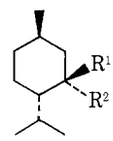
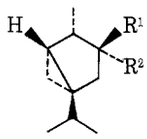
to handle experimentally, we have also investigated a number of these (Table II) for comparison with the respective amines.



(3*R*)-**11**, $R^1 = NH_2$; $R^2 = H$
(3*S*)-**12**, $R^1 = H$; $R^2 = NH_2$



(3*S*)-**13a**, $R^1 = NH_2$; $R^2 = H$
(3*R*)-**14a**, $R^1 = H$; $R^2 = NH_2$

The optical yield (2.3%) of (*S*)-α-phenylbutyric acid [(*S*)-**2a**] using (*R*)-**3a** is the maximum obtained from 15 experiments under a variety of conditions (variations of reaction time and of molar ratios of anhydride to amine and pyridine to anhydride). The range of optical yields in these experiments was 0.9–2.3% and (*S*)-**2a** was always obtained. Thus the earlier conclusion[6,7] that the phenyl group exceeds the methyl group in steric requirement is verified. Alkylarylcarbinamines (*S*)-**4** and (*S*)-**5a** also give the expected result that in steric requirements the benzyl and 1-naphthyl groups are larger than the methyl group. Also the observed extent of asymmetric synthesis with the alkylphenylcarbinamines gives an order of group steric requirement: *tert*-butyl > cyclohexyl ≅ isopropyl > ethyl ≅ phenyl > methyl.

For the alkylarylcarbinamine hydrochlorides evaluated, it also appears that the 1-naphthyl group is effectively larger than the methyl group, and the phenyl group has an apparent steric requirement greater than that of the methyl, ethyl, isopropyl, and cyclohexyl groups, similar to that observed with the corresponding carbinols.[6]

Each chiral alkylamine gave partially resolved α-phenylbutyric acid (**2a**) of the configuration predicted on the basis of group steric requirements of ethyl > methyl, and $R_2CH$ > $RCH_2$. However, isothujylamine nitrate [(3*S*)-**13b**] and neoisothujylamine *p*-toluenesulfonate [(3*R*)-**14b**] gave **2a** of opposite configuration to that obtained using the respective amines.

These observations show that, while in certain cases correlation of absolute configuration of chiral amines with results from the Horeau procedure is possible, there are cases in which steric requirement of the substituents of the carbinamine carbon atom is not the decisive factor in the kinetic resolution. Consequently, assignment of absolute configuration to chiral amines by this method is hazardous and such assignment must be substantiated by direct chemical correlation or by unambiguous circular dichroism measurements.[1]

## Experimental Section

Melting points were taken in open capillary tubes and are corrected. Boiling points are not corrected. Optical rotations were obtained using a visual polarimeter and a 1-dm sample tube. The elemental analysis was done by Galbraith Laboratories, Inc., Knoxville, Tenn.

**(*S*)-α-(1-Naphthyl)ethylamine hydrochloride** [(*S*)-**5b**] was prepared in ether from (*S*)-**5a**, $[\alpha]^{24}D$ −74.5° (neat) [lit.[11] $[\alpha]^{24}D$ −74.5° (neat)], and dry hydrogen chloride and was recrystallized from methanol. (*S*)-**5b** sublimed without melting near 175° and had $[\alpha]^{26}D$ −10° (*c* 2.0, absolute $C_2H_5OH$).

*Anal.* Calcd for $C_{12}H_{14}ClN$: Cl, 17.07. Found: Cl, 17.11.

**(*R*)-α-Phenylisobutylamine hydrochloride** [(*R*)-**8b**] **and (*R*)-α-cyclohexylbenzylamine hydrochloride** [(*R*)-**9b**] were prepared in ether from (*R*)-**8a**, $[\alpha]^{19}D$ +8.5° (*c* 2.1, $C_6H_6$) and (*R*)-**9a**, $[\alpha]^{24}D$ +9.8° (*c* 2.0, $C_6H_6$), respectively, and dry hydrogen chloride. The precipitated salts were collected by filtration, dried, and used without further purification.

**Reaction of an Optically Active Amine or Amine Salt with (±)-α-Phenylbutric Anhydride.** A weighed amount of amine or amine salt (0.73–0.99 mmol) was added to a 40–90% excess of (±)-α-phenylbutyric anhydride (1.18–1.62 mmol), bp 105–108° (8 mm), prepared by the procedure reported for acetic propionic anhydride,[12] in pyridine (6.6–9.8 mmol). After thorough mixing, the mixture was allowed to stand at room temperature for 4 hr. It was then diluted with benzene (5 ml) and water (5 ml) and stirred for 10–15 min. Solid sodium hydroxide was added until the mixture was basic, the benzene layer was removed, and the aqueous layer was extracted three times with benzene. The aqueous layer was acidified with hydrochloric acid and extracted three times with benzene. These latter benzene solutions were combined, dried ($Na_2SO_4$), and evaporated to 1.0 ml for determination of the optical rotation. In the few cases where approximately 2-mmol quantities of amine or amine salt and correspondingly larger quantities of anhydride and pyridine were used, the volume of the benzene solution used for determination of the optical rotation was adjusted to 2.0 ml.

Assuming 100% reaction of the amine and total recovery of the optically active α-phenylbutyric acid, the per cent asymmetric synthesis was calculated as

$$\text{asymmetric synthesis, \%} = \frac{(\alpha D)(\text{volume of benzene solution, ml})}{(\pm 158°)(\text{moles of amine or amine salt})}$$

In the equation, ±158° is the molecular rotation of optically pure α-phenylbutyric acid in benzene.[13]

**Acknowledgment.** We thank the National Science Foundation for a grant (GP-5772) supporting part of this work.

**Registry No.**—(±)-**2a**, 7782-29-8; (*R*)-**2a**, 938-79-4; (*S*)-**2a**, 4286-15-1; (*R*)-**3a**, 3886-69-9; (*R*)-**3b**, 10277-86-8; (*S*)-**4**, 51-64-9; (*S*)-**5a**, 10420-89-0; (*S*)-**5b**, 51600-24-9; (*S*)-**6a**, 513-49-5; (*R*)-**7a**, 3082-64-2; (*R*)-**7b**, 19068-33-8; (*R*)-**8a**, 23844-66-8; (*R*)-**8b**, 51600-25-0; (*R*)-**9a**, 32908-33-1; (*R*)-**9b**, 32908-34-2; (*R*)-**10**, 3082-71-1; (3*R*)-**11**, 51743-63-6; (3*S*)-**12**, 20706-69-8; (3*S*)-**13a**, 5033-81-8; (3*S*)-**13b**, 51731-30-7; (3*R*)-**14a**, 5033-82-9; (3*R*)-**14b**, 51600-26-1; (±)-α-phenylbutyric anhydride, 1519-21-7.

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# Axially Disposed Phenyl Groups in Geminally Substituted Cyclohexanes

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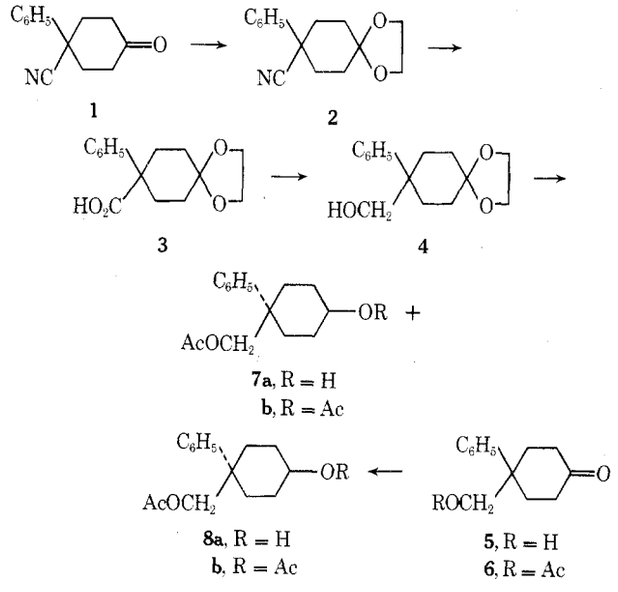
The common assignment of the aromatic groups of 1,4-disubstituted cyclohexanes to the equatorial position rests on the relatively large free-energy difference (3.0 ± 0.1 kcal/mol)[1] between axial and equatorial phenyl. There is evidence that the introduction of additional substitution

