over silica gel and nylon, there was obtained 250 mg of methyl caffeate (*cis* and *trans*), 200 mg of phloroglucinol, 100 mg of starting material, and 300 mg of eriodictyol (**3i**): mp 264–266° (lit.[27] 267°); nmr 2.8–3.6 (m, H-3's), 5.6 (qu, H-2) 5.9 (s, H-6 and H-8), and 6.6–6.8 (m, 3 B-ring H's); λ_{max} 289 and 330, identical with that of an authentic sample. The chalcone was originally present but it isomerized completely during the nylon powder chromatography.

Phloroglucinol 3-Methoxy-4-hydroxycinnamate (1j).—Protection of 3-methoxy-4-hydroxycinnamic acid yielded the 3-methoxy-4-methoxymethyleneoxycinnamic acid, mp 137–139°. The protected acid (5 g) was converted into the phloroglucinol monoester (2.3 g): mp 166–168°; nmr spectrum, 3.4 (s, 3 H's), 3.85 (s, 3 H's), 5.22 (s, 2 H's), 6.07 (s, 3 H's), 6.72 and 7.75 (each a d, J = 16 cps, 1 H), 7.0–7.5 (3 H's), and 9.47 (2 H's). Removal of the protecting group yielded the free ester **1j**: mp 234–236; 3.83 (s, 3 H's), 6.07 (s, 3 H's), 6.63 and 7.75 (each a d, J = 16 cps, 1 H), 6.9–7.4 (3 H's), 9.4 (2 OH's), and 9.6 (1 OH). Treatment with acetic anhydride–pyridine yielded a triacetate: mp 111–112°; nmr ($CDCl_3$) 2.18 (s, 6 H's), 2.23 (s, 3 H's), 3.75 (s, 3 H's), 6.32 and 7.6 (each a d, J = 16 cps, 1 H), 6.73 (3 H's), and 6.9–7.1 (3 H's). A solution of 1.5 g of **1j** in 200 ml of methanol was irradiated for a period of 17 hr at 253.7 nm. Chromatography over silica gel yielded 250 mg of methyl 3-methoxy-4-hydroxycinnamate (*cis* and *trans*). The remainder was chromatographed over nylon powder, and yielded 500 mg of starting material, 200 mg of phloroglucinol, and 400 mg of chalcone **2j**, which was further purified by paper chromatography. It had mp 205–208° (lit.[28] 210–212°); nmr 3.8 (s, 3 H's), 5.8 (s, 2 H's), 6.6–7.1 (3 H's), and 7.5 and 7.9 (each a d, J = 16 cps, 1 H); λ_{max} 373 (log ϵ 4.52), shifted to 384 with NaOAc, to 406 with $AlCl_3$.

Phloroglucinol 3,4-Dimethoxycinnamate (1k).—The acid chloride from 10.0 g of 3,4-dimethoxycinnamic acid in 100 ml of benzene was added dropwise with stirring and cooling to a solution of 30.0 g of phloroglucinol in benzene–pyridine (10:3). After 4 hr, the upper layer was worked up as above, and it yielded a mixture which was chromatographed over silica gel. The di- and triesters were eluted with $CHCl_3$, while elution with ethyl acetate–chloroform (1:9) gave 6.0 g of monoester **1k**: mp 204–205; nmr 3.83 (s, 6 H's), 6.0 (3 H's), 6.67 and 7.73 (each a d, J = 16 cps, 1 H), 6.9–7.4 (m, 3 H's), and 9.47 (2 OH's). Acetic anhydride–pyridine treatment yielded a diacetate: mp 146–147°; nmr ($CDCl_3$) 2.3 (s, 6 H's), 3.93 (s, 6 H's), 6.47 and 7.85 (each a d, J = 16 cps, 1 H), and 6.9–7.3 (m, 6 H's). Irradiation of a solution of 2.0 g of **1k** in 300 ml of methanol for 36 hr at 253.7 nm gave, after chromatography over silica gel and nylon, 550 mg of methyl 3,4-dimethoxycinnamate (*cis* and *trans*), 400 mg of starting material, 400 mg of phloroglucinol, and 450 mg of chalcone **2k**, which was recrystallized from methanol and had mp 173: nmr 3.8 (s, 6 H's), 5.9 (s, 2 H's), 7.0–7.3 (3 H's), and 7.65 and 8.1 (each a d, J = 16 cps, 1 H); λ_{max} 366 (log ϵ 4.51), shifted to 378 with NaOAc, and to 400 nm with $AlCl_3$.

