790. *Hydropyrimidines. Part II.*[1] *A New General Synthesis of Substituted* 1,4,5,6-*Tetrahydropyrimidines.*

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Several 1,3-diamines (aliphatic and aromatic), when condensed with amidine salts, gave good yields of reduced pyrimidine salts. The infrared spectra of the hydrohalides differed significantly from those of the chloromercurates because hydrogen bonding in the latter is strongly diminished.

1,4,5,6-Tetrahydropyrimidine acetate is formed by condensation of trimethylenediamine with formamidine acetate.[1] Because easy methods for preparing formamidine acetate [2] and hydrochloride [3] are now available, it seemed desirable to develop this reaction [1] into a general synthesis of hydropyrimidines. Representative combinations of formamidine, *NN'*-dimethylformamidine, acetamidine, pivalamidine, benzamidine, phenylacetamidine, and guanidine salts were tried with the following diamines: trimethylenediamine and its *N*-methyl, *NN*-dimethyl, and *NN'*-dimethyl derivatives as well as 1,3-diaminobutane, DL-α*γ*-diaminobutyric acid, and 1,8-naphthylenediamine. It was found that the anion (acetate, hydrochloride, hydrobromide, and picrate) of the amidine salt had no effect on the nature of the final product, but the acetates of the tetrahydropyrimidines were frequently deliquescent. The product from 1,8-diaminonaphthalene was the free hydropyrimidine, because it was a weaker base than the ammonia also formed; in this case, better results were obtained with formamidine acetate than with the hydrochloride.

Formamidine salts converted trimethylenediamine and 1,3-diaminobutane into the corresponding salts of 1,4,5,6-tetrahydropyrimidine and its 4-methyl derivative. DL-α*γ*-Diaminobutyric acid, in which the α-amino-group is probably protonated, reacted with formamidine acetate to produce the zwitterion, 1,4,5,6-tetrahydropyrimidine-4-carboxylic acid.

When *N*-methylated trimethylenediamines were condensed with formamidine salts, ammonia (and not methylamine or dimethylamine) was evolved, showing that the nitrogenous groups are expelled from the amidine. This was proved by paper-chromatographic examination of the evolved gas, collected as the hydrochloride. 3-Methylaminopropylamine with formamidine hydrochloride, hydrobromide, or acetate afforded ammonia and the 1,4,5,6-tetrahydro-1-methylpyrimidine salt. *NN'*-Dimethyltrimethylenediamine similarly gave ammonia and a tetrahydropyrimidine derivative which was a quaternary salt lacking an NH group. Tertiary amino-groups did not take part in the condensation. Thus 3-dimethylaminopropylamine reacted only at the primary amino-group, with both formamidine and benzamidine hydrochloride.

The *C*-substituted formamidines reacted readily with trimethylenediamine at 80°, affording the corresponding 2-substituted 1,4,5,6-tetrahydropyrimidine hydrochlorides. Guanidine hydrochloride first formed an addition complex with trimethylenediamine in which the double bond was still present and which was readily broken up by picric acid.

[1] Part I, *J.*, 1962, 527.
[2] Taylor and Ehrhart, *J. Amer. Chem. Soc.*, 1960, **82**, 3138.
[3] Brown, *J. Appl. Chem.*, 1952, **2**, 202.

At 140°, however, elimination of ammonia occurred and 2-amino-1,4,5,6-tetrahydropyrimidine hydrochloride resulted. The corresponding sulphate was obtained by using *S*-methylisothiourea sulphate (*O*-methylisourea hydrochloride was less satisfactory since it had a greater tendency to react at both ends of the trimethylenediamine molecule).

Finally, an *NN'*-dimethylformamidine salt was obtained from formamidine acetate and methylamine, and this (when heated with trimethylenediamine) lost methylamine to yield a 1,4,5,6-tetrahydropyrimidine salt. Dimethylamine did react with formamidine acetate but the product (*NNN'N'*-tetramethylformamidinium acetate) decomposed under the experimental conditions.

