The Preparation of 3-Phenyl-1-chloropropane.[16]—3-Phenyl-1-propanol (100 g., 0.735 mole) was allowed to react with thionyl chloride (120 g., 1.0 mole) in 64 g. (0.80 mole) of anhydrous pyridine using the conditions described for 3-methyl-3-phenyl-1-chlorobutane. The product was obtained in a yield of 81.4 g. (52.8%), b.p. 85° at 8 mm., n^{20}_{D} 1.5207 (reported[17] b.p. 89–93° at 6 mm., n^{20}_{D} 1.5160).

Preparation of 2-Methyl-2,4-diphenylpentane.—The olefin from the dehydration of 4-methyl-2,4-diphenyl-2-pentanol was obtained using the method of Bergmann, Taubadel and Weiss.[18] The olefin which boiled at 165° at 9 mm., n^{20}_{D} 1.5682 (reported[18] b.p. 170–171° at 17 mm.) was produced in an over-all yield of 54% based on the starting 4-methyl-4-phenyl-2-pentanone.

This olefin (50.0 g., 0.231 mole) was selectively hydrogenated using 5 g. of copper–chromite catalyst at 116–154° in a 450-ml. rotating autoclave with an initial hydrogen pressure of 115 atm. The yield of 2-methyl-2,4-diphenylpentane was 36 g. (65%), b.p. 158° at 9.5 mm., n^{20}_{D} 1.5471.

Preparation of 1,1,3-Trimethyl-3-phenylindan.—This compound was prepared from 10 g. of the above-described olefin, by allowing it to stand for 24 hr. with 1 g. of stannic chloride.[18] The yield of product was 7.26 g. (73%), b.p. 161–165° at 12 mm., m.p. 52–53° (recrystallized from methanol) (reported[18] b.p. 166–167° at 25 mm., m.p. 52–53°).

Preparation of 2-Methyl-2-phenyl-4-*p*-tolylpentane.[19]—The method of preparation of this hydrocarbon, b.p. 139° at 3 mm., n^{20}_{D} 1.5431, was identical with that for 2-methyl-2,4-diphenylpentane except for the substitution of *p*-tolylmagnesium bromide for phenylmagnesium bromide in the reaction with 4-methyl-4-phenyl-2-pentanone.

Preparation of 2,5-Dimethyl-2,5-diphenylhexane.—β-Chloro-*t*-butylbenzene (neophyl chloride) was prepared in a yield of 69% using hydrogen fluoride as a catalyst.[20] The material boiled at 126° at 40 mm., n^{20}_{D} 1.5244 (reported[21] b.p. 97° at 13 mm., n^{20}_{D} 1.5250). 2,5-Dimethyl-2,5-diphenylhexane cannot be prepared by a Wurtz reaction of this chloride[21] nor can it be prepared by coupling of neophyl radicals[22] because rearrangements take place, although Urry and Kharasch did isolate some dimer of uncertain structure, m.p. 129°, from the cobaltous chloride-catalyzed dimerization of neophylmagnesium chloride.[22] On attempted coupling the tosylate of neophyl alcohol (prepared by bubbling oxygen into neophylmagnesium chloride) with neophylmagnesium chloride gave only a trace of high boiling material. It was found, however, that the reaction of neophyl chloride with magnesium did give some of the desired product. Neophyl chloride (135 g., 0.80 mole) was allowed to react with 9.72 g. (0.40 g. atom) of magnesium in 200 ml. of anhydrous ether, and the mixture was refluxed for 72 hours. There is no evidence, however, that additional reaction of the chloride with the Grignard reagent takes place during this period. Then 9.72 g. of magnesium was added to react with the excess chloride and the solution was refluxed for an additional 3 hours. The products consisted of *t*-butylbenzene, b.p. 167–169°, n^{20}_{D} 1.4923, 90.2 g. (84%), and the desired product, b.p. 175–177° at 10 mm., n^{20}_{D} 1.5395, 3.41 g. (3.2%). This material solidified on cooling and melted at 62–63° when recrystallized from methanol.

