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Two Independent Intermolecular 1*D*-Polymeric *H*-Bonds between Each Enantiomer in Octahydro-1*H*-Xanthene-1,8(2*H*)-Diones and Bis-Xanthen Analogues: Synthesis and Crystal Structure

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Reaction of 1,3-cyclohexanedione, aldehydes, and cyanogen bromide leads to the selective formation of octahydro-1*H*-xanthene-1,8(2*H*)-diones in moderate to good yields at room temperature under basic condition. The reaction of dialdehydes such as phthalaldehyde and terphthalaldehyde give tetrahydrodibenzo[*b*,*e*]oxepin-1(2*H*)-one and bifunctiolalized linked bis-xanthene analogues, respectively. All structures were characterized by FT IR, ^{1}H and ^{13}C NMR spectroscopy and mass analysis techniques. The structure of 3c was analyzed by X-ray crystallography. The pKa and hydrogen bond strength (E_{HB}) were determined in results of ≈11.7 and ≈5 kcal mol^{-1}, respectively, *via* *d*(O·····O) distance.

Keywords: 1,3-Cyclohexanedione, Octahydro-1*H*-xanthene-1,8(2*H*)-dione, One-pot, Xanthene, Polymeric H-bond

INTRODUCTION

Xanthene derivatives of 1,8-dioxo-octahydroxanthenes are an important class of heterocycle containing oxygen atom in which an aryl substituted pyran ring is fused on either side with two cyclohexenone rings. Recently, several works have been reported in the synthesis of this class of compounds, because the number of its applications has increased, both in the field of medicinal chemistry and material science [1-4]. 1,8-Dioxo-octahydroxanthenes have shown useful biological activities such as anti-inflammatory, antibacterial, and antiviral activities [5]. They have also found applications in biodegradable agrochemicals [6,7], cosmetics and pigments [8], fluorescent materials [9], photodynamic therapy [10], luminescent sensors [11] and laser technologies [12]. Octahydroxanthene derivatives containing a structural unit of benzopyrans can be used as the antispasm [13] and fluorescent fuel [14].

There are several reagents and routes reported for the synthesis of xanthene derivatives, such as $SO4^{2-}/SnO_2$-catalyzed efficient one-pot synthesis of 7,8-dihydro-2*H*-chromen-5-ones by formal [3+3] cycloaddition and 1,8-dioxo-octahydroxanthenes *via* a Knoevenagel condensation [15] ferric hydrogen sulfate [16], [Fe(III)(Salen)Cl] complex [17], primary amino alcohols [18], selectfluor™ [19], using *p*-dodecyl-benezenesulfonic acid (DBSA) or sodium dodecyl sulfate (SDS) [20], Fe_3O_4 nanoparticles [21], nano-Fe_3O_4 encapsulated-silica particles bearing sulfonic acid groups [22] in the presence of [bmim]ClO_4 [23], $SmCl_3$ [1], in refluxing acetic acid [24], in refluxing acetonitrile [25] and *etc*.

In the present research, we investigate the reaction of 1,3-cyclohexanedione with various aldehydes in the presence of BrCN and sodium ethoxide as the basic media, and the corresponding crystallographic structure is also described.

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MATERIALS AND METHODS

General

All structures were drawn using ChemDraw Ultra 8.0 and there numenclatures were performed using ChemBioDraw Ultra 12.0 versions, respectively. Melting points were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. The IR spectra were determined in the region 4000-400 cm^{-1} on a NEXUS 670 FT IR spectrometer by preparing KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on Bruker 400 FT-NMR at 400 and 100 MHz, respectively (Isfahan University, Isfahan, Iran) and 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). The ^1H and ^{13}C NMR spectra were obtained in solutions of DMSO-d_6 and/or $CDCl_3$ as the solvents using TMS as the internal standard. The ^1H and ^{13}C NMR spectra of 4 were obtained on solution in D_2O. The data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad singlet, coupling constant(s) in Hz, integration. All reactions were monitored by TLC with silica gel-coated plates (EtOAc: n-hexane/8:10/ v:v). The flame photometry analyzing Na^+ in 4 was recorded on CORNING 410 flame photometer (Urmia University, Urmia, Iran). Cyanogen bromide was synthesized based on the reported references in literature [26]. Compounds 1, all aldehydes, sodium and used solvents were purchased from Merck and Aldrich without further purification.

General Procedures for the Preparation of 3a-3g, 16a, 16b, 17b, 17c, 18b and 18c

The physical and spectral data of the selected compounds from 3a-3g, 16a, 16b, 17b, 17c, 18b and 18c are as follows (see also Table 1).

In a 25 ml round bottom flask equipped by a magnetically stirrer, dissolved 0.05 g (0.48 mmol) cyanogen bromide (BrCN) in 2 ml methanol at 0 °C. Then separately, 0.13 g (0.96 mmol) 1,3-cyclohexanedione and 0.05 g (0.48 mmol) benzaldehyde were dissolved in 10 ml methanol in an Erlenmeyer, 0.04 g (0.63 mmol) triethylamine was added into solution and then was transferred into a separatory funnel, then it was added drop wise into solution of BrCN in round bottom flask at 0 °C to room temperature. (Caution! The cyanogen bromide is toxic. Reactions should be carried out in a well-ventilated hood). The progression of reaction was monitored by thin layer chromatography (TLC). After outstanding 24 h, the crystalline solid was precipitated, filtered off, washed with few ml methanol and dried.

2-Bromocyclohexane-1,3-dione sodium salt (4). White crystaline solid; ^1H NMR (300 MHz, D_2O) δ: 4.69 (s, DOH), 2.35 (t, 4H, -CO-CH_2-), 1.76 (quin, 2H, -CO-CH_2-CH_2-); ^{13}C NMR (75 MHz, D_2O) δ: 20.6 (-CO-CH_2-**C**H_2-), 35.9 (-CO-**C**H_2-), 97.9 (C-Br), 192.1 (C=O); FT IR (KBr, cm^{-1}): 3431 (HO), 2953, 1569 (a shoulder at the peak's left side), 1495, 1338, 1191, 972, 801, 598, 453.

10a-Hydroxy-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3a). White crystaline solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.8 (bs, 2H, OH), 3.5 (bs, 4H), 2.5 (m, 5H, -CH_2-CO-, overlapped with the peak of DMSO's H_2O), 1.85 (m, 6H, -CH_2-octahydro-5H-xanthene and -CH_2-CH_2-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.4 (-CH-), 16.6 (-CH_2-), 16.8 (-CH_2-), 17.0 (-CH_2-), 36.6 (-CH_2-CO), 37.2 (-CH_2-CO), 90.5 (-C(OH)O-), 96.0 (C=C-C=O), 178.0 (-O-C=C-C=O), 191.5 (C=O), 204.9 (C=O); FT IR (KBr, cm^{-1}): 3321, 2932, 1589 (a shoulder at the peak's left side), 1387, 1099, 745.

10a-Hydroxy-9-phenyl-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3b). White crystaline solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.29 (s, 0.5H, OH), 12.02 (bs, 0.5H, OH), 7.03-7.21 (m. 5H, Ph-H), 5.40 (s, 1H, benzylic C-H), 2.00-2.60 (m, 7H, diastereotopic -CH_2-), 1.93-1.99 (m, 4H, diastereotopic -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1 (-CH_2-), 28.8 (-CH-), 32.9 (-CH_2-), 33.0 (-CH_2-), 33.5 (-CH_2-), 35.0 (-CH_2-CO), 40.0 (-CH_2-CO), 59.5 (-CH-CO), 116.4 (-C(OH)O-), 126.5 (C=C-C=O), 126.7 (C-ar.), 128.2 (C-ar.), 129.5 (C-ar.), 137.8 (C-ar.), 190.9 (-O-C=C-C=O), 192.1 (C=O), 219.4 (C=O); FT IR (KBr, cm^{-1}): 3303, 3053, 3024, 2958, 2918, 2824, 1721, 1634, 1600, 1493, 1377, 1192, 1106, 1035, 948, 693, 597.

10a-Hydroxy-9-(2-nitrophenyl)-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3c). White crystaline solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.87 (d, 1H, J = 8 Hz, ar.-H), 7.10-7.45 (m, 3H, ar.-H), 4.73 (3s, 1H, benzylic C-H), 1.15-2.48 (m, 12H, diastereotopic -CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.4, 20.7, 20.9, 27.6, 28.9, 29.1, 33.4, 35.2, 37.0, 37.3, 100.3, 101.7, 111.0, 114.8, 124.4, 124.6, 126.4, 127.2, 128.4, 132.4, 132.8, 133.0,

39.0, 148.9, 150.6, 169.0, 170.6, 195.5, 196.4, 205.2, 205.8 (a mixtures of two diastereomers); FT IR (KBr, cm^{-1}) 3380, 3050, 2962, 2878, 1713, 1611, 1524, 1424, 1383, 1343, 1081, 741, 595.

10a-Hydroxy-9-(3-nitrophenyl)-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3d). White crystaline solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.05-8.02 (m, 3H, ar.-H), 7.05 (d, 1H, J = 11.2 Hz, ar.-H), 4.44 (s, 1H, benzylic C-H), 4.00 (d, 1H, J = 10.4 Hz, CH, diastereotopic -CH_2-), 3.35 (bs, 1H, OH), 3.28 (s, 1H, diastereotopic -CH_2-), 3.16 (d, 1H, J = 10.8 Hz, diastereotopic -CH_2-), 1.55-2.51 (m, 12H, diastereotopic-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.7, 20.0, 20.3, 20.6, 28.4, 28.6, 31.4, 32.8, 33.1, 34.6, 36.0, 36.4, 58.2, 58.8, 100.1, 101.1, 110.0, 114.6, 120.1, 120.4, 122.6, 123.0, 128.6, 128.7, 135.0, 135.6, 147.0, 147.1, 147.3, 147.4, 168.5, 170.0, 195.5, 196.1, 205.1, 205.4 (a mixtures of two diastereomers); FT IR (KBr, cm^{-1}) 3400, 3159, 2953, 2873, 1724, 1602, 1525, 1427, 1382, 1347, 1254, 1226, 1189, 1110, 1035, 995, 945, 881, 844, 809, 726, 680, 638, 586, 534, 498, 454.

