320. *The Preparation of Pyrazoles by Reaction between β-Diketones and Ethyl Diazoacetate.*

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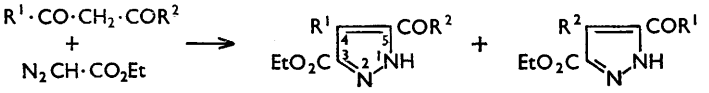
The preparation of pyrazoles by reaction between β-diketones and ethyl diazoacetate, first used by Klages, has been modified and two isomers have been isolated on use of unsymmetrical diketones. The orientations of these isomers have been established by oxidation of acetylpyrazoles with sodium hypoiodite and of aroylpyrazoles by oxidation with peracetic acid. It has been shown that 3-carboxyl groups in the pyrazole nucleus can be replaced by bromine, and that methylation of *N*-unsubstituted pyrazoles produces both *N*-methyl isomers.

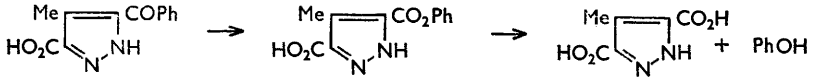
Klages [1] showed that acetylacetone and propionylacetone condense with ethyl diazoacetate in dilute aqueous sodium hydroxide solution to give 3,4,5-trisubstituted pyrazoles. We have now found that using ethanolic potassium hydroxide gives better results and we have examined the reaction with acetylacetone, benzoylacetone, *p*-methoxybenzoylacetone, and dibenzoylmethane. Two products may be produced from unsymmetrical diketones, and these have been isolated, but in each case there was very little of one isomer. Benzoylacetone gave ethyl 5-acetyl-4-phenylpyrazole-3-carboxylate [2] (isolated as the corresponding acid) with a small amount of ethyl 5-benzoyl-4-methylpyrazole-3-carboxylate [2] and 4-phenylpyrazole-3-carboxylate.[3] The last product is believed to arise

[1] Klages, *J. prakt. Chem.*, 1902, **65**, 387.
[2] Wolff, *Annalen*, 1902, **325**, 129.
[3] Kohler and Steele, *J. Amer. Chem. Soc.*, 1919, **41**, 1104.

by reaction between ethyl diazoacetate and acetophenone produced by alkaline fission of the diketone; this reaction, which has not been previously observed, was confirmed by



the formation of this pyrazole (in very poor yield) from acetophenone and ethyl diazoacetate in methanolic potassium hydroxide. In methanolic potassium hydroxide benzoylacetone and ethyl diazoacetate gave a smaller yield of the 5-acetyl-4-phenyl product, and



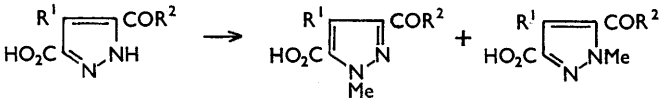
none of the 5-benzoyl-4-methyl product, but a larger yield of 4-phenylpyrazole-3-carboxylic acid (isolated as its methyl ester [4]).

The orientations of the pyrazolyl ketones were confirmed in two ways: (*a*) Determination of the acetyl group with sodium hypoiodite was satisfactory for *N*-unsubstituted 3-acetylpyrazoles, but for the *N*-methyl derivatives the results were low. (*b*) Oxidation of 5-benzoyl-4-methylpyrazole-3-carboxylic acid with peracetic acid [5] gave a phenyl ester which, after hydrolysis, gave phenol and 4-methylpyrazole-3,5-dicarboxylic acid.[2]

p-Methoxybenzoylacetone and ethyl diazoacetate gave 5-acetyl-4-*p*-methoxyphenyl- and small amounts of 5-*p*-methoxybenzoyl-4-methyl- and 4-*p*-methoxyphenyl-pyrazole-3-carboxylic acid. The last-named pyrazole was also prepared (in very small yield) from *p*-methoxyacetophenone and ethyl diazoacetate. The 5-acetyl acid gave a quantitative result for the acetyl estimation with sodium hypoiodite, and the 5-benzoyl acid gave 4-methylpyrazole-3,5-dicarboxylic acid [2] and *p*-methoxyphenol when treated with peracetic acid.

