Neoaspergillic Acid (II)——Colorless needles, mp 126—127.5° from ethanol. Reddish brown with $FeCl_3$. UV λ_{max}^{EtOH} nm (ε) 234 (10557), 330 (8143). IR KBr cm^{-1}: 3430, 2960, 2440, 2040, 1638, 1584, 1567, 1240, 1157. NMR in $CDCl_3$ δ ppm: 0.99 (6H, doublet, $J=7.0$), 0.94 (6H, doublet, $J=7.0$), 1.96—2.44 (2H, multiplet), 2.67 (4H, triplet, $J=7.0$), 9.71 (1H, broad singlet). MS *m/e* (%): 224(30), 207(63), 193(28), 166(40), 153(43), 123(61), 43 (23).

β-Hydroxyneoaspergillic Acid (V)——Colorless amorphous, mp 143—144° (from ethylacetate). $C_{12}H_{20}N_2O_3$ (*m/e* Found: 240.146, Calcd: 240.1473). UV λ_{max}^{EtOH} nm (ε): 237 (16238), 333 (12511). IR KBr cm^{-1}: 3350, 2955, 2925, 2870, 2060, 1640, 1575, 1235, 990, 720. NMR in $CDCl_3$ δ ppm: 0.95 (6H, doublet, $J=6$), 1.34 (6H, singlet), 2.18 (1H, multiplet), 2.69 (2H, doublet, $J=8$), 2.99 (2H, singlet), 7.39 (1H, singlet). MS *m/e* (%): 240(M^+, 20), 182(38), 166(32), 123(100), 59(100), 43(38), 41(31). Catalytic reduction of V over Raney-Ni in MeOH at room temperature gave crystals (mp 112—117°) by following purification through silica gel column chromatography. The product was negative for $FeCl_3$ test and its UV spectrum was identical with those of IV. Identified with authentic deoxy-β-hydroxyneoaspergillic acid by mixed fusion.

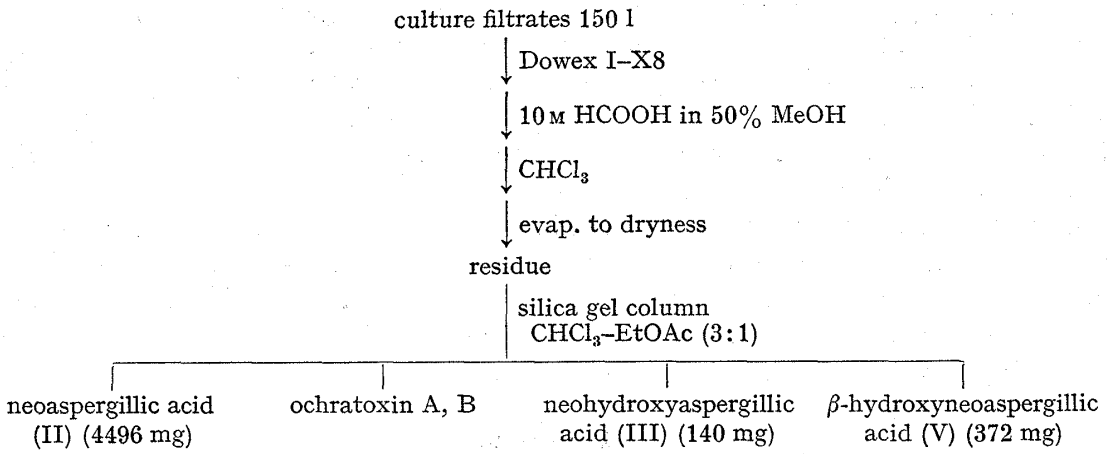

Chart 2

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Reaction of Some Halogenated Aromatic N-Heterocycles with Hexamethylphosphoric Triamide

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Some halogenated pyrazines, pyridines, and quinolines were heated with hexamethylphosphoric triamide at 200° to yield the corresponding dimethylamino derivatives in a high yield.

