930. *Fluorescent Whitening Agents. Part I. 1,3-Diaryl-2-pyrazolines.*

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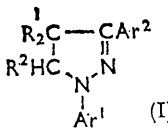
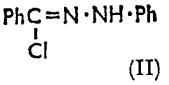
The preparation is described of 55 2-pyrazolines, mostly by reaction of an arylhydrazine with a Mannich base, or a β-chloro or αβ-unsaturated ketone. Arylation of 1-phenylpyrazolines is employed in a few instances. A route to 4,4-disubstituted 1,3-diaryl-2-pyrazolines is developed.

As part of a search for new fluorescent whitening agents we prepared a number of 1,3-diaryl-2-pyrazolines (I), which as a class seem particularly suitable in this connection.[1] Unlike most types of fluorescent agent, this series can be prepared very pure and with a wide range of substituents, and so it has proved possible to study in some detail the effect of structure both upon spectral properties and upon the affinity of the dyes for fibres; but only the preparative aspects of the investigation are considered here. Furthermore the pyrazolines reported (Tables 1 and 2) exclude those bearing a carboxyl function (to be described later).

1,3-Diaryl-2-pyrazolines are normally synthesised [2] from an arylhydrazine and an αβ-unsaturated ketone or its potential progenitor, such as the corresponding β-chloro-ketone or Mannich base ($ArCO{\cdot}CH_2{\cdot}CH_2X$; X = Cl or NR^1R^2). Reaction presumably proceeds in all cases through an intermediate phenylhydrazone, although it is only in certain instances, particularly when electron-withdrawing groups are present,[3] that such intermediates are insolable. Two valuable additional methods have been developed in recent years, namely the arylation [4] of 1-aryl-2-pyrazolines in the 3-position with diazonium salts, and the 1,3-dipolar addition [5] of the R–C=N–N–R′ moiety to olefinic compounds. All the above methods have been used in this work. A further route involving formation of the N–N bond by dehydration of suitable anilino-oximes has recently been described [6] but seems to be of limited applicability.



(I)



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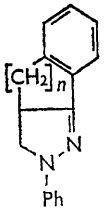

(III a: $n = 1$; b: $n = 2$)

The majority of the 1,3-diphenyl-2-pyrazolines (Table 1) were prepared conveniently and in good yield from the appropriate acetophenone via a Mannich base. Pyrazolines bearing a nitro-group on the 1-phenyl ring were better prepared from the chloro-ketone, since under neutral conditions Mannich bases gave the nitrophenyl hydrazones, and in the presence of alkali dark by-products were formed. For compounds in which an electronegative substituent was present in the 3-phenyl ring, and for which, in general, the unsaturated ketone or its equivalent is not readily available, we employed the arylation route.[4] Thus, 1-phenyl-2-pyrazoline gave, with diazotised sulphanilamide and diazotised *p*-nitroaniline, the 3-*p*-sulphonamido- and 3-*p*-nitro-phenyl derivatives, respectively. The usefulness of this interesting approach is limited by the availability of 1-aryl-2-pyrazolines

[1] B.P. 669,590, 670,857, and 712,764 (to Ilford); 808, 113 and 832,239 (to Farbenfabriken Bayer); 883,826 (to Unilever).
[2] Elderfield, " Heterocyclic Compounds," Chapman and Hall Ltd., London, 1957, Vol. V, p. 45.
[3] Auwers and Voss, *Ber.*, 1909, **42**, 4411; Nisbet, *J.*, 1945, 125; Curtis, Hassall, and Weatherston, *J.*, 1962, 3831.
[4] Duffin and Kendall, *J.*, 1954, 408.
[5] Huisgen, Seidel, Wallbillich, and Knupfer, *Tetrahedron*, 1962, **17**, 3.
[6] Hassner and Michelson, *J. Org. Chem.*, 1962, **27**, 298.

TABLE 1.

Substituted 1,3-diphenyl-2-pyrazolines (I).

