THE SYNTHESES OF NOVEL 2-(2-QUINOXALINYL)PYRIDAZIN-3(2H)-ONES

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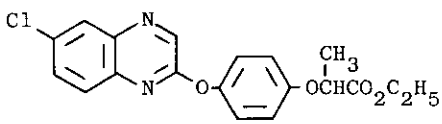
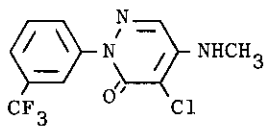
Abstract - The first syntheses of 4-chloro-2-(2-quinoxalinyl)-pyridazin-3(2H)-one derivatives are reported. They could be synthesized from 2-hydrazinoquinoxaline derivatives as starting materials.

Quinoxaline derivatives are widely used as pharmaceutical and agricultural chemicals,[1-4] particularly, ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]-propanoate (NCI-96683, quizalofop-ethyl) has recently attracted special interest as a selective herbicide.[1] It is effective for controlling gramineous weeds without any phytotoxicity to broadleaf crop plants as well as broadleaf weeds especially in a post emergence treatment. Quinoxaline moiety of this compound is used as a building block for the biological activities.[5]

On the other hand, 4-chloro-5-methylamino-2-(3-trifluoromethylphenyl)pyridazin-3(2H)-one (monometflurazone) and its related compounds are used as a pre emergence herbicide.[6] It is known that these pyridazin-3(2H)-one derivatives inhibit chlorophyl formation and a chlorine atom of monometflurazone is essential for the herbicidal activities.

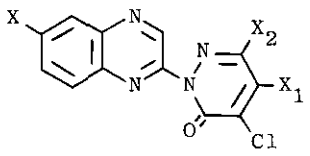


quizalofop-ethyl



monometflurazone

In this paper, we now describe the syntheses of novel and biologically interesting 4-chloro-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (4-9) from 2(1H)-quinoxalinones (1a-c)[7-9] via 2-hydrazinoquinoxalines (3a-c).



