A NEW HETEROCYCLIC RING SYSTEM: SYNTHESIS OF PYRAZOLO[3',4':4,5]-PYRIMIDO[2,1-*a*]PHTHALAZINE DERIVATIVES°

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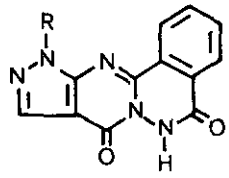
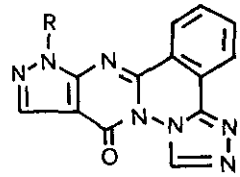
Abstract - Derivatives (**5**-**7**) of a new heterocyclic system containing the pyrimido[2,1-*a*]phthalazine skeleton were obtained by condensation of phthalic anhydride with the appropriate hydrazides (**2**-**4**). Moreover the preparation of 9-substituted 1*H*-pyrazolo[3',4':4,5]pyrimido[2,1-*a*][1,2,4]-triazolo[4,3-*c*]phthalazin-12-ones (**20**) and (**21**) is described.

In previous papers[1,2] we reported the synthesis of polyheterocycles containing the pyrimido[2,1-*a*]phthalazine skeleton in expectation of some biological activities. Following this research line, we describe here a synthesis of new heterocyclic systems corresponding to the general formulae (A) and (B):



A



B

The preparation of the (A) type compounds (**5**-**7**) was carried out in an analogous way to that described by us.[1,2] The condensation of phthalic anhydride (**1**) with the hydrazides (**2**),(**3**),(**4**) in DMAC gave the pyrazolo[3',4':4,5]pyrimido[2,1-*a*]phthalazinediones (**5**),(**6**),(**7**) and 5-aminopyrazole-4-[*N*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)]carboxamides (**8**),(**9**),(**10**), respectively (Scheme 1). The carboxamides (**8**,**9**, **10**) were transformed into compounds (**5**,**6**,**7**), respectively, by heating in 1,2-dichlorobenzene in the presence of DBU. In an alternative synthetic route, the condensation of *N*-aminophtalimide (**11**) with the 5-amino-1-phenylpyrazole-4-carbonyl

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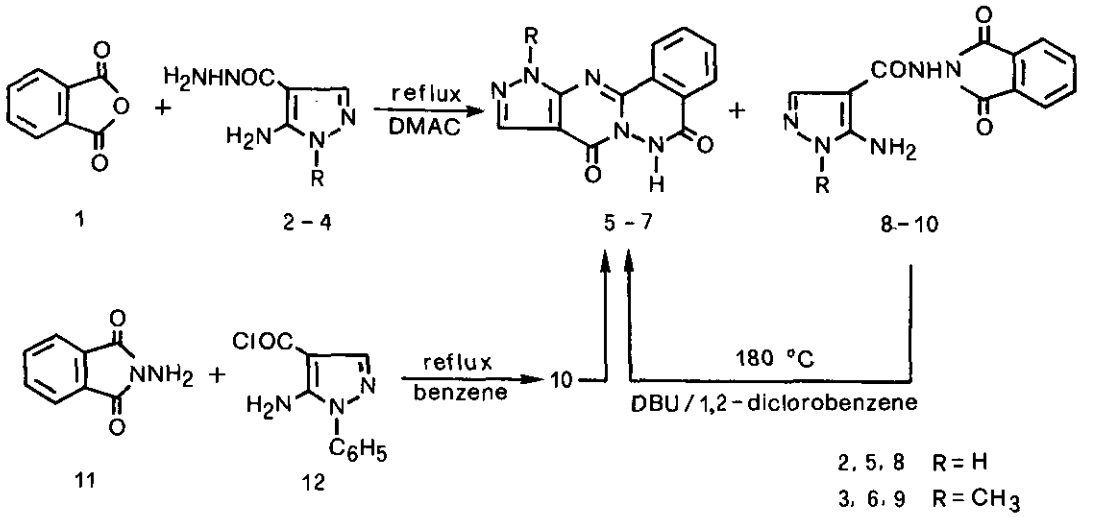
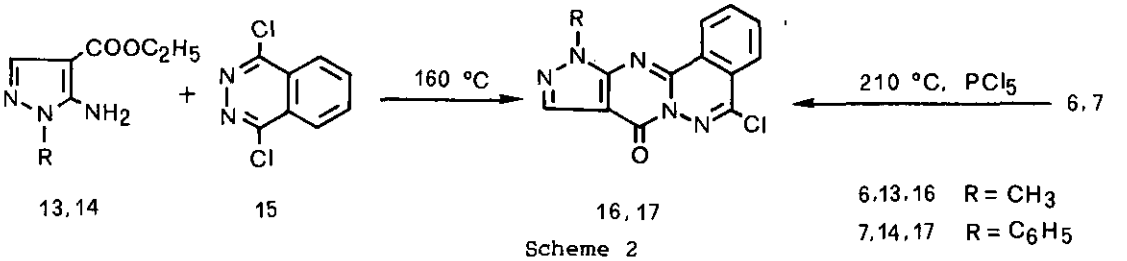
chloride (12) in benzene gave intermediate (10) whose subsequent cyclization afforded the 11-phenyl derivative (7). This alternative synthetic pathway supports the structures of compounds (7) and (10) and also compounds (5,6, and 8,9). The structure of the heterocycles (5-7) and carboxamides (8-10) was ascertained by ir, ^{1}H-nmr, electron impact mass spectra and elemental analyses.



