matographic analysis of the resulting hydrocarbons on a DEGS column showed the mixture to contain the same products in the same ratio as obtained from dichloromethylation of indane. Hydrogenation of the recrystallized dibromomethylindane and vapor phase chromatographic analysis showed it to be at least 95% pure and consisting of the same hydrocarbon derived from 5,6-dichloromethylindane.

Indane-5,6-dicarboxaldehyde.—5,6-Dibromomethylindane, 21 g. (0.069 mole), was added to a solution of sodium 2-nitropropionate prepared by dissolving sodium metal, 3.1 g. (0.135 g.-atom) in 300 ml. of absolute ethanol and then adding 2-nitropropane, 12.2 g. (0.141 mole). The mixture was shaken vigorously from time to time and the temperature was controlled so that it did not exceed 25°. After 12 hr. the reaction mixture, which had turned bright yellow, was concentrated to an oil on a rotary evaporator, the temperature again being maintained below 25°. The solid–oil residue was extracted first with 100 ml. of ether, and then the remaining solid with 500 ml. of water. The two solutions were placed in a separatory funnel and the aqueous layer was withdrawn. The ether solution was then washed with 100 ml. of a 1% sodium hydroxide solution, concentrated to *ca.* 20 ml., and extracted with a 40% solution of sodium bisulfite. Addition of formaldehyde (34% aqueous solution) caused the separation of a yellow oil which was taken up in ether. Evaporation of the ether gave a yellow oil which crystallized from ligroin as yellow needles, 2.39 g. (19.8%), m.p. 50.5–52.5°.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.70; H, 5.82. Found: C, 75.63; H, 5.85.

Indano[5′,6′-4,5]-2,7-dicarboethoxytropone.—Indane-5,6-dialdehyde, 1.78 g. (0.01 mole), and diethyl acetonedicarboxylate 2.02 g. (0.01 mole, Aldrich), were dissolved in 40 ml. of 95% ethanol. Diethylamine, 2 drops, was added, causing the solution to warm slightly. After *ca.* 20 min., crystals started to precipitate. The reaction mixture was allowed to stand for 14 hr. and then concentrated to *ca.* 20 ml. with an air stream. The crystals were collected on a filter and washed with a few milliliters of 95% ethanol to give 0.585 g. Concentration of the mother liquor to an oil and chromatography on alumina (Merck neutral) using 50:50 benzene–ligroin gave an additional crystalline product which was recrystallized from 95% ethanol to give an additional 0.510 g. of tropone derivative (total 1.095 g., 32%). Recrystallization from 95% ethanol gave pale yellow needles: m.p. 176–177.5°; ultraviolet spectrum in 95% ethanol, 282 (ε 47,400) and 246 mμ (28,200).

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.51; H, 6.23.

Work-up of the mother liquor of the initial recrystallization after chromatography, by concentration, and cooling produced 0.456 g. (8.5%) of the bis adduct as white prisms, m.p. 143–145.5°.

Anal. Calcd. for $C_{29}H_{34}O_{19}$: C, 64.19; H, 6.32. Found: C, 64.33; H, 6.30.

1′-Bromoindano[5′,6′-4,5]-2,7-dicarboethoxytropone.—Indano-[5′,6′-4,5]-2,7-dicarboethoxytropone, 400 mg. (1.17 mmoles), N-bromosuccinimide, 220 mg. (1.24 mmoles), and azobisisobutyronitrile, 2 mg., were added to 8 ml. of carbon tetrachloride. After the mixture had been refluxed for 20 min., succinimide was floating at the surface. The succinimide was filtered off. Cooling of the resulting solution produced a white crystalline precipitate, 341 mg. (69%), which was satisfactory for further reaction. Recrystallization from carbon tetrachloride gave white needles: m.p. 150–152°; ultraviolet spectrum in 95% ethanol, 283 (ε 43,200) and 249 mμ (26,200).

Anal. Calcd. for $C_{20}H_{19}BrO_5$: C, 57.29; H, 4.57; Br, 19.06. Found: C, 57.07; H, 4.66; Br, 19.96, 19.73.

