Non-Steroidal Antiinflammatory Agents. 3 [1]. Synthesis of 3-Hydroxy-3-hydroxyphenyl-2,4-dioxo-1,2,3,4-tetrahydroquinolines

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The acid-catalyzed condensation of quinisatines **5a-c** or their aminals **4a-c** with phenols **6a-i** led to a number of 3-hydroxy-3-hydroxyphenyl-2,4-dioxo-1,2,3,4-tetrahydroquinolines **7a-s** which were considered as potential antiinflammatory agents.

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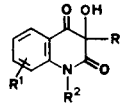
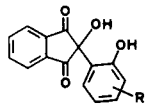
In our search for novel classes of non-steroidal antiinflammatory agents derivatives of 4-hydroxyquinolin-2-ones were investigated. In the case of their 3-monosubstituted derivatives we recently reported synthetic pathways to 3-acetic- [1b] and 3-propionic acids [1a].

Our interest in 3,3-disubstituted derivatives of 2,4-dioxo-1,2,3,4-tetrahydroquinoline was attracted by the work of Budzikiewicz [3] who found their 3-hydroxy-3-alkyl derivatives (type I) to be inherent compounds of bacteria. A subsequent investigation [4] made a number of these compounds in a preparative scale available, however, the substituent R in compounds of type I was always an alkyl- or an unsubstituted phenyl group.



I



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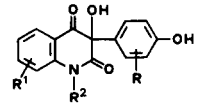

III

In 1979 Poupelin and coworkers [5] synthesized a number of 2-hydroxy-2-(2-hydroxyphenyl)indane-1,3-diones (type II) by the condensation of ninhydrin with some selected phenols. Besides a low toxicity they reported a moderate antiinflammatory action of some of their derivatives. This prompted us to synthesize compounds of type III for pharmacological testing, which should possess less GI irritation because of their lower acidity compared to carboxylic acids.

Compounds of this type were first synthesized in the later 1960's by condensation of quinisatine or its stable hydrate and phenol under strongly acidic conditions [6]. It was also found that it is possible to start with the aminals **4** which are readily hydrolyzed *in situ* to the corresponding triketones without loss of yield.

For the synthesis of the novel quinisatine **5a** we started from the readily available dichloro compound **3a** [7], which was nitrated to give the 6-nitro derivative **3e** [8]. According to known procedures the chloro atoms were substituted with morpholine [9] to yield the 6-nitroquinisatine

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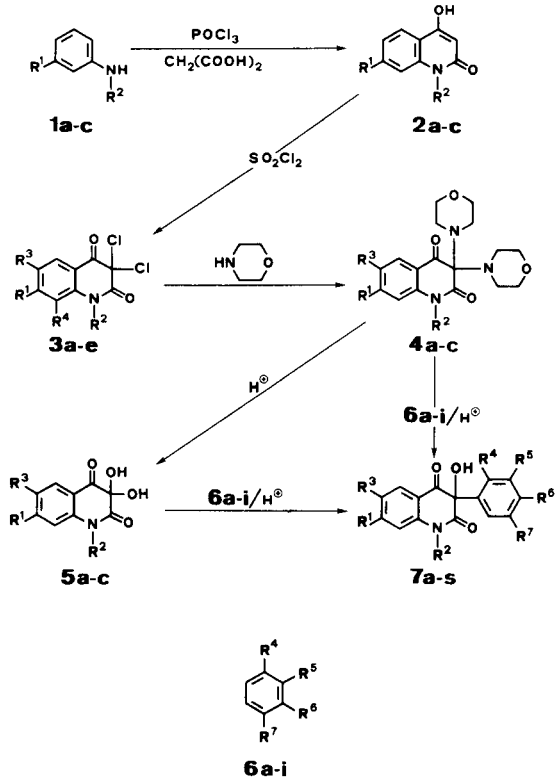

R-Key see Table 1

aminal **4a**, which served as a starting material for our syntheses. All attempts to isolate either 6-nitroquinisatine itself or its hydrate **5a** were unsuccessful hence decomposition took place upon isolation.

