Some Derivatives of 2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine.*

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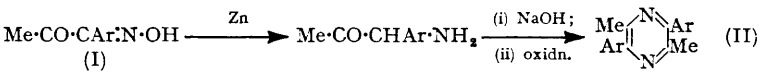
[Reprint Order No. 6344.]

Condensation of diazonium salts with hydroxyiminoacetone affords derivatives of 1-hydroxyimino-1-phenylacetone which, on reduction followed by self-condensation, give aryl-substituted 2 : 5-dimethylpyrazines. Nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine and of its *NN'*-dioxide yields principally di-*m*-nitro-derivatives.

Condensation of diazonium salts with hydroxyiminoacetone (Borsche, *Ber.*, 1907, **40**, 737; Philipp, *Annalen*, 1936, **523**, 285) yields arylated derivatives of the latter (1-aryl-1-hydroxyiminoacetone) (I), which are convenient intermediates for syntheses of 3 : 6-



(II)

diaryl-2 : 5-dimethylpyrazines (II). This versatile method does not appear to have been described previously, although the less readily accessible α-hydroxyiminopropiophenones, Ar·CO·CMe:N·OH, have often been used for similar purposes (cf. Spring, *Ann. Reports*, 1945, **42**, 188).

Benzenediazonium chloride and derivatives bearing methyl, methoxy-, chloro-, methoxycarbonyl, and acetamido-substituents were condensed with hydroxyiminoacetone in aqueous sodium acetate in the presence of a cupric sulphate–sodium sulphite catalyst to give moderate to good yields of 1-hydroxyimino-1-phenylacetone derivatives. Diazotised 3-aminopyridine likewise gave 1-hydroxyimino-1-3′-pyridylacetone. When these compounds were reduced and the products subjected to self-condensation in the presence of oxidising agents, 3 : 6-diaryl-2 : 5-dimethylpyrazines were obtained.

As nitro-derivatives of 3 : 6-diaryl-2 : 5-dimethylpyrazines cannot be obtained from the nitroanilines by this method, the nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine was examined. Nitration with nitric–sulphuric acid gave 2 : 5-dimethyl-3 : 6-di-*m*-nitrophenylpyrazine, identified by reduction to the diamine and conversion by the Sandmeyer reaction into the dichloro-compound, which was identical with that prepared from *m*-chloroaniline. As the nitration of pyridine *N*-oxide is stated to occur almost exclusively in the 4-position (Hertog and Overhoff, *Rec. Trav. chim.*, 1950, **69**, 468) it was of interest to determine whether the nitration of 2 : 5-dimethyl-3 : 6-diphenylpyrazine 1 : 4-dioxide would yield the di-*p*-nitro-derivative: such was not the case, however, the principal nitration product being again the di-*m*-nitrophenyl compound.

Experimental

Hydroxyiminoacetone.—The following modification of Charrier's method (*Gazzetta*, 1907, **37**, II, 145) was used. Ethyl acetoacetate (260 g.) was shaken with a cold solution of potassium hydroxide (130 g.) in water (1300 c.c.). After 24 hr. at 15—25°, sodium nitrite (161 g.) was added with stirring followed by dilute sulphuric acid (244 c.c. containing 122 c.c. of acid of *d* 1·84) at 0—8°. The solution was basified with aqueous 35% sodium hydroxide and shaken with benzene (100 c.c.). The aqueous layer was made just acid to Congo-red by addition of 50% sulphuric acid, and the product was extracted with ether (1 l.). Evaporation of the dried ($MgSO_4$) ethereal extract gave hydroxyiminoacetone (139 g., 80%), m. p. 65—67°.

Condensation of Diazonium Salts with Hydroxyiminoacetone.—(a) 1-*Hydroxyimino*-1-*phenylacetone*. A diazo-solution, prepared from aniline (93 g.), hydrochloric acid (230 c.c.; *d* 1·18), and water (200 c.c.) by treatment with sodium nitrite (69 g.) in water (100 c.c.) at 0—2°, was neutralised (Congo-red) with sodium acetate (88 g.; trihydrate) in water (140 c.c.). The diazonium solution was introduced below the surface of a solution of hydroxyiminoacetone (100 g.), sodium acetate (672 g.), cupric sulphate (25 g.), and sodium sulphite (4 g.; anhydrous) in water (680 c.c.) with stirring at 10—20°. After being stirred for 1 hr. at 20—25°, the solution was filtered and the residue extracted with hot N-sodium hydroxide (1600 c.c.). The extract was clarified (carbon) and the filtrate poured into hot acetic acid (150 c.c.) and water (150 c.c.) with stirring. The product (134 g., 82%) was collected and dried. After crystallisation from water, it had m. p. 165—166° (Found: N, 8·55. Calc. for $C_9H_9O_2N$: N, 8·6%).

