Heterocyclic Imines and Amines. Part XII.[1] Imino-derivatives of Piperazine

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Sodamide in formamide effected addition of ammonia to *N*-benzyliminodiacetonitrile (1a) to yield 4-benzyl-2,6-diiminopiperazine (4), which underwent displacement reactions with water and hydroxylamine, the latter giving 4-benzyl-2,6-dihydroxyiminopiperazine (5a). Similar addition of aniline and 2-aminopyridine to the dinitrile (1a) yielded the 2-imino-6-arylimino-derivatives of (4) which again gave the dioxime (5a) with hydroxylamine. *N*-Benzoyl-, acetyl-, and unsubstituted-iminodiacetonitrile gave the corresponding 2,6-dihydroxyiminopiperazines. Sodamide in formamide with iminodiacetonitrile provided 2,6-bisformyliminopiperazine, and with nitrilotriacetonitrile (10) gave 3,5-di-iminopiperazin-1-ylacetonitrile, which with hydroxylamine produced 3,5-dihydroxyiminopiperazin-1-ylacetamide oxime. The trinitrile (10) with hydroxylamine gave only the acyclic tris(amide oxime).

Spectral evidence for the iminopiperazine structures is discussed.

ADDITION of ammonia, hydroxylamine, and aniline to glutaronitriles gave 2,6-di-imino-piperidine (glutarimidine) and other imino-piperidine products.[2] Iminopiperazines have now been obtained from the glutaronitrile analogue, bis(cyanomethyl)amine (1d) (iminodiacetonitrile), and from *N*-derivatives including nitrilotriacetonitrile (10).

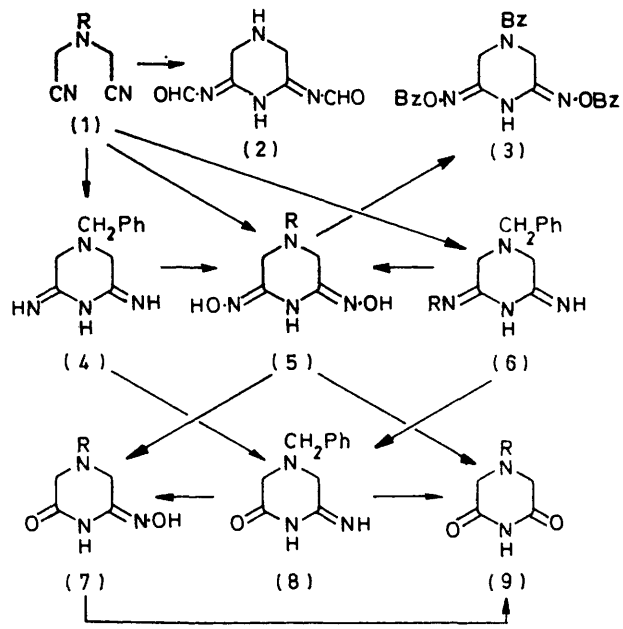
Initially, cycloadditions to the *N*-benzyl derivative (1a) were examined, in case the imino-group of the parent dinitrile (1d) interfered. With methanolic ammonia at 90°, *N*-benzyliminodiacetonitrile (1a) gave the imidine (4), but this was obtained better with sodamide–formamide [3-5] and then was isolated as the crystalline formamide solvate. The cyclic structure (4) was indicated by the absence of nitrile absorption in the i.r. spectrum and confirmed by the similarity of the u.v. spectrum (Table) to that of 2,6-di-iminopiperidine.[2]

U.v. light absorptions [a]

	$\lambda_{max.}$/nm	$10^{-3}\varepsilon$
Imidines		
(4) [b]	250·5	13·8
(6e)	260, 291·5	10·0, 10·5
(6f)	257, 282	17·0, 12·6
(2)	249·5, 347	18·3, 12·65
(12) [b]	250·5	18·0
Imino-imides		
(8)	238	15·0
(13)	238	15·3
Cyclic dioximes		
(5a)	234	14·9
(5b)	232	19·4
(5c)	234	15·0
(5d)	234	15·8
(3)	232, $254_{infl.}$	29, 16·5
Hydroxyiminoamides		
(7a) [or]	$224_{infl.}$	9·4
(7b)	$220_{infl.}$	10·2

[a] In MeOH. [b] In EtOH.

Moreover, hydrolysis gave successively the imino-imide (8) and the known imide (9a).[6] With hydroxylamine in boiling methanol the di-imino-compound (4) condensed as expected to give the dioxime (5a), which was also prepared direct from the dinitrile (1a) and hydroxylamine. Nitrous acid effected partial hydrolysis of the dioxime (5a) to the monoxime (7a), the hydrochloride of which was also prepared from the imino-imide (8) and hydroxylamine hydrochloride. Hydrolysis of both the



dioxime (5a) and the monoxime (7a) with aqueous hydrochloric acid gave the imide (9a), isolated as the hydrochloride. This hydrochloride was also formed by treatment of the dinitrile (1a) in acetic acid with hydrogen chloride, presumably *via* the chloro-imino-imide followed by hydrolysis.

