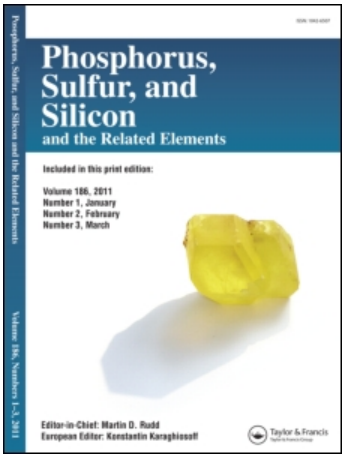

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SYNTHESIS AND SOME REACTIONS OF 2-MERCAPTO-3,5,7-TRIPHENYLPYRIDO[2,3-d]-PYRIMIDINE-4(3H)-ONE

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SYNTHESIS AND SOME REACTIONS OF 2-MERCAPTO-3,5,7-TRIPHENYLPYRIDO[2,3-d]-PYRIMIDINE-4(3H)-ONE

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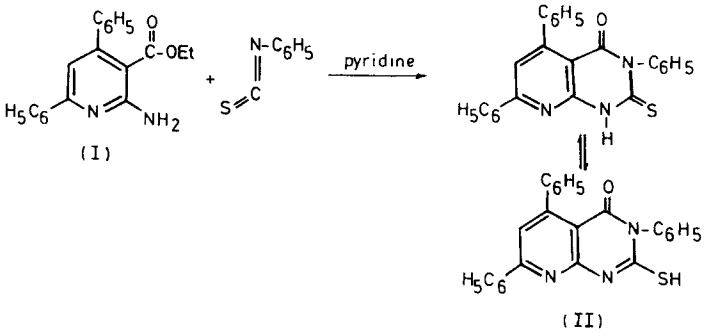
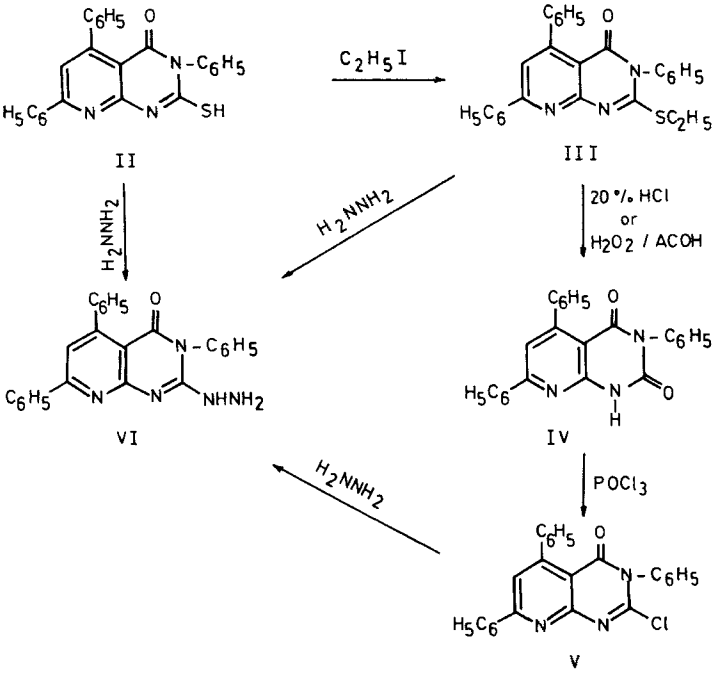
2-Mercapto-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (II) was synthesized by the interaction of ethyl-2-amino-4,6-diphenylincotinate (I) with phenyl isothiocyanate in pyridine. The reaction of II with different reagents was carried out to give some condensed heterocyclic systems.

2-Alkylthiopyrido[2,3-d]pyrimidine-4(3H)-ones possessing long lasting diuretic and selective natgriuretic activities[1] and some pyridopyrimidine thiones having analgesic, antinflammatory and central nervous system depressing activities[2] and it is known in the literature[3–13] that the heterocyclic nucleus containing thiol group was used in the synthesis of several condensed heterocyclic systems. From this point of view, it was very interesting to synthesize 2-mercapto-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (II) to be used as a starting material for the synthesis of pyridopyrimidine derivatives.