Ionisation.—As would be expected from their amidine structures, three 2-substituted 1,4,5,6-tetrahydropyrimidines, the phenyl-, the benzyl- and the amino-compounds, were highly basic, with pK_a 12·8, 13·0, and 14·1, respectively. The pK_a value for the 2-phenyl compound was a little lower than that of the parent 1,4,5,6-tetrahydropyrimidine [1] (13·0). In the cation, strong resonance interaction between the phenyl group and the amidinium system might be expected and this would lead to a pK_a greater than that of the parent. However, 2-phenylpyridine is also less basic than its parent by almost 0·7 pK_a unit. It has been suggested [4] that in the solvated cation the angle between the plane of the rings is larger than in the free base, so that resonance interaction between the phenyl and pyridine nuclei is much less than expected. A similar situation may occur with 1,4,5,6-tetrahydro-2-phenylpyrimidine. The latter compound was also much stable than 1,4,5,6-tetrahydropyrimidine at high pH values, and this is ascribed to the combined effect of

Infrared spectra (cm.$^{-1}$) of substituted 1,4,5,6-tetrahydropyrimidine salts (B).

Subst.	Salt	ν(N⁺=C—N)	ν(NH)	δ(NH)
4-Me	B,HCl	1666	2980, 3120	1581
	B,HHgCl$_3$	1684	3310	1572
4-CO$_2$H	—	1683	2940, 3110	
1-Me	B,HBr	1692	3010, 3160	1557
	B,HHgCl$_3$	1696	3300	1542
	B$_2$,H$_2$PtCl$_6$ *	1697	3320	1545
1,3-Me$_2$	B,HHgCl$_3$	1703	—	—
2-Me	B,HCl	1655	3000, 3150	1625
	B,HHgCl$_3$	1657	3290, 3040	1618
	B$_2$,H$_2$HgCl$_4$	1655	3240, 3280, 3050	1618
	B,HHg$_2$Cl$_5$	1655	3290, 3040	1616
2-Bu^t	B,HCl	1631	3170, 3010, 2970	1600
	B,HHgCl$_3$	1635	3300	1597
	B$_2$,H$_2$HgCl$_4$	1637	3280	1597
2-CH$_2$Ph	B,HCl	1658	3000	1621
	B$_2$,H$_2$HgCl$_4$	1656	3230	1616
2-Ph	B,HCl	1640	2990, 3100	1612
	B$_2$,H$_2$HgCl$_4$	1641	3190	1611
2-NH$_2$	B,HCl	1677	3240, 3340,† 3100	1606
	B$_2$,H$_2$SO$_4$	1674	3230, 3320, 3120	1609
	B,HHg$_2$Cl$_5$	1656	3330	1619
Formamidine	B,HCl	1705	3300, 3110	
,,	B,HBr	1708	3130, 3230	
,,	B,HI	1717	3130, 3320	
,,	B,HHg$_2$Cl$_5$	1713	3360, 3240	
Acetamidine	B,HHgCl$_3$	1678	3410, 3315, 3270	

* Silver chloride disc. † Shoulder.

resonance stabilisation of the C=N grouping by the phenyl group and the latter's steric hindrance to the approach of a nucleophilic hydrolytic species towards C-2. 2-Amino-1,4,5,6-tetrahydropyrimidine (pK_a 14·1) is a heterocyclic base of outstanding strength.

[4] Katritzky and Simmons, *J.*, 1960, 1511.

Spectra.—Prominent bands of the infrared spectra of substituted 1,4,5,6-tetrahydropyrimidine salts are given in the Table, together with results for some formamidine and acetamidine salts. Except for bands due to ionic carboxyl and sulphate ion in two of the spectra, the most intense band in each spectrum is that due to asymmetric $\overbrace{N{=}C{=}N}^{+}$ stretching, which lies in the range of 1631—1717 cm.$^{-1}$. The position of this band is susceptible to changes in the strength of the hydrogen bonding present and, save for the amino-compounds, occurs at a lower frequency for the simple halides than it does for the complex halides where the hydrogen bonding is weaker. Conversely, the NH deformation vibration occurring in the 1540—1640 cm.$^{-1}$ region occurs at a lower frequency for the complex than for the simple halides.

For the hydrohalides, at least two intense N–H stretching bands appear in the 2900—3300 cm.$^{-1}$ region, the low-frequency band being the more intense. With most of the complex halides one sharp intense N–H stretching band appears at much higher frequencies, again because hydrogen bonding is here strongly diminished. When a compound forms more than one chloromercurate, there are but minor differences between the spectra of these.

Experimental

Analyses by Dr. J. E. Fildes and her staff.