10a-Hydroxy-9-(3,4,5-trimethoxyphenyl)-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3e). White crystalin solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.851, 6.858, 6.863 (3s, 1H), 6.46 (s, 2H), 6.36 (s, 1H), 3.70 (s, 6H, 2OMe, major isomer), 3.68 (s, 3H, OMe, major isomer), 3.67 (s, 1H, OMe, minor isomer), 3.60 (s, 1H, OMe, minor isomer), 3.58 (s, 3H, OMe, major isomer), 3.36 (bs, 4H), 1.88-2.47 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.8, 20, 20.5, 20.6, 28.5, 28.6, 32.2, 32.3, 33, 34.4, 35.7, 36.67, 36.7, 38.8, 39.1, 39.3, 39.5, 39.7, 40, 40.11, 40.14, 40.4, 55.6, 59, 59.7, 59.8, 100, 100.9, 103.8, 105.2, 105.5, 111.2, 115.6, 135.1, 140, 140.9, 151.9, 167.3, 169, 195.5, 195.9, 205, 206.2 (a mixtures of two diastereomers); FT IR (KBr, cm^{-1}) 3324, 2946, 2838, 1718, 1651, 1615, 1510, 1459, 1426, 1373, 1329, 1230, 1190, 1122, 1039, 995, 949, 886, 855, 781, 701, 647, 584.

10a-Hydroxy-9-(2-hydroxyphenyl)-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3f). White crystaline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.77 (s, 1H, OH), 7.07-7.11 (m, 1H, ar.-H), 6.93-6.96 (m, 2H, ar.-H), 4.57 (s, 1H, benzylic CH), 2.69 (dt, 1H, J = 18, 4.8 Hz), 2.44-2.57 (m, 3H, CH, diastereotopic -CH_2-), 2.30-2.40 (m, 2H, diastereotopic -CH_2-), 1.88-2.11 (m, 4H, diastereotopic -CH_2-), 1.65-1.82 (m, 2H, diastereotopic -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6 (-CH_2-), 19.9 (-CH-), 28.0 (-CH_2-), 29.7 (-CH_2-), 36.0 (-CH_2-), 37.0 (-CH_2-CO), 77.2 (-CH-CO), 112.3 (–C(OH)O-), 115.5 (C=C-C=O), 119.8 (C-ar.), 124.6 (C-ar.), 127.5 (C-ar.), 128.1 (C-ar.), 150.9 (C-ar.), 171.2 (HO-C-ar.), 172.8 (-O-C=C-C=O), 197.1 (C=O), 201.5 (C=O); FT IR (KBr, cm^{-1}) 3446, 3100, 2952, 2538 (broad), 1642, 1552, 1422, 1373, 1294, 1236, 1193, 993, 773, 495.

9-(4-Fluorophenyl)-10a-hydroxy-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione (3g). White crystalin solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.18 (m, 1H, ar.-H), 6.86-7.03 (m, 3H, ar.-H), 4.40 (s, 1H, benzylic CH), 3.86 (m, 1H, diastereotopic -CH_2-), 3.67 (bs, 4H, OH, diastereotopic -CH_2-), 2.96 (m, 1H, diastereotopic -CH_2-), 1.60-2.41 (m, 10H, CH, diastereotopic -CH_2-),; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.1, 20.9, 21.0, 28.9, 29.0, 32.3, 33.5, 35.3, 36.2, 37.0, 37.2, 60.1, 100.5, 101.4, 114.3, 114.5, 116.0, 129.8, 130.5, 141.0, 141.5, 168.1, 170.0, 196.0, 205.4, (a mixtures of two diastereomers); FT IR (KBr, cm^{-1}) 3315, 3050, 2962, 2850, 1721, 1632, 1598, 1506, 1379, 1221, 1197, 1108, 1036, 950, 532.

5,10a-Dihydroxy-7,8,9,9a,10a,11,12,13,14a,14b-decahydrobenzo[5,6]oxepino[2,3,4-kl]xanthen-14(5H)-one (16a). White crystaline solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.04-7.18 (m, 4H, ar.-H), 6.62 (s, 1H, CHOH), 5.52 (d, 1H, J = 7.2 Hz, benzylic CH), 5.21-5.26 (m, 2H, CH, OH), 4.80 (s, 1H, OH), 2.72-2.81 (m, 1H, diastereotopic-CH_2-), 2.01-2.50 (m, 5H, diastereotopic -CH_2-), 1.90 (m, 2H, diastereotopic -CH_2-), 1.58 (m, 1H, diastereotopic -CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.7, 20.7, 28.2, 33.5, 35.1, 36.9, 65.3 (CH_3, CH_2, CH), 77.2 (CH-C=O), 77.3 (C=C), 101.2 (C(OH)O-C), 112.5, 123.4 (C-ar.), 124.0 (C-ar.), 125.7 (C-ar.), 127.5 (C-ar.), 143.1 (C-ar.), 144.6 (C-ar.), 197.5, 197.6, 205.5 (C=O); FT IR (KBr, cm^{-1}) 3274, 3020, 2948, 2900, 1721, 1625, 1384, 1189, 1080, 1003, 926, 749.

5,10a-Dihydroxy-8,8,12,12-tetramethyl-7,8,9,9a,10a,11,12,13,14a,14b-decahydrobenzo[5,6]oxepino[2,3,4-kl]xanthen-14(5H)-one (16b). Yellow crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.06 (m, 4H, ar.-H), 6.58 (s, 1H, CHOH), 5.49 (s, 1H, benzylic CH), 5.19 (s, 1H, OH), 4.73 (s, 1H, CH), 2.86 (d, 1H, 12.0 Hz, diastereotopic -CH_2-), 2.47-1.93 (m, 8H, diastereotopic-CH_2-), 1.10 (s,

3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 26.6, 27.1, 29.4, 32.3, 32.9, 33.2, 35.1, 42.5, 46.7, 51.1, 52.7 (CH_3, CH_2, CH), 64.6 (CH-C=O), 78.1 (C=C), 101.7 (C(OH)O-C), 111.2 (C-ar.), 123.7 (C-ar.), 124.3 (C-ar.), 126.2 (C-ar.), 127.9 (C-ar.), 143.9 (C-ar.), 145.0 (-O-C=C), 165.6 (C(OH)O-C), 197.8 (-O-C=C), 205.7 (C=O); MS (*m/z*, %) 396 (M^+, 51), 325 (70), 252 (11), 210 (18), 165 (17), 115 (20), 83 (100, base peak), 55 (46), 43 (13); FT-IR (KBr, cm^{-1}) 3204, 2955, 2935, 2870, 1721, 1650, 1618, 1381, 1072.

9,9'-(1,4-Phenylene)bis(10a-hydroxy-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8(2H)-dione) (17c). White crystaline solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.91 (bs, 1H, OH), 9.89 (s, 1H, OH), 7.70 (d, 2H, *J* = 8 Hz, major isomer, ar.-H), 7.42 (d, 2H, *J* = 8 Hz, major isomer, ar.-H), 7.70 (d, 2H, *J* = 8 Hz, minor isomer, overlapped with the peak of major isomer, ar.-H), 7.28 (d, 2H, *J* = 8 Hz, minor isomer, ar.-H), 4.39 (s, 1H, CH), 3.97 (s, 1H), 3.33 (bs, 5H, overlapped with the peak of water), 1.86-2.40 (m, 20H, diastereotopic -CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.6 , 19.9, 20.3, 20.5, 28.4, 28.5, 32.9, 34.67, 34.74, 36.5, 36.6 (CH_2, CH), 59.09, 59.14 (CH-C=O), 110.3, 115.0 (C=C-C=O), 127.1, 128.57, 128.69, 128.75, 128.74, 129.3, 133.6, 133.8, 152.7 (C-ar.), 168.0, 169.1, 192.5, 195.4 (-O-C=C-C=O), 196.0 (C=O), 204.8 (C=O) (a mixtures of two diastereomers); FT-IR (KBr, cm^{-1}): 3095, 2950, 2874, 1719, 1691, 1604, 1426, 1379, 1287, 1255, 1224, 1195, 1163, 1109, 1034, 996, 956, 887, 832, 783, 642, 589, 529.

9,9'-(1,3-Phenylene)bis(10a-hydroxy-3,3,6,6-tetramethyl-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8 (2H)-dione) (18b). White crystalline solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.90 (bs, 1H, OH), 7.19 (t, 1H, *J* = 7.5 Hz), 6.92 (d, 2H, *J* = 7.5 Hz, ar.-H), 6.87 (s, 1H, ar.-H), 5.52 (s, 1H, CH), 2.37-2.25 (m, 8H, diastereotopic -CH_2-), 1.18 (s, 6H, $2CH_3$), 1.07 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.9, 29.1, 31.7, 32.8, 46.4, 47.1 (CH_3, CH_2, CH), 115.7 (C(OH)O-C), 124.4 (C-ar.), 125.4 (C-ar.), 127.8 (C-ar.), 138.3 (C-ar.), 189.3 (C=O), 190.0 (C=O); MS (*m/z*, %) 622 (M^+, 1), 518 (8), 378 (47), 350 (8), 319 (36), 281 (24), 254 (17), 227 (7), 197 (6), 165 (9), 141 (18), 107 (35), 83 (100, base peak), 55 (61); FT-IR (KBr, cm^{-1}) 2958, 2929, 2872, 1594, 1372.

