Regeneration of 5′-O-Acetylthymidine from Its Adduct.—To a solution of 0.1 g of the adduct IX in 5 ml of acetonitrile was added 5 ml of 0.1 *N* silver nitrate. The mixture was stored at room temperature for 2 hr and filtered, and the solvent was removed under reduced pressure. Thin layer chromatography, using the system described above, indicated the complete decomposition of the adduct; the presence of 5′-O-acetylthymidine (R_f 0.75) was demonstrated by use of the solvent system ethanol–acetonitrile–dichloromethane (2:3:5); the same solvent system indicated the absence of thymidine (R_f 0.50) in the reaction mixture.

Stereochemical Studies. IV. Asymmetric Selection *via* Elimination. Formation of Optically Active Olefins During Pyrolyses of Optically Active Esters

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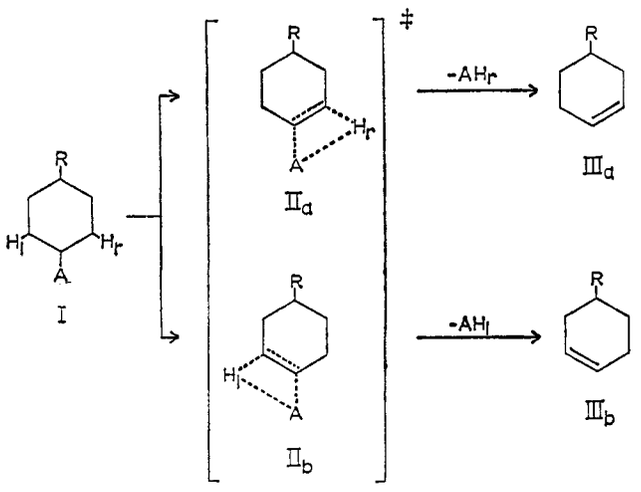
Careful pyrolysis of each of the four possible stereoisomeric 4-methylcyclohexyl hydratropates [*trans*-(−)-(*R*), *trans*-(+)-(*S*), *cis*-(−)-(*R*), and *cis*-(+)-(*S*)] has, in each case, resulted in the formation of optically active 4-methylcyclohexene. The significance of these results are discussed in terms of a possible topological description of the transition state for the pyrolytic *cis* elimination of esters.

While many examples of addition processes involving asymmetric selection[1] have been recorded,[2] asymmetric selection *via* elimination has not received anything like similar attention.

Our interest in asymmetric elimination lay in the realization that such processes could provide a useful tool for configurational correlation and, perhaps more intriguing, that an asymmetric elimination process might be an extremely sensitive probe for information useful in detailing transition state topology.

We envisioned a general model system which, in principal, would allow asymmetric selection during elimination. The system could contain any even-membered ring with substituents (R and A) symmetrically disposed so that neither ring atom bearing a substituent would be asymmetric. The 1,4-disubstituted cyclohexane system (I) meets these requirements (Scheme I).

SCHEME I



Let the relative steric arrangement of R and A be known (*cis* or *trans*), and let A contain an asymmetric atom possessing only one of its two possible configurations. System I would then be optically active by virtue of A.

In addition, the group A must be one which is known to undergo *cis* elimination (ester, amine oxide, sulfoxide, or phosphine oxide). The two transition states for the *cis* elimination of AH from I may then be represented by IIa and IIb. Under the requirements and restrictions set down for I, these transition states must bear a diastereoisomeric relationship to one another, and therefore differ in energy. Consequently, one transition state represents a lower energy pathway for elimination than the other, and the enantiomeric olefin resulting from the lower energy pathway would be expected to predominate, providing optical activity in the product olefin.

We have submitted this concept to experimental test in the case of esters[3] and sulfoxides,[4] are in the process of examining amine oxides,[5] and wish now to report our results on the ester study in detail.

Discussion

At the outset of this work we recognized that the alkaloid hyoscyamine IX possesses all the structural requirements deemed necessary to give rise to an asymmetric elimination process, *i.e.*, production of tropidine, optically active owing to enrichment of one enantiomer (Xa or Xb) (Scheme II) during the elimination of tropic acid.

We, therefore, submitted hyoscyamine to careful pyrolysis under a variety of conditions, but in no case were we able to detect any optical activity present in

(1) Rather than pursue the confusing practice of classification under one of the various and vaguely defined terms used heretofore (asymmetric destruction, induction, synthesis, transformation, etc.), the term asymmetric selection is suggested to mean any chemical reaction that gives rise to partial or absolute enrichment of one enantiomer over the other in the product.

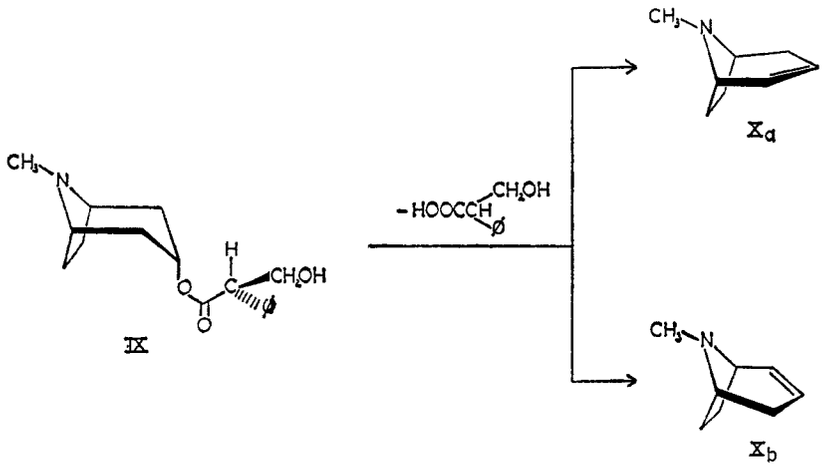
(2) For a partial account of a number of examples, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(3) A preliminary account was reported earlier by S. I. Goldberg and F.-L. Lam [*Tetrahedron Letters*, 1893 (1964)] and presented before the Division of Organic Chemistry, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, p 48S.

