chromatography in benzene–ethyl acetate (4:1) led to crystalline α-formylaminoisovaleronitrile (IV, 43.2 mg.), m.p. 39.5–40°, R_f 0.07.

Anal. Calcd. for $C_6H_{10}N_2O$: N, 22.23. Found: N, 22.24.

This compound showed the typical nitrile absorption at 4.44 μ. The mother liquor of IV contained material with λ_{max} 259 mμ. This material was stable against acid and alkali, and, even after treatment with 0.1 *N* acid or alkali overnight, no change in the spectrum was observed.

Dehydration of Formyl-DL-valylglycine Ethyl Ester (VIIb).—Formyl-DL-valylglycine ethyl ester (230 mg.) and tosyl chloride (700 mg.) were dissolved in pyridine (2 ml.) and the mixture was stirred for 3 hr. at 20°. Within a few minutes the solution took on a wine red color. The pyridine solution was diluted with cold petroleum ether (100 ml.). The precipitated oily material was washed with cold petroleum ether, then extracted ten times with cold ether (25 ml.). The combined ethereal extracts were evaporated and the residue was purified by preparative thin layer chromatography (silicic acid, benzene–ethyl acetate, 4:1 v./v.). A band (R_f 0.45), which showed positive ninhydrin reaction after treatment with ethanol–6.0 *N* hydrochloric acid (1:1 v./v.) and subsequent heating, was eluted with methanol. The viscous isocyanide of VIIb had R_f 0.45 (benzene–ethyl acetate, 1:4) and 0.70 (ethyl acetate–methanol, 5:1); 4.68 (isonitrile) and 5.74 μ (ester).

The purified isocyanide was stable on standing at 20° but reverted partly to decomposition products which gave a yellow coloration with ninhydrin reagent. When ethyl acetate was used in place of ether for the extraction of the isocyanide, there was obtained a decomposition product, R_f 0.28 (ethyl acetate–methanol, 5:1), which after treatment with hot mineral acid gave a positive ninhydrin reaction.

Dehydration of Formyl-DL-valylglycinamide (VIIc).—Formyl-DL-valylglycinamide (194 mg.) and tosyl chloride (900 mg.) in pyridine (3 ml.) were stirred at 20° for 3 hr. and poured into cold ether (100 ml.). The precipitate was washed with cold ether and extracted with cold ethyl acetate (25 ml.) which was quickly concentrated to a sirup under reduced pressure. This extract was purified by thin layer chromatography in ethyl acetate–methanol (5:1, v./v.). A band having R_f 0.67–0.68 was first eluted with chloroform, then with methanol. Both extracts were separately evaporated to dryness and examined. The infrared spectrum of both samples had the characteristic absorption of the isocyanide group at 4.70 μ. In addition the sample from the methanol extract also contained the 4.47-μ absorption peak characteristic of nitriles. When samples of the isocyanide fraction were left standing in chloroform (20°, 1 hr.), thin layer chromatography showed formation of a new compound with the characteristic nitrile absorption.

N-Formyl-DL-valinecyanomethylamide (IX).—From the ether-washed dehydration product of formylvalylglycinamide (216 mg.) and tosyl chloride (992 mg.) in pyridine, the nitrile IX was extracted into ethyl acetate. The residue (242 mg.) was purified by preparative thin layer chromatography. The major band, which was eluted with methanol, after removal of the methanol and trituration in ethyl acetate, yielded colorless crystals, m.p. 137–138.5°.

Anal. Calcd. for $C_8H_{13}N_3O_2$: N, 22.99. Found: N, 22.69.

The Reduction of 1-Benzylmethylpyrazinium Salts with Sodium Borohydride

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The reaction of three 1-benzylalkylpyrazinium salts with sodium borohydride gave the corresponding 1-benzylalkylpiperazines.

The reaction of sodium borohydride with substituted pyridinium salts has been shown to yield di- and tetrahydropyridines as the major products. The enamine system formed by the initial attack of the hydride on the pyridinium ion is attacked by a proton from the solvent and then a second attack by hydride ion to form the tetrahydropyridine.[2] A pyrazinium salt could form only enamine or imine double bonds by hydride ion reaction, and thus it was anticipated that sodium borohydride reduction of pyrazinium salts in protic solvents would form piperazines and not partially reduced pyrazines. No example of the reaction of pyrazinium salts with sodium borohydride has been reported. The benzo derivatives, 1-methyl- and 1-ethylquinoxalinium salts, are reported to form 1-substituted 1,2,3,4-tetrahydroquinoxalines.[3] The reactions of 1 benzyl-3-methyl-, 1-benzyl-3,5-dimethyl-, and 1-benzyl-2,5-dimethylpyrazinium bromides with sodium borohydride now have been shown to give the corresponding piperazines and are the subject of this paper.