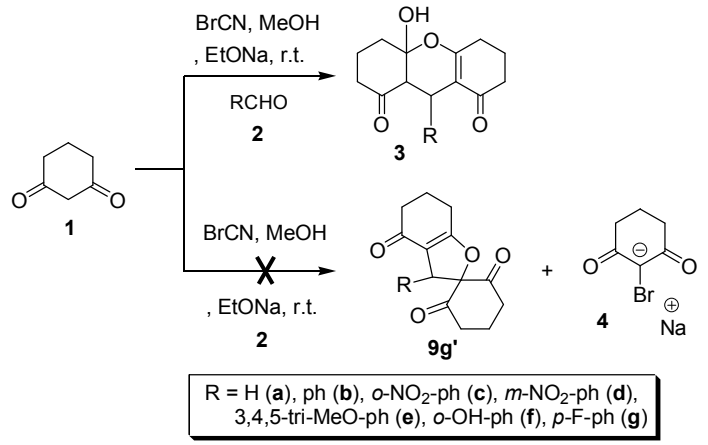
9,9'-(1,4-Phenylene)bis(10a-hydroxy-3,3,6,6-tetramethyl-3,4,5,6,7,8a,9,10a-octahydro-1H-xanthene-1,8 (2H)-dione) (18c). Yellow crystalline solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.87 (s, 2H, OH), 7.03 (s, 4H, ar.-H), 5.49 (s, 2H, CH), 2.48-2.27 (m, 16H, CH, diastereotopic -CH_2-), 1.23 (s, 12H, $4CH_3$), 1.09 (s, 12H, $4CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.5, 29.6, 31.4, 32.4, 46.4, 47.0, 115.5, 126.7, 135.5, 189.3, 190.5; MS (*m/z*, %) 622 (M^+, 2), 588 (11), 552 (10), 518 (11), 494 (6), 451 (4), 423 (5), 378 (47), 353 (5), 328 (5), 295 (15), 266 (24), 236 (22), 207 (17), 177 (29), 148 (48), 107 (100, base peak), 83 (41), 55 (47); FT-IR (KBr, cm^{-1}) 3430, 3054, 2959, 2931, 2871, 2635, 1713, 1596, 1373.

RESULTS AND DISCUSSION

The reaction of 1,3-cyclohexanedione (1) with BrCN and various aldehydes in the presence of sodium ethoxide affords 10a-hydroxy-9-aryl-3,4,5,6,7,8a,9,10a-octahydro-1*H*-xanthene-1,8(2*H*)-dione (3) (Scheme 1 and Table 1).

As a part of our current studies on 1,3-cyclohexanedione 1 and its reaction with BrCN and our interest in the chemistry of BrCN, we discovered the unexpected bromination of 1 by BrCN (in the absence of aldehyde) that afforded the salt of 4. The formation of salt 4 has interesting applications in many chemical transformations. Previously, dimedone has been α-brominated by bromodimethylsulfonium bromide (BDMS) [27]. Cyanation of compounds *via* BrCN is well-known [28-30]. Previously, it was also reported that the reaction of β-dicarbonyl compound with iodine and bromine produce the α-iodinated [31-33] and α-brominated products [34], respectively.

Recently, we have also reported the crystal structure of 9b'b" that is derived from the reaction of 1,3-dimethylbarbituric acid with BrCN and acetone in the presence of Et_3N [35]. We proposed that in these reactions the salts of triethylammonium-5-bromobarbiturates (11) are formed in the reaction of (thio)barbituric acids with aldehydes [36] aromatic dialdehydes [37] and ketones [38] in the presence of BrCN and triethylamine (Fig. 1). The salts of 11 plays a major role for the synthesis of spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine]2,2',4,4',6'(3*H*, 3'*H*,5*H*)-pentaones, 9. According to the mechanism of the formation of 10 and 11 [36-38] it was assumed that the enolic form of 1,3-cyclohexanedione 1 reacted with BrCN is



Scheme 1. Reaction of 1,3-cyclohexanedione (1) with cyanogen bromide and aldehydes in a basic medium

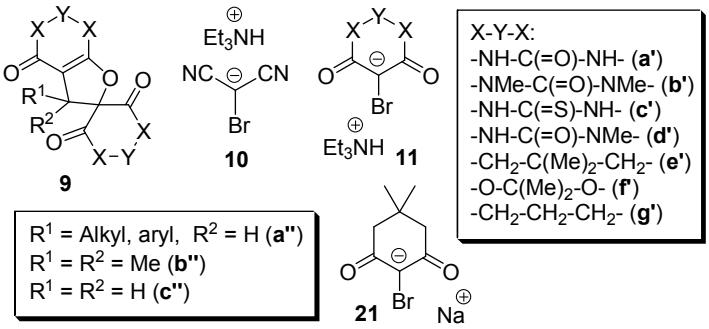
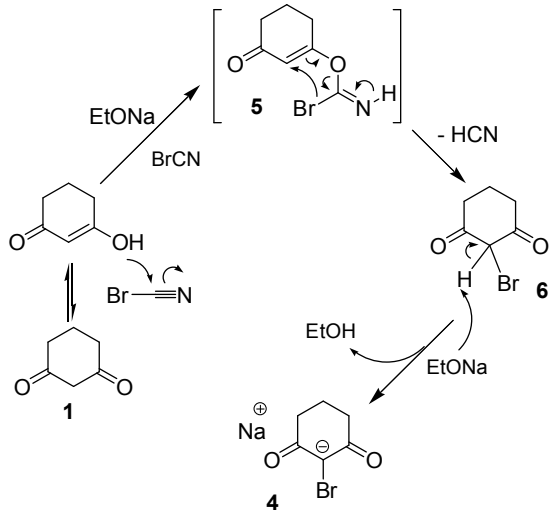


Fig. 1. Structures of spiro[furo[2,3-*d*]pyrimidine-6,5'-pyrimidine] derivative (9) [35], triethylammonium-2-bromo-dicyanomethanid (10) [40], and triethylammonium-5-bromo-(thio)barbiturates (11) [36-38] and 21.



Scheme 2. Proposed mechanism for the formation of 4

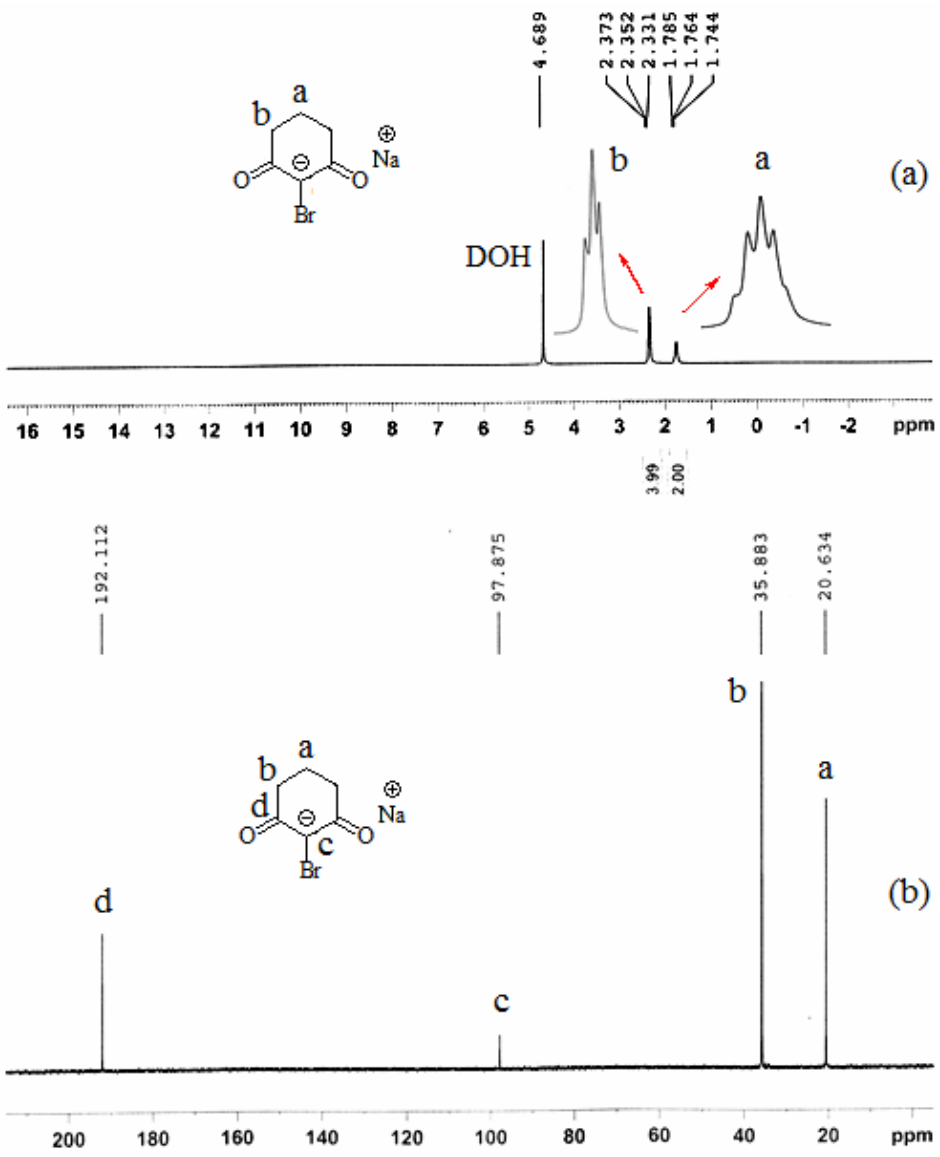
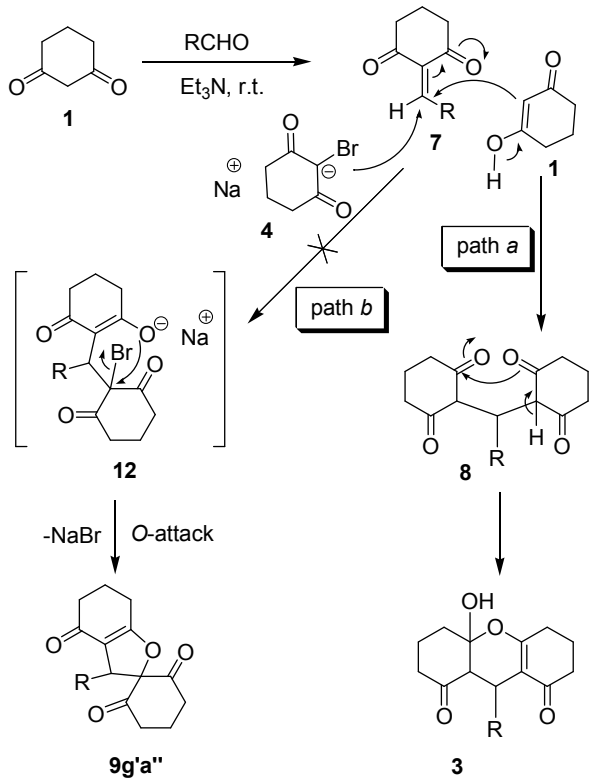
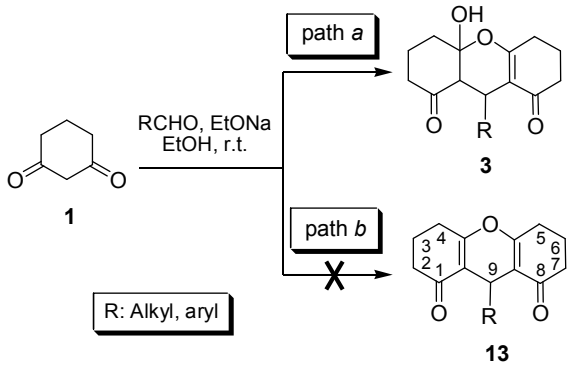


