Thieno[2,3-*d*]pyrimidines as Potential Chemotherapeutic Agents. II.

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The synthesis of the thieno[2,3-*d*]pyrimidines (**2a,b** and **4a,b**) has been accomplished from 2-amino-3-carbethoxy-4,5-tetramethyleno-5-ethylthiophenes (**1a,b**).

2-Mercapto-3-phenyl/benzyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidines have been transformed into their corresponding sulphides (**3a-d**) by interaction with alkyl halides. Reaction of **4a,b** with phosphorus oxychloride gave the corresponding chloro compounds **6a,b** which underwent facile nucleophilic substitution with hydrazine and amines affording products **7** and **8** respectively. Condensation of hydrazine **7** with phthalic anhydride gave the phthalazine derivative **9** whereas condensation with carbonyl compounds gave the hydrazones (**10a-d**). The latter were subsequently cyclized to 3-aryl-1,2,4-triazolo[3,4-*c*]-pyrimido[4,5-*b*]tetrahydrobenzothiophenes (**11a,b**) by reaction with bromine and acetic acid.

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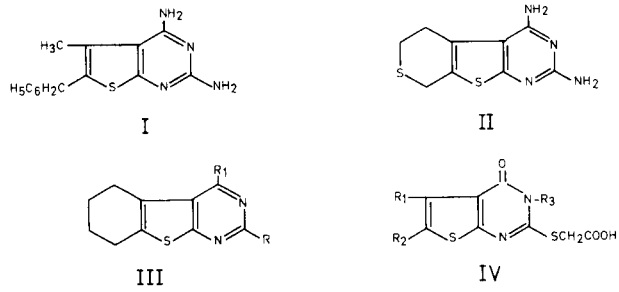
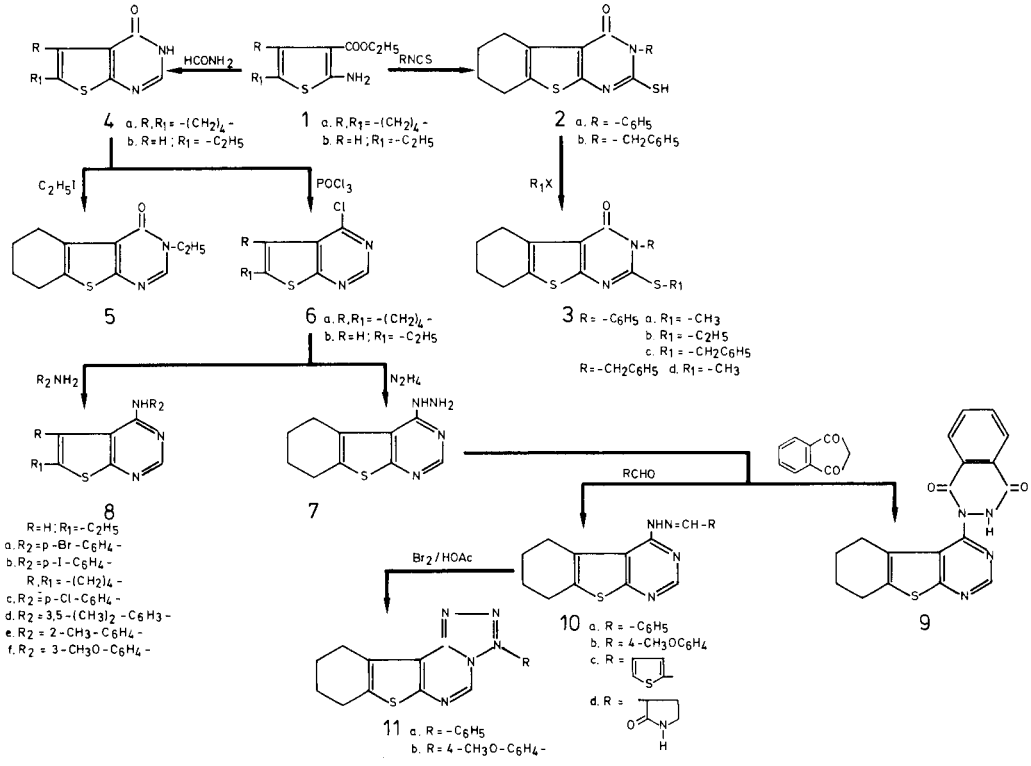
Different biologic activities of condensed pyrimidines *e.g.*, the sedative effect of benzothiophene derivatives (I) and the antibacterial and antimalarial properties of 2,4-diamino-6-benzyl-5-methylthieno[2,3-*d*]pyrimidine (I) and thiopyrano[2,3-*d*]pyrimidine (II) are well documented (2-4). Recently some thieno[2,3-*d*]pyrimidines (III) have been reported to exhibit post-coital antifertility activity in rats (5). Hypocholesterolemic and antitussive properties have been demonstrated by 2-mercapto-3,4-dihydrothieno-



