The Synthesis of *cis*- and *trans*-2-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran[1]

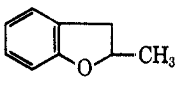
EDWARD C. HAYWARD, D. STANLEY TARBELL,[2] AND L. D. COLEBROOK

Department of Chemistry, University of Rochester, Rochester, New York 14627

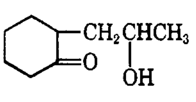
Received June 26, 1967

trans-2-Iodomethyl-3,4-dimethyl-5,7-dichloro-2,3-dihydrobenzofuran (**4b**) has been converted *via* a number of stages to *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**6d**), the configuration being established by its method of synthesis and its nmr spectrum. The *cis* isomer **5** was prepared from 2-isoamyl-3,4-dimethyl-5,7-dichlorobenzofuran by dechlorination followed by reduction of the 2,3 double bond. The configuration assignment and structure are supported by the 100-MHz nmr spectrum. These compounds of known relative stereochemistry offer promising materials for further syntheses in the fumagillin series.

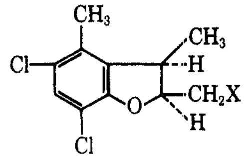
We have shown recently[3] that 2-methyl-2,3-dihydrobenzofuran **1** can be converted by lithium–liquid ammonia reduction, hydrolysis, and catalytic reduction to the hydroxy ketone **2**. We have also described[4] the synthesis and proof of configuration of *cis*- and *trans*-2,3,4-trimethyl-5,7-dichloro-2,3-dihydrobenzofurans (**3a** and **4a**), as well as the corresponding 2-iodomethyl compounds **3b** and **4b**, whose configurations were likewise established.[4,4a] The preparation of analogs of **3a** and **4a**, with an isoamyl group in the 2 position instead of a methyl group, would, by utilization and extension of the procedure of Brust and Tarbell,[3] allow the synthesis of compounds approaching the structure of fumagillin derivatives[5] with good prospects of arriving at the right stereochemistry at the (six) asymmetric centers present in the fumagillin series.



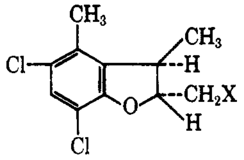
1



2

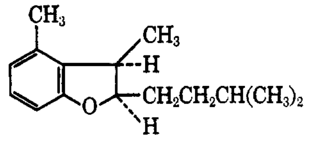


3a, X = H
b, X = I

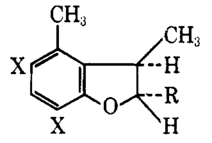


4a, X = H
b, X = I

The present paper reports the synthesis of pure *cis*- and *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**5** and **6d**). The lithium–liquid ammonia reduction of these compounds has been shown to occur, analogous to the previous results.[3]



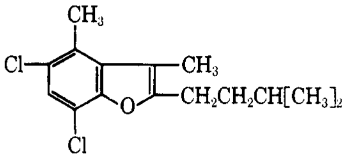
5



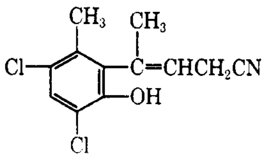
4b, R = CH_2I; X = Cl
6a, R = CH_2CN; X = Cl
b, R = $CH_2COCH[CH_3]_2$; X = Cl

c, R = $CH_2CCH[CH_3]_2$; X = Cl
d, R = $CH_2CH_2CH[CH_3]_2$; X = H
e, R = $CH_2CH_2CH[CH_3]_2$; X = Cl

The conversion of the crystalline *trans*-iodomethyl compound[4] **4b** to the nitrile **6a** by displacement with sodium cyanide gave, in initial runs, a poor yield of the desired product **6a**; the reaction yielded mainly the known benzofuran[5a] **7**, by elimination of HI, and the unsaturated hydroxynitrile **8**. However, in dimethyl sulfoxide at 90°, 60% of the desired product **6a** was obtained, along with 28% of the benzofuran **7**, and a few percent of the unsaturated nitrile **8**.



7



8

The ketone **6b** was obtained, after many orienting runs, as a crystalline product, mp 111–112°, in 51% yield, by the action of isopropylmagnesium bromide on the nitrile **6a**. The carbonyl group in **6b** was reduced by forming the crystalline ethylene dithioketal **6c**, which was desulfurized by treatment with W-2 Raney nickel. This process led to partial removal of the aromatic chlorines, and three pure compounds were isolated by vpc, corresponding to desulfuration with loss of no chlorine (compound **6e**), one chlorine, and both chlorines. Dechlorination could not be made complete by one treatment with Raney nickel,

---

[1] Aided by Grant AI-01138 from the National Institutes of Health.

