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Investigation on the Reaction of Benzazolium Salts with Base[1]

Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima,
and Hisao Sato

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

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N-Methylbenzoxazolium, N-methylbenzothiazolium, and benzimidazolium salts were reacted with triethylamine, potassium *t*-butoxide or dimsyl sodium to give corresponding ketospiran derivatives. Several other products were also characterized and possible mechanisms of these reactions were discussed briefly.

The reaction of thiamine with diethyl benzoylphosphonate in the presence of triethylamine giving 1,4-thiazine derivative was previously reported.[3] This reaction was also manifested by 3,4-dimethylthiazolium,[4] 3-methylbenzothiazolium[4] and 1,3,4-thiadiazolium[5] salts. The present paper deals with the investigation of the behaviors of benzoxazolium, benzothiazolium, and benzimidazolium salts toward triethylamine.

N-Methylbenzoxazolium iodide (Ia) was added 2 mole equivalents of triethylamine in N, N-dimethylformamide (DMF) and allowed to stand overnight to give the crystals of mp 167—168°. This product, $C_{16}H_{14}O_3N_2$, was determined to have the structure as spiro[N-methylbenzoxazoline]-2,2'-[2',3'-dihydro-4'-methyl-3'-oxo-4'H-benz-1',4'-oxazine] (IIa) on the basis of the spectral data. Ultraviolet (UV) spectrum of IIa showed absorption maxima at 242 and 287 mμ, infrared (IR) spectrum exhibited C=O band at 1694 cm^{-1}, and nuclear magnetic resonance (NMR)[6] spectrum showed signals due to N-methyl groups at τ 6.90 and 6.52, and aromatic multiplet (8H) at τ 2.7—3.5. Recently, Wanzlick, *et al.*[7] reported similar reaction giving oxacyanine derivative from three moles of Ia. Their results were produced by different condition.

Ketospiran formation of benzoxazolium salt by the treatment with triethylamine prompted us to investigate the reaction of benzothiazolium and benzimidazolium salts with triethylamine.

Treatment of N-methylbenzothiazolium iodide (Ib) with triethylamine gave ketospiran IIb accompanying by spiran VII and cyclodecane VIII in 7.6, 3, and 52.7% yield, respectively. Spiran VII was confirmed to be identical with an authentic sample synthesized by another route,[8] and cyclodecane VIII showed identical physical constants as reported by Wanzlick, *et al.*[9]

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[1] This paper constitutes Part LXIV in the Study on Pyrimidine Derivatives and Related Compounds (Part LXIII: A. Takamizawa, Y. Hamashima, H. Sato, and S. Sakai *Chem. Pharm. Bull.* (Tokyo), **17**, (1969)).

[2] Location: *Fukushima-ku, Osaka.*

[3] A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966).

[4] A. Takamizawa and H. Sato, Abstracts of Papers of 24th Meeting of the Pharmaceutical Society of Japan, 1967, p.397.

[5] A. Takamizawa and H. Sato, Abstracts of Papers of the 88th Annual Meeting of the Pharmaceutical Society of Japan, 1968, p. 119.

[6] NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ or d_6-DMSO containing TMS as an internal reference. Chemical shifts are presented in a τ value.

[7] H.-W. Wanzlick and H. Steinmans, *Chem. Ber.*, **101**, 244 (1968).

[8] J.J. Vorsanger, *Bull. Soc. Chim. France*, **1964**, 119.

[9] H.-W. Wanzlick, H.-J. Kleiver, and I. Lasch, *Ann.*, **708**, 155 (1967).