I II III IV

SCHEME 1



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[2,3-*d*]pyrimidin-4-one (IV) (6). The therapeutic importance of thieno[2,3-*d*]pyrimidines prompted us to synthesize several analogs by exotic combinations of groups and active moieties. The key intermediates 2-amino-3-carbethoxy-4,5-tetramethyleno-5-ethylthiophenes (**1a,b**) were prepared by the method of Gewald (7). Heating of **1a** with phenyl/benzylisothiocyanates for 15 hours gave the corresponding 2-mercapto-3-phenyl/benzyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidines (**2a,b**) which were transformed into the corresponding sulphides (**3a-c**) by reaction with alkyl halides.

Cyclization of **1a** with formamide afforded 4-oxo-3*H*-5,6-tetramethyleno-6-ethylthieno[2,3-*d*]pyrimidines (**4a,b**). Reaction of **4a** with ethyliodide in alkaline medium gave 3-ethyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**5**).

Reaction of **4** with phosphorus oxychloride in the presence of dimethylaniline as catalyst gave 4-chloro-5,6-tetramethyleno-6-ethylthieno[2,3-*d*]pyrimidines (**6a,b**) which underwent nucleophilic substitution with hydrazine and aromatic amines resulting in 4-hydrazino/arylamino-5,6-tetramethyleno-6-ethylthieno[2,3-*d*]pyrimidines (**7,8**). The hydrazine **7** proved to be an useful precursor for the synthesis of other heterocycles. Thus the reaction of this hydrazine derivative with phthalic anhydride afforded the phthalazine **9**, while condensation of **7** with aromatic aldehydes and isatin gave the corresponding hydrazones **10a-d**. The hydrazones (**10a,b**) were subsequently cyclized to 3-aryl-1,2,4-triazolo[3,4-*c*]pyrimido[4,5-*b*]tetrahydrobenzothiophenes (**11a,b**) by reaction with bromine and acetic acid. The structures of all compounds were confirmed by elemental analyses and spectroscopic studies.

Pesticidal Activity.

Four compounds, *viz.* 4-(*p*-bromoanilino)-6-ethylthieno-[2,3-*d*]pyrimidine (**8a**), 4-(*p*-iodoanilino)-6-ethylthieno-[2,3-*d*]pyrimidine (**8b**), 2-mercapto-3-phenyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**2a**) and 4-(indolin-2-on-3-yl)hydrazono-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**10d**) were screened for their pesticidal activities according to the method described earlier (8).

Only the latter compound (**10d**) showed some herbicidal activity against *Pigweed* (10%), *Velvet leaf* (20%), *Red millet* (20%), *Green foxtail* (10%) and *Soya bean* (20%).

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. Mass spectra were recorded on a Jeol JMS-01SG apparatus operating at 70 eV ionization energy.

2-Mercapto-3-phenyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**2a**).

A mixture of 2-amino-3-carbethoxy-4,5-tetramethylenothiophene (**1a**) (4 g, 18 mmoles) and phenylisothiocyanate (2.4 g, 18 mmoles) was heated for 15 hours at 160-180°. After cooling the residue was dissolved in aqueous sodium hydroxide (8%), filtered and neutralized with dilute hydrochloric acid. The resulting precipitate was filtered off, washed with water and crystallized from a water-ethanol mixture, 27%, mp 148-150° dec, lit (9) mp > 315°; ms: m/e 314.

