Azolopyrimidines and Pyrimidoquinazolines From 4-Chloropyrimidines

A. M. El-Reedy [a], A. S. Ali [b] A. O. Ayyad [a]

[a] Chemistry Department, Faculty of Science, University of Cairo, Giza, A. R. Egypt

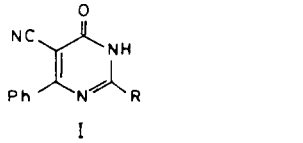
[b] National Research Centre, Dokki, Giza, A. R. Egypt

Received June 8, 1988

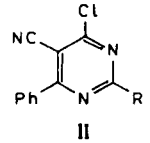
5-Cyano-3,4-dihydro-6-phenyl-2-substitutedpyrimidin-4-ones **Ia-c** reacted with phosphorus oxychloride to give the corresponding 4-chloropyrimidine derivatives **IIa-c**. Compounds **IIa-c** reacted with aniline and hydrazine to yield the 4-anilino, **IIIa,e**, and 4-hydrazino, **IIIb-d** derivatives. The 4-hydrazino analogues **IIIb,c** could be converted into the triazolo[4,3-*c*] and tetrazolo[4,5-*c*]pyrimidines **IV** and **V** by the action of carbon disulphide and nitrous acid, respectively. The reaction of **IIb,c** with phenylhydrazine afforded directly the 5-amino-4,6-diphenyl-6*H*-2-substitutedpyrazolo[3,4-*d*]pyrimidines **VIa,b**. The 4-chloro derivative **IIa** reacted with antrhanilic acid to form the 5-cyano-2,4-diphenyl-6-(*o*-carboxyphenylamino)pyrimidine **VIII**, which could be cyclised into the 4-cyano-1,3-diphenyl-10*H*-pyrimido[6,1-*b*]quinazolin-10-one **IX** by heating with acetic anhydride.

J. Heterocyclic Chem., **26**, 313 (1989).

On scanning the literature it is observed that publications dealing with azolo[-*a*]pyrimidines overnumber those of azolo[-*c*]- and azolo[-*d*]pyrimidines. In continuation to our interest in the synthesis of substituted pyrimidines [1,2] and fused pyrimidines [3,4], we describe here the syntheses of pyrazolo[3,4-*d*]-, triazolo[4,3-*c*]- and tetrazolo-[4,5-*c*]pyrimidines. Also, we report the synthesis of the 10*H*-pyrimido[6,1-*b*]quinazolin-10-one. Thus, refluxing of 5-cyano-3,4-dihydro-6-phenyl-2-substitutedpyrimidin-4-ones **Ia-c** [2,5] with phosphorus oxychloride in dry dioxane afforded the corresponding 4-chloropyrimidine derivatives **IIa-c**. The ir spectra of **IIa-c** showed no absorption in the carbonyl region and the pmr spectrum (DMSO-d_6) of **IIa**, as an example, displayed signals at δ 7.61 ppm (m, 6H, aromatic protons), δ 8.08 ppm (m, 2H, aromatic protons) and δ 8.45 ppm (m, 2H, aromatic pro-tons).



I

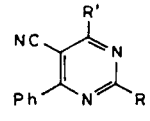


II

a, R = C_6H_5
b, R = NHC_6H_5
c, R = $NHCH_2C_6H_5$

Position 4 in compounds **IIa-c** showed distinct activity and the chlorine atom could be substituted by the use of aniline or hydrazine hydrate. Thus compounds **IIa-c** reacted with aniline or hydrazine hydrate in boiling dioxane to give the corresponding 4-anilino and 4-hydrazino derivatives **IIIa-e**, respectively.

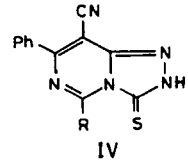
The pmr spectrum (DMSO-d_6) of **IIIc** showed signals at δ 4.50 ppm (s, 2H, CH_2), δ 4.60 ppm (s, 2H, NH_2, disappeared after deuterium oxide exchange), δ 7.28 ppm (m, 5H, aromatic protons), δ 7.50 ppm (m, 3H, aromatic protons), δ 7.71 ppm (m, 2H, aromatic protons), δ 8.18 ppm (broad s, 1H, NH, disappeared after deuterium oxide exchange) and δ 8.62 ppm (broad s, 1H, NH, disappeared after deuterium oxide exchange). The ir spectra of **IIIa-e** displayed absorption bands around 3300 cm^{-1} (NH) and 2220 cm^{-1} (CN).



