The Stereospecific Synthesis of *trans*- and *cis*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (Dihydrotoxol). Dihydrobenzofuran Derivatives in Which $J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$[1]

L. H. ZALKOW AND M. GHOSAL[2]

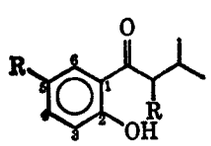
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia

Received September 4, 1968

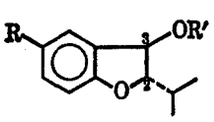
2'-Hydroxy-2,5'-dibromo-3-methylbutyrophenone (II) has been converted into *trans*-2-isopropyl-2-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII) by successive treatment with sodium borohydride in aqueous ethanolic potassium hydroxide, butyllithium, then carbon dioxide and finally methyllithium. When II was reduced with sodium borohydride and the product then treated with potassium hydroxide, *cis*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X) was obtained, which was converted by an identical sequence of reactions into *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (racemic dihydrotoxol, IX). The sodium borohydride reduction of II in alkaline medium is believed to lead first to cyclization to 2-isopropyl-5-bromocoumaran-3-one (XIV) followed by reduction to give the thermodynamically more stable *trans* isomer (III), while in the absence of alkali II is first reduced to give the *erythro* isomer (steric approach control) which then leads to the *cis* isomer (X) by backside displacement of the α-bromo atom by the phenolic OH group. The unexpected observation that $J_{trans\text{-}2,3} > J_{cis\text{-}2,3}$ in the two families of 2,3-dihydrobenzofurans is believed to arise from a stereochemical dependence of the electronegativity effect of the hydroxyl groups in the *cis* series as observed by Booth[10] for six-membered rings.

Rayless goldenrod (*Aplopappus heterophyllus*), a toxic plant indigenous to the Southwestern United States, has been found to contain four benzofuran derivatives: toxol[3] [(2*S*)-isopropenyl-(3*S*)-hydroxy-5-acetyl-2,3-dihydrobenzofuran], dehydrotremetone[3] (2-isopropenyl-5-acetylbenzofuran), tremetone[4] [(2*S*)-isopropenyl-5-acetyl-2,3-dihydrobenzofuran] and 2,5-diacetylbenzofuran.[5] We wish to record here the stereospecific synthesis of racemic dihydrotoxol and its *trans* isomer and to comment on certain unexpected aspects of the nmr spectra of these compounds and their synthetic precursors.

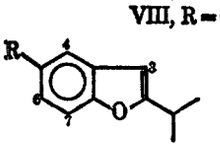
Treatment of phenol with isovaleryl chloride gave phenyl isovalerate, which in turn gave *o*-hydroxyisovalerophenone, I, by the Fries rearrangement. On treatment with bromine in acetic acid, *o*-hydroxyisovalerophenone afforded 2'-hydroxy-2,5'-dibromo-3-methylbutyrophenone, II. Introduction of a bromine atom at C-5 was particularly advantageous since it made possible the later introduction of an acetyl group at this position under nonacidic conditions. Attachment of bromine α to the carbonyl group and at position C-5 was apparent from the nmr spectrum of II. Thus the α proton appeared as a downfield doublet centered at δ 4.83 while the aromatic protons gave a typical ABC pattern expected of a trisubstituted aromatic system such as II with $J_{3,4} = 9$ Hz and $J_{4,6} = 2.5$ Hz.



I, R = H
II, R = Br



III, R = Br; R' = H
IV, R = Br; R' = $COCH_3$
VII, R = CO_2H; R' = H
VIII, R = $COCH_3$; R' = H



V, R = Br
VI, R = H

Reduction of II with sodium borohydride in an aqueous ethanolic solution of potassium hydroxide gave *trans*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III) in 54% yield. The infrared and nmr spectra of III showed it to be a dihydrobenzofuran derivative but the assignment of a *trans* relationship at C-2 and C-3 was not apparent until the *cis* isomer was prepared and the latter correlated with dihydrotremetone as described below. The infrared spectrum showed a strong hydroxyl band at 3340 cm^{-1} and the OH proton appeared as a doublet ($J = 6$ Hz) in the nmr spectrum centered at δ 4.37; the latter signal disappeared on addition of D_2O. The C-3 proton, which appeared as a triplet, in the nmr spectrum, in the absence of D_2O, gave a clean doublet ($J = 6$ Hz) in CD_3COCD_3 in the presence of D_2O, while the C-2 proton gave a quartet ($J = 6$ and 10 Hz) centered at δ 3.99. The aromatic protons and isopropyl group appeared as expected in the nmr spectrum for structure III.

