enamines. Part 8.† Acid-catalysed Transformations in 4,4,6-Trimethyl-1,4-Dihydropyrimidine-2(3*H*)-thione Derivatives and Related Compounds

By **Harjit Singh** * and **Paramjit Singh**, Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India

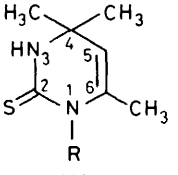
1-Substituted 4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones (2) on heating in 11M-HCl at 100—110° are converted into the corresponding 2-substituted-amino-4,6,6-trimethyl-6*H*-1,3-thiazines (4) and/or thioureas. But at 95—100°, Dimroth rearrangement products, *e.g.* the corresponding 2-substituted-amino-4,4,6-trimethyl-4*H*-1,3-thiazines (3) are formed.

RING transformations of naturally occurring pyrimidines with the ultimate aim of using these transformations in nucleosides have been performed with both nucleophilic and electrophilic reagents. Whereas the nucleophiles replace the N(1)–C(2)–N(3) unit,[1] the electrophiles implement the transformations through attack at the enamine 5,6-double bond.[2-5] The guiding factor in both modes of reaction of pyrimidines (1) is the enamine (>N–C=C) chromophore which helps attack of the nucleophiles at the enamine α-carbon [C(6)] and of the electrophiles at the β-carbon [C(5)].[6,7] Dimroth rearrangements in similar pyrimidine derivatives [8,9] are also the outcome of initial hydrolytic cleavage of enamines and subsequent ring closure.

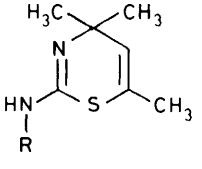
The ring interconversions of such pyrimidines possessing an additional functionality would be of added interest as the incorporation of such pyrimidines and their ring interconversions in nucleosides would provide modified nucleosides of biological interest. 1-Substituted 4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones (2) constitute one such category possessing a thioxo group at



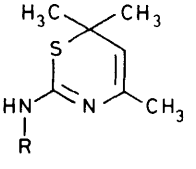
(1)



(2)



(3)



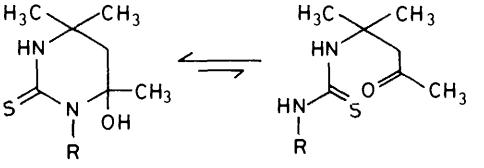
(4)

C(2) and hence we became interested in their acid catalysed transformations. Earlier, Zigeuner and his co-workers [10,11] found that on refluxing in xylene or *NN*-dialkylformamide solutions, (2) is converted into 4-substituted-amino-6,6-dimethyl-5,6-dihydropyridine-2(1*H*)-thiones. Ignatova and her co-workers [12-14] reported that (2) on heating in concentrated HCl rearrange to 2-substituted-amino-4,4,6-trimethyl-4*H*-1,3-thiazines (3). In our preliminary studies,[15] we reported that (2; R = C_6H_5) on treatment with 11M-HCl at 100—110° gives 2-phenylamino-4,6,6-trimethyl-6*H*-1,3-thiazine (4; R = C_6H_5) and phenylthiourea. The object of the present investigation was to examine and rationalise the behaviour of various compounds (2) towards acids under different conditions.

† Part 7, ref. 15.

RESULTS AND DISCUSSION

Earlier, we demonstrated that (4; R = C_6H_5) is formed from (2; R = C_6H_5) on heating in 11M-HCl solution at 100—110° *via* β-elimination of the initial hydrolytic product (5) to mesityl oxide and phenylthiourea which recondense.[15] Now, it has been found that (2; R = C_6H_5), on heating in 11M-HCl at 95—100°, forms only 2-phenylamino-4,4,6-trimethyl-4*H*-1,3-thiazine (3; R = C_6H_5).[12-16] Evidently, at lower temperature under acidic conditions, the intermediate (5) undergoes dehydrative recyclisation involving attack of the thioureido sulphur on the carbonyl carbon instead of β-elimination which is preferred at higher temperature. Hence, the mode of reaction of (2; R = C_6H_5) with 11M-HCl is temperature-dependent and Dimroth rearrangement results at lower temperatures. The treatment of (2; R = C_6H_5), with 0.2M-HCl at any temperature and for any length of time does not bring about any of these changes. Compound (5), on heating at 140—150° also gives the corresponding thioureas.

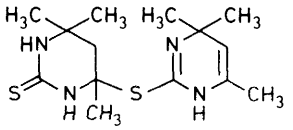


(5b) (5a)

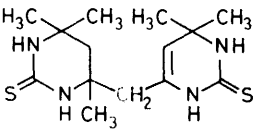
SCHEME 1

4,4,6-Trimethyl-1,4-dihydropyrimidine-2(3*H*)-thione (2; R = H) with 11M-HCl at 100—110° gives the dimer, 4-(1,4-dihydro-4,4,6-trimethylpyrimidin-2-ylthio)-tetrahydro-4,6,6-trimethylpyrimidine-2(1*H*)-thione (6) and 2-amino-4,6,6-trimethyl-6*H*-1,3-thiazine (4; R = H). At lower temperatures this reaction provides only

the dimer (6). Evidently, in (2; R = H), dimerisation is preferred over hydrolytic cleavage.[15] Meanwhile, a report [17] assigning structure (7) to this dimer has come to



(6)



(7)

our notice. We believe that the presence of only one downfield thione carbon signal (δ 173.928 p.p.m.) [18] in the ^{13}C n.m.r. data [15] rules out structure (7).

