Notes

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Benzocoumarins of Steroid-like Structure

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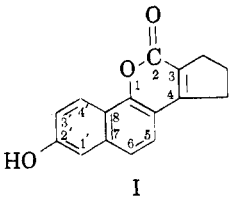
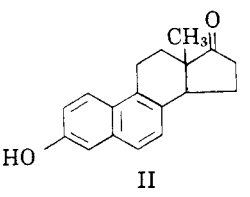
Steroid molecules play an essential role in a wide variety of chemical processes of life, ranging from the control of various endocrine functions and biochemical morphogenesis[1] to the production of cancers. A well-known means of counteracting the effect of hormones and vitamins is to introduce into the body substances with molecular structures similar to those of the hormones or vitamins, but with different biological properties, in order that they may compete with normal metabolites for fixation by the cell receptors. Important steroid metabolites are the estrogens, which are considered as direct or indirect promoters of various cancers; and in view of the growth-inhibiting effects of coumarin on certain tissues,[2] estrogen analogs bearing a coumarin nucleus have been synthesized for biological testing as potential carcinostatic drugs.[3]

1,6-Dihydroxynaphthalene readily condensed with ethyl cyclopentanone-2-carboxylate in ethanol solution in the presence of hydrogen chloride to give 2′-hydroxy-3,4-trimethylene-7,8-benzocoumarin (I) which resembles the natural estrogen equilenin (II)

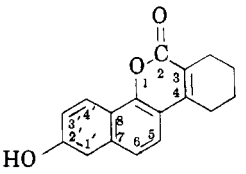


I

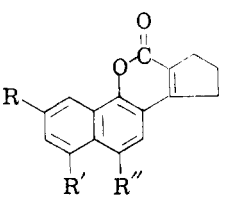


II

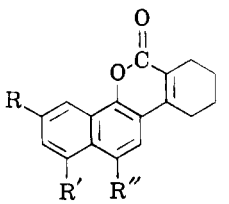
both in molecular shape and in the position of the hydroxyl group. Similar condensation with ethyl cyclohexanone-2-carboxylate afforded 2′-hydroxy-3,4 - tetramethylene - 7,8 - benzocoumarin (III). Under the same conditions, 3′-hydroxy-3,4-trimethylene-(IV) and 3′-hydroxy-3,4-tetramethylene-7,8-benzocoumarin (VII) were obtained from 1,7-dihydroxynaphthalene. The constitution of these four coumarins was deduced from the known fact that α-naphthol reacts with β-keto esters far more easily than does β-naphthol,[4] especially when a weak condensation catalyst such as hydrogen chloride is used. Moreover, 2,6-dihydroxynaphthalene failed to give benzocoumarins with β-keto esters under similar conditions. The same argument applies to naphthoresorcinol (1,3-dihydroxynaphthalene), whose condensation-product with ethyl cyclopentanone-2-carboxylate must have been 5-hydroxy-3,4-trimethylene-7,8-benzocoumarin; with ethyl acetoacetate, 5-hydroxy-4-methyl-7,8-benzocoumarin (X) was obtained.



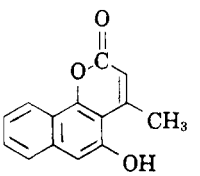
III



IV; R = OH, R′ = R″ = H
V; R′ = OH, R = R″ = H
VI; R″ = OH, R = R′ = H



VII; R = OH, R′ = R″ = H
VIII; R′ = OH, R = R″ = H
IX; R″ = OH, R = R′ = H



X

1,5- and 1,4-Dihydroxynaphthalene condensed with only one molecule of ethyl cyclopentanone- and ethyl cyclohexanone-2-carboxylate to give the corresponding benzocoumarins V, VI, VIII, and IX; cyclic β-keto esters thus behaved like ethyl acetoacetate, which Robinson and Weygand[5] found to react with 1,5-dihydroxynaphthalene in equimolecular amount in the presence of hydrogen chloride. Benzocoumarins V and VIII were also obtained from demethylation with pyridine hydrochloride of their methyl ethers, prepared from 1-hydroxy-5-methoxynaphthalene. From 1-hydroxy-8-methoxynaphthalene, 4′-methoxy-3,4-trimethylene- and 4′-methoxy-3,4-tetramethylene-7,8-benzo-

(1) *Cf.* Needham, *Biochemistry and Morphogenesis*, 2nd Edition, Cambridge University Press, 1950.

