Synthesis and biological activity of some heterocyclic compounds containing quinoxaline and coumarin moieties

I. M. EL-DEEN and M. E. ABD EL-FATTAH*

Faculty of Education, Suez Canal University, Port-Said, Egypt and *Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

(Received 28 June 1999)

2,3-Dichloroquinoxaline (2) condensed with 7,8-dihydroxy-4-methylcoumarin to give the 1,4-dioxane derivative 4. 2,3-Dichloroquinoxaline (2) reacted with 4-hydroxycoumarin, 7-hydroxy-4-methylcoumarin and acetylhydrazide 13 to give either the 2,3-(dihydropyridine-4-methoxy)quinoxaline (6) or the 2,3-di-(4-methylcoumarin-7-methoxy)quinoxaline (7) or the 2-chloro-3-(4-methylcoumarin-7-methoxy)quinoxaline (8) or the 2-chloro-3-(4-methylcoumarin-7-methoxy)quinoxaline (9) or the dithiazoloquinoxaline 14 or the oxadiazinoquinoxaline 16, depending on the relative ratios of the reactants and the reaction conditions.

Keywords: 2,3-dichloroquinoxaline, reaction with coumarin derivatives.

Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important molecules, quinoxalines have played an important role in medicinal chemistry,1–3 anticancer treatment,4 as herbicides,5 as well as for the detection and estimation of metals,6–9 and as heat stable oil additives.10 In view of these and in continuation of our work11–14 in this area, the synthesis of some new heterocyclic compounds containing quinoxaline and coumarin moieties are reported here.

RESULTS AND DISCUSSION

The 2,3-dichloroquinoxaline (2) was prepared by the reaction of o-phenylenediamine with oxalic acid to give 2,3-dihydroxyquinoxaline (1), followed by the treatment of 1 with phosphorus oxychloride. The condensation of 2,3-dichloroquinoxaline (2) with 7,8-dihydroxy-4-methylcoumarin (3) under alkaline conditions15 gave the corresponding 1,4-dioxane derivative 4, (Scheme 1).

One molarequivalent of 2,3-dichloroquinoxaline (2) was allowed to react with two molar equivalent5 of a 7,4-disubstituted coumarin 5, such as 4-hydroxycoumarin or 7-hydroxy-4-methylcoumarin, in alkaline medium affording the corresponding 2,3-(dihydropyridine-4-methoxy)quinoxaline (6) and 2,3-di-(4-methylcoumarin-7-methoxy)quinoxaline (7) (Scheme 2), respectively.
In addition, one molar equivalent of 2,3-dichloroquinazoline (2) reacted with one molar equivalent of a 7,4-disubstituted coumarin 5, such as 4-hydroxycoumarin or 7-hydroxy-4-methylcoumarin, in alkaline medium led to the formation of 2-chloro-3-(coumarin-4-yloxy)quinazoline (8) and 2-chloro-3-(4-methylcoumarin-7-yloxy)quinazoline (9) (Scheme 3), respectively.

An ethanolic solution of 9 when allowed to react with an amine derivative 10, such as 4-aminobenzoic acid or 4-tolysulphonamide, afforded the corresponding 3-(4-carboxyphenylamino)-2-(4-methylcoumarin-7-yloxy)quinazoline (11) and 3-(4-tolylsulphonamido)-2-(4-methylcoumarin-7-yloxy)quinazoline (12) (Scheme 4), respectively.

The ditaizoloquinazoline derivative 14 was obtained by the reaction of one molar equivalent 2,3-dichloroquinazoline (2) with two molar equivalent of 4-
methylcoumarin-7-yl-oxoacetyl hydrazone (13) in dimethyl formamide under reflux (Scheme 5).

