Reaction of 1,2- and 1,3-Dicarbonyl Compounds with 1,3-Diamines: Some New 1,4-Diazepines

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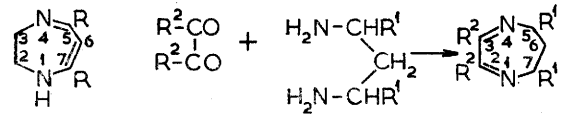
Glyoxal sodium hydrogen sulphite addition compound reacts with 2,4-diaminopentane dihydrochloride to yield 5,7-dimethylhexahydro-1,4-diazepin-2-one, but glyoxal monohydrate reacts with 1,3-diaminopropane and 2,4-diaminopentane under alkaline conditions to produce more complex substances. Cyclohexane-1,2-dione condenses with 1,3-diaminopropane to form 2,3,4,6,7,8-hexahydro-1*H*-1,5-benzodiazepine, but di-imines formed from two molecules of dicarbonyl compound and one of diamine result from the reactions of 1,3-diaminopropane with benzil, camphorquinone, and isatin. Complex products are obtained from *o*-quinones and diaminopropane. 1,3-diketones and 1,3-diamines react to produce open-chain compounds formed from two molecules of ketone and one of amine. 2,3-Dihydro-1*H*-1,4-diazepine is apparently formed from malonaldehyde and ethylenediamine, but 1,2-diaminocyclohexane reacts with malonaldehyde to give 1,2-bis(2-formylvinylamino)-cyclohexane.

MANY 2,3-dihydro-1*H*-1,4-diazepines (I) and 3*H*-1,5-benzodiazepines have been prepared by the reaction of 1,2-diamines with 1,3-dicarbonyl compounds.[1] The reaction of some 1,2-dicarbonyl compounds with 1,3-diamines has now been investigated with a view to obtaining the hitherto unknown 6,7-dihydro-5*H*-1,4-diazepines (II), and comparing them with their isomers of type (I). The desired diazepines (II) corresponding to some of the available 1,2-dicarbonyl compounds are isomers of 2,3-dihydro-1*H*-1,4-diazepines, the preparation of which has not previously been described. Attempts were therefore made to prepare these latter compounds by the established procedure. Apart from making possible comparison of the bond structures in (I) and (II), compounds of type (II) might lead by a suitable substitution–elimination sequence to derivatives of the unknown fully unsaturated 1,4-diazepine; introduction of a third double bond into dihydrodiazepines of type (I) has not proved possible,[1b,2] and attempted formation of a 1,4-diazepine derivative from *cis*-1,2-bisethoxycarbonylaminoethylene and acetylacetone was also unsuccessful.[3]



(I) (II)

Reaction of glyoxal sodium hydrogen sulphite addition compound with 2,4-diaminopentane dihydrochloride (mixture of racemic and *meso* obtained by reduction of acetylacetone dioxime) yielded *cis*-5,7-dimethylhexahydro-1,4-diazepin-2-one (IV) instead of the expected compound (II; $R^1 = Me$, $R^2 = H$), which would be isomeric with the known[4,5] 2,3-dihydro-5,7-dimethyl-1*H*-1,4-diazepine (I; R = Me). The product is presumably formed from the *meso*-diamine; no *trans*-isomer could be isolated from the mother liquor. The diazepinone is basic, and forms a monopicrate and a monobenzoyl derivative. It gives no colouration with ferric chloride, nor does it form an imino-chloride when treated with phosphorus halides. The infrared spectrum (KBr) contains peaks at 1650 (amide CO) and 3200 and 3300 (amido and amino NH) cm.$^{-1}$. In the n.m.r. spectrum (Figure and Table 1), the prominent doublets

TABLE 1

N.m.r. spectrum of 5,7-dimethylhexahydro-1,4-diazepin-2-one (see Figure)

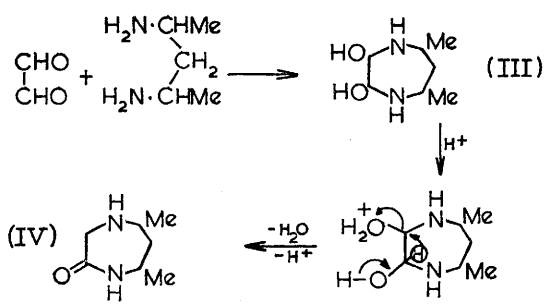
	δ		J(c./sec.)
H_a	3·65 or 3·30	J_{ab}	16·0
H_b	3·30 or 3·65	J_{cd}	6·5
H_c	3·00	J_{ce}	8·0
H_d	1·08 or 1·22	J_{cf}	10·5
H_e	1·80	J_{ef}	14·2
H_f	1·25	J_{eg}	2·0
H_g	3·75	J_{fg}	10·2
H_h	1·22 or 1·08	J_{gh}	6·5

at δ 1·08 and 1·22 p.p.m. are obviously due to the two methyl groups. The protons of the ketomethylene group (H_a and H_b, δ 3·3 and 3·65 p.p.m.) constitute an AB system; the resulting pair of doublets is superimposed on two multiplets due to H_c and H_g. The two quartets δ *ca.* 1·75 and 1·95 p.p.m. are due to H_e, which with H_f constitutes another AB system; the multiplet due to H_f is obscured by the methyl resonances. The magnitudes of the coupling constants J_{ce} and J_{eg} indicate *cis*-coupling while the large values of J_{cf} and J_{fg} indicate *trans*-coupling. This is consistent with the *cis*-disposition of the methyl groups. The n.m.r. spectrum of a solution in deuteriochloroform differs from that in water in that the pair of doublets due to H_a and H_b is replaced by a singlet and the two doublets due to the methyl groups overlap to appear as a 1 : 2 : 1 triplet. The mass spectrum of (IV) is consistent with the structure inasmuch as the major peaks can be accounted for by fragmentations analogous to those of other lactams and amines.[6]