Method	Substituents in Ar¹	Substituents in Ar²	R¹	R²	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N	M. p. (observed)	M. p. (lit.)	Lit. ref.
M	None	4-Ph	H	H	84·2	5·8	9·5	$C_{21}H_{18}N_2$	84·5	6·1	9·4	208—210°	203—205°	*a*
M	,,	4-OH	,,	,,	75·3	5·7	11·6	$C_{15}H_{14}N_2O$	75·6	5·9	11·8	167—168	156—157	*b*
M	,,	2-OH	,,	,,	76·0	6·0	11·6	$C_{15}H_{14}N_2O$	75·6	5·9	11·8	128—129	—	—
E	,,	4-OCOMe	,,	,,	72·6	5·7	9·7	$C_{17}H_{16}N_2O_2$	72·8	5·8	10·0	146—149	—	—
E	,,	4-OCOPh	,,	,,	—	—	8·1	$C_{22}H_{18}N_2O_2$	—	—	8·2	182—183	—	—
M	,,	4-OMe	,,	,,	76·0	6·4	11·0	$C_{16}H_{16}N_2O$	76·2	6·4	11·1	140—141	105 142·5—143	*c* *d*
CK	,,	3,4-$(OMe)_2$	,,	,,	72·5	6·5	10·1	$C_{17}H_{18}N_2O_2$	72·3	6·4	9·9	124	130	*e*
D	,,	4-NO_2	,,	,,	—	—	15·5	$C_{15}H_{13}N_3O_2$	—	—	15·7	151—152	152—152·5	*f*
D	,,	4-$SO_2{\cdot}NH_2$	,,	,,	—	—	13·7	$C_{15}H_{15}N_3O_2S$	—	—	13·9	263—264	—	—
DA	,,	None	,,	CN	—	—	16·7	$C_{16}H_{13}N_3$	—	—	17·0	141—142	138—140	*g*
DA	,,	,,	,,	CO_2Me	—	—	10·2	$C_{17}H_{16}N_2O_2$	—	—	10·0	106—107	—	—
DA	,,	,,	,,	n-$C_{10}H_{21}$	—	—	7·9	$C_{25}H_{34}N_2$	—	—	7·7	65—66	—	—
DA	,,	,,	,,	$BrCH_2$	—	—	8·8	$C_{16}H_{15}BrN_2$	—	—	8·9	91—92	—	—
DA	,,	,,	,,	$C_5H_5\overset{+}{N}CH_2-$, $\overset{-}{Br}$	—	—	11·0	$C_{21}H_{20}BrN_3$	—	—	10·7	218—219	—	—
D	,,	4-Cl	Me	H	71·3	6·1	9·7	$C_{17}H_{17}ClN_2$	71·7	6·0	9·8	109—110	—	—
M	4-Me	None	H	,,	—	—	12·0	$C_{16}H_{16}N_2$	—	—	11·9	130—131	—	—
M	4-Cl	,,	,,	,,	—	—	11·0	$C_{15}H_{13}ClN_2$	—	—	10·9	141—142	—	—
M	3-Cl	,,	,,	,,	—	—	11·2	$C_{15}H_{13}ClN_2$	—	—	10·9	103—104	—	—
M	3,4-Cl_2	,,	,,	,,	—	—	9·8	$C_{15}H_{12}Cl_2N_2$	—	—	9·6	122—123	—	—
M	4-Br	,,	,,	,,	—	—	9·6	$C_{15}H_{13}BrN_2$	—	—	9·3	142—143	—	—
M	4-OMe	,,	,,	,,	76·1	6·5	10·8	$C_{16}H_{16}N_2O$	76·2	6·4	11·1	163—164	—	—
M	2-OMe	,,	,,	,,	76·0	6·5	10·7	$C_{16}H_{16}N_2O$	76·2	6·4	11·1	72—73	—	—
M	4-SO_2NH_2	,,	,,	,,	—	—	13·9	$C_{15}H_{15}N_3O_2S$	—	—	13·9	254—255	—	—
M	4-Me	4-Cl	,,	,,	—	—	10·3	$C_{16}H_{15}ClN_2$	—	—	10·3	207—208	—	—
M	4-Cl	,,	,,	,,	—	—	9·9	$C_{15}H_{12}Cl_2N_2$	—	—	9·6	174—175	—	—
M	,,	4-OMe	,,	,,	—	—	9·5	$C_{16}H_{15}ClN_2O$	—	—	9·8	193—194	—	—
D	,,	4-$SO_2{\cdot}NH_2$	,,	,,	—	—	12·7	$C_{15}H_{14}ClN_3O_2S$	—	—	12·5	212—213	—	—
M	3-Cl	4-Me	,,	,,	—	—	9·9	$C_{16}H_{15}ClN_2$	—	—	10·3	107—108	—	—
M	,,	4-Cl	,,	,,	—	—	9·6	$C_{15}H_{12}Cl_2N_2$	—	—	9·6	124—125	—	—
M	,,	4-OMe	,,	,,	—	—	9·9	$C_{16}H_{15}ClN_2O$	—	—	9·8	123—124	—	—
M	3,4-Cl_2	,,	,,	,,	—	—	8·7	$C_{16}H_{14}Cl_2N_2O$	—	—	8·7	119—120	—	—
M	4-NO_2	4-Cl	,,		—	—	14·1	$C_{15}H_{12}ClN_3O_2$	—	—	13·9	196—197	—	—
M	4-SO_3Na				—	—	7·9	$C_{15}H_{12}ClN_2NaO_3S$	—	—	7·8	>300	—	—
E	4-SO_3H	,,	,,	,,	—	—	8·2	$C_{15}H_{13}ClN_2O_3S$	—	—	8·3	130—131	—	—
E	4-SO_3Me	,,	,,	,,	—	—	8·0	$C_{16}H_{15}ClN_2O_3S$	—	—	8·0	188—189	—	—
M	4-$SO_2{\cdot}NH_2$	,,	,,	,,	—	—	12·3	$C_{15}H_{14}ClN_3O_2S$	—	—	12·5	212—213	218	*h*
M	,,	3,4-Cl_2	,,	,,	—	—	11·3	$C_{15}H_{13}Cl_2N_3O_2S$	—	—	11·3	239—240	233—236	*h*
CK	4-CN	4-Cl	,,	,,	—	—	15·0	$C_{16}H_{12}ClN_3$	—	—	14·9	127—128	183	*i*
CK	,,	3,4-$(OMe)_2$	,,	,,	—	—	13·6	$C_{18}H_{17}N_3O_2$	—	—	13·7	172—173	—	—
M	4-SO_3Na	4-Ph	,,	,,	62·7	4·6	6·6	$C_{21}H_{17}N_2NaO_3S$	63·0	4·3	7·0	>300	—	—
M	,,	4-OMe	,,	,,	—	—	8·0	$C_{16}H_{15}N_2NaO_4S$	—	—	7·9	>300	—	—