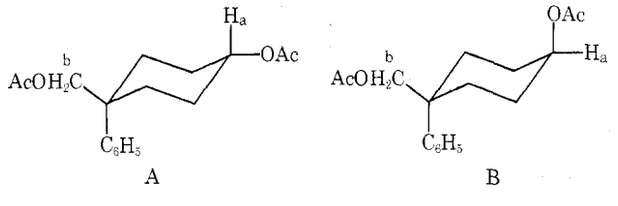
on the carbon bearing the aromatic ring may change the supposed preference; axial phenyls have been reported in 3-aryl-3,5,5-trimethylcyclohexanones,[2] 4-arylpiperidines,[3] and derivatives of the conformationally constrained isomers of 4-*tert*-butyl-1-phenylcyclohex-1-ylamine.[4]




Recently we had occasion to prepare the cyclohexanone **6**. Treatment of the known[5] cyano ketone **1** with ethylene glycol gave the ketal **2**. This was hydrolyzed by means of potassium hydroxide in ethylene glycol and the resulting acid was reduced to the alcohol by means of lithium aluminum hydride. Deketalization followed by acylation gave the desired ketone. Reduction of the carbonyl group with sodium borohydride[6] proceeded smoothly to give the readily chromatographically separable pair of alcohols (**7a**, **8a**) in the ratio of 4.5:1. Each of these was converted to the corresponding diacetate for the purpose of stereochemical assignment by nmr.

Both the splitting pattern of $H_a$ in the major isomer (septet) and chemical shift of that proton ($\delta$ 4.75) relative to $H_a$ of the minor product ($\delta$ 4.84, quintet) lead to the conclusion that the former is the derivative of the equatorial alcohol. There remains the assignment of configuration of the transannular carbon. It is of note first that the difference in chemical shift of $H_a$ between the two isomers ($\delta$ 0.11) is markedly smaller than that observed in analogous isomeric acetate pairs ($\delta$ 0.5–0.6).[7] In addition, the signal for $H_b$ in the axial acetate ($\delta$ 4.08) is shifted downfield from the corresponding protons in the equatorial isomer ($\delta$ 3.98).

These observations can best be accommodated by the assumption that the aromatic ring in each compound occupies the axial position. Thus, the presence of a cis acetate group transannular to $H_a$ in the equatorial acetate (A) would exert a deshielding effect and shift that signal




downfield from its expected position. By the same token, the presence of the ring acetate cis to $H_b$ in the axial isomer (B) will shift the signal for the methylene downfield.

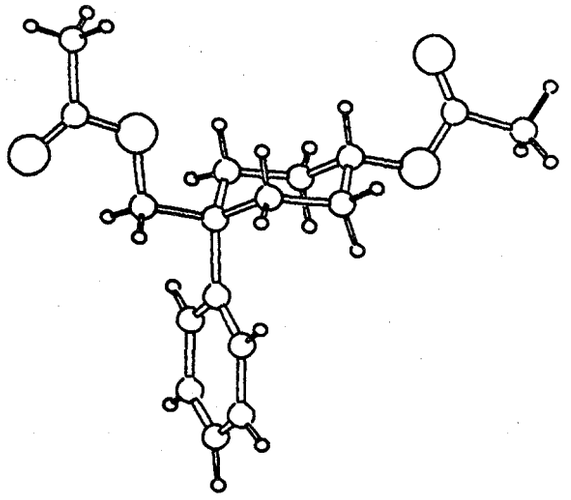
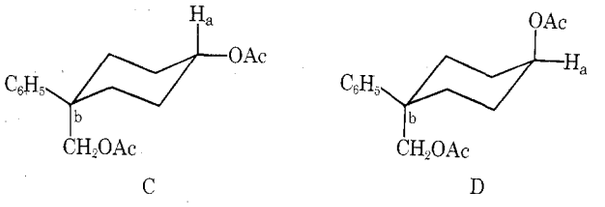


**Figure 1.** Drawing of **7b** from final X-ray coordinates.

Application of the same reasoning to the alternate formulations (C, D) will, of course, lead to the opposite predictions; in this case the axial acetate should show a down-




field shift of $H_a$, while the methylene of the equatorial isomer should show the downfield $H_b$. It is of interest to note in this connection that both isomers seem to have axial phenyls; in the previously reported piperidines,[3] only one of the isomers has the phenyl in this position.

This unexpected finding leans heavily on the assumption that the acetate will exert a shielding effect. We cannot rule out the possibility that the nmr bands in fact represent averaged signals from two rapidly converting conformers, though this assumes a significant population of the axial phenyl molecule. Independent evidence was thus sought for the steric assignment.

