540. *The Orientation of Some Bromo-1-phenylpyrazoles.*

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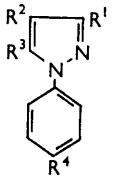
Dibromination of 3-methyl-1-phenylpyrazole in hot acetic acid gives the 4-bromo-1-*p*-bromophenyl derivative and not the 4,5-dibromo-compound as claimed by Michaelis and Behn.[1] Further bromination in nitric acid gave 4,5-dibromo-1-*p*-bromophenyl-3-methylpyrazole; this could not be prepared from 4,5-dibromo-3-methyl-1-phenylpyrazole by bromination in neutral solution but was prepared from it by a Sandmeyer reaction.

Michaelis and Behn [1] prepared 4- (I) and 5-bromo-3-methyl-1-phenylpyrazole (II) and claimed that further bromination of these two compounds produced the same dibromo-compound, 4,5-dibromo-3-methyl-1-phenylpyrazole (III). This is contrary to previous experience in this laboratory [2] where it was expected that compound (I) would form a *p*-phenyl-substituted derivative.

Michaelis and Behn's work was repeated. 3-Methyl-1-phenylpyrazole-5-carboxylic acid [3] (IX) was decarboxylated to the parent (V) and treated with bromine in cold acetic acid. The product, an oil, distilled in the range described by Michaelis for the 4-bromo-compound (I). This, with bromine in hot acetic acid, gave a solid (A) which corresponded, not with the 4,5-dibromo-compound (III), m. p. 92°, as stated by Michaelis and Behn,[1] but with the 4,*p*-dibromo-compound (IV), m. p. 98°, which was prepared as follows. The 4-bromopyrazole (I), on nitration with mixed acids at 12°, gave the *p*-nitro-compound (VI) which was also prepared by nitrating the parent (V) to the known 3-methyl-1-*p*-nitrophenylpyrazole [3,4] (VII) and brominating this in cold acetic acid. The bromo-nitro-compound (VI), on reduction with hydrazine hydrate and palladised charcoal,[5] gave the amine (VIII) which was converted into the dibromo-compound (IV) by the Sandmeyer reaction. This was identical with product (A).

[1] Michaelis and Behn, *Ber.*, 1900, **33**, 2595.
[2] Brain and Finar, *J.*, 1958, 2435.
[3] Finar and Hurlock, *J.*, 1958, 3259.
[4] Knorr, *Annalen*, 1894, **279**, 221.
[5] Dewar and Mole, *J.*, 1956, 2556.

4,5-Dibromo-1-phenylpyrazole (III), the only possible product if the second bromine atom enters the pyrazole nucleus, was prepared by means of the Borodine–Hunsdiecker reaction ($R{\cdot}CO_2Ag + Br_2 \longrightarrow RBr + AgBr + CO_2$). 3-Methyl-1-phenylpyrazole-5-carboxylic acid [3] (IX) was converted into its 4-bromo-derivative [6] (X), and the silver salt



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
(I)	Me	Br	H	H	(VII)	Me	H	H	NO_2	(XIII)	Me	Br	CO_2H	H
(II)	Me	H	Br	H	(VIII)	Me	Br	H	NH_2	(XIV)	CO_2H	Br	Me	H
(III)	Me	Br	Br	H	(IX)	Me	H	CO_2H	H	(XV)	Me	Br	CO_2H	Br
(IV)	Me	Br	H	Br	(X)	Me	Br	CO_2H	H	(XVI)	Me	H	Br	NO_2
(V)	Me	H	H	H	(XI)	Me	Br	CO_2Ag	H	(XVII)	Me	Br	Br	NO_2
(VI)	Me	Br	H	NO_2	(XII)	Me	Br	Br	Br	(XVIII)	Me	Br	Br	NH_2

(XI) of this gave two products when treated with bromine in chloroform solution: the required 4,5-dibromopyrazole (III) and a more highly substituted neutral compound suspected of being a tribromo-compound [7] (XII) (cf. Brain and Finar [2]). The identity of compound (III) was established by its preparation by the Michaelis method [1] through the 5-monobromo-compound (II) (cf. Stoermer and Martinsen [8]), thereby confirming that bromination of 3-methyl-1-phenylpyrazole gives substitution initially in the 4-position of the pyrazole nucleus followed by substitution in the *para*-position of the benzene nucleus.

