Substituted Chromans and Tetrahydrofuro[2,3-*b*]benzofurans (Trapped Tetrahedral Intermediates) from 3-Phenyl-2-benzofuranones.

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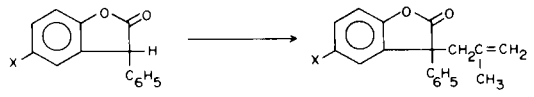
The previously discovered neighboring group reaction has been extended to the synthesis of chroman derivatives (*i.e.*, **4**, **5**, **6**) containing geminal methyls in the 2-position, a feature common to certain physiologically active natural chromans. In two instances, cyclic ortho ester by-products (**8**), not observed in previous work, were formed as a result of the intramolecular trapping of tetrahedral intermediates. Reasons for the incursion of this unexpected side reaction are discussed.

In continuation of the utilization of certain neighboring group reactions for the preparation of compounds of potential pharmacological interest, a series of 2,2-dimethyl-4-phenylchromans has been prepared (1). It was hoped that the addition of the geminal methyl groups to the simpler 4-phenylchroman nucleus previously prepared (2) would impart more physiological activity to the system, in analogy to certain potent naturally occurring chromans (*e.g.*, the cannabinoids). Although this hope was not realized, some of the chemistry encountered in the present work is sufficently different from that of the original work (2) to justify reporting it.

The sodio-derivatives of the three phenylbenzofuranones **1a**, **b**, **c**, were readily alkylated with methallyl chloride in dimethylformamide (85-90% yield).



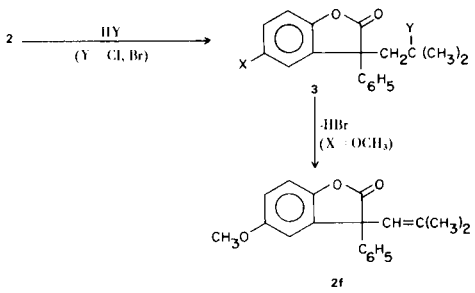
1a, X = H
1b, X = Cl
1c, X = OH

2

It is interesting that the hydroxy derivative **1c** gave exclusive carbon-alkylation. The acidity of the 3-hydrogen atom of **1c** is roughly two orders of magnitude less than that of the phenolic hydrogen (3). Thus the mono-sodium derivative of **1c** must be mostly (> 98%) in the form of the phenoxide salt. The selective formation of **2c** (see Table I) serves as another example of the overwhelming nucleophilic reactivity of most carbanions over most oxyanions. Addition of a second equivalent of base (sodium hydride) to the initial alkylation product **2c**, followed by treatment with dimethyl sulfate or benzyl bromide gave the methyl and benzyl ethers, **2d** and **2e**, respectively.

Addition of halogen acids to the methallyl derivatives **2** occurred smoothly to give the halo-isobutyl compounds **3** (see Table I).

As expected, hydrogen bromide gave better yields than hydrogen chloride, and in all cases addition occurred to give the tertiary halide exclusively. In one instance (**3f**) the

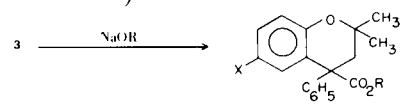


3

2f

isomeric isobutenyl derivative **2f** was isolated as a minor (12%) by-product resulting from elimination in a direction which was not the reverse of the addition.

Treatment of the halides **3** with sodium alkoxides in the usual manner (2, 4) generally gave good yields of the esters **4** (see Table II).