For 7-methoxyquinisatine we started from *m*-anisidine **1b** which was converted to 4-hydroxy-7-methoxy-2-oxo-1,2-dihydroquinoline **2b** using the known procedure [10, 2b]. Chlorination of both of the active hydrogen atoms with sulfuryl chloride using the method mentioned above [7] unfortunately led to an inevitable partial halogenation of the aromatic ring due to its increased activity towards

Table 1

R-Key of Compounds **1-7**

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1a	H	H	—	—	—	—	—
1b	OCH_3	H	—	—	—	—	—
1c	H	CH_3	—	—	—	—	—
2a	H	H	—	—	—	—	—
2b	OCH_3	H	—	—	—	—	—
2c	H	CH_3	—	—	—	—	—
3a	H	H	H	H	—	—	—
3b	OCH_3	H	Cl	H	—	—	—
3c	OCH_3	H	Cl	Cl	—	—	—
3d	H	CH_3	H	H	—	—	—
3e	H	H	NO_2	H	—	—	—
4a	H	H	NO_2	—	—	—	—
4b	OCH_3	H	Cl	—	—	—	—
4c	H	CH_3	H	—	—	—	—
5a	H	H	NO_2	—	—	—	—
5b	OCH_3	H	Cl	—	—	—	—
5c	H	CH_3	H	—	—	—	—
6a	—	—	—	OH	H	H	*t*-Bu
6b	—	—	—	H	CH_3	OH	H
6c	—	—	—	H	OCH_3	OH	H
6d	—	—	—	OH	H	H	CH_3
6e	—	—	—	OCH_3	OCH_3	OCH_3	H
6f	—	—	—	*t*-Bu	H	OH	H
6g	—	—	—	OH	*t*-Bu	H	CH_3
6h	—	—	—	H	H	OH	H
6i	—	—	—	OH	H	OH	H
7a	OCH_3	H	Cl	OH	*t*-Bu	H	CH_3
7b	OCH_3	H	Cl	*t*-Bu	H	OH	H
7c	OCH_3	H	Cl	OCH_3	OCH_3	OCH_3	H
7d	OCH_3	H	Cl	H	H	OH	H
7e	OCH_3	H	Cl	OH	H	OH	H
7f	H	H	NO_2	OH	H	H	*t*-Bu
7g	H	H	NO_2	H	CH_3	OH	H
7h	H	H	NO_2	OH	H	H	CH_3
7i	H	H	NO_2	OH	*t*-Bu	H	CH_3
7k	H	H	NO_2	*t*-Bu	H	OH	H
7l	H	H	NO_2	OCH_3	OCH_3	OCH_3	H
7m	H	CH_3	H	OH	H	H	*t*-Bu
7n	H	CH_3	H	H	CH_3	OH	H
7o	H	CH_3	H	H	OCH_3	OH	H
7p	H	CH_3	H	OH	H	H	CH_3
7q	H	CH_3	H	OH	*t*-Bu	H	CH_3
7r	H	CH_3	H	*t*-Bu	H	OH	H
7s	H	CH_3	H	OCH_3	OCH_3	OCH_3	H

electrophilic attack yielding the trichloro derivative **3b** as major and the tetrachloroquinolone **3c** as minor product. Substitution of both of the active halogens with morpholine to give **4b** occurred as expected and acidic hydrolysis of the aminal [9] led to the stable 6-chloro-7-methoxyquinisatine **5b**.

The *N*-methyl derivative **5c** was prepared by known procedures [1a,2a,11].

Finally, we reacted the quinisatines or their hydrates **5a-c** as well as their aminals **4a-c** without noting a significant change in the yield with phenols **6a-i** to obtain a variety of derivatives **7a-s**. Due to the different properties of some of our products we developed 3 different general procedures (see Experimental).

