Hetarylpyrazoles. II. (1) Reactions of Pyrazol-1′-ylpyridines

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Pyrazol-1′-ylpyridines undergo electrophilic substitution reactions (bromination, chlorination, and nitration) preferentially in the pyrazole ring. There is some evidence of the mutual influence of the pyrazole and the pyridine ring on the reactivity of the system. Some modifications of the substituents were also carried out. A dihydro derivative of a new ring system, pyrazolo[1′,2′-*a*]pyrido[2,1-*c*][1,2,4]triazine was also obtained.

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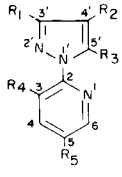
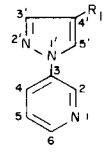
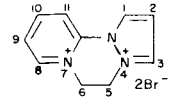
Some years ago we obtained 2-, 3-, and 4-(pyrazol-1′-yl)-pyridines by the Ullmann condensation method (3) and more recently we prepared some more 2-(pyrazol-1′-yl)-pyridines either by the condensation of the respective pyridylhydrazines with 1,3-dicarbonyl compounds or by the arylation of appropriate pyrazoles by halopyridines (1). Except the metallation of 2-(pyrazol-1′-yl)pyridine (4) nothing is known about the chemical reactivity of this system and as such we would now like to report our work on some reactions of these pyrazol-1′-ylpyridines.



I	$R_1=R_2=R_3=R_4=R_5=H$
II	$R_1=R_3=Ph, R_2=R_4=R_5=H$
III	$R_1=R_2=R_3=R_5=H, R_4=NO_2$
IV	$R_1=R_2=R_3=R_4=H, R_5=NO_2$
V	$R_1=R_3=Me, R_2=R_4=H, R_5=NO_2$
VI	$R_1=R_3=Ph, R_2=R_4=H, R_5=NO_2$
VIII	$R_1=R_3=R_4=R_5=H, R_2=Br$
IX	$R_1=R_3=Ph, R_4=R_5=H, R_2=Br$
X	$R_1=R_3=R_5=H, R_2=Br, R_4=NO_2$
XI	$R_1=R_3=R_4=H, R_2=Br, R_5=NO_2$
XII	$R_1=R_3=Me, R_2=Br, R_4=H, R_5=NO_2$
XIII	$R_1=R_3=Ph, R_2=Br, R_4=H, R_5=NO_2$
XIV	$R_1=R_3=R_4=R_5=H, R_2=Cl$
XV	$R_1=R_3=Ph, R_4=H, R_2=R_5=Cl$
XVI	$R_1=R_3=R_5=H, R_2=Cl, R_4=NO_2$
XVII	$R_1=R_3=R_4=H, R_2=Cl, R_5=NO_2$
XVIII	$R_1=R_3=Me, R_2=Cl, R_4=H, R_5=NO_2$
XIX	$R_1=R_3=Ph, R_2=Cl, R_4=H, R_5=NO_2$
XX	$R_1=R_3=R_4=R_5=H, R_2=NO_2$
XXI	$R_1=R_3=R_5=H, R_2=R_4=NO_2$
XXII	$R_1=R_3=R_4=H, R_2=R_5=NO_2$
XXIII	$R_1=R_3=Me, R_4=H, R_2=R_5=NO_2$
XXIV	$R_1=R_3=p\text{-}NO_2C_6H_4, R_2=NO_2, R_4=R_5=H$
XXV	$R_1=R_3=p\text{-}NO_2C_6H_4, R_2=R_5=NO_2, R_4=H$
XXVI	$R_1=R_3=Ph, R_2=R_5=NO_2, R_4=H$
XXXI	$R_1=R_3=R_4=R_5=H, R_2=NH_2$
XXXII	$R_1=R_3=R_4=R_5=H, R_2=NHAc$
XXXIII	$R_1=R_3=R_4=R_5=H, R_2=CN$
XXXV	$R_1=R_3=R_4=R_5=H, R_2=CONH_2$
XXXVI	$R_1=R_3=R_4=R_5=H, R_2=CO_2H$
XXXVII	$R_1=Me, R_2=R_4=H, R_3=Cl, R_5=NO_2$