[2] To whom inquiries should be directed: Department of Chemistry, Vanderbilt University, Nashville, Tenn. 37203.

[3] D. P. Brust and D. S. Tarbell, *J. Org. Chem.*, **31**, 1251 (1966).

[4] D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *ibid.*, **31**, 2192 (1966).

[4a] NOTE ADDED IN PROOF.—A recent note (I. H. Zalkow and M. Ghosal, *Chem. Commun*, 922 (1967)) reports that, for 2,3-dihydrobenzofurans carrying an isopropyl group at the 2 position and a hydroxyl at the 3 position, J_{2H-3H} is greater for the *trans* than for the *cis* isomers. This assignment of configuration is based on oxidation of the related compound toxol (2-isopropenyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran) to (+)-tartaric acid of high optical purity. The implication, that the configurational assignments made in our previous paper[4] on 2,3-dihydro-2,3-dimethylbenzofurans are invalid, is not correct for the following reasons, in our opinion. The assignments made earlier were based primarily on the demonstration that the *cis*- and *trans*-2,3-dihydro-2,3-dimethylbenzofurans could be equilibrated by concentrated sulfuric acid, and the form predominating at equilibrium was considered to be the *trans* form. Furthermore, the results obtained in the formation of the 2-iodomethyl compounds **3b** and **4b** could only be accommodated by the configurations originally assigned. In the present paper, the 2-isoamyl-3-methyl-2,3-dihydro compound **5**, which is formed by catalytic reduction of the 2,3 double bond, is undoubtedly *cis*, in agreement with our other assignments, and also with our use of the Karplus equation. It would appear that in our cases with methyl or alkyl groups at the 2,3 position, J_{2H-3H} is greater for the *cis* than for the *trans*, whereas in the cases studied by Zalkow, with an oxygen function at the 3 position, the reverse is the case.

[5] For establishment of the structures in the fumagillin series, see (a) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961); for stereochemistry and absolute configuration, see (b) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962); for X-ray crystallographic confirmation, see (c) N. J. McCorkindale and J. G. Sime, *Proc. Chem. Soc.*, 331 (1961).

The Synthesis of *cis*- and *trans*-2-Isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran[1]

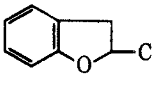
EDWARD C. HAYWARD, D. STANLEY TARBELL,[2] AND L. D. COLEBROOK

Department of Chemistry, University of Rochester, Rochester, New York 14627

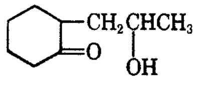
Received June 26, 1967

trans-2-Iodomethyl-3,4-dimethyl-5,7-dichloro-2,3-dihydrobenzofuran (**4b**) has been converted *via* a number of stages to *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**6d**), the configuration being established by its method of synthesis and its nmr spectrum. The *cis* isomer **5** was prepared from 2-isoamyl-3,4-dimethyl-5,7-dichlorobenzofuran by dechlorination followed by reduction of the 2,3 double bond. The configuration assignment and structure are supported by the 100-MHz nmr spectrum. These compounds of known relative stereochemistry offer promising materials for further syntheses in the fumagillin series.

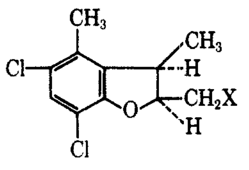
We have shown recently[3] that 2-methyl-2,3-dihydrobenzofuran **1** can be converted by lithium–liquid ammonia reduction, hydrolysis, and catalytic reduction to the hydroxy ketone **2**. We have also described[4] the synthesis and proof of configuration of *cis*- and *trans*-2,3,4-trimethyl-5,7-dichloro-2,3-dihydrobenzofurans (**3a** and **4a**), as well as the corresponding 2-iodomethyl compounds **3b** and **4b**, whose configurations were likewise established.[4,4a] The preparation of analogs of **3a** and **4a**, with an isoamyl group in the 2 position instead of a methyl group, would, by utilization and extension of the procedure of Brust and Tarbell,[3] allow the synthesis of compounds approaching the structure of fumagillin derivatives[5] with good prospects of arriving at the right stereochemistry at the (six) asymmetric centers present in the fumagillin series.