Method: CK, Chloro-ketone; D, diazonium salt; DA, dipolar addition; E, see Experimental section; M, Mannich base.

References: (*a*) Mohrbacher and Cromwell, *J. Amer. Chem. Soc.*, 1957, **79**, 401; (*b*) Zigeuner and Wiesenberger, *Monatsh.*, 1949, **80**, 801; (*c*) Ref. 21; (*d*) Profft, Runge, and Jumar, *J. prakt. Chem.*, 1954, **1**, 57; (*e*) Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 233; (*f*) Wheatley, Fitzgibbon, and Cheyney, *J. Amer. Chem. Soc.*, 1954, **76**, 4490; (*g*) Ref. 5; (*h*) B.P. 808,113; (*i*) B.P. 832,239.

TABLE 2.

Miscellaneous 2-pyrazolines.

Method	Compound	Found (%) C	H	N	Formula	Required (%) C	H	N	M. p. (observed)	M. p. (lit.)	Lit. ref.
E	1-Phenyl-2-pyrazoline	—	—	—	$C_9H_{10}N_2$	—	—	—	50—51°	51—52°	*a*
E	1-*p*-Chlorophenyl-2-pyrazoline	60·0	5·1	15·2	$C_9H_9ClN_2$	59·8	4·8	15·5	73—74	—	—
E	4,4-Dimethyl-1-phenyl-2-pyrazoline	75·7	8·4	15·6	$C_{11}H_{14}N_2$	75·8	8·1	16·1	b. p. 108—110/1 mm.	—	—
M	3-(α-Naphthyl)-1-phenyl-2-pyrazoline	83·8	6·0	9·9	$C_{19}H_{16}N_2$	83·8	5·9	10·3	91—92	167—168	*b*
D	3-(β-Naphthyl)-1-phenyl-2-pyrazoline	83·5	5·5	10·2	$C_{19}H_{16}N_2$	83·8	5·9	10·3	176—177	180—182	*c*
UK	1,5-Diphenyl-3-styryl-2-pyrazoline	—	—	8·5	$C_{23}H_{20}N_2$	—	—	8·6	156—157	152—153	*d*
M	3,3a,4,5-Tetrahydro-2-phenyl-2*H*-benz[*g*]indazole	81·9	6·6	11·6	$C_{17}H_{16}N_2$	82·2	6·5	11·3	129—130	—	—
M	2,3,3a,4-Tetrahydro-2-phenylindeno[1,2,*c*]pyrazole	82·2	5·9	11·9	$C_{16}H_{14}N_2$	82·0	6·0	12·0	172—173	—	—
M	1-Benzothiazol-2′-yl-3-phenyl-2-pyrazoline	68·5	4·6	15·2	$C_{16}H_{13}N_3S$	68·8	4·7	15·0	209—210	—	—
UK	3-(1-Methylbenzimidazol-2-yl)-1,5-diphenyl-2-pyrazoline	78·0	5·8	15·9	$C_{23}H_{20}N_4$	78·4	5·7	15·9	186—187	—	—
UK	5-Benzimidazol-2′-yl-1,3-diphenyl-2-pyrazoline	—	—	16·9	$C_{22}H_{18}N_4$	78·1	5·4	16·6	269—270	—	—
E	3-Amino-1-phenyl-2-pyrazoline	66·9	6·9	26·2	$C_9H_{11}N_3$	67·1	6·9	26·1	168—169	169	*e*
E	Dibenzoyl derivative of 3-amino-1-phenyl-2-pyrazoline	74·8	5·1	10·9	$C_{23}H_{19}N_3O_2$	74·8	5·2	11·4	170—171	—	—
E	3-Benzylideneamino-1-phenyl-2-pyrazoline	77·1	5·9	17·2	$C_{16}H_{15}N_3$	77·1	6·1	16·9	196—197	183	*e*

Methods: D, diazonium salt; E, see Experimental section; M, Mannich base; UK, unsaturated ketone.