Formamidine Salts.—Formamidine acetate was prepared according to Taylor and Ehrhart's [2] directions. The hydrochloride was obtained by passage of an aqueous solution of the acetate through an ion-exchange column (IRA 400; Cl^-) or on saturation of an ethanolic solution of the acetate with hydrogen chloride. The *hydrobromide* resulted when a solution of the acetate (11·2 g.) in water (20 ml.) and 48% hydrobromic acid (20 ml.) was evaporated at 20°/0·2 mm.; repetition of the process afforded a hygroscopic solid which, after repeated crystallisations from propan-1-ol, had m. p. 134—135° (Found: C, 9·9; H, 4·0; Br, 63·8. CH_5BrN_2 requires C, 9·6; H, 4·0; Br, 63·9%). The *hydriodide* was similarly prepared from the acetate (5·2 g.) in water (10 ml.) and hydriodic acid (8 ml.; *d* 1·7). Several crystallisations from propan-2-ol gave plates, m. p. 236—239° (decomp.) (Found: C, 7·05; H, 2·9; I, 73·8; N, 16·1. CH_5IN_2 requires C, 7·0; H, 2·9; I, 73·8; N, 16·3%).

C-*Substituted Formamidine Hydrochlorides.*—Benzamidine and acetamidine hydrochlorides were prepared from the corresponding nitriles according to published procedures.[5] *Acetamidine trichloromercurate*, from the hydrochloride and mercuric chloride in methanol, melted between 130° and 134° (from ethanol) (Found: C, 6·6; H, 1·9; Cl, 29·0; Hg, 54·7; N, 7·6. $C_2H_7Cl_3HgN_2$ requires C, 6·6; H, 1·9; Cl, 29·1; Hg, 54·8; N, 7·65%). *Phenylacetamidine hydrochloride* was similarly obtained from phenylacetonitrile, freshly prepared from benzyl chloride and potassium cyanide.[6] Crystallisation from propan-2-ol–pentyl alcohol–light petroleum (b. p. 60—80°) afforded a specimen with m. p. 149—151° (Found: C, 56·4; H, 6·4; Cl, 20·9; N, 16·4. $C_8H_{11}ClN_2$ requires C, 56·3; H, 6·5; Cl, 20·8; N, 16·4%). *Pivalamidine hydrochloride*, obtained from pivalonitrile [7,8] without isolation of the intermediate imidoate hydrochloride, had m. p. 190—192·5° (from propan-2-ol) (Found: C, 43·9; H, 9·6; Cl, 25·8; N, 20·6. $C_5H_{13}ClN_2$ requires C, 44·0; H, 9·6; Cl, 26·0; N, 20·5%).

1,4,5,6-*Tetrahydropyrimidine Hydrochloride.*—In a typical experiment, trimethylenediamine (1·33 g.) and formamidine hydrochloride (1·45 g.) in propan-2-ol (9 ml.) were heated on the steam-bath for 2 hr. and then evaporated to dryness at 100°/20 mm. The solid (2·13 g.), on crystallisation from ethyl acetate–propan-2-ol at −15°, yielded 1,4,5,6-tetrahydropyrimidine hydrochloride, m. p. 189—190°, converted into the trichloromercurate,[1] m. p. and mixed m. p. 164—165·5°.

Similarly, 1,3-diaminobutane afforded 1,4,5,6-tetrahydro-4-methylpyrimidine hydrochloride,

[5] Dox, *Org. Synth.*, 1948, Coll. Vol. I, p. 5.
[6] Adams and Thal, *Org. Synth.*, 1948, Coll. Vol. I, p. 107.
[7] Brown, *J. Amer. Chem. Soc.*, 1938, **60**, 1325.
[8] Rogers, *J. Amer. Chem. Soc.*, 1947, **69**, 457.

m. p. 147—149·5° (lit.,[9] 149°) (from propan-2-ol) (Found: C, 44·7; H, 8·2; Cl, 26·6; N, 20·8. Calc. for $C_5H_{11}ClN_2$: C, 44·6; H, 8·2; Cl, 26·3; N, 20·8%). The *picrate* (from propan-2-ol) had m. p. 106—108° (Found: C, 40·5; H, 4·05; N, 21·5. $C_{11}H_{13}N_5O_7$ requires C, 40·4; H, 4·0; N, 21·4%). The *trichloromercurate* formed needles, m. p. 92—93·5° (from methanol–ethanol) (Found: C, 14·9; H, 2·7; Cl, 26·3; Hg, 49·5; N, 6·9. $C_5H_{11}Cl_3HgN_2$ requires C, 14·8; H, 2·7; Cl, 26·2; Hg, 49·4; N, 6·9%). The acetate, obtained as a brown oil from formamidine acetate and 1,3-diaminobutane, was identified as the picrate.

