ethoxide. Yields of 73 and 70% of 1-ethoxy-N,N-dimethylvinylamine, b.p. 124–125°, were obtained in runs of 1 and 3 moles, respectively.

1-Ethoxy-N,N,2-trimethylpropenylamine.—The procedure of Meerwein,[4] modified as described above, was applied to the preparation of this compound from N,N-dimethylisobutyramide. The product, b.p. 148–150° (63–65° at 40 mm.), $n^{20}D$ 1.4367, was obtained in 49% yield. Satisfactory elemental analyses were not obtained, possibily because the product reacted with atmospheric moisture. However, its physical properties, including infrared and n.m.r. spectra, were in agreement with the proposed structure. The infrared spectrum contained a strong absorption for >N—C=C< at 5.98 μ. The n.m.r.[5] spectrum consisted of the following absorptions (chemical shift, multiplicity, and assignment are shown): 3.63, quartet, O–CH_2–; 2.64, singlet, N–CH_3; 1.58, singlet, C=C–CH_3; 1.18 p.p.m., triplet, C–CH_3.

N,N,N′,N′,2-Pentamethyl-1-propene-1,1-diamine.—To a solution of N,N-dimethylisobutyramide (57.5 g., 0.5 mole) in tetrahydrofuran (250 ml.) was added phosgene (60 g., 0.6 mole). The resulting mixture was heated at 50–65° with stirring under a Dry Ice-cooled condenser for 1.5 hr., while carbon dioxide was evolved and the mixture separated into two liquid phases. The entire mixture was transferred to a heated dropping funnel and added rapidly to a mixture of dimethylamine (70 g., 1.55 moles), dioxane (150 ml.), and 48 g. of a 50% dispersion of sodium hydride in mineral oil, while the temperature was maintained at 0–10°. The resulting viscous slurry was allowed to stand for 18 days at room temperature, while protected from atmospheric moisture by drying tubes. The mixture was filtered, and the filtrate was distilled *in vacuo* to yield 22.5 g. (32%) of product, b.p. 60–62° (35 mm.), and 15 g. (26%) of recovered amide. Again, satisfactory elemental analyses could not be obtained. However, the infrared spectrum showed a strong absorption at 6.02 μ and the n.m.r. spectrum consisted of singlet absorptions at 2.6 and 1.5 p.p.m. assigned to N–CH_3 and C=C–CH_3 protons, respectively.

Methyl 2,2-Diethoxycyclobutanecarboxylate.—Ketene diethyl acetal (20 g., 0.172 mole), methyl acrylate (15 g., 0.174 mole), and acetonitrile (50 ml.) were combined and refluxed for 190 hr. Distillation of the mixture through a 6-in. Vigreux column gave 22 g. (63%) of methyl 2,2-diethoxycyclobutanecarboxylate, b.p. 52–55° (0.9 mm.), $n^{20}D$ 1.4324. The infrared spectrum showed no absorption between 5.9 and 6.7 μ, and the n.m.r. spectrum showed no olefinic proton absorption.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.4; H, 9.0. Found: C, 59.4; H, 9.2.

The 2,4-dinitrophenylhydrazone (prepared in methanol) melted at 143–145°.

Anal. Calcd. for $C_{12}H_{12}N_4O_6$: C, 46.7; H, 3.9. Found: C, 46.6; H, 4.2.

Hydrolysis of Methyl 2,2-Diethoxycyclobutanecarboxylate.—A mixture of methyl 2,2-diethoxycyclobutanecarboxylate (10 g., 0.049 mole), water (15 ml.), concentrated hydrochloric acid (5 drops), and enough methanol to produce a homogeneous solution was heated on the steam bath for 3.5 hr. in an open beaker. The mixture was cooled and filtered. The solid was recrystallized from benzene to give 4.8 g. (72%) of glutaric acid, which was identical with an authentic sample.