Anal. Calcd. for $C_{16}H_{14}N_2OS_2$: C, 61.1; H, 4.46; N, 8.9. Found: C, 61.2; H, 4.8; N, 9.1.

2-Mercapto-3-benzyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**2b**).

This compound was prepared by heating a mixture of 2-amino-3-carbethoxy-4,5-tetramethylenothiophene (**1a**) (2 g, 8 mmoles) and benzylisothiocyanate (1.32 g, 9 mmoles) for 15 hours at 160-180°. The residue was dissolved in 8% sodium hydroxide and filtered. The filtrate was acidified with dilute hydrochloric acid which gave a white amorphous solid, 38% mp 224-226° dec, lit (9) mp 244-246°; ms: m/e 328.

Anal. Calcd. for $C_{17}H_{16}N_2OS_2$: C, 62.2; H, 4.9; N, 8.5. Found: C, 62.5; H, 5.12; N, 8.65.

2-Methylmercapto-3-phenyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**3a**).

To a solution of **2a** (0.3 g, 0.95 mmole) in aqueous sodium hydroxide (8%), methyliodide was added dropwise at room temperature under vigorous stirring. The reaction mixture was then stirred for 4 hours and filtered. The precipitate was washed several times with distilled water, dried and finally crystallized from a water-ethanol mixture, 52%, mp 222-223°; ms: m/e 328.

Anal. Calcd. for $C_{17}H_{16}N_2OS_2$: C, 62.2; H, 4.9; N, 8.5. Found: C, 62.45; H, 5.2; N, 8.32.

2-Ethylmercapto-3-phenyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**3b**).

This compound was prepared by the reaction of **2a** (0.3 g, 0.95 mmole) with ethyliodide (0.2 g) in alkaline medium and isolated as described in the preceding experiment, 46%, mp 194-195°; ms: m/e 342.

Anal. Calcd. for $C_{18}H_{18}N_2OS_2$: C, 63.15; H, 5.26; N, 8.18. Found: C, 63.51; H, 5.32; N, 8.52.

2-Benzylmercapto-3-phenyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**3c**).

This compound was prepared from **2a** (0.3 g, 0.95 mmole) and benzylchloride (0.13 g, 1 mmole) in aqueous sodium hydroxide as described earlier, 60%, mp 200-201°; ms: m/e 404.

Anal. Calcd. for $C_{23}H_{20}N_2OS_2$: C, 68.31; H, 4.95; N, 6.93. Found: C, 68.51; H, 5.21; N, 7.32.

2-Methylmercapto-3-benzyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**3d**).

This compound was prepared by the reaction of **2b** (0.3 g, 0.91 mmole) and methyliodide (0.2 g) in aqueous sodium hydroxide as described earlier 41%, mp 116-117°; ms: m/e 342.

Anal. Calcd. for $C_{18}H_{18}N_2OS_2$: C, 63.15; H, 5.26; N, 8.18. Found: C, 63.4; H, 5.34; N, 8.52.

4-Oxo-(3*H*)-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**4a**).

This compound was synthesised by cyclisation of **1a** in formamide, by the procedure reported earlier (10), 65%, mp 255-256°; ms: m/e 206.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.21; H, 4.71; N, 13.5.

4-Oxo-(3*H*)-6-ethylthieno[2,3-*d*]pyrimidine (**4b**).

This compound was cyclised by refluxing 2-amino-3-carbethoxy-5-ethylthiophene (**1b**) in formamide, 80%, mp 184-185°; ms: m/e 180.

Anal. Calcd. for $C_8H_8N_2OS$: C, 53.31; H, 4.48; N, 15.54. Found: C, 53.15; H, 4.44; N, 15.5.

3-*N*-Ethyl-4-oxo-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**5**).