Dibenzoylmethane and ethyl diazoacetate gave 5-benzoyl-4-phenylpyrazole-3-carboxylic acid and a trace of 4-phenylpyrazole-3-carboxylic acid. The orientation of the main product was established by oxidation with peracetic acid to 4-phenylpyrazole-3,5-dicarboxylic acid [6] and phenol. It is of interest in this connection that neither ethyl 5-acetyl-4-methylpyrazole-3-carboxylate nor 5-acetyl-4-phenylpyrazole-3-carboxylic acid reacted with peracetic acid under these conditions.

Oxidation of 5-acetyl-4-phenylpyrazole-3-carboxylic acid with bromine in an excess of aqueous sodium hydroxide produced 5-bromo-4-phenylpyrazole-3-carboxylic acid. This seems to occur by replacement of the 5-carboxyl group first produced by oxidation of the acetyl group (bromoform was also isolated) because this bromo-acid is also obtained



when 4-phenylpyrazole-3,5-dicarboxylic acid is treated with bromine under the same conditions. In the latter case, however, a small amount of 3,5-dibromo-4-phenylpyrazole was also isolated. Thus 3(5)-carboxyl groups in the pyrazole nucleus may be replaced directly by bromine (cf. Brain and Finar [7]). 5-Acetyl-4-*p*-methoxyphenylpyrazole-3-carboxylic acid with bromine in aqueous sodium hydroxide also gave 5-bromo-4-*p*-methoxyphenylpyrazole-3-carboxylic acid.

Brain and Finar [8] methylated ethyl 5-acetyl-4-methylpyrazole-3-carboxylate with

[4] von Pechmann and Burkhard, *Ber.*, 1900, **33**, 3596.
[5] Hassall, *Org. Reactions*, 1957, **9**, 73.
[6] Buchner, *Ber.*, 1893, **26**, 260.
[7] Brain and Finar, *J.*, 1958, 2435.
[8] Brain and Finar, *J.*, 1957, 2356.

methyl iodide and ethanolic potassium hydroxide and obtained only ethyl 3-acetyl-1,4-dimethylpyrazole-5-carboxylate. However, 5-acetyl-4-phenyl- and 5-benzoyl-4-methyl-pyrazole-3-carboxylic acid with dimethyl sulphate in aqueous sodium hydroxide produced both methylated isomers in each case. The 5-benzoyl-4-phenyl acid with methyl iodide and ethanolic potassium hydroxide also gave both methylated isomers. The orientations of these isomers have been established by their relative rates of esterification with methanolic hydrogen chloride,[8] the sterically hindered acid being hardly affected under the conditions used.

Experimental

Ethyl 5-Acetyl-4-methylpyrazole-3-carboxylate.—Acetylacetone (2·0 g., 0·02 mole) and ethyl diazoacetate (2·3 g., 0·02 mole) were added, in that order, to a hot solution of potassium hydroxide (1·1 g., 0·02 mole) in absolute ethanol (80 c.c.), and the solution boiled for 10 min. The ethanol was then rapidly distilled off and the residue dissolved in water and acidified with hydrochloric acid, to give the ester which recrystallised from water in needles (1·57 g., 40%), m. p. 124—124·5° (Klages [1] gives 123—124°).

