Non-Steroidal Antiinflammatory Agents. 2 [1]. Synthesis of 4-Hydroxy-1-methyl-2-oxo-dihydroquinolin-3-yl Acetic Acid and Related Tetrazolyl Derivatives

Kurt Faber [2] and Thomas Kappe*

Dedicated to Prof. Dr. J. Schurz, Institut für Physikalische Chemie der Universität Graz, Graz, Austria, on the occasion of his 60th birthday.

Institut für Organische Chemie, Universität Graz, Heinrichstr. 28, A-8010 Graz, Austria

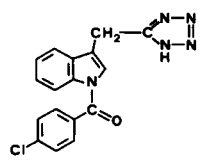
Received April 20, 1984

The synthesis of some potential antiinflammatory compounds, such as the tetrazole derivatives **7** and **9**, as well as the heteroaryl acetic acid **12** and its lactone **13**, has been accomplished starting from the readily available pyronoquinolone **2**.

J. Heterocyclic Chem., **21**, 1881 (1984).

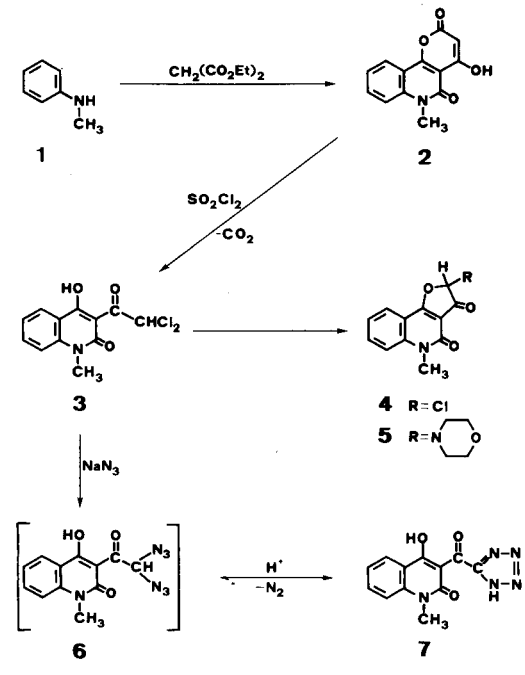
In recent years, the literature on non-steroidal antiinflammatory agents has increased constantly. GI irritation continues to be the principal complication with most developmental, clinical and commercial drugs of this type. The ongoing search for novel classes of non-steroidal antiinflammatory agents reflects the continued inability to separate antiinflammatory action from GI irritation.

We have recently reported a facile synthesis of 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylpropionic and propenoic acids and their γ-lactones, by a Wittig reaction with quinisatines, however, the corresponding acetic acid derivatives could not be obtained by this procedure [1]. Therefore, in the present study, we have synthesized compounds **12** and **13** starting with the readily available pyrono-quinolone **2** as depicted in Schemes 1 and 2. Furthermore, several tetrazole derivatives have been reported to be antiinflammatory agents [3-8]. 5-Amino-1-phenyltetrazole has been shown to be a useful antiinflammatory drug [9] and a number of 5-aryl-2-tetrazolylalkanoic acids and their hydrazine derivatives, like thiosemicarbazides, are known to be anti-inflammatory agents [10-13]. It is also interesting to note that the tetrazolyl group has about the same acidity as an alkanoic acid (compare the pK_a 4.8 of tetrazole itself) and can replace the carboxyl group, as demonstrated with the antiinflammatory activity of intrazol [14] which is closely related to indometacin from a structural point of view. Therefore, we have also considered the intermediate compounds **7** and **9** as candidates for pharmacological testing.