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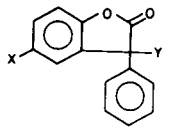
However, conversion of the tertiary halides was much slower than that of the primary halides of the previous work (2). Whereas the primary bromide converted almost instantaneously at room temperature to the chroman in the presence of sodium methoxide in methanol, the halides **3** (bromides as well as chlorides) required hours. Two bromides of the present work (*i.e.*, **3e** and **3f**) did not give

TABLE I

3-Phenyl-2-benzofuranones

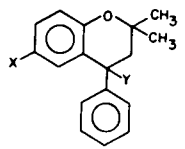


No.	X	Y	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carobn, % Calcd.	Carobn, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2a	H	$CH_2C(CH_3)=CH_2$	49-50 (a)	90	CH_3OH	$C_{18}H_{16}O_2$	81.79	81.62	6.10	6.40
2b	Cl	$CH_2C(CH_3)=CH_2$	70-71 (b)	86	CH_3OH	$C_{18}H_{15}ClO_2$	72.36	72.23	5.06	5.07
2c	OH	$CH_2C(CH_3)=CH_2$	140-141	88	C_6H_6-cyclohexane	$C_{18}H_{16}O_3$	77.12	76.81	5.75	5.75
2d	OCH_3	$CH_2C(CH_3)=CH_2$	64-65	53 (c)	C_2H_5OH	$C_{19}H_{18}O_3$	77.53	77.65	6.16	6.25
2e	$OCH_2C_6H_5$	$CH_2C(CH_3)=CH_2$	99-100	63 (c)	CH_3OH	$C_{25}H_{22}O_3$	81.06	81.11	5.99	6.21
2f	OCH_3	$CH=C(CH_3)_2$	115-116	12 (d)	C_2H_5OH	$C_{19}H_{18}O_3$	77.53	77.31	6.16	6.29
3a	H	$CH_2C(Cl)(CH_3)_2$	99-100	43	$(C_2H_5)_2O$	$C_{18}H_{17}ClO_2$ (e)	71.86	71.71	5.70	5.75
3b	H	$CH_2C(Br)(CH_3)_2$	88-90	89	$(C_2H_5)_2O$-hexane	$C_{18}H_{17}BrO_2$	62.62	62.63	4.96	5.01
3c	Cl	$CH_2C(Cl)(CH_3)_2$	143-144	38	CH_3OH	$C_{18}H_{16}Cl_2O_2$ (f)	64.49	64.15	4.81	4.73
3d	Cl	$CH_2C(Br)(CH_3)_2$	144-145	72	$CHCl_3$	$C_{18}H_{16}BrClO_2$	56.94	57.11	4.25	4.24
3e	OH	$CH_2C(Br)(CH_3)_2$	150-153	67	$CHCl_3$	$C_{18}H_{17}BrO_3$	59.85	60.29	4.75	4.75
3f	OCH_3	$CH_2C(Br)(CH_3)_2$	92-93	74	C_2H_5OH	$C_{19}H_{19}BrO_3$	60.81	60.91	5.10	5.12

(a) B.p. 148-154°/0.5 mm. (b) B.p. 168-169°/0.5 mm. (c) in 2 steps from **1c**. (d) by-product from the preparation of **3f**. (e) *Anal.* Calcd. for Cl: 11.79. Found: 11.65. (f) *Anal.* Calcd. for Cl: 21.15. Found: 21.11.