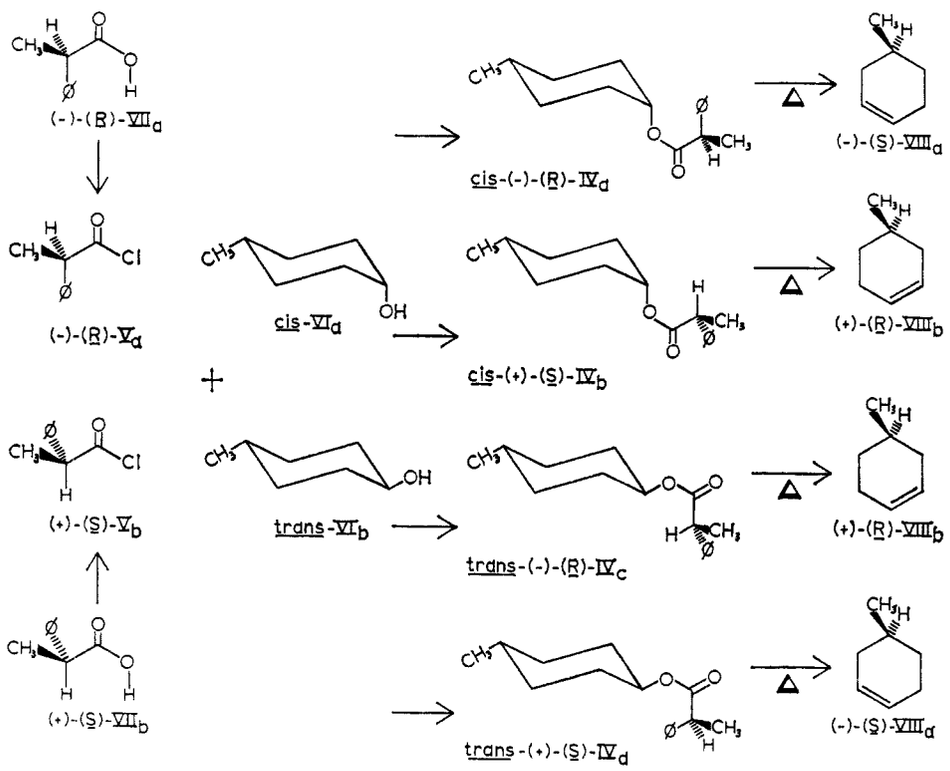
(4) S. I. Goldberg and M. S. Sahli, *Tetrahedron Letters*, 4441 (1965). The observation of stereospecificity in the pyrolysis of steroidal sulfoxides by D. M. Jones and M. A. Sand [*Proc. Chem. Soc.*, 81 (1964)] is probably another example of the general concept.

(5) G. Berti and G. Bellucci [*Tetrahedron Letters*, 3853 (1964)] have reported in preliminary fashion the presence of asymmetric selection during pyrolysis of optically active N-methyl-N-(4-methylcyclohexyl)-N-phenylamine oxide.

SCHEME II



SCHEME III



the tropidine obtained. It soon became apparent, however, that these experiments were inconclusive, for we were able to show that the rate of racemization of hyoscyamine to its optically inactive form, atropine, was at least as fast as its rate of elimination to tropidine and tropic acid. Hyoscyamine was completely racemized during 15 min at 150°, and, since pyrolytic temperatures near 300° were required for even a small yield of tropidine, use of hyoscyamine for an experimental demonstration of our concept of asymmetric selection during elimination seemed hopeless.

The system which actually did provide for successful experimental demonstration of asymmetric elimination was that of the four isomeric 4-methylcyclohexyl hydratropates IVa–d. Each isomeric ester was individually prepared from enantiomeric hydratropyl chloride Va and Vb and isomeric 4-methylcyclohexanol VIa and VIb (Scheme III). The enantiomeric acid chlorides were each obtained from the corresponding enantiomeric hydratropic acid VIIa and VIIb which in turn were obtained *via* strychnine resolution of the racemic acid. It was found that treatment of each enantiomeric acid with oxalyl chloride at room temperature consisted a mild means for preparing acid chloride of high optical activity.

Preparation and separation of *cis*- and *trans*-4-methylcyclohexanol is detailed in the Experimental Section. Also given are the spectral data determined from each isomer which provided confirmation of previous assignments[6] of stereochemistry to these alcohols. This information plus the knowledge of absolute configurations of the enantiomeric hydratropic acids (and therefore the enantiomeric hydratropoyl chlorides)[7]

(6) See L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 1717 (1949), and references therein.

(7) The configuration of hydratropic acid was related to that of glyceraldehyde in 1939 by H. I. Bernstein and F. C. Whitmore [*J. Am. Chem. Soc.*, **61**, 1324 (1939)]. Subsequent determination of the absolute configuration of the latter also placed the former on an absolute basis.

TABLE I

RESULTS OF ESTER PYROLYSES

Ester			4-Methylcyclohexene			
Isomer	$[\alpha]_D$[a]	Optical purity, %	Isomer	Conversion, %	$[\alpha]_D$[b]	Optical yield,[i] %
cis-(−)-(*R*)-IV$_a$	−18.4 ± 0.3[c]	(65.1 ± 1.7)[d]	(−)-(*S*)-VIII$_a$	52	−0.17 ± 0.06[e]	0.24 ± 0.08
cis-(+)-(*S*)-IV$_b$	+28.3 ± 1.2[e]	(100)[f]	(+)-(*R*)-VIII$_b$	36	+0.93 ± 0.09[g]	0.87 ± 0.08
trans-(−)-(*R*)-IV$_c$	−35.7 ± 1.0[h]	(57.5 ± 1.2)[i]	(+)-(*R*)-VIII$_b$	15	+0.35 ± 0.27[h]	0.54 ± 0.41
trans-(+)-(*S*)-IV$_d$	+61.8 ± 0.7[h]	(100)[f]	(−)-(*S*)-VIII$_a$	16	−0.44 ± 0.15[k]	0.41 ± 0.14

[a] Measurements in benzene solution. [b] Measurements in methanol solution. [c] 32°. [d] Based upon assumed 100% optical purity for *cis*-(+)-(*S*)-IV$_b$. [e] 31°. [f] Assumed 100% optical purity. [g] 28°. [h] 26°. [i] Based upon assumed 100% optical purity for *trans*-(+)-(*S*)-IV$_d$. [j] Based upon highest reported specific rotation (107°) of 4-methylcyclohexene [J. Zelikow, *Chem. Ber.*, **37**, 1374 (1904)] and assumed optical purity of the corresponding stereomeric ester. [k] 27°.

allowed for complete description of the absolute stereochemical details of each isomeric ester.