Since structures (2)—(4) (R = H or C_6H_5) were confirmed by unambiguous syntheses,[15,16,19] it was considered appropriate to use the spectral data to deduce a physical parameter which could provide a ready distinction of these isomeric structures. It has been found that (2) can best be distinguished from (3) and (4) by the downfield ^{13}C signal (δ 175—190 p.p.m.) for the thione carbon. The chemical shifts of 5-H in the ^1H n.m.r. spectrum of (3) are downfield from those in isomeric (4) (Table), a difference usually encountered in the chemical shifts of β-CH= of -S-CH=CH- and >N-CH=CH- structural units.[20] Again 5-H of (2) and (4) absorbs at similar chemical shifts.

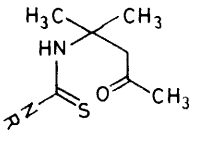
Chemical shifts (δ) of 5-H

R	(2)	(3)	(4)
H	4.44	4.75	4.54
C_6H_5	4.62	5.42	4.62

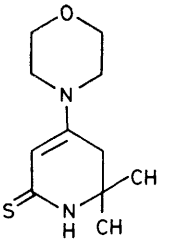
The condensation of methylamine and 2-methyl-2-isothiocyanatopentan-4-one at ambient temperature gave an adduct with molecular formula $C_8H_{16}N_2OS$ and 1,4,4,6-tetramethyl-1,4-dihydropyrimidine-2(3*H*)-thione (2; R = CH_3). The latter in its ^{13}C n.m.r. spectrum exhibited the thione carbon and C(5) signals at δ 177.80 and 110.63 p.p.m. (d) and in the ^1H n.m.r. spectrum, 5-H appeared at δ 4.68 (d, *J* 1.5 Hz). Likewise in the condensation of 2-methyl-2-isothiocyanatopentan-4-one with ethyl- and allyl-amines, adducts with molecular formulae $C_9H_{18}N_2OS$ and $C_{10}H_{16}N_2OS$ along with 1-substituted 4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones (2; R = C_2H_5 or CH_2=$CHCH_2$) were formed.

Because of the absence of carbonyl and the presence of hydroxy absorption bands in the i.r. spectra, the adducts (5) were assigned the carbinolamine structures, 1-methyl-, 1-ethyl-, or 1-allyl-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3*H*)-thione (5b; R = CH_3, C_2H_5, or CH_2=$CHCH_2$). The existence of five-membered cyclic carbinolamines from bicyclic aminoalkanones is on record.[21] The present studies further show that acyclic aminoalkanones also exist as six-membered cyclic carbinolamines. The insufficient solubility of these adducts precluded ^1H n.m.r. spectral determinations, but the i.r. spectra of adducts (5; R = H or C_6H_5) which had not been isolated earlier [15] were studied. Compound (5; R = H) did not show any carbonyl absorption band and existed as carbinolamine (5b; R = H), but (5; R = C_6H_5) absorbed at 1 695 cm^{-1} indicating the aminoketone (5a; R = C_6H_5) structure.[21,22]

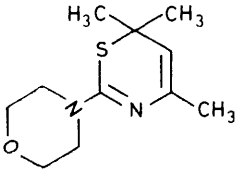
Since compounds (5), which were proposed as intermediates in the acid-catalysed transformations of (2) [15] have now been isolated, we have studied their transformations. On heating at 100—110° for prolonged periods or in 0.2M-HCl solutions for 3—4 h, (5) underwent cyclodehydration to the corresponding derivative (2). We had earlier noticed that adducts (8), obtained



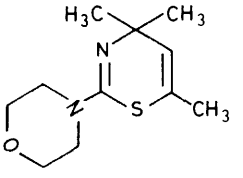
(8)



(9)



(10)



(11)

from secondary amines (morpholine or pyrrolidine) and 2-methyl-2-isothiocyanatopentan-4-one, on heating at 140—150 °C * underwent β-elimination to form almost quantitatively morpholine- and pyrrolidine-*N*-carbothioamides.[23] On similar heating at 150—160°, (5; R = CH_3, C_2H_5, or CH_2=$CHCH_2$) also gave the corresponding thioureas almost quantitatively. Since compounds (5) are obtained in very good yields, from easily available precursors, this observation permits a facile approach to the synthesis of thioureas. Zigeuner [11] reported that (8; R = morpholino) on heating in xylene (b.p. 140 °C) or morpholine (b.p. 128 °C) gave a pyridine derivative (9). We have now noticed that under these conditions a considerable amount of morpholine-*N*-carbothioamide is also formed. Hence at elevated temperatures, adducts (5) and (8) preferred pyrolytic β-elimination over cyclodehydration. Various derivatives of (2), on heating at 150—160 °C, gave a multitude of products and were not investigated.