(27) F. B. Power and F. Tutin, *J. Chem. Soc.*, **91**, 887 (1907).

(28) M. Swaleh, W. Rahman, and M. O. Farooq, *Indian J. Chem.*, **2**, 375 (1964).

Registry No.—**1b**, 531-40-8; **1c**, 22129-63-1; **1f**, 25518-27-8; **1f** (triacetate), 25518-28-9; **1g**, 25568-73-4; **1g** (triacetate) 25518-29-0; **1h**, 25528-10-3; **1i**, 25528-11-4; **1i** (tetraacetate), 25528-12-5; **1j**, 25528-13-6; **1j** (triacetate), 25528-14-7; **1k**, 25528-15-8; **1k** (diacetate), 25528-16-9; **2b**, 25515-42-8; **2c**, 25515-43-9; **2d**, 25515-44-0; **2f**, 25515-45-1; **2g**, 25515-46-2; **2j**, 25515-47-3; **2k**, 25515-48-4; **3e**, 6307-93-3; **3h**, 480-43-3; **3i**, 4049-38-1; phloroglucinol monocinnamate, 28867-41-0; phloroglucinol (diacetate), 25528-21-6; 3-methoxy-4-methoxymethyleneoxycinnamic acid, 25528-22-7.

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A New Preparation of Coumarans

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A new reaction for the formation of 2,2-dialkylcoumarans has been discovered. When phenols are allowed to react with 2,2-disubstituted aldehydes in the presence of an acid catalyst, 2,2-dialkylcoumarans are formed in one step.

As part of an investigation of the reaction of various aldehydes with phenol and substituted phenols, the sulfuric acid catalyzed interaction of isobutyraldehyde with phenol in refluxing toluene was observed to give a substantial amount of 2,2-dimethylcoumaran (**3**), which was identified by infrared and nuclear magnetic resonance spectral parameters, elemental analysis, and conversion of the courmaran into the reported[1] solid 5,7-dinitro derivative. In addition an authentic sample of the coumaran (**3**) was prepared from β-methylallyl phenyl ether by the method of Franko-Filipasic.[2]

A number of other aldehydes and substituted phenols were allowed to interact under these same conditions in order to establish the limitations of the method. Isobutyraldehyde reacted with *o*-cresol, *m*-cresol, *p*-cresol, 2,4-xylenol, 4-(1,1,3,3-tetramethylbutyl)phenol, and α-naphthol to give coumarans in yields of 10–62% (Table I). Likewise, 2-ethylhexanal reacted with *m*-cresol to give 2-butyl-2-ethyl-6-methylcoumaran (**6**), but under the same conditions the following aldehydes failed to yield coumarans by reaction with *m*-cresol: acetaldehyde, propionaldehyde, butanal, pentanal, 3-methylbutanal, 2-methyl-2-butenal, and 2-phenylpropionaldehyde. In our hands, the only aldehydes which have produced a coumaran by interaction with a phenol are those which have only one hydrogen atom attached to the second carbon atom of the aldehyde molecule (a 2,2-disubstituted aldehyde).

Each reaction, whether it yielded a coumaran or not, produced varying amounts of resinous materials whose infrared spectra displayed a strong phenolic hydroxyl stretching absorption near 3500 cm^{-1}. Considering the reactants and the reaction conditions, these resins probably have a Novolak-type structure.[3]

The infrared spectra of all the coumarans and of the naphthofuran prepared in this work show a strong ab-

(1) C. D. Hurd and R. Dowbenko, *J. Amer. Chem. Soc.*, **80**, 4711 (1958).

(2) B. R. Franko-Filipasic (to FMC Corp.), U. S. Patent 3,320,286 (May 16, 1967).

(3) L. F. Fieser and M. Fieser, "Organic Chemistry," Reinhold, New York, N. Y., 1956, pp 866–869.

