Acknowledgment.—We are grateful to the Public Health Service (GM-12595) and the Alfred P. Sloan Foundation for support and to the Public Health Service for fellowship support of Tommy L. Chaffin. We wish to thank Professor Ernest Wenkert for samples of podocarpic acid and dehydroabietonitrile, Professor Robert Woody for ORD measurements, and Professor George Schroepfer for stimulating discussions.

Diborane Reductions of Oxygen Heterocycles. Synthesis of 3-Chromanols and 3-Chromanones

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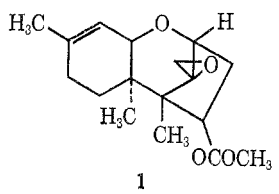
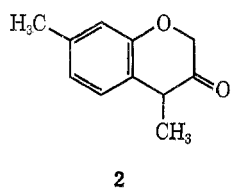
Received December 31, 1969

Hydroboration–oxidation of coumarin and 4,7-dimethylcoumarin affords 3-chromanol and 4,7-dimethyl-3-chromanol. Chrom-2-ene and chromone also afford 3-chromanol, and 3-methylcoumarin yields 3-methyl-4-chromanol. Oxidation of 4,7-dimethyl-3-chromanol with dicyclohexylcarbodiimide and dimethyl sulfoxide produces 4,7-dimethyl-3-chromanone, thus providing a quicker route to this type of ketone than previously reported methods. The three coumarins also yield as products of these reactions 3-(*o*-hydroxyphenyl)propane-1,2-diols. The specificity of these reactions in leading to the vicinal glycols is attributed to the effect of the phenolic oxygen. Reduction of flavone under these conditions leads to no cyclic product, but rather to a dibenzyl alcohol which results from the hydrogenolysis of a benzylic–allylic carbon–oxygen bond.

As part of a program directed toward the synthesis of trichodermin[1] (**1**) and related sesquiterpenes, we required 4,7-dimethyl-3-chromanone (**2**) as an intermediate. Previous syntheses reported for the 3-chromanone system have usually required the preparation of *o*-(carboxymethoxy)phenylacetic acids and their cyclization by either Dieckmann reaction of the corresponding diesters[2–4] or as in the original synthesis of 3-chromanone itself,[5] acetic anhydride catalyzed reaction of the diacid. In these syntheses, however, the particular 3-chromanone involved was generally the ultimate synthetic goal. Thus a lengthy route to a carboxymethylphenylacetic acid was a reasonable price to pay for obtaining the desired ketone. In our case such an expenditure of experimental effort in a multistep route to a synthetic intermediate was clearly undesirable, and we therefore sought a shorter route to **2** from readily available starting materials.



1

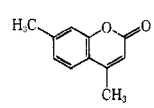
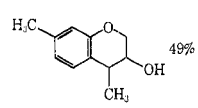
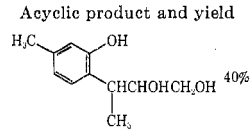
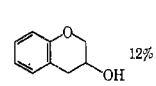
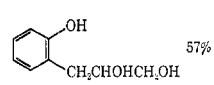
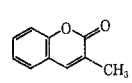
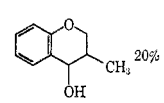
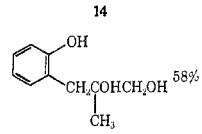
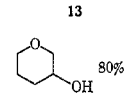
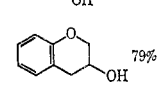
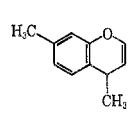
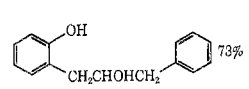


2

One such material is 4,7-dimethylcoumarin (**3**) (Table I), the Pechmann reaction product of *m*-cresol and acetoacetic ester. We have investigated a number of routes for the conversion of **3** to 3-oxygenated chroman systems, but one in particular, hydroboration–oxidation of **3**, has led directly to the desired structural type. Thus, continuous passage of externally generated diborane through a tetrahydrofuran solution of **3** followed by hydrogen peroxide oxidation of the intermediate alkylborane yielded 49% 4,7-dimethyl-3-chromanol (**4**). A second product, the triol **5**, obtained in 40% yield was readily separated from **4** by extraction of the reaction product mixture with aqueous base. The conversion of **4** to 4,7-dimethyl-3-chromanone (**2**) was then effected in 84% yield by Moffat oxidation[6] employing dicyclohexylcarbodiimide, dimethyl sulfoxide, and monophenyl phosphate.

