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Stereochemical Studies in Friedel-Crafts Reactions. I. The Reactions of *cis*- and *trans*-4-Tetrahydrophthalic Acid and Its Dimethyl Ester with Benzene

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The aluminum chloride-catalyzed reactions of *cis*-Δ^4-tetrahydrophthalic acid (**1A**) and its dimethyl ester (**3A**) with benzene gave, stereoselectively, *t*-4-phenyl-*cis*-hexahydrophthalic acid (**2A**) and its dimethyl ester (**12**) respectively. Similarly, the reactions of *trans*-Δ^4-tetrahydrophthalic acid (**1B**) and its dimethyl ester (**3B**) with benzene gave, stereoselectively, *c*-4-phenyl-*trans*-hexahydrophthalic acid (**2B**) and its dimethyl ester respectively, accompanied by a small amount of the *c*-4,*t*-2,*r*-1-isomer. The mechanism can be explained by presuming the interaction of the lone-pair electrons of carbonyl oxygen in the axial carboxyl group with a vacant *p*-orbital of the carbonium ion, which is produced by protonation to the double bond of the cyclohexenes (**1A**, **1B**, **3A**, **3B**).

A number of expensive studies of the directive effect of various remote substituents in hydroboration,[1] oxymercuration,[2] and epoxydation[3] have been reported, but little has been reported on the Friedel-Crafts reaction. Therefore, we have studied the directive effect on the Friedel-Crafts reactions of benzene to the double bond of 4-mono- and 4,5-disubstituted cyclohexenes catalyzed by aluminum chloride. Recently, it was reported[4] that the reaction of *cis*-Δ^4-tetrahydrophthalic acid (**1A**) with benzene catalyzed by aluminum chloride gave quantitatively, 4-phenylhexahydrophthalic acid (**2A**). The stereochemistry of the **2A** acid was not described, however. The present paper will deal with some reactions of benzene with the double bond of such 4,5-disubstituted cyclohexenes as the **1A** acid and its dimethyl ester (**3A**), *trans*-Δ^4-tetrahydrophthalic acid (**1B**), and its dimethyl ester (**3B**).

Results and Discussion

Configuration of 4-*Phenylhexahydrophthalic Acid* (**2A**). The configuration of the acid, **2A**, obtained by the reaction of **1A** with benzene was established on the basis of ring closure, epimerization, and the reaction of 4-phenylhexahydrophthalic acid anhydride (**4A**)[5] with benzene. When the **2A** acid was treated with acetic anhydride or acetyl chloride, the corresponding acid anhydride, **4A**, was obtained in a quantitative yield. Conversely, the hydrolysis of **4A** led to **2A**. The dimethyl ester **12** was converted to a new acid, **2C**, upon treatment with sodium ethoxide, followed by acidification. The **2C** acid is *t*-4,*t*-2,*r*-1-acid with a tri-equatorial structure, which is thermodynamically stable. On the basis of these results, the structure of **2A** was reasonably assumed to be as is shown in Scheme 1.[6]

In order to confirm this *t*-4,*c*–2,*r*–1 configuration of the **2A** acid, the reaction of the **4A** anhydride with benzene was carried out in the presence of aluminum chloride. This reaction gave a mixture of two isomeric keto acids, **5A** and **6A**, both of which were isolated upon fractional recrystallization. The Hunsdiecker reaction of **5A**, followed by treatment with potassium hydroxide in alcohol, gave 4-benzoylbiphenyl.[7] Therefore, the keto acid, **5A**, is 5-phenyl-2-benzoylcyclohexane-1-carboxylic acid. The treatment of **6A** with platinum-black gave 4-phenyl-2-benzylbenzoic acid (**7**). The IR spectrum of **7** shows a strong carbonyl absorption at 1685 cm^{-1}. Its structure was further confirmed by the IR and NMR spectra of the methyl ester, **8**, obtained from **7** and diazomethane. The isomeric keto acid, **5A**, was treated much as **6A** had been to afford the methyl ester **10**. The NMR spectra of the resulting esters exhibited a doublet (J=9.0 Hz[8]) at 8.0 for **8** and a doublet (J=3.0 Hz) at 8.10 ppm for **10**, which were ascribed to Ha in **8** and to Ha′ in **10** respectively.