X= H, Cl, CF_3

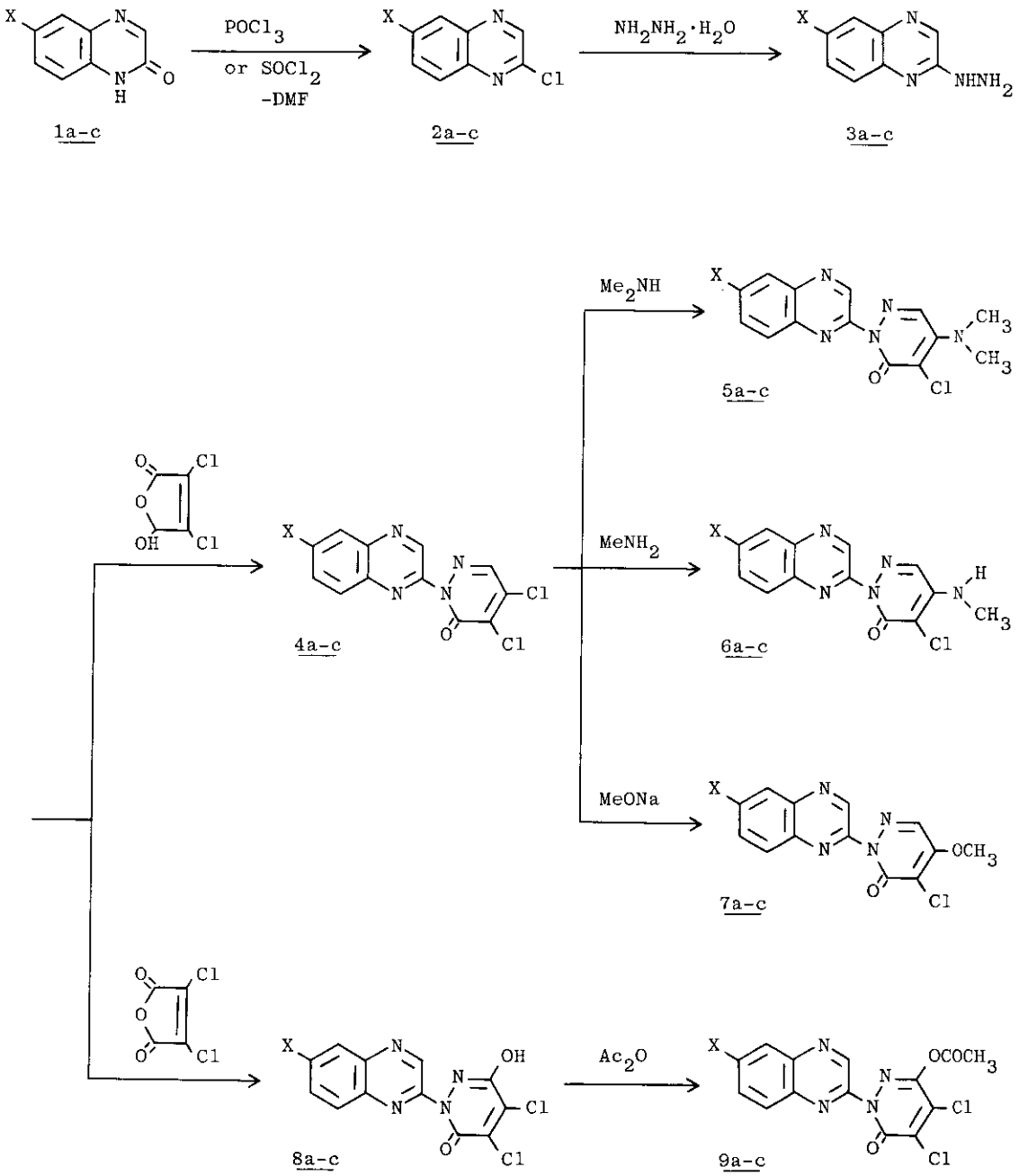
X_1= Cl, OCH_3, $NHCH_3$, $N(CH_3)_2$

X_2= H, OH, $OCOCH_3$

Chlorinations of 1a-c were carried out using phosphoryl chloride or thionyl chloride - DMF to provide 2-chloroquinoxalines (2a-c), whose reactions with hydrazine hydrate in ethanol furnished 3a-c in 87(3a), 93(3b), and 83%(3c) yields, respectively. When 3a-c were allowed to react with mucochloric acid in acetic acid at 110 °C, 4,5-dichloro-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (4a-c) were obtained in 85(4a), 87(4b), and 79%(4c) yields, respectively. Compounds 4a-c were refluxed with excess 40% dimethylamine in ethanol to provide 4-chloro-5-dimethylamino-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (5a-c) in 72(5a), 88(5b), and 80%(5c) yields, respectively. The similar reactions were carried out using an excess of 40% methylamine and 4-chloro-5-methylamino-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (6a-c) were obtained in 96(6a), 97(6b), and 85%(6c) yields, respectively. When 4a-c were refluxed with an equivalent of sodium methoxide in methanol, 4-chloro-5-methoxy-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (7a-c) could be obtained in 85(7a), 71(7b), and 65%(7c) yields, respectively. However, when 4a-c were allowed to react with two fold equivalent of sodium methoxide, 4,5-dimethoxy-2-(2-quinoxalinyl)-pyridazin-3(2H)-ones were not obtained at all but 2-methoxyquinoxalines were afforded in good yields. The reactions were analyzed with HPLC and it was assumed that an equivalent of sodium methoxide reacted with 4a-c similar to the syntheses of 7a-c and next, excess sodium methoxide attacked the 2-position of quinoxaline moieties of the resulting 7a-c.

On the other hand, 3a-c were allowed to react with dichloromaleic anhydride in acetic acid at 100 °C to give 4,5-dichloro-6-hydroxy-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (8a-c) in 91(8a), 87(8b), and 96%(8c) yields, respectively. When 8a-c were refluxed in acetic anhydride, 4,5-dichloro-6-acetoxy-2-(2-quinoxalinyl)-pyridazin-3(2H)-ones (9a-c) were obtained in 73(9a), 76(9b), and 74%(9c) yields, respectively.