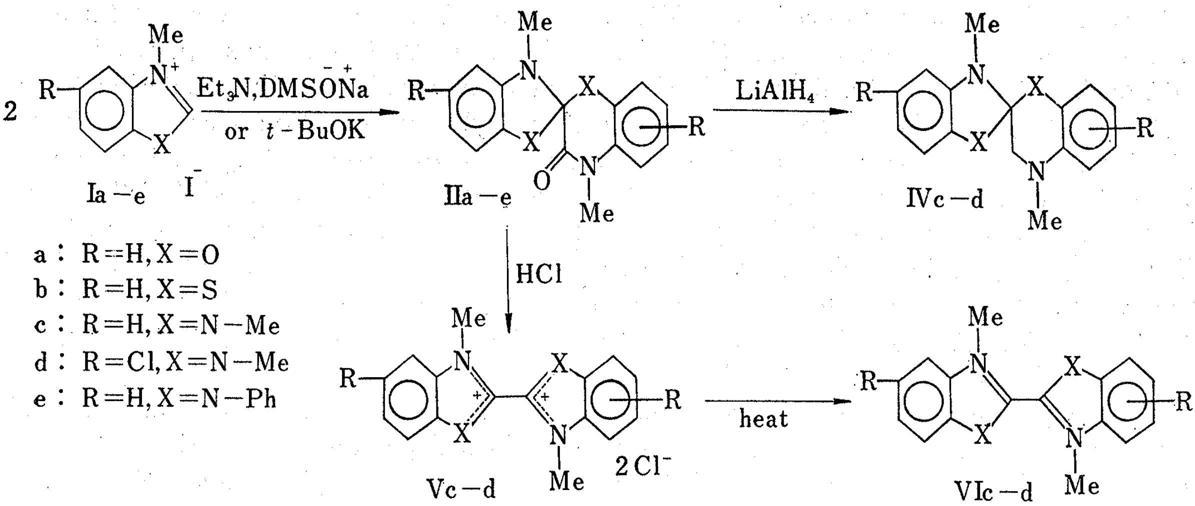

Chart 1

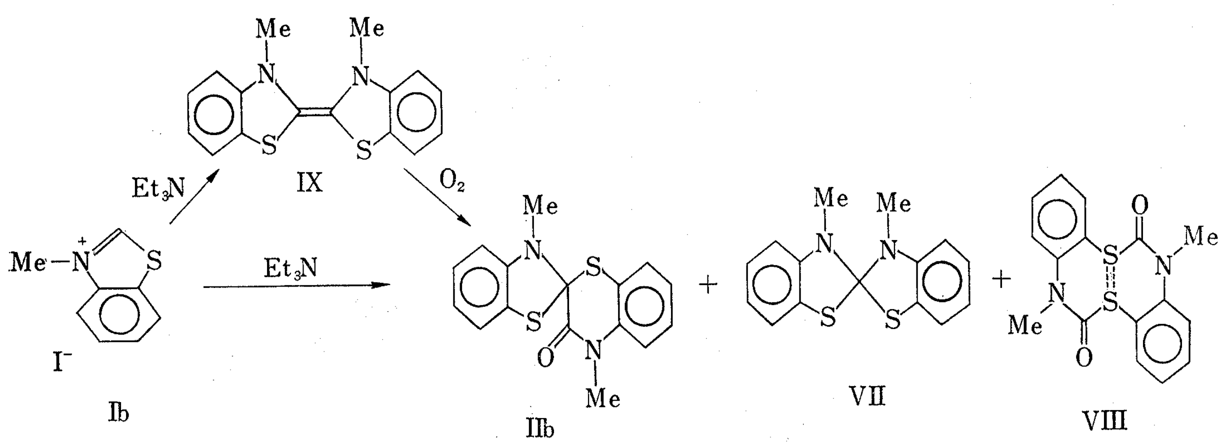

Chart 2

The structure of IIb, $C_{10}H_{14}ON_2S_2$, was confirmed to be spiro [N-methylbenzothiazoline]-2,2′-[2′,3′-dihydro-4′-methyl-3′-oxo-4′H-benzo-1′,4′-thiazine] on the basis of the spectral data. IR spectrum of IIb showed C=O band at 1673 cm^{-1}, and NMR spectrum exhibited N-methyl signals at τ 6.87 and 6.47 and aromatic multiplet (8H) at τ 2.6—3.5.

