Ring Transformations involving Chloroheterocycles. Part II.[1] Reaction of 4-Chloro-1,8-naphthyridines and 4-Chloroquinolines with Substituted Hydrazines

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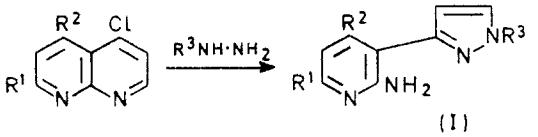
4-Chloro-1,8-naphthyridines and 4-chloroquinolines rearrange on treatment with substituted hydrazines to yield 1,3-pyrazoles. The configuration of the pyrazoles was determined from n.m.r. studies. A mechanism for the rearrangement is proposed.

4-Chloroquinolines [2] and 4-chloro-1,8-naphthyridines [3] rearrange on treatment with hydrazine hydrate in a sealed tube at 150 °C to yield pyrazoles. Similar reactions with substituted hydrazines gave only 1,3-disubstituted pyrazoles; no trace of the corresponding 1,5-isomers was obtained.

With 4-chloroquinoline and phenylhydrazine the product was 3-(2-aminophenyl)-1-phenylpyrazole (IIa) (not 3-anilino-4-aminoquinoline as claimed by Backeberg [4]), converted by deamination into 1,3-diphenylpyrazole (III) (*cf.* ref. 5). For the products (I) from



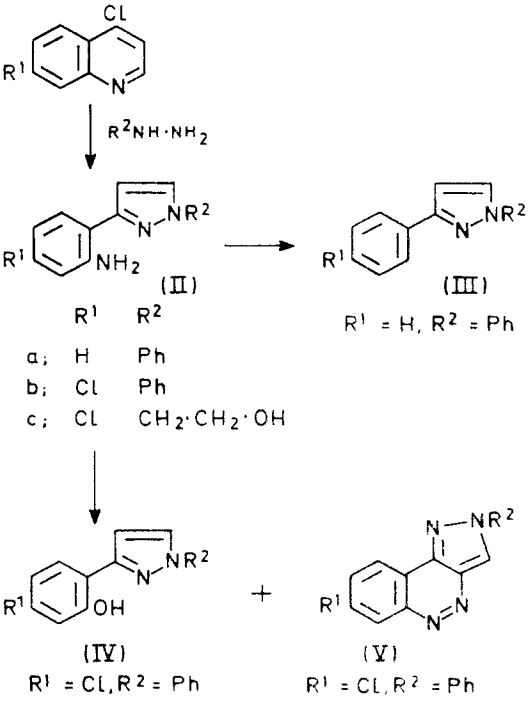
(I)

	R^1	R^2	R^3
a;	Me	H	Ph
b;	Me	H	$CH_2{\cdot}CH_2{\cdot}OH$
c;	Me	H	Me
d;	Me	Me	Ph

4-chloro-1,8-naphthyridines, a chemical proof of structure was more difficult to obtain; their structures were firmly established by n.m.r. spectroscopy.

The n.m.r. studies were an extension of work by Jacquier *et al.*[6] in which protons at positions 3 and 5 of a pyrazole were distinguished by comparison of n.m.r. spectra run in hexamethylphosphoramide (HMP) and [^{2}H]chloroform (DC). Four 1-arylpyrazoles were quoted (phenyl, 4-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trinitrophenyl) in which the H-5 signal shifted downfield by 0·8—1·2 p.p.m. on changing from DC to HMP as solvent whereas the H-3 signal did not shift at all. In 1,3-dimethylpyrazole [6] the H-5 signal shifted downfield by 0·45 p.p.m. whereas the H-3 signal from 1,5-dimethylpyrazole moved upfield by 0·19 p.p.m. It was also shown [6] that $J_{4,5}$ (2·3—2·7 Hz) is always $> J_{3,4}$ (1·5—1·9 Hz).

Using the above methods, we investigated the structures of thirteen novel pyrazoles containing a much wider range of substituents than those examined by the French workers.[6] The pyrazoles were studied as 0·2M-solutions in DC and HMP; eleven of them were shown to be 1,3-disubstituted (Table 1) and the other three were 1,5-disubstituted (Table 2). The coupling



	R^1	R^2
a;	H	Ph
b;	Cl	Ph
c;	Cl	$CH_2{\cdot}CH_2{\cdot}OH$

(II) (III) R^1 = H, R^2 = Ph

(IV) R^1 = Cl, R^2 = Ph (V) R^1 = Cl, R^2 = Ph

constants in all cases agreed with the expected values, 1,3-disubstituted pyrazoles having $J_{4,5}$ in the range 2·33—2·66 Hz and the 1,5-compounds having $J_{3,4}$ in the range 1·78—1·91 Hz. Changing the solvent from DC to HMP deshielded H-5 in the 1,3-compounds by *ca.* 1·1 p.p.m. when R^1 = Ph, and by 0·5 p.p.m. when $R^1 = CH_2{\cdot}CH_2{\cdot}OH$ or Me. In 1,5-compounds, the H-3 signal was virtually unchanged when run in HMP.