In the present investigation it was expected that the reaction of one molar equivalent of 2,3-dichloroquinazoline (2) with one molar equivalent of compound 13 in dimethyl formamide under reflux would produce 2-chloro-3-triazolo [4,3-\(a\)]quinazoline via cyclocondensation. However, the new product proved to be the oxadiazino [2,3-\(b\)]quinazoline derivative (15) (Scheme 6).
Biological activity

Applying the nutrient agar plate diffusing method (Philipp et al., 1994) all of the newly synthesized compounds were screened in vitro for antibacterial activity against Eschericia coli, Salmonella and Staphylococci which were isolated from humans. A few crystals of the tested compounds were placed on the cultivated plates. The plates were incubated at 37 °C/48 h. The activity was determined by measuring the diameter of the inhibition zone. The screening results given in Table 1 indicated that all the compounds exhibited antibacterial activities against one or other type of bacteria. Compounds 6 and 7 gave the very good results with all three types of bacteria.
TABLE I. Antibacterial activity of some synthesized compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Gram–ve</th>
<th>Gram+ve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esch. Coli</td>
<td>Salmonella</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>7</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

- No antibacterial activity, + Mild activity, ++ Moderate activity, +++ Marked activity, ++++ Strong marked activity

EXPERIMENTAL

Melting points were determined on a Boetius hot apparatus. Microanalyses were carried out on an elemental analyzer, Heraeus CHN-O Rapid. IR spectra were recorded on a Perkin-Elmer FTIR 1725 spectrometer. Mass spectra were taken on a VG 12-250 instrument (70 eV El ionization. Source temperature 200 °C). 1H-NMR and 13C-NMR spectra were recorded on a Varian unity 400 spectrometer at 200 MHz, with TMS as the internal standard.

I.4-Dioxane derivative (4)

A solution of 3 (0.01 mol) and sodium hydroxide (0.02 mol) in water (5 mL) was added to a solution of 2 (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2–3 h, then cooled and acidified with hydrochloric acid (1 mol/L). The deposited solid was filtered off and purified by crystallization from benzene to give 4 as pale yellow crystals, yield 73%, m.p. 83 °C. \( \lambda_{\text{max}} \) (KBr): 1712 (C=O), 1630 (C=N), 1209, 1015 cm\(^{-1}\). \( \delta_\text{di} \) (CDCl3): 2.41 (s, 3H, CH3), 7.31–7.96 (m, 7H, Ar-Hand pyranone ring) ppm. \( \delta \) (CDCl3): 160.32 (C-2), 112.38 (C-3), 137.24 (C-4), 126.36 (C-5), 129.63 (C-6), 143.52 (C-7), 150.31 (C-8), 152.27 (C-9), 118.46 (C-10), 32.18 (C-11), 149.01 (C-2'), 3'), 130.01 (C-5', 8'), 130.21 (C-6', 7'), 143.61 ppm. M/z (%): 319 (M+1, 31), 318 (M+1, 52), 190 (100), 160 (65), 161 (69), 159 (5), 156 (4), 148 (2), 147 (11), 144 (3), 144 (7), 119 (20), 118 (3), 105 (36), 103 (15), 92 (4), 91 (2), 90 (9), 77 (15), 65 (11). Anal. C\(_7\)H\(_{10}\)NO\(_4\). Calcld.: C, 67.92; H, 3.15; N, 8.81. Found: C, 67.69; H, 3.01; N, 8.58.

2,3-(Diocoumarin-4-yloxy)quinazoline (6)

A solution of 5a or 5b (0.02 mol) and sodium hydroxide (0.02 mol) in water (5 mL) was added to a solution of 2 (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2–3 h, then cooled and acidified with hydrochloric acid (1 mol/L). The solid obtained was filtered off and purified by crystallization from ethanol to give 6 or 7. \( \lambda_{\text{max}} \) (KBr): 2095, 1710–1720, 1630–1620, 1260, 1095 cm\(^{-1}\).

