EXPERIMENTAL

Microanalyses are by Drs. Weiser and Strauss, Oxford and M/s B.N. Anand and L.K. Khullar, Chemistry Department, Panjab University, Chandigarh.

I.R. spectra were recorded on Perkin-Elmer I.R.S.

NMR spectra were run on a varian A-60 instrument.

PART I

Syntheses of 4:11-thiopegan derivatives (p. 41-80)

Section A: Syntheses of 4:11-thiopegan-9-ene derivatives (p. 41-56)

1. 2-(p'-amino-4':5'-methylene dioxy phenyl)thiazolidine (XCIII, p. 44)

(a) A solution of 6-amino piperonal (XCII, 6 g., 0.036 mole) in ethanol (30 ml.) was mixed with a solution of freshly prepared β-mercaptop ethyl amine (XC, 2.8 g., 0.036 mole) (68) in the same solvent (10 ml.). It was allowed to stand
at room temperature for 3 hours and then cooled in an
ice salt mixture. A yellow solid separated out was collected
which on crystallisation from ethyl acetate gave pale yellow
needles, m.p. 177-78° (4 g. 48%).

(b) Dry H₂S gas was passed through an ice cooled solution
of ethylene imine (3.6 g., 0.08 mole) in anhydrous ethanol
(30 ml.) for 3 hours. To this was then added a solution of
6-amino piperonal (8.25 g., 0.05 mole) in ethanol (30 ml.)
and the reaction mixture was worked up as in (a) above. It
did not depress the melting point of the product obtained from
(a) on admixture. The yield being 6.6 g. (56%).

Found : N, 12.96, Calcd. for C₁₀H₁₁N₂O₂S : N, 12.5 %.

2. Attempted synthesis of 6;7-methylene dioxy-10-methyl-
4;11-thiopeta-9-ene (CII, p. 47); formation of 6-N-
acetamino piperonal (XCVI, p. 46).”

2(2'-Amino-4';5'-methylene dioxy phenyl) thiazolidine
(XCIII, 2.5 g.) was dissolved in acetic anhydride (10 ml.)
and the resulting solution heated on a steam bath for half
an hour. The acetic anhydride was removed under reduced
pressure and the residue treated with ice-cold water and
filtered. The yellow coloured product (1.6 g.) was
crystallised from ethanol, m.p. 159-60°. It gave a negative
test for sulphur and did not depress the melting point of the
authentic sample of 6-N-acetamino piperonal (XCVI) (69) on
admixture.
3. Attempted synthesis of 6,7-methylenedioxy-4H-thiopega-10-one (CI, p. 47); formation of 6-N-carbethoxy amino piperonal (ACV, p. 46)

2(6′-Amino-4′:5′-methylenedioxy phenyl)thiazolidine (XCIII, 2.24 g, 0.01 mole) was dissolved in dioxan (30 ml.) containing sodium carbonate (2.2 g.) in water (5 ml.). To this solution was then added ethyl chloroformate (1.1 g., 0.01 mole) and the contents heated on a steam bath for half an hour. After cooling to room temperature the reaction mixture was added with stirring to water (100 ml.) whereupon a yellow coloured precipitate was formed. It was collected, washed with water and dried. It weighed (1.8 g.). It was crystallised from ethanol, m.p. 136°. This compound was identified to be 6-N-carbethoxy amino piperonal (ACV) by its undepressed mixed melting point with the authentic sample and through analysis.

Found: N, 6.2; Calcd. for C_{11}H_{11}NO_5: N, 5.9%.

4. Preparation of 6-N-carbethoxy amino piperonal (ACV)

A solution of 6-amino piperonal (16.5 g., 0.1 mole) in ethanol (100 ml.) containing sodium carbonate (8 g., 0.15 mole) was set to refluxing on a steam bath. To the refluxing solution was then added ethyl chloroformate (13.5 g., 0.125 mole) during 4-5 minutes. Separation of a yellow product started after 5 minutes. It was heated for
a total period of 20 minutes cooled and precipitate (17.5 g.) collected under suction. The filtrate on dilution with water (100 ml.) gave 2.6 g. of less pure product. It was crystallised from ethanol, m.p. 134-35\(^\circ\), the overall yield being 20 g. (87%).