To a solution of **4a** (0.8 g, 3.8 mmoles) in 8% sodium hydroxide ethyl iodide was slowly added and stirred for 2 hours. The precipitate thus obtained was filtered off and crystallized from ethanol, 28%, mp 117-118°;

ms: m/e 234.

Anal. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.5; H, 5.6; N, 11.9. Found: C, 61.45; H, 5.71; N, 12.2.

4-Chloro-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**6a**).

Chlorination of **4a** with phoshorus oxychloride in the presence of dimethylaniline as catalyst gave the title compound in 60% yield as reported (10), mp 101-102°; ms: m/e 224.

Anal. Calcd. for $C_{10}H_9ClN_2S$: C, 53.46; H, 4.04; N, 12.47. Found: C, 53.40; H, 4.00; N, 12.5.

4-Chloro-6-ethylthieno[2,3-*d*]pyrimidine (**6b**).

This compound was prepared by refluxing **4b** with phosphorus oxychloride as described earlier (10) mp 47-48°; ms: m/e 198.

Anal. Calcd. for $C_8H_7ClN_2S$: C, 48.58; H, 3.56; N, 14.11. Found: C, 48.70; H, 3.52; N, 14.0.

4-Hydrazino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**7**).

This compound was prepared by the reaction of **6a** with hydrazine as reported earlier (11), 62%, mp 180-181°; ms: m/e 220.

Anal. Calcd. for $C_{10}H_{12}N_4S$: C, 54.49; H, 5.49; N, 25.43. Found: C, 54.70; H, 5.40; N, 25.4.

General Preparation of 4-Arylamino-5,6-tetramethyleno-6-ethylthieno-[2,3-*d*]pyrimidines (**8**).

A mixture of **6** (1 mmole) and an appropriate amine (2 mmoles) in ethanol was refluxed for 6-8 hours. The excess of solvent was removed under reduced pressure and the residue was washed with water. The crude material gave on trituration with petroleum ether or methanol a solid which was crystallized from a suitable solvent, yield 60-80%.

4-(4-Bromophenyl)amino-6-ethyl[2,3-*d*]pyrimidine (**8a**).

This compound was obtained in a yield of 65%, mp 215-216°; ms: m/e 334.

Anal. Calcd. for $C_{14}H_{12}BrN_3S$: C, 50.31; H, 3.62; N, 12.56. Found: C, 50.42; H, 3.60; N, 12.4.

4-(4-Iodophenyl)amino-6-ethyl[2,3-*d*]pyrimidine (**8b**).

This compound was obtained in a yield of 68%, mp 197-198° ; ms: m/e 381.

Anal. Calcd. for $C_{14}H_{12}SIN_3$:C, 44.11; H, 3.17; N, 11.03. Found: C, 43.98; H, 3.10; N, 11.3.

4-(4-Chlorophenyl)amino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**8c**).

This compound was obtained in a yield of 70%, mp 144-145°; ms: m/e 315.

Anal. Calcd. for $C_{16}H_{14}ClN_3S$: C, 60.86; H, 4.49; N, 13.31. Found: C, 60.81; H, 4.37; N, 13.2.

4-(3,5-Dimethylphenyl)amino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**8d**).

This compound was obtained in a yield of 65%, mp 184-185°; ms: m/e 309.

Anal. Calcd. for $C_{18}H_{19}N_3S$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.71; H, 6.10; N, 13.6.

4-(2-Methylphenyl)amino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**8e**).

This compound was obtained in a yield of 72%, mp 135-136°; ms: m/e 295.

Anal. Calcd. for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.33; H, 5.62; N, 14.43.

4-(3-Methoxyphenyl)amino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**8f**).

This compound was obtained in a yield of 55%, mp 110-111°; ms: m/e 311.

Anal. Calcd. for $C_{17}H_{17}N_3OS$: C, 65.58; H, 5.50; N, 13.49. Found: C, 65.72; H, 5.61; N, 13.22.

4-(3,8-Dioxo-1,2,3,8-tetrahydrophthalazin-1-yl)-5,6-tetramethylenothieno-[2,3-*d*]pyrimidine (**9**).