TABLE I

HYDROBORATION–OXIDATION PRODUCTS OF OXYGEN HETEROCYCLES

Substrate	Cyclic product and yield	Acyclic product and yield
 **3**	 49% **4**	 40% **5**
Coumarin	 12%	 57% **14**
 **12**	 20% **13**	 58% **15**
Dihydropyran	 80%	
Chromone	 79%	
 **6**	**4** 88%	
Flavone		 73% **19**

The structural assignments of **4**, **5**, and **2** follow from their spectral characteristics. The nmr spectrum of **4**, for example, displays a two-proton multiplet at 3.71 ppm for the C_2-methylene group as well as a doublet for the C_4-methyl group at 1.12 ppm, and two one-proton multiplets at 2.53 and 3.43 ppm for the C_3

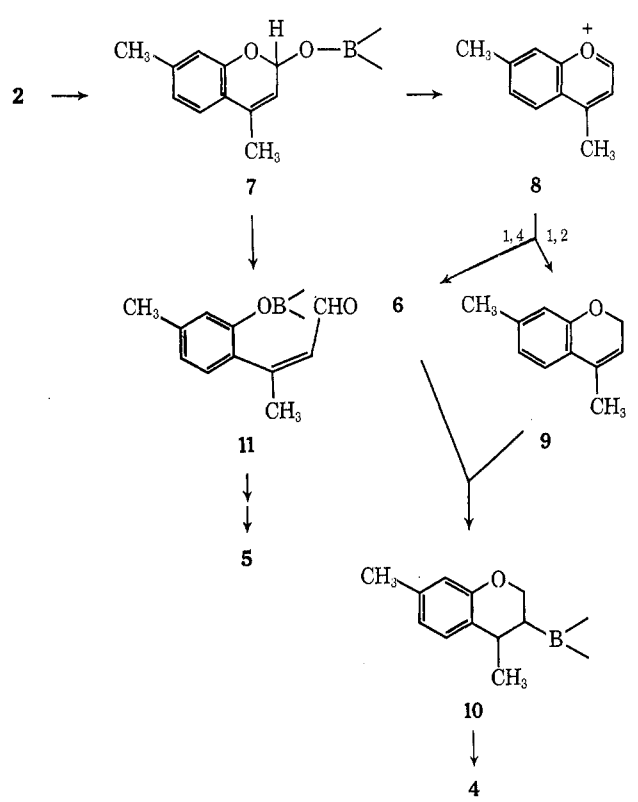
(1) S. Abrahamsson and B. Hilsson, *Proc. Chem. Soc.*, 188 (1964).
(2) A. Robertson and G. Rusby, *J. Chem. Soc.*, 212 (1936).
(3) N. S. Vul'fson, T. N. Podrezova, and L. B. Senyavina, *Zh. Obsch. Khim.*, **34**, 2676 (1964).
(4) M. Miyano and M. Matsui, *Bull. Chem. Soc. Jap.*, **31**, 267 (1958).
(5) P. Pfeiffer and E. Enders, *Chem. Ber.*, **84**, 247 (1951).
(6) K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **87**, 5661 (1965).

and C_4 protons, respectively. The C_2- and C_4-proton resonances show appropriate downfield shifts from the values given above in the spectrum of the oxidation product **2**, and the signal for the C_2-methylene group occurs as an AB pattern in the latter spectrum. Chemical evidence for the structure of **4** was obtained by the demonstration that 4,7-dimethyl-2-chromene (**6**), prepared by the pyrolysis of 4,7-dimethyl chromane-2-acetate,[7] was converted to the same alcohol **4** by the action of diborane and hydrogen peroxide, and dihydropyran under the same conditions gave tetrahydropyran-3-ol.[8]

The nmr spectrum of the triol **5** shows that the two aliphatic hydroxyl groups must have a vicinal relationship since the signal for the benzylic methyl group occurs as a doublet. In addition, the mass spectrum of **5** shows prominent peaks at *m/e* 165 and 135 for loss of the fragments $\cdot CH_2OH$ and $\cdot CHOHCH_2OH$, respectively.

A likely pathway for the multistep reduction of 4,7-dimethylcoumarin can be described by the sequences shown in Scheme I. Thus, production of a 3-chromanol

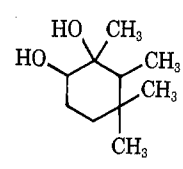
SCHEME I



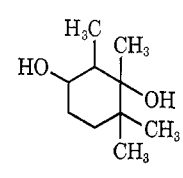
from **3** would appear to require first hydride reduction to yield a hemiacetal borate **7** followed by dissociation of the latter to a pyrylium salt **8**. This species should then undergo rapid reduction by either 1,4 or 1,2 addition of hydride to yield **6** or **9**. The final reduction step, hydroboration of the double bond of either **6** or **9**, would then produce the 3-chromanylborane **10**. The second product of the overall reduction sequence, **5**, would appear to arise from the alternative pathway described in Scheme I. If **7** undergoes ring opening, the resulting aldehyde **11** would suffer further reduction to eventually yield a borane convertible to **5**.