Keywords——HMPA; halogeno N-heterocycles; pyrazine; pyridine; quinoline; dimethylamino N-heterocycles

Although hexamethylphosphoric triamide (HMPA) is one of the most widely used polar solvents, it is also applicable to dimethylamination reaction. As reported by Pedersen and his co-workers, potential substituents[2] of some benzene derivatives and 2-hydroxyl group[3]

1) Location: *1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.*
2) E.B. Pedersen, J. Perregard, and S.-O. Lawesson, *Tetrahedron*, **29**, 4211 (1973).
3) E.B. Pedersen and S.-O. Lawesson, *Tetrahedron*, **30**, 875 (1974).

of 2-hydroxyquinolines can be converted to dimethylamino group by heating with HMPA. The present investigation was undertaken to prepare some dimethylaminopyrazines, starting from chloropyrazines which are readily obtained from the corresponding pyrazine N-oxides or diketopiperazines.

A mixture of 2-chloro-5,6-diphenylpyrazine and HMPA was heated at 200° for 1 hr and the reaction product was purified by column chromatography to give 2-dimethylamino-5, 6-diphenylpyrazine in a high yield. This reaction was carried out also at 170° to afford the same product in a good yield, but the starting material was completely recovered by the reaction at 100°. On the basis of this result, reactions of some monochloro- and dichloropyrazines were carried out by heating with HMPA at 200° and the corresponding dimethylaminopyrazines were obtained in a good yield. Results of these reactions are shown in Table I.

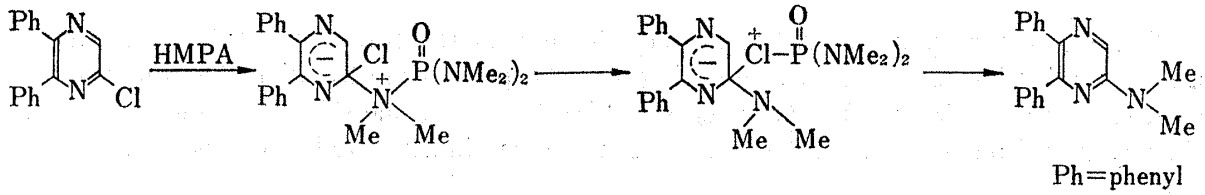

Chart 1

Table I. Reaction of Monochloro- and Dichloro-pyrazines with HMPA

Chloropyrazines	Reaction time (hr)	DMA-pyrazines	Yield (%)
2-Cl-3,6-diethyl-[a]	3	2-DMA-3,6-diethyl-	37
2-Cl-3,6-diisobutyl-[b]	4	2-DMA-3,6-diisobutyl-	43
2,5-DiCl-3,6-dipropyl-[c]	2	2-Cl-5-DMA-3,6-dipropyl-	81
2,5-DiCl-3,6-diisopropyl-[d]	3	2-Cl-5-DMA-3,6-diisopropyl-	63
2,5-DiCl-3,6-diisobutyl-[b]	2	2-Cl-5-DMA-3,6-diisobutyl-	81
2-Cl-5-phenyl-[e]	1	2-DMA-5-phenyl-	64
2-Cl-3,5-diphenyl-[f]	2	2-DMA-3,5-diphenyl-	71
2-Cl-3,6-diphenyl-[f]	2	2-DMA-3,6-diphenyl-	98
2-Cl-5,6-diphenyl-[g]	1	2-DMA-5,6-diphenyl-	95
2,6-DiCl-3,5-diphenyl-[h]	3	2,6-Bis-DMA-3,5-diphenyl-	64

DMA=dimethylamino.

a) Colorless oil, bp 96—100°/10 Torr. Prepared from α-aminobutyric acid anhydride by treatment with a mixture of phosphorylchloride and phosphorous pentachloride.
b) A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **16**, 1160 (1968).
c) Colorless prisms (MeOH), mp 34°, bp 103—105°/7 Torr. Prepared from DL-norvaline anhydride by the same manner as described in (a).
d) Colorless prisms (MeOH), mp 52—53°. Prepared from DL-valine anhydride as described before.
e) S. Sugiura, S. Inoue, T. Kishi, and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969).
f) P.J. Lont and H.C. Van Der Plas, *Rec. Trav. Chim. Pays-Bas*, **92**, 449 (1973).
g) J.K. Landquist, *J. Chem. Soc.*, **1956**, 1885.
h) A. Ohta, *et al.*, Abstracts of Papers, 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974, II, p. 145.

Some halogenated pyridines and quinolines were also submitted to this reaction under the same condition. As shown in Table II, halogens at 2- and 4-positions of pyridine and quinoline rings were converted smoothly into dimethylamino group in a high yield. In contrast, the reaction did not progress at all in the case of 3-bromopyridine and 3-bromoquinoline. This reaction seemed to be a nucleophilic substitution by the dimethylamino group[2] and this result might lend support to this hypothesis.