Diethyl 3,3-Diethoxy-1,2-cyclobutanedicarboxylate.—A mixture of ketene diethyl acetal (30 g., 0.259 mole), diethyl fumarate (41 g., 0.24 mole), and acetonitrile (75 ml.) was refluxed for 190 hr. Distillation of the mixture through a 3-in. Vigreux column gave 12 g. (17%) of diethyl 3,3-diethoxy-1,2-cyclobutanedicarboxylate, b.p. 103–109° (0.2 mm.), $n^{20}D$ 1.4421.

Anal. Calcd. for $C_{14}H_{24}O_6$: C, 58.3; H, 8.4. Found: C, 58.5; H, 8.3.

3,3-Diethoxy-4,4-dimethyl-1,1,2,2-cyclobutanetetracarbonitrile.—Dimethylketene dimethyl acetal (4.4 g., 0.038 mole) was added over a 5-min. period to ethenetetracarbonitrile (3.2 g., 0.025 mole) in acetonitrile (25 ml.). The temperature rose to 38° and then dropped to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from acetone–hexane to give 5.2 g. (85%) of 3,3-dimethoxy-4,4-dimethyl-1,1,2,2-cyclobutanetetracarbonitrile, m.p. 136–137°.

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 58.9; H, 5.0. Found: C, 59.0; H, 5.3.

Methyl 5-Dimethylamino-5-ethoxy-4-pentenoate.—Methyl acrylate (25.8 g., 0.3 mole) was combined with N,N-dimethyl-1-ethoxyvinylamine (34.5 g., 0.3 mole). The temperature of the mixture rose to 60° over a 0.5-hr. period and then dropped slowly to room temperature. Distillation gave 38 g (61%) of methyl 5-dimethylamino-5-ethoxy-4-pentenoate, b.p. 63–67° (1 mm.), $n^{20}D$ 1.4574. The infrared spectrum showed, besides the ester band, a strong absorption at 6.04 μ, and the n.m.r. spectrum contained an olefinic proton triplet at 3.2 p.p.m.

Anal. Calcd. for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0. Found: C, 60.0; H, 9.5; N, 6.9.

The same product was formed when the reaction was carried out at 10° and, on the basis of infrared spectral data, was present prior to distillation. When the analogous compound from ethyl acrylate, b.p. 67–70° (0.5 mm.), $n^{20}D$ 1.4536, was dissolved in ethanol and the resulting solution was added to dilute hydrochloric acid, there was obtained on distillation a 58% yield of diethyl glutarate, identical with an authentic sample.

Methyl 2-Dimethylamino-3,3-dimethyl-1-cyclobutene-1-carboxylate.—A mixture of 1-ethoxy-N,N,2-trimethylpropenylamine (24.8 g., 0.17 mole), methyl acrylate (15 g., 0.17 mole), and acetonitrile (75 ml.) was refluxed for 16 hr. Distillation of the reaction mixture gave 10 g. (40% recovery) of the ethoxyamine starting material and 8.5 g. (44% based on unrecovered starting material) of the product, b.p. 65–68° (0.8 mm.), $n^{20}D$ 1.5121.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.5; H, 9.3; N, 7.6. Found: C, 65.7; H, 9.3; N, 7.4.

The infrared spectrum showed strong bands at 6.0 and 6.2 μ, and the n.m.r. spectrum was compatible with the proposed structure.

The compound gave the 2,4-dinitrophenylhydrazone of methyl 3,3-dimethyl-2-oxocyclobutanecarboxylate, m.p. 128.5–130°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8; N, 16.6. Found: C, 50.3; H, 5.1; N, 16.3.

Methyl 2-dimethylamino-3,3-dimethyl-1-cyclobutene-1-carboxylate also was obtained in 23% yield from methyl acrylate and N,N,N′,N′,2-pentamethyl-1-propene-1,1-diamine. Some of the diamine was recovered, apparently admixed with methyl 3-dimethylaminopropionate, which was formed by addition of dimethylamine to methyl acrylate.

(5) N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane.

Evidence Supporting the Occurrence of a 4,5-Dehydropyrimidine in Aminations of Halopyrimidines[1]

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The elimination–addition (benzyne) mechanism for nucleophilic aromatic substitution has been invoked in many heterocyclic systems; included among these are pyridines,[2] quinolines,[3] and pyridazines.[4] This mode of substitution apparently has not been postulated yet for such transformations in pyrimidines.