TABLE I
COUMARANS FORMED FROM VARIOUS PHENOLS AND ISOBUTYRALDEHYDE

Phenol	Coumaran[a]	Density, d^{20}_4	$n^{20}D$	Yield, %	Calcd, % C	Calcd, % H	Calcd, % O	Found, % C	Found, % H	Found, % O	Bp, °C (mm)	Ref[b]
Phenol	2,2-Dimethylcoumaran	0.9956	1.51234	35	81.04	8.16	10.79	81.04	8.06	10.92	109 (50)	1, c
o-Cresol	2,2,7-Trimethylcoumaran	0.9807	1.51598	46	81.43	8.69	9.86	81.78	8.60	9.92	123 (50)	c
m-Cresol	2,2,6-Trimethylcoumaran	0.9763	1.51405	62	81.43	8.69	9.86	81.59	8.29	9.76	131 (50)	c, d
p-Cresol	2,2,5-Trimethylcoumaran	0.9812	1.51327	22	81.43	8.69	9.86	81.34	8.64	10.23	123 (50)	c
2,4-Xylenol	2,2,5,7-Tetramethylcoumaran	0.9667	1.51303	54	81.77	9.14	9.07	81.72	9.01	9.19	116 (19)	
4-(1,1,3,3-Tetramethylbutyl phenol	2,2-Dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran		1.50680	10	83.02	10.84	6.14	83.16	10.17	6.99	153 (10)	
α-Naphthol	2,3-Dihydro-2,2-dimethylnaphtho[1,2-*b*]furan	1.0176	1.60465	40	84.81	7.11	8.07	84.82	7.01	8.20	138 (1)	

[a] All of the coumarans listed in this table are liquids at room temperature. [b] A reference indicates an alternate and previously reported synthesis of the coumaran. When no reference given, the coumaran is apparently new or has not been previously reported. [c] Q. R. Bartz, R. F. Miller, and R. Adams, *J. Amer. Chem. Soc.*, **57**, 371 (1935). [d] F. Bohlmann and C. Zdero, *Tetrahedron Lett.*, No. 33, 3683 (1968).

sorption band near 1260 cm^{-1}, assignable to aromatic ether absorption. Absorption bands assignable to carbonyl and hydroxyl stretching frequencies are absent. The nuclear magnetic resonance spectra display no unusual features.[4]

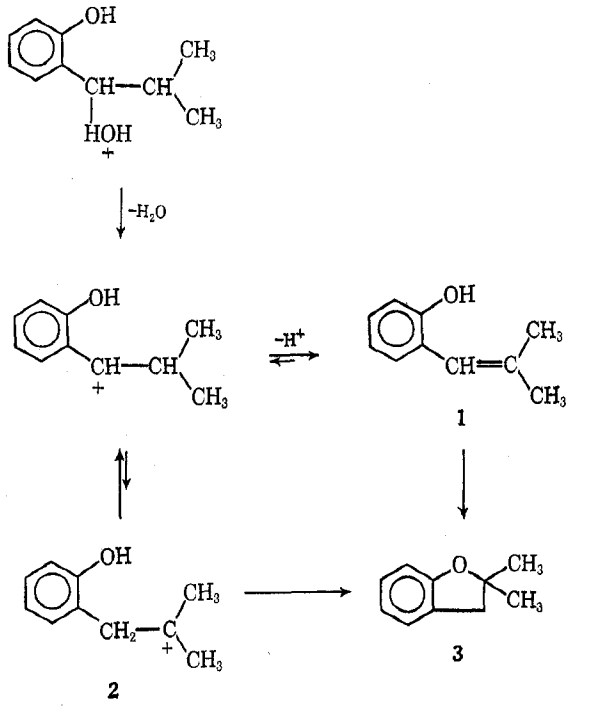
While a detailed study of the mechanism of this reaction was not made, we have observed several general aspects of the reaction which point to a carbonium ion pathway. First, the reaction is catalyzed by strong acids, including sulfuric, phosphoric, hydrochloric, and chlorosulfonic acids and a sulfonic acid type of ion-exchange resin. Nitric acid did not catalyze the production of coumarans, possibly because of its ability to act as an oxidizing agent. Sodium hydroxide was also ineffective as a catalyst.

A second aspect of the reaction is that refluxing benzene, toluene, and xylene are all successful solvents for the reaction, but water is not. This is reasonable because the reactants have limited solubility in water, and because the strong acid catalyst would protonate water in preference to a reactant species.