In order to test the validity of these reaction schemes and to explore the generality of the reduction process, we undertook the investigation of the reaction of diborane with a number of oxygen heterocycles. Table I lists the compounds reduced and the products isolated in each case. In the cases of reduction of three coumarins, a 2-chromene, and dihydropyran, the chromanol type of product is clearly the result of the usual directive effects that operate in hydroboration reactions, that is, production of the least substituted alcohol from an unsymmetrically substituted olefin[9] or formation of the β-ol product from a vinyl ether system.[10] Thus, 4,7-dimethylcoumarin (**3**), 4,7-dimethyl-2-chromene (**6**), and coumarin yield 3-chromanols, and 3-methylcoumarin (**12**) affords 3-methyl-4-chromanol (**13**). The last result also indicates that reduction of the proposed pyrylium salt shown in Scheme I for the reduction of **3** occurs by a 1,2 rather than by a 1,4 process. If a 2-chromene, the product of 1,4 addition, were an intermediate in these reactions, then each of these examples should have yielded a 3-chromanol.

The second series of products shown in Table I, the ring-opened compounds **5**, **14**, and **15** all appear to arise as suggested in Scheme I by hydroboration of an intermediate *o*-hydroxycinnamyl system. In all three cases the product is a vicinal diol despite the fact that **15** must arise from carbon–boron bond formation at the *most* substituted position of a double bond. A recent study[11] of the hydroboration of cyclic conjugated enones has shown that these systems yield vicinal diols also. The authors of this work showed that the first step in these reactions was the reduction of a cyclohexenone to the corresponding allylic borate, and they ascribed their results to the directive influence of the oxygen atom of this first reduction product. None of the cases studied, however, featured alkyl substitution (as in **12**) which could be expected to counter the suggested directive effect of the borate oxygen. There are, furthermore, a number of other reports that suggest that this directive effect is less general than has been suggested.[11] For example, hydroboration of 2,3,4,4-tetramethylcyclohex-2-enone has been shown[12] to yield **16** and **17** in the ratio of approximately 2:1, and the reduction of cinnamyl alcohol with diborane has been reported[13] to lead to a mixture of 3-phenylpropane-1,2- and -1,3-diols.



16



17

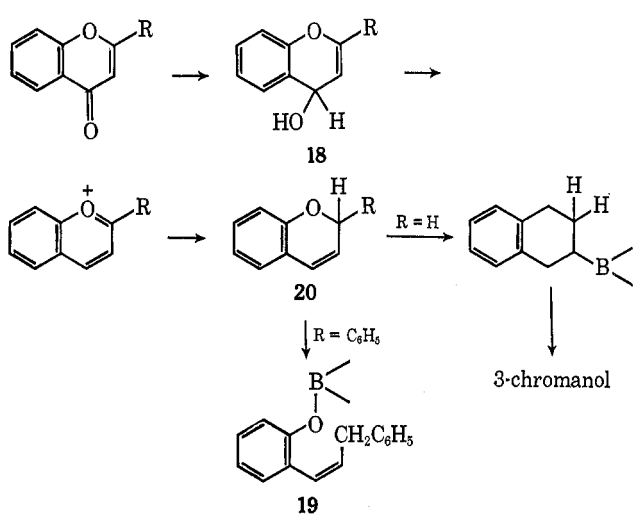
In our cases, the key to the specificity that we have found appears to be the presence of an oxygen atom conjugated with the reducible double bond. This type of effect has been shown previously to occur in the

(7) W. E. Parham and L. D. Huestis, *J. Amer. Chem. Soc.*, **84**, 813 (1962).
(8) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).
(9) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960).
(10) D. J. Pasto and C. C. Cumbo, *ibid.*, **86**, 4343 (1964).
(11) J. Klein and E. Dunkleblum, *Tetrahedron*, **24**, 5701 (1968).
(12) A. Uzarewicz, I. Uzarewicz, and W. Zacharewicz, *Rocz. Chem.*, **39**, 19 (1965).
(13) K. Kratzl and P. Claus, *Monatsh. Chem.*, **94**, 1140 (1963).

hydroboration of substituted styrenes by Brown and Sharp[14] who found that styrene, *o*-methoxystyrene, and *p*-methoxystyrene afford 81, 86, and 93%, respectively, of the β-ol product. The latter two results were correlated with the electron-donating resonance effects of *o*- and *p*-methoxyl substituents. In the examples investigated in the present work this effect, now of an *o*-borate substituent, coupled with that of the aliphatic borate group,[11] is apparently sufficient to produce only the β-ol product regardless of the position of alkyl substitution on the double bond.