On heating in 11M-HCl at 100—110° for 1.5 h, (5; R = CH_3) gave methylthiourea and a product, m.p. 86—87 °C, which on further heating was converted into methylthiourea.[24] The new product showed *m/e* 170 (M^+) and δ 1.67 (3 H, d, *J* 1.5 Hz) and 4.75 (1 H, d, *J* 1.5 Hz) (), supporting a structure formed by cyclodehydration of (5). The absence of a thione carbon signal in the ^{13}C n.m.r. spectrum coupled with the 5-H signal at δ 4.75 in ^1H n.m.r. spectrum, supported the 6*H*-1,3-thiazine structure (4; R = CH_3). The struc-

* We had erroneously reported the temperature as 100° earlier.

tural assignment was supported by the formation of this product along with (2; R = CH_3) in the condensation of mesityl oxide and methylthiourea.[25] Earlier, Mathes [26] had assigned structure (2; R = CH_3) to the product, m.p. 86—87°, obtained by refluxing (5; R = CH_3) in 25% H_2SO_4. But the present work and Willems' synthesis [27] of (2; R = CH_3), m.p. 160—161°, by base-catalysed condensation of methylthiourea and mesityl oxide confirmed the structure (4; R = CH_3) for the product, m.p. 86—87°. Likewise, (5; R = C_2H_5, CH_2=$CHCH_2$, H, or C_6H_5) on heating in 11M-HCl solution at 100—110° for 1.5 h, gave both the corresponding derivatives (4) and thioureas but after 3.0 h, thioureas were the only products. Similarly (2; R = CH_3, C_2H_5, or CH_2=$CHCH_2$) on heating in 11M-HCl at 100—110° initially changed to the corresponding (5) which subsequently underwent the above transformations. Compounds (4; R = CH_3, C_2H_5, CH_2=$CHCH_2$, or C_6H_5), on similar treatment, also gave corresponding thioureas. The adduct (8; R = morpholino) on heating in 11M-HCl at 100—110° gave solely morpholine-*N*-carbothioamide and 2-morpholino-4,6,6-trimethyl-6*H*-1,3-thiazine (10) was not formed. However (10) was obtained by the acid-catalysed condensation of morpholine-*N*-carbothioamide and mesityl oxide.

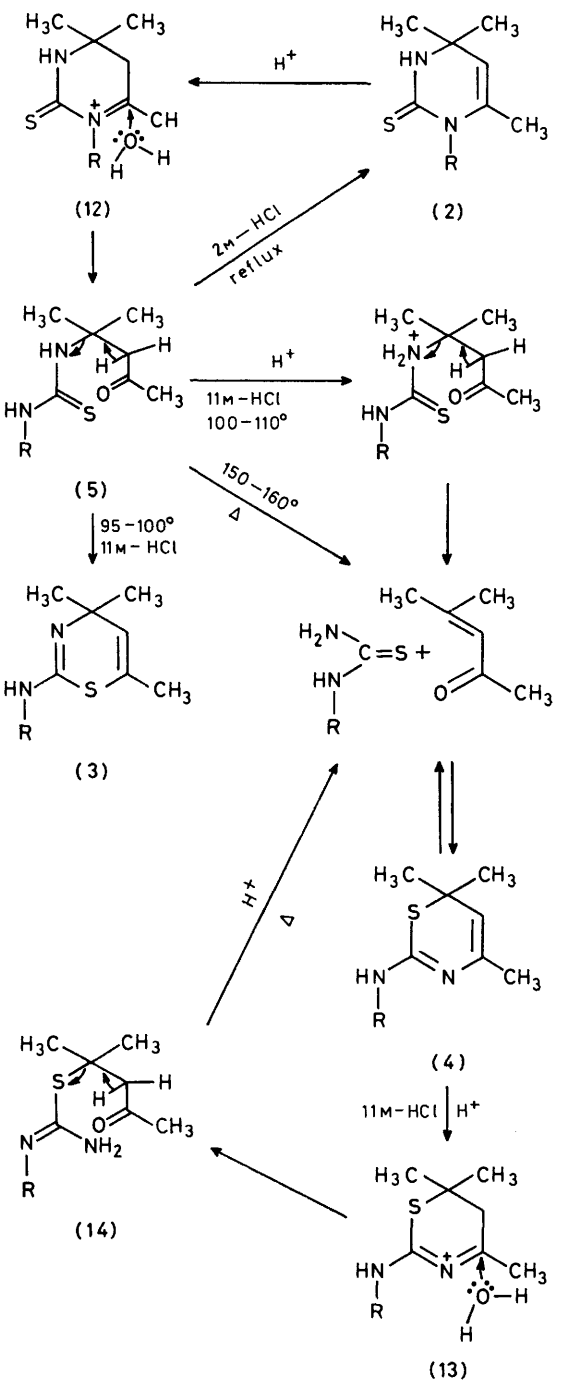
From the above studies it became evident that the transformations of (5) and thereby those of (2) were dependent both on the concentration of the acid and on the temperature of the reaction. Since Ignatova and her co-workers had obtained (5) from (2) [12-14] and the exact conditions for this reaction were not available, we heated (2; R = CH_3) in 11M-HCl solution at 95—100°. After 1.5 h (5; R = CH_3) and a product, m.p. 69—70°, which was assigned the structure, 2-methylamino-4,4,6-trimethyl-4*H*-1,3-thiazine (3; R = CH_3) from its mass, ^{13}C n.m.r., ^1H n.m.r., spectral data, were formed. On heating for 2.5 h, (5; R = CH_3) was completely converted into (3; R = CH_3) which itself did not undergo any change. Thus, other derivatives (2; R = C_2H_5, CH_2=$CHCH_2$, and C_6H_5) and (5; R = C_2H_5, CH_2=$CHCH_2$, and C_6H_5) were converted into the corresponding compounds (3) and the adduct (8; R = morpholino) gave 2-morpholino-4,4,6-trimethyl-4*H*-1,3-thiazine (11).