Distillation of the mother liquor remaining after removal of crystalline III gave 2-isopropyl-5-bromobenzofuran (V) as an unstable liquid which rapidly decomposed. The nmr spectrum of V showed the characteristic C-3 proton as a sharp doublet ($J = 1$ Hz) centered at δ 6.15. The previously reported[6] 2-isopropylbenzofuran (VI) was found to show infrared and nmr spectra similar to that observed for V. Protons at

(1) Presented at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1-3, 1967. A portion of this material has appeared in preliminary form: L. H. Zalkow and M. Ghosal, *Chem. Commun.*, 922 (1967).

(2) Postdoctoral Fellow, Jan 1965-Sept 1966.

(3) L. H. Zalkow, N. Burke, G. Cabat, and E. A. Grula, *J. Med. Chem.*, **5**, 1342 (1962).

(4) Unpublished work M. Ghosal and L. H. Zalkow, Georgia Institute of Technology.

(5) C. T. Ramming, Masters Thesis, Oklahoma State University, Stillwater, Okla., 1965.

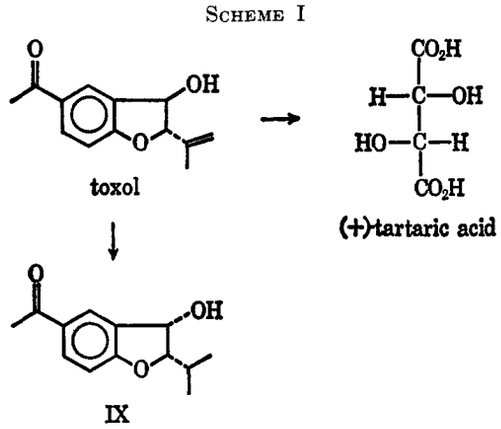
(6) J. I. DeGraw, Jr., and W. A. Bonner, *Tetrahedron*, **18**, 1311 (1962).

C-6 and C-7 in V were found to have the same chemical shift when the nmr spectrum was measured in carbon tetrachloride. On refluxing in benzene in the presence of a crystal of iodine III also gave V. The formation of V lends further support to the assignment of a dihydrobenzofuran structure to III. On treatment with acetic anhydride in pyridine III gave IV. Again the infrared and nmr spectra were consistent with the assigned structure. Of particular significance was the observed coupling of 6 Hz for the C-2 and C-3 protons in the nmr spectrum of IV.

Treatment of *trans*-2-isopropyl-3-hydroxyl-5-bromo-2,3-dihydrobenzofuran with butyllithium followed by carbon dioxide led to 2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (VII). The latter acid was converted into racemic *trans*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII) upon treatment with methyllithium.

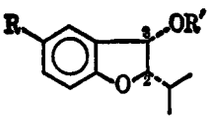
The nmr spectrum of VIII showed a coupling constant of $J = 6$ Hz for the C-2 and C-3 protons and VIII was found to differ in infrared and nmr spectra from dihydrotoxol (IX) prepared by hydrogenation of toxol.[7] Ozonolysis of toxol has been shown to yield (+)-tartaric acid.[7] This established the configuration of toxol and therefore dihydrotoxol at C-2 and C-3 as indicated in Scheme I. The alternative explanation

SCHEME I



that toxol, and therefore dihydrotoxol, possess a *trans* relationship at C-2 and C-3 and epimerization occurs at C-2 during ozonolysis is seen to be invalid since the configuration at C-2 in toxol has been established by independent correlation with (+)-dihydrocoumarilic acid and with rotenone.[7] Thus a *trans* relationship can be assigned to VIII and the cyclic precursors leading to VIII. However, a slight variation in the experimental conditions lead to dihydrotoxol as described below.

When the reduction of 2'-hydroxy-2,5'-dibromo-3-methylbutyrophenone (II) with sodium borohydride was conducted in ethanol in the absence of potassium hydroxide, and then the crude product treated with ethanolic potassium hydroxide, *cis*-2-isopropyl-3-hydroxyl-5-bromo-2,3-dihydrobenzofuran (X) was obtained in good yield. Alcohol X differed in the fingerprint region of its infrared spectrum from isomer III and the nmr spectra of the two isomers were different. Thus the isopropyl methyl groups in X were magnetically equivalent and appeared at higher field (δ 0.88) than those of III (δ 1.09 and 1.15). Likewise, the isopropyl proton in X (δ 1.68) appeared at higher field than the corresponding proton in III (δ 2.2) but of even greater significance was the observation that the coupling constant for the C-2 and C-3 protons in X was only 4 Hz as compared to 6 Hz in III. Likewise, the coupling constant of the C-2 and isopropyl protons in X (6 Hz) was less than that in III (10 Hz). In X the C-3 proton (δ 4.71) was more highly shielded than the corresponding proton in III (δ 5.08).