As noted above hydroboration–oxidation of coumarins leads to both chromanols and 3-phenylpropanediols. In contrast, the chromone system ought to yield only the cyclic product since the initial product of reduction of a chromone, **18** (Scheme II), cannot

SCHEME II



tautomerize to an open-chain isomer. This conclusion was borne out by the result of hydroboration of chromone itself which was the production of 3-chromanol in 79% yield. When the same procedure was applied to flavone, however, no cyclic alcohol product was obtained. Instead we found that the dihydroxy compound **19** was produced in 73% yield. As suggested in Scheme II the reduction sequence with chromones follows the same course as the reduction of coumarins through the step involving hydride addition to the intermediate pyrylium salt to yield a chromene **20**. At this point, however, an additional hydride transfer step appears to take place in the case of the phenylchromene that results in cleavage of the heterocycle. That this step should occur in the reduction of the flavone and not in that of chromone itself is not surprising in view of the benzylic–allylic nature of the carbon–oxygen bond which suffers hydrogenolysis in the flavone case.

Experimental Section

All melting points were determined on an Arthur A. Thomas Co. Uni-Melt capillary melting point instrument. Analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. Infrared spectra were taken on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were recorded on a Varian Associates T-60 spectrometer and data are reported in parts per million from internal tetramethylsilane (TMS). All mass spectra were obtained on a Varian Associates M-66 spectrometer, and precise mass calculations were performed on a Digital, Inc., PDP-9 computer. Precise mass data are given for the molecular ion unless otherwise specified.

4,7-Dimethylcoumarin (3).—*m*-Cresol (300 g, 2.00 m) was allowed to react with acetoacetic ester (260 g, 2.78 mol) according to the method of Fries and Klostermann,[15] and the crude product was recrystallized from methanol to yield blunt needles (254 g, 73%), mp 129–130° (lit.[15] mp 132°).

4,7-Dimethyldihydrocoumarin.—4,7-Dimethylcoumarin (20 g, 0.15 mol) was dissolved in 200 ml of acetic acid containing 10% palladium on charcoal (3 g). This mixture was shaken with hydrogen at 50 psi until the theoretical amount (0.15 m) of the gas had been adsorbed (3–5 hr). The catalyst was then removed by filtration through Celite 545 and the solvent was evaporated to yield a yellow oil. This crude product was distilled *in vacuo* to give a clear oil (19.4 g, 96%): bp 122° (1.25 mm); ir (neat 1754 cm^{-1} (C=O); nmr (CCl_4) 6.95 (m, 3), 3.12 (m, 1), 2.55 (m, 2), 2.33 (s, 3), 1.27 (d, 3, J = 6 Hz).

4,7-Dimethylchroman-2-ol.—Lithium aluminum hydride (3.42 g, 0.090 mol) and 50 ml of anhydrous tetrahydrofuran were placed in a 250-ml three-neck flask fitted with an addition funnel, stirrer and reflux condenser and cooled to 0°. Anhydrous *t*-butyl alcohol (19.9 g, 0.27 mol) was added dropwise with stirring over a 1-hr period; the mixture was allowed to warm to room temperature and then stirred an additional 30 min. This hydride solution ws then diluted with an additional 100 ml of anhydrous tetrahydrofuran and transferred to an addition funnel. 4,7-Dimethyldihydrocoumarin (15.9 g, 0.090 mol) was dissolved in 100 ml of anhydrous tetrahydrofuran and cooled to −60° in a Dry Ice–acetone bath. The hydride solution was then added dropwise over a period of 2 hr and the mixture was allowed to warm to room temperature. After pouring the mixture into ice water, the precipitated salts were filtered from the solution using Celite 545, and the filtrate was extracted four times with ether. The salts were then refluxed with 200 ml of ether, the salts filtered, and all extracts combined, washed, and dried (Na_2SO_4). The solvent was removed to give a yellow oil which was distilled *in vacuo* to yield 12.9 g (82%) of a transparent oil: bp 138° (1.0 mm); ir (neat) 3420 cm^{-1} (O–H); nmr ($CDCl_3$) 6.94 (m, 3), 5.54 (t, 1, J = 4 Hz), 3.91 (s, 1, OH), 3.05 (m, 1), 2.35 (s, 3), 1.77 (m, 2), 1.28 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.28; H, 8.09.