The ^{13}C n.m.r. spectra recorded only for isomers (2)—(4) (R = CH_3) complemented the ^1H data as 4*H*-1,3-thiazine (3) exhibited a C(5) signal (δ 125.83 p.p.m.) downfield from those for 6*H*-1,3-thiazine (4) (δ 108.12 p.p.m.) and pyrimidine-2(3*H*)-thione (2) (δ 110.63 p.p.m.) derivatives. Thus (2) and (4) exhibited enhanced enamine character [28] at C(5) and should give reactions characteristic of this chromophore. One such reaction of (2) with dichlorocarbene has been reported.[5]

The possible mechanisms of these transformations are depicted in Scheme 2. Compounds (2) and (4) undergo hydrolytic cleavage to (5) and (14) *via* attack of water on immonium salts (12) and (13) formed by protonation at the enamine carbon. Subsequently the intermediates (5) and (14) * undergo cyclodehydration or β-elimination reactions under different conditions.

EXPERIMENTAL

M.p.s were determined in capillaries and are uncorrected. ^1H N.m.r. spectra were recorded on a Tesla BS 487C 80 MHz instrument using tetramethylsilane as internal standard.



SCHEME 2

Elemental analyses were performed at the Australian Microanalytical Service, Melbourne. I.r. spectra were recorded with a CZ Specord-7 spectrophotometer. Mass spectra were run on a Hitachi–Perkin-Elmer RMU-60D instrument. For t.l.c., plates coated with silica gel G were run in chloroform–

* The intermediate (14) could not be characterised.

methanol (5 : 3) and spots were developed in an iodine chamber. The progress of all the reactions were monitored through t.l.c. of portions of the reaction mixtures drawn at regular intervals.

Transformations of 4,4,6-*Trimethyl*-1,4-*dihydropyrimidine*-2(3H)-*thione* (2; R = H).—A solution of (2; R = H) (1.56 g, 0.01 mol) in 11M-HCl was heated on a water-bath (95—100°). The progress of the reaction was very slow. After 60 h the mixture was cooled and was diluted with water (100 ml). A solid separated and was collected. On purification by chromatography over alumina it gave (6) (0.68 g, 90%), identical with an authentic sample (R_F, mixed m.p.).[15] No additional product was detected. After refluxing in 0.2M-HCl solution for 12 h (2; R = H) was recovered unchanged.

Transformations of 1-*Phenyl*-4,4,6-*trimethyl*-1,4-*dihydropyrimidine*-2(3H)-*thione* (2; R = C_6H_5).—(a) *In* 11M-HCl. A solution of (2; R = C_6H_5) (2.32 g, 0.01 mol) in 11M-HCl was heated on a boiling water-bath (95—100 °C). After 75 min it completely changed to (5; R = C_6H_5) and (3; R = C_6H_5) (t.l.c.). After another 2.5 h (5; R = C_6H_5) changed. The mixture was cooled, neutralised with an aqueous solution of sodium hydrogencarbonate, and extracted with chloroform (3 × 50 ml). After chromatography over alumina (3; R = C_6H_5) (2.2 g, 95%), m.p. 129—130 °C,[16] was obtained, *m/e* 232 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.62 (3 H, d, *J* 1.5 Hz, 6-CH_3), 5.42 (1 H, m, *J* 1.5 Hz, 5-H), and 7.00—7.37 (5 H, m, aromatic H).

(b) *In* 0.2M-HCl. A solution of (2; R = C_6H_5) (2.32 g, 0.01 mol) in 0.2M-HCl, even after refluxing for 12 h was recovered unchanged.

4,4,6-*Trimethyl*-1,4,5,6-*tetrahydro*-6-*hydroxypyrimidine*-2(3H)-*thione* (5b; R = H).—Liquid ammonia was added dropwise to 2-methyl-2-isothiocyanatopentan-4-one at 20 °C. The solid product thus separated was collected, washed with ether, and dried as such under reduced pressure, $\nu_{max.}$ (KBr) 3 300 (OH) and 3 200 (NH) cm^{-1}.

1-*Phenyl*-4,4,6-*trimethyl*-1,4,5,6-*tetrahydro*-6-*hydroxypyrimidine*-2(3H)-*thione* (5b; R = C_6H_5).—Aniline (0.93 g, 0.01 mol) was mixed with 2-methyl-2-isothiocyanopentan-4-one (1.57 g, 0.01 mol) and the reaction temperature was kept below 20 °C. The solid product separated was collected, washed with ether, and dried under reduced pressure, $\nu_{max.}$ (KBr) 3 100, 2 900 (CH), and 1 695 (C=O) cm^{-1}.

1-*Substituted* 4,4,6-*Trimethyl*-1,4,5,6-*tetrahydro*-6-*hydroxypyrimidine*-2(3H)-*thiones* (5b; R = CH_3, C_2H_5, CH_2=$CHCH_2$).—2-Methyl-2-isothiocyanatopentan-4-one (1.57 g, 0.01 mol) was mixed with an equivalent amount of methylamine. An exothermic reaction took place giving a solid mixture consisting of two components, R_F 0.5 and 0.7. On crystallization from methanol the major product, 1,4,4,6-tetramethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3*H*)-thione (5b; R = CH_3) (1.67 g, 89%), m.p. 161°, was obtained,[27] δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.7 (3 H, s, 6-CH_3), 2.06 (2 H, s, CH_2), 3.5 (3 H, s, N-CH_3), and 7.8 (1 H, m, 6-OH exchanged with D_2O), $\nu_{max.}$ (KBr) 3 060 (OH) and 3 040 (NH) cm^{-1}.

