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Systemic Fungicides. The Synthesis of Certain Pyrazole Analogues of Carboxin

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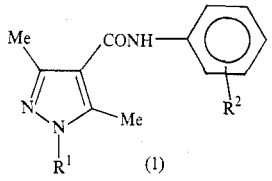
Abstract

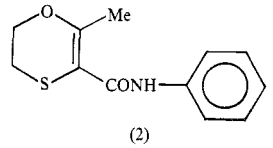
Methods are described for the synthesis of 1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide (3) and the isomeric 1,5-dimethyl compound (4), structural analogues of the systemic fungicide carboxin. Evidence confirming the structural assignment of the compounds is presented, and a convenient method for the removal of the amino group from some aminopyrazoles is described.

Introduction

The fungicidal activity of a series of pyrazole derivatives (1), structurally related to the commercially important systemic fungicide carboxin (2), was reported in 1976.[1]



(1)



(2)

Certain of these pyrazoles, e.g., (1; R^1 = Me, R^2 = H; R^1 = Me, R^2 = 3-Me), showed systemic antifungal activity of the same order as did carboxin against wheat and broad bean rusts, although this activity was generally accompanied by higher levels of phytotoxicity.[1] Further research in this area has shown that these compounds provide useful control of bunt and smuts, as well as rust, in cereals. They are comparable to the best commercially available materials for the control of damping-off (*Rhizoctonia solani*) in cotton seedlings.[2]

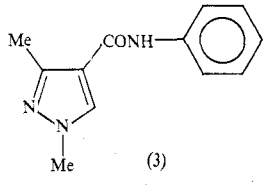
To provide further information on structure–activity relationships within the pyrazole series, we were anxious to obtain compounds of the type (1; R^1 = Me, R^2 = H), in which one of the methyl groups flanking the anilide group had been removed, i.e., compounds (3) and (4).

[1] Carter, G. A., Huppatz, J. L., and Wain, R. L., *Ann. Appl. Biol.*, 1976, **84**, 333.
[2] Huppatz, J. L., Phillips, J. N., and Witrzens, B., *Plant Disease*, 1983, **67**, 45.

Results and Discussion

The Synthesis of Anilide (3) and its Analogues

Our initial approach to the pyrazole (3) involved, as starting material, 1,3-dimethylpyrazolin-5-one (5), which was obtained from ethyl acetoacetate and methylhydrazine.[3] With phenyl isocyanate in the presence of triethylamine,[1] compound (5) gave the corresponding 4-anilide (6). As with the pyrazolin-5-one (5),[4] the anilide (6) is capable of existing in other tautomeric forms. In fact, the ^{1}H n.m.r. spectrum [$(CD_3)_2SO$] indicates that, at least in polar media, the anilide exists in either the NH (6a) or OH (6b) form.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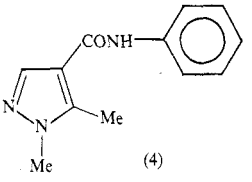
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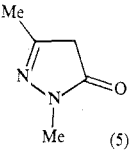
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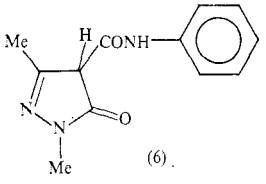
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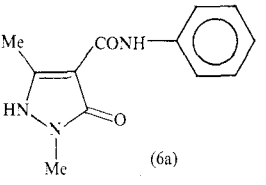
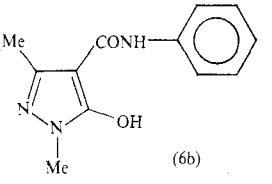

(6a)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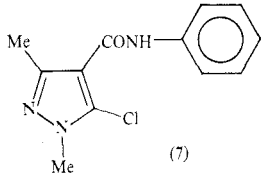
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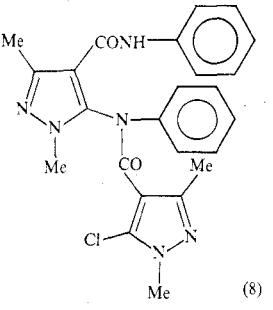
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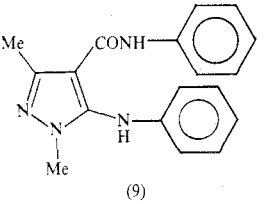
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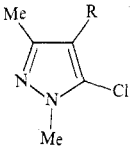
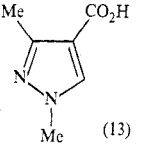

(10) R = CO_2H
(11) R = CHO
(12) R = CO_2Et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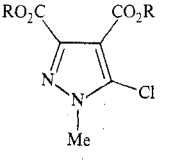

(14) R = H
(15) R = Et

Reaction with phosphoryl chloride was then expected to give the 5-chloro compound (7). Although this compound was readily isolated from the reaction mixture, the yield was only moderate (30–50%). When the residue was examined by column chromatography, the major by-product of the reaction was found to be a high-molecular-weight compound, obviously resulting from self-condensation during the

[3] Auwers, K. von, *J. Prakt. Chem.*, 1925, **110**[2], 182.
[4] Katritzky, A. R., and Maine, F. W., *Tetrahedron*, 1964, **20**, 299.

reaction. The structure (8) of this product followed from its analytical and spectral data, and from the nature of the products obtained on its hydrolysis. Elemental analysis was consistent with a molecular formula of $C_{24}H_{23}ClN_6O_2$, and the mass spectrum showed a molecular ion at m/z 462 and fragmentations consistent with the assigned structure. The ^1H n.m.r. spectrum showed two NMe singlets and two CMe singlets. Hydrolysis with sodium hydroxide in aqueous ethanolic solution produced two readily separable products. The first, a neutral compound which precipitated from the basic reaction medium, showed analytical and spectral data consistent with those required for the 5-anilinopyrazole (9). The second product, isolated on acidification of the basic solution obtained after removal of compound (9), contained a chlorine atom but no aryl group. This compound proved identical to authentic 5-chloro-1,3-dimethylpyrazole-4-carboxylic acid (10), prepared by an alternative route (see below).

Self-condensation reactions in the presence of phosphoryl chloride are not unusual[5] and have been observed previously with pyrazole derivatives.[6] However, in the present case, it is difficult to visualize the mechanism of the reaction, since the formation of compound (8) appears to involve nucleophilic displacement of a relatively unreactive chlorine atom (or phosphorus-containing precursor group). Moreover, prolonged boiling with phosphoryl chloride indicated that, once formed, the chloro compound (7) was inert to the action of the reagent. This observation implies that both compounds (7) and (8) may be formed from a common intermediate.

