Natural Product Chemistry. Part **158** [1]. Reactions of Ethyl 4-Hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate with 1,4-Dibromo-2-methyl-2-butene

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Ethyl 4-hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**1**) which is obtained conveniently by the condensation of *N*-methylisatoic anhydride with diethyl malonate [4], was reacted with 1,4-dibromo-2-methylbutene (**2**) to give the main products **3** and **4** and the dimeric derivatives **5** and **6**.

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Previous investigations [5] on alkylation of ethyl 4-hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**1**) with 3-bromoprop-1-yne under Claisen conditions [6] led to a 3- and to a 4-alkylated product.

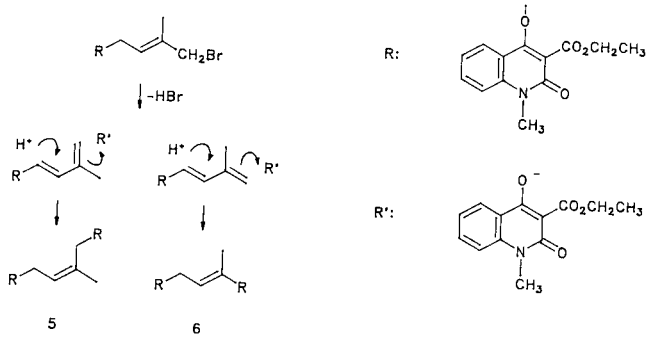
The yields of the products were improved by using a catalytic amount of a crown ether. The increase in yield of the *C*-alkylated product was found to be higher.

Treatment of **1** with 1,4-dibromo-2-methyl-2-butene (**2**) under the same conditions [2] afforded ethyl (*E*)-4[(4-bromo-3-methyl-2-butenyl)oxy]-1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylate (**4**) as the main product.

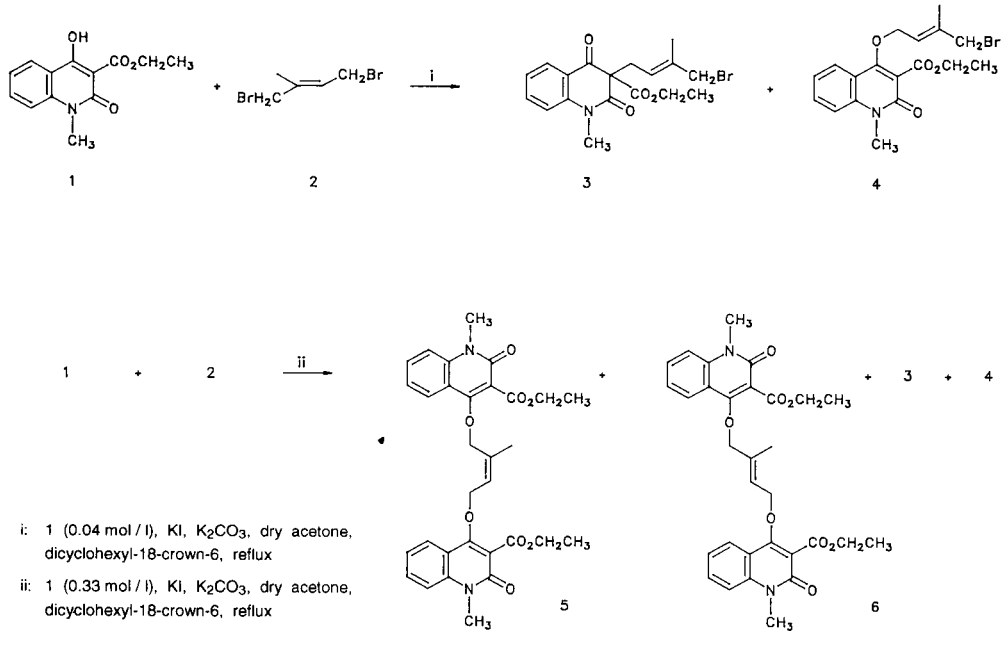
The *C*-alkylated ethyl (*E*)-3-(4-bromo-3-methyl-2-butenyl)-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-quinolinecarboxylate (**3**) which can be regarded as a precursor to tricyclic [7] and dimeric quinoline alkaloids [8] was also obtained.

If the concentration of **1** in the reaction mixture was changed from 0.04 mole/ℓ to 0.33 mole/ℓ an increase in yield of product **3** was observed. Furthermore two new compounds, **5** and **6**, could be isolated. The two isomeric diethyl 4,4'-[(2-methyl-2-butene-1,4-diyl)bis(oxy)]bis[1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylates **5** and **6** were probably formed by the reaction of **4** with **1**.

