360. *The Preparation of Some Pyrazole Derivatives.*

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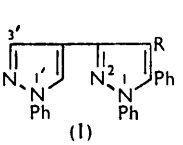
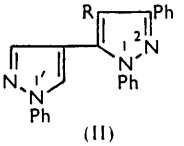
Various pyrazoles have been formylated, and these derivatives oxidised to the corresponding acids. Thionyl chloride reacts directly with 1-phenylpyrazole to give the dipyrazolyl sulphoxide which has been oxidised to the sulphone. 4-Formyl-1-phenylpyrazole gives the expected alcohols with Grignard reagents, except that ethylmagnesium halide gave 4-propenyl-1-phenylpyrazole and a dimer. The alcohols have been oxidised to the ketones, and some of these reduced to alkyl compounds by the Clemmensen method. Both 4-formyl-1-phenylpyrazole and 1-phenylpyrazole-4-carboxylic acid have been reduced by lithium aluminium hydride to 4-hydroxymethyl-1-phenylpyrazole. Two bipyrazolyls and one terpyrazole have also been prepared.

DIMETHYLFORMAMIDE and phosphoryl chloride [1] have been used to formylate 1-phenyl- and 1-methyl-pyrazole, but these reagents failed with pyrazole and 1-benzoyl- and 1-benzenesulphonyl-pyrazole.[2] It has now been shown that formylation fails with 1-*p*-nitrophenyl- and 1-(2 : 4-dinitrophenyl)-pyrazole,[3] and with 1 : 5 : 1′-triphenyl-3 : 4′-bipyrazolyl (I; R = H), but is successful with 1-*m*-nitrophenylpyrazole,[3] giving the 4-formyl derivative and with 1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = H) to give (II; R = CHO). Both formyl compounds, on oxidation, give the corresponding acids. Thionyl chloride [4] has been used instead of phosphoryl chloride, and when this reaction was carried out with 1-phenylpyrazole, only di-(1-phenyl-4-pyrazolyl) sulphoxide (III; $x = 1$) was obtained. This compound was also formed in the absence of dimethylformamide and, on oxidation, was converted into the sulphone (III; $x = 2$). The formation of the sulphoxide by the direct action of thionyl chloride is interesting since in the sulphoxide preparations from thionyl chloride previously investigated Friedel–Crafts conditions have been used.[5]


(I)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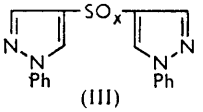
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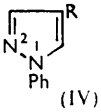
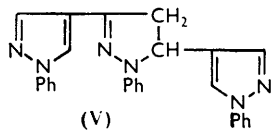

(IV)

A number of 1-phenyl-4-pyrazolylalkanols were prepared by reaction between 4-formyl-1-phenylpyrazole and the appropriate Grignard reagent (see Table 1). Some of these were oxidised in acetone solution with acid dichromate to the corresponding ketones (see Table 2). Under the same conditions, 2-methyl- and 2 : 2-dimethyl-1-4′-pyrazolylpropan-1-ol gave 1-phenylpyrazole-4-carboxylic acid,[6] but at 5—10° the corresponding ketones

[1] Campaigne and Archer, *J. Amer. Chem. Soc.*, 1953, **75**, 989.
[2] Finar and Lord, *J.*, 1957, 3314.
[3] Finar and Hurlock, *J.*, 1957, 3024.
[4] Smith, *J.*, 1956, 3842.
[5] Schönberg, *Ber.*, 1923, **56**, 2275; Smiles and Le Rossignol, *J.*, 1906, 696; Colby and McLoughlin, *Ber.*, 1887, **20**, 195; Loth and Michaelis, *Ber.*, 1894, **27**, 2547.
[6] Finar and Godfrey, *J.*, 1954, 2293.

were obtained. A few of these ketones have been reduced with amalgamated zinc and hydrochloric acid to the corresponding 4-alkyl derivatives (Table 3). Attempts to reduce 4-formyl-1-phenylpyrazole under the same conditions resulted in a resin. Reduction of the 4-formyl compound and of the 4-carboxylic acid with lithium aluminium hydride produced 4-hydroxymethyl-1-phenylpyrazole,[6] and this was converted into di-(1-phenyl-4-pyrazolyl)methane [6] when heated with 1-phenylpyrazole, phosphoric acid, and dilute acetic acid.

