Heterocyclic Imines and Amines. Part XVI.[1] 2,6-Diaminopyrazine and its 1-Oxide from Iminodiacetonitrile

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With palladium–charcoal, 2,6-bishydroxyiminopiperazine (made from iminodiacetonitrile and hydroxylamine at 70°) underwent hydrogen transfer to yield 2,6-diaminopyrazine, characterised as the diacetyl derivative. From iminodiacetonitrile and hydroxylamine in the cold, the bis(amide oxime) resulted but in the hot with added hydroxylamine hydrochloride—conditions which effected a cycloaddition even to nitrilotriacetonitrile—a hydrated complex of 2,6-bishydroxyiminopiperazine and hydroxylamine hydrochloride was formed, together with 2-amino-6-hydroxyaminopyrazine 1-oxide. Reduction of the latter afforded 2,6-diaminopyrazine 1-oxide, which was acetylated to 2,6-diacetamidopyrazine 1-oxide; the latter was deoxygenated to 2,6-diacetamidopyrazine. Attempts to prepare the mono(amide oxime) of iminodiacetonitrile led to a self-condensation product of aminoacetamide oxime, namely 2,5-bishydroxyiminopiperazine. In comparative experiments, *o*-cyanobenzyl cyanide gave with hydroxylamine 1-amino-3-hydroxyaminoisoquinoline, and with a mixture of hydroxylamine and its hydrochloride in the hot, 1,2,3,4-tetrahydro-1,3-bishydroxyiminoisoquinoline. Aspects of the mass spectra of the various compounds are reported.

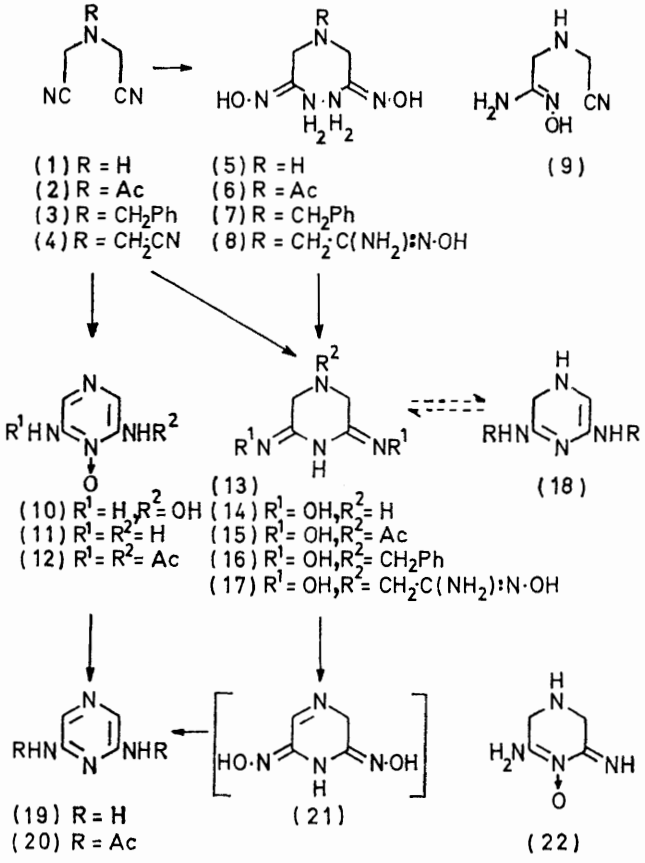
2,6-Di-iminopiperazines[2] (13) are formal tautomers of 2,6-diamino-dihydropyrazines (18) and so ought to aromatise under dehydrogenative conditions. Our first studies of this possibility have led to two new routes to the relatively inaccessible 2,6-diaminopyrazine[3] (19).

[1] Part XV, J. A. Elvidge and A. P. Redman, *J.C.S. Perkin I*, 1972, 2820.

[2] N. R. Barot and J. A. Elvidge, *J.C.S. Perkin I*, 1972, 1009.

[3] K. H. Schaaf and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1949, **71**, 2043.

Catalytic Aromatisation.—Attempts to aromatise 2,6-bishydroxyiminopiperazine (14), available [2] from hydroxylamine and iminodiacetonitrile (1), by using



hydroxylamine in acid medium as a hydrogen acceptor (the base was clearly useless), and also hydrogen peroxide–iron(II) chloride,[4] were abortive, the cyclic dioxime (14) being recovered. Use of palladium–charcoal, however, was moderately successful and when the dioxime (14) was heated with this catalyst in boiling *o*-dichlorobenzene, water was evolved; cooling the solution then afforded yellow 2,6-diaminopyrazine (19) which was characterised as the stable diacetyl derivative (20). It seemed likely that the catalyst abstracted hydrogen from the ring of 2,6-bishydroxyiminopiperazine (14) and that the immediate product (21) tautomerised to 2,6-bishydroxyaminopyrazine which was reduced by the hydrogen on the catalyst to water and the diamine (19). The mass spectrum of the crude diamine (M^+ 110) provided evidence for this. It showed the presence of the intermediate 2-amino-6-hydroxyaminopyrazine (M^+ 126) with a fragmentation pattern similar, below *m/e* 126, to that of the 1-oxide (10) encountered subsequently. Because of the hydrogen deficiency on the catalyst, the maximum yield of the diamine (19) could only be 50%: the observed yield was 20% of that. When cyclohexene or tetralin was added to the reaction mixture as an additional source of transferable hydrogen,[5] no improvement in the yield of diamine (19) resulted. However, the sensitive 2,6-diaminopyrazine (19) was no longer contaminated by any reaction intermediate, the mass spectrum indicating that the diamine was pure. As with other aromatic amines, the primary fragmentation process undergone by the molecular ion was loss of HCN.

