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Reactions of 2-methylindole with morpholinals of substituted salicylaldehydes

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Fusion of 2-methylindole with morphinals of substituted salicylaldehydes (in a ratio of 1 : 1) afforded 3-[(2-hydroxyaryl)morpholinomethyl]-2-methylindoles as normal products of the Mannich reaction. In some cases, the reactions with an excess of 2-methylindole resulted in unusual condensation accompanied by the replacement of the OH group by the morpholino group to form bis(2-methylindol-3-yl)(2-morpholinoaryl)methanes.

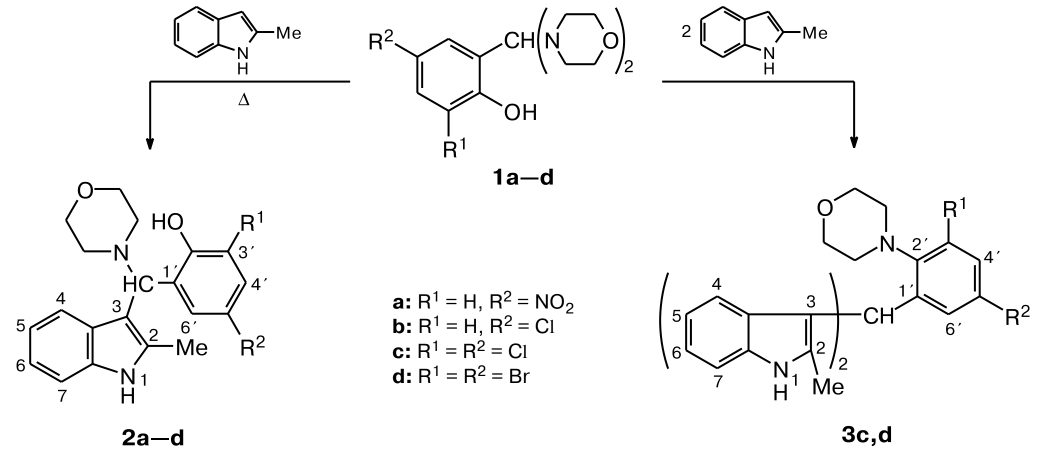
Key words: 2-methylindole, morpholinals of substituted salicylaldehydes, 3-[(2-hydroxyaryl)morpholinomethyl]-2-methylindoles, bis(2-methylindol-3-yl)(2-morpholinoaryl)methanes.

Earlier,[1] we have reported the synthesis of substituted Mannich bases from aminals of aromatic aldehydes and 2,6-di-*tert*-butylphenol. The reactions of morpholinals of substituted salicylaldehydes **1** with 2-methylindole performed under the same conditions afforded not only the expected Mannich bases **2** but also, in some cases, unusual condensation products **3**, whose yields increased with an excess of 2-methylindole (Scheme 1).

The condensation resulted in the replacement of the hydroxy group by the morpholino group. It is known[2] that the replacement of the OH groups by amino groups readily proceeds in phenols capable of undergoing the phenol-quinoid tautomerism.

Aminals, azomethines, and Mannich bases prepared from salicylaldehyde and its derivatives are characterized by the presence of intramolecular hydrogen bonds, which facilitate the proton transfer from the O atom to the N atom.[3] The complete proton transfer to the nitrogen atom in the aminals under consideration and elimination of the amine should give rise to *o*-quinomethides. Such reversible processes can occur in solutions, which has been confirmed by spectroscopic studies.[4,5]

Scheme 1



1a—d

a: $R^1 = H, R^2 = NO_2$
b: $R^1 = H, R^2 = Cl$
c: $R^1 = R^2 = Cl$
d: $R^1 = R^2 = Br$

