CHAPTER-I

BENZO-PYRIMIDO THIADIAZEPINES

INTRODUCTION

The interest in the field of seven-membered heterocyclic compounds like benzodiazepines has been rapidly increasing because of their significant pharmacological properties. Benzodiazepine systems like Librium, Valium, Serax and Megadon have assumed prominence as psychosedative and tranquilizing agents. Recent synthesis of pharmacologically active thiazolo-diazepine and oxazolo diazepine derivatives has considerably broadened the interest in the field.

A brief review relating to the bridge-head seven membered heterocyclic compounds is given below.
BRIEF REVIEW

Fused 5/7 ring systems:

During the investigation of the structure of Lupine alkaloids, Clemo and Ramage(1) found that quinolizidin-1-one(I) underwent the Wolff-Kishner reduction to yield norlupinane(II) and Clemmensen reduction to yield pyrrolo-[2,1-a]azepine(III).

Leonard et al.(2-4) have also developed alternative methods for the synthesis of III.

By treatment of IV with chloral and hydroxylamine, Astill and Boekelheide(5) obtained V, which was converted to azepo-[h,i] indole. VI.

Collington and Jones(6) have described the synthesis of...
azepo- 1,2-α indole starting from 3-methyl indolide ion which reacted with 4-tolyl sulphonyl oxobutyl chloride to give the chlorobutyl indole(VII). VII was converted by sodium cyanide in dimethyl sulfoxide to the nitrile(VIII). The hydrolysis of the nitrile gave a high yield of the acid IX, which was cyclised by polyphosphoric acid to cyclic ketone(X).

\[
\begin{align*}
\text{VII, } R &= (\text{CH}_2)_4\text{Cl} \\
\text{VIII, } R &= (\text{CH}_2)_4\text{CN} \\
\text{IX, } R &= (\text{CH}_2)_4\text{COOH}
\end{align*}
\]

While investigating the Stevens rearrangement, Wittig and Ludwig(7) found that XI could be converted to azepo[a]benz[f] isoindole(XII) by reacting with phenyl lithium.

10,11-Dihydro-5-nitroso-5H-dibenz-[b,f]-azepine with lithium aluminium hydride gave a 5-amino compound XIII, which reacted
with aldehydes and ketones to give hydrazones. Fischer cyclisation of these hydrazones gave indolo-\[1,7-\text{ab}\]-benzazepines (XIV) (8).

Stolle, Merkle and Hanusch (9) have reported that the treatment of XV with 2-bromo-ethylamine hydrobromide gives XVI.

Nair and Adams (10) have synthesised benzimidazo[1,2-\text{a}]azepine XVIII by oxidative cyclisation of aromatic amines XVII with peroxy trifluoroacetic acid.
Bistrzycki and Fassler(11) have prepared dibenzo-[c, e]-benzimidazo-[1,2-α]azepine-15-one (XIX) by treating diphenic anhydride with o-phenylenediamine.

Duncan and Helsley(12,13) have prepared indolo-[1,2-a][1,4]-benzodiazepine-6-ones (XX) by the reaction of the corresponding 2-(2'-aminophenyl)-indole and chloro acetyl chloride and subsequent cyclisation of the chloro-acetamide compound in the presence of sodium hydride.

Robinson and Suginome(14) have reported that heating XXI in xylene solution yields chiefly pyrrolo-[3',2',3,2; 2',1'-α]indolo-[1,2-β][2,4]-benzodiazepine XXII.

\[ R = H, CH_3, CH_2CH_2OH \]
\[ R_1 = Cl, Br, H. \]
Scheuing and Walach have found that certain oxime esters or lactim esters such as XXIII react with acyl hydrazines to yield triazolo derivatives XXIV.

Thiazolo-[3,2-b][2,4]-benzodiazepines (XXV) have been prepared by reacting 1,2,4,5-tetrahydro-3H-benzo[2,4]diazepine-3-thione with halomethyl aryl ketones.

Fused 5/7 ring system with two extra hetero atoms:
Benzimidazo-\([1,2-\alpha][1,2]\) -benzodiazepine-6(5H)-ones (XXVI) have been synthesised according to the scheme given below (17). Dehydrochlorination of XXVII gives (18) imidazo-\([1,2-\alpha][1,3]\) -diazepine (XXVIII).

