NEW HETEROCYCLO-SUBSTITUTED PYRAZOLO[3,4-*b*]PYRIDINE DERIVATIVES

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A literature survey has revealed that several annelated pyridines isolated from natural sources have found broad spectrum of clinical applications[1,2] and as pesticidal agents[3,4]. Moreover, they were used for inhibition of aldose reductase activity and cataract formation in diabetes[5].

In this investigation and in continuance with our previous work in synthesis of some heterocyclic compounds fused with pyridine moiety[6 - 8], we used 3-amino-4,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (*II*) as starting material to synthesize many heterocyclic compounds containing pyrazolopyridine moiety.

EXPERIMENTAL

All melting points were uncorrected. IR spectra (ν, cm^{-1}) were recorded on Pye–Unicam SP 3-100 spectrophotometer using KBr wafer technique. The ^1H NMR spectra were obtained with a Varian EM-390 (90 MHz) spectrometer. The chemical shifts (δ) are reported in ppm, using TMS as internal reference. Elemental analysis was determined on a Perkin–Elmer 240 C microanalyzer.

3-Amino-4,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (*II*)

A mixture of 2-chloro-4,6-diphenylpyridine-3-carbonitrile (*I*) (0.01 mol) and hydrazine hydrate (0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 4 h, then the reaction mixture was allowed to cool. The solid product was collected and recrystallized from ethanol in 95% yield. IR spectrum: 3 360, 3 260, 3 150 (NH and NH_2), no C≡N group band.

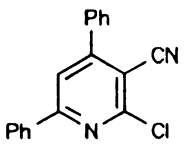
Diazotization of Compound *II*

Compound *II* (0.01 mol) was dissolved in concentrated hydrochloric acid (3 ml) and ice cooled to 0 – 5 °C. Sodium nitrite solution (1.5 g in 10 ml of water) was added dropwise during a period of 10 min and the reaction mixture was stirred for 30 min.

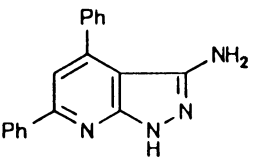
Coupling of Diazonium Salt *III* with the Active Methylene Reagents

To ice cooled mixture of the compound containing active methylene (0.01 mol) and sodium acetate (0.04 mol) in ethanol (50 ml), diazotized amino compound *III* solution (0.01 mol) was added dropwise with stirring

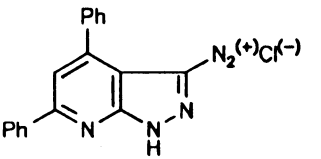
over a period of 30 min. The stirring was continued for 30 min and then reaction mixture was allowed to stand for 3 h. The solid product was collected and recrystallized from ethanol to give the corresponding products *IV* – *VIII*. Compound *IV*, IR spectrum: 3 400(NH), 2 180 (C≡N) and 1 695 (C=O); ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.3 t, 3 H (CH_3), 4.1 q, 2 H (CH_2) 6.7 s, 1 H (pyridine CH). Compound *V*, IR spectrum: 3 310, 3 160 (2 × NH), 2 220 – 2 200 (C≡N); ^{1}H NMR spectrum ($(CD_3)_2SO$): 7.1 s, 1 H (pyridine CH); 13.0 and 11.0 2s, 2 H (2 × NH). Compound *VI*, IR spectrum: 3 400 (NH), 1 730 – 1 700 (CO); ^{1}H NMR spectrum ($(CD_3)_2SO$): 1.4 – 1.2 m, 6 H (2 × CH_3); 4.20 m, 4 H (2 × CH_2) and 7.30 s, 1 H (pyridine CH). Compound *VII*, IR spectrum: 3 300 – 3 200 (NH), 1 750 – 1 720 (CO). ^{1}H NMR spectrum (CF_3COOH): 1.30 t, 3 H (CH_3); 2.30 s, 3 H ($COCH_3$); 4.20 q, 2 H (CH_2); 7.3 s, 1 H (pyridine CH); 8.0 and 10.10 2s, 2 H (2 × NH). Compound *VIII*, IR spectrum: 3 400 – 3 200 (NH), 1 720 – 1 690 (C=O). ^{1}H NMR spectrum (CF_3COOH): 3.30 and 3.10 2s, 6 H (2 × $COCH_3$); 7.40 s, 1 H (pyridine CH).