III

a, R = C_6H_5 ; R' = NHC_6H_5
b, R = C_6H_5 ; R' = $NHNH_2$
c, R = $NHCH_2C_6H_5$; R' = $NHNH_2$
d, R = NHC_6H_5 ; R' = $NHNH_2$
e, R = NHC_6H_5 ; R' = NHC_6H_5

Compounds **IIIb,c** reacted with carbon disulphide in ethanolic potassium hydroxide solution to yield 8-cyano-2,3-dihydro-7-phenyl-5-substituted-1,2,4-triazolo[4,3-*c*]pyrimidine-3-thione, **IVa,b**.



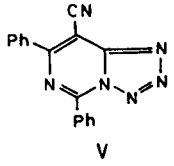
IV

a, R = C_6H_5
b, R = $NHCH_2C_6H_5$

The ir spectra of **IVa,b** displayed absorption bonds around 3300 cm^{-1} (NH) and 2220 cm^{-1} (CN) and the pmr spectrum (DMSO-d_6) of **IVa** showed signals at δ 3.45 ppm

(broad s, 1H, NH, disappeared after deuterium oxide exchange), δ 7.60 ppm (m, 6H, aromatic protons), δ 8.09 ppm (m, 2H, aromatic protons) and δ 8.53 ppm (m, 2H, aromatic protons).

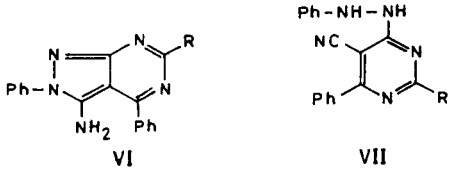
When compounds **IIIb** was treated with nitrous acid at 0°, there was obtained 8-cyano-5,7-diphenyltetrazolo-[4,5-*c*]pyrimidine **V**.



V

The ir spectrum of **V** displayed an absorption band at 2220 cm^{-1} (CN) and showed no absorption in the NH region and its pmr spectrum (DMSO-d_6) showed signals corresponding to aromatic protons only.

In contrast to the action of hydrazine, phenylhydrazine reacted with each of **IIb,c** to give the 5-amino-4,6-diphenyl-6*H*-2-substitutedpyrazolo[3,4-*d*]pyrimidines **VIa,b**. Formation of **VI** may be took place *via* the non-isolable intermediate **VII**.

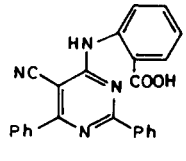


VI VII

a, R = NHC_6H_5
b, R = $NHCH_2C_6H_5$

The ir spectra of **VIa,b** displayed absorption bands around 3300, 3200 and 1640 cm^{-1} (NH_2) and showed no bands for CN group. The pmr spectrum (DMSO-d_6) of **VIb** showed signals at δ 4.65 ppm (s, 2H, CH_2), δ 5.07 ppm (s, 2H, NH_2, disappeared after deuterium oxide exchange), δ 7.05-7.92 ppm (m, 13H, aromatic protons) and δ 8.10 ppm (m, 3H, 2 aromatic protons + NH, exchangeable after deuterium oxide).

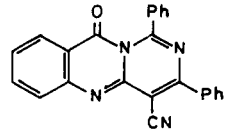
Compound **IIa** reacted with anthranilic acid in refluxing acetic acid to give the 5-cyano-2,4-diphenyl-6-(*o*-carboxyphenylamino)pyrimidine **VIII**.



VIII

The ir spectrum of **VIII** displayed absorption bands at 3100 cm^{-1} (broad, NH and OH), 2220 cm^{-1} (CN) and 1660 cm^{-1} (CO) and its pmr spectrum (DMSO-d_6) showed signal at δ 11.76 ppm (broad s, 1H, COOH, disappeared after deuterium oxide exchange).