Reaction of the pyrazolin-5-one (6) with phosphoryl chloride was carried out under a variety of conditions in an attempt to increase the yield of the chloro compound (7) and to suppress formation of the by-product. The use of a solvent (chloroform or toluene) proved ineffective as little or no reaction occurred. Addition of phosphorus pentachloride to the phosphoryl chloride failed to increase the yield. However, diethylaniline in phosphoryl chloride, a reagent commonly used in pyrimidine chemistry to effect chlorination,[7] resulted in a 70% yield of the chloro compound (7) without concomitant formation of the self-condensation product (8).

Removal of the chlorine substituent from (7) by catalytic hydrogenolysis completed the synthesis of the anilide (3).

Unavailability of some substituted phenyl isocyanates and limitations imposed by the final hydrogenation step restricted the range of substituents which could be incorporated into derivatives of the anilide (3). To overcome these shortcomings, an alternative route to the anilide (3) was investigated. The pyrazolin-5-one (5) was formylated according to the method of Porai-Koshits and coworkers.[8] The product, the pyrazole-4-carbaldehyde (11), was then oxidized with alkaline potassium permanganate to the corresponding acid (10).[8] Oxidation of the aldehyde (11) was dependent on the temperature of the reaction. A crude sample of the acid (10), prepared by oxidation of the aldehyde (11) in refluxing alkaline potassium permanganate, was esterified. The crude product was distilled under vacuum to give 70%

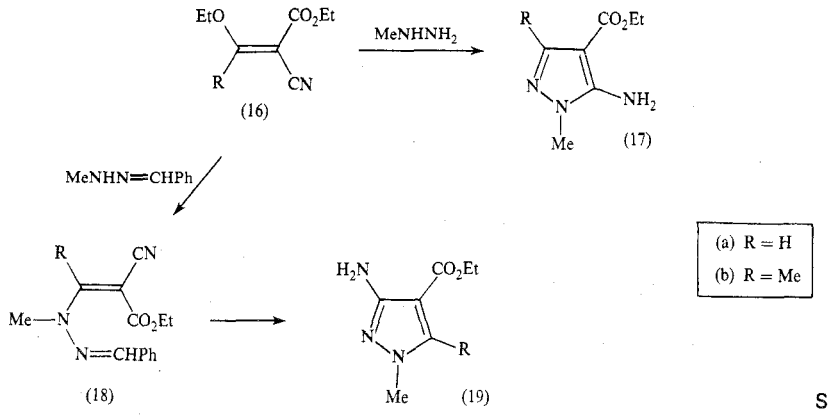
[5] Cossey, A. L., Harris, R. L. N., Huppatz, J. L., and Phillips, J. N., *Aust. J. Chem.*, 1976, **29**, 1039; Harris, R. L. N., Huppatz, J. L., and Phillips, J. N., *Aust. J. Chem.*, 1977, **30**, 2213.

[6] Plescia, S., Daidone, G., Sprio, V., Aiello, E., Dattolo, G., and Cirrincione, G., *J. Heterocycl. Chem.*, 1978, **15**, 1339.

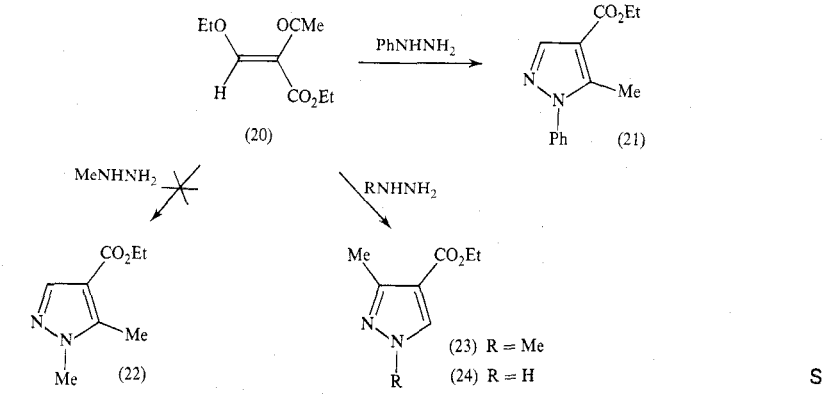
[7] Brown, D. J., 'The Pyrimidines' p. 163 (Interscience: New York 1962).

[8] Porai-Koshits, B. A., Kvitko, I. Ya., and Shutkova, E. A., *Khim.-Farm. Zh.*, 1970, **4**, 19 (*Chem. Abstr.*, 1970, **73**, 3844).

of the expected ester (12). The residue gave a second, higher-boiling product (13%), which was shown by ^{1}H n.m.r. to contain no *C*-methyl substituent but two ethyl ester groups. Obviously, the conditions used in the oxidation had resulted in the formation of about 15% of the diacid (14), which was then converted into the diester (15) on esterification. The yield of the pure acid (10) was optimized by holding the temperature of the oxidation reaction at 60° for 1 h. Catalytic hydrogenation readily removed the chlorine atom from compound (10), affording the carboxylic acid (13). By conversion into the acid chloride, followed by reaction with the appropriate aniline derivative, this compound was used to prepare a number of substituted anilides related to compound (3).



Scheme 1



Scheme 2

The Synthesis of Anilide (4) and its Analogues

The work of Schmidt and coworkers[9] offered an attractive approach to the isomeric anilide (4). Schmidt *et al.* prepared the aminopyrazoles (17a) and (19a) by the reaction sequences outlined in Scheme 1. Reaction of ethyl 2-cyano-3-ethoxyacrylate (16a) with methylhydrazine (the reaction appears to be general for alkyl- or aryl-hydra-

[9] Schmidt, P., Eichenberger, K., Wilhelm, M., and Druey, J., *Helv. Chim. Acta*, 1959, **42**, 349.

zines[10]) gave the 5-aminopyrazole (17a), whereas reaction with the appropriate hydrazone, followed by acid hydrolysis of the intermediate (18a), gave the isomeric 3-aminopyrazole (19a).[9]

Success of a similar approach with ethyl ethoxymethyleneacetoacetate (20) seemed assured, particularly as phenylhydrazine was reported to react with the ethoxymethylene compound (20) to give ethyl 5-methyl-1-phenylpyrazole-4-carboxylate (21)[11] (Scheme 2). Surprisingly, reaction of methylhydrazine with compound (20) gave the pyrazole (23) as major product. The ^{1}H n.m.r. spectrum was identical with that of a sample of compound (23) obtained by dehalogenation of the chloro compound (12). However, minor signals in the spectrum of the crude product indicated the presence of 5–10% of the isomeric pyrazole (22).