References: (*a*) Ref. 7; (*b*) Ref. 14; (*c*) Kenner and Statham, *Ber.*, 1936, **69**, 16; (*d*) Ruheman and Watson, *J.*, 1904, **85**, 1179; (*e*) Ref. 4.

and by the poor-to-moderate yields obtained (10—40% in our instances) in the arylation step. 1-Phenyl-2-pyrazoline can be obtained [7] in poor yield from acraldehyde and phenylhydrazine and we prepared the *p*-chloro-compound in a similar way, but the synthesis of higher-molecular-weight analogues is impeded by the need for steam-distillation owing to substantial amounts of resinous by-products. Limited attempts to develop alternative syntheses were unsuccessful. Reduction of 1-phenylpyrazole with sodium in ethanol [8] gave some 1-phenyl-2-pyrazoline together with other reduction products and unchanged pyrazole. Attempts to reduce the pyrazole catalytically failed, although Thoms and Schnupp [9] have reported that this pyrazole could be hydrogenated to the pyrazolidine in the presence of palladium on barium sulphate and that the uptake showed a break at one molecule of hydrogen. The arylation stage was somewhat improved by the introduction into the work-up of a reduction step so that the simultaneously formed azo-dyes (presumably 3-arylazo-derivatives) could be removed as amines by acid-washing, the 1,3-diaryl-2-pyrazolines being only very weakly basic.

1,3-Diphenyl-2-pyrazolines bearing substituents at the 5-position were readily prepared in high yield by 1,3-addition.[5] Thus acrylonitrile, methyl acrylate, n-dodec-1-ene, and allyl bromide reacted with ω-chlorobenzaldehyde phenylhydrazone (II) and triethylamine in benzene at room temperature to give 5-cyano-, 5-methoxycarbonyl-, 5-n-decyl-, and 5-bromomethyl-1,3-diphenyl-2-pyrazoline, respectively. Each product appeared to be a

[7] Fischer and Knoevenagel, *Annalen*, 1887, **239**, 196.
[8] Balbiano, *Gazzetta*, 1888, **18**, 358.
[9] Thoms and Schnupp, *Annalen*, 1923, **434**, 305.

single substance, and substituents were assigned the 5- rather than the 4-position by analogy with related authenticated examples.[5] The last of these with pyridine gave (1,3-diphenyl-2-pyrazolin-5-yl)methylpyridinium bromide. 1,3-Diaryl-2-pyrazolines substituted at position 4 with a single substituent are readily available (*e.g.*, from propiophenones) but those with 4,4-dialkyl groups, an example of which we required for a special study, are clearly not accessible through any reaction involving an olefinic intermediate. Furthermore, the corresponding Mannich base (the phenylhydrazone of which could conceivably undergo ring-closure by direct elimination of secondary amine, *i.e.*, not involving an olefinic intermediate) did not seem promising, since isobutyrophenone is reported [10] not to give a Mannich base even under vigorous conditions. The most hopeful approach seemed to be through a 1-aryl-4,4-dimethyl-2-pyrazoline, the only recorded example of which appeared to be *p*-(4,4-dimethyl-2-pyrazolin-1-yl)benzoic acid, prepared [11] by briefly heating the *p*-carboxyphenylhydrazone of β-hydroxypivalaldehyde in glacial acetic acid. We were unable to repeat this ring-closure, the hydrazone being recovered in good yield. When, however, the same hydroxy-aldehyde was converted to its toluene-*p*-sulphonate and treated with phenylhydrazine in ethanolic alkali, 4,4-dimethyl-1-phenyl-2-pyrazoline was obtained in 43% yield. Alkyl migrations are not unlikely in such neopentyl systems but the n.m.r. spectrum fully supports the proposed structure. When the condensation was carried out under " neutral " (no added alkali) or mildly acid conditions by-products were formed, one of which, from n.m.r. evidence, appeared to be the 5,5-dimethyl analogue. The shift of one alkyl group had seemed *a priori* more likely but the shift of both could conceivably be due to an intermediate phenylazocyclopropane. Coupling of the dimethylpyrazoline with diazotised *p*-chloraniline gave, though in low yield, the 3-*p*-chlorophenyl derivative, which appears to be the only known example of a 1,3-diarylpyrazoline bearing a gem-dialkyl group in the 4-position, although the more accessible 5,5-dialkyl analogues are recorded in several instances.