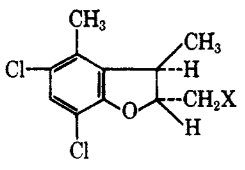
1



2

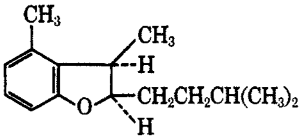


3a, X = H
b, X = I

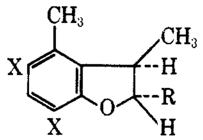


4a, X = H
b, X = I

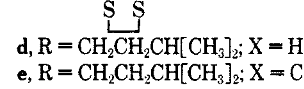
The present paper reports the synthesis of pure *cis*- and *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**5** and **6d**). The lithium–liquid ammonia reduction of these compounds has been shown to occur, analogous to the previous results.[3]



5

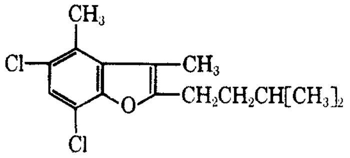


4b, $R = CH_2I$; $X = Cl$
6a, $R = CH_2CN$; $X = Cl$
b, $R = CH_2COCH[CH_3]_2$; $X = Cl$

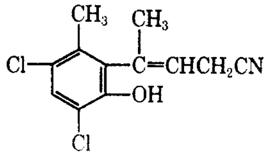


c, $R = CH_2CCH[CH_3]_2$; $X = Cl$
d, $R = CH_2CH_2CH[CH_3]_2$; $X = H$
e, $R = CH_2CH_2CH[CH_3]_2$; $X = Cl$

The conversion of the crystalline *trans*-iodomethyl compound[4] **4b** to the nitrile **6a** by displacement with sodium cyanide gave, in initial runs, a poor yield of the desired product **6a**; the reaction yielded mainly the known benzofuran[5a] **7**, by elimination of HI, and the unsaturated hydroxynitrile **8**. However, in dimethyl sulfoxide at 90°, 60% of the desired product **6a** was obtained, along with 28% of the benzofuran **7**, and a few percent of the unsaturated nitrile **8**.



7



8

The ketone **6b** was obtained, after many orienting runs, as a crystalline product, mp 111–112°, in 51% yield, by the action of isopropylmagnesium bromide on the nitrile **6a**. The carbonyl group in **6b** was reduced by forming the crystalline ethylene dithioketal **6c**, which was desulfurized by treatment with W-2 Raney nickel. This process led to partial removal of the aromatic chlorines, and three pure compounds were isolated by vpc, corresponding to desulfuration with loss of no chlorine (compound **6e**), one chlorine, and both chlorines. Dechlorination could not be made complete by one treatment with Raney nickel,

---

(1) Aided by Grant AI-01138 from the National Institutes of Health.

(2) To whom inquiries should be directed: Department of Chemistry, Vanderbilt University, Nashville, Tenn. 37203.

(3) D. P. Brust and D. S. Tarbell, *J. Org. Chem.*, **31**, 1251 (1966).

(4) D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *ibid.*, **31**, 2192 (1966).

(4a) NOTE ADDED IN PROOF.—A recent note (I. H. Zalkow and M. Ghosal, *Chem. Commun*, 922 (1967)) reports that, for 2,3-dihydrobenzofurans carrying an isopropyl group at the 2 position and a hydroxyl at the 3 position, J_{2H-3H} is greater for the *trans* than for the *cis* isomers. This assignment of configuration is based on oxidation of the related compound toxol (2-isopropenyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran) to (+)-tartaric acid of high optical purity. The implication, that the configurational assignments made in our previous paper[4] on 2,3-dihydro-2,3-dimethylbenzofurans are invalid, is not correct for the following reasons, in our opinion. The assignments made earlier were based primarily on the demonstration that the *cis*- and *trans*-2,3-dihydro-2,3-dimethylbenzofurans could be equilibrated by concentrated sulfuric acid, and the form predominating at equilibrium was considered to be the *trans* form. Furthermore, the results obtained in the formation of the 2-iodomethyl compounds **3b** and **4b** could only be accommodated by the configurations originally assigned. In the present paper, the 2-isoamyl-3-methyl-2,3-dihydro compound **5**, which is formed by catalytic reduction of the 2,3 double bond, is undoubtedly *cis*, in agreement with our other assignments, and also with our use of the Karplus equation. It would appear that in our cases with methyl or alkyl groups at the 2,3 position, J_{2H-3H} is greater for the *cis* than for the *trans*, whereas in the cases studied by Zalkow, with an oxygen function at the 3 position, the reverse is the case.