Compound 6 as colourless crystals, yield 72%, m.p. 168 °C. \( \delta_\text{di} \) (DMSO-\( \text{d}_{6} \)): 7.21–7.98 (m, 14H, Ar-Hand pyranone ring) ppm. \( \delta \) (DMSO-\( \text{d}_{6} \)): 160.32 (C-2), 112.35 (C-3), 150.36 (C-4), 128.42 (C-5), 122.72 (C-6), 131.63 (C-7), 116.32 (C-8), 153.89 (C-9), 118.62 (C-10), 149.35 (C-2', 3').
130.00 (C-5, 8), 130.22 (C-6, 7), 143.68 (C-9, 10) ppm. m/z (%): 451 (M+ + 1, 11), 450 (M+), 189 (8), 161 (100), 119 (75), 92 (85), 91 (43), 76 (35), 65 (12). Anal. C26H14N2O5. Calcld.: C, 69.33; H, 3.11; N, 6.22. Found: C, 69.06; H, 3.02; N, 6.03.

Compound 7 as colourless crystals, yield 74%, m.p.: 153 °C. χ (DMSO-d6): 2.41 (s, 6H, 2x CH3), 7.20–7.97 (m, 12H, Ar–H and pyranone ring) ppm. χ (DMSO-d6): 160.83 (C-2), 111.92 (C-3), 140.32 (C-4), 129.72 (C-5), 114.03 (C-6), 159.63 (C-7), 105.32 (C-8), 154.80 (C-9), 111.63 (C-10), 32.12 (C-11), 149.30 (C-2, 3), 130.02 (C-5, 8), 130.20 (C-6, 7), 143.52 (C-9, 10) ppm. m/z (%): 479 (M+ + 1, 16), 478 (M+), 176 (100), 175 (51), 161 (10), 146 (36), 128 (10), 118 (56), 104 (15), 91 (59), 65 (50). Anal. C28H18N2O6. Calcld.: C, 70.29; H, 3.76; N, 5.86. Found: C, 70.01; H, 3.52; N, 5.31.

2-Chloro-3-(coumarin-4-yl)oxazoline (8)
2-Chloro-3-(4-methylcoumarin-7-yl)oxazoline (9)

A solution of 5a or 5b (0.01 mol) and sodium hydroxide (0.01 mol) in water (54 mL) was added to a solution of 2 (0.01 mol) in methanol (70 mL). The reaction mixture was heated on a water bath for 2–3 h, then cooled and acidified with hydrochloric acid (1 mol/L). The deposited solid was filtered off and purified by crystallization from ethanol to give 8 or 9. λmax (KBr): 2905, 1711–1718, 1623–1618, 1210, 1100 cm⁻¹.

Compound 8 as colourless crystals, yield 63%, m.p.: 138 °C. δ (CDCl3): 7.27–7.98 (m, 9H, Ar–H and pyranone ring) ppm. m/z (%): 326 (M+ + 2, 17), 324 (M+, 31), 163 (15), 162 (100), 161 (33), 129 (17), 120 (85), 92 (40), 63 (14). Anal. C17H16Cl2N2O3. Calcld.: C, 62.96; H, 2.77; N, 8.64; Cl, 10.80. Found: C, 62.71; H, 2.48; N, 8.40; Cl, 10.52.

Compound 9 as colourless crystals, yield 68%, m.p.: 105 °C. δ (CDCl3): 2.44 (s, 3H, CH3), 7.25–7.98 (m, 8H, Ar–H and pyranone ring) ppm. m/z (%): 340 (M+ + 2, 18), 338 (M+, 18), 336 (M+, 48), 176 (100), 175 (50), 164 (18), 163 (29), 147 (33), 144 (9), 130 (14), 126 (48), 118 (62), 104 (41), 91 (60), 77 (48), 65 (33). Anal. C23H16Cl2N2O3. Calcld.: C, 63.91; H, 3.25; N, 8.28; Cl, 10.36. Found: C, 63.60; H, 3.05; N, 7.98; Cl, 10.01.