Intrazol

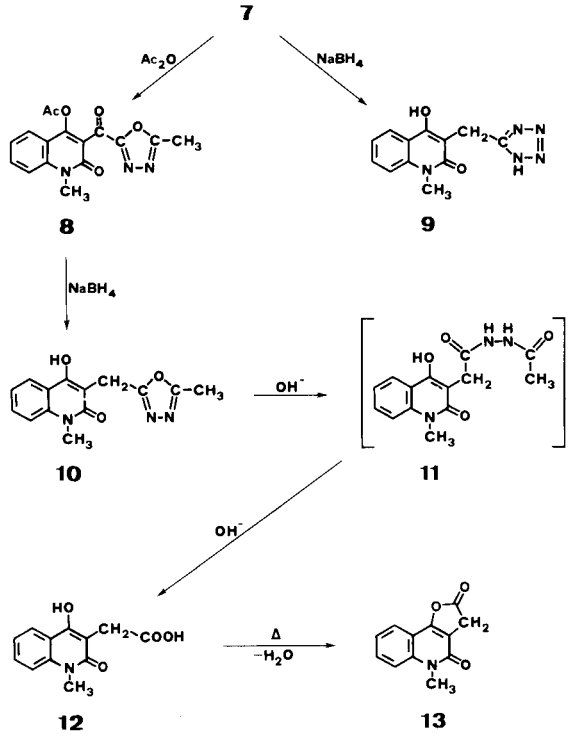
SCHEME 1



From our experiences with pyrono-quinolones of type **2** and their susceptibility for various ways of stepwise degradation [2,15,16] we considered **2** as a good starting material for the synthesis of **12** and **13**. Compound **2** has previously been synthesized by Bowman *et al.* [17] and Bosson *et al.* [18] by the action of an excess of diethyl malonate on *N*-methylaniline at elevated temperatures. By a modification of the procedure we were able to increase the yield of **2** considerably (see Experimental). Chlorination of **2** with sulfuryl chloride afforded - after hydrolytic ringopening of the dichloro-pyrone ring system and decarboxylation - the dichloroacetyl derivative **3** [16]. Nucleophilic substitution of the chloro atoms in **3** with potassium cyanide could not be achieved, instead ring-closure to **4** occurred. An excess

of cyanide and more drastically reaction conditions did not exchange the remaining chloro atom in **4**. The action of an excess of morpholine on **3** afforded **5**. Unfortunately, the attempted hydrolysis of **5** with mineral acids led to decomposition and not to the expected α-hydroxylactone. (It is known that dichloroacetyl-o-hydroxy-acetophenone leads to o-hydroxy-mandelic acid lactone with this sequence of reactions [19]). The reaction of **3** with sodium azide in dimethylformamide occurs at room temperature, and the intermediate diazido compound **6** yielded the tetrazole **7** under the loss of nitrogen.

SCHEME 2



The action of acetic anhydride on **7** led not only to an acetylation of the 4-hydroxy group of the quinolone, but also converted the tetrazole moiety to the oxadiazole ring system yielding **8**. The complex mechanism for this type of reaction has been elucidated many years ago by Huisgen and his coworkers [20] for other tetrazoles. The reduction of **7**, as well as **8**, with sodium borohydride converted the keto group in these compounds smoothly to the methylene moiety leading to **9** and **10**, respectively (under the conditions used during work-up the acetoxy group of **8** was also hydrolized). Hydrolysis of **10** with refluxing 2 *N* sodium hydroxide solution yielded the acetic acid derivative **12**, a compound which was previously prepared by Hörlein [21] *via* a different route. Under the conditions employed the assumed intermediate **11** (analogous hydrazides have been obtained by the hydrolysis of other oxadiazoles [22]) could not be isolated. Finally, heating of **12** led to the required γ-lactone **13** in high yield.

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Büchi-Tottoli melting point apparatus and are uncorrected. 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.

4-Hydroxy-6-methyl-5,6-dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]quinoline (**2**) [17,18].

A mixture of 107 g of *N*-methylaniline (1.0 mole, 135 ml) and 321 g of diethyl malonate (2.0 moles, 378 ml) was heated in an oil bath in a distillation apparatus. At about 160° liberation of ethanol took place and the temperature was increased slowly to about 220°, where it was kept until no more ethanol was formed. Then the mixture was allowed to cool to room temperature by remaining in the oil-bath overnight. The precipitate was filtered and washed with xylene or dioxane to yield 137 g (55%), mp 255-256° (xylene or dioxane) [17], yield 41%, mp 253-254° [18], yield 29%, mp 255-256°.

3-Dichloroacetyl-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline (**3**).

To a suspension of **2** (31 g, 0.128 mole) in 100 ml of dioxane sulfuryl chloride (33 ml, 0.41 mole) was added portionwise, while the temperature was not allowed to rise above 50°, where it was then kept for additional 10 minutes. The mixture was quickly heated to the boil and poured into 500 ml of ice-water to yield 18.6 g (51%), mp 188-190° (toluene).

Anal. Calcd. for $C_{12}H_9Cl_2NO_5$: C, 50.37; H, 3.17; Cl, 24.78; N, 4.90; O, 16.78. Found: C, 50.60; H, 3.10; Cl, 24.30; N, 4.82; O, 17.00.