It is interesting to note that we always found a *para*-substitution of the phenols used (only in cases where this position was blocked by a substituent it was forced to occur in the *ortho* position), which is opposite to the observation of Poupelin and coworkers [5], who found preferably *ortho*-substitution in the case of condensations with ninhydrin.

EXPERIMENTAL

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 spectrometer using samples in potassium bromide disks. The nmr spectra were measured in hexadeuteriodimethylsulfoxide (unless otherwise stated) and with TMS as an internal standard; the instruments used were the Varian A-60A or the 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 a Varian MAT 111 (with 80 eV).

3,3-Dichloro-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**3e**).

To a mixture of 2.3 g (10 mmoles) of dichloro compound **3a** [7] and 2.9 ml of nitric acid (d = 1.40), concentrated sulfuric acid (1.74 ml) was slowly added, while the temperature rose to about 70°. After being kept there for 8 minutes the solution was poured on ice (25 g) whereupon the oily product crystallized if stirring was continued to yield 2.30 g of **3e** (84%), mp 202° (xylene); ir: 3260 m (NH), 1740 s (CO), 1700 s (lactam CO) 1620 s, 1595 s, 1530 s, 1490 s, 1320 s ($ArNO_2$) cm^{-1}; ^1H nmr: δ 7.3 (d, J = 8 Hz, 1H at C-8), 8.15-8.45 (m, 2H at C-5 and C-7), 11.85 (s, NH); ms: m/e (relative intensity) 278 (M^+, ^{37}Cl, 9), 277 (6), 276 (M^+, ^{37}Cl, ^{35}Cl, 50), 275 (11), 274 (M^+, ^{35}Cl, 80), 242 (40), 240 (100), 211 (49), 210 (21), 191 (22), 166 (26), 165 (51), 164 (19), 134 (18), 106 (21), 102 (34), 90 (22), 75 (38), 63 (29).

Anal. Calcd. for $C_9H_4Cl_2N_2O_4$: C, 39.30; H, 1.47; Cl, 25.78; N, 10.18. Found: C, 39.21; H, 1.40; Cl, 25.95; N, 10.06.

4-Hydroxy-7-methoxy-2-oxo-1,2-dihydroquinoline (**2b**).

To a mixture of malonic acid (10.5 g, 0.1 mole) and *m*-anisidine (12.3 g, 0.1 mole) in 500 ml Erlenmeyer flask phosphorus oxychloride (10 ml, 0.11 mole) was added. The temperature was slowly brought to 95° while the reaction took place with vigorous foaming. After cooling the crude mass was powdered and triturated with ice-water (700 ml). The precipitate thus formed was collected and washed with water until free from acid. The pure product was extracted from the crude with 300 ml of 2*N* sodium hydroxide, some insoluble 3,3'-dimethoxymalonic acid dianilide was removed by filtration and after the addition of some ethanol to the filtrate **2b** was precipitated by acidification to *p*H = 5 with 2*N* hydrochloric acid. The yield was 15 g (78%), mp 318° dec (dimethylformamide); ir: 3300-2700 m, 1690 s, 1640 s (lactam CO), 1620 s, 1560 m, 1490 s cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 3.45 (s, OCH_3), 6.05 (d, J = 2 Hz, 1H at C-8), 6.6 (s, 1H at C-3), 6.75 (dd, J = 2 and 7 Hz, 1H at C-6), 7.7 (d, J = 7 Hz, 1H at C-5), 10.3 (s, NH); ms: m/e (relative intensity) 191 (M^+, 52), 169 (14), 178 (10), 150 (41), 149 (100), 135 (15), 122 (32), 105 (21), 97 (25), 95 (24), 94 (25), 88 (29), 85 (29), 84 (27), 83 (36), 81 (28), 79 (61).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.71; N, 7.33. Found: C, 62.70; H, 4.60; N, 7.20.

7-Methoxy-3,3,6-trichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**3b**).