Reaction of ethyl ethoxymethyleneacetoacetate (20) with methylhydrazine provides another example (cf.[12,13]) of a condensation in which the effect of electronic and steric factors is difficult to evaluate; consequently, structural assignment of the product is uncertain. Studies of the reaction of alkyl- and aryl-hydrazines with ethyl 2-cyano-3-ethoxyacrylate (16a) indicate that condensation is initiated by conjugate addition of the unsubstituted nitrogen atom of the hydrazine to the substrate.[9,10] Reaction with ethyl ethoxymethyleneacetoacetate (20), on the other hand, conforms with the prediction[14] that initial conjugate addition by the more nucleophilic, substituted nitrogen atom of methylhydrazine would be preferred. Problems in identifying isomeric *N*-alkylpyrazoles have often arisen, e.g. the products obtained from the reaction of methylhydrazine with tetracyanoethylene,[14–17] and of ethyl hydrazinoacetate with 1-ethoxy-2-phenylbut-1-en-3-one[12] and benzoylacetonitrile.[13] Hence, there is a need for caution in assigning structure where ambiguity is possible.

An attempt to obtain compound (22) by direct *N*-methylation was then made. The ethoxymethylene compound (20) and hydrazine hydrate reacted smoothly to give ethyl 3(5)-methylpyrazole-4-carboxylate (24). Methylation of this compound with methyl iodide in the presence of sodium ethoxide gave a mixture of the isomeric pyrazoles (22) and (23) in the approximate ratio 1 : 1. Careful fractional distillation failed to achieve any significant separation of the isomeric mixture. This result is in accord with literature experience, since it has consistently proved both difficult and tedious to separate isomeric mixtures of pyrazole derivatives.

The reaction sequence shown in Scheme 1 offered an alternative route to the isomers (22) and (23). The cyanoethoxycrotonate (16b), readily prepared by the reaction of triethyl orthoacetate with ethyl cyanoacetate, reacted smoothly with methylhydrazine to give the 5-aminopyrazole (17b). The isomeric 3-amino compound (19b) was prepared via the hydrazone (18b) according to a method similar to that of Schmidt and coworkers.[9]

[10] Schmidt, P., Eichenberger, K., and Druey, J., *Helv. Chim. Acta*, 1958, **41**, 1052; Schmidt, P., and Druey, J., *Helv. Chim. Acta*, 1956, **39**, 986.
[11] Grob, C. A., and Camenisch, K., *Helv. Chim. Acta*, 1953, **36**, 37.
[12] Moore, J. A., and Habraken, C. L., *J. Org. Chem.*, 1965, **30**, 1889.
[13] Elnagdi, M. H., Hafez, E. A. A., El-Fahham, H. A., and Kandeel, E. M., *J. Heterocycl. Chem.*, 1980, **17**, 73.
[14] Dickinson, C. L., Williams, J. K., and McKusick, B. C., *J. Org. Chem.*, 1964, **29**, 1919.
[15] Hecht, S. M., and Werner, D., *J. Chem. Soc., Perkin Trans. 1*, 1973, 1903.
[16] Hecht, S. M., Werner, D., and Traficante, D. D., *J. Org. Chem.*, 1975, **40**, 1815.
[17] Earl, R. A., Pugmire, R. J., Revankar, G. R., and Townsend, L. B., *J. Org. Chem.*, 1975, **40**, 1882.

Deamination of the 5-aminopyrazole (17b) by diazotization in acetic acid/concentrated sulfuric acid, followed by decomposition of the diazonium salt with copper powder, gave the ester (23), identical with the product obtained by other routes described above. Similarly, deamination of the 3-amino compound (19b) afforded the required isomeric pyrazole ester (22). This compound was then converted via the corresponding acid and acid chloride into the anilide (4). Some related substituted anilides are also described in the Experimental section.

Comments on Deaminations

The method used for the deamination of compounds (17b) and (19b) requires some further comment. The long-established procedures for the deamination of aromatic amines, involving reduction of the corresponding diazonium salt with, most commonly, ethanol or hypophosphorous acid,[18] have been supplemented by more recent methods involving reduction of stable diazonium salts[19–23] and a method involving use of alkyl nitrites.[24] These methods are not without disadvantages; some are two-step procedures,[19,20,22] whereas others employ exotic reagents.[21,23]

The formation of low yields of deaminated material, together with the expected cyclization products, from the copper-catalysed decomposition of diazonium salts derived from certain *N*-benzyl-*o*-phenylenediamines,[25] suggested that deamination could be dominant if competing cyclization reactions were no longer possible. Reactions in the acetic acid/sulfuric acid medium used were generally efficient and free from the by-products typically associated with diazonium salt decompositions.[25,26] Accordingly, the 5-aminopyrazole (17b) was diazotized in the mixed-acid medium, and the diazonium salt decomposed with freshly prepared copper. Simple workup gave the deaminated compound (23) in 94% yield. Similarly, the isomeric 3-aminopyrazole (19b) deaminated smoothly to form compound (22), although the yield (80%) was somewhat lower.

Deamination of the aminopyrazole (17a) gave ethyl 1-methylpyrazole-4-carboxylate in almost quantitative yield. Pyrazoles bearing an ester substituent in position 4 are not readily accessible,[27] and Schmidt's synthesis (Scheme 1), followed by deamination, would appear to be the method of choice for the preparation of these compounds. The use of the copper-catalysed deamination reaction thus provides a useful, high-yielding alternative to established procedures. It may well provide a particularly attractive method for amines which are difficult to diazotize in aqueous media.

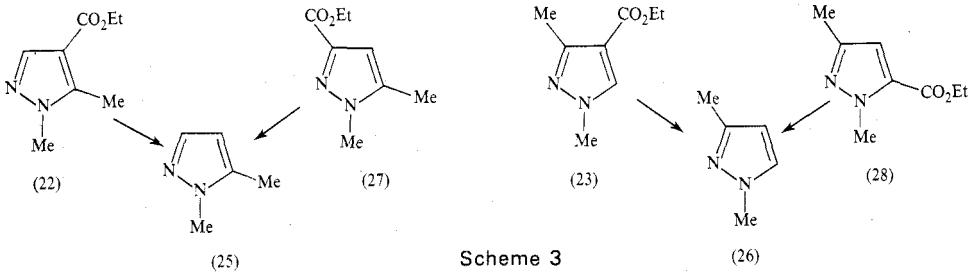
Confirmation of Structures

Although the structures of compounds (3) and (4) follow from assignments accepted in the literature, an element of uncertainty, which has beset attempts to assign unambiguous structures to the *N*-alkyl derivatives of unsymmetrical pyrazoles, still exists.

[18] Kornblum, N., *Org. React.*, 1944, **2**, 262.
[19] Hendrickson, J. B., *J. Am. Chem. Soc.*, 1961, **83**, 1251.
[20] Rutherford, K. G., and Redmond, W. A., *J. Org. Chem.*, 1963, **28**, 569.
[21] Nakayama, J., Yoshida, M., and Simamura, O., *Tetrahedron*, 1970, **26**, 4609.
[22] Newman, M. S., and Hung, W. M., *J. Org. Chem.*, 1974, **39**, 1317.
[23] Katritzky, A. R., Chermprapai, A., Bravo, S., and Patel, R. C., *Tetrahedron*, 1981, **21**, 3603.
[24] Cadogan, J. I. G., and Molina, G. A., *J. Chem. Soc., Perkin Trans. 1*, 1973, 541.
[25] Huppatz, J. L., and Sasse, W. H. F., *Aust. J. Chem.*, 1963, **16**, 417.
[26] Huppatz, J. L., and Sasse, W. H. F., *Aust. J. Chem.*, 1964, **17**, 1406; 1965, **18**, 206.
[27] Jones, R. G., and Mann, M. J., *J. Am. Chem. Soc.*, 1953, **75**, 4048.

This continuing problem has been discussed in detail by Habraken and Moore,[28] who attempted to verify the earlier assignments for 1,5- (25) and 1,3-dimethylpyrazole (26) suggested by von Auwers and Hollmann[29] and by Rojahn.[30] Their approach, in common with structural assignments made herein, rested on the correct assignment of the pyrazolone (5). However, assignment of structure to the products of the reaction of methylhydrazine with a β-keto ester is subject to the same ambiguities as were discussed earlier, although formulation of the products from reactions of this type as pyrazolin-5-ones is generally accepted.[31] To provide additional evidence for the structures assigned to compounds (3) and (4), they have been related to another series of pyrazole derivatives, the structures of which follow from definitive spectral data.

Ethyl acetopyruvate and methylhydrazine reacted smoothly in ethanol to give an approximately equal mixture of the 1,5- (27) and 1,3-dimethylpyrazole (28). In this case, the isomers could be separated by careful fractional distillation. They were readily identified by comparison of their ^{1}H n.m.r. spectra with those recorded in the literature.[32] Significantly, the NMe signal in the spectrum of (28) appeared at δ 4·13, downfield with respect to the corresponding signal (δ 3·86) in the spectrum of (27); this observation indicates that the ester group is in position 5 of the former compound.



Scheme 3

Each isomer was then degraded by hydrolysis of the ester group and thermal decomposition of the resultant pyrazolecarboxylic acid (Scheme 3). The identities of the dimethylpyrazoles [(25) from (27) and (26) from (28)] were confirmed by their ^{1}H n.m.r. spectral data, which were in agreement with the literature values.[28,32] A similar degradative procedure was then applied to the ethyl pyrazole-4-carboxylates (22) and (23). The 1,5-isomer (22) produced (25), identical with the compound formed by degradation of the 3-carboxylate (27). Likewise, hydrolysis and decarboxylation of (23) gave 1,3-dimethylpyrazole (26), identical with the pyrazole obtained by degradation of (28).

The transformations described above clearly establish the relationship between the ethyl pyrazole-4-carboxylates (22) and (23) and the corresponding 5- and 3-methyl derivatives (27) and (28). Whereas ^{1}H n.m.r. spectra of the ethyl pyrazole-4-carboxylates (22) and (23) differed so little from one another that structural assignments could

[28] Habraken, C. L., and Moore, J. A., *J. Org. Chem.*, 1965, **30**, 1892.
[29] Auwers, K. von, and Hollmann, H., *Ber. Dtsch. Chem. Ges.*, 1926, **59**, 601, 1282.
[30] Rojahn, C. A., *Ber. Dtsch. Chem. Ges.*, 1926, **59**, 607.
[31] Wiley, R. H., and Wiley, P., 'Pyrazolones, Pyrazolidines and Derivatives' p. 14 (Interscience: New York 1964).
[32] Tensmeyer, L. G., and Ainsworth, C., *J. Org. Chem.*, 1966, **31**, 1878.

not be made, the relationship shown between these esters and the corresponding 5(3)-derivatives (27) and (28), respectively, clearly establishes unequivocally the structures of compounds (22) and (23).

Experimental

Analyses were performed by the Australian Microanalytical Service, Melbourne. ^{1}H n.m.r. spectra were obtained on a Varian A60-D and a Jeol FX90Q [compounds (22)–(28)] spectrometer with tetramethylsilane as internal reference and $CDCl_3$ as solvent unless otherwise stated. Melting points were determined in unsealed capillary tubes and are uncorrected.

1,3-Dimethyl-5-oxo-*N*-phenyl-4,5-dihydropyrazole-4-carboxamide (6)

1,3-Dimethylpyrazolin-5-one[3] (11·2 g) was suspended in dry benzene (100 ml) containing triethylamine (10·2 g). Phenyl isocyanate (12·0 g) was added dropwise with stirring. The mixture was protected from moisture and stirred overnight at room temperature. Water (100 ml) was added, the mixture shaken, and the aqueous layer separated (filtration through Celite was sometimes necessary at this stage to remove a small amount of insoluble material). The benzene layer was extracted with two further portions (50 ml) of water, and the combined aqueous extracts were acidified with concentrated hydrochloric acid. The mixture was chilled, and the precipitate collected and air-dried.

*1,3-Dimethyl-5-oxo-*N*-phenyl-4,5-dihydropyrazole-4-carboxamide* (18·9 g, 72%) was obtained as a colourless powder, m.p. 239–241° (Found: C, 62·1; H, 5·7; N, 18·0. $C_{12}H_{13}N_3O_2$ requires C, 62·3; H, 5·7; N, 18·2%). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·47, s, 3H, CMe; 3·38, s, 3H, NMe; 6·85–7·80, m, 5H, ArH; 10·87, s, 1H, exchangeable.

5-Chloro-1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide (7)

(*a*) *Reaction of (6) with $POCl_3$*

The following experiment was typical. The pyrazolin-5-one (6) (6·9 g) was added to phosphoryl chloride (30 ml), and the mixture boiled under reflux for 2 h. After cooling, the mixture was poured slowly into ice-water, and the product extracted with chloroform (3 × 50 ml). The chloroform extracts were washed with water, dried and evaporated. The crude product was then dissolved in hot ethanol (*c.* 50 ml), and the solution chilled. The product was collected and recrystallized from ethanol to give *5-chloro-1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide* (7) (2·7 g, 36%) as colourless needles, m.p. 150–152° (Found: C, 57·7; H, 4·9; N, 17·1. $C_{12}H_{12}ClN_3O$ requires C, 57·7; H, 4·8; N, 16·8%). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·30, s, 3H, CMe; 3·75, s, 3H, NMe; 6·80–7·73, m, 5H, ArH; 9·77, s, 1H, NH.

