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Norbornadiene-Fused Heterocycles: Synthesis and Bromination Reaction of 5,8-Dihydro-5,8-methanoquinoxaline Derivatives

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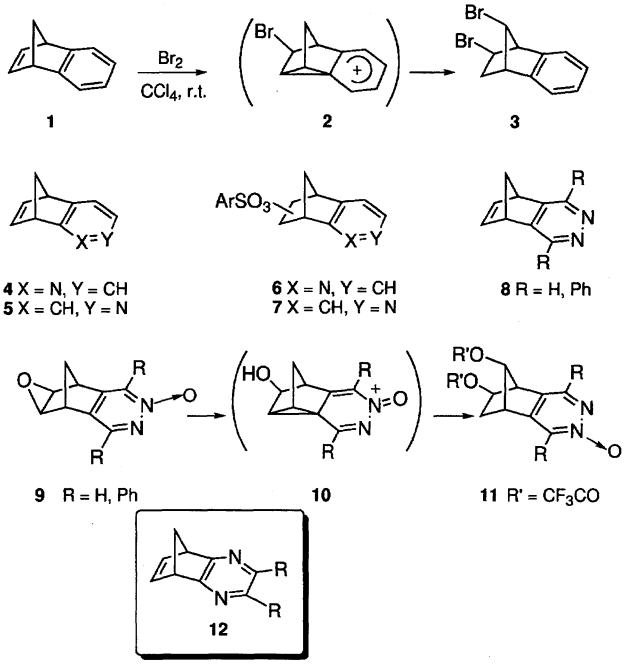
A norbornadiene-fused pyrazine was prepared by the condensation reaction of bicyclo[2.2.1]hept-5-ene-2,3-dione with ethylenediamine followed by oxidation. Treatments of the norbornadiene-fused pyrazine and its benzo derivative with bromine in carbon tetrachloride or in dioxane afforded *trans*-adducts as major products, accompanied by the formations of *cis*-adducts and dibromo derivatives derived from Wagner–Meerwein type skeletal rearrangement, while bromination of a fused dicyanopyrazine in carbon tetrachloride gave only a *trans*-adduct. In contrast, a fused pyrazine with an electron-donating *N*-oxide group gave a 7,9-dibromo derivative as the main component. The possibility of the intervention of a 2*H*-pyrazinium ion for the formation of the skeletally rearranged products is discussed together with the results of ab-initio (3-21G*) calculations.

The participation of a remote aryl group in the formation of a cationic intermediate has been recognized already.[1] As a typical example, the bromination reaction of 1,4-dihydro-1,4-methanonaphthalene (**1**) has been known to give exclusively the 6,9-dibromo derivative **3** via the benzenium ion intermediate **2** (Scheme 1).[2—5] In contrast, the ability of a neighboring six-membered heteroaromatic group to assist the formation of a carbenium ion is considered to be low due to its electron deficiency, but the intermediacy of heteroarenium ions seems to be insufficiently studied. Previously, the intervention of benzenium type ions by participation of the pyridine ring of (tosyloxyalkyl)pyridines was implied by the mass spectroscopic studies.[6] Tanida et al. investigated hydration reactions of the norbornadiene-fused pyridines **4** and **5** and solvolyses of the corresponding sulfonates **6** and **7**,[7—9] and the existence of bridged cationic intermediates incorporated with a pyridine ring was assumed on the basis of *exo* orientation of products. However, skeletal rearrangements of the fused pyridines **4** and **5** by electrophilic reactions on the olefin moiety have not been reported.

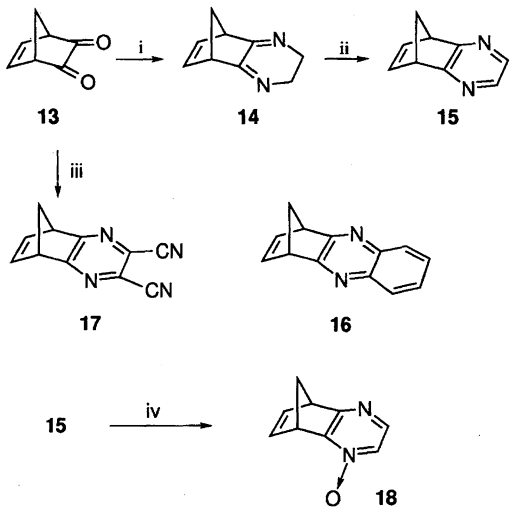


Scheme 1.

In the course of our reports concerning norbornadiene- and bicycloalkene-fused heteroaromatics,[10—15] we recently explained that the epoxide **9**, on treatment with trifluoroacetic acid, underwent a regioselective ring opening followed by Wagner-Meerwein type rearrangement to give the 6,9-bis(trifluoroacetoxy) derivative **11**; we suggested the intermediacy of the 2*H*-pyridazinium ion **10**.[14] Although this reaction is the first example of Wagner–Meerwein rearrangement for the norbornadiene-fused heteroaromatic systems, the electron-donating *N*-oxide group is considered to assist the formation of the bridged ion intermediate **10**. We attempted bromination of the fused pyridazines **8**, but this reaction provided a complex mixture, probably due to the basicity of pyridazines affording quaternary salts.[16] Pyrazine (pK_a 0.65) is known to be a considerably weak base compared with pyridazine (pK_a 2.3) and pyridine (pK_a 5.2).[17] Thus, we expected that bromination reaction of fused pyrazines **12** would afford stable bromine adducts. We wish to report here the synthesis and bromination reaction of norbornadiene-fused pyrazines **12**.