These reactions are shown in Scheme 1 and novel compounds 4-9 synthesized in the present study are summarized in Table 1.



Scheme 1. X: a= H, b= Cl, c= CF_3

Table 1. 4-Chloro-2-(2-quinoxalinyl)pyridazin-3(2H)-ones (4-9)

Compound	X	X_1	X_2	mp(°C)
4a	H	Cl	H	198.0-199.0
4b	Cl	Cl	H	212.0-213.0
4c	CF_3	Cl	H	215.0-216.0
5a	H	NMe_2	H	147.0-148.0
5b	Cl	NMe_2	H	207.5-209.0
5c	CF_3	NMe_2	H	206.0-207.0
6a	H	NHMe	H	245.0-246.0
6b	Cl	NHMe	H	265.5-267.0
6c	CF_3	NHMe	H	221.0-223.0
7a	H	OMe	H	224.0-225.0
7b	Cl	OMe	H	234.0-235.0
7c	CF_3	OMe	H	223.0-224.0
8a	H	Cl	OH	110.0-111.0
8b	Cl	Cl	OH	115.5-117.0
8c	CF_3	Cl	OH	230.0-231.0
9a	H	Cl	OAc	126.0-127.0
9b	Cl	Cl	OAc	172.5-174.0
9c	CF_3	Cl	OAc	165.0-166.0

EXPERIMENTAL

Pmr spectra were obtained on a JEOL FX-90 Spectrometer locked on tetramethylsilane as an internal reference. Ir spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA-3500 and DX-300, JMA-3100. Elemental analyses were measured on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione). Chemical purities were determined on a Shimazu Liquid Chromatograph LC-3A. All melting points are uncorrected.

In the assignment of pmr spectra, the symbol q and p indicate quinoxaline and pyridazine ring, respectively. All new compounds 4-9 gave satisfactory elemental analyses.

The syntheses of 4a-c from 1a-c. A solution of 1b (36.1 g, 200 mmol) was refluxed in phosphoryl chloride (360 ml) for 1.5 h. After removal of excess phosphoryl chloride under reduced pressure, a crude product was dissolved in chloroform. The chloroform solution was washed with 1% aqueous sodium hydroxide, then with water and dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was recrystallized from n-hexane/acetonitrile (10/1) to afford 33.0 g (83%) of 2b, mp 154.0-155.0 °C; pmr($CDCl_3$) δ 7.73(1H, d d, J= 8.9, 2.2 Hz, H-7), 7.96 (1H, d, J= 8.9 Hz, H-8), 8.09(1H, d, J= 2.2 Hz, H-5), and 8.77(1H, s, H-3); ms m/z 198(M^+, base peak), 163, and 136.

A solution of 2b (10.0 g, 50.3 mmol) and 100% hydrazine hydrate (25.0 g, 500 mmol) in ethanol (300 ml) was refluxed for 1 h, the reaction mixture was cooled, and the resulting solid was collected, washed with water, then with a small amount of ethanol and dried in vacuo to afford 9.10 g (93%) of 3b, mp 235.5-237.0 °C; ir(KBr): 3150, 1610, 1583, 1538, 1402, 1328, 1304, 1182, 1077, 1040, 988, 900, and 829 cm^{-1}; pmr($CDCl_3$) δ 7.49(2H, br s, H-7 and H-8), 7.72(1H, br s, H-5), and 8.33 (1H, s, H-3); ms m/z 194(M^+, base peak), 179, 177, 164, and 137.

A mixture of 3b (6.81 g, 35.0 mmol) and mucochloric acid (5.94 g, 35.1 mmol) in acetic acid (200 ml) was stirred at 110 °C for 5.5 h. After cooling, the reaction mixture was poured onto water. The resulting solid was collected, washed with water, and then with ethanol. It was dried in vacuo to afford 10.0 g (87%) of 4b. ir(KBr): 3425, 1678, 1652, 1578, 1481, 1305, 1220, 1158, 1072, 979, 942, and 832 cm^{-1}; pmr($CDCl_3$) δ 7.81(1H, d d, J= 8.4, 2.4 Hz, H-7q), 8.07(1H, s, H-6p), 8.13 (1H, d, J= 8.4 Hz, H-8q), 8.23(1H, d, J= 2.4 Hz, H-5q), and 9.21(1H, s, H-3q); ms m/z 326(M^+, base peak), 291, 264, and 263.