Fig. 2. ^{1}H (a) and ^{13}C NMR spectra of salt 4 (in D_2O).

formed via intermediate 5. Intramolecular rearrangement of 5 afforded 6 followed by the loss of HCN. The proton capturing of acidic methylene proton of 6 forming salt 4 under basic condition (Scheme 2). Unfortunately, all attempts failed to separate or characterize 5 and 6. For instance, the structure of 4 was characterized by IR, ^{1}H and ^{13}C NMR, spectroscopy. The ^{1}H NMR spectrum of 4 consists of a quintet at δ 1.76 ppm and a triplet at δ 2.35 ppm corresponding to methylene groups (assigned as *a* and *b* in Fig. 2) in 1,3-cyclohexanedione ring moiety in 4, respectively. A singlet at δ 4.69 ppm corresponds to DOH derived from deuterium exchanging with a water molecule absorbed in the salt molecules. The ^{13}C NMR spectrum is in a good agreement with the molecular structure and shows four distinct peaks. Two peaks at δ 20.6 and at 35.9 ppm correspond to methylene groups on 1,3-cyclohexanedione ring moiety, respectively. The peaks at δ 97.9 and at 192.1 ppm correspond to C-Br and two equivalent carbonyl



Scheme 3. Knoevenagel condensation, Michael addition and cyclization mechanism for the formation of 3 (Favored path a) and unfavored path *b*



Scheme 4. Formation of 3 (path *a*) and unfavored formation of xanthene derivatives (13) from the reaction of 1,3-cyclohexanedione 1 with various aldehydes in the absence of BrCN under basic condition (path *b*).

groups on 1,3-cyclohexanedione ring moiety, respectively (Fig. 2 and see also experimental and supplementary information). The formation of 4 (the existence of bromine atom in this molecule) was also verified by the Beilstein test and the wet silver nitrate test [39] (precipitate of pale yellow silver bromide). The flame photometry experiment for confirmation of 4 was also performed.

Recently, we have reported the selective formation of spiro dihydrofurans (9e'a'') in the reaction of various aldehydes with dimedone (DM, 14) and BrCN in a basic

medium [41]. Based on the results derived from dimedone, unexpectedly, no spiro dihydrofuran was derived from 1,3-cyclohexandione (9g'a") under the same condition. Instead, octahydro-1*H*-xanthene-1,8(2*H*)-diones (3) were found in results. Whereby, these unexpected results encouraged us to investigate the role of BrCN and the reaction circumstances.

The proposed mechanism for the formation of 3 is shown in Scheme 3. First, the Knoevenagel condensation of 1 with an aldehyde afforded 2-alkylidene and/or 2-arylidenecyclohexane-1,3-dione (7), then the Michael addition of compound 7 with 1 gave the intermediate (8). Finally, an intramolecular nucleophilic attacking in 8 afforded 3 in a good yield. Unfortunately, all attempts failed to separate or characterize 8.

In this work, unexpectedly, the pKa value of 1,3-cyclohexanedione (5.26) [42] is lower than that of DM 14 (5.23) [43]. So, in the reaction of 14 with an aldehyde and BrCN, in the presence of a base, compound 14 first reacts with BrCN to form the salt of 11e', instead, compound 1 reacts with aldehyde to form Knoevenagel adduct 7, and then the second molecule of 1 attacked to the Knoevenagel adduct 7 in competition with the salt 4. Therefore, for the formation of 9g'a", the path *b* is unfavored (Scheme 3).

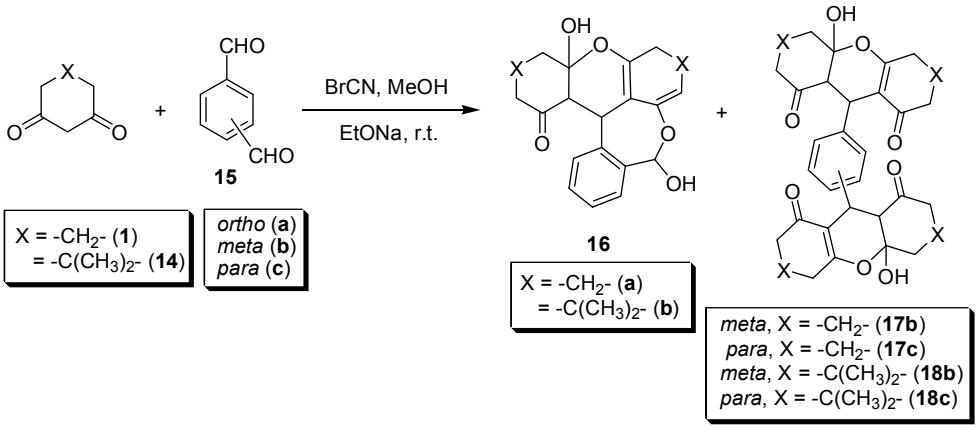
1,3-Cyclohexanedione and its derivatives like 14 were most often studied as C-nucleophiles. This compound gives mono- and bis-condensation products with aldehydes [43,44]. We also performed the reaction of 1 with BrCN and EtONa in the absence of aldehyde so we only obtained the salts of 4. To understand the role of BrCN, the reaction of 1 with aldehydes was performed in the absence of BrCN under the same condition. In this reaction, no 9-alkyl- and/or 9-aryl-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-diones (13) was obtained (Scheme 4) [45-47].

Next, a variety of aldehydes were selected (under optimum condition) to react with 1,3-cyclohexanedione (Table 1, entries 1-7). Various aromatic aldehydes possessing electron-donating and electron-withdrawing substituents reacted smoothly and efficiently under the basic condition, affording the corresponding 3 in good yields. The aldehyde with an electron-withdrawing substituent gave a higher yield than those bearing an electron-donating substituent. Aliphatic aldehydes, including formaldehyde (2a) gave the same results (see experimental information, Table 1, and entry 1).

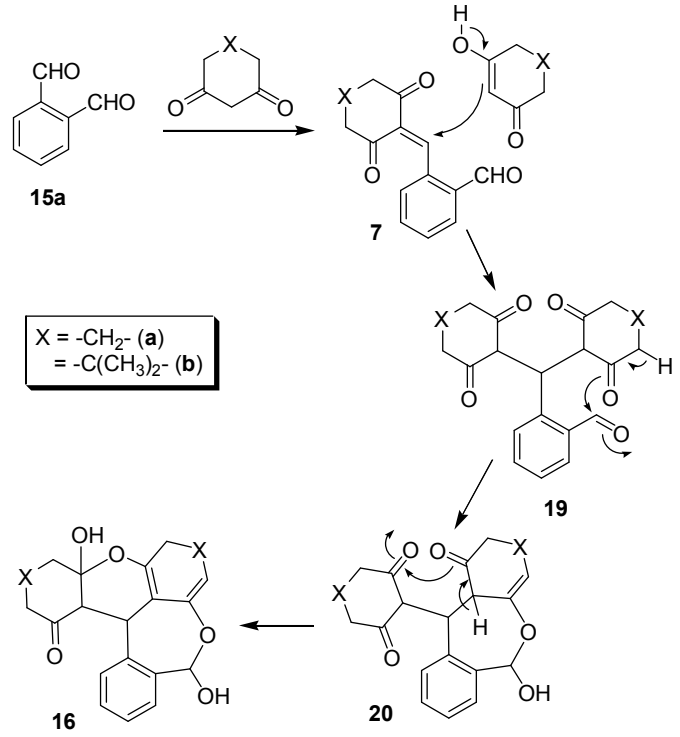
We performed the reaction of 1 with dialdehydes (15) in a basic medium under the same condition similar to Scheme 1. The new reaction of 1 with dialdehydes, such as isophthalaldehyde (15b) and terphthalaldehyde (15c) in the presence of BrCN and Et_3N, afforded 9,9'-(1,3- and 9,9'-(1,4-phenylene)bis(10*a*-hydroxy-3,4,5,6,7,8*a*,9,10*a*-octahydro-1*H*-xanthene-1,8(2*H*)-dione) at room temperature, respectively. In contrast, the reaction of phthalaldehyde (15a) with 1 afforded 6-hydroxy-11-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-3,4,6,11-tetrahydrodi-benzo[*b*,*e*]oxepin-1(2*H*)-one (16a) under the same condition (Scheme 5). For the further investigation about the reaction of dialdehydes, we also performed the reaction of DM 14 with dialdehydes 15b and 15c in the presence of BrCN and EtONa and/or Et_3N (basic condition). Surprisingly, similar to the reaction of 1 with dialdehydes, these reactions were also afforded bis octahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives at room temperature under the same condition. In contrast, the reaction of 15a with 14 afforded 5,10*a*-dihydroxy-8,8,12,12-tetramethyl-7,8,9,9*a*,10a,11,12,13,14*a*,14*b*-decahydrobenzo[5,6]oxepino[2,3,4-*kl*]xanthen-14(5*H*)-one (16b) under the same condition (Scheme 5). The proposed mechanism of the formation of 15a is shown in Scheme 6. Presumably, compounds 1 and/or 14 can attack as Michael addition to the Knoevenagel adduct of 2-alkylidene and/or 2-arylidene cyclohexane-1,3-dione (7) prior to formation of salts 4 and/or 21 (Scheme 6 and Fig. 1). The hindrance effect can also be an effective factor in the formation of 16.

