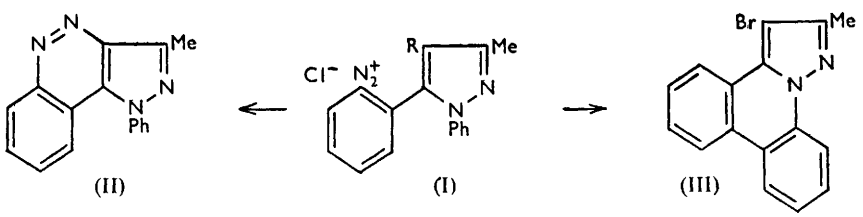
42. *The Reaction between Aroylacetones and Arylhydrazines.*

By I. L. Finar and Alma B. Simmonds.

o-, *m*-, and *p*-Nitrobenzoylacetones react with phenylhydrazine to form 3-methyl-5-*o*-, -*m*-, and -*p*-nitrophenyl-1-phenylpyrazoles only, whereas benzoylacetone and 2 : 4-dinitrophenylhydrazine give both 3- and 5-methyl-1-(2 : 4-dinitrophenyl)-5- and -3-phenylpyrazole. Evidence is given for the orientation of these pyrazoles and also of 3-*o*-aminophenyl-5-methyl-1-phenylpyrazole obtained from 4-chloroquinaldine and phenylhydrazine.

Misleading and inaccurate statements occur in various textbooks regarding the reaction of unsymmetrical β-diketones with monosubstituted hydrazines. Contrary to their expected behaviour, the simple β-diketones, R·CO·CH_2·COR′, do not generally form two isomeric pyrazoles. Only three such examples have so far been recorded: benzoylacetone and methylhydrazine,[1] 1-phenyl-4-*cyclo*propylbutane-1 : 3-dione and 2 : 4-dinitrophenylhydrazine,[2] and 3-benzoylacetyl-1 : 5-diphenylpyrazole and phenylhydrazine.[3] Further, when only one pyrazole has been isolated on reaction of an aroylacetone and an arylhydrazine, it has often been assumed to be the 1 : 5-diaryl-3-methylpyrazole,[4] by analogy with the reaction of benzoylacetone and phenylhydrazine.[5,6,7] So far, this assumption has been shown to be correct for the reaction between benzoylacetone and the three mononitrophenylhydrazines,[8] and for the three mononitrobenzoylacetones and phenylhydrazine.

The orientation of the 3-methyl-5-*m*- and -*p*-nitrophenyl-1-phenylpyrazoles was established by reduction to the amine, followed by diazotisation and treatment with hypophosphorous acid to give 3-methyl-1 : 5-diphenylpyrazole. In the same way, 3-methyl-5-*p*-nitrophenyl-1-phenylpyrazole-4-carboxylic acid can be reduced and deaminated to the known 3-methyl-1 : 5-diphenylpyrazole-4-carboxylic acid. On the other hand, 3-methyl-5-*o*-nitrophenyl-1-phenylpyrazole, when reduced, diazotised, and treated with hypophosphorous acid, gave 3′-methyl-1′-phenylpyrazolo(4′ : 5′-3 : 4)cinnoline (II),



(II) (I) (III)

instead of the expected methyldiphenylpyrazole. Cyclisation of the diazonium salt (I; R = H) is inhibited by concentrated acid and takes place spontaneously in dilute acid (cf. the Widman–Stoermer cinnoline synthesis [9]). Sodium hydroxide solution precipitated the cinnoline and also the ethanol-insoluble sodium diazoate. To prevent the formation of the cinnoline, the *o*-nitro-compound was converted into the 4-bromo-derivative. Reduction to the amine, followed by diazotisation and treatment of the

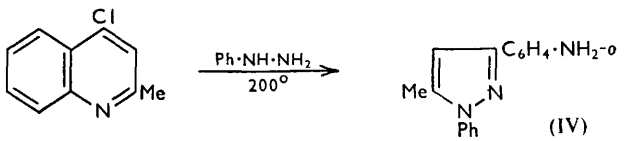
[1] Auwers and Stuhlmann, *Ber.*, 1926, **59**, 1054.
[2] Smith and Rogier, *J. Amer. Chem. Soc.*, 1951, **73**, 3834.
[3] Finar, *J.*, 1955, 1205.
[4] Bülow and Huss, *Ber.*, 1918, **51**, 399; Bull and Fuson, *J. Amer. Chem. Soc.*, 1933, **55**, 269; Schmid and Meyer, *Helv. Chim. Acta*, 1948, **31**, 748; Baker and Butt, *J.*, 1949, 2147; Schmid and Bolleter, *Helv. Chim. Acta*, 1950, **33**, 917.
[5] Knorr, *Ber.*, 1887, **20**, 1098.
[6] Drumm, *Proc. Roy. Irish Acad.*, 1931, **40**, *B*, 94.
[7] Knorr and Duden, *Ber.*, 1893, **26**, 111.
[8] Barry, Finar, and Simmonds, *J.*, 1956, 4974.
[9] Simpson, *J.*, 1943, 447.

