(8) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley, New York, N.Y., 1965, p 115.
(9) R. Bucourt, *Top. Stereochem.*, **8**, 159–224 (1974).
(10) We are investigating the solution conformation of cycloheximide by ^{1}H NMR spectroscopy.

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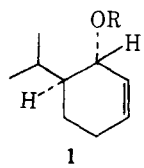
Concerning the Stereochemistry of the S_N2' Reaction in Cyclohexenyl Systems

Sir:

Over 20 years ago,[1] we examined the stereochemistry of the S_N2' reaction of piperidine with the 2,6-dichlorobenzoate of *trans*-6-isopropyl-2-cyclohexen-1-ol (**1**, R = 2, 6-dichlorobenzoyl). We have now reexamined this reaction and have further extended the inquiry to a variety of other situations. We can now report the following: (1) The detailed scrutiny now possible with analytical tools which were unavailable at the time of the original study has confirmed the conclusion that S_N2' displacement on cyclohexenyl esters **1** with piperidine leads to (predominant) syn entry of the displacing group with formation of the amine **2.** (2) Extension of the study to the cis isomer of **1,** shows exclusive syn entry of the piperidine in the S_N2' product (**3**, R = aroyl → **4**). (3) When the displacing



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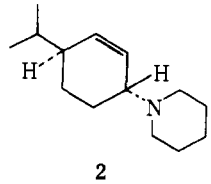

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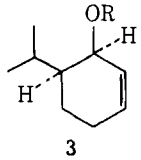

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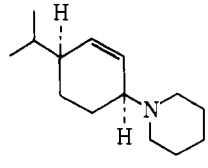

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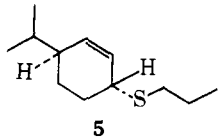
group was changed from piperidine to propanethiolate, a major product was the sulfide from simple S_N2 displacement. The rearranged sulfide component was again largely formed by syn displacement (**1** → **5**). Remarkably, however, this was accompanied by varying amounts of the epimer **6** from anti displacement: the ratio of **5** to **6** varied from ~10:1 down to ~2:1,



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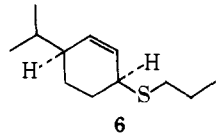

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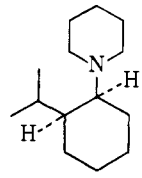
depending on the departing aroyl group R in **1** and on the reaction solvent. (4) The cis isomer **3,** R = aroyl, in striking contrast to its clean syn allylic displacement with piperidine (**3** → **4**) led, in 1-butanol, to either a predominance of anti S_N2' product (**3** → **5, 6**) with the sodium salt of propanethiol (**5:6** ~65:35), or to essentially equal amounts of syn and anti displacement with the corresponding lithium salt.

We now report the experimental evidence and correlations which form the basis for these conclusions.

trans 6-Isopropyl-2-cyclohexen-1-ol (**1,** R = H) was prepared by lithium aluminum hydride reduction[2] of the corresponding enone and purified as reported[1] (NMR; δ 0.83, 3 H, d, *J* = 7 Hz; 0.94, 3 H, d, *J* = 7 Hz; 5.63, 2 H, s). The 2,6-dichlorobenzoate **1,** R = 2,6-dichlorobenzoyl, mp 65–67 °C (reported[1] 66.5–67.2 °C), had NMR: δ 0.92, 3 H, d, *J* = 6 Hz; 0.99, 3 H, d, *J* = 6 Hz; 5.83, 2 H, s. The liquid mesitoate **1** (R = 2,4,6-trimethylbenzoyl) from the lithium salt of **1,** R = H, and mesitoyl chloride (−20 °C → room temperature overnight, 78%)[3] had NMR: δ 0.88, 3 H, d, *J* = 6 Hz; 0.97, 3 H, d, *J* = 6 Hz; 5.78, 2 H bs.

cis-6-Isopropyl-2-cyclohexen-1-ol (**3,** R = H) was best prepared from the corresponding enone with triisobutylaluminum in toluene to give a 92/8 mixture of **3** and **1,** R = H. The pure **3,** R = H, mp 43–45 °C,[3] had NMR: δ 0.93, 3 H, d, *J* = 6 Hz; 0.97, 3 H, d, *J* = 6 Hz. The structure was confirmed by reduction with diimide to *cis*-2-isopropylcyclohexanol,[4] also obtained by lithium tri-*sec*-butylborohydride (L-Selectride)[5] reduction of 2-isopropylcyclohexanone. The mesitoate **3,** R = 2,4,6-trimethylbenzoyl, mp 71–73 °C,[3] had NMR: δ 0.93, 3 H, d, *J* = 6 Hz; 0.98 3 H, d, *J* = 6 Hz; 5.45, 1 H, m; 6.02 2 H, m (CH=CH).[6]

A reference mixture of the two 1-piperidinoisopropylcyclohexanes was prepared starting with the catalytic hydrogenation of 2-isopropylcyclohexanone oxime (platinum oxide in acetic acid) to a mixture (largely cis)[7] of the primary amines (kugelrohr 110 °C/35 mm, 71% yield) which were then cycloalkylated with 1,5-dibromopentane (40 h reflux in ethanol with potassium carbonate). The product (kugelrohr 100 °C/0.5 mm, 60% yield) was an 86:14 mixture of the cis and trans isomers of 1-piperidino-2-isopropylcyclohexane, **7** and **8,** respectively.[8] The cis and trans 4-piperidinoisopropylcyclohexanes **9** and **10** were synthesized, as previously described,[1] by displacement with piperidine of the tosylates of trans and cis 4-isopropylcyclohexanol. The latter were prepared from 4-isopropylcyclohexanone with lithium aluminum hydride[9] (trans:cis = 80:20) or with L-Selectride[5] (trans:cis = 7:93).