The residue obtained after the removal of the solvent from the mother-liquor was crystallized from benzene and gave 1,4,4,6-tetramethyl-1,4-dihydropyrimidine-2(3*H*)-thione (2; R = CH_3) (0.12 g, 7%), m.p. 160—161 °C, *m/e* 170 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.67 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.52 (3 H, s, NCH_3), and 4.68 (1 H, m, *J* 1.5 Hz, 5-H), δ_C ($CDCl_3$) 177.80 (>C=S), 132.66 (C-6), 110.63 (C-5) and 51.54, 36.12, 30.83, 27.90, and 19.59 (sp^3 C) p.p.m., off resonance proton-decoupled spectrum, δ 177.56 (s, >C=S), 132.63 (s, C-6), 110.50 (d, *J* 95 Hz, C-5), 51.59 (s, C-4), 36.04 (q, *J* 88 Hz, CH_3), 30.39 (q, *J* 60 Hz, CH_3), 27.59 (q, *J* 50 Hz, CH_3), and 19.51 (q, *J* 60 Hz, CH_3), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}.

Likewise, using ethyl- and allyl-amine the corresponding derivatives (5b) and (2) were formed.

Compound (5b; R = C_2H_5) had m.p. 132—135 °C (methanol) (Found: C, 53.6; H, 8.95; N, 14.2. $C_9H_{18}N_2OS$ requires C, 53.45; H, 8.9; N, 13.85%), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.37 (3 H, t, *J* 7 Hz, NCH_2CH_3), 1.65 (3 H, s, 6-CH_3), 2.07 (2 H, s, 5-CH_2), 4.00 (2 H, q, *J* 7 Hz, NCH_2CH_3), and 7.6 (1 H, m, 6-OH, exchangeable with D_2O), $\nu_{max.}$ 3 050 (OH) and 3 030 (NH) cm^{-1}. Compound (2; R = C_2H_5) had m.p. 148—149 °C (benzene), *m/e* 184 (M^+), δ ($CDCl_3$) 81.25 (6 H, s, *gem*-Me_2), 1.67 (3 H, d, *J* 1.5 Hz, 6-CH_3), 1.15 (3 H, t, *J* 7 Hz, NCH_2CH_3), 4.12 (2 H, q, *J* 7 Hz, NCH_2CH_3), and 4.7 (1 H, m, *J* 1.5 Hz, 5-H), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}. Compound (5b; R = CH_2=$CHCH_2$) had m.p. 135—137 °C,[27] δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.65 (3 H, s, 6-CH_3), 2.07 (2 H, s, 5-CH_2), 5.12—7.75 (allyl H), and 7.85 (1 H, m, 6-OH, exchanged with D_2O), $\nu_{max.}$ (Nujol) 3 180 (NH) cm^{-1}. Compound (2; R = CH_2=$CHCH_2$ had m.p. 128—129 °C (benzene), *m/e* 196 (*M*), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.86 (3 H, d, *J* 1.5 Hz, 6-CH_3), and 6.15—4.67 (6 H, m, allyl 5-H), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}.

Transformations of Compound (5b).—(a) *By dry heating at* 100—110 °C. 1,4,4,6-Tetramethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3*H*)-thione (5b; R = CH_3) (1.88 g, 0.01 mol) was heated in an oil-bath at 100—110 °C. After 30 min a new product, R_F 0.7, started forming and it took 7 h (t.l.c.) for the completion of the reaction. Compound (2; R = CH_3) (R_F, mixed m.p.) (1.69 g, 95%) was obtained after crystallization.

Likewise compounds (5b; R = C_2H_5) (2.02 g, 0.01 mol) and (5b; R = CH_2=$CHCH_2$) (2.14 g, 0.01 mol) formed the corresponding derivative (2) in 95 and 98% yields, respectively.

(b) *By dry heating at* 150—160 °C. Compound (5b; R = CH_3) (1.88 g, 0.01 mol) was heated at 150—160 °C in a dry test tube for 7—8 h. The product thus obtained on crystallization from methanol gave methylthiourea (0.85 g, 92%). Likewise compounds (5b; R = C_2H_5) (2.02 g, 0.01 mol) and (5b; R = CH_2=$CHCH_2$) (2.14 g, 0.01 mol) gave ethylthiourea (0.95 g, 95%) and allylthiourea (1.13 g, 98%), respectively.

(c) *In* 0.2M-HCl. A solution of (5b; R = CH_3) (1.88 g, 0.01 mol) in 0.2M-HCl (50 ml) was heated on a boiling water-bath (95—100°). After 40 min a product, R_F 0.7, started forming. After 8 h the mixture was cooled and the solid product (2; R = CH_3) (R_F, mixed m.p.) (1.5 g, 88%) was collected by filtration. Compounds (5b; R = C_2H_5) (2.2 g, 0.01 mol) and (5b; R = CH_2=$CHCH_2$) (2.14 g, 0.01 mol) were also similarly converted into (2; R = C_2H_5) (1.60 g, 87%) and (2; R = CH_2=$CHCH_2$) (1.66 g, 85%), respectively.