TABLE II

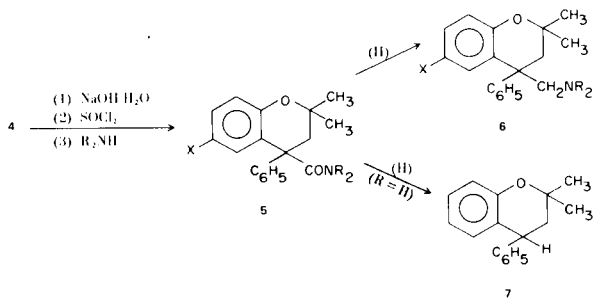
2,2-Dimethyl-4-phenylchromans



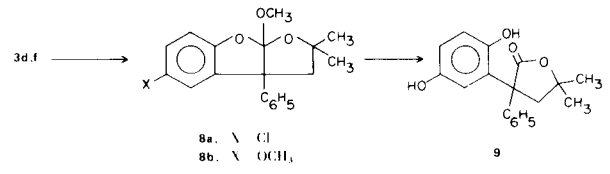
No.	X	Y	M.p., °C	Yield Purified, %	Purification Solvent	Formula	Analyses Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
4a	H	CO_2CH_3	108-109	63	CH_3OH	$C_{19}H_{20}O_3$	77.00	77.21	6.81	6.99		
4b	H	$CO_2CH_2CH_2N(CH_3)_2 \cdot HCl$	162-163	60	C_2H_5OH-$(C_2H_5)_2O$	$C_{22}H_{28}ClNO_3$	67.77	67.44	7.24	7.57	3.59	3.57
4c	H	$CO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$	196-197	58	C_2H_5OH-$(C_2H_5)_2O$	$C_{24}H_{32}ClNO_3$	68.98	69.68	7.72	8.00	3.35	3.44
4d	H	CO_2H	195-196	98	C_6H_6	$C_{18}H_{18}O_3$	76.57	76.32	6.42	6.62		
4e	Cl	CO_2CH_3	121-123	67	CH_3OH	$C_{19}H_{19}ClO_3$	68.98	68.63	5.79	5.82		
4f	Cl	CO_2H	184-185	94	C_2H_5OH-H_2O	$C_{18}H_{17}ClO_3$	68.25	67.85	5.41	5.43		
4g	OH	CO_2CH_3	156-157	28	$(C_2H_5)_2O$-pentane	$C_{19}H_{20}O_4$	73.06	73.22	6.45	6.75		
4h	OCH_3	CO_2H	124-126	93	Cyclohexane	$C_{19}H_{20}O_4$	73.06	73.12	6.45	6.52		
5a	H	$CONH_2$	206-208	88	2-Butanone	$C_{18}H_{19}NO_2$	76.85	77.14	6.81	6.96	4.98	4.90
5b	H		159-161	82	CH_3OH	$C_{23}H_{28}N_2O_2$	75.79	75.98	7.74	7.95	7.69	7.82
5c	Cl	$CONH_2$	184-185	75	C_2H_5OH	$C_{18}H_{18}ClNO_2$	68.46	68.30	5.75	5.84	4.44	4.42
5d	Cl	$CON(CH_3)_2$	115-117	74	CH_3OH	$C_{20}H_{22}ClNO_2$	69.86	69.93	6.45	6.60	4.07	4.09
5e	Cl		140-142	92	C_2H_5OH	$C_{22}H_{24}ClNO_2$	71.44	71.21	6.54	6.58	3.79	3.69
5f	Cl		163-165	87	CH_3OH	$C_{23}H_{27}ClN_2O_2$	69.25	69.59	6.82	6.98	7.02	7.15
5g	OCH_3	$CON(CH_3)_2$	85-86	70	Pentane	$C_{21}H_{25}NO_3$	74.31	74.48	7.42	7.77	4.13	4.11
5h	OCH_3		109-110	65	C_2H_5OH	$C_{23}H_{27}NO_3$	75.59	75.63	7.45	7.64	3.83	3.79
5i	OCH_3		120-121	70	C_2H_5OH	$C_{24}H_{30}N_2O_3$	73.07	73.23	7.66	7.90	7.10	7.07
6a	H		253-255	67	C_2H_5OH	$C_{23}H_{32}Cl_2N_2O$	65.24	64.82	7.62	7.85	6.62	6.70
6b	Cl	$CH_2N(CH_3)_2 \cdot HCl$	235-236	25	C_2H_5OH	$C_{20}H_{25}Cl_2NO$	65.57	65.20	6.88	6.95	3.82	3.93
6c	Cl		248-251	60	C_2H_5OH	$C_{22}H_{27}Cl_2NO$	67.35	67.37	6.94	7.03	3.57	3.52
6d	Cl		244-245	31	C_2H_5OH	$C_{23}H_{30}Cl_2N_2O$	65.55	65.55	7.18	7.38	6.65	6.55
6e	OCH_3	$CH_2N(CH_3)_2 \cdot HCl \cdot H_2O$	121-123	52	C_2H_5OH	$C_{21}H_{30}ClNO_3$	66.39	66.84	7.96	8.25	3.69	3.60
6f	OCH_3		232-234	72	C_2H_5OH	$C_{23}H_{30}ClNO_2$	71.21	70.82	7.79	8.01	3.61	3.55
7	H	H	119-120	53	C_2H_5OH	$C_{17}H_{18}O$	85.67	85.49	7.61	7.71		

good yields of **4** under the usual conditions. The free phenolic group in **3e**, by rapid formation of the oxyanion, undoubtedly tends to inhibit further attack by methoxide ion elsewhere in the molecule. The methoxy derivative **3f** gave good yields of **4** (X = OCH_3, R = CH_3) only by treatment with sodium methoxide in dimethyl sulfoxide. Reasons for this are discussed below.