The condensation of phenylhydrazine and acrylonitrile led under appropriate conditions either [4,12] to 3- or [13] to 5-amino-1-phenyl-2-pyrazoline. Somewhat surprisingly, the former gave, with benzoic anhydride in pyridine or with benzoyl chloride under Schotten–Baumann conditions, a dibenzoyl derivative. We did not determine whether both acyl groups were attached to the same nitrogen atom. By contrast, acetylation of the amine gave only a monoacetate.[4]

The pyrazoline (m. p. 91—92°) derived from α-acetonaphthone, presumably the 3-α-naphthyl-1-phenyl derivative, did not correspond to that (m. p. 167—168°) recorded by Mayer and Müller [14] from their supposed 2-chloroethyl α-naphthyl ketone, and their product may have been a mixture of α- and β-isomers. The Mannich bases derived from α-hydrindone and α-tetralone led to the interesting bridged structures, 2,3,3a,4-tetrahydro-2-phenylindeno[1,2-*c*]pyrazole (IIIa) and 3,3a,4,5-tetrahydro-2-phenyl-2*H*-benz[*g*]indazole (IIIb), respectively.

In view of the success of certain fluorescent agents containing the benzimidazole group [15] it was of interest to prepare examples of benzimidazolylpyrazolines. Lactic acid and *N*-methyl-*o*-phenylenediamine were condensed in acid conditions [16] to give 2-α-hydroxyethyl-1-methylbenzimidazole which was oxidised to the ketone and treated with benzaldehyde to give 2-cinnamoyl-1-methylbenzimidazole. Reaction with phenylhydrazine then gave 3-(1-methylbenzimidazol-2-yl)-1,5-diphenyl-2-pyrazoline. Condensation of benzimidazole-2-aldehyde with acetophenone gave the unsaturated ketone, which with phenylhydrazine afforded 5-(benzimidazol-2-yl)-1,3-diphenyl-2-pyrazoline. The required

[10] Winstein, Jacobs, Seymour, and Linden, *J. Org. Chem.*, 1946, **11**, 215.
[11] Veibel, *Acta Chem. Scand.*, 1947, **1**, 67.
[12] Zaretskii, U.S.S.R.P. 113,120; Pietra, *Boll. sci. Fac. Chim. ind. Bologna*, 1953, **11**, 78.
[13] Schmidt and Druey, *Helv. Chim. Acta*, 1958, **41**, 306.
[14] Mayer and Müller, *Ber.*, 1927, **60**, 2278.
[15] *E.g.*, B.P. 861,431.
[16] Phillips, *J.*, 1929, 2826.

benzimidazole-2-aldehyde was conveniently made by condensing *o*-phenylenediamine with tartaric acid to give 1,3-bis(benzimidazol-2-yl)ethane-1,2-diol, followed by oxidation of the diol with sodium metaperiodate. 1-Methylbenzimidazole-2-aldehyde was similarly prepared.

Experimental

All figures for percentage compositions (" calculated " and " required ") were obtained on an IBM 1620 computer.

Preparation of Mannich Bases.—β-Dimethylaminopropiophenone hydrochloride, m. p. 155—157°, was prepared according to Maxwell.[17] The following analogues were similarly prepared from the appropriate acetophenone, paraformaldehyde, and dimethylamine hydrochloride: *p*-Cl, m. p. 173—174° (lit.,[18] 174—175°); *p*-Me, m. p. 165—166° (lit.,[19,20] 158—159°, 168°); *p*-MeO, m. p. 178—179° (lit.,[21] 181°); *o*-HO, m. p. 174—175° (lit.,[22,23] 156°, 176°); *p*-HO, m. p. 191—192° (lit.,[24] 192°); *p*-Ph, m. p. 183—185° (lit.,[25,22] 176—177°, 192°); 3,4-Cl_2, m. p. 193—194° (Found: N, 4·7. $C_{11}H_{14}Cl_3NO$ requires N, 5·0%).

The following were also prepared: 2-dimethylaminoethyl α-naphthyl ketone hydrochloride, m. p. 153—155° (lit.,[26] 156·8—158·1°); 2-dimethylaminomethyl-1-tetralone hydrochloride, m. p. 149—151° (lit.,[27,28] 144°, 158—159°); 2-morpholinomethylindan-1-one hydrochloride, m. p. 161—162° (lit.,[29] 162°).

Preparation of β-Chloro-ketones.—β-Chloro-3,4-dimethoxypropiophenone (m. p. 113—114°) and 4,β-dichloropropiophenone (m. p. 49—50°) were prepared by a Friedel–Crafts reaction from β-chloropropionyl chloride, aluminium trichloride (1·1 mol.), and the appropriately substituted benzene.