The bromination of **6A** gave the mono-bromo ketone **11** (γ_{CO} 1680 cm^{-1}), which, on treatment with hydroiodic acid, afforded **6A**. Under similar conditions, **5A** was recovered unchanged. Since the ease of bromination depends on the respective rate of enolization,[9] the difference in behavior of **5A** and **6A** should be attributed to the presence of the axial benzoyl group in **6A** and the equatorial one in **5A**. The methyl ester of **5A** gave a mixture of the **5B** isomeric acid upon epimerization with sodium ethoxide, followed by acid hydrolysis. The recrystallization

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1) a) J. Klein, E. Dundelbrum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967); b) D. J. Dasto and F. M. Klein, *ibid.*, **33**, 1468 (1968).

2) H. B. Henbest and B. Nichollis, *J. Chem. Soc.*, **1959**, 227.

3) a) H. B. Henbest, B. Nichollis, W. R. Jackson, R. A. L. Wilson, N. S. Crossley, M. B. Meter, and R. S. McElhinney, *Bull. Soc. Chem. Fr.*, **1960**, 1365; b) N. S. Crossley, A. C. Darby, H. B. Henbest, J. J. McCullough, B. Nicollis, and M. F. Slewart, *Tetrahedron Lett.*, **1961**, 398; c) H. B. Henbest and J. J. McCullough, *Proc. Chem. Soc.*, **1962**, 74.

4) E. Schefczik, *Chem. Ber.*, **98**, 1270 (1965).

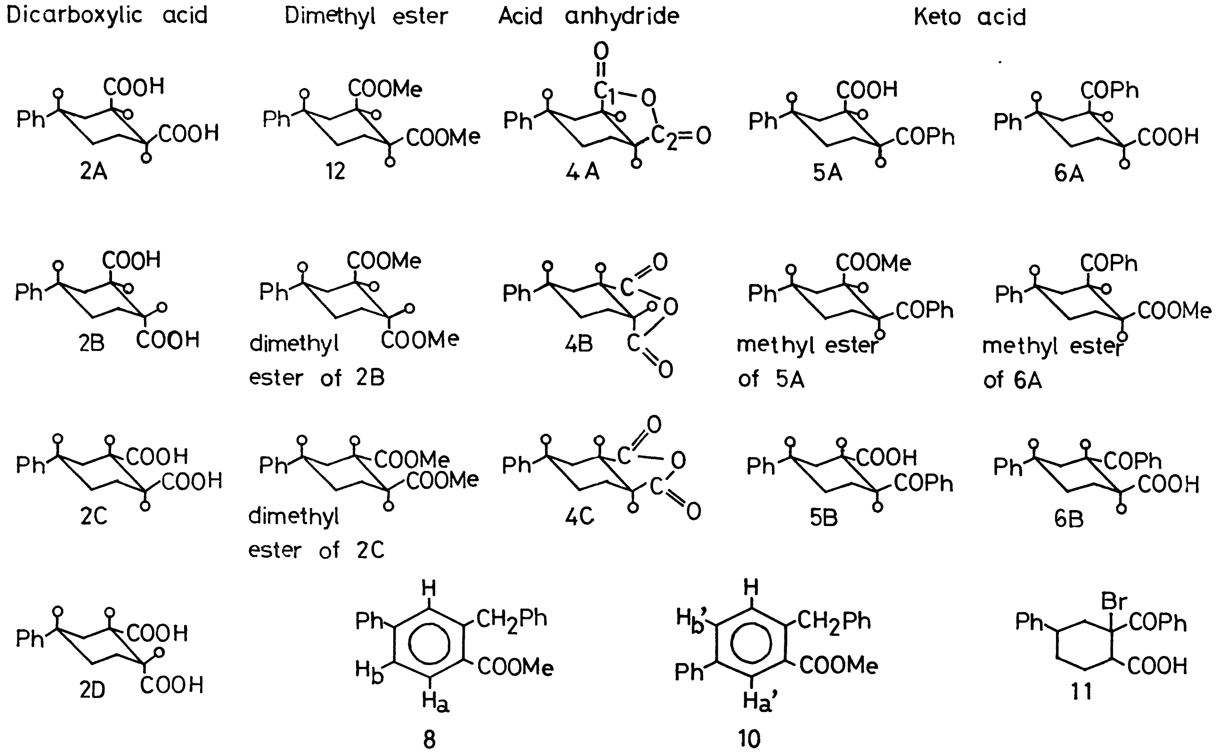
5) Since it has been reported that[a,b] the phenyl group had a substantially greater A value than the benzoyl, methoxycarbonyl, and carboxyl groups, it is supposed that the phenyl group in this paper has an equatorial conformation. a) E. L. Eliel, N. L. Allinger, S. T. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y. (1965), p. 236; b) E. W. Garbish, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).