(d) *In* 11M-HCl *at* 95—100 °C. A solution of (5b; R = CH_3) (1.88 g, 0.01 mol) in 11M-HCl (25 ml) was heated on a boiling water-bath. After 15 min (3; R = CH_3) † started forming. Heating was continued and (5b; R = CH_3)

† For (3) and (4), the nomenclature and structures used in refs. 10—14 have been followed. But the absence of any splitting for NH signal in the n.m.r. spectra of the alkylamino derivatives suggest the corresponding 2-substituted-imino structures.

vanished completely after 1.5 h. The reaction mixture was neutralised with aqueous solution of sodium hydrogencarbonate and extracted with chloroform. On chromatography (3; R = CH_3) (1.6 g, 95%) was isolated, m.p. 60—70° (benzene), *m/e* 170 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.92 (3 H, d, *J* 1.5 Hz, 6-CH_3), 2.85 (3 H, s, NCH_3), and 5.45 (1 H, m, *J* 1.5 Hz, 5-H), δ_C ($CDCl_3$) 149.18 (s, >C=N), 125.83 (s, C-5), 124.69 (C-6), 56.55 (s, C-4), 29.73 (s, 2 × CH_3), and 22.04 p.p.m. (s, 2 × CH_3), off resonance proton decoupled spectrum, δ_C 124.62 (d, 80 Hz, C-5), 31.28—27.99 (2 × q, 2 × CH_3), and 23.44—20.68 (2 × q, 2 × CH_3), $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) cm^{-1}. Similarly, compounds (5b; R = C_2H_5) (2.02 g, 0.01 mol) and (5b; R = CH_2=$CHCH_2$) (2.14 g, 0.01 mol) gave (3; R = C_2H_5) * (1.66 g, 90%) and (3; R = CH_2=$CHCH_2$) * (1.8 g, 92%), respectively. Compound (3; R = C_2H_5) was a brown oil, *m/e* 184 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.15 (3 H, s, *J* 7 Hz, NCH_2CH_3), 1.67 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.32 (2 H, q, *J* 7 Hz, NCH_2CH_3), and 5.45 (1 H, m, *J* 1.5 Hz, C_5H), $\nu_{max.}$ ($CHCl_3$) 3 485 (NH) cm^{-1}. Compound (3; R = CH_2=$CHCH_2$) was a brown oil, *m/e* 196 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.92 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.9—5.9 (allyl H), and 5.5 (1 H, m, *J* 1.5 Hz, 5-H), $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) cm^{-1}.

(e) *In* 11M-HCl *at* 100—110 °C. (i) A solution of 1,4,4,6-tetramethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3*H*)-thione (5b; R = CH_3) (1.88 g, 0.01 mol) in 11M-HCl (25 ml) was heated at 100—110 °C in an oil-bath. It was completely consumed after 1.5 h. The mixture was cooled to room temperature, neutralised with aqueous sodium hydrogencarbonate, and then extracted with ethyl acetate (2 × 100 ml). After removal of the solvent a semisolid residue consisting of two components, R_F 0.52 and 0.05 (chloroform–methanol, 5 : 3), was obtained. The products were separated by chromatography over neutral alumina using benzene–chloroform (6 : 3) as eluant. The component of R_F 0.52 was 2-methylamino-4,6,6-trimethyl-6*H*-1,3-thiazine (4; R = CH_3) (1.2 g, 70.6%), m.p. 86—87 °C [27] (benzene–light petroleum), *m/e* 170 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.67 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.0 (3 H, s, NCH_3), and 4.75 (1 H, m, *J* 1.5 Hz, 5-H), δ_C ($CDCl_3$) 154.43 (s, >C=N), 143.82 (s, C-2), 108.12 (s, C-5), 43.735 (s, C-4), and 30.01, 29.69, 29.32, and 23.53 p.p.m. (4 × CH_3), off resonance proton decoupled spectrum, 154.29 (s, >C=N), 143.69 (s, C-6), 107.98 (d, *J* 95 Hz, 5-H), 43.60 (s, 4-C), and 31.18—23.00 p.p.m. (4 × q, 4 × CH_3), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}. The component of R_F 0.05 (0.2 g, 22.2%) was methylthiourea, m.p. 114 °C (methanol). It could not be extracted completely because of its solubility in water, *m/e* 90 (M^+) (Found: C, 26.9; H, 6.4; N, 30.8; S, 35.9. $C_2H_6N_2S$ requires C, 26.65; H, 6.65; N, 31.1; S, 35.55%).

Compound (4; R = C_2H_5) had m.p. 40—41 °C (benzene), δ ($CDCl_3$) 81.31 (6 H, s, *gem*-Me_2), 1.19 (3 H, t, *J* 7 Hz, NCH_2CH_3), 1.87 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.44 (2 H, q, *J* 7 Hz, NCH_2CH_3), and 4.70 (1 H, m, *J* 1.5 Hz, 5-H), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}. Compound (4; R = CH_2=$CHCH_2$) was a semisolid, *m/e* 196 (M^+), δ ($CDCl_3$) 1.25 (6 H, s, *gem*-Me_2), 1.68 (3 H, d, *J* 1.5 Hz, 6-CH_3), 4.72 (1 H, m, *J* 1.5 Hz, 5-H), and 4.2—5.2 (5 H, m, allyl H), $\nu_{max.}$ ($CHCl_3$) 3 500 (NH) cm^{-1}.

