Studies on the Syntheses of Heterocyclic Compounds. Part DCXII (1). A Simple Synthesis of Benzopyran and Dibenzopyran Derivatives

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trans-2-(3-Hydroxyphenyl)cyclohexanol (Ib) was converted into 6-methyl-6-phenylbenzopyran (IIa) and 6-spirocyclohexanobenzopyran (IIb) by phenolic cyclization or under acidic condition. This type of reaction was also applied to the synthesis of 3,4-dihydro-6-methoxy-1-methoxycarbonyl-1-methyl-1*H*-2-benzopyran (IV).

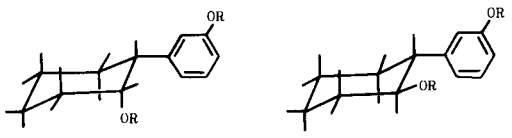
Previously we have reported that heating 3-hydroxyphenethylamine derivatives with various carbonyl compounds without acidic catalyst gave the corresponding 1,2,3,4-tetrahydro-6-hydroxyisoquinolines having mono- or disubstituents at C-1 position and we had proposed that this type of non-acidic reaction be called "Phenolic Cyclization" because a phenolic hydroxyl group played an important role in this reaction (3). Furthermore, this type of reaction was applied to the synthesis of 2-benzazepine (4), phthalazine (5), and 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (6) derivatives.

We have investigated the extension and generalization of the phenolic cyclization and here wish to report a synthesis of hexahydro-6*H*-dibenzopyrans by this reaction of *trans*-2-(3-hydroxyphenyl)cyclohexanol (Ib) with various carbonyl compounds and also a simple synthesis of dibenzopyran derivatives by a similar type of reaction.

Previously Cornubert reported that Ladenburg reduction (7) of 2-phenylcyclohexanone gave only *trans*-2-phenylcyclohexanol whereas hydrogenation in the presence of Raney nickel or platinum catalyst afforded only the *cis*-derivative in quantitative yield. On the contrary, Ladenburg reduction of 2-(3-hydroxyphenyl)cyclohexanone (III) gave a separable mixture of *cis*- (Ia), m.p. 114°, and *trans*-2-(3-hydroxyphenyl)cyclohexanol (Ib), m.p. 144-145°, in a ratio of 1:4 (8) in 90% yield. On the other hand, catalytic hydrogenation of III in the presence of palladium-charcoal afforded a mixture of Ia and Ib, in a ratio of 20:1 in 21% yield, which was separated by column and thin layer chromatography.

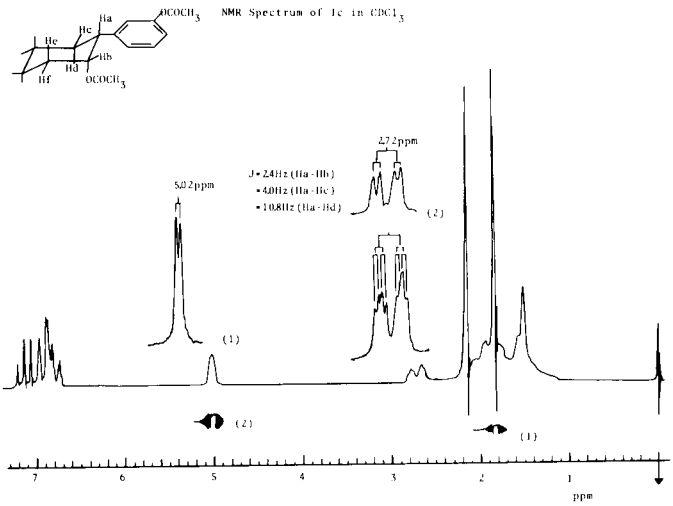
The acetylation of both alcohols with acetic anhydride at 100° for 3 hours gave a *cis*-acetate Ic [ν max (liquid) 1730 and 1760 cm^{-1}; δ (carbon tetrachloride) 1.84 and 2.16] and a *trans*-acetate Id [ν max (liquid) 1730 and 1760 cm^{-1}; δ (carbon tetrachloride) 1.90 and 2.16)], respectively. The stereochemistry of both acetates is determined by nmr spectral considerations. The methine proton at the C-2 position of the *trans*-acetate Id resonated at 2.3 ppm as a sextet having J 10.8, 10.8 and 3.6 Hz and the C-1 methine proton at 4.8 ppm as a sextet with J

