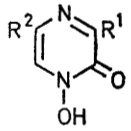
Pyrazines. Part IV.[1] 2,6-Dihydroxy-3,5-diphenylpyrazine and Related Compounds †

By G. W. H. Cheeseman* and R. A. Godwin, Department of Chemistry, Queen Elizabeth College, London W8 7AH

2,6-Dihydroxy-3,5-diphenylpyrazine was prepared by treatment of 1-hydroxy-3,5-diphenylpyrazin-2-one (Ia) with a mixture of acetic anhydride and acetic acid, followed by deacetylation of the resulting 2,6-diacetoxy-3,5-diphenylpyrazine with potassium hydrogen carbonate in methanol. The reaction of the hydroxypyrazinone with phosphoryl chloride gave 2-chloro-6-hydroxy-3,5-diphenylpyrazine. The 1-hydroxy-5(or 3)-methyl-3(or 5)-phenylpyrazinones (Ib and c) underwent similar reactions with phosphoryl chloride, but with acetic anhydride no ring-substituted products were isolated.

In an earlier paper [2] we discussed several unsuccessful attempts to prepare 2,6-dihydroxypyrazine. We now report the successful synthesis of 2,6-dihydroxy-3,5-diphenylpyrazine (5) from 1-hydroxy-3,5-diphenylpyrazin-2-one (1a). 1-Hydroxypyrazin-2-ones are readily prepared by condensation of α-amino-hydroxamic acids with 1,2-dicarbonyl compounds;[3] in the course of our work we also prepared the hydroxypyrazinones (1b and c). 1-Hydroxypyrazin-2-ones are tautomeric with the corresponding 2-hydroxypyrazine 1-oxides and resemble *N*-oxides in most of their reactions.

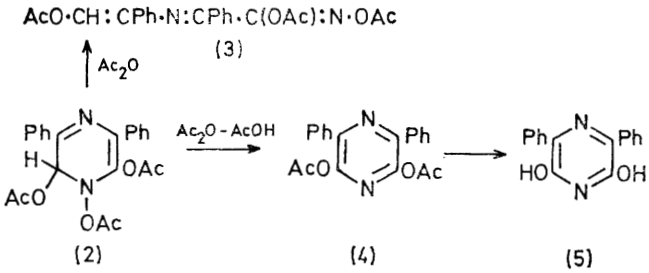


a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = Me$
c; $R^1 = Me$, $R^2 = Ph$

(1)

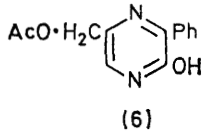
When 1-hydroxy-3,5-diphenylpyrazin-2-one (1a) was heated under reflux with excess of acetic anhydride, a crystalline triacetoxy-compound was obtained which we believe to have the open-chain structure (3). This assignment is consistent with the ^1H n.m.r. spectrum ($CDCl_3$), which showed three methyl singlets at τ 7·4, 7·85, and 8·4, and with carbonyl-stretching i.r. absorptions at 1730, 1750, and 1770 $cm.^{-1}$. When the hydroxypyrazinone (1a) was boiled with a mixture of acetic anhydride and acetic acid, a symmetrical diacetoxy-derivative was obtained, τ ($CDCl_3$) 7·75 (6H, s, 2 × Me), identified as 2,6-diacetoxy-3,5-diphenylpyrazine (4). It is possible that both the di- and tri-acetoxy-compounds are formed from the common intermediate (2). We originally thought that the triacetoxy-compound had the non-aromatic structure (2), but this now seems unlikely since attempts to convert it into the diacetoxy-compound (4) by treatment with acetic anhydride and acetic acid or by heating failed. It may be that the role of the acetic acid in promoting the formation of the diacetoxy-compound (4) from compound (2) is to provide an electrophile (H^+ or its equivalent) to assist in the aromatisation step.

The deacetylation of the 2,6-diacetoxy-compound (4) was attempted by treatment both with methanolic ammonia at 0°, and with potassium hydrogen carbonate in methanol. The former method gave a product shown by its mass spectrum to contain material of molecular weight greater than 500, but the latter was successful and gave 2,6-dihydroxy-3,5-diphenylpyrazine (5). The dihydroxy-compound was isolated as an orange crystalline solid, M^+ 264 (78%), ethanolic solutions of which showed absorption maxima at 278, 354, and 415 nm. but were decolourised on exposure to light. Treatment of the dihydroxy-compound with acetic anhydride regenerated the diacetoxy-compound (4) and reaction with diazomethane gave a mixture of products from which only 2,6-dimethoxy-3,5-diphenylpyrazine was isolated. Ethanolic solutions of the dimethoxy-compound showed absorption maxima at 233, 278, and 346 nm., indicating that the dihydroxy-compound exists predominantly in an alternative tautomeric form in solution. Glutarimide, a pyridine analogue of 2,6-dihydroxy-3,5-diphenylpyrazine, has been found to exist mainly in the monohydroxypyridone form at pH 2·6.[4]