Further proof for the assignments was obtained from the positions of the phenolic hydroxy-proton signals in compounds (IV), (VIIa), (VIIb), and (VIc). In the 1,3-disubstituted pyrazoles the hydroxy-group is in a favourable position for intramolecular hydrogen bonding to the 2-nitrogen atom (VIII), whereas for the 1,5-compounds, intermolecular hydrogen bonding is

[1] Part I, R. A. Bowie, M. J. C. Mullan, and J. F. Unsworth, preceding paper.
[2] C. Alberti, *Gazzetta*, 1957, **87**, 772.
[3] R. A. Bowie, *Chem. Comm.*, 1970, 565.
[4] O. G. Backeberg, *J. Chem. Soc.*, 1938, 1083.
[5] I. L. Finar and A. B. Simmonds, *J. Chem. Soc.*, 1958, 200.
[6] J. Elguero, R. Jacquier, and H. C. N. Tien Duc, *Bull. Soc. chim. France*, 1966, **12**, 3727.

more favourable (IX). Proof of intramolecular hydrogen bonding was obtained by studying solutions of two concentrations (0·2 and 0·1M); the position of the hydroxy-signal was unchanged (Table 1). Of the 1,5-isomers, only compound (VIc) was soluble in DC {(VIa and b) hydrogen bond to [$^2H_6$]acetone and [$^2H_6$]-dimethyl sulphoxide}, and it showed the hydroxy-signal as a broad peak at δ 6·8 p.p.m. (0·2M-soln.) or 5·8 p.p.m. (0·1M-soln.), thus confirming intermolecular hydrogen bonding. However, compound (VIa) was sufficiently soluble in chloroform for i.r. studies and it was shown that only intermolecular hydrogen bonding occurred. Two peaks, at 3250 (bonded) and 3520 cm^{-1} (unbonded), were obtained for the hydroxy-group, and the latter peak increased in relative intensity as the concentration fell from 0·02 to 0·005M. I.r. studies on compound (VIIa) in chloroform showed only one peak, at 3140 cm^{-1}, which was independent of concentration (0·1—0·01M).

Similar structural assignments for the compounds (Ia—d) and (IIb) were obtained from the chemical shifts of the amino-group, although the peaks tended to be broad. At different concentrations, there was no change in chemical shift, further confirming the 1,3-isomeric structure (Table 1).

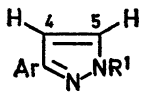
The pyrazoles (Ia—d) and (IIa—c) were prepared by heating the appropriate chloroheterocycles and substituted hydrazines in sealed tubes at 150 °C for 5 h. 2-Amino-6-methyl-3-(1-phenylpyrazol-3-yl)pyridine (Ia) was also prepared by heating 5-chloro-2-methyl-1,8-naphthyridine and phenylhydrazine in anisole for 3—4 h.

Diazotisation of 3-(2-amino-4-chlorophenyl)-1-phenylpyrazole (IIb) and addition to hypophosphorous acid yielded 1,3-diphenylpyrazole (III) which proved the isomeric structure of (IIb). However, diazotisation of 3-(2-amino-4-chlorophenyl)-1-phenylpyrazole (IIb) in the presence of dilute sulphuric acid gave a mixture of two products which, after separation by column chromatography, were shown to be 3-(4-chloro-2-hydroxyphenyl)-1-phenylpyrazole (IV) and 7-chloro-2-phenyl-2*H*-pyrazolo[4,3-*c*]cinnoline (V).

