# Synthesis of hexa-, tetra-, and dihydroxanthene derivatives from salicylaldehyde aminals

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Salicylaldehyde aminals react with cyclohexanone upon heating to form tetrahydroxanthene derivatives. The structure of one of these derivatives, *viz.*, 5,7-dichloro-4a-morpholino-1,2,3,4-tetrahydro-4a*H*-xanthene, was established by X-ray diffraction analysis. The scheme of the reaction was suggested, which involves cycloaddition of intermediate *o*-methylenequinone (from aminal) and enamine (from cyclohexanone). The reactions of salicylaldehyde aminals with enamines that formed from cyclohexanone can successively afford derivatives of hexahydroxanthene, tetrahydroxanthene, and dihydroxanthene. Procedures were developed for the synthesis of these compounds. *N*-Substituted 4a-amino-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthenes were also prepared by the reactions of dialkylammonium 2-formyl-4-nitrophenoxides with the above-mentioned enamines.

**Key words:** salicylaldehyde aminals, cyclohexanone, enamines, *o*-methylenequinones, dialkylammonium 2-formyl-4-nitrophenoxides, cycloaddition, hexa-, tetra-, and dihydroxanthene derivatives.

As part of continuing studies[1–7] of synthetic potentialities of salicylaldehyde aminals (**1**), we found that these compounds readily and rapidly react with cyclohexanone (Scheme 1) to form derivatives of 4a-aminotetrahydroxanthene (method *A*).

It is known[8] that aldehyde aminals are key intermediates in the Mannich reaction. However, in the case under consideration this reaction is excluded because it would give derivatives of 9-aminotetrahydroxanthene.

We suggested that the mechanism of the reaction under study involves the following steps. When dissolved in cyclohexanone upon heating, aminal **1** dissociates into *o*-methylenequinone **2** and amine. The latter reacts with cyclohexanone to form enamine **3**, which enters into the cycloaddition reaction with *o*-methylenequinone **2** to give hexahydroxanthene **4**. The latter eliminates amine to form tetrahydroxanthene **5**, which should be converted into dihydroxanthene **6** as a result of elimination of the remaining amine molecule (see Scheme 1). All steps of Scheme 1 were confirmed experimentally.

Previously,[9,10] we have reported reversible dissociation of Mannich bases, prepared from salicylaldehyde aminals, in polar organic solvents into methylenequinone and amine. Dissociation is accompanied by the appearance of bands in the long-wavelength region of the UV spectra due to absorption of methylenequinones. The degree of dissociation increases and, consequently, the intensities of the long-wavelength bands increase as the temperature increases.

Analogous patterns are also observed in the UV spectra of aminals of substituted salicylaldehydes. The UV spectra of morpholinals of salicylaldehyde, 5-chlorosalicylaldehyde, and 5-nitrosalicylaldehyde in benzene are characterized by absorption bands in the long-wavelength region at 331 ($\varepsilon$ 3750), 343 ($\varepsilon$ 1980), and 299 nm ($\varepsilon$ 9500), respectively. The absorption spectrum of salicylaldehyde morpholinal in a polar solvent (MeCN) is identical with that in benzene. The spectrum of 5-chlorosalicylaldehyde morpholinal has an additional low-intensity band at 400 nm. 5-Nitrosalicylaldehyde morpholinal, which possesses pronounced acidic properties, gives a new strong absorption band in the same region (413 nm). The intensity of this band increases as the temperature increases and regains its initial value as the temperature decreases.

Only in the case of salicylaldehyde morpholinal, whose UV spectra had no evidence of its dissociation, did we fail to perform the above-described reaction.

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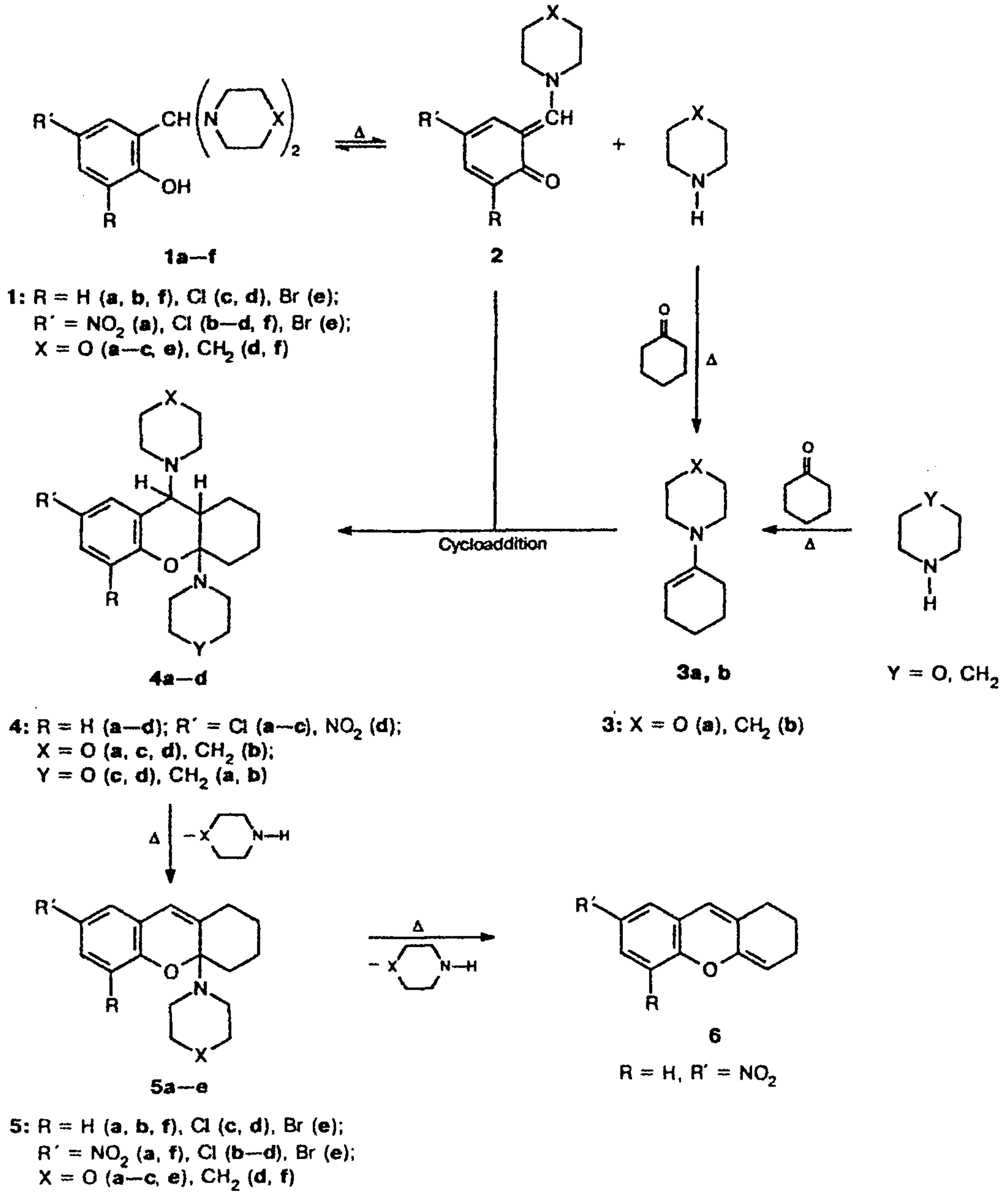
**Scheme 1**