All attempts to isolate 1-(1-phenyl-4-pyrazolyl)propane-1-ol on reaction between ethylmagnesium iodide and 4-formyl-1-phenylpyrazole failed; the products were 4-propenyl-1-phenylpyrazole and a dimer which may be *trans*-3 : 4-di-(1-phenyl-4-pyrazolyl)hex-3-ene. These could be formed from 1-(1-phenyl-4-pyrazolyl)propan-1-ol which is produced first. The presence of this alcohol in the reaction mixture was shown by the isolation of some ethyl pyrazolyl ketone when the crude Grignard reaction product was oxidised. Reduction of this ketone with sodium borohydride gave an oil which was shown to contain the alcohol, but a pure specimen of the latter could not be isolated.



(V)

Ketones were prepared by condensing acetophenone with 4-formyl-1-phenylpyrazole, and benzaldehyde and 4-formyl-1-phenylpyrazole with 4-acetyl-1-phenylpyrazole. Each was condensed with phenylhydrazine, forming the 4 : 5-dihydro-derivatives of compounds (II) and (I), and the dipyrazolylpyrazoline (V). All three pyrazolines were oxidised to the corresponding pyrazoles by potassium permanganate in pyridine.

Experimental

4-Formyl-1-m-nitrophenylpyrazole.—A mixture of 1-*m*-nitrophenylpyrazole [3] (4·25 g., 0·022 mole), dimethylformamide (9·1 g., 0·125 mole), and phosphoryl chloride (5·0 g., 0·33 mole) was heated on the steam-bath for 4 hr., poured on ice, and filtered. The precipitate (2·35 g.) was unchanged nitropyrazole. The filtrate was treated with sodium hydroxide solution to pH 4, and after 12 hr. filtered, giving *4-formyl-1-m-nitrophenylpyrazole* (0·45 g., 9%) as colourless needles (from acetone), m. p. 180° (Found: C, 55·3; H, 3·5; N, 19·2. $C_{10}H_7O_3N_3$ requires C, 55·4; H, 3·2; N, 19·3%).

4-Formyl-1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = CHO).—A mixture of 1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = H) (1·5 g., 0·004 mole), dimethylformamide (5·4 g., 0·074 mole), and phosphoryl chloride (1·67 g., 0·011 mole) was treated as above, but in this case the precipitate was the *formylbipyrazolyl* (the filtrate gave only a negligible amount). This, on crystallisation from ethanol and then benzene–light petroleum (b. p. 40—60°), gave needles (1·35 g., 83%), m. p. 169—169·5° (Found: C, 76·5; H, 4·7; N, 14·8. $C_{25}H_{18}ON_4$ requires C, 77·0; H, 4·6; N, 14·4%).

Oxidation of the Formyl Compounds.—The formylnitropyrazole, on oxidation with hot alkaline potassium permanganate solution, gave colourless needles of 1-m-*nitrophenylpyrazole-4-carboxylic acid* (from aqueous ethanol), m. p. 253—254° (Found: C, 51·3; H, 3·2; N, 17·8. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%). A pyridine solution of the formylbipyrazolyl (II; R = CHO) was refluxed with potassium permanganate and, on working up, gave colourless needles of 1 : 3 : 1′-*triphenyl-5 : 4′-bipyrazolyl-4-carboxylic acid* (II; R = CO_2H) (from aqueous ethanol), m. p. 212—213° (decomp.) (Found: C, 73·7; H, 4·7; N, 13·9. $C_{25}H_{18}O_2N_4$ requires C, 73·9; H, 4·4; N, 13·8%).

Di-(1-phenyl-4-pyrazolyl) Sulphoxide (III; $x = 1$).—A mixture of 1-phenylpyrazole (5·8 g., 0·04 mole) and thionyl chloride (14·0 g., 0·13 mole) was refluxed for 3 hr., the excess of thionyl chloride evaporated, and the cooled solution then poured into water (150 c.c.). The precipitate was collected, washed with water, and recrystallised from acetone, to give colourless plates of the *sulphoxide* (1·0 g., 14·5%), m. p. 154° (Found: C, 64·5; H, 4·1; N, 16·8; S, 9·7. $C_{18}H_{14}ON_4S$ requires C, 64·7; H, 4·2; N, 16·75; S, 9·6%).

Di-(1-phenyl-4-pyrazolyl) Sulphone (III; $x = 2$).—The sulphoxide (3·1 g.), acetic acid (60 c.c.), and 100-vol. hydrogen peroxide (40 c.c.) were heated on the steam-bath for 3 hr., then

poured into water (200 c.c.). The precipitate was collected, washed with water, and recrystallised from ethanol, to give colourless plates of the *sulphone* (2·4 g.; 74%), m. p. 180° (Found: C, 61·6; H, 4·3; N, 15·9; S, 8·9. $C_{18}H_{14}O_2N_4S$ requires C, 61·75; H, 4·0; N, 16·0; S, 9·1%).