XXX

VII	$R_1=H$
XXVII	$R_1=Br$
XXVIII	$R_1=Cl$
XXIX	$R_1=NO_2$
XXXIV	$R_1=CN$

Electrophilic reactions (bromination, chlorination and nitration) were carried out on various 2-(pyrazol-1′-yl)-pyridines (I-VI) and 3-(pyrazol-1′-yl)pyridine (VII). The bromination of I was carried out both in chloroform and in acetic acid leading to the 4′-bromo derivative (VIII). The yield of VIII was much higher when the bromination was carried out in acetic acid. The mass spectrum of VIII exhibited molecular ion peaks corresponding to m/e 223 and 225 and in the proton magnetic resonance spectrum the triplet at δ 6.40 due to the 4′ proton of the pyrazole ring of I disappeared while the doublets for the protons 3′ and 5′ were reduced to singlets thus confirming the substituition at the 4′ position of the pyrazole ring of I. Bromination of II-VI similarly gave the 4′ substituted bromo derivatives (IX-XIII) confirmed by their elemental analyses as well as by their proton magnetic resonance spectra. These bromo derivatives are presented in the tables 1-2.

Chlorination of I-VI were carried out in acetic acid with hypochlorous acid. With the exception of II the corresponding 4′-chloro products (XIV, XVI-XIX) were obtained in each case (Tables 1 and 2). When II was chlorinated a dichloro compound was isolated from the reaction which, based on its elemental analysis, pmr and mass spectra, is tentatively assigned the structure XV.

In the nitration of I, III, IV and V either with a mixture of nitric and sulfuric acid at 10-15° or with acetyl nitrate at 0-5° mononitration products were isolated. The nitration products were identified as being 4′-nitro derivatives (XX-XXIII). Attempts at further nitration of these products failed under conditions of higher temperatures or longer periods of nitrations. The compounds XX and

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Table 1

Pyrazol-1'-ylpyridines

Compound No.	Yield	M.p. °C	Crystallization Solvent (a)	Formula	Analyses (b) % C	H	N
VIII	97	74-75	A	$C_8H_6BrN_3$	42.90 (42.88)	2.64 (2.70)	18.94 (18.75)
IX	89	108-109	A	$C_{20}H_{14}BrN_3$	63.85 (63.85)	3.66 (3.75)	10.96 (11.17)
X	97	133-134	A	$C_8H_5BrN_4O_2$	35.55 (35.71)	1.99 (1.87)	20.62 (20.82)
XI	79	195-195.5	A	$C_8H_5BrN_4O_2$	35.64 (35.71)	1.97 (1.87)	20.67 (20.82)
XII	92	132-133	A	$C_{10}H_9BrN_4O_2$	40.25 (40.42)	3.04 (3.05)	18.66 (18.86)
XIII	91	180-181	A	$C_{20}H_{13}BrN_4O_2$	56.98 (57.02)	3.24 (3.11)	13.18 (13.30)
XIV	70	64-65	A	$C_8H_6ClN_3$	53.21 (53.50)	3.38 (3.37)	23.16 (23.40)
XV	65	191-192	A	$C_{20}H_{13}Cl_2N_3$	65.52 (65.58)	3.87 (3.58)	11.24 (11.49)
XVI	68	117-118	A	$C_8H_5ClN_4O_2$	42.90 (42.78)	2.38 (2.24)	24.72 (24.95)
XVII (c)	9	163-165	A	$C_8H_5ClN_4O_2$	—	—	—
XVIII	79	151	A	$C_{10}H_9ClN_4O_2$	47.64 (47.54)	3.80 (3.59)	21.98 (22.18)
XIX	63	157-158	A	$C_{20}H_{13}ClN_4O_2$	63.53 (63.75)	3.61 (3.48)	14.94 (14.87)
XX (d)	69	160-160.5	B	—	—	—	—
XXI	53	122-123	A	$C_8H_5N_5O_4$	40.62 (40.86)	2.32 (2.14)	29.50 (29.78)
XXII (e)	85	206-207	A	—	—	—	—
XXIII	91	159-160	C	$C_{10}H_9N_5O_4$	45.79 (45.63)	3.55 (3.45)	26.89 (26.61)
XXIV	94	101-101.5	C	$C_{20}H_{12}N_6O_6$	55.59 (55.56)	2.89 (2.80)	19.37 (19.44)
XXV	94	188-190	C	$C_{20}H_{11}N_7O_8$	49.09 (50.32)	2.27 (2.32)	20.38 (20.54)
XXVI (c)	91	154-155	C	$C_{20}H_{13}N_5O_4$	—	—	—
XXVII	54	127-128	A	$C_8H_6BrN_3$	42.91 (42.88)	2.76 (2.70)	19.00 (18.75)
XXVIII	22	120-121	A	$C_8H_6ClN_3$	53.60 (53.50)	3.70 (3.37)	23.71 (23.40)
XXIX	21	156-157	D	$C_8H_6N_4O_2$	50.27 (50.53)	3.35 (3.18)	29.19 (29.46)
XXXII	52	84-85	A	$C_{10}H_{10}N_4O$	59.70 (59.40)	5.06 (4.98)	27.53 (27.71)
XXXIII	46	140	E	$C_9H_6N_4$	63.11 (63.52)	3.63 (3.55)	32.45 (32.53)
XXXIV	28	109	B	$C_9H_6N_4$	63.25 (63.52)	3.69 (3.55)	32.63 (32.53)
XXXV	—	218-219	A	$C_9H_8N_4O$	57.18 (57.44)	4.32 (4.28)	29.86 (29.77)
XXXVI	—	182-183	F	$C_9H_7N_3O_2$	57.06 (57.14)	3.75 (3.73)	22.07 (22.21)
XXXVII	18	102	A	$C_9H_7ClN_4O_2$	45.53 (45.30)	2.78 (2.96)	23.46 (23.48)