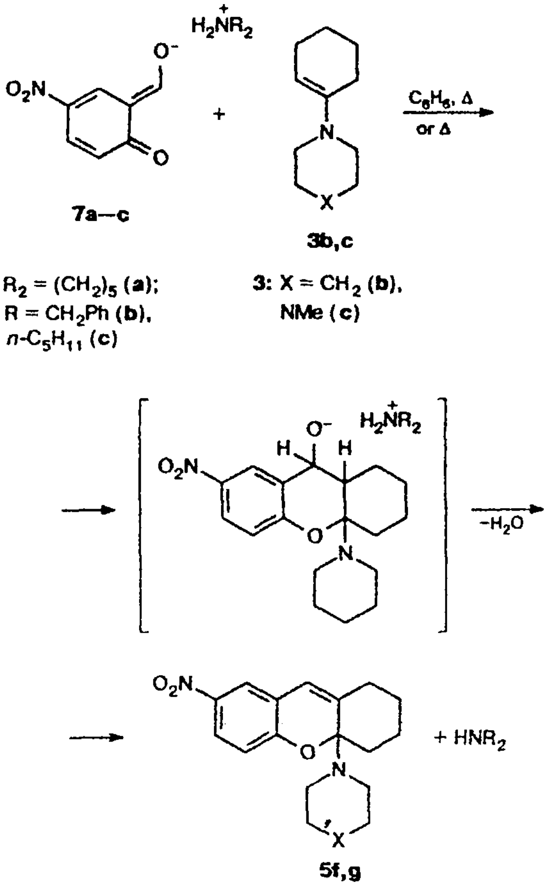
The above-mentioned stages of Scheme 1 were confirmed by the reactions of aminals **1** with enamines. These reactions, unlike those with cyclohexanone, can give hexahydroxanthenes containing various amine substituents (for example, compound **4a**). In Scheme 1, the heterocycles of enamines, which were introduced into the reactions with aminals, contain Y fragments (unlike X in the case of enamines formed *in situ* from aminals). The reactions were performed in acetonitrile (method *B*), in benzene (method *D*), and without a solvent (method *C*). Heating of aminals **1a,c,e** with enamine **3a** in MeCN afforded tetrahydroxanthenes **5a,c,e**, respectively.

The reaction of aminal **1b** with enamine **3a** under the same conditions yielded hexahydroxanthene **4c**. In the absence of a solvent, the reactions of pairs **1b** + **3b** and **1f** + **3b** stopped at the stage of formation of hexahydroxanthenes **4a** and **4b**, respectively (in both cases, position 9 of hexahydroxanthenes is occupied by the piperidine residue). Under these conditions, the reactions of pairs **1a** + **3a** and **1c** + **3a**, which would give hexahydroxanthenes containing the morpholine substituents at position 9, afforded tetrahydroxanthenes **5a,c**, *i.e.*, morpholine was eliminated.

The reactions of pairs **1f** + **3b**, **1b** + **3a**, and **1a** + **3a** in benzene yielded hexahydroxanthenes **4b—d**, respectively.

It is known[11] that 5-nitrosalicylaldehyde, which exhibits increased acidity, does not form aminals with strongly basic aliphatic secondary amines. In these reactions, the phenol proton is completely transferred to the imine N atom to form ionic phenoxides **7** with the substantially delocalized negative charge in the anion. The reactions of phenoxides **7a,b** with 1-piperidinocyclohexene **3b** both in benzene and in the absence of a solvent yielded the same tetrahydroxanthene **5f**. We believe that compounds **7** enter into the reactions with enamines in the *o*-quinoid form (Scheme 2). (A substantial contribution of the quinoid form to the structure of anion **7a** was established by X-ray diffraction analysis.[11])

**Scheme 2**



**7**: $R_2 = (CH_2)_5$ (**a**); $R = CH_2Ph$ (**b**), $n$-$C_5H_{11}$ (**c**)

**3**: $X = CH_2$ (**b**), NMe (**c**)

**5**: $X = CH_2$ (**f**), NMe (**g**)

The reaction of phenoxide **7a** with 1-morpholinocyclohexene **3a** also yielded tetrahydroxanthene **5f** as the major product with an admixture of compound **5a** (~25% according to the $^1$H NMR spectra). This fact indicates that the less basic morpholine ($pK_a = 8.33$)[12] was replaced by the more basic piperidine ($pK_a = 11.12$)[12] in the course of the reaction. This exchange was also observed in the reaction of 5-chlorosalicylaldehyde piperidinal with 1-morpholinocyclohexene (**3a**) in benzene. In the latter case, the major product was hexahydroxanthene **4b**, containing two piperidine residues. In the reaction of the "reverse" pair, *viz.*, in the reaction of 5-chlorosalicylaldehyde morpholinal **1b** with piperidinocyclohexene **3b**, this exchange did not occur and the reaction afforded hexahydroxanthene **4a** containing two different amine substituents. Therefore, we observed exchange in the cases when the more basic cyclic amine, *viz.*, piperidine, was a component of aminal that dissociated in the course of the reaction, while the less basic cyclic amine, *viz.*, morpholine, was incorporated into enamine. The same behavior of piperidine was observed in the reaction of piperidinium 4-nitro-2-formylphenoxide (**7a**) with 1-morpholinocyclohexene (**3a**). Thus, the content of morpholine derivative **5a** in the mixture of the final products was only ~25% ($^1$H NMR spectral data), while the replacement product **5f** was obtained as the major component (~75%).