The mother liquors were evaporated, and the yellow, gummy residue chromatographed on a silica gel column (30 by 3 cm). With chloroform as eluent, the first fractions gave the chloropyrazole (7) (0·4 g, 5%), which, when crystallized from ethanol, had m.p. 149–152°, alone or when mixed with the material obtained above. Subsequent fractions, obtained with chloroform/ethanol (10 : 1) as eluent, gave *5-chloro-*N*-[1,3-dimethyl-4-(phenylcarbamoyl)pyrazol-5-yl]-1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide* (8) (2·0 g, 29%), colourless prisms, m.p. 138–140°, after crystallization from ethanol (Found: C, 62·0; H, 5·1; Cl, 7·6; N, 18·0. $C_{24}H_{23}ClN_6O_2$ requires C, 62·3; H, 5·0; Cl, 7·7; N, 18·2%). ^{1}H n.m.r.: δ 2·09, 2·44, s, 2 × 3H, CMe; 3·63, 3·70, s, 2 × 3H, NMe; 6·90–7·62, m, 10H, ArH; 7·88, s, 1H, NH. Mass spectrum: *m/z* 462 (M, 2%), 370 (3), 334 (3), 288 (8), 213 (5), 159 (36), 157 (100), 123 (10).

The chloropyrazole (7) (1 g) was dissolved in phosphoryl chloride (5 ml), and the solution boiled under reflux for 2 h. After workup as described above, the product was crystallized from ethanol to afford unchanged starting material (0·9 g). The mother liquor was examined by t.l.c. on silica gel plates. No trace of the self-condensation product (8) could be detected.

(*b*) *Reaction of (6) with $POCl_3$/Diethylaniline*

The pyrazolin-5-one (6) (11·5 g) was added to phosphoryl chloride (40 ml) containing diethylaniline (7·5 g). The mixture was boiled under reflux for 0·5 h and then treated as described in (*a*) above. The crude product was dissolved in boiling ethanol (100 ml), and the dark green solution set aside to crystallize. The product was collected and washed with cold ethanol to yield the chloropyrazole (7) as colourless needles (8·8 g, 70%), m.p. and m.m.p. 150–152°.

Hydrolysis of Compound (8)

A solution of compound (8) (2·3 g) in ethanol (10 ml) was heated under reflux with a solution of sodium hydroxide (4 g) in water (20 ml) for 2 h. Water (10 ml) was added and the mixture cooled slowly to 0°. The precipitated solid was collected, dried, and crystallized from ethanol. *5-Anilino-1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide* (9) was obtained as colourless needles, m.p. 177–179° (Found: C, 70·5; H, 6·0; N, 18·6. $C_{18}H_{18}N_4O$ requires C, 70·6; H, 5·9; N, 18·3%). ^{1}H n.m.r. [$(CD_3)_2SO$] δ 2·42, s, 3H, CMe; 3·58, s, 3H, NMe; 6·56–7·60, m, 10H, ArH; 8·2, s, 1H, NH; 9·2, s, 1H, NH.

The filtrate was then acidified with concentrated hydrochloric acid, and the precipitate collected and dried. After crystallization from aqueous ethanol, 5-chloro-1,3-dimethylpyrazole-4-carboxylic acid (10) was obtained as colourless needles (0·8 g, 92%), m.p. 196–198°, alone or when mixed with a sample prepared as described below.

1,3-Dimethyl-*N*-phenylpyrazole-4-carboxamide (3)

The 5-chloro compound (7) above (2·5 g) was dissolved in ethanol (50 ml) containing anhydrous sodium acetate (1 g), and hydrogenated at room temperature and 2 atm pressure with Pd/C (5%) as catalyst. The catalyst was removed by filtration through Celite and the solvent evaporated. Water (50 ml) was added to the residue and the product extracted with chloroform (3 × 25 ml). After washing with water, the extracts were dried and evaporated leaving a colourless oil which subsequently solidified. Crystallization from ethyl acetate/light petroleum (b.p. 60–80°) afforded *1,3-dimethyl-*N*-phenylpyrazole-4-carboxamide* (3) (1·95 g, 91%) as colourless prisms, m.p. 116–117° (Found: C, 66·8; H, 6·1; N, 19·5. $C_{12}H_{13}N_3O$ requires C, 66·9; H, 6·1; N, 19·5%). ^{1}H n.m.r. δ 2·54, s, 3H, CMe; 3·54, s, 3H, NMe; 6·70–7·15, m, 5H, ArH; 7·25, s, 1H, H5; 8·60, s, 1H, NH.

5-Chloro-1,3-dimethylpyrazole-4-carbaldehyde (11)

This compound was prepared from 1,3-dimethylpyrazolin-5-one (5) according to the literature procedure.[8] The crude product had m.p. 74–76°. After crystallization from light petroleum (b.p. 60–80°), it was obtained as clusters of colourless prisms, m.p. 77–78° (lit.[8] 78–79°). ^{1}H n.m.r. δ 2·43, s, 3H, CMe; 3·82, s, 3H, NMe; 9·85, s, 1H, CHO.

5-Chloro-1,3-dimethylpyrazole-4-carboxylic Acid (10)

The following were optimum conditions. The aldehyde (11) was suspended in water (75 ml) containing sodium carbonate (7 g) and potassium permanganate (8 g). The mixture was vigorously stirred and maintained at 60° for 1 h. Excess permanganate and the manganese dioxide were destroyed by addition of sodium metabisulfite. The mixture was then made strongly alkaline with sodium hydroxide solution, filtered through Celite, and the filtrate acidified with concentrated hydrochloric acid. 5-Chloro-1,3-dimethylpyrazole-4-carboxylic acid (10) (8·2 g, 94%) was obtained as a white powder, m.p. 191–194°. Crystallization from aqueous acetic acid gave the product as colourless cubic crystals, m.p. 198–199° (lit.[8] 197–198°).

