Non-Steroidal Antiinflammatory Agents. 1. Synthesis of 4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl Alkanoic Acids by the Wittig Reaction of Quinisatines.

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Dedicated to Prof. Dr. K. Schlögl, Institut für Organische Chemie der Universität Wien, Austria, on the occasion of his 60th birthday.

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The Wittig reaction of quinisatines (**1a,b**) with 1-ethoxycarbonylethyliden- (**2a**) and ethoxycarbonylmethylenetriphenylphosphorane (**2b**) has been investigated. In both cases unusual reaction products (**3a,b** and **12a,b** respectively) were isolated in high yields and converted to potential antiinflammatory acids **6, 8, 15** and lactones **4, 7**.

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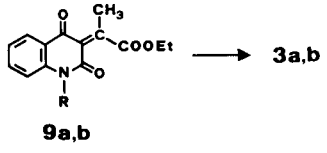
Arylacetic and arylpropionic acids have been extensively studied as antiinflammatory agents. Many compounds of this type, including heteroaryl derivatives, are now in use as therapeutic agents. However, lactones of *o*-hydroxyphenylacetic acids are rarely mentioned in the literature [3], and it was only recently that Closse, Haefliger and Hauser [4] discovered an unusually strong activity in the series of γ-lactones attached to an aromatic ring system. This prompts us to describe our earlier results [1,2] with γ-lactones of 2-quinolones.

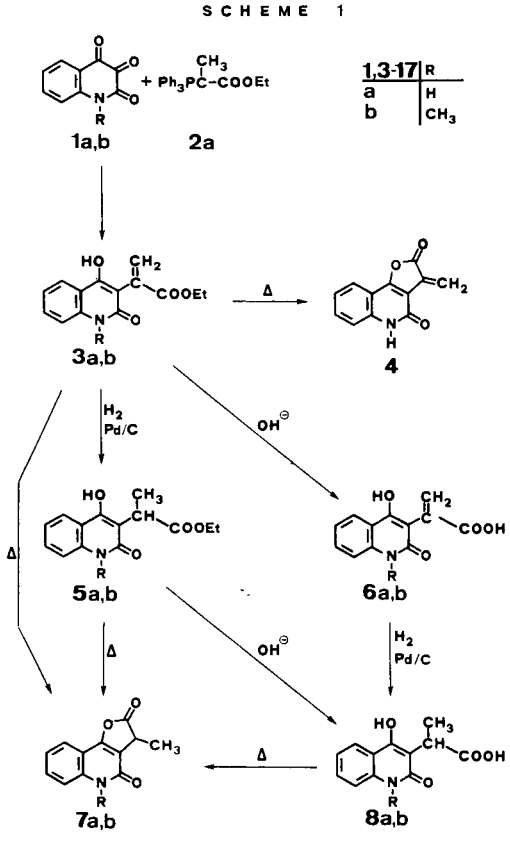
Our approach to these ring systems utilized a Wittig reaction of the readily available quinisatine **1a** [5] and its *N*-methyl derivative **1b** [6,7] with 1-ethoxycarbonylethylidenen-triphenylphosphorane (**2a**) or the methylid **2b**. The Wittig synthesis with the ylid **2a** and the consecutive reactions with the products **3a,b** are depicted in Scheme 1. Surprisingly the double bond in the isolated products of the exothermic Wittig reaction of **1a,b** with **2a** is not in the expected position; obviously the primary condensation product **9** is stabilized to the 4-hydroxycarbostyril system of **3** by a 1,5-shift of a hydrogen atom from the methyl



group to the oxygen at C-4. It should be noted that the stable hydrates of the quinisatines **1a,b** can be used with the same result in the reaction with the ylid **2a**.

Hydrogenation of **3a,b** over palladium on charcoal yields **5a,b** and subsequent hydrolysis of the ester with 2 *N* sodium hydroxide gives the target compounds, the propionic acids **8a,b**. The sequence of the reactions has no influence on the total yields: thus the esters **3a,b** can first be hydrolized to **6a,b** and subsequently hydrogenated to