The individual stereoisomeric esters were pyrolyzed at 425° in a nitrogen stream using a vertical column packed with glass helices.[8] The pyrolysate was condensed from the effluent stream, and the product olefin, 4-methylcyclohexene, was separated and collected *via* gas chromatographic methods. In each case, olefin with low, but measurable, optical activity was obtained. Under the conditions used, the enantiomeric *cis* esters gave rise to higher olefin conversions than did the *trans* esters, but the optical yield in each case was fractional. These data are presented in Table I.

While great care was exercised during preparation of each stereomeric ester, using acid chloride of high optical purity[9] with isomerically pure alcohol, it was not possible to determine the enantiomeric purity of the esters obtained. Indeed, the absence of a consistent pattern of rotatory magnitude within each enantiomeric pair (Table I) indicated the presence of partial racemization during preparation and/or work-up. In order to estimate an optical yield of the predominate enantiomeric olefin obtained in each case, an optical purity of 100% was assumed for each of the higher rotatory diastereomeric esters (IVb and d, Table I). This assumption is, of course, highly conservative, leading to optical yields of olefins (Table I) probably more unfavorable than was actually the case. Nevertheless, it is certain that the degree of asymmetric selection was low, but a low degree of asymmetric selection in this system is not surprising.

The asymmetric α-carbon atom and its substituents (phenyl, methyl, and hydrogen) would not be a part of the bonding sequence which is directly involved in the changes inherent during the pyrolytic elimination process. That is to say, the α carbon would not be directly involved in the transition state. The configurational restrictions present at the α carbon would, therefore, not be expected to exert an effect upon the transition state as great as it might if the asymmetric atom were an intimate part of the bonding sequence undergoing change in the transition state. This consideration is supported by results obtained from pyrolyses of 4-methylcyclohexyl-containing amine oxides and sulfoxides, similar systems in which the asymmetric atom, nitrogen and sulfur, respectively, must be more directly involved in the transition state than the α carbon of the corresponding ester system. Thus, Berti and Bellucci[5] observed, in a 60% conversion, optically active 4-methylcyclohexene with $[\alpha]_{578}^{18}$ +34.7°, and in work in this laboratory with sulfoxides,[4] formation of optically active 4-methylcyclohexene, in 13% conversion, with a D-line specific rotatory magnitude of 74.8°, was recently established.

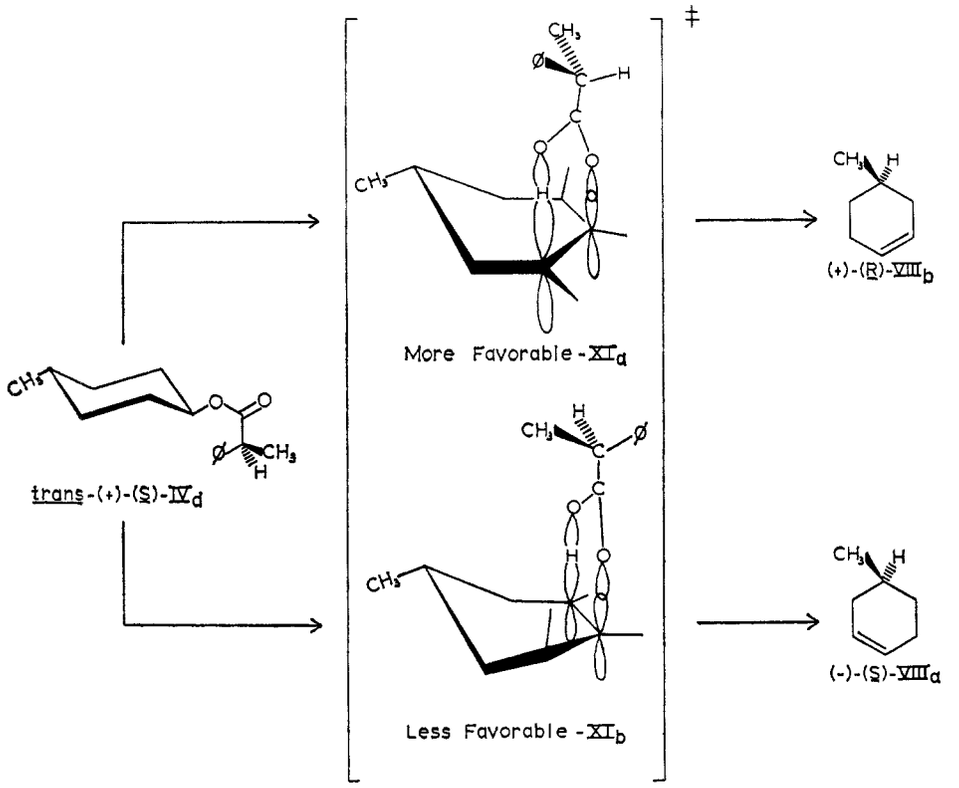
However, while a low degree of asymmetric selection may be a reasonable expectation during pyrolytic *cis* elimination of optically active esters, the difficult question is how low. The actual observation of the very low degree of asymmetric selection in the present study would probably be a rather shaky foundation upon which to base conclusions regarding the electronic nature of the transition state of the pyrolytic, *cis*-elimination process in esters. The results of the present study do, however, establish the presence of asymmetric selection during the process, but the choice among a cyclic, noncharged transition state, a tight, ion-pair transition state, and a tight, radical-pair transition state cannot be made without a quantitative basis for evaluation of the degree of asymmetric selection to be expected within each transition state description. Nevertheless, the accumulated evidence to date seems to be best accommodated within a cyclic, concerted transition state,[10] although an argument has been recently advanced in favor of an ionic description.[11]

If a cyclic, concerted transition state is operative, and if the degree of asymmetric selection observed in the present study does reflect the degree of influence which the asymmetric, α-carbon atom bears upon the process, then it is possible to formulate the absolute topology of the transition state model, for the model must reconcile the known absolute stereochemical details of each starting ester with that of each predominate, enantiomeric olefin[12] obtained. For example, the present results may be used to choose between two transition state topologies.