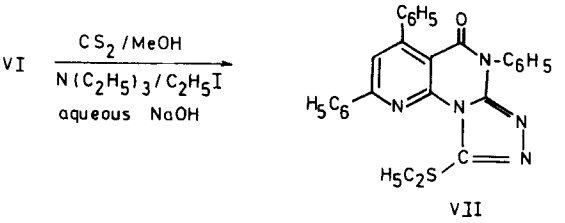


Treatment of II with ethyl iodide gave 2-ethylmercapto-3,5,7-triphemylpyrido-[2,3-d]pyrimidine-4(3H)-one (III) which was converted to 3,5,7-triphenyl-pyrido[2,3-d]pyrimidine-2,4[1(H), 3(H)]-dione (IV) under the effect of dilute hydrochloric acid or hydrogen peroxide and acetic acid.[14] Reaction of IV with phosphoryl chloride afforded 2-chloro-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (V). Compounds II, III and V reacted with hydrazine hydrate to give 2-hydrazino-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (VI) (Scheme 1). The structural assignments of compounds I to VI were based on elemental and spectral analyses.



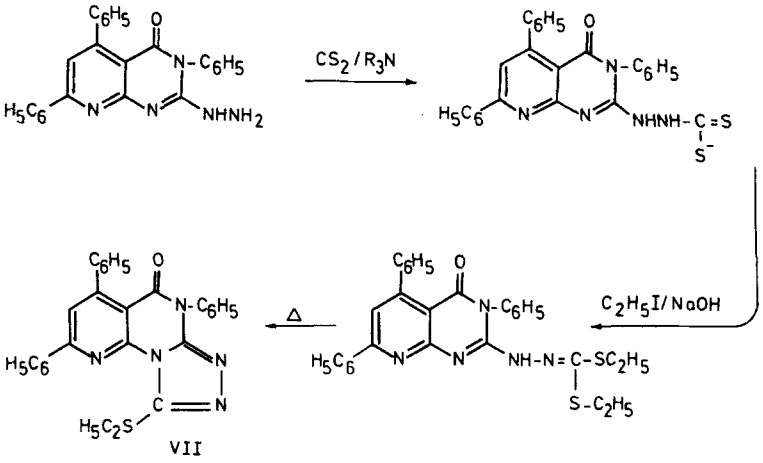
SCHEME 1

The reaction of VI with carbon disulfide in the presence of ethyl iodide, triethylamine, sodium hydroxide in aqueous methanol yielded 9-ethylmercapto-2,4,6-triphenylpyrido[3,2-e][1,2,4]-triazolo[4,3-a]pyrimidine 5(6H, 8H)-one (VII).



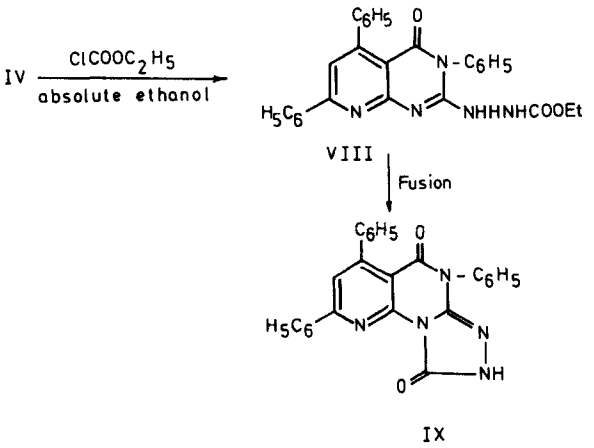
The formation of the cyclic ethylmercapto derivative VII could be explained as shown in Scheme 2. The structure of compound VII was established by elemental and spectral analyses.

Also the reaction of VI with ethyl chloroformate in absolute ethanol gave 2-(ethoxycarbonylhydrazino)-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (VIII) which upon fusion eliminates ethanol giving 2,4,6-triphenylpyrido[3,2-e][1,2,4]triazolo-[4,3-a]pyrimidine-5,9[6(H),8(H)]-dione (IX). The chemical structure of compounds VIII and IX was elucidated from their analytical and spectral data.



VII

SCHEME 2



EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance spectra were measured on EM-360 90 MHZ spectrophotometer. Infrared spectra were measured on a Perkin–Elmer 599 B spectrophotometer. The mass spectra were carried out at the chemistry Department, University College, Cardiff CFI, IXL, U.K.