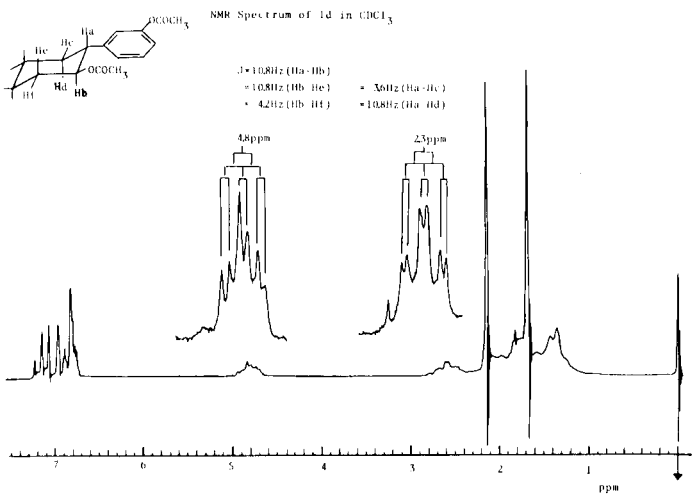
Chart 1



Ia R = H
Ic R = Ac

Ib R = H
Id R = Ac

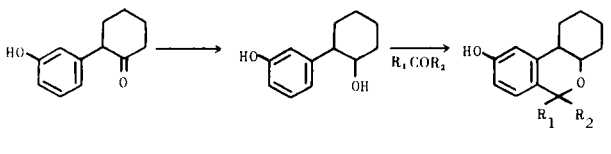




10.8, 10.8 and 4.2 Hz. Thus $J_{1,2}$ should be 10.8 Hz and the dihedral angle for C-1 and C-2 proton is 180°. On the other hand, the C-1 and C-2 methine protons in the *cis*-acetate Ic were observed at 5.02 ppm as a broad signal and at 2.72 ppm as an octet showing J 10.8, 4.0 and 2.4 Hz, respectively. On irradiation of the C-1 proton, the C-2 proton showed a double doublet having J 10.8 and 4.2 Hz, and a decoupling experiment of C-1 proton with C-6 methylene protons at 1.83 ppm revealed that the C-1 proton appeared as a doublet showing J 2.4 Hz. Thus $J_{1,2}$ is 2.4 Hz which indicates that the dihedral angle for the C-1 and the C-2 proton to be 60°.

Heating *trans*-alcohol Ib with acetophenone in boiling ethanol for 15 hours without an acidic catalyst gave 1,2,3,4,4a,10b-hexahydro-6-methyl-6-phenyl-6*H*-dibenzo-[*b*,*d*]pyran-9-ol (IIa), m.p. 128-130° [δ (dimethylsulfoxide-d_6) 6.83 (1H, dd, J = 8.3 and 2.3 Hz), 6.93 (1H, d, J = 2.3 Hz) and 7.15 (1H, d, J = 8.3 Hz)]. Similarly the reaction of the *trans*-alcohol Ib with cyclohexanone gave 1,2,3,4,4a,10b-hexahydro-6-spirocyclohexano-6*H*-dibenzo[*b*,*d*]pyran-9-ol (IIb), m.p. 179-180° [δ (dimethylsulfoxide-d_6) 6.65 (1H, d,d, J = 8.3 and 2.3 Hz, C_7-H)], which was also obtained in 85.1% yield by condensation of Ib with cyclohexanone in the presence of concentrated hydrochloric acid.