(5) For establishment of the structures in the fumagillin series, see (a) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **83**, 3096 (1961); for stereochemistry and absolute configuration, see (b) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962); for X-ray crystallographic confirmation, see (c) N. J. McCorkindale and J. G. Sime, *Proc. Chem. Soc.*, 331 (1961).

insoluble solid (5.5 g, fraction 1) was crystallized from 20 ml of 95% ethanol, giving 4.5 g (46%) of white crystalline nitrile, mp 136–137°. Evaporation of the filtrate to 5 ml, followed by cooling, yielded no further product. The remaining ethanol (5 ml) was removed at reduced pressure, the residual oil was combined with the petroleum ether soluble material (above) and chromatographed on neutral alumina (activity II). Elution with 1:1 petroleum ether–benzene gave 2.7 g (fraction 2) of a white solid in the first 100 ml and 1.2 g (fraction 3) of an oil that slowly crystallized in the next 100 ml of eluent; elution with 100 ml of benzene gave 89 mg (fraction 4) of a white solid; finally, elution with 300 ml of ether yielded 208 mg (fraction 5) of an oil that also partly crystallized on standing. Fraction 2 was identified as 5,7-dichloro-2,3,4-trimethylbenzofuran[4] by comparison of the melting point (no depression of a mixture melting point) and infrared spectrum with those of an authentic sample; the yield was 31%.

Both fractions 3 and 4 showed a nitrile band at 2230 cm^{-1}. Vapor phase chromatography on a 5 ft × 0.025 m 20% Apiezon column (column temperature was 195° with a flow rate of 100 cc He/min) showed that the major component of both fractions had the same retention time of 19 min. Fractions 3 and 4 were combined and recrystallized from 5 ml of 95% ethanol to give 1.0 g of product, mp 135.5–136.5°. This product, combined with the crystalline fraction 1, gave a total yield of the cyanomethyl compound **6a** of 58%. Analytically pure product, mp 136.5–137°, was obtained by a further crystallization from ethanol, followed by chromatography on Florisil. The infrared spectrum showed the characteristic nitrile band at 2230 cm^{-1}. The nmr spectrum showed a singlet at 7.28 (Ar–H), a multiplet at 4.68 (2-H), a multiplet at 3.50 (3-H), a multiplet at 2.77 (2-CH_2CN), a singlet at 2.35 (Ar–CH_3), and a doublet at 1.57 (2-CH_3).

Anal. Calcd for $C_{12}H_{11}Cl_2NO$: C, 56.27; H, 4.33; Cl, 27.69; N, 5.47. Found: C, 56.30; H, 4.58; Cl, 27.86; N, 5.31.

Fraction 5 was recrystallized from 3:1 petroleum ether–ether, giving a white, crystalline solid, mp 119–119.5° (sealed capillary). This compound was identified as the conjugated nitrile **8** from the elemental analysis and infrared and nmr spectra. The infrared spectrum showed absorption at 3500 (hydroxyl group), 2220 (nitrile group), 860 (pentasubstituted aromatic ring), and 830 cm^{-1} (trisubstituted alkene) in agreement with the assigned structures. The nmr spectrum showed a multiplet at 1.98 ($CH_3C{=}C$), a singlet at 2.18 (Ar–CH_3), a multiplet at 2.78 (CH_2CN), a broad multiplet at 5.50 (hydroxyl and vinyl protons overlapped), and finally a singlet at 7.29 (aromatic proton).

Anal. Calcd for $C_{12}H_{11}Cl_2NO$: C, 56.27; H, 4.33; Cl, 27.68; N, 5.47. Found: C, 56.34; H, 4.63; Cl, 27.67; N, 5.77.

