Preparation, absolute configuration, and thermolysis of (*3R*:*5R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline

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Thermolysis of (*3R*:*5R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline produces 25.6% of *trans*-1,2-dimethylcyclopropane of 23% optical purity having the *S*:*S* configuration. Thermolysis mechanisms which explain the racemization and the double inversion process are discussed. The absolute configuration of *active*-2,4-pentanediol and 2,4-dibromopentane is correlated with that of 4-hydroxy-1-pentene.

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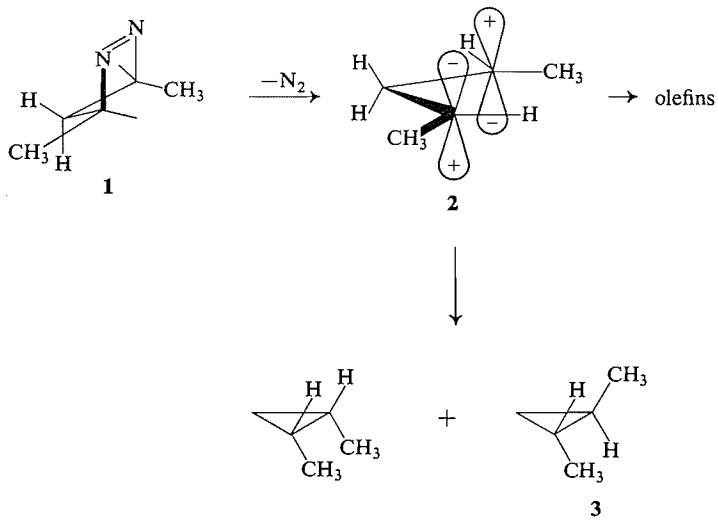
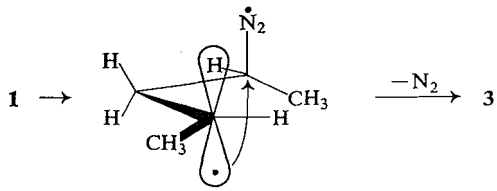


SCHEME 1

Introduction

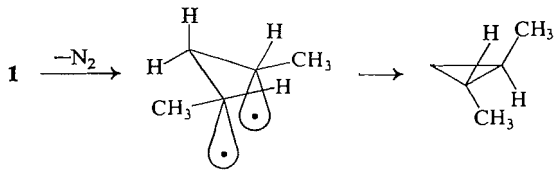
The gas-phase thermolysis of 1-pyrazoline has been shown to proceed by cleavage of both carbon–nitrogen bonds (1) to produce a hydrocarbon intermediate which in turn produces propylene and cyclopropane (2). The intermediate suggested for the thermolysis is such that the two hydrogen atoms attached to each end of the trimethylene species are in the plane defined by the three trimethylene carbon atoms. This has been referred to as the O,O-trimethylene configuration and extended Hückel molecular orbital calculations support the suggestion that it represents an energy minimum (3).

The thermolysis of *trans*-3,5-dimethyl-1-pyrazoline (**1**) produces 73% *cis*-1,2-dimethylcyclopropane, 25% of the *trans* isomer (**3**), and 1% each of *cis*- and *trans*-2-pentene. These products were rationalized as in Scheme 1 (2). The stereochemistry of the intermediate (**2**) is such that optically active **1** on thermolysis should generate racemic **3** if **2** is an intermediate. Recently alternative mechanisms have been proposed which may account for the minor product. Roth and Martin (4) have observed what is essentially inversion at both carbons (to which the azo nitrogens are attached) in the thermolysis of *exo*,*exo*-5,6-dideuterio-2,3-diazabicyclo[2·2·1]hept-2-ene, and by analogy the **3** produced upon thermolysis of active **1** should be optically active and involve inversion at each of its asymmetric centers (Scheme 2). Allred and Smith (5) using a similar bicyclic system have proposed a recoil mechanism by which **1** would be expected to produce a pyramidal diradical intermediate (**4**) which could close to produce **3**.



SCHEME 2

Again optically active **1** would be expected to produce **3** by inversion at both asymmetric centers (Scheme 3).