Preparation of α,β-Unsaturated Ketones.—(*a*) *2-Benzimidazol-2-ylvinyl phenyl ketone.* To benzimidazole-2-aldehyde (7·3 g.) and acetophenone (6 g.) in methanol (100 ml.) was added aqueous sodium hydroxide (4 g. in 10 ml.). The mixture was shaken until the reactants had dissolved, kept overnight at room temperature, and made just acid with glacial acetic acid. The vinyl ketone was filtered off, washed with water, and recrystallised from ethanol (62%), m. p. 159—160° (lit.,[30] 159—160°). The required benzimidazole-2-aldehyde was initially prepared (cf. ref. 31) by oxidation of 2-arabitylbenzimidazole [32] with sodium metaperiodate but the following modification proved more convenient and economical. A mixture of (+)-tartaric acid (150 g.), *o*-phenylenediamine (216 g.) and 40% sulphuric acid (1 l.) was boiled under reflux for 18 hr., cooled, and filtered. The sulphate of 1,2-di(benzimidazol-2-yl)ethane-1,2-diol was washed with water and with ethanol, suspended in water, and converted into the base (140 g., 48%) with aqueous ammonia (Found: C, 65·4; H, 5·0; N, 18·9. Calc. for $C_{16}H_{14}N_4O_2$: C, 65·3; H, 4·8; N, 19·1%). The compound showed no definite m. p. [lit.,[33] 245° (decomp.)]. Oxidation of the diol with periodate (1·0 mol.) gave benzimidazole-2-aldehyde (74%, m. p. 233—237°) identical to that obtained from 2-glucosylbenzimidazole. The oxime (Found: N, 26·0. Calc. for $C_8H_7N_3O$: N, 26·1%) had m. p. 213—214° (lit.,[31] 215°). Methylation of the above diol with dimethyl sulphate in aqueous ethanolic alkali, followed by periodate oxidation, gave 1-methylbenzimidazole-2-aldehyde, m. p. 120—121° (lit.,[30] 121°) (Found: C, 67·6; H, 5·2; N, 17·4. Calc. for $C_9H_8N_2O$: C, 67·5; H, 5·0; N, 17·5%).

(*b*) *1-Methyl-2-benzimidazolyl styryl ketone.* Condensation of *N*-methyl-*o*-phenylenediamine and lactic acid by the method of Phillips [16] gave 2-1′-hydroxyethyl-1-methylbenzimidazole, m. p.

[17] Maxwell, *Org. Synth.*, Coll. Vol. III, p. 305.
[18] Adamson and Billinghurst, *J.*, 1950, 1039.
[19] Kost and Ershov, *Zhur. obshchei Khim.*, 1957, **27**, 1155.
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[28] G.P. 514,418.
[29] Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 284.
[30] B.P. 874,209.
[31] Huebner, Lohmar, Dimler, Moore, and Link, *J. Biol. Chem.*, 1945, **159**, 503.
[32] Moore and Link, *J. Org. Chem.*, 1940, **5**, 637.
[33] Wang and Joulié, *J. Amer. Chem. Soc.*, 1957, **79**, 5706.

82—83° (lit.,[16] 80°), which on oxidation with chromium trioxide as described [34] for the α-hydroxybenzyl analogue gave 2-*acetyl*-1-*methylbenzimidazole*, m. p. 75—76° (Found: N, 16·2. $C_{10}H_{10}N_2O$ requires N, 16·1%). The *oxime* had m. p. 219—220° (Found: C, 63·5; H, 5·9. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·8%). To the ketone (8·7 g.) and benzaldehyde (5·3 g.) in methanol (50 ml.) were added a few drops of 20% aqueous sodium hydroxide. After being kept overnight, the mixture was neutralised with acetic acid and the crude benzimidazol-2-yl styryl ketone condensed with phenylhydrazine.

(*c*) *Distyryl ketone.* This was prepared according to Conard and Dolliver's method.[35]

Phenylhydrazines.—These were either bought or prepared by reduction of the appropriate diazonium salt with stannous chloride.

Formation of Pyrazolines.—(*a*) *From Mannich bases.* The Mannich base hydrochloride (0·01 mol.), the phenylhydrazine (0·012 mol.), and sodium hydroxide (*ca.* 0·012 mol.) in 40% aqueous ethanol (25 ml.) were boiled under reflux for 2—3 hr. The pyrazoline normally crystallised during the reaction or on cooling and was filtered off, washed with a little aqueous alcohol, and recrystallised. When the phenylhydrazine was employed as its hydrochloride a further equivalent of base was used. Yields were 50—75% of recrystallised material.