Condensation of Benzoylacetone with Ethyl Diazoacetate.—Benzoylacetone (48·7 g., 0·3 mole) and ethyl diazoacetate (34·2 g., 0·3 mole) were added to a hot solution of potassium hydroxide (16·8 g., 0·3 mole) in absolute ethanol (700 c.c.). After 0·5 hour's refluxing, the ethanol was distilled off, and the residue cooled and dissolved in water (750 c.c.). A small amount of oil was precipitated, and this was extracted with ether (2 × 100 c.c.; fraction A). The aqueous solution was acidified with glacial acetic acid and extracted with ether. The ether solution was washed with 5% aqueous sodium hydrogen carbonate, the ether evaporated, and the residue dissolved in N-sodium hydroxide (700 c.c.) and steam-distilled for 1·5 hr. to remove acetophenone and to hydrolyse the pyrazole ester. The solution was cooled and acidified with hydrochloric acid, to give 5-acetyl-4-phenylpyrazole-3-carboxylic acid which, on recrystallisation from hot water, yielded the pure acid (32·2 g., 46%), m. p. 214·5—215° (Wolff [2] gives 208°). Fraction A was extracted with 2N-sodium hydroxide (10 × 25 c.c.), the aqueous extract acidified with hydrochloric acid, and the precipitated oil extracted with ether. The dried ether solution (Na_2SO_4) was evaporated. The residual dark viscous oil (6·8 g.), when dissolved in 2N-sodium hydroxide (50 c.c.), left a residue of crystals (0·35 g.), m. p. 159—161°. The filtered solution was diluted to 250 c.c. and brought nearly to precipitation point by adding 2N-acetic acid. A fractional precipitation was then carried out by adding N-acetic acid in small portions and collecting the precipitate after each addition. In this way were collected: (*a*) 0·6 g. of a brown powder, which on recrystallisation from aqueous ethanol gave light brown crystals (0·45 g.), m. p. 166—167°. These, on hydrolysis with 2N-sodium hydroxide, gave 4-phenylpyrazole-3-carboxylic acid (0·35 g.), m. p. 256° (decomp.), and this, on recrystallisation from aqueous acetic acid, had m. p. 257° (decomp.) (Knorr [4] gives 252—254°). The small insoluble residue (above), when hydrolysed, also gave this acid. (*b*) 1·7 g. of a pale brown powder which on recrystallisation from aqueous ethanol gave ethyl 5-benzoyl-4-methylpyrazole-3-carboxylate (1·35 g.), m. p. 121—121·5° (Wolff [2] gives 119—120°). The ester was hydrolysed with 2N-sodium hydroxide; the acid, recrystallised twice from aqueous ethanol, had m. p. 239—240° (Wolff [2] gives 233°).

4-Phenylpyrazole-3-carboxylic Acid.—Acetophenone (6·0 g., 0·05 mole) and ethyl diazoacetate (5·7 g., 0·05 mole) were refluxed with methanol (50 c.c.), and a solution of potassium hydroxide (2·8 g., 0·05 mole) in methanol (50 c.c.) was run in slowly with stirring during 45 min. The methanol was then distilled off, the residue cooled, and water (250 c.c.) added. The pH was adjusted to 9, and the solution extracted with ether (3 × 30 c.c.). The ether was evaporated, and the residue dissolved in 2N-sodium hydroxide and steam-distilled for 2 hr. Acidification gave 4-phenylpyrazole-3-carboxylic acid which on recrystallisation from aqueous acetic acid (0·15 g.) had m. p. 257° (decomp.), unchanged in mixed m. p. with an authentic specimen prepared by the method of Kohler and Steele [3] who give m. p. 252—253°.

Condensation between Dibenzoylmethane and Ethyl Diazoacetate.—Dibenzoylmethane (22·4 g., 0·1 mole) was condensed with ethyl diazoacetate (11·4 g., 0·1 mole) and potassium hydroxide (5·6 g., 0·1 mole) in absolute ethanol, and the main product worked up as for benzoylacetone. Recrystallisation from aqueous acetic acid and then from aqueous ethanol gave *5-benzoyl-4-phenylpyrazole-3-carboxylic acid* (12·6 g., 43%), m. p. 211—211·5° (Found: C, 70·2; H, 4·1; N, 9·5. $C_{17}H_{12}O_3N_2$ requires C, 69·9; H, 4·1; N, 9·6%). The *ethyl ester* was also isolated; it had m. p. 128—128·5° (from ethanol–light petroleum) (Found: N, 8·6. $C_{19}H_{16}O_3N_2$ requires N, 8·7%).

The ether extract of an aqueous solution of the condensation product contained mainly this ester, but fractional precipitation afforded a very small amount of ethyl 4-phenylpyrazole-3-carboxylate, m. p. and mixed m. p. 168—169° (Kohler and Steele [3] give 164—165°).