No evidence of this exchange was observed in the reactions of enamines with phenoxides of acyclic secondary amines. The reaction of dibenzylammonium 4-nitro-2-formylphenoxide (**7b**) with 1-morpholinocyclohexene (**3a**) afforded pure 4a-morpholino-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthene (**5a**), while the reaction of dipentylammonium 4-nitro-2-formylphenoxide (**7c**) with 1-(4-methylpiperazin-1-yl)cyclohexene (**3c**) yielded 4a-(4-methylpiperazin-1-yl)-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthene (**5g**).

Hexahydroxanthenes **4** containing three asymmetric carbon atoms can, in principle, exist as four enantiomeric pairs. The $^1$H NMR spectrum of compound **4b** is indicative of the presence of two isomers in a ratio of 1 : 1. According to the $^1$H NMR spectral data, the morpholine analog of this dihydroxanthene (**4c**) obtained in benzene by method ***D*** was also a mixture primarily of two isomers (~65% and ~30%) with a small admixture of a third isomer (~5%). The fundamentally different situation was observed in the reaction performed in MeCN (**4c**, method ***B***), namely, although the product obtained was of the same elemental composition, it did not contain the isomer which accounted for ~65% of the mixture formed in benzene. The major component of the latter mixture (~80%) was the isomer whose content in the products obtained in the reaction in benzene was ~30%, and ~20% of the mixture was accounted for by the isomer which was obtained in benzene as an insignificant admixture (~5%).

Based on the experimental data, certain conclusions can be made about the effect of various factors on the results of the reactions. The reactions of aminal **1a** with enamine **3a** in acetonitrile and benzene, which boil at virtually the same temperature, afforded tetrahydroxanthene **5a** and hexahydroxanthene **4d**, respectively, *i.e.*, a polar solvent favors elimination of amine from hexahydroxanthene. However, this elimination did not occur in the reaction of **1b** with **3b** and the reactions in both solvents gave hexahydroxanthene **4c**. The synthesis of compound **5b** according to method *A* coupled with the above-mentioned data clearly demonstrate the role of temperature. Thus, hexahydroxanthene **4c** remained unchanged in boiling acetonitrile (81.5 °C) for 2 h, while when boiled in cyclohexanone (155 °C), it eliminated morpholine to form **5b** over 2—3 min.

In the reactions under consideration one target product was formed from another product. This raised the question about the purity of the resulting compounds. In some instances, the results of $^1$H NMR spectroscopy demonstrated that compounds isolated in these reactions contained admixtures, which were not isomers of the target compounds. Generally, these were small admixtures of tetrahydroxanthenes **5** in hexahydroxanthenes **4**. In addition, virtually all "crude" tetrahydroxanthenes **5** contained insignificant admixtures that gave a characteristic doublet of triplets in the $^1$H NMR spectra (for example, for **5b** (method *A*) in $CDCl_3$: δ 5.11, $J$ = 4.7 and 1.8 Hz). We attributed this signal to the C(4)H proton of dihydroxanthene formed from tetrahydroxanthene as a result of elimination of an amine molecule, which was confirmed by the synthesis of 4a-morpholino-7-nitro-2,3-dihydro-1*H*-xanthene (**6**) (Scheme 3).

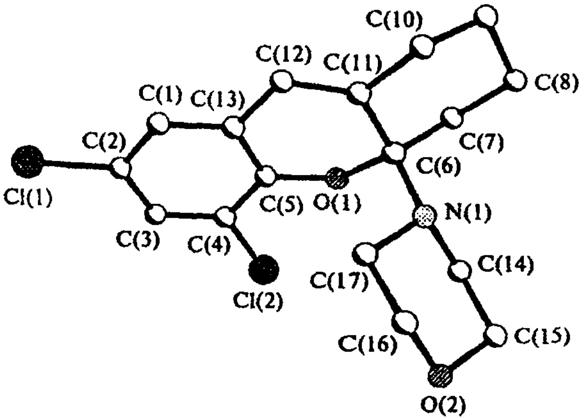
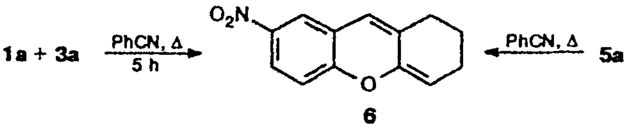


**Fig 1.** Overall view of molecule **5c**.

**Scheme 3**



In an independent experiment, it was demonstrated that compound **6** was formed upon prolonged boiling of tetrahydroxanthene **5a** in benzonitrile.

The structure of compound **5c** was established by X-ray diffraction analysis (Fig. 1, Tables 1—3). The

**Table 1.** Bond lengths ($d$) in the structure of **5c**

| Bond | $d$/Å |
|---|---|
| Cl(1)—C(2) | 1.740(2) |
| Cl(2)—C(4) | 1.727(2) |
| O(1)—C(5) | 1.356(2) |
| O(1)—C(6) | 1.483(2) |
| O(2)—C(16) | 1.417(3) |
| O(2)—C(15) | 1.416(4) |
| N(1)—C(6) | 1.447(3) |
| N(1)—C(17) | 1.464(3) |
| N(1)—C(14) | 1.470(3) |
| C(1)—C(2) | 1.382(4) |
| C(1)—C(13) | 1.387(3) |
| C(2)—C(3) | 1.382(4) |
| C(3)—C(4) | 1.388(3) |
| C(4)—C(5) | 1.384(3) |
| C(5)—C(13) | 1.401(3) |
| C(6)—C(11) | 1.519(3) |
| C(6)—C(7) | 1.529(3) |
| C(7)—C(8) | 1.518(4) |
| C(8)—C(9) | 1.514(4) |
| C(9)—C(10) | 1.518(4) |
| C(10)—C(11) | 1.502(3) |
| C(11)—C(12) | 1.328(3) |
| C(12)—C(13) | 1.454(3) |
| C(14)—C(15) | 1.505(4) |
| C(16)—C(17) | 1.503(3) |