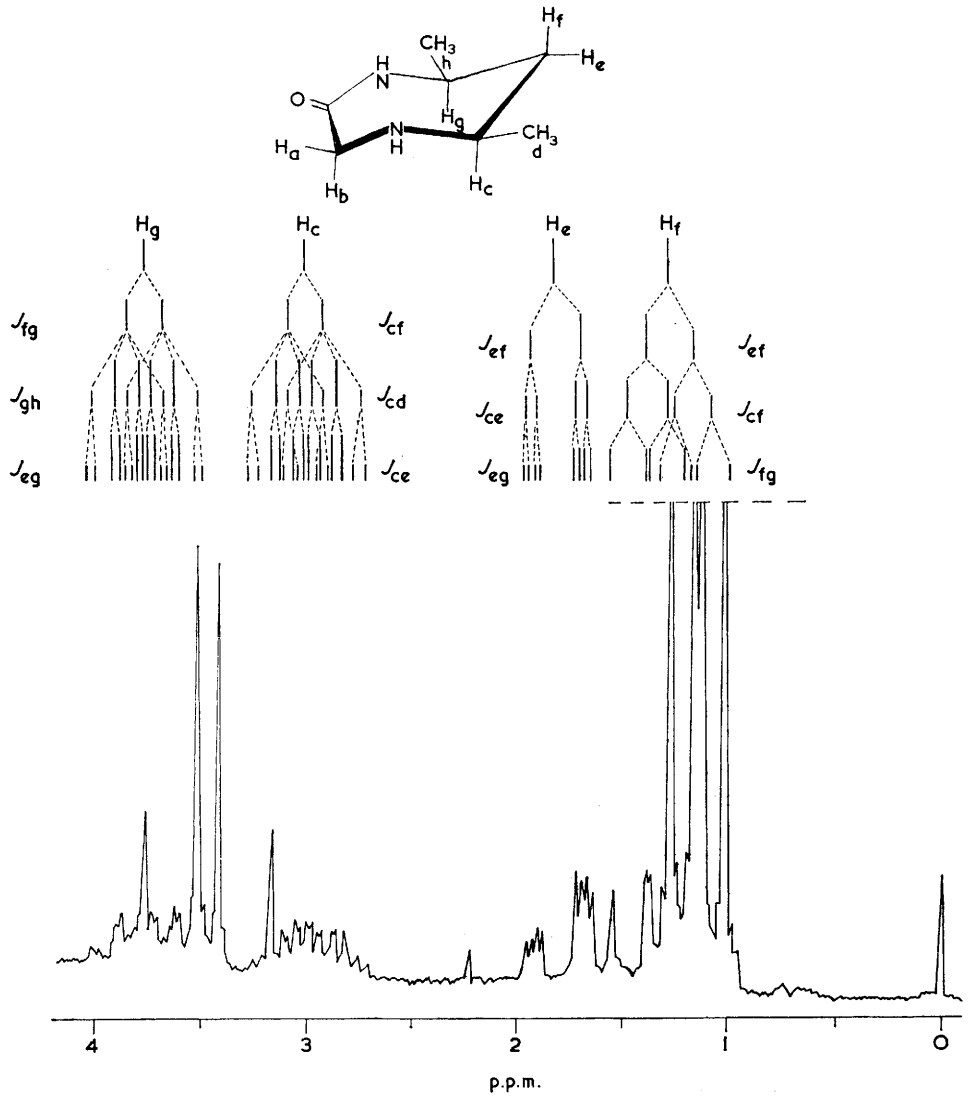
The dimethylhexahydrodiazepinone could be formed by the route shown, involving a migration of hydrogen

[1] (*a*) S. H. Malik, Ph.D. Thesis, London, 1967; (*b*) R. H. McDougall, Ph.D. Thesis, St. Andrews, 1962.
[2] D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.*, 1965, 3785.
[3] R. H. McDougall and S. H. Malik, unpublished work.
[4] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1139.
[5] D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 1956, 2597.
[6] *E.g.* A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1964, **86**, 5536; A. M. Duffield, L. Wise, and L. A. Paquette, *J. Org. Chem.*, 1966, **31**, 1599.

analogous to the acid-catalysed pinacol–pinacolone rearrangement. It is significant that (IV) is formed only under acidic conditions. The isolation of cyclic *vic*-dihydroxy-compounds from the reaction of glyoxal with amides [7] provides evidence for the formation of (III) as an intermediate.



Attempts to synthesise (IV) from chloroacetyl chloride and 2,4-diaminopentane yielded only polymeric material.



N.m.r. spectrum of *cis*-5,7-dimethylhexahydro-1,4-diazepin-2-one in deuterium oxide

obtained sufficiently pure to give a useful n.m.r. spectrum.

No simple product could be obtained from the reaction of glyoxal sodium hydrogen sulphite addition compound with 1,3-diaminopropane dihydrochloride under conditions similar to those which lead to formation of the diazepinone (IV).

The reaction of glyoxal monohydrate with 1,3-diamines takes a different course from that of the sodium hydrogen sulphite adduct. No reaction with 1,3-diaminopropane or 2,4-diaminopentane occurred at pH 4 or 7, but at pH 11 two products could be isolated in each case. The less soluble product from diaminopropane

[7] A. C. Currie, A. H. Dinwoodie, G. Fort, and J. M. C. Thompson, *J. Chem. Soc.* (*C*), 1967, 491.

was a base, $C_{10}H_{18}N_4O$, the formation of which corresponds to the equation

$$2C_3H_{10}N_2 + 2C_2H_2O_2 \longrightarrow C_{10}H_{18}N_4O + 3H_2O$$

It is not the imine (V), since the u.v. spectrum shows only end absorption. The more soluble product from diaminopropane is also basic and has the formula $C_{12}H_{18}N_4O_2$; * its formation corresponds to the equation

$$2C_3H_{10}N_2 + 3C_2H_2O_2 \longrightarrow C_{12}H_{18}N_4O_2 + 4H_2O$$

The two products obtained from 2,4-diaminopentane and glyoxal monohydrate, $C_{14}H_{26}N_4O$ and $C_{16}H_{26}N_4O_2$,* are exactly analogous to the above compounds. No structural information could be derived from the n.m.r. spectra of any of these substances.

While the reaction of 1,3-diaminopropane with glyoxal derivatives was being investigated, an attempt was

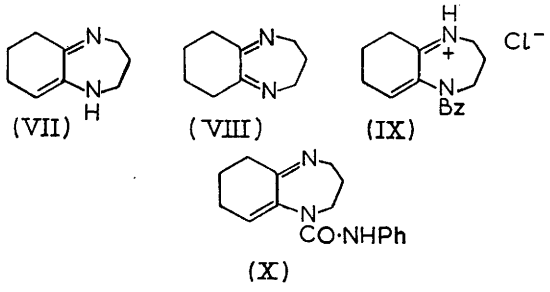
$H_2N{\cdot}[CH_2]_3{\cdot}N{:}CH{\cdot}CH{:}N{\cdot}[CH_2]_3{\cdot}N{:}CH{\cdot}CHO$
(V)

$BzCPh{:}N{\cdot}[CH_2]_3{\cdot}N{:}CPhBz$
(VI)

made to prepare the unsubstituted 2,3-dihydro-1*H*-1,4-diazepine (I; R = H), the isomer of the desired dihydrodiazepine (II; $R^1 = R^2 = H$). The preparation of 2,3-dihydro-1*H*-1,4-diazepine has not been described, although the u.v. maximum of the cation has been recorded; † by analogy with known methods for the formation of compounds of type (I), it should result from the reaction of ethylenediamine with malonaldehyde (generated from 1,1,3,3-tetraethoxypropane). Under most conditions, only starting materials or tarry products were isolated, but in methanolic perchloric acid a crystalline product containing much ethylenediamine perchlorate, but having a u.v. maximum at *ca.* 320 nm. and an inflection at 339 nm. (in water) was obtained. (2,3-Dihydro-5,7-dimethyl-1*H*-1,4-diazepinium perchlorate has $\lambda_{max.}$ 325 nm. in water.[1b]) The chromium(III)–malonaldehyde complex [8] might be expected to liberate malonaldehyde under both acidic and alkaline conditions, whereas 1,1,3,3-tetraethoxypropane is hydrolysed only under acidic conditions. However, no evidence for diazepine formation was obtained when the complex was treated with ethylenediamine under various conditions.