By conventional procedures, the methyl esters **4** were converted to corresponding amides **5** (Table II) which were reduced either by lithium aluminum hydride or diborane to the amines **6** (Table II). However, hydride reduction of the primary amide **5a** (X = R = H) persistently resulted in exclusive carbonyl cleavage to give the 4-phenylchroman **7**.



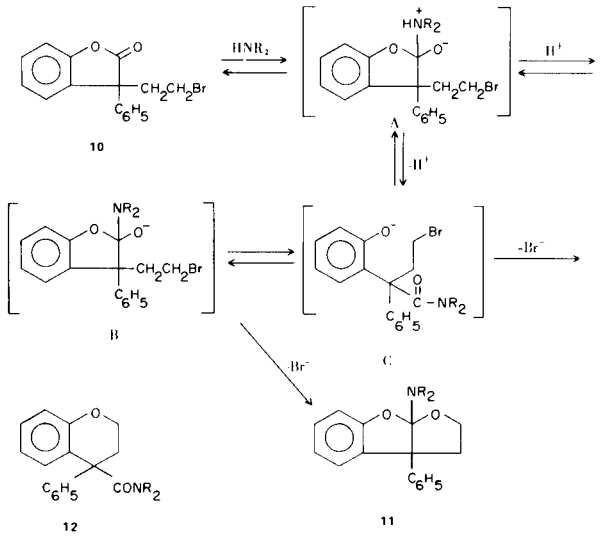
The most surprising outcome of the present work arose from the identification of ortho-ester by-products **8** in the reaction of two of the bromides **3d** and **3f** with sodium methoxide in methanol. Both could be isolated in 15% yield, and pmr analysis showed that 25% of the crude



product obtained from **3f** consisted of the ortho ester **8b** (the remainder was the normal ester **4**). Fusion of **8b** with anhydrous pyridine hydrochloride gave the lactone **9** possessing the infrared spectral properties previously found (5) to be characteristic of this structural type.

Although treatment of the primary bromide **10** with secondary amines previously had been found (6) to lead to trapped tetrahedral intermediates of type **11**, no such products were identifiable from the reaction with methoxide in methanol.

It was assumed that the tetrahedral intermediate B was more stable than the one involving methoxide in place of NR_2, with the result that when methoxide ion was used, phenoxide was more rapidly expelled from B (*i.e.*, intermediate of type C) and the sole product was the chroman ester analogous to **12**. Aside from any effects due to the geminal methyl groups, which are probably important, the results of the present work suggest that at least two other factors influence product ratios (*i.e.*, type **11** *vs.* type **12**).



A donor substituent *para* to the oxygen atom in C, especially *p*-methoxy, destabilized the phenoxide ion (*i.e.*, favors B *vs.* C), but also increases the nucleophilic reactivity of the oxygen anion relative to that of the unsubstituted phenoxide ion. In hydroxylic solvents, hydrogen-bonded solvation of the *p*-methoxy phenoxide ion reduces its nucleophilic reactivity sufficiently to allow the reaction type B → **11** to compete significantly with the reaction type C → **12**. In the poor anion solvator DMSO such attenuation of reactivity does not occur and the sole product is the normal ester **4** (*i.e.*, reaction type C → **12**).

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 521 spectrophotometer and wave numbers are reported in cm^{-1}. The Raman spectrum was recorded on a Jarrell-Ash Model 500 spectrometer. Pmr spectra were recorded on a Varian T-60 (60 MHz) spectrometer. Chemical shifts are reported as δ relative to TMS (δ = 0.000 ppm), using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. The mass spectrum was obtained in a AEI Model MS902 spectrometer.