Found: N, 6.4; Calcd. for C\(_{11}\)H\(_{11}\)NO\(_5\) : N, 5.9%.

5. Formation of \(2(\varepsilon'-\text{amino-4:5'-methylene dioxy-phenyl})\)-carbethoxy-thiamolidine (\(\text{CV, } \text{CH}_3\text{COOC}_2\text{CH}_3\) : p. 49).

A solution of ethyl ester of cystein hydrochloride (\(\text{CIV, } \text{CH}_3\text{COOC}_2\text{CH}_3\) : 3.7 g., 0.02 mole) (70) and pyridine (5 ml.) in water (10 ml.) was added with stirring to a solution of \(6\)-amino piperonal (3.3 g., 0.02 mole) in ethanol (30 ml.). It was warmed on a water bath for 2-3 minutes and then allowed to stand overnight. A pale yellow product separated out was collected which after crystallisation from ethanol dioxan mixture furnished white needles m.p. 198-99\(^\circ\) (1.9 g., 40%).

Found: N, 9.57; Calcd. for C\(_{13}\)H\(_{16}\)NO\(_5\) : N, 9.45%.

6. \(2(\varepsilon'-\text{Amino-4:5'-methylene dioxy phenyl})\)-4-carbethoxy thiamolidine (\(\text{CV, } \text{CH}_3\text{COOC}_2\text{H}_5\))

This was prepared by a procedure similar to the one adopted in experiment 5 by reacting together methyl ester of
cysteine hydrochloride and 6-amino piperonal. Crystallised from methyl ethyl ketone and ethanol mixture, m.p. 174-75\(^\circ\).

Found: N, 10.1, Calcd. for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_4\)S: N, 9.8E.  

7. Attempted synthesis of 3-carbethoxy or 3-carboxy-6\(^\text{a}\)-7-methylene dioxo-10-methyl-4:11-thiopeta-9-one

(CVI, \(R = \text{COOC}_{3}H_{7}, \text{SOOC}_{3}H_{5}, R^{1} = \text{CH}_{3}, p.53\)); formation of 6-N-acetamino piperonal (CVI)

2(2\(^\prime\)-Amino-4\(^\prime\):6\(^\prime\)-methylene dioxo phenyl)-4-carbethoxy or 4-carboxy-thioamidines were treated with acetic anhydride in a similar manner as given in experiment 2 on page 132. 6-N-acetamino piperonal was the only product isolated in both the cases.

8. Attempted synthesis of 3-carbethoxy or 3-carboxy-6\(^\text{a}\)-7-methylene dioxo-4:11-thiopeta-10-one (CVI, \(R = \text{COOC}_{3}H_{7}, \text{SOOC}_{3}H_{5}\)); formation of 6-N-carbethoxy amino piperonal (CVI)

Here also the procedure followed was similar to the one adopted in experiment 3 on page 133. The products isolated were identified to be 6-N-carbethoxy amino piperonal through their unpressed mixed melting point with the authentic sample.

Attempted synthesis of 6\(^\text{a}\)7-methylenedioxy-4:11-thiopeta-10-one (CVI, \(R = H, \text{COOC}_{3}H_{7}, \text{SOOC}_{3}H_{5}\))
9. Condensation of 6-α-carbethoxy amino piperonal (ACV) with β-mercapto ethylamine (AC); formation of 2(2'-carbethoxy amino 4:8'-methylene dioxy phenyl) thiazolidine (CVI, R = H, p. 51)

A solution of 6-α-carbethoxy amino piperonal (2.37 g., 0.01 mole) and freshly prepared β-mercapto ethyl amine (0.77 g., 0.01 mole) in ethanol (40 ml.) was heated on a water bath for 30 minutes. This was then kept overnight and the product reported was crystallised from acetone into white needles changing colour to pale yellow on standing, m.p. 156-57°C (2.0 g., 67%).