SCHEME 3

Correlations of Configurations

Chart 1 shows the method of synthesis, rotations, and absolute configurations of each of the compounds used in the sequence from (*R*)-(−)-4-hydroxy-1-pentene (6) to (*3R*:*5R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline. The 4-hydroxy-1-pentene was resolved via the brucine salt of the phthalate half ester (6*b*). Oxymercuration (7) of the hydroxy-1-pentene followed by borohydride reduction gave an 80% yield of 2,4-pentanediol consisting of a 30:70 mixture of *meso* and *active* forms. This mixture was not separated but converted directly to the dibromide using the procedure of Pritchard and Vollmer (8). The ratio of *active* to *meso* remained essentially that of the reactant, suggesting that the dibromide was produced by inversion of both centers in a clean manner (8, 9). The dibromide was then converted to the pyrazolidine and oxidized to the pyrazoline without characterization of rotation at the pyrazolidine stage (the latter is air sensitive and generally contains some of the 1-pyrazoline). The magnitude of rotation of each of these compounds was put on a firm basis by the resolution of *rac-trans*-3,5-dimethylpyrazolidine using (+)-10-camphorsulfonic acid, the pyrazolidine thus resolved was oxidized to give **1** with $[\alpha]_D^{25}$ +605°.

Thermolysis of 1

The resolved pyrazoline **1** on thermolysis produced *cis*- and *trans*-2-butene (1% each), *cis*-1,2-dimethylcyclopropane (73%) and *trans*-1,2-dimethylcyclopropane (25%); only the latter product has an asymmetric center and thus, to minimize losses, the hydrocarbon products were isolated and the total hydrocarbon fraction examined. The proportion of *cis* and *trans* isomers was then determined by gas–liquid chromatography (g.l.c.) and upon correction for the percentage of *cis*-3,5-dimethyl-1-pyrazoline in the starting material the optical activity of the **3** produced from *active*-**1** was calculated. Table I gives the results of several runs carried out in this manner. The percentage of *cis*-3,5-dimethyl-1-pyrazoline in the initial mixture was determined by 100 MHz nuclear magnetic resonance (n.m.r.) spectroscopy. This ratio was verified by the g.l.c. analysis of the cyclopropane

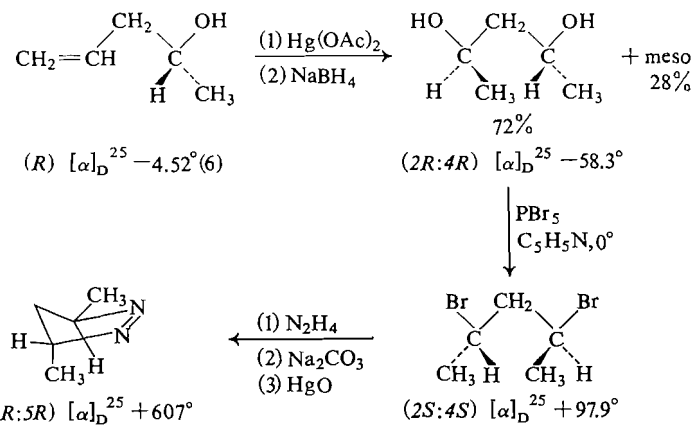
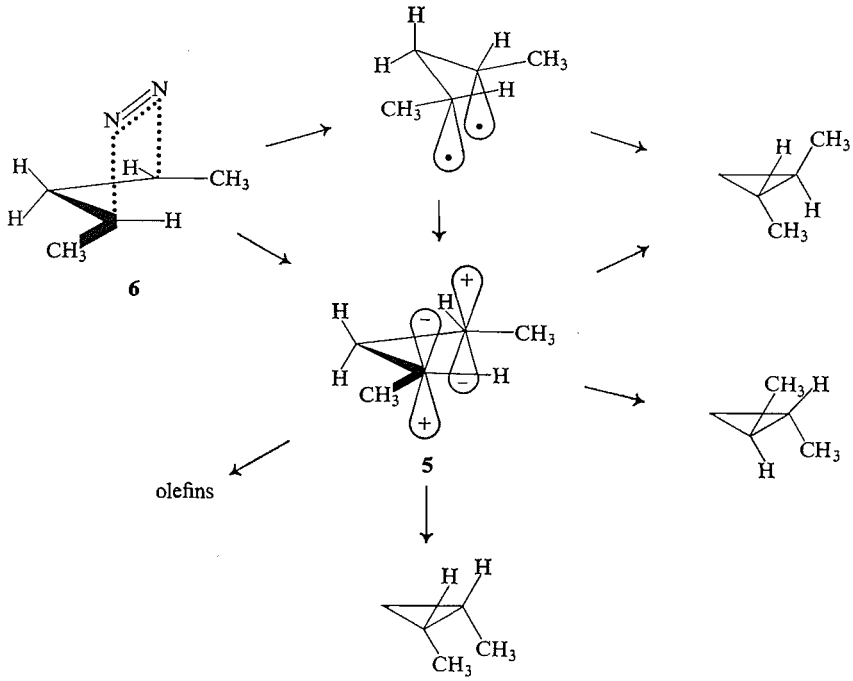


CHART 1: Preparation of (3*R*,5*R*)-(+)-*trans*-3,5-dimethyl-1-pyrazoline with maximum observed rotations.