Aromatisation with Hydroxylamine.—The 2,6-bishydroxyiminopiperazine (14) used for the foregoing new preparation of 2,6-diaminopyrazine had been obtained [2] from the dinitrile (1) and hydroxylamine at 70° in only 14% yield, much resin being formed, so better conditions were sought. At ambient temperature the reaction proceeded a stage less far and gave acyclic iminobis(acetamide oxime) (5) in 50% yield. Similarly, the *N*-acetyl- and -benzyl-iminodiacetonitriles (2) and (3) afforded the corresponding bis(amide oximes), (6) and (7), which cyclised under mildly acidic conditions to the known 2,6-bishydroxyiminopiperazines (15) and (16). These two compounds had earlier been prepared [2] in good yield directly from the 4-substituted iminodiacetonitriles (2) and (3), by use of a mixture of hydroxylamine and its hydrochloride in boiling aqueous methanol. The effectiveness of these cyclisation conditions was further shown by the production of the imide dioxime (17) from nitrilotriacetonitrile (4), other attempts at cycloaddition of hydroxylamine having failed.[2] Incidentally, it was found that the compound thought [2] to have been (17) was in fact its hydrochloride. Application of these conditions to iminodiacetonitrile itself (1) and to iminobis(acetamide oxime) (5) unexpectedly afforded a hydrated molecular complex (C) of the cyclic dioxime (14) and hydroxylamine hydrochloride, with the composition $(C_4H_8N_4O_2)_2,(\overset{+}{N}H_3OH\ \bar{C}l),H_2O$. This complex dissociated on dissolution in hot methanol and the cyclic dioxime (14) crystallised out. The complex (C) was reformed by cooling a hot saturated solution of the dioxime (14) and hydroxylamine hydrochloride. The dioxime hydrochloride hydrate, prepared in the course of elucidating the nature of the complex (C), had different m.p. and i.r. spectrum, and was stable to recrystallisation.

As the yield of the cyclic dioxime complex (C) from iminodiacetonitrile was only 40%, further product was sought in the filtrate. From this, the pale yellow monohydrate of 2-amino-6-hydroxyaminopyrazine 1-oxide (10) was isolated in 20% yield. This formed a hydrated picrate, but various attempts at acetylation gave black resin. Dehydration of the base hydrate occurred at 90—102° as shown by thermogravimetric analysis. Being a hydroxylamine, the compound (10) reduced Fehling's solution and Tollens' reagent [6]

[4] K. Pfister, A. P. Sullivan, J. Weijlard, and M. Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4955.

[5] R. P. Linstead, E. A. Braude, P. W. D. Mitchell, K. R. H. Wooldridge, and L. M. Jackman, *Nature*, 1952, **169**, 100.

[6] *Cf.* A. Kirpal and E. Reiter, *Ber.*, 1925, **58**, 699.

and gave a purple-red colour immediately with triphenyltetrazolium chloride and alkali.[7] As a 2-amino-1-aza-arene 1-oxide, the product (10) gave a pure blue colour [8,9] with iron(III) chloride. This colour changed to turquoise with an excess of the reagent, a colour indicative of 2-hydroxyamino-1-aza-arenes.[8] The intense maximum at 338 nm in the u.v. spectrum of compound (10) supported an aromatic structure, as did the ^{1}H n.m.r. spectrum, which showed that the ring was unsymmetrically substituted, there being separate signals (near τ 2·45) from the 3- and 5-protons on the ring. The expected weak coupling was observed in the spectrum of a solution in trifluoroacetic acid. The mass spectrum of the 2-amino-6-hydroxyaminopyrazine 1-oxide (10) indicated that loss of O from the molecular ion (*m/e* 142) was a favourable process, as for some other *N*-oxides.[10] The product ion with *m/e* 126 was responsible for the base peak. There was then loss of HCN to give an ion with *m/e* 99, the process giving rise to a metastable peak at *m/e* 78. A minor process, for which there was a weak metastable peak at 110, was loss of OH from the molecular ion (presumably from the hydroxyamino-group) to give an ion with *m/e* 125, from which loss of NH, NO, and HNO gave ions with *m/e* 110, 95, and 94. Further fragmentation of the ions with *m/e* 99—94 then gave ions with *m/e* 83, 82, 67, 66, 55, 41, and 40.

Catalytic reduction of the 2-amino-6-hydroxyaminopyrazine 1-oxide (10) in acetic acid with Adams catalyst effected an uptake of 1 molecular proportion of hydrogen and gave a product $C_4H_6N_4O$. Reduction of the hydroxyamino- rather than the *N*-oxide function was expected.[11] That the product was indeed 2,6-diaminopyrazine 1-oxide (11) was indicated by the pure blue colour given with iron(III) chloride. Moreover, the test with triphenyltetrazolium chloride and alkali was now negative. Confirmation of the constitution (11) came from the equivalence of the 3- and 5-protons, shown by the ^{1}H n.m.r. spectrum, and by the strong i.r. absorption at 1225 and 841 cm^{-1} characteristic of heteroaromatic *N*-oxide stretching and deformation.[12] In the mass spectrum of 2,6-diaminopyrazine 1-oxide (11), the base peak at *m/e* 126 arose from the molecular ion and a weak peak at *m/e* 110 showed that loss of O from the *N*-oxide was here a minor process.[10] The major fragmentation, for which there was a metastable peak at *m/e* 78, was 126 ⟶ 99 as before, and this was followed by a fragmentation similar to that observed in the spectrum of compound (10).