To a suspension of 10 g of **2b** (56 mmoles) in 50 ml of dioxane 12.5 ml

(150 mmoles) of sulfuryl chloride was added dropwise with cooling. The solution was filtered from some insoluble starting material and poured on ice-water (300 ml). The crude product was recrystallized from chlorobenzene to yield 7.5 g of **3b** (45%), mp 225° dec; ir: 3200 s (NH), 1720 s (CO), 1680 s (lactam CO), 1580 s cm^{-1}; ^1H nmr (tetradeuteriomethanol): δ 4.0 (s, OCH_3), 6.7 (s, 1H at C-8), 7.9 (s, 1H at C-5).

Anal. Calcd. for $C_{10}H_6Cl_3NO_3$: C, 40.78; H, 2.05; Cl, 36.11; N, 4.76. Found: C, 40.90; H, 2.00; Cl, 36.20; N, 4.70.

7-Methoxy-3,3,6,8-tetrachloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**3c**).

The mother liquor from the recrystallisation of **3b** was evaporated and the remaining oil was recrystallized from ethyl acetate to give 5 g tetrachloro derivative **3c** (27%), mp 165-167°; ir: 3200 s (NH), 1720 s (CO), 1680 s (lactam CO), 1580 s cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.2 (s, OCH_3), 8.15 (s, 1H at C-5).

Anal. Calcd. for $C_{10}H_5Cl_4NO_3$: C, 36.51; H, 1.53; Cl, 43.11; N, 4.26. Found: C, 36.71; H, 1.62; Cl, 42.96; N, 4.30.

3,3-(Dimorpholin-4-yl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**4a**).

Using the procedure described in ref [9] we obtained **4a** from **3e** in 81% yield, mp 184° dec (ethanol); ir: 3000 w, 1715 s (CO), 1680 s (lactam CO), 1625 s, 1605 s, 1545 s, 1535 m cm^{-1}; ^1H nmr: δ 2.6 (t, J = 7 Hz, morpholine NCH_2), 3.55 (t, J = 7 Hz, morpholine OCH_2), 7.35 (d, J = 8 Hz, 1H, at C-8) 8.35-8.65 (m, 2H at C-5 and C-7).

Anal. Calcd. for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.88. Found: C, 54.00; H, 5.33; N, 14.70.

6-Chloro-3,3-(dimorpholin-4-yl)-7-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**4b**).

Following the procedure described in ref [9] we obtained **4b** from **3b** in 86% yield, mp 130° dec (methanol); ir: 3450 s (NH), 1690 s (CO), 1660 s (lactam CO), 1600 s cm^{-1}.

Anal. Calcd. for $C_{18}H_{22}Cl_3N_3O_5$: C, 54.76; H, 5.62; Cl, 8.98; N, 10.64. Found: C, 54.80; H, 5.60; Cl, 9.20; N, 10.60.

6-Chloro-3,3-dihydroxy-7-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**5b**).

Using the procedure described in ref [9] we obtained **5b** from **4b** in 96% yield, which turns red above 120° upon the formation of 6-chloro-7-methoxyquinisatine. Recrystallization from water; ir: 3520 s, 3370 s, 3310 s, 1740 s (CO), 1660 s (lactam CO), 1610 s, 1510 m, 1490 s cm^{-1}; ^1H nmr: δ 3.95 (s, OCH_3), 6.8 (s, 1H at C-8), 7.3 (s, 2 OH), 7.75 (s, 1H at C-5), 10.65 (s, NH).

Anal. Calcd. for $C_{10}H_8ClNO_5$: C, 46.62; H, 3.13; Cl, 13.76; N, 5.44. Found: C, 46.48; H, 3.15; Cl, 13.89; N, 5.35.

General Procedures for the Preparation of 3-Hydroxy-3-hydroxyphenyl Derivatives **7a-s**.

Method A.

Quinisatines **5** (10 mmoles), or their corresponding aminals **4** (10 mmoles) were dissolved in a cooled mixture of glacial acetic acid (22.5 ml), water (0.25 ml) and concentrated sulfuric acid (3.75 ml). The appropriate phenol **6** (20 mmoles) was added in small portions and the mixture stirred at room temperature for 1.5-2 hours. The crystalline product **7** was filtered and recrystallized.