6) The possibility of **2D** could not be excluded at this stage, but it was rejected on the basis of subsequent experiments. (*vide infra*).

7) L. M. Long and H. R. Henze, *J. Amer. Chem. Soc.*, **63**, 1939 (1941).

8) J. W. Emsley, J. Feeney, and L. H. Sulchiffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergaman Press, Oxford (1966), p. 770.

9) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549(1955).



Scheme 1.

of this mixture gave a new acid, **5B**, in a 40% yield. The epimerization of the methyl ester of **6A** similarly gave another new acid, **6B**. These results support the **5A** and **6A** structures shown. Furthermore, the all-equatorial isomers, that is, the **5B** and **6B** keto acids are considered to be *t*-2-benzoyl-*c*-5-phenyl-*r*-1-cyclohexanecarboxylic acid and *t*-2-benzoyl-*t*-4-phenyl-*r*-1-cyclohexanecarboxylic acid respectively.

As is shown in Scheme 1, **6A** was obtained as a result of the attack by benzene an C–1 in **4A**, while **5A** was formed by the reaction of benzene at C–2. When **5A** or **6A** was treated with aluminum chloride in benzene under reflux, both were recovered unchanged. On the basis of the observed reaction of the acid anhydride **4A** with benzene, the configuration of **4A** can reasonably be assumed to be *c*–2, *t*–4, *r*–1 and the alternative structure, **4B**, can be excluded. As the hydrolysis of the acid anhydride **4A** gives the **2A** acid, the configuration of **2A** must be the same as **4A**.

The Reaction of Cyclohexenes with Benzene. The aluminum chloride-catalyzed reaction of various 4,5-disubstituted cyclohexenes with benzene was carried out. The results are shown in Table 1.

The reaction of dimethyl *cis*-Δ^4-tetrahydrophthalate (**3A**) with benzene gave a viscous oil in an 82% yield. The oil proved to be homogeneous on gas-chromatographic analysis and was identified as the dimethyl ester of **2A** by a comparison of the IR spectra. Therefore, the reaction gave, stereoselectively, dimethyl *t*-4-phenyl-*cis*-hexahydrophthalate (**12**) or the dimethyl ester of **2A**. The reaction of *trans*-Δ^4-tetra-

Table 1. Aluminum chloride-catalyzed addition reaction of benzene with 4,5-disubstituted cyclohexene

Cyclohexene	Product	Bp (Mp)	Yield (%)	Product distribution[a)] (min)
1B	Crystalline solid[b)]	(149—154°C)	90	b)
3A	**12**[c)]	153—154°C/3 mmHg (53— 54°C)	82	single peak (69)
3B	Viscous oil[d)]	154—155°C/3 mmHg	80	80 (60) : 20 (65)

a) By gas-chromatographic analysis. The ratio was calculated from the peak areas. (retention).

b) Fractional recrystallization from 40% acetic acid gave **2B** (70%), mp 162—164°C, and *t*-4, *t*-2, *r*-1-acid (**2C**) (8%), mp 215—217°C. IR of **2B**: (KBr) 2700—2400 (-OH), 1690 (carboxyl) and 1600 cm^{-1} (aromatic). Found: C, 67.08; H, 6.39%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. The dimethyl ester of **2B** was obtained by the treatment of **2B** with diazomethane in ether. IR: (neat) 1730 (ester) and 1605 cm^{-1} (aromatic. NMR: δ ($CDCl_3$) 2.30—1.60 (m, 6, $3CH_2$), 2.95—2.55 (m, 1, CH), 3.45—3.00 (m, 2, 2CH), 3.75 (s, 6, $2CH_3$) and 7.22 ppm (s, 5, aromatic). The *t*-4, *t*-2, *r*-1-acid (**2C**) was identified by a mixed-melting-point determination and by a comparison of its IR spectrum with those of an authentic sample.