Results and Discussion

Synthesis. The most expedient synthesis of norbornadiene-fused pyrazines seems to be that by condensation reactions of an α-diketone and ethylenediamines. As expected, bicyclo[2.2.1]hept-5-ene-2,3-dione[18] (**13**) smoothly condensed with ethylenediamine to give 2,3,5,8-tetrahydro-5,8-methanoquinoxaline (**14**). The oxidation reaction of **14** with nickel peroxide was found to give the best yield (86%) of 5,8-dihydro-5,8-methanoquinoxaline (**15**), whereas the use of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), MnO_2, or Pd–C gave a lower yield of **15**. The fused dicyanopyrazine **17** was obtained in good yield by the condensation reaction of **13** with diaminomaleonitrile (Scheme 2). The fused quinoxaline **16** was prepared as described in the literature.[18] 5,8-Dihydro-5,8-methanoquinoxaline 1-oxide (**18**) was prepared by the oxidation reaction of **15** with *m*-chloroperbenzoic acid. In the ^{1}H NMR spectrum of **18**, the bridgehead proton at the 8-position appeared at $\delta = 4.45$, which is rather deshielded relative to the bridgehead proton at the 5-position ($\delta = 4.00$) and that of **15** ($\delta = 3.89$). The deshielding should be due to the anisotropic effect of the neighboring *N*-oxide group, which also deshields the proton at the 2-position.[19]

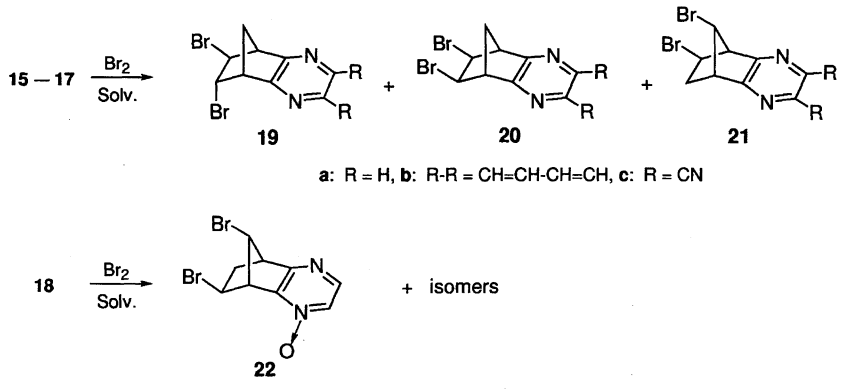


Scheme 2. Reagents and conditions: i, $NH_2CH_2CH_2NH_2$, *p*-TsOH, benzene reflux, 5 h, 60%; ii, NiO_2, benzene reflux, 4 h, 86%; iii, diaminomaleonitrile, THF room temp 3.5 h, reflux 3.5 h, 96%; iv, MCPBA, CH_2Cl_2, room temp 24 h, 77%.

Bromination Reaction. Treatment of the pyrazine **15** with bromine in CCl_4 gave a mixture of three bromine adducts: **19a**, **20a**, and **21a** in a ratio of 20 : 1 : 5 (Table 1 and Scheme 3), which was determined by integration of the ^{1}H NMR spectrum. An attempted separation of these isomers by medium pressure liquid chromatography (MPLC) with a silica gel or ODS (octadecylsilanated) silica gel column was unsuccessful. However, signals assignable to those products were extractable from the ^{1}H NMR spectrum of the mixture (see Experimental). The structures of the products were deduced from careful analysis of the ^{1}H NMR data as well as the comparison of the ^{1}H NMR data reported for bromination products of **1**.[5] For the *trans*-isomer **19a**, the stereochemical assignment for the *exo*-bromine atom at the 7-position is supported by the presence of a coupling attributable to the W-arrangement between the CHBr proton at the 7-position ($\delta = 4.00$, $^4J = 3$ Hz, 7-H_{endo}) and the methylene proton (9-H_s) *syn* to the pyrazine ring. For the *exo-cis* isomer **20a**, the presence of a coupling ($^4J = 2$ Hz) between the CHBr protons and 9-H_s, the absence of the vicinal coupling between the CHBr protons and the bridgehead protons, and the ^{1}H signals indicating the presence of C_s symmetry support the *exo-cis* orientation of the bromine atoms. For the 6,9-dibromo derivative **21a**, the relatively large geminal coupling constant (14 Hz) for the methylene protons at the 7-position compared with those reported for the bridge methylene protons of norbornene skeletons,[20] the AA′B splitting pattern for 6-H and 7-H's, and the presence of the W-coupling between 6-H and 9-H_s ($^4J = 1$ Hz) support the structure

Table 1. Bromination Reaction of Norbornadiene-Fused Pyrazines

Compd	Solvent	Products (Yield and Products ratio)		
15	CCl_4	**19a**+**20a**+**21a** (86%, 20 : 1 : 5)		
15	Dioxane	**19a**+**20a**+**21a** (88%, 19 : 1 : 11)		
16	CCl_4	**19b** (52%)	**20b**+**21b** (26%, 1 : 4)	
16	Dioxane	**19b** (27%)	**20b**+**21b** (33%, 1 : 12)	
17	CCl_4	**19c** (96%)	**20c** (0%)	**21c** (0%)
17	Dioxane	**19c** (59%)	**20c** (10%)	**21c** (0%)