(a) A, ethanol; B, chloroform; C, acetic acid; D, benzene; E, aqueous ethanol; F, methanol. (b) Figures in parentheses represent calculated values. (c) Identified through mass spectrum. (d) Lit. (1) m.p. 160-160.5°. (e) Lit. (1) m.p. 206-207°.

Table 2

Spectroscopic Properties of 2-(Pyrazol-1'-yl)pyridines

Compound No.	Pmr (chemical shifts in δ; J in Hz) H-3'/R_1	H-4'/R_2	H-5'/R_3	H-3/R_4	H-4	H-5/R_5	H-6	Solvent (a)	Ir cm^{-1}
I	7.75 (d) J = 1.5	6.40 (t) J = 3.0 and 1.5	8.53 (d) J = 3.0	7.78 (dd) J = 8.0 and 1.4	7.95 (dd) J = 8.0	7.10 (dd) J = 8.0 and 5.0	8.35 (dd) J = 5.0 and 1.5	A	—
VIII	7.63 (s)	—	8.55 (s)	7.70-8.20 (m)	7.70-8.20	7.12 (dd) J = 8.0 and 5.0	8.34 (d) J = 5.0	A	3140, 3080, 1592, 1575, 1470, 1450, 1380, 960, 820, 775
IX	7.38 (s)	—	7.38 (s)	7.00-7.90 (m)	8.00 (dd) J = 8.0 and 2.5	7.00-7.90 (m)	8.28 (dd) J = 5.0 and 1.5	A	3060, 1590, 1575, 1482, 1448, 1360, 970, 770, 695
X	7.61 (s)	—	8.35 (s)	—	7.98 (dd) J = 8.0 and 1.5	7.32 (dd) J = 8.0 and 5.0	8.53 (dd) J = 5.0 and 1.5	A	3160, 3060, 1592, 1580, 1530 (NO_2), 1470, 1370, 1335 (NO_2), 965, 815, 760
XI	7.71 (s)	—	8.60 (s)	8.05 (d) J = 9.0	8.58 (dd) J = 9.0 and 2.5	—	9.22 (d) J = 2.5	A	3150, 3130, 3105, 1603, 1580, 1519 ($NO_2$8), 1470, 1435, 1345 (NO_2), 932, 860, 855, 780
XII	2.30 (s)	—	2.72 (s)	8.07 (d) J = 9.0	8.55 (dd) J = 9.0 and 2.5	—	9.23 (d) J = 2.5	A	3120, 3080, 2930, 2860, 1610, 1580, 1530 (NO_2), 1465, 1405, 1345 (NO_2), 1140, 1040, 865, 765
XIII	7.39 (s)	—	7.39 (s)	7.98 (d) J = 9.0	8.45 (dd) J = 9.0 and 2.5	—	8.88 (d) J = 2.5	A	3070, 3030, 1603, 1585, 1519 (NO_2), 1470, 1410, 1345 (NO_2), 970, 860, 840, 770, 695
XIV	7.60 (s)	—	8.51 (s)	7.50-8.10 (m)	7.50-8.10 (m)	7.00-7.40 (m)	8.36 (dd) J = 5.0 and 1.5	A	3115, 3080, 3050, 1600, 1580, 1480, 1450, 1375, 1345, 975, 955, 850, 775
XV	7.38 (s)	—	7.38 (s)	7.00-8.50 (m)	7.00-8.50 (m)	—	7.00-8.50 (m)	A	3060, 1585, 1470, 1450, 1400, 1215, 980, 830, 788, 695
XVI	7.98 (s)	—	8.79 (s)	—	8.52 (dd) J = 8.0 and 1.8	7.69 (dd) J = 8.0 and 5.0	8.75 (dd) J = 5.0 and 1.8	B	3160, 3120, 3080, 1592, 1580, 1535 (NO_2), 1475, 1400, 1370, 1340 (NO_2), 1150, 970, 860, 810, 750
XVII	7.70 (s)	—	8.57 (s)	8.08 (d) J = 9.0	8.60 (dd) J = 9.0 and 2.5	—	9.23 (d) J = 2.5	A	3170, 3120, 3040, 1610, 1580, 1535 (NO_2), 1475, 1440, 1380, 1352 (NO_2), 1115, 950, 855, 815, 765