(2) Kuhn, Jerchel, Moewus, and Möller, *Naturwissenschaften*, **31**, 468 (1943); Veldstra and Havinga, *Enzymologia*, **11**, 373 (1945).

(3) For experimental inhibition of the carcinogenic activity of hydrocarbons by similarly built inactive polycyclic molecules, see Lacassagne, Buu-Hoï, and Rudali, *Brit. J. Exptl. Pathol.*, **26**, 5 (1945); Kotin, Falk, Lijinsky, and Zechmeister, *Science*, **123**, 102 (1956).

(4) Appel, *J. Chem. Soc.*, 1031 (1935).

(5) Robinson and Weygand, *J. Chem. Soc.*, 386 (1941); Shamshurin, *J. Gen. Chem. U.S.S.R.*, **14**, 885 (1944).

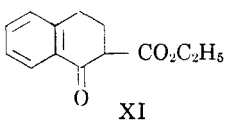
TABLE I

NEW 7,8-BENZOCOUMARINS

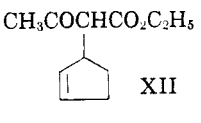
-7,8-Benzocoumarin	No.	Formula	M.P., °C.	Analyses Calc'd C	Calc'd H	Found C	Found H
2'-Hydroxy-3,4-tetramethylene-	III	$C_{17}H_{14}O_3$	330	76.7	5.3	76.6	5.1
3'-Hydroxy-3,4-trimethylene-	IV	$C_{16}H_{12}O_3$	294	76.2	4.8	75.9	4.8
3'-Hydroxy-3,4-tetramethylene-	VII	$C_{17}H_{14}O_3$	311	76.7	5.3	76.5	5.1
3'-Hydroxy-4-methyl-		$C_{14}H_{10}O_3$	285	74.3	4.5	74.0	4.3
1'-Hydroxy-3,4-trimethylene-	V	$C_{16}H_{12}O_3$	341	76.2	4.8	76.0	5.0
1'-Hydroxy-3,4-tetramethylene-	VIII	$C_{17}H_{14}O_3$	304	76.7	5.3	76.4	5.1
6-Hydroxy-3,4-trimethylene-	VI	$C_{16}H_{12}O_3$	206	76.2	4.8	76.0	4.7
6-Hydroxy-3,4-tetramethylene-	IX	$C_{17}H_{14}O_3$	216	76.7	5.3	76.4	5.5
1'-Methoxy-3,4-trimethylene-		$C_{17}H_{14}O_3$	171	76.7	5.3	76.6	5.3
1'-Methoxy-3,4-tetramethylene-		$C_{18}H_{16}O_3$	164	77.1	5.8	77.0	5.6
4'-Methoxy-3,4-trimethylene-		$C_{17}H_{14}O_3$	252	76.7	5.3	77.0	5.5
4'-Methoxy-3,4-tetramethylene-		$C_{18}H_{16}O_3$	188	77.1	5.8	77.3	5.7
5-Hydroxy-4-methyl-	X	$C_{14}H_{10}O_3$	298	74.3	4.5	74.3	4.2

coumarin were likewise readily prepared and dealkylated.

Despite the ease of the above syntheses, the hydrogen chloride-catalyzed condensation of cyclic β-keto esters with dihydroxynaphthalenes to benzocoumarins was not successful in every instance. Thus, ethyl 1-keto-1,2,3,4-tetrahydronaphthalene-2-carboxylate (XI) failed to condense with any of the dihydroxynaphthalenes tried. Nor did ethyl α-Δ^2-cyclopentenylacetoacetate (XII) (prepared



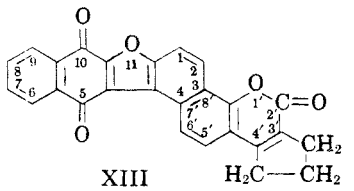
XI



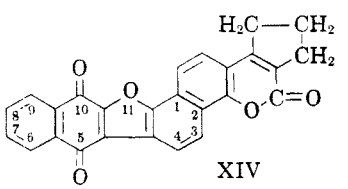
XII

by alkylation of the sodio derivative of ethyl acetoacetate with Δ^2-cyclopentenyl bromide) react with 1,5-dihydroxynaphthalene.