Dimer IX was obtained from Ib by the treatment with triethylamine under N_2 stream, and ice-cooling. Wanzlick, *et al.*[9] reported that only cyclodecane VIII was obtained from IX by air oxidation. However, we obtained IIb and VII in addition to VIII. These facts suggested the participation of dimer IX in the formation of IIb from Ib. Further treatment of cyclodecane VIII with triethylamine failed to give IIb and recovered starting material dennying the course *via* VIII as intermediate.

Treatment of benzimidazolium salts (Ic, d, e) with strong base dimsyl sodium or potassium *t*-butoxide gave ketospiran IIc, d, e accompanied by benzimidazolone IIIc, d, e. The structures of IIc, d, e were confirmed by elemental analyses, molecular weight determinations,[10] and spectral data. IIc, d, e showed UV maxima at about 230 and 310 mμ, and IR absorption bands due to C=O groups at 1660—1675 cm^{-1}. NMR signals due to N-methyl or N-phenyl groups and aromatic protons also supported these structures. Benzimidazolones IIIc, d was confirmed to be identical with authentic samples prepared by other routes.[11]

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10) Molecular weights were determined by Vapor Pressure Osmometer Model 301A, Michrohlab Inc.
11) *a*) H. Wahl, *Compt. Rend.*, **241**, 1949 (1955): *b*) R.L. Clark and A.A. Pessolano, *J. Am. Chem. Soc.*, **80**, 1657 (1958).

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Ketospirans IIc, d were reduced by $LiAlH_4$ to spirane IVc, d in good yields. IR spectra of IVc, d showed no C=O bands and NMR signals due to methylene groups appeared at about τ 6.78. Treatment of IIc, d with EtOH–HCl gave bis-benzimidazolium chloride Vc, d as pentahydrates, and NMR signals due to four N-methyl groups of Vc appeared as singlet at τ 5.71 and no signal was appeared at low field besides aromatic protons on benzene rings. Elemental analyses and molecular weight determination also supported "bis" structure. On heating of Vc, d above melting points, products VIc, d were obtained quantitatively. Elemental analyses and molecular weight determinations showed the loss of 2 moles of CH_3Cl from Vc, d. NMR signals due to two N-methyl groups appeared as slightly splitting doublet at 5.70 and 5.69 (VIc) or singlet at τ 5.69 (VId). These facts showed that VIc, d had bis-imidazole structures.

The mechanisms of these reactions might be explained as shown in Chart 3.[9] Peroxides were derived from dimers and the electron migrations depending on the ring hetero atoms and substituting groups occurred in different ways to give ketospirans and other products.

