

Synthesis of Hydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones

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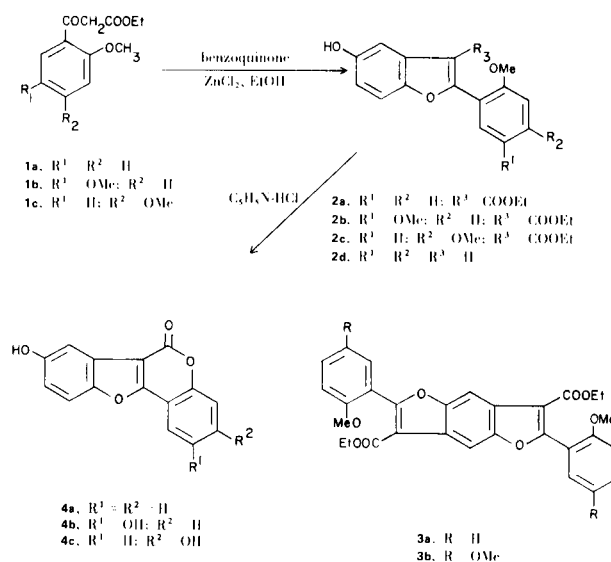
The Micheal addition of ethyl 2-methoxy-, 2,4-dimethoxy- and 2,5-dimethoxybenzoylacetates with benzoquinone leads to ethyl 2-(methoxy or dimethoxy phenyl)-5-hydroxybenzofuran 3-carboxylates. Treatment of the benzofuran derivatives with anhydrous pyridine hydrochloride at 190-195° leads to hydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones.

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Several methods have been used to synthesize the title compounds (coumestans), some of which occur in nature. 3,9-Dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestrol) occurs in some forage plants and has been reported to have estrogenic activity. Several analogs of naturally occurring coumestans have been prepared with the aim of finding compounds with estrogenic, antifungal or growth promoting activity (2,3).

The scheme shown below was used to synthesize 8-hydroxy-, 2,8-dihydroxy- and 3,8-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones. The synthesis of the 3,8-dihydroxy- compound represents a shortening of the published procedure which involved three reactions starting with 2,5-dihydroxybenzaldehyde and 2', 4'-bis(benzyloxy)-2-methoxyacetophenone (4).

Carbomethoxylation of the appropriate methoxy substituted acetophenone derivatives with diethyl carbonate-sodium hydride gave the substituted benzoylacetates (1*a-c*) which were characterized by forming their 3-substituted-1-phenyl-2-pyrazolin-5-one derivatives. Condensation of the benzoylacetates with benzoquinone in boiling alcoholic zinc chloride solution resulted in the formation of substituted ethyl 5-hydroxybenzofuran 3-carboxylates (2*a-c*). The formation of compounds 2*a* and 2*b* were accompanied by low yields of the benzo[1,2-*b*:4,5-*b'*]difurans 3*a* and 3*b*, respectively. Treatment of compounds 2*a-c* with anhydrous pyridine hydrochloride at 190-195° effected demethylation, ester hydrolysis and lactonization to afford 8-hydroxy-, 2,8-dihydroxy- and 3,8-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-ones (4*a-c*). Compound 4*a* was also prepared by treating compound 2*a* with boiling hydriodic-acetic acids. Also formed in the reaction was 5-hydroxy-2-(2-methoxyphenyl)benzofuran (2*d*) in low yield.



EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were determined on a Perkin Elmer IR 337. Mineral oil mulls were used for solid samples. Nmr spectra were determined on a Hitachi-Perkin Elmer R20B spectrometer with TMS as internal reference. Elemental analyses were performed both in the analytical unit of the Department of Chemistry and Atlantic Microlab, Inc.

Ethyl 2-Methoxybenzoylacetate (1*a*).

