Acetylene Chemistry. Part 25 [1]. Reactions of Ethyl 4-Hydroxy-3-quinolin-2(1*H*)-onecarboxylates with 3-Bromoprop-1-yne

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Ethyl 4-hydroxyquinolin-2(1*H*)-onecarboxylates **1a** and **1b** which are obtained conveniently by the condensation of isatoic anhydride and diethylmalonate [4], were reacted with 3-bromoprop-1-yne (**2**) to obtain mono- and dialkylated derivatives.

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It is known that, 3-prenylquinolinones are the precursors for the biosynthesis of tricyclic alkaloids in the family *Rutaceae* [5].

The introduction of radioactive labelled side chains to the quinolinone ring would be of interest in the biosynthetic studies. Previous investigations on alkylation of 4-hydroxyquinolin-2(1*H*)-ones gave 3,3-dialkylated compounds as the major products [6,7]. The dialkylation is accomplished because the reactivity of the 3-position is increased after monoalkylation in order to accept another alkyl substituent [8].

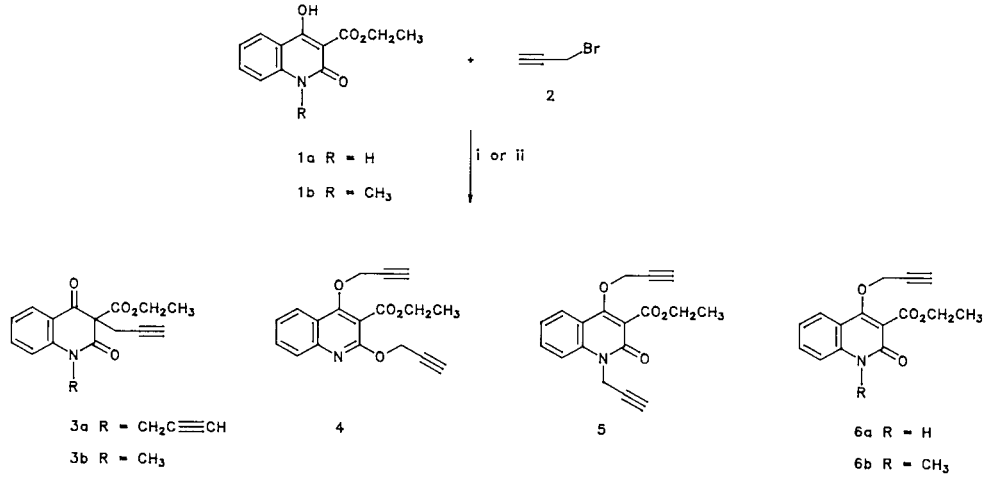
The starting materials **1a** and **1b** were obtained from the condensation reaction of diethyl malonate with isatoic anhydride and *N*-methylisatoic anhydride respectively [4]. The carbethoxy group can easily be removed after alkylation with potassium carbonate in ethanol [6]. The reaction of **1a** with 3-bromoprop-1-yne (**2**) under Claisen conditions [9] leads to the dialkylated products, ethyl 1,3-di-(2-propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxylate (**3a**), ethyl 2,4-di-(2-propynyl)oxy-3-quinolinecarboxylate (**4**) and ethyl 1-(2-propynyl)-4-(2-propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**5**) and to the monoalkylated product, ethyl 4-(2-propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**6a**).