2-Chloro-5-methyl-3,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline (**4**).

A suspension of 0.5 g of dichloroacetyl derivative **3** (1.75 mmoles) and 0.35 g of potassium cyanide (5.4 mmoles) in 100 ml of acetone was heated under reflux for 2 hours. (A trace of potassium iodide accelerates the reaction). After the mixture was filtered and the filtrate was taken to dryness *in vacuo* the remaining residue was recrystallized from ethanol to give 0.157 g (36%), mp 220°; ir: 3145 w, 3020 w, 1745 s (CO on C-3), 1665 s (quinolone-CO), 1630 s, 1570 s, 1520 m cm^{-1}; ^1H nmr: δ = 3.62 (s, NCH_3), 6.95 (s, 1H on C-2), 7.25-7.95 (m, 3ArH), 8.1 (dd, J = 2 and 7 Hz, peri H); ms: m/e (relative intensity) 251 (M^+, 13), 249 (M^+, 47), 215 (25), 214 (80), 186 (18), 185 (18), 184 (18), 157 (22), 132 (31), 129 (95), 128 (67), 114 (47), 105 (25), 104 (35), 103 (51), 102 (100), 101 (86), 97 (22), 92 (35), 89 (47), 88 (47), 87 (29), 77 (56), 76 (44), 75 (65), 74 (47), 51 (40).

Anal. Calcd. for $C_{12}H_8ClNO_5$: C, 57.73; H, 3.23; Cl, 14.20; N, 5.61. Found: C, 57.58; H, 3.24; Cl, 13.78; N, 5.47.

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

To a suspension of **3** (2.86 g, 10 mmoles) in 20 ml of anhydrous toluene morpholine (4.35 g, 4.3 ml, 50 mmoles) was added. The mixture was then stirred for an hour at 40°. After removal of the solvent *in vacuo* morpholine hydrochloride was extracted from the residue with water (5 ml) and the remaining precipitate was recrystallized from ethanol to yield 0.84 g (28%), mp 228°; ir: 3660-3300 w, 3000 w, 2880 w, 1740 s (CO on C-3), 1665 s (quinolone CO), 1640 s, 1590 m, 1565 s, 1520 s cm^{-1}; ^1H nmr: δ = 2.8 (t, J = 7 Hz, 2 morpholine NCH_2), 3.55 (s, NCH_3), 3.65 (t, J = 7 Hz, 2 morpholine OCH_2), 5.8 (s, H on C-2), 7.35-7.85 (m, 3ArH), 8.05 (dd, J = 2 and 7 Hz, peri H).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.53; H, 5.38; N, 9.05.

(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl) (Tetrazol-5-yl) Ketone (**7**).

To a solution of 2.86 g of **3** (10 mmoles) in 50 ml of dimethylformamide, sodium azide (3.25 g, 50 mmoles) was added. The mixture was stirred at room temperature for 24 hours (on a larger scale for 48 hours) and then diluted with 50-100 ml of water. By the addition of 2*N* hydrochloric acid until the *p*H was about 4, (caution, hydrazoic acid is liberated!) the product precipitated, yield 1.7 g (63%), mp 232° (1-butanol); ir: 3110 w, 1625 s (quinolone and ketone CO), 1600 s, 1550 s, 1510 m cm^{-1}; ^1H nmr: δ = 3.5 (s, NCH_3), 7.1-7.95 (m, 3ArH), 8.1 (dd, J = 2 and 7 Hz, peri H), 13.5 (broad, 1, acidic H).

Anal. Calcd. for $C_{12}H_9N_5O_3$: C, 53.14; H, 3.34; N, 25.82. Found: C, 53.63; H, 3.40; N, 25.99.

(4-Acetoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl) (5-Methyl-1,3,4-oxadiazol-2-yl) Ketone (**8**).