2'-Hydroxy-3,4-trimethylene-7,8-benzocoumarin (I), being a β-naphthol with a free adjacent α-position, reacted with one molecule of 2,3-dichloro-1,4-naphthoquinone in pyridine medium to give a furan



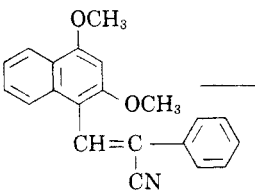
XIII



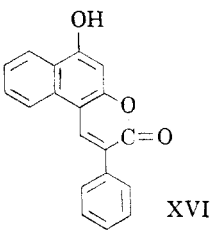
XIV

derivative,[6] 3',4'-trimethylenecoumarino(7',8'-4,-3)brasan-5,10-quinone (XIII), and a similar compound was obtained from coumarin III. From coumarin V, which is an α-naphthol with a free adjacent β-position, 3',4'-trimethylenecoumarino-(7',8'-1,2)brasan-5,10-quinone (XIV) was prepared. These furoquinones represent new types of oxygen-containing heterocycles, with the properties of vat-dyes.

In the course of this work, attention was paid to the chemistry of 1,3-dihydroxynaphthalene. This compound could be readily dialkylated with dimethyl sulfate in aqueous sodium hydroxide to give 1,3-dimethoxynaphthalene, without any appreciable C-methylation. Formylation of this diether with dimethylformamide afforded 2,4-dimethoxy-1-naphthaldehyde; 1-phenyl-2-(2,4-dimethoxy-1-naphthyl)acrylonitrile (XV), prepared by an alkali-



XV



XVI

catalyzed condensation of this aldehyde with benzyl cyanide, was readily converted by pyridine hydrochloride[7] to 7-hydroxy-3-phenyl-5,6-benzocoumarin (XVI).

EXPERIMENTAL

2'-Hydroxy-3,4-trimethylene-7,8-benzocoumarin (I). In a water-cooled solution of 40 g. of 1,6-dihydroxynaphthalene and 58 g. of ethyl cyclopentanone-2-carboxylate in 400 ml. of ethanol, dry hydrogen chloride was bubbled for 3 hours, and the mixture was kept overnight at room temperature. The precipitate which formed was collected, washed with cold ethanol, dried, and recrystallized from nitrobenzene (charcoal), giving shiny, green-tinged, sublimable needles, m.p. 333° (yield, 90–95%). This compound dissolved in aqueous alkalis to give greenish-yellow solutions.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 76.0; H, 4.7.

The other hydroxylated benzocoumarins, listed in Table I, were prepared in the same way and with similar yields.

(6) *Cf.* Buu-Hoï, *J. Chem. Soc.*, 489 (1952); Buu-Hoï and Demerseman, *J. Chem. Soc.*, 4699 (1952).

(7) *Cf.* Buu-Hoï and Lavit, *J. Org. Chem.*, 21, 21 (1956).

The methoxybenzocoumarins were also prepared according to the same procedure, except that they were precipitated from their ethanol solution by means of water, and were recrystallized from ethanol or benzene.

3',4'-Trimethylenecoumarino(7',8'-4,3)brasan-5,10-quinone (XIII). To a solution of 1.5 g. of 2'-hydroxy-3,4-trimethylene-7,8-benzocoumarin in 100 ml. of dry pyridine, 1.4 g. of 2,3-dichloro-1,4-naphthoquinone was added, and the mixture was refluxed for 30 minutes. After cooling, the brown precipitate was collected, washed first with ethanol then with water, dried, and recrystallized from nitrobenzene, giving brown-red sublimable needles (70–75% yield) which did not melt below 360°, and gave a deep violet halochromy in sulfuric acid.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.5; H, 3.2.

3',4' - Tetramethylenecoumarino(7',8' - 4,3)brasan - 5,10 quinone, similarly prepared from 2'-hydroxy-3,4-tetramethylene-7,8-benzocoumarin, crystallized from nitrobenzene in brown-red sublimable needles, m.p. above 360°, giving a deep violet halochromy in sulfuric acid.

Anal. Calc'd for $C_{27}H_{16}O_5$: C, 77.1; H, 3.8. Found: C, 76.8; H, 3.6.

3',4'-Trimethylenecoumarino(7',8'-3,4)brasan-5,10-quinone crystallized from nitrobenzene in dark brown needles, which sublimed to brown-red microcrystals, m.p. above 360°. The coloration in sulfuric acid was likewise a deep violet.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.6; H, 3.2.

3',4'-Trimethylenecoumarino(7',8'-1,2)brasan-5,10-quinone (XIV). This compound crystallized from nitrobenzene in brown needles, m.p. above 360°; its brown-violet halochromy in sulfuric acid was markedly different from that of the above quinones.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.7; H, 3.3.