First attempts to prepare *N*-phenyl derivatives of the imidine by previous methods [2] failed. Th is fusion of *N*-benzyliminodiacetonitrile (1a) with aniline hydrochloride gave only intractable tarry material, as did treatment of the imine (4) with aniline, even under anaerobic conditions

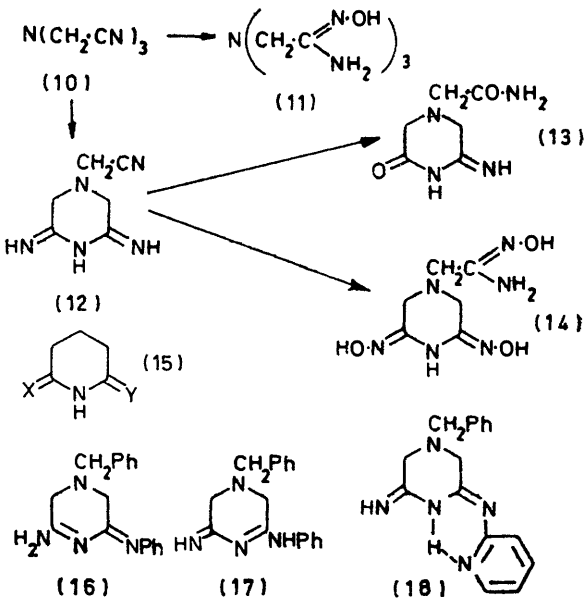
[1] Part XI, J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc.* (*C*), 1968, 1297.
[2] J. A. Elvidge, R. P. Linstead, and A. M. Salaman, *J. Chem. Soc.*, 1959, 208.
[3] *Cf.* Baeyer Farbenfabriken, Indian P. 43,679/1952.
[4] J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1954, 442.
[5] G. E. Ficken and R. P. Linstead, *J. Chem. Soc.*, 1955, 3525.
[6] J. V. Dubsky and E. Dingemanse, *Ber.*, 1921, **54**, 2659.

and excluding light. However, by heating the dinitrile (1a) with aniline in ethanolic sodium ethoxide under nitrogen, the mono-*N*-phenylimine (6e) was obtained in low yield, whilst superior yields resulted from the use of sodio-aniline in benzene or an excess of aniline. Similarly, by treating the dinitrile (1a) with the sodio-derivative of 2-aminopyridine, the analogue (6f) resulted. The cyclic, unsymmetrical structures (6e and f) were confirmed by the absence of nitrile absorption in the i.r. spectrum and the presence of 3 two-proton signals in the ^{1}H n.m.r. spectra.

Efforts to obtain the *NN'*-disubstituted derivatives from compounds (6e and f) by extensions of the foregoing reactions failed, the unsubstituted imino-function in (6e and f) being unreactive under the basic conditions employed. This lack of reactivity persisted also under acidic conditions, acid hydrolysis of (6e) yielding the imino-imide (8) rather than the *N*-phenylimino-imide as expected from previous results.[4,7] With hydroxylamine hydrochloride, however, the *N*-phenyl-imidine (6e) underwent replacement of both imino-substituents to give the dioxime (5a); there are precedents for this behaviour, however.[8]

Although acyl groups were unlikely to be as satisfactory as benzyl for protection of the imino-function in iminodiacetonitrile, nevertheless the benzoyl and acetyl derivatives (1b and c) were examined since these were so accessible. With methanolic ammonia or sodamide, the benzoyl group in *N*-benzoyliminodiacetonitrile (1b) was rapidly removed as benzamide. Hydroxylamine, however, did not affect the acyl groups in compounds (1b and c) but reacted with the nitrile functions, as hoped, to give the cyclic dioximes (5b and c). These structures were confirmed by the i.r. and ^{1}H n.m.r. spectra and by chemical degradations. With nitrous acid, the benzoyl dioxime (5b) afforded the partial hydrolysis product, the piperazine oxime (7b), whilst the acetyl compound (5c) gave the known 4-acetylpiperazine-2,6-dione (9c). Boiling aqueous hydrochloric acid hydrolysed the dioximes (5b and c) to piperazine-2,6-dione (9d), which was isolated as the hydrochloride. In the former case, benzoic acid was also recovered.

Attempts to add ammonia to iminodiacetonitrile itself (1d) gave intractable material, but with sodamide in formamide under nitrogen at room temperature and in the dark, the cyclic bisformylimino-compound (2) slowly separated, rather than the expected imidine. There must be equilibration of amide and formamide anion in the medium, either of which can attack the dinitrile reversibly, so the isolation of the diformyl derivative is presumably an accident of its low solubility. With hydroxylamine, iminodiacetonitrile (1d) gave the cyclic dioxime (5d), though the yield was poor compared with the yields of products obtained similarly from the *N*-derivatives (1a—c). Supporting evidence for the structure (5d) came from the spectra, the hydrolysis with nitrous acid to the imide (9d), and the benzylation and acetylation in pyridine to yield the compounds (5a) and (5c) already encountered. Benzoylation afforded a tribenzoyl derivative for which structure (3) was indicated by the spectra.



Nitrilotriacetonitrile (10) was readily available [9] and was also used for some comparative experiments. In contrast to the behaviour of the other iminodiacetonitriles with hydroxylamine, the trinitrile (10) gave the acyclic tris(amide oxime) (11). This was reminiscent of glutaronitrile yielding a bis(amide oxime) under mild conditions.[2] The last-named compound was cyclised by sublimation to the dioxime (15; X = Y = NOH) and we now find that the cyclic product is obtained direct under mild conditions by interaction of glutaronitrile with a mixture of hydroxylamine and its hydrochloride. Extension of these reactions was unsuccessful, however, and a cyclic dioxime was not obtained from the nitrile (10). Even treatment of the tris(acetamide oxime) (11) with acetic anhydride gave only an acyclic triacetyl derivative. Nevertheless the nitrile (10) readily gave with sodamide in formamide the di-imino-nitrile (12), from which a picrate was made. In the i.r. spectrum, this new nitrile showed no nitrile stretching absorption (which is sometimes vanishingly weak [10]) but the u.v. absorption was closely similar to that of the imidine (4), providing strong evidence for the cyclic structure (12). Water effected rapid hydrolysis to a compound $C_6H_{10}N_4O_2$ which was assigned the structure (13). The u.v. absorption was the same as that of the imino-imide (8), the i.r. absorption indicated the presence of the side-chain amide function, and the ^{1}H n.m.r.