Under the same conditions as **1a** above, **1b** was reacted with 3-bromoprop-1-yne (**2**) to give ethyl 4-(2-propynyl)oxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**6b**) in 35% yield and ethyl 3-(2-propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-1-methyl-3-quinolinecarboxylate (**3b**) in 5% yield. The yields were improved by using a catalytic amount of a crown ether, in the reaction. Consequently **6b** and **3b** were obtained in 45% and 17% yield respectively. The increase in yield of the *C*-alkylated product was found to be higher.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 ir spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform at 200 MHz with

Scheme



i: k_2CO_3, ki, acetone, reflux

ii: i, dicyclo-hexyl-18-crown-6

tetramethylsilane as the internal reference on a Varian Gemini 200 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV. Silica gel 60 F_{254} (precoated, aluminium sheets, 0.2 mm thickness, Merck 5549) were used for analytical tlc. Column chromatography was carried out on silica gel 60 (particle size 0.063-0.200 mm, Merck 7734). 3-Bromoprop-1-yne was obtained from Ega-Chemie, Germany. Isatoic anhydride and *N*-methylisatoic anhydride (Janssen, Germany) were used after recrystallisation from dimethyl acetamide.

Alkylation of Ethyl 4-Hydroxy-3-quinolin-2(1*H*)-onecarboxylate (**1a**) with 3-Bromoprop-1-yne (**2**).

To a stirred mixture of ethyl 4-hydroxy-3-quinolin-2(1*H*)-onecarboxylate (0.50 g, 2 mmoles) containing potassium carbonate (1.40 g, 10 mmoles) and potassium iodide (0.03 g) in dry acetone, 3-bromoprop-1-yne (0.36 g, 3 mmoles) was added dropwise. The reaction mixture was heated under reflux for 10 hours, was allowed to cool and filtered. The filtrate was evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (dichloromethane-methanol 98:2) to give **3a**, **4**, **5** and **6a**.

Ethyl 1,3-Di-(2-propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxylate (**3a**).

The first eluate of the column (dichloromethane-methanol 98:2) afforded ethyl 1,3-di-(2-propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxylate (0.05 g, 8.1%) (**3a**), which was isolated from dichloromethane-methanol as colourless prisms, mp 116-117°; ir (potassium bromide): 3050, 3030 (≡CH), 2100 (C≡C), 1750 (C=O, ester), 1700, 1670 (C=O), 1595, 1480, 1375, 1230, 765 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.79 (t, J = 2.7 Hz, 1H, H-3''), 2.28 (t, J = 2.3 Hz, 1H, H-3'), 3.30 (d, J = 2.7 Hz, 2H, H-1''), 4.16 (dq, J = 7.1, 1.5 Hz, $CO_2CH_2CH_3$), 4.91 (dq, J = 2.3, 18.0 Hz, 2H, H-1'), 7.27 (t, J = 7.8 Hz, 1H, H-6), 7.41 (d, J = 8.2 Hz, 1H, H-8), 7.74 (m, 1H, H-7), 8.09 (dd, J = 1.7, 7.8 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 13.8 ($CO_2CH_2CH_3$), 24.8 (C-1''), 32.3 (C-1'), 63.1 ($CO_2CH_2CH_3$), 66.8 (C-2''), 71.6 (C-3'), 71.9 (C-2'), 72.8 (C-3''), 77.2 (C-4a), 115.8 (C-8), 120.7 (C-3), 123.9 (C-6), 128.6 (C-5), 136.9 (C-7), 142.1 (C-8a), 161.8 (C-4), 166.2 (C-2), 189.2 ($CO_2CH_2CH_3$); ms: m/z 309 (M^+, 37), 295 (7), 270 ($M^+ - CH_2C\equiv CH$, 5), 236 ($M^+ - CO_2CH_2CH_3$, 100), 224 (17), 208 (14), 198 (14), 180 (20), 156 (36), 146 (16), 128 (28), 114 (11), 102 (29), 90 (22), 77 (32), 63 (15), 51 (39).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.86; H, 4.91; N, 4.50.

Ethyl 2,4-Di-(2-propynyl)oxy-3-quinolinecarboxylate (**4**).