Method B.

The reaction was carried out as described in method A but the separation of the product **7** was accomplished by dilution of the reaction mixture with 75 ml of water. Crystallization took place if stirring was continued overnight.

Method C.

The reaction was carried out as described in method A. When the reaction mixture was diluted with water (75 ml) the product was separated by bringing the *p*H close to 6 with 2*N* sodium hydroxide. The crude oil crystallized if stirring was continued overnight.

6-Chloro-3-hydroxy-7-methoxy-3-(2-hydroxy-5-methyl-3-*t*-butylphenyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7a**).

Following method A, **7a** was obtained from **4b** and **6g** in 83% yield, mp 293° (ethanol); ir: 3450 s, 2960 s, 1690 s (CO), 1680 s (lactam CO), 1620 m, 1590 s cm^{-1}; ^1H nmr: δ 1.3 (s, *t*-butyl), 2.2 (s, $ArCH_3$), 3.8 (s, OCH_3), 6.55 (s, 1H at C-8), 6.9 (m, 2 ArH and 1 OH), 7.6 (s, 1H at C-5), 10.45 (s, NH).

Anal. Calcd. for $C_{21}H_{22}ClNO_5$: C, 62.45; H, 5.49; Cl, 8.79; N, 3.47. Found: C, 62.78; H, 5.52; Cl, 8.62; N, 3.41.

6-Chloro-3-hydroxy-7-methoxy-3-(4-hydroxy-2-*t*-butylphenyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7b**).

Following method B, **7b** was obtained from **4b** and **6f** in 65% yield, mp 281° (ethanol); ir: 3440 s, 3205 m, 2960 m, 1695 s (CO), 1650 s, (lactam CO), 1605 s, 1580 s cm^{-1}; ^1H nmr: 1.25 (s, *t*-butyl), 3.9 (s, OCH_3), 6.6-7.55 (m, 4 ArH and 1 OH), 7.7 (s, 1H at C-5), 9.3 (s, 1 OH), 10.8 (s, NH).

Anal. Calcd. for $C_{20}H_{20}ClNO_5$: C, 61.62; H, 5.17; Cl, 9.10; N, 3.59. Found: C, 61.35; H, 5.17; Cl, 9.26; N, 3.76.

6-Chloro-3-hydroxy-7-methoxy-3-(2,3,4-trimethoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7c**).

Following method B, **7c** was obtained from **4b** and **6e** in 78% yield, mp 246° (ethanol/water); ir: 3390 s, 2940 w, 1705 s (CO), 1650 s (lactam CO), 1610 s, 1595 s cm^{-1}; ^1H nmr: δ 3.45 (s, OCH_3), 3.68 (s, OCH_3), 3.82 (s, OCH_3), 3.95 (s, OCH_3), 6.7-7.4 (m, 3 ArH and 1 OH), 7.7 (s, 1H at C-5), 10.85 (s, NH).

Anal. Calcd. for $C_{19}H_{18}ClNO_7$: C, 55.96; H, 4.45; Cl, 8.69; N, 3.43. Found: C, 55.71; H, 4.53; Cl, 8.63; N, 3.45.

6-Chloro-3-hydroxy-3-(4-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7d**).

Following method B, **7d** was obtained from **4b** and **6h** in 90% yield, mp 315° dec (diluted acetic acid); ir: 3400 s, 1700 s (CO), 1650 s (lactam CO), 1600 s cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClNO_5$: C, 57.59; H, 3.62; Cl, 10.62; N, 4.20. Found: C, 57.32; H, 3.60; Cl, 10.68; N, 4.14.

6-Chloro-3-hydroxy-3-(2,4-dihydroxyphenyl)-7-methoxy-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7e**).