(2) (3) (4) (5)

Our attempts to prepare 2,6-dihydroxypyrazines from the hydroxypyrazinones (1b and c) were frustrated; on treatment of these compounds with either acetic anhydride alone or acetic anhydride–acetic acid mixtures, only monoacetoxy derivatives were obtained. These were the acetoxymethyl compounds (6) and (7) [τ 4·85 (s, CH_2) and 7·8 (s, Me)].



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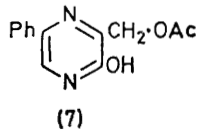


(7)

† A preliminary account of some of this work was presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 1969.

[1] Part III, G. W. H. Cheeseman and R. A. Godwin, preceding paper.

[2] G. W. H. Cheeseman and E. S. G. Törzs, *J. Chem. Soc.*, 1965, 6681.

[3] G. Dunn, J. A. Elvidge, G. T. Newbold, D. W. C. Ramsey, F. S. Spring, and W. Sweeny, *J. Chem. Soc.*, 1949, 2707.

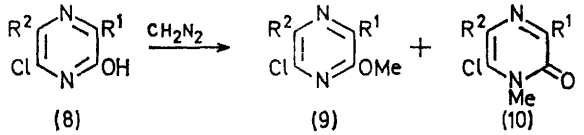
[4] A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc.* (*B*), 1966, 562.

Treatment of the 1-hydroxypyrazinones (1a—c) with phosphoryl chloride gave the 2-chloro-6-hydroxypyrazines (8a—c). The possible formation of the isomeric 2-chloro 1-*N*-oxides was excluded because the products of phosphoryl chloride reaction showed i.r. absorptions characteristic of cyclic amides and no N–O stretching absorptions. Also in their mass spectra a loss of 28 mass units from the molecular ion was observed, rather than the loss of 16 mass units typical of *N*-oxides. The chloro-hydroxy-compounds (8a—c) reacted as expected with ethereal diazomethane to give mixtures of *O*- and *N*-methyl derivatives. Comparison of the u.v. spectra of the parent hydroxy-compounds with those of their *O*- and *N*-methyl derivatives (Table) indicates that in ethanolic solution the

U.v. spectra of chloro-hydroxypyrazines and their fixed tautomers in ethanol

	$\lambda_{max.}$ [nm. (ε)]
(8a)	234 (20,150), 265 (16,200), 339 (17,100)
(9a)	234 (20,100), 265 (19,000), 334 (18,700)
(10a)	244sh (14,200), 272 (19,900), 374 (17,200)
(8b)	252 (11,000), 332 (15,100)
(9b)	254 (14,600), 326 (19,500)
(10b)	237 (9000), 258 (10,400), 370 (19,800)
(8c)	255 (10,100), 314 (8300)
(9c)	254 (12,600), 312 (10,400)
(10c)	265 (15,000), 339 (7900)

predominant tautomers are the hydroxy-forms. Katritzky and his colleagues [5] have previously found that, in ethanol, 2-chloro-6-hydroxypyridine also exists predominantly in the hydroxy-form. These results contrast with the marked preference of unsubstituted 2-hydroxypyrazine [6] and 2-hydroxypyridine [7] to exist in the pyrazinone and pyridone form, respectively. A chloro-substituent is thought to favour hydroxy-forms because of its base-weakening effect.



(8) (9) (10)

a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = Me$
c; $R^1 = Me$, $R^2 = Ph$

The chlorine atom in the *N*-methylpyrazinone (10a) was readily displaced with methanolic sodium methoxide; however, acidification of the reaction mixture with dilute hydrochloric acid to pH 2 gave the hydrochloride of 6-hydroxy-1-methyl-3,5-diphenylpyrazin-2-one. This ready hydrolysis of the intermediate 6-methoxy-derivative was not anticipated. An attempt to displace the chlorine atom from 2-chloro-6-hydroxy-3,5-diphenylpyrazine (8a) by high temperature reaction with methanolic sodium methoxide, which might, by analogy with the reported preparation of 2,5-dihydroxy-3,6-diphenylpyrazine,[8] have produced 2,6-dihydroxy-3,5-diphenylpyrazine (5), instead gave the known 2-hydroxy-3,5-diphenylpyrazine.