1-p-*Carboxyphenyl*-1-*hydroxyiminoacetone*. A diazonium solution, prepared from ethyl *p*-aminobenzoate (165 g.), hydrochloric acid (230 c.c.; *d* 1·18), sodium nitrite (69 g.), water (300 c.c.), and ice (250 g.) in the usual manner, was condensed with hydroxyiminoacetone (100 g.) as described for benzenediazonium chloride. The crude product was boiled under reflux for 1 hr. with 2N-sodium hydroxide (1500 c.c.) and the extract was clarified (carbon) and filtered. Acidification of the filtrate with hydrochloric acid afforded crude 1-p-*carboxyphenyl*-1-*hydroxyiminoacetone* (145 g., 70%), m. p. 174—176°, which, after crystallisation from water (3300 c.c.), melted at 186° (Found: C, 57·5; H, 4·45; N, 6·75. $C_{10}H_9O_4N$ requires C, 57·95; H, 4·35; N, 6·75%).

The other *derivatives* of 1-hydroxyimino-1-phenylacetone shown in the Table were prepared similarly. [The m. p. (72°) given in the literature (D.R.-P. 294,159) for 4-amino-2-methoxyacetanilide is erroneous. A sample of the amine had m. p. 120—121° after crystallisation from butan-1-ol (Found: C, 60·1; H, 6·75; N, 15·55; OMe, 16·85. Calc. for $C_9H_{12}O_2N_2$: C, 60·0; H, 6·65; N, 15·55; OCH_3, 17·2%).]

1-*Hydroxyimino*-1-3′-*pyridylacetone*. A solution of 3-aminopyridine (23·5 g.) in hydrochloric acid (68 c.c.; *d* 1·18) and water (50 c.c.) was treated with sodium nitrite (17·5 g.) in water (25 c.c.) at 0°. The diazonium solution was condensed with hydroxyiminoacetone (25 g.) in water (215 c.c.) in the presence of sodium acetate (204 g.), cupric sulphate (6·25 g.), and sodium sulphite (1 g.; anhydrous) in the usual manner. The crude product was extracted

with boiling N-sodium hydroxide, the solution was clarified with carbon, and the product (24·5 g., 60%) reprecipitated by addition of acetic acid. Recrystallisation from methanol afforded long, silky needles of *1-hydroxyimino-1-3′-pyridylacetone*, m. p. 201—202° (Found: C, 59·0; H, 5·2; N, 17·0. $C_8H_8O_2N_2$ requires C, 58·55; H, 4·9; N, 17·1%).

1-Hydroxyimino-1-phenylacetone derivatives.

R in Me·CO·CR:N·OH	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
o-C_6H_4Me	134—135°	$C_{10}H_{11}O_2N$	68·1	6·3	8·4	67·8	6·2	7·9
m-C_6H_4Cl	145	$C_9H_8O_2NCl$	—	—	7·0	—	—	7·1
p-C_6H_4Cl	177	$C_9H_8O_2NCl$ *	54·8	4·7	7·25	54·7	4·2	7·1
p-NHAc·C_6H_4	187—188	$C_{11}H_{12}O_3N_2$	—	—	12·8	—	—	12·75
p-NO_2·C_6H_4	202	$C_9H_8O_4N_2$	52·3	4·05	13·8	51·9	3·85	13·45
4 : 3-NHAc·C_6H_3(OMe)	213—215 ‡	$C_{12}H_{14}O_4N_2$ †	57·4	5·8	11·55	57·6	5·6	11·2

* Found: Cl, 18·45. Reqd.: Cl, 17·95%. † Found: OMe, 12·7. Reqd.: OMe, 12·4%.
‡ With decomp.

Preparation of Pyrazine Derivatives.—2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine.* Zinc dust (80 g.) was added portionwise to a stirred solution of 1-hydroxyimino-1-phenylacetone (60 g.) in 5N-sodium hydroxide (600 c.c.) at 25—30°. The mixture was stirred for 2 hr., then diluted with water (600 c.c.) and filtered. The product was extracted with hot chloroform (500 c.c.), and air was bubbled through the extract for 15 min. After being dried ($MgSO_4$), the solution was evaporated and the residue was distilled at 1 mm. The gummy distillate was rubbed with a little ether, and the resulting solid crystallised from dilute acetic acid, giving 2 : 5-dimethyl-3 : 6-diphenylpyrazine (19·1 g., 40%), m. p. 126° (Kolb, *Annalen*, 1896, **291**, 267, gives m. p. 125—126°).