Following method B with 2 g of *p*-toluenesulfonic acid instead of sulfuric acid **7e** was obtained from **4b** and **6i** in 56% yield, mp 260° dec (diluted acetic acid); ir: 3400 s, 3280 s, 1690 s (CO), 1650 s (lactam CO), 1600 s cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}ClNO_6$: C, 54.95; H, 3.46; Cl, 10.13; N, 4.01. Found: C, 55.12; H, 3.50; Cl, 10.20; N, 3.97.

3-Hydroxy-3-(2-hydroxy-5-*t*-butyplphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7f**).

Following method A, **7f** was obtained from **4a** and **6a** in 62% yield, mp 214° dec (ethanol/water); ir: 3370 m, 3000 s, 1700 s (CO and lactam CO), 1610 s, 1545 s, 1495 s cm^{-1}; ^1H nmr: δ 1.25 (s, *t*-butyl), 6.6 (d, J = 8 Hz, 1H at C-3'), 7.2 (dd, J = 2.5 and 8 Hz, 1H at C-4'), 7.35 (d, J = 9 Hz, 1H at C-8), 7.7 (d, J = 2.5 Hz, 1H at C-6'), 8.5 (dd, J = 2.5 and 9 Hz, 1H at C-7), 8.55 (s, 1H at C-5), 9.55 (s, 1 OH), 11.65 (s, NH).

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.63; H, 4.86; N, 7.57. Found: C, 61.53; H, 4.85; N, 7.55.

3-Hydroxy-3-(4-hydroxy-5-methylphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7g**).

Following method C, **7g** was obtained from **4a** and **6b** in 32% yield, mp 264° dec (ethanol/water); ir: 3465 s, 1740 s (CO), 1690 s (lactam CO), 1640 m, 1600 s, 1545 s, 1520 m, 1505 m cm^{-1}; ^1H nmr: δ 2.05 (s, $ArCH_3$), 6.3 (s, 1 OH), 6.7 (d, J = 8 Hz, 1H at C-5'), 6.95 (dd, J = 2 and 8 Hz, 1H at C-6'), 7.1 (d, J = 7 Hz, 1H at C-2'), 7.25 (d, J = 9 Hz, 1H at C-8), 8.4 (dd, J

= 2.5 and 9 Hz, 1H at C-7), 8.45 (s, 1H at C-5), 9.65 (s, 1 OH), 11.65 (s, NH).

Anal. Calcd. for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.69; N, 8.54. Found: C, 58.63; H, 3.77; N, 8.50.

3-Hydroxy-3-(2-hydroxy-5-methylphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7h**).

Following method A, **7h** was obtained from **4a** and **6d** in 58% yield, mp 218° (ethanol/water); ir: 3275 s, 1700 s (CO and lactam CO), 1610 s, 1545 s, 1500 s cm^{-1}; ^1H nmr: δ 2.25 (s, $ArCH_3$), 6.5 (d, J = 8 Hz, 1H at C-3'), 6.95 (dd, J = 2 and 8 Hz, 1H at C-4'), 7.35 (d, J = 9 Hz, 1H at C-8), 7.45 (d, J = 2 Hz, 1H at C-6'), 8.45 (dd, J = 2.5 and 9 Hz, 1H at C-7), 8.55 (s, 1H at C-5), 9.55 (s, 1 OH), 11.55 (s, NH).

Anal. Calcd. for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.69; N, 8.53. Found: C, 58.39; H, 3.70; N, 8.47.

3-Hydroxy-3-(2-hydroxy-5-methyl-3-*t*-butylphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7i**).

Following method A, **7i** was obtained from **4a** and **6g** in 55% yield, mp 255-258° dec (ethanol/water); ir: 3375 m, 3000 m, 1700 s (CO), 1635 s (lactam CO), 1550 s, 1515 s, 1490 m cm^{-1}; ^1H nmr: δ 1.3 (s, *t*-butyl), 2.25 (s, $ArCH_3$), 6.85-7.05 (m, 3 ArH at C-8, C-4' and C-6'), 7.15 (s, 1 OH), 7.95 (s, 1 OH), 8.2 (dd, J = 2 and 7 Hz, 1H at C-7), 8.55 (d, J = 2 Hz, 1H at C-5), 11.15 (s, NH).