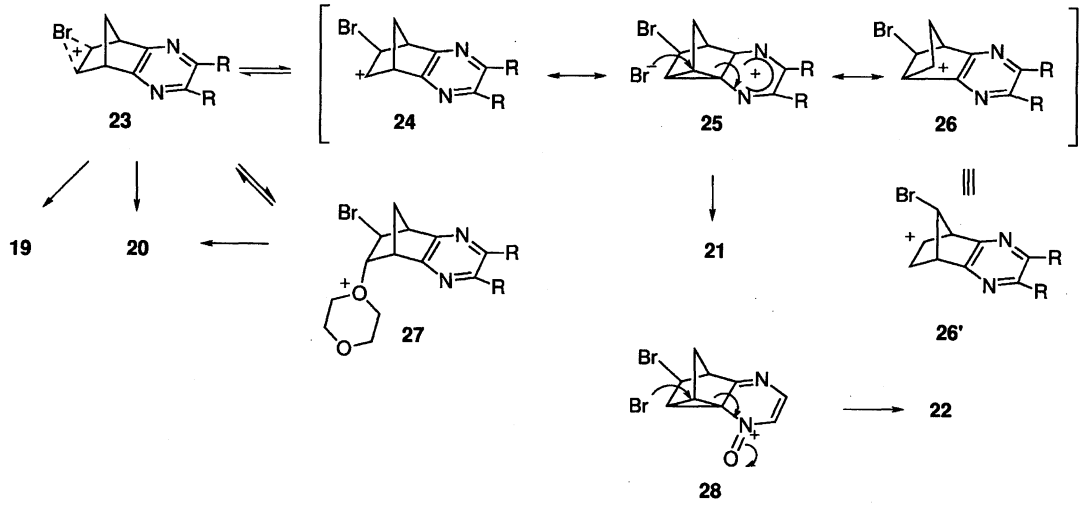
Scheme 3.

of **21a**. A similar reaction of **15** with bromine in dioxane also gave a mixture of three bromine adducts **19a**, **20a**, and **21a** in 88% yield, while the ratio of **21a** is somewhat increased, as shown in Table 1.

Treatment of the fused quinoxaline **16** with bromine in CCl_4 or in dioxane resulted in the formation of the *trans*-isomer **19b** and a mixture of the *cis*-isomer **20b** and the 2,11-dibromo derivative **21b**. The trend of products ratio seems not to be significantly changed compared with that of the bromination reactions of **15**. The ^{1}H NMR spectrum of the *trans*-isomer **19b** shows a coupling between 3-H_{endo} (δ = 4.14, ^4J=3 Hz) and 11-H_s, which supports the stereochemical assignment to be **19b**. We could not separate the mixture of **20b** and **21b** by chromatographic techniques. The ^{1}H NMR spectrum of the mixture revealed the presence of the *cis*-isomer **20b** and the rearranged product **21b**. The presence of AA′B pattern at 2-H and 3-H's clearly indicates the formation of the 2,11-dibromo derivative **21b**. On the other hand, the reaction of the dicyanopyrazine **17** with bromine in CCl_4 gave exclusively the *trans*-adduct **19c**. A similar reaction of **17** in dioxane gave the *trans*-isomer **19c** (57%) and the *cis*-isomer **20c** (17%). In these reactions, the formation of the 6,9-dibromo derivative **21c** could not be observed: Substitution of electron-withdrawing cyano groups on the pyrazine ring suppresses the formation of rearranged products.

The bromination reaction of the *N*-oxide **18** in CCl_4 gave a mixture of three bromine adducts (77%) in a ratio of 20 : 13 : 10. The mixture contained the 7,9-dibromo derivative **22** as a main component, judging from the presence of an AA′B pattern assignable to the 6-H and 7-H protons in the ^{1}H NMR spectrum. The unequivocal assignments of **22** as well as structure determinations of other isomers are unattainable due to overlapping of peaks. A similar reaction of **18** in dioxane provided a mixture of four bromine adducts (80%) in a ratio of 8 : 4 : 1 : 1, and the main component was judged also to be **22**. Careful recrystallization of the mixture twice from ethanol succeeded in the isolation of **22**. The ^{1}H NMR spectrum of **22** shows the peak assignable to 8-H (δ = 4.31), which is rather deshielded by the anisotropic effect of the *N*-oxide group compared to that of 5-H (δ = 3.70). The AA′B splitting pattern assignable to 6-H's and 7-H supports the structure of the 7,9-dibromo derivative **22**.

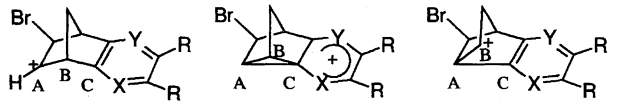
A plausible mechanism for the bromination reactions of the fused pyrazines is illustrated in Scheme 4. The formation of the *trans*-isomers **19** would be derived from the *anti* addition via the bromonium ion **23**. The *cis*-isomers **20** could be formed by direct collapse of ion pairs[21] or by the *exo* attack of a bromide ion toward the solvated intermediate **27** when dioxane was used. The skeletally rearranged products **21** would be formed by intermediacy of the cationic intermediate (**24**⟷**25**⟷**26**). Although we could not eliminate the possibility of 1,2-aryl migration from **24** to the classical cationic intermediate **26** (=**26′**), the attack of a bromide ion from the *exo* face of **26′** seems to be sterically hindered by the bulky bromo substituent. It has been reported that there is a fairly regular trend of a greater amount of *syn* addition in the more polar solvents for bromination reactions of some alkenes.[21] When dioxane was used as the solvent in the present bromination reactions, the dicyanopyrazine **17** was found to provide the *cis*-isomer **20c**, which was not formed in the reaction in carbon tetrachloride. However, in the reactions of **15** and **16** in dioxane, the ratios of the *cis*-isomers seem not to be substantially changed, but instead those of the rearranged products are somewhat increased. The results would suggest that the *anti* collapse of the bromonium ion **23** occurs at a rate competitive with a ring opening of **23** to give the cation (**24**⟷**25**⟷**26**) which would lead to *cis*-isomers and skeletally rearranged products in a ratio depending on the contribution of the bridged 2*H*-pyrazinium ion **25** to the resonance stabilization, and that the use of dioxane would forward the formation of the resonance hybrid (**24**⟷**25**⟷**26**) by the solvent effect of a polar aprotic solvent. For the bromination reaction of the *N*-oxide **18**, a contribution of the bridged cation **28** would be increased by the electron-donating *N*-oxide group, and this effect favors the regioselective formation of the 7,9-dibromo derivative