More vigorous conditions resulted in further oxidation; the following experiment is illustrative. The crude acid (10) (26·1 g), prepared by treatment of (11) with alkaline permanganate at 100° for 3 h and workup as above, was suspended in ethanol (300 ml), and concentrated sulfuric acid (5 ml) added. The mixture was boiled under reflux for 48 h. The ethanol was removed under vacuum, water (200 ml) was added, and the product extracted with chloroform (3 × 100 ml). The combined extracts were washed twice with sodium bicarbonate solution (5%), then with water; they were dried and the solvent was removed. The crude product (27 g) was distilled under vacuum to give, initially, *ethyl 5-chloro-1,3-dimethylpyrazole-4-carboxylate* (12) as a colourless oil (21·3 g, 70%), b.p. 80–82°/0·01 mm, which subsequently solidified to a colourless solid, m.p. 38–39° (Found: C, 47·2; H, 5·5; N, 13·6. $C_8H_{11}ClN_2O_2$ requires C, 47·4; H, 5·5; N, 13·8%). ^{1}H n.m.r. δ 1·36, t, 3H, CH_2CH_3; 2·43, s, 3H, CMe; 3·81, s, 3H, NMe; 4·34, q, 2H, CH_2CH_3. Continued distillation afforded *diethyl 5-chloro-1-methylpyrazole-3,4-dicarboxylate* (15) as a colourless oil (5·1 g, 13%), b.p. 124–125°/0·01 mm (Found: C, 46·1; H, 5·0; N, 10·6. $C_{10}H_{13}ClN_2O_4$ requires C, 46·1; H, 5·0; N, 10·8%). ^{1}H n.m.r. δ 1·36, dt, 6H, 2 × CH_2CH_3; 3·94, s, 3H, NMe; 4·42, dq, 4H, 2 × CH_2CH_3.

1,3-Dimethylpyrazole-4-carboxylic Acid (13)

5-Chloro-1,3-dimethylpyrazole-4-carboxylic acid (10) (3·5 g) was dissolved in sodium carbonate solution (5%, 50 ml), and hydrogenated at room temperature and 2 atm pressure with Pd/C (5%) as catalyst. The catalyst was removed by filtration through Celite and the volume of the aqueous solution reduced by half under vacuum. The solution was then acidified with concentrated hydrochloric acid, chilled, and the precipitate collected. *1,3-Dimethylpyrazole-4-carboxylic acid* (13) (2·6 g, 93%) was obtained as colourless needles after crystallization from water, m.p. 190–191° (Found: C, 51·2; H, 5·8; N, 19·8. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·8; N, 20·0%).

Analogues of the Anilide (3)

The carboxylic acid (13) above (10 mmol) was boiled under reflux with thionyl chloride (5 ml) and, after removal of excess reagent, the acid chloride was treated with a solution of the appropriate substituted aniline (12 mmol) in pyridine solution (5 ml). After 30 min at 100°, the mixture was diluted with water, and the crude product separated by filtration. The following compounds were prepared.

N-(*3-Chlorophenyl*)-*1,3-dimethylpyrazole-4-carboxamide*, m.p. 137–138°, colourless prisms from ethyl acetate/light petroleum (b.p. 40–60°) (Found: C, 57·6; H, 4·8; N, 16·8. $C_{12}H_{12}ClN_3O$ requires C, 57·7; H, 4·8; N, 16·8%).

N-(*3-Methoxyphenyl*)-*1,3-dimethylpyrazole-4-carboxamide*, m.p. 92–93°, colourless prisms from chloroform/light petroleum (b.p. 40–60°) (Found: C, 63·6; H, 6·2; N, 17·0. $C_{13}H_{15}N_3O_2$ requires C, 63·7; H, 6·2; N, 17·1%).

1,3-Dimethyl-N-(*3-tolyl*)*pyrazole-4-carboxamide*, m.p. 127–129°, colourless needles after crystallization from ethyl acetate/light petroleum (b.p. 60–80°) (Found: C, 68·0; H, 6·5; N, 18·1. $C_{13}H_{15}N_3O$ requires C, 68·1; H, 6·6; N, 18·3%).

Ethyl 1,3-Dimethylpyrazole-4-carboxylate (23)

Ethyl 5-chloro-1,3-dimethylpyrazole-4-carboxylate (12) (20·2 g) was hydrogenated as described for the preparation of (3) above. Distillation of the crude product gave *ethyl 1,3-dimethylpyrazole-4-carboxylate* (23) (15·6 g, 93%) as a colourless oil, b.p. 85–86°/0·1 mm, which subsequently solidified, m.p. 58–59° (Found: C, 57·1; H, 7·1; N, 16·8. $C_8H_{12}N_2O_2$ requires C, 57·1; H, 7·2; N, 16·7%). ^{1}H n.m.r. δ 1·34, t, 3H, CH_2CH_3; 2·46, s, 3H, CMe; 3·85, s, 3H, NMe; 4·30, q, 2H, CH_2CH_3; 7·83, s, 1H, H 5.

Reaction of Compound (20) with Methylhydrazine

Ethyl ethoxymethyleneacetoacetate (20) (18·6 g) was dissolved in ether (250 ml), and the solution cooled to −5°. Methylhydrazine (5 g) was added dropwise with stirring at such a rate that the temperature of the mixture did not exceed 0°. The mixture was then stirred at this temperature for 15 min, followed by 1 h at room temperature. The solvent was removed and the product distilled under vacuum. The distillate (15·8 g, 94%) consisted mainly of ethyl 1,3-dimethylpyrazole-4-carboxylate, which was obtained initially as a colourless oil, b.p. 86–89°/0·2 mm, but which subsequently solidified, m.p. 49–55°. The ^{1}H n.m.r. spectrum of this product was virtually identical with that reported above for (23), except that a shoulder at δ 2·55 (5-Me group) indicated approximately 5–10% of the corresponding 1,5-dimethyl isomer (22).

Ethyl 3(5)-Methylpyrazole-4-carboxylate (24)

The ethoxymethylene compound (20) (46·5 g) in ethanol (300 ml) was treated dropwise with hydrazine hydrate (15 g) at −10°. After the addition was complete, the temperature of the mixture was allowed to rise to ambient, whereupon the ethanol was removed under vacuum. Chloroform (300 ml) was added, and the solution washed with saturated sodium chloride solution (100 ml) and water (50 ml). After drying and removal of the solvent, the crude product was distillled. Ethyl 3(5)-methylpyrazole-4-carboxylate (24) (31·8 g, 83%) was obtained as a colourless oil, b.p. 159–160°/4 mm, which solidified, m.p. 49–52° (lit.[33] 54°).

[33] Dains, F. B., and Harger, R. N., *J. Am. Chem. Soc.*, 1918, **40**, 562.