(ii) Alternatively, the above solution of (5b; R = CH_3) (1.88 g, 0.01 mol) was heated at 100—110 °C in an oil-bath for 3.5 h. The reaction on work-up as in (i) gave methylthiourea (0.7 g, 77%). Similarly (5b; R = C_2H_5) (1.02 g, 0.01 mol) and (5b; R = allyl) (2.14 g, 0.01 mol) gave ethylthiourea and allylthiourea in (0.78 g, 75%) and (0.69 g, 60%) yields, respectively.

Condensation of Methylthiourea and Mesityl Oxide.—Mesityl oxide (0.8 g, 0.01 mol) was added to a stirred solution of methylthiourea (0.9 g, 0.01 mol) in methanol (30 ml) saturated with anhydrous HCl gas at room temperature. The mixture was kept overnight. The solvent was removed under reduced pressure and the reaction mixture was neutralised with aqueous sodium hydrogencarbonate solution to give a product mixture consisting of two components which were isolated by chromatography over neutral alumina. The component of R_F 0.7 (0.17 g, 10%) was eluted with benzene and was found to be identical (R_F, mixed m.p.) with (2; R = CH_3). The component of R_F 0.52 (1.4 g, 82%) was eluted with benzene–chloroform (6 : 1) mixture and was found to be identical with (4; R = CH_3).

Similar condensations of ethylthiourea (1.04 g, 0.01 mol) and allylthiourea (1.16 g, 0.01 mol) with mesityl oxide furnished (2; R = C_2H_5) (0.09 g, 5%), (2; R = allyl) (0.14 g, 7%), (4; R = C_2H_5) (1.66 g, 90%), and (4; R = allyl) (1.67 g, 85%), respectively.

Acid-catalysed Transformations of (2).—(a) *In* 11M-HCl *at* 95—100 °C. A solution of (2; R = CH_3) (3.4 g, 0.02 mol) in 11M-HCl (50 ml) was heated at 95—100 °C on a boiling water-bath. After 1.5 h (2; R = CH_3) was completely consumed giving (3; R = CH_3) (40%) and (5b; R = CH_3) (60%) (t.l.c.). Heating was continued and after 2.5 h (5b; R = CH_3) was also consumed giving only (3; R = CH_3). The mixture was cooled and neutralised with aqueous sodium hydrogencarbonate solution. After column chromatography over neutral alumina using benzene–chloroform (6 : 2) as eluant, (3; R = CH_3) (3.3 g, 98%) was obtained. Similarly, the reactions of (2; R = C_2H_5) (3.8 g, 0.02 mol) and (2; R = allyl) (3.92 g, 0.02 mol) gave corresponding (3) in 98 and 95% yields.

(b) *In* 11M-HCl *at* 100—110 °C. A solution of (2; R = CH_3) (3.4 g, 0.02 mol) in 11M-HCl (50 ml) was heated in an oil-bath at 100—110 °C. The progress of the reaction was monitored by t.l.c. of aliquot portions of the mixture at regular intervals. After 1.15 h, (2; R = CH_3) was completely consumed and (5; R = CH_3) which started forming after 15 min and was present in *ca.* 70% yield (t.l.c.) after 1.5 h vanished after 3.0 h. Methylthiourea and (4; R = CH_3) started forming after 1.15 and 1.30 h, respectively. After 4 h (4; R = CH_3) also vanished. At this stage the mixture was worked up and was extracted with ethyl acetate (5 × 50 ml) giving methylthiourea (1.6 g, 90%).

Similarly, (2; R = C_2H_5) (3.68 g, 0.01 mol) and (2; R = CH_2=$CHCH_2$) (3.92 g, 0.02 mol) gave the corresponding thioureas both in 90% yields.

In another set of experiments the mixtures were worked up after 2.5 h. The product mixtures obtained after extraction with chloroform were chromatographed on alumina using benzene–ethyl acetate (9 : 1) as eluant and the corresponding (4; R = CH_3) (60%), (4; R = C_2H_5) (50%), and (4; R = CH_2=$CHCH_2$) (55%) were obtained. In these experiments the respective thioureas formed were not isolated.

Transformations of 2-*Substituted-amino*-4,6,6-*trimethyl*-6H-1,3-*thiazines* (4).—A solution of (4; R = CH_3) (1.7 g, 0.01 mol) in 11M-HCl (25 ml) was heated at 100—110 °C. After 30 min, it was completely changed to methylthiourea (0.35 g, 92%) (t.l.c.). Similarly, quantitative yields of

* Footnote as on page 1016.

ethyl- and allyl-thiourea were obtained by carrying out transformations of (4; R = C_2H_5) (1.84 g, 0.01 mol) and (4; R = CH_2=$CHCH_2$) (1.96 g, 0.01 mol), respectively.

Transformations of (8; R = *morpholino*).—(i) On refluxing a solution of (8) in xylene or morpholine, compound (9) was formed in 60% yield. The other product formed was morpholine-*N*-carbothioamide (30—35%).

(ii) On heating (8) at 140—150°, a new product (t.l.c.) started forming after 25 min and (8) was converted completely into this product after 2 h. It was found to be identical (R_F, mixed m.p.) with morpholine-*N*-carbothioamide.