2-(Substituted amine)-3-(4-methylcoumarin-7-yl)oxazolines (11 and 12)

A solution of 9 (0.01 mol) and an amine derivative 10a or 10b (0.01 mol) (such as 4-aminobenzoic acid or 4-tolysulphonamide) in ethanol (70 mL) was heated under reflux for 6 h. The solution obtained after cooling was filtered off and recrystallized from ethanol to give 11 and 12.

Compound 11 as pale yellow crystals, yield 67%, m.p.: 265 °C. λmax (KBr): 3220 (NH), 3325 – 2890 (broad OH), 1705–1718 (C=O), 1625 (C=N), 1280, 1030 cm⁻¹. δ (DMSO-d6): 2.38 (s, 3H, CH3), 7.20–7.98 (m, 12H, Ar–H and pyranone ring) ppm. δ (DMSO-d6): 160.62 (C-2), 112.01 (C-3), 139.65 (C-4), 129.68 (C-5), 114.10 (C-6), 159.51 (C-7), 106.32 (C-8), 154.73 (C-9), 111.53 (C-10), 32.16 (C-11), 149.35 (C-12), 145.09 (C-13), 130.01 (C-5', 8'), 130.21 (C-7', 10'), 143.62 (C-9', 11'), 143.82 (C-1', 11'), 114.21 (C-2', 6'), 129.95 (C-3', 5'), 129.43 (C-4'), 172.25 (C-7') ppm. m/z (%): 439 (M+, 17), 438 (M+ – 1, 12), 395 (12), 394 (10), 265 (7), 264 (34), 221 (5), 220 (18), 174 (5), 145 (7), 144 (4), 104 (7), 102 (6), 90 (11), 77 (5). Anal. C27H18N3O3S. Calcld.: C, 68.34; H, 3.87; N, 9.57. Found: C, 68.02; H, 3.62; N, 9.28.

Compound 12 as pale yellow crystals, yield 65%, m.p.: 120 °C. λmax (KBr): 3240 (NH), 1712 (C=O), 1625 (C=N), 1205, 1030 cm⁻¹. δ (DMSO-d6): 2.30 (s, 3H, CH3), 2.43 (s, 3H, CH3), 7.15 – 7.96 (m, 12H, Ar–H and pyranone ring) ppm. δ (DMSO-d6): 160.65 (C-2), 112.1 (C-3), 139.72 (C-4), 129.67 (C-5), 114.16 (C-6), 159.53 (C-7), 106.30 (C-8), 154.70 (C-9), 111.52 (C-10), 32.13 (C-11), 149.36 (C-12), 145.10 (C-13), 130.00 (C-5', 8'), 130.21 (C-6', 7'), 143.61 (C-9', 10'), 142.60 (C-1', 11'), 125.71 (C-2', 6'), 129.40 (C-3', 5'), 139.58 (C-4'), 21.0 (C-7') ppm. m/z (%): 473 (M+, 25), 298 (25), 234 (45), 175 (100), 145 (23), 90 (16), 77 (31). Anal. C28H19N3O3S. Calcld.: C, 63.42; H, 4.02; N, 8.88; S, 6.76. Found: C, 63.17; H, 3.86; N, 8.58; S, 6.49.
**Ditiazoloquinoline (14)**

A mixture of 2 (0.01 mol) and acyl hydrazide 13 (0.02 mol) in dimethyl formamide (50 mL) was refluxed for 16 h. The reaction mixture was cooled and then poured onto water. The solid that separated was crystallized from acetic acid to give 14 as yellow crystals, yield 73%, m.p. 280–281 °C. 