2a—d

3c,d

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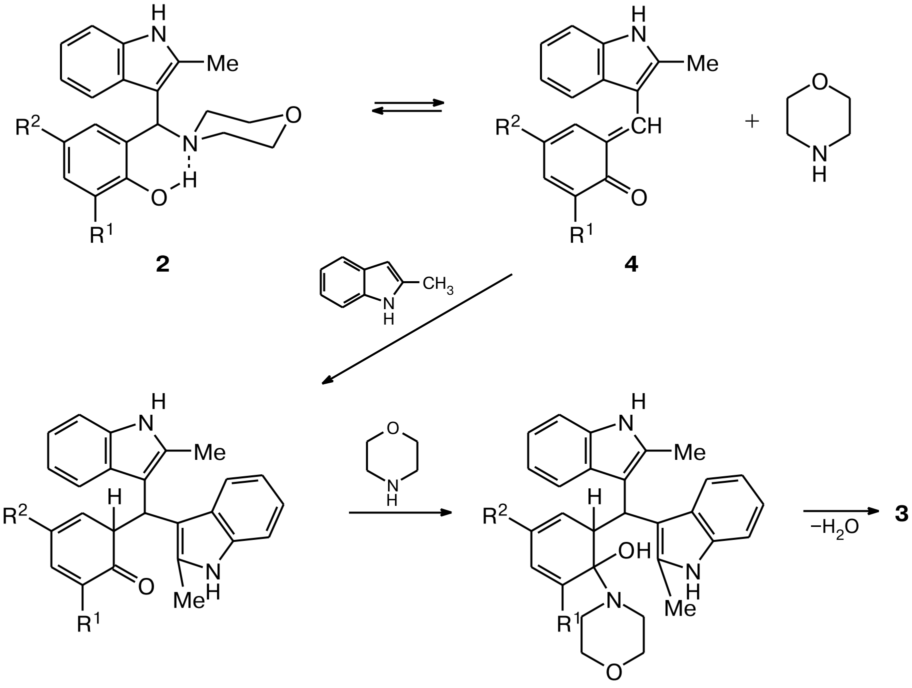
Scheme 2



The assumed sequence of the reactions yielding the final product **3** is shown in Scheme 2. Dissociation of the Mannich base **2** afforded quinomethide **4**. The C-nucleophile present in the equilibrium system can add to compound **4**.

The structures of compounds **2a—d** and **3c,d** were established based on the data from elemental analysis and IR and ^{1}H NMR spectroscopy. The structure of aminal **1a** synthesized earlier[6] was confirmed by X-ray diffraction analysis.

The ^{1}H NMR spectrum of compound **3d** differs from the spectrum of compound **3c** in that it has not only the major signals for the methylene protons of the morpholine fragment (triplets at δ 2.93 and 3.74) but also contains minor signals with identical spin-spin coupling constants (triplets at δ 3.26 and 3.66) (Table 1). This fact is most probably accounted for by the presence of a minor conformer (~15%) in a solution of **3d**.

The ^{1}H NMR spectrum of compound **2d**, unlike that of compound **2c**, also has additional signals for the methylene protons of the morpholine fragment (δ 3.21 and 3.97), although their intensities are much lower than those in the spectrum of **3d**.

X-ray diffraction study of compound **1a** [6] (Fig. 1) revealed the presence of a strong O(1)—H(10)......N(2) intramolecular hydrogen bond (O.........N, 2.601(3) Å; H......N; 1.686(3) Å; O—H......N angle, 155(2)°). As a result, the valent bonds of the N(2) atom are somewhat longer than the corresponding bonds of the N(3) atom (Table 2). The morpholine rings adopt chair conformations (the torsion angles are in the ranges of 56.0(4)—61.8(4) and 53.3(4)—61.4(4)°, respectively). The N(2) and N(3) atoms have pyramidal configurations (the sums of the bond angles at the N(2) and N(3) atoms are 331.0 and 338.0°, respectively, Table 2). The angle between the planes of the nitro group and the benzene ring is 17.4°. The remaining geometric parameters of molecule **1a** have standard values.[7]

In the crystal, the molecules are linked through van der Waals interactions, other short intermolecular contacts being absent (Fig. 2).

Experimental

The IR spectra were measured on a Specord IR-75 instrument in Nujol mulls. The ^{1}H NMR spectra were recorded on a Varian UNITY-300 spectrometer.