(*b*) *From β-chloro-ketones.* The following is typical: 4,β-Dichloropropiophenone (7·5 g.), *p*-nitrophenylhydrazine (6 g.), and pyridine (20 ml.) in ethanol (100 ml.) were boiled under reflux for reflux for 4 hr. The pyrazoline (7·0 g.) separated on cooling and had m. p. 184—186°, raised to 189—190° on recrystallisation from ethanolic chloroform.

(*c*) *From αβ-unsaturated ketones.* The ketone and phenylhydrazine (1·2 equiv.) in ethanol containing a few drops of conc. hydrochloric acid were boiled under reflux for 2 hr.

(*d*) *By 1,3-dipolar addition.* The method is basically that of Huisgen [5] and his co-workers. To ω-chlorobenzaldehyde phenylhydrazone (2·3 g., 0·01 mol.) in benzene (40 ml.) was added triethylamine (3 ml., 0·03 mol.) followed by the olefinic compound (0·05 mol.). After 2 hr. at room temperature the mixture was filtered and the filtrate evaporated to dryness under reduced pressure; the residue was recrystallised from aqueous ethanol. Yields were 50—85% (calc. from phenylhydrazone).

(*e*) *By the arylation of 1-phenyl-2-pyrazolines with diazonium salts.* (i) Preparation of 1-phenyl-2-pyrazolines. 1-Phenyl- [7] and 1-*p*-chlorophenyl-2-pyrazoline were prepared in low (20—25%) yield from acraldehyde and the phenylhydrazine. Steam-distillation from acid solution was essential in both cases to achieve separation from resinous by-products. 4,4-Dimethyl-1-phenyl-2-pyrazoline was made as follows. To β-hydroxypivalaldehyde [36] (63 g.) in dry pyridine (200 ml.) was added toluene-*p*-sulphonyl chloride (130 g., 1·1 mol.) and the mixture kept at room temperature overnight. The toluene-*p*-sulphonate (128 g., 81%), isolated in the usual way, was obtained as a straw-coloured viscous oil which decomposed on attempted distillation. To the ester (36 g.) in ethanol (75 ml.) was added aqueous sodium hydroxide (9 g. in 40 ml.) followed by phenylhydrazine (36 g.). The mixture was heated under reflux for 3 hr., made slightly acid with N-sulphuric acid and steam-distilled. Extraction of the distillate (5 l.) with ether followed by evaporation of the dried extract gave the crude *pyrazoline* (10 g., 43%) which on distillation gave pure material (6·6 g.), b. p. 108—111°/1 mm., n_D^{20} 1·5722.

The n.m.r. spectrum (*ca.* 1·2M in CCl_4) showed single-line absorptions at τ values of 8·85, 6·65, and 3·60 p.p.m., in the ratio 6 : 2 : 1, attributable to the $-CH_2{\cdot}CH_2-$, $-CH_2-$, and $-CH=$ protons of the pyrazoline ring respectively. The phenyl-proton resonance was spin-coupled in a complex manner and appeared between 2·50 and 3·50 p.p.m.

The use of the ester with phenylhydrazine (2·4 mol.) in ethanol in the absence of alkali gave, in similar yield, a product A (b. p. 100—104°/1 mm., n_D^{23} 1·5736). A similar reaction using 50% aqueous acetic acid as solvent gave a product B (b. p. 110—114°/1·2 mm., n_D^{23} 1·5739). The n.m.r. spectrum of product A showed peaks centred at the following τ values additional to those of the pure 4,4-dimethylpyrazoline: 8·70 p.p.m. (singlet), 7·35 p.p.m. (doublet) in the intensity ratio of 3 : 1, together with a weak triplet at 3·49 p.p.m. These are tentatively attributed to the presence of about 25% of the isomeric 5,5-dimethyl-1-phenyl-2-pyrazoline. Product B showed bands due to a similar impurity (*ca.* 15%), together with a strong peak at 7·86 which was barely detectable in A.

(ii) Arylation of 1-phenyl-2-pyrazolines. The method is essentially that of Duffin and

[34] Bistrzycki and Przeworski, *Ber.*, 1912, **45**, 3492.
[35] Conard and Dolliver, *Org. Synth.*, Coll. Vol. II, p. 167.
[36] Stiller, Harris, Finkelstein, and Keresztesy, *J. Amer. Chem. Soc.*, 1940, **62**, 1787.