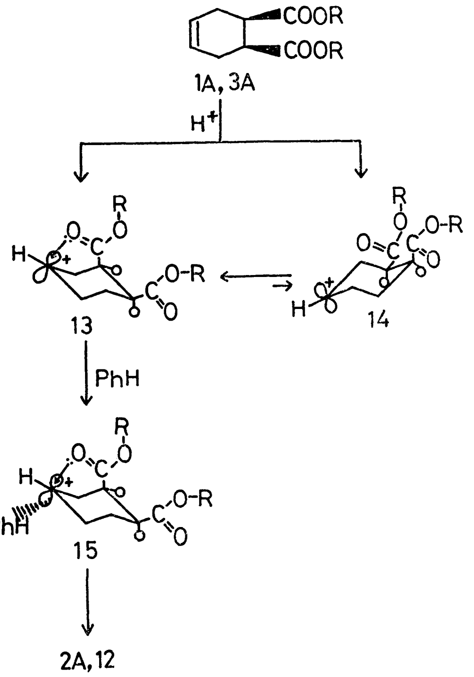
c) The product crystallized on cooling. Found: C, 69.74; H, 7.45%. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30%.

d) IR: (neat) 1730 (ester) and 1605 cm^{-1} (aromatic). Found: C, 69.75; H, 7.38%. Cald for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30%.

hydrophthalic acid (**1B**) and benzene gave a mixture of acids in a 90% yield, from which **2B** was isolated in a 70% yield and *t*-4-phenyl-*trans*-hexahydrophthalic acid (**2C**) in an 8% yield. Finally, the reaction of dimethyl *trans*-Δ^4-tetrahydrophthalate (**3B**) gave, in an 80% yield, a viscous oil which showed two peaks (area ratio 4 : 1) on gas-chromatography. The GC retention time indicated that the major component was the dimethyl ester of **2B**, and the minor one, the dimethyl ester of **2C**. In short, *trans*-4,-5disusbstituted cyclohexene (**1B**, **3B**) reacted with benzene to give **2B** and the dimethyl ester of **2B** contaminated with the *t*–4,*t*–2,*r*–1–isomer (**2C**, dimethyl ester of **2C**); this is in contrast to the behavior of the *cis*-4,5-disubstituted cyclohexene isomers (**1A**, **3A**). The configuration of the **2B** acid was established on the basis of the analogous epimerization and ring closure described above. The dimethyl ester of **2B** was converted to *t*–4,*t*–2,*r*–1–acid (**2C**) with sodium ethoxide, followed by acidification. This indicated that the **2B** and **2C** acids are stereoisomeric with each other. The **2B** acid was converted to **4A** in a quantitative yield with acetic anhydride, while **2B** was recovered unchanged upon treatment with acetyl chloride. The **2C** acid gave **4A** in a quantitative yield upon treatment with acetic anhydride and gave a new acid anhydride (**4C**) in quantitative yield when treated with acetyl chloride. In spite of the stereochemical differences in these acids (**2A**, **2B**, **2C**) in ring closure, the same product (**4A**) was obtained. In view of these facts, **2B** was identified as *c*-4-phenyl-*trans*-hexahydrophthalic acid having both carboxyl groups in an anti-axial conformation; this should explain the unsuccessful dehydration to anhydride.

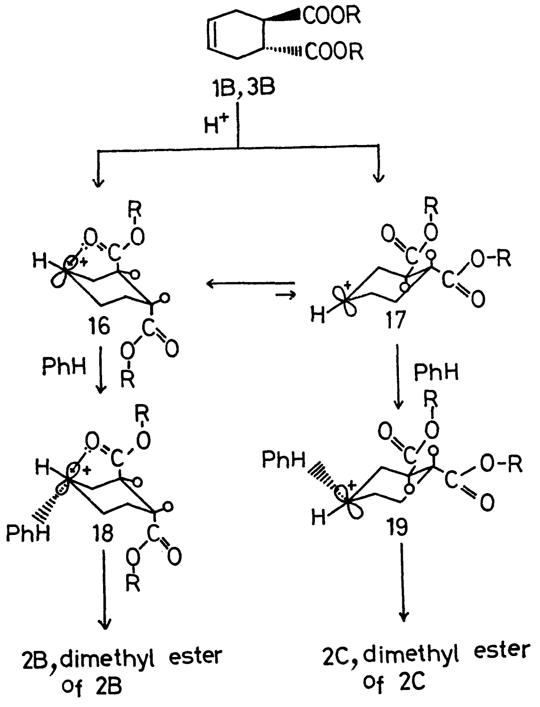
Mechanism. It is generally known[10] that the alkylation of aromatics with olefins catalyzed by Lewis acids is initiated by the protonation of the double bond, thus forming a carbonium ion which then reacts with the aromatic rings.