Table II. Reaction of Halogenated Pyridines and Quinolines with HMPA

Compound	Reaction time (hr)	Product	Yield (%)
2-Br-pyridine[a]	2	2-DMA-pyridine[6]	85
3-Br-pyridine[a]	2	recovered	
2-Cl-quinoline[a]	1	2-DMA-quinoline[5]	45
3-Br-quinoline[b]	1	recovered	
4-Cl-quinoline[c]	2	4-DMA-quinoline[4]	72
2,4-DiCl-quinoline[d]	3	2,4-Bis-DMA-quinoline[7]	69

DMA=dimethylamino.
a) Commercially obtained.
b) R.H. Baker, C.J. Albisetti, Jr., R.M. Dodson, G.R. Lappin, and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1532 (1946).
c) M. Hamana, *Yakugaku Zasshi*, **71**, 263 (1951).
d) A. Bayer and F. Bloem, *Chem. Ber.*, **15**, 2147 (1882).

Some of dimethylamino N-heterocycles have hitherto been prepared by heating halogenated quinolines with dimethylamine in a sealed tube,[4] by methylation of aminopyridines,[5] or through the Tschitschibabin type reaction.[6,7] However, one might conclude that HMPA is highly useful reagent for dimethylamination of some halogenated N-heterocycles.

Experimental[8]

All experiments were carried out at 200° and worked up in the same manner. The reaction of 2-chloro-5,6-diphenylpyrazine will be described as an example.

Reaction of 2-Chloro-5,6-diphenylpyrazine with HMPA——A mixture of 100 mg (0.37 mmol) of 2-chloro-5,6-diphenylpyrazine and 0.5 ml of HMPA was heated at 200° (bath temp.) for 1 hr in a flask equipped with an air condenser. When cooled, the reaction mixture was diluted with a small amount of H_2O and extracted several times with ether. The ether layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on 3 g of Wakogel C-200 and the column was developed with a mixture of hexane and benzene to give 98 mg (95%) of 2-dimethylamino-5,6-diphenylpyrazine, which was recrystallized from MeOH to give colorless prisms, mp 133°. *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.22. Found: C, 78.57; H, 6.09; N, 15.31. MS *m/e*: 275 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 228 (4.23), 295 (4.24), 364 (3.94). NMR ($CDCl_3$) δ: 3.20 (6H, s).

2-Dimethylamino-3,6-diethylpyrazine——Colorless oil of bp 100—102°/8 Torr (bath temp.). *Anal.* Calcd. for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 66.89; H, 9.70; N, 23.97. MS *m/e*: 179 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 257.5 (3.87), 285 (3.51), 327 (3.72). NMR ($CDCl_3$) δ: 2.82 (6H, s).

2-Dimethylamino-3,6-diisobutylpyrazine——Pale yellow oil of bp 150°/20 Torr (bath temp.). *Anal.* Calcd. for $C_{14}H_{25}N_3$: C, 71.44; H, 10.71; N, 17.85. Found: C, 71.41; H, 10.91; N, 17.76. MS *m/e*: 235 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 258 (3.85), 327.5 (3.73). NMR ($CDCl_3$) δ: 2.84 (6H, s).

2-Chloro-5-dimethylamino-3,6-dipropylpyrazine——Pale yellow oil of bp 160°/10 Torr (bath temp.). *Anal.* Calcd. for $C_{12}H_{20}N_3Cl$: C, 59.61; H, 8.34; N, 17.38. Found: C, 59.72; H, 8.42; N, 17.09. MS *m/e*: 241 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 262 (3.97), 333 (3.75). NMR ($CDCl_3$) δ: 2.84 (6H, s).

2-Chloro-5-dimethylamino-3,6-diisopropylpyrazine——Colorless oil of bp 150°/10 Torr (bath temp.). *Anal.* Calcd. for $C_{12}H_{20}N_3Cl$: C, 59.61; H, 8.34; N, 17.38. Found: C, 59.34; H, 8.30; N, 17.47. MS *m/e*: 241 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 260.5 (3.94), 330 (3.73). NMR ($CDCl_3$) δ: 2.80 (6H, s).