Fused 5/7 ring systems with three extra hetero atoms:

S-triazolo-\([4,3-a][1,4]\) benzodiazepines (XXIX) have been prepared from XXX and \(R^2CONH-NH_2\) (19). XXX was prepared from the corresponding 2-oxoanalogue of XXX by refluxing it with...
phosphorous pentasulphide in pyridine.

\[
\begin{align*}
\text{XXIX} & \quad \text{XXX} \\
R = \text{Cl}, \\
R^2 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{C}_6\text{H}_5
\end{align*}
\]

6-Phenyl-4H-s-triazolo-[4,3-a][1,4]-benzodiazepines (XXXII) have been prepared by heating 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione (XXXI) with CH\textsubscript{3}CONNH\textsubscript{2} in ethanol (20).

Meguro et al (21) have reported an interesting observation that 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine (XXXIII)
can easily be converted to the corresponding 2-hydrazino-1, 4-benzo-diazepine (XXXIV) by reaction with hydrazine hydrate in methanol in the presence of an acid catalyst at room temperature. XXXIV is easily cyclised by treatment with ethyl orthoformate in presence of sulphuric acid, giving rise to s-triazolo[4,3-\(\text{b}\)][1,3]-benzo diazepine(XXXV).
Fused 5/7 ring systems with four extra hetero atoms:

Kochhar (22) has successfully prepared s-triazolo-[4,3-b][1,2,4]-triazepines as represented by structure XXXVI and XXXVII.

George et al. (23) have reported that refluxing of the sodium salt of XXXVIII in dioxane gives 3-ethyl-8-nitro-s-triazolo-[3,4-b][1,3,4]-benzothiadiazepine (XXXIX).

Sidhu et al. (24) have reported that condensation of \( \text{O}_2\text{N-C}_6\text{H}_4-\text{CH(NHCICO)}_2 \) with hydrazine hydrate in alcohol yields 5,6-dihydro-5-(2'-nitrophenyl)-4H-1,2,4,6-tetrazepine XL which, on reduction and subsequent oxidation, gives 1H-1,2,4,6-tetrazepo[4,5-b]-indazole (XLI).
Fused 6/7 ring systems:

Leonard and Goode (25) have obtained XLIII by hydrogenation of XLII over a copper chromite catalyst at 265° and 350 atmospheric pressure.

1,3-Dioxo-2-benzyl-2,3,7,8-tetrahydro-1H-quinolo-[8,8a,1-ab]-benz[f]azepine (26) (XLIV) was obtained by heating iminodibenzyl with benzyl malonic acid.
Leonard, Swann and Fuller (27) have obtained azepo-\[1,2-\text{B}\]isoquinoline (XLVI) from the Dieckmann cyclisation of XLV. The Clemmensen reduction of XLVI gave the rearranged product, benzقة pyrido a azepine (XLVII).

1,2-dihydro-8-phenyl-3\text{H}-pyrido-\[3,2,1-\text{jk}\] \[1,4\]-benzodiazepin-5(6\text{H})-one (XLIX) has been prepared (28) by condensing 8-benzoyl-1,2,3,4-tetrahydroquinoline (XLVIII) with H₂NCH₂COOEt-HCl in refluxing pyridine.
Mueller and Zeller (29) have synthesised 6,7,9,10-tetrahydro-6-oxo-5H-isooquinolo-[2,1-\(d\)][1,4]benzodiazepinium bromide (L).  

Calder et al. (30) have reported that the reaction of 2,2'-bipyridyl with methylene sulphate in nitrobenzene followed by treatment with \(\text{H}_2\text{O}\) and \(\text{NaI}\) gives 6,8-dihydro dipyrido-[1,2-\(e\):2',1'-\(e\)]-1,3,6-oxadiazepinium diiodide (LI).
REFERENCES

-(13b)-

Importance and extensive use of Librium, Valium, Serax and Megadon containing seven membered ring system as psychosedative and tranquilizing agents prompted the author to prepare similar seven membered ring systems fused to different types of physiologically active heterocyclic nuclei. Studies in this field were also considered worth-while in view of the challenging interests they offer with regard to their synthesis and structure elucidation. It was planned to use spectral methods specially mass spectral technique for structural elucidation and that forms one of the most important aspects of the present investigation. Interpretation and rationalisation of the mass spectral peaks are described in Chapter IV.

This chapter describes the synthesis of 2,2,4-trimethyl-2H-benzo-[1,2-d] pyrimido [1,2-\(d\) [1,3,6]-thiadiazepines(I).