Chart 2

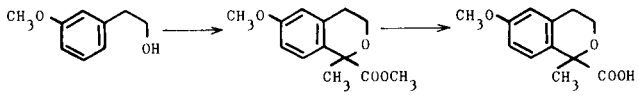


III I II

IIa: R_1 = CH_3, R_2 = Ph
IIb: R_1,R_2 = $-(CH_2)_5-$

On the other hand, the reaction of 2-(3-methoxyphenyl)ethanol (V) with methyl pyruvate without an acidic catalyst allowed recovery of the starting material, but 3,4-dihydro-6-methoxy-1-methoxycarbonyl-1-methyl-1*H*-2-benzopyran (IV) [ν max (liquid) 1730 cm^{-1}; δ (carbon tetrachloride) 1.60 (3H, s, ≡C-Me), 6.5 ~ 6.9 (2H, m, aromatic protons) and 7.26 (1H, d, J = 8.3 Hz, C_8-H)] could be obtained in 80% yield by condensation in the presence of a catalytic amount of *p*-toluenesulfonic acid. This suggests that this type of reaction is one type of phenolic cyclization. Thus, we have developed a new and simple synthetic method for benzopyrans.

Chart 3



V VI IV

EXPERIMENTAL

Melting and boiling points were not corrected. Ir spectra were taken with a Hitachi-215 spectrophotometer and nmr spectra with a JEOL MH-60 and PS-100 spectrophotometers.

2-(3-Hydroxyphenyl)cyclohexanol (I).

a) To a solution of 2-(3-hydroxyphenyl)cyclohexanone (III) (1.1 g.) in ethanol (50 ml.), metallic sodium (2.2 g.) was added in small portions within 2 hours. After heating under reflux for 1 hour, followed by removal of the solvent, water (50 ml.) was added to the above residue. The resulting solution was washed twice with ether, then acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over magnesium sulfate and distilled to give a pale yellow mixture of *cis*- Ia and *trans*-isomers Ib in a ratio of 1:4 (8). Recrystallization from ethanol gave colorless prisms (1.0 g., 90.0%) (Ia:Ib = 1:6), whose separation by tlc on silica gel using ether-petroleum ether (2:1) as eluant afforded Ib (750 mg., 67.6%) as colorless prisms, m.p. 144-145°; nmr δ (dimethylsulfoxide-d_6): 3.4 (1H, singlet, > CHO*H*), 4.15 (1H, doublet, > C*H*OH, J = 6 Hz), 6.45 ~ 6.7 (3H, multiplet, aromatic protons), 7.05 (1H, triplet, aromatic protons, J = 7.8 Hz), 9.10 (1H, broad signal, PhO*H*).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.34. Found: C, 75.08; H, 8.64.

b) A solution of III (2 g.) in ethanol (50 ml.) was hydrogenated in the presence of 30% palladium-charcoal (1 g.). After the usual treatment of the reaction mixture, the residue was purified by column chromatography on silica gel (length, 20 cm) using benzene-ether (5:1) to give Ia (405 mg., 20.0%) as colorless prisms, m.p. 114°; nmr δ (dimethylsulfoxide-d_6): 3.82 (1H, singlet, > CHO*H*), 4.30 (1H, doublet, > C*H*OH, J = 4 Hz), 6.4 ~ 6.7 (3H, multiplet, aromatic protons), 7.00 (1H, triplet, aromatic proton, J = 8 Hz), 9.20 (1H, singlet, PhO*H*).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: 75.03; H, 8.64.

Furthermore, the other fraction gave Ib (20 mg., 1.0%) which was identical with the authentic sample prepared by method (a) by mixed melting point and comparison of the spectral data.