SCHEME 1

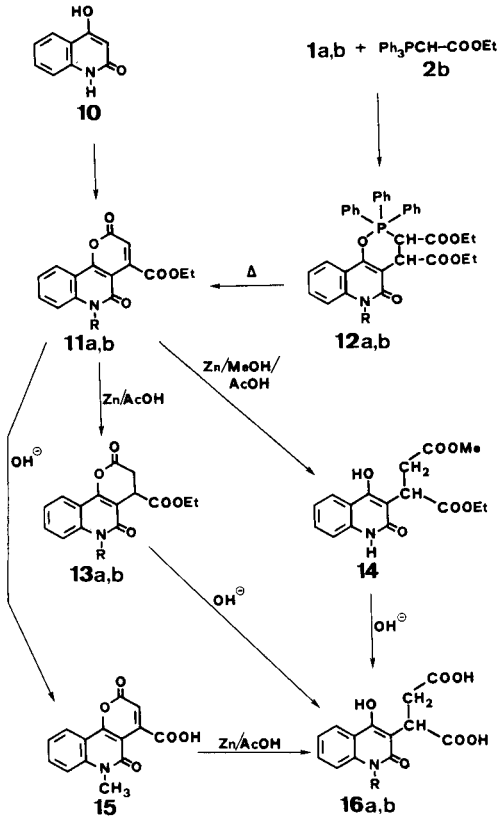


8a,b. The γ-lactones **7a,b** in turn are readily obtained from the esters **5** as well as from the free acids **8** by heating to about 220-230° and purification by sublimation. On the other hand, heating of the unsaturated ester **3a** in boiling xylene gave only traces of the methylene lactone **4**. Interestingly, the ester **3b** gave a small yield (about 10%) of the saturated lactone **7b** after being heated to 230° and no methylene lactone corresponding to **4**.

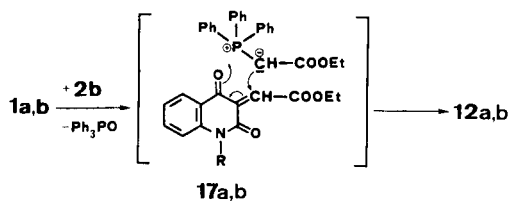
The reaction of the quinisatines **1a,b** with ethoxycarbonylmethylenetriphenylphosporane (**2b**) represents anoth-

er, even more interesting variation of the Wittig reaction (Scheme 2). As in the case with the ylid **2a** the primary condensation products **17a,b** seem to be instable and highly

SCHEME 2

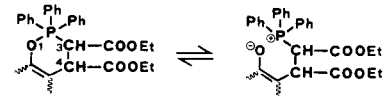


reactive. However, a stabilization just by prototropy, as in the former case, is not possible for **17**, instead the intermediates **17** are trapped in a Michael type addition of the



starting ylid yielding the phosphorus containing compounds **12a,b**. These are the only products formed regardless of the ratio of the reactants employed.

The structure of compounds **12** is elucidated by ^{1}H nmr and ^{31}P nmr spectroscopy. The ^{31}P nmr shows a chemical shift δ = +13.6 ppm (phosphoric acid as δ = 0.0 ppm) which indicates a high contribution of the zwitterionic form **B** [7a]. (For the reason of simplicity we have used the ringclosed form **A** for the nomenclature, see Experimental). The proton at C-3 of the "oxaphosphorin" ringsystem



shows a P-H coupling constant of $^2J_{PH}$ = 18 Hz, and a ^3J_H = 0.5 Hz coupling constant with the proton at C-4; the latter indicating a dihedral angle between both hydrogens of about 90°, resulting in a "trans" position of the two ester groups.

Both of the phosphorus heterocycles **12a,b** are unstable above 40°. A quantitative decomposition under the loss of triphenylphosphine and ethanol is performed at 70° yielding the pyronoquinolones **11a,b**. Proof of structure for **11a** was accomplished by an independent synthesis starting with 4-hydroxy-2(1*H*)-quinolone (**10**), using our recently developed modification of the Pechmann reaction [8]; thus heating of **10** with diethyl 2-oxosuccinate in the presence of ammonium acetate at 220° produces **11a** in moderate yield. The double bond moiety of the pyrone ring in **11** can be reduced with zinc in acetic acid to obtain the esters **13a,b**. Carrying out the reduction of **11a** in methanol as solvent yields the mixed succinate **14**. Alkaline saponification of **13** as well as **14** leads to the succinic acids **16a,b**. Also the reduction of **15**, which in turn is obtained by the hydrolysis of **11b**, leads to **16b**.