Reaction of 1,3-diaminopropane with biacetyl yields only non-basic tars, but with benzil the di-imine (VI) is formed. The i.r. spectrum has maxima at 1670 (C=O) and 1630 (C=N) $cm.^{-1}$. The n.m.r. spectrum consists of a multiplet centred at δ 7·3 p.p.m. (20H, phenyl groups), a triplet at 3·3 (4H, outer methylene protons), and a quintet at 1·7 p.p.m. (2H, inner methylene protons).

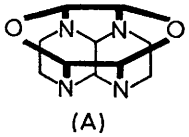
Cyclic 1,2-diketones should be more likely to react with diamines to give cyclic products than open-chain diketones, since the ring structure would be expected to keep the carbonyl groups in a conformation more conducive to cyclisation. In conformity with this prediction, cyclohexane-1,2-dione (which exists largely as the mono-enol) reacts with 1,3-diaminopropane to yield the hexahydro-1,5-benzodiazepine (VII). This structure, rather than the isomeric (VIII), is supported by the i.r. spectrum: $\nu_{max.}$ 3400 (NH) and 1645 and 1625 (C=C and C=N) $cm.^{-1}$, and also by the u.v. spectrum: $\lambda_{max.}$ 287 nm. (log ε 2·65); cyclohexanedione mono-enol has $\lambda_{max.}$ 264 nm. (log ε 3·84), and the diketo-form, prepared in solution from the sodium hydrogen sulphite adduct,[9] has a low-intensity maximum at 412 nm. 1,3-Diaminopropane reacts with a solution of the diketo-form to yield only (VII). The hexahydrobenzodiazepine did not isomerise



on treatment with sodium ethoxide, and no 1,5-benzodiazepine was produced on attempted dehydrogenation with chloranil. It was hydrolysed to cyclohexanedione and diaminopropane under acidic or alkaline conditions. Reaction with benzoyl chloride in dry benzene yielded a hygroscopic crystalline material which decomposed on absorption of atmospheric moisture; its composition corresponded approximately to that of the salt (IX). The diazepine (VII) reacted with phenyl isocyanate to form a crystalline product which decomposed when warmed in solution. The crude material had the correct C to N ratio for the phenylcarbamoyl derivative (X).

Bromination of the diazepine (VII) in carbon tetrachloride produced a hygroscopic solid which contained chlorine as well as bromine, presumably as the result of a free-radical reaction involving solvent molecules. Reaction with bromine in bromoform yielded a crystalline product, believed to be (XI), which rapidly changed

* The formulae $C_{12}H_{18}N_4O_2$ and $C_{16}H_{26}N_4O_2$ are analogous to that of the compound $C_{10}H_{14}N_4O_2$ formed in aqueous alkaline buffer from two molecules of ethylenediamine and three molecules of glyoxal, and shown by *X*-ray crystallography to have structure (A) (J. M. Edwards, U. Weiss, R. D. Gilardi, and I. L. Karle, *Chem. Comm.*, 1968, 1649).


(A)

† The reported value of 339 nm. for the absorption maximum of 2,3-dihydro-1,4-diazepinium perchlorate (C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd, and D. R. Marshall, *J. Chem. Soc.* (*C*), 1966, 93) is a misprint; further details, including the preparation of the perchlorate, have now been published: C. Barnett, D. R. Marshall, and D. Lloyd, *J. Chem. Soc.* (*B*), 1968, 1536.

[8] (*a*) J. P. Collman and E. T. Kittleman, *J. Amer. Chem. Soc.*, 1961, **83**, 3529; (*b*) J. P. Collman, E. T. Kittleman, W. S. Hurt, and N. A. Moore, *Inorg. Synth.*, 1966, **8**, 141.

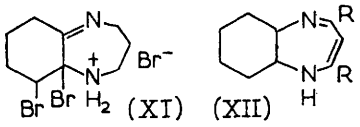
[9] R. Bakule and F. A. Long, *J. Amer. Chem. Soc.*, 1963, **85**, 2309.

to a dark tar on absorption of atmospheric moisture. No tractable product was obtained on attempted bromination of (VII) with *N*-bromosuccinimide or pyridinium bromide perbromide.

The diazepine (VII) is isomeric with the 2,3-dihydro-1*H*-1,4-diazepine (XII; R = H), which has not been prepared, although 5a,6,7,8,9,9a-hexahydro-2,4-dimethyl-1*H*-1,5-benzodiazepine (XII; R = Me) has previously been made from 1,2-diaminocyclohexane and acetylacetone.[2] An attempt to prepare (XII; R = H) for comparison with (VII) by reaction of *trans*-1,2-diaminocyclohexane with malonaldehyde yielded instead the monohydrate of *trans*-1,2-bis-(2-formylvinylamino)-cyclohexane (XIII) or the tautomeric structure. The i.r. spectrum (KBr) contains broad bands at 3300 (hydrogen-bonded NH or OH) and 1600 (chelated C=O or C=N and C=C) cm.$^{-1}$.

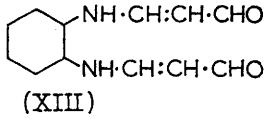
Unlike cyclohexane-1,2-dione, cyclopentane-1,2-dione reacts with 1,3-diaminopropane to give tars, even under nitrogen. Camphorquinone, which can be regarded as a cyclo-hexane- or -pentane-1,2-dione incapable of enolisation, reacts with diaminopropane to give the di-imine (XIV). Camphorquinone reacts with carbonyl reagents at the 3-position, and so structure (XIV) is assumed rather than the isomeric structure involving reaction of the carbonyl groups at the 2-position.

Cycloheptane-1,2-dione and diaminopropane reacted with formation of a product which appeared to be (XV), but which could not be freed from unchanged ketone and/or water.