diazonium salt (I; R = Br) with hypophosphorous acid, gave 4'-bromo-3'-methylpyrazolo(5' : 1'-9 : 10)phenanthridine [8] (III).

In accordance with the directions of Koenigs and Freund,[10] *o*-nitrobenzoylacetone and phenylhydrazine were heated together in ethanol at 30—40°. Bright yellow crystals of the phenylhydrazone, m. p. 156°, were obtained. When, however, the diketone and phenylhydrazine were heated together in ethanol on a steam-bath, a colourless form of the phenylhydrazone, m. p. 136°, was obtained and 3-methyl-5-*o*-nitrophenyl-1-phenylpyrazole was isolated from the mother-liquor. A solution of the phenylhydrazone, m. p. 136°, in boiling ethanol, when quickly cooled, gave the phenylhydrazone, m. p. 156°. Both phenylhydrazones slowly formed 3-methyl-5-*o*-nitrophenyl-1-phenylpyrazole when heated in ethanol on a steam-bath.

When *o*-nitrobenzoylacetone or its phenylhydrazone was heated with an excess of phenylhydrazine, no trace of a bisphenylhydrazone was found. Gevekoht [11] claimed to have prepared the bisphenylhydrazone, m. p. 120°, but his analytical figures do not agree with the calculated values for it. Since our colourless phenylhydrazone melted at 120° when first isolated from the reaction mixture, Gevekoht's compound is probably an impure form of the monophenylhydrazone, m. p. 136°. To add to the confusion, Cohn has recorded Gevekoht's compound as 3-methyl-5-*o*-nitrophenyl-1-phenylpyrazole in his " Tabellarische Übersicht der Pyrazolderivate," Braunschweig, 1897. The formation of bisphenylhydrazones from β-diketones has not been observed, even when ring closure to a pyrazole is impossible as in the reaction between benzoylacetone and *N*-methyl-*N*-phenylhydrazine.[1]

When Koenigs and Freund [10] condensed *o*-nitrobenzoylacetone and phenylhydrazine in ethanol on a steam-bath, they obtained only the pyrazole which they named by analogy with the pyrazole formed from benzoylacetone and phenylhydrazine. Unfortunately, they followed Knorr's earlier ideas on the orientation of the isomeric methyldiphenylpyrazoles [5] and had overlooked the proofs of orientation given by Knorr and Duden,[7] and by Auwers and Mauss,[12] thus incorrectly naming their product 5-methyl-3-*o*-nitrophenyl-1-phenylpyrazole. Since their product gave on reduction a different amine from that formed by heating 4-chloroquinaldine with an excess of phenylhydrazine in a sealed tube at 200°, they named the product from the latter reaction as 5-*o*-aminophenyl-3-methyl-1-phenylpyrazole. We, however, have shown it to be 3-*o*-aminophenyl-5-methyl-1-phenylpyrazole (IV) by deamination to 5-methyl-1 : 3-diphenylpyrazole.

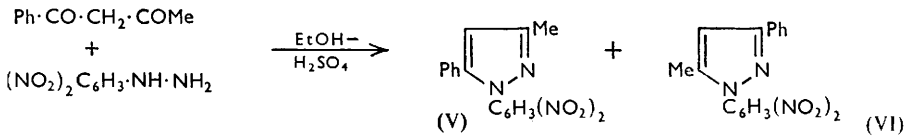


(IV)

We have now found another example of a simple β-diketone, benzoylacetone, which forms two pyrazoles with 2 : 4-dinitrophenylhydrazine. When Brady [13] carried out this reaction he obtained only one pyrazole, m. p. 151°, which he named 3(or 5)-methyl-1-(2 : 4-dinitrophenyl)-5(or 3)-phenylpyrazole. On the other hand Borsche and Reid [14] obtained from this reaction a pyrazole, m. p. 128—129°, and stated that it was 3-methyl-1-(2 : 4-dinitrophenyl)-5-phenylpyrazole. By this reaction we have isolated two isomeric pyrazoles, m. p. 154° and m. p. 137°, with the latter predominating. On several occasions, the product melted at 128°, but in every case it was separated into the two pyrazoles. Therefore, Borsche and Reid's product was undoubtedly a mixture. Henbest [15] prepared