SCHEME 4

and olefin products obtained upon thermolysis, and agreement to within 1% was obtained for the amount of *cis*- and *trans*-3,5-dimethyl-1-pyrazoline. Because the rotation of the hydrocarbon product was the same in sign as that of the reactant, and because of the magnitude of the rotation of **1** relative to that of **3**, it was necessary to be sure that unreacted **1**, or its tautomer, was not a contaminant. This was achieved by passing the whole product mixture through a 20 ft Carbowax 20M column and by collection of only the hydrocarbon fraction.

The results from Table I indicate an excess of double inversion to retention of absolute configuration of 23.6 ± 1.7% for the *trans*-1,2-dimethylcyclopropane (10) produced from *active*-**1**. The most concise scheme that fits the kinetic and stereochemical data is that shown as Scheme 4. This incorporates the pyramidal diradical suggested by Allred and Smith (5) to account for the optically active portion of the **3** produced, which is 6% of the total product. The racemic **3**, *cis*-1,2-dimethylcyclopropane and olefins are believed to arise from the trimethylene intermediate **5**. The present data cannot distinguish between **5** being formed directly from **1** via the transition state **6**, and a small fraction going via the pyramidal diradical or whether all of the material goes via the pyramidal diradical, 94% of which in turn produces **5**. Similarly the possibility exists that the 6% optically active *trans*-1,2-dimethylcyclopropane is produced via a mechanism similar to that suggested by Roth and Martin (4).

Experimental

The nuclear magnetic resonance spectra were obtained using a Varian A-60 and a Varian HA 100 spectrometer. Optical rotations were measured using a 1.00 dm cell in a Perkin–Elmer Model 141 spectropolarimeter and a Jasco ORD-UV5 spectrophotometer. A Wilkens Aerograph Autoprep was used for the preparative g.l.c. and a Gow-Mac Model TR-11-B,w thermal conductivity cell with a Gow-Mac Model 40-05C power supply was used on a vacuum line for analytical g.l.c. and the trapping of hydrocarbon samples (11).

Resolution of trans-3,5-Dimethylpyrazolidine and its Conversion to trans-3,5-Dimethyl-1-pyrazoline (1)

trans-3,5-Dimethylpyrazolidine was originally resolved through its *N,N'*-bishydroxymethylene-(+)-camphor derivative (2). However, regeneration of the pyrazolidine from this derivative proved to give too low a yield to be useful in this work. Among the different acids employed for an attempted salt formation, (+)-10-camphorsulfonic acid was found to be the most suitable.

TABLE I

Stereochemistry of the thermolysis product **3**

Source	Reactant		Time at 200° (h)	Hydrocarbon product			% optical purity of **3**
	Optical purity*	Weight (mg)		Weight† (mg)	α_D^{25}	Calcd. max.‡	
1. Direct resolution	10·2% (*R*:*R*) $[\alpha]_D^{25}$ +61·5°‖	115	5	75	+0·018° ±0·002°	0·089°	20·3§
2. 84·3% *trans*	93·4% (*S*:*S*)	160	10	101·6	−0·240°¶ ±0·002°	0·940°	25·5
3. 84·3% *trans*	93·4% (*S*:*S*)	167	15	99·0	±0·002° −0·212°¶ ±0·002°	0·910°	23·2
4. 88·4% *trans*	50·6% (*S*:*S*)	128·4	10	74·0	+0·085°¶ ±0·002°	0·385°	22·1

*Calculated on the basis of $[\alpha]_D^{25}$ +607°.
†Represents 95, 94, 87, and 84% of theoretical amount of C_5H_{10}.
‡Calculated using $[\alpha]_D^{25}$ for 3 of 46°, if all 3 from optically pure 1 was active (see Experimental).
§Rotation taken in methanol; value 46° from diglyme assumed.
‖Diluted with racemic material.
¶Diglyme used as solvent.