Representatively, first, the Knoevenagel condensation of 1 with one of aldehyde group of 15a afforded 7, then Michael addition of 1 to 7 as the key intermediate gave the intermediate (19). Finally, an intramolecular nucleophilic *O*-attack of the carbonyl group of cyclohexane-1,3-dione ring moiety to the carbonyl group on phenyl ring in 19 (formation of an oxepin ring) afforded 16a through triketoform of 20 in a good yield (Scheme 6, see experimental and supplementary information). Unfortunately, all attempts failed to separate or characterize 19 and 20.

Representatively, the FT IR spectrum of 16b showed the stretching frequencies of 3204 and 1721 cm^{-1} for hydroxyl and carbonyl groups, respectively. The ^1H NMR



Scheme 5. Reaction of 1 and 14 with dialdehydes (15) in the presence of BrCN in a basic medium.



Scheme 6. Proposed mechanism for the formation of 16a and 16b

spectrum of this compound showed four diastereotopic methyl groups at δ 1.10 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H) ppm (Fig. 3). This compound showed four distinct singlets for hemiacetalic, benzylic and two kinds of hydroxyl protons at δ 6.58 (s, 1H), 5.49 (s, 1H), 5.19 (s, 1H), 4.73 (s, 1H) ppm, respectively. The ^{13}C NMR spectrum of 16b showed twenty four distinct peaks for carbon atoms (Fig. 4).

Mass spectrom of this compound presented ion molecular, *m/z* 396. The plausible mass fragmentation of 16b is shown in Scheme 7. Ion molecular of *m/z* 396 converts to *m/z* 340 *via* Retro Diels-Alder reaction by loss

Table 1. The Product Structures, Physical Properties and Yields Derived from 1,3-Cyclohexanedione 1 and DM 14 with Various Mono- and Dialdehydes in a Basic Medium (EtONa)

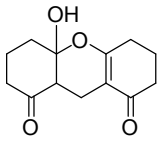
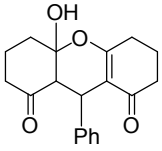
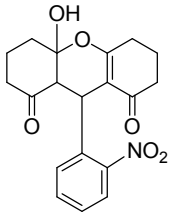
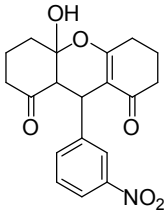
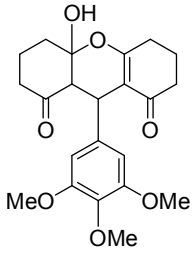
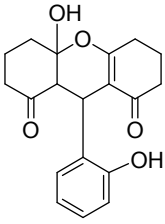
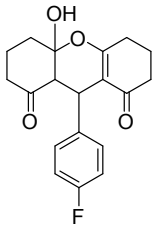
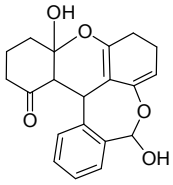
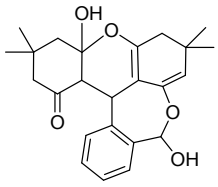
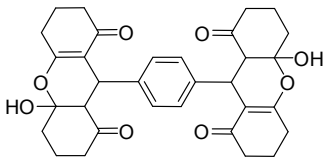
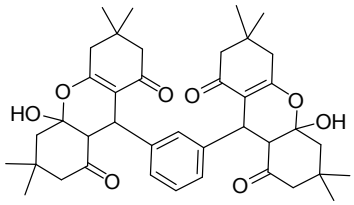
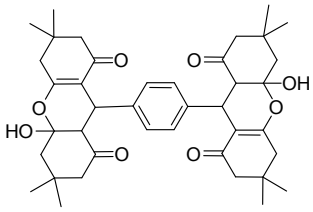
Entry	Product	m.p. (°C)	Yield (%)
1	 (3a)	182-184	50
2	 (3b)	212-214	75
3	 (3c)	175-178	60
4	 (3d)	210-212	75
5	 (3e)	93-95	75
6	 (3f)	212-214	60

Table 1. Continued

7	 (3g)	236-237	70
8	 (16a)	226-228	60
9	 (16b)	234-235	70
10	 (17c)	207-209	55
11	 (18b)	229-231	65
12	 (18c)	278-280	55

of isobutylene. The base peak (*m/z* 83) derives from the fragmentation of *m/z* 340 followed by loss of methyl radical then carbon monoxide and finally, by McLaferty fragmentation (Scheme 7). These data confirmed the characterization of 16b structure (See experimental and Supplementary information).

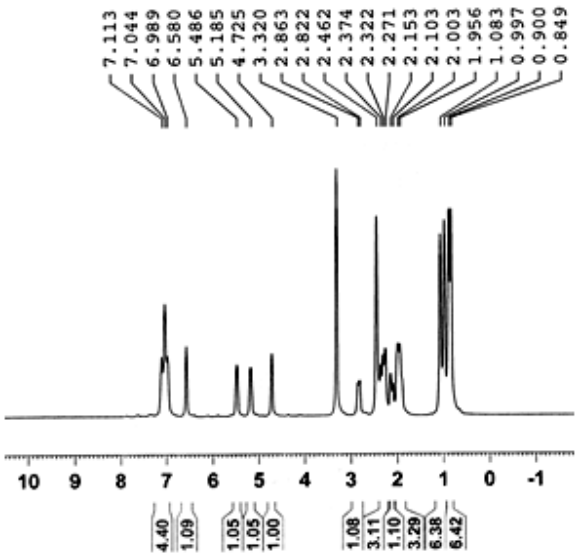


Fig. 3. The ^{1}H NMR spectrum of 16b (DMSO-d_6).

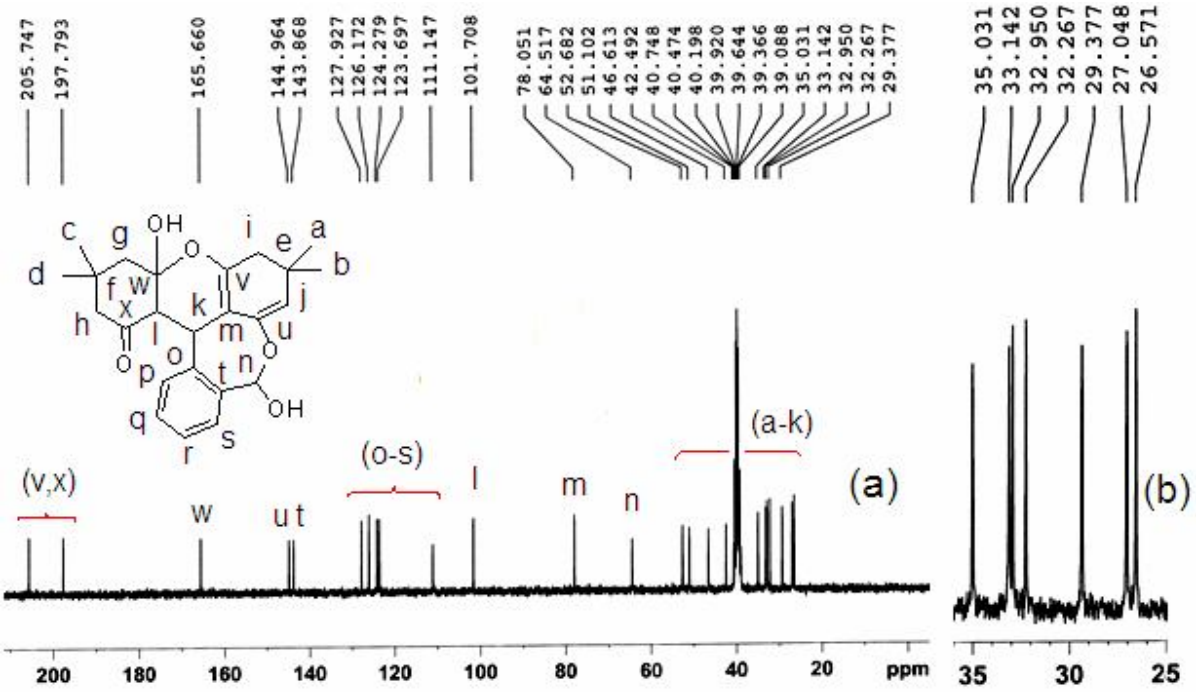
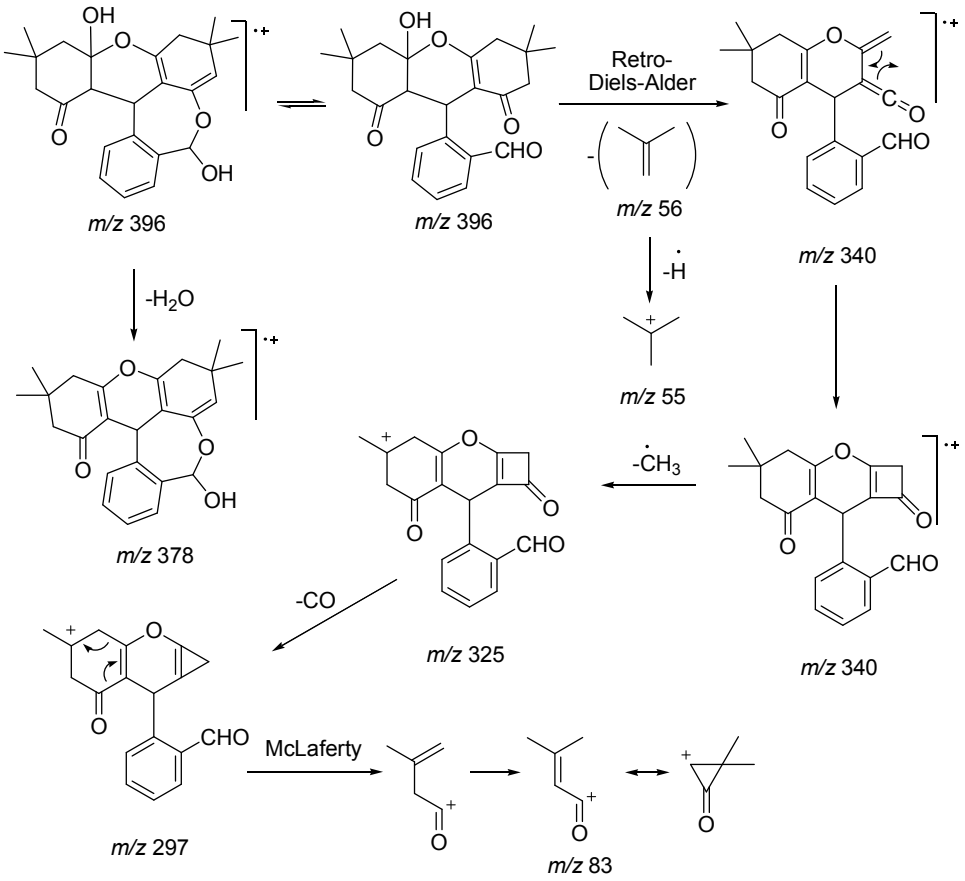
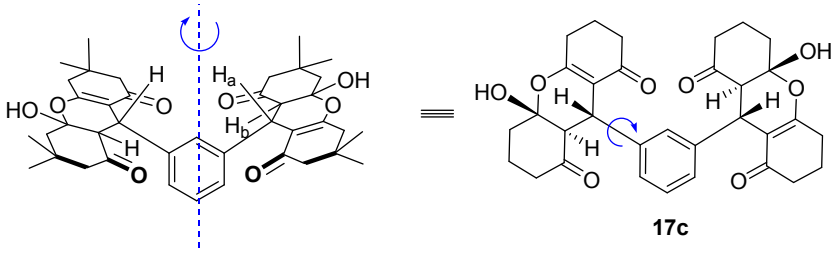