Anal. Calcd. for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 89.78; H, 9.87.

Preparation of 1,4-Diphenylbutane.[16]—1,4-Diphenyl-1-butanol was prepared by the Grignard method using 15.4 g. (0.10 mole) of 3-phenyl-1-chloropropane and 2.6 g. (0.11 g. atom) of magnesium with 10.6 g. (0.10 mole) of benzaldehyde in 150 ml. of anhydrous ether. The yield of product was 12.2 g. (55%), b.p. 175.5° at 5 mm., m.p. 45.5–47° (reported[23] m.p. 45–46°).

1,4-Diphenylbutane was prepared from the above alcohol, (11.8 g., 0.052 mole) by means of hydrogenolysis using 1 g. of copper–chromite catalyst at 211–239° in a 114-ml. rotating autoclave with an initial hydrogen pressure of 105 atm. The yield of product was 8.8 g. (80%), m.p. 52–52.5° (reported[24] 52–52.5°).

Acknowledgment.—The authors wish to express their appreciation to Miss H. Beck for the elemental analysis and to Professor D. F. Mason of the Chemical Engineering Department, Northwestern University, for the mass spectral gas analysis.

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EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Synthesis of Coumestrol, 3,9-Dihydroxy-6H-benzofuro[3,2-c][1]benzopyran-6-one[1]

BY O. H. EMERSON AND E. M. BICKOFF

RECEIVED MARCH 10, 1958

A practical synthesis of coumestrol is described. 2,4-Dimethoxyphenylacetonitrile is condensed with resorcinol to give α-(2,4-dimethoxyphenyl)-2,4-dihydroxyacetophenone. Treatment of this compound with methyl chloroformate yields 3-(2,4-dimethoxyphenyl)-4,7-dihydroxycoumarin which, on heating with aniline hydrochloride, yields coumestrol in an over-all yield of about 17%. Coumestrol is easily acetylated to give the diacetate, m.p. 235–236°, which crystallizes well from acetonitrile or acetic acid, and from which coumestrol can be regenerated readily. An improved preparation of 2,4-dimethoxyphenylacetonitrile from 2,4-dimethoxybenzaldehyde and rhodanine is reported also, giving an over-all yield of about 62%.

Previous work in this Laboratory[2-4] resulted in the isolation of an estrogen from ladino clover and alfalfa which was shown to have the empirical formula $C_{15}H_8O_5$, and for which structural formula I and the name coumestrol were proposed. It was felt most desirable to synthesize the substance, both to confirm the structure and to make it accessible for pharmacological study.

Although the substance is new, a number of closely related compounds are well known. Thus

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[1] We wish to thank Dr. Leonard T. Capell of the staff of "Chemical Abstracts" for the systematic name.

[2] E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. DeEds, *Science*, **126**, 967 (1957).

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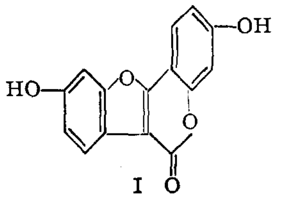
[4] E. M. Bickoff, R. L. Lyman, A. L. Livingston and A. N. Booth, THIS JOURNAL, **80**, 3969 (1958).

3-(2,4-dimethoxyphenyl)-4-hydroxy-7-methoxycoumarin (IIa)[5] could be expected to yield coumestrol by simultaneous ring closure and demethylation through the action of hydriodic acid.[6,7]



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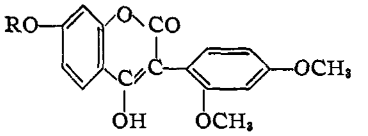

IIa, R = CH_3
IIb, R = H

This was found to be the case. The chromatographic properties and biological assays of the natural and synthetic products were indistinguishable. The ultraviolet absorption spectra of a sample of natural coumestrol purified by Craig distribution and a sample of synthetic material regenerated from the acetate[3] were substantially identical. Coumestrol crystallizes with difficulty and melts with decomposition at about 385°. However, the acetates crystallized nicely, melted at 235-236° singly and on admixture, and were identical crystallographically and in X-ray diffraction pattern.[8] The ultraviolet and infrared absorption spectra were identical within the errors of measurement (Figs. 1 and 2).