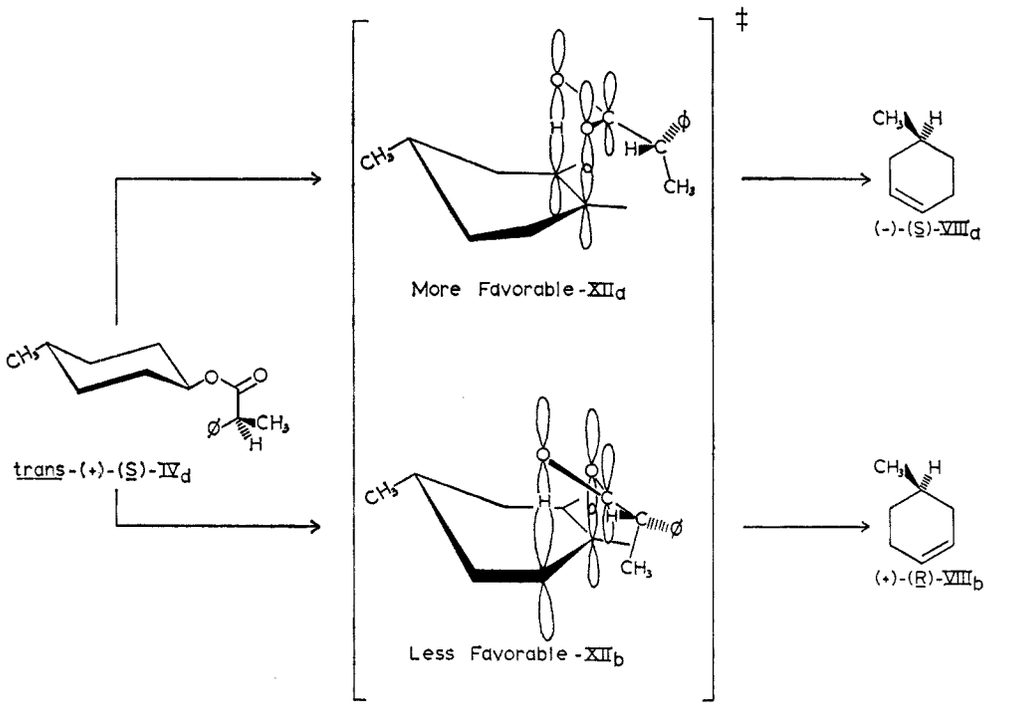
The first, depicted by structure XI in Scheme IV, and which may be referred to as the "perpendicular plane" model, would be rejected because it leads to prediction of formation of predominate enantiomeric olefin oposite to that observed experimentally. This may be illustrated with one example, that of (+)-(*S*)-IVd, which gave rise experimentally to (−)-(*S*)-4-methylcyclohexene (VIIIa) as the predominate enantiomer.

(8) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955).
(9) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961).
(10) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).
(11) J. C. Sheer, E. C. Kooyman, and F. L. J. Sixma, *Rec. Trav. Chim.*, **82**, 1123 (1963).
(12) See, S. I. Goldberg and F.-L. Lam, *J. Org. Chem.*, **31**, 240 (1966), for results which corroborate previous correlation of rotatory sign and configuration of the enantiomeric 4-methylcyclohexenes.

SCHEME IV



SCHEME V



For evaluation[13] of each of the diastereomeric transition states XIa and XIb, only those conformations of the phenylcarbopropoxy group in which the smallest α substituent (hydrogen) is eclipsing an oxygen are considered. This assumption reduces the possibilities to those depicted by XIa and XIb. Evaluation of the small difference between XIa and XIb leads to the conclusion that XIa should be the more favorable on the basis of interaction with the nearest cyclohexyl proton (β axial), but XIa leads to prediction of (+)-(*R*)-VIIIb enrichment, while enrichment of (−)-(*S*)-VIIIa was experimentally observed.

The second transition-state model, the "parallel plane" model, is depicted by XII. In this model it is assumed that, for the orbital reorganization which takes place during the ester pyrolysis, the transition

(13) "Framework Molecular Orbital Models," obtained from Prentice-Hall, Inc., were used to construct and evaluate these transition state models. Normal bond distances and normal π-bond diameters (scale, 1 in. = 1 A) were assumed to be valid.

state may be represented with the p orbitals of the leaving oxygen function *linearly* overlapped with the p orbitals of the developing double bond. The resulting topology is then one in which the leaving carbalkoxy group and the forming olefin essentially define two parallel planes. While this arrangement results in closer nonbonded interaction between alkyl (cyclohexyl) protons and the α substituents on the carbalkoxy (phenylcarbopropoxy) group than in the "perpendicular plane" model, the more favorable orbital overlap in the former may be the more important factor. (See Scheme V.)

Examination of scale molecular models[13] of XII indicates that the most significant nonbonded interaction is that between the α substituents and the C-1 cyclohexyl proton. If the two diastereomeric transition states XIIa and XIIb are evaluated in terms of this interaction, again only considering those conformers in which the smallest α substituent, hydrogen, is eclipsing oxygen, then XIIa is judged the more favorable, and XIIa leads to prediction of product enrichment with that enantiomeric olefin VIIIa which was in fact experimentally observed. Similar evaluation of the three other stereomeric esters used in this study lead, in each case, to prediction of enrichment of that enantiomeric 4-methylcyclohexene which was experimentally found.

Experimental Section[14]

Racemic Hydratropic Acid. A. *Via* **Oxidation of Racemic Hydratropaldehyde.**—To 200 ml of mechanically stirred 10% aqueous potassium hydroxide solution, containing silver oxide (60 g, 0.26 mole), was slowly added (3 hr) racemic hydratropaldehyde[15] (30.5 g, 0.228 mole). After the addition was complete and the initial exothermic reaction had subsided, the reaction mixture was stirred during an additional 10-hr period at room temperature. Filtration of the basic aqueous reaction mixture was followed by ether extraction of the filtrate in order to remove neutral components. These ether extracts were discarded. The aqueous residue was made strongly acidic by addition of concentrated sulfuric acid, and the acidic solution was submitted to exhaustive ether extraction. Evaporation of the dried and filtered combined ether extracts left an oily residue, which, upon distillation, gave rise to racemic hydratropic acid: 8.70 g, 25.4% yield; bp 112–114° (1 mm), lit.[9,16] bp 147° (11 mm) and 159° (25 mm). An infrared spectrum (neat) determined from this material was found to be superimposable upon that obtained from the more thoroughly characterized acid prepared *via* hydratroponitrile.