Scheme 1

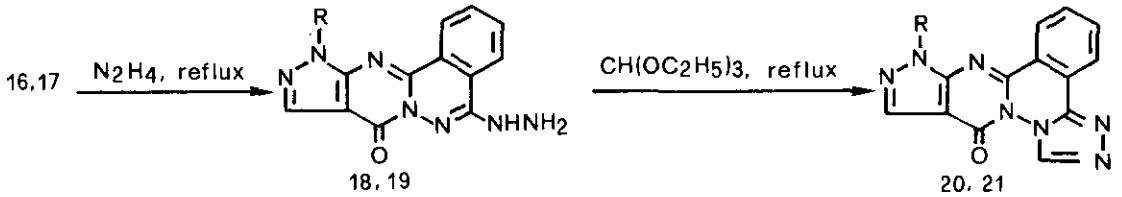
The reaction of compounds (6) and (7) with phosphorus pentachloride gave the corresponding 5-chloro derivatives (16) and (17), identical to those obtained by the condensation of the esters (13) and (14) with 1,4-dichlorophthalazine (15), respectively (Scheme 2). Analytical and spectral data of the 5-chloro derivatives (16) and (17) are in agreement with the proposed structures. Under reaction conditions adopted for 11-methyl (6) and 11-phenyl (7) derivatives, the 11-unsubstituted compound (5) was not chlorinated with phosphorus pentachloride.



Scheme 2

Moreover, the reaction of the 5-chloro derivatives (16) and (17) with hydrazine hydrate gave the 5-hydrazino derivatives (18) and (19) whose heating with triethyl orthoformate furnished the pyrazolo[3',4':4,5]pyrimido[2,1-*a*][1,2,4]triazolo[4,3-*c*]-phthalazin-12-one (20) and (21), respectively (Scheme 3). The ir spectra of these

pentacycles (20) and (21) showed the strong carbonyl absorption bands at 1735 cm^{-1} and 1740 cm^{-1}, respectively. Their electron impact mass spectra showed the intense molecular ion peaks at m/z 291 and 353, respectively.



16, 18, 20 R = CH_3
17, 19, 21 R = C_6H_5

Scheme 3

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 spectrophotometer in KBr disks. Elemental analyses for C, H and N were obtained on a Carlo Erba 1106 analyzer. The low resolution mass spectra were recorded by direct insertion into ion source on a VG-2AB2SE mass spectrometer under the following conditions:ionization energy,70 eV; source temperature 250-300°C; trap current 60 μA. The sample temperature ranged from room temperature to 300°C. The ^{1}H-nmr spectra were recorded in DMSO-d_6 on Bruker AC-80 spectrometer operating at 250.13 MHz. Chemical shifts are reported in δ ppm from DMSO as internal standard.

General procedure for the preparation of the derivatives of pyrimido[2,1-*a*]phthalazine-5,8-diones (5, 6, and 7) and of the carboxamides (8, 9, and 10).

A solution of the requisite derivatives (2[3]),(3[4]) or (4[5])(0.02 mol) and phthalic anhydride (1) (2.9 g, 0.02 mol) in 20 ml of DMAC(*N,N*-dimethylacetamide) was heated at reflux for 2 h. After cooling, the precipitate was filtered off, washed with ethanol, dried and recrystallized from the appropriate solvent. The carboxamides (8, 9 and 10) were isolated from the reaction filtrates by dilution with water, and collected, washed with ethanol, dried and recrystallized from appropriate solvent.