1-(1-*Phenyl*-4-*pyrazolyl*)*ethanol*.—To methylmagnesium iodide (magnesium, 3·39 g., 0·139 mole; methyl iodide, 19·6 g., 0·139 mole) in ether (100 c.c.) was added dropwise 4-formyl-1-phenylpyrazole (20·0 g., 0·116 mole) in benzene (300 c.c.) during 1 hr. with stirring. The mixture was gently refluxed for a further 2 hr., cooled, and hydrolysed by the dropwise addition of 25% ammonium chloride solution (100 c.c.). The benzene–ether layer was separated from the aqueous layer which was extracted with ether (3 × 100 c.c.). The benzene solution and ethereal extracts were combined, washed with water, dried (Na_2SO_4), and evaporated. The residual red oil was extracted with hot ligroin (b. p. 100—120°) which, on evaporation, left a pale yellow oil (20·6 g.). This was distilled rapidly and the fraction (9·3 g.), b. p. 172—176°/0·06 mm., was redistilled to give the *pyrazolylethanol* (7·8 g., 53·3%), b. p. 152—153°/0·04 mm. (Found: C, 70·6; H, 6·35; N, 15·2. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%). The other alkanols (see Table 1) were similarly prepared, in 49—79% yield (no extraction with ligroin was used for these compounds).

TABLE 1.

Alkanol (IV) R =	Halide for Grignard	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
$CHPr^n{\cdot}OH$	PrI	73·5—74° *	72·5	7·45	13·1	$C_{13}H_{16}ON_2$	72·2	7·4	13·0
$CHPr^i{\cdot}OH$	Pr^iI	75·5—76 †	72·4	7·3	13·0				
$CHBu^n{\cdot}OH$	Bu^nBr	68—69 *	73·1	7·7	12·2	$C_{14}H_{18}ON_2$	73·1	7·8	12·15
$CHBu^t{\cdot}OH$	Bu^tCl	99—99·5 *	72·8	7·9	12·4				
CHPh·OH	PhBr	120—121 *	76·5	5·6	11·5	$C_{15}H_{14}ON_2$	76·8	5·6	11·2

* Recrystallised from aqueous methanol. † Recrystallised from benzene–light petroleum.

4-*Acetyl*-1-*phenyl*-4-*pyrazole*.—1-(1-Phenyl-4-pyrazolyl)ethanol (IV; 5·4 g.) in acetone (25 c.c.) was added slowly, with stirring, to cold acid dichromate solution (150 c.c.; 100 g. of sodium dichromate, 250 c.c. of concentrated sulphuric acid, 750 c.c. of water). The temperature of the mixture was not allowed to exceed 50°. After ½ hr., the solution was diluted with water, and the precipitate collected, washed with water, and recrystallised from ethanol to give the ketone (4·85 g., 91%), m. p. 129° (Balbiano [7] gives m. p. 121·5—122·5°). The other ketones (see Table 2) were similarly prepared, in 69—87% yield (the temperature was kept between 5—10° for the first, second, and fifth).

TABLE 2.

Ketone (IV) R =	M. p.*	Found (%) C	H	N	Formula	Required (%) C	H	N
Ac	109—109·5°	71·6	5·9	13·9	$C_{12}H_{12}ON_2$	72·0	6·0	14·0
$COPr^n$	114	72·7	6·4	12·9	$C_{13}H_{14}ON_2$	72·9	6·5	13·1
$COPr^i$	117·5—118	72·3	6·5	12·8				
$COBu^n$	110·5—111·5	73·6	7·0	12·5	$C_{14}H_{16}ON_2$	73·7	7·0	12·3
$COBu^t$	99·5—100	73·8	6·9	12·1				
Bz	126—126·5 †							

* All compound recrystallised from aqueous ethanol. † Balbiano [7] gives m. p. 123°.

Clemmensen Reduction of the Ketones.[8]—Freshly prepared amalgamated zinc (10 g.) and the ketone (0·01 mole) were refluxed for 2 hr. with 5N-hydrochloric acid (15 c.c.), further acid (12 c.c.) being added during this period. When cool, the solution was decanted from the zinc residue, the latter was washed with water and then ether, and the decanted liquid and washings were combined, saturated with sodium chloride, and extracted with ether (3 × 75 c.c.). The ethereal extract was dried (Na_2SO_4), the ether evaporated, and the residual oil distilled *in vacuo*, to give the 4-*alkyl*-1-*phenylpyrazoles* in 42—59% yield (Table 3).