[7] P. F. Clark, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1953, 3593.
[8] P. F. Clark, J. A. Elvidge, and J. H. Golden, *J. Chem. Soc.*, 1956, 4135.
[9] W. Eschweiler, *Annalen*, 1893, **278**, 230.
[10] J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc.* (*C*), 1971, 2424; L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1958, p. 265.

spectrum supported the latter and demonstrated the presence of 3 non-equivalent methylene groups. With hydroxylamine, the di-imino-nitrile (12) underwent substitution in the imino-groups as well as addition to the nitrile to afford 3,5-bishydroxyiminopiperazin-1-yl-acetamide oxime (14).

Structures. The light absorptions of the imino-piperazines (see Table) are closely similar to those of the corresponding compounds in the glutarimidine series.[2] Previously, it was concluded that 2,6-di-iminopiperidine, and the derived dioxime, imino-imide, and hydroxyimino-imide were best represented by structures with exocyclic double bonds as (15; X = Y = NH; X = Y = NOH; X = NH, Y = O; and X = NOH, Y = O, respectively). It follows therefore that the corresponding piperazine derivatives have the structures (4), *etc.*, as depicted with exocyclic double bonds.

The *N*-aryl substituted imidines (6e and f) have higher wavelength absorption (see Table) and so might have had a different fine structure to the preceding compounds. However, the *N*-phenyl compound (6e) has $\nu_{max.}$ 3430 and 3070 cm^{-1} attributable to the ring and substituent N–H stretchings respectively, by comparison with data for the foregoing simpler compounds. The amino-tautomer (16) is thus excluded, whilst the alternative, substituted amino-tautomer (17) is unlikely because the *N*-pyridyl compound (6f), with similar u.v. absorption and hence similar bond structure, shows an additional, chelated N–H absorption at 3310 cm^{-1}, accommodated by structure (18). Hence it is concluded that the *N*-aryldi-iminopiperazines have the structures (6e and f) as shown, with exocyclic double bonds. Because the corresponding *N*-phenyl-2,6-di-iminopiperidines [2] have similar u.v. absorptions, these likewise are evidently best represented by structures with exocyclic double bonds.

EXPERIMENTAL

I.r. spectra were measured for Nujol mulls (except where indicated) with a Unicam SP 200 spectrophotometer. U.v. and ^1H n.m.r. spectra were measured respectively with a Unicam SP 800B and Perkin-Elmer R10 60 MHz spectrometer.

N-Benzyliminodiacetonitrile (1a) had m.p. 41° and sometimes m.p. 45° (lit.,[11] 41—41·5° and [6] 45—45·5°) (Found: C, 71·35; H, 5·95. Calc. for $C_{11}H_{11}N_3$: C, 71·05; H, 6·0%), *m/e* 185, $\nu_{max.}$ 2270 (C≡N), 1610w, 1590w, 1508, 1438, 1352w, 1336, 1308w, 1290w, 1215w, 1148, and 1135s cm^{-1}.

4-*Benzyl*-2,6-*di-iminopiperazine* (4).—(a) To *N*-benzyliminodiacetonitrile (2·77 g) in dry methanol (10 ml), liquid ammonia (10 ml) was added cautiously and the solution heated in a Carius tube at 90° for 24 h. Evaporation of the solution and washing of the solid with ethyl acetate and ether gave the di-iminopiperazine (1·5 g, 50%) with closely similar i.r. absorption to that of the sample next prepared.

(b) *N*-Benzyliminodiacetonitrile (11·1 g) in formamide (40 ml) was added to sodamide (6 g) in formamide (40 ml) with stirring under nitrogen and exclusion of light. After 1 h, the crystalline *piperazine–formamide complex* was collected and washed with formamide, butanol, ethyl acetate, and then ether; yield 10·3 g (85%), m.p. 157—159° (decomp.) (Found: C, 57·8; H, 6·8; N, 27·8. $C_{11}H_{14}N_4$,$HCONH_2$ requires C, 58·3; H, 6·9; N, 28·0%), *m/e* 202, $\nu_{max.}$ 3400—3000 (NH), 1690 (C=N), 1620, 1558s, 1446, 1345s, 1305w, 1207, 1150, 1105s, 1028w, 934s, 910, 897, 753s, and 698s cm^{-1}.

The *picrate* crystallised from ethanol as yellow needles, m.p. 237° (decomp.) (Found: C, 47·2; H, 4·0; N, 23·0. $C_{17}H_{17}N_7O_7$ requires C, 47·3; H, 3·9; N, 22·7%).

The *dihydrochloride hydrate* (0·5 g, 83%), obtained by addition of concentrated hydrochloric acid (2 ml) to the di-imine (0·4 g) in butanol (10 ml) and then washing with butanol, had m.p. 340° (charring) (Found: C, 45·5; H, 5·8; N, 19·1. $C_{11}H_{18}Cl_2N_4O$ requires C, 45·1; H, 6·1; N, 19·1%), $\nu_{max.}$ 3280s (N–H), 2530 ($\overset{+}{N}$–H), 3400—2200 (OH, NH), 1667 (C=N), 1520s,br, 1345, 1318, 1215s, 1187, 1100, 1083w, 1048s, 1015, and 930 cm^{-1}.

4-*Benzyl*-6-*iminopiperazin*-2-*one* (8).—(a) *Formation.* 4-Benzyl-2,6-di-iminopiperazine (2·02 g) was dissolved in warm water (25 ml). Ammonia was evolved, and next day the product was recrystallised from aqueous ethanol to give needles, m.p. 192—194°, of 4-*benzyl*-6-*iminopiperazin*-2-*one* (1·9 g, 93%) (Found: C, 65·2; H, 6·5; N, 20·6. $C_{11}H_{13}N_3O$ requires C, 65·0; H, 6·4; N, 20·7%), *m/e* 203, $\nu_{max.}$ 3320s (ring N–H), 1652s (C=O), 1600br, 1525s, and 1353s cm^{-1}, $\tau(CF_3CO_2H)$ 5·36 (s), 5·21 (s), 5·07 (s, each CH_2), and 2·46 (s, Ph).