Musante and Berretti [6] have brominated 3-methyl-1-phenylpyrazole-5-carboxylic acid in cold acetic acid to a monobromo-acid which, although unidentified, was proved not to be 1-*p*-bromophenyl-3-methylpyrazole-5-carboxylic acid. We have repeated this and attempted to dibrominate the acid in hot acetic acid but without success. Decarboxylation of this bromo-acid gave an oil which, when brominated in hot acetic acid gave 4-bromo-1-*p*-bromophenylpyrazole (IV). Musante and Berretti's unidentified bromo-acid must therefore have been the 4-bromo-acid (X). Attempts to brominate the 4-bromo-3-acid (XIV) further also failed. It appears that a 5-bromo- or 3- or 5-carboxyl group inhibits normal dibromination in neutral solution. However, on addition of bromine to an aqueous solution of the sodium salt of the 5-acid (IX) or (X), a dibromo-acid is obtained. Decarboxylation of this gives the dibromo-compound (IV). The tribromo-derivative (XII) was also formed and is moreover obtained on addition of bromine to the sodium salt of the dibromo-acid (XV) (cf. Finar and Walter [9]).

The 4,5-dibromopyrazole (III) could not be further brominated in neutral solution. It was, however, nitrated in sulphuric acid, giving the *p*-nitro-derivative (XVII). The dibromo-compound (IV) similarly could not be further brominated in neutral solution. But in 8N-nitric acid bromination proceeded readily at room temperature to form the tribromopyrazole (XII). This was synthesised by means of the Sandmeyer reaction. The 5-bromopyrazole (II) gave the known *p*-nitrophenyl compound [1] (XVI). Bromination of this gave the 4-bromo-derivative (XVII) which was also prepared from the 4,5-dibromopyrazole (III) by nitration. Reduction of this with hydrazine hydrate and palladised charcoal [5] gave the amine (XVIII) and thence by the Sandmeyer reaction the tribromopyrazole (XII).

Experimental

4-Bromo-3-methyl-1-p-nitrophenylpyrazole.—(*a*) A mixture of sulphuric acid (35 c.c.; *d* 1·84) and nitric acid (35 c.c.; *d* 1·42) was added dropwise to 4-bromo-3-methyl-1-phenylpyrazole [1] (9·44 g., 0·04 mole) in sulphuric acid (45 c.c.; *d* 1·84) at 75° during 0·5 hr., with stirring. The solution was kept at 12° for 0·5 hr., then poured on ice. The pale yellow solid was washed and dried (10·56 g., 93%; m. p. 192—195°). On repeated recrystallisation from acetone, it gave *4-bromo-3-methyl-1-p-nitrophenylpyrazole* as pale yellow needles, m. p. 200—201° (Found:

[6] Musante and Berretti, *Gazzetta*, 1949, **79**, 668.
[7] Michaelis and Schwabe, *Ber.*, 1900, **33**, 2612.
[8] Stoermer and Martinsen, *Annalen*, 1907, **352**, 322.
[9] Finar and Walter, *J.*, 1960, 1588.

C, 42·3; H, 2·7; Br, 28·55; N, 14·6. $C_{10}H_8BrN_3O_2$ requires C, 42·6; H, 2·9; Br, 28·3; N, 14·9%).