1,4,5,6-*Tetrahydropyrimidine-4-carboxylic acid*, obtained from DL-αγ-diaminobutyric acid and formamidine acetate in aqueous ethanol, had m. p. >270° (Found: C, 46·7; H, 6·2; N, 22·0. $C_5H_8N_2O_2$ requires C, 46·9; H, 6·3; N, 21·9%). The most intense band in the infrared spectrum (potassium bromide disc) occurred at 1620 cm.$^{-1}$, due to ionic carboxyl.[10]

Perimidine, obtained from 1,8-naphthylenediamine and formamidine acetate in ethanol, had m. p. 219—222° (from benzene) (lit.,[11] 224°) (Found: C, 78·75; H, 4·9; N, 16·7. Calc. for $C_{11}H_8N_2$: C, 78·5; H, 4·8; N, 16·7%). Substitution of formamidine hydrochloride for the acetate gave a mixture of ammonium chloride and perimidine, separable by fractional crystallisation from propan-2-ol.

1,4,5,6-*Tetrahydro-1-methylpyrimidine Hydrobromide*.—A mixture of 3-methylaminopropylamine[12] (4·9 g.) in water (22 ml.) with formamidine hydrobromide (6·26 g.) in ethanol (78 ml.) was refluxed for 2 hr., while a current of nitrogen swept evolved gases into 2N-hydrochloric acid (100 ml.). Evaporation of the mixture at 100°/20 mm. gave an oil, which crystallised at 4° over phosphorus pentoxide in 6 days. Repeated crystallisations from propan-1-ol gave the deliquescent *hydrobromide*, m. p. 70—75° (Found: C, 33·6; H, 6·1; Br, 44·6; N, 15·5. $C_5H_{11}BrN_2$ requires C, 33·5; H, 6·2; Br, 44·6; N, 15·6%). From one of the solutions was deposited a small quantity of 3-*methylaminopropylamine dihydrobromide*, m. p. 182·5—184° (from methanol–ethanol) (Found: C, 19·0; H, 5·6; N, 11·2. $C_4H_{14}Br_2N_2$ requires C, 19·2; H, 5·6; N, 11·2%). Evaporation of the 2N-hydrochloric acid solution at 100°/20 mm. gave ammonium chloride (4·75 g., 89%) which was examined on Whatman No. 1 paper, by the ascending technique, in 5N-acetic acid–butan-1-ol (3 : 7 v/v). Development with ninhydrin at 100° did not reveal a purple spot, although control experiments revealed that as little as 0·1% of methylamine hydrochloride in ammonium chloride gave a positive reaction. Similarly no methylamine was evolved during the 1 hour's refluxing of 3-methylaminopropylamine (1·71 g.) and formamidine acetate (2·02 g.) in ethanol (27 ml.). Evaporation of the solution furnished 1,4,5,6-tetrahydro-1-methylpyrimidine acetate as an oil (2·93 g., 95%), part of which on treatment with hydrogen chloride and mercuric chloride yielded the *trichloromercurate*, m. p. 110—111° (from methanol) (Found: C, 14·8; H, 2·9; Hg, 49·3; N, 6·9. $C_5H_{11}Cl_3HgN_2$ requires C, 14·8; H, 2·7; Hg, 49·4; N, 6·9%). The oil, treated with hydrogen chloride followed by chloroplatinic acid, gave the *hexachloroplatinate*, m. p. 195—196° (decomp.) (from methanol) (Found: C, 19·9; H, 3·6; Cl, 35·2; N, 9·3; Pt, 32·2. $C_{10}H_{22}Cl_6N_4Pt$ requires C, 19·8; H, 3·7; Cl, 35·1; N, 9·2; Pt, 32·2%). Picric acid converted the oil into the picrate, which from ethanol had m. p. 106—107° (lit.,[1] 104—106°) (Found: C, 40·4; H, 3·9; N, 21·7. Calc. for $C_{11}H_{13}N_5O_7$: C, 40·4; H, 4·0; N, 21·4%).

No methylamine was evolved when formamidine hydrochloride in place of the acetate or hydrobromide was used in the condensation. 1,4,5,6-Tetrahydro-1-methylpyrimidine hydrochloride was isolated as an oil which was converted into the above picrate and hexachloroplatinate.