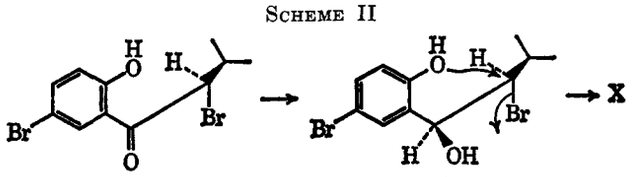


IX, R = $COCH_3$; R' = H
X, R = Br; R = H
XI, R = Br; R' = $COCH_3$
XII, R = CO_2H; R' = H
XIII, R = $COCH_3$; R' = $COCH_3$

As previously described, X was converted into acetate XI, the nmr spectrum of which again showed the isopropyl groups (δ 0.92, 0.97) at higher field than in the isomeric acetate IV (δ 0.97, 1.15). The couplings of the C-2 and C-3 protons ($J = 3.5$ Hz) and the C-2 proton and isopropyl proton ($J = 6$ Hz) were also less than that observed for IV ($J = 6$ and 9.5 Hz, respectively). Acetate XI was converted into *cis*-2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (XII) by the action of butyllithium followed by treatment with solid carbon dioxide. On treatment with methyllithium, XII gave after distillation racemic dihydrotoxol (IX) identical in every way, except for optical rotation, with active dihydrotoxol prepared by hydrogenation of natural toxol.[7] In addition to IX, a dehydrated product, presumably 5-acetylbenzofuran was obtained in the above distillation. Dihydrotoxol acetate (XIII) was obtained when IX was treated with acetic anhydride and pyridine and the synthetic sample was again identical with the naturally derived material on infrared and nmr spectral comparisons. As observed in X and XI, the C-2 and C-3 proton coupling in IX, XII and XIII was 4 Hz while the C-2, isopropyl proton coupling was 6 Hz.

The slight change in experimental conditions, which allowed preparation of either *trans*- (VIII) or *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX) can be explained as follows. In the two-step conversion of II into X, the carbonyl group is reduced in the first step and ring closure occurs in the second step. By application of Cram's rule,[8] using Dreiding models, one would expect to get predominantly the *erythro* alcohol; backside displacement of the bromine atom by the phenolic OH group would then lead to the *cis* isomer, as illustrated in Scheme II. In the one step,

SCHEME II

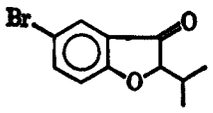


erythro

(7) W. A. Bonner, N. I. Burke, W. E. Fleck, R. K. Hill, J. A. Joule, B. Sjoberg, and L. H. Zalkow, *Tetrahedron*, **20**, 1419 (1964).

(8) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

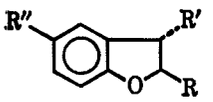
conversion of II into III, ring closure apparently occurs first to give XIV, which is then reduced under these



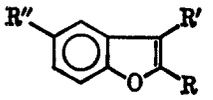
XIV

conditions to give the thermodynamically more stable *trans* product III (product-development control). In support of the latter postulation is the observation that XIV prepared by treatment of II with diethylamine gave only III on reduction with sodium borohydride in aqueous ethanolic potassium hydroxide.

During earlier attempts to synthesize dihydrotoxol, some interesting observations were made.[9] Thus reaction of *trans*-3-hydroxy- (XV) or 3-acetoxy-2-isopropyl-2,3-dihydrobenzofuran (XVI) with acetic anhydride and trifluoracetic acid or stannic chloride lead to 2-isopropyl-5-acetylbenzofuran (XVII), while similar conditions failed to lead to acetylation at C-5 in the case of 3-acetoxy-2-isopropylbenzofuran (XVIII). As previously reported,[7] reduction of toxol (*cis*-2-isopropenyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran) with 5% rhodium-on-alumina catalyst gave dihydrotoxol; under similar conditions, however, 2-carbethoxy-3-acetylbenzofuran (XIX) gave 2-carbethoxy-2,3-dihydrobenzofuran (XX). An attempt to oxidize (5′-acetyl-2′-dihydrobenzofuryl)-2-propyl acetate at C-3 with chromium trioxide in acetic anhydride at 0° led