In a similar manner, 4a and 4c were synthesized.

4a; ir(KBr): 3410, 1664, 1570, 1488, 1300, 1220, 1152, 970, 939, 800, and 762 cm^{-1}; pmr($CDCl_3$) δ 8.03(1H, s, H-6p), 9.18(1H, s, H-3q), and 7.70-8.40(4H, m, aromatic protons); ms m/z 292(M^+, base peak), 257, 230, 229, and 129.

4c; ir(KBr): 3440, 1649, 1580, 1565, 1463, 1404, 1330, 1312, 1274, 1224, 1192, 1160, 1122, 1080, 1060, 980, 948, 898, 841, and 749 cm^{-1}; pmr(DMSO-d_6) δ 8.09 (1H, d d, J= 9.0, 2.4 Hz, H-7q), 8.32(1H, s, H-6p), 8.34(1H, d, J= 9.0 Hz, H-8q), 8.49(1H, d, J= 2.4 Hz, H-5q), and 9.33(1H, s, H-3q); ms m/z 360(M^+, base peak), 325, 298, and 297.

The syntheses of 5a-c from 4a-c. A solution of 4b (1.00 g, 3.05 mmol) and 40% aqueous dimethylamine (10.0 g, 88.9 mmol) in ethanol (10 ml) was refluxed for

0.5 h. After cooling, the resulting solid was collected, washed with water, and then with ethanol. It was dried in vacuo to afford 0.90 g (88%) of 5b. ir(KBr): 3425, 1648, 1605, 1522, 1338, 1319, 1144, 1066, and 817 cm^{-1}; pmr($CDCl_3$) δ 3.25 (6H, s, $-N(CH_3)_2$), 7.71(1H, d d, J= 9.0, 2.4 Hz, H-7q), 7.90(1H, s, H-6p), 8.09 (1H, d, J= 9.0 Hz, H-8q), 8.16(1H, d, J= 2.4 Hz, H-5q), and 9.31(1H, s, H-3q); ms m/z 335(M^+), 300, 273, 163, and 103(base peak).

In a similar manner, 5a and 5c were synthesized.

5a; ir(KBr): 3425, 1652, 1605, 1520, 1321, 1308, 1138, 799, and 752 cm^{-1}; pmr($CDCl_3$) δ 3.23(6H, s, $-N(CH_3)_2$), 7.88(1H, s, H-6p), 9.26(1H, s, H-3q), and 7.50-8.30(4H, m, aromatic protons); ms m/z 301(M^+, base peak), 266, and 239.

5c; ir(KBr): 3440, 1645, 1600, 1562, 1523, 1460, 1404, 1311, 1185, 1158, 1126, and 1059 cm^{-1}; pmr(DMSO-d_6) δ 3.24(6H, s, $-N(CH_3)_2$), 8.14(3H, br s, H-7q, H-8q, and H-6p), 8.44(1H, br s, H-5q), and 9.26(1H, s, H-3q); ms m/z 369(M^+, base peak), 334, 307, 197, and 103.

The syntheses of 6a-c from 4a-c. A solution of 4b (1.00 g, 3.05 mmol) and 40% aqueous methylamine (10.0 g, 129 mmol) in ethanol (10 ml) was refluxed for 15 min. After cooling, the resulting solid was collected and washed with water, and then with ethanol. It was dried in vacuo to afford 0.95 g (97%) of 6b. ir(KBr): 3350, 1608, 1524, 1481, 1442, 1338, 1304, 1185, 1102, 968, and 828 cm^{-1}; pmr(DMSO-d_6) δ 3.05(3H, d, J= 5.0 Hz, $-NHCH_3$), 7.04(1H, br d, J= 5.0 Hz, $-NHCH_3$), 8.13(1H, s, H-6p), 9.18(1H, s, H-3q), and 7.60-8.40(3H, m, H-5q, H-7q, and H-8q); ms m/z 321 (M^+, base peak), 286, 259, and 205.