2 : 5-*Dimethyl*-3 : 6-*di*-o-*tolylpyrazine*, prepared similarly from 1-hydroxyimino-1-*o*-tolylacetone (36 g.), 5N-sodium hydroxide (320 c.c.), and zinc dust (43 g.), had m. p. 110—111° after recrystallisation from acetone, methanol, and dilute acetic acid (Found: C, 82·8; H, 6·8; N, 10·1. $C_{20}H_{20}N_2$ requires C, 83·3; H, 6·9; N, 9·7%).

2 : 5-*Di*-m-*chlorophenyl*-3 : 6-*dimethylpyrazine* was prepared similarly from 1-*m*-chlorophenyl-1-hydroxyiminoacetone. After crystallisation from acetic acid and from acetone the *compound* had m. p. 160° (Found: C, 66·0; H, 4·25; N, 8·8; Cl, 21·3. $C_{18}H_{14}N_2Cl_2$ requires C, 65·65; H, 4·25; N, 8·5; Cl, 21·6%).

2 : 5-*Di*-p-*chlorophenyl*-3 : 6-*dimethylpyrazine*, also prepared similarly, melted at 224—225° (Found: C, 65·65; H, 4·15; N, 8·35; Cl, 21·15%).

2 : 5-*Dimethyl*-3 : 6-*di*-3′-*pyridylpyrazine* was prepared from 1-hydroxyimino-1-3′-pyridylacetone (17·7 g.) and 5N-sodium hydroxide (185 c.c.) by treatment with zinc dust (25 g.) in the above manner. The crude product was extracted with chloroform and air was bubbled through the extract for 15 min. The chloroform was removed, the residue was dissolved in hot 2N-hydrochloric acid (100 c.c.), and the extract was clarified with carbon and basified with sodium hydroxide. The precipitated product (7·65 g., 54%) recrystallised from methanol or ethanol, after which the *compound* melted at 202—203° (Found: C, 73·1; H, 5·1; N, 21·35. $C_{16}H_{14}N_4$ requires C, 73·3; H, 5·25; N, 21·35%).

When boiled under reflux with methyl iodide (125 c.c.) for 16 hr., the compound (6·38 g.) yielded the *dimethiodide* (6·2 g.), m. p. 250° (decomp.) (Found: C, 39·25; H, 3·7; N, 10·0; I, 46·8. $C_{18}H_{20}N_4I_2$ requires C, 39·6; H, 3·65; N, 10·25; I, 46·5%).

2 : 5-*Di*-p-*carboxyphenyl*-3 : 6-*dimethylpyrazine.* A cooled (ice-bath) solution of 1-*p*-carboxyphenyl-1-hydroxyiminoacetone (104 g.) in 5N-sodium hydroxide (1 l.) was treated with zinc dust (106 g.), added portionwise below 30°. The mixture was diluted with water (1 l.) and filtered at 90—95°. Hydrochloric acid (*d* 1·18) was added until the filtrate was no longer alkaline to Brilliant-yellow; the alkalinity was just restored by addition of sodium carbonate, and the solution was filtered. A hot solution of mercuric chloride (280 g.) in water (800 c.c.) was added to the filtrate, which had been brought to pH 7—7·5 with acetic acid, at 40° with stirring. After 5 min., sodium carbonate was added until the solution was alkaline to Brilliant-yellow. The filtrate was acidified (Congo-red) with hydrochloric acid and the precipitate was collected and redissolved in hot, dilute sodium carbonate (1 l.). After filtration through kieselguhr, the solution was acidified with hydrochloric acid, and the crude product (55—60 g.) was collected and dried. After crystallisation from boiling pyridine, the *compound* (40—45 g., 50%) had

m. p. >320° (Found : C, 68·5; H, 4·75; N, 7·65. $C_{20}H_{16}O_4N_2$ requires C, 68·95; H, 4·6; N, 8·05%).

2 : 5-*Di*-p-*carbamoylphenyl*-3 : 6-*dimethylpyrazine*.—2 : 5-Di-*p*-carboxyphenyl-3 : 6-dimethylpyrazine (3·5 g.) was boiled under reflux with phosphorus pentachloride (4·5 g.) and phosphoryl chloride (30 c.c.) until completely dissolved. After removal of the latter by distillation under reduced pressure, the residue was warmed with an excess of aqueous ammonia (*d* 0·88) for 10 min. The *compound* (2·9 g.) was collected, washed with water, and dried; it had m. p. >340° (Found : N, 15·7. $C_{20}H_{18}O_2N_4$ requires N, 16·2%).