XVIII	2.29 (s)	—	2.70 (s)	8.05 (d) J = 9.0	8.50 (dd) J = 9.0 and 2.5	—	9.21 (d) J = 2.5	A	3105, 3095, 1600, 1580, 1515 (NO_2), 1485, 1470, 1340 (NO_2), 1235, 1115, 1040, 860, 800, 765
XIX	7.10-7.60 (m)	—	7.10-7.60 (m)	8.02 (d) J = 9.0	8.48 (dd) J = 9.0 and 2.5	—	8.90 (d) J = 2.5	A	3080, 1600, 1580, 1519 (NO_2), 1475, 1342 (NO_2), 1160, 970, 8.00, 760
XXI	8.38 (s)	—	9.30 (s)	—	8.45 (dd) J = 8.0 and 1.5	7.72 (dd) J = 8.0 and 5.0	8.75 (dd) J = 5.0 and 1.5	C	3160, 3120, 3080, 1595, 1540 (NO_2), 1470, 1440, 1405, 1325 (NO_2), 1000, 950, 850, 815, 750
XXIII	2.61 (s)	—	3.12 (s)	8.18 (d) J = 9.0	8.69 (dd) J = 9.0 and 2.5	—	9.33 (d) J = 2.5	A	3120, 3100, 3080, 1601, 1580 (NO_2), 1500, 1465, 1405, 1380, 1340 (NO_2), 1050, 855, 805, 770
XXIV	7.70-9.00 (m)	—	7.70-9.00 (m)	7.70-9.00 (m)	7.70-9.00 (m)	7.30-7.65 (m)	7.70-9.00 (m)	B	3100, 1590, 1530 (NO_2), 1470, 1440, 1350 (NO_2), 870, 840 785

Table 2 continued

XXV	7.70-9.10 (m)	—	7.70-9.10 (m)	7.70-9.10 (m)	7.70-9.10 (m)	—	7.70-9.10 (m)	B	3100, 1605, 1580, 1525 (NO_2), 1470, 1350 (NO_2), 870, 860, 750
XXVI	7.00-9.00 (m)	—	7.00-9.00 (m)	7.00-9.00 (m)	7.00-9.00 (m)	—	7.00-9.00 (m)	B	3080, 1602, 1570, 1530 (NO_2), 1470, 1340 (NO_2), 860, 750
XXXI	7.32 (s)	3.00-4.30 (br.)	7.83 (s)	7.50-8.10 (m)	7.50-8.10 (m)	7.22 (dd) J = 9.0 and 5.0	8.34 (d) J = 5.0	B	3500 and 3200 (NH_2), 3140, 1595, 1580, 1475, 1435, 1125, 955, 780
XXXII	7.76 (s)	2.16 (s), 7.50-8.20 (m)	8.78 (s)	7.50-8.20 (m)	7.50-8.20 (m)	6.90-7.30 (m)	8.33 (d) J = 5.0	A	3500-3100 (NH_2), 1650 (C=O), 1600, 1580, 1475, 1455, 810, 790
XXIII	7.70-8.20 (m)	—	8.96 (s)	7.70-8.20 (m)	7.70-8.20 (m)	7.30 (dd) J = 8.0 and 5.0	8.43 (dd) J = 5.0 and 1.2	A	3140, 3120, 3080, 2240 (C≡N). 1600, 1580, 1475, 1460, 1210, 1055, 955, 880, 780
XXXV	7.80-8.30 (m)	3.00-4.00 (br)	8.90 (s)	7.80-8.30 (m)	7.80-8.30 (m)	7.20-7.60 (m)	8.50 (dd) J = 5.0 and 1.5	B	3380 and 3230 (NH_2), 3140 3120, 1690 and 1670 (C=O), 1630, 1600, 1560, 1480, 1440, 1320, 960, 875, 780
XXXVI	7.70-8.30 (m)	3.20-4.20 (m)	9.19 (br)	7.70-8.30 (m)	8.45 (br)	7.00-7.70 (m)	8.95 (br)	B	3200-2500 (br., OH), 3130, 1680 (C=O), 1595, 1560, 1480, 1440, 1280, 990, 950, 770, 760
XXXVII	2.31 (s)	6.28 (s)	—	7.96 (d) J = 9.0	8.55 (dd) J = 9.0 and 2.5	—	9.29 (d) J = 2.5	A	3140, 3080, 1600, 1580, 1525 (NO_2), 1475, 1430, 1390, 1345 (NO_2), 1010, 860, 840, 800