It should be noted that the Wittig reaction of quinisatine (**1a**) with fluorenylidentriphenylphosphorane has already been tried by A. Schönberg [9] in 1973, however, without success.

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Büchi-Tottoli melting point apparatus and are uncorrected; those marked with an asterik (*) were determined by inserting the capillary approximately 20° below the actual melting point. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The nmr spectra were recorded in hexadeuteriodimethylsulfoxide (unless otherwise indicated) and with TMS as an internal standard; the instruments used were the Varian A-60A or EM 360 at 60 MHz, the HA-100D at 100 MHz and the XL 200 at 200 MHz. Mass spectra were performed with an AEI MS 20 (with 70 eV) or Varian MAT 111 (with 80 eV); and uv spectra with a Perkin-Elmer-Hitachi 200.

2-[3-(4-Hydroxy-2-oxo-1,2-dihydroquinolinyl)]-2-propenoic acid Ethyl Ester (**3a**).

To a stirred suspension of 5.25 g (30 mmoles) **1a** in 30 ml of dry ethanol were added 11.0 g (30 mmoles) of **2a** in small portions. After heating to 50° for 30 minutes the solution was concentrated *in vacuo* to approximately 5 ml and cooled to give **3a** as a yellow precipitate. The yield was 4.73 g (60%), mp 180°* dec (methanol); ir: 3300-2400 b, 1725 s (ester CO), 1645 s (lactam CO), 1600 s, 1500 w, 1480 m cm^{-1}; nmr: δ = 1.2 (t, J = 7 Hz, CH_3), 4.15 (q, J = 7 Hz, CH_2), 5.9 (d, J = 1.5 Hz, 1H, $=CH_2$), 6.5 (d, J = 1.5 Hz, 1H, $=CH_2$), 7.0-7.6 (m, 3ArH), 7.9 (dd, J = 2 and 7 Hz, *peri*-H), 11.4 (b, 2 acidic H); ms: m/e 259 (M^+, 63), 213 (100), 185 (100), 129 (21), 120 (17), 92 (15).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.18; H, 5.12; N, 5.46.

2-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolinyl)]-2-propenoic Acid Ethyl Ester (**3b**).

To a stirred suspension of 0.5 g (2.65 mmoles) **1b** in 17 ml of dry chloroform 0.96 g (2.65 mmoles) **2a** were added while the temperature rises to about 40° to affect solution. After 20 minutes at room temperature **3b** precipitates or is extracted with 15 ml of 2*N* sodium hydroxide solution. The aqueous layer is again extracted with little ether or toluene and after filtration the *p*H is brought to 3-4 to yield **3b** which crystallizes if stirring is continued. The yield was 0.55 g (76%), mp 167°* (chloroform or 1-butanol); ir: 3390-2720 b, 1735 s, 1720 m (ester CO), 1640 s (lactam CO), 1620 s, 1585 s, 1515 m cm^{-1}; ^1H nmr: δ 1.2 (t, J = 7 Hz, CH_3), 3.55 (s, NCH_3), 4.15 (q, J = 7 Hz, CH_2), 5.8 (d, J = 1.5 Hz, 1H, $=CH_2$), 6.4 (d, J = 1.5 Hz, 1H, $=CH_2$), 7.1-7.75 (m, 3ArH), 8.05 (dd, J = 2 and 7 Hz, *peri*-H at C-5).

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.00; H, 5.53; N, 4.95.

2-[3-(4-Hydroxy-2-oxo-1,2-dihydroquinolinyl)]-2-propionic Acid Ethyl Ester (**5a**).

A solution of 1.04 g (4 mmoles) **3a** in 150 ml of methanol was hydrogenated in the presence of palladium (10%) on charcoal at an initial pressure of 50 psi in a Parr-Shaker for 17 hours. The solution was filtered from the catalyst and evaporated to yield 1.03 g (99%), mp 185°* dec. (methanol); ir: 3550-2550 b, 1690 m (ester CO), 1645 s (lactam CO), 1575 m, 1510 w cm^{-1}; ^1H nmr: δ = 1.02 (t, J = 7 Hz, CH_3), 1.35 (d, J = 7 Hz, CH_3), 4.08 (q, J = 7 Hz, CH_2), 4.12 (q, J = 7 Hz, 1H at C-2), 7.0-7.7 (m, 3 ArH), 8.02 (dd, J = 2 and 7 Hz, *peri*-H), 10.5 (s, 1 acidic H), 11.4 (s, 1 acidic H); ms: m/e (relative intensity) 261 (M^+, 21), 215 (36), 188 (100), 170 (12), 146 (27), 130 (20), 120 (24), 115 (20), 92 (27).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.27; H, 5.89; N, 5.28.