Crude *trans*-3,5-dimethylpyrazolidine (6 g, 0.06 mole) was dissolved in ether (50 ml) and then added to a solution of (+)-10-camphorsulfonic acid (25 g, 0.11 mole) in ether (1500 ml). The reaction mixture containing the salt was stirred at room temperature for 2 h and the solids were separated by filtration (about 20 g). The salt was dissolved in methanol (300 ml) and ether (1500 ml) was added to precipitate an impurity having a wide melting point range, from 195–210°. The bulky filtrate was evaporated to dryness on a rotary evaporator and the residue was dissolved in a minimum volume of methanol, and ether (400 ml) was added to precipitate the salt (6 g, m.p. 120–125°). Dissolution of this substance in methanol (10 ml) and reprecipitation by ether gave 3.5 g of the salt m.p. 128–132°. Recrystallizations were repeated until the m.p. was found to be constant at 135–137°. The n.m.r. spectrum of the salt in deuteriochloroform indicated that the pyrazolidine and the sulfonic acid were present in the ratio 1:2 respectively.

The salt was decomposed with aqueous potassium carbonate solution until the solution became basic and it was then extracted three times with ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The product was oxidized by mercuric oxide to the 1-pyrazoline, which was separated by g.l.c. on a 20 ft column of 10% Uconinsoluble on Fluoropak; $[\alpha]_D^{25}$ +605° (CH_3OH, *c*, 7.5 × 10^{-3} g/ml).

Larger quantities of **1** were prepared from the active glycol as described below.

R(−)-4-Hydroxy-1-pentene and S(+)-4-Hydroxy-1-pentene

4-Hydroxy-1-pentene was prepared by the method of Whitmore (12) from allyl bromide and acetaldehyde. This compound was converted to its acid phthalate ester and resolved through its brucine salt according to the procedure of Levene (6*c*).

The acid phthalate ester (crude, 130 g) was dissolved in warm acetone (50 ml) and then added to a suspension of brucine (200 g) in warm acetone (700 ml). The solution thus obtained was filtered and slow crystallization was allowed to occur at room temperature after it was seeded with the proper diastereomeric crystal. The crystals thus obtained had a m.p. of 144–146°; yield 140 g. Three more recrystallizations in progressively larger volumes of acetone gave a product having m.p. 148–149°, yield 125 g. The alcohol was recovered from the salt in about 90% yield.

The *S*(+)-alcohol corresponded to an optical purity of 93.4% (6). The *R*(−)-alcohol obtained from the mother liquor had an optical purity of 50.6%.

2,4-Pentanediol

This compound was prepared from 4-hydroxy-1-pentene, following the method of Brown and Geoghegan (7).

Starting with 4-hydroxy-1-pentene (17.2 g, 200 mmole) and mercuric acetate (64 g, 200 mmole) dissolved in a mixture of water (200 ml) and tetrahydrofuran (THF) (200 ml), the oxymercuration was conducted for 12 min at room temperature. A sodium hydroxide solution (200 ml, 3 *M*) was added, followed by a sodium borohydride solution (200 ml of 0.5 *M* $NaBH_4$ in 3 *M* sodium hydroxide). The reaction mixture was saturated with sodium chloride and the THF layer separated. The aqueous layer was extracted three times with THF (100 ml) and the combined THF solutions were dried over anhydrous potassium carbonate. Removal of the solvent and distillation gave the glycol (16 g, 80%), b.p. 70–74°/3mm. Analysis of the diol by g.l.c. on a polyethyleneimine column gave the ratio of the *active* to *meso* isomers.

R(−)-4-hydroxy-1-pentene of 50.6% optical purity gave the diol mixture of α_D^{25} −21.1° (methanol; *c*, 4.43 × 10^{-2} g/ml). Since the percentage of the *active* form was 71.6 ± 0.2%, the minimum rotation of (*2R*:*4R*)-(−)-2,4-pentanediol is $[\alpha]_D^{25}$ −58.3°.

S(+)-4-hydroxy-1-pentene of 93.4% optical purity gave the diol mixture of $[\alpha]_D^{25}$ +35.8° (methanol; *c*, 2.5 × 10^{-2} g/ml). Since the *active* form in the mixture was 64.8 ± 0.3%, the minimum rotation of (*2S*:*4S*)-(+)-2,4-pentanediol is +59.1°.

2,4-Dibromopentane

This compound was prepared by the method of Pritchard and Vollmer (6) by the action of phosphorus pentabromide on 2,4-pentanediol. A sample of *(2S:4S)*-(+)-2,4-pentanediol of 93.4% optical purity gave the 2,4-dibromopentane $[\alpha]_D^{25}$ +65.1° (CCl_4; *c*, 1.5×10^{-2} g/ml).