This compound **4** was obtained as colourless needles from dichloromethane-methanol, 0.09 g (15%), mp 113-115°; ir (potassium bromide): 3230 (≡CH), 2980, 2100 (C≡C), 1705 (C=O, ester), 1600, 1310, 1210, 1135, 1080, 995, 965, 735 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.46 (t, J = 2.4 Hz, 1H, H-3'), 2.62 (t, J = 2.5 Hz, 1H, H-3''), 4.48 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.92 (d, J = 2.5 Hz, 2H, H-1''), 5.11 (d, J = 2.4 Hz, 2H, H-1'), 7.44 (m, 1H, H-6), 7.68 (m, 1H, H-7), 7.81 (m, 1H, H-8), 8.13 (ddd, J = 0.5, 1.5, 8.3 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 14.2 ($CO_2CH_2CH_3$), 54.3 ($CO_2CH_2CH_3$), 62.3 (C≡*C*H), 62.4 (C≡*C*H), 74.6 (2 x $CH_2C\equiv CH$), 77.1 (C-2''), 79.1 (C-2'), 109.7 (C-4a), 120.9 (C-3), 123.5 (C-8), 125.1 (C-6), 127.8 (C-5), 131.6 (C-7), 147.4 (C-8a), 158.3 (C-4), 161.3 (C-2), 165.5 ($CO_2CH_2CH_3$); ms: (m/z) 309 (M^+, 24), 295 (3), 270 ($M^+ - CH_2C\equiv CH$, 9), 236 ($M^+ - CO_2CH_2CH_3$, 100), 224 (21), 208 (19), 197 (19), 180 (35), 156 (19), 146 (10), 128 (21), 102 (9), 84 (30), 77 (12), 63 (9), 57'(34).

Anal. Calcd. $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.90; H, 4.69; N, 4.60.

Ethyl 1-(2-Propynyl)-4-(2-propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**5**).

The third eluate of the column (dichloromethane-methanol 98:2) gaves ethyl 1-(2-propynyl)-4-(2-propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**5**), which was obtained from dichloromethane-*n*-pentane as colourless needles, 0.13 g (21%), mp 95-98°; ir (potassium bromide): 3280 (≡CH), 3000, 2130 (C≡C), 1745 (C≡O, ester), 1682, 1650 (C=O, 2-quinolinone), 1595, 1468, 1370, 1220, 1010, 938, 860, 680, 640, 520 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.4 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.3 (t, J = 2.5 Hz, 1H, H-3'), 2.7 (t, J = 2.5 Hz, 1H, H-3''), 4.9 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.93 (d, J = 2.5 Hz, 2H, H-1''), 5.07 (d, J = 2.5 Hz, 2H, H-1'), 7.31 (m, 1H, H-6), 7.51 (dd, J = 0.6, 8.6 Hz, 1H, H-8), 7.68 (m, 1H, H-7), 8.07 (dd, J = 0.5, 6.5 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 14.1 ($CO_2CH_2CH_3$), 31.8 (C-1'), 60.9 (C-3'), 62.3 (C-3''), 72.7 (C-1''), 77.1 (C-2'), 77.6 (C-2''), 112.5 (C-4a), 114.6 (C-8), 117.1 (C-3), 122.8 (C-6), 125.2 (C-5), 132.4 (C-7), 138.3 (C-8a), 159.3 (C-4), 160.0 (C-2), 165.0 ($CO_2CH_2CH_3$); ms: (m/z) 309 (M^+, 5), 264 ($M^+ - OCH_2CH_3$, 8), 236 ($M^+ - CO_2CH_2CH_3$, 90), 208 (19), 198 (18), 186 (15), 169 (9), 156 (100), 128 (24), 102 (9), 84 (15), 77 (7), 51 (13).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.61; H, 4.86; N, 4.45.

Ethyl 4-(2-Propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**6a**).