In a similar manner, 6a and 6c were synthesized.

6a; ir(KBr): 3440, 3280, 1645, 1624, 1539, 1342, 1315, 810, and 758 cm^{-1}; pmr (DMSO-d_6) δ 3.08(3H, d, J= 5.4 Hz, $-NHCH_3$), 7.00(1H, br d, J= 5.4 Hz, $-NHCH_3$), 8.12(1H, s, H-6p), 9.16(1H, s, H-3q), and 7.70-8.40(4H, m, aromatic protons); ms m/z 287(M^+, base peak), 252, 225, and 171.

6c; ir(KBr): 3430, 1652, 1618, 1564, 1458, 1405, 1310, 1272, 1190, 1152, 1122, and 1059 cm^{-1}; pmr(DMSO-d_6) δ 3.03(3H, d, J= 5.4 Hz, $-NHCH_3$), 7.05(1H, br d, J= 5.4 Hz, $-NHCH_3$), 8.10(1H, s, H-6p), 8.15(2H, br s, H-7q and H-8q), 8.42(1H, br s, H-5q), and 9.25(1H, s, H-3q); ms m/z 355(M^+, base peak), 320, 293, and 239.

The syntheses of 7a-c from 4a-c. To a solution of sodium methoxide (0.18 g, 3.33 mmol) in dry methanol (40 ml) 4b (1.00 g, 3.05 mmol) was added at room temperature. The reaction mixture was refluxed for 1 h. After cooling, the resulting solid was collected and washed with water, and then with ethanol. It was

dried in vacuo to afford 0.70 g (71%) of 7b. ir(KBr): 3420, 1652, 1600, 1480, 1390, 1299, 1248, 1152, 1071, 973, 946, and 824 cm^{-1}; pmr(DMSO-d_6) δ 4.18(3H, s, -OCH_3), 7.84(1H, d d, J= 8.4, 2.4 Hz, H-7q), 8.12(1H, d, J= 8.4 Hz, H-8q), 8.21 (1H, d, J= 2.4 Hz, H-5q), 8.50(1H, s, H-6p), and 9.18(1H, s, H-3q); ms m/z 322(M^+, base peak), 287, 280, 259, 163, and 103.

In a similar manner, 7a and 7c were synthesized.

7a; ir(KBr): 3425, 1662, 1605, 1382, 1298, 1252, 1150, 972, 942, 807, and 771 cm^{-1}; pmr(DMSO-d_6) δ 4.24(3H, s, -OCH_3), 8.61(1H, s, H-6p), 9.27(1H, s, H-3q), and 7.78-8.45(4H, m, aromatic protons); ms m/z 288(M^+, base peak), 253, 245, and 225.

7c; ir(KBr): 3420, 1660, 1601, 1450, 1381, 1306, 1259, 1181, 1159, 1132, 1055, 970, and 852 cm^{-1}; pmr(DMSO-d_6) δ 4.19(3H, s, -OCH_3), 8.04(1H, d d, J= 8.0, 2.4 Hz, H-7q), 8.28(1H, d, J= 8.0 Hz, H-8q), 8.45(1H, d, J= 2.4 Hz, H-5q), 8.48(1H, s, H-6p), and 9.29(1H, s, H-3q); ms m/z 356(M^+, base peak), 321, 314, 293, 197, and 103.

The reaction of 4b with two fold equivalent of sodium methoxide. A solution of 4b (1.00 g, 3.05 mmol) and sodium methoxide (0.33 g, 6.11 mmol) in dry methanol (40 ml) was refluxed and the reaction was analyzed with HPLC. In the beginning of the reaction, 4b was converted into 7b and 6-chloro-2-methoxyquinoxaline was not detected. Reflux was continued for 1 h and it became clear that the resulting 7b decreased with increasing 6-chloro-2-methoxyquinoxaline. After cooling, the reaction mixture was poured onto water. The resulting solid was collected, washed with water, and then with a small amount of ethanol. It was dried in vacuo to afford 0.46 g (78%) of 6-chloro-2-methoxyquinoxaline, mp 87.5-89.0 °C; ir(KBr): 3400, 1602, 1581, 1568, 1458, 1380, 1309, 1219, 1179, 1016, and 824 cm^{-1}; pmr ($CDCl_3$) δ 4.07(3H, s, -OCH_3), 7.55(1H, d d, J= 8.4, 2.4 Hz, H-7), 7.77(1H, d, J= 8.4 Hz, H-8), 7.98(1H, d, J= 2.4 Hz, H-5), and 8.45(1H, s, H-3); ms m/z 194 (M^+, base peak), 166, and 165.