1,4,5,6-*Tetrahydro*-1,3-*dimethylpyrimidinium Salts*.—Toluene-*p*-sulphonyl chloride (190·5 g.) was added with stirring, in 4½ hr., to trimethylenediamine (42 ml.) in N-sodium hydroxide (1 l.) on the steam-bath. The mixture was cooled and the solid filtered off, yielding 1,3-ditoluene-*p*-sulphonamidopropane (163 g., 88%), m. p. 144—148° (lit.,[13] 148°). Dimethyl sulphate (61·9 ml.) was added in 1 hr. to a stirred solution of the propane derivative (84·5 g.) in 0·8N-sodium hydroxide (1·1 l.). The mixture was stirred for a further ½ hr., then cooled to 0° and the supernatant liquid was decanted. The residual gel was washed with aqueous sodium hydroxide

[9] Smith and Christensen, *J. Org. Chem.*, 1955, **20**, 829.
[10] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen and Co., London, 1960, p. 240.
[11] Grundmann and Kreutzberger, *J. Amer. Chem. Soc.*, 1955, **77**, 6559.
[12] Tarbell, Shakespeare, Claus, and Bunnett, *J. Amer. Chem. Soc.*, 1946, **68**, 1217.
[13] Howard and Marckwald, *Ber.*, 1899, **32**, 2038.

and with water and crystallised from ethanol (55 ml.) (yield, 72 g., 88%). After six recrystallisations from ethanol, NN'-*dimethyl*-NN'-*ditoluene*-p-*sulphonyltrimethylenediamine* had m. p. 86—90° (Found: C, 55·3; H, 6·4; N, 6·9; S, 15·4. $C_{19}H_{26}N_2O_4S_2$ requires C, 55·6; H, 6·4; N, 6·8; S, 15·6%).

This compound (103 g.) was refluxed in concentrated sulphuric acid (385 ml.) and water (282 ml.) for 5 hr., during which the reflux temperature fell from 165° to 135°. The mixture was cooled, diluted with water (500 ml.), poured into aqueous sodium hydroxide (623 g. in 1246 ml.), and steam-distilled. The distillate (9 l.) was neutralised with concentrated hydrochloric acid and evaporated to dryness, affording crude *NN'*-dimethyltrimethylenediamine dihydrochloride (44 g.). After repeated crystallisations from aqueous methanol it had m. p. 257—262° (lit.,[14] 262—263°).

A mixture of this dihydrochloride (3·84 g.) and sodium hydroxide in water (8 ml.) was distilled at 20°/0·1 mm. A mixture of the distillate and formamidine acetate (2·29 g.) in ethanol (22 ml.) was refluxed on the steam-bath for 2½ hr. while a current of nitrogen swept evolved gases into 2N-hydrochloric acid (50 ml.). Evaporation of the acid solution yielded ammonium chloride (1·98 g., 84%) which was shown by paper chromatography to be free from methylamine hydrochloride. The mixture was evaporated to dryness at 100°/20 mm. and the residual oil, on treatment with picric acid, afforded 1,4,5,6-*tetrahydro*-1,3-*dimethylpyrimidinium picrate*, m. p. 116·5—118·5° (from methanol–propan-2-ol) (Found: C, 41·9; H, 4·4; N, 20·5. $C_{12}H_{15}N_5O_7$ requires C, 42·2; H, 4·4; N, 20·5%). When the reaction was repeated with formamidine hydrochloride, again no methylamine was evolved. A deliquescent oil was obtained which, on treatment with methanolic mercuric chloride, yielded 1,4,5,6-*tetrahydro*-1,3-*dimethylpyrimidinium trichloromercurate* as needles, m. p. 101—102·5° from methanol (Found: C, 17·0; H, 3·0; Cl, 24·8; N, 6·65. $C_6H_{13}Cl_3HgN_2$ requires C, 17·2; H, 3·1; Cl, 25·3; N, 6·7%). Decomposition of the chloromercurate in aqueous methanol with hydrogen sulphide, followed by treatment with picric acid, afforded the same picrate.

Reaction of Formamidine Hydrochloride with 3-*Dimethylaminopropylamine*.—A mixture of the diamine (2·32 g.) and formamidine hydrochloride (1·82 g.) in propan-2-ol (20 ml.) was refluxed for 1¾ hr. while a stream of nitrogen swept evolved gases into 2N-hydrochloric acid (50 ml.). Paper chromatography of the acid solution revealed no dimethylamine hydrochloride, although in synthetic mixtures as little as 1% (w/w) of this hydrochloride in ammonium chloride could be thus detected. Evaporation of the mixture gave an oil (3·23 g.), which with picric acid (10·4 g.) in boiling ethanol (60 ml.) gave a solid. After extractions with boiling ethanol (2 × 50 ml.), methanol (2 × 100 ml.), and water (1 × 100 ml.) this yielded NN'-*bis*-(3-*dimethylaminopropyl*)*formamidine picrate*, m. p. 189° (decomp.) (Found: C, 38·9; H, 3·6; N, 19·8. $C_{29}H_{33}N_{13}O_{21}$ requires C, 38·7; H, 3·7; N, 20·2%).