**Table 2.** Bond angles (ω) in the structure of **5c**

| Angle | ω/deg |
|---|---|
| C(5)—O(1)—C(6) | 120.8(2) |
| C(16)—O(2)—C(15) | 109.3(2) |
| C(6)—N(1)—C(17) | 113.6(2) |
| C(6)—N(1)—C(14) | 114.9(2) |
| C(17)—N(1)—C(14) | 108.2(2) |
| C(2)—C(1)—C(13) | 120.4(2) |
| C(1)—C(2)—C(3) | 121.4(2) |
| C(1)—C(2)—Cl(1) | 119.5(2) |
| C(3)—C(2)—Cl(1) | 119.1(2) |
| C(2)—C(3)—C(4) | 118.1(2) |
| C(5)—C(4)—C(3) | 121.5(2) |
| C(5)—C(4)—Cl(2) | 118.9(2) |
| C(3)—C(4)—Cl(2) | 119.5(2) |
| O(1)—C(5)—C(4) | 118.8(2) |
| O(1)—C(5)—C(13) | 121.5(2) |
| C(4)—C(5)—C(13) | 119.7(2) |
| N(1)—C(6)—O(1) | 110.1(2) |
| N(1)—C(6)—C(11) | 110.1(2) |
| O(1)—C(6)—C(11) | 111.7(2) |
| N(1)—C(6)—C(7) | 112.5(2) |
| O(1)—C(6)—C(7) | 103.8(2) |
| C(11)—C(6)—C(7) | 108.5(2) |
| C(8)—C(7)—C(6) | 112.3(2) |
| C(9)—C(8)—C(7) | 110.3(2) |
| C(8)—C(9)—C(10) | 111.2(2) |
| C(11)—C(10)—C(9) | 113.0(2) |
| C(12)—C(11)—C(10) | 124.6(2) |
| C(12)—C(11)—C(6) | 121.3(2) |
| C(10)—C(11)—C(6) | 114.1(2) |
| C(11)—C(12)—C(13) | 122.2(2) |
| C(1)—C(13)—C(5) | 118.9(2) |
| C(1)—C(13)—C(12) | 123.9(2) |
| C(5)—C(13)—C(12) | 117.2(2) |
| N(1)—C(14)—C(15) | 110.2(2) |
| O(2)—C(15)—C(14) | 112.8(2) |
| O(2)—C(16)—C(17) | 111.0(2) |
| N(1)—C(17)—C(16) | 111.0(2) |

**Table 3.** Coordinates of nonhydrogen atoms (×10$^4$) and hydrogen atoms (×10$^3$) and equivalent isotropic thermal parameters ($U_{eq}$×10$^3$) in the structure of **5c**

| Atom | *x* | *y* | *z* | $U_{eq}$/Å$^2$ |
|---|---|---|---|---|
| Cl(1) | 5270(1) | 4334(1) | 3728(1) | 91(1) |
| Cl(2) | 3111(1) | 7082(1) | 1434(1) | 66(1) |
| O(1) | 507(2) | 7331(1) | 2759(1) | 44(1) |
| O(2) | 2648(2) | 10223(1) | 3704(1) | 61(1) |
| N(1) | 215(2) | 8734(1) | 3672(1) | 37(1) |
| C(1) | 2633(3) | 5467(2) | 4064(2) | 54(1) |
| C(2) | 3889(3) | 5248(2) | 3462(2) | 57(1) |
| C(3) | 4064(3) | 5737(2) | 2648(2) | 54(1) |
| C(4) | 2931(3) | 6453(2) | 2443(2) | 45(1) |
| C(5) | 1649(3) | 6674(1) | 3028(1) | 39(1) |
| C(6) | −525(2) | 7829(1) | 3441(1) | 38(1) |
| C(7) | −2224(3) | 7930(2) | 2957(2) | 49(1) |
| C(8) | −3523(3) | 8360(2) | 3576(2) | 63(1) |
| C(9) | −3738(3) | 7753(2) | 4421(2) | 68(1) |
| C(10) | −2083(3) | 7595(2) | 4921(2) | 55(1) |
| C(11) | −741(3) | 7241(1) | 4303(1) | 42(1) |
| C(12) | 175(3) | 6472(2) | 4462(2) | 47(1) |
| C(13) | 1505(3) | 6183(1) | 3858(1) | 44(1) |
| C(14) | 416(3) | 9383(3) | 2894(2) | 54(1) |
| C(15) | 1104(4) | 10317(2) | 3223(2) | 66(1) |
| C(16) | 2444(3) | 9611(2) | 4464(2) | 54(1) |
| C(17) | 1825(3) | 8656(2) | 4159(2) | 47(1) |
| H(1) | 259(4) | 515(2) | 462(2) | 74(9) |
| H(3) | 494(4) | 561(2) | 224(2) | 72(8) |
| H(7A) | −211(3) | 826(2) | 241(2) | 60(7) |
| H(7B) | −259(4) | 734(2) | 280(2) | 66(8) |
| H(8A) | −315(3) | 899(2) | 378(2) | 59(7) |
| H(8B) | −457(4) | 842(2) | 328(2) | 67(8) |
| H(9A) | −423(4) | 716(3) | 427(2) | 84(10) |
| H(9B) | −454(4) | 799(3) | 486(3) | 92(10) |
| H(10A) | −168(3) | 819(2) | 520(2) | 54(6) |
| H(10B) | −219(4) | 721(2) | 537(2) | 71(9) |
| H(12) | 1(3) | 614(2) | 496(2) | 55(7) |
| H(14A) | −67(4) | 950(2) | 257(2) | 72(8) |
| H(14B) | 112(4) | 907(2) | 246(2) | 68(8) |
| H(15A) | 135(4) | 1074(2) | 270(2) | 82(9) |
| H(15B) | 25(4) | 1061(2) | 365(2) | 72(8) |
| H(16A) | 166(4) | 992(2) | 489(2) | 71(8) |
| H(16B) | 357(4) | 955(2) | 478(2) | 61(7) |
| H(17A) | 265(3) | 837(2) | 379(2) | 48(6) |
| H(17B) | 164(3) | 827(2) | 467(2) | 59(7) |

