HYDROPYRIMIDINES

V.* HEXAHYDROPYRIMIDINES. THE REACTION OF ALDEHYDES AND KETONES WITH 1,3-DIAMINOPROPANES†

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Summary

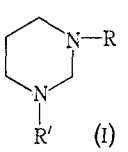
Hexahydropyrimidine and some *N*-alkylated derivatives have been obtained from the reaction of the corresponding trimethylenediamine or its monoprotonated salt with formaldehyde. A variety of spectroscopic evidence supports a cyclic structure for these compounds in preference to a tautomeric open-chain form. The chemical behaviour of hexahydropyrimidine is explicable in terms of a cyclic di-secondary amine structure.

The cyclic structure is destabilized with respect to the open-chain form if the hydrogen atoms attached to C2 of the hexahydropyrimidine ring are replaced by alkyl groups and cannot be detected when, in addition, one of the hydrogen atoms attached to nitrogen is replaced by the bulkier t-butyl group.

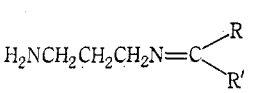
Hexahydro-2-methylpyrimidine is dehydrogenated to 1,4,5,6-tetrahydro-2-methylpyrimidine on shaking with Adams catalyst and hydrogen under laboratory conditions. Hexahydropyrimidines which are tautomeric mixtures are reduced to the corresponding *N*-alkyl-1,3-diaminopropanes, while those possessing cyclic structures are inert.

Introduction

Reaction of trimethylenediamine monohydrochloride or acetate with aqueous formaldehyde is claimed[1,2] to give an equilibrium mixture of the salts of hexahydropyrimidine (I; R = R′ = H) and its open-chain tautomer, 3-methyleneaminopropylamine (II; R = R′ = H). Free hexahydropyrimidine, on account of its



(I)



(II)

polymerization properties, is also believed to exhibit ring-chain tautomerism. Continuing our interest in hydropyrimidines, this reaction was reinvestigated and extended to include other diamines, aldehydes, and ketones. The various products

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† Some of the information in this paper was presented at the Heterocyclic Symposium at Monash University, August 1965.

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[1] Titherley, A. W., and Branch, G. E. K., *J. chem. Soc.*, 1913, **103**, 330.

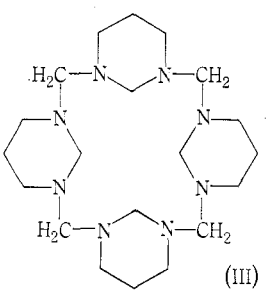
[2] Branch, G. E. K., *J. Am. chem. Soc.*, 1916, **38**, 2466.

were examined by a variety of spectroscopic methods in order to determine structures and enumerate the factors governing the phenomenon of ring-chain tautomerism in hexahydropyrimidines.

Methods and Results

The majority of the diamines required for condensation with the carbonyl compounds were commercial specimens or were prepared by methods described in the literature.[3] 3-n-Butylaminopropylamine was obtained in small yield from the alkylation of trimethylenediamine monohydrochloride with n-butyl chloride. Although the nucleophilic properties of a nitrogen atom are suppressed on protonation, in this case alkylation occurred on both nitrogen atoms because in solution the monohydrochloride exists in equilibrium with the dihydrochloride and free trimethylenediamine. Indeed recrystallization of the monohydrochloride affords the dihydrochloride. 1,3-Bis(t-butylamino)propane was prepared from the reaction of t-butylamine with trimethylene dibromide (in place of the dichloride[4]) since reaction of trimethylenediamine with t-butyl chloride involved elimination of hydrogen chloride only. There was no nucleophilic displacement of nitrogen on the tertiary carbon atom as was observed with hydrazine.[5] An alternative route to the propane compound from methylmagnesium iodide and 1,3-bis(isopropylideneamino)propane could not be tried, since the desired intermediate was not obtained from the condensation of trimethylenediamine and acetone.

Repetition of the condensation of trimethylenediamine monohydrochloride with formaldehyde in aqueous solution afforded a solution which was shown by paper-chromatographic examination to contain at least two nitrogeneous constituents, one of which was trimethylenediamine dihydrochloride. This could indeed be isolated by removal of the solvent under very mild conditions.



(III)

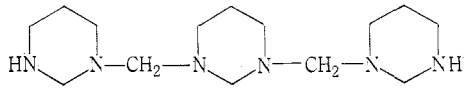
A concentrated aqueous solution of hexahydropyrimidine was obtained on treatment of the condensation solution with excess solid sodium hydroxide. Anhydrous hexahydropyrimidine was obtained for the first time on removal of the water by azeotropic distillation with benzene. Unfortunately both water and benzene formed azeotropes with hexahydropyrimidine so that the yield of anhydrous base diminished considerably during the dehydration procedure. Hexahydropyrimidine

[3] Tarbell, D. S., Shakespeare, N., Claus, C. J., and Bunnett, J. F., *J. Am. chem. Soc.*, 1946, **68**, 1217.

[4] Zienty, F. B., *J. Am. chem. Soc.*, 1946, **68**, 1388.

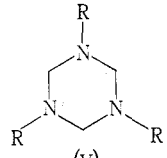
[5] Westphal, O., *Ber. dt. chem. Ges.*, 1941. **74B** 759.

was a colourless fuming liquid which was monomeric in benzene solution at room temperature. Contrary to earlier reports it did not form a polymer at room temperature. However, it did react further with formaldehyde to form 1,3,7,9,-13,15,19,21-octaazapentacyclo[19,3,1,$1^{3,7}$,$1^{9,13}$,$1^{15,19}$]octacosane (III), which was also obtained from the direct condensation of trimethylenediamine with two moles of formaldehyde.[6] Hexahydropyrimidine during its isolation was accompanied by higher-boiling material, from which a solid could be isolated. This compound (IV) seemed to be formed from the condensation of three moles of hexahydropyrimidine and two moles of formaldehyde, or three moles of trimethylenediamine and six moles of formaldehyde. Either this condensation occurred in aqueous solution during the



(IV)

preparation of hexahydropyrimidine—when both free hexahydropyrimidine and trimethylenediamine were present—or after treatment with alkali when unchanged formaldehyde in the wet base could have caused further condensation. No evidence could be produced for the formation of a hexahydro-1,3,5-triazine compound (V; R = $CH_2CH_2CH_2NH_2$) by trimerization of the open-chain tautomer (II; R = R′ = H)



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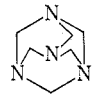


(VI)

Formation of derivatives of hexahydropyrimidine on treatment of the polymers with various reagents was explained by hydrolytic fission of the requisite –N–CH_2–N– linkages. This must occur for example with hexamethylenetetramine (VI), which can afford derivatives of 1,3,5-hexahydrotriazine (V; R = H) or open-chain compounds with benzoyl chloride.[7]

Reaction of trimethylenediamine monohydrochloride with acetaldehyde or acetone yielded the expected hexahydro-2-methyl- or -2,2-dimethyl-pyrimidines which were accompanied by some unreacted trimethylenediamine. Benzaldehyde, however, did not give hexahydro-2-phenylpyrimidine but 1,3-bis(benzylideneamino)-propane. Pentan-3-one and trimethylenediamine monoacetate gave a mixture of hexahydro-2,2-diethylpyrimidine and 1,3-bis(pent-3-ylideneamino)propane as judged from its behaviour upon reduction and in the mass spectrometer.

3-n-Butylamino- and 3-t-butylamino-propylamine monohydrochlorides condensed in the expected manner with formaldehyde, affording the corresponding

[6] Krässig, H., *Makromol. Chem.*, 1956, **17**, 77.

[7] Imolin, E. M., and Rapoport, L., "s-Triazines and Derivatives." p. 548. (Interscience: New York 1959.)

1-alkyl hexahydropyrimidines. With the 1-t-butylhexahydropyrimidine further condensation with formaldehyde occurred,[8] affording bis(3-t-butyl-1,3-diazacyclohexyl)methane. Hence it was inferred that some free 1-t-butylhexahydropyrimidine must have been present in the aqueous reaction mixture.

Since trimethylenediamine monohydrochloride in aqueous solution gives rise to trimethylenediamine anyway, it was of interest to elucidate the course of the reaction between the free base and carbonyl containing compounds. Trimethylenediamine and formaldehyde afforded substance (III), which tenaciously retained benzene when crystallized from that solvent. Acetaldehyde and acetone furnished hexahydro-2-methyl- and -2,2-dimethyl-pyrimidines respectively. The Schiff base 1,3-bis(isopropylideneamino)propane may have been formed to a small extent in the reaction with acetone, since the mass spectrum of the reduction product showed a peak at *m/e* 158 which could have been due to 1,3-bis(isopropylamino)propane. The analogous double Schiff base was the sole product of the reaction between the diamine and benzaldehyde, even with equimolar quantities of reactants. Pentan-3-one under similar conditions formed the double Schiff base predominantly.