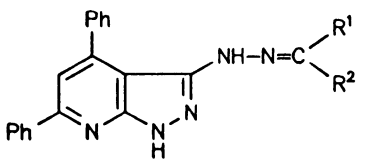
I



II

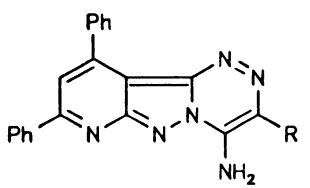


III

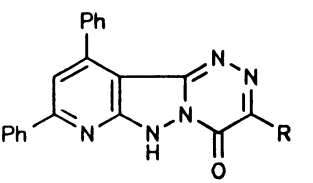


IV–VIII

	R^1	R^2
IV	CN	$CO_2C_2H_5$
V	CN	CN
VI	$CO_2C_2H_5$	$CO_2C_2H_5$
VII	$COCH_3$	$CO_2C_2H_5$
VIII	$COCH_3$	$COCH_3$



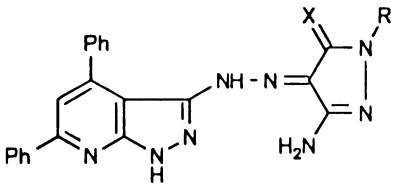
IX, R = $CO_2C_2H_5$
X, R = CN



XI, R = $CO_2C_2H_5$
XII, R = $COCH_3$

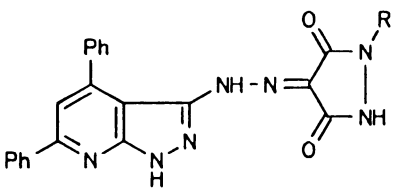
Cyclization of Compounds *IV – VII*

A mixture of compounds *IV – VII* (0.01 mol) in acetic acid (20 ml), was heated under reflux for 1 h, then allowed to cool. The solid product was collected and recrystallized from ethanol. The physical and analytical data are listed in Table I. Compound *IX*, IR spectrum: 3 350 – 3 200 (NH_2), 1 700 (CO). ^1H NMR spectrum (CF_3COOH) 1.80 t, 3 H (CH_3); 4.50 q, 2 H (CH_2), 7.50 s, 1 H (pyridine CH); 9.20 and 9.80 2s, 2 H (NH_2). Compound *X*, IR spectrum: 3 300 – 3 200 (NH_2), 2 220 (C≡N). ^1H NMR spectrum (CF_3COOH): 7.30 s, 1 H (pyridine CH); 9.80 s, 2 H (NH_2). Compound *XI*, IR spectrum: 1 720 and 1 700 (CO); ^1H NMR spectrum ($CDCl_3$): 1.30 t, 3 H (CH_3); 4.20 q, 2 H (CH_2); 7.40 s, 1 H (pyridine CH). Compound *XII*, IR spectrum: 1 700 (CO). ^1H NMR spectrum ($CDCl_3$): 2.30 s, 3 H ($COCH_3$).