(b) *Hydrolysis.* The imino-imide (8) (0·4 g) in water (10 ml) containing 3 drops of concentrated hydrochloric acid was heated under reflux for 2 h. Treatment with charcoal, filtration, and evaporation gave 4-benzyl-piperazine-2,6-dione (9a) (0·2 g, 49%), m.p. 105—106° (from aqueous ethanol) (lit.,[6] 106°) (Found: N, 13·9. Calc. for $C_{11}H_{12}N_2O_2$: N, 13·7%), *m/e* 204, $\nu_{max.}$ 3180w and 3080w (ring N–H), 1722 and 1690s (C=O), 1405, 1320, 1280br, 1193, 1150, 1100, 1024, 840br, 760s, and 705s cm^{-1}, $\tau(CDCl_3)$ 6·62 (s, 2 × CH_2), 6·34 (s, CH_2), and 2·69 (s, Ph).

4-*Benzyl*-2,6-*bishydroxyiminopiperazine* (5a).—(a) *Formation.* (i) 4-Benzyl-2,6-di-iminopiperazine (2·02 g), hydroxylamine hydrochloride (1·38 g), and methanol (30 ml) were heated together under reflux for 2 h. After removal of ammonium chloride, treatment with charcoal, filtration and cooling, 4-*benzyl*-2,6-*bishydroxyiminopiperazine* separated (1·4 g, 60%), m.p. 196—197° (decomp.) (from aqueous ethanol) (Found: C, 56·3; H, 6·05; N, 24·1. $C_{11}H_{14}N_4O_2$ requires C, 56·4; H, 6·0; N, 23·9%), *m/e* 234, $\nu_{max.}$ 3440 (ring N–H), 3400—2400 (OH), 1667s (C=N), 1505w, 1403sh, 1322w, and 1110 cm^{-1}, $\tau(CF_3CO_2H)$ 5·28 (d, *J* 4 Hz, 3- and 5-H_2 coupled to $\overset{+}{N}H$), 4·47 (s, 4-CH_2), and 2·46 (Ph). The dioxime gave a reddish violet colour with iron(III) chloride in aqueous ethanol.

(ii) *N*-Benzyliminodiacetonitrile (1·85 g) in ethanol (5 ml) was heated with ethanolic hydroxylamine [10 ml; from the hydrochloride (1·38 g)] for 14 h under reflux. Evaporation and crystallisation of the residue from aqueous ethanol afforded the dioxime (5a) (1·17 g, 50%), m.p. and mixed m.p. 196—198°, and i.r. absorption identical with that above.

(b) *Hydrolysis.* 4-Benzyl-2,6-bishydroxyiminopiperazine (1·17 g) was heated under reflux in 3N-hydrochloric acid (10 ml) for 1·5 h and then the solution was treated with

[11] H. S. Mosher, J. Cornell, O. L. Stafford, and T. Roe, *J. Amer. Chem. Soc.*, 1953, **75**, 4949.

charcoal and evaporated. Recrystallisation of the residue (0·3 g, 30%) from 96% ethanol gave flakes, m.p. 243—244° (decomp., darkening from 230°), of *4-benzylpiperazine-2,6-dione hydrochloride* (Found: C, 54·6; H, 5·5; N, 11·65. $C_{11}H_{13}ClN_2O_2$ requires C, 54·9; H, 5·4; N, 11·65%), *m/e* 204 and (amongst others) 18·5 and 17·5, $\nu_{max.}$ 3150w (ring N–H), 2490s and 2420 ($\overset{+}{N}$–H), 1735s (C=O), 1417, 1334, 1280s, and 1205 cm^{-1}, $\tau(D_2O)$ 5·84 (s, 2 × CH_2), 5·53 (s, CH_2), and 2·46 (s, Ph).

4-Benzyl-6-hydroxyiminopiperazin-2-one (7a).—(a) *Formation.* (i) The preceding dioxime (5a) (0·7 g) in ethanol (7·5 ml), dioxan (15 ml), and water (7·5 ml) was treated with 10% sodium nitrite (6 ml), followed by 2N-hydrochloric acid (6 ml). Next day, evaporation and crystallisation of the residue from aqueous ethanol gave *4-benzyl-6-hydroxyiminopiperazin-2-one hydrochloride* (0·5 g, 77%), m.p. 194—195° (decomp.), *m/e* 219 (21), 190 (8·4), 128 (10·9), 100 (13·4), 91 (100%), and 18·5, 17·5 in ratio 35 : 100, $\nu_{max.}$ 3250s (ring N–H), 3150 (OH), 2710w and 2560s ($\overset{+}{N}$–H), 1734s (C=O), 1680 (C=N), 1350s, and 1300 cm^{-1}.

Treatment of the hydrochloride (255 mg) in ethanol (3 ml), water (3 ml), and dioxan (6 ml) with silver nitrate (85 mg) in water, filtration and evaporation gave *4-benzyl-6-hydroxyiminopiperazin-2-one* (110 mg, 50%) as needles, m.p. 200—201° (decomp.) (from aqueous ethanol) (Found: C, 60·7; H, 6·0; N, 19·55. $C_{11}H_{13}N_3O_2$ requires C, 60·3; H, 5·9; N, 19·2%), *m/e* 219, $\nu_{max.}$ 3250s,br (NH, OH), 1680sh (C=N), 1659s (C=O), 1402, 1320w, and 1298 cm^{-1}. This monoxime gave a yellow-brown colour with iron(III) chloride in aqueous ethanol.