The rationale for the different fragments obtained by the fission of these compounds in the mass spectra is described in Chapter IV.
General method of synthesis of benzo-pyrimido thiadiazepines:

Benzo pyrimido thiadiazepines reported here have been synthesised according to the scheme outlined below:

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 + \text{S=C} \quad \text{N} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{O=CH} \quad \text{CH}_3 \\
\text{NH}_2 & \quad \text{N} \quad \text{NH}_2 \quad \text{B} \\
\text{CH}_3 & \quad \text{A} \\
\text{RCOOH/Ac}_2\text{O} & \quad \text{Conc. H}_2\text{SO}_4
\end{align*}
\]

\[R = H, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5-\text{CH}_2\]

Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-aminophenyl)-pyrimidine-2-thiol:

1-(o-Aminophenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol(II) was obtained by the condensation of o-phenylene-diamine with 2-methyl-2-isothiocyanato-4-pentanone according
to the method described by Mathes et al. (1,2). It was noticed that protonic catalysts (H₂SO₄ or HCl) were necessary to promote the reaction between aromatic amine and isothiocyanate to furnish 2-mercapto pyrimidine (II). 1-(o-aminophenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol (II) showed three strong bands in IR spectrum at 3210, 3350 and 3400 cm⁻¹ for NH₂ group.

The structure (II) was supported by NMR taken in DMSO at 100 MHz which has an interestingly separated triplet for gem-dimethyl between δ 8.88 to 8.87 (6H); CH₃ is centered at δ 8.55 (3H) and a singlet for -NH₂ is situated at δ 7.95 (2H); the -SH and allylic protons H are at δ 1.68 (1H) and δ 5.1 (1H) respectively. The aromatic protons appear in the form of a multiplet at δ 3.58 to 2.97 (4H).

The structure (II) was further confirmed by mass spectra, the fragmentation pattern of which is discussed in Chapter IV.

A special characteristic of III was that it did not undergo coupling reaction after diazotisation, rather it cyclised immediately to V(3).
Synthesis of benzo-1,2-d] pyrimido-1,2-f] 1,3,6 thia diazenine(V) from 1-(o-amino phenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiols(II):

The conversion of II to IV involves the interposition of a carbon atom between the -NH₂ group of nucleus A and -SH group of nucleus B of II with the resulting formation of a -N=C=X- linkage giving the corresponding heterocyclic system.

It may not be out of place to describe how the interposition of a carbon atom to bring about the -N=C=X- linkage from -NH₂ and HX (X = O, S, NH) resulting in different types of heterocyclic systems has been carried out by other workers.

(i) A number of imidazo quinolines(VII) have been prepared by the condensation of 8-amino quinoline(VI) with carboxylic acid or their derivatives(3,4).

(ii) Cavalieri et al.(5) have prepared adenine(IX) in 35-40% yield by cyclisation of 4,5,6-triamino pyrimidine(VIII) with aqueous formic acid(6). It is now known that conversion to adenine is most readily accomplished by heating(VIII) with
formic acid in anhydrous formamide.

(iii) Heterocyclic compounds such as X which possess a hydrazino group ortho to a ring nitrogen have been condensed with organic acids, acid chlorides and acid anhydrides to give the desired \( s \)-triazolo quinoxalines (XI) (7); in some cases, however, only the acetylated intermediates have been isolated, depending on the nature of the heterocyclic compound (8).
(iv) Potts and Hussain have directly synthesised XIII by the cyclisation of 4-methyl-2-thiazolyl hydrazine(XII) with formic, acetic or propionic acids(9).

\[
\text{XII} \quad \text{XIII}
\]

\[
R_1 = H, \text{CH}_3, \text{C}_2\text{H}_5
\]

(v) Various benzimidazoles, benzoazoles and benzothiazoles(XV) have been synthesised by the condensation of XIV with carboxylic acids in the presence of (10) or in the absence of mineral acids (11,12) and this reaction has been shown to be pH dependent(13).

\[
\text{XIV} \quad \text{XV}
\]

\[
X = O, S, \text{NH}
\]

(vi) The use of carboxylic acids for the formation of \(-\text{N=O-S-}\) has also been reported by Elion et al. who succeeded in obtaining XVII from XVI(14).
Two routes are possible for the formation. The final products with $-\text{N} = \text{C} - X$ bond may be obtained directly from the reaction mixture; alternatively the intermediate $N$-acyl derivatives may be isolated and cyclised to the final products after dehydration(15-17).

Method employed for convenience II to IV in the present investigation:

A number of attempts were made to achieve the synthesis of IV in one single step via the intermediate III, but all these attempts were unsuccessful leading either to III or the starting material II.