The syntheses of 8a-c from 3a-c. A mixture of 3b (1.95 g, 10.0 mmol) and dichloromaleic anhydride (1.67 g, 10.0 mmol) in acetic acid (35 ml) was stirred at 100 °C for 3 h. After cooling, the reaction mixture was poured onto water. The resulting solid was collected and washed with water, and then with ethanol. It was dried in vacuo to afford 3.00 g (87%) of 8b. ir(KBr): 3345, 1740, 1604, 1580, 1375, 1393, 1208, 1179, 1110, and 880 cm^{-1}; pmr(DMSO-d_6) δ 7.59(2H, br s, H-7q and H-8q), 7.96 (1H, br s, H-5q), 8.67(1H, s, H-3q), and 10.05(1H, br s, -OH); ms m/z 342(M^+, base peak), 297, and 263.

In a similar manner, 8a and 8c were synthesized.

8a; ir(KBr): 3375, 1742, 1610, 1580, 1292, 1208, 1121, 882, and 770 cm^{-1}; pmr (DMSO-d_6) δ 8.59(1H, s, H-3q), 10.40(1H, br s, -OH), and 7.15-8.15(4H, m, aromatic protons); ms m/z 308(M^+, base peak), 263, and 229.

8c; ir(KBr): 3360, 1742, 1606, 1580, 1318, 1282, 1188, 1157, and 1120 cm^{-1}; pmr (DMSO-d_6) δ 7.73(2H, br s, H-7q and H-8q), 8.18(1H, br s, H-5q), 8.70(1H, s, H-3q), and 10.44(1H, br s, -OH); ms m/z 376(M^+), 331, 297(base peak), and 213.

The syntheses of 9a-c from 8a-c. A solution of 8b (1.50 g, 4.37 mmol) was refluxed in acetic anhydride (40 ml) for 1 h. After removal of excess acetic anhydride under reduced pressure, crude product was purified with column chromatography (silica gel, $CHCl_3$) to afford 1.28 g (76%) of 9b. ir(KBr): 3410, 1811, 1750, 1720, 1599, 1479, 1440, 1367, 1290, 1248, 1210, 1118, 972, 880, 838, 723, and 710 cm^{-1}; pmr($CDCl_3$) δ 2.39(3H, s, $-OCOCH_3$), 7.65(2H, br s, H-7q and H-8q), 8.08(1H, br s, H-5q), and 9.70(1H, s, H-3q); ms m/z 384(M^+), 342(base peak), 297, and 263.

In a similar manner, 9a and 9c were synthesized.

9a; ir(KBr): 3420, 1811, 1752, 1714, 1600, 1557, 1490, 1363, 1260, 1213, 1105, 971, 881, 770, 724, and 703 cm^{-1}; pmr($CDCl_3$) δ 2.38(3H, s, $-OCOCH_3$), 9.69(1H, s, H-3q), and 7.50-8.30(4H, m, aromatic protons); ms m/z 350(M^+), 308(base peak), 263, and 229.

9c; ir(KBr): 3425, 1810, 1749, 1720, 1600, 1559, 1451, 1362, 1324, 1250, 1212, 1190, 1170, 1130, 1103, 1058, 972, 882, 839, 727, and 703 cm^{-1}; pmr($CDCl_3$) δ 2.38 (3H, s, $-OCOCH_3$), 7.79(2H, br s, H-7q and H-8q), 8.33(1H, br s, H-5q), and 9.75 (1H, s, H-3q); ms m/z 418(M^+), 376(base peak), 331, and 297.

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