$\text{r}_{\text{max}}$(KBr): 1716, 1630, 1305, 1215, 1095 cm$^{-1}$. $\delta$ (DMSO-d$_6$): 2.41 (s, 6H, 2x CH$_3$), 4.53 (s, 4H, 2x –CH$_2$O–), 7.21–7.98 (m, 12H, Ar-H and pyranone ring) ppm. $\delta$ (DMSO-d$_6$): 155.34 (C-2, 5), 130.08 (C-5, 8), 130.23 (C-6, 7), 143.43 (C-9, 10), 154.86 (C-5a), 57.82 (C-6a), 160.63 (C-2'), 112.15 (C-3'), 139.70 (C-4'), 129.58 (C-5'), 114.15 (C-6'), 159.36 (C-7'), 106.27 (C-8'), 154.71 (C-9'), 111.50 (C-10'), 32.15 (C-11'). ppm. $m/z (%):$ 562 (M$^+$, 17), 388 (13), 387 (19), 175 (100), 147 (97), 146 (79), 130 (14), 118 (11), 102 (27), 91 (24), 77 (15), 65 (12). Anal: C$_9$H$_2$NO. Caled.: C 64.06; H, 3.91; N, 14.95. Found: C, 63.89; H, 3.62; N, 14.70.

**Oxadiazino 2,3-b'quinoxaline (16)**

A mixture of 2 (0.01 mol) and acyl hydrazide 13 (0.01 mol) in dimethyl formamide (30 mL) was heated under reflux for 12 h. The reaction mixture was cooled and then poured onto water yielding the crude product which was filtered and purified by recrystallization from acetic acid to give 16 as pale yellow crystals, yield 74%, m.p. 264 – 265 °C. $\text{r}_{\text{max}}$(KBr): 3240 (NH), 1714, 1625, 1201, 1095 cm$^{-1}$. $\delta$ (DMSO-d$_6$): 2.42 (s, 3H, CH$_3$), 4.51 (s, 2H, –CH$_2$O–), 7.21–7.97 (m, 8H, Ar-H and pyranone ring), 10.4 (s, 1H, NH) ppm. $\delta$ (DMSO-d$_6$): 158.52 (C-2), 155.31 (C-5), 143.41(C-7, 12), 130.02 (C-8, 11), 130.22 (C-9, 10), 158.76 (C-14), 57.63 (C-15), 160.54 (C-2'), 112.20 (C-3'), 139.72 (C-4'), 129.56 (C-5'), 114.12 (C-6'), 159.53 (C-7'), 106.24 (C-8'), 154.59 (C-9'), 111.32 (C-10'), 32.13 (C-11'), ppm. $m/z (%):$ 375 (M$^+$ + 1, 2), 374 (M$^+$, 5), 233 (12), 226 (17), 199 (11), 176 (100), 175 (7), 147 (81), 131 (10), 128 (3), 120 (15), 102 (10), 91 (21), 77 (9), 65 (8). Anal. C$_9$H$_2$NO. Caled.: C, 64.17; H, 3.74; N, 14.97. Found: C, 64.01; H, 3.49; N, 14.61.

**ИЗВОД**

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ НЕКИХ ХЕТЕРОЦИКЛИЧНИХ ЈЕДИЊЕА КОЈА САДРЖЕ ХИННОКСАЛИНСКО И КУМАРИНСКО ЈЕЗГРО

I. M. EL-DEEN и M. E. ABD EL-FATTAH

Faculty of Education, Suez Canal University, Port Said, Egypt, and Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

Конденсацијом 2,3-дигидрокахиноксалина (2) и 7,8-дигидрокахиноксалина добијен је 1,4-дигидроксикарнин 4. Релацијом 2 са 4-дигидроксикарним 7-дигидроксикарним и хидразидом 3 добијен је 2,3-(дици максима 4-илокси) хиноксалин (6), 2,3-(4-метилгидроксикарни-7-илокси) хиноксалин (7), 2-хидроксикарном 4-илокси). Хиноксалин (8), 2-хидроксикарном 7-илокси) хиноксалин (9), односно дигидроксикарном и оксидизованом хиноксалин (14) или оксидизованом хиноксалин (26), у зависности од могућих реактних одбиса реактаната и услова реакције.

(Примјено 28. јуна 1999)

**REFERENCES**

7. Q. S. Soper, U.S. Pat., 364779 [C. A. 77 (1972) 30339z]