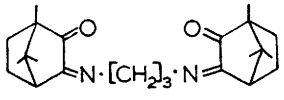


(XI)

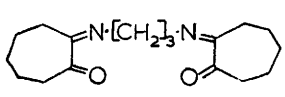
(XII)



(XIII)



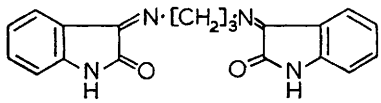
(XIV)



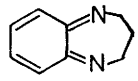
(XV)

Isatin reacted with 1,3-diaminopropane to yield a product the composition and spectroscopic data of which are consistent with the structure (XVI).

When ninhydrin was treated with diaminopropane under various conditions, dark, sparingly soluble substances were formed, none of which had the composition of the expected diazepine or di-imine. A similar product was formed when indane-1,2,3-trione was used. The reaction of ninhydrin with aliphatic αω-diamines has previously been studied by Yamageshi and Yoshida,[10] who considered that the amines were oxidised to aldehydes, but that the reaction with ethylenediamine was different from that of longer-chain diamines; the reaction with 1,3-diaminopropane was not mentioned. Moubasher and Othman,[11] however, claim that 1,3-diaminopropane reacts with ninhydrin in aqueous solution to yield a blue solution from which hydrindantine can be isolated; no experimental evidence for the fate of the diamine was given.



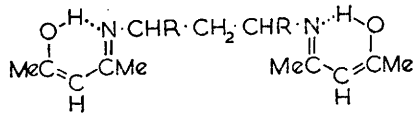
(XVI)



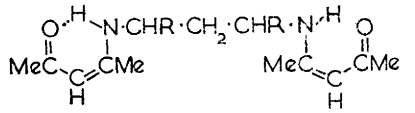
(XVII)

In view of the fact that cyclohexane-1,2-dione condenses with 1,3-diaminopropane to form a diazepine, *o*-quinones might be expected to yield initially compounds of type (XVII), which should rearrange readily to 2,3-dihydro-1*H*-1,5-benzodiazepines. 1,3-Diaminopropane was treated with tetrachloro-*o*-benzoquinone, 1,2-naphthoquinone, sodium 1,2-naphthoquinone-4-sulphonate, phenanthrenequinone, and acenaphthenequinone, but in all cases the products were insoluble, high-melting materials, the compositions of which corresponded neither to the desired diazepines nor to the di-imines formed from two molecules of quinone and one of diamine. A complex reaction between true quinones and diamines is not unexpected, but the failure of phenanthrenequinone and acenaphthenequinone to yield identifiable products is more surprising in view of the fact that benzil and diaminopropane undergo a simple condensation reaction.

Although 1,3-diketones react with 1,2-diamines to yield diazepines, reaction with 1,3-diamines is unlikely to produce eight-membered ring analogues. In fact, acetylacetone reacts with 2,4-diaminopentane in alkaline buffer solution to give (XVIIIa or b; R = Me); no reaction with 1,3-diaminopropane occurs under these conditions, but under different conditions the compound (XVIIIa or b; R = H) is formed (*cf.* ref. 12). The solid-phase i.r. spectra of the compounds (XVIII; R = Me and R = H) both contain a very broad, low-intensity band between 2000 and 4000 cm.$^{-1}$ (OH or NH groups with extensive hydrogen bonding), a doublet at 1570 and 1620 cm.$^{-1}$ (chelated C=O or C=N), and a band at 738 cm.$^{-1}$ (C=C). The spectra of solutions in bromoform



(XVIIIa)



(XVIIIb)

contain bands at 3300 and 3500 cm.$^{-1}$. The n.m.r. spectra of these products can be interpreted in terms of the enamine structure (XVIIIb) (Table 2). Complete

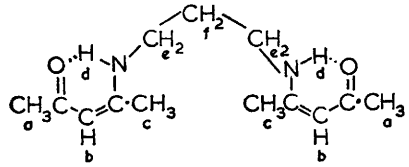
[10] M. Yamageshi and T. Yoshida, *J. Pharm. Soc. Japan*, 1954, **74**, 1075 (*Chem. Abs.*, 1955, **49**, 1488).

[11] R. Moubasher and A. M. Othman, *J. Amer. Chem. Soc.*, 1950, **72**, 2666.

[12] (*a*) P. J. McCarthy, R. J. Hovey, K. Ueno, and A. E. Martell, *J. Amer. Chem. Soc.*, 1955, **77**, 5820; (*b*) A. E. Martell, R. L. Belford, and M. Calvin, *J. Inorg. Nuclear Chem.*, 1958, **5**, 170; (*c*) G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, 1961, **83** 2099.

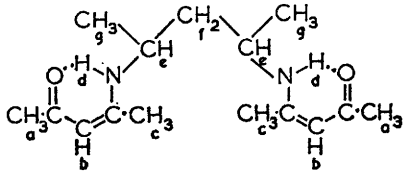
TABLE 2

N.m.r. spectra of products from acetylacetone and 1,3-diamines (p.p.m. from tetramethylsilane)



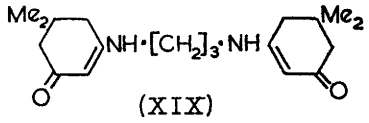
Solvent:						
CCl_4	1·90		4·83	10·90	3·33, 3·43	Under CH_3
C_6H_6	1·42	2·02	4·86	11·10	2·59, 2·68	1·05(m)
Assignment	H_c	H_a	H_b	H_d	H_e	H_f

(*cf.* ref. 12c)



Solvent:								
$CDCl_3$	1·16, 1·26	1·79	1·99	4·92	10·80	3·70 (m)	*ca.* 1·75
Assignment	H_g	H_c	H_a	H_b	H_d	H_e	H_f

analysis of the spectrum of (XVIII; R = Me) is not possible since the resonance due to the methylene protons is largely obscured by the methyl resonances. Dimedone reacts with 1,3-diaminopropane to give the compound (XIX), or its tautomer, the i.r. spectrum (KBr) of which contains a broad band between 1500 and 1600 cm.$^{-1}$, presumably due to conjugated C=O, C=N, and C=C groups. Only polymeric material was obtained from the reaction of malonaldehyde with diaminopropane.



(XIX)

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer Infracord model 137 or a Hilger-Watts Infrascan spectrophotometer, and u.v. spectra with a Unicam SP 700 or an Optica CF4R spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer R10 instrument with tetramethylsilane as internal standard. Molecular weights in solution were measured with a Mechrolab vapour pressure osmometer.

2,4-*Diaminopentane*.—A mixture of (±)- and *meso*-2,4-diaminopentane dihydrochloride was prepared by reduction of acetylacetone dioxime with sodium and ethanol.[13] The base was obtained by treating the salt with saturated sodium hydroxide solution and extraction with ether.