Scheme 4.

22 as the main component.

MO calculations on the three cationic species **29**, **30**, and **31** were carried out by the ab-initio (3-21G*) method (Chart 1).[22] PM3-MNDO calculations on these species afforded the optimized structures corresponding to **29**, **30**, and **31** for all the aromatic systems. Ab-initio (3-21G*) calculations were performed with the PM3-optimized structures as input geometries. The results are shown in Table 2. For the benzene-fused system, the benzenium ion **30a** was obtained as the sole structure with an energy minimum starting from every cation **29a**, **30a**, and **31a**. The atomic distances A–C and B–C are slightly longer than that of A–B, and a contribution of the resonance structures **29a** and **31a** to the bridged structure might still exist. On the other hand, the optimization on the fused pyrazine and the fused dicyanopyrazine systems gave nonbridged structures, either **29** or **31**, and no energy minimum was observed for the bridged ion structures **30b** and **30c**. In contrast, the fused pyrazine bearing *N*-oxide group gave the bridged ion structure **30d** as the only stable cation. The electron-donating *N*-oxide group seems to enhance the formation of the bridged cation, as suggested in the TFA-induced reaction of the epoxide **9**.[14]



29 **30** **31**

a: X = Y = CH, R = H; **b**: X = Y = N, R = H;
c: X = Y = N, R = CN; **d**: X = NO, Y = N, R = H

Chart 1.

In conclusion, we have shown the first example of the Wagner–Meerwein skeletal rearrangement by the electrophilic addition reactions of norbornadiene-fused heteroaromatic systems. The ratio of the skeletally rearranged products was found to be dramatically changed depending on the substituents on the pyrazine ring, probably due to their mesomeric effects. Although we don't have any concrete evidence for the intervention of a 2*H*-pyrazinium ion, the substituent effects as well as the stereoselectivity for the formation of the skeletally rearranged products would suggest the contribution of bridged 2*H*-pyrazinium ions such as **25**.

Experimental

General. All the melting points were determined with a Yanagimoto hot-stage apparatus and are uncorrected. IR spectra were obtained with a JEOL Diamond 20 spectrometer. NMR spectra were recorded either with JEOL JNM-LA300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or JEOL JNM-LA400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers. Assignments of the ^{1}H and ^{13}C signals are based on DEPT, H-H COSY, and C-H COSY measurements. Mass spectra were measured with a Shimadzu GCMS-QP1000EX spectrometer operating in the electron impact mode (70 eV). Elemental analyses were performed with a Perkin–Elmer Model 240 apparatus. MPLC separations were carried out by a Yamazen YFLC-600-10V system

Table 2. Ab-initio (3-21G*) Calculations of Cationic Intermediates

Compd	**29**	**30**	**31**
		E (total energy, au)	
a: X=Y=CH, R=H		−2980.02420	
Atomic distance (Å)			
A–B		1.435	
A–C		1.669	
B–C		1.666	
	E (au)		*E* (au)
b: X=Y=N, R=H	−3011.77983		−3011.77799
Atomic distance (Å)			
A–B	1.491		1.449
A–C	2.236		1.585
B–C	1.558		2.098
	E (au)		*E* (au)
c: X=Y=N, R=CN	−3194.17742		−3194.17294
Atomic distance (Å)			
A–B	1.536		1.568
A–C	2.339		1.503
B–C	1.535		2.542
		E (au)	
d: X=NO, Y=N, R=H		−3086.13866	
Atomic distance (Å)			
A–B		1.456	
A–C		1.606	
B–C		1.609	

with Yamazen Ultra Pack™ Columns (Si-40B or ODS-S-50B). Solvents were dried and purified by standard methods.

2,3,5,8-Tetrahydro-5,8-methanoquinoxaline (14): A solution of bicyclo[2.2.1]hept-5-ene-2,3-dione (**13**) (1.00 g, 8.2 mmol), ethylenediamine (0.58 g, 9.7 mmol), and *p*-toluenesulfonic acid (0.16 g, 0.9 mmol) in benzene (80 cm^3) was refluxed for 5 h while the produced water was removed by a Dean–Stark trap. The mixture was washed with aqueous sodium hydrogencarbonate and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was distilled under vacuum to give the tetrahydromethanoquinoxaline **14** (0.72 g, 60%) as yellow oil: Bp 195 °C (3 Torr, 1 Torr = 133.322 Pa, bath temp by Kugelrohr distillation); IR (neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.96 (1H, d, J = 9 Hz, 9-H_s), 2.33 (1H, d, J = 9 Hz, 9-H_a), 3.34—3.58 (4H, m, 2-H and 3-H), 6.37 (2H, s, 6-H and 7-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.4 (C-2 and C-3), 48.0 (C-5 and C-8), 49.5 (C-9), 136.7 (C-6 and C-7), 163.3 (C-4a and C-8a); MS *m/z* (rel intensity) 146 (M^+; 43), 119 (19), 92 (30), 66 (cyclopentadiene; 100). Found: C, 73.57; H, 6.59; N, 19.04%. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16%.