Compound **VIII** was cyclised on heating with acetic anhydride to yield 4-cyano-1,3-diphenyl-10*H*-pyrimido[6,1-*b*]-quinazolin-10-one **IX**.



IX

The ir spectrum of **IX** showed no absorption in the NH region and the signal corresponding to the carboxylic proton, in **VIII**, disappeared in its pmr spectrum.

EXPERIMENTAL

Melting points were taken on a Kofler apparatus and are uncorrected. Infrared (ir) spectra were determined as potassium bromide pellets with a Perkin-Elmer Infracord 137 instrument. The ^{1}H-nmr spectra were determined with a Perkin-Elmer R12A instrument.

2-Anilino-5-cyano-3,4-dihydro-6-phenylpyrimidin-4-one **Ia** and the phenyl derivative **Ib** were prepared as described in literature [2,5].

2-Benzylamino-5-cyano-3,4-dihydro-6-phenylpyrimidin-4-one **Ic**.

A mixture of 2.43 g (0.01 mole) of 5-cyano-3,4-dihydro-2-methylthio-6-phenylpyrimidin-4-one [5] and 1.28 g (0.012 mole) of benzylamine was heated in an oil bath at 200° for 2 hours. The reaction mixture was left to cool and the solid separated was crystallized from dioxane to yield 2.42 g (80%) of **Ic**, mp 263°; ir: 3250 (NH), 2220 (CN), 1660 cm^{-1} (CO).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.50; H, 4.66; N, 18.55. Found: C, 71.5; H, 4.6; N, 18.5.

4-Chloro-5-cyano-6-phenyl-2-substitutedpyrimidines **IIa-c**. General Procedure.

A mixture of 0.01 mole of **Ia-c**, 50 ml of dioxane and 25 ml of phosphorus oxychloride was heated under reflux for one hour. The solution was cooled and poured into ice water. The solid separated was collected, washed with water, dried and crystallized from ethanol to give **IIa-c**. See Tables I and III.

Table I

4-Chloro-5-cyano-6-phenyl-2-substitutedpyrimidines

Compound	Mp °C	Yield %	Formula	Analysis % Calcd./Found C	H	Cl	N
IIa	180	87	$C_{17}H_{10}ClN_3$	69.99	3.45	12.16	14.40
				70.0	3.5	12.0	14.4
IIb	168	75	$C_{17}H_{11}ClN_4$	66.55	3.61	11.56	18.28
				66.7	3.5	11.6	18.4
IIc	157	80	$C_{18}H_{13}ClN_4$	67.39	4.08	11.05	17.47
				67.2	4.0	10.9	17.4

5-Cyano-2,4-disubstituted-6-phenylpyrimidines **IIIa-e**. General Procedure.

A mixture of 0.01 mole of **IIa-c**, 0.02 mole of aniline or hydrazine hydrate and 40 ml of dioxane was heated under reflux for 2 hours. The reaction mixture was cooled and poured into water. The solid separated was collected and crystallized from the proper solvent. Tables I and III.

8-Cyano-2,3-dihydro-7-phenyl-5-substituted-1,2,4-triazolo[4,3-*c*]pyrimidine-3-thione **IVa,b**.

Table II

5-Cyano-2,4-disubstituted-6-phenylpyrimidines

Compound	Mp °C	Yield %	Solvent	Formula	Analysis % Calcd./Found C		
IIIa	226	79	Dimethyl-formamide	$C_{23}H_{16}N_4$	79.29 79.4	4.63 4.5	16.08 16.0
IIIb	252	75	Dilute dioxane	$C_{17}H_{13}N_5$	71.05 71.1	4.56 4.4	24.39 24.5
IIIc	159	75	Benzene	$C_{18}H_{16}N_6$	68.33 68.2	5.10 5.2	26.57 26.6
IIId	174	70	Benzene	$C_{17}H_{14}N_6$	67.52 67.7	4.66 4.6	27.82 27.7
IIIe	168	65	Ethanol	$C_{23}H_{17}N_5$	76.01 75.9	4.72 4.7	19.27 19.3

A mixture of 1 g of each of **IIIb,c**, 50 ml of ethanol, 0.3 g of potassium hydroxide and 3 ml of carbon disulphide was refluxed for 4 hours. After removal of ethanol, water was added and the alkaline solution was filtered. The clear filtrate was acidified with dilute hydrochloric acid and the formed precipitate was collected and crystallized from dioxane.