The three benzofuranone starting materials **1a** (7), **1b** (8), and **1c** (7) were prepared by published methods.

3-Methallyl-3-phenyl-2-benzofuranone (**2a**) and Analogs.

To a stirred suspension of sodium hydride (0.4 mole, washed from mineral oil with benzene) in dry dimethylformamide (250 ml.), under an atmosphere of nitrogen, solid **1a** (84 g., 0.4 mole) was added in portions over one hour, keeping the temperature between 20° and 30° by means of a cold water bath. After addition was complete, stirring was continued for 30 minutes and then methallyl chloride (40 g., 0.44 mole) was added dropwise to the clear red solution over a period of 15 minutes, during which time the temperature rose from 24° to 45°. After stirring at room temperature overnight, the reaction mixture was heated at 90-95° for 2 hours, cooled, and poured into ice (1 kg.). The precipitated oil was taken up in ether (900 ml.), washed with water (2 x 300 ml.), decolorized by treatment with Norite, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distil-

lation gave an orange colored oil (112 g.) that crystallized on cooling in ice. This was taken up in a minimum quantity of hot methanol, cooled and seeded. There was obtained 94.5 g. (90% yield) of **2a**, m.p. 49-50°.

In like manner were prepared the two 5-substituted derivatives **2b** and **2c** (see Table I for properties), except that for the preparation of **2c**, the sodium hydride (in benzene suspension) was added in a cold (10°) solution of **1c** and methallyl chloride in dimethylformamide.

The methoxy (**2d**) and benzyloxy (**2e**) derivatives were best prepared without isolation of **2c**. After completion of the methallylation of **1c**, an equivalent quantity of dimethyl sulfate (for **2d**) or benzyl bromide (for **2e**) was added followed by another equivalent of sodium hydride (at 10°). Stirring at room temperature overnight was sufficient to complete the final etherification step.

3-(2-Bromoisobutyl)-3-phenyl-2-benzofuranone (**3b**) and Analogs.

A stirred solution of **2a** (30 g., 0.114 mole) and diphenylamine (0.3 g.) in 60 ml. of cyclohexane was treated with a rapid stream of anhydrous hydrogen bromide. The temperature rose from 25° to 34° and after 2 hours the mixture set to a semi-solid mass. After standing overnight, the product was collected at the filter, washed with a little cold ether, taken up in 300 ml. of warm ether, decolorized with charcoal, and the solution was concentrated to 100 ml. Addition of 80 ml. of hexane followed by seeding gave 30.5 g. (89%) of pure **3b**, m.p. 88-90°.

The other bromides, **3d**, **3e**, and **3f** (see Table I) were prepared similarly except that chloroform instead of cyclohexane was used as solvent in all cases. Also to minimize ether cleavage, the synthesis of **3f** was carried out at ice-bath temperature.

The chloro-compounds **3a** and **3c** were obtained, respectively, by treating **2a** in cyclohexane and **2b** in chloroform with hydrogen chloride in the presence of a catalytic amount of boron trifluoride etherate.

3-(2-Isobutenyl)-5-methoxy-3-phenyl-2-benzofuranone (**2f**).

From the ethanol filtrate remaining after crystallization of the bromide **3f** (from an 0.19 mole run), a solid deposited which was not **3f**. Recrystallization once from ethanol gave 6.6 g., m.p. 115-116°; ir (deuteriochloroform): 1800 (ν C=O); Raman (solid): 1665 (ν CH=C<); pmr (deuteriochloroform): δ 1.40 (d, 3H, J = 1 Hz, =CCH_3), δ 1.80 (d, 3H, J = 1 Hz, =CCH_3), δ 3.83 (s, 3H, OCH_3), δ 5.67-5.80 (m, 1H, =CH), δ 6.7-7.4 (m, 8H, ArH).

2,2-Dimethyl-4-phenyl-4-chromancarboxylic Esters (**4**).