When the method of Phillips(10) i.e. the condensation of II with carboxylic acids in presence of hot dilute hydrochloric acid was employed, an intractable material which defied all attempts of its purification was obtained. The condensation of II with ethyl ortho-esters/ acetic anhydride, acid chlorides, carboxylic acids/ acetic anhydride, carboxylic acids/ polyphosphate ester according to the methods suggested by Taylor et al. and Yokoyama et al.,(19), led invariably to
the intermediate III. Also the reaction did not proceed either on refluxing II with carboxylic acids in presence of polyphosphoric acid or with carboxylic acid alone; the starting material was recovered unchanged. The characteristic features of the IR spectra of the intermediate III are the presence of $\text{NH}$ and $\text{C=O}$ vibration at 3250 and 1670 cm$^{-1}$ in III ($R=H$), at 3220 and 1650 cm$^{-1}$ in III ($R=CH_3$) and at 3300 and 1675 cm$^{-1}$ respectively in III ($R=C_2H_5$).

Structure III ($R=H$) is supported by its NMR spectrum (Plate I) and it possesses a doublet at $\tau 8.55(6H)$ due to $\text{CH}_3$, a singlet at $\tau 8.17(3H)$ for $\text{CH}_3$, the one H signal for and for $\text{S-H}$ approximately at $\tau 6.5(1H)$ and $\tau 0.9$ respectively. The aromatic protons are expected to appear in the form of a multiplet at $\tau 3.26 - 2.78$.

The NMR spectrum of III ($R=CH_3$) (Plate II) taken in CDCl$_3$ possesses a doublet at $\tau 8.55(6H)$ due to $\text{CH}_3$, a singlet at $\tau 8.2(3H)$ for $\text{CH}_3$ and another singlet at $\tau 7.52(3H)$ due to $\text{CH}_3-C$. The $\text{S-H}$ and allylic protons are situated at $\tau 0.78(1H)$ and $\tau 6.4(1H)$ respectively. The aromatic protons lie at $\tau 3.18 - 2.72(4H)$ in the form of a multiplet.

The cyclisation of intermediate III to benzopyrimido thiadiazepines (IV) was attempted with a variety of cyclodehydration agents. They either hydrolysed the intermediate III or were ineffective. Treatment of the intermediate III with
phosphoryl chloride and thionyl chloride resulted in a carbonaceous material which resisted all attempts at purification. Refluxing the intermediate III with PPA/POCl₃, PPA/P₂O₅/Chloroform, Na₂CO₃/ethanol resulted in the starting material. Heating the compound III above its melting point and again solidifying had no effect. While refluxing III with sodium acetate and acetic acid for 2 hours had no effect, the increase of refluxing period (10 hrs) resulted in the hydrolysis of III to II. Ultimately conc. sulphuric acid was employed for the cyclisation of III to IV. However, in some cases, the products were found contaminated with the starting material.

The pure samples were isolated by passing it through alumina column and eluting with acetone - petroleum ether (60-80°b.p).

Possible Mechanism:

A number of mechanisms may be considered for the conversion of II to IV via III. Addition of amine to the carboxylic acid may give the adduct II(i) which can eliminate water in the usual way leaving the intermediate III. Subsequent intramolecular nucleophilic attack by the thiol group would lead to the cyclic carbinolamine II(ii) which, by elimination of water, gives benzopyrimido thiadiazepines(IV). It is also possible that the initial adduct may cyclise directly to the carbinolamine.
-(23)-

II →

II(i)

II(iii)

II(iv)

III

III(i)

IV
Alternatively, further acylation of monoacyl compounds (III) leading to the diacyl compound III(i) may, by cyclisation and facile hydrolysis, give the final product IV. Of course it is also possible that the initial reaction takes place at the -S-H instead of at the amino group leading to the parallel reaction sequence involving adduct II(iii) and monoacyl derivative II(iv). Cyclisation or further acylation will give rise to the same intermediate II(ii) or III(i). In order to examine the route from III(i) to IV and from II(iv) to IV, a number of attempts were made to prepare the diacyl derivative III(i) and monoacyl derivative II(iv). But they all proved unsuccessful. This may be due to the formation of unstable compounds of the type XVIII as suggested by Amundsen et al. (20), or due to weak nucleophilicity of -S-H.

![Image of XVIII]

Furthermore, the route III(i) to IV can be ruled out on other considerations. The diacyl derivatives decompose too slowly to provide significant quantities of the final product. Studies of the decomposition of various diacyl derivatives have shown (21) that they hydrolyse initially to the monoacyl compounds.