Synthesis of compound **1a** has been described earlier.[6] Compounds **1b—d** were prepared according to a modified method.[2]

(5-Chloro-2-hydroxyphenyl)dimorpholinomethane (1b). 5-Chlorosalicylaldehyde (6 g, 38 mmol) was dissolved in Pr^{i}OH (15 mL) with heating and morpholine (7 mL, 80 mmol) was added. The reaction mixture was heated to boiling and then cooled to ~20 °C, after which light petroleum (10 mL) was added, a crystal seed of the aminal was introduced, and the reaction mixture was triturated with a rod on cooling in ice. The precipitate that formed was filtered off, washed with light petroleum, dried, and used in the syntheses without additional purification. After recrystallization from Pr^{i}OH, the yield of **1b** was 8 g (66%), colorless crystals, m.p. 110—115 °C. Found (%): C, 57.23; H, 7.18; N, 8.56; Cl, 11.64. $C_{15}H_{21}ClN_2O_3$. Calculated (%): C, 57.60; H, 6.77; N, 8.96; Cl, 11.33.

Table 1. Spectroscopic parameters of compounds **2a—d** and **3c,d**

Compound	IR, ν/cm^{-1} (Nujol mulls)	^{1}H NMR ($CDCl_3$, δ, J/Hz)
2a	3380, 3326, 3300 (OH, NH); 1714 (w); 1614, 1548, 1514, 1487 (arom.), 1580, 1341 (NO_2)	2.48 (s+t, 7 H, CH_3+CH_2N); 3.65 (t, 4 H, CH_2O, J = 4.5); 5.12 (s, 1 H, CH); 6.84 (d, 1 H, C(3´)H, J = 9.0); 6.80—7.00 (m, 2 H, C(5)H+C(6)H); 7.20 (d, 1 H, C(4)H, J = 7.8); 7.56 (d, 1 H, C(7)H, J = 7.7); 7.88 (dd, 1 H, C(4´)H, ^3J = 9.0, ^4J = 2.85); 8.22 (d, 1 H, C(6´)H, J = 2.85); 10.86 (s, 1 H, OH); 12.58 (s, 1 H, NH).
2b	3380, 3313, 3287 sh (OH, NH), 1607, 1581, 1554 (arom.), 1107 (C—O—C)	2.47 (s, 3 H, CH_3), 2.56 (m, 4 H, CH_2N); 3.74 (m, 4 H, CH_2O); 5.03 (s, 1 H, CH); 6.78 (d, 1 H, C(3´)H, J = 8.7); 6.85 (d, 1 H, C(6´)H, J = 2.6); 7.04 (dd, 1 H, C(4´)H, ^3J = 8.7, ^4J = 2.6); 7.11 (m, 2 H, C(5)H+C(6)H); 7.27 (d, 1 H, C(4)H, J = 7.9); 7.57 (d, 1 H, C(7)H, J = 7.9); 8.00 (s, 1 H, NH); 12.77 (s, 1 H, OH)
2c	3313 (OH, NH), 1594, 1561, 1547 (arom.), 1114 (C—O—C)	2.44 (s, 3 H, CH_3); 2.60 (m, 4 H, CH_2N); 3.80 (m, 4 H, CH_2O); 5.10 (s, 1 H, CH); 6.77 (d, 1 H, C(6´)H, J = 2.4); 7.00—7.15 (m, 2 H, C(5)H+C(6)H); 7.20 (d, 1 H, C(4´)H, J = 2.4); 7.28 (d, 1 H, C(4)H, J = 7.9); 7.49 (d, 1 H, C(7)H, J = 7.9); 8.00 (s, 1 H, NH); 14.00 (s, 1 H, OH)
2d	3319 (OH, NH); 1594, 1567, 1554 (arom.), 1114 (C—O—C)	2.46 (s, 3 H, CH_3); 2.59 (m, 4 H, CH_2N); 3.75 (m, 4 H, CH_2O); 5.08 (s, 1 H, CH); 6.95 (d, 1 H, C(6´)H, J = 1.5); 7.00—7.16 (m, 2 H, C(5)H+C(6)H); 7.28 (d, 1 H, C(4)H, J = 8.0); 7.49 (two d, 1 H each, C(7)H+C(4´)H); 8.03 (s, 1 H, NH); 14.15 (s, 1 H, OH)
3c	3447, 3393 (NH), 1634, 1621, 1581, 1557 (arom.), 1114 (C—O—C)	2.07 (s, 6 H, CH_3); 2.83 (t, 4 H, CH_2N, J = 4.7); 3.65 (t, 4 H, CH_2O, J = 4.7); 6.07 (s, 1 H, CH); 6.85—7.25 (m, 10 H, CH_{arom}); 7.80 (s, 2 H, NH)
3d	3447, 3400 (NH); 1641, 1621, 1574, 1560 (arom.); 1114 (C—O—C)	2.06 (s, 6 H, CH_3); 2.93 (t, 3.4 H, CH_2N, J = 4.7); 3.26 (t, 0.6 H, CH_2N, J = 4.7); 3.66 (t, 0.6 H, CH_2O, J = 4.7); 3.74 (t, 3.4 H, CH_2O, J = 4.7); 6.05 (s, 1 H, CH); 6.85—7.10 (m, 6 H, CH_{arom}); 7.11 (d, 1 H, C(6´)H, J = 2.3); 7.25 (d, 2 H, C(7)H, J = 8.0); 7.53 (d, 1 H, C(4´)H, J = 2.3); 7.81 (s, 2 H, NH)