The tetrazole **7** (2.71 g, 10 mmoles) was heated under reflux with 30-40 ml of acetic anhydride for 2 hours, on a larger scale until dissolution was complete. After the solvent was removed *in vacuo* the residue was recrystallized from 1-butanol to yield 2.42 g (74%), mp 228°; ir: 1760 s (acetyl CO), 1700 m, 1680 s (ketone CO), 1640 s (quinolone CO), 1575 s, 1525 w cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.25 (s, acetyl CH_3), 2.28 (s, oxadiazole CH_3), 3.65 (s, NCH_3), 7.1-7.7 (m, 3ArH), 7.85 (dd, J = 2 and 7 Hz, peri H); ms: m/e (relative intensity) 327 (M^+, 14), 285 (51), 242 (20), 215 (77), 202 (23), 201 (79), 186 (17), 185 (48), 159 (29), 158 (66), 133 (35), 129 (27), 105 (60), 104 (45), 102 (14), 90 (13), 89 (13), 83 (37), 78 (24), 77 (36), 76 (18), 56 (22), 51 (24), 50 (14), 44 (17), 43 (100), 42 (17), 41 (21), 39 (13).

Anal. Calcd. for $C_{16}H_{13}N_3O_5$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.50; H, 4.08; N, 12.67.

(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(tetrazol-5-yl)methane (**9**).

The reduction of the ketone **7** (2.71 g, 10 mmoles) in 50 ml of anhydrous methanol was accomplished by the portionwise addition of 7.6 g of sodium borohydride (20 mmoles). After the solution was diluted with 50 ml of water and filtered, it was acidified with 2*N* hydrochloric acid to yield 1.36 g (52%). To increase the yield the methanol may be evaporated, mp 244°, dec (dimethylformamide); ir: 3600-3340 w, 3000 w, 1650 s (quinolone CO), 1635 m, 1595 m, 1520 m cm^{-1}; ^1H nmr: δ = 3.45 (s, NCH_3), 3.8 (s, CH_2), 7.3-7.6 (m, 3ArH), 7.8 (dd, J = 2 and 7 Hz, peri H), 7.9 and 8.0 (s, each 1 acidic H); ms: m/e (relative intensity) 200 (M^+-HN_4, 38), 199 (100), 198 (96), 170 (46), 168 (44), 149 (46), 143 (26), 142 (26), 140 (16), 115 (88), 105 (20), 104 (24), 101 (20), 94 (56), 87 (40), 85 (30), 83 (31), 77 (44), 74 (38), 73 (78), 72 (50), 69 (39), 57 (78), 55 (64), 50 (34).

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.02; H, 4.31; N, 27.23. Found: C, 55.55; H, 3.76; N, 26.72.

(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(5-methyl-1,3,4-oxadiazol-2-yl)methane (**10**).

To a suspension of 0.33 g of ketone **8** (1.4 mmoles) in 20 ml of anhydrous methanol sodium borohydride was added in small portions until dissolution was complete (about 1.1 g, 2.8 mmoles). After standing overnight at room temperature the mixture was diluted with 50 ml of water and by bringing the *p*H to about 2 with 2*N* hydrochloric acid **10** was isolated after some hours until crystallisation was complete. The yield was 0.22 g (81%). Purification was accomplished by dissolution in 2*N* sodium hydroxide and reprecipitation with 2*N* hydrochloric acid, mp 167°. ir: 3400-2800 w, 1650 s (quinolone CO), 1610 m, 1580 s, 1515 m cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.5 (s, oxadiazole CH_3), 3.55 (s, NCH_3), 4.25 (s, CH_2), 6.85-7.65 (m, 3ArH), 7.9 (dd, J = 2 and 7 Hz, peri H).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.71; H, 4.78; N, 15.17.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolinyl-3-acetic Acid (**12**) [21].

A solution of 2.71 g of oxadiazolyl methane **10** (10 mmoles) in 100 ml of 2*N* sodium hydroxide was refluxed for 4-5 hours. After cooling and filtering the mixture was acidified with 2*N* hydrochloric acid to yield 1.91 g (82%), mp 228-232° (acetic acid) [21], mp 232-234°; ir: 3400-2800 m, 1720 s (acid CO), 1650 s (quinolone CO), 1620 s, 1575 s cm^{-1}; ^1H nmr: δ = 3.6 (s, NCH_3 and CH_2), 7.1-7.75 (m, 3ArH), 8.05 (dd, J = 2 and 7 Hz, peri H), 12.3 (broad, 1 acidic H).

5-Methyl-2,4-dioxo-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline (**13**).

