The Preparation of *cis*- and *trans*-4-*tert*-Butylcyclohexyl-1-carbinols

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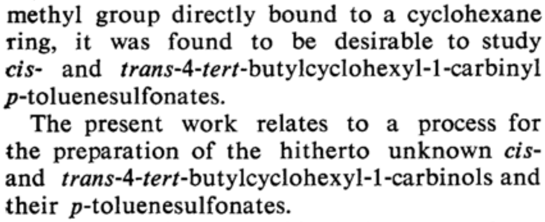
In the course of the investigation[1] concerning the conformation of a toluenesulfoxymethyl group directly bound to a cyclohexane ring, it was found to be desirable to study *cis*- and *trans*-4-*tert*-butylcyclohexyl-1-carbinyl *p*-toluenesulfonates.

The present work relates to a process for the preparation of the hitherto unknown *cis*- and *trans*-4-*tert*-butylcyclohexyl-1-carbinols and their *p*-toluenesulfonates.

The *cis*- and *trans*-carbinols have now been prepared from 4-*tert*-butylbenzoic acid by hydrogenating them over platinum oxide in acetic acid and over Raney nickel in neutral aqueous medium, respectively. The resulting *cis*- and *trans*-4-*tert*-butylhexahydrobenzoic acids were converted into their ethyl esters which were treated with lithium aluminum hydride to give the *cis*- and *trans*-carbinols respectively, and they were converted into the *p*-toluenesulfonates. The process carried out is shown in the following scheme.



tert-Butylbenzoic acid (I) used as starting material was obtained by reacting dry benzene with *tert*-butyl alcohol over aluminum chloride[2], brominating the resulting *tert*-butylbenzene with bromine over iron powder[3] and treating a Grignard reagent of the 4-*tert*-butylbromobenzene with carbon dioxide according to the method[4] for the conversion of *tert*-butyl chloride into *tert*-butylacetic acid.

The hydrogenation of substituted benzene compounds in neutral medium with Raney nickel generally gives thermodynamically stable hydrogenated benzene compounds as main products and on the contrary in acetic acid with platinum oxide less stable stereoisomers. For example, the hydrogenation[1,5] of 4-methyl- or isopropylbenzoic acid over Raney nickel gives mainly the corresponding *trans*-hexahydrobenzoic acid melting at a higher temperature and over platinum oxide the corresponding cis-isomer melting at a lower temperature. The hydrogenation of the 4-isopropylbenzoic acid by either of the above methods does not proceed so readily as with the 4-methylbenzoic acid. The 4-methylbenzoic acid is completely hydrogenated with Raney nickel under an initial pressure of 90 atm. at 180~200°C in 2 hr. to give the hexahydrobenzoic acid, while the hydrogenation of the isopropylbenzoic acid[5] is effected under 150~200 atm. 200°C for 4~5 hr. On the other hand, the hydrogenation[1,5] of the methyl- and isopropylbenzoic acids with platinum oxide is completed under atmospheric pressure in 2~4.5 and 6 hr., respectively.

In the present work, the butylbenzoic acid (I) was hydrogenated in a neutral aqueous solution with Raney nickel under an initial pressure of 90 atm. 250~260°C in 5 hr., although the uptake of hydrogen was not complete and this reaction was probably accompanied by hydrogenolysis, and the *trans*-hexahydrobenzoic acid melting at 175~176°C after recrystallization was obtained in a 40% yield. On the other hand, the butylbenzoic acid (I) was not hydrogenated in acetic acid with platinum oxide within 4 hr. at 60~70°C under atmospheric pressure, but the uptake of hydrogen was very readily and completely effected under an initial pressure of 60 atm. at about 100°C in 1 hr. and the *cis*-hexahyrobenzoic acid (IIb) was obtained as scales, m. p. 115~117°C after recrystallization, in a good yield. The difficulty in hydrogenation of these 4-alkylbenzoic acids increases as the alkyl group goes from methyl to *tert*-butyl. These acids were converted into their anilides by the method without the danger of isomerization.

The above acids were converted into their ethyl esters by refluxing in ethyl alcohol with a small amount of sulfuric acid in a short

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[1] N. Mori, This Bulletin, **34**, 1299 (1961).

[2] C. S. Marvel et al., *J. Am. Chem. Soc.*, **66**, 914 (1944).

[3] R. C. Huston, W. B. Fox and M. N. Binder, *J. Org. Chem.*, **3**, 251 (1938).

[4] H. Gilman and R. H. Kirby, "Organic Syntheses", Coll. Vol. I, Second edition (1941), p. 361.

[5] R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, **1939**, 1245.

period. The refractive index and the density of the cis-ester (IIIb) are higher than those of the trans-ester (IIIa). In Table I, the physical constants of the *cis*- and *trans*-4-*tert*-butylhexahydrobenzoic acids and their derivatives obtained in the present work are shown with those of 4-methyl and isopropylhexahydrobenzoic acids and their derivatives for comparison.

