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Potential Non-Steroidal Estrogens and Antiestrogens, I[1] Synthesis of Some 7-Methoxy-2-(1*H*)-quinolone Derivatives

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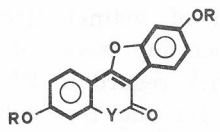
Reaction of 4-hydroxy-7-methoxy-2(1*H*)-quinolone (*1*) with iodosobenzenes, prepared *in situ* from the dichloroiodo compounds *2a,b*, afforded the iodoniumylides *3a,b* in good yields. Their thermal rearrangement produced the 3-iodo-4-aryloxy-quinolones *4a,b*. Reductive deiodination of *4a,b* gave the corresponding arylethers *5a,b*. By photocyclization *4a* as well as *5a* yielded the benzofuro--quinolone *6a* (*4b* or *5b* could not be cyclized to *6b*). Acid catalyzed »transylidation« of the iodonium-ylides *3a,b* with triphenylphosphane, pyridine and isoquinoline as nucleophiles produced the corresponding *P*- and *N*-ylides *8*, *9a,b*, respectively. The pyridinium- (*9a*) and isoquinolinium-ylid (*9b*) were also prepared from the 3-chloro-4-hydroxy-2-quinolone *7a*, which in turn could be obtained by the action of hydrochloric acid on *3a,b* (*7b* was obtained by careful reaction of HBr with *3a*).

Estrogen receptor, a specific, high-affinity binding protein present in estrogen-sensitive tissues, is the principal mediator of estrogen activity. Human breast tumors are also known to have significant levels of estrogen receptor.[2] Some synthetic estrogens, such as stilbestrol and hexestrol, show a similar binding activity as the natural hormone.[3] Some non-steroidal estrogen antagonists have already been successfully introduced in the treatment of advanced breast cancer.[4]



A: COUMESTROL, Y = O; R = H

B: "AZACOUMESTROL", Y = NH; R = H

Coumestrol (*A*) represents an estrogenic factor occurring naturally in forage crops.[5] It is easily observed that the 4,4'-dihydroxy-E-stilben moiety (bold faced) is present in this structure.[6] Some years ago we published a simple synthesis of *A* by cyclodehydrogenation of the corresponding 4-hy-

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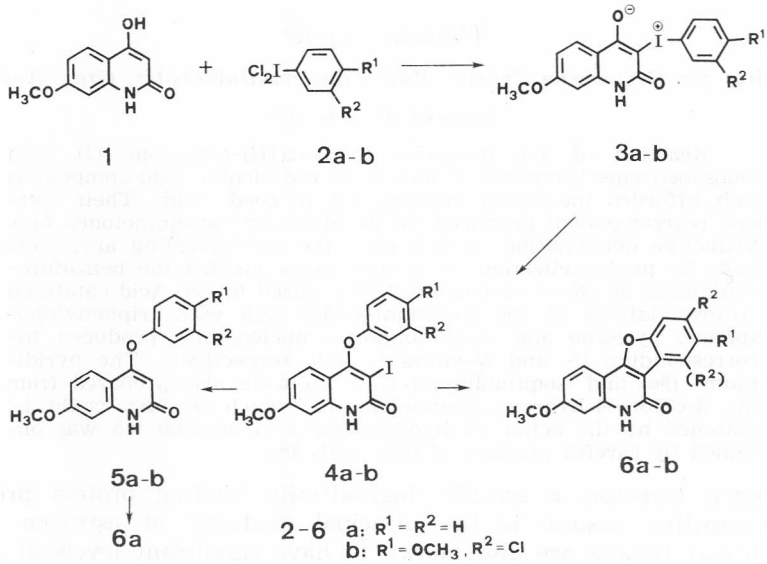
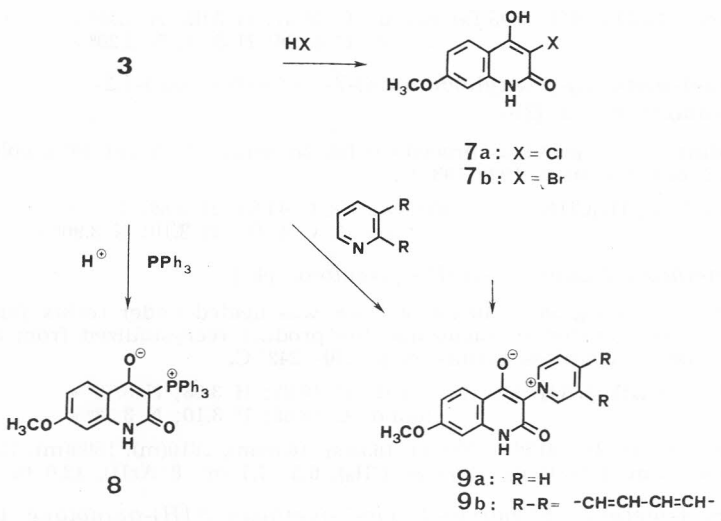
droxy-3-aryl-coumarin.[7] Later, we have shown that the coumestan ringsystem can also be obtained by photocyclization of 4-phenyloxy-coumarin.[8] In the present work we have tried to use the latter approach to the synthesis of »Azacoumestrol« (*B*) derivatives.