[10] Koenigs and Freund, *Chem. Ber.*, 1947, **80**, 143.
[11] Gevekoht, *Annalen*, 1883, **221**, 323.
[12] Auwers and Mauss, *Ber.*, 1926, **59**, 611.
[13] Brady, *J.*, 1931, 756.
[14] Borsche and Reid, *Annalen*, 1943, **554**, 269.
[15] Henbest, *J.*, 1952, 4536.

(2 : 4-dinitrophenyl)-5-methyl-1-3-phenylpyrazole (VI), m. p. 154°, from phenyl propargyl ketone and 2 : 4-dinitrophenylhydrazine and gave evidence for its orientation. Brady's pyrazole is therefore (VI). The orientation of the isomeric pyrazole (V), m. p. 137°, has been independently established by reduction to the nitro-amine, followed by deamination to the known 3-methyl-1-*o*-nitrophenyl-5-phenylpyrazole.[8]



Experimental.

Additional Evidence for the Orientation of 3-*Methyl*-1 : 5-*diphenylpyrazole.*—The pyrazole was oxidised by boiling potassium permanganate in aqueous pyridine to 1 : 5-diphenylpyrazole-3-carboxylic acid which melted (alone or when mixed with an authentic specimen [3]) at 186°.

3-*Methyl*-5-o-*nitrophenyl*-1-*phenylpyrazole.*—*o*-Nitrobenzoylacetone (2·35 g., 0·0114 mole) and phenylhydrazine (1·3 g., 0·0114 mole), heated in ethanol at 35—40° for 10 min., gave bright yellow crystals (3·17 g., 93%) of the phenylhydrazone, m. p. 156° (Koenigs and Freund [10] give 163°) (Found: N, 14·3. Calc. for $C_{16}H_{15}O_3N_3$: N, 14·2%).

When, however the diketone (10 g., 0·05 mole) and phenylhydrazine (5·4 g., 0·05 mole) were separately dissolved in ethanol and then heated together on a steam-bath for 5 min., another form of the *phenylhydrazone* (6·4 g., 43%) was obtained as colourless flakes, m. p. 136° (Found: C, 64·4; H, 5·1; N, 14·0. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·2%), and the pyrazole [10, 16] (7·5 g., 54%) of m. p. 95° was obtained from the mother-liquor. When the phenylhydrazone, m. p. 136°, was dissolved in boiling ethanol and quickly cooled, it was converted into the yellow form, m. p. 156°. Both phenylhydrazones slowly formed the pyrazole, m. p. 95°, when heated in ethanol on a steam-bath or recrystallised from chloroform, acetic acid, or benzene.

3-*Methyl*-5-m-*nitrophenyl*-1-*phenylpyrazole.*—*m*-Nitrobenzoylacetone (2·3 g., 0·011 mole) and phenylhydrazine (1·2 g., 0·011 mole), refluxed in ethanol for 3 hr., gave the *pyrazole* as pale yellow crystals (2·9 g., 93%), m. p. 102—103° (Found: C, 68·8; H, 4·8; N, 14·7. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·8; N, 15·0%).

Ethyl p-*Nitrobenzoylacetoacetate.*—Bülow and Hailer [17] prepared this ester by reaction between *p*-nitrobenzoyl chloride, ethyl acetoacetate, and sodium in ethanol. We found it difficult to obtain a pure specimen by their method. A good sample of the ester was obtained by using methanol instead of ethanol, and by pouring the reaction mixture into ice-water to precipitate methyl *p*-nitrobenzoate. The filtrate was then poured into cooled glacial acetic acid and extracted with ether (yield 48%).

3-*Methyl*-5-p-*nitrophenyl*-1-*phenylpyrazole*-4-*carboxylic Acid.*—This acid was prepared from *p*-nitrobenzoylacetoacetic ester by Knorr and Jödicke's method [16]; it had m. p. 210° (Knorr and Jödicke give 202°).