Scheme II



Scheme I



The loss of hydrogen bromide led to the intermediate butadienyl derivatives **7** and **8** to react with **1** to give the (*E*)- and the (*Z*)-isomer respectively.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were 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 tetramethylsilane as the internal reference on a Varian Gemini 200 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV and high resolution mass spectra on a Finnigan MAT 8230. Silica gel 60 F_{254} (precoated, aluminum 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). *N*-Methylisatoic anhydride (Janssen, Germany) was used after recrystallisation from dimethylacetamide. The synthesized compounds must be protected against light and moisture.

Alkylation of Ethyl 4-Hydroxy-1-methyl-3-quinolin-2(1*H*)-onecarboxylate (**1**) with 1,4-Dibromo-2-methyl-2-butene (**2**).

Method A.

To a stirred mixture of ethyl 4-hydroxy-1-methyl-3-quinolin-2(1*H*)-carboxylate (**1**) (1.00 g, 4 mmoles) containing potassium carbonate (2.76 g, 20 mmoles), potassium iodide (0.67 g) and a catalytic amount of the crown ether dicyclohexyl-18-crown-6 in 100 ml of dry acetone, 1,4-dibromo-2-methyl-2-butene (**2**) was added dropwise. The reaction mixture was heated under reflux for 18 hours. Then the mixture 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 **3** and **4**.

Ethyl (*E*)-3(4-Bromo-3-methyl-2-butenyl)-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-quinolinecarboxylate (**3**).

The first eluate of the column (dichloromethane-methanol 98:2) afforded ethyl (*E*)-3(4-bromo-3-methyl-2-butenyl)-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-3-quinolinecarboxylate (**3**), which was isolated from chloroform-methanol as colourless needles, 198 mg (4%), mp 99°; ir (potassium bromide): 2975 (CH), 1742 (C=O, ester), 1689 (C=O, 2-quinolinone), 1652 (C=O, 4-quinolinone), 1596 (C=C, aromat), 1467 (CH), 1360, 1251, 1151, 1070, 1040, 770, 755, 663, 608, 416 cm^{-1}; ^1H nmr: δ 1.19 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.68 (d, J = 1.3 Hz, 3H, CCH_3), 3.10 (m, J = 7.5, 7.9, 15.6 Hz, 2H, H-1'), 3.50 (s, 3H, N-CH_3), 3.68 (s, br, 2H, CH_2Br), 4.21 (dq, J = 1.0, 7.1 Hz, 2H, $CO_2CH_2CH_3$), 5.30 (dt, br, J = 1.3, 7.9 Hz, 1H, H-2'), 7.18-7.28 (m, 2H, H-6, H-8), 7.69 (ddd, J = 1.7, 7.4, 8.4 Hz, 1H, H-7), 8.02 (dd, J = 1.7, 8.2 Hz, 1H, H-5); ^{13}C nmr: δ 13.87 ($CO_2CH_2CH_3$), 14.87 (=CCH_3), 29.86 (N-CH_3), 35.87, 40.18 (C-1', C-4'), 62.66 ($CO_2CH_2CH_3$), 115.45 (C-4a), 115.69 (C-8), 120.65 (C-3), 122.93 (C-2'), 123.83 (C-6), 128.38 (C-5), 137.28 (C-7), 137.78 (C-3'), 143.99 (C-8a), 166.87 (C-4), 168.53 (C-2), 192.08 ($CO_2CH_2CH_3$); ms: m/z 315 (M^+ +H-Br, 27), 314 (M^+ -Br, 100), 313 (M^+ -$CO_2CH_2CH_3$, 33), 240 (313 -CO_2-CH_2CH_3, 71), 226 (241 -CH_3, 30), 146 (2), 134 (21), 133 (11), 105 (34), 104 (42), 91 (20), 79 (31), 78 (36), 77 (75), 76 (20), 67 (32), 51 (22); ms: (ci, NH_3) m/z 414 (M^+ (^{81}Br) + NH_4 + H, 11), 413 (M^+ (^{79}Br) + NH_4, 51), 412 (M^+ (^{81}Br) + NH_3, 13), 411 (M^+ (^{79}Br) + NH_4, 48), 396 (M^+ (^{81}Br) + H, 7), 394 (M^+ (^{79}Br) + H, 7), 314 (M^+ -Br, 6), 249 (15), 248 (100), .242 (4); hrms: (ci, NH_3) Calcd. for $C_{18}H_{20}{}^{79}BrNO_4$ + NH_4: 411.091943. Found: 411.091797.

Ethyl (*E*)-4[(4-Bromo-3-methyl-2-butenyl)oxy]-1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylate (**4**).