1,3-Dialkylhexahydropyrimidines were readily formed from the condensation of both 1,3-di-n-butyl- and -t-butyl-aminopropanes with formaldehyde, but there was little, if any, reaction between the t-butyl diamine and pentan-3-one. Reaction of some 3-alkylaminopropylamines with formaldehyde but not with other aldehydes is known to give 1-alkylhexahydropyrimidines.[8] In this work, 3-t-butylaminopropylamine condensed with benzaldehyde to afford 1-benzylideneamino-3-t-butylaminopropane, i.e. the open-chain tautomer of 1-t-butyl-3-phenylhexahydropyrimidine. Similar open-chain compounds were formed with acetone or pentan-3-one in place of formaldehyde. The products from the reaction of acetone with 3-methylaminopropylamine seemed to be the hexahydropyrimidine containing a small amount of the open-chain tautomer.

In its chemical reactions, hexahydropyrimidine behaved as a disecondary amine, being readily di-benzoylated, -tosylated, and -nitrosated, and forming a bisphenylureido derivative. Reaction with phenylmagnesium bromide did not give the product to be expected from the addition of the Grignard reagent to the double bond of the open-chain tautomer (II; $R = R' = H$). The chemical behaviour of other hexahydropyrimidines with two hydrogen atoms or one hydrogen atom and one methyl group at C 2 was also in accord with their possession of cyclic structures. Hexahydro-2,2-dimethylpyrimidine gave dibenzoyl and other derivatives of trimethylenediamine but no *N*-nitroso compound, indicating that in this and similar cases the molecule reacted in the open-chain form (II; $R = R' = CH_3$) with its readily hydrolysable aliphatic Schiff base group.[9] Nitrous acid would cause deamination of the primary amino groups. Again no product formed by the addition of phenylmagnesium bromide to the double bond of the open-chain tautomer could be isolated from the reaction of this Grignard compound with hexahydro-2,2-dimethylpyrimidine.

[8] Riebsomer, J. L., and Morey, G. H., *J. org. Chem.*, 1950, **15**, 245.

[9] Allen, C. F. H., and Blatt, A. H., in "Organic Chemistry: An Advanced Treatise." (Ed. H. Gilman.) Vol. I, p. 659. (John Wiley: New York 1943.)

Only those hexahydropyrimidines with a 2,2-dimethyl grouping underwent catalytic reduction under mild conditions to afford 3-alkylaminopropylamines, which suggests that it was the double bond of the open-chain tautomer which was being reduced. Better yields were obtained if the reduction were effected with sodium borohydride, a reagent which also caused reductive fission in those hexahydropyrimidines not reduced catalytically. The poor yields in the latter type of reduction, especially with compounds containing the $-\overset{|}{N}-CH_2-\overset{|}{N}-$ group, implied that the reduction involved a different mechanism from reduction of the double bond in an open-chain tautomer, e.g. the iminium ion mechanism postulated by Wilson.[10] Hexahydro-2-methylpyrimidine was unique among the reduced pyrimidines examined, since on shaking with Adams catalyst and hydrogen under laboratory conditions, it underwent dehydrogenation to the 1,4,5,6-tetrahydro stage.

The $-\overset{|}{N}-CH_2-\overset{|}{N}-$ grouping is labile towards acid and this was reflected in the instability of hexahydropyrimidine monohydrochloride, prepared *in situ*, which slowly deposited trimethylenediamine dihydrochloride at room temperature. Attempts to form the "di-" series of salts, even in non-aqueous solutions, caused ring opening and formation of the corresponding trimethylenediamine salts. Replacement of NH by NCH_3 in the parent compound increased the stability towards acid, since it was now possible to isolate both mono- and di-valent salts, but only from non-aqueous solutions. Even then, attempts to recrystallize the salts caused ring fission and formation of the 1,3-bis(methylamino)propane salts. Hexahydro-1,3-dimethylpyrimidine formed a monoquaternary salt, even with excess methyl iodide; coulombic repulsion between two positively charged centres separated by only one carbon atom is probably great enough to prevent formation of the diquaternary salt.[11] The chair conformation of this diquaternary salt would also have additional strain stemming from 1,3 axial–axial repulsions of two of the methyl groups.[12]

Dehydrogenation of hexahydro-1,3-dimethylpyrimidine with chloranil afforded a complex mixture from which a small amount of 1,3-bis(methylamino)propane dihydrochloride was isolated. Chloride ion could be produced from the chloranil by nucleophilic displacement with the pyrimidine base, while ring opening could have been caused by the highly acidic tetrachloroquinol produced by hydrogen transfer to the chloranil.[13]

Ionization

The monocations of hexahydropyrimidine and its 1,3-dimethyl homologue were sufficiently stable in aqueous solution for a pK_a to be measured. The value found for hexahydropyrimidine (9·75) is close to that (9·5) predicted[14] for the cyclic structure (I; R = R′ = H) on the basis that it is the pK_a for a typical secondary aliphatic amine (11·15) which contains a ring (ΔpK_a 0·2), two groups which have equal probabilities of accepting a proton (ΔpK_a 0·3), and an alkylamine

[10] Wilson, E. M., *Chemy Ind.*, 1965, 472.
[11] Evans, R. F., Kynaston, W., and Jones, J. I., *J. chem. Soc.*, 1963, 4031.
[12] Pfleiderer, W., private communication.
[13] Jackman, L. M., *Adv. org. Chem.*, 1960, **1**, 329.
[14] Clark, J., and Perrin, D. D., *Q. Rev. chem. Soc.*, 1964, **18**, 295.

group both one ($-\Delta pK_a$ 1·7) and three carbon atoms ($-\Delta pK_a$ 0·45) away from the site of protonation. It is impossible to predict a pK_a value for the primary amino group of the open-chain tautomer (II; R = R′ = H) on account of the absence of pertinent data. However, the ring-opened covalent hydrated species $NH_2(CH_2)_3N$-HCH_2OH would be expected to have a pK_a of 10·3 since it can be regarded as a typical primary aliphatic amine (pK_a 10·77) containing an alkylamino group three carbon atoms away from the site of protonation ($-\Delta pK_a$ 0·45). The long chain of three carbon atoms could conceivably reduce the electronic effects of the $-N{=}CH_2$ and $-NHCH_2OH$ groups on the amino group to approximately the same level. The pK_a value to be expected for the open-chain tautomer (II; R = R′ = H) would not be very different from the pK_a predicted for the ring-opened covalent hydrated species. Better agreement exists between the pK_a value (8·40) found for hexahydro-1,3-dimethylpyrimidine and that predicted for a cyclic structure (8·65), which is a typical tertiary aliphatic amine (pK_a 10·5) modified by all the factors mentioned in connection with hexahydropyrimidine, together with the extra effect ($-\Delta pK_a$ 0·2) of an *N*-methyl group.

The two pK_a values (11·27 and 9·34 respectively) found for the two basic groups in 1,3-bis(t-butylamino)propane also agree closely with predicted values. A value of 11·0 would be predicted for the higher pK_a, since it is that of an aliphatic secondary amine (pK_a 11·15) in which there are two sites possessing equal probabilities of protonation (ΔpK_a 0·3) and an alkylamino group three carbon atoms away from the site of protonation ($-\Delta pK_a$ 0·45). The second pK_a would be predicted to have a value of 9·05, since it refers to an aliphatic secondary amine which contains a positively charged alkylamino group three carbon atoms distant from the site of protonation ($-\Delta pK_a$ 1·8). However, a statistical factor comes into play ($-\Delta pK_a$ 0·3), for although the proton can attack only one site in the monocation, it can be lost from either of two sites in the symmetrical dication.

Spectra

Infrared Spectra

The infrared spectrum of hexahydropyrimidine exhibits one prominent peak at 3270 cm^{-1} which can be assigned to the NH stretching vibration of a secondary amine.[15a] There is no sharply defined absorption in the 1600–1700 cm^{-1} which could be described as a –C=N– stretching vibration, so that the infrared spectrum strongly supports the cyclic structure (I; R = R′ = H) rather than the open-chain form (II; R = R′ = H) for hexahydropyrimidine. Other hexahydropyrimidine derivatives whose infrared spectra exhibit no absorption in the double-bond stretching region and for which open-chain structures must be precluded, include the hydrochloride and the 1-n-butyl-, the 1-t-butyl-, the 2-methyl-, the 4,4,6-trimethyl, and the 1-isopropyl-4,4,6-trimethyl homologues. Hexahydro-2,2-dimethylpyrimidine, however, gave a weak absorption at 1670 cm^{-1}, which may safely be described as a ν(C=N) vibration,[15b] since comparable values for this vibration (which is now an intense one) are observed in the spectra of t-butylazomethane (1665 cm^{-1}), of

[15] Bellamy, L. J., "The Infrared Spectra of Complex Molecules." (*a*) p. 248; (*b*) p. 268. (Methuen: London 1960.)