1,4,5,6-*Tetrahydro*-2-*methylpyrimidine Hydrochloride*.—The mixture of acetamidine hydrochloride (8·4 g.) and trimethylenediamine (6·58 g.) at 100° evolved ammonia, and after four crystallisations from ethanol–ethyl acetate at −15°, afforded hygroscopic 1,4,5,6-tetrahydro-2-methylpyrimidine hydrochloride, m. p. 146—149° (lit.,[9] 139°) (Found: C, 44·4; H, 8·3; N, 20·6. Calc. for $C_5H_{11}ClN_2$: C, 44·6; H, 8·2; N, 20·8%). It was converted into the picrate, m. p. 154—156° (lit.,[15] 157°). The hydrochloride with methanolic mercuric chloride yielded (*a*) the *trichloromercurate*, m. p. 90° (Found: C, 14·9; H, 2·75; Cl, 26·4; Hg, 49·3; N, 6·9. $C_5H_{11}Cl_3HgN_2$ requires C, 14·8; H, 2·7; Cl, 26·2; Hg, 49·4; N, 6·9%). (*b*) the *tetrachloromercurate*, m. p. 130—131° (Found: C, 22·2; H, 4·0; N, 10·3. $C_{10}H_{22}Cl_4HgN_4$ requires C, 22·2; H, 4·1; N, 10·4%), and (*c*) the *pentachlorodimercurate*, m. p. 122—124·5° (Found: C, 8·8; H, 1·6; Hg, 59·2; N, 4·1. $C_5H_{11}Cl_5Hg_2N_2$ requires C, 8·9; H, 1·6; Hg, 59·2; N, 4·1%). The reaction between acetamidine acetate (from the hydrochloride and sodium acetate in methanol) and trimethylenediamine gave deliquescent 1,4,5,6-tetrahydro-2-methylpyrimidine acetate, characterised by conversion into the above picrate.

1,4,5,6-*Tetrahydro*-2-*t*-*butylpyrimidine Hydrochloride*.—The product (4·55 g.) from pivalamidine hydrochloride (2·8 g.), trimethylenediamine (1·73 ml.), and ethanol (15 ml.), after two crystallisations from propan-2-ol at −15°, afforded the *hydrochloride*, m. p. 254—256° (Found: C, 54·5; H, 9·65; Cl, 20·1; N, 15·8. $C_8H_{17}ClN_2$ requires C, 54·4; H, 9·6; Cl, 20·1; N, 15·9%). The *picrate*, from the hydrochloride and picric acid in propan-2-ol, formed yellow needles, m. p. 158—160° (Found: C, 45·65; H, 5·1; N, 18·8. $C_{14}H_{19}N_5O_7$ requires C, 45·5; H, 5·2;

[14] Gibson, Harley-Mason, Litherland, and Mann, *J.*, 1942, 163.
[15] Aspinall, *J. Amer. Chem. Soc.*, 1940, **62**, 2160.

N, 19·0%). The hydrochloride, with 0·5 and 1 mol. of methanolic mercuric chloride, yielded, respectively, (*a*) the *tetrachloromercurate*, m. p. 171—174° (needles from methanol–propan-2-ol) (Found: C, 30·7; H, 5·5; Cl, 22·8; Hg, 32·0; N, 8·9. $C_{16}H_{34}Cl_4HgN_4$ requires C, 30·8; H, 5·5; Cl, 22·7; Hg, 32·1; N, 9·0%), and (*b*) the *trichloromercurate*, m. p. 134—135° (prisms from methanol–propan-2-ol) (Found: C, 21·3; H, 3·9; N, 6·2. $C_8H_{17}Cl_3HgN_2$ requires C, 21·4; H, 3·8; N, 6·25%).

2-*Benzyl*-1,4,5,6-*tetrahydropyrimidine hydrochloride* (20·5 g., 97%), obtained from phenylacetamidine hydrochloride (17·1 g.), trimethylenediamine (9·3 ml.) and ethanol (150 ml.), had m. p. 212—213° after repeated crystallisation from propan-2-ol and from ethanol–light petroleum (b. p. 60—80°) (Found: C, 62·8; H, 7·1; Cl, 16·8; N, 13·4. $C_{11}H_{15}ClN_2$ requires C, 62·75; H, 7·2; Cl, 16·8; N, 13·3%). The *picrate*, formed in ethanol, had m. p. 176—177° (Found: C, 50·65; H, 4·2; N, 17·3. $C_{17}H_{17}N_5O_7$ requires C, 50·6; H, 4·25; N, 17·4%). The *tetrachloromercurate*, formed in methanol, had m. p. 136—137° (Found: C, 37·7; H, 4·15; N, 8·0. $C_{22}H_{30}Cl_4HgN_4$ requires C, 38·1; H, 4·4; N, 8·1%).