Finally, in several of the acid-catalyzed reactions of phenols with isobutyraldehyde a small amount of product, up to 5%, was identified as a phenol bearing an isobutenyl substituent. Because of this, equimolar amounts of *m*-cresol and isobutyraldehyde were heated in refluxing toluene solution for 27 days in the absence of any catalyst to give recovered starting materials, 12% 2-isobutenyl-5-methylphenol, and a trace of 2,2,6-trimethylcoumaran (**4**). The 2-isobutenyl-5-methylphenol was then smoothly cyclized to **4** by heating it in the presence of a catalytic amount of anhydrous magnesium chloride.

A reaction path which is consistent with these observations is illustrated by the reaction of phenol with isobutyraldehyde to give 2,2-dimethylcoumaran (**3**) (Scheme I). Our data are insufficient to comment upon the relative importance of 2-isobutenylphenol (**1**) and the ion (**2**).

SCHEME I

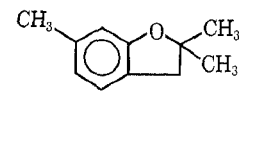


This mechanism helps to explain why aldehydes such as butanal or 3-methylbutanal which have secondary hydrogen atoms at the 2 position fail to form coumarans upon reaction with *m*-cresol, especially if the reaction path is predominantly through **2**. In such cases, the reaction would require formation of a secondary rather than a tertiary carbonium ion from the much more stable benzylic carbonium ion. We are unable to explain the failure of the reaction of 2-phenylpropionaldehyde with *m*-cresol to give a coumaran on this basis.

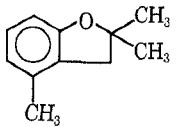
Two isomeric coumarans may result from the reaction of *m*-cresol with aldehydes. Thus, isobutyraldehyde and *m*-cresol produced a coumaran which might be 2,2,6-trimethylcoumaran (**4**) or 2,2,4-trimethylcoumaran (**5**). The coumaran from 2-ethylhexanal

(4) All of the coumarans listed in Table I, including the naphthofuran, are 2,2-dimethyl derivatives. These two methyl groups appear in all cases at 1.3 ppm (δ) in the nuclear magnetic resonance spectra as a single absorption line when observed in carbon tetrachloride solution. The adjacent two hydrogen atoms at the C-3 position appear as a singlet at 2.8–2.9 ppm. The aromatic protons appear in all of the coumarans in Table I as a multiplet at 6.2–7.1 ppm except those of 2,2,5,7-tetramethylcoumaran where the two aromatic protons appear as a single line at 6.7 ppm. The aromatic protons of the naphthofuran appear as a multiplet at 7.0–7.8 ppm. The methyl groups attached to the aromatic ring in those coumarans derived from *o*-cresol *m*-cresol, *p*-cresol, and 2,4-xylenol all appear as a singlet at 2.2 ppm. The 1,1,3,3-tetramethylbutyl group of 2,2-dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran shows additional absorption at 0.7 ppm due to its terminal *t*-butyl moiety, a singlet at 1.6 ppm due to the single methylene group in this chain, and a single line at 1.3 ppm assignable to the two methyl groups which are attached to the carbon atom which is joined to the aromatic ring.

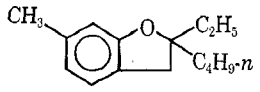
and *m*-cresol could be 2-butyl-2-ethyl-6-methylcoumaran (**6**) or 2-butyl-2-ethyl-4-methylcoumaran (**7**).



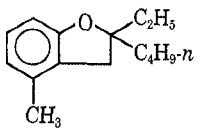
4



5



6



7

The nuclear magnetic resonance spectra showed that the pattern of the aromatic multiplets at 6.2–6.9 ppm (δ) is identical for both reaction products. This is conclusive evidence that the position of the aromatic methyl group in the coumaran from each reaction is the same. That is, the products are either **4** and **6** or **5** and **7**. The aromatic multiplet consists of a doublet centered at 6.8 ppm which integrates for 1 proton, a second doublet centered at 6.4 ppm, and a singlet at 6.3 ppm which nearly superimposes one peak of this latter doublet; this combination of the doublet at 6.4 and singlet at 6.3 integrates for 2 protons. Such a pattern indicates that the coumaran obtained from *m*-cresol and isobutyraldehyde is **4** and that the coumaran obtained from *m*-cresol and 2-ethylhexanal is **6**.