(*b*) A mixture of bromine (1·6 g., 0·01 mole) in acetic acid (5 c.c.) was added dropwise to 3-methyl-1-*p*-nitrophenylpyrazole [4] (2·03 g., 0·01 mole) in acetic acid (50 c.c.). After 1 hr. at room temperature the needles deposited were collected, washed, and dried. The mother-liquor, when poured into water, gave more solid which was collected and dried (total 2·4 g., 85·7%; m. p. 193—194°). Recrystallisation from acetone gave 4-bromo-3-methyl-1-*p*-nitrophenylpyrazole, m. p. and mixed m. p. 199—200°.

1-p-*Aminophenyl*-4-*bromo*-3-*methylpyrazole*.—4-Bromo-3-methyl-1-*p*-nitrophenylpyrazole was refluxed with ethanol (250 c.c.), 60% hydrazine hydrate (4 c.c.), and 5% palladised charcoal [5] (0·40 g.) for 1 hr. The catalyst was filtered off, and the filtrate evaporated to small bulk, diluted with water, and set aside. Yellow plates of 1-*p*-aminophenyl-4-bromo-3-methylpyrazole separated (2·4 g., 72%), having m. p. 85—88°, raised to 86—88° on recrystallisation from methanol–water. Since the amino-compound was unstable the *acetyl derivative*, m. p. 220·5—221·5°, was analysed (Found: C, 48·7; H, 3·9; Br, 26·9; N, 14·0. $C_{12}H_{12}BrN_3O$ requires C, 49·0; H, 4·1; Br, 27·2; N, 14·3%).

4-*Bromo*-1-p-*bromophenyl*-3-*methylpyrazole*.[7]—1-*p*-Aminophenyl-4-bromo-3-methylpyrazole (5·06 g., 0·02 mole) was dissolved in 70% w/w sulphuric acid (120 c.c.) and diazotised at 5° with sodium nitrite (1·9 g., 40% excess) in sulphuric acid (6·5 c.c.; *d* 1·84). The diazonium sulphate solution was added dropwise during 20 min. to a boiling solution of cuprous bromide (7·7 g.), prepared by heating a mixture of copper sulphate pentahydrate (3·2 g.), copper turnings (1 g.), sulphuric acid (0·82 c.c.; *d* 1·84) and water (50 c.c.) for 4 hr., and adding sodium hydrogen sulphite until the solution was yellow. Steam-distillation removed solid (3 g., 48%) that on recrystallisation from methanol gave 4-bromo-1-*p*-bromophenyl-3-methylpyrazole as pale yellow needles, m. p. 97—98°, undepressed on admixture with the product of bromination of 4-bromo-3-methyl-1-phenylpyrazole in hot acetic acid (Michaelis and Schwabe [7] give m. p. 98°).

4-*Bromo*-3-*methyl*-1-*phenylpyrazole*-5-*carboxylic Acid*.[6]—3-Methyl-1-phenylpyrazole-5-carboxylic acid was brominated as described by Musante and Berretti [6] to give a monobromo-acid (m. p. 179—180°) as shown by their analysis, but unidentified by them. This bromo-acid (4 g.) was decarboxylated at 185—190°. The product, dissolved in ether, washed with 2N-sodium carbonate, dried (Na_2SO_4), and recovered, was an oil (2 g.). It was treated in chloroform with bromine and kept on a steam-bath for 1 hr., then giving a solid, which on recrystallisation from aqueous ethanol gave 4-bromo-1-*p*-bromophenyl-3-methylpyrazole. Since 1-*p*-bromophenyl-3-methylpyrazole [7] is a solid, m. p. 94°, the initial bromine atom must be in position 4 of the pyrazole nucleus.