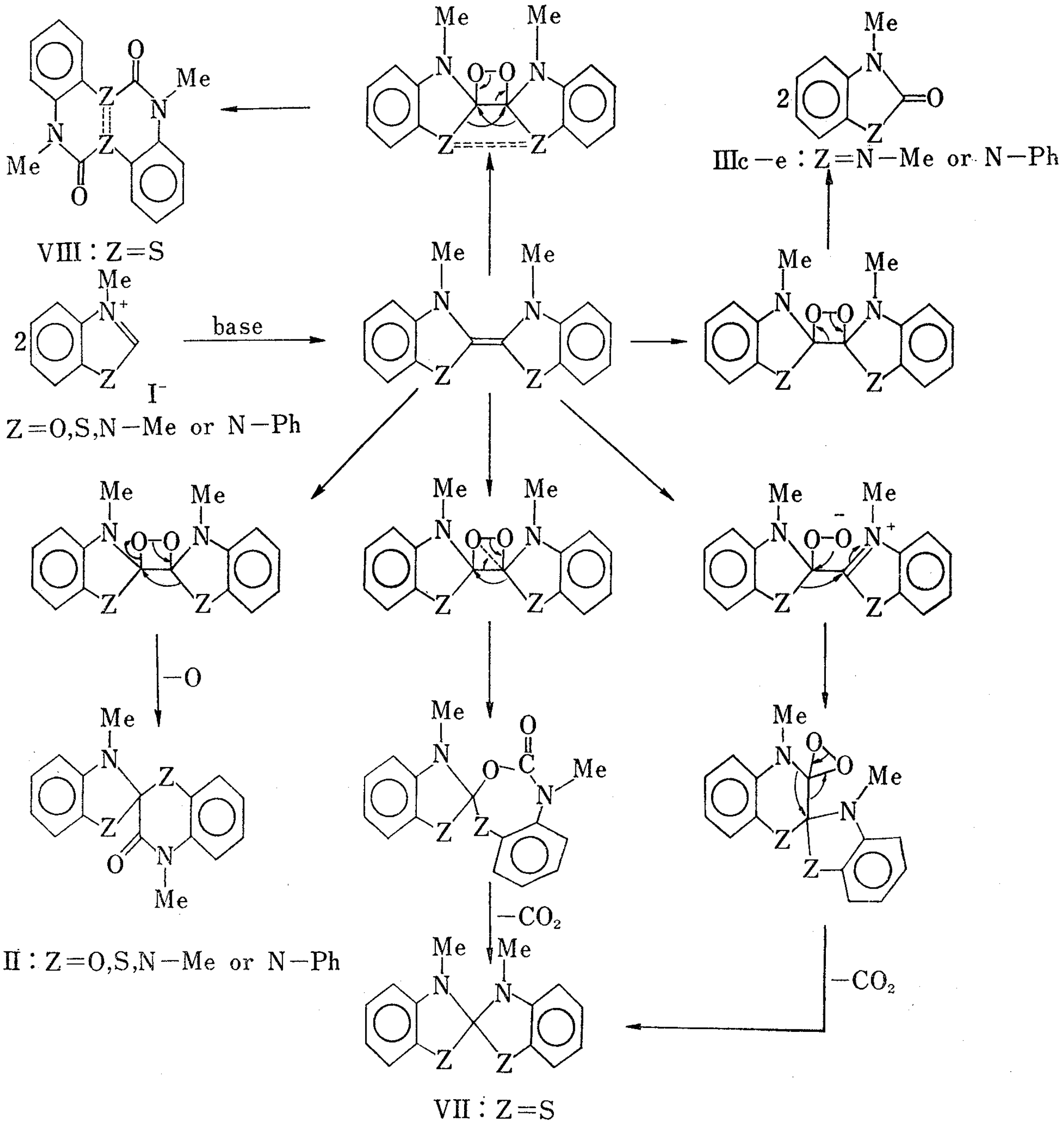

Chart 3

Experimental[12]

Spiro[N-methylbenzoxazoline]-2,2′-[2′,3′-dihydro-4′-methyl-3′-oxo-4′H-benz-1′4′-oxazine] (IIa)——To a suspension of 1.0 g (3.83 mmole) of N-methylbenzoxazolium iodide (Ia) in 5 ml of anhydrous DMF, 0.7 g (6.93 mmole) of triethylamine was added dropwise with stirring under ice-cooling. After stirring for 0.5 hr, reaction mixture was allowed to stand overnight at room temperature, and evaporated *in vacuo* to remove DMF below 50°. The residue was extracted with $CHCl_3$ and the extract was washed with 10% NaOH and H_2O successively. After drying over anhydrous Na_2SO_4, $CHCl_3$ was removed and the residue was treated with a mixture of MeOH and ligroin to give 0.113 g of IIa as pale yellow crystals, mp 150—160°. Recrystallization from MeOH gave colorless prisms, mp 167—168°. The filtrate of the crude crystals was subjected to column chromatography on Al_2O_3 with AcOEt to give 0.043 g of IIa, mp 155—160°. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.07; H, 5.00; O, 17.00; N, 9.92; M.W. 282.3. Found: C, 68.01; H, 4.99; O, 16.92; N, 10.03; M.W. ($CHCl_3$) 288. UV λ_{max}^{EtOH} mμ (log ε): 242 (4.18), 287 (4.02). IR λ_{max}^{Nujol} cm^{-1}: 1694 (C=O). NMR ($CDCl_3$) τ: 6.90^s (Me), 6.52^s (Me) $2.7—3.5^m$ (aromatic 8H).