XV, R = isopropyl; R′ = OH; R″ = H
XVI, R = isopropyl; R′ = acetoxy; R″ = H
XX, R = carbethoxy; R′ = R″ = H
XXI, R = 2-(2-acetoxy)propyl; R′ = H; R″ = acetyl
XXIV, R = isopropyl; R′ = H; R″ = Br or OH



VII, R = isopropyl; R′ = H; R″ = acetyl
XVIII, R = isopropyl; R′ = acetoxy; R″ = H
XIX, R = carbethoxy; R′ = acetoxy; R″ = H
XXII, R = isopropyl; R′ = H; R″ = acetyl
XXIII, R = 2-(2-hydroxy)propyl; R′ = R″ = H

instead to 5-acetylsalicyclic acid. Attempts to functionalize the C-3 position of dihydrotremetone *via* the ketal by reaction with N-bromosuccinimide gave, after hydrolysis, 2-isopropyl-5-acetylbenzofuran (XXII). The later substance, in the form of its ketal, when treated with lead tetraacetate, gave, after hydrolysis, 2-(5′-acetyl-2′-benzofuryl)-2-propanol (XXIII). An attempt to hydroborate 2-isopropylbenzofuran did not meet with success while treatment of 2-isopropyl-2,3-dihydrobenzofuran (XXIV, R″ = H) with N-bromosuccinimide or Fenton reagent lead to attack in the aromatic ring (XXIV, R″ = Br or OH).

(9) For details of these experimental conditions, see N. Burke, Ph.D. Dissertation, Oklahoma State University, Stillwater, Okla., 1965.

A comparison of the nmr spectra of the two series of benzofuran derivatives provides some unexpected information. Thus the coupling constants for the C-2 and C-3 protons in the *cis* series (IX, X, XI, XII, XIII) are always smaller (J = 3–4 Hz) than in the *trans* (III, IV, VII, VIII) series (J = 5–6 Hz). The observed low value for $J_{2,3}$ in the *cis* isomers may be due to the stereochemical dependence of the electronegativity effect pointed out by Booth[10] for six-membered rings. Thus, in the *cis* isomers, as the C-2 and C-3 substituents bend away from each other to remove steric compression, the angle between the C-3 hydroxyl group and the C-2 proton approaches 180°, the angle of maximum electronegativity effect and minimum $J_{2,3}$. In the case of 2-alkyl-3-methyl-2,3-dihydrobenzofurans, Tarbell, *et al.*,[11] have observed that $J_{cis\text{-}2,3} > J_{trans\text{-}2,3}$ as expected. However, an isomer of 2-phenyl-3-hydroxyl-2,3-dihydrobenzofuran in which $J_{2,3}$ = 6 Hz has been assigned as *cis* relationship of the C-2 and C-3 groups.[12] Since only one isomer was obtained in the later case it is not worthwhile commenting further on this example at this time; however, it is clear that assignment of stereochemistry in systems such as 2,3-dihydrobenzofurans solely on the basis of the size of coupling constants can be misleading.

Experimental Section

Melting points were taken on a Kofler block and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., or by Dr. A. Bernhardt, Mülheim, Germany. Infrared spectra were recorded with a Perkin-Elmer Model 237B Infracord spectrophotometer and nmr spectra were recorded with a Varian A-60 spectrometer, using TMS as an internal standard (δ 0).

Preparation of 2′-Hydroxy-2,5′-dibromo-3-methylbutyrophenone (II).—*o*-Hydroxyisovalerophenone was prepared following the procedure previously described[13] for the preparation of *o*-hydroxypropiophenone. Isovalerylchloride (150 g) was added slowly to 117 g of phenol and after the evolution of hydrogen chloride ceased, the reaction mixture was heated on the steam bath for 12 hr. The crude phenyl isovalerate thus obtained was slowly added to a well-stirred suspension of aluminum chloride (184.2 g) in carbon disulfide (201 ml). After refluxing on the steam bath for 3 hr, the carbon disulfide was removed by distillation and the residue was heated with an oil bath at 170–180° for 1 hr. The solid mass was then hydrolyzed with dilute hydrochloric acid (360 ml, 1:1 concentrated HCl–water) by warming on the steam bath, then diluted with water (300 ml) and steam distilled. The steam distillate was extracted with ether; the ether extract was washed with water, dried over anhydrous $MgSO_4$, and finally concentrated. Distillation of the residue gave 162 g of *o*-hydroxyisovalerophenone (I) {bp 73° (0.4 mm); ν_{max}^{film} 3500–2900 (OH), 1637 (C=O), 1370–1170 (five strong bands, C–O stretch), 750 cm^{-1}; nmr (CCl_4) δ 0.96 (d, 6, J = 6 Hz), 2.26 (septet, 1, J = 6), 2.76 (d, 2, J = 6), 6.67–8.35 (complex pattern, integrating for four protons, identical with that observed for the four aromatic protons in *o*-hydroxyacetophenone)} which was brominated without further purification.