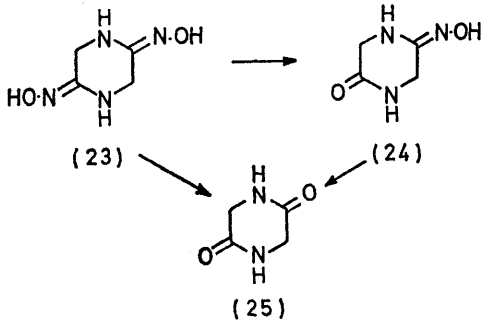
By keeping the diaminopyrazine 1-oxide (11) with acetic anhydride, 2,6-diacetamidopyrazine 1-oxide (12) was obtained quantitatively. This still showed *N*-oxide absorption in the i.r. but the NH_2 bands had been replaced by amide absorption and the compound gave no specific colouration with iron(III) chloride. Deoxygenation of this *N*-oxide (12) with sodium dithionite then afforded 2,6-diacetamidopyrazine (20), which showed no *N*-oxide bands in the i.r. and had the expected ^{1}H n.m.r. and mass spectra. The mass spectrum showed loss of CH_2CO twice from the molecular ion (*m/e* 194), to give ions with *m/e* 152 and 110, and then fragmentation to ions with *m/e* 83, 82, 67, 66, 55, and 40. The base peak was at *m/e* 43, corresponding to Ac^+. The mass spectrum of the precursor (11) exhibited similar features. For example, the molecular ion (*m/e* 210) lost CH_2CO twice to give ions with *m/e* 168 and 126, and there was a metastable peak at *m/e* 134 corresponding to the first of these fragmentations. The fragment ion with *m/e* 126 had the same composition as diaminopyrazine 1-oxide (11) and indeed fragmented further similarly. The loss of O from the molecular ion of diacetamidopyrazine 1-oxide (12) to give an ion with *m/e* 194 hardly occurred but neither was there loss of OH as with the oximes or hydroxyamino-compounds.

Mechanism of Formation of the Pyrazine Oxide (10).—The formation of the substituted pyrazine 1-oxide (10) from iminodiacetonitrile (1) and a mixture of hydroxylamine and its hydrochloride appeared not to involve dehydrogenation of intermediately formed 2,6-bishydroxyiminopiperazine (14). This compound might have given a pyrazine, not a pyrazine 1-oxide, but in fact was stable under the reaction conditions. The acyclic bis(amide oxime) (5) was not implicated as an intermediate because it cyclised under the conditions solely to the dioxime (14), which was isolated as the molecular complex (C) already described. In attempts to obtain the mono(amide oxime) (9) from iminodiacetonitrile (1) and hydroxylamine, only the bis(amide oxime) (5) was isolated. Nevertheless, the mono(amide oxime) (9) remained a likely first reaction product which could cyclise to a 2-amino-6-iminotetrahydropyrazine 1-oxide (22), substitution of which and dehydrogenation by hydroxylamine would give the observed end-product (10). There are ample precedents in this Series for such substitutions at non-aryl imino-groups. $\alpha\alpha'$-Diaminoaza-arenes are not in general prone to such substitutions, and so the formation from dicyano-amidines and hydroxylamine of 2,6-diaminotriazine 1-oxides,[13] rather than amino-hydroxyamino-compounds (analogously to our reaction), is explicable.

Further efforts to prepare the possible first intermediate, the mono(amide oxime) (9), starting from glycolonitrile, chloroacetonitrile, or aminoacetonitrile all failed. The last nitrile did react cleanly but the immediate product, presumably aminoacetamide oxime, at once underwent self-condensation to precipitate

[7] M. A. T. Rogers, *J. Chem. Soc.*, 1955, 769.
[8] G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1949, S133.
[9] W. Sharp and F. S. Spring, *J. Chem. Soc.*, 1951, 932; G. T. Newbold, W. Sharp, and F. S. Spring, *ibid.*, p. 2679; R. Adams and S. Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 2785.
[10] R. Gigg and B. G. Odell, *J. Chem. Soc.* (*B*), 1966, 218.
[11] E. Ochiai, 'Aromatic Amine Oxides,' Elsevier, New York, 1967, pp. 9, 185.
[12] A. D. Cross and R. A. Jones, 'An Introduction to Practical Infrared Spectroscopy,' Butterworth, London, 1969, p. 93; R. T. Conley, 'Infrared Spectroscopy,' Allyn and Bacon, Boston, 1966, p. 169.
[13] J. T. Shaw, *J. Org. Chem.*, 1962, **27**, 3890.