The last fraction of the column (dichloromethane-methanol) contained ethyl 4-(2-propynyl)oxy-3-quinolin-2(1*H*)-onecarboxylate (**6a**), which could be recrystallised as colourless needles from dichloromethane, 0.01 g (1.8%), mp 136-139°; ir (potassium bromide): 3450 (NH), 3280 (≡CH), 2950, 2130 (C≡C), 1750 (C=O, ester), 1640 (C=O, 2-quinolinone) 1598, 1238, 1090, 758 cm^{-1}; ^1H nmr (deuteriochloroform): 1.45 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.65 (t, J = 2.4 Hz, 1H, C≡C*H*), 4.43 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.94 (d, J = 2.4 Hz, 2H, $CH_2C\equiv CH$), 7.21-7.40 (m, 2H, H-6, H-8), 7.50-7.61 (m, 1H, H-7), 7.97 (dd, J = 1.1, 8.1 Hz, 1H, H-5), 12.0 (s, br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.2 ($CO_2CH_2CH_3$), 61.2 ($CO_2CH_2CH_3$), 62.3 ($CH_2C\equiv CH$), 77.1 (C≡*C*H), 77.3 (*C*≡CH), 115.6 (C-4a), 116.2 (C-8), 118.4 (C-3), 122.9 (C-6), 124.4 (C-5), 132.3 (C-7), 138.3 (C-8a), 161.1 (C-2), 162.8 (C-4), 165.2 ($CO_2CH_2CH_3$); ms: (m/z) 271 (M^+, 7), 242 ($M^+ - CH_2CH_3$, 8), 226 (12), 212 (6), 198 ($M^+ - CO_2CH_2CH_3$, 100), 187 (8), 170 (28), 146 (21), 130 (20), 119 (42), 115 (22), 102 (15), 92 (33), 77 (21), 63 (19), 51 (19); hrms calcd. for $C_{15}H_{13}NO_4$: 271.0845. Found: 271.0840.

Alkylation of Ethyl 4-Hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**1b**) with 3-Bromoprop-1-yne (**2**).

The alkylation of **1b** (0.49 g, 2 mmoles) took place under the same conditions as for **1a**. The reaction mixture was stirred under reflux for 18 hours, cooled, filtered and the filtrate was evaporated *in vacuo*. Separation of the residue by column chromatography on silica gel (dichloromethane) afforded the compounds **3b** and **6b**.

Ethyl 3-(2-Propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-1-methyl-3-quinolinecarboxylate (**3b**).

This compound was obtained as colourless plates from dichloromethane-*n*-pentane, 0.03 g (5%), mp 124°; ir (potassium bromide): 3210 (≡CH), 3000, 2110 (C≡C), 1740 (C=O, ester), 1620 (C=O), 1600 (C=O), 1330, 1280, 1195, 980, 765 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.78 (t, J = 2.7 Hz, 1H, C≡C*H*), 3.28 (d, J = 2.7 Hz, 2H, $CH_2C{\equiv}CH$), 3.56 (s, 3H, N-CH_3), 4.16 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 7.20-7.28 (m, 2H, H-6, H-8), 7.68-7.77 (m, 1H, H-7), 8.07 (dd, J = 1.6, 8.0 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 13.8 ($CO_2CH_2CH_3$), 25.1 (N-CH_3), 30.1 ($CH_2C{\equiv}CH$), 63.1 ($CO_2CH_2CH_3$), 66.9 (C≡CH), 71.6 (C≡*C*H), 78.1 (C-4a), 115.5 (C-8), 120.8 (C-3), 123.8 (C-6), 128.7 (C-5), 137.4 (C-7), 144.1 (C-8a), 165.5 (C-4), 167.5 (C-2), 190.4 ($CO_2CH_2CH_3$); ms: (m/z) 285 (M^+, 32), 256 ($M^+ - CH_2CH_3$, 3), 240 ($M^+ - OCH_2CH_3$, 6), 212 ($M^+ - CO_2CH_2CH_3$, 100), 198 (5), 184 (12), 132 (9), 104 (18), 77 (13), 51 (7).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.45; H, 5.23; N, 4.89.

Ethyl 4-(2-Propynyl)oxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**6b**).