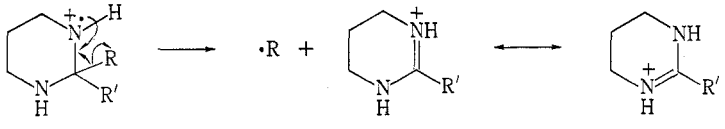
1,2,5,6-tetrahydro-2,2,4,4,6-pentamethylpyrimidine (1670 cm^{-1}), of 1,3-bis(benzylideneamino)propane (1647 cm^{-1}), and 1,3-bis(pent-3-ylideneamino)propane (1663 cm^{-1}). However, only one NH stretching vibration is observed at 3275 cm^{-1}, so that the open-chain form (II; R = R′ = CH_3) must be present as a minor constituent, and the two NH stretching vibrations associated with the primary amine group (which in the spectrum of trimethylenediamine occur at 3365 (ν_{as}) and 3290 (ν_s) cm^{-1} respectively) must be obscured by the broad NH stretching band of the cyclic tautomer (I; R = R′ = CH_3). The spectrum of anhydrous hexahydro-2,2,4,4,6-pentamethylpyrimidine exhibits similar features (ν(NH) at 3279 cm^{-1}, ν(C=N) at 1653 cm^{-1}), and it is concluded that again in the liquid state a small proportion of open-chain isomer is present in a tautomeric mixture.

Replacement of one NH group by an NCH_3 group makes little difference to the tautomeric equilibria, for the spectrum of hexahydro-1,2,2-trimethylpyrimidine resembles that of the 2,2-dimethyl compound in having both a ν(NH) band at 3260 cm^{-1} and a weak ν(C=N) band at 1665 cm^{-1}. By contrast, introduction of one *N*-t-butyl group shifts the tautomeric equilibrium strongly in favour of the open-chain form when groups other than hydrogen are attached to C2. The spectra of 1-t-butyl-hexahydro-2,2-dimethyl-, -2,2-diethyl-, and -2-phenyl-pyrimidines exhibit weak ν(NH) bands around 3300 cm^{-1} while the ν(C=N) band around 1650 cm^{-1} is now the strongest band in the whole spectrum, indicating that these three compounds should properly be regarded as the open-chain tautomeric 1-alkylideneamino-3-t-butylaminopropanes.

Since the intense ν(C=N) band at 1670 cm^{-1} in the spectrum of 1,2,5,6-tetrahydro-2,2,4,4,6-pentamethylpyrimidine persisted in that of the monohydrate, it was concluded that no covalent hydration[16] of the C=N group had occurred.

Mass Spectra

Although a detailed consideration of the mass spectra of the hexahydropyrimidines will be deferred,[17] it is pertinent to comment here upon a salient feature of the cracking patterns. A hexahydropyrimidine containing hydrogen atoms attached to C2 gives a molecular ion peak ($M^{+\cdot}$) of low intensity which is accompanied by a peak of high intensity (one of the most intense in the whole spectrum), which is due to a molecular species one unit of mass lighter than the molecular ion. Expulsion of

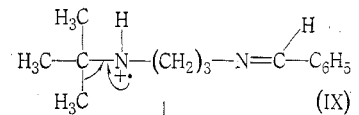


(VII) (VIII)

a hydrogen atom from a cyclic molecular ion (VII; R = R′ = H) will give a resonance-stabilized amidinium cation (VIII). The high stability of this amidinium ion has already been noted,[18] since it is responsible for the high pK_a values for 1,4,5,6-tetrahydro-

[16] Albert, A., and Armarego, W. L. F., *Adv. heterocycl. Chem.*, 1965, **4**, 1.
[17] Evans, R. F., and Porter, Q. N., unpublished data.
[18] Brown, D. J., and Evans, R. F., *J. chem. Soc.*, 1962, 527.

pyrimidines. The mass spectrum of a hexahydropyrimidine possessing two methyl groups attached to C2 contains a weak molecular ion peak which is accompanied by an intense peak due to a mass 15 units lighter. This is again readily explained by the formation of a resonance-stabilized amidinium ion following the expulsion of a methyl radical from the molecular ion (e.g. VIII; R = R′ = CH_3). The molecular ion $M^{+\cdot}$ of hexahydro-2-methylpyrimidine (VII; R = H; R′ = CH_3) may lose either a hydrogen atom or a methyl radical to afford two different amidinium ions, which are stabilized by resonance to comparable extents. In this case the stability of the ejected neutral fragment is the deciding factor. The methyl radical, being more stable, is preferentially eliminated and the ratio of peak heights is $(M-15)^+$: $(M-1)^+ : M^{+\cdot} = 18 : 5 : 1$.



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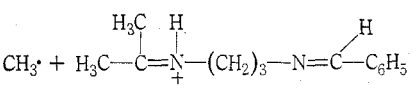


(X)

Those hexahydropyrimidines whose infrared spectra indicate the presence of a small amount of open-chain tautomer in the liquid phase give cracking patterns explicable solely in terms of the cyclic structure. On the other hand, those hexahydropyrimidines whose infrared spectra indicate that they are mainly, if not exclusively, open-chain compounds give mass spectra strongly supporting such indications. No peak corresponding to a cyclic amidinium ion is apparent. Thus in 1-benzylideneamino-3-t-butylaminopropane the molecular ion peak corresponding to (IX) is small compared with that due to its first decomposition product (X) which is formed by the expulsion of a methyl radical from the t-butyl group.[19]

TABLE 1

N.M.R. SPECTRA OF TRIMETHYLENEDIAMINE AND SALTS IN HEAVY WATER

τ Values

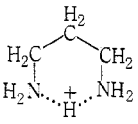
	CCH_2C	NCH_2CCH_2N
Diamine	8·23–8·73	7·28, 7·38, 7·50
Diamine,1HCl	8·07–8·32	6·97, 7·10, 7·22
Diamine,2HCl	7·7 –8·2	6·75, 6·87, 7·00

Nuclear Magnetic Resonance Spectra

The τ values for certain absorption peaks in the n.m.r. spectra of trimethylenediamine, hexahydropyrimidine, and related compounds are given in Tables 1 and 2.

[19] Budzikiewicz, H., Djerassi, C., and Williams, D. H., "Interpreptation of Mass Spectra of Organic Compounds." (Holden-Day: San Francisco 1964.)

The spectrum of trimethylenediamine (and of its cations) consists of two groups of peaks, a triplet in the 6·75–7·50 τ (4 protons) assigned to the protons of both methylene groups next to the nitrogen atoms, and a multiplet (quintet or sextet) in the 7·7–8·7 τ region (2 protons), which is due to the protons of the central methylene group of the three carbon atom chain. It is apparent that free rotation about C–C and C–N bonds has rendered the various conformations of the molecule equivalent so that simple-type spin multiplets have resulted.[20] The τ values diminish as the number of positive charges in the molecule increases, reflecting the inductive effect of the positively charged nitrogen. The spectrum of the monocation indicates that this species has a symmetrical, presumably hydrogen-bonded, structure (XI).


(XI)

If the absorption peaks due to the *N*-substituents are ignored, the *N*,*N*′-dialkyl derivatives of hexahydropyrimidine (which of necessity must have cyclic structures) exhibit in their n.m.r. spectra the absorption pattern of a trimethylenediamine together with a new singlet peak (2 protons) considerably further downfield. The

TABLE 2

N.M.R. SPECTRA OF HEXAHYDROPYRIMIDINE AND DERIVATIVES

τ Values

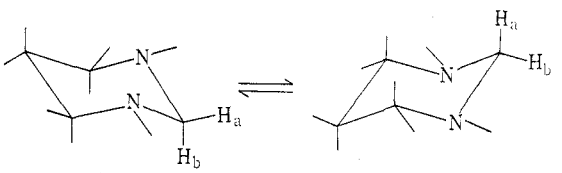
1,3-Substituents	Solvent	CCH_2C	NCH_2CCH_2N	NCH_2N
H; H	D_2O	8·33–8·69	7·02, 7·15, 7·24	6·37
H; H,HCl	D_2O	8·00–8·37	6·75, 6·83, 6·93	5·81
H; Bu^n	CCl_4	under Bu^n peaks	7·19–7·60	6·78
H; Bu^t	CCl_4	8·25–8·60	7·21, 7·31, 7·39	6·54
Me; Me	$CDCl_3$	8·12–8·42	(7·27) 7·49, 7·57, 7·67 (7·83)	7·00
Me; Me,MeI	D_2O	7·96	(1) 6·51, 6·61, 6·71	6·16
			(2) 7·21, 7·30, 7·40	
Bu^n; Bu^n	CCl_4			6·98
Bu^t; Bu^t	CCl_4	8·42–8·64	7·84, 7·90, 7·96	7·37
PhCO; PhCO	$CDCl_3$	8·00–8·38	6·12, 6·21, 6·29	4·85
Ts; Ts	$CDCl_3$	8·53–9·02	6·72, 6·82, 6·91	5·31
NO; NO	$CDCl_3$	7·82–8·33	5·96, 6·07, 6·17, 6·27 (4·32)[a]	3·50
			5·40, 5·42, 5·49, 5·52 (4·62)[a]	4·07
			5·59, 5·62 (5·01)[a]	4·58
H; H(4,4,6-Me_3)	D_2O	8·32–8·59		6·35

[a] C_6H_6.

new peak must be due to the protons of the methylene group between the two nitrogen atoms and falls in the range observed with other compounds containing the same group. Thus the ring protons of the hexahydro-1,3,5-triazine (V; R = $(CH_3)_2NCH_2CH_2CH_2$–) give rise to one sharp peak at 6·81 τ. These measurements were made at slightly above room temperature, which is well above the temperature

[20] Jackman, L. M., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry." p. 23. (Pergamon: Oxford, 1959.)