Table I. Physical constants of isomeric 4-alkyl-hexahydrobenzoic acids and their derivatives

4-Alkyl	Free acid M. p., °C	Anilide M. p., °C	Ethyl ester	
			n_D^{20}	d_4^{20}
trans-tert-Bu	175∼176	139.5	1.4515	0.9282
cis-tert-Bu	115∼117	191	1.4593	0.9400
trans-isoPr[5]	94	—	—	—
cis-isoPr[5]	liq.	—	1.4491	—
trans-Me[6]	111	—	1.4392	0.9361
cis-Me[6]	13	—	1.4425	0.9448

These trans- and cis-esters IIIa and IIIb were converted into the corresponding carbinols IVa and IVb by treatment with lithium aluminum hydride, according to the method[1] for the conversion of the isomeric 4-methylhexahydrobenzoic acid ethyl esters into their carbinols. It is well known that hydrogenolysis of esters with lithium aluminum hydride proceeds with complete retention of configuration while that with sodium in alcohol and over copper chromite catalyst proceeds with some isomerization. The purified *cis*-carbinol is in needles melting at 56∼57°C and the trans-isomer is in needles of m. p. 25∼27°C. The refractive index and the density of the *cis*-carbinol which was in a super-cooled liquid form before purification are higher than those of the super-cooled *trans*-carbinol, as shown in Table II, which also includes those of 4-methyl- and isopropyl-cyclohexyl-1-carbinols for comparison, and this fact is in accordance with the Auwers-Skita rule[7].

Table II. Physical constants of isomeric 4-alkylcyclohexyl-1-carbinols and their tosylates

4-Alkyl	Carbinol		Tosylate M. p., °C
	n_D^{20}	d_4^{20}	
trans-tert-Bu	1.4683	0.9092	83 ∼84
cis-tert-Bu	1.4781	0.9243	95 ∼95.5
trans-isoPr[5]	1.4661*	0.9007*	—
cis-isoPr[5]	1.4682*	0.9051*	—
trans-Me[5]	1.4578*	0.8962*	44.5∼44.7[1]
cis-Me[5]	1.4617*	0.9074*	30.5∼31.0[1]

* Values at 30°C.

Experimental

4-*tert*-Butylbenzoic Acid (I).—A Grignard reagent solution was prepared in the usual way by adding dropwise 4-*tert*-butyl-bromobenzene (70 g.) in dry ether (200 cc.) to magnesium strips (8 g.) covered with ether (50 cc.) while warming on steam bath and stirring. The solution was cooled to −15∼−10°C in an ice-salt bath and then treated with a stream of dry carbon dioxide until the temperature rose no more. The reaction mixture was decomposed with dilute sulfuric acid and the ethereal layer was washed with aqueous sodium hydroxide solution. The aqueous layer separated was acidified with concentrated hydrochloric acid to give an acid product which melted at 163∼164.4°C (lit.[2] 164°C) after one recrystallization from aqueous methanol.

***trans-tert*-Butylhexahydrobenzoic Acid (IIa).**—A solution (pH=8.0) of the butylbenzoic acid (12 g.) in 7% sodium hydroxide solution was hydrogenated in the presence of Raney nickel (6 g.) under an initial pressure of 90 atm. at 250∼260°C. The reaction was stopped after 5 hr. although the uptake of hydrogen was not complete. After removal of the catalyst, the solution was acidified with concentrated hydrochloric acid and the precipitated material (10 g.) was repeatedly recrystallized from aqueous methanol to give the pure *trans*-hexahydrobenzoic acid (3 g.) as plates, m. p. 175∼176°C (lit.[8] 174°C).

Found: C, 71.8; H, 10.9. Calcd. for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9%.

A part of the acid was converted into an anilide by refluxing for 10 min. with one equivalent each of thionyl chloride and pyridine in dry benzene and then for 2 min. with two equivalents of aniline. Recrystallization of the anilide from aqueous ethanol readily gave fine plates, m. p. 139.5°C.

Found: N, 5.6. Calcd. for $C_{17}H_{25}ON$: N, 5.4%.

***cis-tert*-Butylhexahydrobenzoic Acid (IIb).**—A solution of the butylbenzoic acid (10 g.) in purified glacial acetic acid (60 cc.) was hydrogenated with platinum oxide (0.5 g.) under an initial pressure of 60 atm. at 90∼100°C until no more hydrogen was absorbed. After removal of the catalyst and the solvent, the crystalline residue was taken up in a small volume (about 20 cc.) of petroleum ether and the undissolved parts were filtered off. The filtrate was concentrated and cooled. The separated plates were filtered off and recrystallized repeatedly from aqueous methanol to give the pure *cis*-hexahydrobenzoic acid (6 g.) as scales, m. p. 115∼117°C (lit.[8] 116°C).