The readily available 4-hydroxy-7-methoxy-2(1*H*)-quinolone (*1*)[9] reacts at room temperature in water with iodosobenzene or 3-chloro-4-methoxy--iodosobenzene, both generated *in situ* by the action of a sodium carbonate solution on the dichloro-iodobenzenes *2a, b* to give the iodonium-ylides *3a, b* in good yields. (The trichloro compound *2b* was prepared by the action of sulfuryl chloride on 4-iodo-anisole). Thermal rearrangement of *3a, b* in boiling *N,N*-dimethylformamide afforded the 3-iodo-4-phenoxy-2(1*H*)-quinolones *4a, b*. Reductive deiodination of *4a, b* with zinc dust and acetic acid in ethanol produced high yields of *5a, b*.



Photocyclization[8] of *5a* in the presence of one equivalent of iodine gave the benzofuro-quinolone *6a* in low yield. About the same yield (20%) could obtained using *4a* directly (without addition of iodine) after irradiation. Unfortunately, irradiation of *4b* did not produce any traces of compound *6b* (in principle the formation of two isomers with regard to R^2 are possible), which would have been a simple precursor for the free dihydroxy compound with potential estrogenic or antiestrogenic properties. In related papers[10,11] the presence of halogen and a change of the position of the oxygen function (from position 4 to 3) in bis(hydroxyphenyl)-ethanes brought about an increase in antiestrogenic activity. Furthermore, this type of compounds could also act as breast tumor imaging agents.[11] Therefore, we are presently planning another approach to structure *6b*.



Having at hand the readily available iodonium-ylides *3*, we performed some of their typical reactions[12] leading to compounds *7*—*9*. Thus, 3-haloquinolones *7a,b* were obtained by the reaction with hydrochloric or hydrobromic acid, respectively.[13] Acid catalyzed »trans-ylidation«[12] with triphenylphosphate yielded the phosphonium-ylid *8*,[14] and the reaction with pyridine or isoquinoline afforded the pyridinium-ylid *9a* or the isoquinolinium-ylid *9b*.[15] The latter two compounds could also be obtained by the heating of *7a* with pyridine or isoquinoline.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi-Tottoli melting point apparatus, melting points above 200 °C were determined using a hot metal block and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 421, the ^{1}H NMR spectra on a Varian EM-360 spectrometer with TMS as internal standard. Mass spectra were obtained with a Finnigan 4021 instrument.

2-Chloro-4-dichloroiodo-anisole (2b)

To a solution of 4.7 g (20 mmol) of 4-iodo-anisole in 5 ml of glacial acetic acid an excess of sulfuryl chloride (5 ml) was added all at once. The reaction mixture was left with constant stirring for one hour. The precipitation of *2b* was completed by adding 10 ml of petrol ether (b. p. 40—60 °C), yield 6.0 g (88%), m. p. 73 °C (dec.). The compound, which is stable in the refrigerator for only a few days, proved to be identical (TLC, IR, mixed m. p.) to a compound previously[16] obtained by the action of chlorine on 2-chlor-4-iodo-anisole in carbon tetrachloride.

Anal. $C_{16}H_{12}INO_3$ (393.19) calc'd.: C 48.87; H 3.08; N 3.56%
found: C 49.26; H 3.44; N 3.20%

3-(3-Chloro-4-methoxy-phenyliodonium)-7-methoxy-2-oxo-1,2--dihydroquinolin-4-olat (3b)

According to the previous procedure for *3a* using *2b*. Yield 49%, colorless crystals from 1-butanol, m. p. 192—193 °C.

Anal. $C_{17}H_{13}ClINO_3$ (457.65) calc'd.: C 44.62; H 2.86; N 3.06%
found: C 45.01; H 3.10; N 3.90%

3-Iodo-7-methoxy-4-phenoxy-2(1H)-quinolone (4a)

A solution of 1.0 g *3a* in 10 ml of DMF was heated under reflux for one hour. The solvent was removed *in vacuo* and the product recrystallized from acetic acid. Yield 0.90 g (90%), colorless prisms, m. p. 240—242 °C.