2-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolinyl)]-2-propionic Acid Ethyl Ester (**5b**).

The reduction of **3b** is carried out in the same manner as described for **3a** to give a 99% yield of **5b**, mp 86°; ir: 3620-2840 b, 1745 s (ester CO), 1640 s (lactam CO), 1615 s, 1580 s, 1510 m cm^{-1}; ^1H nmr: δ 1.15 (t, J = 7 Hz, CH_3), 1.4 (d, J = 7 Hz, CH_3), 3.6 (s, NCH_3), 4.05 (q, J = 7 Hz, CH_2), 4.18 (q, J = 7 Hz, 1H at C-2), 7.1-7.75 (m, 3ArH), 8.1 (dd, J = 2 and 7 Hz, *peri*-H), 10.5 (s, broad, OH).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.23; N, 5.09. Found: C, 65.21; H, 5.96; N, 5.17.

2-[3-(4-Hydroxy-2-oxo-1,2-dihydroquinolinyl)]-2-propenoic Acid (**6a**).

A solution of **3a** (0.92 g, 4 mmoles) was refluxed in 20 ml of 2*N* sodium hydroxide for 2 hours. After cooling to room temperature **6a** is precipitated with hydrochloric acid to yield 0.80 g (98%), mp 290°* dec. (methanol); ir: 3700-2200 b, 1705 m (acid CO), 1650 s (lactam CO), 1615 s, 1510 w cm^{-1}; ^1H nmr: δ = 5.85 (d, J = 1.5 Hz, 1H, $=CH_2$), 6.45 (d, J = 1.5 Hz, 1H, $=CH_2$), 7.0-7.6 (m, 3ArH), 7.9 (dd, J = 2 and 7 Hz, *peri*-H), 10.6-11.9 (broad, 3 acidic H).

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.03; H, 3.86; N, 5.86.

2-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolinyl)]-2-propenoic Acid (**6b**).

Hydrolysis of **3b** (2.73 g, 10 mmoles) was performed with 100 ml of 2 *N* sodium hydroxide solution yielding 2.16 g (88%). Purification was accomplished by dissolution in 5% sodium bicarbonate solution and precipitation with 2 *N* hydrochloric acid, mp 238°* dec; ir: 3570-3200 b, 1710 s (acid CO), 1645 s (lactam CO), 1615 s, 1570 s, 1515 s cm^{-1}; ^1H nmr: δ = 3.6 (s, NCH_3), 5.8 (d, J = 1.5 Hz, 1H, $=CH_2$), 6.5 (d, J = 1.5 Hz, 1H, $=CH_2$), 7.1-7.85 (m, 3ArH), 8.05 (dd, J = 2 and 7 Hz, *peri*-H).

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.61; H, 4.60; N, 5.69.

3-Methyl-2,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline (**7a**).

A) The ester **5a** (0.5 g, 2 mmoles), was heated for about 15 minutes in a small erlenmeyer in an oil bath to 220° until no more ethanol was liberated. The residue was crystallized from 1-butanol to yield 0.40 g (97%), mp 291° dec.

B) The ester **5a** (0.5 g, 2 mmoles), was heated in a small sublimation apparatus in an oil bath at 240°/17mm to yield 0.40 g (97%) of **7a** as sublimate. ir: 3250-2600 b, 1840 s, 1825 sh (lactone CO), 1680 s (lactam CO), 1645 m, 1620 w, 1590 m, 1515 m cm^{-1}; ms: m/e (relative intensity) 215 (M^+, 40), 187 (60), 186 (100), 168 (42), 149 (91); uv (ethanol): λ max (log ϵ) 327 (3.80), 318 (3.85), 306 sh (3.74), 283 (3.85), 275 (3.84) nm.

Anal. Calcd. for: $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.96; H, 4.19; N, 6.49.

3,5-Dimethyl-2,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline (**7b**).

A) The ester **3b** (1.4 g, 5 mmoles) was heated in a sublimation apparatus in an oil bath. At about 220-230°/18mm 0.11 g (9.7%) of **7b** sublimed, mp 206° (after repeated sublimation).