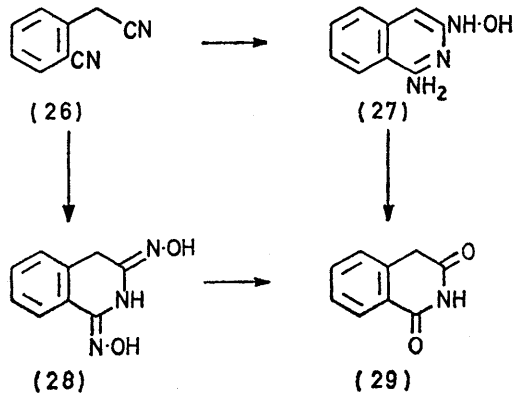
2,5-bishydroxyiminopiperazine (23). This showed i.r. absorption similar in the 3500—2500 and 930 cm^{-1} regions to that of analogous oximes,[2] and, like the imide dioxime (14), gave a positive test with triphenyltetrazolium chloride and alkali. There was no absorption between 1300 and 1100 cm^{-1}, demonstrating the absence of a true *N*-oxide function, although the compound (23) confusingly gave a blue colour with iron(III) chloride like a 2-amino-1-aza-arene 1-oxide. The u.v. absorption maximum at 213 nm, shown by a solution of the compound (23) in methanol, indicated some interaction between the chromophores across the ring. the open-chain tris(amide oxime) (8) being transparent to shorter wavelengths. The ^1H n.m.r. spectrum of the dioxime (23) showed the presence of the two equivalent methylene groups and of two kinds of exchangeable proton. Strong support for the structure (23) also came from the mass spectrum. In this, a metastable peak at *m/e* 112 corresponded to fragmentation of the molecular ion, *m/e* 144, into a fragment ion, *m/e* 127, by loss of OH, features present also in the spectrum of the isomeric 2,6-bishydroxyiminopiperazine (14). However, subsequent fragmentation differed. In neither spectrum was there an initial peak gap of 16 mass units corresponding to loss of O as there was in the spectra of the



N-oxides already discussed. Hydrolysis of the 2,5-bishydroxyiminopiperazine (23) with dilute hydrochloric acid gave the hydrochloride of the mono-oxime (24) whilst nitrous acid converted the dioxime (23) into piperazine-2,5-dione (25).

The foregoing results showed that iminodiacetonitrile and hydroxylamine afforded, according to the conditions, acyclic bis(amide oxime) (5), the imide dioxime (14), or 2-amino-6-hydroxyaminopyrazine 1-oxide (10). Some interest attached therefore to re-examining the reaction between *o*-cyanobenzyl cyanide (26) and hydroxylamine, which in boiling aqueous methanol had given not an *N*-oxide but 1-amino-3-hydroxyaminoisoquinoline (27), as indicated by ^1H n.m.r., u.v., and i.r. spectroscopy.[14] New support for this hydroxyamino-structure (27) came from the hydrolysis with acid to homophthalimide (29), the turquoise colour given with iron(III) chloride, the positive test with triphenyltetrazolium chloride and alkali, and the mass spectrum, which showed that the molecular ion, *m/e* 175, underwent initial losses of O, OH, and H_2O.

When *o*-cyanobenzyl cyanide was treated with hydroxylamine under milder conditions, the same product (27) resulted, no acyclic amide oxime being detected. With a mixture of hydroxylamine and its hydrochloride in boiling aqueous methanol, homophthalimide dioxime (28) was produced, analogously



to the formation of other imide dioximes under these conditions. The new dioxime (28) gave a typical reddish brown colour with iron(III) chloride, and had the expected i.r. absorption and ^1H n.m.r. characteristics. Acidic hydrolysis afforded homophthalimide (29).

EXPERIMENTAL

I.r. spectra (Nujol), u.v. spectra (ethanol), and ^1H n.m.r. spectra were measured respectively with a Unicam SP 200, a Unicam SP 800B, and a Perkin-Elmer R10 60 MHz spectrometer. Mass spectrometric results were obtained with an A.E.I. MS12 instrument.

Concerning Dehydrogenation of 2,6-Bishydroxyiminopiperazine.—(*a*) The piperazine [2] (14) (0·43 g) in methanol (10 ml) and dioxan (3 ml) was heated with hydroxylamine [from the hydrochloride (0·35 g)] in water (5 ml) under reflux in nitrogen for 7 h. Evaporation of the solution to half bulk under reduced pressure provided the molecular complex (C) (i.r. spectrum).

(*b*) The piperazine (14) (0·72 g), 10% hydrogen peroxide (1·7 ml), and iron(II) chloride (3 mg) were stirred together under nitrogen at 60° for 1 h. Brown material separated (0·6 g), identified after recrystallisation (MeOH–H_2O) as compound (14), by mixed m.p. 225° (decomp.) and i.r. spectrum.[2]

(*c*) The piperazine (14) (1 g) and 10% palladium–charcoal (0·2 g) were heated in *o*-dichlorobenzene (100 ml) under reflux in nitrogen for 3 h. Filtration and cooling afforded crude yellow 2,6-diaminopyrazine [3] (19) (0·1 g), *m/e* 150, 148, 146 (1 : 6 : 5 : 10, *o*-dichlorobenzene), 126 (amino-hydroxyaminopyrazine), and 110 (diaminopyrazine). With an excess of acetic anhydride (3 ml) this afforded during 24 h yellow 2,6-diacetamidopyrazine (20) (0·15 g), which was sublimed at 190—200° and 0·2 mmHg (identified by i.r. spectrum; see later).

(*d*) 2,6-Bishydroxyiminopiperazine (14) (1 g), suspended in *o*-dichlorobenzene (80 ml) containing 1,2,3,4-tetrahydronaphthalene (0·5 ml), was heated under reflux in nitrogen for 3 h with 10% palladium–charcoal (0·2 g), more tetralin (0·5 ml) being added at half-time. Filtration and cooling afforded pale yellow 2,6-diaminopyrazine

[14] J. M. Cox, J. A. Elvidge, and D. E. H. Jones, *J. Chem. Soc.*, 1964, 1423.