Indeno[5′,6′-4,5]-2,7-dicarboethoxytropone.—1-Bromoindane-[5′,6′-4,5]-2,7-dicarboethoxytropone, 275 mg. (0.656 mmole) was dissolved in a suspension of 2 g. of sodium iodide in 15 ml. of N,N-dimethylformamide and allowed to stand at room temperature for 36 hr. under nitrogen. During this time the solution had turned red-orange. The reaction mixture was diluted with 25 ml. of chloroform and then 50 ml. of distilled water was added. The chloroform layer was separated and again washed with 50 ml. of water. After the chloroform solution had been dried with magnesium sulfate it was evaporated down to give a brown-red solid residue. This solid was recrystallized from 95% ethanol to give orange plates, 82 mg. (36%). A second recrystallization from 95% ethanol gave pale yellow plates: m.p. 165.5–168°; ultraviolet spectrum in 95% ethanol, 286 (ε 37,600), 255 (27,800), and 248 mμ (27,500). Attempts to obtain carbon and hydrogen analyses gave erratic results indicating carbon values *ca.* 1% too low. These results are attributed to the decomposition referred to in the discussion. When this compound was treated with hydrogen and palladium-on-carbon catalyst, 2.89 moles of hydrogen were absorbed. This hydrogenation product was identical with that obtained by hydrogenation of indano-[5′,6′-4,5]dicarboethoxytropone, which was verified by identical infrared spectra and mixture melting point determination.

Acknowledgment.—The author wishes to express his indebtedness to the National Science Foundation for Grant NSF GP 758 which supported this work.

Anthocyanins and Related Compounds. IV. The Synthesis of Coumestrol and Related Coumarinobenzofurans from Flavylium Salts

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Received May 19, 1964

Coumestrol and related coumarinobenzofurans have been synthesized by hydrogen peroxide oxidation of appropriately substituted 2′-hydroxy-3-methoxyflavylium salts.

Following the structural elucidation[2] of wedelolactone I in 1957, a number of phenolic coumarinobenzofuran derivatives have been identified in plant extracts. However, with the exception of the elegent wedelolactone synthesis recently described by Wanzlick and coworkers,[2] a satisfactory, generally applicable, synthetic route to these phenolic and partially O-alkylated coumarinobenzofurans has not previously been developed.[3]

Coumestrol, a constituent of alfalfa and other forage crops,[4] is of particular interest because of its estrogenic properties.[5] In a preliminary communication[6] a synthesis of coumestrol from 2′,4′,7-trihydroxy-3-methoxyflavylium chloride (II) was reported briefly. This flavylium salt, oxidized with hydrogen peroxide in

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) T. R. Govindachari, K. Nagarajan, B. R. Pai, and P. C. Parthasarathy, *J. Chem. Soc.*, 545 (1957); (b) H. W. Wanzlick, R. Gritzky, and H. Heidepriem, *Chem. Ber.*, **96**, 305 (1963).

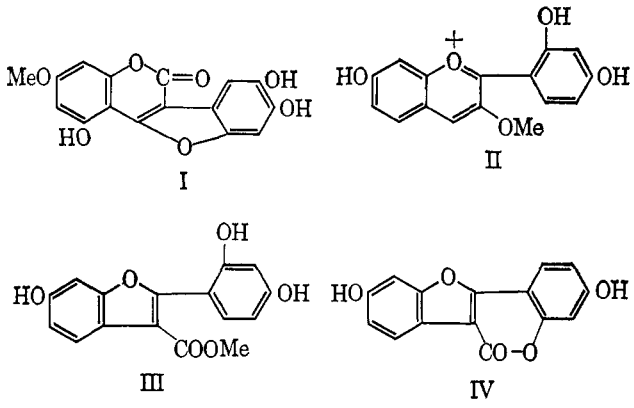
(3) For representative synthetic approaches, see T. R. Govindachari, K. Nagarajan, and P. C. Parthasarathy, *J. Chem. Soc.*, 548 (1957); O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958); C. Deschamps-Vallet and C. Mentzer, *Compt. rend.*, **251**, 736 (1960); Y. Kawase, *Bull. Chem. Soc. Japan*, **32**, 690 (1959), *Chem. Abstr.*, **56**, 1437 (1962).