The reaction of benzyl bromide with the methyl pyrazines gave a single salt in each instance. It was assumed on the basis of steric grounds that the less hindered nitrogen had undergone salt formation giving IIa, b, and c. Proton magnetic resonance spectroscopy did not assist in the characterization, for the difference in chemical shifts of the methyl resonance peaks was not great.[4]

The reaction of 1-benzyl-3-methylpyrazinium bromide (IIa) and 1-benzyl-3-5-dimethylpyrazinium bromide (IIb) with sodium borohydride in water gave products homogenous to gas chromatography. Elemental analyses and infrared and proton magnetic resonance spectra were consistent with complete saturation of the heterocyclic ring to the piperazine. The single isomer of 1-benzyl-3,5-dimethylpiperazine which formed had the methyl groups *cis* and equatorial, for only this conformation was consistent with the proton magnetic resonance spectrum. In common with IIIa the methyl protons appeared as a doublet (0.91 p.p.m., J = 7 c.p.s.), the benzyl methylene hydrogen as a singlet (3.39 p.p.m.), the aromatic hydrogens as a singlet (7.22 p.p.m.), and the amino hydrogen at *ca.* 1.2 p.p.m. The axial and equatorial hydrogens at positions 2 or 6 of IIIb are nonidentical. The axial hydrogens appear as a triplet at 1.49 p.p.m.; the coupling constants of the axial hydrogens with the geminal equatorial hydrogens and with the adjacent axial hydrogens at positions 3 (or 5) are approximately equal (11 c.p.s.). The 2,6-equatorial hydrogens appear as a quartet at about 2.66 p.p.m. and the 3,5-diaxial

(1) This work is a portion of the research of J. J. T. to be presented to the Graduate Faculty of the University of New Hampshire in partial fulfillment of the Doctor of Philosophy degree.

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TABLE I

PROPERTIES OF THE METHYLPYRAZINIUM SALTS (II)

Pyrazinium bromide	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1-Benzyl-3-methyl (a)	50	151.0–153.5	$C_{12}H_{13}BrN_2$	54.35	4.94	53.88	5.31
1-Benzyl-3,5-dimethyl (b)	88	246–248	$C_{13}H_{15}BrN_2$	55.94	5.42	55.95	5.50
1-Benzyl-2,5-dimethyl (c)	63	172–174.5	$C_{13}H_{15}BrN_2$	55.94	5.42	55.87	5.72

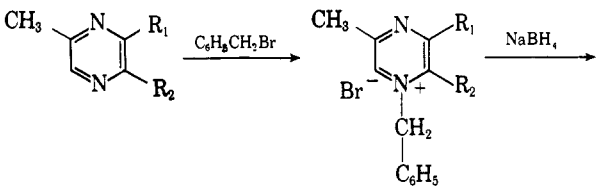
TABLE II

PRODUCTS OF THE REDUCTION OF PYRAZINIUM SALTS (II) WITH SODIUM BOROHYDRIDE

							Phenylthioureas			
			Calcd., %		Found, %			Calcd., %		Found, %	
III	Yield, %	B.p., °C. (mm.)	C	H	C	H	M.p., °C.	C	H	C	H
a	33	108 (2.6)	75.74	9.54	75.79	9.79	130–131	70.12	7.12	70.08	7.23
b[a]	61	100–103 (1.6)	76.42	9.86	76.62	10.05	126–127	70.75	7.42	70.95	7.45
c[b]	66	112–113 (2.7)	76.42	9.86	76.71	9.57	114–115	70.75	7.42	71.03	7.39

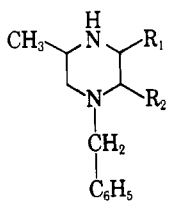
[a] 1-Benzyl-3,5-dimethylpiperazine (IIIb) was hydrogenolyzed to 2,6-dimethylpiperazine, m.p. 114–115°, following the procedure of Cignarella.[7] The picrate of IIIb melted at 245–246°, lit.[7] m.p. 245–247°. [b] This mixture of isomers was resolved by recrystallization of the picrate (m.p. 224–226°) from aqueous ethanol to give a single isomer (m.p. 234–236°).

hydrogens produce a multiplet at about 2.9 p.p.m.[5] The large coupling constant of the triplet at 1.49 p.p.m. is consistent with geminal and adjacent diaxial hydrogens.[6] Thus the conformation of the methyl groups is also defined by this spectrum.