Compound **IVa** was obtained in 60% yield, mp 270°; ir: 3420, 3180 (NH), 2220 (CN).

Anal. Calcd. for $C_{18}H_{11}N_5S$: C, 65.63; N, 3.36; N, 21.28; S, 9.72. Found: C, 65.7; H, 3.3; N, 21.3; S, 9.6.

Compound **IVb** was obtained in 65% yield, mp 266°; ir: 3300, 3150 (NH); 2220 (CN); ^{1}H-nmr (deuteriodimethylsulfoxide): δ 4.8 ppm (s, 2H, CH_2), δ 7.15-7.57 ppm (m, 9H, 8 aromatic protons + NH, exchangeable after deuterium oxide), δ 7.85 ppm (m, 2H, aromatic protons), δ 11.1 ppm (broad s, 1H, NH, disappeared after deuterium oxide exchange).

8-Cyano-5,7-diphenyltetrazolo[4,5-*c*]pyrimidine **V**.

A solution of 1 g of **IIIb** in 50 ml of acetic acid was cooled to 0° and a cold solution of 0.5 g of sodium nitrite in 10 ml of water was gradually added. The reaction mixture was kept at 0-5° with stirring for 2 hours, left overnight and diluted with water whereupon precipitation took place. The solid, that precipitated, was collected and crystallized from dioxane to give 0.61 g 65% of **V**, mp 201°; ir: 2220 cm^{-1} (CN); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.64 ppm (6H, aromatic protons), δ 8.05 ppm (m, 2H, aromatic protons), δ 8.25 ppm (m, 2H, aromatic protons).

Anal. Calcd. for $C_{17}H_{10}N_6$: C, 68.43; H, 3.38; N, 28.19. Found: C, 68.5; H, 3.4; N, 28.1.

5-Amino-4,6-diphenyl-6*H*-2-substitutedpyrazolo[3,4-*d*]pyrimidine **VIa,b**.

A solution of 0.005 mole of each of **IIb,c** in 30 ml of dry dioxane was treated with 0.54 g (0.005 mole) of phenylhydrazine was refluxed for 10 hours. The solution was left to cool, poured into water and crystallized from ethanol.

Compound **VIa** was obtained in 73% yield, mp 230°; ir: 3300 cm^{-1} (NH), 1640 cm^{-1} (NH_2); ^{1}H-nmr: δ 5.10 ppm (s, 2H, NH_2, disappeared after deuterium oxide exchange), δ 6.9-7.9 ppm (m, 13H, aromatic protons), δ 8.15 ppm (m, 2H, aromatic protons), δ 9.82 ppm (s, 1H, NH, disappeared after deuterium oxide exchange).

Compound **VIb** was obtained in 74% yield, mp 184°.

5-Cyano-2,4-diphenyl-6-(*o*-carboxyphenylamino)pyrimidine **VIII**.

To a solution of 2.92 g (0.01 mole) of **IIa** in 50 ml of acetic acid, 1.37 g (0.01 mole) of anthranilic acid were added. The solution was refluxed for 4 hours. Compound **VIII** which precipitated during reflux was collected and crystallized from dioxane to yield 3.49 g (89%) of **VIII**, mp 296°, ir: 3100 (broad, OH & NH), 2220 (CN), 1660 (CO); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.48 ppm (m, 9H, aromatic protons), δ 7.92 ppm (m, 3H, 2 aromatic protons + NH, exchangeable after deuterium oxide), δ 8.28 ppm (m, 2H, aromatic protons), δ 8.80 ppm (m, 1H, aromatic proton), δ 11.76 ppm (s, 1H, COOH, disappeared after deuterium oxide exchange).