B. *Via* **Hydrolysis of Hydratroponitrile.**[16]—To a combined solution of racemic hydratropaldehyde (53.0 g, 0.397 mole, in 160 ml of ethanol) and hydroxylamine hydrochloride (33.0 g, 0.474 mole, in 40 ml of water) was slowly added 32 ml of 19 *N* aqueous sodium hydroxide solution. After the mixture was stirred during 3 hr, it was cooled by addition of about 200 ml of crushed ice and allowed to warm to, and remain at (overnight), room temperature. The basic reaction mixture was then exhaustively extracted with ether, and the combined ether extracts, after drying and evaporation, yielded racemic hydratropaldoxime: 45 g (76% yield); colorless oil; bp 110° (3.5 mm) or 96° at (1.5 mm), lit.[16] 133° (11 mm); infrared spectrum, ν_{max}^{neat} 3220 and 1300 cm^{-1} (bonded OH),[17] 1960, 1870, 1805, 1745, 1600, and 1490 cm^{-1} (monosubstituted phenyl),[17] and 1670 cm^{-1} (C=N).[17]

The oxime (45 g, 0.30 mole) was then heated with acetic anhydride under reflux during 0.5 hr. After the orange reaction mixture was allowed to cool to room temperature and neutralized with aqueous sodium bicarbonate, it was extracted with ether. Evaporation of the combined and dried ether extracts provided racemic hydratroponitrile as a colorless oil: 28 g (71% yield); bp 74° (0.5 mm), lit.[16] bp 106° (12 mm); infrared spectrum, ν_{max}^{neat} 2245 cm^{-1} (C≡N),[17] 1955, 1870, 1760, 1605 and 1492 cm^{-1} (monosubstituted phenyl).[17]

Racemic hydratroponitrile (28 g, 0.21 mole) was suspended in concentrated aqueous sodium hydroxide solution and heated under gentle reflux during 18 hr. The reaction mixture was then cooled and carefully acidified with hydrochloric acid, and the resulting acidic solution was extracted with ether. Evaporation of the combined and dried ether extracts provided **racemic hydratropic acid**: 24 g (76% yield); bp 113° (1.3 mm), lit.[9,16] bp 147° (11 mm) and 159° (25 mm); infrared spectrum, ν_{max}^{neat} 2960 and 1702 cm^{-1} (carboxyl group),[17] 1945, 1870, 1805, 1603, and 1492 cm^{-1} (monosubstituted phenyl).[17]

Resolution of Racemic Hydratropic Acid.—Racemic hydratropic acid (24 g) and strychnine (44 g) were dissolved in 200 ml of 75% (v/v) aqueous ethanol, and the resulting solution was kept in the refrigerator (*ca.* 10°) during 3 days. The crystallized strychnine hydratropate was collected, redissolved in fresh 75% aqueous ethanol, and allowed once again to crystallize slowly in the refrigerator. This procedure was repeated through the sixth recrystallization since the fifth and sixth recrystallizations did not give rise to any improvement in the melting point (176–177°) of the white, crystalline salt. The constant-melting strychnine hydratropate was taken up in 6 *N* hydrochloric acid, and the liberated organic acid was extracted into ether. Distillation of the oily residue obtained from evaporation of the combined and dried ether extracts gave (+)-(*S*)-**hydratropic acid (VIIb)**: 4.5 g; bp 101–103° (0.4 mm); $[\alpha]^{23}D$ +75.2 ± 0.7° (*c* 1.76, chloroform), lit.[9] $[\alpha]D$ +76.3 ± 0.6° (*c* 1.613, chloroform).

The mother liquors and washings obtained from the six recrystallizations of the strychnine hydratropate described above were combined and acidified, and the liberated hydratropic acid was extracted into ether. The combined and dried ether extracts yielded an oily residue upon evaporation, which afforded partially resolved, levorotatory hydratropic acid {$[\alpha]^{25}D$ −24.0 ± 0.1° (*c* 6.75, acetone)}, upon distillation: 8.5 g, bp 120–121° (4 mm). This sample of partially resolved acid was dissolved in hot acetone containing quinine (18.6 g), and the resulting solution was allowed to cool slowly to room temperature and remain there during several days to ensure complete crystallization of quinine hydratropate. The white, crystalline salt displayed a melting point of 176–177° and a specific rotation of −123°, both of which were improved after successive recrystallizations of the salt from hot acetone, giving, after the third and fourth recrystallizations, material which possessed a melting range of 178–179° and a rotation of $[\alpha]^{27}D$ −99.2 ± 0.8 (*c* 0.870, chloroform).

This material was taken up in 6 *N* hydrochloric acid, and the freed organic acid was extracted into ether. After drying and evaporation of the combined ether extracts, distillation of the residue gave (−)-(*R*)-**hydratropic acid (VIIa)**: 3.0 g, $[\alpha]^{27}D$ −77.0 ± 0.3° (*c* 2.380, chloroform), lit.[9] $[\alpha]^{25}D$ −76.1 ± 0.6 (*c* 1.599, chloroform).

(−)-(*R*)-(Va) and (+)-(*S*)-Hydratropoyl Chlorides (Vb).—The optically active acid chlorides were obtained *via* treatment of each enantiomeric acid with oxalyl chloride according to the following procedure.

Hydratropic acid (1 equiv) was added to 2 or 3 equiv of pure oxalyl chloride at room temperature. An immediate effervescence took place and continued during about 40 min while the reaction mixture was stirred. Stirring was continued for an additional hour even though no gas evolution was apparent. The reaction mixture was then submitted to reduced pressure at room temperature, and the excess oxalyl chloride was slowly pumped off during about 2 hr. Careful distillation of the residue gave hydratropoyl chloride usually in better than 90% yield: bp 93–94° (9 mm), lit.[9] bp 81–83° (10 mm); infrared spectrum, ν_{max}^{neat}

(14) Temperatures are uncorrected. Combustion analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined with a Perkin-Elmer, Model 337, grating spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian, A-60, spectrometer near room temperature, using chloroform-*d* solvent containing 4% (v/v) tetramethylsilane (TMS) internal standard. Chemical shifts are reported under the δ convention in parts per million relative to TMS (0 ppm). Polarimeter measurements were carried out with an O. C. Rudolph and Sons, Inc. (Caldwell, N. J.), instrument, Model 80, sodium light source.