The acetyl derivatives of the (±)- and *meso*-diamines could not be separated by t.l.c. on silica gel.

cis-5,7-*Dimethylhexahydro*-1,4-*diazepin*-2-*one*.—A solution of glyoxal sodium hydrogen sulphite addition compound (2·84 g.) and 2,4-diaminopentane dihydrochloride (1·75 g.) in 50% aqueous ethanol (50 ml.) was refluxed for 2 hr., and then concentrated to half its volume under reduced pressure, basified with sodium hydroxide, and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to yield cis-5,7-*dimethylhexahydro*-1,4-*diazepin*-2-*one* (0·7 g.) as a yellow solid, m.p. 141—146°. Five recrystallisations from acetone gave white crystals, m.p. 181—182° [Found: C, 59·3; H, 9·9; N, 19·5%; *M* (mass spectrometry), 142. $C_7H_{14}N_2O$ requires C, 59·2; H, 9·9; N, 19·7%; *M*, 142], *M* (solution) 147 (acetone and ethanol), 150 (chloroform), and 277 (water), *M* (Rast) 285. No pure stereoisomer could be isolated from the mother liquors from the recrystallisation.

No product soluble in organic solvents was obtained by using glyoxal monohydrate instead of the hydrogen sulphite adduct, or by using 1,3-diaminopropane dihydrochloride instead of diaminopentane dihydrochloride.

Derivatives of cis-5,7-*Dimethylhexahydro*-1,4-*diazepin*-2-*one*.— 4-*Benzoyl*-5,7-*dimethylhexahydro*-1,4-*diazepin*-2-*one* was prepared under Schotten-Baumann conditions; m.p. 243—245° (from ethanol) (Found: C, 68·2; H, 7·3; N, 11·6. $C_{14}H_{18}N_2O_2$ requires C, 68·3; H, 7·2; N, 11·4%). The *acetyl derivative*, obtained as an oil, could not be induced to crystallise. The *picrate* had m.p. 251—253° (from ethanol) (Found: C, 42·0; H, 4·6; N, 19·0. $C_{13}H_{17}N_5O_8$ requires C, 42·05; H, 4·6; N, 18·9%). The diazepinone did not react with phosphoryl chloride, and no tractable product could be separated from the dark solutions obtained by treatment with phosphorus pentachloride in toluene or xylene on a water-bath.

Reduction of cis-5,7-*Dimethylhexahydro*-1,4-*diazepin*-2-*one*.—A suspension of the diazepinone (0·5 g.) in dry tetrahydrofuran (30 ml.) was added to a stirred solution of lithium aluminium hydride (0·27 g.) in dry tetrahydrofuran (30 ml.) at such a rate as to maintain gentle boiling. The solution was then refluxed for a further 3 hr. and left overnight at room temperature. After dropwise addition of water to destroy the excess of hydride, the solution was basified with sodium hydroxide, and the organic layer separated and dried (KOH). Evaporation of solvent under reduced pressure yielded cis-5,7-*dimethylhexahydro*-1,4-*diazepine* as a brown oil (0·2 g., 21·9%). The *picrate*, prepared by addition of a solution of picric acid in benzene, had m.p. 229—230° (from ethanol) (Found: C, 39·3; H, 3·7; N, 19·4. $C_{19}H_{22}N_8O_{14}$ requires C, 38·9; H, 3·75; N, 19·1%).

Reaction of Glyoxal Monohydrate with 1,3-*Diaminopropane*.—Glyoxal monohydrate (0·76 g., 0·01 mole) and 1,3-diaminopropane (0·74 g., 0·01 mole) were dissolved in pH 11 buffer (20 ml.) and set aside overnight. The precipitated *product* (A) (0·6 g.) was filtered off; m.p. 171—172° (from aqueous acetone) [Found: C, 52·6; H, 8·9; N, 24·6%; *M* (mass spectrometry), 210·1471. $C_{10}H_{18}N_4O,H_2O$ requires C, 52·6; H, 8·8; N, 24·6%; *M* (for $C_{10}H_{18}N_4O$), 210·1480]. A second *product* (B) (0·4 g.) was isolated by extracting the aqueous mother liquor with chloroform, drying the extract ($MgSO_4$), and evaporating at room temperature. The residue was purified by dissolution in chloroform and reprecipitation with acetone; m.p. 240—243° [Found: C, 55·0; H, 8·4; N, 25·5%; *M* (mass spectrometry), 250; *M* solution), 470 (ethanol), 555 (carbon tetrachloride), 960 (water). $C_{12}H_{18}N_4O_2,H_2O$ requires C, 53·7; H, 7·5; N, 20·9%; *M* (for $C_{12}H_{18}N_4O_2$), 250]. No detectable reaction occurred between glyoxal monohydrate and diaminopropane in solutions of pH 4 or 7. The substances (A) and (B) showed only end absorption in the u.v. region; the i.r. spectra of both contained a broad band *ca.* 3300 cm.$^{-1}$ (hydrogen-bonded NH or OH) and a peak at 1640 cm.$^{-1}$.

[13] C. J. Dippel, *Rec. Trav. chim.*, 1931, **50**, 525.

Both substances gave glyoxal bis-2,4-dinitrophenylhydrazone, m.p. and mixed m.p., 327°, when treated with Brady's reagent or a solution of 2,4-dinitrophenylhydrazine in bis-(2-hydroxyethyl) ether containing a few drops of acetic acid,[14] but no reaction occurred with hydroxylamine, semicarbazide, or dimedone. Product (B) was decomposed by heating in organic solvents as well as by cold aqueous acid or alkali. The *dihydrochloride* of (A) was precipitated by passing dry hydrogen chloride through an ethanolic solution of (A), and recrystallised from aqueous acetone; m.p. 193—195° (Found: C, 37·8; H, 7·7; Cl, 22·5; N, 17·4. $C_{10}H_{18}N_4O,2HCl,2H_2O$ requires C, 37·6; H, 7·5; Cl, 22·3; N, 17·6%). Product (A) was converted to its *picrate*, m.p. 157—159°, by addition of cold saturated alcoholic picric acid (Found: C, 39·7; H, 4·0; N, 20·5. $C_{10}H_{18}N_4O,2C_6H_3N_3O_7$ requires C, 39·5; H, 3·6; N, 20·95%). A hygroscopic *hydrochloride* and a *picrate* were similarly obtained from the substance (B), but neither could be obtained pure. Product (A) did not react with benzoyl chloride in pyridine, but with benzoyl chloride and sodium hydroxide a dark oil was produced.