Phthalic anhydride (75 mg, 0.5 mmole) and 4-hydrazino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (100 mg, 0.45 mole) in acetic acid was refluxed for 6 hours. The reaction mixture after cooling was poured into cold water. The precipitate thus obtained was filtered off, washed with water and crystallized from a water-ethanol mixture, 51%, mp 247-248°, ms: m/e 350.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.43; H, 4.00; N, 16.00. Found: C, 61.5; H, 3.85; N, 16.2.

4-Benzalhydrazino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**10a**).

To a solution of **7** (0.2 g, 0.90 mmole) in alcohol, benzaldehyde (0.11 g, 1 mmole) was added and the resulting mixture was refluxed for 1 hour. The solid thus obtained, was filtered off and crystallized from ethanol, 98%, mp 105-106°; ms: m/e 308.

Anal. Calcd. for $C_{17}H_{16}N_4S$: C, 66.2; H, 5.1; N, 18.1. Found: C, 66.31; H, 5.33; N, 18.25.

4-(*p*-Anisalhydrazino-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**10b**).

A mixture of **7** (0.2 g, 0.90 mole) and *p*-anisaldehyde (0.13 g, 1 mmole) in ethanol was refluxed for 1 hour. The precipitate thus obtained was filtered off and crystallized from dimethylformamide, 82%, mp, 184-185°; ms: m/e 338.

Anal. Calcd. for $C_{18}H_{18}N_4OS$: C, 63.9; H, 5.3; N, 16.5. Found: C, 64.1; H, 5.23; N, 16.46.

4-(2-Thiophenalhydrazino)-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**10c**).

Condensation of **7** (0.2 g, 0.90 mmole) with thiophene-2-aldehyde (0.12 g, 1 mmole) in ethanol afforded the title compound, 71%, mp. 179-180°; ms: m/e 314.

Anal. Calcd. for $C_{15}H_{14}N_4S_2$: C, 57.32; H, 4.4; N, 17.83. Found: C, 57.51; H, 4.62; N, 18.1.

4-(Indolin-2-on-3-yl)hydrazono-5,6-tetramethylenothieno[2,3-*d*]pyrimidine (**10d**).

Isatin (0.15 g, 1 mmole) was condensed with **7** (0.2 g, 0.90 mmole) in ethanol by refluxing for 1 hour. The precipitate thus obtained was filtered off and crystallized from dimethylformamide, 70%, mp 272-273°; ms: m/e 349.

Anal. Calcd. for $C_{18}H_{15}N_5OS$: C, 61.8; H, 4.3; N, 20.05. Found: C, 61.58; H, 4.5; N, 20.3.

3-Phenyl-1,2,4-triazolo[3,4-*c*]pyrimido[4,5-*b*]tetrahydrobenzothiophene (**11a**).

To a solution of **10a** (0.28 g, 0.90 mmole) and sodium acetate in acetic acid (2 ml), bromine (0.1 ml) dissolved in the same solvent (1 ml) was added dropwise till a clear solution was obtained. The reaction content was left at room temperature for half an hour and filtered. The filtrate was neutralized with aqueous sodium carbonate and the solid thus obtained was filtered off, and washed with water. The crude product was crystallized from a water-acetic acid mixture, 80%, mp, 152-153°; ms: m/e 306.

Anal. Calcd. for $C_{17}H_{14}N_4S$: C, 66.6; H, 4.5; N, 18.3. Found: C, 66,81; H, 4.65; N, 18.12.

3-(*p*-Anisyl-1,2,4-triazolo[3,4-*c*]pyrimido[4,5-*b*]tetrahydrobenzothiophene (**11b**).

This compound was prepared by oxidative cyclisation of **10b** (0.18 g, 0.53 mmole) with bromine in acetic acid as described in the preceding experiment. The crude product was crystallized from acetic acid, 67%, mp 120-121°; ms: m/e 336.

Anal. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.28; H, 4.76; N, 16.66. Found: C, 64.51; H, 4.65; N, 16.7.

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