2-Chloro-5-dimethylamino-3,6-diisobutylpyrazine——Pale yellow oil of bp 145°/5 Torr (bath temp.). *Anal.* Calcd. for $C_{14}H_{24}N_3Cl$: C, 62.32; H, 8.97; N, 15.57. Found: C, 62.61; H, 9.27; N, 15.44. MS *m/e*: 269 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 263.5 (4.00), 336 (3.76). NMR ($CDCl_3$) δ: 2.82 (6H, s).

4) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 42 (1964).
5) H. Gilman, N.N. Crounse, S.P. Massie, Jr., R.A. Benkeser, and S.M. Spatz, *J. Am. Chem. Soc.*, **67**, 2106 (1945).
6) A.E. Tschitschibabin and I.L. Knunianz, *Ber.*, **61**, 427 (1928).
7) S. Fatulla, M. Mauro, and C. Pasin, *Ric. Sci, Part 2, Sez. A*, **8**, 736 (1965).
8) All melting and boiling points are uncorrected. NMR spectra were taken with JEOL JNM-PS-100, using tetramethylsilane as an internal standard, and mass spectra were measured with Hitachi RMU-7L spectrometer.

2-Dimethylamino-5-phenylpyrazine——Pale yellow needles of mp 96—98° (MeOH). *Anal.* Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.30; H, 6.57; N, 21.27. MS *m/e*: 199 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 223 (3.95), 293 (4.35), 362 (3.90). NMR ($CDCl_3$) δ: 3.20 (6H, s).

2-Dimethylamino-3,5-diphenylpyrazine——Pale yellow needles of mp 95—96° (MeOH). *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.41; 6.31; N, 15.40. MS *m/e*: 275 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 231 (4.21), 309 (4.22), 368.5 (3.96). NMR ($CDCl_3$) δ: 2.82 (6H, s).

2-Dimethylamino-3,6-diphenylpyrazine——Yellow prisms of mp 79° (EtOH–H_2O). *Anal.* Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.67; H, 6.20; N, 15.18. MS *m/e*: 275 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 235.5 (4.26), 270 (4.18), 372.5 (4.07). NMR ($CDCl_3$) δ: 2.84 (6H, s).

2,6-Bis-dimethylamino-3,5-diphenylpyrazine——Pale yellow prisms of mp 160° (MeOH). *Anal.* Calcd. for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.24; H, 7.05; N, 17.77. MS *m/e*: 318 (M^+). UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 242 (4.25), 331.5 (4.07), 381 (4.20). NMR ($CDCl_3$) δ: 2.83 (6H, s).

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On the Relationship between C-13 Nuclear Magnetic Resonance Chemical Shift and Stability of Molecule in Methyl-Substituted N,N-Dimethylpiperidinium Salts[1]

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Among positional and conformational isomers of mono- and di-methyl derivatives of N,N-dimethylpiperidinium ions, a linear relationship was found between the sum of C-13 nuclear magnetic resonance chemical shifts of all the constituent carbons of molecule and the total energy of molecule calculated by MINDO/2 method.

Keywords——methylpiperidinium salts; total C-13 chemical shift; total energy; MINDO/2; conformation

Attention has recently been paid to the correlation of the C-13 NMR chemical shifts of all the carbons constituting the molecule (total chemical shift, $\sum_n \delta_n$) with the conformational stability of molecule.[3–7] Although a linear relationship has been found in some classes of compounds such as methylcyclohexanes,[3] cyclohexanols,[4,5] and chain alkanes,[6] its applicability to stereochemical problems has not fully been demonstrated. This paper shows the correlation between the total chemical shift and the configurational and/or conformational

1) This paper constituents Part VII of a series entitled "Stereochemistry in Solution." Part V: M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **18**, 2499 (1970). Part VI: *idem*, *ibid.*, **22**, 809 (1974).

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3) A.S. Perlin and H.J. Koch, *Canad. J. Chem.*, **48**, 2639 (1970).

4) A.S. Perlin, B. Casu, and H.J. Koch, *Canad. J. Chem.*, **48**, 2597 (1970).

5) A.S. Perline, *Canad. J. Chem.*, **49**, 1972 (1971).

6) K. Okada, I. Morishima, and T. Yonezawa, Read at the 10th NMR symposium in Tokyo, 1970.

7) M. Tsuda, *Farumashia*, **9**, 756 (1973).