EXPERIMENTAL

I.r. spectra were measured on a Perkin-Elmer 237 instrument for Nujol mulls and u.v. spectra on a Unicam SP 800 spectrometer. ^1H N.m.r. spectra were measured on a Perkin-Elmer R10 machine operating at 60 MHz and mass spectra on an A.E.I. MS9 spectrometer.

1-Hydroxy-5-methyl-3-phenylpyrazin-2-one (1b).—To a suspension of 2-amino-2-phenylacetohydroxamic acid (12·0 g., 0·072 mole) in methanol (100 ml.) and water (80 ml.) was added a 40% solution of methylglyoxal (12·5 ml., 0·07 mole) in methanol (100 ml.) at −60°. 5N-Sodium hydroxide (20 ml.) was then slowly added at −30° and the mixture was allowed to warm to 0°. It was kept overnight at 0°, then filtered, acidified to pH 2 with 2N-hydrochloric acid, and cooled to 0°. Crystals of the *hydroxypyrazinone* (7·42 g., 52%), m.p. 144—145°, separated. Recrystallisation twice from benzene gave a sample, m.p. 149—150° (Found: C, 65·3; H, 5·0; N, 14·15. $C_{11}H_{10}N_2O_2$ requires C, 65·3; H, 5·0; N, 13·85%).

The Action of Acetic Anhydride on 1-Hydroxy-3,5-diphenylpyrazin-2-one (1a).—Acetic anhydride (15 ml.) was added to 1-hydroxy-3,5-diphenylpyrazin-2-one [3] (1·0 g.) and the mixture was heated under reflux for 1 hr. The solvent was removed under reduced pressure and to the residue was added a small quantity of methanol (0·5 ml.) to promote crystallisation. Recrystallisation from methanol afforded a solid (0·85 g., 55%), m.p. 170—171° (Found: C, 65·1; H, 5·0; N, 6·9. Calc. for $C_{22}H_{20}N_2O_6$: C, 64·7; H, 5·0; N, 6·9%).

2,6-Diacetoxy-3,5-diphenylpyrazine (4).—(*a*) Acetic anhydride (15 ml.) and acetic acid (3 ml.) were added to 1-hydroxy-3,5-diphenylpyrazin-2-one (1·0 g.) and the mixture was heated under reflux for 1 hr. The solvent was removed under reduced pressure and to the residue was added a small quantity (0·5 ml.) of methanol to promote crystallisation. Recrystallisation from methanol afforded *2,6-diacetoxy-3,5-diphenylpyrazine* (0·60 g., 46%), m.p. 171—172° (Found: C, 69·0; H, 4·7; N, 7·9. $C_{20}H_{16}N_2O_4$ requires C, 68·9; H, 4·6; N, 8·0%).

(*b*) Acetic anhydride (5 ml.) was added to 2,6-dihydroxy-3,5-diphenylpyrazine (0·2 g.) and the mixture was heated under reflux for 1 hr. The solvent was evaporated off under reduced pressure and the residue was recrystallised from methanol to give 2,6-diacetoxy-3,5-diphenylpyrazine (0·14 g., 53%), m.p. 169—170°, identical with the foregoing sample.

2,6-Dihydroxy-3,5-diphenylpyrazine (5).—2,6-Diacetoxy-3,5-diphenylpyrazine (1·0 g.) in methanol (100 ml.) and potassium hydrogen carbonate (1·0 g.) were heated under reflux for 3 hr. The mixture was adjusted to pH 3 with hydrochloric acid, filtered, and evaporated to dryness under reduced pressure. Recrystallisation of the residue from acetone and then nitromethane afforded *2,6-dihydroxy-3,5-diphenylpyrazine* (0·49 g., 65%), m.p. 258—259° (decomp.) (Found: C, 72·7; H, 4·6; N, 10·6. $C_{16}H_{12}N_2O_2$ requires C, 72·7; H, 4·6; N, 10·6%).

2,6-Dimethoxy-3,5-diphenylpyrazine.— Diazomethane

[5] A. R. Katritzky, J. D. Rowe, and S. K. Roy, *J. Chem. Soc.* (*B*), 1967, 758.
[6] G. W. H. Cheeseman, *J. Chem. Soc.*, 1960, 242.
[7] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 311.
[8] G. Karmas and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1957, **79**, 680.