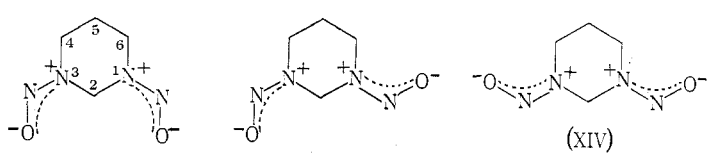
where ring inversion between two equivalent chain forms is slow enough to cause differentiation between axial and equatorial hydrogen atoms.[21]



The spectra of both hexahydropyrimidine and its hydrochloride in heavy water exhibit the three separate groups of peaks to be expected for the cyclic structure (I; R = R′ = H). No open-chain form (II; R = R′ = H) can be present because the methyleneamino protons would give rise to absorptions at τ values considerably lower than 5·8 τ. Thus the methylene protons of t-butylazomethane[22] were found to give rise to the four peaks of an AB system (τ_A 2·61, τ_B 2·99, J 17 c/s) at the lower end of the range (2·8–3·6 τ) previously observed for various formaldoxime derivatives.[23]

The peak associated with the protons of the NCH_2N group is readily observable furthest downfield in the spectra of the two 1-alkylhexahydropyrimidines examined, and there is no indication of the presence of an open-chain tautomer form. A similar peak is noted in the spectra of other *N*,*N*′-disubstituted derivatives besides the alkyl ones. Electron-withdrawing substituents cause it to be shifted downfield. The positive charge in the methiodide of hexahydro-1,3-dimethylpyrimidine has such an effect. It also introduces an element of dissymmetry into the molecule enabling one to differentiate between the separate triplets due to the end-methylene groups of the trimethylene chain, the triplet at lower field being assigned to the methylene group nearest the positively charged nitrogen.

The *N*,*N*′-dinitroso compound affords a complicated spectrum when examined in a number of solvents. However, on heating in *o*-dibromobenzene, for example, changes in this spectrum become apparent at 80°, and by 160° the spectrum is transformed into three broad peaks centred at *c.* 4, 6, and 8 τ respectively. When the solution is cooled to room temperature, the original complicated spectrum appears. This is analogous to that obtained in deuterochloroform and for which results are given in Table 2. The phenomenon is associated with the restriction of rotation



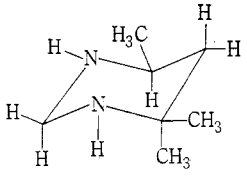
(XII) (XIII) (XIV)

about the N–N bond of *N*-nitrosamines which causes hexahydro-1,3-dinitrosopyrimidine to exist, at room temperature, in three molecular configurations (XII–XIV).

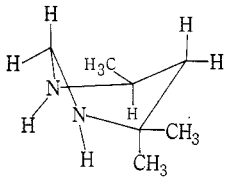
[21] Riddell, F. G., and Lehn, J. M., *Chem. Commun.*, 1966, 375.
[22] Hurwitz, M. D., U.S. Pat., 2,582,128 (*Chem. Abstr.*, 1952, **46**, 8146).
[23] Shapiro, B. L., Ebersole, S. J., and Kopchik, R. M., *J. molec. Spectrosc.*, 1963, **11**, 326.

If protons resonate at higher fields when nearer the partially negatively charged oxygen atom of the nitroso group, the methylene group at C2 of molecules with configuration (XII) gives rise to the peak at τ 4·68, and similarly the same group of molecules with configurations (XIII) and (XIV) will be associated with peaks at 4·07 and 3·5 τ respectively. From the respective peak heights, it was possible to calculate that at room temperature in deuterochloroform, the species (XII), (XIII), and (XIV) were present in the proportions of 6 : 16 : 21. The six peaks between 5·40 and 5·62 τ consist of two almost overlapping sets of triplets assigned to the protons belonging to the 4- and 6-methylene groups of configuration (XII) and to the 4-methylene group of isomer (XIII). The remaining protons of the 6-methylene group of (XIII) and of the 4- and 6-methylene groups of (XIV) give rise to the remaining four peaks between 5·96 and 6·27 τ, two of the expected pair of triplets being coincident. This assignment is strengthened by calculating the ratio of the peak heights of the two groups of peaks (i.e. 5·40–5·62 τ against 5·96–5·27 τ) to be expected from the 6 : 16 : 21 proportions of isomers present in the solution. It was 0·48 compared with an actual value of 0·51. As noted elsewhere,[24] when the solvent was changed to benzene, protons *trans* to the nitroso group experienced a greater upfield shift.

Hexahydro-4,4,6-trimethylpyrimidine had no absorption below 6 τ so that no open-chain tautomer was present. However, two doublets at 8·32, 8·37 and 8·51, 8·59 τ respectively, indicated that the protons attached to C5 were not identical. It was inferred that the methyl groups, one of which must be axial, forced the molecule to oscillate between the chair (XV) and boat (XVI) conformations:



(XV)



(XVI)

The protons attached to C2 gave one peak only so that this end of the molecule must be oscillating between two conformations at such a rate that, on the n.m.r. time scale, the two protons are indistinguishable. Since it is unavoidable that one methyl group will have to take up an axial position, it is inferred that these two conformations may be a chair form of the type (XV) and a boat form (XVI). This results in a fixed arrangement of C4, C5, and C6 and hence in differentiation of the two protons attached to C5.

Although hexahydro-2-methylpyrimidine was not obtained free from trimethylenediamine, the n.m.r. spectrum of the mixture did not absorb below 5 τ, so that again no open-chain tautomeric form (II; R = H, R′ = CH_3) of the pyrimidine was present. The AX_3 pattern of absorption for the protons of the $CHCH_3$ group was readily discernible, a methyl doublet centred at 8·93 τ (J 6 c/s) and a single proton quartet centred at 6·53 τ. A similar feature was observed in the n.m.r.

[24] Karabatsos, G. J., and Taller, R. A., *J. Am. chem. Soc.*, 1964, **86**, 4373.

spectrum of solutions of the mixed hydrochlorides of trimethylenediamine and hexahydro-2-methylpyrimidine, and it was concluded that the latter substance preferred the cyclic structure.

The *gem*-dimethyl group at C2 in hexahydro-2,2-dimethylpyrimidine gave rise, in carbon tetrachloride solution, to a sharp peak at 8·83 τ (6H) in the n.m.r. spectrum.

The *gem*-dimethyl group of the open-chain tautomer (II; R = R′ = CH_3) would be expected to give rise to two peaks depending upon whether a methyl group was *syn* or *anti* with respect to the C=N–CH_2– part of the molecule.[25] The spectrum of the sample, after treatment with heavy water, lost its NH peak at 9·15 τ (2H) and a small peak at 7·93 τ increased in height considerably. The latter referred to the two methyl groups of acetone, which would be formed readily in water by the hydrolysis of the open-chain isomer, with its aliphatic Schiff base structure. However, trimethylenediamine would also be produced in this hydrolysis but no peaks attributable to this substance appear in the spectrum. It is likely, however, that with two polar groups in the molecule there is an adverse distribution of the diamine between the aqueous phase and carbon tetrachloride. The protons of the two –N–CH_2– groups give rise to a triplet of peaks at 7·03, 7·12, 7·22 τ respectively, strongly indicating that there is no difference between the two methylene groups. The corresponding methylene groups in the open-chain tautomer (II; R = R′ = CH_3) are obviously not equivalent chemically or magnetically and would be expected to give rise to two sets of triplet peaks as was found with 1-benzylideneamino-3-t-butylaminopropane (see below). It thus seems that n.m.r. was not a sensitive enough technique to distinguish peaks due to the small amount of open-chain tautomer which, on the infrared evidence, is believed to be present.