4,7-Dimethyl Chromane-2-acetate.—4,7-Dimethylchroman-2-ol (60 g, 0.337 mol) and 19 ml of pyridine were dissolved in 220 ml of acetic anhydride and stirred for 3 days at room temperature. The acetic anhydride and pyridine were then removed to yield a brown oil which upon vacuum distillation gave the colorless acetate (62 g, 84%): bp 130° (1.0 mm); ir (neat) 1749 cm^{-1} (C=O); nmr (CCl_4) 6.95 (m, 3), 6.40 (t, 1, J = 2 Hz), 2.95 (m, 1), 2.23 (s, 3), 1.94 (d, 3, J = 2 Hz), 1.89 (m, 2), 1.35 (d, 1.5, J = 7 Hz), 1.31 (d, 1.5, J = 7 Hz).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.63; H, 7.24.

4,7-Dimethyl-4H-chromene (6).—4,7-Dimethyl chromane-2-acetate (50 g, 0.227 mol) was placed in a 100-ml flask along with several boiling chips. The flask was then fitted with a 12-in. Johnson pyrolysis column[16] packed with glass helices, upon which was a 12-in. heated spiral metal fractionating column and still-head. The lower column was heated to 450° and the upper column to 70°, and the system was evacuated (0.60–1.00 mm). The acetate was then heated to a fast reflux such that the lower boiling prouct was distilled while any unreacted starting material was returned to the flask through the side arm of the Johnson column. Crude product distilled from the column at 90° (1.00 mm) and was finally redistilled to yield a colorless oil (32 g, 79%): bp 50° (0.75 mm); ir (neat 1668 cm^{-1} (C=C); nmr (CCl_4) 6.95 (m, 3); 6.45 (d, 1, J = 6 Hz), 4.80 (d, 0.5, J = 6 Hz), 4.84 (d, 0.5, J = 6 Hz), 3.42 (m, 1), 2.23 (s, 3), 1.31 (d, 3, J = 7 Hz).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.26; H, 7.50.

Chromone.—2-Hydroxyacetophenone (28 g, 0.206 mol) was

(14) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851 (1966).

(15) K. Fries and W. Klostermann, *Chem. Ber.*, **39**, 871 (1906).

(16) K. L. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S. Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

allowed to react with 120 ml of ethyl formate according to the procedure given by Schonberg and Sina.[17] The crude product was recrystallized from ether–hexane to yield fine needles (21.4 g, 71%), mp 58° (lit.[17] mp 59°).

4,7-Dimethylchroman-3-ol (4).—Sodium borohydride (23 g, 0.6 mol) and 100 ml of diglyme were placed in a 500-ml three-neck flask fitted with an addition funnel containing 100 g of boron trifluoride etherate, a magnetic stirrer, and two gas inlet–outlet adapters. One adapter was connected to a nitrogen tank and the other to the gas dispersion column which was filled with anhydrous tetrahydrofuran (600 ml) as were both the side bulb and chamber below the fritted disk. All joints were then secured with pressure clamps, the column was heated to approximately 50°, and **3** (60 g, 0.345 mol) was dissolved in the tetrahydrofuran. The system was then well purged with nitrogen while cooling the column to 40 ± 5° where it was maintained throughout the addition. The nitrogen was cut off and the boron trifluoride etherate added dropwise with stirring over a period of not less than 6 hr, at all times keeping the gas flow relatively slow. Occasionally, starting material crystallized in the fritted disk of the column. When this occurred, tetrahydrofuran was added from the side bulb to dissolve the obstructing material and thereby prevent pressure buildup in the generating flask. When approximately 60% of the diborane had been added, the tetrahydrofuran solution turned intensely yellow and the color persisted until shortly before the addition was completed. The solution was then transferred to a 2-l. flask and allowed to stand overnight. Aqueous sodium hydroxide (320 ml, 3 *N*) and 320 ml of 30% hydrogen peroxide were added with cooling as necessary, and the mixture was stirred for 6 hr at room temperature. The mixture as then acidified with dilute hydrochloric acid and extracted three times with ether. The combined extracts were extracted with 5% aqueous sodium hydroxide an additional three times and the aqueous was layer set aside. The ethereal layer was washed with saturated sodium chloride solution and water and dried (Na_2SO_4), and the solvent was removed to give a thick yellow oil which, upon vacuum distillation, yielded a thick colorless oil which solidified upon standing. This was recrystallized from hexane to give fine needles (29 g, 47%): bp 128–132° (0.5 mm); mp 60°; ir ($CHCl_3$) 3380 cm^{-1} (O–H); nmr (CCl_4) 6.62 (m, 3), 3.71 (m, 2), 3.43 (q, 1, J = 4 Hz), 3.07 (s, 1, OH), 2.53 (m, 1), 2.16 (s, 3), 1.12 (d, 3, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 178 (10), 152 (1), 150 (1), 135 (7), 134 (10), 133 (5), 105 (3), 91 (5), 77 (1).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.25; H, 7.81: precise mass, 178.09930. Found: C, 74.30; H, 8.09; precise mass, 178.09804.