Anal. Calcd. for $C_{24}H_{16}N_4O_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.4; H, 4.1; N, 14.3.

Cyclisation of **VII**. Formation of **IX**.

A solution of 1 g of **VIII** in 10 ml of acetic anhydride was heated under reflux for 10 hours. The solid that separated while boiling was collected and crystallized from dimethylformamide to give 0.58 g 61% of

Table III

IR and PMR Data of Products in Tables I and II

Compound	IR [cm^{-1}]	PMR δ ppm
IIa	2220 (CN)	7.61 (m, 6H, aromatic protons), 8.08 (m, 2H, aromatic protons), 8.45 (m, 2H, aromatic protons)
IIb	3310 (NH), 2220 (CN)	
IIc	3320 (NH), 2220 (CN)	5.95 (s, 2H, CH_2), 7.21 (s, 5H, aromatic protons), 7.50 (m, 3H, aromatic protons), 7.80 (m, 2H, aromatic protons), 9.21 (broad s, 1H, NH, disappeared after deuterium oxide exchange)
IIIa	3300 (NH), 2220 (CN)	7.20-7.71 (m, 11H, aromatic protons), 7.96 (m, 2H, aromatic protons), 8.24 (m, 2H, aromatic protons), 9.57 (s, 1H, NH, disappeared after deuterium oxide exchange)
IIIb	3300 (NH), 2220 (CN), 1640 (NH_2)	4.92 (s, 1H, NH, disappeared after deuterium oxide exchange), 7.55 (m, 6H, aromatic protons), 7.96 (m, 4H, 2 aromatic protons + NH_2 exchangeable after deuterium oxide), 8.48 (m, 2H, aromatic protons)
IIIc	3340 (NH), 2210 (CN), 1640 (NH_2)	4.50 (s, 2H, CH_2), 4.60 (s, 2H, NH_2, disappeared after deuterium oxide exchange), 7.28 (m, 5H, aromatic protons), 7.50 (m, 3H, aromatic protons), 7.71 (m, 2H, aromatic protons), 8.18 (broad s, 1H, NH, disappeared after deuterium oxide exchange), 8.62 (broad s, 1H, NH, disappeared after deuterium oxide exchange)
IIId	3300 (NH), 2210 (CN), 1650 (NH_2)	4.60 (broad s, 2H, NH_2, disappeared after deuterium oxide exchange), 6.95-7.85 (m, 11H, 10 aromatic protons + NH exchangeable after deuterium oxide), 9.71 (s, 1H, NH, disappeared after deuterium oxide exchange)
IIIe	3350 (NH), 2220 (CN)	7.0-7.97 (m, 16H, 15 aromatic protons + NH exchangeable after deuterium oxide), 11.0 (s, 1H, NH, disappeared after deuterium oxide exchange)

IX, mp >300°; ir: 2220 (CN), 1690 (CO); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.35-7.70 ppm (m, 9H, aromatic protons), δ 7.85-8.18 ppm (m, 5H, aromatic protons).

Anal. Calcd. for $C_{24}H_{14}N_4O$: C, 76.98; H, 3.77; N, 14.98. Found: C, 77.0; H, 3.7; N, 15.0.

REFERENCES AND NOTES

[1] H. A. Daboun and A. M. El-Reedy, *Z. Naturforsch.*, **38b**, 1686 (1983).

[2] A. M. Abdel-Fattah, S. M. Hussain, A. M. El-Reedy and N. M. Yousif, *Tetrahedron*, **39**, 3197 (1983).

[3] S. M. Hussain, A. M. El-Reedy, A. M. Hassan Rezk and Kh. A. Sife El-Dien, *J. Heterocyclic Chem.*, **24**, 1605 (1987).

[4] S. M. Hussain, A. M. El-Reedy and S. A. El-Sharabasy, *Tetrahedron*, **44**, 241 (1988).

[5] S. M. Hussain, A. A. Elbarbary and S. A. Mansour, *J. Heterocyclic Chem.*, **22**, 169 (1985).