The methyl esters **4a**, **4e**, and **4g** were prepared by treating the corresponding bromides **3b**, **3d**, and **3e**, respectively, with equivalent quantities of sodium methoxide in methanol at room temperature, essentially according to the method previously described (2) for the synthesis of the simple 4-phenylchroman carboxylic ester lacking the geminal methyl groups. Whereas the primary bromide reacted in a matter of minutes (2), the tertiary bromides of the present work required many hours (24-48) for the production of optimum yields. As expected from the likelihood of elimination, heating the mixtures was usually counter-productive. Likewise, using the chloride **3a** as starting material resulted in slightly lower yields of **4a** (54% *vs.* 63% from the bromide **3b**).

The basic esters **4b** and **4c** also were prepared by treating the bromide **3b** with the sodium derivative of the appropriate amino alcohol in dimethylformamide solution, essentially as described previously (4) for the simpler chroman ring system.

Treatment of the methoxy bromide **3f** with sodium methoxide *in methanol* gave poor yields of the corresponding **4** (X = OCH_3, R = CH_3) along with appreciable amounts of the ortho ester **8**. The following procedure was devised to optimize the yield of the former ester.

Methyl 6-Methoxy-2,2-dimethyl-4-phenyl-4-chromancarboxylate (**4**, X = OCH_3, R = CH_3).

To a stirred solution of sodium methoxide (0.03 mole; prepared from 0.69 g. of sodium) in dry dimethyl sulfoxide (80 ml.) was added 7.50 g. (0.02 mole) of solid **3f**. The resulting red solution warmed to 40°. It was allowed to stand at room temperature overnight and then was poured into ice-water. The precipitated product was taken up in ether, washed with water several times, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation left a viscous yellow oil (4.3 g., 65% yield) that could not be crystallized; pmr (deuteriochloroform): δ 1.20 (s, 3H, CCH_3), δ 1.30 (s, 3H, CCH_3), δ 2.10 [d, 1H, J = 14 Hz, C(H)H], δ 3.00 [d, 1H, J = 14 Hz, CH(H)], δ 3.67 (s, 3H, OCH_3), δ 3.83 (s, 3H, OCH_3), δ 6.7-7.5 (m, 8H, ArH).

Furthermore, the ir spectrum showed carbonyl absorption only at 1725 cm^{-1} (ester C=O; none at 1800 cm^{-1}, characteristic of the benzofuranone C=O) and the pmr spectrum contained none of the peaks characteristic of the ortho ester **8**. (The only foreign peak was due to a trace of DMSO.) The identity and purity of this ester was further established by the fact that it could be hydrolyzed to the pure acid **4h** in 93% yield.

5-Chloro-8a-methoxy-2,2-dimethyl-3a-phenyl-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (**8a**).

To a stirred solution of sodium methoxide (0.15 mole, prepared from 3.45 g. of sodium) in methanol (500 ml.) was added, in portions over 30 minutes, 57.0 g. (0.15 mole) of the solid bromide **3d**. After being stirred overnight at room temperature, the precipitated product was collected at the filter and dried. There was obtained 30.2 g. of the normal ester **4e**, m.p. 121-123°; ir (deuteriochloroform): 1725 (ν C=O); pmr (deuteriochloroform): δ 1.20 (s, 3H, CCH_3), δ 1.33 (s, 3H, CCH_3), δ 2.10 [d, 1H, J = 14 Hz, C(H)H], δ 3.00 [d, 1H, J = 14 Hz, CH(H)], δ 3.83 (s, 3H, OCH_3), δ 6.7-7.4 (m, 8H, ArH).

