

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

1-Phenylcyclohexene from *trans*-2-Phenylcyclohexyltrimethylammonium Hydroxide by *cis* Elimination¹BY ARTHUR C. COPE, GLENN A. BERCHTOLD² AND DANIEL L. ROSS

RECEIVED MARCH 3, 1961

trans-1-Dimethylamino-2-phenylcyclohexane-3,3,6,6-*d*₄ has been synthesized from butadiene-1,1,4,4-*d*₄, obtained from the base-catalyzed equilibration with deuterium oxide and subsequent pyrolysis of 2,5-dihydrothiophene-1,1-dioxide (butadiene sulfone). The quaternary base derived from this amine decomposed thermally forming 1-phenylcyclohexene without loss of deuterium, proving that this Hofmann elimination is a *cis* elimination in which only the β -hydrogen atom in the 2(benzyl)-position is lost.

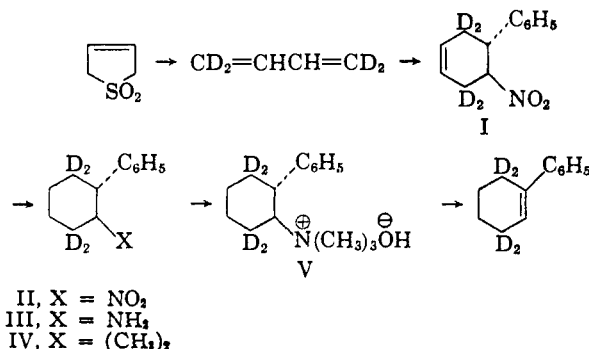
The thermal degradation of *trans*-2-phenylcyclohexyltrimethylammonium hydroxide has been reported to give pure 1-phenylcyclohexene.³ It was suggested that 3-phenylcyclohexene is first formed by a normal *trans* elimination and that this product then undergoes a base-catalyzed prototropic shift to the more stable conjugated system. Examples of such a rearrangement which had been observed previously are the formation of 1,3-pentadiene in the exhaustive methylation of piperidine⁴ and the isolation of propenylbenzene from the exhaustive methylation of 3-phenylpropylamine.⁵

A subsequent study indicated, however, that under the conditions of the reaction the rate of isomerization of 3-phenylcyclohexene is sufficiently slow so as to preclude this route, and a direct *cis* elimination of the hydrogen atom attached to the benzyl carbon atom was proposed.^{6,7}

More recently, Cristol and Stermitz have studied the reaction of *cis*- and *trans*-2-phenylcyclohexyltrimethylammonium iodide with ethanolic potassium hydroxide and observed second-order elimination of the *trans* compound to give an olefin mixture containing approximately 97% of the conjugated isomer.⁸ Bordwell and co-workers have observed analogous *cis* eliminations in cyclic systems.^{9,10} For example, *trans*-2-(*p*-tolylsulfonyl)-cyclohexyl *p*-toluenesulfonate underwent bimolecular *cis* elimination to give 1-(*p*-tolylsulfonyl)-cyclohexene, and the possibility that the reaction proceeds by a two-step mechanism involving an intermediate carbanion was considered unlikely on the basis of kinetic data.^{6,9}

In order to establish which hydrogen atom is eliminated to form 1-phenylcyclohexene in this reaction, *trans*-2-phenylcyclohexyl-3,3,6,6-*d*₄-trimethylammonium hydroxide (V) was prepared and thermally decomposed.

Equilibration of 2,5-dihydrothiophene-1,1-dioxide with deuterium oxide in dioxane containing a trace of anhydrous potassium carbonate gave the deute-



rated sulfone containing 3.99 atoms of deuterium per molecule. Pyrolysis of the sulfone yielded butadiene-1,1,4,4-*d*₄ which was shown by mass spectrographic analysis to consist of 95.5% tetradeuterated and 4.5% trideuterated species. The deuterated butadiene underwent a Diels-Alder reaction with β -nitrostyrene as previously described for the undeuterated compound^{11,12} to produce *trans*-4-nitro-5-phenylcyclohexene-3,3,6,6-*d*₄ (I) (3.93 atoms of deuterium per molecule). Catalytic hydrogenation of I in acetic acid in the presence of 10% palladium-on-carbon produced III but resulted in considerable scrambling of the positions of deuterium substitution. Consequently, an alternate route was undertaken. Hydroboration of I and hydrolysis of the resulting trialkylborane with acetic acid produced II (4.00 atoms of deuterium per molecule). This hydrolysis was carried out at room temperature to prevent any isomerization of the trialkylborane. Reduction of II with stannous chloride in hydrochloric acid produced III (3.86 atoms of deuterium per molecule). Mass spectrographic analysis of III showed it to consist of 1% dideuterated species, 6% trideuterated species, 93% tetradeuterated species and less than 1% pentadeuterated species. The tertiary amine IV (3.99 atoms of deuterium per molecule) was prepared from III by methylation with formic acid and formaldehyde. Reaction with methyl iodide converted IV to the methiodide (4.00 atoms of deuterium per molecule).

Pyrolysis of the quaternary base V proceeded vigorously at 60–80° at 1 mm. Gas chromatography of the distillate, before separation of the neutral and basic products, showed the hydrocarbon fraction to contain only 1-phenylcyclohexene; 3-phenylcyclohexene was not present.

(11) D. Nightingale and V. Tweedie, *ibid.*, **66**, 1968 (1944).(12) C. F. H. Allen, A. Bell and J. W. Gates, Jr., *J. Org. Chem.*, **8**, 373 (1944).

(1) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

(2) Postdoctoral Fellow, 1959–1960.

(3) R. T. Arnold and P. N. Richardson, *J. Am. