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Synthesis of Wieland-Miescher Ketone Analogues-Potential Substrates for the Carbocyclic Frameworks

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Synthesis of Wieland-Miescher Ketone Analogues-Potential Substrates for the Carbocyclic Frameworks

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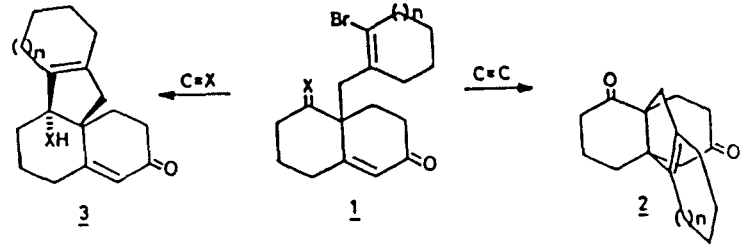
Abstract: The synthesis of the hitherto unknown 3,4,8,8a-tetrahydro-8a(2-bromo-1-cyclo-alkenylmethyl)-1,6(2H,7H)-naphthalene-diones are reported.

Wieland-Miescher ketone[1] is a substrate often being used in organic synthesis and has a unique structural frame work, which exists in many natural products. The recent reports on its preparation in optically active form[2] has made the substrate much more attractive to organic chemists and in fact has been widely used as a building block in the chiral synthesis of natural products.[3] The ketone has also been used in the oxy - Cope rearrangement studies, which interestingly led to the formation of ring enlarged products.[4]

In one of our recent publication, we have reported the use of bicyclo(2.2.2)octenone[5] for the construction of carbocyclic intermediate. In continuation of our efforts towards the development of new methods for the stereocontrolled construction of carbocycles, we have envisaged that Wieland-Miescher ketone analogues 1 are excellent candidates for our study, which will provide a new entry into the propellane 2 type and angularly fused 3 polyquinanes from a single intermediate, depending upon the mode of cyclisation (Scheme 1).

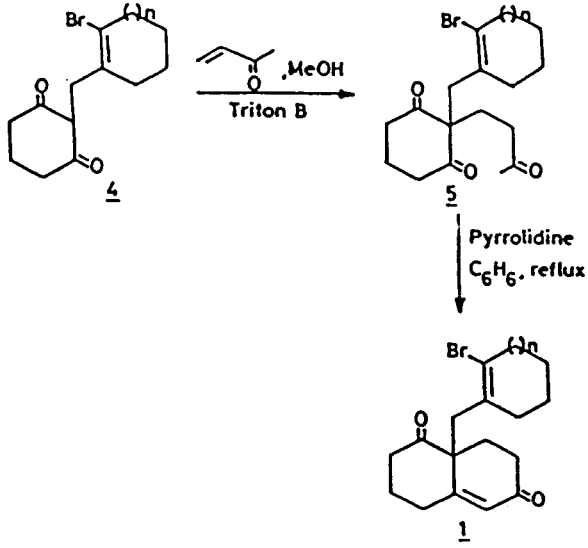
Scheme 1



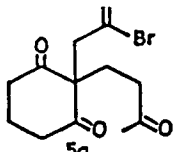
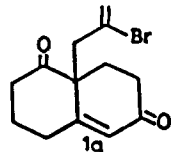
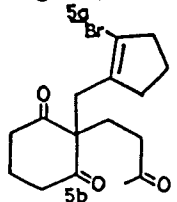
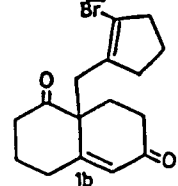
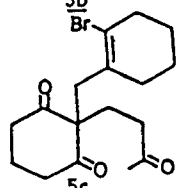
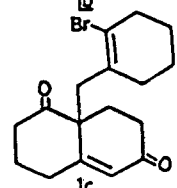
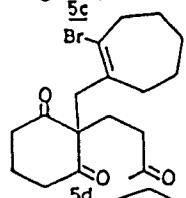
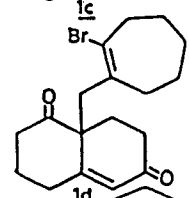
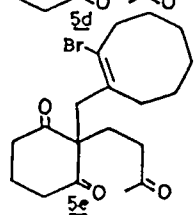
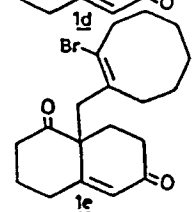
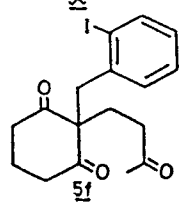
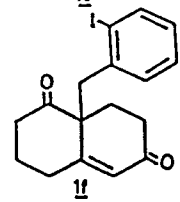
In order to realise our synthetic strategy, we were in need of various hitherto unknown derivatives of the 3,4,8,8a-tetrahydro-8a(2-bromo-1-cycloalkenylmethyl)-1,6(2H,7H)-naphthalenediones. In this communication we report the synthesis of various analogues of Wieland-Miescher ketone, to establish the generality of our route and to bring out wider scope for our further studies.