5,8-Dihydro-5,8-methanoquinoxaline (15): A mixture of the tetrahydromethanoquinoxaline **14** (0.20 g, 1.4 mmol) and nickel peroxide (1.73 g, 19.2 mmol) in benzene (30 cm^3) was refluxed for 4 h. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was distilled under vacuum to give the fused pyrazine **15** (0.17 g, 86%): Bp 150 °C (3 Torr, bath temp by Kugelrohr distillation); IR (KBr) 1581 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.54 (1H, d, J = 8 Hz, 9-H_s), 2.66 (1H, dt, J = 8 and 2 Hz, 9-H_a), 3.89 (2H, t, J = 2 Hz, 5-H and 8-H), 6.90 (2H, d, J = 2 Hz, 6-H and 7-H), 7.87 (2H, s, 2-H and 3-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 50.0 (C-5 and C-8), 67.5 (C-9), 137.3 ($^1J_{C-H}$ = 183 Hz, C-2 and C-3), 142.9 ($^1J_{C-H}$ = 176 Hz, C-6 and C-7), 168.6 (C-4a and C-8a); MS *m/z* (rel intensity) 144 (M^+; 100), 118 (51), 90 (36), 66 (43). Picrate: yellow needles (from ethanol); mp 129—130 °C. Analysis of the picrate, Found: C, 48.51; H, 3.13; N, 18.74%. Calcd for $C_{15}H_{11}N_5O_7$: C, 48.27; H, 2.97; N, 18.76%.

1,4-Dihydro-1,4-methanophenazine (16):[18] Colorless needles (from ethanol); mp 130—132 °C (lit,[18] mp 133 °C); IR 1585, 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.58 (1H, d, J = 9 Hz, 11-H_s), 2.72 (1H, d, J = 9 Hz, 11-H_a), 3.97 (2H, s, 1-H and 4-H), 6.88 (2H, s, 2-H and 3-H), 7.63 (2H, m, 7-H and 8-H), 7.90 (2H, m, 6-H and 9-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 49.5 (C-1, and C-4), 62.9 (C-11), 128.5, 128.6, 139.0 (C-5a and C-9a), 142.2 (C-2 and C-3), 166.3 (C-4a and C-10a); MS *m/z* (rel intensity) 194 (M^+; 100), 168 ($M - C_2H_2$; 21), 66 (41).

2,3-Dicyano-5,8-dihydro-5,8-methanoquinoxaline (17): A solution of bicyclo[2.2.1]hept-5-ene-2,3-dione (**13**) (100 mg, 1 mmol) and diaminomaleonitrile (141 mg, 1.3 mmol) in THF (2 cm^3) was stirred at room temperature for 3.5 h and then refluxed for 3.5 h. The solution was concentrated and the residue was separated by column chromatography (silica gel, hexane–ethyl acetate 1/1) to give the fused dicyanopyrazine **17** (187 mg, 96%): Colorless needles (from hexane); mp 110—111 °C; IR (KBr) 2239, 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.65 (1H, d, J = 9 Hz, 9-H_s), 2.84 (1H, dt, J = 9 and 2 Hz, 9-H_a), 4.06 (2H, quint, J = 2 Hz, 5-H and 8-H), 6.79 (2H, t, J = 2 Hz, 6-H and 7-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ = 49.8 (C-5 and C-8), 66.2 (C-9), 114.0 (CN), 128.0 (C-2 and C-3), 143.0 (C-6 and C-7), 172.3 (C-4a and C-8a); MS *m/z* (rel intensity) 194 (M^+; 100), 168 ($M - CN$; 57), 115 (17), 91 (25). Found: C, 68.00; H, 3.03; N, 29.10%. Calcd for $C_{11}H_6N_4$: C, 68.04; H, 3.11; N, 28.85%.

5,8-Dihydro-5,8-methanoquioxaline 1-Oxide (18). A solution of the fused pyrazine **15** (200 mg, 1.4 mmol) and *m*-chloroperbenzoic acid (80%, 300 mg, 1.4 mmol) in dichloromethane (14 cm^3) was stirred at room temperature for 24 h. The organic layer was washed with aqueous sodium hydrogensulfate and aqueous sodium thiosulfate, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by TLC (silica gel, ethyl acetate) to give **18** (170 mg, 77%): Colorless needles (from hexane); mp 84—85 °C; IR (KBr) 1587, 1317 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.52 (1H, d, J = 8 Hz, 9-H_s), 2.58 (1H, dt, J = 8 and 2 Hz, 9-H_a), 4.00 (1H, quint, J = 2 Hz, 5-H), 4.45 (1H, quint, J = 2 Hz, 8-H), 6.96 (2H, t, J = 2 Hz, 6-H and 7-H), 7.64 (1H, d, J = 5 Hz, 3-H), 7.88 (1H, d, J = 5 Hz, 2-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 44.7 (C-8), 51.2 (C-5), 67.0 (C-9), 130.8 (C-3), 141.1 (C-2), 141.7 (C-6 or C-7), 143.5 (C-7 or C-6), 152.7 (C-4a), 173.9 (C-8a); MS *m/z* (rel intensity) 160 (M^+; 100), 143 ($M - OH$; 75). Found: C, 67.66; H, 4.95; N, 17.60%. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49%.