Ethyl-2-amino-4,6-diphenylnicotinate (I) was prepared according to the literature procedure.[15]

2-Mercapto-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (II). A mixture of (0.01 mole) ethyl-2-amino-4,6-diphenylnicottinate and (0.01 mole) of phenyl isothiocyanate was dissolved in pyridine. The reaction mixture was refluxed in an oil bath for 12 hours, then cooled and poured into ice bath. The product was precipitated, filtered, washed with water, dried and crystallized from benzene to give II as colourless crystals in 70% yield, mp 255–257°C; ir (KBr): 1220 cm^{-1} (C=S), 1700 cm^{-1} (>C=O), 3400 cm^{-1} (NH), 1550 cm^{-1} (N—C=S); pmr ($CDCl_3$): δ7.2 (s, 1H, pyridine), 7.3–8 (m, 15 H, aromatic), 10.9–11.1 (s, 1 H, 5 H); ms, m/z (% rel. int.): 407 (78), 406 (100), 354 (1), 346 (6); 272 (38). Analysis calcd. for: $C_{25}H_{17}N_3OS$: C, 73.71; H, 4.18; N, 10.32; S, 7.86 Found: C, 73.81; H, 4.23, N, 10.45; S, 7.66.

2-Ethylmercapto-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (III). Ethyl iodide (0.012 mole) was added during 2–5 minutes to a stirred solution of II (0.01 mole) in sodium hydroxide solution. The mixture was stirred for further 2 hours. The solid which separated was filtered, washed with water, dried and crystallized from benzene as pale yellow crystals in 75% yield; ir (KBr): 1685 cm^{-1} (>C=O), 1600 cm^{-1} (C=N), 3060 cm^{-1} (CH aliphatic); pmr ($CDCl_3$): δ1.7 (t, 3 H, CH_3), 3.5 (q, 2 H, CH_2), 7.7 (s, 1 H, pyridine), 7.3–7.6 and 8.2–8.4 (m, 15 H, aromatic); ms m/z (% rel. int) 435 (80), 406 (100). Analysis calcd. for $C_{27}H_{21}N_3OS$: C, 74.48; H, 4.82; N, 9.65; S, 7.35 Found: C, 74.52; H, 4.71; N, 9.55; D, 7.41.

3,5,7-Triphenylpyrido[2,3-d]pyrimidine-2,4[(1 H), (3 H)]-dione (IV). A mixture of (1.0 g, 0.0023 mole) 2-ethylmercapto-3,5,7-triphenyl[2,3-d]pyrimidin-4(3 H)-one (III) and 36 ml of 20% hydrochloric acid solution was refluxed for 8 hours. During the reflux period, a white precipitate was formed, filtered off, washed with water, dried and crystallized from aqueous dioxan as colourless crystals in 60% yield, mp 285–7°C; ir (KBr) 1730 cm^{-1}, 1680 cm^{-1} (two >C=O), 3100 cm^{-1} (NH); ms, m/z (% rel. int.) 390 (90) Analysis Calcd. for $C_{25}H_{17}N_3O_2$: S, 76.72; H, 4.34; N, 10.74 Found: C, 76.62; H, 4.28; N, 10.73.

2-Chloro-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (V). A mixture of (0.5 gm, 0.0013 mole) of IV and 2 ml of phosphrus oxychloride was refluxed for 8 hours. During the reflux period the colour changed from yellow to orange then brown. The brown product collected, washed with petroleum ether (40–60°C) then ethanol and crystallized from ethanol-benzene mixture (1:1) to give colourless crystals in 80% yield, mp 273–5°C; ir (KBr) 1690 cm^{-1}. Analysis Calcd. For $C_{25}H_{16}N_3OCl$: C, 73.17; H, 3.90; N, 10.24; Cl, 8.67 Found: C, 73.10; H, 3.82; N, 10.12; Cl, 8.50.