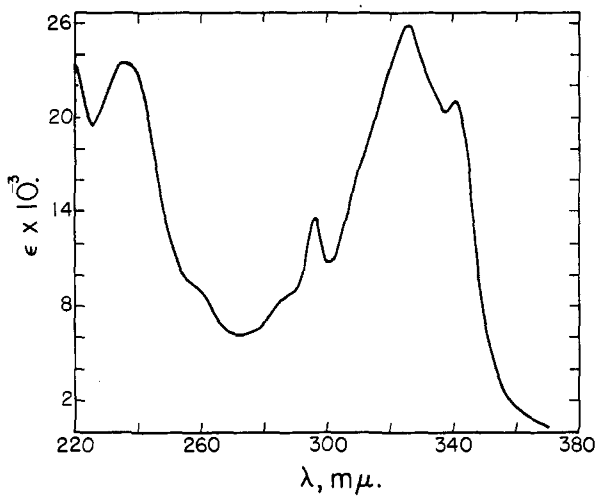

Fig. 1.—Coumestryl acetate, ultraviolet absorption spectrum in methanol; 0.30 mg./10 ml.; Cary recording spectrophotometer model 14PM.

Coumarin IIa was obtained by the following transformations. 2,4-Dimethoxyphenylacetonitrile was condensed with resorcinol (Hoesch) to give α-(2,4-dimethoxyphenyl)-2,4-dihydroxyacetophenone which was methylated to the corresponding 2-hydroxy-4-methoxyphenyl ketone. This, on condensation with methyl carbonate and sodium, gave IIa. A distinct improvement resulted from the finding by Robertson and co-workers[9] that hydroxylated coumarins can be obtained by condensing the proper phenylacetophenone with methyl chloroformate in the presence of potassium carbonate, thus making 3-(2,4-dimethoxyphenyl)-4,7-dihydroxy-coumarin (IIb) readily accessible. This is the more advantageous, since the methoxyl group in 7-position might be difficult to cleave.[10] Further, we found aniline hydrochloride[11] much more satisfactory than hydriodic acid for demethylation and ring closure.

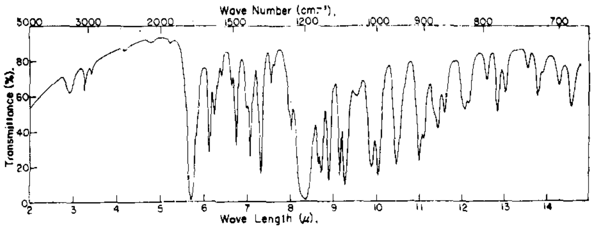

Fig. 2.—Coumestryl acetate, infrared absorption spectrum, potassium bromide pellet, Beckman I.R. 3

Since 2,4-dimethoxyphenylacetonitrile is an intermediate in the synthesis, some attention was paid to its preparation. The most elegant-appearing synthesis[12] involved condensing 2,4-dimethoxybenzaldehyde with nitromethane, reducing the ω-nitrostyrene with hydrogen over palladium-on-charcoal in pyridine solution to the oxime, which was dehydrated with acetic anhydride to the nitrile. In our hands the hydrogenation gave very poor yields in spite of use of large amounts of catalyst.

The commonly used procedure for the preparation of this nitrile[13] is to condense 2,4-dimethoxybenzaldehyde with hippuric acid in acetic anhydride to give the azlactone. This was cleaved with alkali to the corresponding phenylpyruvic acid, which was oximated. Treatment with acetic anhydride effected decarboxylation and dehydration to the nitrile in an over-all yield of 30-35%. By using rhodanine in place of hippuric acid[14,15] it was possible to raise the over-all yield of nitrile to 62%.

Experimental

All melting points are corrected. A Kofler block was often used.