B) The ester **5b** or the acid **8b** were sublimed at about 240°/15mm to yield 95% and 90%, respectively, of **7b**, mp 206°; ir: 1825 s (lactone CO), 1675 s (lactam CO), 1645 s, 1605 w, 1580 w, 1515 w cm^{-1}; ^1H nmr: δ = 1.7 (d, J = 7 Hz, CH_3 at C-3), 3.7 (s, NCH_3), 3.9 (q, J = 7 Hz, 1H at C-3), 7.15-7.6 (m, 3ArH), 7.85 (dd, J = 1.5 and 8 Hz, *peri*-H at C-9); ms: m/e (relative intensity) 229 (M^+, 52), 215 (33), 201 (56), 200 (100), 187 (29), 186 (29), 158 (19), 144 (21), 134 (27), 132 (25), 130 (39), 115 (17), 107 (14), 106 (42), 105 (62), 79 (37), 78 (62), 77 (17), 64 (19); uv (ethanol): λ max (log ϵ) 329 (3.84), 319 (3.89), 307 sh (3.77), 288 (3.89), 2.79 (3.87) nm.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.87; H, 5.07; N, 5.97.

2-[3-(4-Hydroxy-2-oxo-1,2-dihydroquinolinyl)]-2-propionic Acid (**8a**).

A) The ester **5a** (1.04 g, 4 mmoles) was refluxed in 20 ml of 2 *N* sodium hydroxide for 2 hours. After cooling to room temperature and filtration the solution was acidified with 2 *N* hydrochloric acid to yield 0.92 g (99%). Purification was accomplished by dissolution in 5% sodium bicarbonate solution and precipitation with hydrochloric acid, mp 240° dec.

B) The acid **6a** (0.92 g, 4 mmoles) was hydrogenated in 150 ml of acetic acid in the presence of 10% palladium on charcoal for 15 hours in a Parr-Shaker at an initial pressure of 50 psi. The yield was quantitative, mp 240° dec; ir: 3600-2300 b, 1700 s (acid CO), 1640 s (lactam CO), 1600 s, 1560 s, 1500 m cm^{-1}; ^1H nmr: δ = 1.35 (d, J = 7 Hz, CH_3), 4.12 (q, J = 7 Hz, 1H at C-2), 7.0-7.7 (m, 3ArH), 8.02 (dd, J = 2 and 7 Hz), *peri*-H), 9.5-11.5 (broad, 3 acidic H).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.76; N, 6.01. Found: C, 61.52; H, 4.73; N, 5.96.

2-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolinyl)]-2-propionic Acid (**8b**).

A) Following the procedure described for the hydrogenation of **6a**, **8b** was obtained in quantitative yield from **6b**, mp. 226°.

B) Following the procedure described for the hydrolysis of **5a**, **5b** (2.75 g, 10 mmoles) were saponified in 150 ml of 2 *N* sodium hydroxide to give 2.19 g (89%) of **8b**, mp 226°; ir: 3700-2800 b, 1695 (acid CO), 1650 s (lactam CO), 1615 s, 1565 s cm^{-1}; ^1H nmr: δ = 1.35 (d, J = 7 Hz, CH_3), 3.6 (s, NCH_3), 4.1 (q, J = 7 Hz, 1H at C-2), 7.1-7.85 (m, 3ArH), 8.1 (dd, J = 2 and 7 Hz, *peri*-H), 10.5 (s, broad, 2 acidic H).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.29; N, 5.67. Found: C, 62.78; H, 5.10; N, 5.66.

5-Oxo-2,2,2-triphenyl-3,4,5,6-tetrahydro-2*H*-1,2-oxaphosphorino[5,6-*c*]-quinolinyl-3,4-dicarboxylic Acid Diethyl Ester (**12a**).