Further evidence for this conclusion is provided by the infrared spectra of **4** and **6**, which display bands and patterns characteristic of a 1,2,4-trisubstituted benzene.[5]

To show more conclusively that the product of the reaction of *m*-cresol with isobutyraldehyde is the coumaran (**4**), this coumaran was converted in a four-step sequence to 2,2,6-trimethyl-3-coumaranone by following a published procedure in which 2,2-dimethylcoumaran was converted to 2,2-dimethyl-3-coumaranone.[6] The 2,2,6-trimethyl-3-coumaranone is a known compound with a reported[7] melting point of 52°; it gives a semicarbazone derivative reported[7] to melt at 250°. The coumaranone which we prepared from the product of *m*-cresol and isobutyraldehyde melts at 51.5–52.5°; it gave a semicarbazone derivative which melts at 244–246°.

Experimental Section

Melting and boiling points are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 221 spectrometer. All nmr spectra were recorded in carbon tetrachloride solution on a Varian HA 60-IL spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane: s = singlet, d = doublet, t = triplet, and m = multiplet.

General Preparation of Coumarans. 2,2,6-Trimethylcoumaran (4).—This reaction will serve as an example for the preparation of all the coumarans and the naphthofuran listed in Table I, since each of these compounds is prepared in the same manner as 2,2,6-trimethylcourmaran.

A solution of 216 g (2.0 mol) of *m*-cresol, 144 g (2.0 mol) of isobutyraldehyde, 120 ml of toluene, and 6.5 g of concentrated sulfuric acid was refluxed for 3 hr, water being removed azeotropically as it was formed through use of a Barrett trap. The reaction mass was then distilled at 20° (4 mm), collecting the total distillate in a single receiver. The distillate was washed with 20% sodium hydroxide solution to remove unreacted *m*-cresol, then with water, and dried over calcium sulfate. It was then distilled again to give 200 g (62%) of 2,2,6-trimethylcourmaran (**4**), bp 131° (50 mm).

Preparation of 2-Isobutenyl-5-methylphenol.—A solution of 570 g (5.0 mol) of *m*-cresol, 360 g (5.0 mol) of isobutyraldehyde, and 250 ml of toluene was allowed to reflux for 27 days in the absence of a catalyst and was then distilled to give recovered starting materials, 121 g (12%) of 2-isobutenyl-5-methylphenol [bp 150° (50 mm)], and 5.0 g of 2,2,6-trimethylcoumaran (**4**) which was identified by its ir spectrum. The mass spectrum of 2-isobutenyl-5-methylphenol showed a parent ion at *m/e* 162 which corresponds to a molecular formula of $C_{11}H_{14}O$; nmr spectrum (CCl_4) δ 1.7 (s, 3, CH_3 group on double bond), 1.9 (s, 3, CH_3 group on double bond), 2.2 (s, 3, C_5 CH_3), 5.4 (s, 1, C_1 OH), 6.1 (s, 1, H on double bond), 6.5–7.0 (m, 3, aromatic); ir spectrum (NaCl) 3500 and 1180 cm^{-1} (phenolic OH), 795 and 1580 cm^{-1} (trisubstituted olefin where the double bond is conjugated with the aromatic ring). On high dilution (CCl_4) the band at 3500 cm^{-1} was observed as two bands, one at 3608 cm^{-1} ("free" OH stretching frequency) and another at 3540 cm^{-1} (intra hydrogen bonding to the π bond of the 2-isobutenyl substituent).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.47; H, 9.00. Found: C, 81.44; H, 8.70.

Cyclization of 2-Isobutenyl-5-methylphenol.—A mixture of 50 g of 2-isobutenyl-5-methylphenol from the previous reaction and 0.5 g of anhydrous magnesium chloride was heated at 184–194° for 8.5 hr and then distilled *in vacuo* to give 84% 2,2,6-trimethylcoumaran (**4**), identified by vpc retention time and by comparison of its ir spectrum with that of **6** prepared in one step from *m*-cresol and isobutyraldehyde (Table I).