A mixture of 2'-methoxyacetophenone (47.0 g., 0.31 mole), sodium hydride (21.0 g. of 57% mineral oil dispersion) and 350 ml. of dry diethyl carbonate was refluxed for 5 hours. The mixture was cooled, poured into cold dilute hydrochloric acid and the organic phase separated. The aqueous layer was extracted with benzene, combined with the organic phase, dried (calcium chloride) and evaporated *in vacuo* to a pale orange liquid which was repeatedly washed with petroleum ether to remove the mineral oil. Vacuum

distillation afforded the ester as a faintly yellow liquid, b.p. 134-142°/0.3 mm (52%); ir: 1740 and 1670 cm^{-1} ; nmr (deuteriochloroform): δ 1.23 (t CH_3 , $J = 7.5$ Hz), 3.87 (s CH_3O), 3.93 (s CH_2), 4.13 (q CH_2 , $J = 7.5$ Hz) and 6.8-7.9 (m 4H).

Condensation of the β -keto ester with hydrazine in acetic acid afforded 3-(2-methoxyphenyl)-1-phenyl-2-pyrazolin-5-one as colorless needles, m.p. 133.5-134.0° (ethyl alcohol); lit. m.p. 133-134° (5).

Ethyl 2,5-Dimethoxybenzoylacetate (1b).

This compound, a pale yellow liquid, b.p. 162-172°/0.2 mm, was prepared in 63% yield by the condensation of 2',5'-dimethoxyacetophenone, diethyl carbonate and sodium hydride; ir: 1740 and 1665 cm^{-1} ; nmr (carbon tetrachloride): δ 1.20 (t CH_3 , $J = 7$ Hz), 3.72, 3.80 and 3.82 (s CH_2 and 2 CH_3O), 4.10 (q CH_2 , $J = 7$ Hz) and 6.8-7.4 (m 3H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_5$: C, 61.90; H, 6.39. Found: C, 61.76; H, 6.39.

Condensation of the β -keto ester with hydrazine in acetic acid afforded 3-(2,5-dimethoxyphenyl)-1-phenyl-2-pyrazolin-5-one as colorless needles, m.p. 140-141° (ethyl alcohol); ir: 1705 cm^{-1} ; nmr (deuteriochloroform): δ 3.73 (s 2 CH_3O), 3.84 (s CH_2) and 6.8-8.2 (m 8H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.46; N, 9.48.

Ethyl 2,4-Dimethoxybenzoylacetate (1c).

This compound, a pale yellow liquid, b.p. 160-172°/0.2 mm, was prepared in 51% yield by the condensation of 2',4'-dimethoxyacetophenone, diethyl carbonate and sodium hydride; ir: 1740 and 1670 cm^{-1} ; nmr (carbon tetrachloride): δ 1.22 (t CH_3 , $J = 7$ Hz), 3.82 and 3.84 (s 2 CH_3O), 3.87 (s CH_2), 4.21 (q 2H, $J = 7$ Hz), 6.4-6.7 (m, H-3 and H-5) and 7.85-8.05 (d of d, H-6).

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_5$: C, 61.90; H, 6.39. Found: C, 61.84; H, 6.50.

Condensation of the β -keto ester with hydrazine in acetic acid afforded 3-(2,4-dimethoxyphenyl)-1-phenyl-2-pyrazolin-4-one as pale yellow needles, m.p. 124-125° (ethyl alcohol); ir: 1700 cm^{-1} ; nmr (deuteriochloroform): δ 3.74 (s 2 CH_3O), 3.77 (s CH_2), 6.2-6.6 (m 2H), 6.9-7.5 (m 3H) and 7.8-8.1 (m 3H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.86; H, 5.45; N, 9.43.

Ethyl 5-Hydroxy-2-(2-methoxyphenyl)benzofuran-3-carboxylate (2a) and Diethyl 2,6-Bis(2-methoxyphenyl)benzo[1,2-b:4,5-b']-difuran-3,7-dicarboxylate (3a).