In the presence of a trace amount of water, the protonation of the double bond of *cis*-4,5-disubstituted cyclohexene (**1A**, **3A**) gives a carbonium ion[11] which may be in either one of the two conformations (**13**, **14**) shown in Scheme 2. The conformation of **13** seems to be more stable than **14** since **13** is stabilized by the interaction of the lone-pair electorons of carbonyl oxygen in the axial carboxyl group with the vacant *p*-orbital. On the other hand, **14** does not have an axial carboxyl which might serve to stabilize the carbonium ion. The above explanation may be acceptable in view of the fact that a 1,3-interaction of this type has previously been established.[12,13] Thus, the stereoselective formation of **2A** and **12** can presumably be explained by a route which involves the **15** transition state. Scheme 3 summarizes the reac-



R=H, Me

Scheme 2.



R=H, Me

Scheme 3.

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[10] S. H. Patinkin and B. S. Friedman, "Friedel-Crafts and Related Reaction," vol. 2, Part 1, ed. by G. A. Olah, John Wiley, New York (1964), p. 3.

[11] The ester carbonyl can be coordinated by aluminum chloride:

$$\genfrac{}{}{0pt}{}{\diagdown}{R\text{-}O\diagup}C{=}O\cdots AlCl_3 \longleftrightarrow \genfrac{}{}{0pt}{}{\diagdown}{R\text{-}O\diagup}C{=}\overset{\oplus}{O}\ \overset{\ominus}{Al}Cl_3$$

This coordination may antagonize the above-mentioned carbonium-ion stabilization by *n*-electrons on carbonyl oxygen. Possibly, the stereochemistry involved in the present work suggests that such a coordination is not important in the product-determining step of the Friedel-Carfts reaction.

[12] N. Baggett, J. S. Brimacombo, A. B. Foster, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, **1960**, 2574.

[13] a) B Dobinson and A. B. Foster, *ibid.*, **1961**, 2338; b) N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehamann, and J. M. Webber, *ibid.*, **1963**, 4157.

tion of *trans*-4,5-disubstituted cyclohexenes (**1B**, **3B**). The intermediary carbonium ions can be either bridged, **16**, stabilized by an axial carboxyl group or a usual carbonium ion, **17**. The reaction of benzene with the carbonium ion **16** proceeds in a manner similar to that described in the case of **13** to give the *c*–4,*t*–2,*r*–1 configuration (**2B**, the dimethyl ester of **2B**) stereoselectively. The equatorial attack of benzene and the carbonium ion, **17**, proceeds *via* the most favorable transition state, **19**, in which the two substituents and benzene all occupy equatorial positions, so that the *t*–4,*t*–2,*r*–1 configuration (**2C**, the dimethyl ester of **2C**) is formed.

Experimental[14]

Materials. Commercially-avalilable *cis*-Δ^4-tetrahydrophthalic acid (**1A**) was used. Dimethyl *cis*-Δ^4-tetrahydrophthalate (**3A**) was prepared by the procedure reported by Nazarov and Kucherov;[15] bp 107—109°C/5 mmHg (lit,[15] bp 110—111°C/5mmHg). *trans*-Δ^4-Tetrahydrophthalic acid (**1B**) was prepared by the procedure reported by Nazarov and Kucherov;[15] mp 169—170°C (lit,[15] mp 170—171°C). Dimethyl *trans*-Δ^4-tetrahydrophthalate (**3B**) was prepared by the procedure reported by Nazarov and Kucherov;[15] bp 110—111°C/5mmHg (lit,[15] bp 137°C/20mmHg).

t-*4-Phenyl-*cis-*hexahydrophthalic Acid (**2A**).* This was prepared by the procedure reported by Schefczik;[4] mp 190—191°C (lit,[4] 194°C).