Condensation between p-*Methoxybenzoylacetone and Ethyl Diazoacetate.*—*p*-Methoxybenzoylacetone (45 g., 0·235 mole) was condensed as above, and the residue, after distillation of the ethanol, was dissolved in 1·2 l. of water. The secondary products were extracted with ether (2 × 120 c.c.) but examination of the aqueous solution showed that removal was not complete. The main product was therefore isolated as follows. 2N-Acetic acid (10 c.c.) was added to the aqueous solution, and the precipitated oil removed by extraction with ether and rejected. More 2N-acetic acid (50 c.c.) was added to bring the solution to pH 9, and the precipitated oil extracted in ether, recovered, dissolved in 2N-sodium hydroxide, and steam-distilled for 2 hr. Acidification gave 5-*acetyl*-4-p-*methoxyphenylpyrazole*-3-*carboxylic acid* (18·7 g., 31%), m. p. 222·5—223° (from water) (Found: C, 60·0; H, 4·65; N, 10·6. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%). The ether solution containing the secondary products was extracted with 2N-sodium hydroxide (9 × 20 c.c.). As the extraction proceeded fine crystals separated and floated at the interface. These were run off with the aqueous layer, and at the end of the extraction the combined aqueous extract was filtered to give the ester (0·6 g.), m. p. 171—173°, which, on hydrolysis with 2N-sodium hydroxide followed by recrystallisation from aqueous acetic acid, gave 4-p-*methoxyphenylpyrazole*-3-*carboxylic acid*, m. p. 265° (decomp.) (Found: C, 60·4; H, 4·7; N, 12·6. $C_{11}H_{10}O_3N_2$ requires C, 60·6; H, 4·6; N, 12·8%). The filtered aqueous layer was acidified with glacial acetic acid, and the precipitate was collected, dissolved in 2N-sodium hydroxide (60 c.c.), and diluted with water (340 c.c.). The solution was brought near to precipitation point with 2N-acetic acid, and fractional precipitation was then carried out with N-acetic acid. Three fractions were collected, combined, and recrystallised from 50% aqueous ethanol, the mother-liquor being retained. The main crop of crystals was hydrolysed with 2N-sodium hydroxide and gave, on repeated recrystallisation from aqueous ethanol, 5-p-*methoxybenzoyl*-4-*methylpyrazole*-3-*carboxylic acid* (1·3 g.), m. p. 220·5—221° (Found: C, 59·7; H, 4·8; N, 10·6%). The retained mother-liquor was evaporated to dryness, and the residue hydrolysed and recrystallised from glacial acetic acid to give a small amount of 4-*p*-methoxyphenylpyrazole-3-carboxylic acid (total 0·4 g.). This acid was also obtained from *p*-methoxyacetophenone (7·5 g.) and ethyl diazoacetate (5·7 g.) in methanolic potassium hydroxide (0·15 g.).

Oxidations with Peracetic Acid.[5]—To 5-benzoyl-4-phenylpyrazole-3-carboxylic acid (2·92 g., 0·01 mole) in glacial acetic acid (25 c.c.) and concentrated sulphuric acid (15 c.c.) at 0° was added 38% w/w peracetic acid in a thin stream, with shaking. After 24 hr. at room temperature the solution was poured on ice. The oil which was precipitated was allowed to solidify, collected, and hydrolysed with 2N-sodium hydroxide. The hydrolysate was acidified with 50% sulphuric acid and steam-distilled to remove phenol. The residual liquid was evaporated to small bulk and filtered, to give 4-phenylpyrazole-3,5-dicarboxylic acid (1·6 g.), m. p. (from water), 249—250° (decomp.) (Buchner [6] gives 243°). 5-Benzoyl-4-methylpyrazole-3-carboxylic acid (1·85 g.), treated as above and worked up after 3 days, gave phenol and 4-methylpyrazole-3,5-dicarboxylic acid, m. p. 316—316·5° (decomp.) (Wolff [2] gives 315°).

5-*p*-Methoxybenzoyl-4-methylpyrazole-3-carboxylic acid (1·1 g.), worked up after 24 hr., gave *p*-methoxyphenol, isolated as the benzoate, m. p. 89—89·5°, and 4-methylpyrazole-3,5-dicarboxylic acid.