Fig. 4. ^{13}C NMR spectrum of 16b (a) and expanded aliphatic upfield section for clarity (b).

The ^{1}H NMR spectrum of compound 18b showed two singlets at δ 11.89 (s, 2H) and 5.14 ppm (s, 2H) for two hydroxyl groups and two equivalent benzylic protons, respectively. There are two kinds of methyl groups in chemical shifts view of points at δ 1.18 (s, 12H) and 1.07 ppm (s, 12H) (See experimental and Supplementary information). The possible stereostructures for 18b are shown in Scheme 8. An attempt to formation of single



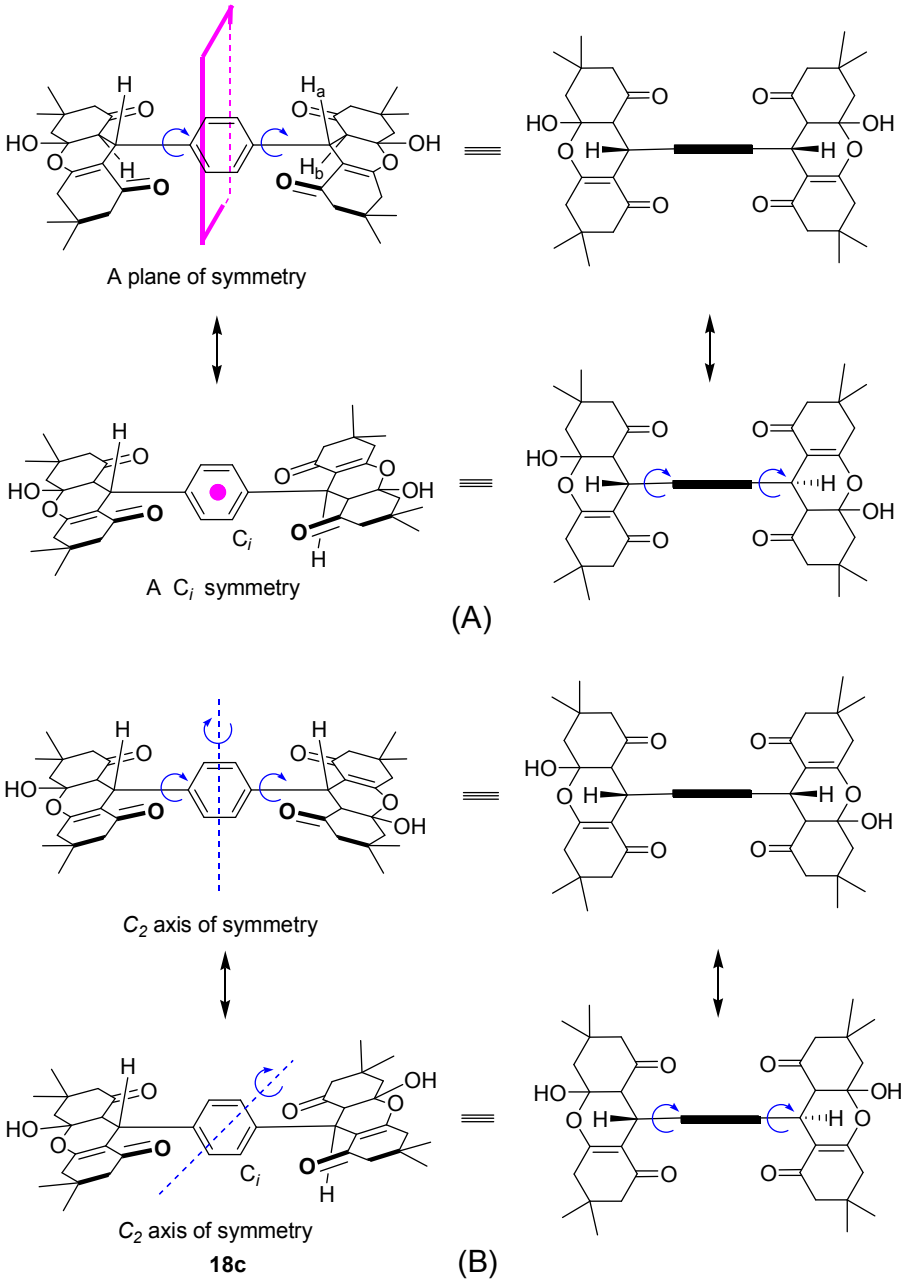
Scheme 7. Plausible mass fragmentation of 16b



Scheme 8. Possible stereoisomer (rotamer) of 18b

crystal of these compounds derived from dialdehydes were filed.

Possible stereoisomers of 18b and 18c are shown in Schemes 8 and 9, respectively. Owing to the dihedral angles of H7-C7-C8-H8 (in enantiomer A) and H38-C38-C26-H26 (in enantiomer B), adopted at 84.04° and -84.75°, respectively (see the X-ray data for 3c later), the coupling constant (*J*) between H7 and H8 (also between H26 and H38) to be condoned with judging to the ^{1}H NMR spectrum of 3c confirmed this phenomenon. Similar to coupling constant in 3c, no coupling constant was shown between the benzylic proton and the vicinal tertiary proton in 18b and 18c and these protons are assigned to H_a and H_b in 18b and 18c (See experimental and Supplementary

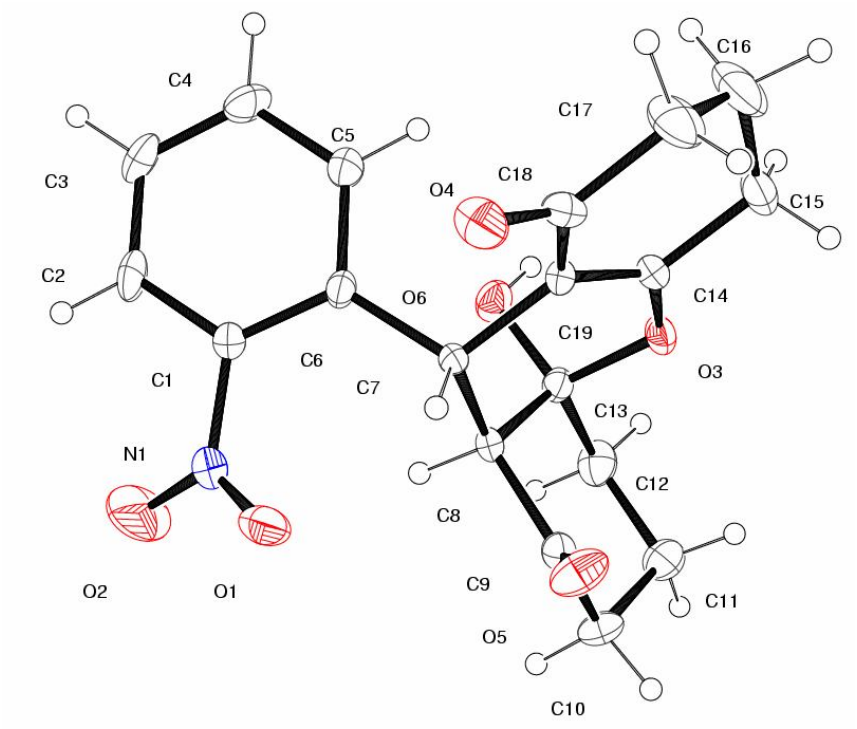


Scheme 9. Possible two stereoisomers (rotamers) for 18c. A plane (σ) and a *Ci* symmetries (a) and C_2 axis of symmetry (b) (*Ci* assigned as a violet dot (●)).