2*H*-pyran ring adopts a distorted sofa boat. The C(6) and C(11) atoms deviate from the plane through the remaining atoms of the ring by 0.41 and 0.25 Å, respectively. The cyclohexane and morpholine rings adopt a chair conformation. The C(6) and C(9) atoms deviate from the C(7)C(8)C(10)C(11) plane by 0.67 and −0.64 Å, respectively. The N(1) and O(2) atoms deviate from the C(14)C(15)C(16)C(17) plane by −0.67 and 0.65 Å, respectively. The morpholyl substituent is in the pseudoaxial orientation (the C(12)—C(11)—C(6)—N(1) torsion angle is 110.4(2)°) and is located virtually perpendicular to the C(6)—O(1) bond. Apparently, this orientation of the heterocycle is governed by shortened intramolecular H(7A)...C(14) and H(7A)...H(14A) contacts (2.66 and 2.11 Å, respectively; the sums of the van der Waals radii[13] are 2.87 and 2.32 Å, respectively).

In the crystal, there are also shortened intermolecular contacts: Cl(2)...Cl(1)′ (1 − *x*, 0.5 + *y*, 0.5 − *z*), 3.45 Å (3.60 Å); and Cl(2)...H(17A)′ (*x*, 1.5 − *y*, −0.5 + *z*), 2.86 Å (2.96 Å).

## Experimental

The IR spectra were recorded on a Specord IR-75 instrument as Nujol mulls. The UV spectra were measured on a Specord M-40 spectrophotometer. The $^1$H NMR spectra (in $CDCl_3$) were obtained on a Varian UNITY-300 spectrometer (except for compound **6a**, whose spectrum was obtained on a Bruker DPX-250 spectrometer). The aminals were synthesized according to procedures developed by us previously.[2,3,6,9] The enamines were synthesized according to a known procedure.[14]

**4a-Morpholino-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthene (5a).** *A.* A mixture of aminal **1a** (0.65 g, 2 mmol) and cyclohexanone (0.35 g, 3.4 mmol) was heated until the exothermic reaction started (70—80 °C), in the course of which the temperature increased to 120 °C. The mixture was kept at this temperature for 2 min and then propan-2-ol (3 mL) was added. The mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold propan-2-ol, and dried. Pale-yellow crystals were obtained in a yield of 0.2 g (31%), m.p. 136—139 °C (from MeOH). .

*C.* A mixture of aminal **1a** (0.32 g, 1 mmol) and enamine **3a** (0.4 mL, 2 mmol) was heated at 140—150 °C for 2 min and cooled. Then MeOH (3 mL) was added and the reaction mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was ~0.32 g (quantitative), m.p. 140 °C (from MeOH). Found (%): C, 64.53; H, 6.54; N, 9.06. $C_{17}H_{20}N_2O_4$. Calculated (%): C, 64.54; H, 6.37; N, 8.86. IR, ν/cm$^{-1}$: 1607, 1581 (arom.); 1514, 1341 ($NO_2$); 1114 (C—O—C). $^1$H NMR, δ: 1.50—2.80 (m, 12 H, $CH_2$, $CH_2N$); 3.62 (m, 4 H, 2 $CH_2O$); 6.28 (s, 1 H, C(9)H); 6.72 (d, 1 H, C(5)H, *J* = 8.9 Hz); 7.78 (d, 1 H, C(8)H, *J* = 2.7 Hz); 7.95 (dd, 1 H, C(6)H, $^3J$ = 8.9 Hz, $^4J$ = 2.7 Hz).

**7-Chloro-4a-morpholino-1,2,3,4-tetrahydro-4a*H*-xanthene (5b).** *A.* A mixture of aminal **1b** (0.62 g, 2 mmol) and cyclohexanone (0.4 mL, ~0.4 mmol) was refluxed for 3 min and cooled. Then EtOH (1.5 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold EtOH, and dried. Colorless crystals were obtained in a yield of 0.13 g (21%), m.p. 164—166 °C (from MeOH). (The crude product contained an admixture of dihydroxanthene. Before analyzing and recording the $^1$H NMR spectrum, the compound was twice recrystallized from MeOH.) Found (%): C, 67.06; H, 6.42; N, 4.63; Cl, 11.37. $C_{17}H_{20}ClNO_2$. Calculated (%): C, 66.77; H, 6.59; N, 4.58; Cl, 11.59. IR, ν/cm$^{-1}$: 1480, 1474 (arom.); 1114 (C—O—C). $^1$H NMR, δ: 1.50—2.60 (m, 8 H, $CH_2$); 2.65—2.80 (m, 4 H, 2 $CH_2N$); 3.60 (m, 4 H, 2 $CH_2O$); 6.16 (d, 1 H, C(9)H, *J* = 1.8 Hz); 6.61 (d, 1 H, C(5)H, *J* = 8.4 Hz); 6.82 (d, 1 H, C(8)H, *J* = 2.6 Hz); 6.95 (dd, 1 H, C(6)H, $^3J$ = 8.4 Hz, $^4J$ = 2.6 Hz).

**5,7-Dichloro-4a-morpholino-1,2,3,4-tetrahydro-4a*H*-xanthene (5c).** *A.* A mixture of aminal **1c** (0.7 g, 2 mmol) and cyclohexanone (0.35 mL, ~3.5 mmol) was heated at 120—

130 °C for 2 min and then cooled. Two drops of water and EtOH (2 mL) were added. The mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with aqueous EtOH, and dried. Colorless crystals were obtained in a yield of 0.2 g (29%), m.p. 145—148 °C.

***B.*** A mixture of aminal **1c** (0.35 g, 1 mmol) and enamine **3a** (0.25 mL, 1.25 mmol) in acetonitrile (5 mL) was refluxed for 2.5 h and then cooled. The resinous precipitate that formed upon treatment with water rapidly crystallized out upon cooling and rubbing. The yield of the crude product was ~0.34 g (quantitative).