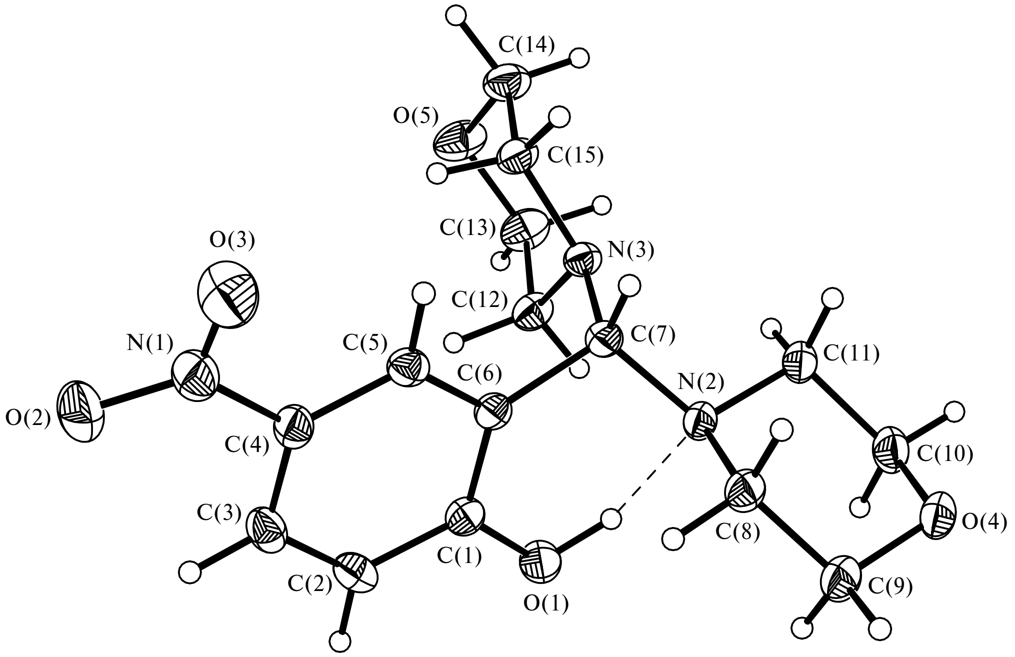


Fig. 1. Molecular structure of compound **1a** with 30% probability ellipsoids; a hydrogen bond is indicated by a dashed line.