2-(2-Oxo-3-methylbutyl)-5,7-dichloro-2,3-dihydro-3,4-dimethylbenzofuran (6b).—A 300% excess of isopropylmagnesium bromide[12] was prepared from 27.3 g of isopropyl bromide in 60 ml of ether and 4.9 g of magnesium turnings in 40 ml of ether. The finely ground cyanomethyl compound was added to the Grignard reagent at room temperature with stirring during 40 min. After an additional 40 min, the reaction mixture was decomposed by the careful addition of aqueous ammonium chloride. The ether was removed by heating on the steam bath, and, to ensure complete hydrolysis, the heating was continued for an additional 2 hr. The product was extracted with ether, and the ether solution was washed with sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the ether was removed at a reduced pressure, leaving 13.6 g of an oily orange solid. Vapor phase chromatography of the crude solid on a 5 ft × 0.25 in. 20% Apiezon column (column temperature was 200° with a flow rate of 100 cc of He/min) showed peaks at 17.2, 26, and 32 min. The largest peak, at 26 min, was collected, giving a white solid, mp 111–112°, which was identified from its spectral properties and elemental analysis as the desired ketone **6b**. The infrared spectrum showed strong carbonyl absorption at 1706 and the characteristic *gem*-dimethyl absorption at 1385 and 1368 cm^{-1}. The nmr spectrum showed singlets at 7.20 (Ar–H) and at 2.25 (Ar–CH_3), a multiplet at 3.20 (3-H), a doublet at 1.34 (3-CH_3), and a pair of doublets at 1.11 and 1.09 ($CH(CH_3)_2$). The protons adjacent to the carbonyl group and the proton attached to the number two carbon atom (2-H) overlapped, forming a complex absorption pattern at 2.90, totaling four protons.

Anal. Calcd for $C_{15}H_{18}Cl_2O_2$: C, 59.81; H, 6.01. Found: C, 59.66; H, 5.93.

The vpc peak at 17.2 min was indicated by coinjection to be the starting nitrile; the 32-min peak was not identified.

The crude, orange solid above was chromatographed on grade II alumina, the fractions being analyzed by vpc. Collection of several fractions, followed by a second chromatography on alumina yielded, after recrystallization from petroleum ether, 7.7 g of the ketone, mp 110–111.5°, with properties identical with those of the sample isolated by vpc; no depression on mixture melting point was observed. A total of 1.8 g of starting material was recovered, making the yield of ketone 51%.

The more polar fractions from the column chromatography consisted of a viscous, yellow oil that partially crystallized on standing. The combined fractions amounted to 20% of the material chromatographed and showed bands in the infrared at 3560, 3400, 2230, 2200, and 1705 cm^{-1}. The infrared spectrum suggested that this fraction was a mixture of a β,γ-unsaturated ketone, and an α,β- and the β,γ-unsaturated nitrile **8**. No attempt was made to isolate the latter from the mixture.

2-(2-Oxo-3-methylbutyl)-5,7-dichloro-2,3-dihydro-3,4-dimethylbenzofuran thioketal (6c) was prepared from 4.6 g of the ketone and 4 ml of ethanedithiol in chloroform at room temperature with boron trifluoride etherate as the catalyst.[13] After 10 hr, the mixture was washed with aqueous base and dried, and the residue (6.4 g), after removal of solvent, was chromatographed on activity I alumina. Elution with petroleum ether–benzene (20:1) gave 5.74 g of oil, which, when dissolved in petroleum ether (20 ml) gave 4.8 g (84%) of white crystals, mp 84–85°. Analytically pure material, mp 85°, was obtained by a further crystallization. The infrared spectrum showed no carbonyl absorption, and the nmr spectrum was in agreement with the expected structure.

Anal. Calcd for $C_{17}H_{22}Cl_2OS_2$: C, 54.10; H, 5.88. Found: C, 53.85; H, 5.86.

***trans*-5,7-Dichloro-2-isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (6e).**—A solution of 4.7 g of the thioketal **6c** in 40 ml of absolute ethanol was refluxed with a large excess of W-2 Raney nickel for 3 hr; the nickel was removed by filtration and was washed with several portions of ethanol. Evaporation of the ethanol at reduced pressure gave 2.3 g of a light yellow oil, which when examined by vpc on a 20% Apiezon column (column temperature was 195° with a flow rate of 100 cc He/min) showed three major peaks at 5, 11, and 21.5 min.

The material eluting at 5 min was identified as the *trans*-2-isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (**6d**). The infrared spectrum showed a strong band at 772 and a medium band at 740 cm^{-1} (1,2,3-trisubstituted benzene). The nmr spectrum is given above.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.53; H, 10.16. Found: C, 82.58; H, 10.02.

The material eluting at 11 min was identified as a monochloroisoamyldihydrobenzofuran. The infrared spectrum showed a medium band at 804 cm^{-1} (1,2,3,4 aromatic substitution).