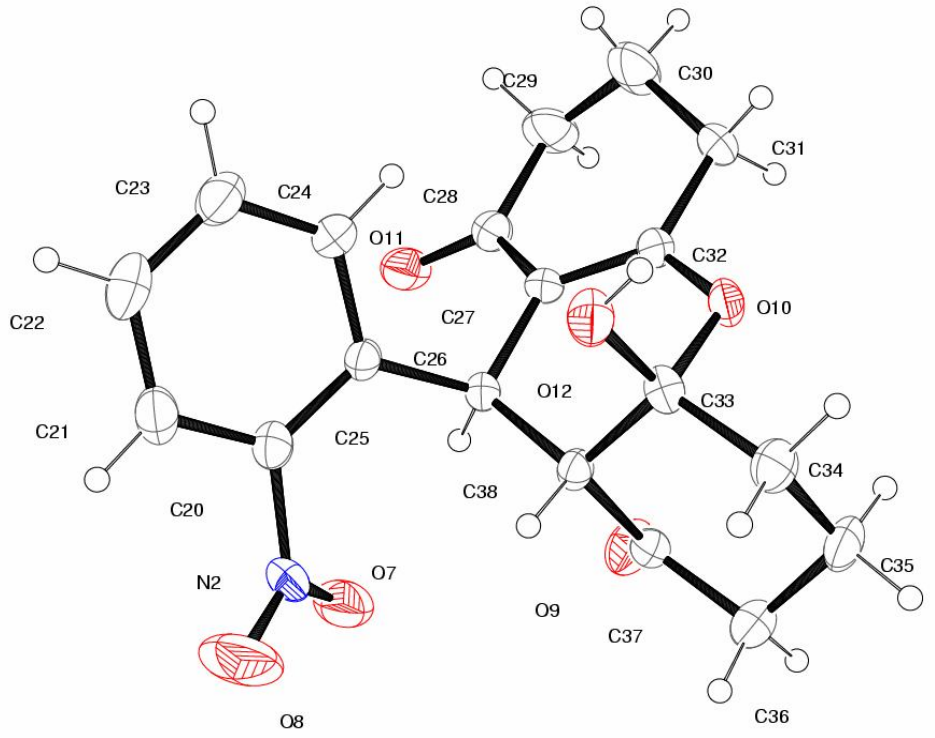
information).

X-ray Diffraction Analysis of 3c

For further study, an X-ray diffraction analysis of 3c was undertaken (Fig. 5). The single crystal of 3c was obtained as a colorless crystal by slow evaporation from MeOH at room temperature. Compound 3c crystallizes in the triclinic space group *P*-1 with two enantiomers in the asymetric unit. Each enantiomer in the structure exists in 1D polymeric form. In the molecule, the fused cyclohexanone and cyclohexenone ring moieties have chair and distorted conformations, respectively. The 3,4-dihydro-2*H*-pyran ring moiety has also



(A)



(B)

Fig. 5. ORTEP drawing of the racemat 3c. Thermal ellipsoids are drawn at the 40% probability level.

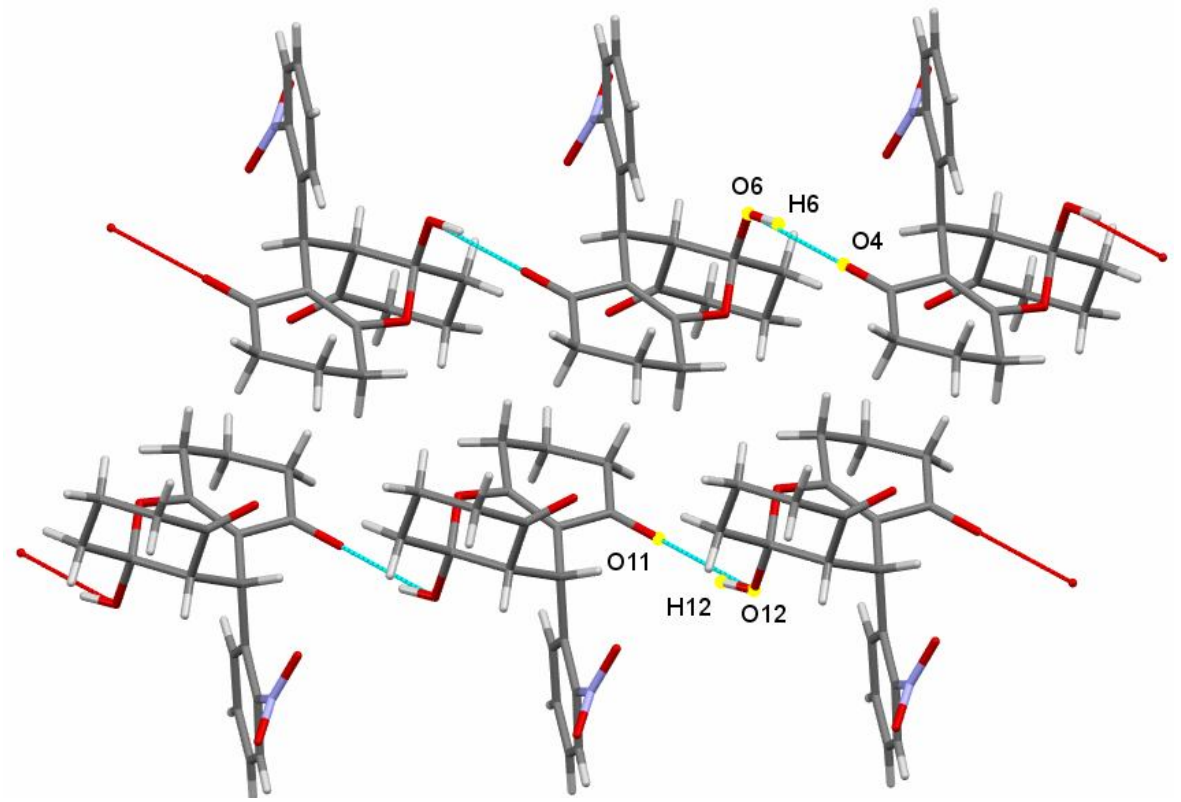


Fig. 6. Two independent intermolecular 1*D*- polymeric *H*-bonds between each enantiomer along the *a*-axis.

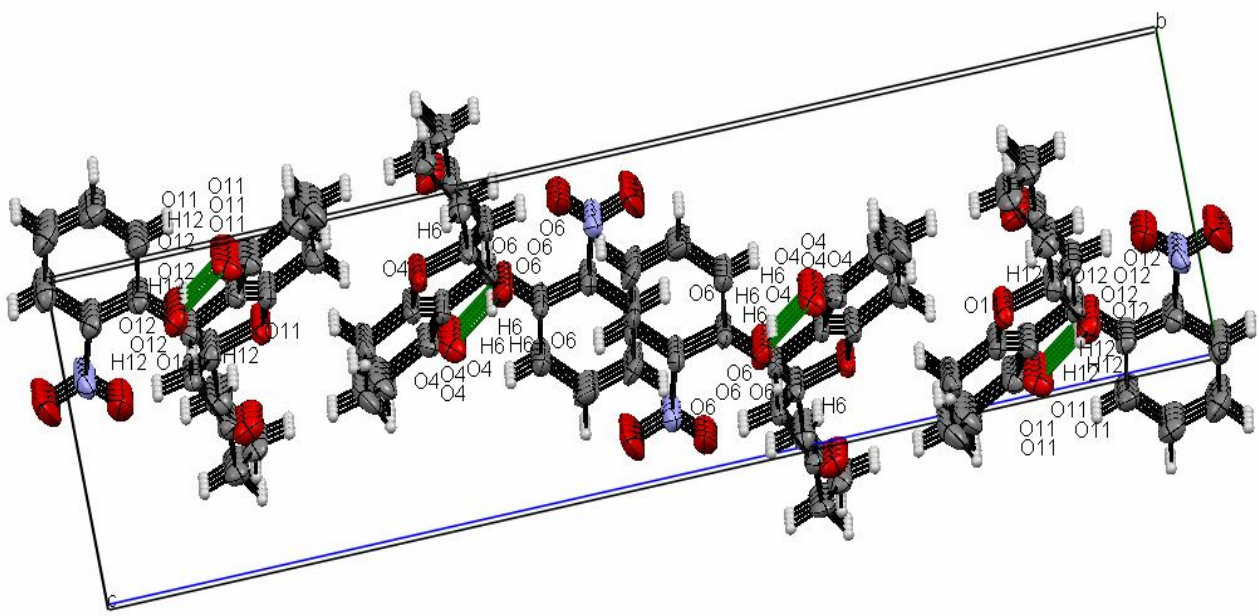


Fig. 7. Crystal packing diagram of 3c dimer (*H*-bonds are assigned as green colors).

Table 2. Two Independent Intermolecular *H*-bond Lengths and Angles in 3c

D-H·····A	*d*(D-H)	*d*(H·····A)	*d*(D·····A)	<(DHA)	Directionality
O6-H6·····O4^{i}	0.82	2.037	2.847	169.84	Weak
O12-H12·····O11^{ii}	0.82	2.065	2.854	161.47	Weak

Symmetry codes: i) -1-x,y,z. ii) 1+x,y,z.