Attempted Preparation of 1-(1-*Phenyl*-4-*pyrazolyl*)*propan*-1-*ol*.—4-Formyl-1-phenylpyrazole (15 g.) was added to ethylmagnesium iodide (31·45 g.) as described above for the pyrazolylethanol. The oil obtained on evaporation of the benzene–ether solvent was extracted with cold light petroleum (400 c.c.) which was then chromatographed on alumina. The mother-liquor

[7] Balbiano, *Gazzetta*, 1889, **19**, 128.
[8] Clemmensen, *Ber.*, 1914, **47**, 51; Brewster and Harris, *J. Amer. Chem. Soc.*, 1930, **52**, 4886.

TABLE 3.

Alkylpyrazole (IV) R =	B. p./mm.	Found (%) C	H	N	Formula	Required (%) C	H	N
CHEt	102—103°/0·5	77·2	7·0	16·3	$C_{11}H_{12}N_2$	76·8	7·0	16·3
Pr^n	133—134°/0·6	77·6	7·2	15·1	$C_{12}H_{14}N_2$	77·4	7·5	15·1
Bu^n	136—137°/0·7	78·1	7·8	14·0	$C_{13}H_{16}N_2$	78·0	8·0	14·0
n-C_5H_{11}	150—152°/0·9	78·5	8·3	13·2	$C_{14}H_{18}N_2$	78·5	8·4	13·1

(of light petroleum) gave, on evaporation, a liquid which, on cooling to 0°, solidified. When the temperature was raised to 20° some solid melted. The fine white needles of 1-*phenyl*-4-*propenylpyrazole* had m. p. 39—40° (Found: C, 78·4; H, 6·2; N, 15·4. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). A chloroform solution of the pure compound rapidly absorbed bromine, and on oxidation with acid dichromate at 0—5° gave 1-phenylpyrazole-4-carboxylic acid. The infrared spectrum of the propenylpyrazole was similar to that of 1-phenyl-4-propylpyrazole, the main difference being the presence in the former of a shoulder at 966 $cm.^{-1}$; this shoulder, which is quite pronounced, has been assigned to a CH out-of-plane deformation frequency in a *trans*-disubstituted ethylene group since such a structure is known to give a strong absorption band at 970—960 $cm.^{-1}$.[9]

When, instead of extraction with light petroleum, the product (oil) was distilled, the small fraction of b. p. 110—112°/0·05 mm. gave, on oxidation at 0—5°, 1-phenylpyrazole-4-carboxylic acid. The non-volatile residue was chromatographed in ligroin on alumina. Elution with benzene, followed by evaporation of the solvent, gave a solid, m. p. 104—105° (Found: C, 78·1; H, 6·45; N, 15·2%). Molecular-weight determination cryoscopically in benzene showed it to be a dimer of the propenylpyrazole. This dimer absorbed half the amount of bromine required for the monomer, and oxidation at 50° gave 1-phenyl-4-propionylpyrazole and 1-phenylpyrazole-4-carboxylic acid. The structure 3 : 4-di-(1-phenyl-4-pyrazolyl)hex-3-ene is in keeping with these results and is supported by absorption bands in the 1680—1620 $cm.^{-1}$ region, thereby indicating symmetrical (*trans*-)tetrasubstitution [9] of the type $(CRR')_2$.

Since attempts to isolate the pyrazolylpropanol as a derivative failed, the crude alkanol was oxidised to the ketone (see Table 2) which was then reduced by sodium borohydride [10] to a yellow oil which was too impure to give a correct analysis, but its infrared spectrum was very similar to that of 1-(1-phenyl-4-pyrazolyl)ethanol. One impurity in this compound was 1-phenyl-4-propenylpyrazole since there was a shoulder at 966 $cm.^{-1}$.

4-*Hydroxymethyl*-1-*phenylpyrazole*.[6]—This was prepared by reducing 4-formyl-1-phenylpyrazole (77% yield) or 1-phenylpyrazole-4-carboxylic acid (81% yield) with an excess of lithium aluminium hydride.[11] Reduction of the formyl compound with sodium borohydride [10] gave a yield of 81%.

Di-(1-*phenyl*-4-*pyrazolyl*)*methane*.[6]—4-Hydroxymethylpyrazole (2·55 g., 0·015 mole), 1-phenylpyrazole (4·2 g., 0·03 mole), glacial phosphoric acid (7·5 c.c.), glacial acetic acid (15 c.c.) and water (15 c.c.) were heated on the steam-bath for 12 hr., then cooled, diluted with water (75 c.c.), and set aside for 12 hr. The precipitate was collected, washed with water, and recrystallised from methanol (charcoal), to give the dipyrazolylmethane (53·5%), m. p. 113—114°.