The bromomethylcycloalkenyl halides used in this work were prepared via the Vilsmeier-Haack bromoformylation[6] of the parent cyclic ketones and the 2-iodobenzyl bromide was prepared from 2-iodobenzoic acid. The alkylation of the reactive bromides with cyclohexane-1,3-dione furnished the mono- alkylated products 4 in good yields. The Michael addition of the alkyldione to methyl vinyl ketone in the presence of Triton B gave nearly quantitative yields of the Michael adducts 5. Subsequent annulation reaction using pyrrolidine as a catalyst in refluxing benzene provided the desired 8a(2-bromo-1-cycloalkenyl) analogues 1 (Scheme 2). The cycloalkenyl groups employed and the yields of the final products are given in the Table.

Scheme 2



Table

Entry	Michael Adduct	Product	yield
1	 5a	 1a	80
2	 5b	 1b	80
3	 5c	 1c	85
4	 5d	 1d	83
5	 5e	 1e	73
6	 5f	 1f	77

We are currently invesitgating the vinyl radical cyclisation of Wieland-Miescher ketone analogues.

EXPERIMENTAL

All the melting points are uncorrected. Infrared spectra were recorded on Perkin Elmer 1310; ^{1}H and ^{13}C nmr were recorded on GEOL GSX 400, Brucker 400 and Varian 300 spectrometers; Mass spectra were scanned on GCMS-QP1000A.

General experimental procedure: To the 10 mmol of the mono- alkylated dione 4[7] in 6 ml of methanol was added 15 mmol of the methyl vinyl ketone followed by 1 mmol of 40% solution of Triton B (benzyltrimethylammonium hydroxide) in methanol, the reaction was stirred at 60°C for 4 to 6h and then at room temperature for overnight, concentration of the reaction mixture and purification gave the desired prodcuts in high yields. The Michael adducts (10 mmol) in 50 ml of dry benzene was added pyrrolidine 1 mmol and was refluxed with azeotropic removal of water for 3 to 5h and stirring at room temperature for overnight, usual workup and after neccessary purification furnished the Wieland-Miescher ketones in good yields (Table).

2(2-Bromopropenyl)-2(3-oxobutyl)cyclohexane-1,3-dione (5a).

IR neat cm^{-1} : 3010,2950,1700,1618,1410,1360,1165,1100, 900.

^{1}H NMR ($CDCl_3$, 300 MHz): δ : 5.55(dt, J=1.82,0.92 Hz, 1H); 5.46(d, J=1.82 Hz, 1H); 3.04(s, 2H); 2.71(t, J=6.68 Hz, 4H); 2.38(t, J=7.17 Hz, 2H); 2.11(s, 3H); 2.07(m, 2H); 2.02(t, J=7.12 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ : 209.42(2s); 207.65(s); 131.49(s); 124.62(t); 67.62(s); 44.57(t); 39.20(2t); 37.45(t); 32.61(t); 29.92(q); 17.43(t).

MS: 221(44.9),161(52.3),146(35.2),145(49.3),121(21.5), 79(26.4),77(21.1),65(22.4),55(100).

m.p. 66-67°C

Analysis required C:51.84, H:5.69; found C:52.02, H:5.83.

2(2-Bromo-1-cyclopentenylmethyl)-2(3-oxobutyl)cyclohexane-1,3-dione (5b).

IR neat cm^{-1}: 2930,1700,1435,1340,1210,1100,925.

^{1}H NMR ($CDCl_3$, 400 MHz): δ : 2.8-2.54(m, 10H); 2.31(t, J=7.18 Hz, 2H); 2.10(t, J=7.18 Hz, 2H); 1.95(s, 3H); 2.09-1.80(m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 209.20(2s); 207.63(s); 135.59(s); 121.31(s); 67.09(s); 39.74(t); 38.75(t); 38.57(2t); 36.54(t); 35.12(t); 29.92(q); 28.02(t); 22.04(t); 17.29(t).