(iii) A solution of (8) (2.26 g, 0.01 mol) in 11M-HCl (50 ml) was heated on a boiling water-bath (95—100 °C). The reaction was monitored through t.l.c. After 20 min, a new product started forming and the conversion was complete after 2.5 h, giving the only product 2-morpholino-4,4,6-trimethyl-4*H*-1,3-thiazine (11), m.p. 50—51 °C (benzene), *m/e* 226 (M^+), δ ($CDCl_3$) 1.21 (6 H, s, *gem*-Me_2), 1.97 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.3—3.7 (8 H, m, morpholine H), and 5.45 (1 H, m, *J* 1.5 Hz, 5-H).

(iv) On heating a solution of (8) (2.26 g, 0.01 mol) in 11M-HCl (50 ml) at 100—110°, it changed completely to morpholine-*N*-carbothioamide (t.l.c.) after 2.5 h.

*Condensation of Mesityl Oxide and Morpholine-*N*-carbothioamide.*—Mesityl oxide (0.08 g, 0.01 mol) was added to a solution of morpholine-*N*-carbothioamide (1.46 g, 0.01 mol) in methanol saturated with HCl gas. It was refluxed for 0.5 h and the solvent was removed under reduced pressure. The residue thus obtained was neutralized with aqueous sodium hydrogencarbonate solution and extracted with chloroform. After chromatography (10) was obtained as a brown oil (1.8 g) in 80% yield, δ ($CDCl_3$) 1.26 (6 H, s, *gem*-Me_2), 1.85 (3 H, d, *J* 1.5 Hz, 6-CH_3), 3.62 (8 H, s, morpholino H), and 4.62 (1 H, m, *J* 1.5 Hz, 5-H).

[9/1068 *Received, 9th July,* 1979]

REFERENCES

[1] K. A. Watanabe and J. J. Fox, *J. Org. Chem.*, 1978, **43**, 1193.
[2] A. M. Michelson, ' The Chemistry of Nucleosides and Nucleotides ', Academic Press, London, 1963.
[3] T. Kunieda and B. Witkop, *J. Amer. Chem. Soc.*, 1971, **94**, 3478.
[4] H. P. M. Thiellier, J. Koomen Gerrit, and U. K. Pandit, *Tetrahedron*, 1977, **33**, 2609.
[5] H. Singh and P. Singh, *Chem. and Ind.*, 1978, 804.
[6] G. Lauer, W. Schafer, and A. Schweig, *Tetrahedron Letters*, 1975, 3939 and references therein.
[7] A. G. Cook, ' Enamines: Synthesis, Structure and Reactions ', Marcel Dekker, New York, 1969.
[8] E. C. Taylor and A. McKillop, ' The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles ', Interscience, New York, 1970.
[9] B. S. Thyagarajan, ' Mechanism of Molecular Migrations,' Interscience, New York, 1969, vol. 1.
[10] G. Zigeuner, W. Bernd Lintschinger, A. Fuchsgruber, and K. Kollmann, *Mh. Chem.*, 1976, **107**, 155.
[11] G. Zigeuner and K. Schweiger, *Mh. Chem.*, 1976, **107**, 1361.
[12] L. A. Ignatova, P. L. Overchhin, and V. V. Unkouskii, *Zhur Vses, Khim. Ova*, 1970, **15**, 208 (*Chem. Abs.*, 1970, **73**, 25,408j).
[13] B. V. Unkovskii and L. A. Ignatova, *Khim. Geterotsikl Soedinenii*, 1969, **5**, 896, (*Chem. Abs.*, 1970, **72**, 111,396q).
[14] B. V. Unkovskii, L. A. Ignatova, P. L. Overchhin, and A. I. Vinogradova, *Khim. Geterotsikl. Soedinenii*, 1970, **12**, 190 (*Chem. Abs.*, 1971, **74**, 2307).
[15] H. Singh, P. Singh, and R. K. Mehta, *Austral. J. Chem.*, 1978, **31**, 2307.
[16] H. Singh and R. K. Mehta, *J. Indian Chem. Soc.*, 1976, **53**, 1223.
[17] G. Zigeuner, A. Frank, M. Dujmovits, and W. Adams, *Mh. Chem.* 1970, **101**, 1415.
[18] U. Vogeli, W. Von Philipborn, and K. Nagarajan, *Helv. Chim. Acta*, 1978, **61**, 607.
[19] H. Singh and S. Singh, *Austral. J. Chem.*, 1973, **26**, 2453.
[20] L. M. Jackman and S. Sternhell, ' Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry ', Pergamon, New York, 1969, p. 209.
[21] (*a*) H. Singh and S. Singh, *Tetrahedron Letters*, 1970, 585; (*b*) L. Lang, M. Barcazi-Beke, and D. Beke, *Magyar Kem. Folyoirat*, 1961, **67**, 364, (*Chem. Abs.*, 1962, **56**, 10,205g).
[22] A. E. Alper and A. Taurins, *Canad. J. Chem.*, 1967, **45**, 2903.
[23] H. Singh and R. K. Mehta, *Indian J. Chem.*, 1977, **15B**, 786.
[24] H. Singh and P. Singh, *Chem. and Ind.*, 1976, 984.
[25] S. N. Pandeya and G. V. Nair, *Indian J. Chem.*, 1965, **3**, 165.
[26] R. A. Mathes, *J. Amer. Chem. Soc.*, 1953, **75**, 1747.
[27] J. Willems and A. Vandenberghe, *Ind. Chim. belge*, 1958, 476.
[28] S. Rajappa and K. Nagarajan, *J.C.S. Perkin II*, 1978, 912.