The crystal structure of **7b**, the diacetate of the major isomer, was determined by X-ray diffraction techniques. The crystals are orthorhombic with unit-cell parameters $a$ = 9.903, $b$ = 12.419, $c$ = 12.908 Å. Even though the molecule itself is not chiral, it crystallized in an acentric space group, $P2_12_12_1$. Diffraction intensities, 1804 reflections, were measured on an automated diffractometer. Trial positions for carbon and oxygen atoms were obtained by a computerized direct-methods procedure using computer programs developed in our laboratories. Structural parameters, including coordinates and isotropic temperature factors of hydrogen atoms, were refined by least squares to $R$ = 0.079.[8]

The configuration and conformation found by X-ray (Figure 1) are of isomer A, in agreement with the preceding nmr argument. The phenyl is axial; the ring-flipped conformer (isomer D) is not found in the crystal. The phenyl is oriented with its flat side toward the axial hydrogens on its side of the cyclohexane ring, although not exactly so. The slight twist is seen in torsion angles about the phenyl–cyclohexane bond (relating the methylene carbon of the acetoxymethyl to the ortho phenyl carbons) which are 82.2 and 94.6°, whereas 90° would correspond to no twist. The phenyl–cyclohexane bond is slightly out of the plane of the phenyl ring. The acetate at $C_1$ is twisted

about the $C_1$–oxygen bond about 16° from being eclipsed by the axial hydrogen on $C_1$.

Strain-energy calculations[9] were performed on structures A–D in order to compare their strain energies and to gain some insight as to whether the crystal conformational details mentioned above are the result of crystal packing or inherent in the structure of the molecule. For the saturated hydrocarbon portion, the potential functions recently published by Engler, Andose, and Schleyer[10] were used. Other force-field parameters were from a set developed locally. This force field gives a calculated energy difference between axial and equatorial phenylcyclohexane of 4.1 kcal/mol, which appears high, but is similar to the 3.7 kcal/mol reported previously by Allinger and Tribble.[11] As a further check on the potential functions, we calculated molecule **7c** in an environment simulating the crystal packing observed by X-ray. As expected, the atoms moved from X-ray positions (maximum shift ~0.3 Å). All shifts appear explainable in terms of thermal motion in the crystal. A comparison with low-temperature X-ray results should produce a closer fit.

For the free molecules, our calculations give energy differences between the axial and equatorial phenyl conformations (A *vs.* D or B *vs.* C) which are quite small, about 1 kcal/mol in favor of the axial isomers in both cases. If the apparent bias against the axial isomer in phenylcyclohexane carries over to these molecules, we should interpret this as an underestimate.

More can be said about the conformational details within isomer A. The phenyl and acetate groups have large barriers to free rotation about their bonds to the cyclohexane ring. The acetate has two minima about 44° on either side of eclipsing the hydrogen at $C_1$, with a low (1.8 kcal/mol) barrier to interconversion *via* transition through the eclipsing conformation. The acetoxymethyl has three minima when rotated about its bond to the cyclohexane moiety, with a relatively low (~5 kcal/mol) barrier to rotation. The minimum corresponding to the crystal conformation is about 0.5 kcal/mol less stable than the two alternate minima.[8]

## Experimental Section[12]

**8-Cyano-8-phenyl-1,4-dioxaspiro[4.5]decane (2).** A mixture of 10.0 g (0.05 mol) of 4-cyano-4-phenylcyclohexanone,[5] 2.85 ml of ethylene glycol, and 0.12 g of *p*-toluenesulfonic acid was stirred at reflux under a Dean-Stark trap for 4.5 hr. The solution was then allowed to cool, washed in turn with saturated $NaHCO_3$, $H_2O$, and brine, and taken to dryness. The residue was recrystallized from cyclohexane to afford 11.27 g (93%) of product, mp 120–122.5°.

*Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.10; H, 6.98; N, 5.77.

**8-Phenyl-1,4-dioxaspiro[4.5]decane-8-carboxylic Acid (3).** A mixture of 11.27 g (0.046 mol) of the nitrile and 11.3 g of potassium hydroxide in 90 ml of ethylene glycol was heated at reflux for 18 hr. The mixture was allowed to cool and diluted with 300 ml of ice–water. The solution was covered with 200 ml of ether and cautiously acidified with concentrated HCl. The organic layer was separated and the aqueous layer was extracted again with ether. The extracts were combined, washed with brine, and taken to dryness. The residual solid was recrystallized from methylene chloride–Skellysolve B[13] to yield 10.51 g (86%) of acid, mp 136–140.5°.

*Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.33; H, 6.90.

**8-Hydroxymethyl-8-phenyl-1,4-dioxaspiro[4.5]decane (4).** A solution of 10.51 g (0.040 mol) of the acid in 200 ml of THF was added to a well-stirred suspension of 3.6 g of lithium aluminum hydride in 53 ml of THF. The mixture was stirred at reflux for 5 hr, and then cooled in ice. There was then added in order 3.6 ml of $H_2O$, 3.6 ml of 15% sodium hydroxide, and 10.8 ml of $H_2O$. The inorganic gel was collected on a filter and the filtrate was taken to dryness. The residue solid was recrystallized from ethyl acetate–cyclohexane to afford 8.94 (90%) of product, mp 120–122°.

*Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.15. Found: C, 72.53; H, 8.15.

**4-Acetoxymethyl-4-phenylcyclohexanone (6).** A solution of 31.6 g (0.13 mol) of the ketal and 30 ml of 2.5 *N* HCl in 300 ml of acetone was allowed to stand at room temperature for 18 hr. The bulk of the solvent was removed under vacuum and the residue was partitioned between ether and $H_2O$. The organic layer was washed with saturated aqueous sodium bicarbonate and brine and taken to dryness. The product was obtained as a waxy solid.

A solution of the crude hydroxy ketone and 70 ml of acetic anhydride in 200 ml of pyridine was allowed to stand at room temperature for 16 hr. The mixture was then poured onto ice–water. The precipitated solid was recrystallized from Skellysolve B to afford 13.1 g (41%) of product, mp 75–77.5°.

*Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.07; H, 7.32.

**"*cis*-" and "*trans*"-4-Acetoxymethyl-4-phenylcyclohexanol (7a, 8a).** To a solution of 3.62 g (0.0147 mol) of keto acetate in 50 ml of 95% isopropyl alcohol there was added 0.25 g sodium borohydride. At the end of 2 hr the bulk of the solvent was removed under vacuum. The precipitated gum was taken up in ether. The organic layer was washed in turn with $H_2O$ and brine and taken to dryness. The residue was chromatographed on silica gel (elution with 5% acetone in methylene chloride). Those fractions which were the same by tlc were then combined. There was obtained first the isomer **7a**, which was recrystallized from petroleum ether to give 2.12 g (58%) of solid, mp 69–71.5°.

*Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.58; H, 7.44.

This was followed by isomer **8a**; this too was recrystallized from petroleum ether. There was obtained 0.49 g (13%) of compound, mp 60–63°.

*Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 7.95.

***trans*-4-Acetoxymethyl-4-phenylcyclohexyl Acetate (8b).** A solution of 2.48 g (0.012 mol) of the alcohol in 10 ml of acetic anhydride and 25 ml of pyridine was allowed to stand overnight at room temperature. The mixture was poured onto ice–water and the precipitated solid was collected on a filter. This was recrystallized from Skellysolve B to afford 3.07 g (88%) of diacetate, mp 68–69°.

*Anal.* Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.05; H, 7.70.

***cis*-4-Acetoxymethyl-4-phenylcyclohexyl Acetate (7b).** A solution of 402 mg of diol in 1 ml of acetic anhydride and 5 ml of pyridine was allowed to stand at room temperature overnight. The mixture was poured onto ice–water and the solid was collected on a filter. A single recrystallization from petroleum ether (cooling in freezer) gave the product, mp 47–48.5°.

*Anal.* Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.60; H, 7.67.

**Registry No.**—**1**, 25115-74-6; **2**, 51509-98-9; **3**, 51509-99-0; **4**, 51510-00-0; **5**, 51510-01-1; **6**, 51510-02-2; **7a**, 51510-03-3; **7b**, 51510-04-4; **8a**, 51510-05-5; **8b**, 51510-06-6.

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(6) This reaction was carried out in 95% *i*-PrOH; this completely obviated the ester interchange when the reaction was run in EtOH.
(7) See, for example, D. Lednicer, D. E. Emmert, R. Lahti, and A. D. Rudzik, *J. Med. Chem.*, **15**, 1239 (1972).
(8) Details of the X-ray investigation and the strain-energy calculations will be reported at a later date.
(9) See, for example, J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968), for a general review of method.
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(12) All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. Nmr spectra were determined in deuteriochloroform on a Varian A-60D nmr spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental analyses.
(13) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.