(a) A, deuteriochloroform; B, DMSO-d_6; C, deuteriochloroform/DMSO-d_6.

Table 3

Spectroscopic Properties of 3-(Pyrazol-1'-yl)pyridines

	Pmr (chemical shifts in δ; J in Hz)								
Compound No.	H-3'	H-4'/R_1	H-5'	H-2	H-4	H-5	H-6	Solvent (a)	Ir cm^{-1}
VII	7.70 (d) J = 1.5	6.49 (t) J = 3.0 and 1.5	8.10 (d) J = 3.0	9.02 (d) J = 3.0	7.90-8.20 (m)	7.36 (dd) J = 8.0 and 5.0	8.48 (d) J = 5.0	A	—
XXVII	7.69 (s)	—	7.95 (s)	8.92 (d) J = 3.0	7.80-8.10 (m)	7.36 (dd) J = 8.0 and 5.0	8.55 (dd) J = 5.0 and 1.5	A	3142, 3105, 3060, 1590, 1580, 1480, 1453, 1375, 1325, 960, 815, 595, 700
XXVIII	8.00 (s)	—	8.98 (s)	9.20 (br)	8.30-8.80 (m)	7.82 (dd) J = 8.0 and 5.0	8.30-8.80 (m)	B	3120, 3090, 3050, 1590, 1580, 1500, 1440, 1360, 1255, 1040, 970, 805
XXIX	8.28 (s)	—	8.68 (s)	9.01 (d) J = 2.5	8.06 (d) J = 8.0	7.44 (dd) J = 8.0 and 5.0	8.50-8.80 (m)	A	3140, 3090, 3030, 1598, 1588, 1510 (NO_2), 1485, 1420, 1340 (NO_2), 1260, 950, 895, 810, 755, 700
XXXIV	7.00-8.05 (m)	—	7.00 8.05 (m)	8.34 (d) J = 2.5	7.00-8.05 (m)	7.00-8.05 (m)	7.00-8.05 (m)	A	3150, 3140, 3000, 3095, 2240, (C≡N), 1580, 1540, 1490, 1435, 1355, 1225, 955, 815, 800, 700

(a) A, deuteriochloroform; B, DMSO-d_6.

XXII obtained in these nitrations were identical with the compounds earlier reported by us (1). On nitrating II with nitric and sulfuric acid at 0-5° position 4' of the pyrazole ring as well as the *para* positions of the 3'- and 5'-phenyl substituents were nitrated leading to XXIV (pmr and mass spectra). Such a nitration in the *para* positions of the 3-and 5-phenyl derivatives of pyrazole had earlier been reported (5). Treating VI with a mixture of acetic

anhydride and fuming nitric acid, a mixture of XXVI and a trinitrated product (mass spectrum of the mixture showed molecular ion peaks at m/e 477 and 432, respectively) was obtained. While nitration of VI with a mixture of sulfuric and nitric acid at 0° gave XXV.