Anal. Calcd for $C_{15}H_{21}ClO$: C, 71.27; H, 8.37. Found: C, 71.26; H, 8.53.

The material eluting at 21.5 min was identified as *trans*-5,7-dichloro-2-isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (**6e**). The infrared spectrum showed a medium band at 860 cm^{-1} (pentasubstituted aromatic ring). The nmr spectrum showed multiplets at 4.30 (2-H), 3.15 (3-H), and 1.42 (methylene and methine protons of the side chain). Also present were a singlet at 7.18 (Ar–H), a singlet at 2.25 (Ar–CH_3), a doublet at 1.28 (3-CH_3), and a doublet at 0.88 (–$CHC(CH_3)_2$).

Anal. Calcd for $C_{15}H_{20}Cl_2O$: C, 62.72; H, 7.02. Found: C, 63.00; H, 7.24.

No attempt was made to separate these three components on a preparative scale. The crude product was used directly in the next reaction.

***trans*-2-Isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (6d).**—The crude product (2.3 g) obtained above was hydrogenated at atmospheric pressure in 10 ml of absolute ethanol containing 1.1 g of sodium acetate, over 0.38 g of 5% palladium on carbon. The product was purified by chromatography on activity II alumina; elution with petroleum ether gave 2.0 g (74%) of a colorless oil, giving a single peak on vpc. The infrared spec-

---

[12] See R. L. Shriner and T. A. Turner, *J. Am. Chem. Soc.*, **52**, 1267 (1930), and C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *ibid.*, **70**, 426 (1948), for reactions between aliphatic nitriles and Grignard reagents.

[13] *Cf.* L. F. Fieser, *ibid.*, **76**, 1945 (1954).

trum and the vpc retention time were identical with those of the *trans*-2-isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (**6d**) whose structure and configuration are established above.

α-(1-Methoxy-2,4-dichloro-5-methylphenyl)propionaldehyde (**7b**).—To a stirred solution of 8.00 g of the allylphenol methyl ether **7a**, 0.51 g of the aldehyde **7b** (obtained from previous incomplete reactions), and 100 mg of osmium tetroxide in 100 ml of dioxane (which had been distilled from potassium hydroxide and then from sodium *immediately before* the reaction), and 50 ml of distilled water was added 14.5 g of sodium metaperiodate[14] over a period of 1 hr. The reaction mixture was then allowed to stir for an additional 3 hr, during which time an additional 75 ml of water was added. The above conditions must be adhered to extremely closely; if the aldehyde is omitted or the dioxane is not sufficiently pure, the reaction will not go to completion.

The reaction mixture was initially brown (black indicates that the reaction is not proceeding properly) and turned yellow after 45 min. If the reaction mixture is not bright yellow at this point, no water should be added until it turns so. Water (300 ml) was added, the solution was extracted with ether, and the ether was dried and removed on the steam bath. The residue was distilled at 160° (*ca.* 0.1 mm) to yield 4.06 g (48%) of product; the nmr spectrum showed among others the aldehyde proton near 10, and the infrared showed strong carbonyl absorption at 1720 and the aldehyde C–H at 2720 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.90. Found: C, 53.63; H, 4.98.

The **semicarbazone** melted at 197–198°.

Anal. Calcd for $C_{12}H_{15}Cl_2N_3O_2$: C, 47.38; H, 4.97. Found: C, 47.59; H, 4.93.

Oxidation of the aldehyde with chromic acid–sulfuric acid in acetone gave the corresponding acid,[4] mp and mmp 133–135°.

1,5-Dimethyl-2-hydroxy-1-(1-methoxy-2,4-dichloro-5-methylphenyl)heptane (**7c**).—To the Grignard reagent prepared from 1.10 g of magnesium, 6.75 g of isoamyl bromide, and 50 ml of absolute ether was added dropwise 5.0 g of the aldehyde in 50 ml of ether. After refluxing for 2 hr, the solution was hydrolyzed with ice–10% sulfuric acid, and the product was isolated in the usual way. The liquid product (5.66 g, 88%) showed strong hydroxyl absorption. The analysis was run on material with two vpc peaks, probably diastereoisomers.

Anal. Calcd for $C_{16}H_{24}Cl_2O_2$: C, 60.19; H, 7.58. Found: C, 60.19; H, 7.49.