2 : 5-*Di*-p-*methoxycarbonylphenyl*-3 : 6-*dimethylpyrazine*.—2 : 5-Di-*p*-carboxyphenyl-3 : 6-dimethylpyrazine (60·9 g.) was boiled under reflux with thionyl chloride (260 c.c.) and pyridine (2 c.c.) until completely dissolved. After removal of excess of thionyl chloride by distillation, the residue was boiled under reflux with methanol (435 c.c.) for 3 hr. The solution was cooled and the ester was collected. After the crude product had been extracted with further methanol (100 c.c.), the residue (63·3 g., 96%) was crystallised from acetic acid and from dioxan. The pure *ester* (46·6 g., 71%) had m. p. 243—244° (Found : C, 70·15; H, 5·15; N, 7·65. $C_{22}H_{20}O_4N_2$ C, 70·2; H, 5·3; N, 7·45%).

2 : 5-*Di*-p-*aminophenyl*-3 : 6-*dimethylpyrazine*.—(*a*) 2 : 5-Di-*p*-carbamoylphenyl-3 : 6-dimethylpyrazine (2·8 g.) was added to sodium hypobromite prepared from sodium hydroxide (4 g.), water (35 c.c.), and bromine (1 c.c.). After being stirred for 5 min., the mixture was diluted with water (10 c.c.), heated on the steam-bath for 30 min., and cooled. The product was collected and dissolved in warm 2N-hydrochloric acid. The solution was clarified with carbon and added to a slight excess of boiling 2N-sodium hydroxide. The *diamine* (1·4 g., 60%) was collected and dried. It separated from 2-ethoxyethanol as pale yellow crystals, m. p. 277° (Found : N, 18·85. $C_{18}H_{18}N_4$ requires N, 19·3%).

(*b*) Zinc dust (40 g.) was added portionwise to a stirred solution of 1-*p*-acetamidophenyl-1-hydroxyiminoacetone (40 g.) in acetic acid (200 c.c.) and water (200 c.c.) at 60—75°. The solution was filtered at 55° and the filtrate was treated with ammonium chloride (80 g.) and excess of aqueous ammonia (*d* 0·88). The product was dissolved in hot acetic acid (400 c.c.), and the solution was filtered. The filtrate was diluted with water (1 l.) and basified with sodium hydroxide. The precipitate was collected and redissolved in hot acetic acid (400 c.c.) and the solution was diluted with water. Crystallisation of the product (14·3 g., 42%) from nitrobenzene afforded 2 : 5-*di*-p-*acetamidophenyl*-3 : 6-*dimethylpyrazine*, white needles, m. p. >300° (Found : C, 71·0; H, 5·8; N, 15·25. $C_{22}H_{22}O_2N_4$ requires C, 70·6; H, 5·9; N, 14·95%).

The acetyl compound (10·4 g.) was boiled under reflux with hydrochloric acid (100 c.c.; *d* 1·18) and water (100 c.c.) for 2 hr. The solution was cooled and basified with sodium hydroxide. The diamine (7·9 g.), after crystallisation from 2-ethoxyethanol, had m. p. and mixed m. p. 277°.

2 : 5-*Di*-(4-*amino*-3-*methoxyphenyl*)-3 : 6-*dimethylpyrazine*.—Zinc dust (141 g.) was added portionwise to a solution of 1-(4-acetamido-3-methoxyphenyl)-1-hydroxyiminoacetone (141 g.) in acetic acid (705 c.c.) and water (705 c.c.) with stirring at 60—75°. The mixture was filtered at 60° and the filtrate was treated with ammonium chloride (240 g.) and excess of aqueous ammonia (*d* 0·88). The product was collected and extracted with boiling acetic acid (1800 c.c.). The solution was filtered from tar, and the filtrate was diluted with water (5 l.). 2 : 5-*Di*-(4-*acetamido*-3-*methoxyphenyl*)-3 : 6-*dimethylpyrazine* (32·7 g., 27%) was collected; after crystallisation from acetic acid, it melted at 322° (Found : N, 12·95. $C_{24}H_{26}O_4N_4$ requires N, 12·9%).

The acetyl compound (32·5 g.) was boiled under reflux with 5N-hydrochloric acid (750 c.c.) for 1·5 hr.; the solution was basified with sodium hydroxide and the *amine* was collected. After crystallisation from 2-ethoxyethanol, it melted at 221—223° (Found : N, 15·5. $C_{20}H_{22}O_2N_4$ requires N, 16·0%).