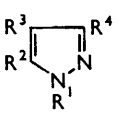
Oxidations with Sodium Hypobromite.—5-Acetyl-4-phenylpyrazole-3-carboxylic acid (6·0 g.) was added with stirring to an ice-cold solution of sodium hypobromite (bromine, 13·8 g.; sodium hydroxide, 12·5 g.; water, 80 c.c.). After being kept at 0° for 0·5 hr., the solution was left at room temperature for 2 hr., boiled to remove bromoform, diluted with water (30 c.c.), and acidified with concentrated hydrochloric acid. The precipitate was collected and the mother-liquor retained. Ether-extraction of the latter yielded crude 4-phenylpyrazole-3,5-dicarboxylic acid (1·2 g.), m. p. 235—238° (decomp.). The precipitate was dissolved in ether and extracted with 5% sodium hydrogen carbonate solution. Acidification gave needles (from aqueous ethanol) of 5-*bromo*-4-*phenylpyrazole*-3-*carboxylic acid* (4·0 g.), m. p. 223—223·5° (Found: C, 45·2; H, 2·9; N, 10·3; Br, 29·6. $C_{10}H_7O_2N_2Br$ requires C, 44·9; H, 2·6; N, 10·5; Br, 30·0%).

In the same way, 5-acetyl-4-*p*-methoxyphenylpyrazole-3-carboxylic acid gave 5-*bromo*-4-p-*methoxyphenylpyrazole*-3-*carboxylic acid*, m. p. 217·5—218° (from aqueous ethanol) (Found: C, 44·5; H, 2·9; N, 9·2; Br, 26·5. $C_{11}H_9O_3N_2Br$ requires C, 44·4; H, 3·0; N, 9·4; Br, 26·9%).

4-Phenylpyrazole-3,5-dicarboxylic acid (0·75 g.) was added to an ice-cold solution of bromine (0·2 c.c., 0·58 g.) and sodium hydroxide (1 g.) in water (6 c.c.). After 2 hr. the solution was acidified, boiled, and cooled, and the precipitate was collected, dissolved in ether, and extracted with 5% sodium hydrogen carbonate solution. The aqueous extract, on acidification, yielded 5-bromo-4-phenylpyrazole-3-carboxylic acid (0·45 g.), m. p. 221—222° (undepressed when mixed with a sample of the acid obtained from the acetylpyrazole).

3,5-Dibromo-4-phenylpyrazole.—5-Bromo-4-phenylpyrazole-3-carboxylic acid (2·67 g.) was dissolved in 2N-sodium hydroxide (5 c.c.) and added to an ice-cold solution of bromine (2·34 g.) and sodium hydroxide (2 g.) in water (30 c.c.). After 2 hr. at room temperature the cloudy solution was diluted with water (20 c.c.) and washed with ether (20 c.c.). The aqueous solution was then acidified with concentrated hydrochloric acid, boiled, and cooled, and the precipitate collected and dissolved in ether. After being washed with 5% sodium hydrogen carbonate solution (15 c.c.) the ether solution was dried (Na_2SO_4) and evaporated. The residue, on recrystallising 3 times from benzene–light petroleum, gave *3,5-dibromo-4-phenylpyrazole*, m. p. 157—157·5° (Found: C, 36·1; H, 2·0; N, 9·2; Br, 52·8. $C_9H_6N_2Br_2$ requires C, 35·8; H, 2·0; N, 9·3; Br, 53·0%).

Determination of the Acetyl Group.—0·6—0·7 Milliequivalent of the pyrazole acid was dissolved in N-sodium hydroxide (50 c.c.), and a 25% excess of ~0·1N-iodine was added dropwise during 5—10 min. The flask was stoppered and kept in the dark for 1 hr., then 2N-hydrochloric acid (30 c.c.) was added, and the liberated iodine was titrated against 0·1N-sodium thiosulphate (starch). Results were as tabulated.