*Reaction of **4A** with Benzene.* Into a solution of **4A** (21.5 g) in dry benzene (87 m*l*), we stirred aluminum chloride (33 g) over a five-minute period below 10°C. Stirring was continued for one hour without further cooling and then for 20 additional minutes under reflux. Then the reaction mixture was poured onto icewater. The evaporation of solvent gave a mixture of carboxylic acids (27 g, 93%), mp 160—186°C. Fractional recrystallization from 95% alcohol gave **5A** (3 g, 11%) and **6A** (18 g, 67%). The recrystallization of **5A** from 85% alcohol gave colorless prisms; mp 182—183°C. IR: (KBr) 2700—2400 (-OH), 1700 (carboxyl), 1680 (Ketone) and 1600 cm^{-1} (aromatic). Found: C, 77.61; H, 6.66%. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%. The recrystallization of **6A** from 95% alcohol gave colorless prisms; mp 202—203°C. IR: (KBr) 2700—2400 (–OH), 1700 (carboxyl), 1680 (ketone) and 1600 cm^{-1} (aromatic). Found: C, 77.82; H, 6.43%. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%.

*The Methyl Esters of **5A** and **6A*** were obtained by the treatment of **5A** and **6A** with diazomethane in ether.

4-Benzoylbiphenyl was prepared by the procedure reported by Long and Henze;[7] mp 100—101°C (lit,[7] 103—104°C).

*4-Benzoylbiphenyl from **5A**.* To a solution of sodium hydroxide (3 g) in water (70 m*l*), **5A** was added (20 g). The mixture was heated to reflux until a clear solution was observed. The solution was cooled to room temperature and filtered. Nitric acid was added, drop by drop, to this filtrate until it reached incipient turbidity. Then a few drops of aqueous sodium hydroxide were added just to clear the solution up again. The slow stirring in of a solution of silver nitrate (13 g) in water (30 m*l*) produced a copious precipitate of the silver salt, which was then collected, washed with water, and carefully dried in a vacuum desiccator. The silver salt was obtained quantitatively. To a suspension of the dry silver salt (20 g) in dry chloroform (100 m*l*), a solution of bromine (9.6 g) in dry chloroform (20 m*l*) was added at room temperature. After this mixture had been refluxed for three hours, a suspension was obtained. After cooling, the suspension was filtered, and the silver bromide in the filter was washed with chloroform. The combined filtrate was washed with an aqueous sodium thiosulfate solution, an aqueous sodium hydroxide solution, water, and brine. Then the solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The distillation of the reaction residue gave an oily product (4 g), bp 220—245°C/2 mmHg. This oil was added to a solution of potassium hydroxide (3 g) in ethyl alcohol (60 m*l*) and refluxed for two hours. Subsequent recrystallization from alcohol gave 4-benzoylbiphenyl (2.5 g, 16%), mp 99—101°C. The structure was confirmed by a mixed-melting-point determination and by a comparison of the IR spectra with those of an authentic sample.[7]

*4-Phenyl-2-benzylbenzoic Acid (**7**).* A mixture of **6A** (1.6 g) and platinum-black (0.5 g) was heated under nitrogen at 305—310°C for four hours. The reaction mixture was then separated and the ether was extracted. The ether layer was treated with 5% sodium hydrogencarbonate and then acid. Recrystallization from alcohol gave **7** (1.0 g, 67%); mp 170—171°C. IR: (KBr) 2700—2400 (-OH), 1685 (carboxyl) and 1600 cm^{-1} (aromatic). Found: C, 84.20; H, 5.52%. Calcd for $C_{20}H_{20}O_2$: C, 84.48; H, 5.67%.

*Methyl Ester of **7** (**8**).* This was obtained by the treatment of **7** with diazomethane in ether. NMR: δ($CDCl_3$) 3.85 (3H, s, CH_3), 4.48 (2H, s, CH_2), 7.20 (5H, s, aromatic), 7.60—7.30 (7H, m, aromatic) and 8.00 ppm (H, d, $J=$ 9 Hz, CH).

*5-Phenyl-2-benzylbenzoic Acid (**9**).* A mixture of **5A** (1.6 g) and platinum-black (0.5 g) was worked up similarly. Recrystallization from alcohol gave **9** (0.8 g, 52%); mp 156—157°C. IR: (KBr) 2700—2400 (-OH), 1695 (carboxyl) and 1600 cm^{-1} (aromatic). Found: C, 84,34; H, 5.77%. Calcd for $C_{20}H_{16}O_2$: C, 84.48; H, 5.67%.

*Methyl Ester of **9** (**10**).* This was obtained by the treatment of **9** with diazomethane in ether. NMR: δ ($CDCl_3$) 3.80 (3H, s, CH_3), 4.40 (2H, s, CH_2), 7.20 (5H, s, aromatic), 7.70—7.30 (7H, m, aromatic) and 8.10 ppm (H, d, $J=3$ Hz, CH).