1,2,3,4,4a,10b-Hexahydro-6-spirocyclohexano-6*H*-dibenzo[*b*,*d*]-pyran-9-ol (IIb).

a) A mixture of Ib (1 g.), ethanol (20 ml.) and cyclohexanone (5 ml.) was heated at 200° in an autoclave for 48 hours and the solvent was then distilled off. The residue was purified by column chromatography on silica gel using ether-benzene to afford IIb (390 mg., 27.5%) as colorless prisms, m.p. 179 ~ 180°, nmr δ (dimethylsulfoxide-d_6): 3.2 (1H, broad signal, > C*H*OH), 6.65 (1H, double doublet, aromatic proton, J = 2.3 and 8.3 Hz), 6.75 (1H, doublet, aromatic proton, J = 2.3 Hz), 6.95 (1H, doublet, aromatic proton J = 8.3 Hz), 8.61 (1H, singlet, PhO*H*). Furthermore, the starting material (420 mg.) was recovered.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.46; H, 8.88.

b) A mixture of Ib (1 g.), ethanol (50 ml.), cyclohexanone (5 ml.) and concentrated hydrochloric acid (1 ml.) was refluxed for 15 hours. After removal of the solvent, the residue was recrystallized from benzene-hexane to give colorless prisms (1.2 g., 85.1%), m.p. 179-180°, which was identical with the above authentic sample prepared by method (a).

1,2,3,4,4a,10b-Hexahydro-6-methyl-6-phenyl-6*H*-dibenzo[*b*,*d*]-pyran-9-ol (IIa).

a) A mixture of Ib (1 g.), ethanol (50 ml.) and acetophenone (5 ml.) was refluxed for 24 hours. After removal of the solvent, the reaction mixture was extracted with benzene (50 ml.). The organic layer was washed with water and extracted with 10% sodium hydroxide solution. The resulting aqueous solution was washed twice with benzene, acidified with hydrochloric acid and then extracted with benzene. The extract was dried over magnesium sulfate and then evaporated to give a syrup, which was purified by column chromatography on silica gel (length, 20 cm) using benzene-ether (1:1). Recrystallization of the resulting solid from benzene gave a small amount of IIa as colorless needles, m.p. 128 ~ 130°; nmr δ (dimethylsulfoxide-d_6): 3.3 ~ 3.8 (1H, broad signal, -OC*H*<), 6.83 (1H, double doublet, aromatic proton, J = 2.3 and 8.3 Hz), 6.93 (1H, doublet, aromatic proton, J = 2.3 Hz), 7.15 (1H, doublet, aromatic proton, J = 8.3 Hz).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.86; H, 7.72.

b) A mixture of Ib (2 g.), ethanol (80 ml.), acetophenone (10 ml.) and concentrated hydrochloric acid (3 ml.) was refluxed for 24 hours. After removal of the solvent the residue was extracted with benzene (50 ml.), the extract of which was washed twice with water and then extracted with 10% sodium hydroxide solution. The resulting alkaline aqueous solution was washed twice with benzene, acidified with hydrochloric acid and again extracted with benzene. The extract was dried over magnesium sulfate and evaporated to give a syrup, which was recrystallized from benzene to afford colorless needles (2.3 g., 75.1%), m.p. 128 ~ 130°, identical with the above authentic sample prepared by method (a).

1-Acetoxy-2-(3-acetoxyphenyl)cyclohexane (Ic and Id).

A solution of Ia (100 mg.) in acetic anhydride (2 ml.) was heated at 100° for 3 hours. After evaporation of acetic anhydride under reduced pressure, the residue was mixed with benzene (50 ml.) and then distilled. This procedure was carried out three times, thus the acetate Ic (135 mg., 93.8%) being obtained as a colorless oil; ir ν (liquid): 1730 and 1760 cm^{-1} (C=O); nmr δ (carbon tetrachloride): 1.84 (3H, singlet, >CHOCOCH_3), 2.16 (3H, singlet, PhOCOCH_3), 2.72 (1H, octet, PhC*H*, J = 10.8, 4.0 and 2.4 Hz), 5.02 (1H, distorted singlet, AcOC*H*<), 6.7~7.2 (4H, multiplet, aromatic protons).