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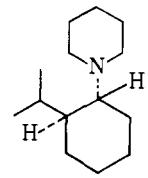

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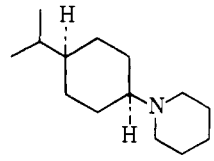

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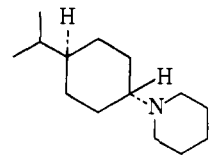

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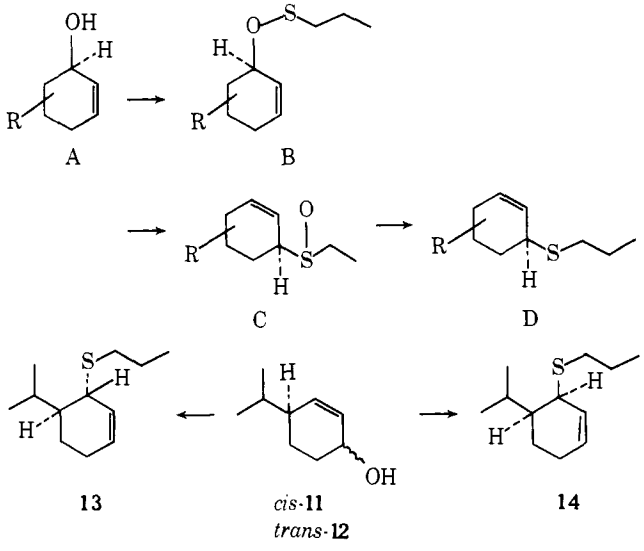
The authentic *trans*- and *cis*-3-isopropyl-6-propylthiocyclohexene, **5** and **6,** were prepared via the stereospecific Mislow rearrangement[10] of the propylsulfenates of **1** and **3,** R = H, to the sulfoxides, followed by lithium aluminum hydride reduction to the desired thioethers (A → B → C → D). The *trans*- and *cis*-4-isopropyl-3-propylthiocyclohexenes **13** and **14**[11] were prepared similarly from *trans*- and *cis*-4-isopropyl-2-cyclohexen-ols, themselves made by the lithium aluminum hydride reduction of the corresponding enone.[12] Separation on silica gel gave the more rapidly eluted cis alcohol[13] (~20%) **11,** followed by the trans isomer **12** (~80%).

Displacement of the ester **1,** R = 2,6-dichlorobenzoyl, in neat piperidine (24 h, 130 °C), as previously described,[1] did indeed result in the formation of the product of syn allylic displacement, the unsaturated amine **2.** It was, however, accompanied by the isomer **4** (**2:4** = 61:23). We suspected that the correct ratio might be more in favor of the syn product **2**



than these numbers imply because the starting dichlorobenzoate, in contrast to the earlier conclusion, was not entirely stable to the reaction conditions: the recovered ester fraction (~30%) was 20% rearranged.[14] This hypothesis was supported by carrying out the reaction for only 1 h: under these conditions of very low conversion (3.5% reaction). The two amines **2** and **4**, which made up 90% of the amine fraction, were formed in a 10:1 ratio in favor of **2**, the product of syn displacement. More definitive results were obtained by utilizing a more stable ester, **1**, R = 2,4,6-trimethylbenzoyl. Displacement with piperidine, *under conditions* (24 h, 130 °C; 25% completion) *which caused no rearrangement in the starting mesitoate or in the reaction products*, led to an amine fraction consisting very largely (92%) of the product **2** of syn S_N2' displacement in addition to ~2% of **4**.

We have extended this finding to the cis isomer **3**, R = 2,4,6-trimethylbenzoyl, and find that under the above conditions (28% completion), the major product is that of syn S_N2' displacement, **4** (80%), accompanied by 20% of the (inverted) S_N2 product. The product of anti S_N2' displacement was not found. This last result rules out a common intermediate in the reactions of the esters corresponding to **1** and **3** and also shows that product stability is not a factor in determining the product stereochemistry.