To a hot solution (oil bath at 85-90°) of 10.5 g. of anhydrous zinc chloride in 15 ml. of absolute ethyl alcohol was added dropwise a solution of ethyl 2-methoxybenzoylacetate (16.68 g., 0.075 mole) in 40 ml. of dry ether. The ether was removed by distillation. A solution of benzoquinone (8.07 g., 0.075 mole) in 250 ml. of dry ether was added dropwise with simultaneous distillation of the ether. The mixture was stirred and heated for 19 hours. After cooling, the brown paste was mixed with water, filtered, dried and dissolved in a large volume of hot benzene. The solution was partially evaporated to afford a tan powder (12.44 g., m.p. 169-172°) which was sublimed *in vacuo*. Recrystallization of the sublimate from benzene gave compound 2a (51%) as colorless crystals, m.p. 173-175°. The analytical sample had m.p. 175-176°; ir: 3340 and 1665 cm^{-1} ; nmr (deuteriochloroform): δ 1.14 (t CH_3 , $J = 7.5$ Hz), 6.19 (s OH) and 6.8-7.6 (m 7H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_5$: C, 69.22; H, 5.16. Found: C, 69.18; H, 5.33.

The brown benzene filtrate was evaporated to a small volume

and the solution chromatographed over silica gel. Elution with chloroform afforded the uv-fluorescent material, 3a, which was obtained as colorless spars after recrystallization from chloroform-ethyl alcohol, m.p. 193-194° (1.5%); ir: 1700 cm^{-1} ; nmr (deuteriochloroform): δ 1.27 (t 2 CH_3 , $J = 7.5$ Hz), 3.79 (s 2 CH_3O), 4.30 (q 2 CH_2 , $J = 7.5$ Hz), 6.85-7.7 (m 8H) and 8.03 (s 2H).

Anal. Calcd. for $\text{C}_{30}\text{H}_{26}\text{O}_8$: C, 70.03; H, 5.09. Found: C, 69.90; H, 5.13.

Further elution of the silica gel column with chloroform gave an additional 9% of compound 2a.

Ethyl 2-(2,5-Dimethoxyphenyl-5-hydroxybenzofuran-3-carboxylate (2b) and Diethyl 2,6-Bis(2,5-dimethoxyphenyl)benzo[1,2-b:4,5-b']difuran-3,7-dicarboxylate (3b).

Benzoquinone was condensed with compound 1b in alcoholic zinc chloride solution in the same manner as the condensation of compound 1a and benzoquinone. Compound 2b was obtained as colorless needles (39.6%), m.p. 163-164° (ethyl alcohol); ir: 3400 and 1685 cm^{-1} ; nmr (deuterioacetone): δ 1.22 (t CH_3 , $J = 7$ Hz), 3.77 and 3.82 (s 2 CH_3O), 4.26 (q CH_2 , $J = 7$ Hz), 6.8-7.5 (m 6H) and 8.38 (s OH).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_6$: C, 66.66; H, 5.30. Found: C, 66.71; H, 5.39.

The acetate derivative of compound 2b had m.p. 101.5-103° (ethyl alcohol); ir: 1760 and 1710 cm^{-1} ; nmr (deuteriochloroform): δ 1.27 (t CH_3 , $J = 7$ Hz), 2.22 (s CH_3CO), 3.75 and 3.81 (s 2 CH_3O), 4.32 (q CH_2 , $J = 7$ Hz) and 6.9-8.0 (m 6H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_7$: C, 65.62; H, 5.24. Found: C, 65.59; H, 5.34.

Compound 3b, colorless rods, m.p. 200-201° (chloroform-ethyl alcohol), was obtained as a uv-fluorescent material in 4.7% yield after chromatography over alumina (Alcoa F-20) and recrystallization; ir: 1695 cm^{-1} ; nmr (deuteriochloroform): δ 1.30 (t 2 CH_3 , $J = 7$ Hz), 3.80 (s 2 CH_3O), 3.86 (s 2 CH_3O), 4.36 (q 2 CH_2 , $J = 7$ Hz), 6.9-7.3 (m 6H) and 8.23 (s 2H).

Anal. Calcd. for $\text{C}_{32}\text{H}_{30}\text{O}_{10}$: C, 66.90; H, 5.16. Found: C, 66.71; H, 5.35.