(ii) 4-Benzyl-6-iminopiperazin-2-one (8) (0·2 g) and hydroxylamine hydrochloride (69 mg) in methanol (5 ml) was heated under reflux for 2 h. Filtration and cooling afforded 4-benzyl-6-hydroxyiminopiperazin-2-one (0·12 g, 51%), which after recrystallisation from aqueous ethanol had m.p. and mixed m.p. 201—202° (decomp.), and correct i.r. absorption.

(b) *Hydrolysis.* 4-Benzyl-6-hydroxyiminopiperazin-2-one (0·219 g), after heating under reflux in 3N-hydrochloric acid (3 ml), afforded (as from the dioxime above), 4-benzylpiperazine-2,6-dione hydrochloride (0·14 g, 70%), m.p. and mixed m.p. 242—244° (decomp., darkening from 232°). The same compound (i.r. spectrum), m.p. and mixed m.p. 243—244° (decomp., darkening from 230°) was obtained after 120 h in 40% yield by saturating a solution of *N*-benzyliminodiacetonitrile in glacial acetic acid with dry hydrogen chloride.

4-Benzyl-2-imino-6-phenyliminopiperazine (6e).—(a) *Formation.* (i) Aniline (5·58 g, 0·06 mol) was added slowly to sodamide (3 g) suspended in benzene (40 ml) under nitrogen and the mixture was heated under reflux for 2·25 h to drive off ammonia (*cf.* ref. 12). *N*-Benzyliminodiacetonitrile (5·55 g, 0·03 mol) in benzene (10 ml) was added and the heating under nitrogen continued for 0·5 h. After filtration, the solution was evaporated under reduced pressure, and the dark residue triturated with ether to give a pale yellow product (6·75 g, 80%), m.p. 125° (decomp.). *4-Benzyl-2-imino-6-phenyliminopiperazine* crystallised as fine pale yellow needles, m.p. 129° (decomp.) (from aqueous methanol) (Found: C, 73·4; H, 6·55; N, 20·0. $C_{17}H_{18}N_4$ requires C, 73·4; H, 6·5; N, 20·1%), *m/e* 278, $\nu_{max.}$ 3460s (ring N–H), 3070s,br (2-NH), 1665s and 1648s (C=N), 1595w, 1575s, 1493, 1340, 1318s, 1300s, 1278w, 1243, 1223w, 1205, 1165w, and 1115s cm^{-1}, $\tau(CDCl_3)$ 6·99 (d, *J* 1·5 Hz, 3-H_2 coupled to NH), 6·70 (s, 5-H_2), 6·42 (4-CH_2), 3·3—2·4 (m, PhN), 2·65 (s, Ph), and 4·2br (2 × NH).

(ii) Sodamide (2 g) was added cautiously to a solution of benzyliminodiacetonitrile (3·7 g, 0·02 mol) in aniline (7·28 g, 0·08 mol) under nitrogen and with exclusion of light. After 3 h stirring, the thick brown liquid was poured into deoxygenated water and the mixture extracted with chloroform. By pouring the chloroform into dry ether, the pale yellow mono-*N*-phenylpiperazine was obtained (3·9 g, 70%), m.p. and mixed m.p. 127—129° (decomp.), with correct i.r. spectrum.

(iii) To sodium ethoxide from the metal (0·23 g) and ethanol (30 ml), aniline (5·58 g, 0·06 mol) and *N*-benzyliminodiacetonitrile (5·55 g, 0·03 mol) were added and the solution was heated under reflux for 19 h under nitrogen. Excess of ethanol was evaporated, the dark residue was poured into air-free water, and the mixture was extracted with chloroform. The extract was dried (Na_2SO_4), evaporated, and treated with dry ether to give the product (1·8 g, 25%), m.p. 126—127° (decomp.) raised to 129—130° by recrystallisation from aqueous methanol: identity with compound (6e) was shown by i.r. and mixed m.p.

(b) *Hydrolysis.* 4-Benzyl-2-imino-6-phenyliminopiperazine (278 mg), methanol (5 ml), and concentrated hydrochloric acid (2 drops) were heated together under reflux for 2 h. Next day, crystals were collected (50 mg), and shown by the i.r. spectrum to be 4-benzyl-6-iminopiperazin-2-one (8).

(c) *Reaction with hydroxylamine.* 4-Benzyl-2-imino-6-phenyliminopiperazine (278 mg) and hydroxylamine hydrochloride (138 mg, 2 mmol) were heated under reflux in methanol for 1·5 h. Filtration and cooling afforded 4-benzyl-2,6-bishydroxyiminopiperazine (150 mg, 64%), m.p. 196° (decomp.) from aqueous ethanol and mixed m.p. 196—197°, and i.r. spectrum identical with authentic material.

4-Benzyl-2-imino-6-(2-pyridyl)iminopiperazine (6f).—(a) *Preparation.* Sodamide (2 g) was added to a stirred solution of *N*-benzyliminodiacetonitrile (3·7 g, 2 mmol) and 2-aminopyridine (3·76 g, 4 mmol) in *NN*-dimethylaniline (15 ml) under nitrogen with exclusion of light. After 4 h, the dark liquid was poured into air-free water and the mixture was extracted with chloroform and the extract was dried (Na_2SO_4). Evaporation and treatment with dry ether gave pale yellow needles of *4-benzyl-2-imino-6-(2-pyridyl)iminopiperazine* (3·52 g, 62%), m.p. 144—145° (decomp.) (from acetone) (Found: C, 68·5; H, 6·0; N, 24·9. $C_{16}H_{17}N_5$ requires C, 68·8; H, 6·1; N, 25·1%), *m/e* 279, $\nu_{max.}$ 3300s,br (ring N–H, bonded), 3080s (2-NH), 1665 and 1635s (C=N), 1595, 1540s, 1428, 1357, 1335s, 1310w, 1283, 1262, 1238w, and 1148 cm^{-1}, $\nu_{max.}$ (CCl_4) 3410 and 3310 (free and bonded ring N–H), 3050 (2-NH), 2920 and 2800 (CH) cm^{-1}, $\tau(CDCl_3)$ 6·63br (3-H_2 coupled to NH), 6·51 (s, 5-H_2), 6·33 (s, 4-CH_2), 2·65 (s, Ph), 3·2—2·0 (m, 3′-, 4′-, and 5′-H of pyridyl ring), 1·60 (*ca.* dd, 6′-H of pyridyl ring), and 3·2—2·0br (2 × NH).