Three 1,5-disubstituted pyrazoles were synthesised for comparison of their n.m.r. spectra with those of the 1,3-isomers already prepared. Treatment of

TABLE 1

N.m.r. data for 1,3-disubstituted pyrazoles



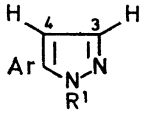
Compound	Solvent *	δ (p.p.m.) H-4	δ (p.p.m.) H-5	$J_{4,5}$/Hz	δ_{OH} or δ_{NH_2} (p.p.m.) 0·2M-soln.	δ_{OH} or δ_{NH_2} (p.p.m.) 0·1M-soln.
(Ia)	DC	6·77	7·94	2·62	6·45br	6·45br
	HMP	7·20	9·05			
(Ib)	DC	6·45	7·44	2·36	6·25br (NH_2)	6·25br
	HMP	6·70	7·92			
(Ic)	DC	6·47	7·30	2·35	6·3	6·3
	HMP	6·74	7·99			
(Id)	DC	6·56	8·02	2·40	5·3br	5·3br
	HMP	6·55	9·07			
(IIa)	DC	6·80	7·93	2·62	5·15br	5·15br
	HMP	7·00 [a]	9·03			
(IIb)	DC	6·75	7·92	2·58		
	HMP	7·10 [a]	9·06			
(IIc)	DC	6·52	7·45	2·34		
	HMP	6·65	7·92			
(III)	DC	6·78	7·93	2·48		
	HMP	7·07	9·02			
(IV)	DC	6·80	7·96	2·66	10·96 (ArOH)	10·96
	HMP	7·15 [a]	8·96			
(VIIa)	DC	6·55	7·48	2·33	10·75	10·75
	DA	6·82	7·73			
	HMP	7·00	8·02			
(VIIb)	DC	6·58	7·52	2·55	10·65	10·65
	HMP	7·00 [a]	7·93			

* DC = [^2H]chloroform; HMP = hexamethylphosphoramide; DA = [$^2H_6$]acetone.

[a] Values are approximate.

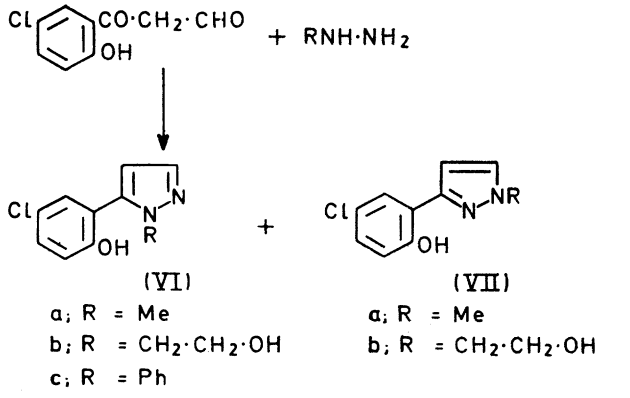
TABLE 2

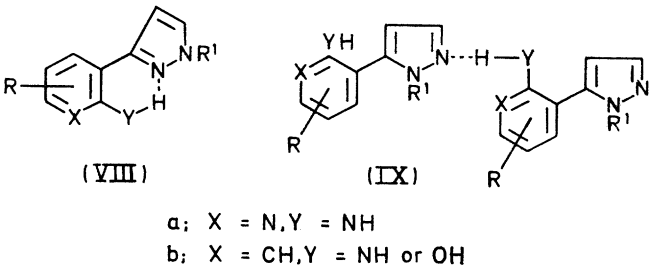
N.m.r. data for 1,5-disubstituted pyrazoles



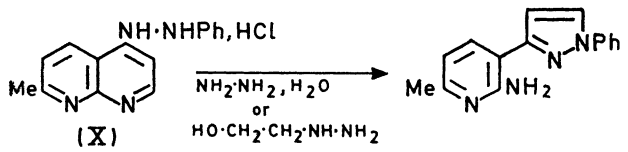
Compound	Solvent *	δ (p.p.m.) H-3	δ (p.p.m.) H-4	$J_{3,4}$/Hz	δ_{OH} (p.p.m.) 0·2M-soln.	δ_{OH} (p.p.m.) 0·1M-soln.
(VIa)	DA	7·53	6·28	1·79		
	HMP	7·33	6·16			
(VIb)	DMSO	7·48	6·23	1·78		
	DA	7·53	6·28			
	HMP	7·37	6·13			
(VIc)	DC	7·70	6·51	1·91	6·8	5·8
	HMP	7·68	6·48			

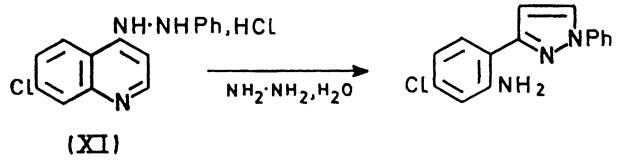
* See Table 1; DMSO = [$^2H_6$]dimethyl sulphoxide.