2-Hydrazino-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (IV). To a solution of II (0.03 mole), in dry pyridine hydrazine hydrate 98% (0.006 mole) was added and the reaction mixture was refluxed for 2 hours, whereby yellow product was separated. The product was collected, washed with a mixture of benzene-petroleum ether 1:1 and dried to give VI in 55% yield, mp. 310–312°C; ir (KBr) 3260, 3320 cm^{-1} ($NHNH_2$), 1690 cm^{-1} (C=O); ms, m/z (rel. int.): 405 (90), 389 (14), 374 (9), 313 (10), 298 (8), 271 (6), 149 (38), 57 (100), 55 (98). Analysis Calcd. for $C_{25}H_{19}N_5O$: C, 74.07; H, 4.69; N, 17.28. Found: C, 74.13; H, 4.71; N, 17.34. This compound was also obtained by heating III (0.03 mole) with excess hydrazine hydrate (2 ml, 98%) on a water bath for 3 hours or by heating a mixture of V (0.001 mole) with hydrazine hydrate (0.02 mole) in 20 ml ethanol on a water bath for 3 hours. The product was identical in all aspects with the above one.

9-Ethylmercapto-2,4,6-triphenylpyrido[3,2-e][1,2,4]triazole[4,3-a]pyrimidine-5(6H) one (VII). A one gram (0.0025 mole) of the hydrazino compound VI was suspended in methanol then 0.2 ml (0.0025 mole) of triethylamine and 5 ml of carbon disulfide were added. The reaction mixture was refluxed for 10 hours. During the reflux period a yellow resin was separated which dissolved in aqueous sodium hydroxide solution and 0.2 ml (0.0025 mole) of ethyl iodide was added. The reaction mixture was stirred for 3 hours at room temperature whereby a pale yellow product was formed, filtered, washed with water and crystallized from benzene as yellow crystals in 70% yield, mp > 360°C; ir (KBr): 1685 cm^{-1} (C=O), 1600 cm^{-1} (C=N), 3060 cm^{-1} (Ch aliphatic), pmr ($CDCl_3$): δ1.7 (t, 3 H, CH_3), 3.5 (q, 2 H, CH_2), 7.7 (s, 1 H, pyridine), 7.3, 7.6 and 8.2–8.4 (m, 15 H aromatic). Analysis Calcd. for: $C_{28}H_{21}N_5OS$: C, 70.74; H, 4.42; N, 14.74; S, 6.74, Found: C, 70.52; H, 4.48; N, 14.68; S, 6.75.

2-(Ethoxycarbonylhydrazino)-3,5,7-triphenylpyrido[2,3-d]pyrimidine-4(3H)-one (VIII). A one g (0.0025 mole) of VI was suspended in absolute ethanol then 0.3 ml (0.0025 mole) of ethyl chloroformate was added. The reaction mixture was refluxed for 5 hours. The ethanol was removed under reduced pressure whereby a pale yellow product was separated and crystallized from benzene-petroleum ether mixture as yellow crystals in 50% yield, mp. 193–95°C; ir (KBr): 1730 cm^{-1} (>C=O ester), 1270 cm^{-1} (C—O ester), 1700 cm^{-1}(C=O pyrimidine ring), 3400 cm^{-1} & 3270 cm^{-1} (NHNH), 3070 cm^{-1} (CH aliphatic), pmr ($CDCl_3$): δ1.2 (t, 3 H, CH_3), 4.1 (q, 2 H, CH_2), 7.7 (s, 1 H, pyridine), 7.2–7.5 and 8.2–8.4 (m, 15 H aromatic). Analysis Calcd. for: $C_{28}H_{23}N_5O_3$: C, 70.44; H, 4.82; N, 14.67, Found: C, 70.32; H, 4.75; N, 14.61.

2,4,6-Triphenylpyrido[3,2-e][1,2,4]triazolo[4,3-a]pyrimidine-5,9[6(H), 8(H)]-dione (IX). Compound VIII 0.5 g was heated in an oil bath at 200°C for 30 minutes. The resulting material was crystallized from dioxane-water mixture as white crystals in 50% yield, mp > 360°C; ir (KBr): 1740 cm^{-1} (>C=O for triazolo ring), 1700 cm^{-1} (>C=O of pyrimidine ring), 3240 cm^{-1} (NH, pmr ($DMSOd_6$):

δ7.7 (s, 1 H), 7.2–7.5 and 8.2–8.4 (m, 15 H aromatic). Analysis Calcd. for: $C_{26}H_{17}N_5O_2$: C, 72.38; H, 3.94; N, 16.24. Found C, 72.32; H, 3.81; N, 16.12.

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