(80 mg) which was dried under nitrogen, *m/e* 111 (6% of M^+), 110 (M^+) 109, and 83.

Repetition, substituting cyclohexene (2 × 0·3 ml) for the tetralin, gave 2,6-diaminopyrazine (75 mg), *m/e* 110.

Iminobis(acetamide oxime) (5) *and Analogues.*—Iminodiacetonitrile (9·5 g) in methanol (80 ml) was mixed with a solution of hydroxylamine prepared in water (90 ml) from the hydrochloride (27·8 g) and sodium carbonate (21·2 g). After 42 h at 25°, the solution was partially evaporated under reduced pressure, sodium chloride was filtered off, and the filtrate was further concentrated to yield iminobis(acetamide oxime) (8·2 5g, 51%), m.p. 138° (decomp.) (from aqueous methanol) [lit.,[15] 126—127° (decomp.)] (Found: C, 29·65; H, 6·8; N, 43·5. Calc. for $C_4H_{11}N_5O_2$: C, 29·8; H, 6·8; N, 43·5%), *m/e* 161, $\nu_{max.}$ 3398s and 3310 (NH_2), 3205s (NH), 3080—2400 (OH), 1678s (C=N), 1660s (NH def.), 1606, 1103, 980, and 930 (N–O stretch) cm^{-1}, τ (D_2O) 6·79 (s, 2 × CH_2). In aqueous methanol with iron(III) chloride, the compound gave a brown colour, which changed to olive green and then turquoise on addition of more reagent.

Similarly, *N*-acetyliminodiacetonitrile[16] (2) (2·74 g) in methanol (15 ml) with hydroxylamine [from the hydrochloride (5·36 g)] in water (18 ml) afforded in 48 h *acetyliminobis(acetamide oxime)* (6) (3·85 g, 96%), m.p. 165—171° (decomp.) (from methanol–water) (Found: C, 35·0; H, 6·3; N, 33·8. $C_6H_{13}N_5O_3$ requires C, 35·5; H, 6·4; N, 34·5%), *m/e* 203, $\nu_{max.}$ 3400s and 3300s (NH_2), 3140—2200 (OH), 1663s (C=N), 1638 (CO), 1600, 1253s, 1000, 968, 936 (N–O stretch), and 735 cm^{-1}, τ (D_2O) 7·83 (s, Me) and 5·91 (s, 2 × CH_2).

On keeping *N*-benzyliminodiacetonitrile[2] (3) (3·7 g) in methanol (60 ml) with hydroxylamine [from the hydrochloride (5·36 g)] in water (18 ml) overnight, the *hemihydrate* of *benzyliminobis(acetamide oxime)* (7) (2·65 g, 51%) crystallised out, m.p. 171—172° (decomp.) (from methanol–water) (Found: C, 51·2; H, 6·7; N, 27·1. $C_{11}H_{17}N_5O_2,0{\cdot}5H_2O$ requires C, 50·8; H, 6·9; N, 26·9%), *m/e* 251, $\nu_{max.}$ 3430s and 3330s (NH_2), 3300—2400 (OH), 1662s (C=N), 1648w, 1600, 1578, 1240, 1070, 992, 922s and 916s (N–O def.), 893, 878, 742s, and 698s cm^{-1}, τ(D_2O + 1 drop $CF_3{\cdot}CO_2H$) 6·57(s, 2 × CH_2), 6·33(s, CH_2), and 2·60(s, Ph). To nitrilotriacetonitrile[17] (4) (1·34 g, 0·01 mol) in ethanol (150 ml), hydroxylamine hydrochloride (4·17 g, 0·06 mol) and sodium hydrogen carbonate (3·87 g, 0·04 mol) in water (50 ml) were added, and the solution was heated under reflux for 2 days. After being concentrated under reduced pressure to *ca.* 80 ml, the solution was kept at 0° and tar then removed. Evaporation of the filtrate, extraction of the residue with boiling methanol (25 ml), and concentration and cooling of the extract provided prisms (0·48 g, 22%) of 3,5-*bishydroxyiminopiperazin*-1-*ylacetamide oxime*[2] (17), m.p. 186° (decomp.) (from aqueous methanol) (Found: C, 33·2; H, 5·9; N, 38·8. $C_6H_{12}N_6O_3$ requires C, 33·3; H, 5·55; N, 38·9%), $\lambda_{max.}$ 234 nm (ε 15,500), τ [$(CD_3)_2SO$] 7·06 (s, 1-CH_2), 6·78(s, 2-, 6-H_2), 4·69br (NH_2), 1·76(s, ring NH), 0·94(s, NOH of 1-substituent), and −0·08(s, 3-, 5-NOH) [the last four signals vanished on addition of D_2O (1 drop)], *m/e* 199 [$(M - 17)^+$)] 184, 183, 164, 157, and 143. The compound previously described[2] as the foregoing was the *hydrochloride*, m.p. 222° (decomp.), *m/e* 216 [$(M - HCl)^+$] *etc.*, 18·5, and 17·5.