6*H*,11*H*-Pyrazolo[3',4':4,5]pyrimido[2,1-*a*]phthalazine-5,8-dione(5).

This compound was obtained as white needles in 30% yield, mp>340°C(DMF); ir: ν 3100(NH), 1690(CO) cm^{-1}; ms: (m/z) 253(M^+); Anal. Calcd for $C_{12}H_7N_5O_2$: C,56.91; H,2.78; N,27.65. Found: C,56.50; H,2.60; N,28.00.

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

This compound was obtained as white needles in 30% yield, mp 309-310°C(dioxane); ir: ν 3100(NH), 1715 and 1665(CO) cm^{-1}; ms: (m/z) 267(M^+); Anal. Calcd for $C_{13}H_9N_5O_2$: C,58.42; H,3.39; N,26.20. Found: C,58.40; H,3.25; N,26.70.

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

This compound was obtained as white powder in 35% yield, mp 274-275°C(dioxane); ir: ν 3100(NH), 1730 and 1660(CO) cm^{-1}; ms: (m/z) 329(M^+); Anal. Calcd for $C_{18}H_{11}N_5O_2$: C,65.65; H,3.36; N,21.26. Found: C,65.55; H,3.34; N,20.75.

5-Aminopyrazole-4-[*N*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)]carboxamide(8).

This compound was obtained as white powder in 50% yield, mp 273-275°C (decompt.) (ethanol); ir: ν 3480, 3370 and 3270(NH), 1800, 1730 and 1660(CO) cm^{-1}; ms: (m/z) 271(M^+); ^{1}H-nmr: 5.86(s, 2H, NH_2), 7.88(s, 1H, pyrazole C_3-H), 7.91-7.99(m, 4H, C_6H_4), 10.49(s, 1H, NHCO), 11.99(s, 1H, pyrazole N_1-H); Anal. Calcd for $C_{12}H_9N_5O_3$: C,53.13; H,3.34; N,25.82. Found C,53.25; H,3.30; N,25.85.

5-Amino-1-methyl-pyrazole-4-[*N*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)carboxamide(9).

This compound was obtained as white powder in 40% yield, mp 272-273°C(dioxane); ir: ν 3430, 3280,3220 and 3160(NH), 1795, 1740 and 1650(CO) cm^{-1}; ms: (m/z) 285(M^+); ^{1}H-nmr: 3.54(s, 3H, CH_3), 6.27(s, 2H, NH_2), 7.78(s,

1H, pyrazole C_3-H), 7.94-7.99(m, 4H, C_6H_4), 10.51(s, 1H, NHCO); Anal. Calcd for $C_{13}H_{11}N_5O_3$: C,54.73; H,3.88; N,24.55. Found: C,54.25; H,3.80; N,24.35.

5-Amino-1-phenyl-pyrazole-4-[*N*-(1,3-dihydro-1,3-dioxo-2-*H*-isoindol-2-yl)carboxamide(10).

This compound was obtained as white powder in 50% yield, mp 253-255°C(ethanol); ir: ν 3480, 3440, 3350 and 3260(NH), 1790, 1740 and 1670(CO) cm^{-1}; ms (m/z) 347(M^+); ^{1}H-nmr: 6.43(s, 2H, NH_2), 7.38-7.46 and 7.50-7.58(m, 5H, C_6H_5) 7.91-8.01(m, 4H, C_6H_4) 8.07(s, 1H, pyrazole C_3-H), 10.72(s, 1H, NHCO); Anal. Calcd for $C_{18}H_{13}N_5O_3$: C,62.24; H,3.77; N,20.16. Found: C,61.75; H,3.65; N,19.80.

Cyclization of carboxamides (8,9 and 10) to compounds (5,6 and 7).General procedure.

A mixture of the appropriate carboxamides (8,9 or 10) (0.01 mol), 1,2-dichlorobenzene (5 ml) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (0.1 ml) was heated in an oil bath at 180°C for 2 h. After cooling, the solid was collected, washed with ethanol, dried and recrystallized from suitable solvent to give compounds (5,6, and 7), respectively.

Synthesis of 5-amino-1-phenyl-pyrazole-4-[*N*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)carboxamide(10).

A mixture of 5-amino-1-phenyl-pyrazole-4-carbonyl chloride(12)[6] (2.2 g, 0.01 mol) and *N*-aminophthalimide(11) (3.2 g, 0.02 mol) in dry benzene (20 ml) was refluxed for 6 h. After cooling, the solid was collected, washed with benzene and recrystallized from ethanol to give compound (10) (0.8 g, yield 25%).