Reaction of Glyoxal Monohydrate with 2,4-Diaminopentane.—The reaction was carried out as with diaminopropane. The precipitated *product* (C) (0·5 g.) was purified by washing with methanol and ether; m.p. 136—139° [Found: C, 60·3; H, 10·0; N, 18·9%; *M* (mass spectrometry), 266. $C_{14}H_{26}N_4O,H_2O$ requires C, 59·2; H, 9·9; N, 19·7%; *M* (for $C_{14}H_{26}N_4O$), 266]. The soluble *product* (D) (1·2 g.) was isolated and purified as for (B); m.p. 160—162° [Found: C, 59·1; H, 8·8; N, 18·05%; *M* (mass spectrometry), 306; *M* (solution), 277 (ethanol), 274 (acetone), 555 (carbon tetrachloride). $C_{16}H_{26}N_4O_2,H_2O$ requires C, 59·3; H, 8·6; N, 17·3%; *M* (for $C_{16}H_{26}N_4O_2$), 306].

Reaction of Ethylenediamine with Malonaldehyde.—A solution of 1,1,3,3-tetraethoxypropane (1·88 g.) and ethylenediamine (0·6 g.) in methanol (50 ml.) containing perchloric acid (70%; 1 ml.) was refluxed for 2 hr. Evaporation of solvent yielded an oil which was taken up in acetone. The perchlorate which separated after 1 hr. was filtered off and recrystallised from water; m.p. 164—166° (Found: C, 39·8; H, 7·1; Cl, 14·7; N, 11·4%). Reaction of the perchlorate with benzoyl chloride and alkali yielded *NN'*-dibenzoylethylenediamine, m.p. and mixed m.p. 244°. During benzoylation, the reaction mixture darkened, possibly owing to liberation, and subsequent polymerisation, of malonaldehyde (*cf.* reaction of 2,3-dihydro-5,7-dimethyl-1*H*-1,4-diazepinium salts under similar conditions [15]).

Attempted reaction of Tris(propanedialato)chromium with Ethylenediamine.—Tris(propanedialato)chromium was prepared by the method of Collman and his co-workers,[8b] but in lower yield. Solutions of the complex (0·1 g.) and ethylenediamine (0·1 g.) in methanol (5 ml.) were acidified with hydrochloric acid or basified with sodium hydroxide, and left for 24 hr. at room temperature; the u.v. spectrum was recorded at intervals. In no case was evidence of reaction obtained.

1,3-*Bis*-(α-*benzoylbenzylideneamino*)*propane.*—A solution of benzil (4·2 g., 0·02 mole) and 1,3-diaminopropane (0·74 g., 0·01 mole) in methanol (30 ml.) was refluxed for 4 hr., concentrated to 10 ml., and left overnight at 0°. The solid which separated gave yellow crystals of 1,3-*bis*-(α-*benzoylbenzylideneamino*)*propane* (2·5 g., 54·6%), m.p. 106—108° (from methanol), $\lambda_{max.}$ (MeOH) 251 nm. (log ε 3·84) (Found: C, 81·45; H, 5·8; N, 6·5. $C_{31}H_{26}N_2O_2$ requires C, 81·2; H, 5·7; N, 6·1%). The compound reacts with Brady's reagent to form benzil bis-2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 315—317°, but is unaffected by aqueous alkali or acid chlorides.

2,3,4,6,7,8-*Hexahydro*-1H-1,5-*benzodiazepine.*—Cyclohexane-1,2-dione (1·12 g., 0·01 mole) was dissolved in water (10 ml.) containing a few drops of ethanol, and added to a solution of 1,3-diaminopropane (0·74 g., 0·01 mole) in water (10 ml.). After 8 hours at room temperature, the yellow *diazepine* was filtered off and recrystallised from methanol; yield 0·8 g. (53·3%), m.p. 180—182° (Found: C, 72·0; H, 9·5; N, 18·6. $C_9H_{14}N_2$ requires C, 72·0; H, 9·3; N, 18·7%).

The same product was obtained by treating a solution in dioxan of the diketo-form of cyclohexane-1,2-dione, prepared by the method of Bakule and Long,[9] with aqueous or methanolic solutions of diaminopropane. The diazepine is hydrolysed to cyclohexane-1,2-dione and diaminopropane by aqueous acid or alkali, and with Brady's reagent it yields cyclohexane-1,2-dione bisdinitrophenylhydrazone, m.p. and mixed m.p. 233—234°.

Bromination of 2,3,4,6,7,8-*Hexahydro*-1H-1,5-*benzodiazepine.*—(*a*) A solution of bromine (0·8 g.) in carbon tetrachloride (15 ml.) was added dropwise to the diazepine (1·5 g.) in carbon tetrachloride (15 ml.). The precipitated solid (0·9 g.), m.p. *ca.* 70° (decomp.), contained chlorine as well as bromine, decomposed on attempted recrystallisation, and rapidly absorbed atmospheric moisture, with decomposition.

(*b*) The diazepine (1·5 g.) in bromoform (20 ml.) was treated dropwise with a solution of bromine in bromoform until no further precipitation of 9,9a-*dibromo*-2,3,4,6,7,8,9,9a-*octahydro*-1H-1,5-*benzodiazepinium bromide* occurred. The product (1·3 g., 33%) decomposed on absorption of atmospheric moixture, and on attempted recrystallisation; it was purified by washing with bromoform and ether; m.p. 170—173° (Found: C, 30·3; H, 3·8; Br, 63·45; N, 7·1. $C_9H_{15}Br_3N_2$ requires C, 27·6; H, 3·8; Br, 61·4; N, 7·2%).

(*c*) *N*-Bromosuccinimide (1·7 g.) and diazepine (1·5 g.) were dissolved in carbon tetrachloride or chloroform (150 ml.) and the solution was refluxed with and without u.v. irradiation. Black solids of indefinite m.p. separated.

(*d*) Pyridinium bromide perbromide (1·95 g.) dissolved in acetonitrile (10 ml.) was added to the diazepine (0·75 g.) in acetonitrile (10 ml.) and the solution was warmed on a water-bath. Black tar separated; no tractable product could be isolated.

Other Derivatives of 2,3,4,6,7,8-*Hexahydro*-1H-1,5-*benzodiazepine.*—Addition of benzoyl chloride to a solution of the diazepine in dry benzene yielded a precipitate of 1-*benzoyl*-2,3,4,6,7,8-*hexahydro*-1H-1,5-*benzodiazepinium chloride*, m.p. 237—240°. The compound decomposed rapidly on exposure to air, and on basification (Found: C, 62·0; H, 7·0; Cl, 12·4; N, 9·8. $C_{16}H_{19}ClN_2O$ requires C, 66·2; H, 6·5; Cl, 12·1; N, 9·6%). Attempted formation of the acetyl derivative in the same way yielded a semi-solid precipitate which immediately decomposed to a dark tar when filtered off.