*4-Phenyl-2-benzoyl-2-bromocyclohexane-1-carboxylic Acid (**11**).* To a solution of **6A** (1.0 g) in acetic acid (160 m*l*), bromine (0.8 g) was added at room temperature. The solution was kept at 80°C for 10 min and then cooled. It was poured onto cracked ice and filtered. The precipitate was washed with water and dried. It gave a yellow product (1.1 g); mp 169—175°C. Recrystallization from 80% alcohol gave **11** as colorless prisms (0.9 g, 70%); mp 184—185°C. The melting point of the product was depressed by mixing with **6A**. IR: (KBr) 2700—2400 (-OH), 1700 (carboxyl), 1680 (benzoyl) and 1600 cm^{-1} (aromatic). Found: C, 62.16; H, 4.80%. Calcd for $C_{20}H_{19}OBr$: C, 62.02; H, 4.95%.

*Bromination of **5A**.* The treatment of **5A** with bromine was carried out in a manner similar to that used in the experiment described above except for the condition of acetic acid (50 m*l*). A crystalline material was thus ob-

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[14] All the melting points and boiling points are uncorrected. The IR spectra were taken on a Hitachi EPI-S spectrometer. The NMR spectra were obtained on a Japan Electron Optics C-60-H spectrometer. The glpc analyses were carried out with a Shimazu GC-4AP appratus using Silicon Grease as the stationary phase.

[15] I. N. Nazarov and V. F. Kucherov, *Otdel. Khim. Nauk*, 1954, 329; *cf. Chem. Abstr.*, 49, 5328 (1955).

tained quantitatively; mp 176—180°C. The melting point of the product, without any purification, was identical with that of **5A**. The IR spectra of the product were identical with that of **5A**.

*Debromination of **11** with 47% Hydroiodic Acid.* To a solution of **11** (50 mg) in acetone (3 m*l*), 47% hydroiodic acid (0.1 m*l*) was added. The solution was then kept at about 50°C for three minutes. After the iodine had been destroyed by the addition of a small quantity of sodium thiosulfate, 5 m*l* of water was added to give a precipitate. The precipitate was collected by filtration with water and dried. It gave a white product (35 mg, 88%); mp 197—199°C. The structure of the product, without any purification, was confirmed by a mixed-melting-point determination and by a comparison of the IR spectra with those of **6A**.

*Treatment of **5A** and **6A** with Aluminum Chloride.* This was done similarly except that the reaction time was one hour. In the case of **5A**: **5A** (3.1 g), aluminum chloride (1.5 g) and benzene (10 m*l*). A crystalline material (2.7 g, 87%) was obtained (mp 176—180°C). The recrystallization of the product from 85% alcohol gave colorless prisms, mp 180—181°C. The melting point of the product was not depressed by mixing with **5A**. The IR spectra of the product were identical with those of **5A**. In the case of **6A**: **6A** (3.1 g), aluminum chloride (1.5 g) and benzene (10 m*l*), a crystalline material (2.6 g, 84%) was obtained (mp 194—198°C). The recrystallization of the product from 95% alcohol gave colorless prisms, mp 201—202°C. The melting point of the product was not depressed by mixing with **6A**. The IR spectra of the product were identical with those of **6A**.

*Aluminum Chloride-catalyzed Reaction of 4,5-Disubstituted Cyclohexene (**1B**, **3A**, **3B**) with Benzene. General Procedure*: Into a solution of 4,5-disubstituted cyclohexene (0.03 M) in dry benzene (0.3 M) we stirred aluminum chloride (0.06 M) over a five-minute period below 10°C. Stirring was continued for one hour without further cooling, and for two additional hours under reflux. Then the reaction mixture was poured onto icewater. The benzene solution was dried over anhydrous magnesium sulfate and evaporated. The product was purified by recrystallization or distillation. The results are given in Table 1.

General Epimerization Procedure: To a sodium ethoxide solution prepared from absolute ethanol (50 m*l*) and sodium ((200 mg) for the dimethyl ester of **2A** (**12**) and the dimethyl ester of **2B**, (100 mg) for **5A**, the methyl ester of **5A**, **6A**, and the methyl ester of **6A**), we added the sample (500 mg). The solution was refluxed for five hours and cooled. After the addition of water (100 m*l*) to the reaction mixture, the resulting mixture was acidified and filtered. The results are shown in Table 2.