Reaction of **1**, R = 2,4,6-trimethylbenzoyl (1 M in refluxing butanol), with the sodium salt of propanethiol (2 equiv, 4 h) gave complete reaction.[15] The sulfides formed resulted largely from S_N2 displacement (**14**, 68.5%). The S_N2' products were formed in a ~9:1 ratio in favor of syn displacement (28% **5**, 3.5% **6**). The ratio in favor of syn S_N2' displacement was decreased in hexamethylphosphoramide (0.1 M in **1**, R = 2,4,6-trimethylbenzoyl, 70 °C, 21 h, 9 equiv of PrSNa) to ~60:40 (28% **5**, 12% **6** in addition to 60% S_N2 product **14**).[16] Finally, in opposition to the exclusive syn S_N2' result with piperidine and **3**, R = 2,4,6-trimethylbenzoyl, the latter compound now gave, under the propylthiolate in butanol conditions, a syn to anti ratio of 35:65 (17.5% **5**, 32.5% **6**; in addition to 50% S_N2 product, **13**). All these ratios are completely different from those obtained under solvolysis conditions (refluxing with propanethiol for 18 h) which, in contrast to the bimolecular displacement above, gave both **13** and **14** from the mesitoates corresponding to either **1** or **3**.[17]

It is clear that there appears to be a spectrum of S_N2' reactions in cyclohexenyl systems. Because of the very real possibility of a bias particular to the six-membered system, it is highly desirable to consider the situation in acyclic cases. The next communication deals with this problem.

Acknowledgment. We thank the National Science Foundation for its support of this work.

References and Notes

(1) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **75**, 4119 (1953); **78**, 4609 (1956).
(2) The reaction gave a mixture consisting, in order of decreasing retention times on 5% FFAP: **1**, R = H (59%); **3**, R = H (20%); *trans*-2-isopropylcyclohexanol (13%); *cis*-2-isopropylcyclohexanol (6%); 2-isopropylcyclohexanone (2%).
(3) Purified by silica gel chromatography using 95:5 pentane–ether. All identifications were by NMR, IR, VPC, and GC–MS (the latter on a Finnigan Model 3300 spectrometer).
(4) G. Vavon and A. Callier, *Bull. Soc. Chim. Fr.*, **41**, 357 (1927).
(5) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
(6) Unlike the 2,6-dichlorobenzoates, the mesitoates derived from **1**,**3**, **13**,**14**, R = H, were stable to VPC. They had retention times of 11.4, 10.31, 15.0, and 22.1 min, respectively, on 1.5% OV-101 at 190 °C. They, and the dichlorobenzoates, could be reconverted to the pure parent alcohol by reduction with diisobutylaluminum hydride. Lithium aluminum hydride was not suitable, giving partially isomerized products.
(7) P. Anziani and R. Cornubert, *Bull. Soc. Chim. Fr.*, 857 (1948).
(8) The four isomeric saturated amines **7**, **8**, **9**, and **10** were cleanly separated by gas phase chromatography and showed retention times of 6.19, 5.81, 7.19, and 8.06 min, respectively, on 5% SE 30 at 190 °C.
(9) M. M. Green and B. B. Roy, *J. Am. Chem. Soc.*, **92**, 6368 (1970).
(10) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968). The intermediate sulfenates were made by reaction of the lithium salts of the alcohols with *S*-propyl *p*-toluenethiosulfonate made with propyl iodide in dimethylformamide; cf. J. P. Weidner and S. S. Block, *J. Med. Chem.*, **7**, 671 (1964).
(11) The allylic sulfides, **5**, **6**, **13**, and **14**, were obtained as colorless liquids after silica gel chromatography (pentane elution). Their respective retention times (5% FFAP) were **13** < **14** < **6** < **5**.
(12) A. K. Macbeth and J. S. Shannon, *J. Chem. Soc.*, 2852 (1952).
(13) The cis alcohol was also the more rapidly eluted isomer on vapor phase chromatography (5% FFAP, 175 °C).
(14) The rearranged dichlorobenzoates were those corresponding to **12** and **3** (16 and 4%) as determined by gas chromatography of the allylic alcohols from Dibal reduction of the recovered esters.
(15) Starting mesitoates and product sulfides were shown to be stable under the reaction conditions. Identification of products was by gas chromatography–mass spectrometry (cf. footnotes 6 and 11).
(16) There was only 5% of attack at carbonyl (with formation of **1**, R = H) in this case, in contrast to 39% from the reaction in butanol.
(17) The four sulfides **5**, **6**, **13**, and **14** were obtained in the relative percentages 22, 38, 10, and 30% and 14, 54, 15, and 17% from **1** and **3**, R = mesitoyl, respectively.

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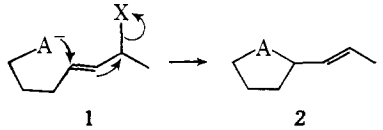
Concerning the Stereochemistry of the S_N2' Reaction. "Concerted" Allylic Displacement in an Acyclic System: Anti Displacement with Thiolate Anion

Sir:

"Concerted" displacement with rearrangement in allylic cyclohexenyl systems (S_N2') takes place largely with syn relationship of the entering and departing groups, when the displacing group is piperidine. With thiolate anion, however, considerable product from anti displacement is obtained.[1] This communication reports our findings that the internal counterpart of the S_N2' reaction (S_N') with thiolate anion (**1**, A = S, → **2**) takes place anti to the departing group in an acyclic system. The choice of an internal displacement was made to avoid complications relating to partition of products between S_N2 and S_N2' types and also because of the existence of a previous, apparently well-authenticated case,[2] of this type in



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