Conversion of β-Methylallyl Phenyl Ether to 2,2-Dimethylcoumaran.—According to an established procedure,[2] a mixture of β-methylallyl phenyl ether (76.5 g, 0.5 mol) and 0.76 g of anhydrous magnesium chloride was purged with nitrogen and then stirred and heated at 180–186° for 6 hr under a nitrogen atmosphere. The reaction mass was distilled to give a 70% yield of 2,2-dimethylcoumaran, identified by vpc retention time and by comparison of its ir spectrum with that of the coumaran prepared from phenol and isobutyraldehyde (Table I).

Nitration of 2,2-Dimethylcoumaran.—Following the exact procedure of Hurd and Dowbenko,[1] a solution of 10 ml of concentrated sulfuric acid and 10 ml of concentrated nitric acid was employed to convert 1.5 g of 2,2-dimethylcoumaran, which had been prepared from phenol and isobutyraldehyde (Table I), into 2,2-dimethyl-5,7-dinitrocoumaran, yellow crystals, mp 150–151° from ethanol (lit.[2] 149–150°). This same dinitrocoumaran was then prepared as just described from the 2,2-dimethylcoumaran which had been obtained by cyclization of β-methylallyl phenyl ether. A mixture melting point of the dinitrocoumaran prepared by both methods showed no depression.

Preparation of 2-Butyl-2-ethyl-6-methylcoumaran (6).—A solution of 216 g (2.0 mol) of *m*-cresol, 256 g (2.0 mol) of 2-ethylhexanal, 108 ml of toluene, and 6.6 g of concentrated sulfuric acid was refluxed for 70 min, water being removed azeotropically as it was formed through use of a Barrett trap. The reaction mass was then distilled until a temperature of 200° at 2 mm had been obtained, collecting all of the distillate in a single receiver. The distillate was washed with 20% sodium hydroxide solution, then water, dried over calcium sulfate, and distilled again to give 172 g (39%) of 2-butyl-2-ethyl-6-methylcoumaran (**6**): bp 160° (22 mm); nmr spectrum (CCl_4) δ 0.9 (t, 6, ethyl- and butyl CH_3), 1.0–1.8 (m, 8, ethyl and butyl CH_2), 2.2 (s, 3, C_6 CH_3), 2.8 (s, 2, C_3 H), 6.8 (d, 1, aromatic), 6.4 (d, 1, aromatic), 6.3 (s, 1, aromatic).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16; O, 7.33. Found: C, 82.68; H, 9.90, O, 7.51.

2,2,6-Trimethyl-3-coumaranone.—This sequence of reactions

(5) 2,2,5-Trimethylcoumaran is a 1,2,4-trisubstituted benzene. Its infrared spectrum shows strong bands at 810 and 880 cm^{-1} (out-of-plane CH deformation vibrations) and a weak absorption pattern of three bands (overtone and combination bands) in the 2000–1650-cm^{-1} range, all of which are characteristic of a 1,2,4-trisubstituted benzene (L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 67, 78, 90). The spectra of **4** and **6** in these regions are essentially identical.

(6) C. D. Hurd and R. Dowbenko, *J. Amer. Chem. Soc.*, **82**, 3662 (1960).

(7) K. v. Auwers, *Justus Liebigs Ann. Chem.*, **439**, 132 (1924).

was carried out in a manner very similar to that used by Hurd and Dowbenko[6] to convert 2,2-dimethylcoumaran to 2,2-dimethyl-3-coumaranone. Thus a mixture of 8.1 g (0.05 mol) of 2,2,6-trimethylcoumaran (4), 8.9 g (0.05 mol) of N-bromosuccinimide, 0.05 g of benzoyl peroxide, and 150 ml of dry carbon tetrachloride was refluxed for 2 hr and processed in the manner of Hurd and Dowbenko to give 7.6 g (63%) of 3-bromo-2,2,6-trimethylcoumaran as a colorless liquid: bp 80–81° (1.5 mm); nmr spectrum (CCl_4) δ 1.3 (s, 3, C_2 CH_3), 1.5 (s, 3, C_2 CH_3), 2.2 (s, 3, C_6 CH_3), 4.9 (s, 1, C_3 H), and 6.3–7.2 (m, 3, aromatic).