Treatment of N-Methylbenzothiazolium Iodide (Ib) with Triethylamine——To a suspension of 3.1 g (11.18 mmole) of Ib in 20 ml of anhyd. DMF, 2.3 g (22.4 mmole) of triethylamine (dried over sodium wire) was added dropwise at 0—2° during 0.5 hr, stirred for 1 hr at 0—1°, and allowed to stand overnight at room temperature. DMF was removed *in vacuo* below 43°, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was subjected to column chromatography on Al_2O_3 (240 g) with benzene. First fraction gave 0.048 mg (3.0%) of colorless crystals, mp 208—205°. IR spectrum showed to be identical with an authentic sample of VII.[8] Second fraction gave 0.136 mg (7.75%) of spiro[N-methylbenzothiazoline]-2,2′-[2′,3′-dihydro-4′-methyl-3′-oxo-4′H-benzo-1,4′-thiazine] (IIb) as colorless crystals of mp 150—152°. Recrystallization from acetone gave colorless sticks, mp 154—156°. *Anal.* Calcd. for $C_{16}H_{14}ON_2S_2$: C, 61,.14; H, 4.49; N, 8.91; S, 20.35; M.W. 314.3. Found: C, 60.98; H, 4.44; N, 8.91; S, 20.46; M.W. 313 (in $CHCl_3$). UV λ_{max}^{EtOH}: 224, 307 mμ. IR λ_{max}^{Nujol}: 1673 cm^{-1} (C=O). NMR ($CDCl_3$) τ: 6.87^s (Me), 6.47^s (Me), $2.6—3.5^m$ (aromatic 8H). Third fraction gave 0.973 g (52.7%) of VIII[9] as colorless crystals of mp 205—213°. Recrystallization from acetone gave colorless sticks, mp 212—213°. *Anal.* Calcd. for $C_{16}H_{14}O_2N_2S_2$: C, 58.18; H, 4.27; O, 9.68; N, 8.48; S, 19.39; M.W. 330.3. Found: C, 58.47; H, 4.45; O, 9.29; N, 8.54; S, 19.52; M.W. (in $CHCl_3$) 326. IR λ_{max}^{Nujol}: 1657, 1647 cm^{-1} (C=O). NMR ($CDCl_3$) τ: 6.97^s (Me×2), $2.2—2.8^m$ (aromatic 8H).

Air Oxidation of IX——A suspension of 1.43 g (4.8 mmole) of IX and 0.5 g of Norit in 200 ml of acetone was refluxed for 4 hr under introducing dry air. After filtration, the filtrate was concentrated *in vacuo* and the residue was subjected to Al_2O_3 column chromatography with benzene to give 0.037 g (2.7%) of VII, 0.271 g (18.0%) of IIb, and 0.53 g (33.5%) of VIII.

Spiro[1,3-dimethylbenzimidazoline]-2,2′-[1′,4′-dimethyl-3′-oxo-1′,2′,3′,4′-tetrahydroquinoxaline] (IIc)——To a solution of dimsyl sodium prepared from 0.511 g of NaH (47% oil suspension) in 40 ml of dimethyl sulfoxide (DMSO), 2.74 g of 1,3-dimethylbenzimidazolium iodide (Ic) was added and stirred for 2 hr at room temp. After standing overnight, DMSO was removed *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was washed with H_2O and evaporated. Al_2O_3 column chromatograhy of the residue with $CHCl_3$ gave 0.035 g (2.5%) of IIc. Recrystallization from ether–acetone gave crystals of mp 172—174°. *Anal.* Calcd. for $C_{18}H_{20}ON_4$: C, 70.10; H, 6.54; O, 5.19; N, 18.17. Found: C, 70.19; H, 6.46; O, 5.32; N, 17.79. UV λ_{max}^{EtOH}: 229, 309 mμ. IR λ_{max}^{Nujol}: 1660 cm^{-1} (C=O) NMR ($CDCl_3$) τ: 7.39^s (Me×2); 7.13^s (Me); 6.52^s (Me), $2.84—3.82^m$ (aromatic 8H).