In all the above nitrations the pyridine ring of the 2-(pyrazol-1′-yl)pyridines resisted nitration even under vigorous conditions. However, when 4′-bromo-2-(pyrazol-1′-yl)pyridine (VIII) was nitrated with sulfuric and nitric acids at room temperature, a mixture consisting of unreacted VIII, XI and XXII was obtained. The formation of XI and XXII in this reaction indicates the activation towards nitration of the pyridine ring by the bromo-substituted pyrazole ring. In this reaction the nitration of the pyridine ring of VIII must precede the "ipso" nitration (6) at 4′ position of the pyrazole ring since as mentioned above 4′-nitro-2-(pyrazol-1′-yl)pyridine (XX) is resistant to further nitration even under vigorous conditions. This type of "ipso" attack at the 4 position of the pyrazole ring has earlier been observed in the nitration of 4-bromo-1-methylpyrazole with sulfuric and nitric acid when 1-methyl-4-nitropyrazole was isolated from the reaction (7).

An attempt to formylate the 2-(pyrazol-1′-yl)pyridine under Vilsmeir-Haack reaction's conditions failed. Diverse experimental conditions were tried but without success. It seems that the molecule of I behaves like 1-*o*-, and 1-*p*-nitrophenylpyrazole which are resistant to attack in this reaction (8).

3-(Pyrazol-1′-yl)pyridine (VII) was also subjected to above mentioned electrophilic reactions and compounds XXVII-XXIX were obtained in good yields (Tables 1 and 3). Once again no evidence of substitution in the pyridine ring of VII was obtained.

From the results of these electrophilic substitution reactions it may be deduced that both the pyrazole and the pyridine rings in these pyrazol-1′-ylpyridines mutually influence the reactivity, the pyridine ring having a deactivating influence in the formylation reaction while, through mesomeric effect of the halogens in the 4′ position of the pyrazole, pyridine ring is activated for the halogenation and nitration reaction. We are continuing further studies in this direction.

Some other reactions were also carried out with I. Alkylation of I with 1,2-dibromoethane gave a dihydro derivative (XXX) of a hitherto unreported heterocyclic system, pyrazolo[1′,2′-*a*]pyrido[2,1-*c*][1,2,4]triazine and somewhat resembles "diquat" (9). The structure of XXX was confirmed from its elemental analysis and its pmr spectrum: a sharp singlet at δ 5.35 for the four equivalent protons of $=\overset{+}{N}\text{-}(CH_2)_2\text{-}\overset{+}{N}=$, a doublet (J = 3 Hz) at δ 9.89 for H-3 of the pyrazole ring was highly deshielded as compared to the parent I (H-3′, δ 7.75) and as expected H-2 was also at a lower field, δ 7.51 (as compared with H-4′ of I at δ 6.40). Such a deshielding for all the protons of XXX has its parallel when the pmr spectrum of 2,2′-bipyridyl is compared with the biquaternary 2,2′-bipyridyl systems (10).

The substituent groups of various pyrazol-1′-ylpyridines either obtained by synthesis or from reactions were modified to afford further derivatives. Thus reduction of XX by tin and hydrochloric acid gave the corresponding amino compound (XXXI) which was rather difficult to purify and hence was transformed to the acylamino compound (XXXII) for easy characterization.

The bromo compounds VIII and XXVII were treated with cuprous cyanide in dimethylsulfoxide solvent (11) to give the corresponding 4′-cyano derivatives XXXIII and XXXIV respectively. When hydrolyzed in sulfuric acid at room temperature, XXXIII afforded the carboxamide (XXXV) while heating with a solution of sodium hydroxide XXXIII was converted into its corresponding acid (XXXVI).

Chlorodeoxygenation of 3′-methyl-5-nitro-2-(pyrazol-1′-yl)pyridin-5′-one (1) was also carried out. Heating under reflux converted it into the 5′-chloro derivative (XXXVII).

EXPERIMENTAL

The pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer model R-20B using tetramethylsilane as an internal reference. Infrared absorption spectra were measured on a Perkin-Elmer model 180, samples were examined as potassium bromide pellets. The melting points were observed on a Fisher-Johns apparatus and are uncorrected.