Found: C, 71.7; H, 10.6. Calcd. for $C_{11}H_{20}O_2$: C, 71.7; H, 10.9%.

The anilide of the cis-acid was obtained by the method used for the trans-acid as long needles from aqueous methanol and ligroin, m. p. 191°C which was depressed to 124∼127°C on admixture with the trans-anilide.

Found: N, 5.6. Calcd. for $C_{17}H_{25}ON$: N, 5.4%.

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[6] G. H. Keats, ibid., **1937**, 2003.

[7] K. von Auwers, *Ann.*, **420**, 84 (1920); A. Skita, *Ber.*, **53**, 1792 (1920); A. Skita and W. Faust, ibid., **64**, 2878 (1931).

[8] Eliel and Acharya reported that the acids were first obtained by Stolow, but the details of preparation are not described. See E. L. Eliel and R. V. Acharya, *J. Org. Chem.*, **24**, 151 (1959).

Ethyl *trans-tert*-Butylhexahydrobenzoate (IIIa).—The trans- acid (3 g.) was refluxed in ethanol (30 cc.) with concentrated sulfuric acid (0.5 cc.) for 2 hr. After concentration of the reaction mixture, the residue was taken up in ether, washed with water, 10% sodium carbonate solution and then water, dried with sodium sulfate and concentrated. The residue was distilled under reduced pressure to give the ethyl ester (3 g.) which boiled at 125∼137°C (mainly 135∼136°C)/25 mmHg and had n_D^{20} 1.4522. Redistillation gave the pure ester which had b. p. 146∼148°C/29 mmHg, n_D^{20} 1.4515 d_4^{20} 0.9282 and MR_D 61.70 (Calcd. 61.69).

Ethyl *cis-tert*-Butylhexahydrobenzoate (IIIb).—The cis- acid (3.5 g.) gave similarly the cis-ethyl ester (3.5 g.) which, after redistillation, had b. p. 134∼137°C/28 mmHg, n_D^{20} 1.4593, d_4^{20} 0.9400 and MR_D 61.74 (Calcd. 61.69).

***trans-tert*-Butylcyclohexylcarbinol (IVa).**—The trans-ester (2.5 g.) in dry ether (30 cc.) was added dropwise to a suspension of lithium aluminum hydride (1.0 g.) in dry ether (60 cc.) at 0∼5°C and the reaction mixture was stirred for another hour. This mixture was then treated with a small amount of cold dilute sulfuric acid until the ether layer was clear and then filtered. The filtrate and washings of the filter cake were combined, dried with potassium carbonate and concentrated. The residue was distilled to give the carbinol (1.8 g.) as a viscous oil which had b. p. 140∼140.5°C/28.5 mmHg, n_D^{20} 1.4683, d_4^{20} 0.9092, MR_D 52.13 (Calcd. 52.32), which solidified in a refrigerator and melted at 25∼27°C.

Found: C, 77.5; H, 12.9. Calcd. for $C_{11}H_{22}O$: C, 77.6; H, 13.0%.

The carbinol (1.1 g.) was treated with *p*-toluenesulfonyl chloride (1.5 g.) in dry pyridine (5 cc.) by the usual way[1] at 0∼5°C and allowed to stand overnight in a refrigerator with occasional shaking. The mixture was poured into a mixture of ice and concentrated hydrochloric acid. The separated crystalline solid was filtered off and recrystallized twice from aqueous ethanol to give the *trans-p*-toluenesulfonate (1.4 g.) as needles, m. p. 83∼84°C.

Found: C, 66.8; H, 8.6. Calcd. for $C_{18}H_{28}O_3S$: C, 66.6; H, 8.66%.

***cis-tert*-Butylcyclohexylcarbinol (IVb).**—A similar treatment of the cis-ester (3.0 g.) with lithium aluminum hydride (1.2 g.) gave the *cis*-carbinol (1.4 g.) as a viscous oil, b. p. 133∼136°C/27 mmHg, n_D^{20} 1.4781, d_4^{20} 0.9243 and MR_D 52.16 (Calcd. 52.32), which soon partially solidified on being allowed to stand in a refrigerator. The semi-solid mass was pressed on a porous tile and recrystallized from aqueous ethanol to give the pure *cis*-carbinol as long needles, m. p. 56∼57°C.

Found: C, 78.2; H, 12.8. Calcd. for $C_{11}H_{22}O$: C, 77.6; H, 13.0%.

The pure carbinol was treated by the method used for the *trans*-carbinol with *p*-toluenesulfonyl chloride to give the *cis-p*-toluenesulfonate. Recrystallization from methanol gave needles, m. p. 95∼95.5°C.

Found: C, 66.7; H, 8.8. Calcd. for $C_{18}H_{28}O_3S$: C, 66.6; H, 8.66%.

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