Following fraction gave 0.37 g (22.8%) of IIIc. IR spectrum showed to be identical with an authentic sample.[11a]

Spiro[1,3-dimethyl-5-chlorobenzimidazoline]-2,2′-[1′,4′-dimethyl-3′-oxo-6′ (or 7′)-chloro-1′,2′,3,4′-tetrahydroquinoxaline] (IId)——1,3-Dimethyl-5-chlorobenzoimidazolium iodide (Id) (1.54 g) was added to dimsyl sodium solution prepared from 0.256 g of NaH (47% oil suspension) and 20 ml of DMSO and treated as above. First fraction of Al_2O_3 column chromatography ($CHCl_3$) gave 0.21 g (20.5%) of IId as colorless rhombs, mp 177—178° (from acetone-ether). *Anal.* Calcd. for $C_{18}H_{18}ON_4Cl_2$: C, 57.30; H, 4.81; O, 4.24; N, 14.85; Cl, 18.50; M.W. 377.27. Found: C, 57.36; H, 4.89; O, 4.42; N, 14.93; Cl, 18.61; M.W. 393 (acetone). IR λ_{max}^{EtOH}: 232, 316 mμ. IR λ_{max}^{Nujol}: 1663 cm^{-1} (C=O). NMR ($CDCl_3$) τ: 7.38^s (Me×2), 7.12^s (Me), 6.53^s (Me), $3.05—4.00^m$ (aromatic 6H).

Following fraction gave 0.098 g (10%) of IIId. IR spectrum showed to be identical with an authentic sample.[8b]

Spiro[1-methyl-3-phenylbenzimidazoline]-2,2′-[1′-phenyl-4′-methyl-3′-oxo-1′,2′,3′,4′-tetrahydroquinoxaline] (IIe)——1-Methyl-3-phenylbenzimidazolium iodide (Ie) (3.36 g) was added below 15° to dimsyl sodium solution prepared from 0.437 g of NaH (47% oil suspension) and 20 ml of DMSO, and stirred for 6 hr at room temperature. After evaporation, the residue was extracted with $CHCl_3$. The extract was washed with H_2O,

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[12] All melting points are uncorrected.

dried over anhyd. Na_2SO_4, and evaporated to give 2.5 g of oil. Al_2O_3 column chromatography of this oil gave 0.21 g of IIe. Recrystallization from ether gave colorless needles, mp 131—134°. *Anal.* Calcd. for $C_{28}H_{24}ON_4$: C, 77.75; H, 5.59; O, 3.70; N, 12.96. Found: C, 77.68; H, 5.68; O, 3.86; N, 12.67. UV λ_{max}^{EtOH}: 230, 313 mμ. IR λ_{max}^{Nujol}: 1675 cm^{-1} (C=O). NMR ($CDCl_3$) τ: 7.30^s (Me), 6.82^s (Me), 2.97^s (Ph), $2.25—3.90^m$ (Ph and aromatic 8H).

Following fraction gave 1-methyl-3-phenylbenzimidazoline (IIIe). Recrystallization from ether gave colorless rhombs, mp 127—129°. *Anal.* Calcd. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.38; O, 7.14; N, 12.49. Found: C, 75.00; H, 5.43; O, 7.27; N, 12.53. IR λ_{max}^{Nujol}: 1700 cm^{-1} (C=O). NMR ($CDCl_3$) τ: 6.52^s (Me), $2.35—3.0^m$ (aromatic 9H).

Spiro[1,3-dimethylbenzimidazoline]-2,2′-[1′,4′-dimethyl-1′,2′,3′,4′-tetrahydroquinoxaline] (IVc)——To a suspension of 0.02 g of $LiAlH_4$ in 10 ml of abs. ether, a solution of 0.103 g of IIc in 10 ml of abs. ether was added dropwise with stirring under cooling. After refluxing for 6 hr, sat. NH_4Cl was added and ether layer was evaporated *in vacuo*. The residue was recrystallized from ether to give 0.064 g of colorless rhombs, mp 163—164°. *Anal.* Calcd. for $C_{18}H_{22}N_4$: C, 73.43; H, 7.53; N, 19.03; M.W. 294.39. Found: C, 73.75; H, 7.40; N, 19.23; M.W. 301 ($CHCl_3$). UV λ_{max}^{EtOH}: 227, 266, 311 mμ. NMR ($CDCl_3$) τ: 7.48^s (Me), 7.25^s (Me $\times$ 3), 6.78^s (CH_2), $3.3—4.0^m$ (aromatic 8H).