Nitration of 2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine*.—A solution of 2 : 5-dimethyl-3 6-diphenylpyrazine (5·6 g.) in sulphuric acid (25 c.c.; *d* 1·84) was treated with a mixture of nitric acid (2·2 c.c.; *d* 1·5) and sulphuric acid (7 c.c.; *d* 1·84) at 5—10°. The temperature rose spontaneously to 40—42° and the mixture was stirred for a further 5 min. The solution was poured on ice, and the product collected. Crystallisation from pyridine (100 c.c.) afforded 2 : 5-*dimethyl*-3 : 6-*di*-m-*nitrophenylpyrazine* (4·72 g., 61%), m. p. 284—285°. After recrystallisation from pyridine, it had m. p. 285—286° (Found : C, 62·0; H, 4·05; N, 15·8. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0; N, 16·0%).

The nitro-compound (4·72 g.) was boiled under reflux with a solution of stannous chloride (30 g.) in hydrochloric acid (100 c.c.; *d* 1·18) until completely dissolved (2 hr.). The solution was cooled and the product collected. Treatment with concentrated aqueous sodium hydroxide

followed by continuous extraction with ethanol afforded 2 : 5-*di*-m-*aminophenyl*-3 : 6-*dimethylpyrazine* (2·7 g., 69%), m. p. 235—236° (from ethanol) (Found: C, 74·8; H, 6·15; N, 19·6. $C_{18}H_{18}N_4$ requires C, 74·5; H, 6·2; N, 19·3%).

The diamine (2·42 g.) was dissolved in water (80 c.c.) and hydrochloric acid (5 c.c.; *d* 1·18), and the solution was diazotised at 25° by 2N-sodium nitrite (8·3 c.c.). The diazonium solution was added to cuprous chloride (2·5 g.) in hydrochloric acid (75 c.c.; *d* 1·18), the solution diluted with water, and the product collected. After reprecipitation from acetic acid solution and crystallisation from acetic acid and from acetone, it had m. p. 160°, not depressed in admixture with a previous sample of 2 : 5-di-*m*-chlorophenyl-3 : 6-dimethylpyrazine (Found: C, 65·55; H, 4·0; N, 8·5; Cl, 21·1. Calc. for $C_{18}H_{14}N_2Cl_2$: C, 65·65; H, 4·25; N, 8·5; Cl, 21·6%).

2 : 5-*Dimethyl*-3 : 6-*diphenylpyrazine* 1 : 4-*Dioxide*.—2 : 5-Dimethyl-3 : 6-diphenylpyrazine (10·4 g.) was heated at 55—60° for 24 hr. with 30% hydrogen peroxide (18 c.c.) and acetic acid (90 c.c.). Further peroxide (46 c.c.) was added and heating was continued for a further 24 hr. The solution was diluted with water (1 l.) and basified with sodium hydroxide; the *dioxide* (10·12 g., 87%) was collected and dried. After recrystallisation from methanol or ethanol, it had m. p. 259—260° (Found: C, 73·85; H, 5·5; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·5%).

Nitration. A mixture of nitric acid (3 c.c.; *d* 1·5) and sulphuric acid (12 c.c.; *d* 1·84) was added dropwise to a solution of the dioxide (8·76 g.) in sulphuric acid (36 c.c.; *d* 1·84) with stirring at 5—10°. The solution was stirred for 0·5 hr., the temperature rising to 25°; it was then poured on ice and the product (9·25 g.) was collected. Crystallisation from acetic acid afforded 2 : 5-*dimethyl*-3 : 6-*di*-m-*nitrophenylpyrazine* 1 : 4-*dioxide* (5·5 g., 48%), m. p. *ca.* 300° (decomp.) (Found: C, 56·8; H, 3·9; N, 14·5. $C_{18}H_{14}O_6N_4$ requires C, 56·55; H, 3·65; N, 14·65%).

Reduction of this nitro-compound (5·5 g.) by boiling it under reflux with granulated tin (20 g.) and hydrochloric acid (100 c.c.; *d* 1·18) for 1 hr., basifying the solution with sodium hydroxide, and removing the tin with hydrogen sulphide gave 2 : 5-di-*m*-aminophenyl-3 : 6-dimethylpyrazine, m. p. and mixed m. p. 235—236°. Tetrazotisation of this product followed by the Sandmeyer reaction afforded 2 : 5-di-*m*-chlorophenyl-3 : 6-dimethylpyrazine, m. p. and mixed m. p. 160°.

The author thanks Dr. H. Gudgeon for helpful advice and criticism.

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