(4) E. M. Bickoff, R. L. Lyman, A. L. Livingston, and A. N. Booth, *J. Am. Chem. Soc.*, **80**, 3969 (1958).

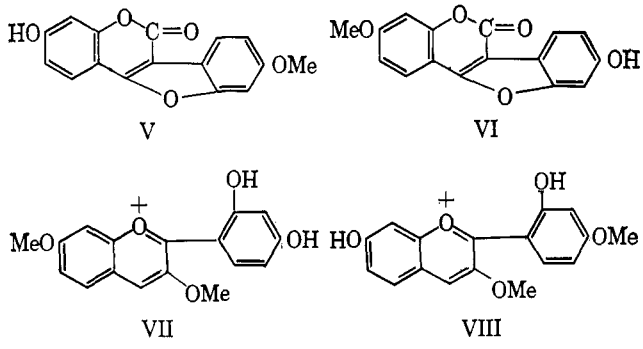
(5) E. M. Bickoff, A. L. Livingston, and A. N. Booth, *Arch. Biochem. Biophys.*, **88**, 262 (1960).

(6) L. Jurd, *Tetrahedron Letters*, **No. 18**, 1151 (1963).

aqueous methanol, gives the 3-carbomethoxybenzofuran III which rapidly lactonizes on acidification to coumestrol (IV, 50% yield). 4′-O-Methylcoumestrol (V) and 7-O-methylcoumestrol (VI), previously prepared only from coumestrol by selective alkylation techniques,[7] have now been synthesized by a similar oxidation of 2′,4′-dihydroxy-3,7-dimethoxyflavylium chloride[5] (VII) and 2′,7-dihydroxy-3,4′-dimethoxyflavylium chloride (VIII). The orientation of methoxyl and hydroxyl groups in these two important monomethyl derivatives, formerly assigned on the basis of ultraviolet spectral shifts, has thus been confirmed unequivocally.

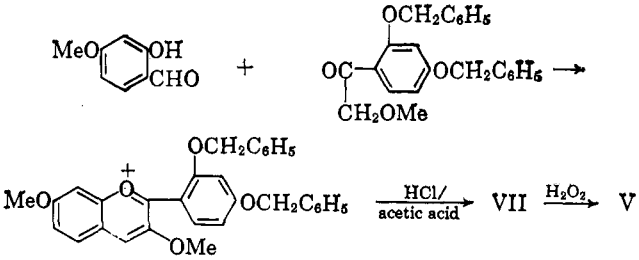


I II III IV



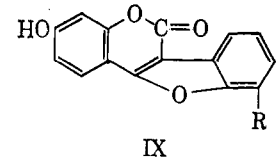
V VI VII VIII

The 2′-hydroxyflavylium salts required in this oxidation process are readily prepared by acid condensation of appropriate *o*-hydroxybenzaldehydes with ω-methoxy-2-benzyloxyacetophenones. Protective benzyl groups in the resulting 2′-benzyloxyflavylium salts are subsequently hydrolyzed to yield 2′-hydroxyflavylium salts.



Attempts to condense the *o*-hydroxy aldehydes directly with ω-methoxy-2,4-dihydroxyacetophenone without protecting the 2-hydroxyl group of the acetophenone gave highly colored, unidentified compounds which were not, however, the desired flavylium salts. This behavior has been noted[8] in the acid condensation of other *o*-hydroxyacetophenones. An exception to this generalization was observed in the present case with salicylaldehyde. This condensed "normally" with ω-methoxy-2,4-dihydroxyacetophenone to yield chiefly 3-methoxy-2′,4′-dihydroxyflavylium chloride.

In the course of this investigation the coumarinobenzofurans IX (R = MeO– and R = H) were prepared by oxidation and subsequent debenzylation of 3,8-dimethoxy-2′,4′-dibenzyloxyflavylium chloride and 3-methoxy-2′,4′-dibenzyloxyflavylium chloride, respectively. The benzofuran IX (R = H) was recently



IX

synthesized by Govindachari[9] but as indicated in the Experimental section there are some discrepancies in the properties of his product and that obtained by the above oxidation process.