A typical procedure for the preparation of 2′-hydroxy-2,5′-dibromo-3-methylbutyrophenone (II) was as follows. A solution of bromine (3.1 ml) in acetic acid (40 ml) was added over a period of 1 hr with stirring to a solution of *o*-hydroxyisovalerophenone (4.9 g) in acetic acid (100 ml) cooled in ice

(10) H. Booth, *Tetrahedron Lett.*, 411 (1965).
(11) E. C. Hayward, D. S. Tarbell, and L. D. Colebrook, *J. Org. Chem.*, **33**, 399 (1968).
(12) S. P. Pappas and J. E. Blackwell, Jr., *Tetrahedron Lett.*, 1171 (1966).
(13) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 543.

water. After this stood at room temperature for 1 hr most of the acetic acid was removed by distillation at reduced pressure and the residue was poured into ice water. The solid which crystallized was collected by filtration, washed with water, dried and recrystallized from petroleum ether (bp 60–90°) to give 7.3 g of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II), mp 85–86°. Repeated recrystallization from petroleum ether (bp 30–60°) gave the analytical sample: mp 88.5–90°, ν_{max}^{Nujol} 1634, 1370–1150 (six bands), 750, 695 cm^{-1}; nmr (CCl_4) δ 1.05 (d, 3, J = 6 Hz), 1.25 (d, 3, J = 6), 4.83 (d, 1, J = 9), 6.93 (d, 1, J = 9), 7.59 (q, 1, J = 9, 2.5), 7.90 (d, 1, J = 2.5).

Anal. Calcd for $C_{11}H_{12}O_2Br_2$: C, 39.29; H, 3.57. Found: C, 39.13; H, 3.48.

The above procedure was not found to be efficient for the bromination of more than 5 g of the ketone and the following modification was used for larger quantities. To a stirred solution of *o*-hydroxyisovalerophenone (20 g) in 400 ml of acetic acid was added approximately one-half of a solution prepared by the addition of 12.4 ml of bromine to 100 ml of acetic acid over a period of 7 min. After the reddish color of bromine disappeared (about 20 min), the remainder of the bromine solution was added over a period of 15 min; the solution was allowed to stand at room temperature for 15 min, then heated for 20 min at 100°, when the initial rapid evolution of hydrogen bromide ceased. The solution was concentrated to about 300 ml under reduced pressure, then diluted with water until 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone(23.5 g) crystallized. After washing with water it gave mp 81.5–83°.

Preparation of *trans*-2-Isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III).—A solution of potassium hydroxide (4 g) in water (30 ml) was added to a suspension of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II, 10 g) in ethanol (100 ml). Sodium borohydride (1.5 g) was added to the clear solution thus obtained and the resulting solution was stirred at room temperature for 24 hr. The pale yellow solution was filtered and the filtrate was acidified with acetic acid (5 ml), then concentrated under reduced pressure and diluted with water to give shiny white crystals of *trans*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (III). Recrystallization from ethanol–water gave 3.5 g, mp 106–108°. Concentration of the mother liquid gave an additional 1 g of III, which after recrystallization from ethanol–water gave 0.6 g, mp 106–108°. The analytical sample, prepared by further recrystallization from ethanol–water, gave mp 112–113°; ν_{max}^{KBr} 3340, 1605, 1475, 1245, 1185, 1062, 988, 952, 825 cm^{-1}; nmr (CD_3COCD_3) δ 1.09 (d, 3, J = 6 Hz), 1.15 (d, 3, J = 6), 3.99 (q, 1, J = 6, 10), 4.37 (d, 1, J = 6, disappears on addition of D_2O), 5.08 (t, 1, J = 6, changes to doublet on addition of D_2O), 6.68 (d, 1, J = 8.5), 7.23 (q, 1, J = 8.5, 2), 7.43 (d, 1, J = 2), the isopropyl proton appeared as an ill-defined multiplet centered about 2.2.

Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.36 H, 5.06. Found: C, 51.70; H, 5.15.