The same treatment of Ib (100 mg.) afforded the acetate Id (137 mg., 95.1%); ir ν (liquid): 1730 and 1760 cm^{-1} (C=O); nmr δ (carbon tetrachloride) 1.90 (3H, singlet, >CHOCOCH_3), 2.16 (3H, singlet, PhOCOCH_3), 2.30 (1H, sextet, PhC*H*<, J = 10.8, 10,8 and 3.6 Hz), 4.80 (1H, sextet, AcOC*H*<, J = 10.8, 10.8 and 4.2 Hz), 6.72~7.24 (4H, multiplet, aromatic protons).

2-(3-Methoxyphenyl)ethyl Alcohol (V).

To a solution of 3-methoxyphenethylamine hydrochloride (9) (10 g.) in acetic acid (25 ml.) and water (75 ml.) a solution of sodium nitrite (10 g.) in water was added dropwise under cooling. After addition, the mixture was stirred at 0° for 2 hours and then heated at 80° for 1 hour. After cooling, the reaction mixture was basified with 10% sodium hydroxide and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give an oil, which was distilled *in vacuo* to afford a colorless oil (6.9 g., 85.2%), b.p. 132~135° (12 mm Hg) [lit. (10), b.p. 129~133° (11 mm Hg)]; ir ν (liquid): 3400 cm^{-1} (OH); nmr δ (carbon tetrachloride): 2.75 (2H, triplet, PhCH_2CH_2, J = 7.5 Hz), 3.76 (3H, singlet, OCH_3).

3,4-Dihydro-6-methoxy-1-methoxycarbonyl-1-methyl-1*H*-2-benzopyran (VI).

A mixture of V (0.5 g.), methyl pyruvate (3 ml.) and *p*-toluenesulfonic acid (0.1 g.) was heated at 100° for 10 hours. After the reaction, an excess of methyl pyruvate was removed by distillation *in vacuo* to give an oil, which was dissolved in ether (20 ml.). The extract was washed with water, dried over sodium sulfate, and evaporated to afford a pale yellowish oil (6.2 g., 80.0%); ir ν (liquid): 1730 cm^{-1} (C=O); nmr δ (carbon tetrachloride): 1.60 (3H, singlet, ≡C-CH_3), 2.80 (2H, distorted triplet, PhCH_2CH_2), 3.65 (3H, singlet, PhOCH_3), 3.70 (3H, singlet, CO_2CH_3), 4.05 (2H, distorted triplet, OCH_2CH_2), 6.5~6.9 (2H, multiplet, aromatic protons), 7.26 (1H, doublet, aromatic proton, J = 8.3 Hz).

1-Carboxy-3,4-dihydro-6-methoxy-1-methyl-1*H*-2-benzopyran (IV).

A mixture of VI (3 g.) and 10% sodium hydroxide solution (20 ml.) was heated at 100° for 1 hour and the cooled reaction mixture was washed with ether. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The extract was dried over sodium sulfate and evaporated to afford a syrup, which was purified by column chromatography on silica gel (length, 20 cm) using chloroform-ethanol (9:1) to give a caramel-like material (2.1 g., 75.0%); ir ν (potassium bromide): 1700 cm^{-1} (C=O); nmr (deuteriochloroform): 1.7 (3H, singlet, ≡C-CH_3), 2.7 (2H, distorted triplet, PhCH_2CH_2), 3.7 (3H, singlet, PhOCH_3), 4.0 (2H, distorted triplet, OCH_2CH_2), 6.5~6.9 (2H, multiplet, aromatic protons), 7.4 (1H, doublet, aromatic proton, J = 8.3 Hz), 10.5 (1H, singlet, CO_2*H*).

Acknowledgement

We thank Dr. K. Fukumoto, Pharmaceutical Institute, Tohoku University, for his kind discussion and President Mr. A. Yanagisawa and Director Mr. O. Takagi, Grelan Pharmaceutical Company Ltd. for their kind encouragement. We also thank Miss R. Kato, Miss R. Suenaga and Miss Y. Yokahama, Pharmaceutical Institute, Tohoku University for their kind help in the preparation of this manuscript.

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