***C.*** A mixture of aminal **1c** (0.35 g, 1 mmol) and enamine **3a** (0.25 mL, 1.25 mmol) was refluxed for 2 min and cooled. Then MeOH (1.5 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was 0.2 g (59%), m.p. 151—153 °C (from isooctane). Found (%): C, 60.15; H, 5.56; N, 4.39; Cl, 21.05. $C_{17}H_{19}Cl_2NO_2$. Calculated (%): C, 60.01; H, 5.63; N, 4.12; Cl, 20.84. IR, ν/cm$^{-1}$: 1560, 1480 (sh), 1467 (arom.); 1114 (C—O—C). $^1$H NMR, δ: 1.50—2.60 (m, 8 H, $CH_2$); 2.60—2.85 (m, 4 H, 2 $CH_2N$); 3.62 (m, 4 H, 2 $CH_2O$); 6.17 (s, 1 H, C(9)H); 6.75 (s, 1 H, C(8)H); 7.08 (s, 1 H, C(6)H).

**5,7-Dichloro-4a-piperidino-1,2,3,4-tetrahydro-4a*H*-xanthene (5d).** ***A.*** A mixture of aminal **1d** (0.7 g, 2 mmol) and cyclohexanone (0.7 mL, 7 mmol) was refluxed for 3 min and cooled. Then MeOH (4 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The colorless crystalline precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was 0.37 g (55%), m.p. 105 °C (from MeOH). Found (%): C, 64.19; H, 6.24; N, 4.35; Cl, 20.87. $C_{18}H_{21}Cl_2NO$. Calculated (%): C, 63.91; H, 6.26; N, 4.14; Cl, 20.96. IR, ν/cm$^{-1}$: 1567, 1480 (sh), 1467 (arom.). $^1$H NMR, δ: 1.40—2.80 (m, 18 H, $CH_2$, $CH_2N$); 6.11 (s, 1 H, C(9)H); 6.73 (d, 1 H, C(8)H, *J* = 2.3 Hz); 7.05 (d, 1 H, C(6)H, *J* = 2.3 Hz).

**5,7-Dibromo-4a-morpholino-1,2,3,4-tetrahydro-4a*H*-xanthene (5e).** ***B.*** A mixture of aminal **1e** (0.44 g, 1 mmol) and enamine **3a** (0.25 mL, 1.25 mmol) in MeCN (2 mL) was refluxed for 2 h and cooled. Then MeOH (6 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The colorless crystalline precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was 0.14 g (32.5%), m.p. 130—132 °C (from a 1 : 3 MeCN—MeOH mixture). Found (%): C, 47.74; H, 4.16; N, 3.18; Br, 36.92. $C_{17}H_{19}Br_2NO_2$. Calculated (%): C, 47.58; H, 4.46; N, 3.26; Br, 37.24. IR, ν/cm$^{-1}$: 1554, 1467, 1454 (arom.); 1120 (C—O—C). $^1$H NMR, δ: 1.40—3.20 (m, 12 H, $CH_2$, $CH_2N$); 3.61 (m, 4 H, 2 $CH_2O$); 6.14 (d, 1 H, C(9)H, *J* = 1.9 Hz); 6.92 (d, 1 H, C(8)H, *J* = 2.3 Hz); 7.36 (d, 1 H, C(6)H, *J* = 2.3 Hz).

**7-Chloro-9-morpholino-4a-piperidino-1,2,3,4,9,9a-hexahydro-4a*H*-xanthene (4a).** ***C.*** A mixture of aminal **1b** (0.31 g, 1 mmol) and enamine **3b** (0.3 mL, 1.5 mmol) was heated at 140 °C for 3 min and cooled. Then MeOH (3 mL) was added and the mixture was heated to boiling, cooled with ice, and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold MeOH, and dried. Colorless crystals were obtained in a yield of 0.21 g (69%), m.p. 120—123 °C (from EtOH). Found (%): C, 68.00; H, 8.18; N, 6.89; Cl, 9.06. $C_{22}H_{31}ClN_2O_2$. Calculated (%): C, 67.59; H, 7.99; N, 7.17; Cl, 9.07. IR, ν/cm$^{-1}$: 1574, 1480 (sh), 1467 (arom.); 1114 (C—O—C). $^1$H NMR, δ: 1.52—3.70 (m, 27 H, CH, $CH_2$, $CH_2N$, $CH_2O$); 3.93 (d, 1 H, CH, C(9)H, *J* = 9.3 Hz); 6.63 (d, 1 H, C(5)H, *J* = 8.6 Hz); 7.00 (dd, 1 H, C(6)H, $^3J$ = 8.6 Hz, $^4J$ = 2.3 Hz); 7.45 (d, 1 H, C(8)H, *J* = 2.3 Hz).

**7-Chloro-4a,9-di(piperidino)-1,2,3,4,9,9a-hexahydro-4a*H*-xanthene (4b).** ***C.*** A mixture of aminal **1c** (0.31 g, 1 mmol) and enamine **3b** (0.25 mL, 1.25 mmol) was heated at 120 °C for 2 min. Then MeOH (3 mL) was added. The mixture was refluxed, rubbed with a glass rod until a crystalline precipitate formed, and cooled. The precipitate was filtered off, washed with MeOH, and dried. Colorless crystals were obtained in a yield of 0.32 g (82%), m.p. 128—129 °C (from MeCN).

***D.*** A mixture of aminal **1c** (0.31 g, 1 mmol) and enamine **3b** (0.25 mL, 1.25 mmol) in benzene (2 mL) was refluxed for 1 h and then MeOH (10 mL) was added. The mixture was cooled with ice and rubbed with a glass rod. The abundant colorless precipitate that formed was filtered off, washed with MeOH, and dried. The yield was 0.22 g (56%), m.p. 123—126 °C (from MeOH). Found (%): C, 70.83; H, 8.16; N, 7.35; Cl, 8.74. $C_{23}H_{33}ClN_2O$. Calculated (%): C, 71.02; H, 8.55; N, 7.20; Cl, 9.11. IR, ν/cm$^{-1}$: 1581, 1487 (sh), 1467, 1447 (sh) (arom.). (The IR spectra of the compounds obtained in benzene and in the absence of solvent were identical.) $^1$H NMR, δ: 1.30—2.90 (m, 29 H, CH, $CH_2$, $CH_2N$); 3.92 (d, ~0.5 H, C(9)H, *J* = 9.7 Hz); 4.32 (d, ~0.5 H, C(9)H, *J* = 5.0 Hz); 6.60 (d, ~0.5 H, C(5)H, *J* = 8.6 Hz); 6.68 (d, ~0.5 H, C(5)H, *J* = 8.6 Hz); 7.00 (m, 1 H, C(6)H); 7.36 (d, ~0.5 H, C(8)H, *J* = 2.6 Hz); 7.45 (d, ~0.5 H, C(8)H, *J* = 2 Hz).