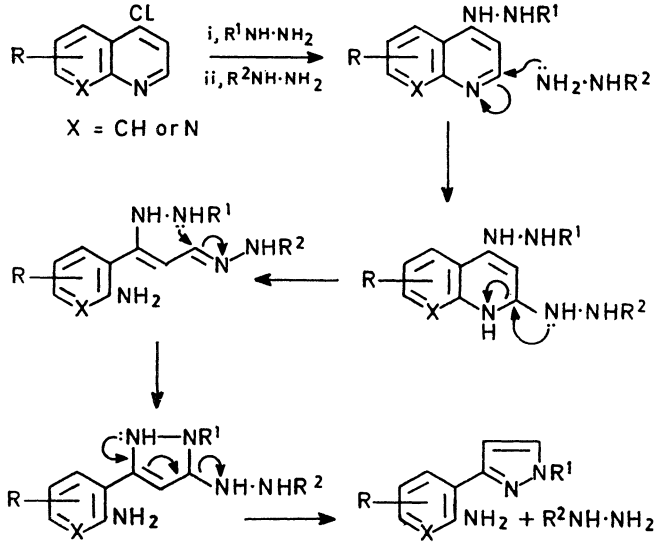
5-chloro-2-hydroxybenzoylacetaldehyde with phenylhydrazine in hot methanol yielded only 5-(5-chloro-





2-hydroxyphenyl)-1-phenylpyrazole (VIc), in high yield. However, with methylhydrazine and hydroxyethylhydrazine mixtures of the corresponding 1,3- and 1,5-disubstituted pyrazoles (VIa and b) and (VIIa and b) were obtained, which were easily separated by crystallisation.

A mechanism for the rearrangement of 4-chloro-1,8-naphthyridines and 4-chloroquinolines with substituted hydrazines to give 1,3-disubstituted pyrazoles is suggested (see Scheme). We have shown that 2-methyl-5-(2-phenylhydrazino)-1,8-naphthyridine hydrochloride (X) reacts with hydrazine hydrate or β-hydroxyethylhydrazine to give 2-amino-6-methyl-3-(1-phenylpyrazol-



SCHEME

3-yl)pyridine (Ia), and that 7-chloro-4-(2-phenylhydrazino)quinoline hydrochloride (XI) reacts with hydrazine hydrate to yield 3-(2-aminophenyl)-1-phenylpyrazole (IIa). These results prove that (*a*) a two-step reaction mechanism is involved and (*b*) the hydrazino-group in the 5-position of the 1,8-naphthyridine (4 in the quinoline) determines the final product of the rearrangement. The attack of the second hydrazino-group at position 7 of the 1,8-naphthyridine (position 2 in the quinoline) only serves to open the pyridine ring (Scheme). This mechanism ($R^1 = R^2 = H$, X = N) also accounts for the formation of pyrazoles from chloronaphthyridines and hydrazine hydrate,[1] since it has been shown[1] that 2-amino-6-methyl-3-pyrazol-5-ylpyridine is obtained from the reaction of 5-hydrazino-2-methyl-1,8-naphthyridine and hydrazine hydrate.

EXPERIMENTAL

N.m.r. spectra were determined with Varian A-60 or HA-100 instruments (tetramethylsilane as internal reference). I.r. spectra are for Nujol mulls unless otherwise stated and were recorded with a Perkin-Elmer model 157 spectrophotometer or model 457 grating spectrophotometer.

2-Amino-3-(pyrazol-3-yl)pyridines (Ia—d).—*Method A.* The 4-chloro-1,8-naphthyridines (3·0 g) and substituted hydrazines (10 ml) were heated in sealed tubes at 130—150 °C for 5 h. Removal of the excess of hydrazine by distillation and crystallisation of the residue from aqueous ethanol gave the 1,3-disubstituted pyrazoles (Table 3).

Method B. A mixture of 5-chloro-2-methyl-1,8-naphthyridine (5·34 g), phenylhydrazine (9·75 g), and anisole (10 ml) was heated in an oil-bath. At about 90 °C an exothermic reaction occurred and the internal temperature rose to 195 °C. The mixture was heated for a further 3 h at 160—170 °C, then cooled, and aqueous sodium carbonate was added until the mixture was basic. Excess of phenylhydrazine was removed by steam distillation and the solid (75%) which precipitated was crystallised from light petroleum (b.p. 100—120°) and shown to be compound (Ia), m.p. 136—137°.