Bromination Reaction of 5,8-Dihydro-5,8-methanoquinoxaline (15). To a solution of the fused pyrazine **15** (100 mg, 0.7 mmol) in carbon tetrachloride (2 cm^3) was added a solution of bromine (166 mg, 1 mmol) in carbon tetrachloride (2 cm^3). The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated and the residue was purified by MPLC (silica gel, hexane–ethyl acetate 1/1) to give a mixture of three bromine adducts (180 mg, 86%): **19a**, **20a**, and **21a** in a ratio of 20 : 1 : 5. Colorless plates (from hexane); mp 72—75 °C; IR (neat) 1602, 1365 cm^{-1}. For 6-*endo*,7-*exo*-dibromo-5,6,7,8-tetrahydro-5,8-methanoquinoxaline (**19a**) (from mixture), ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.41 (1H, ddt, J = 11, 3, and 2 Hz, 9-H_s), 2.62 (1H, dt, J = 11 and 2 Hz, 9-H_a), 3.72 (1H, m, 5-H), 3.75 (1H, m, 8-H), 4.00 (1H, t, J = 3 Hz, 7-H), 4.78 (1H, ddd, J = 4, 3, and 1 Hz, 6-H), 8.28 (1H, d, J = 3 Hz, 2-H or 3-H), 8.32 (1H, J = 3 Hz, 3-H or 2-H). For 6,7-*exo-cis*-dibromo-5,6,7,8-tetrahydro-5,8-methanoquinoxaline (**20a**) (from mixture), ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.34 (1H, m, 9-H_s), 2.81 (1H, dt, J = 10 and 2 Hz, 9-H_a), 3.79 (2H, t, J = 2 Hz, 5-H and 8-H), 4.30 (2H, d, J = 2 Hz, 6-H and 7-H), 8.24 (2H, s, 2-H and 3-H). For 6-*exo*-9-*anti*-dibromo-5,6,7,8-tetrahydro-5,8-methanoquinoxaline (**21a**) (from mixture), ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.37 (1H, m, 7-H_{endo}), 2.99 (1H, dt, J = 14 and 5 Hz, 7-H_{exo}), 3.70 (1H, m, 8-H), 3.88 (1H, ddd, J = 8, 5, and 1 Hz, 6-H), 3.94 (1H, dd, J = 2 and 1 Hz, 5-H), 4.32 (1H, t, J = 1 Hz, 9-H), 8.26 (1H, d, J = 2 Hz, 2-H or 3-H), 8.27 (1H, d, J = 2 Hz, 3-H or 2-H). For the mixture of **19a**, **20a**, and **21a**, ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.1, 41.8, 43.5, 45.1, 51.5, 52.0, 52.1,53.5, 53.9, 54.2, 55.2, 57.2, 142.2, 142.6, 143.0, 143.2, 143.5, 158.0, 159.0, 159.1, 159.6, 160.2 (one sp^3 carbon missing); MS *m/z* (rel intensity) 306 (M^+; 8), 304 (M^+; 16), 302 (M^+; 8), 144 (**15**; 100). Found: C, 35.80; H, 2.65; N, 9.09%. Calcd for $C_9H_8N_2Br_2$: C, 35.56; H, 2.65; N, 9.22%.

A similar reaction of **15** (100 mg, 0.7 mmol) and bromine (166 mg, 1 mmol) in dioxane (4 cm^3) gave a mixture of three bromine adducts (185 mg, 88%, colorless plates from hexane, mp 73 —77 °C): **19a**, **20a**, and **21a** in a ratio of 19 : 1 : 11. Found: C, 35.29; H, 2.51; N, 9.23%. Calcd for $C_9H_8N_2Br_2$: C, 35.56; H, 2.65; N, 9.22%.

Bromination Reaction of 1,4-Dihydro-1,4-methanophenazine (16). To a solution of the fused quinoxaline **16** (194 mg, 1 mmol) in carbon tetrachloride (4 cm^3) was added a solution of bromine (192 mg, 1.2 mmol) in carbon tetrachloride (4 cm^3). The mixture was stirred at room temperature for 8 h. The mixture was concentrated and the residue was separated by MPLC (silica gel, dichloromethane) to give **19b** (185 mg, 52%) and a mixture of **20b** and **21b** (93 mg, 26%) in a ratio of 1 : 4.

2-*endo*, 3-*exo*-Dibromo-1, 2, 3, 4-tetrahydro-1, 4-methnaophenazine (19b): Colorless needles (from hexane); mp 144—145 °C; IR (KBr) 2978, 2970, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.46 (1H, dd, J = 11 and 3 Hz, 11-H_s), 2.77 (1H, d, J = 11 Hz, 11-H_a), 3.83 (1H, d, J = 3 Hz, 1-H), 3.87 (1H, br s, 4-H), 4.14 (1H, t, J = 3 Hz, 3-H), 4.86 (1H, tm, J = 3 Hz, 2-H), 7.76 (2H, m, 7-H and 8-H), 8.05 (1H, m, 6-H or 9-H), 8.12 (1H, m, 9-H or 6-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.5 (C-11), 52.4 (C-1), 54.0 (C-3), 54.2 (C-4), 54.4 (C-2), 129.2, 129.4, 129.5, 129.6, 141.6 (C-6a or C-9a), 141.9 (C-9a or C-6a), 158.8 (C-4a or C-10a), 159.0 (C-10a or C-4a); MS *m/z* (rel intensity) 356 (M^+; 9), 354 (M^+; 18), 352 (M^+; 9), 194 (**16**; 100). Found: C, 44.26; H, 3.00; N, 7.88%. Calcd for $C_{13}H_{10}N_2Br_2$: C, 44.10; H, 2.85; N, 7.91%.