Methylation of Ethyl 3(5)-Methylpyrazole-4-carboxylate (24)

Sodium (4·6 g) was dissolved in ethanol (200 ml), and the pyrazole (24) (27 g) added. Methyl iodide (28·4 g) was added dropwise, with stirring, to the solution at room temperature. The mixture was then boiled gently under reflux for 2 h. Most of the ethanol was removed under vacuum, and sodium chloride solution (5%, 200 ml) added to the residue. The product was extracted with chloroform (3 × 100 ml), and the combined extracts were washed with water, dried and evaporated. The crude product was distilled under vacuum, an efficient fractionating column being used. The distillate (26·0 g), b.p. 85–87°/0·5 mm, proved to be an equal mixture of the isomers (22) and (23). ^{1}H n.m.r. δ 1·34, t, 3H, CH_2CH_3; 2·46 (23), 2·55 (22), 2s, 3H, CMe; 3·80 (22), 3·85 (23), 2s, 3H, NMe; 4·30, q, 2H, CH_2CH_3; 7·86, s, 1H, H 3 (22) and H 5 (23).

Ethyl 2-Cyano-3-ethoxycrotonate (16b)

This compound was prepared by reaction of ethyl cyanoacetate (0·2 mol), triethyl orthoacetate (0·2 mol) and acetic anhydride (0·4 mol) as described previously.[34] It was obtained in 55% yield as a colourless oil, b.p. 115–118°/0·3 mm, which solidified, m.p. 73–75° (lit.[35] 74–75°).

Ethyl 5-Amino-1,3-dimethylpyrazole-4-carboxylate (17b)

The ethoxymethylene compound (16b) (8·5 g) was dissolved in ethanol (50 ml), methylhydrazine (2·5 g) added, and the mixture boiled under reflux for 3 h. Removal of the solvent afforded a pale yellow oil which was distilled under vacuum. *Ethyl 5-amino-1,3-dimethylpyrazole-4-carboxylate* (17b) (8·6 g, 94%) was obtained as a colourless oil, b.p. 133–135°/0·4 mm, which immediately solidified. Crystallization from ethyl acetate afforded colourless cubic crystals, m.p. 111–113° (Found: C, 52·4; H, 7·2; N, 22·8. $C_8H_{13}N_3O_2$ requires C, 52·4; H, 7·2; N, 22·9%). ^{1}H n.m.r. δ 1·34, t, 3H, CH_2CH_3; 2·32, s, 3H, CMe; 3·55, s, 3H, NMe; 4·30, q, 2H, CH_2CH_3; 5·46, br s, 2H, NH_2.

Ethyl 3-Amino-1,5-dimethylpyrazole-4-carboxylate (19b)

(i) Benzaldehyde methylhydrazone[36] (13·4 g) and the ethoxymethylene compound (16b) (18·3 g) were dissolved in toluene (100 ml), and the mixture boiled under reflux for 2 h. The toluene was removed under vacuum, and the residue triturated with light petroleum (b.p. 60–80°). The solid product was recovered by filtration and crystallized from aqueous methanol. *Ethyl 3-*(N^2*-benzylidene-*N^1*-methylhydrazino)-2-cyanocrotonate* (18b) was obtained as pale yellow plates (23·3 g, 86%), m.p. 103–104° (Found: C, 66·1; H, 6·2; N, 15·4. $C_{15}H_{17}N_3O_2$ requires C, 66·4; H, 6·3; N, 15·5%).

(ii) The benzylidene compound (18b) (16·3 g) was suspended in ethanol (150 ml) containing concentrated hydrochloric acid (10 ml), and the mixture boiled under reflux for 30 min. The solvent was removed, water (100 ml) and concentrated hydrochloric acid (20 ml) were added, and the mixture extracted with chloroform (3 × 25 ml). The aqueous layer was then basified with sodium hydroxide solution (10%), and the product extracted with chloroform (3 × 50 ml). The combined extracts were washed with water, dried and evaporated.

Ethyl 3-amino-1,5-dimethylpyrazole-4-carboxylate (19b) (10·2 g, 93%) was obtained as colourless needles after crystallization from ethyl acetate, m.p. 103–105° (Found: C, 52·3; H, 7·2; N, 22·7. $C_8H_{13}N_3O_2$ requires C, 52·4; H, 7·2; N, 22·9%). ^{1}H n.m.r. δ 1·35, t, 3H, CH_2CH_3; 2·43, s, 3H, CMe; 3·60, s, 3H, NMe; 4·30, q, 2H, CH_2CH_3; 4·76, br s, 2H, NH_2.

Ethyl 1,5-Dimethylpyrazole-4-carboxylate (22)

Sodium nitrite (2·5 g) was added to a mixture of glacial acetic acid (22·5 ml) and concentrated sulfuric acid (15 ml) which had been cooled to 0°. A solution of the 3-aminopyrazole (19b) (5·5 g) in glacial acetic acid (90 ml) and concentrated sulfuric acid (25 ml) was added dropwise with stirring so that the temperature of the mixture was maintained between 0 and 5°. After stirring 30 min at this temperature, freshly prepared copper, from copper sulfate pentahydrate (10 g) and zinc powder (3·5 g),[25] was added. The mixture was stirred for a further 30 min while the temperature was allowed to rise to ambient, then poured into ice water (500 ml), and basified with ammonia solution. The

[34] Huppatz, J. L., Phillips, J. N., and Rattigan, B. M., *Agric. Biol. Chem.*, 1981, **45**, 2769.
[35] Popp, F. D., and Catala, A., *J. Org. Chem.*, 1961, **26**, 2738.
[36] Todd, D., *J. Am. Chem. Soc.*, 1949, **71**, 1353.

product was extracted with ether (3 × 100 ml), and the combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was distilled under vacuum affording *ethyl 1,5-dimethylpyrazole-4-carboxylate* (22) (4·05 g, 80%) as a colourless oil, b.p. 78–80°/0·05 mm (Found: C, 57·0; H, 7·2; N, 16·7. $C_8H_{12}N_2O_2$ requires C, 57·1; H, 7·2; N, 16·7%). ^{1}H n.m.r. δ 1·34, t, 3H, CH_2CH_3; 2·55, s, 3H, CMe; 3·80, s, 3H, NMe; 4·30, q, 2H, CH_2CH_3; 7·83, s, 1H, H3.

Deaminations of (17a,b)

Ethyl 5-amino-1,3-dimethylpyrazole-4-carboxylate (17b) was diazotized and the diazonium salt decomposed as described above. Ethyl 1,3-dimethylpyrazole-4-carboxylate (23) was obtained in 94% yield and was identical (m.p., ^{1}H n.m.r., mass spectrum) with the sample obtained by hydrogenolysis of the ester (12) described above.