To a well stirred suspension of **1a** (0.88 g, 5 mmoles) in anhydrous dioxane (40 ml) at room temperature **2b** (3.48 g, 10 mmoles) was added in small portions, at such a rate that the temperature does not rise above 40°. Solution takes place and after about 1 minute at 40° a colorless precipitate appears and the reaction is complete after 5 minutes. The precipitate is collected and washed with a small amount of acetone to yield 2.73 g (91%), mp 127°* dec, **12a** could not be recrystallized because decomposition occurs slowly in solution above 50°; ir: 3200-2740 b, 1735 s,

1730 sh (ester CO), 1645 s (lactam CO), 1610 s, 1530 w cm^{-1}; ^1H nmr: δ = 0.5 (t, J = 7 Hz, 1 ester CH_3), 1.2 (t, J = 7 Hz, 1 ester CH_3), 3.5 (d, J = 0.5 Hz, 1H at C-4), 3.6 (q, J = 7 Hz, 1 ester CH_2), 4.04 (q, J = 7 Hz, 1 ester CH_2), 4.55 (dd, J = 0.5 Hz and J_{PH} = 18 Hz, 1H at C-3), 7.0-8.0 (m, 19ArH), 11.0 (s, NH): ^{31}P nmr (hexadeuteriodimethylsulfoxide, phosphoric acid as external standard): δ = +13.6; ms: m/e (relative intensity) 285 (M^+- Ph_3P, -ethanol, = **11a**, 51%), 264 (21), 262 (47, = triphenylphosphine), 240 (30), 213 (90), 212 (40), 185 (100), 183 (34), 156 (30), 152 (19), 108 (21), 93 (26), 92 (28), 85 (26), 77 (17).

Anal. Calcd. for $C_{35}H_{32}NO_6P$: C, 70.81; H, 5.43; N, 2.36; O, 16.17. Found: C, 70.39; H, 5.26; N, 2.34; O, 15.79.

6-Methyl-5-oxo-2,2,2-triphenyl-3,4,5,6-tetrahydro-2*H*-1,2-oxaphosphorino[5,6-*c*]quinolinyl-3,4-dicarboxylic Acid Diethyl Ester (**12b**).

To a well stirred and cooled suspension of **1b** (1.0 g, 5.3 mmoles) in anhydrous dioxane (50 ml) **2b** (3.7 g, 11 mmoles) was added portionwise while the temperature was not allowed to rise above 25°. After 30 minutes the solvent is removed *in vacuo* (bath temperature not above 30°!) and the oily residue was triturated with some cyclohexane to afford crystallization. The yield was 2.7 g (85%), mp 92-96°* dec; ir: 3110 w, 3020 w, 1745 s (ester CO), 1675 w, 1645 s (lactam CO), 1630 s, 1600 m, 1585 w, 1500 w cm^{-1}; ^1H nmr (deuteriochloroform): δ = 0.5 (t, J = 7 Hz, 1 ester CH_3), 1.1 (t, J = 7 Hz, 1 ester CH_3), 3.4 (s, NCH_3), 3.68 (d, J = 0.5 Hz, 1H at C-4), 3.7 (q, J = 7 Hz, 1 ester CH_2), 4.1 (q, J = 7 Hz, 1 ester CH_2), 4.9 (dd, J = 0.5 Hz and J_{PH} = 16 Hz, 1H at C-3), 7.0-8.05 (m, 18ArH), 8.25 (dd, J = 2 and 7 Hz, *peri*-H).

Anal. Calcd. for $C_{36}H_{34}NO_6P$: C, 71.16; H, 5.64; N, 2.31. Found: C, 70.74; H, 5.59; N, 1.94.

2,5-Dioxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolinyl-4-carboxylic Acid Ethyl Ester (**11a**).

A) Solid **12a** (1.19 g, 2 mmoles) was heated in an oven at 70° for 4 hours. The resulting oil crystallized by the addition of methanol to yield 0.56 g (98%), mp 257° (1-butanol).

B) A mixture of 8.0 g (50 mmoles) of **10**, 10.0 g (53 mmoles) of diethyl 2-oxo-succinate, 12.0 g ammonium acetate and 50 ml of nitrobenzene was heated in an oil bath to 220° for 30 minutes. After filtration the solvent was removed *in vacuo*. The remaining oily residue crystallized by the addition of little methanol to yield 3.55 g (25%), mp 257° (1-butanol); ir: 3200-2800 b, 1780 sh, 1750 s (ester and lactone CO), 1670 s (lactam CO), 1550 m, 1500 w cm^{-1}; ^1H nmr: δ = 1.35 (t, J = 7 Hz, CH_3), 4.4 (q, J = 7 Hz, CH_2), 6.6 (s, 1H, at C-3), 7.2-8.1 (m, 4ArH), 12.05 (s, NH); ms: m/e (relative intensity) 285 (M^+, 60), 257 (7), 240 (27), 213 (100), 185 (97), 156 (24), 146 (12).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.02; H, 3.95; N, 5.02.