The Mixture of 20b and 21b (1 : 4): White powder (from hexane); mp 118—122 °C; IR (KBr) 1508, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.39 (0.2H, d, J = 11 Hz, **20b** 11-H_s), 2.50 (0.8H, dd, J = 14 and 8 Hz, **21b** 3-H_{endo}), 2.96 (0.2H, d, J = 11 Hz, **20b** 11-H_a), 3.10 (0.8H, dt, J = 14 and 5 Hz, **21b** 3-H_{exo}), 3.80 (0.8H, m, **21b**, 4-H), 3.92 (0.4H, s, **20b** 1-H and 4-H), 4.00 (0.8H, dd, J = 8 and 5 Hz, **21b** 2-H), 4.05 (0.8H, s, **21b** 1-H), 4.40 (1.2H, **21b** 11-H, **20b** 2-H, and **20b** 3-H), 7.75 (2H, m), 8.03 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz), δ = 36.1 (**21b** C-3), 41.7, 41.8 (**20b** C-11), 51.7, 52.2, 52.4, 55.6, 57.6, 129.1, 129.2, 129.3, 129.7, 129.8, 130.0, 141.9, 142.1, 142.2, 157.6, 158.5, 159.7; MS *m/z* (rel intensity) 356 (M^+; 12), 354 (M^+; 23), 352 (M^+; 11), 194 (**16**; 100). Found: C, 44.27; H, 2.91; N, 7.86%. Calcd for $C_{13}H_{10}N_2Br_2$: C, 44.10; H, 2.85; N, 7.91%.

A similar reaction of **16** (194 mg, 1 mmol) and bromine (192 mg, 1.2 mmol) in dioxane (8 cm^3) gave **19b** (116 mg, 33%, mp and mixed mp 142—143 °C) and a mixture of **20b** and **21b** (95 mg, 27%, 1 : 12): White powder (from hexane): mp 143—149 °C. Found: C, 44.24; H, 2.74; N, 7.79%. Calcd for $C_{13}H_{10}N_2Br_2$: C, 44.10; H, 2.85; N, 7.91%.

Bromination Reaction of 2,3-Dicyano-5,8-dihydro-5,8-methanoquinoxaline (17) in Carbon Tetrachloride. To a solution of the dicyanopyrazine **17** (100 mg, 0.51 mmol) in carbon tetrachloride (2 cm^3) was added a solution of bromine (100 mg, 0.63 mmol) in carbon tetrachloride (2 cm^3). The mixture was stirred at room temperature for 6 h and concentrated. The residue was crystallized from hexane to give 6-*endo*,7-*exo*-dibromo-2,3-dicyano-5,6,7,8-tetrahydro-5,8-methanoquinoxaline: (19c) (175 mg, 96%): Colorless needles (from hexane); mp 161—162 °C; IR (KBr) 2985, 2241 (CN), 1466, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.52 (1H, br d, J = 11 Hz, 9-H_s), 2.81 (1H, d, J = 11 Hz, 9-H_a), 3.90 (1H, d, J = 3 Hz, 5-H), 3.91 (1H, br s, 8-H), 3.98 (1H, t, J = 3 Hz, 7-H), 4.80 (1H, t, J = 3 Hz, 6-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 45.1 (C-9), 51.2 (C-7), 51.6 (C-6), 52.3 (C-5), 53.8 (C-8), 113. 2 (CN), 113.3 (CN), 131.7 (C-2 or C-3), 132.1 (C-3 or C-2), 162.7 (C-4a or C-8a), 163.7 (C-8a or C-4a); MS *m/z* (rel intensity) 356 (M^+; 10), 354 (M^+; 19), 352 (M^+; 10), 194 (**17**; 100). Found: C, 37.34; H, 1.70; N, 16.03%. Calcd for $C_{11}H_6N_4Br_2$: C, 37.32; H, 1.71; N, 15.83%.

Bromination Reaction of 2,3-Dicyano-5,8-dihydro-5,8-methanoquinoxaline (17) in Dioxane. To a solution of the dicyanopyrazine **17** (100 mg, 0.51 mmol) in dioxane (2 cm^3) was added a solution of bromine (240 mg, 1.5 mmol) in dioxane (2 cm^3). The mixture was stirred at room temperature for 24 h and concentrated. The residue was separated by MPLC (silica gel, hexane–ethyl acetate 4/1) to give **19c** (108 mg, 59%, mp and mixed mp 159—160 °C) and 6,7-*exo-cis*-dibromo-2,3-dicyano-5,6,7,8-tetrahydro-5,8-methanoquinoxaline (**20c**) (19 mg, 10%): Colorless needles (from hexane); mp 213—214 °C; IR (KBr) 2245 (CN), 1454, 1336 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.46 (1H, d, J = 11 Hz, 9-H_s), 2.99 (1H, d, J = 11 Hz, 9-H_a), 3.95 (2H, br s, 1-H and 4-H), 4.27 (2H, br s, 2-H and 3-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 43.7 (C-9), 49.2 (C-1 and C-4), 55.2 (C-6 and C-7), 113.3 (CN), 132.1 (C-2 and C-3), 163.8 (C-4a and C-8a); MS *m/z* (rel intensity) 356 (M^+; 7), 354 (M^+; 13), 352 (M^+; 7), 194 (**17**; 63), 168 (**17** − CN; 100). Found: C, 37.21; H, 1.70; N, 15.60%. Calcd for $C_{11}H_6N_4Br_2$: C, 37.32; H, 1.71; N, 15.83%.