Kendall,[4] but the use of a reduction stage (where possible) during the work-up to remove azo-compounds facilitated isolation of the product. Thus *p*-chloroaniline (6·4 g.) was diazotised in 5N-hydrochloric acid with sodium nitrite (3·75 g.) and added dropwise to a stirred solution of 4,4-dimethyl-1-phenyl-2-pyrazoline (9 g.) in 3% ethanolic sodium hydroxide (50 ml.) at 0—5°. The mixture was stirred for a further 10 min. at 5—10°, poured into water (500 ml.) and extracted with chloroform. To the residue after evaporation of the water-washed extracts was added ethanol (20 ml.), 5N-hydrochloric acid (40 ml.) and stannous chloride (20 g.) and the mixture boiled under reflux for 10 min. The neutral organic fraction was chromatographed on alumina to give, on elution with light petroleum (60—80°)/benzene (19 : 1), 3-*p*-chlorophenyl-4,4-dimethyl-1-phenyl-2-pyrazoline as pale yellow needles (1·5 g.), m. p. 109—110°. Yields of 1,3-diaryl-2-pyrazolines from the coupling of 1-phenyl- or 1-*p*-chlorophenyl-2-pyrazoline were somewhat higher (20—40%).

(*f*) *Miscellaneous methods.* (i) The acetate and benzoate of 3-*p*-hydroxyphenyl-1-phenyl-2-pyrazoline were prepared by conventional acylation of the hydroxypyrazoline. (ii) 3-Amino-1-phenyl-2-pyrazoline, prepared [4] from phenylhydrazine and acrylonitrile in ethanolic alkali, titrated as a mono-acidic base (perchloric acid in acetic acid) and gave a benzylidene derivative, m. p. 197° (from ethanol), but m. p. 170° (from dioxan). Duffin and Kendall record m. p. 182° (from dioxan). The aminopyrazoline with benzoic anhydride (1 mol.) in refluxing pyridine gave the dibenzoyl derivative (Table 2), and the same compound was isolated when a mixture of the amine and benzoyl chloride in acetone was shaken with portions of aqueous alkali. (iii) The isomeric 5-amino-1-phenyl-2-pyrazoline was prepared [13] from phenylhydrazine *via* *N*-2-cyanoethyl-*N'*-phenylhydrazine. The free amine proved unstable and readily eliminated ammonia on storage. The hydrochloride, m. p. 234—235° (lit., 236—238°) was stable. (iv) (1,3-Diphenyl-2-pyrazolin-5-yl)methylpyridinium bromide. 5-Bromomethyl-1,3-diphenyl-2-pyrazoline (1 g.) in pyridine (5 ml.) was boiled under reflux for 2 hr., cooled, and diluted with ether. Recrystallisation from ethanol/ether gave the pure pyridinium salt, m. p. 218—219°. (v) Methyl 4-(3-*p*-chlorophenyl-2-pyrazolin-1-yl)benzenesulphonate. The sodium salt (1 g.) was dissolved in cold water (100 ml.) and concentrated hydrochloric acid (50 ml.) added. The acid (m. p. 126°) was filtered off and recrystallised from N-hydrochloric acid to give pure material (0·6 g., 64%), m. p. 130—131°. To the acid (1·7 g.) suspended in chloroform (50 ml.) was added excess of diazomethane in ether (750 ml.) at 0°. The mixture was kept overnight at room temperature, warmed to 50° for 5 min., and acetic acid added to destroy residual diazomethane. Evaporation of the solvent and recrystallisation of the residue from ethanol gave the methyl ester (1·08 g., 60%), m. p. 188—189°.

Attempted Reduction of Pyrazoles and Pyrazolones.—1-Phenylpyrazole was prepared by a similar method to that described [37] for 1-2'-hydroxyethylpyrazole. Phenylhydrazine (18·8 g., 0·174 mol.) and concentrated hydrochloric acid (32·5 ml.) were mixed and cooled. 1,1,3-Triethoxy-3-methoxypropane (35·5 g., 0·174 mol.) in ethanol (35 ml.) was added and the mixture boiled under reflux for 1 hr., cooled, and taken up in ether. After being washed with aqueous sodium carbonate, with 2N-hydrochloric acid, and with water, the ethereal solution was evaporated and the residue distilled under reduced pressure. 1-Phenylpyrazole (15·2 g., 60%) was collected as the main fraction, b. p. 125—128°/17 mm. The acetoxymercury derivative had m. p. 190—191° (lit.,[38] 191°).

Reduction of the pyrazole (5 g.) with sodium (5 g.) in ethanol (70 ml.) (cf. Balbiano [8]) gave a basic fraction (not examined), 1-phenylpyrazoline (1·7 g., 34%) (volatile in steam), and 1-phenylpyrazole (1·1 g., 22%). No hydrogen was taken up when the pyrazole in glacial acetic acid was shaken in an atmosphere of hydrogen in the presence of 5% palladium on barium sulphate, 5% palladium–charcoal, or platinum black.

Only starting material could be isolated after an attempted reduction of 1,3-diphenylpyrazol-5-one (2·4 g.) with lithium aluminium hydride (0·5 g.) in dry tetrahydrofuran (24 hr. under reflux).

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