General procedure for the preparation of 5-chloro-8*H*-pyrazolo[3',4':4,5]pyrimido[2,1-*a*]phthalazin-8-ones (16) and (17).

Method A. A mixture of the appropriate amino ester (13[7] or 14[8]) (0.02 mol) and 1,4-dichlorophthalazine (15)[9] (2.0 g, 0.01 mol) was heated in an oil bath at 160°C under stirring until the evolution of hydrogen chloride was completed. After cooling, the reaction mixture was treated with a small amount of warm ethanol and filtered. The solid collected was poured into 5% sodium hydrogen carbonate (100 ml) and filtered off. After washing with water, the solid was collected, dried and crystallized from appropriate solvent.

Compound(16). This compound was obtained as yellow powder in 40% yield, mp 309-310°C(dioxane); ir: ν 1735(CO) cm^{-1}; ms: (m/z) 285(M^+); Anal. Calcd for $C_{13}H_8N_5Cl$: C,54.65; H,2.82; N,24.51. Found: C,54.90; H,2.90; N,24.30.

Compound(17). This compound was obtained as yellow crystals in 55% yield, mp 248-249°C(dioxane); ir: ν 1735(CO) cm^{-1}; ms: (m/z) 347(M^+); Anal. Calcd for $C_{18}H_{10}N_5Cl$: C,62.16; H,2.89; N,20.13. Found: C,62.35; H,2.90; N,20.20.

Method B. A mixture of the appropriate compound (6) or(7) (0.01 mol) and phopsphorus pentachloride (10.4 g, 0.05 mol) was heated in an oil bath at 210°C for 6 h. The cooled reaction mixture was then poured onto crushed ice and the resulting suspension neutralized with 10% sodium hydroxide. The residue was filtered, washed with water, dried and crystallized from appropriate solvent to give compounds (16 or 17).

General procedure for the preparation of 5-hydrazino-8*H*-pyrazolo[3',4':4,5]pyrimido[2,1-*a*]phthalazin-8-ones (18) and (19).

A mixture of 5-chloro derivative (16) or (17) (0.01 mol) and hydrazine hydrate (5.0 g, 0.1 mol) in dioxane (20 ml) was heated under reflux for 2 h. After cooling, a solid was collected, washed with ethanol, dried and crystallized from appropriate solvent.

Compound(18). This compound was obtained as yellow crystals in 30% yield, mp 313-315°C (decompt.) (*N,N*-dimethylformamide); ir: ν 3290 and 3260(NH), 1725(CO) cm^{-1}; ms: (m/z) 281(M^+); Anal. Calcd for $C_{13}H_{11}N_7O$: C,55.51; H,3.94; N,34.85. Found: C,55.20; H,4.00; N,34.50.

Compound(19). This compound was obtained as yellow crystals in 30% yield, mp 290°C (decompt.)(*N,N*-dimethylformamide); ir: ν 3330 and 3300(NH), 1700(CO) cm^{-1}; ms: (m/z) 343(M^+); Anal. Calcd for $C_{18}H_{13}N_7O$: C,62.96; H,3.81; N,28.55. Found: C,63.15; H,3.75; N,28.60.

General procedure for the preparation of 12*H*-pyrazolo[3',4':4,5]pyrimido[2,1-*a*][1,2,4]triazolo[4,3-*c*]phthalazin-12-ones (20) and (21).

A mixture of 5-hydrazino derivative (18) or (19) (0.01 mol) and triethyl orthoformate (5 ml, 30 mmol) was refluxed for 3 h. After cooling, the solid was collected, washed with ethanol and crystallized from appropriate solvent.

Compound(20). This compound was obtained as orange powder in 40% yield, mp 270-271°C(ethanol/dioxane); ir: ν 1735(CO) cm^{-1}; ms: (m/z) 291(M^+); Anal. Calcd for $C_{14}H_9N_7O$: C,57.73; H,3.11; N,33.66. Found: C,57.69; H,3.13; N,33.48.

Compound(21). This compound was obtained as orange powder in 35% yield, mp 263-264°C(ethanol/dioxane); ir: ν 1740(CO) cm^{-1}; ms: (m/z) 353(M^+); Anal. Calcd for $C_{19}H_{11}N_7O$: C,64.58; H,3.13; N,27.74. Found: C,65.07; H,3.17; N,27.89.

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