The following starting materials were obtained by the condensation of pyridylhydrazines with 1,3-dicarbonyl compounds or by the arylation of pyrazoles (1): 2-(pyrazol-1′-yl)pyridine (I), 2-(3′,5′-diphenylpyrazol-1′-yl)-pyridine (II), 3-nitro-2-(pyrazol-1′-yl)pyridine (III), 5-nitro-2-(pyrazol-1′-yl)-pyridine (IV), 2-(3′,5′-dimethylpyrazol-1′-yl)-5-nitropyridine (V), 2-(3′,5′-diphenylpyrazol-1′-yl)-5-nitropyridine (VI), 3-(pyrazol-1′-yl)pyridine (VII) (3), and 3′-methyl-5-nitro-2-(pyrazol-1′yl)pyridin-5′-one.

General Procedures.

Brominations.

A solution of 1 ml. of bromine in 6 ml. of acetic acid was slowly added to a solution of 0.005 mole of a pyrazol-1′-ylpyridine in 10 ml. of acetic acid at room temperature and let stand for 1.5 to 5 hours. After this period the solution was added to ice-cold water and treated with a saturated aqueous solution of sodium bisulfite. The precipitate was filtered off and crystallized.

Alternately the bromination could be carried out in chloroform solution at room temperature. After the reaction is over the solution is washed three times with a saturated solution of potassium carbonate and the chloroform layer separated, washed and dried. The solvent is evaporated to give the brominated product which is crystallized. The best results were obtained using acetic acid as the reaction solvent and the products VIII-XIII and XXVII were obtained (Tables 1, 2, and 3).

Chlorinations.

To a solution of 0.005 mole of a pyrazol-1′-ylpyridine in acetic acid (10-100 ml.), 10 ml. of an aqueous solution of commercial sodium hypochlorite (≈ 5%) was added and let stir for a period of 2 hours (in the case of II and IV stirring was continued for 24 hours) and then added to ice-cold water and extracted with chloroform. The chloroform extract was washed first with saturated solution of potassium carbonate and then

with water. The chloroform layer was separated, dried and the solvent evaporated off to give a residue which was crystallized to give the chloro compounds XIV-XIX and XXVIII (Tables 1, 2, and 3).

Nitrations.

With Acetic Anhydride-Nitric Acid.

To a solution of 0.005 mole of a pyrazol-1'-ylpyridine in acetic anhydride cooled to -5° was added 2 ml. of fuming nitric acid at such a rate that the temperature did not rise above 5° (dry ice was used to control the temperature). After 1 hour the reaction mixture was inverted over crushed ice and left for a few hours when the precipitate was filtered off, washed with water, dried and crystallized. In this manner XX (65%) and XXVI were obtained from the nitration of I and VI, respectively.

With Sulfuric and Nitric Acid.

A pyrazol-1'-ylpyridine (0.005 mole) was dissolved in 10 ml. of concentrated sulfuric acid and to the solution a mixture of 5 ml. of concentrated sulfuric and 5 ml. of concentrated nitric acid was added dropwise at 0-5°. The reaction mixture was left to stir for 2 to 24 hours at different temperature and then inverted over crushed ice, filtered, washed with water, dried and crystallized from a suitable solvent. In this manner, from I-V and VII the products (reaction time and temperature) XX (2 hours, room temperature), XXI (2 hours, room temperature), XXII (12 hours, room temperature), XXIII (12 hours, 10°), XXIV (2 hours, 10°), XXV (21 hours, 5°), and XXIX (2 hours, 15°) were obtained and are presented in the Tables 1-3.

Nitration of 4'-Bromo-2-(pyrazol-1'-yl)pyridine.

A mixture of 2 ml. of concentrated sulfuric and 2 ml. of concentrated nitric acid was added dropwise at 0-5° to a solution of 0.5 g. of VIII in 10 ml. of concentrated sulfuric acid. The reaction mixture was stirred at this temperature for a period of 1 hour and then inverted over crushed ice. The precipitate formed was filtered, washed with water and dried giving a mixture which was crystallized from ethanol giving 0.23 g. (38%) of 4'-bromo-5-nitro-2-(pyrazol-1'-yl)pyridine (XI), m.p. 195-195.5°. This was identical (m.p., mixed m.p., pmr and infrared spectra) with a sample obtained from the bromination of IV. The solvent was removed from the mother liqour and the residue thus obtained was crystallized from acetic acid/water giving 0.26 g. (49%) of XXII, m.p. 206-207°, identical (m.p., mixed m.p., pmr and infrared spectra) with the sample obtained from the nitration of IV above and from the arylation of 4-nitropyrazole (1).