Ia, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$

IIa, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$

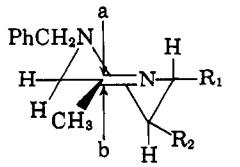


IIIa, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$

The synthesis of *cis*-1-benzyl-3,5-dimethylpiperazine (IIIb) by a cyclization route was recently described.[7] The refractive index and high-melting picrate were the only constants of IIIb, useful for comparison, given in the reference. The value reported for the refractive index ($n^{20}D$ 1.5363) differed considerably from the refractive index of the product of sodium borohydride reduction of IIb ($n^{19}D$ 1.5271). The melting point of the picrate of the reduction product corresponded with the literature value. Hydrogenolysis of the 1-benzyl group of the reduction product of IIb gave a solid whose melting point agreed with that reported for *cis*-2,6-dimethylpiperazine.[7]

The product of the reduction of 1-benzyl-2,5-dimethylpyrazinium bromide (IIc) with sodium borohydride gave elemental analyses corresponding to those of the piperazine; however, the gas chromatographic analysis indicated two components to be present. The major isomer (about 90%) was purified by preparation of the picrate, m.p. 234–236°, and recrystallization from aqueous ethanol. The amine, regenerated from the picrate, gave a single major peak on gas chromatographic analysis and indicated less that 0.5% contamination by the other isomer. The n.m.r. spectrum was too complex to be used to determine the stereochemistry of this isomer. One feature of interest, however, was the nonidentity of the benzylic protons resulting in an AB pattern. The major product from the reduction of IIc was shown to be *trans* IIIc by hydrogenolysis of the 1-benzyl substituent to give a solid identical, by melting point, mixture melting point, and infrared spectrum, with *trans*-2,5-dimethylpiperazine (IVc).[8]

The formation of the geometrical isomers of IIIb and IIIc having the methyl groups both equatorial probably does not result from thermodynamic control of the reaction, for the protonation and reduction steps should not be reversible under the conditions.[2,9] The stereochemistry is probably established by the attack of hydride from a borohydride ion on an imine such as V. If the preferred conformation is as represented by V, then attack along route b would require a "boat-like" transition state while attack along route a would proceed *via* an energetically favored "chair-like" transition state.[10]



Va, $R_1 = CH_3$; $R_2 = H$
b, $R_2 = H$; $R_2 = CH_3$

(5) Compare with spectra 477, 478, and 479 in N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "N.M.R. Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963.

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(8) The authors wish to express appreciation to the Wyandotte Chemical Co. for authentic samples of *cis*- and *trans*-2,5-dimethylpiperazine (IVc).

(9) R. Lyle and P. Anderson in "Advances in Heterocyclic Chemistry," Vol. VI, A. Katritzky, Ed., Academic Press Inc., New York, N. Y., in press.

(10) Compare with the electrophilic attack on cyclohexanone enols [E. J. Corey, *Experientia*, **9**, 329 (1953); J. Valls and E. Toromnaoff, *Bull. soc. chim. France*, 758 (1961)] or the conjugate addition of cyanide ion to $\Delta^{5,6}$ and $\Delta^{12,13}$ keto steroids [W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, **No. 11**, 461 (1962)].

Experimental

Pyrazinium Salts (IIa, b, and c, Table I).—A solution of 0.2 mole of the pyrazine I and 0.2 mole of benzyl bromide in 125 ml. of acetone was heated under reflux for 2 hr. The pyrazinium salt which precipitated was removed by filtration. The filtrate was heated under reflux to cause precipitation of additional pyrazinium salt II. The process was repeated to give three crops of salt. The combined yield of II (a, b, or c) was stirred with acetone, and the suspension was separated by filtration. The solid was dried to give the salt II, in analytical purity.

Reduction of the Pyrazinium Salts (II) with Sodium Borohydride.—A solution of 0.06 mole of the pyrazinium salt (II) in 100 ml. of water was added slowly to a solution of 2.4 moles (9.1 g.) of sodium borohydride in 50 ml. of water. The mixture was stirred for 10 min. after the addition was complete, and then 10% hydrochloric acid was added until effervescence ceased. The solution was heated under reflux for 2 hr. to hydrolyze the amine boranes, and, with cooling, the solution was neutralized with sodium hydroxide. Sodium chloride was added to decrease the solubility of the amine, and the mixture was extracted with ether. After drying, the ether extracts were concentrated and the residue was distilled. The products are listed in Table II.