The spectrum of hexahydro-2,2,4,4,6-pentamethylpyrimidine in heavy water was complicated by the presence of bands belonging to decomposition (e.g. acetone at 7·81 τ) products or the starting material from which it was prepared, 1,2,5,6-tetrahydro-2,2,4,6,6-pentamethylpyrimidine. The latter had the same spectrum as its hydrate when either was dissolved in pyridine, indicating either that no covalent hydration of the double bond had occurred or if it had that the hydrate was completely dissociated in solution.

1-Benzylideneamino-3-t-butylaminopropane afforded an n.m.r. spectrum completely in accord with its open-chain structure. The aldimine proton gave rise to an easily recognizable peak centred at 1·83 τ, split into three (*J c.* 1·4 c/s) by long-range coupling with the –CH_2– group next to the doubly bound nitrogen atom which was probably situated *syn* with respect to the double bond on account of steric reasons.[25] The protons of this methylene group gave rise to a triplet at 6·35 τ and each triplet peak was in turn split into two (*J* 1–1·2 c/s) by coupling with the aldimine proton. The methylene group next to the NH grouping gave rise to a triplet at 7·25, 7·35, and 7·47 τ, thus confirming that it was differently situated.

Thus it is concluded that a hexahydropyrimidine bearing two hydrogen atoms at C2 in the molecule will exist solely as the cyclic form and will exhibit the chemical

[25] Staab, H. A., Vögtle, F., and Mannschreck, A., *Tetrahedron Lett.*, 1965, 697.

properties of a cyclic amine. It is possible to replace one of these hydrogen atoms by a methyl group and still retain the cyclic structure and its accompanying chemical behaviour. However, introduction of two alkyl groups at C2 causes destabilization of the cyclic structure on steric grounds, and an open-chain tautomeric form begins to make its appearance. As a consequence of this, the compound prefers to react in the open-chain form. Because this possesses a readily hydrolysable aliphatic Schiff base grouping, the hexahydropyrimidine gives derivatives not of itself but of the corresponding 1,3-diaminopropane. Complete destabilization of the cyclic structure results when, in addition to the *gem*-dialkyl group at C2, a large alkyl group is attached to one of the nitrogen atoms.

Experimental

Microanalyses were performed by Dr W. Zimmermann and his staff of the Australian Microanalytical Service, Melbourne. Substances were examined chromatographically on Whatman paper No. 1 in (A) butan-1-ol/5N aqueous acetic acid (70 : 30 v/v) or (B) propanol/0·2N ammonia (30 : 10 v/v) by the ascending technique, and the papers were viewed after exposure to iodine vapour. Light petroleum refers to the fraction b.p. 60–80°.

The method for the measurement of ionization constants at 20° was described earlier.[26] Infrared spectra were measured with a Perkin–Elmer 421 spectrophotometer either as thin films (liquids) or KCl or KBr disks (solids). The 60-Mc/s nuclear magnetic resonance spectra were obtained either with a Varian A60 or a Varian HR60 spectrometer, and were calibrated by the sideband technique using Muirhead–Wigan decade oscillators.

The mass spectra were recorded on an A.E.I. MS9 high-resolution mass spectrometer. Molecular weights in solution were determined with a Mechrolab 301A vapour-pressure osmometer.

Starting Materials

(i) *1-n-Butylaminopropylamine.*—n-Butyl bromide (27·4 g), trimethylenediamine monohydrochloride (22·1 g) in ethanol (40 ml), and water (5 ml) were refluxed for 2½ hr and evaporated at 100°/20 mm. The residue in water (20 ml) was mixed with sodium hydroxide (40 g) in water (40 ml) and the upper layer (31 g) separated and distilled. The fraction (13 g), b.p. up to 160°/30 mm, was redistilled giving 3-n-butylaminopropylamine, b.p. 190–202° (1·7 g, 7%), picrate m.p. 149–152° (lit.[3] 150–151°), and 1,3-bis(butylamino)propane (4·6 g), b.p. 202–230°.

(ii) *1,3-Bis(t-butylamino)propane.*—Only *trimethylenediamine monohydrochloride* (2 g) separated from a mixture of diamine (7·4 g) and t-butyl chloride (37 g) in ethanol (100 ml), which had stood at room temperature for 24 hr, been refluxed for 3½ hr, and then cooled. It melted between 115 and 129° (Found: C, 32·45; H, 9·8; Cl, 31·7; N, 25·0. $C_3H_{11}ClN_2$ requires C, 32·6; H, 10·0; Cl, 32·0; N, 25·3%) and afforded the dihydrochloride, m.p. 248–254° (dec.) on crystallization from ethanol. The original reaction mixture deposited trimethylenediamine dihydrochloride on acidification with hydrochloric acid.

Consequently t-butylamine (19·6 g), trimethylene dibromide (13·6 g), and ethanol (25 ml) were refluxed for 4½ hr and cooled. *1,3-Bis(t-butylamino)propane dihydrobromide* (15·1 g) separated from this solution A, m.p. 317° (from ethanol) (Found: C, 38·25; H, 8·2; Br, 46·1; N, 8·0. $C_{11}H_{28}Br_2N_2$ requires C, 37·9; H, 8·1; Br, 45·9; N, 8·0%). The hydrobromide (15 g) in water (30 ml) was mixed with sodium hydroxide (10 g) in water (50 ml), and the mixture extracted with ether (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and distilled. The residue (6·3 g) crystallized from ether at 0° to give *1,3-bis(t-butylamino)propane hydrate*, m.p. 73–75°, b.p. 207–212°/765 mm (Found: N, 13·2. $C_{11}H_{28}N_2O$ requires N, 13·7%). τ 8·96 (Bu^t); 7·33, 7·44, and 7·54 ($-CH_2-N$) and 7·92–8·75 ($-C-CH_2-C$ and NH) pK_{aI} 11·3; pK_{aII} 9·3. The *picrate* had m.p. 209–211° (dec.) (from methanol/propan-2-ol) (Found: C, 46·1; H, 6·0; N, 17·3.

[26] Albert, A., and Serjeant, E. P., "Ionization Constants." (Methuen: London, 1962.)

$C_{11}H_{26}N_2,1{\cdot}5C_6H_3N_3O_7$ requires C, 45·3; H, 5·8; N, 17·2%). Solution A was evaporated at 100° and the residue on treatment with aqueous alkali as above afforded a further 5·5 g of base hydrate bringing the yield up to 86%.

(iii) *1,2,5,6-Tetrahydro-2,2,4,6,6-pentamethylpyrimidine* and its hydrate were obtained by the procedure of Bradbury *et al.*[27] The hydrate had m.p. 51–55° (ether) (lit.[27] 43–44°) (Found: C, 62·5; H, 11·3; N, 16·0. Calc. for $C_9H_{18}N_2,H_2O$: C, 62·7; H, 11·7; N, 16·3%). The *chloroplatinate* had m.p. 181–183° (dec.) (from methanol) (Found: C, 19·45; H, 3·9; N, 5·0; Pt, 34·0. $C_9H_{20}Cl_6N_2Pt$ requires C, 19·2; H, 3·6; N, 5·0; Pt, 34·6%). The infrared spectrum (thin film) of the anhydrous base had a ν(NH) band at 3300 cm^{-1} and a strong ν(C=N) peak at 1670 cm^{-1}, which was also exhibited by the hydrate (KBr disk made without application of a vacuum). The n.m.r. spectra of the base and its hydrate in pyridine were identical (tetramethylsilane internal standard). Peaks occurred at 8·94 τ (3H, CH_3–), 8·56 τ (2H, $-CH_2-C{=}N$), 8·26 τ (6H, $-C-C(CH_3)_2-N-$), and 8·08 τ (6H, $-N-C(CH_3)_2-N-$). The pK_a, obtained by measurement of pH after rapid addition of base to dilute hydrochloric acid, was 8·11 ± 0·05. The n.m.r. spectrum of the oximino derivative in deuterochloroform had peaks at 7·78 τ (3H, $CH_3-C{=}N$); 8·53 τ (6H, $N-C(CH_3)_2-N$); and 8·53 τ (6H, $C-C(CH_3)_2-N$). Hexahydro-2,2,4,4,5-pentamethylpyrimidine was isolated as its hydrate[28] from the reduction of the analogous 1,2,5,6-tetrahydro compound with sodium and alcohol. Hexahydro-4,4,6-trimethylpyrimidine was obtained following Bradbury *et al.*[27]

Hexahydropyrimidine

An ice-cold solution of trimethylenediamine (17·0 ml, 0·2 mole) in water (50 ml) was stirred magnetically while it was slowly titrated with concentrated hydrochloric acid (*c.* 40 ml) to a methyl orange end-point in a fume cupboard. Trimethylenediamine (17·0 ml) was added, the temperature brought to and maintained at 20–25° (ice), and the solution was titrated with formalin (30·0 ml of 40%, 0·4 mole) over ½ hr. The solution gave two spots on paper, R_F values 0·10 and 0·46 respectively (A), the former being due to trimethylenediamine dihydrochloride. Evaporation of the mixture at 0°/0·1 mm afforded an oil which partly solidified. Extraction with cold methanol left the solid, identified as trimethylenediamine dihydrochloride by melting point, mixed melting point, and infrared spectrum. Evaporation of the extract at 20°/0·1 mm gave an oil which again partly solidified on standing. The process of extraction and evaporation was repeated with ethanol and propan-2-ol, and after each extraction, about 30% of the product remained and was identified as trimethylenediamine dihydrochloride. The residue obtained from the evaporation of the propan-2-ol extract was used immediately for spectroscopic examination. No significant bands were observed in the 1600–1700 cm^{-1} region (thin film).