Found: C, 52.60; H, 5.05; NS, 10.75; Calc. for C_{13}H_{16}N_2O_8 S

C, 52.70; H, 5.40; S, 10.31%.

IR (nujol) 2970-2835, 1730, 1650, 1510, 1550, 1620, 1460,
1375, 1300, 1245, 1238, 1213, 1180, 1170, 1100,
1048, 990, 976, 950, 930, 865, 785, 768, 715 cm\(^{-1}\)

10. 2(2'-Carbethoxy amino-4:8'-methylene dioxy phenyl)-4-carbethoxy or 4-carbethoxy thiazolidines (CVI, \(R = CH_3COOC_2H_5\)) were prepared by reacting together equivalent amounts of 6-N-carbethoxy amino piperonal and methyl or ethyl ester of cysteine hydrochloride in presence of sodium acetate. The products were worked up as in experiment 9 (Table II, p. 52).
11. Attempted cyclisation of \( \text{2(2'-carbethoxy amino}- \)
\( \text{4'-6'-methylene dioxy phenyl)4-carbethoxy thiamolidine} \)
(CVI, \( R = \text{COOC}_2H_5 \))

(a) An ethanolic solution of (CVI, \( R = \text{COOC}_2H_5; 1.0 \) g.) was refluxed on a steam bath for 3 hours. On cooling the product separated (0.8 g.) m.p. 119-20° was crystallised from ethanol. It melted at 192° and did not depress the melting point of the authentic sample on admixture indicating that ring closure had not taken place.

(b) In another experiment (CVI, \( R = \text{COOC}_2H_5 \)) was heated in an oil bath at 150°, cooled and crystallised from ethanol, m.p. 133-34°, undepressed on admixture with 6-N-carbethoxy amino piperonal (LCV).

(c) Alternatively the thiamolidine intermediate (CVI, \( R = \text{COOC}_2H_5; 1.0 \) g.) was heated in vacuum (1 mm.) at 100-110° for 2 hours. Some vapours condensed on the cooler parts of the flask. On crystallisation from ethanol, a sticky mass was separated, which could not be characterised.

Synthesis of 6,7-methylene dioxy-10-methyl-4:11-thioperga-
gone (GXI, \( \text{A} = \text{H}_3; \text{A'} = \text{CH}_3 \), p. 52)
Condensation of 6-N-acetamino piperonal (XCVI) with -mercapto ethylamine (XU); isolation of 2(2'-acetamino-4':5'-methylene dioxy phenyl) thiaxolidine (CVII, R = H, R' = CH₃) and isolation of 6:7-methylene dioxy-10-methyl-4:11-thiopega-9-one (CXI, R = H, R' = CH₃)

A mixture of freshly prepared β-mercapto ethylamine (2.3 g, 0.03 mole) and 6-N-acetamino piperonal (6.2 g, 0.03 mole) was heated on a steam bath in ethanol (50 ml) for 15 minutes and then allowed to stand at room temperature overnight. The precipitated solid was filtered and crystallised twice from ethanol yielding (5 g, 62.5%) of white needles of 2-(2'-acetamino-4':5'-methylene dioxy phenyl thiaxolidine, m.p. 156-57°.

Found: C, 58.31; H, 5.12; N, 10.87, Calc. for C₁₂H₁₄N₂O₃S
C, 58.12; H, 5.26; N, 10.52 %.

I.R. (Nujol) 2380, 2910, 2840, 1606, 1560, 1500, 1460, 1415, 1376, 1315, 1280, 1226, 1200, 1170, 1160, 1120, 1066, 1030, 985, 930, 895, 880, 840, 745, 725, 715, 700 cm⁻¹

The filtrate from above was added with stirring to water (100 ml) and a small amount of solid separated, collected under suction. On crystallisation from ethanol it gave white needles of 6:7-methylene dioxy-10-methyl-4:11-
thiopega-9-ene (CXL) m.p. 178°.

Found: C, 68.64; H, 5.12; N, 11.28, Calcd. for C_12H_12N_2O_2S

C, 68.06; H, 4.84; N, 11.29.