1,4,5,6-*Tetrahydro*-2-*phenylpyrimidine Hydrochloride*.—The product (89%) from benzamidine hydrochloride and trimethylenediamine, on recrystallisation from ethanol–light petroleum (b. p. 60—80°), afforded the hydrochloride, m. p. 244—246° (lit.,[16] 243·5°) (Found: C, 61·1; H, 6·6; Cl, 18·0; N, 14·4. Calc. for $C_{10}H_{13}ClN_2$: C, 61·05; H, 6·6; Cl, 18·0; N, 14·2%), $\lambda_{max.}$ at pH 7, 227·5 mμ (log ε 4·16), $\lambda_{infl.}$ 274 mμ (log ε 2·80), but after 15 min. in N-potassium hydroxide $\lambda_{max.}$ 222 mμ (log ε 4·08), $\lambda_{infl.}$ 260 mμ (log ε 3·47). Acidification of the alkaline solution caused the spectrum to revert to that at pH 7·0.

The tetrachloromercurate, formed in methanol, had m. p. 181—184° (Found: C, 36·0; H, 3·75; N, 8·3. Calc. for $C_{20}H_{26}Cl_4HgN_4$: C, 36·1; H, 3·9; N, 8·4%). The picrate, formed in ethanol, had m. p. 180—181° (lit.,[15] m. p. 181°).

Reaction of Benzamidine Hydrochloride with 3-*Dimethylaminopropylamine*.—Anhydrous benzamidine hydrochloride (obtained by distilling the dihydrate, 2·21 g., with benzene, 20 ml., and ethanol, 100 ml.), the diamine (1·15 g.), and ethanol (34 ml.) were refluxed for 1 hr. Evolved gases were free from dimethylamine. With picric acid, the oil (2·69 g.) from evaporation of the reaction mixture gave NN′-*bis*-(3-*dimethylaminopropyl*)*benzamidine picrate*, m. p. 168—170° (from methanol) (Found: C, 43·4; H, 4·0; N, 18·5. $C_{35}H_{39}N_{13}O_{21}$ requires C, 43·0; H, 4·0; N, 18·6%).

2-*Amino*-1,4,5,6-*tetrahydropyrimidine Salts*.—(*a*) The mixture obtained by refluxing guanidine hydrochloride (2·45 g.), trimethylenediamine (1·9 g.), and ethanol (15 ml.) for 1 hr. was evaporated. The oil (4·05 g.), crystallised from propan-2-ol, afforded an addition *complex*, m. p. 108—110° (Found: C, 23·0; H, 8·4; Cl, 26·7; N, 41·8. $C_5H_{22}Cl_2N_8$ requires C, 22·7; H, 8·4; Cl, 26·7; N, 42·3%). From it, picric acid precipitated guanidine picrate identified by mixed m. p. The infrared spectrum of the complex (potassium bromide disc) had a broad band at 1630—1660 cm.$^{-1}$.

(*b*) The diamine (2·2 g.) and guanidine hydrochloride (2·15 g.) were heated at 140° for 3 hr., evolving ammonia which was isolated as ammonium chloride (2·33 g., 97%). Recrystallisation of the solid from propan-2-ol gave 2-*amino*-1,4,5,6-*tetrahydropyrimidine hydrochloride*, m. p. 152—157° (Found: C, 35·2; H, 7·45; N, 30·7. $C_4H_{10}ClN_3$ requires C, 35·4; H, 7·4; N, 31·0%). The hydrochloride was converted into the picrate, m. p. 185—186° (lit.,[17] 185—186°), and a *pentachlorodimercurate*, m. p. 117—118·5° (from methanol) (Found: C, 7·1; H, 1·45. $C_4H_{10}Cl_5Hg_2N_3$ requires C, 7·1; H, 1·5%), which, after decomposition with hydrogen sulphide and treatment with picric acid, gave the same picrate.