To obtain the free base, the original solution, after addition of formalin, stood at room temperature for 2 hr and was made alkaline by addition of sodium hydroxide pellets (80 g). The cold mixture was filtered through a sintered-glass funnel, and the upper layer (45 g) separated. This was refluxed with benzene (100 ml) under a Dean–Stark water separator for 2 hr (12·9 g water collected). The benzene solution was decanted and fractionally distilled, affording fractions (*a*) b.p. 59–62°/32 mm, m.p. 10° (9·7 g, 28%), (*b*) b.p. 59–110°/23 mm (3·7 g), (*c*) b.p. 95–185°/0·1 mm (2·9 g), and a residue (4·1 g). Redistillation of (*a*) afforded anhydrous *hexahydropyrimidine*, b.p. 58–60°/20 mm (Found: C, 55·6; H, 11·7; N, 32·8. $C_4H_{10}N_2$ requires C, 55·8; H, 11·7; N, 32·5%) ν(NH) 3270 cm^{-1}; no ν(C=N); pK_a 9·5.

Picric acid and chloroplatinic acid, with fraction (*a*), gave solids which on crystallization from methanol afforded the corresponding salts of trimethylenediamine (m.p., mixed m.p., or infrared spectrum). The *ditoluene-*p*-sulphonamido derivative*, prepared under Schotten–Bauman conditions, had m.p. 145–147° (ethanol) (Found: C, 54·85; H, 5·6; N, 7·0. $C_{18}H_{22}N_2O_4S_2$ requires C, 54·8; H, 5·6; N, 7·1%). τ (CH_3) 7·56; τ (C_6H_4) 2·17, 2·21, 2·29, 2·31, 2·60. The dibenzoyl derivative prepared similarly had m.p. 92–96° (benzene) (lit.[1] m.p. 94°), τ (C_6H_5) 2·65. Methanolic mercuric chloride/hydrogen chloride converted the base into *trimethylenediamine*

[27] Bradbury, R. B., Hancox, N. C., and Hatt, H. H., *J. chem. Soc.*, 1947, 1394.
[28] Matter, E., *Helv. chim. Acta*, 1947, **30**, 1114.

tetrachloromercurate m.p. 241–244° (Found: C, 8·7; H, 2·85; Cl, 33·55; Hg, 47·9; N, 6·65. $C_3H_{12}Cl_4HgN_2$ requires C, 8·6; H, 2·9; Cl, 33·9; Hg, 47·9; N, 6·7%). With 1 or 2 equiv. of phenyl isocyanate, hexahydropyrimidine yielded hexahydro-1,3-bis(3′-phenylureido)pyrimidine m.p. 222–224° (ethanol) (Found: C, 66·2; H, 6·2; N, 17·35. $C_{18}H_{20}N_4O_2$ requires C, 66·7; H, 6·2; N, 17·3%). The higher-boiling fractions (*b*) and (*c*) above also yielded the same phenylureido derivative.

From an earlier preparation, a fraction, b.p. 110–170°/0·8 mm, was isolated which afforded a solid, m.p. 55–57° after two crystallizations from light petroleum (Found: C, 58·3; H, 11·0; N, 29·0; mol. wt., 254–274. Calc. for $C_{14}H_{30}N_2,0·33H_2O$: C, 58·3; H, 10·65; N, 29·2%; mol. wt., 288).

Reaction with formaldehyde.—Hexahydropyrimidine (2·53 g), formalin (2·2 ml, 40%), and ethanol (11 ml) were refluxed for 4 hr and evaporated at 100°/20 mm and at 170–180°/0·4 mm. The residue on crystallization from benzene afforded crystals, m.p. 160–165·5°, identical with (mixed m.p., infrared spectrum) the product from the reaction of trimethylenediamine and formaldehyde.[6]

Reaction with phenylmagnesium bromide.—No 3-benzylaminopropylamine could be isolated from the reaction of hexahydropyrimidine (0·86 g) in ether (100 ml) with phenylmagnesium bromide prepared from bromobenzene (6·3 g), magnesium turnings (0·96 g), and ether (100 ml).

Nitrosation.—Ice-cold 1N hydrochloric acid (71 ml) was added in one portion to an ice-cold solution (30 ml) of sodium nitrite (4·9 g) and hexahydropyrimidine (3·05 g) which stood at 0° for 6 hr and then overnight at room temperature. Cooling to 0° caused the oil which had separated to solidify, and the solid (0·42 g) was filtered off and dissolved in ether. The filtrate was saturated with sodium chloride and continuously extracted with ether. The combined ether solutions were dried ($MgSO_4$) and evaporated, affording semi-solid material (3·5 g, 69%) R_F 0·84 (A). A 5% solution in benzene was passed through alumina. Evaporation of the eluate at 30°/20 mm afforded a residue which on crystallization from benzene/light petroleum and benzene/toluene gave pale yellow *hexahydro-1,3-dinitrosopyrimidine*, m.p. 61·5–64·5° (Found: C, 33·7; H, 5·8; N, 38·5; mol. wt., 143±4 (benzene). $C_4H_8N_4O_2$ requires C, 33·3; H, 5·6; N, 38·9%; mol. wt., 144·1). A slightly better yield (74%) resulted when hexahydropyrimidine hydrochloride was used.

Condensations between Monoprotonated Diamines and Carbonyl Compounds

The general procedure consisted of titrating the diamine (0·5 mole) dissolved in water to a methyl orange end-point with concentrated hydrochloric acid or dissolved in methanol with glacial acetic acid and adding an equal quantity of diamine to the mixture. The carbonyl compound (1 mole) was added at such a rate and with external cooling so that the temperature was kept at 20–25°. With benzaldehyde, sufficient methanol was also added to keep the solution homogeneous. This was removed by evaporation at 20°/20 mm prior to work-up after several hours standing by addition of solid sodium hydroxide. The upper layer was either taken up in benzene (and dehydrated by refluxing under a Dean–Stark water separator) or extracted into ether and dried (Na_2SO_4). In either case the product was isolated by fractional distillation.

Thus 3-t-butylaminopropylamine monohydrochloride (20 ml of 0·85N) was converted into *1-t-butylhexahydropyrimidine* (0·54 g, 23%), b.p. 80–90/16 mm (Found: C, 67·0; H, 12·6; N, 20·5. $C_8H_{18}N_2$ requires C, 67·6; H, 12·75; N, 19·7%). ν(NH) occurred at 3270 cm^{-1} and $\tau(Bu^t)$ at 8·93.

Similarly aqueous 3-n-butylaminopropylamine monohydrochloride (5 ml of 2·34N) gave *1-n-butylhexahydropyrimidine*, b.p. 92–100°/18 mm (50%) (Found: C, 67·3; H, 12·5; N, 19·4. $C_8H_{18}N_2$ requires C, 67·6; H, 12·75; N, 19·7%). ν(NH) 3265 cm^{-1}.

The product of the reaction between acetone (0·2 mole) and aqueous trimethylenediamine monohydrochloride (50 ml of 4N) led, after azeotropic drying with benzene to *hexahydro-2,2-dimethylpyrimidine* (43%), b.p. 57–61°/71 mm (Found: C, 62·8; H, 12·35; N, 24·45. $C_6H_{14}N_2$ requires C, 63·1; H, 12·1; N, 24·5%). ν(NH) 3280 cm^{-1}, ν(C=N) 1670 cm^{-1}. Attempts to form derivatives with picric acid, benzoyl chloride, toluene-*p*-sulphonyl chloride, or with phenyl isocyanate afforded the corresponding trimethylenediamine derivatives. No nitroso compound

could be isolated upon treatment with sodium nitrite and hydrochloric acid, nor 3-(dimethylbenzylamino)propylamine from the reaction with phenylmagnesium bromide.