Analysis of the dibromide by g.l.c. using a Carbowax 20M column indicated the *active* form to be 71.2 ± 0.5%, thus *(2R:4R)*-(+)-2,4-dibromopentane has $[\alpha]_D^{25}$ +97.9°.

3,5-Dimethyl-1-pyrazoline (1)

This compound was prepared as previously described (2). The ratio of the *trans* to *cis* isomers was determined by measuring the absorptions due to the methyne protons at C-3 and C-5 in the 100 MHz n.m.r. spectrum of the sample.

This ratio was verified by the analysis of cyclopropane and olefin products obtained by the thermal decomposition of the mixture. Since the product ratios from each of pure *cis*- and *trans*-3,5-dimethyl-1-pyrazolines are known, the ratio actually obtained can be used to solve the percentage of individual components present in the mixture. The values from n.m.r. and g.l.c. agreed within 1%. The value from n.m.r. was used to calculate the stereospecifity of the thermal decomposition and optical rotation. The *active* dihalide reacts more readily than the *meso* compound and thus there is a slight enrichment in the percent *trans*.

(*a*) The dihalide sample derived from *(S)*-(+)-4-hydroxy-1-pentene of 93.4% optical purity produced a sample of 3,5-dimethyl-1-pyrazoline (84.3 ± 0.5% *trans* by n.m.r.; 84.8 ± 1.0% by g.l.c.) α_D^{25} −0.851° (CH_3OH; *c*, 1.83×10^{-3} g/ml); $[\alpha]_D^{25}$ −588°.

(*b*) The dihalide sample derived from *(R)*-(−)-4-hydroxy-1-pentene of 50.6% optical purity produced a sample of 3,5-dimethyl-1-pyrazoline (88.4 ± 0.8% *trans* by n.m.r.; 88.3 ± 0.3% by g.l.c.) α_D^{25} +0.623° (CH_3OH; *c*, 1.83×10^{-3} g/ml); $[\alpha]_D^{25}$ +630°.

(*c*) The dihalide sample derived from *(R)*-(−)-4-hydroxy-1-pentene of 31% optical purity produced a sample of 3,5-dimethyl-1-pyrazoline (85% *trans* by n.m.r.) $\alpha_D^{25°}$ +0.366° (CH_3OH; *c*, 2.21×10^{-3} g/ml); $[\alpha]_D^{25}$ +603°.

The average value of 607 ± 21° agrees with the value of 605° obtained by direct resolution from the pyrazolidine.

Thermal Decomposition of Optically Active trans-3,5-Dimethyl-1-pyrazoline

Decomposition of the optically active compound was affected by transferring it to a glass bulb with a break-seal and then degassing the system thoroughly before sealing. The pressure at the temperature of decomposition varied from 1–2 atm. After the decomposition was over, the container was connected to a vacuum line and the seal broken. Nitrogen was pumped off and the other products trapped by liquid nitrogen. This was later transferred to a system suitable for g.l.c. analysis. The whole mixture was passed through a 20 ft column of Carbowax 20M to ensure that only the hydrocarbon products were collected. Hydrocarbon products collected were later weighed and transferred into 1 ml of diglyme and their optical rotation measured.

The column marked calculated maximum for the hydrocarbon product in Table I was calculated using $[\alpha]_D^{25}$ +46° for *trans*-1,2-dimethylcyclopropane (10). The theoretical maximum of *active-trans*-1,2-dimethylcyclopropane present was calculated from the known amount of optically pure **1** that was present in the sample on the basis that all of the 25.6% of **3** produced would be optically active.

Controls

A sample of *(3S:5S)*-(−)-3,5-dimethyl-1-pyrazoline, containing 15.6% of the *cis* isomer, was heated to 205° for 10 min (63% reaction for the *trans* isomer and 48.4% reaction for the *cis* isomer (2)) then quenched. The n.m.r. spectrum of the unreacted material indicated 81 ± 1% *trans* and 19 ± 1% *cis*. The values calculated from the rate data are 80% *cis* and 20% *trans*. The original sample had a rotation of $[\alpha]_D^{25}$ −588°, the recovered sample had a rotation of $[\alpha]_D^{25}$ −592°. Thus the reactants do not isomerize under the reaction conditions. *Active-trans*-1,2-dimethylcyclopropane was similarly recovered unchanged.

Acknowledgments

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