6-Methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolinyl-4-carboxylic Acid Ethyl Ester (**11b**).

A) Solid **12b** (3.0 g, 5 mmoles) was heated in an oven at 80-90° for 2 hours. The oily residue crystallized upon the addition of cyclohexane, the product was filtered and washed with little ether. The yield was 1.38 g (92%), mp 183° (ethanol).

B) If the thermolysis followed directly the Wittig reaction without isolation of **12b** the oily residue which was obtained after removal of the dioxane was heated to 80-90° for 2 hours. Addition of ether afforded crystallization of **11b** in 78% yield, mp 183° (ethanol); ir: 1765 s (lactone CO), 1740 s (ester CO), 1665 s (lactam CO), 1610 m, 1585 w, 1560 s, 1505 w cm^{-1}; ^1H nmr (deuteriochloroform): δ = 1.45 (t, J = 7 Hz, CH_3), 3.7 (s, NCH_3), 4.5 (q, J = 7 Hz, CH_2), 6.3 (s, 1H at C-3), 7.2-7.9 (m, 3ArH), 8.2 (dd, J = 2 Hz and 7 Hz, *peri*-H).

Anal. Calcd. for $C_{16}H_{14}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.59; H, 4.38; N, 4.67.

2,5-Dioxo-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*c*]quinolinyl-4-carboxylic Acid Ethyl Ester (**13a**).

A solution of 2.0 g (7 mmoles) **11a** in 50 ml acetic acid is reduced by the addition of 1 g zinc dust in small portions over a period of 30 minutes at reflux temperature. After cooling the solvent is removed *in vacuo*, the residue washed with water (20 ml) and the remaining product is purified by sublimation to yield 1.9 g (94%), mp 234° dec; ir: 3300-2600 b, 1810 s (lactone CO), 1730 s (ester CO), 1670 s (lactam CO), 1640 sh, 1620 m, 1590 m, 1510 m cm^{-1}; ^1H nmr: δ = 1.1 (t, J = 7 Hz, CH_3), 2.8-3.8 (m, $1CH_2$), 3.8-4.3 (m, ester CH_2 and 1H at C-4), 7.0-8.0 (m, 4ArH), 11.8 (s, NH).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.56; N, 4.88. Found: C, 62.88; H, 4.48; N, 4.65.

6-Methyl-2,5-dioxo-3,4,5,6-tetrahydro-2*H*-pyrano[3,2-*c*]quinolinyl-4-carboxylic Acid Ethyl Ester (**13b**).

The ester **11b** was reduced with zinc in acetic acid as described for **11a**. The remaining oil after removal of the solvent could be crystallized from ethyl acetate-cyclohexane yielding 84% **13b**, mp 181°; ir: 3700-2820 b, 1745 s (lactone CO), 1705 s (ester CO), 1640 s (lactam CO), 1620 sh, 1600, 1510 m cm^{-1}; ms: m/e (relative intensity) 301 (M^+, 14), 228 (M^+ - CO_2Et, 33), 87 (10), 69 (14), 57 (30), 56 (100), 55 (28), 54 (15), 44 (37), 43 (99), 42 (99), 41 (44), 40 (38).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.96; H, 5.10; N, 4.70.

2-(4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)succinic Acid 1-Ethyl Ester 4-Methyl Ester (**14**).

In a mixture of 20 ml of acetic acid and 10 ml of methanol 1.0 g (3.5 mmoles) of **11a** was reduced by the portionwise addition of 1.0 g zinc dust over a period of 30 minutes at reflux temperature. After cooling and filtration the solvents were removed *in vacuo*. The remaining solid was washed with water (20 ml) and filtered to yield 1.07 g (96%), mp 156° (toluene); ir: 3400-2500 b, 1750 m, 1700 m (2 ester CO), 1650 s (lactam CO), 1620 sh, 1580 m, 1510 m cm^{-1}; ^1H nmr: δ = 1.1 (t, J = 7 Hz, CH_3), 2.8-3.5 (m, CH_2), 3.6 (s, CH_3), 4.0 (q, J = 7 Hz, CH_2), 4.3-4.7 (m, CH), 6.9-7.7 (m, 3ArH), 7.9 (dd, J = 2 Hz and 7 Hz, *peri*-H), 10.7 (s, acidic H), 11.5 (s, acidic H); ms: m/e (relative intensity) 319 (M^+, 36), 287 (15), 277 (25), 273 (36), 241 (21), 214 (59), 186 (29), 179 (21), 167 (22), 149 (66), 101 (100), 98 (45), 83 (45), 73 (57).