The entire amount of 3-bromo-2,2,6-trimethylcoumaran was dissolved in a mixture of 12 ml of glacial acetic acid and 7.5 g of freshly fused potassium acetate. The mixture was heated at 120° for 10 min, allowed to stand at room temperature overnight, and then heated on a steam bath for 3 hr. The crude product, 3-acetoxy-2,2,6-trimethylcoumaran, was isolated in the same way that Hurd and Dowbenko isolated 3-acetoxy-2,2-dimethylcourmaran except that the product was not distilled. Instead, the crude acetoxycoumaran was dissolved in a solution of 50 ml of methanol and 5.0 g of potassium hydroxide, and the solution was refluxed for 1 hr. It was then diluted with 100 ml of water, saturated with sodium chloride, and extracted with ether. After drying the ethereal extract, solvent was removed and the crude product, 3-hydroxy-2,2,6-trimethylcoumaran (3.1 g), solidified spontaneously. After recrystallization from hexane, the hydroxycoumaran appeared as colorless crystals, mp 66–66.5°; its ir spectrum (NaCl) showed the expected hydroxyl stretching vibration at 3370 cm^{-1} and a band at 1280 cm^{-1} assignable to the ether stretching vibration.

The 3-hydroxy-2,2,6-trimethylcoumaran (2.5 g) in 20 ml of pyridine was added to a slurry of chromium trioxide (4.5 g) in 45 ml of pyridine at 20°. The reaction mixture was allowed to stand overnight at 20–25° and was then diluted with 200 ml of water. The mixture was extracted with ether. The ethereal extract was washed with dilute aqueous hydrochloric acid, then water, and dried over calcium sulfate. Evaporation of the ether gave 2.1 g of 2,2,6-trimethyl-3-coumaranone as colorless needles, mp 51.5–52.5° from hexane (lit.[7] 52°), whose ir spectrum showed a strong carbonyl stretching vibration at 1725 cm^{-1}. The coumaranone formed a semicarbazone derivative, mp 244–246° from ethanol (lit.[7] 250°).

Registry No.—6, 25594-08-5; 2-isobutenyl-5-methylphenol, 25594-09-6; 3-bromo-2,2,6-trimethylcoumaran, 25594-10-9; 3-hydroxy-2,2,6-trimethylcoumaran, 25594-11-0; 2,2,5,7-tetramethylcoumaran, 25594-12-1; 2,2-dimethyl-5-(1,1,3,3-tetramethylbutyl)coumaran, 25594-13-2; 2,3-dihydro-2,2-dimethylnaphtho[1,2-*b*]-furan, 25594-14-3.

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Synthesis and Characterization of C_3 and C_{17} Steroidal Amines

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The synthesis and characterization of 5α-androstane C_3 and C_{17} amines are reported. Primary, tertiary, and quaternary mono- and diammonium salts of 5α-androstane have been synthesized. The salts are found to interact selectively with nucleic acids.[3]

For the past three years, considerable work has been devoted in our laboratory to the elucidation of the interaction specificity of nucleic acid systems with mono- and polyammonium salts.[2] It is well known that these compounds interact very strongly with polynucleotides. This paper reports the synthesis and characterization of steroidal amines, of 5α-androstane, *i.e.*, primary, tertiary, and quaternary ammonium salts as well as various epimers (3α, 3β, 17α, and 17β). The interaction specificity of these salts with various nucleic acids has been studied by proton magnetic resonance, ultraviolet, circular dichroism, viscometry, and T_m of helix–coil transitions. While this is reported elsewhere,[3] the results indicate that the steroidal amines selectively stabilize the DNA helical structure, while causing the ribose-containing acids to unravel and denature. The temperature-dependent pmr experiments show that single-stranded random coils interact with the steroidal amines *via* electrostatic and hydrogen- and hydrophobic-type bonding. The capacity to form H bonding in the random coils is shown to be greater than that of the helix.[3]

Results and Discussion

The synthetic scheme for the preparation of the steroidal amines is straightforward and is outlined in Schemes I and II. The 3-amino-17-oxo-(5α)-androstane derivatives, **1** and **2**, were synthesized by an SN2 reaction of dimethylamine with the appropriate 3-tosylate 17-oxo-(5α)-androstane precursor. For example, the 3β-tosylate 17-oxo intermediate was allowed to react with dimethylamine in a sealed tube to give the 3α-dimethylamino-17-oxo-(5α)-androstane product as the tosylate salt. Conversion to the free base and acidification with HCl afforded the salt **2**. In a similar manner, the 3β epimer was obtained. The stereochem-

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