Treatment of **6** (5.0 g, 0.037 mol) with diborane by the procedure described above yielded 5.0 g (88%) of **4**.

4,7-Dimethylchroman-3-one (2).—4,7-Dimethylchroman-3-ol (1.78 g, 0.01 mol) was dissolved in a mixture of 15 ml of anhydrous DMSO and 15 ml of anhydrous benzene containing 6.20 g (0.03 m) of dicyclohexylcarbodiimide. A 2-ml portion of a 2.5 *M* solution of anhydrous monophenyl phosphate in DMSO was then added dropwise. After 4 min a white precipitate formed. The mixture was stirred for 2.5 hr following which 25 ml of ethyl acetate and 2.7 g of oxalic acid in 25 ml of methanol were added; stirring was continued for an additional 30 min. The mixture was then filtered, and the filtrate was washed with water, refiltered, and finally washed with aqueous sodium bicarbonate and dried over sodium sulfate. Removal of the solvent left 2.65 g of a crude oil.

The oil was chromatographed on 20 g of silica gel (100–200 mesh) with elution by a 1:4 ether–hexane mixture. The resulting material was distilled to yield 1.5 g (84%) of ketone: bp 106° (0.5 mm); ir (neat liquid) 1730 cm^{-1} (C=O); nmr (CCl_4) 6.80 (m, 4), 4.20 (AB q, 2, J = 9 Hz), 3.35 (q, 1, J = 7 Hz), 2.26 (s, 3), 1.34 (d, 3, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 176 (9), 161 (2), 133 (10), 105 (7).

For analytical purposes the ketone **2** was converted to its semicarbazone derivative, mp 216° dec.

Anal. Calcd for $C_{12}H_{15}O_2N_3$: C, 61.80; H, 6.44. Found: C, 62.02; H, 6.38.

5-Methyl-2-(1′-methyl-2′,3′-dihydroxypropyl)phenol (5).—The sodium hydroxide layer from the preparation of **4** above was acidified with dilute hydrochloric acid and extracted three times with ether. The combined extracts were then washed with water, dried (Na_2SO_4), and evaporated to give a thick green oil. This was chromatographed on 500 g of Silicar CC-7, eluting with 40:60 ether–hexane to yield a colorless translucent oil (23.6 g, 35%): ir (neat) 3330 cm^{-1} (O–H); nmr ($CDCl_3$) 6.79 (m, 3), 4.44 (s, 1, OH), 4.27 (s, 1, OH), 2.70–3.78 (m, 4), 2.25 (s, 3), 1.23 (d, 3, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 196 (10), 165 (3), 136 (7), 135 (10), 121 (5), 117 (1), 115 (1), 100 (5), 91 (1).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16; precise mass, 196.10985. Found: C, 67.18; H, 8.07; precise mass, 196.10757.

3-Methylchroman-4-ol (13).—3-Methylcoumarin (5 g, 0.031 mol) was allowed to react according to the method described for **3**. Removal of solvent from the ethereal layer yielded a clear oil which rapidly crystallized on standing. This was recrystallized from hexane to yield large blunt needles (1.3 g, 20%): mp 96°, ir ($CHCl_3$) 3580 and 3430 cm^{-1} (O–H); nmr ($CDCl_3$) 7.05 (m, 4), 4.00 (m, 3), 2.27 (s, 1, OH), 1.94 (m, 1), 0.96 (d, 3, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 164 (10), 122 (10), 121 (9), 100 (2).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32; precise mass, 164.08366. Found: C, 73.35; H, 7.45; precise mass, 164.08213.