Coumestrol from 3-(2,4-Dimethoxyphenyl)-4-hydroxy-7-methoxycoumarin.—*The coumarin IIa*[4] *(390 mg.)* was refluxed with 10 ml. of hydriodic acid, sp. gr. 1.70, and 5 ml. of acetic acid in an atmosphere of carbon dioxide as long as methyl iodide was evolved (about 1 hour). The reaction mixture was cooled, diluted with water, and filtered. The crude coumestrol was purified by distribution in a Craig apparatus as previously described.[3] The product was assayed biologically and compared with natural coumestrol

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(6) W. B. Whalley, personal communication.

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by chromatographing on silicic acid chromatostrips[16] using a mixture of ether–petroleum ether, b.p. 63–70°, 7:3 v:v. Both natural and synthetic coumestrol had an R_f of 0.36, and showed the same intense violet-blue fluorescence.

2,4-Dimethoxybenzalrhodanine.—2,4-Dimethoxybenzaldehyde (50 g.), rhodanine[17] (40 g.), anhydrous sodium acetate (150 g.) and 200 ml. of acetic acid were heated in an oil-bath at 130° and maintained at that temperature for half an hour. The product is very sparingly soluble, and the contents of the flask rapidly became almost solid. The mixture was cooled, an equal volume of water was added, and the product filtered and washed with water. Extraction with 250 ml. of hot ethanol removed some dark-colored impurities. The yield was 79 g. (93% of theory), melting at 267–270° to a black tar. Because of the slight solubility in the common solvents, recrystallization is impractical except for small amounts of material.

The analytical sample was recrystallized from butanol, of which 150 ml. was needed to dissolve 1 gram. It separated in tufts of orange-yellow needles, m.p. 275°.

Anal. Calcd. for $C_{12}H_{11}NO_3S_2$: C, 51.21; H, 3.95. Found: C, 51.4; H, 3.92.

2,4-Dimethoxyphenylthiopyruvic Acid.—The above dimethoxybenzalrhodanine (20 g.) was suspended in a mixture of 80 ml. of 15% aqueous sodium hydroxide and 20 ml. of 14% sodium sulfide and heated with swirling under nitrogen on a steam-bath until all the solid dissolved (*ca.* 7 minutes), then for 5 minutes more. The mixture was cooled in an ice-bath, then acidified with 100 ml. of 10% hydrochloric acid. The precipitate was filtered, washed, and extracted with 200 ml. of ethyl acetate. After removing the water, the ethyl acetate was concentrated under slightly reduced pressure to about 70 ml. and allowed to stand. The product separated in well formed yellow-to-orange crystals, which were washed with toluene. The combined filtrates were concentrated for second and third crops. The acid can be recrystallized very conveniently from toluene; m.p. 168–170° with some decomposition, yield 13.6 g. (82% of theoretical).

Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 54.98; H, 5.04. Found: C, 55.2; H, 5.11.

2,4-Dimethoxyphenylpyruvic Acid Oxime.—To a solution of 8 g. of sodium in 240 ml. of ethyl alcohol was added a concentrated aqueous solution of 24 g. of hydroxylamine hydrochloride. The hydroxylamine filtrate was added to 24 g. of the above acid, and the solution was refluxed as long as hydrogen sulfide was evolved (about 1 hour). The alcohol was removed under reduced pressure, and the residue extracted with an excess of 5% sodium hydroxide solution, and filtered from a small amount of 2,4-dimethoxyphenylacetonitrile. The filtrate was acidified to *p*H 2.0 with hydrochloric acid[18] and the precipitate filtered off. As the oximino acid is appreciably soluble in water, the filtrate was extracted with 200 ml. of ethyl acetate, which was then used to dissolve the product. The ethyl acetate was then concentrated to about 100 ml. and two volumes of benzene were added. The oximino acid separated in large white needles which can be further purified by recrystallization from that solvent mixture. This is a better solvent for some of the impurities than ethyl acetate–petroleum ether recommended by Mitter and Maitra.[13] The yield was 20.4 g. (86% of theoretical), m.p. 149°.[19]

2,4-Dimethoxyphenylacetonitrile was prepared as described.[13] The exothermic reaction, once started, goes rapidly to completion in almost quantitative yield. The product can be recrystallized very satisfactorily from 2-propanol.