[from methylnitrosourea (13·5 g.) in ether (110 ml.)] was slowly added at 0° to a stirred solution of 2,6-dihydroxy-3,5-diphenylpyrazine (1·43 g.) in methanol (100 ml.). The mixture was stirred for 4 hr. at 0° and 16 hr. at room temperature. The slight precipitate was then filtered off and the solvent was removed under reduced pressure. The residue was recrystallised from methanol to yield 2,6-*dimethoxy*-3,5-*diphenylpyrazine* (0·23 g., 15%), m.p. 98—99° (Found: C, 73·8; H, 5·4; N, 9·4. $C_{18}H_{16}N_2O_2$ requires C, 73·9; H, 5·5; N, 9·6%).

5-*Acetoxymethyl*-2-*hydroxy*-3-*phenylpyrazine* (6).—Acetic anhydride (15 ml.) was added to 1-hydroxy-5-methyl-3-phenylpyrazin-2-one (1·0 g.) and the mixture was heated under reflux for 1 hr. The solvent was removed under reduced pressure and to the residue was added a small quantity of methanol (0·5 ml.) to promote crystallisation. The solid (0·50 g., 41%), was filtered off, washed with methanol, and dried. Recrystallisation from toluene afforded 5-*acetoxymethyl*-2-*hydroxy*-3-*phenylpyrazine*, m.p. 186—187° (Found: C, 63·9; H, 5·2; N, 11·2. $C_{13}H_{12}N_2O_3$ requires C, 63·9; H, 4·95; N, 11·5%).

3-*Acetoxymethyl*-2-*hydroxy*-5-*phenylpyrazine* (7).—Acetic anhydride (15 ml.) was added to 1-hydroxy-3-methyl-5-phenylpyrazin-2-one (1·0 g.) and the mixture was heated under reflux for 1 hr. The solvent was removed under reduced pressure and to the residue was added a small quantity of methanol (0·5 ml.) to promote crystallisation. The solid (0·22 g., 18%) was filtered off, washed with methanol, and dried. Recrystallisation from toluene afforded 3-*acetoxymethyl*-2-*hydroxy*-5-*phenylpyrazine*, m.p. 187—188° (Found: C, 64·2; H, 4·95; N, 11·2%).

2-*Chloro*-6-*hydroxypyrazines* (8).—1-Hydroxy-3,5-diphenylpyrazin-2-one (8·0 g.) was added to phosphoryl chloride (60 ml.) and the mixture was heated under reflux for 1 hr., then concentrated to one-third bulk and poured into well stirred ice–water. The solid product was filtered off, dried, and extracted with benzene to give a pale yellow solid (5·09 g., 60%). Three recrystallisations from 96% ethanol afforded 2-*chloro*-6-*hydroxy*-3,5-*diphenylpyrazine* (8a), m.p. 244—246° (Found: C, 68·1; H, 3·7; N, 9·8. $C_{16}H_{11}ClN_2O$ requires C, 68·0; H, 3·9; N, 9·9%).

Similarly were prepared 2-*chloro*-6-*hydroxy*-5-*methyl*-3-*phenylpyrazine* (8c) (55%), m.p. 181—182° (decomp.) (Found: C, 60·1; H, 4·0; N, 12·6. $C_{11}H_9ClN_2O$ requires C, 59·9; H, 4·1; N, 12·7%), and 2-*chloro*-6-*hydroxy*-3-*methyl*-5-*phenylpyrazine* (8b) (31%), m.p. 185—186° (Found: C, 58·9; H, 4·0; N, 12·35%). Both compounds were crystallised from benzene.

2-*Chloro*-6-*methoxy*-3,5-*diphenylpyrazine* (9a) *and* 6-*Chloro*-1-*methyl*-3,5-*diphenylpyrazin*-2-*one* (10a).—Diazomethane [from methylnitrosourea (18·0 g.) in ether (150 ml.)] was slowly added at 0° to a stirred suspension of 2-chloro-6-hydroxy-3,5-diphenylpyrazine (4·0 g.) in methanol (110 ml.). The mixture was stirred for 4 hr. at 0° and 9 hr. at room temperature. Insoluble material was then filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallised from methanol to give a first crop (1·21 g.), m.p. 145—147°, and a second crop (1·49 g.), m.p. 87—88°. Three recrystallisations of the first crop afforded 6-*chloro*-1-*methyl*-3,5-*diphenylpyrazin*-2-*one*, m.p. 159—160° (Found: C, 68·6; H, 4·3; N, 9·4. $C_{17}H_{13}ClN_2O$ requires C, 68·8; H, 4·4; N, 9·4%). Two recrystallisations of the second crop afforded 2-*chloro*-6-*methoxy*-3,5-*diphenylpyrazine*, m.p. 95—96° (Found: C, 68·9; H, 4·6; N, 9·4%).