13. Cyclisation of 2(2'-acetamino-4':5'-methylene dioxy phenyl thiomaleidine (CVIII); formation of 6:7-methylene dioxy-10-methyl-4:11-thiopega-9-ene (CXL)

2(2'-acetamino-4':5'-methylene dioxy phenyl)thiomaleidine (5.0 g.) obtained in experiment 12 was refluxed in ethanol for 2 hours. On cooling a solid separated out which was collected and crystallised from ethanol yielding (3 g., 65 %) of (CXL) m.p. 178°. It did not depress the melting point of the already obtained sample (m.p. 178°) from the previous experiment on admixture.

14. Synthesis of 3-carboxethoxy or 3-carbethoxy-6:7-methylene dioxy-10-methyl or phenyl-4:11-thiopega-9-ene (CXL, R = COOC_3H_7; COOC_6H_5; R' = CH_3, C_6H_5; p. 63)

**General procedure**: 6-N-Acyl amino piperonal (XCVI, R' = CH_3, C_6H_5) in ethanol was added to a solution of equivalent amounts of methyl or ethyl ester of L-cysteine hydrochloride and
sodium acetate in water. The reaction mixture was refluxed for 2 hours and kept overnight. The product separating was collected and purified (Table I:1, p. 56).

Section B: Synthesis of 2:3-benzo-4:11-thiopeta-9-ene derivatives (CXXV, R = H, CH₃, Cl; p. 57-58)

15. 2-Amino-5-methyl and 5-chloro thiophenols were prepared according to the directions given in the literature (71).

16. Condensation of 2-amino-thiophenols (CXXI, R = H, CH₃, Cl) with 6-N-acetaminopiperonal; formation of 2:3-benzo-6:7-methylene dioxy-4:11-thiopeta-9-ene (CXXV, R = H, CH₃, Cl)

General Procedure: A mixture of equivalent amounts of 6-N-acetaminopiperonal and appropriate 2-amino thiophenol in ethanol was refluxed on a steam bath. Separation of a pale yellow solid started within half an hour and increased with time. The contents were refluxed for a total period of 2 hours, cooled and filtered. The products obtained were crystallised from appropriate solvent. The data regarding these compounds is tabulated in Table IV, p. 59.

Section C:

A. Syntheses of 4-carboxy-4:11-thiopeta-9-ene derivatives (CXXX, p. 58-61)
17. Condensation of N-acetyl isatinic acid (CXLII, $R' = CH_3$; $R'' = H$) with methyl ester of l-cysteine hydrochloride (CIV, $R = COOCH_3$); formation of 3-carboxymethoxy-4-carboxy-10-methyl-4:11-thiopenta-9-one (CXLIX, $R = COOCH_3$; $R' = CH_3$; $R'' = H$)

To a solution of N-acetyl isatinic acid (1.3 g., 0.066 mole) (72) in ethanol (8 ml.) was added methyl ester of l-cysteine hydrochloride (1.14 g., 0.066 mole) and sodium acetate (0.9 g., 0.066 mole) dissolved in water (6 ml.). The contents were refluxed on a steam bath. Separation of a white crystalline product started within half an hour. It was heated for one and a half hour more, cooled and the product separated was collected under suction. It was crystallized from dilute ethanol in white needles, m.p. 220° (0.7 g., 34.3%).

Found: C, 55.13; H, 4.59; N, 9.53; S, 10.66; Calc. for C$_{14}$H$_{14}$N$_2$O$_5$S: C, 54.90; H, 4.57; N, 9.25; S, 10.45%.

The same procedure was adopted for the synthesis of other members of the series (Table V, p. 62).

8. Attempted synthesis of 4-methyl-4:11-thiopenta-9-one (CXLII)

18. Preparation of 6-amino-3:4-dimethyl acetophenone

This was prepared by reducing 3:4-dimethyl 6-nitro acetophenone with conc. HCl and stannous chloride. The amine was
isolated by usual methods, m.p. 131°. The amine obtained was converted into its acetyl derivative by treating it with acetic anhydride at room temperature for 2 hours, m.p. 98-99° (73).