2-(2′-Methyl-2′,3′-dihydroxypropyl)phenol (15).—The sodium hydroxide layer from above was worked up according to the method described for **5**. The crude product was chromatographed on 30 g of Silicar CC-7 eluting with 50:50 ether–hexane to yield a transparent oil which crystallized on standing. This was recrystallized from ether–hexane to give fine white needles (3.26 g, 58%): mp 93°; ir (KBr) 3410 and 3240 cm^{-1}; nmr (DMSO-d_6) 6.90 (m, 4), 4.99 (s, 1, OH), 4.72 (t, 1, J = 5 Hz, OH), 3.20 (d, 2, J = 5 Hz), 2.70 (s, 2), 1.00 (s, 3); mass spectra (70 eV), *m/e* (rel intensity) 182 (3), 151 (5), 133 (3), 131 (2), 109 (2), 108 (10), 107 (7), 105 (2), 100 (5).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.70; precise mass, 182.09421. Found: C, 65.89; H, 7.92; precise mass, 182.09407.

Chroman-3-ol.—Coumarin (10 g, 0.0685 mol) was allowed to react with diborane using the same method as in preparation of **4**. Removal of the solvent from the ethereal layer gave a clear oil which on crystallization from hexane gave fine needles (1.23 g, 12%): mp 79°; ir ($CHCl_3$) 3565 and 3420 cm^{-1} (O–H); nmr ($CDCl_3$) 6.95 (m, 4), 4.16 (s, 1, OH), 4.03 (d, 2, J = 2 Hz), 2.71 (m, 3); mass spectrum (70 eV) *m/e* (rel intensity) 150 (10), 131 (2), 121 (1), 119 (1), 107 (9), 106 (2), 91 (2), 78 (3).

Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.67; precise mass, 150.06802. Found: C, 72.19; H, 6.77; precise mass, 150.06685.

Chromone (5.0 g, 0.034 m) under the same conditions yielded 4.08 g (79%) of chroman-3-ol.

2-(2′,3′-Dihydroxypropyl)phenol (14).—The basic layer from above on acidification and extraction with ether gave a thick yellow oil. This was chromatographed on 60 g of Silicar CC-7 eluting with 50:50 ether–hexane to yield a clear thick oil (6.45 g, 57%): ir (neat) 3350 cm^{-1} (O–H); nmr (DMSO-d_6) 6.95 (m, 4), 4.50 (s, 2, OH), 3.70 (m, 1), 3.41 (d, 2, J = 2 Hz), 2.70 (d, 2, J = 5 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 168 (5), 150 (1), 137 (4), 132 (2), 119 (3), 108 (10), 107 (10), 100 (2), 91 (5).

Anal. Calcd for $C_9H_{12}O_3$: C, 63.79; H, 7.14; precise mass, 168.07857. Found: C, 63.73; H, 7.12; precise mass, 168.07905.

Tetrahydropyran-3-ol.—3,4-Dihydropyran (30 g, 0.35 mol) was allowed to react with diborane using a method analogous to that of **3**. Evaporation of the ethereal layer gave a clear yellow oil which was vacuum distilled to yield a colorless oil (27.3 g, 80%): bp 83° (10 mm) [lit.[7] bp 70–72 (0.1 mm)]; ir (neat) 3320 cm^{-1} (O–H); nmr (CCl_4) 5.80 (s, 1, OH), 3.08–3.79 (m, 5), 1.25–1.87 (m, 4).

Anal. Calcd for $C_5H_{10}O_2$: C, 58.82; H, 9.81. Found: C, 58.60; H, 9.93.

2-(3′-Phenyl-2′-hydroxypropyl)phenol (19).—Flavone (5 g, 0.025 mol) was allowed to react with diborane by a procedure analogous to that of **3**. Acidification and extration with ether of the sodium hydroxide layer gave a thick yellow oil. This was vacuum distilled to yield a clear oil which was then crystallized from carbon tetrachloride to give fine transparent needles (4.2 g, 74%): mp 93°; bp 182° (0.17 mm); ir (KBr) 3390 and 3180 cm^{-1} (O–H); nmr (DMSO-d_6) 7.36 (s, 5), 6.87 (m, 4), 5.20 (d, 1, J = 4 Hz, OH), 3.60 (m, 1), 2.43 (d, 2, J = 6 Hz), 1.87 (d, 2, J = 7 Hz); mass spectrum (70 eV), *m/e* (rel intensity) 228 (1), 211 (6), 210 (10), 209 (8), 195 (7), 193 (6), 181 (1), 121 (1), 120 (1), 119 (7), 107 (8), 104 (8), 100 (2), 91 (7), 79 (6), 77 (8).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.95; H, 7.02; precise mass ($M^+ - H_2O$), 210.10439. Found: C, 78.69; H, 7.22; precise mass, 210.10257.