MS: 261(75.6),243(48.8),233(20.4),203(23.7),183(24.1), 147(100),139(22.7),105(20.7),91(36.1),80(21.2),79(92.2), 77(45.2),71(20.6),55(74.4),53(21.9).

2(2-Bromo-1-cyclohexenylmethyl)-2(3-oxobutyl)cyclohexane-1,3-dione (5c).

IR neat cm^{-1}: 2940,1700,1445,1375,1300,1210.

^{1}H NMR ($CDCl_3$, 300 MHz): δ : 2.8(s, 2H); 2.9-2.4(m, 6H); 2.05(s, 3H); 2.3-2.0(m, 4H); 1.9(m, 2H); 1.6(m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): 209.42(2s); 207.65(s); 131.49(s); 124.62(s); 67.62(s); 44.57(t); 39.42(t); 39.20(2t); 37.45(t); 32.61(t); 28.31(q); 24.78(t); 25.02(t); 22.90(t); 17.47(t).

MS: 275(100),217(43.6),205(21.2),183(21.1),161(57.7), 139(22.5),93(66),91(72),79(42.5),77(58.2),71(21.7), 67(25.4),65(23.4),55(81.1),53(24.6).

m.p. 55-56°C

Analysis required C:57.47, H:6.53; found C:57.43, H:6.82.

2(2-Bromo-1-cycloheptenylmethyl)-2(3-oxobutyl)cyclohexane-1,3-dione (5d).

IR neat cm^{-1}: 2920,2845,1710,1690,1440,1350,1318,1215, 1165,1030,965,908.

^{1}H NMR ($CDCl_3$, 400 MHz): δ : 2.84(ddd, J=16.60,10.74,5.37 Hz, 2H); 2.76(m, 2H); 2.73(s, 2H); 2.62(ddd, J=16.60,6.35, 4.88 Hz, 2H); 2.18(s, 4H); 2.13(m, 2H); 2.09(s, 3H); 1.84(m, 1H); 1.72(m, 2H); 1.55(m, 2H); 1.45(m, 2H); 0.88(m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 209.48(2s); 207.83(s); 136.73(s); 128.17(s); 67.88(s); 47.33(t); 41.51(t); 39.36(t); 39.16(2t); 34.48(t); 31.27(t); 29.67(q); 26.77(t); 25.10(t); 24.77(t); 17.10(t).

MS: 371(15.7),369(15.8),290(21.2),271(30.4),175(36.2), 115(27.7),107(51.4),105(33.1),97(32.8),93(26.4),

91(75.2),89(31.4),85(31.7),81(46.2),79(76.7),77(32.9), 71(100),69(48),67(38.7),65(29.6).

2(2-Bromo-1-cyclooctenylmethyl)-2(3-oxobutyl)cyclohexane-1,3-dione (5e).

IR neat cm^{-1}: 2920,2845,1710,1685,1440,1350,1320,1225, 1165,1110,1095,1025.

^1H NMR ($CDCl_3$, 400 MHz): δ : 2.81-2.60(m, 7H); 2.26-2.07(m, 9H); 1.88(m, 1H); 1.62-1.34(m, 10H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 209.98(2s); 208.05(s); 133.95(s); 127.79(s); 67.86(s); 43.98(t); 39.75(2t); 39.51(t); 37.87(t); 32.31(t); 30.02(t); 29.22(q); 28.18(t); 27.97(t); 26.42(t); 26.10(t); 17.33(t).

MS: 385(15.1),383(15.3),303(73),285(42),245(36.4), 189(36.8),183(100),121(39.6),105(22.5),93(35.8), 91(43.3),81(23.7),79(53.6),77(24.7),67(28.8),55(66.1).

2(2-Iodobenzyl)-2(3-oxobutyl)cyclohexane-1,3-dione(5f).

IR neat cm^{-1}: 3010,2950,1700,1460,1440,1350,1160,1010.