Ethyl 2-(2,4-Dimethoxyphenyl)-5-hydroxybenzofuran-3-carboxylate (2c).

Condensation of benzoquinone with compound 1c in alcoholic zinc chloride solution afforded compound 2c in 20% yield as cream colored needles, m.p. 182-183° (ethyl alcohol), after sublimation *in vacuo* and recrystallization; ir: 3400 and 1680 cm^{-1} .

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_6$: C, 66.66; H, 5.30. Found: C, 66.44. H, 5.37.

8-Hydroxy-6H-benzofuro[3,2-c][1]benzopyran-6-one (4a).

Heating compound 2a with anhydrous pyridine hydrochloride at 190-195° for 40 minutes, followed by dilution with water, filtration and recrystallization, afforded compound 4a as needles (84%), m.p. 313-315° (methyl alcohol); ir: 3330 and 1690 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_8\text{O}_4$: C, 71.43; H, 3.20. Found: C, 71.42; H, 3.14.

The acetate derivative of compound 3a was obtained as pale yellow needles, m.p. 210-211° (methylene chloride); ir: 1730 cm^{-1} ; nmr (deuteriochloroform); δ 2.34 (s CH_3CO) and 7.9-8.0 (m 7H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{10}\text{O}_5$: C, 69.38; H, 3.43. Found: C, 69.59; H, 3.52.

2,8-Dihydroxy-6H-benzofuro[3,2-c][1]benzopyran-6-one (4b).

Heating compound 2b with anhydrous pyridine hydrochloride at 190-195° for 2.5 hours afforded compound 4b (59%) as a light

tan solid from acetic acid, m.p. $>325^{\circ}$ (partial sublimation $>280^{\circ}$); ir: 3300 and 1705 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_8\text{O}_4$: C, 67.17; H, 3.01. Found: C, 67.17; H, 3.03.

The diacetate of compound **4b** was obtained as off-white crystals, m.p. $238\text{--}240^{\circ}$ (chloroform-ethyl alcohol); ir: 1750 cm^{-1} (broad); nmr (deuteriochloroform): δ 2.38 (s 2 CH_3CO) and 7.1-7.9 (m 6H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{12}\text{O}_7$: C, 64.77; H, 3.44. Found: C, 64.52; H, 3.28.

3,8-Dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (**4c**).

Heating compound **2c** with anhydrous pyridine hydrochloride at $190\text{--}195^{\circ}$ for one hour afforded compound **4c** (55%) as a light tan powder from diethylformamide, m.p. $>330^{\circ}$ (partial sublimation $>285^{\circ}$). Lit. m.p. $>350^{\circ}$ (**4a**); ir: 3300 and 1720 cm^{-1} .

The diacetate of compound **4c** was obtained as colorless needles, m.p. $258\text{--}260^{\circ}$ (chloroform-ethyl alcohol); ir: 1750 and 1730 cm^{-1} ; lit. m.p. $243\text{--}244^{\circ}$ (**4b**), 253° (**4a**).

5-Hydroxy-2-(2-methoxyphenyl)benzofuran (**2d**).

Compound **2a** (3.85 g.), acetic acid (50 ml.) and 30 ml. of 47% hydriodic acid were heated at 120° for 2 hours. The cooled mixture was diluted with water, filtered, and the solid recrystallized from methyl alcohol to afford compound **3a** (1.20 g.). Evaporation

of the methanolic filtrate almost to dryness gave 0.53 g. of material which partially sublimed at $110\text{--}115^{\circ}/0.05\text{ mm}$. The sublimation residue was recrystallized from benzene to afford 5.4% starting material. The sublimate (0.20 g., m.p. $118\text{--}123^{\circ}$) was twice recrystallized from carbon tetrachloride and twice sublimed *in vacuo* to yield compound **2d** with m.p. $127\text{--}129^{\circ}$; ir: 3350 cm^{-1} ; nmr (deuterioacetone): δ 4.03 (s CH_3O) and 6.7-8.2 (m 9H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.99; H, 5.03. Found: C, 74.74; H, 5.10.

REFERENCES AND NOTES

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