The second eluate obtained ethyl 4-(2-propynyl)oxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**6b**), which was recrystallised from dichloromethane-*n*-pentane to give colourless needles, 0.20 g (35%), mp 121-122°; ir (potassium bromide): 3210 (≡CH), 2120 (C≡C), 1717 (C=O, ester), 1616 (C=O, 2-quinolinone), 1582, 1494, 1397, 1275, 1121, 1022, 752 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.67 (t, J = 2.5 Hz, 1H, C≡C*H*), 3.67 (s, 3H, N-CH_3), 4.46 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.91 (d, J = 2.5 Hz, 2H, $CH_2C{\equiv}CH$), 7.26-7.39 (m, 2H, H-6, H-8), 7.65 (m, 1H, H-7), 8.07 (dd, J = 1.5, 8.2 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 14.2 ($CO_2CH_2CH_3$), 29.6 (N-CH_3), 61.1 and 62.4 ($CH_2C{\equiv}CH$ and $CO_2CH_2CH_3$), 77.3 (C≡*C*H), 77.5 (*C*≡CH), 113.5 (C-4a), 114.5 (C-8), 117.1 (C-3), 122.7 (C-6), 125.3 (C-5), 132.7 (C-7), 140.0 (C-8a), 159.1 (C-4), 161.3 (C-2), 165.7 ($CO_2CH_2CH_3$); ms: (m/z) 285 (M^+, 17), 256 ($M^+ - CH_2CH_3$, 9), 240 ($M^+ - OCH_2CH_3$, 20), 226 (11), 212 ($M^+ - CO_2CH_2CH_3$, 100), 201 (15), 184 (42), 172 (13), 156 (10), 146 (20), 132 (44), 117 (18), 104 (64), 91 (18), 77 (54), 69 (15), 51 (21).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.02; H, 5.20; N, 4.90.

Alkylation of Ethyl 4-Hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**1b**) with 3-Bromoprop-1-yne (**2**) in the Presence of a Catalytic Amount of Dicyclohexyl-18-crown-6.

A mixture of ethyl 4-hydroxy-1-methyl-3-quinolin-2(1*H*)-one carboxylate (0.49 g, 2 mmoles) (**1b**), potassium carbonate (1.4 g, 10 mmoles), potassium iodide (0.03 g) and dicyclohexyl-18-crown-6 (0.07 g, 0.2 mmole) in dry acetone was stirred 1 hour before 3-bromoprop-1-yne (**2**) (0.36 g, 3 mmoles) was added dropwise. The reaction mixture was then heated under reflux for 18 hours, cooled and filtered. The filtrate was evaporated *in vacuo*. The separation of the remaining residue by column chromatography lead to 0.10 g (17%) ethyl 3-(2-propynyl)-2,4-dioxo-1,2,3,4-tetrahydro-1-methyl-3-quinolinecarboxylate (**3b**) and to 0.26 g (45%) ethyl 4-(2-propynyl)oxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**6b**). The spectral data of the two compounds were identical to those described previously.

REFERENCES AND NOTES

[1] Part **24**: J. Reisch and S. Dittmann, *J. Heterocyclic Chem.*, **30**, 379 (1993).

[2] M. Iding, parts of the Dissertation, Universität Münster, 1993.

[3] D. Schönweiler passed away during this research programme.

[4] L. A. Mitscher, G. W. Clark, T. Suzuki and M. S. Batala, *Heterocycles*, **3**, 913 (1975).

[5] K. Mothes, H. R. Schütte and M. Luckner, Biochemistry of Alkaloids, VEB, Berlin, 1985.

[6] J. Reisch, M. Müller and I. Mester, *Z. Naturforsch. Teil B*, **36**, 1176 (1981).

[7] J. Reisch and A. Bathe, *Arch. Pharm. (Weinheim, Ger.)*, **320**, 737 (1987).

[8] I. Gruda, *Can. J. Chem.*, **50**, 18, (1972).

[9] L. Claisen and O. Eisleb, *Liebigs Ann. Chem.*, **401**, 21 (1913).