The second eluate of the column (dichloromethane-methanol 98:2) gave ethyl (*E*)-4[4-bromo-3-methyl-2-butenyl)oxy]-1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylate (**4**), which was obtained from chloroform-methanol as colourless needles, 698 mg (44%), mp 104-105°; ir (potassium bromide): 2985 (CH), 1725 (C=O, ester), 1628 (C=O, 2-quinolinone), 1590, 1499, 1458, 1318, 1080, 985, 860, 753 cm^{-1}; ^1H nmr: δ 1.43 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.84 (s, br, 3H, CCH_3), 3.66 (s, 3H, N-CH_3), 4.00 (s, br, 2H, CH_2Br), 4.45 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.82 (d, J = 6.7 Hz, 2H, CH_2CH=), 5.95 (t, br, J = 6.7 Hz, 1H, CH=), 7.24-7.28 (m, 1H, H-7), 7.32 (d, J = 8.5 Hz, 1H, H-8), 7.56-7.65 (m, 1H, H-7), 7.96 (dd, J = 1.5, 8.1 Hz, 1H, H-5); ^{13}C nmr: δ 14.00 ($CO_2CH_2CH_3$), 15.19 (C-5'), 29.29 (N-CH_3), 38.94 (C-4'), 62.16 ($CO_2CH_2CH_3$), 68.73 (C-1'), 111.36 (C-4a), 114.27 (C-8), 116.84 (C-3), 122.37 (C-6), 124.27 (C-2'), 124.75 (C-5), 132.29 (C-7), 138.14 (C-3'), 139.68 (C-8a), 158.85 (C-4), 161.38 (C-2), 166.21 ($CO_2CH_2CH_3$); ms: (ci, NH_3) m/z 397 (M^+ (^{81}Br) + 2H, 17), 396 (M^+ (^{81}Br) + H, 84), 395 (M^+ (^{81}Br), 23), 394 (M^+ (^{79}Br) + H, 73), 314 (M^+ -Br, 27), 249 (16), 248 (100), 243 (13), 242 (64); hrms: (ci, NH_3) Calcd. for $C_{18}H_{20}{}^{79}BrNO_4$ + H: 394.065394. Found: 394.069090.

Method B.

The educt **1** (1 g, 4 mmoles) was reacted with 1,4-dibromo-2-methyl-2-butene under the same conditions like method A but in 12 ml of dry acetone. After 18 hours the reaction mixture was allowed to cool, filtered and the filtrate was evaporated *in vacuo*. Separation of the residue on a column of silica gel (chloroform-methanol 98:2) and preparative tlc (chloroform-methanol 98:2) yields **3** (268 mg, 17%), **4** (64 mg, 4%), **5** (180 mg, 8%) and **6** (180 mg, 8%).

The spectral data about the compounds **3** and **4** are identical to those described previously.

Diethyl (*Z*)-4,4'-[(2-Methyl-2-butene-1,4-diyl)-bis(oxy)]bis[1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylate (**5**).

This compound **5** was obtained from chloroform-methanol as colourless needles, 180 mg (8%), mp 94-95°; ir (potassium bromide): 2925 (CH), 1723 (C=O, ester), 1623 (C=O, 2-quinolinone), 1589 (C=C, aromat), 1496, 1458, 1363, 1311, 1240 (C-O, ether), 1178, 1079, 1021, 755 cm^{-1}; ^1H nmr: δ 1.43 (t, J = 7.2 Hz, 6H, 2 x $CO_2CH_2CH_3$), 1.86 (d, J = 1.3 Hz, 3H, CCH_3), 3.70 (s, 6H, 2 x N-CH_3), 4.47 (2q, J = 7.2 Hz, 4H, 2 x $CO_2CH_2CH_3$), 4.72 (s, 2H, $OCH_2C(CH_3)$=), 4.92 (d, J = 6.8 Hz, 2H, OCH_2CH=), 6.02 (dt, J = 1.3, 6.8 Hz, 1H, CH=), 7.23-7.67 (m, 6H, 2 x H-6, 2 x H-7, 2 x H-8), 8.01 (m, 2H, 2 x H-5); ^{13}C nmr: δ 14.10 ($CO_2CH_2CH_3$), 14.18 ($CO_2CH_2CH_3$), 14.49 (CH_3C=), 29.37 (N-CH_3), 29.47 (N-CH_3), 62.15 (2 x $CO_2CH_2CH_3$), 68.38 (OCH_2CH=), 76.81 (=$C(CH_3)$-CH_2O), 111.24 (C-4a, C-4a'), 114.10, 114.19 (C-8, C-8'), 116.85, 116.93 (C-3, C-3'), 122.25 (C-6, C-6'), 122.93 (CH=CCH_3), 124.54, 124.72 (C-5, C-5'), 132.14 (C-7, C-7'), 136.37 (=$C(CH_3)$-CH_2), 139.60 (C-8a, C-8a'), 158.53, 158.72 (C-4, C-4'), 161.26 (C-2, C-2'), 165.94 ($CO_2CH_2CH_3$), 166.05 ($CO_2CH_2CH_3$); ms: m/z 487 (M^+ -$CO_2CH_2CH_3$, 18), 315 (14), 314 (M^+ -$C_{13}N_{12}NO_4$, 70), 270 (11), 269 (M^+ -OCH_2CH_3, 2), 242 (86), 241 (314 -CO_2CH_2-