1-Substituted 3-(2-Aminophenyl)pyrazoles (IIa—c).—The 4-chloroquinolines (3·0 g) and substituted hydrazines (10 ml) were treated as in method A to give the 1,3-disubstituted pyrazoles (Table 3). The products (IIa—c) crystallised from aqueous ethanol.

1,3-Diphenylpyrazole (III).— 3-(2-Aminophenyl)-1-phenylpyrazole (0·6 g) was dissolved in concentrated hydrochloric acid (3 ml) and diazotised with sodium nitrite (0·3 g) in water (0·5 ml) at 15 °C. After 60 min the solution was poured into 30% hypophosphorous acid (7 ml) and stored at 0 °C overnight. Basification with sodium hydroxide solution and extraction with chloroform gave, after drying ($MgSO_4$), crude 1,3-diphenylpyrazole, which was purified by column chromotography (silica gel; benzene as eluant); m.p. 84—86° (lit.,[7] 85—86°). Authentic specimens were prepared (for comparison purposes) by two independent routes.[7,8]

3-(4-Chloro-2-hydroxyphenyl)-1-phenylpyrazole (IV) *and 7-Chloro-2-phenyl-2H-pyrazolo[4,3-c]cinnoline* (V).—3-(2-Amino-4-chlorophenyl)-1-phenylpyrazole (1·0 g) was suspended in glacial acetic acid (20 ml) and diazotised with aqueous sodium nitrite (0·4 g). An orange colour was produced and the solution was stirred for 1 h at room temperature. Water (200 ml) and concentrated sulphuric acid (5 ml) were added and the solution was heated under

[7] R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.*, 1968, **101**, 536.

[8] N. K. Kochetkov, E. D. Khomutova, O. B. Mikhailova, and A. N. Nesmeyanov, *Izvest. Akad. Nauk S.S.S.R. Otdel. khim. Nauk*, 1957, 1181 (*Chem. Abs.*, 1958, **52**, 6324g).

reflux for a few minutes. On cooling, a yellow solid precipitated which was purified by column chromatography [silica gel (20 g)]. The column was eluted with benzene first to give *compound* (IV) (0·2 g), m.p. 120—122° (Found: C, 66·6; H, 4·25; Cl, 13·4; N, 10·3%; M^+, 270. $C_{15}H_{11}ClN_2O$ requires C, 66·55; H, 4·05; Cl, 13·15; N, 10·35%; *M*, 270). Elution with chloroform then gave *compound* (V) (0·4 g), m.p. 262—263° (Found: C, 63·9; H, 3·4; Cl, 12·9; N, 19·8%; M^+, 280. $C_{15}H_9ClN_4$ requires C, 64·15; H, 3·2; Cl, 12·65; N, 19·95%; *M*, 280), δ [$(CD_3)_2SO$] 10·05 (1H, s, pyrazole proton), 8·62 (1H, d, H-6), 7·95 (1H, dd, *J* 8·0 Hz, H-8), 8·45 (1H, d, H-9), 8·17 (2H, m, *ortho*-aromatic H), and 7·6 p.p.m. (3H, m, aromatic).

Reaction of 5-*Chloro*-2-*hydroxybenzoylacetaldehyde* [9] *with Hydrazines.*—(a) *Methylhydrazine.* The aldehyde (2·0 g) was dissolved in hot methanol (30 ml) and methylhydrazine (2·0 g) was added slowly. The resulting solution was heated under reflux for 2 h. Water was then added and the precipitate crystallised from propan-2-ol to give 3-(5-*chloro*-2-*hydroxyphenyl*)-1-*methylpyrazole* (VIIa) (0·5 g). Addition of water to the propan-2-ol gave 5-(5-*chloro*-2-*hydroxyphenyl*)-1-*methylpyrazole* (VIa) (1·0 g).

(b) β-*Hydroxyethylhydrazine.* The reaction was carried out as in (a) and the methanolic solution was poured on ice. The precipitate crystallised from benzene to give 5-(5-*chloro*-2-*hydroxyphenyl*)-1-β-*hydroxyethylpyrazole* (VIb) (1·2 g). The benzene solution was evaporated and the residue crystallised from light petroleum (b.p. 80—100°) to give 3-(5-*chloro*-2-*hydroxyphenyl*)-1-β-*hydroxyethylpyrazole* (VIIb) (0·8 g).

(c) *Phenylhydrazine.* The reaction was carried out as in (b). The precipitate was collected, dried, and crystallised twice from benzene to give only one isomer, 5-(5-*chloro*-2-*hydroxyphenyl*)-1-*phenylpyrazole* (VIc) (2·8 g).