The acid **12** was slowly heated in a sublimation apparatus in an oil-bath. At 205-225°/18 mm the lactone sublimed in a yield of 89%, mp 189-190°. Purification was accomplished by repeated sublimation at 160-180°/18 mm; ir: 2980 w, 1840 s (lactone CO), 1675 s, 1650 s (quinolone CO), 1605 s, 1575 s, 1515 m cm^{-1}; ^1H nmr (deuteriochloroform): δ = 3.72 (s, NCH_3), 3.75 (s, 2H on C-3), 7.15-7.65 (m, 3ArH), 7.80 (dd, J = 2 and 7 Hz, peri H); uv (ethanol) [23]; λ max (log ϵ) = 329 sh (3.75), 319 (3.83), 305 sh (3.68), 284 (3.89), 276 (3.88).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.05; H, 4.17; N, 6.53.

REFERENCES AND NOTES

[1] Part 1: K. Faber, H. Stückler and Th. Kappe, *J. Heterocyclic Chem.*, **21**, 1177 (1984). The present work also represents Part 2 in the series Organic Azides in Heterocyclic Synthesis; Part 1: Th. Kappe, G. Lang and E. Pongratz, *J. Chem. Soc., Chem. Commun.*, 338 (1984).

[2] K. Faber, Ph. D. Thesis, University of Graz, 1981.

[3] T. Y. Shen and C. P. Dorn, German Patent 1,815,451 (1969); *Chem. Abstr.*, **71**, 91488v (1969).

[4] C. Hoffmann and A. Dordilly, German Patent 1,934,551 (1970); *Chem. Abstr.*, **72**, 90476y (1970).

[5] P. F. Juby and T. W. Hudyman, *J. Med. Chem.*, **12**, 396 (1969); P. F. Juby, T. W. Hudyman and M. Brown, *ibid.*, **15**, 1179 (1972).

[6] R. Aries, French Patent 1,580,970 (1970); *Chem. Abstr.*, **72**, 132737s (1970); French Patent 1,584,861 (1972); *Chem. Abstr.*, **74**, 3634y (1972).

[7] J. S. Shukla, I. Ahmad and S. Saxena, *Indian J. Pharm. Sci.*, **41**, 70 (1979).

[8] L. Chausse, French Patent 2,068,411 (1971); *Chem. Abstr.*, **77**, 34531d (1972).

[9] L. I. Wiesel, *Arthritis Rheum.*, **9**, 551 (1966); *J. New Drugs*, **5**, 263 (1965).

[10] R. T. Buckler, S. Hayao, O. J. Lorenzetti, L. F. Sancilio, H. E. Hartzler and W. G. Strycker, *J. Med. Chem.*, **13**, 725 (1970).

[11] S. S. Parmar, V. Kishore and B. Ali, *Agents/Actions*, **3/5**, 386 (1973).

[12] CIBA Ltd., French Patent 1,533,763 (1968); *Chem. Abstr.*, **71**, 101573k (1969).

[13] K. Rahman, S. S. Parmar and S. P. Singh, *J. Heterocyclic Chem.*, **17**, 1137 (1980).

[14] S. J. Fleming, M. E. Bierwagen, A. W. Pircio and M. H. Pindell, *Arch. Int. Pharmacodyn. Ther.*, **178**, 423 (1969); *Chem. Abstr.*, **72**, 41376g (1970).

[15] O. Schmut, Ph. D. Thesis, University of Graz, 1971.

[16] Th. Witoszynskij, Ph. D. Thesis, University of Graz, 1972.

[17] R. E. Bowman, A. Campbell and E. Tanner, *J. Chem. Soc.*, 444 (1959).

[18] J. A. Bosson, M. Rasmussen, E. Ritchie, A. V. Robertson and W. C. Taylor, *Aust. J. Chem.*, **16**, 480 (1963).

[19] Th. Kappe, E. Lender and E. Ziegler, *Monatsh. Chem.*, **99**, 990 (1968).

[20] R. Huisgen, J. Sauer and H. J. Sturm, *Angew. Chem.*, **70**, 272 (1968); R. Huisgen, J. Sauer, H. J. Sturm and J. H. Markgraf, *Chem. Ber.*, **93**, 2106 (1960); R. Huisgen, *Angew. Chem.*, **72**, 364 (1960); J. Sauer, R. Huisgen and H. J. Sturm, *Tetrahedron Letters*, 241 (1960).

[21] U. Hörlein, *Arch. Pharm.*, **304**, 81 (1971).

[22] G. Lang, Ph. D. Thesis, University of Graz, 1972.

[23] W. Stadlbauer and Th. Kappe, *Z. Naturforsch.*, **36b**, 739 (1981).