The mother liquor remaining after the removal of crystalline III was freed of volatile solvent and distilled under reduced pressure to give 2-isopropyl-5-bromobenzofuran (V) [bp 75–76° (0.075 mm); R_f 0.54 on thin layer chromatography (10 cm) on silica gel G in petroleum ether (bp 60–90°) with detection in iodine vapor]: ν_{max}^{film} 1590, 1260, 1162, 1050, 942, 795 cm^{-1}; nmr (CCl_4) δ 1.26 (d, 6, J = 6.5 Hz), 7.98 (quintuplet, 1, J = 6.5), 6.15 (d, 1, J = 1), 7.15 (d, 2, J = 1), 7.43 (t, 1, J = 1). A product of identical ir and nmr spectra and of identical R_f was obtained by refluxing III (250 mg) in benzene in the presence of a crystal of iodine for 5.5 hr followed by washing with aqueous thiosulfate and then water, drying, and evaporation of solvent. Owing to its rapid decomposition, even in a sealed tube, a satisfactory elemental analysis could not be obtained for V. However, for comparison purposes 2-isopropylbenzofuran (VI) was prepared as previously described[6] and was found to show infrared and nmr spectra very similar to that observed for V. Thus the C-3 proton in VI appeared as a sharp doublet (J = 1) centered at δ 6.0 in its nmr spectrum (neat) and the infrared spectrum of VI (film) also showed strong bands at 1590, 1260, 1162, 942 and 795 cm^{-1}; in addition both V and VI showed a characteristic pair of bands at 738 and 758 cm^{-1}.

Preparation of *trans*-2-Isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (IV).—Acetic anhydride (3 ml) was added to a solution of 0.9 g of III in 15 ml of pyridine. After standing at room temperature overnight, the usual work-up gave 0.8 g of *trans*-2-isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (IV), which after recrystallization from ethanol gave mp 90°; ν_{max}^{Nujol} 1731, 1241 cm^{-1}; nmr (CCl_4) δ 0.97 (d, 3, J = 6 Hz), 1.15 (d, 3, J = 6), 1.97 (s, 3), 4.0 (q, 1, J = 9.5, 6.0), 6.01 (d, 1, J = 6.0), 6.65 (d, 1, J = 8.5), 7.26 (q, 1, J = 8.5, 2), 7.43 (d, 1, J = 2).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.17; H, 5.02. Found: C, 52.40; H, 5.14.

Preparation of 2-Isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (VII).—To a solution of 1.03 g of III in 10 ml of ether, cooled in an ice–water bath, was added 15 ml of 0.8 *N* butyllithium in ether solution. The cooling bath was removed after 15 min and the solution was allowed to stand at room temperature for an additional 45 min, then it was poured over solid carbon dioxide. After sublimation of the excess solid carbon dioxide, the residue was taken up in excess 10% aqueous potassium hydroxide; the latter solution was filtered and the filtrate was acidified with acetic acid and then extracted with ether. The ethereal extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue crystallized from aqueous ethanol to afford 0.37 g of 2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran, mp 189–190°. Recrystallization from aqueous ethanol gave the analytical sample: mp 196–197°; ν_{max}^{Nujol} 3322, 1686 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 65.05; H, 6.29.