Table 3 gives analytical data for the products (VIa—c) and (VIIa and b).

2-*Methyl*-5-(2-*phenylhydrazino*)-1,8-*naphthyridine.*— To 5-chloro-2-methyl-1,8-naphthyridine (5·0 g) in ethanol (30 ml) was added phenylhydrazine (9·7 g); the solution was heated under reflux for 30 min, cooled, and basified with ammonia. Precipitation occurred on addition of water. The *solid* (70%), crystallised from aqueous ethanol, had m.p. 161—162° (Found: C, 71·8; H, 5·6; N, 22·1%; M^+, 250. $C_{15}H_{14}N_4$ requires C, 72·0; H, 5·6; N, 22·4%; *M*, 250), δ [$(CD_3)_2SO$] 8·84 (1H, d, $J_{6,7}$ 8·0 Hz, H-6), 6·66 (1H, d, H-7), 7·42 (1H, d, $J_{3,4}$ 7·0 Hz, H-3), 7·95 (1H, d, H-4), 6·7—7·4 (5H, m, aromatic), 8·83 (1H, s, NH), and 2·60 p.p.m. (3H, s, Me).

TABLE 3

Analytical data

Compound	Yield (%)	M.p. (°C)	Found (%) C	H	N	Cl	Formula	Required (%) C	H	N	Cl	ν_{NH_2}/cm^{-1}
(Ia)	75	136—137	72·0	5·6	22·5		$C_{15}H_{14}N_4$	71·95	5·65	22·4		3400, 3300
(Ib)	60	116—117	60·3	6·5	25·8		$C_{11}H_{14}N_4O$	60·55	6·45	25·65		3420, 3320
(Ic)	75	148—149	64·0	6·4	29·6		$C_{10}H_{12}N_4$	63·8	6·45	29·75		3430, 3250
(Id)	55	131—132	72·5	6·1	21·4		$C_{16}H_{16}N_4$	72·7	6·1	21·2		3430, 3300
(IIa)	60	123—124	76·8	5·5	17·9		$C_{15}H_{13}N_3$	76·55	5·55	17·85		3420, 3300
(IIb)	72	151	66·9	4·3	15·7	13·0	$C_{15}H_{12}ClN_3$	66·8	4·45	15·6	13·15	3430, 3320
(IIc)	60	90—91	55·7	5·1	17·6	15·1	$C_{11}H_{12}ClN_3O$	55·6	5·05	17·7	14·95	3420, 3300
												Solvent of cryst.
(VIa)	40	181—182	57·3	4·4	13·2	17·1	$C_{10}H_9ClN_2O$	57·55	4·3	13·45	17·0	Pr^iOH
(VIb)	45	158—159	55·2	4·5	11·8	15·0	$C_{11}H_{11}ClN_2O_2$	55·35	4·6	11·75	14·85	PhH
(VIc)	90	269—270	66·4	4·0	10·3	13·3	$C_{15}H_{11}ClN_2O$	66·55	4·05	10·35	13·1	PhH
(VIIa)	40	94—95	57·5	4·5	13·2	17·0	$C_{10}H_9ClN_2O$	57·55	4·3	13·45	17·0	Pr^iOH–H_2O
(VIIb)	40	91—92	55·3	4·5	11·7	14·9	$C_{11}H_{11}ClN_2O_2$	55·35	4·6	11·75	14·85	LP †

† Light petroleum (b.p. 100—120°)

Reactions of Phenylhydrazino-derivatives (X) *and* (XI).—(*a*) 2-Methyl-5-(2-phenylhydrazino)-1,8-naphthyridine hydrochloride (X) (2·0 g) was heated in a sealed tube with hydrazine hydrate (10 ml) at 150 °C for 5 h. After cooling, water was added and the resulting solid (50%) was crystallised from light petroleum (b.p. 100—120°) to give the pyrazolylpyridine (Ia). Similarly the (X) and β-hydroxyethylhydrazine gave (Ia) (40%).

(*b*) 7-Chloro-4-(2-phenylhydrazino)quinoline [4] hydrochloride (XI) (2·0 g) and hydrazine hydrate (10 ml) were heated in a sealed tube at 150 °C for 5 h to give the phenylpyrazole (IIb) (40% yield after crystallisation from aqueous ethanol).

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[9] G. Wittig, F. Bangert, and H. E. Richter, *Annalen*, 1925, **446**, 155.