α-(2,4-Dimethoxyphenyl)-2,4-dihydroxyacetophenone.—The procedure of Boyd and Robertson[5] was modified somewhat. Hoesch condensations involving phloroglucinol or resorcinol may give better yields if no zinc chloride is used.[15,20,21] 2,4-Dimethoxyphenylacetonitrile (4.4 g.) and 8 g. of resorcinol were dissolved in 50 ml. of anhydrous ether, saturated with dry hydrogen chloride at 0° and kept 5 days in an ice-box. The ketimine hydrochloride was worked up as described[4] and the ketone crystallized from 60% alcohol, and then from toluene. The yield was 3.6 g. (50% of theoretical), m.p. 156° as reported by Späth and Schläger.[22]

3-(2,4-Dimethoxyphenyl)-4,7-dihydroxycoumarin.—α-(2,4-Dimethoxyphenyl)-α-2,4-dihydroxyacetophenone (6.69 g.) and 4.1 ml. of methyl chloroformate were refluxed together in 150 ml. of acetone over 17 g. of potassium carbonate for 4 hours. The cooled mixture was diluted with two volumes of water and acidified with hydrochloric acid. The product was filtered off and the mother liquors concentrated for a second crop. The united precipitates (7.7 g.) were dissolved in 100 ml. of methanol, a little alizarin yellow added, heated to boiling in a nitrogen atmosphere, and 20% methanolic potassium hydroxide added dropwise until the indicator stayed a strong orange, and refluxed for 10 minutes. The cooled reaction mixture was diluted with two volumes of water and acidified with hydrochloric acid. The product was recrystallized from ethanol; yield 5.50 g. (75% of theoretical), m.p. 263–264°.

Anal. Calcd. for $C_{17}H_{14}O_6$: C, 64.95; H, 4.49. Found: C, 65.0; H, 4.50.

Coumestryl Acetate (by Aniline Hydrochloride Fusion).—The above coumarin (1.00 g.) was heated with 2 g. of aniline hydrochloride in a carbon dioxide atmosphere in an oil-bath heated to 210–220° for 3.5 hours. The aniline hydrochloride was leached out with water from the cooled reaction mixture and the insoluble material was washed with a small amount of ethyl acetate and acetone, which removed some dark red material. A chromatogram showed that there was no unaltered starting material, and only a small amount of coumestryl monomethyl ether. Without further attempts at purification, the crude product was acetylated by boiling it 5 minutes with acetic–anhydride and sodium acetate, and the crude reaction product washed with a small amount of acetone, which removed some highly colored material. The coumestryl acetate was recrystallized from acetonitrile and melted at 235–236°. The yield was 620 mg. (55%). For large amounts of material, acetic acid is preferable to acetonitrile for recrystallization.

Anal. Calcd. for $C_{19}H_{12}O_7$: C, 64.75; H, 3.44. Found: C, 64.7; H, 3.51.

Coumestrol Regenerated from the Acetate.—Coumestryl acetate (100 mg.) was refluxed 40 minutes with 10 ml. of 6% methanolic potassium hydroxide in an atmosphere of nitrogen. The cooled mixture was diluted with an equal volume of water, acidified with diluted hydrochloric acid, and concentrated in a stream of carbon dioxide to force out the coumestrol. The product was dissolved in acetone–methanol mixture and boiled a few minutes with 15 mg. of charcoal, filtered, and concentrated to a volume of about 3 ml., and allowed to stand about an hour. The coumestrol was filtered and dried in a vacuum desiccator. It appeared as a pale buff mass of birefringent granules. The absorption spectrum of this material was identical with that reported for the natural product[2] in the range from 230–350 mμ, but was slightly more transparent than the natural in the region from 360–390 mμ, and again at 220 mμ. Thus the value for ε at 380 mμ for the synthetic product was 1600 compared with 2100 for the natural.

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ALBANY, CALIF.

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