Anal. Calcd. for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.55; H, 5.56; N, 4.36.

6-Methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolinyl-4-carboxylic Acid (**15**).

The ester **11b** (1.5 g, 5 mmoles), or the oxaphosphorin **12b** (3 g, 5 mmoles), were heated with 150 ml of 2*N* sodium hydroxide for 2 hours. After cooling the free acid was precipitated with 2 *N* hydrochloric acid to yield 1.14 g (84%), respectively, 0.97 g (72%) if **12b** was used. Purification was accomplished by dissolution in 5% sodium bicarbonate solution and precipitation with hydrochloric acid, mp 262°; ir: 3500-2760 b, 1750 s (lactone CO), 1735 m, 1700 s (acid CO), 1660 s (lactam CO), 1640 m, 1615 s, 1570 s, 1520 s cm^{-1}; ^1H nmr: δ = 3.6 (s, CH_3), 6.9 (s, 1H at C-3), 7.1-7.75 (m, 3ArH), 8.05 (dd, J = 2 Hz and 7 Hz, *peri*-H), 10.5-11.5 (s, broad, COOH).

Anal. Calcd. for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.17. Found: C, 61.53; H, 3.71; N, 5.17.

2-(4-Hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)succinic Acid (**16a**).

The ester **13a** (1.9 g, 6.6 mmoles) was heated under reflux in 20 ml of 2 *N* sodium hydroxide. After cooling the succinic acid was precipitated with dilute hydrochloric acid to give 1.7 g (92%). Purification was accomplished by dissolution in 5% sodium bicarbonate and reprecipitation with 2 *N* hydrochloric acid. In the same manner and in the same yield **16a** was obtained when **14** was hydrolized, mp 226°; ir: 3700-2200 b, 1740 s, 1700 s (acid CO), 1645 s (lactam CO), 1610 s, 1560 s, 1510 m cm^{-1}; ^1H nmr: δ 2.1-3.5 (m, CH_2), 4.3 (m, CH), 6.9-7.75 (m, 3ArH), 8.0 (dd, J = 2 Hz and 7 Hz, *peri*-H), 11.5 (broad, 3 acidic H), 12.3 (broad, 1 acidic H); ms: m/e (relative intensity) 277 (M^+, 67), 231 (19), 220 (33), 210 (22), 205 (33), 199 (36), 188 (28), 181 (31), 177 (75), 169 (50), 149 (94), 119 (69), 111 (56), 109 (64), 100 (89), 97 (72), 93 (83), 83 (94), 77 (100).

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05; Found: C, 55.95; H, 4.07; N, 4.85.

2-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)succinic Acid (**16b**).

A) The hydrolysis of **13b** (1.5 g, 5 mmoles) was performed in 100 ml of boiling 2 *N* sodium hydroxide as described for **13a**. The yield was 1.26 g (87%).

B) A solution of 2.0 g (7 mmoles) of the acid **15** in 100 ml of acetic acid was treated with 2.0 g of zinc dust in small portions during 15 minutes at reflux temperature. After filtration the solvent was removed *in vacuo* and the oily residue dissolved in 50 ml of cold 5% sodium bicarbonate solution. Acidification with 2 *N* hydrochloric acid yields 1.56 g (73%), of **16b**, mp 178°; ir: 3700-2760 b, 1735 s (acid CO), 1680 s (lactam CO), 1610 s, 1565 s, 1505 w cm^{-1}; ^1H nmr: δ 3.15 (m, CH_2), 3.6 (s, NCH_3), 4.5 (t, J = 7 Hz, CH), 7.15-7.9 (m, 3ArH), 8.1 (dd, J = 2 Hz and 7 Hz, *peri*-H).

Anal. Calcd. for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 58.00; H, 4.52; N, 4.89.

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[7a] Note added in proof: For literature see M. Schlosser and H. B. Tuong, *Angew. Chem.*, **91**, 675 (1979); *Angew. Chem., Int. Ed. Engl.*, **18**, 637 (1979); M. Schlosser, H. B. Tuong, and C. Tarchini, *Chimia*, **31**, 219 (1977).

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