^1H NMR ($CDCl_3$, 300 MHz): δ : 7.80(d, J=7.53 Hz, 1H); 7.19(t, J=7.51 Hz, 1H); 6.87(d, J=7.54 Hz, 1H); 6.86(t, J=7.43 Hz, 1H); 3.24(s, 2H); 2.61(ddd, J=16.73,7.58,5.25 Hz, 2H); 2.47(ddd, J=16.73, 8.41,5.62 Hz, 2H); 2.26(t, J=6.55 Hz, 2H); 2.17(t, J=6.55 Hz, 2H); 2.08(s, 3H); 1.87(m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ : 209.47(2s); 206.89(s); 140.24(d); 139.34(s); 129.94(d); 128.56(d); 128.05(d); 102.36(s); 68.18(s); 45.95(t); 39.71(2t); 38.75(t); 29.67(t,q); 16.70(t).

MS: 381(17.5),271(100),217(67.3),213(22.9),185(22.5), 157(68),129(26.5),128(32.40,116(23.4),115(44.9), 91(26.6),90(46.4),89(26.9),55(69.5).

m.p. 70-71°C

Analysis required C:51.27, H:4.81; found C:51.35, H:4.88.

3,4,8,8a-Tetrahydro-8a(2-bromopropenyl)-1,6(2H,7H)-naphthalenedione (1a).

IR neat cm^{-1}: 3010,2950,1705,1660,1615,1440,1340,1145, 900.

^1H NMR ($CDCl_3$, 400 MHz): δ : 5.92(s, 1H); 5.64(m, 2H); 3.17(d, J=14.87 Hz, 1H); 3.01(d, J=14.87 Hz, 1H); 2.93-2.77(m, 2H); 2.63-2.45(m, 4H); 2.41-2.34 (m, 1H); 2.23-2.14(m, 2H); 1.80-1.67(m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 208.87(s); 197.74(s); 163.94(s); 127.24(d); 126.47(s); 122.32(t); 54.77(s); 46.60(t); 39.06(t); 33.59(t); 32.26(t); 26.18(t); 23.80(t).

MS: 203(100),143(24.4),105(27.2),91(49.7),79(30), 77(38.9), 65(24.1),55(88.8),51(21.9).

m.p. 101-102°C

Analysis required C:55.14, H:5.34; found C:54.87, H:5.29.

3,4,8,8a-Tetrahydro-8a(2-bromo-1-cyclopentenylmethyl)-1,6(2H,7H)-naphthalenedione (1b).

IR neat cm^{-1}: 3010,2950,1702,1660,1610,1435,1310,1220, 1140,920.

^1H NMR ($CDCl_3$, 400 MHz): δ : 5.91(s, 1H); 2.92(dd, J=14.65,5.86 Hz, 1H); 2.88(d, J=14.16 Hz, 1H); 2.82(ddd,

J=14.65,4.88,1.46 Hz, 1H); 2.68(dd, J=13.67,5.37 Hz, 1H); 2.62(m, 2H); 2.55(m, 1H); 2.51(m, 1H); 2.45(dt, J=17.58,4.39 Hz, 1H); 2.28-2.07(m, 5H); 1.83-1.95(m, 2H); 1.73(dt, J=13.67,3.91 Hz, 1H); 1.67(dt, J=13.67,4.39 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 210.29(s); 198.38(s); 164.84(s); 135.61(s); 126.85(d); 122.53(s); 54.96(s); 39.82(t); 38.75(t); 36.35(t); 34.47(t); 34.06(t); 32.20(t); 26.47(t); 23.89(t); 22.12(t).

MS: 243(30.6),165(29.70),164(92.9),163(26.1),159(24.2), 136(30.3),91(24.7),90(26.3),79(100),77(56.6),55(33.4), 51(21.7).

m.p. 89-90°C

Analysis required C:59.45, H:5.93; found C:59.55, H:6.00

3,4,8,8a-Tetrahydro-8a-(2-bromo-1-cyclohexenylmethyl)-1,6(2H,7H)-naphthalenedione (1c).

IR neat cm^{-1}: 2925,2850,1700,1650,1603,1440,1422,1350, 1340,1320,1305,1255,1220,1178,1140,1100,963,888.

^{1}H NMR ($CDCl_3$, 400 MHz): δ : 5.91(s, 1H); 3.00(d, J=14.16 Hz, 1H); 2.95-2.80(m, 2H); 2.84(d, J=14.16 Hz, 1H); 2.69(ddd, J=18.07,13.19,5.37 Hz, 1H); 2.55(m, 4H); 2.44(dt, J=17.09,4.39 Hz, 1H); 2.27(dt, J=14.16,4.89 Hz, 1H); 2.23-2.11(m, 3H); 2.02(m, 2H); 1.76-1.56(m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 210.59(s); 198.48(s); 164.86(s); 131.71(s); 126.83(d); 124.75(s); 55.13(s); 43.52(t); 38.90(t); 37.28(t); 34.17(t); 32.37(t); 31.69(t); 26.89(t); 24.42(t); 23.80(t); 22.54(t).