3-*Methyl*-5-p-*nitrophenyl*-1-*phenylpyrazole.*—(*a*) The pyrazole was prepared by heating the 4-carboxylic acid for about 3 hr. at 240—250°. The pyrazole had the m. p. 111—112° (Knorr and Jödicke [16] obtained an oil). (*b*) *p*-Nitrobenzoylacetone (2 g., 0·01 mole) and phenylhydrazine (1·1 g., 0·01 mole), refluxed together in ethanol, gave the pyrazole (1·0 g., 36%) as yellow needles, m. p. 111° (Found: C, 68·8; H, 4·6; N, 14·9%).

1-(2 : 4-*Dinitrophenyl*)-3(*and* 5)-*methyl*-5(*and* 3)-*phenylpyrazoles.*—Benzoylacetone (20 g., 0·12 mole) in ethanol was added to a hot solution of 2 : 4-dinitrophenylhydrazine (16 g., 0·08 mole) in ethanol (350 c.c.) and 98% sulphuric acid (32 c.c.) and heated on a steam-bath for 10 min. Yellow plates of 1-(2 : 4-dinitrophenyl)-5-methyl-3-phenylpyrazole (VI) (2·1 g., 8%), m. p. 154° (from ethanol or acetic acid), were decanted from yellow needles of 1-(2 : 4-*dinitrophenyl*)-3-*methyl*-5-*phenylpyrazole* (V) (15·3 g., 67%), m. p. 137° (from ethanol or acetic acid) (Found: C, 59·2; H, 3·7; N, 16·8. $C_{16}H_{12}O_4N_4$ requires C, 59·3; H, 3·7; N, 17·3%).

[16] Knorr and Jödicke, *Ber.*, 1885, **18**, 2259.
[17] Bülow and Hailer, *Ber.*, 1902, **35**, 932.

4-Bromopyrazoles.—The pyrazole in glacial acetic acid was treated with an excess of bromine at room temperature. The precipitate was dissolved in chloroform, washed with sodium carbonate solution and water, and allowed to crystallise. 3-Methyl-5-*o*-nitrophenyl-1-phenylpyrazole (5 g.) gave the *4-bromo-derivative* (5·5 g., 86%), m. p. 141° (Found: Br, 22·0. $C_{16}H_{12}O_2N_3Br$ requires Br, 22·2%). 1-(2 : 4-Dinitrophenyl)-3-methyl-5-phenylpyrazole (V) (2·5 g.) gave the *4-bromo-derivative* (2·9 g., 93%), m. p. 176° (Found: Br, 19·9. $C_{16}H_{11}O_4N_4Br$ requires Br, 19·8%). 1-(2 : 4-Dinitrophenyl)-5-methyl-3-phenylpyrazole (VI) (1·15 g.) gave the *4-bromo-derivative* (1·3 g., 91%), m. p. 158° (Found: Br, 19·9%).

5-Aminophenyl-3-methyl-1-phenylpyrazoles.—The nitro-compound (1 mol.) in ethanol was heated on a steam-bath with stannous chloride (8 mol.) in concentrated hydrochloric acid for 1 hr. The solution was made alkaline with 30% ammonia solution, and the amine was extracted with ether and recrystallised from ethanol. The *m*-nitro-compound gave pale yellow crystals of the *amine*, m. p. 161·5° (Found: C, 77·0; H, 6·0; N, 16·3. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·0; N, 16·9%). The *p*-nitro-compound gave colourless crystals of the amine, m. p. 93°. The *o*-nitro-compound gave the amine,[10] m. p. 96° (yield 50%); a better product, m. p. 99°, was obtained when a solution of the *o*-nitro-compound (17·5 g.) in ethanol–hydrazine hydrate solution (60%; 10 c.c.) was heated in the presence of palladised charcoal (2 g.) on a steam-bath (yield 13 g., 83%).

5-o-Aminophenyl-4-bromo-3-methyl-1-phenylpyrazole.—The nitro-compound (10 g.), reduced with stannous chloride as above, gave colourless crystals of the *amine* (5·1 g., 54%), m. p. 135° (Found: C, 58·6; H, 4·4; N, 12·4; Br, 24·1. $C_{16}H_{14}N_3Br$ requires C, 58·5; H, 4·3; N, 12·8; Br, 24·4%).

5-p-Aminophenyl-3-methyl-1-phenylpyrazole-4-carboxylic Acid.—This compound, prepared by the method of Knorr and Jödicke,[16] had m. p. 261° (Knorr and Jödicke give m. p. 251°).