Because reactions involving a benzyne-type intermediate generally occur in cases of nonactivated aryl halides, 2-methyl-5-chloropyrimidine (I) was selected as a precursor for the 4,5-dehydropyrimidine. The C-5 of the pyrimidine ring is relatively electron-rich

(1) This investigation was supported by Grant CA-02857 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) For pertinent references, see (a) T. Kauffmann and F.-P. Boettcher, *Chem. Ber.*, **95**, 1528 (1962); (b) R. J. Martens and H. J. den Hertog, *Tetrahedron Letters*, **No. 15**, 643 (1962).

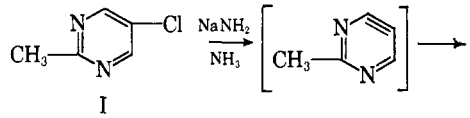
(3) T. Kauffmann, F.-P. Boettcher, and J. Hansen, *Ann.*, **659**, 102 (1962).

(4) T. Kauffmann and A. Risberg, *Tetrahedron Letters*, **No. 22**, 1459 (1963).

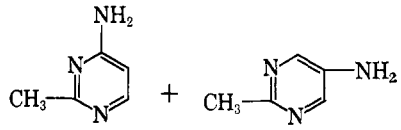
and hence less susceptible to reaction through the addition–elimination mechanism of substitution.

The chloro compound (I) was prepared by the decarboxylation of 2-methyl-4-carboxy-5-chloropyrimidine (II)[5] which was obtained from the condensation of acetamidine with mucochloric acid.

Treatment of I with sodium amide in liquid ammonia would be expected to yield 2-methyl-4-aminopyrimidine (III) and 2-methyl-5-aminopyrimidine (IV), providing the elimination–addition mechanism is operative.



I



III IV

Authentic samples of III and IV were prepared by the following procedures. Condensation of ethyl sodium formylacetate with acetamidine gave 2-methyl-4-hydroxypyrimidine (V).[6] Treatment of V with phosphorus oxychloride gave 2-methyl-4-chloropyrimidine (VI),[6] which was converted to III with aqueous ammonia. Urban and Schnider reported the preparation of IV by the reductive dehalogenation of 2-methyl-5-amino-4,6-dichloropyrimidine (VII).[7] We have synthesized IV by the decarboxylation of 2-methyl-4-carboxy-5-aminopyrimidine (VIII), which was obtained by the amination of 2-methyl-4-carboxy-5-bromopyrimidine (IX)[5] with aqueous ammonia. The bromo acid (IX) was prepared by condensing acetamidine with mucobromic acid.[5] The sample of IV obtained by the decarboxylation of VIII was identical with one prepared by the reduction of VII.[8]

2-Methyl-5-chloropyrimidine was treated with sodium amide in liquid ammonia for 2 hr., and the reaction mixture was analyzed by vapor phase chromatography. 2-Methyl-4-aminopyrimidine (III) was identified as a component of the mixture. This component was shown to have the same retention time as an authentic sample of III and when isolated exhibited an infrared spectrum identical with that of III. The presence of 2-methyl-5-aminopyrimidine (IV) can only be inferred. A component of the reaction mixture with a retention time identical with that of an authentic sample of IV was observed. The quantity obtained, however, was not sufficient for spectral comparison. Control experiments with III and IV indicated that interconversion of the two aminopyrimidines did not occur under the reaction conditions.

The formation of 2-methyl-4-aminopyrimidine (III) from I is consistent with a benzyne-type mechanism.[9] The determination of relative quantities of III and IV is precluded at this time by poor yields.

(5) Z. Budesinsky, *Collection Czech. Chem. Commun.*, **14**, 223 (1949).
(6) S. Gabriel, *Ber.*, **37**, 3638 (1904).
(7) R. Urban and O. Schnider, *Helv. Chim. Acta*, **41**, 1806 (1958).
(8) The authors are indebted to O. Schnider, R. Hoffmann-LaRoche and Co., Basel, Switzerland, for a sample of this compound.
(9) H. Heaney, *Chem. Rev.*, **62**, 81 (1962).