Propenones.—4-Formyl-1-phenylpyrazole (30 g., 0·175 mole) in ethanol (200 c.c.) was added dropwise, with stirring, to a cooled solution of sodium hydroxide (12 g., 0·52 mole) [in water (80 c.c.) and ethanol (40 c.c.)] and acetophenone (21 g., 0·175 mole) at 10—15°. The mixture was kept for 12 hr., and the solid then collected, washed well with water, dried at 110°, and recrystallised twice from benzene–light petroleum, to give needles of 1-*phenyl*-3-(1-*phenyl*-4-*pyrazolyl*)*prop*-2-*en*-1-*one* (*A*) (38·9 g., 57%), m. p. 181° (Found: C, 78·5; H, 5·3; N, 9·8. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·1; N, 10·2%). In the same way, 4-acetyl-1-phenylpyrazole and benzaldehyde gave 4-*cinnamoyl*-1-*phenylpyrazole* (*B*) (47%), m. p. 170·5—171·5° (from benzene) (Found: C, 78·4; H, 5·1; N, 10·2%); 4-acetyl-1-phenylpyrazole and 4-formyl-1-phenylpyrazole gave 1 : 3-*di*-(1-*phenyl*-4-*pyrazolyl*)*prop*-2-*en*-1-*one* (*C*) (77·5%), m. p. 250—250·5° (from benzene–light petroleum) (Found: C, 74·6; H, 4·7; N, 16·5. $C_{21}H_{16}ON_4$ requires C, 74·2; H, 4·7; N, 16·5%).

Pyrazolines.—Phenylhydrazine (1·6 g., 0·015 mole) in glacial acetic acid (25 c.c.) was added

[9] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, 2nd edn., 1958, pp. 34 *et seq.*
[10] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.
[11] Nystrom and Brown, *ibid.*, 1947, **69**, 1197.

dropwise to a hot solution of the ketone (*A* in preceding paragraph) (3·69 g., 0·014 mole) in glacial acetic acid (50 c.c.), and the mixture heated for a further hour on the steam-bath. It was kept for 12 hr., and the solid then collected, washed with a little ethanol, and recrystallised from ethanol, to give colourless needles of 1 : 3-*diphenyl*-5-(1-*phenyl*-4-*pyrazolyl*)*pyrazoline* (92%), m. p. 192° (Found: C, 78·8; H, 5·5; N, 15·4. $C_{24}H_{20}N_4$ requires C, 79·1; H, 5·5; N, 15·4%). In the same way, the ketone (*B*) and phenylhydrazine gave 1 : 5-*diphenyl*-3-(1-*phenyl*-4-*pyrazolyl*)*pyrazoline* (76%), m. p. 169—170° (from benzene) (Found: C, 78·8; H, 5·5; N, 15·7%); the ketone (*C*) and phenylhydrazine gave 1-*phenyl*-3 : 5-*di*-(1-*phenyl*-4-*pyrazolyl*)-*pyrazoline* (53%), m. p. 227—228° (from chloroform–light petroleum) (Found: C, 75·6; H, 5·1; N, 19·2. $C_{27}H_{22}N_6$ requires C, 75·3; H, 5·1; N, 19·5%). All three pyrazolines gave a blue fluorescence under ultraviolet light.

Pyrazolyls.—A mixture of the 4 : 5-dihydro-derivative of the bipyrazolyl (II; R = H) (3·65 g.), powdered potassium permanganate (3 g.), pyridine (20 c.c.), and water (5 c.c.) was kept for 1·5 hr., then heated at 100° for 20 min. The solid isolated was recrystallised from benzene–light petroleum, to give needles of 1 : 3 : 1′-*triphenyl*-5 : 4′-*bipyrazolyl* (II; R = H) (55%), m. p. 109—110° (Found: C, 79·3; H, 5·2; N, 15·2. $C_{24}H_{18}N_4$ requires C, 79·6; H, 5·0; N, 15·45%). In the same way, the 4 : 5-dihydro-derivative of the bipyrazolyl (I; R = H) gave 1 : 5 : 1′-*triphenyl*-3 : 4′-*bipyrazolyl* (I; R = H) (97%), m. p. 166·5—167° (from aqueous ethanol) (Found: C, 79·3; H, 5·0; N, 15·4%). 1-*Phenyl*-3 : 5-*di*-(1-*phenyl*-4-*pyrazolyl*)*pyrazole* (69%), m. p. 167·5—168° (from benzene–light petroleum) (Found: C, 75·9; H, 4·7; N, 19·3. $C_{27}H_{20}N_6$ requires C, 75·6; H, 4·7; N, 19·6%), was similarly prepared.

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