Preparation of *trans*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (VIII).—To a solution of methyllithium, prepared from 0.113 g of lithium and 0.4 ml of methyl iodide in 5 ml of diethyl ether, cooled in an ice bath was added dropwise a solution of 0.2 g of VII in 15 ml of ether. The ice bath was then removed and the solution was allowed to stand at room temperature for 1.5 hr and then hydrolyzed by the cautious addition of cold water until the initially formed precipitate dissolved. After stirring for 1 additional hr the solution was extracted with ether and the ethereal extract was washed with water, 10% aqueous potassium hydroxide, water again then dried ($MgSO_4$) and evaporated. The viscous residue solidified on addition of petroleum ether (bp 30–60°) and was recrystallized from carbon tetrachloride–petroleum ether (bp 30–60°) to give 50 mg of *trans*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran, mp 104–105°. The analytical sample was prepared after two more recrystallizations from carbon tetrachloride–petroleum ether (bp 30–60°): mp 115°; ν_{max}^{Nujol} 3360, 1658 cm^{-1}; nmr (CD_3COCD_3) δ 1.13 (d, 3, J = 6.5 Hz), 1.18 (d, 3, J = 6.5), 2.52 (s, 3), 4.11 (q, 1, J = 6, 10), 5.38 (d, 1, J = 6), 6.68–8.03 (m, 3).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.79; H, 7.60.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X).—Sodium borohydride (0.44 g) was added in small portions, over a period of 20 min, to a stirred solution containing 10.2 g of 2′-hydroxy-2,5′-dibromo(3-methyl)butyrophenone (II) in 300 ml of ethanol cooled in an ice bath. The resulting colorless solution was diluted with water, acidified with a minimum amount of acetic acid and concentrated on the steam bath under reduced pressure. The cooled turbid solution was extracted with ether, the ether extract washed with dilute sodium carbonate solution and water, then dried (Na_2SO_4) and evaporated to give 9 g of an oily residue to which was added a solution prepared by adding 2.1 g of potassium hydroxide to 70 ml of ethanol. The latter solution was allowed to stand at room temperature for 2 hr, then after filtration to remove potassium bromide the filtrate was diluted with water and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate and evaporated to give 7.1 g of crude *cis*-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran (X) as a viscous liquid. The crude X was dissolved in petroleum ether (bp 60–90°) and chromatographed on Merck acid-washed alumina, activity II. The benzene eluent gave pure X: mp 44.5–45°; ν_{max}^{Nujol} 3289, 1595, 1460, 1235, 1170, 1119, 1055–877 (nine bands; this part of the spectrum differs significantly from that of III), 816 cm^{-1}; nmr (CCl_4) δ 0.88 (d, 6, J = 6 Hz), 3.96 (q, 1, J = 4, 6), 4.20 (d, 1, J = 6.5, disappears on addition of D_2O), 4.71 (d, 1, J = 4, after addition of D_2O), 6.55 (d, 1, J = 8.5), 7.18 (q, 1, J = 8.5, 2), 7.25 (s, 1, $W_{1/2h}$ = 2 cps), the isopropyl proton appeared as a broad pentuplet centered at 1.68.

Anal. Calcd for $C_{11}H_{13}O_2Br$: C, 51.36; H, 5.06. Found: C, 51.42; H, 5.30.

Preparation of *cis*-2-Isopropyl-3-acetoxy-5-bromo-2,3-dihydrobenzofuran (XI).—Crude X (7.1 g), as a viscous liquid, was dissolved in dry pyridine (150 ml) to which was added 20 ml of acetic anhydride. After standing at room temperature overnight the solution was worked up in the usual manner to give the crude acetate as a viscous liquid (8 g). Two fractionations gave the analytical sample: single spot by the tlc, R_f 0.6, ethyl acetate eluent; bp 95° (0.3 mm), 86° (0.01 mm); ν_{max}^{film} 1739, 1233 cm^{-1}; nmr (CCl_4) δ 0.92 (d, 3, J = 6.5 Hz), 0.97 (d, 3, J = 6.5), 2.0 (s, 3), 4.31 (q, 1, J = 6, 3.5), 6.01 (d, 1, J = 3.5), 6.63 (d, 1, J = 8.5), 7.26 (q, 1, J = 8.5, 2) 7.39 (d, 1, J = 2).

Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.17; H, 5.02. Found: C, 52.45; H, 5.02.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran (XII).—To a solution containing lithium metal (2.15 g) in dry ether (50 ml) in a nitrogen atmosphere, cooled in an ice bath, was added a solution containing *n*-butyl bromide (17.2 g) in dry ether (25 ml) with vigorous stirring. When the reaction subsided (~3 hr), the ethereal solution was rapidly filtered through glass wool and to this cooled solution in a nitrogen atmosphere, a solution of XI (4.1 g) in dry ether (25 ml) was added slowly. The reaction mixture was allowed to stand at room temperature for 1.5 hr, then poured on solid carbon dioxide. After the excess carbon dioxide sublimed, the solution was extracted with 5% potassium hydroxide solution; the alkaline solution washed with ether then acidified with acetic acid. The acidic solution was extracted with ether and the ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give a viscous liquid which was taken up in benzene. Trituration with petroleum ether (bp 60–09°) gave 734 mg of crystalline *cis*-2-isopropyl-3-hydroxy-5-carboxy-2,3-dihydrobenzofuran which gave mp 157.5–159° after recrystallization from ethyl acetate–petroleum ether (bp 60–90°); ν_{max}^{Nujol} 3236, 1672 cm^{-1}; nmr (CD_3COCD_3) δ 1.02 (d, 6, J = 6.5 Hz), 4.33 (q, 1, J = 6, 4.5), 5.22 (d, 1, J = 4.5), 6.86 (d, 1, J = 8.5), 7.90 (d, 0.5, J = 2, this represents one-half of the C-6 quartet, the other half lies under the C-4 broad singlet), 8.05 (broad singlet, 1.5).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.54; H, 6.56.