Anal. $C_{16}H_{12}INO_3$ (393.19) calc'd.: C 48.87; H 3.08; N 3.56%
found: C 48.69; H 3.10; N 3.38%

IR spectrum (KBr): 2150—2700(w), 1655(s), 1630(m), 1610(m), 1590(m), 1555(w) cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): 3.75 (s, CH_3), 6.5—7.7 (m, 8 ArH), 12.0 (s, NH).

4-(3-Chloro-4-methoxy-phenoxy)-3-iodo-7-methoxy-2(1H)-quinolone (4b)

According to the previous procedure for *4a* using *3b*. Yield 85%, colorless crystals, m. p. 222—223 °C.

Anal. $C_{17}H_{13}ClINO_4$ (457.65) calc'd.: C 44.62; H 2.86; N 3.06%
found: C 44.62; H 2.83; N 2.97%

7-Methoxy-4-phenoxy-2(1H)-quinolone (5a)

To the boiling solution of 1.97 g (5 mmol) of *4a* in a mixture of 20 ml of ethanol and 20 ml of acetic acid 0.5 g of zinc dust was added in small portions. Heating was continued for one hour and the obtained solution was filtered from the remaining zinc dust. The filtrate was evaporated *in vacuo* to a small volume and water added. Recrystallization from acetic acid afforded 1.15 g (86%) colorless crystals, m. p. 255—256 °C.

Anal. $C_{16}H_{13}NO_3$ (267.30) calc'd.: C 71.89; H 4.91; N 5.24%
found: C 71.79; H 4.92; N 5.16%

IR spectrum (KBr): 3160—2600(w), 1640(s), 1610(sh), 1580(m), 1560(w) cm^{-1}. ^{1}H NMR spectrum (DMSO-d_6): 3.80 (s, CH_3), 5.15 (s, 1H an C-3), 6.8 (m, 2 ArH), 7.2—7.6 (m, 5 ArH), 7.9 (d, $J = 7$ Hz, 1H an C-5), 11.5 (s, NH).

4-(3-Chloro-4-methoxy-phenoxy)-7-methoxy-2(1H)-quinolone (5b)

According to the previous procedure for *5a* using *4b*. Yield 84%, colorless needles from acetic acid, m. p. 262—263 °C.

Anal. $C_{17}H_{14}ClNO_4$ (331.74) calc'd.: C 61.55; H 4.25; Cl 10.69; N 4.22%
found: C 62.00; H 4.34; Cl 10.50; N 4.20%

MS spectrum, *m/e* (%): 333 (M^+ for ^{37}Cl, 24), 331 (M^+ for ^{35}Cl, 100), 316 (M^+—CH_3, 19), 297 (26), 174 (12), 149 (38), 119 (12), 62 (13).

3-Methoxy-5,6-dihydrobenzofuro[3.2-c]quinolin-6-one (6a)

a) A solution of 535 mg (2.0 mmol) of *5a* and 508 mg (2.0 mmol) iodine in 100 ml of benzene was irradiated with a high pressure mercury lamp (300 W) for 4 hours. The organic phase was decolorized with charcoal, washed with 100 ml 2% NaOH, and dried. The residue was crystallized from acetic acid, yielding 110 mg (20.6%) colorless prisms, m. p. 281—284 °C.

b) In the same manner irradiation of *4a*, but without addition of iodine, afforded a 18% yield of *6a*.

Anal. $C_{16}H_{11}NO_3$ (265.27) calc'd.: C 72.45; H 4.18; N 5.28%
found: C 72.03; H 4.10; N 4.99%

MS spectrum, *m/e* (%): 265 (M^+, 100), 237 (21), 149 (23). IR spectrum (KBr): 3200—2700(w), 1660(s), 1600(m), 1560(m) cm^{-1}.

3-Chloro-4-hydroxy-7-methoxy-2(1H)-quinolone (7a)

A suspension of 10 mmol of *3a* or *3b* in 5 ml of ethanol and 5 ml of conc. HCl is slowly heated to 80 °C. After cooling and addition of 50 ml of water the precipitate is collected by filtration. Yield 71%, colorless crystals from acetic acid., m. p. 262—263 °C.

Anal. $C_{10}H_8ClNO_3$ (225.64) calc'd.: C 53.23; H 3.58; Cl 15.71; N 6.21%
found: C 52.93; H 3.63; Cl 15.55; N 5.94%

IR spectrum (KBr): 3300—2700(m), 1630(vs, broad), 1600(s), 1550(m), 1520(m) cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 3.75 (s, CH_3), 6.6—6.75 (m, 2 ArH), 7.70 (d, $J = 9$ Hz, H an C-5), 11.7 (s, NH).