4,5-*Dibromo*-3-*methyl*-1-*phenylpyrazole*.[1]—(*a*) Silver 4-bromo-3-methyl-1-phenylpyrazole-5-carboxylate (12·1 g., 0·03 mole) was prepared by precipitation from a neutral solution of the ammonium salt of the above acid by the addition of silver nitrate solution. It was stirred in boiling carbon tetrachloride (30 c.c.) and bromine (1·66 c.c., 0·03 mole) in carbon tetrachloride (20 c.c.) was added during 20 min. After a further 0·5 hour's refluxing, the silver bromide formed was filtered off. The carbon tetrachloride was evaporated and the residual dark oil (7·1 g.) was dissolved in ether and washed with alkali (3 × 20 c.c.), to extract unchanged acid (2·0 g.). The ether was evaporated and a portion of the residual oil (2 g.) in chloroform was passed down an alumina column and eluted with light petroleum (b. p. 40—60°) to give a white solid (1·3 g.). On rechromatography as above, 4,5-dibromo-3-methyl-1-phenylpyrazole (0·5 g., 44%), m. p. 90—91° (Michaelis and Behn [1] give m. p. 92°), was separated from a small quantity of 4,5-dibromo-3-methyl-1-*p*-bromophenylpyrazole.[7]

(*b*) This product was also prepared by the method of Michaelis and Behn,[1] with m. p. 90—92° (Michaelis and Behn give m. p. 92°), undepressed on admixture with the specimen from reaction (*a*) but depressed on admixture with the product of direct bromination of 4-bromo-3-methyl-1-phenylpyrazole.

4-*Bromo*-1-p-*bromophenyl*-3-*methylpyrazole*-5-*carboxylic Acid*.—To a stirred solution of 4-bromo-3-methyl-1-phenylpyrazole-5-carboxylic acid (6·57 g., 0·022 mole) in 0·0967N-sodium hydroxide (250 c.c.) was added bromine (3·9 g., 0·024 mole) during 15 min. Stirring was continued for 2 hr. until the solution had a straw colour. The precipitate was dissolved in ether and extracted with alkali and the alkaline extract acidified to give 4-bromo-1-*p*-bromophenyl-3-methylpyrazole-5-carboxylic acid (5·5 g., 62%), m. p. 237° on recrystallisation (Found: C, 36·6;

H, 2·5; N, 8·0. Calc. for $C_{11}H_8Br_2N_2O_2$: C, 36·7; H, 2·2; N, 7·8%). The ether extract was washed, dried (Na_2SO_4), and evaporated to give a green oil (1·75 g.). Chromatography of this in chloroform on alumina with light petroleum (b. p. 40—60°) as eluent gave a small quantity of white needles, m. p. 140—143°, which on recrystallisation from ethanol gave 4,5-dibromo-1-*p*-bromophenyl-3-methylpyrazole, m. p. 147—148° (Michaelis and Schwabe [7] give m. p. 150°).

Orientation of the Dibromo-3-methyl-1-phenylpyrazole-5-carboxylic Acid.—This dibromo-acid was decarboxylated at 240—250° for 1 hr. The product was dissolved in ether, washed with alkali, dried (Na_2SO_4), and recovered to give a solid which, on recrystallisation, gave pale yellow needles of the 4-bromo-1-*p*-bromophenylpyrazole, m. p. 97—98° undepressed on admixture with specimens previously prepared.

4,5-*Dibromo*-1-p-*bromophenyl*-3-*methylpyrazole*.[7]—(*a*) To a stirred solution of the above dibromo-acid (2·0 g., 0·0055 mole) in 0·0967N-sodium hydroxide (57·00 c.c.) was added bromine (0·9 g., 0·0056 mole) during 15 min. After 72 hr. the mixture was extracted with ether which when washed, dried (Na_2SO_4), and evaporated gave a dark green oil (1·5 g., 68%). This, on chromatography in chloroform on alumina and elution with light petroleum (b. p. 40—60°) gave 4,5-dibromo-1-*p*-bromophenyl-3-methylpyrazole,[7] m. p. 147·5—149° undepressed on admixture with the specimen prepared as above.

