Synthesis of New Polycyclic Systems Containing the Pyrimido[2,1-*a*]phthalazine Skeleton [1]

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The synthesis of new polyheterocycles containing the pyrimido[2,1-*a*]phthalazine system **5**, **6** and **7**, obtained by condensation of phthalic anhydride with the appropriate hydrazides **2**, **3** and **4**, respectively, are reported. It was also synthesized the 14*H*-[1]Benzothieno[3',2':4,5]pyrimido[2,1-*a*][1,2,4]triazolo[4,3-*c*]phthalazin-14-one (**16**).

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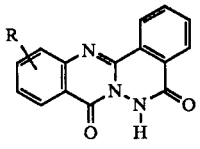
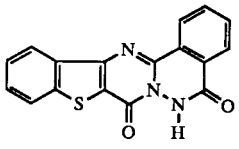
Owing to our interest in polycyclic heterocycles containing the pyrimido[2,1-*a*]phthalazine system that may show biological activities, in a previous study [2] we synthesized some phthalazino[1,2-*b*]quinazoline derivatives corresponding to the general formula **A**.



A

With the aim of determining the entity of the various influences, due the structural differences, on the manifestation of antiinflammatory and antalgic activities the following new heterocyclic systems were prepared:



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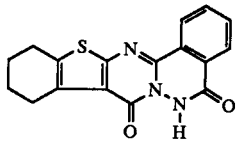

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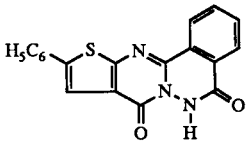

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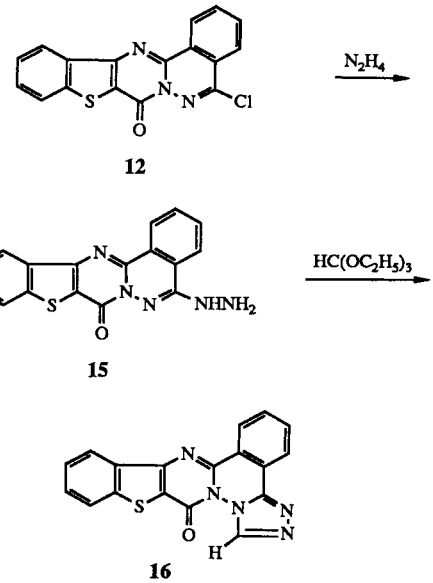
The preparation of compounds **5**, **6** and **7** was carried out using a previous procedure described by us in the case of similar compounds [2] and was based on the condensation of phthalic anhydride (**1**) with the hydrazide of 3-aminobenzo[*b*]thiophene-2-carboxylic acid (**2**), of 2-amino-4,5,6,-7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (**3**) and of 2-amino-5-phenylthiophene-3-carboxylic acid (**4**) respectively.

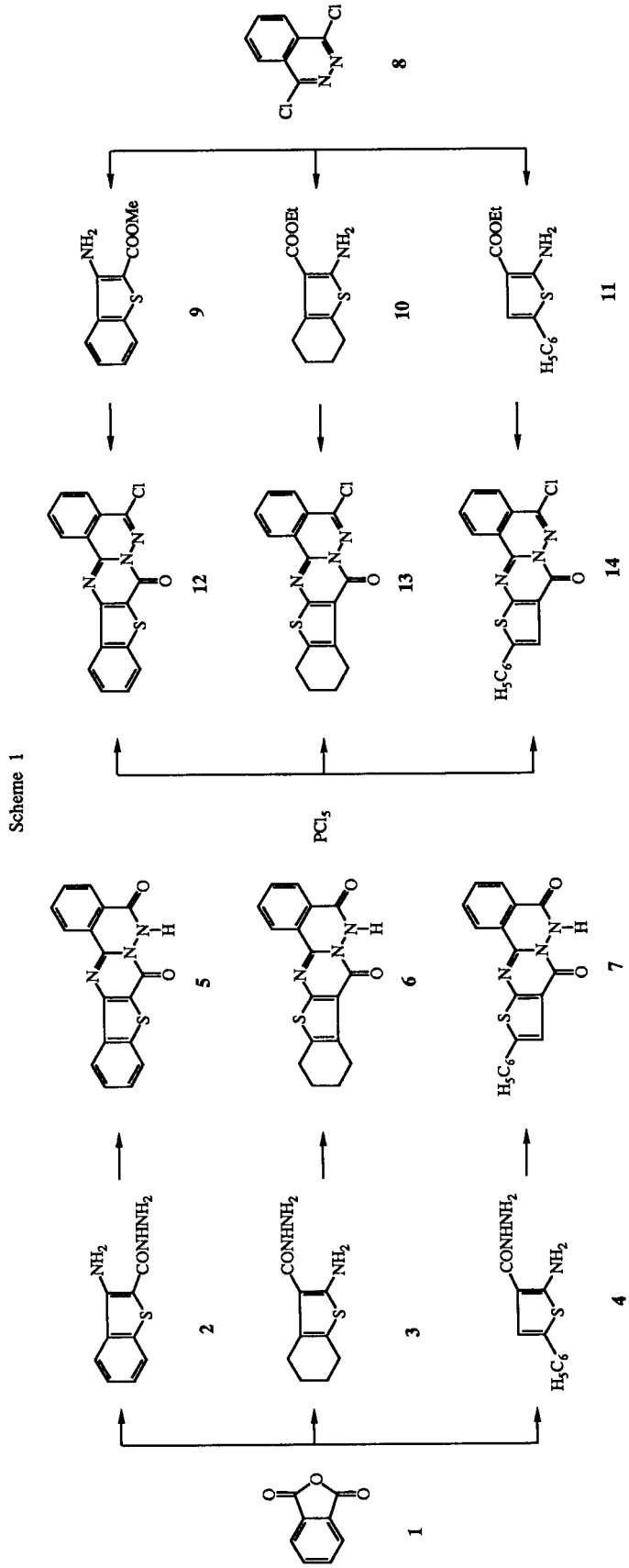
The previously unknown hydrazide **2** was prepared from the methyl ester of the 3-aminobenzo[*b*]thiophene-2-carboxylic acid (**9**) and hydrazine hydrate.