Cyclisation of the Bis(amide oximes).—Acetyliminobis(acetamide oxime) (6) (0·48 g) in 50% aqueous ethanol (15 ml) was heated under reflux with hydroxylamine hydrochloride (0·7 g) for 0·5 h and then the solution was partially evaporated. 4-Acetyl-2,6-bishydroxyiminopiperazine (15) separated (0·29 g), mixed m.p. 203—205° (decomp.), with the correct i.r. spectrum.[2]

Similar treatment of benzyliminobis(acetamide oxime) (7) (0·4 g) in methanol gave 4-benzyl-2,6-bishydroxyiminopiperazine (16) (0·17 g, 50%) as needles (from methanol–water), mixed m.p. 196° (decomp.).[2]

When iminobis(acetamide oxime) (5) (1·61 g) and hydroxylamine hydrochloride (2·8 g) were boiled together in aqueous methanol (40 ml) for 20 min. and the solution was cooled, the product (33%) was the molecular complex (C) next described [mixed m.p. 161° (decomp.) and i.r. spectrum].

Molecular Complex (C) *of* 2,6-*Bishydroxyiminopiperazine and Hydroxylamine Hydrochloride.*—A solution of the cyclic dioxime (14) (0·29 g) in the minimum of hot aqueous methanol was heated under reflux with hydroxylamine hydrochloride (0·28 g) for 1 h. On cooling the solution, the hydrated *complex* (C) crystallised, m.p. 161° (decomp.) [Found: C, 25·8; H, 5·7; N, 33·55. $(C_4H_8N_4O_2)_2,(N^+H_3{\cdot}OH\ Cl^-),H_2O$ requires C, 25·6; H, 5·9; N, 33·5%], $\nu_{max.}$ 3397 (NH) 3210br (NH, OH bonded), 2700—2000 (N^+H), 1672s (C=N), 1640 (NH def.), 1241, 1202, 1025s, 1000s, 990, 950, 938s (N–O str.), and 904 cm^{-1}, τ (D_2O) 6·43 (2 × CH_2).

Attempted recrystallisation of the complex (C) from boiling aqueous methanol afforded 2,6-bishydroxyiminopiperazine (14) as flakes, m.p. 224°, mixed m.p. 225—226° (decomp.), with the correct i.r. spectrum.

2,6-*Bishydroxyiminopiperazine Hydrochloride.*—To aqueous methanolic hydrogen chloride (10 ml; 0·75 N), the cyclic dioxime (14) (0·5 g) was added. After 10 min, with occasional shaking, the *hydrochloride hydrate* had formed (0·54 g, 83%), m.p. 190° (decomp.) (from aqueous methanol) (Found: C, 24·0; H, 5·6; N, 27·5. $C_4H_9ClN_4O_2,H_2O$ requires C, 24·2; H, 5·5; N, 28·2%), $\nu_{max.}$ 3400 [N(1)H], 3210br (OH), 2670 and 2440 (N^+–H), 1680 (C=N), 1642 (NH def.), 1280, 1028s, 1000s, 950, 939s (N–O str.), and 908 cm^{-1}.

Interaction of Iminodiacetonitrile with a Mixture of Hydroxylamine and Its Hydrochloride: Formation of the Pyrazine (10).—Hot solutions of hydroxylamine hydrochloride (111·2 g, 1·6 mol) in methanol (120 ml) and sodium carbonate (21 g, 0·2 mol) in water (80 ml) were mixed and slowly added to iminodiacetonitrile (38 g, 0·4 mol) in boiling methanol (160 ml) under nitrogen. When half had been added (0·5 h), an exothermic reaction began, the solution darkened, and product started separating: heating and addition were then controlled to maintain gentle reflux. After a further 1 h, the solid was collected (27 g, 41%) and washed with methanol to give complex (C) (i.r. spectrum). On treating the filtrate with charcoal (2 ×) and then partially evaporating it by bubbling nitrogen through for 1 h, needles separated (11·65 g, 20·5%) of the *monohydrate* of 2-*amino*-6-*hydroxyaminopyrazine* 1-*oxide*, m.p. 161° (decomp.) (from MeOH–H_2O) (Found: C, 29·8; H, 5·0; N, 35·0. $C_4H_6N_4O_2,H_2O$ requires C, 30·0; H, 5·0; N, 35·0%), *m/e* 142, $\nu_{max.}$ 3520s and 3430s (NH_2), 3250br and 3100 (NHOH), 2700br (bonded OH), 1650 (NH def.), 1633s and 1582br (ring), 1501, 1246, 1200s (N–O str.),

[15] L. P. Eddy, W. W. Levenhagen, and S. K. McEwen, *Inorg. Synth.*, 1968, **11**, 89.

[16] W. J. A. Jongkees, *Rec. Trav. chim.*, 1908, **27**, 287.

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1166w, 1146w, 1059w, 1010, 900—800, and 717br cm^{-1}, $\lambda_{max.}$ 235, 285, and 338 nm (ε 24,300, 2900, and 5500), τ (Me_2SO) 3·21br (NH_2), 2·49(s, 3-H), 2·44(s, 5-H), and 0·92br (NHOH) [the first and last signals vanished on addition of D_2O (2 drops)], τ ($CF_3{\cdot}CO_2H$) 1·97(d, 3-H, *J* 1·7 Hz) and 1·94(d, 5-H). It reduced Fehling's solution, slowly gave a silver mirror with Tollens' reagent at 50°, and in aqueous methanol gave a blue colour with iron(III) chloride, which turned turquoise on addition of more reagent. With dilute alkali, the compound gave a bright yellow colour which gradually darkened; eventually black solid separated.