Treatment of the diazepine, in benzene, with phenyl isocyanate produced a precipitate of a substance, m.p. 120° (decomp.), which decomposed on warming with solvents and could not be recrystallised (Found: C, 64·1: H, 8·7; N, 13·85. Calc. for $C_{16}H_{19}N_3O$: C, 71·3; H, 7·1; N, 15·6%).

[14] H. J. Shine, *J. Org. Chem.*, 1959, **24**, 252, 1790.
[15] D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.* (*C*), 1966, 780.

Attempted Dehydrogenation of 2,3,4,6,7,8-*Hexahydro*-1H-1,5-*benzodiazepine*.—The diazepine (0·75 g.) was dissolved in xylene (10 ml.), chloranil (1·2 g.) in xylene (5 ml.) was added, and the solution was boiled for 30 min. Black solid, m.p. >360°, separated.

trans-1,2-*Bis*-(2-*formylvinylamino*)*cyclohexane*.— 1,1,3,3-Tetraethoxypropane (1·88 g.) and hydrochloric acid (1 ml.) were stirred in water (10 ml.) until the mixture was homogeneous, and then added to *trans*-1,2-diaminocyclohexane (1·12 g.) in pH 5 buffer (20 ml.). After 3 days the solution was basified with sodium hydroxide and extracted with chloroform. The extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure at room temperature, to yield trans-1,2-*bis*(2-*formylvinylamino*)-*cyclohexane monohydrate*, purified by washing with acetone; yield 1·02 g. (45·9%), m.p. 270° (decomp.), $\lambda_{max.}$ 240 and 284 nm. (log ε 2·74 and 3·14) (Found: C, 60·5; H, 7·6; N, 11·4. $C_{12}H_{18}N_2O_2,H_2O$ requires C, 60·0; H, 8·3; N, 11·7%). The same product was obtained in lower yield at pH 7, but no reaction occurred in alkaline buffer. The compound is sensitive to heat and acid.

Attempted Reaction of Cyclopentane-1,2-*dione with* 1,3-*Diaminopropane*.—Cyclopentane-1,2-dione, prepared from cyclopentanone by Acheson's procedure,[16] was treated with 1,3-diaminopropane in methanol, ethanol, or benzene at room and at reflux temperature, and also in aqueous buffer solutions (pH 4, 7, or 11). In all cases, dark tars were obtained, even in a nitrogen atmosphere; no tractable products could be separated by chromatography.

(+)-1,3-*Bis*(2-*oxobornan*-3-*ylideneamino*)*propane*.—A solution of (−)-camphorquinone (1·66 g.) and 1,3-diaminopropane (0·5 ml.) in ethanol (12 ml.) was refluxed for 4 hr., and then concentrated to 5 ml. and chromatographed on silica gel (100 g.), with methanol as eluant. Evaporation of the eluate under reduced pressure left an oil which partially solidified when left in an evacuated desiccator, and which, when stirred with a little ether, yielded pale yellow crystals of (+)-1,3-*bis*(2-*oxobornan*-3-*ylideneamino*)*propane*, which were washed well with ether; yield 0·63 g. (34·1%), m.p. 104—107°, $[\alpha]_D^{20}$ +203° [0·1056 g., chloroform (5 ml.)], $\nu_{max.}$ (KBr or $CHBr_3$) 1750 (C=O) and 1675 (C=N) cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 217, 283, and 376 nm. (log ε 4·16, 2·41, and 1·88) [camphorquinone (MeOH) has $\lambda_{max.}$ 207, 285, and 488 nm. (log ε 3·08, 1·40, and 1·49)] (Found: C, 74·3; H, 9·2; N, 7·6. $C_{23}H_{34}N_2O_2$ requires C, 74·6; H, 9·2; N, 7·6%). The compound cannot be purified by recrystallisation, as it is soluble in all common organic solvents except petroleum, and is hydrolysed with formation of camphorquinone on attempted recrystallisation from a mixture of organic solvent and water.

Reaction of Cycloheptane-1,2-*dione with* 1,3-*Diaminopropane*.—Cycloheptane-1,2-dione was prepared by oxidation of cycloheptanone with selenium dioxide.[17] A mixture of cycloheptane-1,2-dione (1·26 g.) and 1,3-diaminopropane (0·74 g.) was heated under reflux for 1 hr. The residue, which decomposed on attempted vacuum distillation, was dissolved in chloroform (10 ml.) and the solution was chromatographed on alumina (Spence, grade H). Elution with chloroform effected separation into four distinct yellow bands. The first and last contained cycloheptanedione and diaminopropane respectively. The second band yielded a yellow oil, $\nu_{max.}$ 1715 (C=O) and 1660 (C=N) cm.$^{-1}$, together with bands ascribable to unchanged diketone; $\lambda_{max.}$ (MeOH) 294 nm.; [cycloheptane-1,2-dione has $\lambda_{max.}$ 270 nm.] (Found: C, 69·5; H, 9·5; N, 7·95. $C_{17}H_{26}N_2O_2$ requires C, 70·3; H, 9·0; N, 9·6%). A similar oil was obtained from the third band (Found: C, 57·3; H, 8·3; N, 8·85%). The same product mixture was obtained when the reaction was carried out in boiling methanol or ethanol, or in xylene with azeotropic removal of water, or by leaving an aqueous solution of the reactants overnight and then extracting with chloroform.

1,3-*Bis*-(3-*oxindolylideneamino*)*propane*.—A solution of isatin (2·94 g., 0·02 mole) and 1,3-diaminopropane (0·74 g., 0·01 mole) in methanol (50 ml.) was boiled for 1 hr. The precipitate was filtered from the hot solution and washed with hot methanol (in which unchanged isatin is soluble) and with ether to yield 1,3-*bis*-(3-*oxindolylideneamino*)*propane* as a red-brown powder (2·3 g., 93·7%), m.p. 225—227°, $\nu_{max.}$ (KBr) 1650 cm.$^{-1}$ (C=N), $\lambda_{max.}$ (MeOH) 204, 246, 251, 292, and 391 nm. (log ε 4·64, 4·59, 4·56, 3·89, and 3·35) [isatin has $\lambda_{max.}$ (MeOH) 212, 245, 250, 302, and 426 nm. (log ε 4·09, 4·26, 4·18, 3·39, and 2·71)] (Found: C, 68·4; H, 5·1; N, 16·85. $C_{19}H_{16}N_4O_2$ requires C, 68·6; H, 4·8; N, 16·9%). The compound is sparingly soluble in all common organic solvents; recrystallisation from aqueous dimethylformamide was accompanied by decomposition.