Table 2. Bond lengths (*d*) and bond angles (ω) in compound **1a**

Bond	*d*/Å	Bond	*d*/Å	Angle	ω/deg	Angle	ω/deg
O(1)—C(1)	1.349(4)	N(3)—C(12)	1.465(4)	C(9)—O(4)—C(10)	108.3(3)	C(5)—C(4)—N(1)	118.5(3)
O(2)—N(1)	1.237(3)	C(1)—C(2)	1.392(4)	C(13)—O(5)—C(14)	109.0(3)	C(3)—C(4)—N(1)	119.5(3)
O(3)—N(1)	1.228(3)	C(1)—C(6)	1.414(4)	O(3)—N(1)—O(2)	123.5(3)	C(4)—C(5)—C(6)	120.3(3)
O(4)—C(9)	1.418(4)	C(2)—C(3)	1.372(4)	O(3)—N(1)—C(4)	118.9(3)	C(5)—C(6)—C(1)	118.0(3)
O(4)—C(10)	1.422(4)	C(3)—C(4)	1.384(4)	O(2)—N(1)—C(4)	117.7(3)	C(5)—C(6)—C(7)	120.2(3)
O(5)—C(13)	1.420(4)	C(4)—C(5)	1.380(4)	C(11)—N(2)—C(7)	113.6(2)	C(1)—C(6)—C(7)	121.6(3)
O(5)—C(14)	1.421(4)	C(5)—C(6)	1.383(4)	C(11)—N(2)—C(8)	108.0(2)	N(3)—C(7)—N(2)	110.6(2)
N(1)—C(4)	1.460(4)	C(6)—C(7)	1.528(4)	C(7)—N(2)—C(8)	109.4(2)	N(3)—C(7)—C(6)	113.6(2)
N(2)—C(11)	1.472(4)	C(8)—C(9)	1.504(4)	C(7)—N(3)—C(15)	112.1(2)	N(2)—C(7)—C(6)	109.1(2)
N(2)—C(7)	1.478(3)	C(10)—C(11)	1.513(4)	C(7)—N(3)—C(12)	115.2(2)	N(2)—C(8)—C(9)	109.6(3)
N(2)—C(8)	1.485(4)	C(12)—C(13)	1.504(5)	C(15)—N(3)—C(12)	110.7(2)	O(4)—C(9)—C(8)	110.7(3)
N(3)—C(7)	1.463(4)	C(14)—C(15)	1.500(4)	O(1)—C(1)—C(2)	118.3(3)	O(4)—C(10)—C(11)	112.4(3)
N(3)—C(15)	1.463(4)			O(1)—C(1)—C(6)	121.5(3)	N(2)—C(11)—C(10)	109.5(3)
				C(2)—C(1)—C(6)	120.2(3)	N(3)—C(12)—C(13)	109.6(3)
				C(3)—C(2)—C(1)	121.0(3)	O(5)—C(13)—C(12)	110.9(3)
				C(2)—C(3)—C(4)	118.2(3)	O(5)—C(14)—C(15)	111.9(3)
				C(5)—C(4)—C(3)	122.0(3)	N(3)—C(15)—C(14)	110.4(3)

Compounds **1c,d** were prepared analogously.

(3,5-Dichloro-2-hydroxyphenyl)dimorpholinomethane (1c), the yield was 85%, m.p. 140—145 °C. Found (%): C, 51.46; H, 6.21; N, 7.92; Cl, 20.68. $C_{15}H_{20}Cl_2N_2O_3$. Calculated (%): C, 51.88; H, 5.81; N, 8.07; Cl, 20.42.

(3,5-Dibromo-2-hydroxyphenyl)dimorpholinomethane (1d), the yield was 80%, m.p. 135—140 °C. Found (%): C, 40.92; H, 4.28; N, 6.13; Br, 37.07. $C_{15}H_{20}Br_2N_2O_3$. Calculated (%): C, 41.31; H, 4.62; N, 6.42; Br, 36.64.

3-[(2-Hydroxy-5-nitrophenyl)morpholinomethyl]-2-methylindole (2a). A mixture of morpholinal **1a** [6] (3.2 g, 10 mmol) and 2-methylindole (1.4 g, 11 mmol) was ground in a mortar, fused at 140 °C, and cooled to ~20 °C. Then CH_3CN (10 mL) was added and the mixture was triturated with a rod on cooling in