4-Benzoyl-2,6-bishydroxyiminopiperazine (5b).—(a) *Preparation.* A hot solution of *N*-benzoyliminodiacetonitrile [13] (1b) (1·99 g, 0·01 mol) in dioxan (5 ml), methanol (2 ml), and water (3 ml) was treated with hydroxylamine hydrochloride (2·76 g, 0·04 mol) and sodium carbonate (1·06 g, 0·01 mol) dissolved in water (5 ml) and dioxan (2 ml). The

[12] F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 1953, 255.

[13] J. R. Baily and D. F. Snyder, *J. Amer. Chem. Soc.*, 1915, **37**, 935.

solution was heated under reflux for 0·5 h during which *4-benzoyl-2,6-bishydroxyiminopiperazine* separated (1·7 g, 70%), m.p. 198° (decomp.) (from aqueous methanol) (Found: C, 53·4; H, 5·0; N, 22·8. $C_{11}H_{12}N_4O_3$ requires C, 53·2; H, 4·8; N, 22·6%), *m/e* 248, $\nu_{max.}$ 3350s (ring N–H), 3140w (OH), 1675s (C=N), 1642s (C=O), 1503w, 1278s, 1235w, and 1142 cm^{-1}, $\tau(CF_3CO_2H)$ 4·94 (s, 2 × CH_2), 2·43 (s, Ph). This dioxime gave a greyish violet colour in aqueous ethanol with iron(III) chloride.

(b) *Hydrolysis.* The dioxime (0·248 g) was heated under reflux in 3N-hydrochloric acid (3 ml) for 1·25 h. After the solution had cooled, benzoic acid was collected (0·11 g, 90%), identical (i.r. spectrum) with authentic material. Evaporation of the filtrate afforded piperazine-2,6-dione hydrochloride (0·15 g, 100%), m.p. 277—278° (decomp.) from methanol, identified by i.r. spectrum and mixed m.p. with authentic material (see later).

4-Benzoyl-6-hydroxyiminopiperazin-2-one (7b).—The dioxime (5b) (0·496 g) was dissolved in a warm mixture of methanol (5 ml), dioxan (10 ml), and water (5 ml). To the cooled solution, 10% sodium nitrite in water (4 ml) was added and then 3N-hydrochloric acid (4 ml). Next day, [illegible]poration of the solution under reduced pressure gave *4-benzoyl-6-hydroxyiminopiperazin-2-one* (0·18 g, 40%), m.p. 183—184° (decomp.) (from aqueous methanol) (Found: C, 56·85; H, 4·8; N, 17·9. $C_{11}H_{11}N_3O_3$ requires C, 56·65; H, 4·7; N, 18·0%), *m/e* 233, $\nu_{max.}$ 3150br (OH, NH), 1650s,br (C=N, C=O), 1600w, 1505, 1410w, 1350, 1325s, 1282, 1258, 12[illegible] and 1135s cm^{-1}. In aqueous ethanol the mo[illegible]parated as[illegible]ve a yellowish orange colour with iron(III) chl[illegible] methano[illegible]

[illegible]$_3$ requir[illegible]*bishydroxyiminopiperazine* (5c).—(a) *Preparation.* [illegible]420 (ring[illegible]xylamine hydrochloride (11·2 g) and sodium carbonate (4·24 g) were dissolved in warm water (10 ml) and methanol (30 ml), and *N*-acetyliminodiacetonitrile [14] (1c) (5·48 g) was added. After the solution had been heated under reflux for 15 min, *4-acetyl-2,6-bishydroxyiminopiperazine* (3·7 g, 50%) separated as needles, m.p. 202—204° (decomp.) (from aqueous methanol) (Found: C, 38·6; H, 5·5; N, 30·2. $C_6H_{10}N_4O_3$ requires C, 38·7; H, 5·4; N, 30·1%), *m/e* 186, $\nu_{max.}$ 3420 (ring N–H), 3200s,br (OH), 1670s (C=N), 1630s (C=O), 1302w, 1255s, and 1195w cm^{-1}, τ([illegible]lisation of [illegible]yl-2,6-bish[illegible]$_2$H) 7·58 (s, Me), 4·98 (d, *J* 6 Hz, 2 × CH_2 coupled to [illegible]nd mixed [illegible] It gave a grey-violet colour in aqueous ethanol with iron(III) chloride.

(b) *Hydrolysis.* (i) The preceding dioxime (0·744 g) was suspended in methanol (10 ml), water (10 ml), and dioxan (11 ml), and 10% sodium nitrite in water (8 ml) was added, followed by 3N-hydrochloric acid (5 ml). Next day, evaporation of the solution afforded 4-acetylpiperazine-2,6-dione (9c) (0·4 g, 64%) as flakes, m.p. 155—156° (from methanol) (Found: C, 46·2; H, 5·2; N, 17·8. Calc. for $C_6H_8N_2O_3$: C, 46·15; H, 5·1; N, 17·9%) (lit.,[15] m.p. 167—168°), $\nu_{max.}$ 3190 and 3080w (NH), 1730 and 1702s (imide C=O), and 1650 (4-C=O) cm^{-1}.