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.25; N, 7.28. Found: C, 62.71; H, 5.30; N, 7.26.

3-Hydroxy-3-(4-hydroxy-2-*t*-butylphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7k**).

Following method A, **7k** was obtained from **4a** and **6f** in 65% yield, mp 260° dec (ethanol/water); ir: 3500 s, 3240 w, 3130 m, 2990 w, 1750 s (CO), 1695 s (lactam CO), 1625 s, 1600 s, 1540 s, 1505 s, 1490 s cm^{-1}; ^1H nmr: δ 1.3 (s, *t*-butyl), 6.55-7.65 (m, 4 ArH and 1 OH), 8.45 (dd, J = 2 and 7 Hz, 1H at C-7), 8.5 (s, 1H at C-5), 9.55 (s, 1 OH), 11.55 (s, NH).

Anal. Calcd. for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 62.00; H, 4.97; N, 7.49.

3-Hydroxy-3-(2,3,4-trimethoxyphenyl)-6-nitro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7l**).

Following method B, **7l** was obtained from **4a** and **6e** in 82% yield, mp 195° dec (cyclohexane/ethyl acetate); ir: 3460 m, 3280 m, 3180 w, 3000 m, 1695 s (CO), 1610 s (lactam CO), 1545 s, 1500 m cm^{-1}; ^1H nmr: δ 3.5 (s, OCH_3), 3.75 (s, OCH_3), 3.85 (s, OCH_3), 6.75-7.5 (m, 3 ArH and 1 OH), 8.5 (dd, J = 2 and 7 Hz, 1H at C-7), 8.55 (s, 1H at C-5), 11.6 (s, NH).

Anal. Calcd. for $C_{18}H_{16}N_2O_8$: C, 55.67; H, 4.15; N, 7.21. Found: C, 55.46; H, 4.13; N, 7.10.

3-Hydroxy-3-(2-hydroxy-5-*t*-butylphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7m**).

Following method B, **7m** was obtained from **4c** and **6a** in 98% yield, mp 203° (ethanol/water); ir: 3470 s, 3000 s, 1710 s (CO), 1670 s (lactam CO), 1610 s, 1510 s cm^{-1}; ^1H nmr: δ 1.35 (s, *t*-butyl), 3.45 (s, NCH_3), 6.6 (d, J = 7 Hz, 1H at C-3'), 7.1 (s, 1 OH), 7.15 (dd, J = 3 and 8 Hz, 1H at C-4'), 7.25 (d, J = 7 Hz, 1H at C-8), 7.42 (d, J = 7 Hz, 1H at C-6), 7.65 (d, J = 3 Hz, 1H at C-6'), 7.75 (t, J = 7 Hz, 1H at C-7), 7.9 (dd, J = 3 and 7 Hz, 1H at C-5), 9.35 (s, 1 OH).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.43; N, 4.15.

3-Hydroxy-3-(4-hydroxy-3-methylphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7n**).

Following method B, **7n** was obtained from **4c** and **6b** in 69% yield, mp 240° (dimethylformamide/water); ir: 3520 s, 1720 s, (CO), 1670 s (lactam CO), 1610 s, 1520 s cm^{-1}; ^1H nmr: δ 2.13 (s, $ArCH_3$), 3.65 (s, NCH_3), 6.35 (s, 1 OH), 6.55 (d, J = 7.5 Hz, 1H at C-5'), 7.00 (dd, J = 2.5 and 7.5 Hz, 1H at C-6'), 7.10 (d, J = 2.5 Hz 1H at C-2'), 7.30 (t, J = 7 Hz, 1H at C-7), 7.50 (d, J = 7 Hz, 1H at C-8),7.81 (dd, J = 1.5 and 8 Hz, 1H at C-6), 7.90 (dd, J = 2.5 and 8 Hz, 1H at C-5), 9.7 (s, 1 OH).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.70. Found: C, 68.51; H, 5.14; N, 4.80.