At 90—105°, the monohydrate lost weight (Found: 11·0. Loss of $1H_2O$ requires 11·25%) to give 2-*amino*-6-*hydroxyaminopyrazine* 1-*oxide* (10), m.p. 160° (decomp.) (Found: C, 33·3; H, 4·3; N, 39·4. $C_4H_6N_4O_2$ requires C, 33·8; H, 4·3; N, 39·4%), *m/e* 142, $\nu_{max.}$ 3440 and 3360 (NH_2), 3295 (NH), 3160 (bonded NH), 2640br (bonded OH), 1642s, 1585sh, and 1566 (ring), 1510, 1301, 1241, 1200s (N–O str.), 1147, 1061, 921br, and 839s (N–O def.) cm^{-1}.

The *picrate monohydrate* crystallised from methanol as yellow needles, m.p. 158° (decomp.) (Found: C, 30·8; H, 2·9; N, 25·6. $C_{10}H_{11}N_7O_{11}$ requires C, 30·8; H, 2·8; N, 25·2%).

2,6-*Diaminopyrazine* 1-*Oxide* (11).—2-Amino-6-hydroxyaminopyrazine 1-oxide hydrate (6·4 g), glacial acetic acid (200 ml), and Adams catalyst (0·56 g) were shaken together in hydrogen (uptake, allowing for catalyst, 1·04 mol. equiv.). The catalyst was removed, the filtrate evaporated, the residue dissolved in methanol, and the solution treated with charcoal and evaporated under reduced pressure. From water, the 2,6-*diaminopyrazine* 1-*oxide* (3·2 g, 64%) formed needles, m.p. 294—295° (decomp.) (Found: C, 38·05; H, 4·8; N, 44·1. $C_4H_6N_4O$ requires C, 38·1; H, 4·8; N, 44·4%), *m/e* 126, $\nu_{max.}$ 3360 and 3250sh (NH_2), 3160 and 3090br (bonded NH_2), 1608s, 1561, and 1541 (ring), 1260, 1225s (N–O str.), 841s (N–O def.), 818s, 736, and 712br cm^{-1}, τ (Me_2SO) 3·4br (2 × NH_2) and 2·67(s, 3-, 5-H), $\lambda_{max.}$ 230·5, 282, and 336 nm (ε 21,700, 2200, and 9600). It gave a deep blue colour with iron(III) chloride which was discharged by 1 drop of aqueous hydrochloric acid. Solutions in alkali and in concentrated sulphuric acid appeared stable.

2,6-*Diacetamidopyrazine* 1-*Oxide* (12).—2,6-Diaminopyrazine 1-oxide (0·63 g) was suspended in acetic anhydride (20 ml). After 38 h, the 2,6-*diacetamidopyrazine* 1-*oxide* was collected (1·05 g, 100%), washed with ethanol, and recrystallised from boiling aqueous methanol to give needles, m.p. 272—273° (decomp.) (Found: C, 45·65; H, 4·7; N, 26·8. $C_8H_{10}N_4O_3$ requires C, 45·7; H, 4·7; N, 26·7%), *m/e* 210, $\nu_{max.}$ 3270s (NH), 3120w, 1692s (CO), 1570s,br, 1558sh, 1500w, 1336s, 1297s, 1276w, 1230s (N–O str.), 1142, 1060, 958, 885, 861s (N–O def.), 802w, and 700br cm^{-1}, τ [$(CD_3)_2SO$] 7·7(s, 2 × Me), 0·93(s, 2 × ring H), and −0·46br (2 × NH·CO), τ ($CF_3{\cdot}CO_2H$) 7·40(s, 2 × Me) and 0·24 (3-, 5-H), $\lambda_{max.}$ 252, 277infl, and 327 nm (ε 32,600, 10,300, and 8900). No colour was given in aqueous methanol with iron(III) chloride.

2,6-*Diacetamidopyrazine* (20).—2,6-Diacetamidopyrazine 1-oxide (105 mg) and sodium dithionite (0·21 g) were heated under reflux in 70% (v/v) ethanol–water (12 ml) for 20 min.[18] The 2,6-*diacetamidopyrazine* (80 mg, 82%) was collected: it sublimed at *ca.* 300° without melting or decomposing (Found: C, 49·6; H, 5·1; N, 28·9. $C_8H_{10}N_4O_2$ requires C, 49·5; H, 5·15; N, 28·9%), *m/e* 194, $\nu_{max.}$ 3300s (NH), 3160w, 3100w, 1678s (CO), 1566, 1280, 1260, 1240s, 1190, 1157s, 1122, 1040, 1010s, 960, 881, and 810 cm^{-1}, $\lambda_{max.}$ 216·5, 244infl, and 312·5 nm (ε 26,800, 6950, and 12,900). It was not appreciably soluble in alcohols, acetic acid, chloroform, or dimethyl sulphoxide.