Polyheterocycles **5**, **6** and **7** by action of phosphorus pentachloride gave the corresponding 5-chloro derivatives **12**, **13** and **14** identical to those obtained by condensation of the esters **9**, **10** and **11** respectively with 1,4-dichlorophthalazine (**8**) (Scheme 1). Analytical and spectral data of the compounds **5**, **6** and **7**, and of the 5-chloro derivatives **12**, **13** and **14** are also in agreement with the proposed structures.

Moreover reaction of compound **12** with hydrazine hydrate gave 5-hydrazino-8*H*-[1]benzothieno[3',2':4,5]pyrimido[2,1-*a*]phthalazin-8-one (**15**). The hydrazine derivative **15** proved to be a versatile molecule for synthetic realizations. Really the derivative **15** heated with ethyl orthoformate cyclized to 14*H*-[1]benzothieno[3',2':4,5]pyrimido-[2,1-*a*][1,2,4]triazolo[4,3-*c*]phthalazin-14-one (**16**) (Scheme 2). Compound **16** shows a band at 1690 cm^{-1} in the ir spectrum assigned to the carbonyl group and its mass spectrum exhibits an intense peak m/z 343 corresponding to the molecular ion.

Scheme 2





Scheme 1

EXPERIMENTAL

All melting points were taken in open capillaries using a Gallemkamp melting point apparatus with a digital thermometer MFB-595 and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 281 spectrometer in potassium bromide disks. Elemental analyses for C, H and N were obtained on a Carlo Erba 1106 elemental analyzer. The low resolution mass spectra were recorded by direct insertion into the ion source on a VG-2AB2SE mass spectrometer under the following conditions: ionization energy, 70 eV; source temperature 250-300°; trap current 60 μA. The sample temperature ranged from room temperature to 300°.

Hydrazide of 3-Aminobenzo[*b*]thiophene-2-carboxylic Acid (**2**).

A solution of the methyl ester of the 3-aminobenzo[*b*]thiophene-2-carboxylic acid (**9**) [3] (20 g, 0.1 mole) and of hydrazine hydrate (40 ml) in ethanol (50 ml) was refluxed for 15 hours. After cooling the solid was collected, washed with ethanol, dried and recrystallized from aqueous ethanol to give a white powder (7 g, 34%), mp 180-182°; ir: 3420, 3320 and 3260 (NH), 1630 (CO) cm^{-1}.

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.17; H, 4.34; N, 20.28. Found: C, 52.40; H, 4.25; N, 20.00.

General Procedure for the Preparation of the Derivatives of Pyrimido[2,1-*a*]phthalazine-5,8-diones **5**, **6** and **7**.

A solution of the requisite derivative **2**, **3** [4] or **4** [5] (0.02 mole) and of phthalic anhydride (**1**) (0.02 mole) in 20 ml of *N,N*-dimethylacetamide was heated at reflux for 2 hours. After cooling the precipitate was collected, washed with ethanol, dried and recrystallized from the appropriate solvent.

6*H*-[1]Benzothieno[3',2':4,5]pyrimido[2,1-*a*]phthalazine-5,8-dione (**5**).

This compound was obtained as colorless needles in a yield of 55%, mp 333-335° (glacial acetic acid); ir: 3200 (NH), 1660 (CO) cm^{-1}; ms: (m/z) 319 (M^+).

Anal. Calcd. for $C_{17}H_9N_3O_2S$: C, 63.95; H, 2.82; N, 13.16. Found: C, 63.60; H, 2.60; N, 13.00.

9,10,11,12-Tetrahydro-6*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*a*]phthalazine-5,8-dione (**6**).

This compound was obtained as green microcrystals in a yield of 35% mp 285-288° (*N,N*-dimethylformamide/water); ir: 3140 (NH), 1675 (CO) cm^{-1}; ms: (m/z) 323 (M^+).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S$: C, 63.15; H, 4.00; N, 13.00. Found: C, 62.80; H, 4.04; N, 13.18.

10-Phenyl-6*H*-thieno[2',3':4,5]pyrimido[2,1-*a*]phthalazine-5,8-dione (**7**).