Experimental

ω-Methoxy-2,4-dibenzyloxyacetophenone.—A mixture of ω-methoxyresacetophenone[10] (30 g.), benzyl chloride (70 ml.), potassium iodide (15 g.), anhydrous potassium carbonate (60 g.), and acetone (400 ml.) was heated under reflux for 5 hr. and filtered. The filtrate was concentrated to an oil which crystallized on addition of Skellysolve F. Recrystallized from methanol, ω-methoxy-2,4-dibenzyloxyacetophenone separated as colorless prisms, m.p. 103–104°, which did not give a color with alcoholic ferric chloride (49 g.).

Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.2; H, 6.12. Found: C, 76.2; H, 6.16.

7-Hydroxy-3-methoxy-2′,4′-dibenzyloxyflavylium Chloride. A solution of 2,4-dihydroxybenzaldehyde (5.8 g.) and ω-methoxy-2,4-dibenzyloxyacetophenone (15.1 g.) in warm ethyl acetate (100 ml.) was diluted with ether (300 ml.), cooled in an ice bath, and saturated with hydrogen chloride gas for 20 min. On scratching, the flavylium salt began to crystallize. The mixture was kept at 0° overnight and the flavylium salt was then collected (22 g.). Recrystallized from glacial acetic acid–ether, 7-hydroxy-3-methoxy-2′,4′-dibenzyloxyflavylium chloride separated as orange-red prisms: m.p. 217–218°; $\lambda_{max}^{EtOH-0.5\% HCl}$ 499, 267, and 241 mμ.

7,2′,4′-Trihydroxy-3-methoxyflavylium Chloride (II).—The above dibenzyloxyflavylium salt (64 g.) was heated to boiling with glacial acetic acid (420 ml.) and treated with concentrated hydrochloric acid (420 ml.). The mixture was heated for 1 hr. on the steam bath, diluted to 2.5 l. with 10% aqueous HCl, and cooled. A layer of benzene (200 ml., to dissolve benzyl chloride) was added and the crude flavylium salt was collected (41 g.). The crude flavylium salt (24 g.) was digested with methanol (250 ml.) containing 10% aqueous HCl (50 ml.). The undissolved, pure 7,2′,4′-trihydroxy-3-methoxyflavylium chloride was collected (17.0 g.). The filtrate was concentrated and cooled, whereupon a second crop (4.0 g.) of the flavylium salt was obtained. Recrystallized from aqueous methanolic HCl II separated as carmine red needles: $\lambda_{max}^{EtOH-0.5\% HCl}$ 508, 282, 263, and 240 mμ (log ε 4.66, 4.04, 4.02, and 4.35); R_f 0.74 (formic acid–3*N* HCl, 1:1), 0.75 (water–acetic acid–concentrated HCl, 80:40:5).

Coumestrol.—Oxidation of the above flavylium salt (II, 10 g.) as previously described[6] gave coumestrol (4.18 g.) as a yellow, crystalline powder, m.p. >350°. It was chromatographically, estrogenically, and spectrally[7] identical with an authentic specimen of the natural estrogen.

Anal. Calcd. for $C_{15}H_8O_5$: C, 67.1; H, 3.01. Found: C, 67.0; H, 3.21.

(7) L. Jurd, *J. Org. Chem.*, **24**, 1786 (1959).

(8) E. H. Charlesworth, J. J. Chavan, and R. Robinson, *J. Chem. Soc.*, 370 (1933).

(9) T. R. Govindachari, K. Nagarajan, and P. C. Parthasarathy, *Tetrahedron*, **15**, 129 (1961).

(10) W. K. Slater and H. Stephen, *J. Chem. Soc.*, **117**, 309 (1920).

The diacetate of the product separated from tetrahydrofuran–methanol as colorless needles, m.p. 229–230°, undepressed on admixture with coumestrol diacetate. Chromatographically and spectrally, the acetates were identical.

Anal. Calcd. for $C_{18}H_{12}O_7$: C, 64.8; H, 3.43; $2CH_3CO$–, 24.4. Found: C, 64.7; H, 3.47; CH_3CO–, 24.5.