1-(4-Amino-2-nitrophenyl)-3-methyl-5-phenylpyrazole.—The dinitro-compound (V) (8 g.) in ethanol (500 c.c.) and 30% aqueous ammonia solution (15 c.c.) was saturated with hydrogen sulphide and heated on a steam-bath for 1 hr. The solution was evaporated to small bulk and the crystals obtained (5·3 g., 73%) were purified by dissolving them in concentrated hydrochloric acid and filtering. Addition of water gave bright yellow crystals of the *nitro-amine*, m. p. 182° (from ethanol) (Found: N, 18·7. $C_{16}H_{14}O_2N_4$ requires N, 19·0%).

1-(4-Amino-2-nitrophenyl)-5-methyl-3-phenylpyrazole.—The dinitro-compound (VI) (1·4 g.) in ethanol (60 c.c.) and 30% aqueous ammonia (3 c.c.) on reduction with hydrogen sulphide gave the *nitro-amine* (0·7 g., 54%), m. p. 170° (from ethanol or ligroin) (Found: C, 65·6; H, 4·5. $C_{16}H_{14}O_2N_4$ requires C, 65·3; H, 4·7%).

Diazotisation and Hypophosphorous Acid Treatment of the Aminophenylpyrazoles.—The amine (0·6 g.) was dissolved in concentrated hydrochloric acid (3 c.c.) and diazotised with sodium nitrite (0·3 g.) in water (0·5 c.c.). After ½ hr. the solution was poured into 30% hypophosphorous acid (7 c.c.). 5-*m*- and 5-*p*-Aminophenyl-3-methyl-1-phenylpyrazole both gave 3-methyl-1 : 5-diphenylpyrazole which was characterised as its bromo-derivative,[12, 18] m. p. 75°. 5-*p*-Aminophenyl-3-methyl-1-phenylpyrazole-4-carboxylic acid gave 3-methyl-1 : 5-diphenylpyrazole-4-carboxylic acid,[18] m. p. 205°. 3-*o*-Aminophenyl-5-methyl-1-phenylpyrazole (IV) gave 5-methyl-1 : 3-diphenylpyrazole, characterised as its picrate,[12] m. p. 108°. 5-*o*-Aminophenyl-3-methyl-1-phenylpyrazole gave *3′-methyl-1′-phenylpyrazolo(4′ : 5′-3 : 4)cinnoline* (II), m. p. 216°, which was also obtained when the diazonium salt solution was heated with ethanol and Gattermann copper powder or with boiling 50% sulphuric acid, or was made alkaline with sodium hydroxide solution (Found: C, 73·4; H, 4·7; N, 21·2. $C_{16}H_{12}N_4$ requires C, 73·8; H, 4·6; N, 21·5%). 5-*o*-Aminophenyl-4-bromo-3-methyl-1-phenylpyrazole gave 4′-bromo-3′-methylpyrazolo(5′ : 1′-9 : 10)phenanthridine [8] (III), m. p. 140° (Found: C, 61·7; H, 3·9; N, 8·7; Br, 25·3. Calc. for $C_{16}H_{11}N_2Br$: C, 61·7; H, 3·5; N, 9·0; Br, 25·7%). 1-(4-Amino-2-nitrophenyl)-3-methyl-5-phenylpyrazole gave red needles, m. p. 108°; it was successfully deaminated by adding the nitro-amine (1 g.) in glacial acetic acid (12 c.c.) to sodium nitrite (0·3 g.) in concentrated sulphuric acid (1·5 c.c.) at 5°. After ½ hr. the solution was heated with ethanol (20 c.c.) on a steam-bath for ½ hr. Dilution with water and extraction with ether gave pale yellow crystals which melted at 104° alone or when mixed with 3-methyl-1-*o*-nitrophenyl-5-phenylpyrazole.[8]

Knorr's Pyrazoline Reaction.—The aminophenylpyrazoles were reduced with sodium and ethanol, evaporated to dryness, and dissolved in concentrated sulphuric acid. On addition

[18] Knorr and Blank, *Ber.*, 1885, **18**, 316.

of sodium nitrite solution, 5-*o*-, -*m*-, and -*p*-aminophenyl-3-methyl-1-phenylpyrazoles, and 1-*o*-aminophenyl-3-methyl-5-phenylpyrazole [8] gave a red colour whereas 3-*o*-aminophenyl-5-methyl-1-phenylpyrazole gave a blue colour (cf. Knorr [19] and Auwers and Mauss [12]).

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[19] Knorr, *Annalen*, 1887, **238**, 200; *Ber.*, 1893, **26**, 100.