Since the collapse of adducts such as II(i) to amides is
known to be a fast reaction (22), the more probable of the remaining two possibilities is the formation and decomposition of the monoacyl compounds.

IR spectra of IV (R=H, CH₃, C₂H₅) indicate the disappearance of original bands due to NH and C=O and appearance of strong band due to C=N−.

The structures IV (R=H, CH₃) are further supported by the disappearance of −S−H and amideic protons in their NMR spectra.
EXPERIMENTAL

Synthesis of benzo-pyrimido thiadiazepine:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{HSCN} & \quad \rightarrow \\
\text{N} & \quad \text{S} \\
\text{C} & \quad \text{C} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{H}_2\text{SO}_4 \\
\text{C}_6\text{H}_5 & \quad \text{xx} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{RCOCH} + \text{Ac}_2\text{O} \\
\text{C}_6\text{H}_5 & \quad \text{xix} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{xxi} \\
\text{H}_2\text{SO}_4 & \\
\text{R} \quad \text{H,CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5\text{--CH}_2 \\
\end{align*}
\]
I. Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-aminophenyl)-pyrimidine-2-thiol:

2-Methyl-2-isothiocyanato-4-pentanone (1,2) (78.5g, 0.5mole) was added to a solution of o-phenylenediamine (54.0g, 0.5mole) in absolute ethanol (75 ml.) taken in a 250ml flask. A drop of sulphuric acid was added to catalyse the reaction. The mixture was heated under reflux over the steam bath for two hours. The solvent was removed under reduced pressure and the residual brown coloured solid was washed with aqueous sodium carbonate (500 ml.) and then with water. The solid thus obtained on crystallisation from ethanol melted at 226°, the yield being 80.20g.

(Found: C, 63.10; H, 7.00; N, 16.90; S, 12.85, while C_{13}H_{17}N_{3}S requires C, 63.16; H, 6.88; N, 17.0; S, 12.96%)

(i) Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-formylaminophenyl)-pyrimidine-2-thiol (XX, R=H).

1-(o-Aminophenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol (2.0g, 0.008 mole), formic acid (10 ml) and acetic anhydride (10 ml) were taken in a 100 ml. flask and heated under reflux for 2 hours. The clear yellow solution obtained was evaporated to dryness. The solid was crystallised from ethanol; yield - 1.60g., 73%, m.p. 197-98°.

(Found: C, 61.16; H, 6.30; N, 14.98; S, 11.40 while C_{14}H_{17}N_{3}O requires C, 61.09; H, 6.18; N, 15.27; S, 11.64%).
(ii) Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-acetyl-
aminophenyl)-pyrimidine-2-thiol: (XX, R=CH₃).

1-(o-Aminophenyl)-1,4-dihydro-4,4,6-trimethyl-pyrimidine-
2-thiol (2.0g., 0.008 mole) was taken in a 50 ml R.B.Flask and
to it was added acetic acid (10 ml) and acetic anhydride(10ml).
The reaction mixture was heated under reflux for 2 hours and
the clear yellow solution so obtained was evaporated to dryness
under reduced pressure. The solid obtained on addition of ice
cold water to the residue was crystallised from ethanol.

Yield 1.55g.(67%); m.p. 187°

A single spot was obtained on TLC plate when eluted with 70%
rectified spirit and developed in iodine vapour.

(Found: C,62.00; H,6.73; N,13.98 while C₁₅H₁₉N₃S₀ requires
C,62.28, H, 6.57, N, 14.50%).

(iii) Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-propionyl-
aminophenyl)-pyrimidine-2-thiol: (XX, R=C₂H₅).

Propionic acid(10ml) and acetic anhydride(10ml) were
added to 1,4-dihydro-4,4,6-trimethyl-1-(o-aminophenyl)-pyri-
midine-2-thiol, taken in a 100ml R.B.flask. The reaction
mixture was heated under reflux for two hours and the clear
solution, thus obtained, was evaporated to dryness. The solid
obtained by the treatment of the residue with crushed ice and
sodium bicarbonate solution was crystallised from ethanol.