**7-Chloro-4a,9-di(morpholino)-1,2,3,4,9,9a-hexahydro-4a*H*-xanthene (4c).** ***B.*** A mixture of aminal **1b** (0.62 g, 2 mmol) and enamine **3a** (0.5 mL, 2.5 mmol) in MeCN (4 mL) was refluxed for 2 h, cooled with ice, and rubbed with a glass rod. The colorless crystalline precipitate that formed was filtered off, washed with cold MeOH, and dried. Colorless crystals were obtained in a yield of 0.22 g (28%), m.p. 168—172 °C (from MeOH). Found (%): C, 63.50; H, 7.19; N, 7.32; Cl, 8.73. $C_{21}H_{29}ClN_2O_3$. Calculated (%): C, 64.19; H, 7.44; N, 7.13; Cl, 9.02. IR, ν/cm$^{-1}$: 1581, 1480, 1447 (arom.); 1121, 1114 (C—O—C). $^1$H NMR, δ: 1.20—3.20 (m, 16 H, $CH_2$, $CH_2N$); 3.50—3.95 (m, 9 H, C(9a)H, $CH_2O$); 4.16 (d, ~0.2 H, C(9)H, *J* = 6.6 Hz); 4.34 (d, ~0.8 H, C(9)H, *J* = 5.2 Hz); 6.70 (d, ~0.8 H, C(5)H, *J* = 8.6 Hz); 6.77 (d, ~0.2 H, C(5)H, *J* = 8.7 Hz); 7.05 (dd, ~0.8 H, C(6)H, $^3J$ = 8.6 Hz, $^4J$ = 2.4 Hz); 7.15 (dd, ~0.2 H, C(6)H, $^3J$ = 8.8 Hz, $^4J$ = 2.5 Hz); 7.37 (m, 1 H, C(8)H).

***D.*** A mixture of aminal **1b** (0.62 g, 2 mmol) and enamine **3a** (0.5 mL, 2.5 mmol) in benzene (3 mL) was refluxed for 2 h. Then MeOH (5 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The precipitate that formed was filtered off, washed with MeOH, and dried. Colorless crystals were obtained in a yield of 0.65 g (83%), m.p. 143—153 °C (from EtOH). Found (%): C, 63.65; H, 7.03; N, 7.41; Cl, 9.15. $C_{21}H_{29}ClN_2O_3$. Calculated (%): C, 64.19; H, 7.44; N, 7.13, Cl, 9.02. IR, ν/cm$^{-1}$: 1581, 1480 (sh), 1447 (arom.); 1114 (C—O—C). (The fingerprint regions of the IR spectra of specimens of **4c** obtained by different procedures are somewhat different.) $^1$H NMR, δ: 1.20—3.10 (m, 17 H, CH, $CH_2$, $CH_2N$); 3.50—4.36 (m, 9 H, C(9)H, $CH_2O$); 6.64 (d, ~0.65 H, C(5)H, *J* = 8.6 Hz); 6.70 (d, ~0.3 H, C(5)H, *J* = 8.6 Hz); 6.78 (d, ~0.05 H, C(5)H, *J* = 8.7 Hz); 7.00 (m, 1 H, C(6)H); 7.37 (d, ~0.3H, C(8)H, *J* = 2.6 Hz); 7.44 (d, ~0.7 H, C(8)H, *J* = 2 Hz).

**4a,9-Di(morpholino)-7-nitro-1,2,3,4,9,9a-hexahydro-4a*H*-xanthene (4d).** ***D.*** A mixture of aminal **1a** (0.32 g, 1 mmol) and enamine **3a** (0.25 mL, 1.25 mmol) in benzene (2 mL) was refluxed for 3 h. Then MeOH (3 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The crystalline precipitate that formed was filtered off, washed with MeOH, and dried. The yield was 0.27 g (67.5%), m.p. 161—162 °C (from MeCN). The resulting compound is light-sensitive (turned green on storage in the light). Found (%): C, 62.52; H, 6.95; N, 10.70. $C_{21}H_{29}N_3O_5$. Calculated (%): C, 62.51; H, 7.24; N, 10.41. IR, ν/cm$^{-1}$: 1607, 1581, 1487 (arom.); 1514, 1341 ($NO_2$); 1107 (C—O—C). $^1$H NMR, δ: 1.50—1.87 (m, 8 H, $CH_2$); 2.47 (m, 1 H, C(9a)H); 2.79 (m, 8 H, $CH_2N$); 3.71 (m, 8 H, $CH_2O$); 4.07 (d, 1 H, C(9)H, $J$ = 10 Hz); 6.76 (d, 1 H, C(5)H, $J$ = 9 Hz); 7.99 (dd, 1 H, C(6)H, $^3J$ = 8.9 Hz, $^4J$ = 2.8 Hz); 8.50 (d, 1 H, C(8)H, $^4J$ = 2.7 Hz).

### Syntheses of tetrahydroxanthenes 5 from phenoxides 7

**4a-Morpholino-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthene (5a).** A mixture of dibenzylammonium 2-formyl-4-nitrophenoxide (**7b**)[11] (0.32 g, 1 mmol) and enamine **3a** (0.25 mL, 1.25 mmol) in benzene (2 mL) was refluxed for 2 h. Then MeOH (2 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The crystalline precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was 0.23 g (72%), m.p. 140—142 °C (from MeOH). A mixture with the known sample did not give a melting point depression. The IR spectra of the samples are identical.