(*c*) *S*-Methylisothiourea sulphate (2·82 g.) in water (20 ml.) was added during 20 min. to a boiling solution of trimethylenediamine (1·5 g.) in water (7 ml.). After 160 minutes' refluxing, evaporation gave a residual sulphate (2·95 g., 98%), m. p. 300° (decomp.) (from aqueous methanol) (Found: C, 32·2; H, 6·8; N, 28·2; S, 10·9. $C_8H_{20}N_6O_4S$ requires C, 32·4; H, 6·8; N, 28·4; S, 10·8%). The analogous reaction with *O*-methylisourea hydrochloride gave a mixture of substances which included 1,3-*diguanidinopropane dihydrochloride*. This was isolated as follows: the 24 hr.-old solution of trimethylenediamine (0·65 g.) and *O*-methylisourea hydrochloride (1·95 g.) in water (12 ml.) was refluxed for 1 hr. and then evaporated to dryness. The solid (from methanol) had m. p. 197—200° (Found: C, 26·2; H, 7·0; Cl, 30·8. $C_5H_{16}Cl_2N_6$

[16] Lythgoe and Rayner, *J.*, 1951, 2323.
[17] Hafner and Evans, *J. Org. Chem.*, 1959, **24**, 1157.

requires C, 26·0; H, 7·0; Cl, 30·7%). The corresponding *trichloromercurate*, formed in methanol, had m. p. 158·5—160·5° (Found: C, 7·6; H, 2·1; N, 10·7. $C_5H_{16}Cl_6Hg_2N_6$ requires C, 7·8; H, 2·1; N, 10·9%).

Reaction of Formamidine Acetate with Methylamines.—A mixture of formamidine acetate (2 g.), ethanolic 33% methylamine (8 ml.), and ethanol (20 ml.) was heated at 100° for 2 hr. Evaporation gave an oil (2·4 g., 95%), which on treatment with ethanolic picric acid yielded NN′-*dimethylformamidine picrate*, m. p. 164·5—166·5° (from methanol–ethanol) (Found: C, 36·1; H, 3·9; N, 23·7. $C_9H_{11}N_5O_7$ requires C, 35·9; H, 3·7; N, 23·3%). Repetition of the experiment with ethanolic dimethylamine gave no such picrate.

Reaction of Trimethylenediamine with NN′-*Dimethylformamidine Picrate.*—A mixture of the picrate (0·14 g.), trimethylenediamine (0·04 ml.) and ethanol (6 ml.) was refluxed for 1 hr. Concentration and recrystallisation from ethanol afforded 1,4,5,6-tetrahydropyrimidine picrate identified by mixed m. p.

Stability of 1,4,5,6-*Tetrahydro*-2-*phenylpyrimidine in Water.*—The hydrochloride (0·5 g.) in water (100 ml.) was twice shaken with freshly prepared silver oxide (0·35 g.) for 1 hr. After 24 hr. at 20°, the filtrate with ethanolic picric acid gave a little 1,4,5,6-tetrahydro-2-phenylpyrimidine picrate.

pK_a *Determination.*—Ionisation constants at 20° were determined spectrophotometrically with an Optika CF4 instrument. For 2-amino- and 2-benzyl-1,4,5,6-tetrahydropyrimidine, the high pK_a values made it necessary to apply a graphical procedure to obtain the extinction coefficient for the free base. The values obtained for the 1,4,5,6-tetrahydropyrimidine derivatives were: 2-benzyl 13·0; 2-phenyl 12·8; 2-amino 14·1 (values in this region must be considered uncertain). Perimidine had pK_a 6·39 ± 0·05.

Spectra.—Ultraviolet spectra were measured with a Perkin–Elmer Spectracord model 4000-A double-beam spectrophotometer, and the maxima checked with a Hilger Uvispek mark V manual instrument. Infrared spectra were taken with a Perkin–Elmer 21 double-beam spectrophotometer fitted with a sodium chloride prism. The compounds were examined in potassium bromide discs, except for the chloroplatinate which was examined in silver chloride or potassium chloride discs. The behaviour of 1,4,5,6-tetrahydro-1-methylpyrimidine hexachloroplatinate in potassium bromide discs was erratic. Apparent double decomposition occurred in the preparation of one disc and the spectrum observed was that of 1,4,5,6-tetrahydro-1-methylpyrimidine hydrobromide. After 3 months in a desiccator over phosphorus pentoxide, a reverse double decomposition seemed to have occurred and the spectrum observed was that of the hexachloroplatinate. No double decomposition occurred in the preparation of a second disc, but regrinding in a humid atmosphere brought about partial double decomposition and NH stretching bands due to both hydrobromide and hexachloroplatinate were observed. Longer regrinding of the same disc in the same atmosphere brought about a marked diminution in intensity of the NH stretching bands due to the hydrobromide.

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