Table 3. Selected Bond Length (Å), Angles (θ) and Torsion Angles (φ) in two Enantiomers of A and B in 3c

Enantiomer A		Enantiomer B	
O4-C18	1.217 (5)	O11-C28	1.231 (5)
O5-C9	1.208 (5)	O9-C37	1.204 (5)
O6-C13	1.382 (5)	O12-C33	1.401 (5)
O6-H6	0.82	O12-H12	0.82
C6-C7	1.531 (5)	C26-C25	1.531 (5)
O3-C13	1.456 (4)	O10-C33	1.459 (5)
N1-C1	1.458 (5)	N2-C20	1.488 (6)
C13-O6-H6	109.5	C33-O12-H12	109.5
O6-C13-O3	108.2 (3)	O12-C33-O10	108.1 (4)
C14-O3-C13	117.5 (3)	C32-O10-C33	117.3 (3)
C6-C7-H7	107.2	C25-C26-H26	106.2
O1-N1-C1-C6	32.3 (6)	O7-N2-C20-C25	-32.3 (6)
C1-C6-C7-C8	65.9 (5)	C38-C26-C25-C20	-64.0 (5)
O6-C13-C8-H8	59.36	O12-C33-C38-H38	-58.73
H7-C7-C8-H8	84.04	H38-C38-C26-H26	-84.75
C7-C8-C13-O3	58.5 (4)	O10-C33-C38-C26	-58.0 (4)
C18-C17-C16-C15	-44.4 (8)	C32-C31-C30-C29	-44.4 (7)
C9-C10-C11-C12	-52.9 (5)	C34-C35-C36-C37	52.9 (6)

distorted conformation. Each enantiomer of 3c has three stereogenic chiral centers of C7 (*R*), C8 (*S*), C13 (*S*) and C26 (*S*), C38 (*R*) and C33 (*R*) configurations. Polymeric units have an independent intermolecular O-H···O *H*-bond interactions with the same enantiomer in the structure. The *H*-bond distances between enantiomer units are equal to

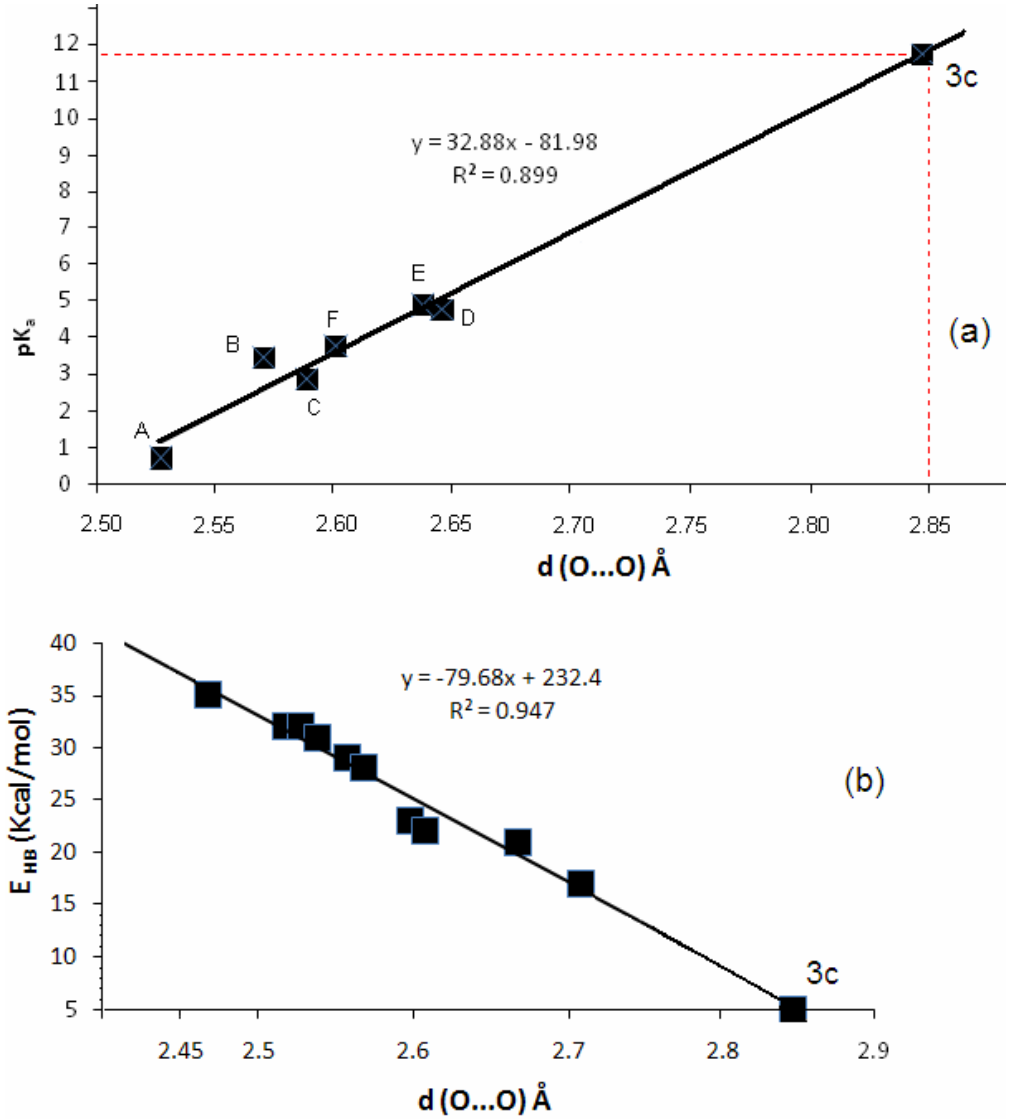


Fig. 8. (a) Correlation of the average distance (2.85 Å) of *d*(O4·····O6, 2.847 Å) and *d*(O11·····O12, 2.854 Å) in 3c with increasing pKa values of trichloroacetic (A), chloroacetic (B), 2,6-dimethoxybenzoic (C), propionic (D), acetic (E) and formic acids (F) [50-53] and estimation of the pKa value for 3c (-----). (b) Hydrogen bond strength (E_{HB}) *versus* average distance *d*(O4·····O6) and *d*(O11·····O12) in 3c [54].

2.848(5) Å (O6-H6····O4[a]) and 2.855(5) Å (O12-H12····O11[b]) [symmetry codes: (a) -1-x,y,z; (b) 1+x,y,z] (Fig. 6 and Table 2). The selected bond lengths (Å), angles (θ) and torsion angles (φ) in enantiomers of A and B in 3c are shown in Table 3. Crystal packing diagram of 3c dimer and the polymeric *H*-bonds assigned as green colors is shown in Fig. 7.

The single-crystal of the compound 3c was used for data collection on a Bruker SMART BREEZE CCD diffractometer. The graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$.

Integration of the intensities, correction of Lorentz and polarization effects and cell refinement was performed using Bruker SAINT (Bruker AXS Inc., 2012) software [48]. The structure was solved by direct methods using *SHELXS-97* [49] and refined by a full-matrix least-squares procedure using the program *SHELXL-97* [49]. The H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* 3c: $C_{19}H_{19}O_6N$; crystal system, space group: triclinic, *P*-1; (no:2); unit cell dimensions: a = 7.1242(4), b = 8.1701(5), c = 29.4333(17) Å, α = 90.086(3), β = 90.690(3), γ = 102.490(2)°; volume: 1672.50(17) Å^3; Z = 2; calculated density: 1.419 g cm^{-3}; absorption coefficient: 0.106 mm^{-1}; F(000): 752; θ range for data collection 1.4-28.3°; refinement method: full-matrix least-square on F^2; data/parameters: 4828/471; goodness-of-fit on F^2: 1.110; final R indices [$I > 2\sigma(I)$]: R_1 = 0.093, wR_2 = 0.234; largest diff. peak and hole: 0.532 and -0.524 e Å^{-3}.

Crystallographic data were deposited in CSD under CCDC-1042147 registration number. These data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif or request to CCDC, 12 Union Road, Cambridge, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).

Comparison of the strength of the *H*-bond in 3c with other carboxylic acids and flavone-acid compounds reported by Wallet *et al.* [50–52] and methyl 2,4-dimethoxysalicilate by Dabbagh *et al.* [53] allows for estimation of the pKa of 3c. They used this method when the experimental pKa determination was impractical. The estimated pKa value for intermolecular *H*-bond of 3c is equal to ≈ 11.7 (Fig. 8, top). Based on correlation between hydrogen bond strength (E_{HB}) and d(O·····O) distance [54,55], the estimated E_{HB} of intermolecular *H*-bond for 3c is equal to ≈ 5 kcal mol^{-1} (Fig. 8, bottom). These observations indicated that the O6-H6·····O4 and O12-H12·····O11 *H*-bonds are weak *H*-bonds (Table 2).

CONCLUSIONS

In summary, a versatile one-pot reaction of 1,3-cyclohexanedione with aldehydes selectively affords octahydro-1*H*-xanthene-1,8(2*H*)-diones in the presence of cyanogen bromide and basic media in good yields. The experimental results indicated that the aromatic aldehydes possessing electron-withdrawing are more reactive than those with electron-donating substituent or aliphatic aldehydes. The notable advantages of this protocol are mild, clean, good yields, simple reaction conditions and no need of chromatographic separations. The reaction of pthalaldehyde with 1,3-cyclohexanedione and dimedone unexpectedly afforded decahydrobenzo[5,6]oxepino[2,3,4-*kl*]xanthen-14(5*H*)-ones. The reaction of isophthalaldehyde and terphthalaldehyde with 1,3-cyclohexanedione and dimedone were afforded 9,9'-(1,3- and 9,9'-(1,4-phenylene)bis(10*a*-hydroxy-3,4,5,6,7,8*a*,9,10*a*-octahydro-1*H*-xanthene-1,8(2*H*)-diones), respectively. The crystal structure of compound 3c was studied and showed a dimmeric form of two enantiomers of A and B. Each enantiomer showed an independent intermolecular *H*-bond between the same enantiomers. The pKa and *H*-bond strength (E_{HB}) values were obtained 11.7 and 5 kcal mol^{-1}, respectively.

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SUPPLEMENTARY INFORMATION

Full characterization data of compounds 3a-3g, 16, 17 and 18 and crystallographic data for 3c are available.

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