2-*Chloro*-6-*methoxy*-5-*methyl*-3-*phenylpyrazine* (9c) *and* 6-*Chloro*-1,3-*dimethyl*-5-*phenylpyrazin*-2-*one* (10c).—Diazomethane [from methylnitrosourea (18·0 g.) in ether (150 ml.)] was slowly added at 0° to a stirred solution of 2-chloro-6-hydroxy-5-methyl-3-phenylpyrazine (3·44 g.) in methanol (100 ml.). The mixture was stirred for 6 hr. at 0° and 12 hr. at room temperature. The slight precipitate was then filtered off, the filtrate was evaporated to dryness under reduced pressure, and the residue in benzene was filtered through a column of silica gel. The chromatogram was developed first with 5% ethyl acetate–benzene to afford 2-*chloro*-6-*methoxy*-5-*methyl*-3-*phenylpyrazine* (1·21 g., 33%), m.p. 80—81° (Found: C, 61·1; H, 4·7; N, 11·6. $C_{12}H_{11}ClN_2O$ requires C, 61·4; H, 4·7; N, 11·9%). Further elution, with 30% ethyl acetate–benzene, gave 6-*chloro*-1,3-*dimethyl*-5-*phenylpyrazin*-2-*one* (1·83 g., 50%), m.p. 132—133° (decomp.) (Found: C, 61·3; H, 4·8; N, 11·8%).

2-*Chloro*-6-*methoxy*-3-*methyl*-5-*phenylpyrazine* (9b) *and* 6-*Chloro*-1,5-*dimethyl*-3-*phenylpyrazin*-2-*one* (10b).—Diazomethane [from methylnitrosourea (13·5 g.) in ether (70 ml.)] was slowly added at 0° to a stirred solution of 2-chloro-6-hydroxy-3-methyl-5-phenylpyrazine (2·74 g.) in methanol (100 ml.). The mixture was stirred for 4 hr. at 0° and 24 hr at room temperature. The slight precipitate was then filtered off, the filtrate was evaporated to dryness under reduced pressure, and the residue in benzene was filtered through a column of silica gel. Elution with 2% ethyl acetate–benzene afforded 2-*chloro*-6-*methoxy*-3-*methyl*-5-*phenylpyrazine* (0·75 g., 26%), m.p. 55—56° (Found: C, 61·6; H, 4·8; N, 11·8%). Further elution, with 8% ethyl acetate–benzene, gave 6-*chloro*-1,5-*dimethyl*-3-*phenylpyrazin*-2-*one* (1·21 g., 42%), m.p. 92—93° (Found: C, 61·6; H, 4·7; N, 12·0%).

6-*Hydroxy*-1-*methyl*-3,5-*diphenylpyrazin*-2-*one Hydrochloride*.—Methanolic sodium methoxide [from sodium (0·7 g.) and methanol (20 ml.)] was added to 6-chloro-1-methyl-3,5-diphenylpyrazin-2-one (1·0 g.). The mixture was heated under reflux for 1 hr., diluted with water (50 ml.), and acidified to pH 2 with hydrochloric acid. 6-*Hydroxy*-1-*methyl*-3,5-*diphenylpyrazin*-2-*one hydrochloride* (0·83 g., 78%) was filtered off; m.p. 230—231° (decomp.) (from methanol) (Found: C, 64·6; H, 4·8; N, 8·9. $C_{17}H_{15}ClN_2O_2$ requires C, 64·9; H, 4·8; N, 8·9%).

2-*Hydroxy*-3,5-*diphenylpyrazine*.—A mixture of 2-chloro-6-hydroxy-3,5-diphenylpyrazine (0·82 g.) and an excess of methanolic sodium methoxide [from sodium (2·15 g.) and methanol (25 ml.)] was heated in a sealed tube at 150° for 56 hr. and then poured into water (30 ml.). The solution was filtered and acidified to pH 7 with acetic acid. The precipitate was filtered off, washed with water, and dried. Recrystallisation from methanol afforded 2-hydroxy-3,5-diphenylpyrazine, m.p. 273—274° (lit.,[3] 270—272°) (Found: N, 11·5. Calc. for $C_{16}H_{12}N_2O$: N, 11·3%).

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