This compound was obtained as bright yellow crystals in a yield of 30%, mp 290-292° (*N,N*-dimethylformamide/water); ir: 3180 (NH), 1690 (CO) cm^{-1}; ms: (m/z) 345 (M^+).

Anal. Calcd. for $C_{19}H_{11}N_3O_2S$: C, 66.10; H, 3.18; N, 12.17. Found: C, 65.80; H, 3.11; N, 12.00.

General Procedure for the Preparation of 5-Chlorothienopyrimido[2,1-*a*]phthalazin-8-ones **12**, **13** and **14**.

Method A.

A mixture of the appropriate amino ester **9** [3], **10** [6] or **11** [6] (5 mmoles) and of 1,4-dichlorophthalazine (**8**) [7] (5 mmoles) was heated in an oil bath under stirring until the evolution of hydrochloric acid was complete. After cooling, the reaction mixture was treated with a small amount of warm ethanol and filtered. The solid collected was poured into about 100 ml of a 5% solution of sodium hydrogen carbonate and filtered off. After washing with water, the solid was collected, dried and crystallized from appropriate solvent.

5-Chloro-8*H*-[1]benzothieno[3',2':4,5]pyrimido[2,1-*a*]phthalazin-8-one (**12**).

This compound was obtained as yellow crystals in a yield of 20%, mp 335-338° (*N,N*-dimethylformamide); ir: 1710 (CO) cm^{-1}; ms: (m/z) 337 (M^+).

Anal. Calcd. for $C_{17}H_8ClN_3OS$: C, 60.45; H, 2.37; N, 12.44. Found: C, 60.00; H, 2.30; N, 12.10.

9,10,11,12-Tetrahydro-5-chloro-8*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*a*]phthalazin-8-one (**13**).

This compound was obtained as a microcrystalline powder in a yield of 20%, mp 285-288° (*N,N*-dimethylformamide/water); ir: 1710 (CO) cm^{-1}; ms: (m/z) 341 (M^+).

Anal. Calcd. for $C_{17}H_{12}ClN_3OS$: C, 59.80; H, 3.51; N, 12.29. Found: C, 60.10; H, 3.65; N, 12.25.

5-Chloro-10-phenyl-8*H*-thieno[2',3':4,5]pyrimido[2,1-*a*]phthalazin-8-one (**14**).

This compound was obtained as a yellow powder in a yield of 20%, mp 263-266 (*N,N*-dimethylformamide); ir: 1710 (CO) cm^{-1}; ms: (m/z) 363 (M^+).

Anal. Calcd. for $C_{19}H_{10}ClN_3OS$: C, 62.70; H, 2.75; N, 11.55. Found: C, 63.05; H, 2.95; N, 11.20.

Method B.

A mixture of the appropriate compound **5**, **6** or **7** (3 mmoles) and of phosphorus pentachloride (17 mmoles) was heated in an oil bath at 210° for 2 hours. The cooled reaction mixture was then poured into crushed ice and the resulting suspension neutralized with a 10% solution of sodium hydroxide. The residue was collected, dried, chromatographed on silica gel, eluting with ethyl acetate/hexane (3:7, v/v), and recrystallized from appropriate solvent to give a compound whose mp and ir spectrum were identical to those of products **9**, **10** and **11**, obtained by Method A, respectively.

5-Hydrazino-8*H*-[1]benzothieno[3',2':4,5]pyrimido[2,1-*a*]phthalazin-8-one (**15**).

A mixture of the 5-chloro derivative **12** (1.0 g, 3 mmoles) and of hydrazine hydrate (0.75 g, 3 mmoles) in ethanol (10 ml) was heated under reflux for 2 hours. After cooling a solid was collected, washed with ethanol, dried and crystallized from *N,N*-dimethylformamide to give a yellow powder (0.7 g, 70%) mp 342-344°; ir: 3370 and 3275 (NH), 1690 (CO) cm^{-1}.

Anal. Calcd. for $C_{17}H_{11}N_5OS$: C, 61.26; H, 3.33; N, 21.02. Found: C, 60.95; H, 3.20; N, 20.75.

14*H*-[1]Benzothieno[3',2':4,5]pyrimido[2,1-*a*][1,2,4]triazolo[4,3-*c*]-phthalazin-14-one (**16**).

A mixture of **15** (0.7 g, 2.0 mmoles) and of triethyl orthoformate (9 ml) was refluxed for 5 hours. After cooling, the solid was collected, washed with ethanol and crystallized from *N,N*-dimethylformamide to give yellow crystals (0.8 g, 87%), mp 365-368°; ir: 1690 (CO) cm^{-1}; ms: (m/z) 343 (M^+).

Anal. Calcd. for $C_{18}H_9N_5OS$: C, 62.97; H, 2.62; H, 20.40. Found: C, 62.45; H, 2.56; N, 20.03.

REFERENCES AND NOTES

[1] This work was presented at the Royal Society of Chemistry-Società Chimica Italiana Joint Meeting on Heterocyclic Chemistry, Catania, 11-14 May 1988, and was supported by the Italian Ministry of Public Education.

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