19. Attempted condensation of 6-N-acetamino-3:4-dimethylacetophenone; with ethyl ester of L-cysteine hydrochloride; attempted formation of 3-carbethoxy-4,6,7,10-tetramethyl 4:11-thiopogas-9-ene

To a solution of 6-N-acetamino-3:4-dimethyl acetophenone (0.05 g., 0.01 mole) in ethanol (35 ml.) was added ethyl ester of cysteine hydrochloride (1.01 g., 0.01 mole) and sodium acetate (0.79 g., 0.01 mole) in water (10 ml.). The contents were heated on a water bath for 2 hours. On dilution with water a white crystalline product (0.6 g.) was obtained which after crystallisation from ethanol melted at 184-86°. It did not contain sulphur. It was analysed for nitrogen and was found to contain 9.6 per cent of nitrogen. The exact nature of this compound is under investigation.

Section D : Syntheses of quaternary 4:11-thiopoges derivatives (p. 64-79)

(1) Syntheses of 3-bromomethyl-4:11-thiopogas-9:11-diene bromides (CXXXI, Table VII)

20. Preparation of 4-quinazolones : These were prepared by heating together anthranilic acid or N-acyl anthranilic
acid (1 mole) and formamide (1-1.5 mole) at a temperature ranging from 120-160, depending upon the N-acetyl anthranilic acid used, for 4 hours. The solid products thus obtained were crystallised from appropriate solvents (74).

21. Preparation of 4-mercapto quinazolines (CXXXIII)

4-Quinazolones (1 mole) and phosphorus pentasulphide (1.1 mole) were refluxed in dry pyridine for 3 hours. The contents were then added with stirring to warm water to decompose excess of phosphorus pentasulphide. The yellow coloured products thus obtained were collected and purified (75).

22. Reaction of 4-mercapto quinazoline (CXXXIII) with allyl chloride (CXXV, R = H); formation of 4(S-allyl) mercapto quinazoline (CXXXVI, Table VI, p. 76)

4-Mercapto quinazoline (8.1 g., 0.06 mole) was dissolved in sodium hydroxide solution (250 ml., 1 %) and filtered to remove any suspended impurity. To this was then added allyl chloride (4.56 g., 0.06 mole) and sufficient ethanol (about 50 ml.) to render the solution homogeneous. The resulting clear solution was stirred for 2-3 minutes when it became turbid and an oily liquid started separating. It was kept at room temperature for half an hour and then
extracted with ether (200 ml.). The combined extract dried over anhydrous sodium sulphate and after removing the solvent the crude oily product was distilled under reduced pressure, b.p. 150° (7.8 mm.), yield 8.1 g. (67%).

Found : C, 65.61; H, 5.05; N, 13.93, Mr. Wt. 195, Cals. for C_{11}H_{10}N_{3}S O, C, 65.34; H, 4.95; N, 13.76 %. Mol. Wt. 202.

23. Ferrate derivatives of (CXXVI) was crystallised from ethanol, m.p. 178-79°.

Found : N, 16.60; Cals. for C_{17}H_{23}N_{6}O_{7} : N, 16.20 %.

24. Treatment of 4(3-allyl)mercapto quinazoline with HCl gas; attempted formation of 3-methyl-4:11-thiopage-9:11-diene chloride (CXXXVIII); formation of 4-quinazolone hydrochloride (CXXXII, R = H)

4(3-Allyl)mercapto quinazoline (CXXVI, 5.0 g.) was dissolved in anhydrous ethanol (50 ml.) and the resulting solution was chilled in an ice-salt mixture. Dry HCl gas was passed through it whereupon a white crystalline solid separated out immediately. It was collected and crystallised from anhydrous ethanol, m.p. 259-60°. It was found to be 4-quinazolone hydrochloride through its analysis and mixed melting point with the original sample on admixture showing
removal of \(-\text{S-CH}_2\text{-CH=CH}_2\) side chain by hydrolysis.