*Ring Closure of 4-Phenylhydrophthalic Acid (**2A**, **2B**, **2C**) with Acetic Anhydride or Acetyl Chloride. General Procedure*: A mixture of 4-phenylhexahydrophthalic acid (9.5 g) and acetic anhydride (40 m*l*) or acetyl chloride (40 m*l*) was refluxed for three hours. After the acetic anhydride (25 m*l*) or acetyl chloride (25 m*l*) had been removed from the reaction mixture, the solution was cooled in an ice-box for three days. We thus obtained a crystalline solid. The crystalline solid was washed with light petroleum ether (bp 30—70°C) and purified by recrystallization. The results are shown in Table 3.

TABLE 2. EPIMERIZATION OF TRISUBSTITUTED CYCLOHEXANE

Sample[a]	Product	Mp	Yield (%)
Dimethyl ester of **2A**	**2C**[b]	220—221°C	400 mg (89)
Dimethyl ester of **2B**	**2C**[b]	218—219°C	400 mg (89)
5A	**5A**[c]	180—181°C	450 mg (90)
Methyl ester of **5A**	**5B**[d]	179—180°C	200 mg (40)
6A	**6B**[e]	241—242°C	450 mg (90)
Methyl ester of **6A**	**6B**[e]	240—242°C	400 mg (80)

a) The corresponding methyl ester was obtained by the treatment of diazomethane in ether.

b) Recrystallization from 60% acetic acid gave **2C** of colorless prisms. IR: (KBr) 2700—2400 (-OH), 1705 (carboxyl) and 1600 cm^{-1} (aromatic). Found: C, 67.82; H, 6.41%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. The dimethyl ester of **2C** was obtained by the treatment of **2C** with diazomethane in ether. IR: (neat) 1730 (ester) and 1600 cm^{-1} (aromatic). NMR: δ($CDCl_3$) 2.95—1.15 (m, 9, 3CH and $3CH_2$), 3.70 (d, 6, $2CH_3$) and 7.22 (s, 5, aromatic).

c) The structure of the product was confirmed by a mixed-melting-point determination and by a comparison of its IR spectra with those of an authentic sample.

d) It gave a white product (430 mg, 90%); mp 160—174°C. Found: C, 78.03; H, 6.68%. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%. Recrystallization from 80% alcohol gave 5B of white prisms. IR: (KBr) 2800—2500 (-OH), 1700 (carboxyl), 1680 (ketone) and 1600 cm^{-1} (aromatic). Found: C, 77.20; H, 6.68%. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%.

e) Recrystallization from 90% alcohol gave **6B** of colorless prims. IR: (KBr) 2700—2400 (-OH), 1700 (carboxyl), 1680 (ketone) and 1600^{-1} (aromatic). The melting point of **6B** was depressed by mixing with **6A**. The IR spectra of **6B** and **6A** were different in the fingerprint region. Found: C, 77.79; H, 6.62%. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%.

TABLE 3. RING CLOSURE OF 4-PHENYLHEXAHYDROPHTHALIC ACID

Sample	Reagent	Product	Mp	Yield
2A	Acetic anhydride	**4A**[a]	105—106°C[b]	quant.
2A	Acetyl chloride	**4A**[a]	106—107°C[b]	8.4 g 89%
2B	Acetic anhydride	**4A**[a]	106—107°C[b]	quant.
2B	Acetyl chloride	**2B**[c]	154—159°C[d]	8.4 g 89%
2C	Acetic anhydride	**4A**[a]	105—106°C[b]	quant.
2C	Acetyl chloride	**4C**[e]	162—163°C[b]	quant.

a) IR: (Nujol 1850, 1780 (acid anhydride) and 1600 cm^{-1} (aromatic)). Found: C, 73.09; H, 6.13%. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.37%.

b) Recrystallization from benzene-ligroin.

c) The structure of the product was confirmed by a mixed-melting-point determination and by a comparison of its IR spectra with those of an authentic sample.

d) Crude product.

e) IR: (Nujol) 1865, 1785 and 1600 cm^{-1}. The melting point of **4C** was depressed upon mixing with **4A**. The IR spectra of **4A** and **4C** were different in the fingerprint region. Found: C, 73.09; H, 6.13%. Calcd for $C_{14}H_{14}O_3$: C, 72.74; H, 6.44%.

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