3-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7o**).

Following method C, **7o** was obtained from **4c** and **6c** in 26% yield, mp 228° (dimethyl formamide/water); ir: 3530 s, 3130 w, 1720 s (CO), 1660 s (lactam CO), 1610 s, 1515 s, 1500 m cm^{-1}; ^1H nmr: δ 3.5 (s, OCH_3), 3.7 (s, NCH_3), 6.35 (s, 1 OH), 6.55 (dd, J = 2 and 8 Hz, 1H at C-6'), 6.65 (d, J = 8 Hz, 1H at C-5'), 6.90 (d, J = 2 Hz, 1H at C-2'), 7.15 (t, J = 7 Hz, 1H at C-7), 7.35 (d, J = 7 Hz, 1H at C-8), 7.65 (d, J = 7 Hz, 1H at C-6), 7.75 (d, J = 7 Hz, 1H at C-5), 9.3 (s, 1 OH).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.33; H, 4.90; N, 4.45.

3-Hydroxy-3-(2-hydroxy-5-methylphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7p**).

Following method A, **7p** was obtained from **4c** and **6d** in 64% yield, mp 199° (ethanol/water); ir: 3275 w, 1710 s (CO), 1670 s (lactam CO), 1610 s, 1500 s cm^{-1}; ^1H nmr: δ 2.3 (s, $ArCH_3$), 3.45 (s, NCH_3), 6.60 (d, J = 7 Hz, 1H at C-3'), 6.85-8.1 (m, 6 ArH and 1 OH), 9.3 (s, 1 OH).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.93; H, 4.98; N, 4.68.

3-Hydroxy-3-(2-hydroxy-5-methyl-3-*t*-butylphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7q**).

Following method A, **7q** was obtained from **4c** and **6g** in 34% yield, mp 192° (dimethyl formamide/water); ir: 3520 s, 3000 m, 1675 s (CO), 1615 s (lactam CO), 1515 w, 1480 s cm^{-1}; ^1H nmr: δ 1.25 (s, *t*-butyl), 2.15 (s, $ArCH_3$), 3.32 (s, NCH_3), 6.65 (s, 1 OH), 6.78 (s, 1H at C-4'), 6.85 (s, 1H at C-6'), 7.05 (d, J = 8 Hz, 1H at C-8), 7.15 (d, J = 8 Hz, 1H at C-6), 7.35 (t, J = 7 Hz, 1H at C-7), 7.45 (s, 1 OH), 7.80 (d, J = 8 Hz, 1H at C-5).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.49; H, 6.62; N, 3.95.

3-Hydroxy-3-(4-hydroxy-2-*t*-butylphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7r**).

Following method B, **7r** was obtained from **4c** and **6f** in 68% yield, mp 178° (cyclohexane/ethyl acetate); ir: 3310 s, 3020 s, 1720 s (CO), 1655 s (lactam CO), 1610 s, 1515 w, 1505 w, 1480 s cm^{-1}; ^1H nmr: δ 1.25 (s, *t*-butyl), 3.4 (s, NCH_3), 6.65-8.0 (m, 7 ArH and 1 OH), 9.35 (s, 1 OH).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; Found: C, 71.03; H, 6.30; N, 4.10.

3-Hydroxy-7-methoxy-3-(2,3,4-trimethoxyphenyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**7s**).

Following method C, **7s** was obtained from **4c** and **6e** in 79% yield, mp 142° (dimethyl formamide/water); ir: 3670 w, 3380 s, 3040 w, 3000 m, 2880 w, 1710 s (CO), 1680 s (lactam CO), 1610 s, 1500 s cm^{-1}; ^1H nmr: δ 3.37 (s, OCH_3), 3.42 (s, NCH_3), 3.8 (s, OCH_3), 6.85 (d, J = 7 Hz, 1H at C-5'), 7.05-8.05 (m, 5 ArH and 1 OH).

Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 64.42; H, 5.40; N, 3.95.

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