Benzaldehyde (0·05 mole) and aqueous trimethylenediamine monohydrochloride (15 ml of 3·3N, diluted with methanol to form a homogeneous solution) afforded 1,3-bis(benzylideneamino)propane (72%).[29]

The reaction mixture from pentan-2-one (9 g) and trimethylenediamine monoacetate (14 g) in methanol (25 ml), after standing at room temperature (24 hr), was decomposed with a solution of sodium (2·4 g) in methanol (45 ml) and filtered. The filtrate was evaporated at 20–35°/3 mm, and the residue decomposed with concentrated aqueous sodium hydroxide and extracted with ether. The dried (Na_2SO_4) ether extract was distilled, affording a fraction (2·4 g, 17%), b.p. 60–140°/28 mm, containing unstable 2,2-diethyl-hexahydropyrimidine.

A solution containing hexahydro-2-methylpyrimidine hydrochloride, R_F 0·62 (A), was obtained by the addition of recently prepared acetaldehyde (8·6 g) to trimethylenediamine monohydrochloride (0·2 mole) in aqueous solution (45 ml). The n.m.r. spectrum of a portion of this solution diluted with deuterium oxide had no significant absorption below the DOH peak at 5·16 τ. The CHMe group gave rise to the AX_3 groups of signals at 8·53 and 8·63 and 5·73, 5·84, 5·94, and 6·04 τ respectively. The mixture was worked up in the usual manner, and after azeotropic drying with benzene, and two distillations, afforded a fraction, b.p. 143–145° (1 g, 5%) rich in hexahydro-2-methylpyrimidine (mass spectrum). It did not exhibit a peak in the C=N stretching region of the infrared spectrum. The n.m.r. spectrum in D_2O again had no peaks below 5 τ and the AX_3 type spectrum caused by the CHMe group led to the easily recognized doublet at 8·88 and 8·98, and the quartet at 6·37, 6·47, 6·58, and 6·67 τ respectively. The *dibenzoyl derivative* had m.p. 193–195° (from benzene and ethanol) (Found: C, 73·3; H, 6·5; N, 8·8. $C_{19}H_{20}N_2O_2$ requires C, 74·0; H, 6·5; N, 9·1%). The n.m.r. spectrum ($CDCl_3$) again contained the recognizable features of an AX_3 type of spectrum—a doublet at 8·40 and 8·51 and a quartet at 6·51, 6·62, 6·72, 6·85 τ respectively.

Addition (5 ml) of ice-cold concentrated hydrochloric acid (10 ml) to an ice-cold solution of sodium nitrite (6·9 g) and hexahydro-2-methylpyrimidine hydrochloride (0·05 mole) in water caused the separation of an oil, which after 1 hr at 0° was extracted into ether (2 × 50 ml). The dried (Na_2SO_4) extract was evaporated at 20°/15 mm and the residue (3·46 g, 44% R_F 0·89(A)) was quickly distilled affording a *fraction*, b.p. 126°/0·05 mm (Found: C, 38·9; H, 6·8; N, 33·2; $M^{+\cdot}$, 158. $C_5H_{10}N_4O_2$ requires C, 38·0; H, 6·4; N, 35·4%; $M^{+\cdot}$, 158). The complicated n.m.r. spectrum ($CDCl_3$) revealed three sets of doublets due to methyl groups at 7·93 and 8·07, 8·37 and 8·49, and 8·76 and 8·87 τ respectively. This suggested the presence of three isomers analogous to those existing in solution with hexahydro-1,3-dinitrosopyrimidine. However, the proton at C2 gave rise not to three quartets, but to an evenly spaced quintet at 2·40, 2·52, 2·63, 2·75, and 2·86 τ so that some of the lines must have overlapped.

Condensations between Free Diamine and Carbonyl Compounds

Trimethylenediamine (8·5 ml) mixed with acetone (46·4 g) was kept at room temperature for 24 hr. The mixture was distilled until the temperature of the distillate reached 150°. The residue was distilled under reduced pressure and the fraction (5·7 g, 50%) boiling between 50 and 103°/17 mm was slowly redistilled. The fraction (2·5 g), b.p. 57–61°/17 mm, was shown to be identical (infrared spectrum) with hexahydro-2,2-dimethylpyrimidine.

Hexahydro-1,3-dimethylpyrimidine.—1,3-Bis(methylamino)propane (12·3 g) and paraformaldehyde (4 g) in ethanol (200 ml) and methanol (50 ml) were refluxed (3 hr) in an apparatus guarded with a soda lime tube. The cold mixture was exactly neutralized with 1N hydrochloric acid (119·9 ml) and concentrated at 20°/0·5 mm to 75 ml. Excess solid potassium hydroxide was added to the ice-cold solution, the upper layer separated, dried (KOH), and distilled, collecting the fraction (3·6 g), b.p. 132–136° (lit.[6] 125–126°). Earlier fractions still contained water (infrared bands at 3400, 3300, and 1650 cm^{-1}). The overall yield was 62%, pK_{aI} 8·40 ± 0·05; pK_{aII} 1·0.

[29] Postovskiĭ, I. Y., and Nosenkova, N. G., *Zh. obshch. Khim.*, 1957, **27**, 526 (*Chem. Abstr.*, 1957, **51**, 15525).

The *monopicrate*, precipitated by 1 equiv. of picric acid in cold ethanol, gave needles melting between 135 and 147° (from ethanol) (Found: C, 42·2; H, 5·0; N, 20·4. $C_{12}H_{15}N_5O_7$ requires C, 42·0; H, 5·0; N, 20·4%). Two equivalents of picric acid precipitated the *dipicrate* needles, m.p. 193–195° (dec.) (from methanol) (Found: C, 37·5; H, 3·6; N, 19·45. $C_{18}H_{20}N_8O_{14}$ requires C, 37·8; H, 3·5; N, 19·6%). The *dihydrochloride*, precipitated from cold ethanolic hydrogen chloride, melted between 192° and 215° (Found: C, 38·2; H, 8·6; Cl, 37·7; N, 15·0. $C_6H_{16}Cl_2N_2$ requires C, 38·5; H, 8·6; Cl, 37·9; N, 15·0%). Recrystallization from ethanol afforded 1,3-bis(methylamino)propane dihydrochloride.

The *tetrachloromercurate*, obtained by addition of base to a slight excess of ethanolic hydrogen chloride/mercuric chloride, melted between 80 and 125° (Found: C, 15·7; H, 4·0; Cl, 31·7; Hg, 41·0; N, 6·8. $C_6H_{16}Cl_4HgN_2$ requires C, 15·7; H, 3·5; Cl, 30·9; Hg, 43·7; N, 6·1%). Recrystallization from ethanol afforded 1,3-*bis(methylamino)propane tetrachloromercurate*, m.p. 158–159° (Found: C, 13·4; H, 3·7; Cl, 32·0; Hg, 45·0; N, 6·3. $C_5H_{16}Cl_4HgN_2$ requires C, 13·5; H, 3·6; Cl, 31·75; Hg, 44·9; N, 63%). The *methiodide*, formed in refluxing propan-2-ol with 1·23 or 2·34 equiv. of methyl iodide, had m.p. 160–161° (dec.) from propan-2-ol/light petroleum (Found: C, 33·0; H, 6·85; I, 49·35; N, 10·9. $C_7H_{17}IN_2$ requires C, 32·0; H, 6·7; I, 49·6; N, 10·9%). τ 7·62 (NCH_3), 6·86 ($^+N(CH_3)_2$).

Dehydrogenation.—Hexahydro-1,3-dimethylpyrimidine (0·13 g) and chloranil (0·27 g) in benzene (30 ml) changed colour from yellow to reddish brown on standing at room temperature overnight. The benzene was evaporated and the residue extracted with propan-2-ol to give a solid, which after repeated crystallizations from propan-2-ol and methanol/acetone (charcoal), had an infrared spectrum (KBr disk) identical with that of authentic 1,3-bis(methylamino)-propane dihydrochloride.

1,3-Di-n-butylhexahydropyrimidine.—1,3-Bis(n-butylamino)propane hydrate was obtained from n-butylamine and trimethylene dibromide instead of the dichloride in the published procedure.[4] The *picrate* had m.p. 196–197° (from ethanol) (Found: C, 43·0; H, 5·2; N, 16·9. $C_{23}H_{32}N_8O_{14}$ requires C, 42·9; H, 5·0; N, 17·4%). The amine hydrate (6 g), paraformaldehyde (1·3 g), and ethanol (10 ml) were refluxed (4 hr) and distilled, affording 1,3-di-n-butylhexahydro-pyrimidine, b.p. 128°/17 mm (6·1 g, 80%) (Found: C, 72·6; H, 12·8; N, 14·75. $C_{12}H_{26}N_2$ requires C, 72·7; H, 13·2; N, 14·1%). The methiodide and butiodide were obtained as oils.

1,3-Di-t-butylhexahydropyrimidine.—The propane base (1·96 g) with paraformaldehyde (0·38 g) in ethanol (10 ml) was refluxed (4 hr) and distilled. The fraction, b.p. 115–117°/20 mm (1·4 g, 66%), was redistilled to give *1,3-di-t-butylhexahydropyrimidine*, b.p. 118°/20 mm (Found: C, 72·7; H, 13·1; N, 14·4. $C_{12}H_{26}N_2$ requires C, 72·7; H, 13·2; N, 14·1%). Picric acid gave the picrate of 1,3-bis(t-butylamino)propane.