The filtrate was concentrated to dryness in a rotating evaporator. the residue was taken up in chloroform, washed with water, treated with charcoal, filtered, and concentrated again to dryness. The residual oil was taken up in a minimum quantity of hot methanol and allowed to cool. An additional quantity (3.0 g., m.p. 121-122°) of the ester **4e** crystallized. Concentration of the filtrate and cooling gave second crop material (6.9 g., m.p. 82-89°) which was recrystallized twice from methanol to give pure **8a**, m.p. 106-107°; ir (deuteriochloroform): no C=O absorption; pmr (deuteriochloroform): δ 1.05 (s, 3H, CCH_3), δ 1.48 (s, 3H, CCH_3), δ 2.55 [d, 1H, J = 13 Hz, C(H)H], δ 2.92 [d, 1H, J = 13 Hz, CH(H)], δ 3.45 (s, 3H, OCH_3), δ 6.8-7.5 (m, 8H, ArH).

Anal. Calcd. for $C_{19}H_{19}ClO_3$: C, 68.98; H, 5.79. Found: C, 69.07; H, 5.83.

5,8a-Dimethoxy-2,2-dimethyl-3a-phenyl-2,3,3a,8a-tetrahydrofuro-[2,3-*b*]benzofuran (**8b**).

Treatment of the methoxy bromide **3f** with sodium methoxide in methanol according to the foregoing procedure gave an oil (65% yield) from which no solid product could be obtained. The pmr spectrum indicated that it was a mixture of the normal ester (75%) and the ortho ester **8b** (25%). A sample of this material (32.6 g., 0.1 mole) was then heated under reflux overnight with a solution of 80 ml. of 45% aqueous potassium hydroxide in 320 ml. of ethanol. The cooled reaction mixture was filtered from insoluble material (6.6 g.) and concentrated to dryness in a rotating evaporator. The brown residue was treated with water, and insoluble

material (4.7 g., m.p. 85-87°) was collected at the filter. One recrystallization from methanol gave 3.9 g. of pure **8b**, m.p. 87-88°; ir (deuteriochloroform): no C=O absorption; pmr (deuteriochloroform): δ 1.05 (s, 3H, CCH_3), δ 1.48 (s, 3H, CCH_3), δ 2.55 [d, 1H, J = 13 Hz, C(H)H], δ 2.92 [d, 1H, J = 13 Hz, CH(H)], δ 3.40 (s, 3H, OCH_3), δ 3.70 (s, 3H, OCH_3), δ 6.5-7.4 (m, 8H, ArH); mass spectrum: (50 eV) m/e molecular ion: 326.1544. Calcd. for $C_{20}H_{22}O_4$: 326.1518.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.29; H, 6.85.

2-(2,5-Dihydroxyphenyl)-4,4-dimethyl-2-phenyl-4-hydroxybutyric Acid γ-Lactone (**9**).

A mixture of the ortho ester **8b** (2.08 g., 0.007 mole) and anhydrous pyridine hydrochloride (3.24 g., 0.028 mole) was heated for 2 hours at 210° under an atomosphere of nitrogen. The light yellow reaction mixture was poured onto ice (~ 200 g.), and the precipitated solid (1.81 g., m.p. 222-225°) was collected at the filter, dried, and recrystallized from aqueous methanol. There was obtained 1.5 g. (72% yield) of pure **9**, m.p. 235-236°; ir (Nujol): 3400-3500 (ν bonded OH), 1705 (ν C=O); pmr (DMSO-d_6): δ 1.08 (s, 3H, CCH_3), δ 1.45 (s, 3H, CCH_3), δ 2.97 (s, 2H, CCH_2C), δ 5.7-6.0 (m, 1H, ArH), δ 6.3-7.0 (m, 2H, ArH), δ 7.2-7.8 (m, 5H, ArH), δ 8.56 (s, 1H, OH), δ 8.94 (s, 1H OH).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.74; H, 6.20.

2,2-Dimethyl-4-phenyl-4-chromancarboxamides (**5**).

All of the amides **5** listed in Table II were prepared by saponification of the corresponding esters **4**, and treatment of the resulting carboxylic acids (see Table II) with thionyl chloride followed by reaction of the crude acid chlorides with ammonia or with the appropriate secondary amine. Details of these routine steps have been described elsewhere (2) for a closely related system.

2,2-Dimethyl-4-phenyl-4-chromanmethylamines (**6**).