(15) Purchased from Columbia Organic Chemicals Co., Inc., and used without further purification.

(16) R. Roger and D. G. Neilson, *J. Chem. Soc.*, 627 (1960).

(17) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958; K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.

1790 and 1705 cm^{-1} (chloroformyl),[17] 1605, 1585, 1500, and 1445 cm^{-1} (monosubstituted phenyl),[17] and 1380 cm^{-1} (methyl on carbon).[17]

(−)-(*R*)-Hydratropic acid (VIIa) was converted to (−)-(*R*)-**hydratropoyl chloride (Va)** {$[\alpha]^{28}D$ −92.4 ± 0.4° (*c* 3.37, benzene)} with indicated optical purity of 90%,[18] while use of the (+)-(*S*)-acid afforded (+)-(*S*)-**hydratropoyl chloride (Vb)** {$[\alpha]^{25}D$ +103.9 ± 0.5° (*c* 3.34, benzene)} of 101%[18] indicated optical purity.

cis- **(VIa) and** *trans*-**4-Methylcyclohexanols (VIb).**—The procedure reported by Jackman and co-workers[6] for catalytic hydrogenation of 4-methylcyclohexanone to a mixture containing 59% *cis*- and 41% *trans*-4-methylcyclohexanol was followed.

The mixture was carefully fractionated, and a sample (20 g) from the heart cut [bp 173–174° (750 mm)], consisting of 69% *cis*- and 31% *trans*-4-methylcyclohexanol,[19] was dissolved in 20 ml of benzene and added to 80 ml of a warm benzene solution containing *p*-nitrobenzoyl chloride (36 g). After the reaction mixture was allowed to remain at room temperature overnight, it was successively washed with several portions of saturated aqueous sodium carbonate solution and water. The residual benzene solution was then dried and evaporated to a mass of yellow crystalline material (35 g) which was taken up in 140 ml of warm methanol. The methanolic solution was allowed to cool slowly while it deposited pale yellow crystals. After crystallization was complete, the *p*-nitrobenzoate was collected in a filter and dried, giving 33.7 g of a mixture of isomeric esters, mp 63–80°. This material was submitted to five more recrystallizations from warm methanol (5 ml of methanol/g of ester). The sixth recrystallization yielded 17.8 g of *cis*-4-methylcyclohexyl *p*-nitrobenzoate, which displayed a melting range (94.5–95.5°, lit.[6] mp 96°) essentially unchanged from that determined from the material of the fourth or fifth recrystallization.

The entire sample of the *cis* ester (17.8 g) was taken up in 300 ml of 10% aqueous potassium hydroxide and heated under conditions of steam distillation. The steam distillate obtained was submitted to continuous extraction by *n*-hexane during 3 days; and the dried hexane extract was evaporated to an oily residue, which upon distillation, yielded pure ***cis*-4-methylcyclohexanol (VIa)**: 6.60 g; bp 34–36° (0.4 mm), lit.[6] bp 52° (2 mm); $n^{22}D$ 1.4607, lit.[6] $n^{20}D$ 1.4614; this material gave rise to a single, symmetrical peak upon gas–liquid partition chromatographic analysis[20]; infrared spectrum, ν_{max}^{neat} 3345 cm^{-1} (bonded OH),[17] 1380 cm^{-1} (methyl on carbon),[17] strong band at 982 cm^{-1} and absence of a band at 1005 cm^{-1} (axial COH)[21]; nmr spectrum, $\nu_{max}^{CDCl_3}$ δ 3.88, multiplet (C-1 equatorial proton),[23] δ 3.46, singlet (O*H*),[26] δ 2.1–1.1, complex array of signals of the remaining nine cyclohexyl protons, δ = 0.92 ppm, unresolved, three-proton signal of methyl group.

***trans*-4-Methylcyclohexanol (VIb)** was obtained through purification of commercially available 4-methylcyclohexanol, containing 94.2% of the *trans* isomer.[27] The commercial material (50 g) in 50 ml of benzene was slowly (40 min) added to a warm benzene solution of *p*-nitrobenzoyl chloride (90 g in 170 ml). The crude *p*-nitrobenzoate (102 g, mp 62–64°) obtained was recrystallized five times from hot methanol; material from the third, fourth, or fifth recrystallization, each displayed mp 64.0–64.5°; lit.[6] mp 64–65°. The final recrystallization yielded 62 g of *trans*-4-methylcyclohexyl *p*-nitrobenzoate, which was hydrolyzed and distilled, in a manner identical with that used to obtain the *cis* isomer, to afford pure ***trans*-4-methylcyclohexanol: (VIb)**; 16 g; bp 173–174° (750 mm), lit.[6] bp 54° (3 mm); $n^{22}D$ 1.4559, lit.[6] $n^{20}D$ 1.4561; infrared spectrum, ν_{max}^{neat} 3350 cm^{-1} (bonded OH),[17] 1380 cm^{-1} (methyl on carbon),[17] 1005 and 983 cm^{-1} (equatorial COH)[21]; nmr, $\nu_{max}^{CDCl_3}$ δ 4.20, singlet (O*H*),[26] 3.40 multiplet (C-1 axial proton),[23] 2.2–1.0, complex array of signals of the remaining nine cyclohexyl protons, 0.88, three-proton signal appearing as an unsymmetrical apparent doublet, assigned to methyl at C-4.

***cis*- and *trans*-4-Methylcyclohexyl Racemic Hydratropates.**—Each stereoisomeric racemic ester was prepared by allowing 1 equiv of racemic hydratropoyl chloride to react with excess (2 or 3 equiv) of alcohol (*cis* or *trans*) during 3 hr at room temperature. Excess alcohol was then evaporated quickly from the reaction mixture under mild conditions [not >40° (0.5 mm)], leaving essentially pure ester.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.02. Found: C, 78.25; H, 9.21.

In each case, however, the racemic stereoisomeric ester was collected from a gas–liquid partition chromatographic column[28] in order to obtain the following data.