**7-Nitro-4a-piperidino-1,2,3,4-tetrahydro-4a*H*-xanthene (5f).** *B.* A mixture of piperidinium 2-formyl-4-nitrophenoxide (**7a**)[11] (0.25 g, 1 mmol) and enamine **3b** (0.25 mL, 1.25 mmol) was heated at 110—120 °C for 2 min and cooled. Then MeOH (3 mL) was added and the mixture was cooled with ice and rubbed with a glass rod. The crystalline precipitate that formed was filtered off, washed with MeOH, and dried. The yield was 0.1 g (32%), m.p. 124—127 °C (from MeOH).

*D.* A mixture of compound **7a** (0.25 g, 1 mmol) and enamine **3b** (0.25 mL, 1.25 mmol) in benzene (2 mL) was refluxed for 1 h. The solvent was evaporated. The residue was triturated with MeOH (3 mL). The crystalline precipitate that formed was filtered off, washed with cold MeOH, and dried. The yield was 0.25 g (64.5%), m.p. 124—127 °C (from MeOH). Found (%): C, 69.11; H, 6.77; N, 8.70. $C_{18}H_{22}N_2O_3$. Calculated (%): C, 68.77; H, 7.05; N, 8.91. IR, ν/cm$^{-1}$: 1667 (C=C); 1607, 1574, 1480, 1474 (arom.); 1514, 1334 ($NO_2$). (The IR spectra of the compounds obtained in benzene and in the absence of solvent were identical.) $^1$H NMR, δ: 1.40—2.60 (m, 14 H, $CH_2$); 2.73 (m, 4 H, 2 $CH_2N$); 6.23 (d, 1 H, C(9)H, $J$ = 1.5 Hz); 6.69 (d, 1 H, C(5)H, $J$ = 8.9 Hz); 7.77 (d, 1 H, C(8)H, $J$ = 2.7 Hz); 7.93 (dd, 1 H, C(6)H, $^3J$ = 8.9 Hz, $^4J$ = 2.7 Hz).

**4a-(4-Methylpiperazin-1-yl)-7-nitro-1,2,3,4-tetrahydro-4a*H*-xanthene (5g).** A mixture of dipentylammonium 2-formyl-4-nitrophenoxide (**7c**)[11] (0.33 g, 1 mmol) and 1-(4-methylpiperazin-1-yl)cyclohexene (**3c**) (0.4 mL, ~2 mmol) was heated at 140 °C over 2 min and cooled. Then MeOH was added (10 mL). The colorless crystalline precipitate that formed upon treatment with water was filtered off and dried. The yield of the crude product (virtually pure according to the IR spectral data) was ~0.33 g (quantitative), m.p. 150—153 °C (from propan-2-ol). Found (%): C, 65.62; H, 6.94; N, 13.10. $C_{18}H_{23}N_3O_3$. Calculated (%): C, 65.63; H, 7.04; N, 12.76. IR, ν/cm$^{-1}$: 1607, 1581, 1487, 1474 (arom.); 1514, 1341 ($NO_2$). $^1$H NMR, δ: 1.40—2.40 (m, 8 H, $CH_2$); 2.25 (s, 3 H, $CH_3$); 2.50 (m, 4 H, 2 $CH_2N$); 2.85 (m, 4 H, 2 $CH_2N$); 6.25 (d, 1 H, C(9)H, $J$ = 1.5 Hz); 6.68 (d, 1 H, C(5)H, $J$ = 8.9 Hz); 7.77 (d, 1 H, C(8)H, $^4J$ = 2.75 Hz); 7.91 (dd, 1 H, C(6)H, $^3J$ = 9.0 Hz, $^4J$ = 2.8 Hz).

**7-Nitro-2,3-dihydro-1*H*-xanthene (6).** A mixture of aminal **1a** (0.64 g, 2 mmol) and enamine **3a** (0.5 mL, 2.5 mmol) in benzonitrile (2 mL) was refluxed for 4 h, cooled with ice, and rubbed with a glass rod. The precipitate that formed was filtered off, washed with cold MeCN, MeOH, and hexane, and dried. Yellow crystals were obtained in a yield of 0.15 g (33%), m.p. 149—151 °C (from MeOH—acetone, 2 : 1). Found (%): C, 68.06; H, 4.71; N, 5.93. $C_{13}H_{11}NO_3$. Calculated (%): C, 68.11; H, 4.84; N, 6.11. IR, ν/cm$^{-1}$: 1647, 1621 (C=C); 1607, 1567 (arom.); 1514, 1334 ($NO_2$). $^1$H NMR, δ: 1.69 (m, 2 H, C(2)H); 2.25 (m, 2 H, C(3)H); 2.44 (m, 2 H, C(1)H); 5.25 (dt, 1 H, C(4)H, $^3J$ = 4.7 Hz, $^5J$ = 1.9 Hz); 6.02 (br.s, 1 H, C(9)H); 6.75 (d, 1 H, C(5)H, $J$ = 8.9 Hz); 7.74 (d, 1 H, C(8)H, $J$ = 2.8 Hz); 7.92 (dd, 1 H, C(6)H, $^3J$ = 8.9 Hz, $^4J$ = 2.8 Hz).

**X-ray diffraction study of compound 5c.** Crystals of **5c** ($C_{17}H_{19}Cl_2NO_2$) are monoclinic, at 20 °C $a$ = 8.017(2) Å, $b$ = 14.128(3) Å, $c$ = 14.572(4) Å, β = 91.11(2)°, $V$ = 1650.1(6) Å$^3$, $d_{calc}$ = 1.370 g cm$^{-3}$, space group $P2_1/c$, $Z$ = 4. The unit cell parameters and intensities of 2903 independent reflections ($R_{int}$ = 0.017) were measured on an automated Siemens P3/PC diffractometer (λ(Mo-Kα), graphite monochromator, θ/2θ scanning technique, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the use of the SHELXTL PLUS program package.[15] The positions of the hydrogen atoms were located from the difference electron density synthesis. The full-matrix least-squares refinement with anisotropic thermal parameters for nonhydrogen atoms (with isotropic thermal parameters for hydrogen atoms) based on $F^2$ converged to $wR_2$ = 0.1066 ($R_1$ = 0.043 using 2180 reflections with $F > 4\sigma(F)$, $S$ = 1.06). The coordinates of nonhydrogen atoms are given in Table 3.

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