Experimental

Melting points were taken on a Mel-Temp apparatus. Infrared spectra were determined using a Beckman IR-5A spectrophotometer. All vapor phase chromatographic analyses were carried out on an F & M Model 500 gas chromatograph with a 0.25-in. o.d., 5-ft. stainless steel column packed with 8% Triton X-305 on Chromosorb W. The analyses were run isothermally at 153° using helium as a carrier gas (100 ml./min.).

Materials.—2-Methyl-5-chloropyrimidine (I),[5] 2-methyl-4-carboxy-5-chloropyrimidine (II),[5] 2-methyl-4-aminopyrimidine (III),[6] 2-methyl-4-hydroxypyrimidine (V),[6] 2-methyl-4-chloropyrimidine (VI),[6] 2-methyl-4-carboxy-5-aminopyrimidine (VIII),[5] and 2-methyl-4-carboxy-5-bromopyrimidine (IX)[5] were prepared according to procedures described in the literature.

2-Methyl-5-aminopyrimidine (IV) was prepared by heating 1.9 g. of VIII at 200° for 3 hr. in an oil bath. The reaction mixture was extracted for 12 hr. with benzene. Upon removal of the benzene *in vacuo* there was obtained a solid weighing 0.1 g. (8%), which was vacuum sublimed at 135° and 28 mm. The melting point of the sublimate was 155–157°. An authentic sample of IV[8] melted at 156–159° and exhibited an infrared spectrum identical with that of the product obtained from the decarboxylation of VIII.

Reaction of 2-Methyl-5-chloropyrimidine (I) with Sodium Amide in Liquid Ammonia.—The reaction conditions were similar to those by Pieterse and den Hertog employed in the amination of 3-chloropyridine.[10] Sodium amide was prepared from 0.37 g. of sodium, 12 ml. of anhydrous liquid ammonia, and 0.1 g. of ferric nitrate.[11] 2-Methyl-5-chloropyrimidine (I, 0.97 g.) was added cautiously to the stirred mixture. After the mixture was stirred and refluxed for 2 hr., the reaction was quenched with 1.0 g. of ammonium chloride. The ammonia was allowed to evaporate, and the resulting residue was extracted with benzene for 36 hr. The benzene was removed *in vacuo*, and the resulting residue was dissolved in methanol and diluted to 1 ml. Authentic samples of 2-methyl-4-aminopyrimidine (III) and 2-methyl-5-aminopyrimidine (IV) were found to have retention times of 13.0 and 14.8 min., respectively, under the column conditions stated above. The methanolic solution contained a component with a retention time of 13.0 min. When this component was collected, it exhibited an infrared spectrum identical with that of III. A component with a retention time identical with that of IV was detected, but it was not present in sufficient amounts for collection and spectral comparisons. By means of a quantitative correlation between weight of pyrimidine and chromatogram peak area, in which authentic samples of the aminopyrimidines were employed, the reaction mixture was found to contain these pyrimidines in only small amounts (<5%).

Control Experiments on 2-Methyl-4-aminopyrimidine (III) and 2-Methyl-5-aminopyrimidine (IV).—The aminopyrimidines were recovered in amounts up to approximately 50% when refluxed with sodium amide in liquid ammonia at −33° for 2 hr. The column conditions for the analysis were the same as those described above. In each instance, the aminopyrimidine under investigation was found to be the only component present in the reaction mixture.

(10) M. J. Pieterse and H. J. den Hertog, *Rec. trav. chim.*, **80**, 1376 (1961).
(11) T. H. Vaughn, R. R. Vogt, and J. Nieuwland, *J. Am. Chem. Soc.*, **56**, 2120 (1934).

Synthesis of 3,5-Diaminopyrazole Hydrochlorides

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In 1894, von Rothenburg[1] reported that the condensation of malononitrile and hydrazine yielded a compound believed to be 3,5-diaminopyrazole (IIIa).

(1) R. von Rothenburg, *Chem. Ber.*, **27**, 685 (1894).