MS: 257(25.9),164(56.9),136(22.9),93(100),91(43.4), 79(30.1), 77(46.3),65(19.4),55(32.4).

m.p. 92-93°C

Analysis required C:60.54, H:6.28; found C:60.31, H:6.35.

3,4,8,8a-Tetrahydro-8a(2-bromo-1-cycloheptenylmethyl)-1,6(2H,7H)-naphthalenedione (1d).

IR neat cm^{-1}: 2920,2840,1700,1665,1610,1440,1350,1338, 1320,1255,1220,1140,965,915.

^1H NMR ($CDCl_3$, 400 MHz): δ : 5.92(s, 1H); 3.02(d, J=13.67 Hz, 1H); 2.82(d, J= 13.67 Hz, 1H); 2.95-2.67(m, 5H); 2.58-2.51(m, 2H); 2.44(dt, 17.09,4.39 Hz, 1H); 2.30(ddd, J=14.64,5.37,3.9 Hz, 1H); 2.22-2.05(m, 4H); 1.76-1.64(m, 3H); 1.57-1.48(m, 2H); 1.47-1.38(m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 210.61(s); 198.83(s); 165.10(s); 137.85(s); 128.40(d); 127.23(s); 55.49(s); 45.93(t); 41.92(t); 39.46(t); 34.62(t); 34.06(t); 32.92(t); 31.46(t); 27.65(t); 25.53(t); 25.10(t); 23.83(t).

MS: 353(17.8),351(18.3),271(73.2),211(37.9),164(69), 163(30.2),153(55.8),136(39.6),135(37.3),109(41.4), 108(46.1),105(54.1),95(30.7),93(48.4),81(51.3),80(38.2) 79(100),78(55.9),77(96.9),71(72.9),67(75.4),65(73.6).

3,4,8,8a-Tetrahydro-8a-(2-bromo-1-cyclooctenylmethyl)-1,6(2H,7H)-naphthalenedione (1e).

IR neat cm^{-1}: 2910,2845,1705,1665,1610,1443,1350,1320, 1260,1220,1140,1020,955,925.

^{1}H NMR ($CDCl_3$, 400 MHz): δ : 5.91(s, 1H); 2.95(d, J=13.67 Hz, 1H); 2.80(d, J=13.67 Hz, 1H); 2.86-2.06(m, 13H); 1.75-1.44(m, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 210.44(s); 198.42(s); 164.72(s); 134.24(s); 127.59(s); 126.88(d); 54.90(s); 41.60(t); 39.14(t); 37.64(t); 34.09(t); 32.66(t); 31.08(t); 28.96(t); 27.85(t); 27.73(t); 26.00(t); 25.83(t); 23.25(t).

MS: 367(21.4),365(23.8),303(24.2),285(32.1),165(92), 121(100),93(71),91(48.7),79(80.8),77(30.2),67(32.1), 55(46.8).

3,4,8,8a-Tetrahydro-8a(2-iodobenzyl)-1,6(2H,7H)-naphthalenediones (1f).

IR neat cm^{-1}: 1310,2940,1700,1650,1610,1460,1350,1240, 1010.

^{1}H NMR ($CDCl_3$, 400 MHz): δ : 7.85(dd, J=7.3,1.46 Hz, 1H); 7.24(dt, J=7.33,1.46 Hz, 1H); 7.07(dd, J=7.32,1.46 Hz, 1H); 6.94(dt, 7.33,1.46 Hz, 1H); 6.00(s, 1H); 3.53(d, J=13.68 Hz, 1H); 3.34(d, J=13.68 Hz, 1H); 2.65-1.53(m, 10H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ : 210.88(s); 198.51(s); 163.91(s); 140.66(d); 139.55(s); 130.67(d); 129.38(d); 128.68(d); 128.62(d); 102.58(s); 56.08(s); 45.90(t); 39.67(t); 34.16(t); 33.16(t); 29.20(t); 22.79(t).

MS: 253(15),217(100),96(26.3),95(26.9),91(27.9), 90(30.8),86(24.4),84(36.4),77(18.5),71(23.5),69(20.9),

57(84.1),55(43.9).

m.p.79-80°C.

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