These amines were prepared by reduction of the corresponding amides **5** either with lithium aluminum hydride or with diborane.

(a) With Lithium Aluminum Hydride. Preparation of **6c**.

To a stirred suspension of lithium aluminum hydride (1.26 g., 0.034 mole) in ether (90 ml.; under an atmosphere of nitrogen) was added 4.98 g. (0.0135 mole) of the solid amide **5e**. The stirred mixture was heated under reflux overnight, cooled in ice and treated successively, with stirring, with 1.3 ml. of water, 1.3 ml. of 50% aqueous sodium hydroxide, and 3.9 ml. of water. The ether solution was decanted from the gelatinous residue which was similarly washed with fresh ether. The combined ether extracts were treated with excess 10% hydrochloric acid and the precipitated salt was collected at the filter, dried and recrystallized from ethanol to give 3.2 g. (60% yield) of pure **6c**.

In a similar manner, the dimethylamino compound **6b** also was prepared. However, it was isolated as a water-soluble salt.

(b) With Diborane. Preparation of **6a**.

To a stirred, ice-cold, 1*M* solution of diborane (20 ml., 0.02 mole) in tetrahydrofuran was added, dropwise and under an atmosphere of nitrogen, a solution of 3.64 g. (0.01 mole) of the amide **5b** in 20 ml. of tetrahydrofuran. The temperature was maintained at 5° or less during the addition which required an hour. The solution was allowed to warm to room temperature and then was heated under reflux overnight. The mixture was cooled in ice again and treated with 15 ml. of methanol followed by 15 ml. of saturated methanol solution of hydrogen chloride. The mixture was heated under reflux for 1.5 hours and cooled in ice. Precipitated product (m.p. 248-250°) was collected at the filter and recrystallized from ethanol. There was obtained 3.1 g. (67%) of pure **6a**, m.p. 253-255°.

In like manner were prepared the three amines, **6d**, **6e**, and **6f**, except that **6e** proved to be soluble in methanol so that the isolation procedure had to be modified accordingly.

2,2-Dimethyl-4-phenylchroman (7).

When the primary amide **5a** was treated with lithium aluminum hydride in ether in the usual manner, essentially no basic product was obtained. When **5a** (0.01 mole) was heated under reflux (24 hours) with lithium aluminum hydride (0.03 mole) in tetrahydrofuran, again no basic product could be isolated. From the neutral fraction, however, a solid (m.p. 110-118°) was obtained which, after 3 recrystallizations from ethanol, gave 1.25 g. (53% yield) of pure **7**, m.p. 119-120°; pmr (deuteriochloroform): δ 1.37 (s, 3H, CCH_3), δ 1.43 (s, 3H, CCH_3), δ 2.02 [d, 2H, J = 10 Hz, $C(H)CH_2C$], δ 4.10 [t, 1H, J = 10 Hz, $Ar_2CHC(H_2)$], δ 6.7-7.4 (m, 9H, ArH).

Compound **7** was the only product isolated (70% yield) when the amide **5a** also was treated under reflux with sodium bis(methoxyethoxy) aluminohydride in benzene.

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REFERENCES

(1) This paper is No. XV in the series, "Neighboring Group Reactions". For paper XIV, see H. E. Zaugg and R. W. DeNet, *J. Org. Chem.*, 35, 3567 (1970).

(2) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *ibid.*, 26, 4821 (1961).

(3) H. E. Zaugg and A. D. Schaefer, *J. Am. Chem. Soc.*, 87, 1857 (1965).

(4) H. E. Zaugg, R. W. DeNet, R. J. Michaels, *J. Org. Chem.*, 26, 4828 (1961).

(5) H. E. Zaugg, R. W. DeNet, R. J. Michaels, W. H. Washburn, and F. E. Chadde, *ibid.*, 26, 4753 (1961).

(6) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, 84, 4567 (1962).

(7) A. Bistrzycki and J. Flatau, *Ber.*, 28, 989 (1895); *ibid.*, 30, 124 (1897).

(8) R. Stoermer, *ibid.*, 44, 1853 (1911).