Ethyl α-Δ²-cyclopentenylacetoacetate (XII). This compound, prepared in 40% yield from the hydrogen chloride adduct with cyclopentadiene, and the sodio derivative of ethyl acetoacetate in toluene medium, was a pale yellow liquid, b.p. 125–126°/13 mm., n_D^{24} 1.4653.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.0; H, 8.5.

A cooled solution of 1.5 g. of 1,5-dihydroxynaphthalene and 2 g. of this keto ester in 100 ml. of acetic acid was saturated with hydrogen chloride, and left to stand for 24 hours at room temperature. On dilution with water, 1,5-dihydroxynaphthalene was recovered unchanged. The use of sulfuric acid as condensing agent was also unsuccessful. Ethyl 1-keto-1,2,3,4-tetrahydronaphthalene-2-carboxylate likewise failed to react.

1,3-Dimethoxynaphthalene. This compound (6 g.), prepared from 8 g. of 1,3-dihydroxynaphthalene, 60 ml. of 10% aqueous potassium hydroxide, and 15 g. of dimethyl sulfate, was a pale yellow, viscous oil, b.p. 172–173°/12 mm.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.7; H, 6.4.

The *picrate* crystallized from ethanol in brown-red needles, m.p. 141°.

Anal. Calc'd for $C_{18}H_{15}N_3O_9$: C, 51.8; H, 3.6. Found: C, 51.8; H, 3.3.

2,4-Dimethoxy-1-naphthaldehyde. A mixture of 5.5 g. of 1,3-dimethoxynaphthalene, 2.8 g. of dimethylformamide, 5.1 g. of phosphorus oxychloride, and 5 ml. of dry toluene was heated for 3 hours on a boiling water-bath. A saturated aqueous solution of sodium hydroxide was added, and the mixture was refluxed for 30 minutes. The reaction product was taken up in toluene, and the toluene solution was washed with hydrochloric acid, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield, 2.8 g. of an aldehyde, b.p. 215–235°/13 mm., crystallizing from ethanol in shiny, colorless needles, m.p. 165°, giving a yellow coloration in sulfuric acid.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 71.9; H, 5.2.

The corresponding thiosemicarbazone crystallized from ethanol in pale yellow needles, m.p. 220° (decomp. above 206°).

1-Phenyl-2-(2,4-dimethoxy-1-naphthyl)acrylonitrile (XV). A solution of equimolar amounts of the foregoing aldehyde and benzyl cyanide in warm ethanol was shaken with a few drops of 20% aqueous sodium hydroxide. After addition of water, the precipitate formed was recrystallized from ethanol, giving pale yellow needles, m.p. 151°.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4. Found: C, 80.1; H, 5.6.

7-Hydroxy-3-phenyl-5,6-benzocoumarin (XVI). A mixture of one part of the foregoing nitrile and five parts of redistilled pyridine hydrochloride was refluxed for 10 minutes. Water was added, and the precipitate which formed was recrystallized from benzene, giving pale yellow needles, m.p. 289°, soluble in aqueous sodium hydroxide to give green solutions.

Anal. Calc'd for $C_{19}H_{12}O_3$: C, 79.2; H, 4.2. Found: C, 793.; H, 4.1.

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D-Bis-(*p*-dimethylaminoisopropylphenyl)-carbodiimide

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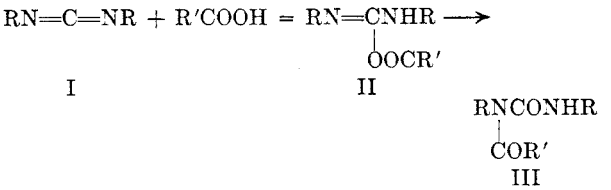
In general, carbodiimides react with carboxylic acids in two ways:[1]

(1) attachment of a proton followed by the attack of the acid anion to form acylurea III:



(2) formation of the urea IV and the acid anhydride:

$$I + 2R'COOH = \underset{IV}{RNHCONHR} + (R'CO)_2O$$

The product depends not only on the structure of both reactants but also on the solvent and the temperature. From a study of a large number of carbodiimides, bis-(*p*-dimethylaminophenyl)carbodiimide (V) and bis-(*p*-tolyl)carbodiimide (VI) have been found to react almost exclusively according to (1) and are therefore suggested as the most suitable reagents for the characterization of carboxylic acids.[2]

(1) H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953).
(2) F. Zetzsche and A. Fredrich, *Ber.*, **73**, 1114 (1940).