CH_3), 30), 240 (M^+ -$C_3H_6O_2$, 100), 227 (12), 226 (241 -CH_3, 35), 213 (5), 212 (15), 202 (31), 201 (43), 200 (45), 198 (226 -CO, 7), 146 (18), 134 (38), 133 (25), 132 (16), 105 (45), 104 (40), 91 (18), 79 (20), 77 (40), 67 (69), 55 (60); ms: (ci, NH_3) m/z 562 (M^+ + 2H, 4), 561 (M^+ + H, 11), 316 (562 -$C_{13}H_{12}NO_4$, 4), 315 (561 -$C_{13}H_{12}NO_4$, 5), 314 (M^+ -$C_{13}H_{12}NO_4$, 24), 249 (15), 248 (100), 242 (26); hrms: (ci, NH_3) Calcd. for $C_{31}H_{32}N_2O_8$ + H: 561.223695. Found: 561.224914.

Diethyl (*E*)-4,4'-[(2-Methyl-2-butene-1,4-diyl)-bis(oxy)]bis[1,2-dihydro-1-methyl-2-oxo-3-quinolinecarboxylate] (**6**).

Compound **6** was separated from the reaction mixture by preparative tlc (chloroform-methanol 98:2), 180 mg (8%), oil; ir (potassium bromide): 2920 (CH), 1724 (C=O, ester), 1630 (C=O, 2-quinolinone), 1589 (C=C, aromat), 1497, 1459, 1362, 1310, 1241 (C-O, ether), 1178, 1078, 1022, 756 cm^{-1}; ^1H nmr: δ 1.35 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.36 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.04 (d, J = 1.5 Hz, 3H, CCH_3), 3.66 (s, 3H, N-CH_3), 3.67 (s, 3H, N-CH_3), 4.39 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.40 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.80 (s, 2H, $OCH_2C(CH_3)$=), 4.84 (dd, J = 0.9, 6.9 Hz, 2H, OCH_2CH=), 5.88 (dt, J = 1.5, 6.9 Hz, 1H, CH_2-CH=), 7.15-7.65 (m, 6H, 2 x H-6, 2 x H-7, 2 x H-8), 7.95 (m, 2H, 2 x H-5); ^{13}C nmr: δ 14.14 (2 x $CO_2CH_2CH_3$), 21.82 (CH_3C=), 29.49 (2 x N-CH_3), 62.16 ($CO_2CH_2CH_3$), 62.24 ($CO_2CH_2CH_3$), 68.03 (OCH_2CH=), 76.94 ($OCH_2C(CH_3)$=), 111.17 (C-4a, C-4a'), 114.09, 114.17 (C-8, C-8'), 116.75, 116.90 (C-3, C-3'), 122.27, 122.38 (C-6, C-6'), 124.50, 124.73 (C-5, C-5', $CH_2C(CH_3)$=), 131.97, 132.08 (C-7, C-7'), 137.12 (CH_2CH=), 139.59 (C-8a, C-8a'), 158.59, 158.66 (C-4, C-4'), 161.19 (C-2, C-2'), 165.86 ($CO_2CH_2CH_3$), 165.91 ($CO_2CH_2CH_3$); ms: m/z 487 (M^+ -CO_2CH_2-CH_3, 17), 315 (20), 314 (M^+-$C_{13}H_{12}NO_4$, 100), 270 (12), 269 (314 -OCH_2CH_3, 10), 268 (54), 242 (89), 241 (314 -$CO_2CH_2CH_3$, 28), 240 (94), 226 (241 -CH_3, 34), 202 (66), 201 (57), 200 (40), 198 (226 -CO, 8), 146 (28), 134 (52), 133 (26), 112 (38), 105 (53), 91 (21), 77 (45), 67 (68), 55 (21); ms: (ci, NH_3) m/z 562 (M^+ + 2H, 3), 561 (M^+ + H, 9), 316 (562 -$C_{13}H_{12}NO_4$, 5), 315 (561 -$C_{13}H_{12}NO_4$, 6), 314 (M^+ -$C_{13}H_{12}NO_4$, 32), 249 (15), 248 (100), 242 (19); hrms: (ci, NH_3) Calcd. for $C_{31}H_{32}N_2O_8$ + H^+: 561.22369. Found: 561.22436.

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