The Stereochemistry of the Product of the Sodium Borohydride Reduction of 1-Benzyl-2,5-dimethylpyrazinium Bromide (IIc).—A solution of 5.1 g. of isomeric 1-benzyl-2,5-dimethylpiperazines (IIIc) from the reduction of IIc dissolved in 60 ml. of ethanol was treated with hydrogen for 11 hr. at atmospheric pressure over 3 g. of 5% palladium on charcoal. The catalyst was removed by filtration, and the filtrate was divided into two portions of 30 ml.

Evaporation of the solvent from one portion gave a solid residue which was purified by sublimation to give 0.2 g. of solid, m.p. 113.5–115.5°. The melting point was not depressed on mixing with authentic *trans*-2,5-dimethylpiperazine,[8] m.p. 114–116°, and the infrared spectra of the solids were identical. The second portion of the hydrogenation product was converted to the picrate by treatment with a saturated alcoholic solution of picric acid. Recrystallization of the solid from ethanol–water gave 1.3 g. of picrate, m.p. 306–307° dec. The picrates of authentic samples of *cis*- and *trans*-2,5-dimethylpiperazine decompose at 272–273° and 307–308°, respectively.

Acknowledgment.—The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by Grant CA-04143 and continuation grants. The n.m.r. spectra were determined using a Varian A-60 spectrometer made available by Grant G 22718 from the National Science Foundation.

Aromatic N-Oxides. II.[1] N-Acetoxypyridinium Perchlorates

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A convenient method for preparing N-acetoxypyridinium perchlorates is reported. Reactions of these salts with water, ethanol, sodium acetate, triethylamine, and potassium cyanide have been studied. The reaction of 2-methylquinoline 1-oxide with acetic anhydride to yield 1-acetoxy-2-methylquinolinium acetate has been found to be reversible.

Many workers have postulated N-acyloxypyridinium ions, for example the cation of I, as intermediates in reactions. A partial list includes three groups[3–5] who have studied the mechanism of the formation of 2-pyridylmethyl acetate from 2-methylpyridine 1-oxide and acetic anhydride. Other workers have obtained products which may be postulated to occur by reaction of an N-acyloxypyridinium ion with cyanide ion,[6] chloride ion,[7] hydrogen and platinum,[8] enolate of ethyl cyanoacetate,[9] enamines,[10] tertiary amines,[11] and carboxylate salts.[12]

While our work was in progress the first report of the isolation of an N-acetoxypyridinium salt, 1-acetoxy-2-methylpyridinium picrate,[13] was made. We have obtained several N-acetoxypyridinium perchlorates as a result of titrating aromatic N-oxides dissolved in acetic anhydride–acetic acid solutions with perchloric acid in acetic acid.[1] By using the foregoing procedure two additional N-acetoxypyridinium perchlorates have been prepared.[14]

A more convenient method for preparing N-acetoxypyridinium perchlorates is the reaction of perchloric acid in acetic anhydride with a pyridine N-oxide dissolved in acetic anhydride and acetic acid. The products are obtained in high yield and generally do not require purification for further use. In this preparation the acylating agent is probably CH_3CO^+ or $(CH_3CO)_2OH^+$ or both.[15,16] The N-acetoxypyridinium perchlorates prepared in this manner are listed in Table I.

The structure assignments of the N-acetoxypyridinium perchlorates were based on their elemental analyses, infrared absorptions about 1830 cm.$^{-1}$,[13] and their hydrolysis to parent N-oxides.

Since pyridine is an excellent leaving group in the reaction of N-acylpyridinium ions[17] with nucleophiles and since aromatic N-oxides are less basic than pyridine,[18] one may expect N-acyloxypyridinium ions, for example the cation of I, to react with nucleophiles at the carbonyl carbon (attack a). The formation of anhydrides[12] from the reaction of the product of

(1) (a) Paper I: C. W. Muth, *et al.*, *Anal. Chem.*, **34**, 1163(1962); (b) from the M.S. Thesis, 1961, and Ph.D. Dissertation, 1964, of R. S. Darlak; (c) presented in part before the Organic Division of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962.

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