Preparation of *cis*-2-Isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (Racemic Dihydrotoxol, IX).—To a solution of methyllithium, prepared from lithium metal (0.25 g) and methyl iodide (1.3 ml), in ether (15 ml) cooled in an ice bath was added a solution containing 250 mg of XII in 15 ml of dry ether in the course of 15 min. After stirring for 1.5 hr water and ether were added to the solution. The ether layer was separated, washed with water, dried and evaporated to give a viscous liquid. Distillation through a long, narrow, horizontal glass tube gave mainly a dehydrated material, presumably 5-acetylbenzofuran, and then racemic *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX): bp 86–91° (0.01 mm); λ_{max}^{film} 3390, 1664 cm^{-1}; nmr (CCl_4) δ 0.98 (d, 6, J = 6 Hz), 2.35 (s, 3), 4.21 (q, 1, J = 4, 6), 4.97 (d, 1, J = 4), 6.60 (d, 1, J = 8.5), 7.62 (q, 1, J = 2, 8.5), 7.78 (d, 1, J = 2). Racemic IX was identical in infrared and nmr spectra with active IX prepared from natural toxol.

Preparation of *cis*-2-Isopropyl-3-acetoxy-5-acetyl-2,3-dihydrobenzofuran (Racemic Dihydrotoxol Acetate, XIII).—A sample of crude *cis*-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran (IX) was converted into the acetate XIII by treatment with acetic anhydride in pyridine. The analytical sample was obtained by distillation at reduced pressure and gave bp 110° (0.05 mm); λ_{max}^{film} 1734, 1675, 1233 cm^{-1}; nmr (CCl_4) δ 0.93 (d, 3, J = 6.5 Hz), 1.0 (d, 3, J = 6.5), 2.02 (s, 3), 2.43 (s, 3), 4.43 (q, 1, J = 3.0, 6), 6.16 (d, 1, J = 3), 6.8–8.05 (three aromatic protons).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.66; H, 7.24.

Synthetic XIII was identical by ir and nmr spectra with a sample prepared from natural toxol by hydrogenation and acetylation as described above. On standing at room temperature, XIII spontaneously lost acetic acid.

Preparation of 2-Isopropyl-5-bromocoumaran-3-one (XIV) and Its Conversion into III.—2′-Hydroxy-2,5′-dibromo-3-methylbutyrophenone (II, 0.5 g) was shaken with 3 ml of diethylamine at room temperature. After 5 min the amine hydrochloride precipitated and after 15 min the reaction mixture was diluted with ether and filtered. The filtrate was washed several times with water, dried and evaporated to give a viscous yellow oil, which on distillation gave 2-isopropyl-5-bromocoumaran-3-one: bp 85° (0.01 mm); single spot by tlc, R_f 0.81, benzene eluent; ν_{max}^{film} 1720 cm^{-1}; nmr (CCl_4) δ 0.88 (d, 1, J = 6.5 Hz), 1.13 (d, 1, J = 6.5) 4.40 (d, 1, J = 4 cps), 7.03 (d, 1, J = 9.5), 7.65 (q, 1, J = 9.5, 2), 7.72 (d, 1, J = 2); mol wt (mass spectrum), 253.992 (Calcd for $C_{11}H_{11}O_2Br$, 253.994).

The 2-isopropyl-5-bromocoumaran-3-one obtained above (0.35 g) was dissolved in ethanol (4 ml) and water (1 ml) and 0.1 g of potassium hydroxide was added to this solution. The solution was cooled to ice bath temperature and sodium borohydride (0.07 g) was added. The solution was allowed to warm to room temperature overnight. On dilution with water and acidification with acetic acid 0.11 g of III identical in all respects with III obtained as previously described was obtained. The filtrate gave only unreacted XIV on extraction with ether.

Registry No.—I, 19019-21-7; II, 19019-22-8; III, 19018-84-9; IV, 19018-85-0; V, 19019-23-9; VII, 19018-86-1; VIII, 19018-87-2; IX, 19018-88-3; X, 19018-89-4; XI, 19018-90-7; XII, 19018-91-8; XIII, 19018-92-9; XIV, 19019-24-0.

Acknowledgments.—We are grateful for financial support to the Public Health Service, National Institute of General Medical Sciences (GM-13654).