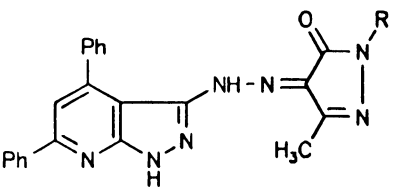


	X	R
XIII	O	H
XIV	NH	H
XV	O	C_6H_5
XVI	NH	C_6H_5

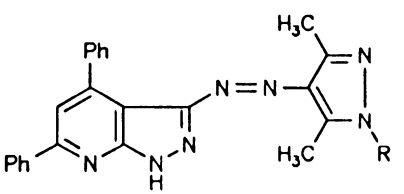
XIII – XVI



XVII, R = H
XVIII, R = Ph



XIX, R = H
XX, R = Ph



XXI, R = H
XXII, R = Ph

TABLE I
Physical constant and analytical data for compounds *II*, *IV* – *XXII*

Compound	M. p., °C (Yield, %)	Formula (M. w.)	Calculated/Found		
			% C	% H	% N
II	205 (78)	$C_{18}H_{14}N_4$ (286.3)	75.51 75.44	4.93 4.84	19.57 19.63
IV	180 (65)	$C_{23}H_{18}O_2N_6$ (410.4)	67.31 67.26	4.42 4.35	20.48 20.57
V	118 (71)	$C_{21}H_{13}N_7$ (363.4)	69.41 69.37	3.61 3.25	26.98 27.04
VI	158 (68)	$C_{25}H_{23}O_4N_5$ (457.5)	65.63 65.82	5.07 5.24	15.31 16.01
VII	190 (65)	$C_{24}H_{21}O_3N_5$ (427.5)	67.44 67.38	4.95 4.86	16.38 16.45
VIII	172 (62)	$C_{23}H_{19}O_2N_5$ (397.4)	69.51 69.61	4.82 4.91	17.62 17.71
IX	228 (58)	$C_{23}H_{18}O_2N_6$ (410.4)	67.31 67.23	4.42 4.50	20.48 20.53
X	270 (61)	$C_{21}H_{13}N_7$ (363.4)	69.41 69.35	3.61 3.53	26.98 26.93
XI	125 (63)	$C_{23}H_{17}O_3N_5$ (411.4)	67.15 67.24	4.17 4.24	17.02 16.96
XII	268 (60)	$C_{22}H_{15}O_2N_5$ (381.4)	69.28 67.34	3.96 4.04	18.36 18.41
XIII	198 (73)	$C_{21}H_{16}ON_8$ (396.4)	63.63 63.72	4.07 4.12	28.27 28.34
XIV	>310 (70)	$C_{21}H_{17}N_9$ (395.4)	63.79 63.84	4.33 4.41	31.88 31.92
XV	165 (72)	$C_{27}H_{20}ON_8$ (472.5)	68.63 68.72	4.27 4.32	23.72 23.66
XVI	182 (75)	$C_{27}H_{21}N_9$ (471.5)	68.78 68.86	4.49 4.52	26.73 26.68
XVII	>300 (70)	$C_{21}H_{15}O_2N_7$ (397.4)	63.47 63.54	3.81 3.75	24.67 24.72
VXIII	284 (73)	$C_{27}H_{19}O_2N_7$ (473.5)	68.49 68.55	4.05 4.11	20.71 20.63
XIX	270 (76)	$C_{22}H_{17}ON_7$ (395.4)	66.82 66.75	4.33 4.42	24.80 24.71
XX	293 (74)	$C_{28}H_{21}ON_7$ (471.5)	71.32 71.23	4.49 4.54	20.79 20.82
XXI	220 (70)	$C_{23}H_{19}N_7$ (393.5)	70.21 70.11	4.87 4.94	24.92 24.87
XXII	320 (73)	$C_{29}H_{23}N_7$ (469.6)	74.18 74.25	4.94 4.85	20.88 20.92

Reaction of Compounds *IV – VIII* with Hydrazine and Phenylhydrazine

A mixture of compounds *IV – VIII* (0.01 mol), hydrazine or phenylhydrazine (0.01 mol) in ethanol (30 ml) was heated under reflux for 4 h. The reaction mixture was allowed to cool, the solid product was collected and recrystallized from ethanol to give *XIII – XXII*, respectively. The physical constants are listed in Table I. The IR spectra of these compounds (*XIII* and *XXII*) showed a characteristic bands at 3 400, 3 300 (NH_2), 2 200 (C≡N), 3 140 (NH), 1 720 – 1 690 (CO). ^{1}H NMR spectra ($CDCl_3$): 9.20 s, 3 H (3 × NH); 6.80 s, 2 H (NH_2); 7.10 – 8.90 m, 11 H (aromatic) for compound *XIII*; 2.10 s, 3 H, (CH_3); 9.20 s, 3 H (3 × NH); 7.10 – 8.70 m, 11 H (aromatic) for compound *XIX*; 2.80 s, 6 H (2 × CH_3); 9.10 s, 2 H (2 × NH); 7.00 – 8.90 m, 11 H (aromatic) for compound *XXI*; 9.60 – 9.20 s, 3 H (3 × NH); 7.20 – 8.60 m, 16 H (aromatic) for compound *XVIII*.

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