(ii) 4-Acetyl-2,6-bishydroxyiminopiperazine (0·186 g) was heated under reflux with 3N-hydrochloric acid (3 ml) for 1 h. Evaporation of the solution and crystallisation of the residue from aqueous methanol gave piperazine-2,6-dione hydrochloride (0·11 g, 73%), m.p. and mixed m.p. 278—279° (decomp.).

2,6-Bisformyliminopiperazine (2).—Iminodiacetonitrile [13,16] (1d) (1·9 g) was dissolved in formamide (40 ml) under nitrogen, and sodamide (2 g) was added cautiously. Next day the solution was concentrated under reduced pressure (0·1 mmHg) on a steam-bath to *ca.* 25 ml and then kept under nitrogen for 7 days. The solid was collected and washed with dioxan and ether, and recrystallised from methanol to give needles, m.p. 196—198° (decomp., with darkening from 190°), of *2,6-bisformyliminopiperazine* (Found: C, 42·7; H, 4·9; N, 33·1. $C_6H_8N_4O_2$ requires C, 42·9; H, 4·8; N, 33·3%), *m/e* 168, $\nu_{max.}$ 3400 (ring N–H), 3380—3000 (4-NH, bonded NH), 1670s and 1630s (C=N, C=O), 1610w, 1565, 1273s, 1213s, 1065, 1025, 990w, 835w, 792w, and 745 cm^{-1}.

2,6-Bishydroxyiminopiperazine (5d).—(a) *Preparation.* Hydroxylamine solution [from the hydrochloride (5·6 g), sodium carbonate (4·24 g), and water (10 ml)] was heated with iminodiacetonitrile (3·8 g) in methanol (15 ml) under nitrogen at 70° overnight. Polymeric matter was removed and the solution treated with charcoal. Evaporation under reduced pressure than gave *2,6-bishydroxyiminopiperazine* (0·8 g, 14%) which crystallised from aqueous methanol as diamond-shaped flakes, m.p. 225° (decomp.) (Found: C, 33·5; H, 5·6; N, 38·7. $C_4H_8N_4O_2$ requires C, 33·3; H, 5·6; N, 38·9%), *m/e* 144, $\nu_{max.}$ 3410 (ring N–H), 3280 (4-N–H), 3100s,br (OH), 1670s (C=N), 1540, 1500, 1445, 1405w, 1335, 1300, 1200w, and 1109 cm^{-1}, $\tau(CF_3CO_2H)$ 5·21 (2 × CH_2). The dioxime gave a reddish brown colour with iron(III) chloride in aqueous ethanol.

(b) *Hydrolysis.* To the preceding dioxime (1·44 g) in methanol (35 ml), dioxan (12 ml), and water (25 ml), 10% sodium nitrite in water (20 ml) was added and then 3N-hydrochloric acid (20 ml). After 3 h, the solution was treated with charcoal and evaporated to give piperazine-2,6-dione hydrochloride (1·16 g, 77%), m.p. 278° (decomp.) (from aqueous methanol) (lit.,[15] carbonises at 260°) (Found: C, 31·9; H, 4·7; N, 18·9. Calc. for $C_4H_7ClN_2O_2$: C, 31·9; H, 4·65; N, 18·6%), $\nu_{max.}$ 3300—2300 (N–H and $\overset{+}{N}$–H), 1725s,br and 1685sh (C=O), 1560w, 1542, 1445, 1400s, 1350, 1300, 1280s, 1238s,br, and 1183s cm^{-1}.

(c) *Benzylation.* To 2,6-bishydroxyiminopiperazine (1·44 g, 0·01 mol) suspended in pyridine (20 ml), benzyl chloride (3·8 g, 0·03 mol) was added. Next day, evaporation of the solution and crystallisation of the residue from aqueous ethanol gave 4-benzyl-2,6-bishydroxyiminopiperazine (5a) (0·4 g, 15%), m.p. and mixed m.p. 196° (decomp.) and the correct i.r. spectrum.

(d) *Acetylation.* Similar treatment but with acetic anhydride and crystallising the residue from methanol gave 4-acetyl-2,6-bishydroxyiminopiperazine (5c) (40%), m.p. and mixed m.p. 204° (decomp.) and the correct i.r. spectrum.

(e) *Benzoylation.* Analogous benzoylation of the dioxime (5d), but for 13 days, afforded [by work-up as in (c)] a solid (0·5 g, 10%) which gave no colour with iron(III) chloride. Recrystallisation from 96% ethanol gave *4-benzoyl-2,6-bisbenzoyloxyiminopiperazine* (3) as clusters of needles, m.p. 172° (with darkening from 170°) (Found: C, 65·7; H, 4·6; N, 12·35. $C_{25}H_{20}N_4O_5$ requires C, 65·8; H, 4·4; N, 12·3%), *m/e* 456, $\nu_{max.}$ 3430 (ring N–H), 1740s (ester C=O), 1660sh and 1638s (C=N and amide C=O), 1600, 1585w, 1405, 1318, and 1247s,br cm^{-1}, $\tau(CDCl_3)$ 5·24 (s, 2 × CH_2), 2·51 (s, 2 × Ph), 2·7—2·3 (m, 3′-, 4′-, and 5′-H of 4-Bz), 1·98 (*ca.* dd, 2′- and 6′-H of 4-Bz), and 1·26br (NH).

[illegible]F_3CO
NH).