3,7-Dimethoxy-2′,4′-dihydroxyflavylium Chloride (VII).—A solution of 4-O-methylresorcylaldehyde (3.04 g.) and ω-methoxy-2,4-dibenzyloxyacetophenone (7.24 g.) in ethyl acetate (50 ml.) and ether (200 ml.), saturated with HCl gas for 20 min. and kept at 0° overnight, deposited 3,7-dimethoxy-2′,4′-dibenzyloxyflavylium chloride as orange needles, m.p. 155° (10.1 g.).

This product (6.0 g.) was heated at 100° for 40 min. with acetic acid (30 ml.) and concentrated HCl (15 ml.). Ten per cent aqueous HCl (150 ml.) was added and the mixture was cooled. The red needles (4.10 g.) which precipitated were recrystallized from aqueous methanolic HCl. 3,7-Dimethoxy-2′,4′-dihydroxyflavylium chloride was obtained as red needles: $\lambda_{max}^{EtOH\text{-}0.5\%\ HCl}$ 502, 283, 267, and 238 mμ.

4′-O-Methylcoumestrol (V).—Thirty per cent hydrogen peroxide (4.0 ml.) was added to a solution of the flavylium salt VII (2.0 g.) in warm methanol (50 ml.) and water (25 ml.). After 10 min., concentrated sulfuric acid (4.0 ml.) was added and the solution was heated on a steam bath for 20 min. The slightly brown, crystalline solid which precipitated was recrystallized from acetone–methanol. 4′-O-Methylcoumestrol separated as fawn-colored needles: m.p. and m.m.p.[7] 337–338° (0.83 g.); λ_{max}^{EtOH} 341, 302, and 243 mμ; λ_{max}^{NaOEt} 378, 310, 269, and 243 mμ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.57. Found: C, 68.1; H, 3.71.

4′-O-Methylcoumestrol acetate separated from acetic acid–methanol as colorless, felted needles: m.p. 240–241° (lit.[7] m.p. 240°); λ_{max}^{EtOH} 337, 302, and 243 mμ.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO–, 9.63. Found: C, 66.7; H, 3.81; MeO–, 9.41.

2′,7-Dihydroxy-3,4′-dimethoxyflavylium Chloride (VIII).—A mixture of ω,4-dimethoxy-2-hydroxyacetophenone[11] (3.6 g.), benzyl chloride (5 ml.), K_2CO_3 (5 g.), KI (1.0 g.), and acetone (50 ml.) was heated under reflux for 3 hr. and filtered. Evaporation of the filtrate gave the benzyl ether as an oil which, after washing with light petroleum, was combined with 2,4-dihydroxybenzaldehyde (3 g.) in ethyl acetate (20 ml.) and ether (50 ml.). Saturation of the solution with HCl gas in the usual way precipitated 3,4′-dimethoxy-2′,7-dibenzyloxyflavylium chloride as orange needles (5.0 g.). A solution of this product in glacial acetic acid (25 ml.) and concentrated HCl (15 ml.) was heated on a steam bath for 2 hr. A mass of red crystals separated. After cooling, the product was collected and recrystallized from methanol containing 10% aqueous HCl. 2′,7-Dihydroxy-3,4′-dimethoxyflavylium chloride separated as red felted needles: $\lambda_{max}^{EtOH\text{-}0.5\%\ HCl}$ 502, 267, and 240 mμ.

7-O-Methylcoumestrol (VI).—The flavylium salt VIII (0.5 g.) was suspended in warm ethanol (10 ml.) and water (5 ml.) and treated with 30% hydrogen peroxide (1.0 ml.). After 5 min. the solution was diluted with water and extracted with ether. The ether extract, washed with water and dried (Na_2SO_4), was evaporated and the residue was heated with glacial acetic acid (5 ml.) and 50% aqueous sulfuric acid (5 ml.) for 20 min. The crystalline product which separated was recrystallized from acetone–methanol to give 7-O-methylcoumestrol as fawn-colored needles, m.p. 275–276°. For purification this product was converted into its acetate which crystallized from acetone–methanol as colorless felted needles: m.p. 201; λ_{max}^{EtOH} 348, 332, 297, and 240 mμ.

(11) P. R. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A22**, 157 1945).

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO–, 9.63. Found: C, 66.6; H, 3.71; MeO–, 9.48.