R^1	R^2	R^3	R^4	Ac (% found)
H	CO_2H	Ph	Ac	99·6
H	CO_2H	*p*-MeO·C_6H_4	Ac	97·9
Me	Ac	Ph	CO_2H	76·2
Me	CO_2H	Ph	Ac	37·8

Methylation of the Pyrazole Acids.—(*a*) 5-Benzoyl-4-phenylpyrazole-3-carboxylic acid (14·6 g., 0·05 mole) was esterified,[8] and the ester was boiled with methyl iodide (10·7 g., 0·075 mole) and potassium hydroxide (2·8 g., 0·05 mole) in ethanol (350 c.c.). The methylated esters were then hydrolysed by boiling the solutions with an excess of potassium hydroxide, and the ethanol was removed by steam-distillation. After acidification, the precipitate was collected and dissolved by shaking it with ether and 5% sodium hydrogen carbonate solution. The ether was rejected and the aqueous layer was acidified with concentrated hydrochloric acid and extracted with 1 : 1 benzene–ether. The solvent layer was dried (Na_2SO_4) and evaporated and the residue refluxed for 3 hr. with 1% methanolic hydrogen chloride (183 g.). The methanol was evaporated, the residue dissolved in ether, and the sterically hindered acid extracted with 5% aqueous sodium hydrogen carbonate. Acidification and recrystallisation of the precipitate from aqueous acetic acid gave *3-benzoyl-1-methyl-4-phenylpyrazole-5-carboxylic acid* (5·6 g.), m. p. 181—182° (Found: C, 71·0; H, 4·7; N, 8·9. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·15%). The ether solution was evaporated, the residue re-esterified twice again, and the final residue recrystallised from aqueous ethanol and then hydrolysed with 2N-sodium hydroxide. Acidification and recrystallisation of the precipitate from aqueous ethanol gave *5-benzoyl-1-methyl-4-phenylpyrazole-3-carboxylic acid* (4·3 g.), m. p. 213° (Found: C, 70·7; H, 4·7; N, 9·0%).

(*b*) To 5-acetyl-4-phenylpyrazole-3-carboxylic acid (11·5 g., 0·05 mole) in 20% aqueous sodium hydroxide (25 c.c.) was added dimethyl sulphate (15·7 g., 0·125 mole) with rapid stirring during 10 min., the temperature being kept at 30—40°. The solution was stirred for a further 50 min., the pH being kept above 11 by further additions of 20% aqueous sodium hydroxide. Water (25 c.c.) was added, the solution acidified, and the oily precipitate left to solidify, collected, and dried at 50°. This was refluxed for 3 hr. with 0·5% methanolic hydrogen chloride (215 g.), and the methanol then distilled off. The residue was dissolved in ether and extracted with 5% sodium hydrogen carbonate solution to remove the sterically hindered acid. Acidification, etc., gave *3-acetyl-1-methyl-4-phenylpyrazole-5-carboxylic acid* (10 g.), m. p. 187—188° (from aqueous ethanol) (Found: C, 64·1; H, 4·85; N, 11·4. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9; N, 11·5%).

The ether solution was evaporated and the residue hydrolysed for 9 hr. on the steam-bath with a mixture of equal volumes (30 c.c. each) of concentrated sulphuric acid, glacial acetic acid, and water. The mixture was then poured into water, the products were extracted with ether,

and the ether was extracted with 5% aqueous sodium hydrogen carbonate, to give the unhindered acid. The esterification and separation process was carried out twice more, to give *5-acetyl-1-methyl-4-phenylpyrazole-3-carboxylic acid* (1·0 g.), m. p. 206° (from aqueous ethanol) (Found: C, 64·0; H, 5·2; N, 11·4%).

5-Acetyl-4-*p*-methoxyphenylpyrazole-3-carboxylic acid (13·0 g., 0·05 mole), treated in the same way, gave *3-acetyl-4-p-methoxyphenyl-1-methylpyrazole-5-carboxylic acid*, m. p. 163° (from benzene–ethyl acetate) (Found: C, 61·0; H, 5·1; N, 10·1. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1; N, 10·2%), and *5-acetyl-4-p-methoxyphenyl-1-methylpyrazole-3-carboxylic acid*, m. p. 184·5—185° (from aqueous ethanol) (Found: C, 61·0; H, 5·1; N, 9·8%).

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