Similarly, ethyl 5-amino-1-methylpyrazole-4-carboxylate (17a)[9] was deaminated to give a 96% yield of ethyl 1-methylpyrazole-4-carboxylate, b.p. 81–83°/0·2 mm (lit.[37] 120°/13 mm).

1,5-Dimethyl-*N*-phenylpyrazole-4-carboxamide (4) and its Analogues

The ester (22) (4·4 g) was dissolved in ethanol (20 ml) and sodium hydroxide solution (20 ml, 10%), and the mixture boiled under reflux for 1 h. The ethanol was removed under vacuum, water (20 ml) was added, and the solution acidified with concentrated hydrochloric acid. The solution was chilled and the product slowly crystallized. 1,5-Dimethylpyrazole-4-carboxylic acid (3·4 g, 92%) was obtained as colourless needles, m.p. 183–184° (lit.[38] 179–181°) (Found: C, 51·3; H, 5·6; N, 19·8. Calc. for $C_6H_8N_2O_2$: C, 51·4; H, 5·8; N, 20·0%).

The above acid was converted into the acid chloride and treated with aniline in pyridine as described above for the preparation of derivatives of the anilide (3). *1,5-Dimethyl*-N-*phenylpyrazole-4-carboxamide* (4) was obtained in 88% yield as pale yellow prisms from chloroform/light petroleum (b.p. 40–60°), m.p. 138–139° (Found: C, 67·0; H, 6·0; N, 19·2. $C_{12}H_{13}N_3O$ requires C, 67·0; H, 6·1; N, 19·5%). ^{1}H n.m.r. δ 2·55, s, 3H, CMe; 3·71, s, 3H, NMe; 7·05–7·76, m, 5H, ArH; 7·81, s, 1H, H3; 8·13, br s, 1H, NH.

The following analogues of the anilide (4) were prepared similarly.

1,5-Dimethyl-N-*(3-tolyl)pyrazole-4-carboxamide*, m.p. 152–153°, colourless prisms from chloroform/light petroleum (b.p. 40–60°) (Found: C, 67·9; H, 6·5; N, 18·1. $C_{13}H_{15}N_3O$ requires C, 68·1; H, 6·6; N, 18·3%).

N-*(3-Chorophenyl)-1,5-dimethylpyrazole-4-carboxamide*, m.p. 145–146°, colourless prisms from ethyl acetate/light petroleum (b.p. 40–60°) (Found: C, 57·6; H, 4·7; N, 17·0. $C_{12}H_{12}ClN_3O$ requires C, 57·7; H, 4·8; N, 16·8%).

N-*(3-Methoxyphenyl)-1,5-dimethylpyrazole-4-carboxamide*, m.p. 132–133°, colourless needles from ethyl acetate/light petroleum (b.p. 40–60°) (Found: C, 63·6; H, 6·0; N, 17·0. $C_{13}H_{15}N_3O_2$ requires C, 63·7; H, 6·2; N, 17·1%).

Reaction of Ethyl Acetopyruvate and Methylhydrazine

Ethyl acetopyruvate (53 g) in ethanol (150 ml) was treated dropwise with stirring with methylhydrazine (16·8 g); external cooling was necessary during the addition. After boiling gently under reflux for 30 min, the solvent was removed and the residue fractionally distilled under vacuum. Ethyl 1,3-dimethylpyrazole-5-carboxylate (28) was obtained as a colourless oil (25·6 g, 46%), b.p. 59–60/0·5 mm (lit.[37] 66–72°/1 mm). ^{1}H n.m.r. δ 1·37, t, 3H, CH_2CH_3; 2·27, s, 3H, CMe; 4·13, s, 3H, NMe; 4·33, q, 2H, CH_2CH_3; 6·60, s, 1H, H4 (corresponding lit.[32] values: 1·36, 2·27, 4·13, 4·32, 6·61). Ethyl 1,5-dimethylpyrazole-3-carboxylate (27) was obtained as an oil (23·0 g, 41%), b.p. 118–119°/0·5 mm, which solidified, m.p. 39–40° (lit.[37] b.p. 108–110°/1 mm, m.p. 40°). ^{1}H n.m.r. δ 1·38, t, 3H, CH_2CH_3; 2·30, s, 3H, CMe; 3·85, s, 3H, NMe; 4·37, q, 2H, CH_2CH_3; 6·55, s, 1H, H4 (corresponding lit.[32] values: 1·36, 2·30, 3·85, 4·36, 6·55).

1,3-Dimethylpyrazole (26) and 1,5-Dimethylpyrazole (25)

(i) The esters (28) and (27) were hydrolysed by boiling with aqueous alcoholic sodium hydroxide solution for 1 h. 1,3-Dimethylpyrazole-5-carboxylic acid, m.p. 211–212° (lit.[29] 210–212°), and

[37] Wijnberger, C., and Habraken, C. L., *J. Heterocycl. Chem.*, 1969, **6**, 545.
[38] Liljefors, T., and Sandström, J., *Acta Chem. Scand.*, 1970, **24**, 3109.

1,5-dimethylpyrazole-3-carboxylic acid, m.p. 174–175° (lit.[29] 174–176°), had ^{1}H n.m.r. spectral data in agreement with data recorded in the literature.[32]

(ii) 1,3-Dimethylpyrazole-5-carboxylic acid was dry-distilled; the distillate was collected, and examined by ^{1}H n.m.r. The following data are in close agreement with data reported[28,32] for 1,3-dimethylpyrazole (26): δ 2·28, s, 3H, CMe; 3·84, s, 3H, NMe; 6·00, d, *J c.* 1·2 Hz, 1H, H4; 7·22, d, *J c.* 1·2 Hz, 1H, H5.

A sample of the pyrazole-4-carboxylic acid (13) was similarly dry-distilled. ^{1}H n.m.r. analysis showed the distillate to be 1,3-dimethylpyrazole (26).

(iii) 1,5-Dimethylpyrazole-3-carboxylic acid was decarboxylated and the distillate examined by ^{1}H n.m.r. The following data are similar to those previously reported[28,32] for 1,5-dimethylpyrazole (25): δ 2·25, s, 3H, CMe; 3·76, s, 3H, NMe; 5·98, d, *J c.* 1 Hz, 1H, H4; 7·34, d, *J c.* 1 Hz, 1H, H3.

Similarly, a sample of 1,5-dimethylpyrazole-4-carboxylic acid was dry-distilled; the distillate exhibited a ^{1}H n.m.r. spectrum which was identical with that of 1,5-dimethylpyrazole (25).

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