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Nitrilotris(acetamide oxime) (11).—Hydroxylamine hydrochloride (5·56 g) and sodium carbonate (2·12 g) were dissolved in water (20 ml), nitrilotriacetonitrile [9] (10) (2·68 g) in ethanol (100 ml) was added and the solution heated under reflux. After 15 min, the solution was cooled and the *trioxime* (3·8 g, 81%) collected, m.p. 172° (decomp.) (from methanol–water) (lit.,[17] 112°) (Found: C, 30·1; H, 6·6; N, 42·2. $C_6H_{15}N_7O_3$ requires C, 30·9; H, 6·4; N, 42·1%), *m/e* 233, $\nu_{max.}$ 3470 and 3380s (NH_2), 3300, 3160w, and 3050br (bonded NH_2 and OH), 1670s (C=N), 1610, 1585s, 1350w, 1340, 1256w, and 1238 cm^{-1}, $\tau(D_2O)$ 6·86 (s, 3 × CH_2). A reddish brown colouration appeared with iron(III) chloride in aqueous ethanol.

A suspension of the trioxime (2·33 g) in acetic anhydride (6·16 g) and pyridine (20 ml) was kept for 27 h. Recrystallisation of the solid (2·26 g, 63%) from water afforded flakes, m.p. 156° (decomp.), of the *triacetyl derivative* (Found: C, 40·3; H, 5·9; N, 27·3. $C_{12}H_{21}N_7O_6$ requires C, 40·1; H, 5·85; N, 27·3%), *m/e* 359, $\nu_{max.}$ 3475s (N–H), 3340br (OH), 1760s (C=O), 1660—1600 (C=N), 1220br, 1008s, and 970s cm^{-1}. This also gave a reddish brown colour with iron(III) chloride.

3,5-*Di-iminopiperazin*-1-*ylacetonitrile* (12).—A solution of nitrilotriacetonitrile (8·04 g) in warm formamide (60 ml) was mixed with a solution of sodamide (7·3 g) in formamide (60 ml) and stirred under nitrogen in the absence of light for 6 h. After the mixture had been kept at 0° for 100 h, 10 ml *di-iminopiperazine* was collected and washed quickly with formamide, ethanol, ethyl acetate, and then dry ether to give crystals (4·43 g, 44%), m.p. 180° (charring) (Found: C, 47·5; H, 6·1; N, 46·1. $C_6H_9N_5$ requires C, 47·7; H, 6·0; N, 46·35%), *m/e* 151 (9), 124 (3), 111 (4), 83 (78), 68 (11), and 42 (100%), $\nu_{max.}$ 3450—3000s (N–H), 1668 and 1626s (C=N), 1570s,br 1365s, 1345s, 1315w, 1292w, 1278, 1260w, 1200, 1170, 1157s, 1138w, and 1115 cm^{-1}.

The *picrate* crystallised from ethanol as yellow needles, m.p. 193—195° (decomp.) (Found: C, 37·9; H, 3·35; N, 29·4. $C_{12}H_{12}N_8O_7$ requires C, 37·9; H, 3·2; N, 29·5%).

5-*Imino*-3-*oxopiperazin*-1-*ylacetamide* (13).—When 3,5-di-iminopiperazin-1-ylacetonitrile (0·84 g) was warmed with water (5 ml), ammonia was evolved. After 10 min, the solution was chilled and the *product* collected (0·5 g, 58%); recrystallisation from hot water gave needles, m.p. 212° (decomp.) (Found: C, 42·2; H, 6·1; N, 33·0. $C_6H_{10}N_4O_2$ requires C, 42·35; H, 5·9; N, 32·9%), *m/e* 170 (10·8), 153 (3·2), 126 (86·5), 112 (29·7), 99 (25·4), 71 (32·4), and 42 (100%), $\nu_{max.}$ 3390s and 3190 (NH_2), 3310s (ring N–H), 1660s,br (2 × C=O), 1520s, 1410, 1340s, 1308, 1247, 1202w, 1160w, 1150, and 1132s cm^{-1}, $\tau(CF_3CO_2H)$ 6·08 (s), 5·89 (s), 5·51 (s, each CH_2), and 2·2br ($CONH_2$).

3,5-*Bishydroxyiminopiperazin*-1-*ylacetamide Oxime* (14).—3,5-Di-iminopiperazin-1-ylacetonitrile (0·51 g) and hydroxylamine hydrochloride (1·24 g) in methanol (10 ml) were heated under reflux for 5 min and the solution was then cooled. 3,5-*Bishydroxyiminopiperazin*-1-*ylacetamide oxime* (0·51 g, 78%) crystallised from aqueous methanol as needles, m.p. 222° (decomp.) [Found: *m/e* 216 (0·04), 199 (47), 183 (14·6), 157 (100), and 143 (23%). $C_6H_{12}N_6O_3$ requires *M*, 216], $\nu_{max.}$ 3390 and 3220 (NH_2), 3180br (OH), 1695s and 1655s (C=N), 1415, 1105s, 990s, 935, 910s, and 865s cm^{-1}. A violet colour, which changed to green, was given with iron(III) chloride.

Reaction of Glutaronitrile with Hydroxylamine and Its Hydrochloride.—Glutaronitrile (1·9 g, 0·02 mol), hydroxylamine hydrochloride (5·56 g, 0·08 mol), and sodium carbonate (2·12 g, 0·02 mol) were heated under reflux in 50% aqueous ethanol (10 ml) for 2 h. The crystalline 2,6-bishydroxyiminopiperidine was filtered off, washed with water, ethanol, and was dried (2·0 g, 71·5%). Recrystallisation from aqueous ethanol gave prisms, m.p. 239—240° (decomp.) [lit.,[2] 240—241° (decomp.)], $\nu_{max.}$ 3410 (N–H), 3100s,br (OH), 1668s (C=N), 1290, 1250w, 1183, 988s, 948, 895, 860, 830s, and 783 cm^{-1}.

[1/2176 *Received*, 17*th November*, 1971]

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