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Registry No.—4,7-dimethyldihydrocoumarin, 18782-15-5; 4,7-dimethylchroman-2-ol, 24454-18-0; 4,7-dimethyl chroman-2-acetate, 24454-19-1; **2** semicarbazone, 24454-20-4; **4**, 24454-21-5; **5**, 24454-22-6; **6**, 24454-23-7; **13**, 24454-24-8; **14**, 24454-25-9; **15**, 24454-26-0; chroman-3-ol, 21834-60-6; tetrahydropyran-3-ol, 19752-84-2; **19**, 1481-82-9; **2**, 24454-30-6.

Acknowledgment.—This work was supported in part by the National Science Foundation (GP-9542).

Configuration and Conformation of 3-Arylideneflavanones

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Received January 12, 1970

The stereochemistry of 3-arylideneflavanones has been established by the preparation of both *cis* (**3a–c**) and *trans* (**2a–c**) isomers. Configurations and conformations are assigned on the basis of nmr spectra. The products obtained by the acid-catalyzed condensation of flavanones and aromatic aldehydes have the *trans* configuration. Ultraviolet irradiation produces the *cis* isomers. Allylic coupling constants show that the *trans* isomers exist in the conformation with the 2-phenyl group axial. The *cis* isomers appear to exist in both conformations. In 2,2-diphenylchromanone (**4**) the steric effect of the second phenyl group causes formation of the *cis* product 2,2-diphenyl-3-benzylidenechromanone (**5**). *o*-Hydroxybenzaldehyde with flavanone does not give the benzylidene derivative but forms *o*-hydroxybenzylflavone.

Flavanones have been condensed with a number of aromatic aldehydes to form 3-arylideneflavanones (termed flavindogenides) in high yield.[1] Flavindogenides have also been isolated as coproducts during the preparation of flavanones by the acid-catalyzed condensation of aromatic aldehydes and substituted *o*-hydroxyacetophenones.[2] Interest in 6-nitro-3-benzylideneflavanones as bacteriostats led Széll and Zarandy to reinvestigate methods for their preparation.[3] Recently two natural products, eucomin and eucomol, related in structure to flavindogenides, were isolated.[4] Eucomin is the first member of the arylidenechromanone family to be found in nature.

Two geometrical isomers are possible for the product from the condensation of aromatic aldehydes and flavanones since the β-aryl groups of the flavindogenide may be either *cis* or *trans* to the carbonyl group. In the reported cases only one of the two possible geometrical isomers was obtained. The condensation of aryl aldehydes with methylene compounds normally yields unsaturated products which have the carbonyl function *trans* to the larger group at the β-carbon atom.[5,6] However, as shown below, there was some evidence to suggest that 3-(2-nitrobenzylidene)flavanone prepared in the normal way had the *cis* configuration. Cromwell and coworkers[7] prepared *trans*-2-(2-aminobenzylidene)-4,4-dimethyltetralone by the reduction of the corresponding nitro compound with iron and acetic acid. This compound was cyclized by refluxing with hydrochloric acid or on treatment with hydrogen chloride to give 5,5-dimethyl-5,6-dihydrobenz[*c*]ac idine. Algar and M'Cullagh[8] were unable to isolate the corresponding amino compound by reduction of 3-(2-nitrobenzylidene)flavanone with stannous chloride in acetic acid saturated with hydrogen chloride but obtained 2,3-(2-phenylchromano-3,4)quinoline directly. This cyclized product was the only product obtained when the flavanone was treated under the conditions described by Bell and Cromwell for formation of the amino compound.[9] These results tended to indicate a *cis* configuration for the 3-arylideneflavanones.

In view of the interest shown in flavindogenides we undertook the present work in order to assign their stereochemistry. The stereochemical assignment was also necessary for our further studies on the epoxidation reactions of flavindogenides.[10] In this paper the results of our study on *cis*- and *trans*-3-arylideneflavanones are presented.[11]

The stereochemistry of the 3-arylideneflavanones has now been unambiguously determined by the synthesis of both the *trans* (**2a–c**) and *cis* (**3a–c**) compounds. Condensation of flavanones (**1a,b**) with benzaldehyde or anisaldehyde forms *trans*-flavindogenides (**2a–c**) in yields approaching 90%. In our study, as in previous reports, only one isomer was obtained. An examination of the reaction mixture using thin layer chromatography showed no trace of a second isomer. The nmr spectra of the crude reaction product also indicated only one isomer.

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