Yield 1.80g (73%); m.p. 197-98°C.
(Found: C, 63.60; H, 6.60; N, 14.19 while requires C, 63.70; H, 6.93; N, 13.86%)

(iv) Synthesis of 1,4-dihydro-4,4,6-trimethyl-1-(o-phenylacetyl aminophenyl)-pyrimidine-2-thiol (XX, \( R = C_6H_5-CH_2- \)):

1-(o-Aminophenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol (2.0 g, 0.008 mole) was taken in a 50 mL R.B. flask and to it was added phenyl acetic acid (1.3 g, 0.01 mole) and acetic anhydride (10 ml). The reaction mixture was heated under reflux for two hours and the clear solution so obtained was evaporated to dryness under reduced pressure. A gummy mass which was left in the flask was washed thoroughly with ice-cold water and crystallised from ethanol to get a white solid.

Yield - 0.5 g (25%), m.p. 115 -17°C.

The solid showed one spot on TLC plate when eluted with 70% rectified spirit and developed in iodine vapour.

III (i) Synthesis of 2,2,4-trimethyl-2\( H \)-benzo[1,2,3]pyrimido[1,2-f][1,3,6]thiadiazepine (XXI, \( R = II \)):

1,4-Dihydro-4,4,6-trimethyl-1-(o-formylamino phenyl)-pyrimidine-2-thiol (1.0 g) was dissolved in concentrated sulphuric acid (4 ml) and allowed to stand over night at room temperature. The reaction mixture after being warmed on steam bath for 15 minutes was poured on crushed ice and basified with 10% aqueous sodium hydroxide solution. The solid obtained was filtered, washed with water and crystallised from aqueous
(30) -ethanol (30: 70). Yield - 0.5 g (54%), m.p. 155°C.
(Found: C, 65.20; H, 6.01; N, 16.47 while C_{14}H_{15}N_{3}S requires C, 65.37; H, 5.83; N, 16.3%).

(ii) Synthesis of 2, 2, 4, 11-tetramethyl-2H-benzo-[1, 2-d] pyrimido-[1, 2-f] [1, 3, 6]-thiadiazepine: (XXI, R=CH₃).

1-(o-Acetylaminophenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol (1.0 g) was dissolved in concentrated sulphuric acid (4 ml) and allowed to stand over-night at room temperature. The reaction mixture, after being heated on steam bath for 15 minutes, was poured on crushed ice and basified with 10% NaOH. Filtered, washed and the air dried product was crystallised from aqueous ethanol or benzene-pet.ether (80-100°C) mixture.

Yield - 0.6 g (64%), m.p. 165°C.
(Found: C, 66.18; H, 6.29; N, 15.81 while C_{15}H_{17}N_{3}S requires C, 66.42; H, 6.27; N, 15.5%).

A single spot was obtained on TLC plate, when eluted with benzene-ethyl acetate mixture in the ratio 3:1 respectively and developed in iodine vapour.

(iii) Synthesis of 2, 2, 4-trimethyl-11-ethyl-benzo-[1, 2-d] pyrimido-[1, 2-f] [1, 3, 6]-thiadiazepine: (XXI, R=C_{2}H_{5}).

1,4-Dihydro-4,4,6-trimethyl-1-(o-propionylaminophenyl)pyrimidine-2-thiol (1.0 g.) was dissolved in concentrated sulphuric acid (4 ml) and allowed to stand over-night. The
reaction mixture was heated on steam bath for 15 minutes and poured on crushed ice and basified with 10% sodium hydroxide solution. The product so obtained was filtered, washed with water, air dried and crystallised from aqueous ethanol or benzene - pet. ether (80-100°).

Yield - 0.45g. (48%), m.p. 160°.

(Found: C, 67.16; H, 7.01; N, 14.90 while C₁₈H₁₉N₃S requires C, 67.36; H, 6.66; N, 14.73%).

(iv) Synthesis of 2,2,4-trimethyl-11-benzyl-2H-benzo[1,2-d]pyrimido[1,2-f][1,3,6]thiadiazepine (XXI, R= C₆H₅-CH₂-).

1-(o-Phenyl acetylamino phenyl)-1,4-dihydro-4,4,6-trimethyl pyrimidine-2-thiol (1.0g) was dissolved in concentrated sulphuric acid (4 ml) and allowed to stand over-night at room temperature. The reaction mixture, after being heated on steam bath for 15 minutes, was poured on crushed ice. It was then basified with 10% NaOH solution and allowed to stand for a few hours. The precipitated solid was filtered, washed and air dried. It was crystallised from aqueous ethanol.

Yield - 0.25g., m.p. 135-37°C.

The solid showed a single spot on TLC plate when eluted with benzene-ethyl acetate (3:1) and developed in iodine vapour.
REFERENCES:

6. Traube, Ann., 64, 331 (1904).