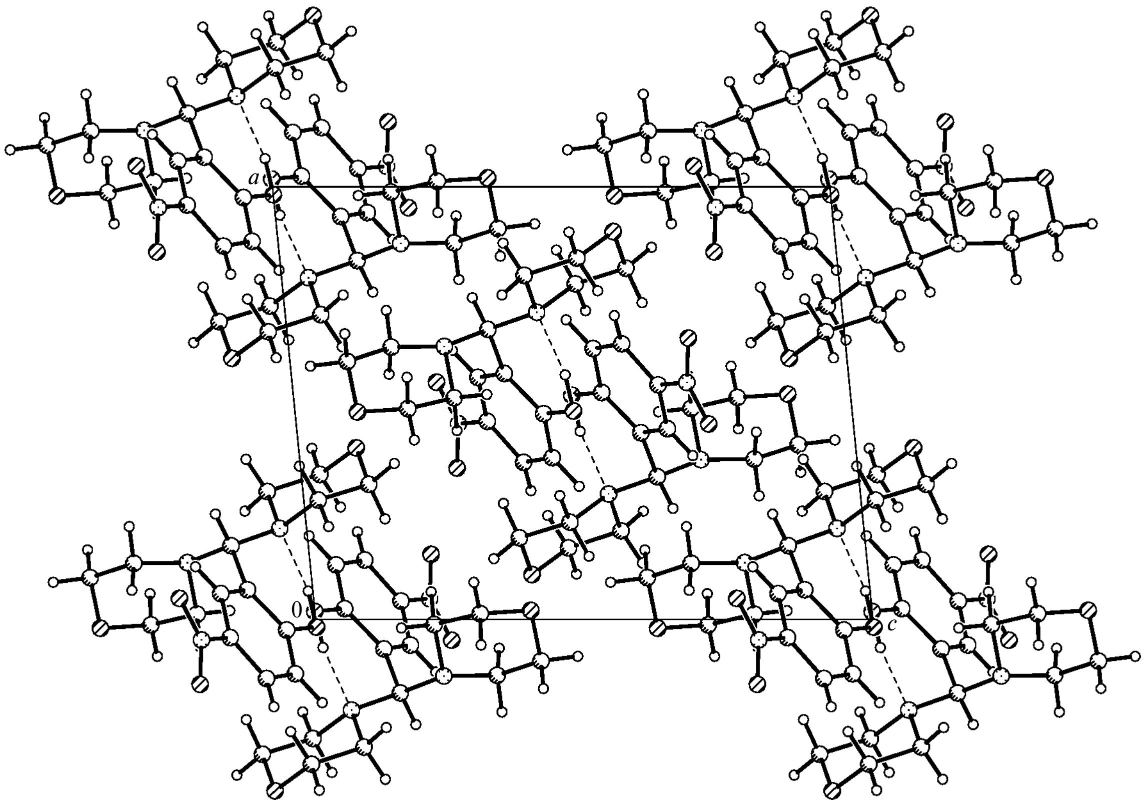


Fig. 2. Crystal packing of molecules **1a** along the *y* axis; the hydrogen bonds are shown by dashed lines.

ice. The precipitate that formed was filtered off, washed with cold MeCN and EtOH, and dried. Compound **2a** was obtained in a yield of 2.74 g (75%) as colorless crystals with m.p. 220—225 °C (decomp.) (from $MeNO_2$). Found (%): C, 65.19; H, 5.84; N, 11.63. $C_{20}H_{21}N_3O_4$. Calculated (%): C, 65.38; H, 5.76; N, 11.44.

3-[(5-Chloro-2-hydroxyphenyl)morpholinomethyl]-2-methylindole (2b). A mixture of morpholinal **1b** (1.25 g, 4 mmol) and 2-methylindole (0.7 g, 5 mmol) was ground in a mortar, fused at 150 °C, and cooled to ~20 °C. Then MeOH (20 mL) was added. The reaction mixture was triturated with a rod on refluxing and cooled in ice. The precipitate that formed was filtered off, washed with MeOH and hexane, and dried. The yield of the crude product was 0.62 g. The product was recrystallized from $MeNO_2$ and washed on a filter with MeOH and hexane. Compound **2b** was obtained in a yield of 0.45 g (31.7%) as colorless crystals with m.p. 207—211 °C. Found (%): C, 67.15; H, 6.21; N, 7.79; Cl, 10.13. $C_{20}H_{21}ClN_2O_2$. Calculated (%): C, 67.32; H, 5.93; N, 7.85; Cl, 9.93.