Spiro[1,3-dimethylbenzimidazoline]-2,2′-[1′,4′-dimethyl-6′ (or 7′)-chloro-1′,2′,-3′,4′-tetrahydroquinoxaline] (IVd)——Treatment as above from 0.126 g of IId and 0.02 g of $LiAlH_4$, 0.07 g of light brown oil was obtained which crystallized slowly and recrystallized from ether–*n*-hexane to give colorless rhombs, mp 117°. *Anal.* Calcd. for $C_{18}H_{20}N_4Cl_2$: C, 59.47; H, 5.55; N, 15.42. Found: C, 59.65; H, 5.62; N, 15.37. UV λ_{max}^{EtOH}: 231, 274, 320 mμ. NMR ($CDCl_3$) τ: 7.47^s (Me), 7.22, 7.20 (Me $\times$ 3), 6.76^s (CH_2), $3.2—4.0^m$ (aromatic 6H).

Bis-1,3-dimethylbenzimidazolium Chloride (Vc)——A solution of 0.1 g of IIc in EtOH·HCl was allowed to stand overnight at room temperature. After evaporation, the residue (0.12 g) was recrystallized from acetone–MeOH to give colorless sticks, mp 260° (decomp.). *Anal.* Calcd. for $C_{18}H_{20}N_4Cl_2 \cdot 5H_2O$: C, 47.75; H, 6.67; N, 12.38; Cl, 15.64. Found: C, 47.99; H, 6.61; N, 12.55; Cl, 16.81. NMR (d_6-DMSO) τ: 6.28^s (H_2O, 10H), 5.71^s (Me $\times$ 4), $1.57—2.13^m$ (aromatic 8H).

Bis-1,3-dimethyl-5-chlorobenzimidazolium Chloride (Vd)——IId (0.09 g) was treated as above to give 0.115 g of colorless crysts, mp 240° (decomp.) (from MeOH–acetone). *Anal.* Calcd. for $C_{18}H_{18}N_4Cl_2 \cdot 5H_2O$: C, 41.45; H, 5.41; O, 15.32; N, 10.72; Cl, 27.18. Found: C, 40.64; H, 5.33; O, 15.07; N, 10.68; Cl, 29.85. NMR (d_6-DMSO) τ: 6.62^s (H_2O, 10H), 5.71, 5.70 (Me $\times$ 4), $1.3—2.2^m$ (aromatic 6H).

Bis-1-methylbenzimidazole (VIc)——Vc (0.075 g) was heated in an oil bath above melting point. After cooling, separated crystals (0.04 g) was recrystallized from acetone to give light brown needles, mp 210—211°. *Anal.* Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36; M.W. 262.30. Found: C, 73.15; H, 5.40; N, 21.22; M.W. 266 ($CHCl_3$). UV λ_{max}^{EtOH}: 236, 316 mμ. NMR ($CDCl_3$) τ: 5.70, 5.69 (Me $\times$ 2), $2.17—2.75^m$ (aromatic 8H).

Bis-1-methyl-5-chlorobenzimidazole (VId)——Vd (0.03 g) was treated as above to give 0.019 g of colorless rhombs, mp 227—233° (decomp.) (from acetone). *Anal.* Calcd. for $C_{16}H_{12}N_4Cl_2$: C, 58.01; H, 3.65; N, 16.92; Cl, 21.41; M.W. 331.22. Found: C, 57.99; H, 3.71; N, 16.67; Cl, 21.31; M.W. 329 ($CHCl_3$). UV λ_{max}^{EtOH}: 238, 328 sh, 334 mμ. NMR ($CDCl_3$) τ: 5.69^s (Me $\times$ 2), $2.03—2.75^m$ (aromatic 6H).

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