Alkaline hydrolysis of the acetate and recrystallization of the product from acetone–methanol gave pure 7-O-methylcoumestrol: m.p. 277° (lit.[7] m.p. 274°); λ_{max}^{EtOH} 342, 303, and 245 mμ; λ_{max}^{NaOEt} 380, 317, and 271 mμ.

3-Methoxy-2′,4′-dibenzyloxyflavylium Chloride.—Salicylaldehyde (2.44 g.) and ω-methoxy-2,4-dibenzyloxyacetophenone (7.24 g.), condensed in ethyl acetate (40 ml.) and ether (200 ml.) with HCl gas, gave the flavylium salt (9.8 g.). Recrystallized from glacial acetic acid–ether, it separated in glistening orange plates with a green reflex, m.p. 142° dec.

7′-Hydroxycoumarino(3′,4′:3.2)benzofuran (**IX, R = H**).—Hydrogen peroxide (30%, 4.0 ml.) was added to a suspension of the above flavylium salt in methanol (120 ml.) at room temperature. After 5 min. water was added to the pale yellow solution and the product was extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and evaporated to an oil. This was dissolved in hot acetic acid (30 ml.) and slowly diluted with concentrated hydrochloric acid (30 ml.). The solution was heated on a steam bath for 30 min. and then diluted with an excess of water. The slightly pink product was collected and recrystallized from methanol, giving slightly brown crystals, m.p. 270–272° (0.6 g.).

The **acetate** of this product crystallized from acetone–methanol as colorless, felted needles, m.p. 208–209°, which migrated as a single, blue fluorescent spot on silicic acid chromatostrips (R_f 0.83 in ether, 0.59 in ether–Skellysolve F, 2:1): λ_{max}^{EtOH} 340, 323, 295, and 236 mμ. For 7′-acetoxycoumarino(3′,4′:3.2)benzofuran, Govindachari, *et al.*,[9] report m.p. 105–106°.

Anal. Calcd. for $C_{17}H_{10}O_5$: C, 69.4; H, 3.40. Found: C, 69.5; H, 3.46.

Alkaline hydrolysis of the above acetate gave 7′-hydroxycoumarino(3′,4′:3.2)benzofuran which crystallized from acetone–methanol as colorless needles: m.p. 276° (lit.[9] m.p. 285°); λ_{max}^{EtOH} 347, 331, 297, and 242 mμ; λ_{max}^{NaOEt} 372, 307, and 247 mμ. On silicic acid chromatostrips the compound migrates as a single spot, R_f 0.72 in ether, 0.44 in ether–Skellysolve F (2:1).

Anal. Calcd. for $C_{15}H_8O_4$: C, 71.4; H, 3.20. Found: C, 71.5; H, 3.33.

The **methyl ether** of the product crystallized from acetone–methanol as cream-colored granular crystals, m.p. 190° (lit.[9] m.p. 195–196°).

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.2; H, 3.79. Found: C, 72.5; H, 3.82.

7′-Hydroxy-7-methoxycoumarino(3′,4′:3.2)benzofuran (**IX, R = MeO**).—3,8-Dimethoxy-2′,4′-dibenzyloxyflavylium chloride, prepared by the condensation of *o*-vanillin and ω-methoxy-2,4-dibenzyloxyacetophenone, crystallized from glacial acetic acid–ether as yellow-orange needles, m.p. 139–140°.

Oxidation of the flavylium salt (3.0 g.) as described above gave the coumarinobenzofuran IX (R = MeO–) (0.30 g.) which separated from acetone–methanol as yellow, granular crystals: m.p. 289°; λ_{max}^{EtOH} 330, 296, 261, and 252 mμ; λ_{max}^{NaOEt} 370, 305, and 262 mμ.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.57; 1 MeO–, 11.0. Found: C, 68.4; H, 3.77; MeO–, 11.0.

The **methyl ether** of the product crystallized from methanol as cream-colored needles: m.p. 195°; λ_{max}^{EtOH} 344, 328, 294, 259, and 250 mμ.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.9; H, 4.08. Found: C, 68.9; H, 4.11.

Acknowledgment.—The author is indebted to L. M. White and Miss G. Secor for elemental analyses and to E. M. Bickoff for a specimen of natural coumestrol.