***cis*-4-Methylcyclohexyl racemic hydratropate** showed infrared spectrum, ν_{max}^{neat} 1730, 1200, and 1168 cm^{-1} (ester),[17] 1605, 1500, and 1455 cm^{-1} (phenyl nucleus),[17] 1380 cm^{-1} (methyl on carbon)[17]; nmr, $\nu_{max}^{CDCl_3}$ δ 7.21, apparent singlet (phenyl protons),[29] 4.88, multiplet (C-1 equatorial proton),[30] 3.62, quartet, *J* = 7.3 cps [OC(O)C*H*(CH_3)C_6H_5],[29] 1.47, doublet, *J* = 7.3 cps [OC(O)CH(C*H*$_3$)C_6H_5],[29] 0.82, unsymmetrical doublet, *J* = 5 cps (C-4 methyl protons),[29] 2–1, complex array (remaining cyclohexyl protons).[29]

***trans*-4-Methylcyclohexyl racemic hydratropate** showed infrared spectrum, ν_{max}^{neat} 1735, 1200, and 1168 cm^{-1} (ester),[17] 1610, 1505, and 1460 cm^{-1} (phenyl nucleus),[17] 1385 cm^{-1} (methyl on carbon).[17] While significant differences in infrared absorption of the two stereoisomeric esters were observed in the region 1150–850 cm^{-1} (see Table II), the generalization suggested by Page[31] for distinguishing axial and equatorial cyclohexyl acetates by means of their absorption in this region does not appear to be applicable in the present case.

The nmr spectrum showed $\nu_{max}^{CDCl_3}$ δ 7.20, apparent singlet (phenyl protons),[29] 4.59, multiplet (C-1 axial proton),[30] 3.58, quartet, *J* = 7.3 cps [OC(O)C*H*(CH_3)C_6H_5],[29] 1.43, doublet, *J* = 7.3 cps [OC(O)CH(C*H*$_3$)C_6H_5],[29] 0.90, partially resolved apparent doublet, *J* = 4.8 cps (C-4 methyl protons),[29] 2–1, complex array (remaining cyclohexyl protons).[29]

Pyrolyses of Enantiomeric *cis* and Enantiomeric *trans* Esters.—Ester pyrolyses were carried out by means of the so-called drop-

(18) Calculation based on highest reported[9] specific rotation.

(19) Calculated from refractive indexes of the pure components ($n^{22}D$ 1.4607, *cis* and $n^{22}D$ 1.4551, *trans*) and the mixture ($n^{22}D$ 1.4586).

(20) A 16 ft × 0.25 in. column, packed with Diatoport-W (60–80 mesh), containing 15% (w/w) Carbowax 20M, run isothermally (110°) with helium at 130 cc/min. Under these conditions *cis*-4-methylcyclohexanol exhibited a retention time of 27.4 min.

(21) The infrared spectrum determined from the *trans*-alcohol displayed bands of moderate intensity at 982 and 1005 cm^{-1}. These absorption patterns appear to be in agreement with the generalization[22] that near the 1000-cm^{-1} region an equatorial COH absorbs at higher frequency than an axial COH.

(22) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 5571 (1952); A. Furst, H. H. Kuhn, R. Scotoni, Jr., and H. H. Gunthard, *Helv. Chim. Acta*, **35**, 951 (1952); W. G. Dauben, E. Hoerger, and N. K. Freeman, *J. Am. Chem. Soc.*, **74**, 5206 (1952); and, H. Rosenkrantz and L. Zablow, *ibid.*, **75**, 903 (1953).

(23) Chemical shifts of the C-1 protons (δ 3.88 and 3.40) clearly confirm the stereochemical assignments to the isomeric 4-methylcyclohexanols. It has been shown[24] and theoretically predicted[25] that an equatorial proton is deshielded relative to the corresponding axial proton by what appears to be an average $\Delta\delta_{ae}$ value of 0.40 ppm. The presently observed value of 0.47 ppm is in good agreement with previous experience.

(24) See, for example, J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).

(25) A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958).

(26) Chemical shift varies with concentration and/or temperature.

(27) Gas–liquid partition chromatographic analysis (under conditions described in ref 20) of a commercial "*cis*-4-methylcyclohexanol" showed the material to consist of 1.3% of an unknown material (retention time 18.3 min), 4.5% of *cis*-4-methylcyclohexanol (VIa) (retention time 27.3 min), and 94.2% of *trans*-4-methylcyclohexanol (VIa) (retention time 29.5 min). Identical analysis of a commercial "*trans*-4-methylcyclohexanol" showed it to be made up of 2.8% of the unknown component (retention time 18.3 min), 63.5% *cis*-4-methylcyclohexanol (VIa) (retention time 27.3 min), and 33.7% *trans*-4-methylcyclohexanol (VIb) (retention time 29.4 min). Consequently, the commercial "*cis* alcohol" was used as our source of *trans*-4-methylcyclohexanol (VIb).

(28) An 8 ft × 0.25 in. column, packed with Diatoport-W (60–80 mesh), containing 5% (w/w) SE-30 silicone rubber, run isothermally (210°) with helium at 100 cc/min. Under these conditions the *cis* ester possessed a retention time of 17.4 min, while that of the *trans* ester was found to be 19.9 min.

(29) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959; G. V. D. Tiers, "Tables of Tau-Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "N.M.R. Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962; N. S. Bhacca, D. P. Hollis, L. J. Johnson, and E. A. Pier, "N. M. R. Spectra Catalog," Vol. 2, 1963.

(30) As in the case of the corresponding alcohols,[23] the chemical shifts of the C-1 protons in the esters allow for definitive assignment of stereochemistry.

(31) J. E. Page, *J. Chem. Soc.*, 2017 (1955).