Cyclization to the dihydrobenzofuran was carried out with concentrated sulfuric acid at room temperature. All runs gave a complex mixture, which showed on vpc on Ucon Polar a considerable fraction (45–51% at a reaction time of 10 sec–1 min) which had the proper analysis for structure **6d** and showed the same nmr spectrum as the sample of **6d** synthesized from the *trans*-iodomethyl compound **4b**.

2-Isoamyl-3,4-dimethyl-5,7-dichlorobenzofuran (**7**) was prepared on a 45-g scale by the previously described method[5a] in 57% yield, mp 52–53°, as reported.[5a]

2-Isoamyl-3,4-dimethylbenzofuran.—A solution of 10.7 g of the chlorinated benzofuran **7** in 150 ml of absolute ethanol containing 3.4 g of anhydrous sodium acetate was hydrogenated at atmospheric pressure and room temperature over 0.68 g of 5% palladium on carbon. When half of the theoretical volume of hydrogen had been absorbed, an additional 3.1 g of anhydrous sodium acetate was added. The absorption of hydrogen was complete within 12 hr. The 8.14 g of product obtained on working up the reaction showed two peaks at 4.5 and 6.7 min, when examined by vpc on a 20% Apiezon column. The 4.5-min peak amounted to *ca.* 10% of the product and was identified by coinjection with authentic material as the *cis*-dihydrobenzofuran **5**. The 6.7-min peak was identified by coinjection with authentic material as the 2-isoamyl-3,4-dimethylbenzofuran. The crude mixture was used for conversion to the *cis*-2,3-dihydro compound **5**.

***cis*-2-Isoamyl-2,3-dihydro-3,4-dimethylbenzofuran** (**5**).—A solution of 8.14 g of 2-isoamyl-3,4-dimethylbenzofuran above in 40 ml of absolute ethanol was refluxed for 6 hr over *ca.* 35 g of W-2 Raney nickel. The catalyst and solvent were removed, the residue was extracted with ether, and the ether solution was washed with water and dried. Removal of the ether gave 8.2 g of oil, which was purified by chromatography on activity II alumina. Elution with 9:1 petroleum ether–benzene gave 7.3 g (90%) of the *cis*-2-isoamyl-2,3-dihydro-3,4-dimethylbenzofuran (**5**). Vapor phase chromatography on a 20% Apiezon column (column temperature was 190° with a flow rate of 100 cc of He/min) showed that this product was greater than 99% pure.

The infrared spectrum of **5** showed a strong band at 769 and a medium band at 740 cm^{-1} (1,2,3-trisubstituted benzene).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.26; H, 10.02.

Treatment of the dichlorobenzofuran **7** with palladium on carbon and hydrogen in a Parr shaker for 9 hr gave a mixture which consisted (from vpc examination) of about 35% of starting material, 60% of the *cis* compound **5**, and 5% of the *trans* compound **6d**.

Spin-Decoupling Experiments.—Spin decoupling of $CDCl_3$ solutions of *cis*- and *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (**5** and **6d**, respectively) was carried out using a JEOLCO 4H-100 spectrometer operating at 100 MHz. For these experiments the spectrometer was used in the frequency sweep mode while locked on internal TMS. A sweep width of 1.80 ppm was employed in recording the decoupled spectrum of the proton on C-3 while the C-3 methyl lines were being irradiated. The frequency of the decoupling sideband was checked by observing the beat pattern as the C-3 methyl doublet was recorded. For the *cis* compound (**5**) and the *trans* compound (**6d**) the decoupling sidebands were 1.05 and 1.30 ppm, respectively, from TMS.

A cleanly decoupled spectrum was obtained for the *cis* isomer, but the decoupled spectrum of the *trans* isomer showed an additional weak line which appeared to be produced by an impurity rather than by incomplete decoupling. This impurity, which also affected other regions of the spectrum, may have been due to some decomposition of the sample during long standing before the spin-decoupling experiments were carried out.

Registry No.—**5**, 14734-10-2; **6a**, 14571-08-5; **6b**, 14571-09-6; **6c**, 14565-20-9; **6d**, 14565-21-0; **6e**, 14638-74-5; **7b**, 14565-22-1; **7b**, semicarbazone, 14565-23-2; **7c**, 14565-24-3; **8**, 14565-25-4.

---

[14] *Cf.* R. Pappo, D. S. Allen, Jr., R. V. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).