Bromination Reaction of 5,8-Dihydro-5,8-methanoquinoxaline 1-Oxide (18). To a solution of the *N*-oxide **18** (80 mg, 0.5 mmol) in dioxane (2 cm^3) was added a solution of bromine (120 mg, 0.8 mmol) in dioxane (2 cm^3). The mixture was stirred at room temperature for 2 h. Dichloromethane was added and the organic phase was washed with aqueous sodium thiosulfate and dried over Na_2SO_4. After removal of the solvent, the residue was purified by TLC (silica gel, ethyl acetate) to give a mixture of four bromine adducts (128 mg, 80%): White powder (from hexane); sublimation at ca. 185 °C (sealed tube). The ratio of the isomers was determined to be 8 : 4 : 1 : 1 judging from the integration of the peaks assignable to pyridazine rings in the ^1H NMR spectrum and the main component was 7-*exo*,9-*anti*-dibromo-5,6,7,8-tetrahydro-5,8-methanoquinoxaline 1-oxide (**22**). For the mixture: ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.15—2.62 (1.43H), 2.99 (0.57H, t, J = 14 and 4 Hz, **22** 6-H_{exo}), 3.48—4.74 (2.86H), 4.31 (0.57H, t, J = 1 Hz, **22** 8-H), 4.33 (0.57H, t, J = 1 Hz, **22** 9-H), 7.82 (0.29H, J = 4 Hz), 7.86 (0.57H, d, J = 4 Hz, **22** 3-H), 7.91 (0.07H, d, J = 4 Hz), 7.93 (0.07H, d, J = 4 Hz), 8.11 (0.29H, J = 4 Hz), 8.17 (0.57H, d, J = 4 Hz, **22**, 2-H), 8.20 (0.07H, d, J = 4H), 8.07 (0.23H, d, J = 4 Hz); MS *m/z* (rel intensity) 322 (M^+; 5), 320 (M^+; 11), 318 (M^+; 5), 134 (M − 2Br − C_2H_2; 100). Found: C, 33.60; H, 2.65; N, 8.60%. Calcd for $C_9H_8N_2OBr_2$: C, 33.78; H, 2.52, N, 8.75%.

Recrystallization of the mixture twice from ethanol gave a small amount (20 mg) of the pure 7,9-dibromo derivative **22**: Colorless plates (from ethanol); sublimation at ca. 196 °C (sealed tube); IR (KBr) 1583, 1425, 1321 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.42 (1H, dd, J = 14 and 8 Hz, 6-H_{endo}), 2.99 (1H, dt, J = 14 and 4 Hz, 6-H_{exo}), 3.70 (1H, m, 5-H), 3.89 (1H, ddd, J = 8, 4, and 1 Hz, 7-H), 4.31 (1H, t, J = 1 Hz, 8-H), 4.33 (1H, t, J = 1 Hz, 9-H), 7.86 (1H, d, J = 4 Hz, 3-H), 8.17 (1H, d, J = 4 Hz, 2-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 35.2 (C-6), 39.9 (C-7), 51.0 (C-8), 52.3 (C-9), 52.6 (C-5), 133.4 (C-3), 143.5 (C-4a), 152.7 (C-2), 173.9 (C-8a); MS *m/z* (rel intensity) 322 (M^+; 3), 320 (M^+; 5), 318 (M^+; 3), 239 (M − Br; 19), 134 (M − 2Br − C_2H_2; 100). Found: C, 34.03; H, 2.44; N, 8.70%. Calcd for $C_9H_8N_2OBr_2$: C, 33.78; H, 2.52; N, 8.75%.

A similar reaction of **18** with bromine in carbon tetrachloride gave a mixture of three bromine adducts (20 : 13 : 10, 77%, white powder from hexane, mp 165—185 °C) of which the main component was **22**. For the mixture: ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.34—2.45 (1H), 2.55—2.62 (0.53H), 2.99 (0.47H, dt, J = 14 and 4 Hz, **22** 6-H_{exo}), 3.70 (0.47H, m, **22** 5-H), 3.72—4.75 (2.12 H), 3.89 (0.47H, ddd, J = 8, 4, and 1 Hz, **22** 7-H), 4.31 (0.47H, t, J = 1 Hz, **22** 8-H), 4.33 (0.47H, t, J = 1 Hz, **22** 9-H), 7.86 (0.47H, d, J = 4 Hz, **22** 3-H), 7.91 (0.23H, d, J = 4 Hz), 7.93 (0.30H, d, J = 4 Hz), 8.17 (0.47H, d, J = 4 Hz, **22** 2-H), 8.20 (0.30H, d, J = 4 Hz), 8.24 (0.23H, d, J = 4 Hz). Found: C, 33.82; H, 2.52; N, 8.71%. Calcd for $C_9H_8N_2OBr_2$: C, 33.78; H, 2.52; N, 8.75%.

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