TABLE II

INFRARED ABSORPTIONS IN THE 1150–850-CM^{-1} REGION OF THE *cis* AND *trans* ESTERS[a]

trans ester, cm^{-1}	*cis* ester, cm^{-1}
1150 (s)	
1125 (m)	1128 (s)
1083 (s)	1086 (m)
1018 (s)	1015 (w)
1010 (s)	1005 (w)
998 (s)	992 (w)
983 (s)	972 (m)
966 (m)	959 (s)
938 (s)	930 (w)
923 (w)	912 (m)
895 (s)	883 (s)
880 (m)	870 (m)

[a] s = strong; m = medium; w = weak.

ping sample method.[8] For this purpose a 10-mm Pyrex tube, having approximately 20 cm of it packed with Pyrex helices, was used. The tube was held vertically with the packed section heated by an electrical furnace,[32] the temperature of which was regulated by a "Temcometer" input controller.[33] The sample was introduced dropwise *via* a hypodermic syringe and passed through a rubber septum at the top of the tube into a stream of nitrogen. Pyrolysate was condensed out of the effluent stream in a trap cooled by an external Dry Ice–acetone bath. The conditions used for pyrolyses of the optically active esters, first worked out with racemic *trans* ester with the purpose of finding the mildest conditions necessary to produce a workable yield of olefin, were as follows. The sample (neat) was added (1 μdrop/sec) at the top of the pyrolysis tube while nitrogen was continually passed (12 cc/min) through the system. The heated section of the tube was maintained at 425 ± 3°. The condensed pyrolysate was analyzed by means of gas–liquid partition chromatography[34] to establish the presence and yield of 4-methylcyclohexene, and then to collect the pure olefin for characterization and polarimeter measurements.

The formation of 4-methylcyclohexene as the olefinic product from each pyrolysis experiment was established by determination of infrared and nuclear magnetic resonance spectra of material collected *via* glpc. In all cases these spectra were found to be superimposable upon those determined from authentic 4-methylcyclohexene.

***trans*-4-Methylcyclohexyl (+)-(*S*)-hydratropate (IVd)** (1.40 g, 5.68 mmoles), $[\alpha]^{26}D$ +61.8 ± 0.7° (*c* 2.02, benzene), gave **(−)-(*S*)-4-methylcyclohexene (VIIIa)** (0.0881 g, 16% conversion), $[\alpha]^{27}D$ −0.44 ± 0.15 (*c* 7.23, methanol).[35]

***trans*-4-Methylcyclohexyl (−)-(*R*)-hydratropate (IVc)** (1.09 g, 4.45 mmoles), $[\alpha]^{26}D$ −35.7 ± 1.0° (*c* 1.32, benzene), gave **(+)-(*R*)-4-methylcyclohexene (VIIIb)** (0.0642 g, 15% conversion), $[\alpha]^{26}D$ +0.35 ± 0.27 (*c* 6.32, methanol).[35]

***cis*-4-Methylcyclohexyl (+)-(*S*)-hydratropate (IVb)** (0.075 g, 2.66 mmoles), $[\alpha]^{31}D$ +28.3 ± 1.2° (*c* 1.91, benzene), gave **(+)-(*R*)-4-methylcyclohexene (VIIIb)** (0.0933 g, 36% conversion), $[\alpha]^{28}D$ +0.93 ± 0.09° (*c* 8.86, methanol).[35]

***cis*-4-Methylcyclohexyl (−)-(*R*)-hydratropate (IVa)** (0.930 g, 3.78 mmoles), $[\alpha]^{32}D$ −18.4 ± 0.3° (*c* 7.36, benzene), gave **(−)-(*S*)-4-methylcyclohexene (VIIIa)** (0.187 g, 52% conversion), $[\alpha]^{31}D$ −0.17 ± 0.06° (*c* 1.41, methanol).[35]

Failure to Observe Asymmetric Selection During Pyrolysis of (−)-Hyoscyamine (IX).—(−)-Hyoscyamine hydrochloride[36] (6.47 g, 19.6 mmoles) was dissolved in 30 ml of water, and the solution was made basic by addition of 10 ml of concentrated aqueous ammonia solution. The basic solution deposited white crystals of hyoscyamine which were collected in a suction filter and washed with several portions of cold water. The material was thoroughly dried under reduced pressure at room temperature, providing reasonably pure (−)-hyoscyamine: 4.52 g (80% yield); mp 103–105°, lit.[37] mp 108–111°; $[\alpha]^{27}D$ −21.7 ± 0.4° (*c* 4.21, 50% aqueous ethanol), lit.[37] $[\alpha]D$ −22° (ethanol-water).

Pyrolyses of (−)-hyoscyamine (IX) to tropidine (X) were initially carried out *via* a distillation technique[38,39] under reduced pressures (80–120 mm) and at temperatures (230–300°) which required 60–90 min for complete reaction. In no case, however, did the tropidine (X) (methiodide, mp 309–310°, lit.[39] mp 310–311°) obtained display any detectable optical activity.

A number of investigators have observed the rather facile racemization of hyoscyamine under a variety of conditions,[37] and experiments during the present investigation have demonstrated that the material undergoes complete racemization after 15 min at 150–155°. Therefore, the distillation pyrolysis method, requiring higher temperature and longer time, offered little hope of the chance of observing an asymmetric selection process. In an effort to circumvent this difficulty and provide a faster, more efficient pyrolysis, we turned to the dropping sample technique for pyrolysis of hyoscyamine.

(−)-Hyoscyamine (IX) (1.50 g, 5.19 mmoles), dissolved in 10 ml of chloroform, was added (2–3 drops/sec), by means of a hypodermic syringe, at the top of the pyrolysis tube into a stream (20 cc/min) of nitrogen. The packed section of the tube (as described above) was maintained at 280 ± 5°, and the pyrolysate was condensed in a cold (−78°) trap. Careful examination of the tropidine (X) obtained from the condensate did not reveal the presence of any measurable optical activity.

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(32) Hoskins Manufacturing Co., Detroit, Mich.

(33) Thermo Electric Manufacturing Co., Dubuque, Iowa.

(34) The detection and collection of 4-methylcyclohexene were carried out on an 8 ft × 0.25 in. column packed with Versamid 900 on Diatoport W [20% (w/w)], run at 75° with helium carrier gas at 100 cc/sec.

(35) Average value of at least five determinations. The lack of precision is a reflection of the difficulty in matching the very small field displayed by the micropolarimeter cell used for these measurements.

(36) Purchased from Mann Research Laboratories, Inc., New York, N. Y.

(37) H. L. Holmes in, "The Alkaloids," Vol. 1, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1950, Chapter VI.

(38) A. A. Bothner-By, R. S. Schultz, R. F. Dawson, and M. L. Solt, *J. Am. Chem. Soc.*, **84**, 52 (1962).

(39) E. Leete, *ibid.*, **84**, 55 (1962).