3-[(5-Dichloro-2-hydroxyphenyl)morpholinomethyl]-2-methylindole (2c). A mixture of morpholinal **1c** (0.5 g, 1.3 mmol) and 2-methylindole (0.2 g, 1.5 mmol) was fused at 135 °C and cooled to ~20 °C. Then MeOH (2.5 mL) was added and the reaction mixture was triturated with a rod on refluxing. Crystallization started from the boiling solution. The reaction mixture was cooled in ice. The precipitate that formed was filtered off, washed with cold MeOH and light petroleum, and dried. The yield was 0.24 g (43%), m.p. 203—206 °C (from $MeNO_2$). Found (%): C, 60.98; H, 5.36; N, 7.23; Cl, 17.87. $C_{20}H_{20}Cl_2N_2O_2$. Calculated (%): C, 61.39; H, 5.15; N, 7.16; Cl, 18.12.

3-[(5-Dibromo-2-hydroxyphenyl)morpholinomethyl]-2-methylindole (2d) was prepared analogously to compound **2c** (a mixture of morpholinal **1d** (1.32 g, 3 mmol) and 2-methylindole (0.45 g, 3 mmol) was fused at 165 °C). The yield was 0.65 g (45%), m.p. 214—216 °C (decomp.) (from $MeNO_2$). Found (%): C, 49.78; H, 4.52; N, 5.69; Br, 33.58. $C_{20}H_{20}Br_2N_2O_2$. Calculated (%): C, 50.02; H, 4.20; N, 5.83; Br, 33.28.

(3,5-Dichloro-2-morpholinophenyl)-bis(2-methylindol-3-yl)methane (3c). A mixture of morpholinal **1c** (1.75 g, 5 mmol) and 2-methylindole (1.5 g, 12 mmol) was ground in a mortar and fused at 155 °C. The product was isolated analogously to compound **2c**. The yield was 1.3 g (51%), m.p. 175—185 °C (from toluene). Found (%): C, 68.73; H, 5.57; N, 8.21; Cl, 14.43. $C_{29}H_{27}Cl_2N_3O$. Calculated (%): C, 69.05; H, 5.39; N, 8.33; Cl, 14.05.

(3,5-Dibromo-2-morpholinophenyl)-bis-3-(2-methylindol-3-yl)methane (3d) was prepared analogously to compound **3c** from morpholinal **1d** (5 mmol) and 2-methylindole (1.5 g, 12 mmol). The yield was 1.5 g (50%), m.p. 165—172 °C (from toluene). Found (%): C, 58.50; H, 4.83; N, 6.84; Br, 27.19. $C_{29}H_{27}Br_2N_3O$. Calculated (%): C, 58.70; H, 4.59; N, 7.08; Br, 26.93.

X-ray diffraction study of morpholinal 1a. The crystals of **1a** ($C_{15}H_{21}N_3O_5$, M = 323.35) are monoclinic, space group $P2_1/n$, at 293 K: a = 10.652(2), b = 10.598(2), c = 13.658(3) Å, β = 95.70(3)°, V = 1534.2(5) Å, Z = 4, d_{calc} = 1.400 mg cm^{-3}, $F(000)$ = 688, μ = 0.106 mm^{-1}. The unit cell parameters and intensities of 2741 reflections were measured on an automated four-circle Siemens P3/PC diffractometer (293 K, λ-Mo-Kα radiation, graphite monochromator, $\theta/2\theta$ scan technique, θ_{max} = 25°). The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. The hydrogen atoms were located from difference Fourier syntheses and refined isotropically. The final reliability factors were as follows: R_1 = 0.0553 for 1456 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.1039 for all 2589 independent reflections. All calculations were carried out with the use of the SHELXTL PLUS program package (Version 5.10).[8]

The tables of the atomic coordinates, bond lengths, bond angles, torsion angles, and anisotropic thermal parameters for compound **1a** were deposited with the Cambridge Structural Database.

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