(*b*) To 4-bromo-1-*p*-bromophenyl-3-methylpyrazole [1] (1·58 g., 0·005 mole) in 8N-nitric acid acid (40 c.c.) was added bromine (0·8 g., 0·005 mole) during 5 min. The mixture was shaken until a dark brown sticky solid was formed. The product was washed and recrystallised from ethanol to give off-white needles of 4,5-dibromo-1-*p*-bromophenyl-3-methylpyrazole (1·63 g., 82%), m. p. 146—148°. Further recrystallisation from ethanol gave pure white needles, m. p. 147—148° undepressed on admixture with the above specimen.

4,5-*Dibromo*-3-*methyl*-1-p-*nitrophenylpyrazole*.—(*a*) Bromine (0·4 g., 0·0025 mole) in acetic acid (20 c.c.) was added during 10 min. to a solution of 5-bromo-3-methyl-1-*p*-nitrophenylpyrazole [1] (0·65 g., 0·0025 mole) in acetic acid (5 c.c.). The solution was kept at room temperature for 1 hr., then poured into an excess of water. The yellow solid was washed and dried (0·8 g., 88·9%). Recrystallisation (charcoal) from ethanol gave 4,5-*dibromo*-3-*methyl*-1-p-*nitrophenylpyrazole*, m. p. 162·5—163° (Found: N, 11·3. $C_{10}H_7Br_2N_3O_2$ requires N, 11·6%).

(*b*) A mixture of sulphuric acid (10 c.c.; *d* 1·84) and nitric acid (10 c.c.; *d* 1·42) was added dropwise with stirring during 0·5 hr. to a cooled solution of 4,5-dibromo-3-methyl-1-phenylpyrazole [1] (4 g., 0·0013 mole) in sulphuric acid (10 c.c.; *d* 1·84). The temperature was kept at $\not>5°$ during the addition and then at 12° for 1 hr., and finally the solution was poured on ice. The precipitate was collected, washed, and dried (4·45 g., 97·6%), m. p. 157—159°. Recrystallisation (charcoal) from ethanol gave white needles, m. p. 162·5—163°, undepressed on admixture with the specimen from (*a*).

1-p-*Aminophenyl*-4,5-*dibromo*-3-*methylpyrazole*.—4,5-Dibromo-3-methyl-1-*p*-nitrophenylpyrazole (4·0 g., 0·011 mole) was refluxed with ethanol (50 c.c.), 60% hydrazine hydrate (4·1 c.c.), and 5% palladised charcoal [5] (0·41 g.) for 1 hr. The catalyst was filtered off; the filtrate, when evaporated to small bulk, diluted, and set aside, deposited a solid (3·2 g., 87·2%). Warming this with 2N-hydrochloric acid and cooling afforded needles of 1-p-*aminophenyl*-4,5-*dibromo*-3-*methylpyrazole hydrochloride*, m. p. 262—263° (decomp.) (Found: C, 32·9; H, 3·0. $C_{10}H_{10}Br_2ClN_3$ requires C, 32·7; H, 2·7%).

4,5-*Dibromo*-1-p-*bromophenyl*-3-*methylpyrazole*.—To a cooled solution of 1-*p*-aminophenyl-4,5-dibromo-3-methylpyrazole (2·2 g., 0·0066 mole) in sulphuric acid (1·5 c.c.; *d* 1·84) and water (10 c.c.) was added sodium nitrite (0·8 g.) in water (10 c.c.). A cuprous bromide solution was prepared by refluxing a mixture of copper sulphate pentahydrate (0·63 g.), copper turnings (0·2 g.), sodium bromide (1·54 g.), water (10 c.c.), and sulphuric acid (0·16 c.c.; *d* 1·84) for 4 hr. The reduction was completed by adding a small quantity of sodium hydrogen sulphite. The cold diazonium solution was added dropwise from a cooled jacketed dropping-funnel into the boiling cuprous bromide, through which steam was passing. Material volatile in steam (0·9 g., 34·6%) afforded, on recrystallisation from ethanol, 1-*p*-bromophenyl-4,5-dibromo-3-methylpyrazole, m. p. 144·5—146° undepressed on admixture with specimens previously obtained.

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