Reactions of Ninhydrin and Indane-1,2,3-*trione with* 1,3-*Diaminopropane*.—Solutions of ninhydrin (1·78 g.) in water (60 ml.) or ethanol (60 ml.) were treated with 1,3-diaminopropane (0·74 g. or 0·37 g.), and either refluxed for 1 hr. or left at room temperature for 24 hr. The dark-coloured products were filtered off; those from aqueous solution were heavily hydrated and lost water *in vacuo* at 100°, but not at room temperature. The solid phase i.r. spectra were poorly resolved, but appeared to show absorption corresponding to C=O and C=N.

Indane-1,2,3-trione, prepared by dehydration of ninhydrin with thionyl chloride,[18] reacted with diaminopropane in boiling dry benzene to produce black solids of indefinite m.p.

Reaction of o-*Quinones with* 1,3-*Diaminopropane*.—Tetrachloro-*o*-benzoquinone, 1,2-naphthoquinone, sodium 1,2-naphthoquinone-4-sulphonate, phenanthrenequinone, or acenaphthenequinone (0·01 mole) was treated with 1,3-diaminopropane (0·74 g., 0·01 mole) in methanol, ethanol, or acetic acid at room or at reflux temperature. *N*-Methyl-2-pyrrolidone (NMP) and *NN*-dimethylformamide were also used as solvents in experiments with the last two quinones, and sodium naphthoquinonesulphonate was also treated with diaminopropane in water. In many cases, dark solids of high (>360°) or indefinite m.p. were formed, but some apparently homogeneous products (Table 3) were precipitated from the hot solutions or on cooling.

2,4-*Bis*(2-*acetyl*-1-*methylvinylamino*)*pentane*.—A solution of 2,4-diaminopentane (1·0 g.) and acetylacetone (2·0 g.) in pH 11 buffer (20 ml.) was left for 24 hr. at room temperature. The precipitated product was filtered off and recrystallised six times from light petroleum (b.p. 60—80°) to yield pure 2,4-*bis*(2-*acetyl*-1-*methylvinylamino*)*pentane* (1·5 g., 56·4%), m.p. 116—118°, $\lambda_{max.}$ (MeOH) 318 nm. (log ε 3·42) [Found: C, 67·6; H, 9·65; N, 10·6%; *M* (mass spectrometry), 266. $C_{15}H_{26}N_2O_2$ requires C, 67·7; H, 9·8; N, 10·5%; *M*, 266]. The compound is hydrolysed in acid solution, and yields green precipitates with methanolic solutions of ferrous, chromic, or cupric salts. There was

[16] R. M. Acheson, *J. Chem. Soc.*, 1956, 4232.
[17] R. W. van der Haar, R. C. Voter, and C. Banks, *J. Org. Chem.*, 1949, **14**, 836.
[18] A. Schönberg and R. Moubasher, *J. Chem. Soc.*, 1943, 71.

TABLE 3

Quinone	Reaction conditions	Product m.p.	Product composition (%)
Tetrachloro-*o*-benzoquinone	EtOH, reflux	290° (decomp.)	C, 25·2; H, 8·3; Cl, 47·45; N, 18·55.
1,2-Naphthoquinone	MeOH, 48 hr., room temp.	210 (decomp.)	C, 69·7; H, 5·3; N, 10·0.
Sodium 1,2-naphthoquinone-4-sulphonate	MeOH, reflux	>360	C, 38·2; H, 3·2; N, 5·3; S, 9·5.
Phenanthrene-quinone	MeOH, reflux	295	C, 84·0; H, 4·7; N, 4·0.
Acenaphthene-quinone	NMP, 24 hr., room temp.	190—193	C, 64·8; H, 4·5; N, 10·75.

no reaction between acetylacetone and diaminopentane in solutions of pH 4 or 7, and reaction in xylene with azeotropic removal of water yielded intractable tars.

1,3-*Bis*-(2-*acetyl*-1-*methylvinylamino*)*propane*.—A solution of acetylacetone (1·0 g.) and 1,3-diaminopropane (0·7 g.) in xylene (30 ml.) was refluxed for 2 hr. with azeotropic removal of water. The xylene was removed under reduced pressure, and the oily residue was dissolved in chloroform (5 ml.) and chromatographed on alumina (Spence, grade H). Elution with chloroform caused separation into three yellow bands, the first of which yielded 1,3-bis(2-acetyl-1-methylvinylamino)propane, (1·0 g., 84%), m.p. 51° (lit.,[12] 51°, 61°) $\lambda_{max.}$ (MeOH) 318 nm. (log ε 3·85) (Found: C, 65·5; H, 9·1; N, 11·6. Calc. for $C_{13}H_{22}N_2O_2$: C, 65·5; H, 9·2; N, 11·8%). The other two bands yielded 1,3-diaminopropane and acetylacetone. Acetylacetone and diaminopropane did not react in aqueous buffer solutions.

1,3-*Bis*-(5,5-*dimethyl*-3-*oxocyclohexenylamino*)*propane*.—Dimedone (2·8 g.) and 1,3-diaminopropane (0·8 g.) were dissolved in ethanol (40 ml.) and the solution was boiled for 2 hr., or in benzene (40 ml.) and the solution was refluxed for 1 hr. with azeotropic removal of water. After evaporation of the solvent, the residue was washed with acetone and recrystallised from methanol, yielding 1,3-*bis*-(5,5-*dimethyl*-3-*oxocyclohexenylamino*)*propane*, (1·8 g., 56·6%) as yellow crystals, m.p. 276—277°, $\lambda_{max.}$ (MeOH) 290 nm. (log ε 4·27) (Found: C, 71·8; H, 9·6; N, 9·0. $C_{19}H_{30}N_2O_2$ requires C, 71·7; N, 9·4; N, 8·8%).

Reaction of Malonaldehyde with 1,3-*Diaminopropane*.—(*a*) 1,1,3,3-Tetraethoxypropane (6·5 g.) was shaken with hydrochloric acid (2N; 7 ml.) until the mixture was homogeneous, and the solution was added to 1,3-diaminopropane (1·1 g.) in xylene (40 ml.). It was refluxed until no more water was removed by azeotropic distillation. A dark tar, insoluble or sparingly soluble in all common solvents, separated.

(*b*) The acetal (6·0 g.) was hydrolysed as in (a), and the solution was neutralised with solid potassium carbonate. The resulting solution was added to 1,3-diaminopropane (1 g.) in pH 11 buffer (55 ml.) and left for 48 hr. The solution darkened; extraction with ether or chloroform produced a brown gum insoluble in common organic solvents except methanol and ethanol.

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