2,5-*Bishydroxyiminopiperazine* (23).—Aminoacetonitrile hydrochloride (18·5 g), hydroxylamine hydrochloride (25·6 g), and sodium carbonate (31·8 g) were dissolved in water (170 ml) under nitrogen. Next day, the pale yellow product (50%) was collected and purified by precipitation from dimethyl sulphoxide with water to afford 2,5-*bishydroxyiminopiperazine*, m.p. 180° (with charring) (Found: C, 33·3; H, 5·55; N, 38·9. $C_4H_8N_4O_2$ requires C, 33·3; H, 5·55; N, 38·9%), *m/e* 144, $\lambda_{max.}$ (MeOH) 213·5 nm, $\nu_{max.}$ 3355 (NH), 3200—2600br (OH), 1678s (C=N), 1338s, 1085, 1017, 930s (N–O str.), 898, and 838 cm^{-1}, τ (Me_2SO) 6·36 (s, 2 × CH_2), 3·69br (2 × NH), and 1·19br (2 × NOH). With iron(III) chloride in aqueous dimethyl sulphoxide it gave a blue colour. The triphenyltetrazolium chloride–alkali test was positive in 2 min.

Hydrolysis of 2,5-*Bishydroxyiminopiperazine.*—(*a*) The dioxime (23) (0·5 g) was heated with 3N-hydrochloric acid (3 ml) on a steam-bath for 1 h; the solution was treated with charcoal and the filtrate neutralised with sodium carbonate and evaporated. Extraction of the residue with methanol, and concentration, afforded 5-*hydroxyiminopiperazin*-2-*one hydrochloride* (0·1 g) (from methanol), charring at *ca.* 200° (Found: C, 29·1; H, 4·8; N, 25·4. $C_4H_8ClN_3O_2$ requires C, 29·15; H, 4·4; N, 24·6%), *m/e* 129 *etc.*, 18·5, and 17·5, $\nu_{max.}$ 3350 and 3200 (NH), 3050br (OH), 2800—2100 (N^+H), 1672s (C=N), 1630 (CO), 1525, 1340s, 1320sh, 1083s, 950 (N–O str.), 925, 848, 820br, and 790 cm^{-1}. It gave a brown colour with iron(III) chloride. The mono-oxime (0·1 g) in water (2 ml) was kept with aqueous 10% sodium nitrite (1 ml) and 3N-hydrochloric acid overnight. Treatment of the solution with charcoal, and evaporation (to 0·2 ml) gave a residue. This was washed with methanol and recrystallised from water to afford piperazine-2,5-dione (25) (60 mg), m.p. 288—290° (decomp.), $\nu_{max.}$ 3100 and 3060 (NH, bonded), 1700s,br (CO), 1075, 920, 845s, and 815 cm^{-1}.

(*b*) The dioxime (23) (0·29 g) in a mixture of water (2 ml), methanol (2 ml), and dioxan (2 ml) was treated with aqueous 10% sodium nitrite (2 ml) and 3N-hydrochloric acid (2 ml). Next day, the solution (charcoal) was evaporated (to 0·5 ml) and the product worked up as before to afford piperazine-2,5-dione (0·18 g), m.p. and mixed m.p. 288—290° (decomp.), *m/e* 114, and the correct i.r. spectrum.[19]

Reactions of o-*Cyanobenzyl Cyanide with Hydroxylamine.*—(*a*) These reagents in boiling methanol afforded 1-amino-3-hydroxyaminoisoquinoline [14] (27) (78% yield), m.p. 95°, *m/e* 175, which gave a turquoise-blue colour with iron(III) chloride in aqueous ethanol, a purple-red colour with triphenyltetrazolium chloride and alkali in 5 min, and a silver mirror with Tollens' reagent at 50°. It reduced Fehling's solution.

(*b*) The same product (27) (m.p., i.r. and ^1H n.m.r. spectra) [14] was formed from the dinitrile in methanol at room temperature with hydroxylamine (1 or 4 mol. equiv.) for 20 h (yields 74 and 84%), and with a mixture of hydroxylamine and its hydrochloride.

(*c*) When the dinitrile (1·42 g) in methanol (16 ml)

[18] *Cf.* J. C. Mason and G. Tennant, *J. Chem. Soc.* (*B*), 1970, 911.
[19] Sadtler Standard Spectra, No. 18335.

was boiled with hydroxylamine hydrochloride (5·6 g) and sodium carbonate (0·8 g) in 40% aqueous methanol (40 ml) for 1·5 h and the solution cooled, 1,2,3,4-*tetrahydro*-1,3-*bis-hydroxyiminoisoquinoline* (28) separated (0·97 g, 51%), m.p. 223—225° (decomp.) (from methanol–water) (Found: C, 56·8; H, 4·8; N, 21·8. $C_9H_9N_3O_2$ requires C, 56·5; H, 4·7; N, 22·0%), *m/e* 191, $\nu_{max.}$ 3380 (ring NH), 3280 and 2705br (OH), 3030 (CH), 1666s and 1644s (C=N), 1604w, 1578w, 1140, 973, 924s (N–O str.), 770, and 721 cm^{-1}, τ (Me_2SO) 6·21(s, CH_2), 2·65 (*ca.* s, 5-, 6-, 7-H), 2·17 (dd, 8-H, *J* 7 and 2·5 Hz), 1·41br (NH), −0·10 (3-NOH); and −0·70 (1-NOH), $\lambda_{max.}$ 238 and 269 nm (16,700 and 7300). It gave a reddish brown colour with iron(III) chloride in aqueous methanol.

Hydrolyses of the Isoquinoline Products.—Boiling of the hydroxyamino-compound (27) (0·35 g) and of the di-oxime (28) (0·4 g) with 3N-hydrochloric acid (4 ml portions) for 1 and 2 h, respectively, treatment of the solutions with charcoal and cooling, gave homophthalimide (29) (0·2 g, 62·5%; 0·25 g, 79%), m.p. 234—235°, with the correct i.r. spectrum.[14]

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