5,6-Dihydropyrazolo[1',2'-*a*]pyrido[2,1-*c*][1,2,4]triazinedium Dibromide (XXX).

A solution of 1 g. of 2-(pyrazol-1'-yl)pyridine in 10 ml. of 1,2-dibromoethane was placed in a flask fitted with a reflux condenser and a calcium chloride guard tube and heated under reflux for 170 hours. The solid formed was filtered and washed with 1,2-dibromoethane and ether to give 0.61 g. (27%) of XXX, m.p. > 300°; pmr (DMSO-d_6): δ 5.35 (s, $=\overset{+}{N}\text{-}(CH_2)_2\text{-}\overset{+}{N}=$), 7.51 (t, J = 3 Hz, H-2), 8.10-8.50 (m, H-9), 8.90-9.10 (m, H-10 and H-11), 9.25-9.45 (m, H-1 and H-8), and 9.89 (d, J = 3 Hz, H-3); ir: 3420, 2900-3100 (br.), 1625, 1580, 1570, 1520, 1440, 1345, 1170, 800, 780 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}Br_2N_3$: C, 33.94; H, 3.12; N, 11.89. Found: C, 34.09; H, 3.19; N, 11.96.

4'-Amino-2-(pyrazol-1'-yl)pyridine (XXXI) and 4'-Acetamido-2-(pyrazol-1'-yl)pyridine (XXXII).

Reduction of 8 g. of XX was carried out by means of 6 g. of tin and 60 ml. of hydrochloric acid. After 8 hours of heating on a water bath the reaction mixture was basified with a 30% sodium hydroxide solution and the amine was extracted with ethyl acetate (3 x 100 ml.). The ethyl acetate extract was dried over anhydrous magnesium sulfate and freed of the solvent giving 5.2 g. (77% yield) of XXXI which on repeated crystallization from benzene and then chromatography on alumina using benzene as eluting solvent afforded crystals m.p. 73-76° which seemed to oxidize with great ease and gave poor elemental analysis. It was, however, characterized through its pmr and ir spectra (Table 2). On treatment with acetic anhydride and anhydrous sodium acetate XXXI was converted into its acetamido derivative (XXXII) (Tables 1 and 2).

4'-Cyano-2-(pyrazol-1'-yl)pyridine (XXXIII).

A mixture of 0.6 g. of 4'-bromo-2-(pyrazol-1'-yl)pyridine (XX) and 0.5 g. of cuprous cyanide in 6 ml. of dimethylsulfoxide was heated at 150° in an atmosphere of nitrogen for a period of 5 hours. After cooling, the reaction mixture was extracted with benzene (3 x 100 ml.). The benzene extract was washed with ammonium hydroxide and then with water, dried with anhydrous magnesium sulfate, filtered and freed of the solvent. The residue was subjected to chromatography on alumina (benzene as eluting solvent) and crystallized giving 0.2 g. of XXXIII, m.p. 140° (Tables 1 and 2).

4'-Cyano-3-(pyrazol-1'-yl)pyridine (XXXIV).

By using similar conditions to those used for the preparation of XXXIII above, XXXIV was obtained from XXVII (Tables 1 and 3).

2-(Pyrazol-1'-yl)pyridine-4'-carboxamide (XXXV).

A small quantity of XXXIII as stirred with concentrated sulfuric acid at room temperature for 24 hours, poured over crushed ice, neutralized with concentrated ammonium hydroxide and extracted with chloroform giving the carboxamide (XXXV), m.p. 218-219° (Tables 1 and 2).

2-(Pyrazol-1'-yl)pyridine-4'-carboxylic Acid (XXXVI).

A small quantity of XXXIII was heated under reflux with a 10% solution of sodium hydroxide for 6 hours. After cooling, the reaction mixture was acidified with hydrochloric acid and the precipitated acid (XXXVI), m.p. 182-183° was collected by filtration (Tables 1 and 2).

5'-Chloro-3'-methyl-5-nitro-2-(pyrazol-1'-yl)pyridine (XXXVII).

A mixture of 2 g. of 3'-methyl-5-nitro-2-(pyrazol-1'-yl)pyridin-5'-one and 10 ml. of phosphoryl chloride was heated under reflux for 2 hours. The excess phosphoryl chloride was distilled off and the residue was treated with ice-cold water and extracted with chloroform to give 0.4 g. of XXXVII (Tables 1 and 2).

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