Found: N, 15.26; Calc. for \(\text{C}_8\text{H}_7\text{ClN}_2\text{O}\); N, 15.37%.

24a. 4-Quinazolone hydrochloride was prepared by passing dry HCl gas through a cooled solution of 4-quinazolone in anhydrous ethanol for 3-4 minutes. It was crystallised twice from anhydrous ethanol m.p. 260° reported 212-215° (76).

Found: N, 15.63; Calc. for \(\text{C}_8\text{H}_7\text{ClN}_2\text{O}\); N, 15.37%.

25. Treatment of (CXXVI) with bromine; formation of 3-bromomethyl-4:11-thiopepa-9:11-diene bromide (CXXIX, Table VII, p. 77)

A solution of 4(S-allyl)mercapto quinazoline (6.0 g., 0.02 mole) in acetic acid (50 ml.) was cooled to 0° in an ice-salt mixture. To this was added with shaking bromine (1.4 ml., 0.028 mole) in the same solvent (10 ml.). It was allowed to stand at room temperature for one hour and then diluted with anhydrous ether (150 ml.) whereupon a pale yellow solid separated out. This was collected and crystallised from acetic acid, m.p. 198° (6.33 g., 70%). The product was freely soluble in water and gave a positive test of halogen with silver nitrate solution.

Found: C, 36.80; H, 2.95; N, 7.92; Calc. for \(\text{C}_9\text{H}_7\text{B}_{11}\text{O}_{10}\text{Cl}\text{N}_2\text{S}\)

C, 36.44; H, 2.76; N, 7.73%.
26. Estimation of ionic bromine in (CXXIX)

A known weight of 3-bromoethyl-4:11-thiopenta-9:11-
diene bromide was dissolved in distilled water and ionic 
bromine estimated by Vohlard's method (77).

Found: Br, 22.89; Calcd. for C_{11}H_{10}Br_2N_2S (calc. ionic Br)

Br, 22.09 %.

(11) Synthesis of 4:11-thiopenta-9:11-diene chlorides
(CXLV, p. 78, Table IX, p. 80)

Preparation of 4-chloro quinazolines

Appropriate 4-keto quinazolines (1 mole) were heated 
with phosphorous pentachloride (1.1 mole) and large excess 
of phosphorus oxychloride at 115-160° depending upon the 
4-keto quinazoline used for 2-3 hours. The excess 
phosphorus oxychloride was removed under reduced pressure 
and the products extracted with chloroform washed with 
dilute sodium hydroxide solution and finally with water 
and dried. After removing the solvent the 4-chloro-
quinozolines were crystallised from appropriate solvents (78).

27. Reaction of 4-chloro-quinazolines (CXLII, R = H) with 
mercapto ethanol(CXLII); formation of 4( -hydroxy ethyl) 
mercapto quinazoline (CXLIII, R = H) Table VIII, p. 80.
4-Chloro quinazoline (1.64 g., 0.01 mole) (78) in acetone (10 ml.) was treated with -mercapto ethanol (0.77 g., 0.01 mole) dissolved in sodium hydroxide solution (0.4 g., 5 ml.) and the reaction mixture stirred vigorously. Heat was produced immediately and the temperature of the reaction mixture rose to 45°. It was stirred for 5-6 minutes more and then diluted with water (30 ml.) when an oily liquid separated, which however, solidified on cooling in ice. The product was collected and crystallised from petroleum ether-benzene mixture, m.p. 75-76° (1.6 g., 77%).

Found: N, 13.1. Calcd. for C_{10}H_{10}N_O_S: N, 13.59%.

28. Treatment of (CXLIII) with thionyl chloride; formation of 4-(9H-thiopyr-9-yl)-10-10-diene chloride (CXLV, R = H)

4-(Hydroxy ethyl) mercapto quinazoline (2.0 g.,) was heated with thionyl chloride (10 ml.) for 4 hours. Excess of thionyl chloride was removed under reduced pressure and the resultant product was crystallised from acetic acid, m.p. 222° (1.6 g., 84%). The product was partially soluble in water and the aqueous extract gave a positive test for...