Reaction of 3-dimethylaminopropylamine with formaldehyde.—The redistilled amine (5·1 g) and aldehyde (1·7 g) reacted vigorously at 100°. Distillation of the mixture afforded *1,3,5-tris-(3-dimethylaminopropyl)hexahydro-1,3,5-triazine* boiling between 140° and 160°/0·4 mm (Found: C, 62·7; H, 12·2; N, 24·2; mol. wt., 312. $C_{18}H_{42}N_6$ requires C, 63·1; H, 12·35; N, 24·5%; mol. wt., 342). τ 6·81 ($N-CH_2-N$) (CCl_4).

The methiodide, formed in propan-2-ol, had m.p. 240–243° (dec.) (from methanol) (Found: C, 27·2; H, 5·9; I, 54·5; N, 8·9. $C_{22}H_{54}I_4N_6,2H_2O$ requires C, 27·9; H, 5·8; I, 53·7; N, 8·9%).

3-Alkylamino-1-alkylideneaminopropanes

(i) 3-Methylaminopropylamine (2·64 g) and acetone (17·4 g) refluxed together (5 hr) and distilled afforded a *fraction*, b.p. 62–64°/15 mm (1·65 g, 43%) (Found: C, 64·2; H, 12·3; N, 22·6; $M^{+\cdot}$, 128. $C_7H_{16}N_2$ requires C, 65·6; H, 12·6; N, 21·8%; $M^{+\cdot}$, 128). The infrared spectrum (thin film) had bands at 3260 cm^{-1} (ν(NH)) and 1665 cm^{-1} (weak) (ν(C=N)).

The analogous reaction between 3-t-butylaminopropylamine and acetone afforded unstable 3-t-butylamino-1-isopropylideneaminopropane, b.p. 93°/16 mm. ν(NH) 3333 cm^{-1} and ν(C=N) 1666 cm^{-1}.

(ii) 3-t-Butylaminopropylamine (6·5 g), with benzaldehyde (5·3 g) and benzene (50 ml), was refluxed under a Dean–Stark water separator (3½ hr). The benzene was distilled away at 760 mm

and the residue distilled at 24 mm. Redistillation of a fraction, b.p. 132–172° (4·1 g, 36%), furnished *1-benzylideneamino-3-t-butylaminopropane*, b.p. 98°/0·3 mm (Found: C, 76·7; H, 10·2; N, 12·4. $C_{14}H_{22}N_2$ requires C, 77·0; H, 10·2; N, 12·8%). The infrared spectrum had a very strong band at 1649 cm^{-1} (ν(C=N) and a band at 3320 cm^{-1} (ν(NH)).

1,3-Bisalkylideneaminopropanes

Condensation of trimethylenediamine (8·5 ml) and pentan-3-one (10·7 g) was effected in refluxing benzene (50 ml, 3 hr), and on working up as described above *1,3-bis(1-ethylpropylideneamino)propane*, b.p. 133–134°/14 mm (7 g, 67%), was obtained (Found: C, 73·9; H, 12·2; N, 13·8. $C_{13}H_{26}N_2$ requires C, 74·2; H, 12·5; N, 13·3%). ν(C=N) 1682 cm^{-1}.

1,3-Bis(benzylideneamino)propane, b.p. 138–140°/0·05 mm (9·9 g, 80%), was obtained from the analogous reaction with benzaldehyde.[29]

Reduction Experiments

(i) *With sodium borohydride.*—In a typical experiment, hexahydropyrimidine (0·43 g) and sodium borohydride (0·37 g) in ethanol/propan-2-ol (20 ml, 1 : 1 v/v) was stirred and allowed to stand overnight at room temperature. Water (5 ml) was added, and the mixture cautiously acidified with concentrated hydrochloric acid, made alkaline with 5N aqueous sodium hydroxide, and evaporated at 100°/20 mm, collecting the distillate in ice-cold hydrochloric acid. The acidic solution was evaporated at 100°/15 mm and the residue (0·76 g, 95%) treated with water (2 ml) and methanol (10 ml) containing mercuric chloride (1·5 g). The precipitate, on fractional crystallization from aqueous methanol, yielded trimethylenediamine tetrachloromercurate, m.p. 249–253° (0·57 g), and 3-methylaminopropylamine tetrachloromercurate (0·08 g, 4%), identified by m.p., mixed m.p., and infrared spectrum. The reduction of hexahydro-2-methyl- and -2,2-dimethyl-pyrimidines was performed in ethanol alone, and the distillate was collected in ethanolic picric acid. In each case, trimethylenediamine dipicrate was separated manually from, respectively, 3-methylaminopropylamine dipicrate (32%), m.p. 191–193° (dec.) (lit.[3] 191–193°), and 3-isopropylaminopropylamine dipicrate (37%), m.p. 186–187° (lit.[3] 185–186·5°). Hexahydro-2,2,4,4,6-pentamethylpyrimidine was reduced to 2-amino-4-isopropylamino-4-methylpentane dihydrochloride (91%), m.p. 250–251° (dec.) (from aqueous propan-2-ol) (lit.[27] m.p. 250° (dec.)). With the two butylhexahydropyrimidines, addition of alkali threw out an upper layer which was extracted with ether, dried (Na_2SO_4), and evaporated. Only with the t-butyl compound did the mass peak (*m/e* 200) of the hydrogenolysed compound appear in the mass spectrum of the product.

The fraction rich in 2,2-diethylhexahydropyrimidine was reduced and distilled to give a fraction, b.p. 200° (35%), which yielded *3-(1-ethylpropylamino)propylamine picrate*, m.p. 183–185° (Found: N, 18·3. $C_{14}H_{23}N_5O_7$ requires N, 18·8%). 1,3-Bis(1-ethylpropylideneamino)propane yielded *1,3-bis(1-ethylpropylamino)propane*, b.p. 136°/14 mm (Found: C, 72·0; H, 13·8. $C_{13}H_{30}N_2$ requires C, 72·8; H, 14·1%). *3-Isopropylamino-1-methylaminopropane*, b.p. 68–70°/18 mm, was obtained from the reduction of 3-isopropylideneamino-1-methylaminopropane (Found: N, 21·2. $C_7H_{18}N_2$ requires N, 21·5%).

(ii) *Catalytic.*—Hexahydro-2,2-dimethylpyrimidine (1·07 g) in methanol (20 ml) was shaken with platinum oxide (0·11 g) and hydrogen under ordinary conditions for 1½ hr (0·94 mole absorbed). The mixture was filtered, distilled, and the fraction, b.p. 52–62°/13 mm, treated with ethanolic picric acid to give trimethylenediamine dipicrate and 3-isopropylaminopropylamine dipicrate which were separated by fractional crystallization from ethanol. Reduction of hexahydro-2,2,4,4,6-pentamethylpyrimidine (1·36 g) in methanol (25 ml) with catalyst (0·1 g) and hydrogen under the usual conditions, for 10½ hr (0·45 mole absorbed) led to the isolation of a fraction, b.p. 175–177° (25%), (lit.[27] b.p. 178°) identified as 2-amino-4-isopropylamino-2-methylpentane by its mass spectrum (molecular ion *m/e* 158). Hexahydropyrimidine, and its 1,3-di-n-butyl and 1,3-di-t-butyl homologues, were recovered unchanged from the reduction mixtures.

When crude hexahydro-2-methylpyrimidine (2·86 g) in methanol (30 ml) was shaken with platinum oxide (0·1 g) and hydrogen under laboratory conditions, reduction of the catalyst

required 1 hr. The mixture then evolved hydrogen (> 0·25 mole in 5 hr). The catalyst was filtered off and the filtrate distilled. The fraction, b.p. 130–144° (1 g), was rich in starting material (mass spectrum). The residue (1 g) solidified on standing but could not be recrystallized. It was identified by treatment with picric acid when 1,4,5,6-tetrahydro-2-methylpyrimidine picrate[30] (m.p. and mixed m.p. 154–157°) was obtained.

Hexahydro-4,4,6-trimethyl-1,3-dinitrosopyrimidine precipitated immediately when ice-cold concentrated hydrochloric acid (3 ml) was added over 2 min to hexahydro-4,4,6-trimethylpyrimidine (1·81 g) and sodium nitrite (1·95 g) in water (20 ml) at 0°. Recrystallized from ethanol it had m.p. 72–76° (Found: C, 45·8; H, 7·4; N, 29·9; *m/e*, 186. $C_7H_{14}N_4O_2$ requires C, 45·2; H, 7·6; N, 30·1; *m/e*, 186).

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[30] Brown, D. J., and Evans, R. F., *J. chem. Soc.*, 1962, 4039.