3-Bromo-4-hydroxy-7-methoxy-2(1H)-quinolone (7b)

According to the previous procedure for *7a*, using 8 ml of ethanol and 2 ml of 40% HBr. Yield 68%, colorless prisms from acetic acid, m. p. 208—210 °C.

Anal. $C_{10}H_8BrNO_3$ (270.10) calc'd.: C 44.45; H 2.97; Br 29.59; N 5.19%
found: C 43.98; H 2.59; Br 29.90; N 4.72%

^1H NMR spectrum (DMSO-d_6): 3.8 (s, CH_3), 6.6—6.8 (m, 2H at C-6 and C-8), 7.7 (d, $J = 9$ Hz, peri-H at C-5), 11.6 (s, NH).

7-Methoxy-2-oxo-3-triphenylphosphonium-1,2-dihydroquinolin-4-olate (8)

A solution of 5 mmol *3a* or *3b* and 5 mmol of triphenylphosphane was heated for 5 hours in 25 ml of methanol and 0.5 ml of acetic acid. The reaction mixture was evaporated to dryness and the residue crystallized from DMF, yielding 82% or 78%, respectively, of *8* in the form of colorless prisms, m. p. 290—291 °C.

Anal. $C_{28}H_{22}NO_3P$ (451.48) calc'd.: C 74.48; H 4.92; N 3.10%
found: C 74.20; H 4.81; N 3.30%

IR spectrum (KBr): 3200—2700(m), 1630/1615(s), 1585(vs), 1540(m), 1510(m) cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 3.7 (s, CH_3), 7.3—7.7 (m, 18 ArH).

7-Methoxy-2-oxo-3-(1-pyridinium)-1,2-dihydroquinolin-4-olate (9a)

a) A solution of 5 mmol *3a* or *3b* was heated with 50 ml of methanol, 1 ml of pyridine and 0.5 ml of acetic acid for 5 hours under reflux. After evaporation, the residue was crystallized form 1-butanol or acetic acid affording a 88% yield of *9a* in the form of yellow crystals, m. p. 300—301 °C.

b) A mixture of 5 mmol of *7a* and 2 ml of pyridine was heated under reflux for 12 hours, and evaporated to dryness. The residue was digested with 50 ml of water containing 0.5 g of sodium bicarbonate, filtered, washed with water and crystallized from 1-butanol. Yield 76%, yellow crystals, m. p. 300 °C.

Anal. $C_{15}H_{12}N_2O_3$ (268.30) calc'd.: C 67.15; H 4.52; N 10.44%
found: C 66.76; H 4.54; N 10.18%

IR spectrum (KBr): 3260—2900(m), 1615(vs), 1595(s), 1530(m) cm^{-1}. ^1H NMR spectrum (DMSO-d_6): 3.8 (s, CH_3), 6.65 (m, H-6 and H-8); 7.80 (d, $J = 7$ Hz, H-5), 8.05 (m, 2 β-PyrH), 8.40 (m, 1 γ-PyrH), 8.95 (dd, $J = 2 + 7$ Hz, 2 α-PyrH), 10.5 (s, NH).*

3-(2-Isoquinolinium)-7-methoxy-2-oxo-1,2-dihydroquinolin-4-olate (9b)

According to the previous procedures for *9a*, using *3a,b* or *7a*. Yields 92%, 90% or 71%, respectively. Yellow crystals, m. p. 275—276 °C (from DMF).

Anal. $C_{19}H_{14}N_2O_3 \cdot H_2O$ (336.40) calc'd.: C 67.84; H. 4.79; N 8.33%
found: C 67.40; H 4.78; N 8.19%

* This spectrum was recorded with a Varian XL-200 at 200 MHz.

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POVZETEK

Potencijalni nesteroidni estrogeni in antiestrogeni, I. Sinteze nekaterih derivatov 7-metoksi-2(1*H*)kinolona

Fatma A. A. El-Mariah in Thomas Kappe

Pri reakciji med 4-hidroksi-7-metoksi-2(1*H*)kinolonom in jodozobenzeni, katere pripravimo in situ iz ustreznih diklorojodo spojin, nastanejo jodonijevi ilidi z dobromi izkoristki. Po termični premestitvi nastanejo 3-jodo-4-ariloksikinoloni in po reduktivni odstranitvi joda dobimo ustrezne ariletre. Nekateri od te se pri fotociklizaciji pretvorijo v benzofurokinolone. Nekateri jodonijevi ilidi se pretvorijo z zmesjo trifenilfosfana, piridina in izokinolina v ustrezne *P*- in *N*-ilide.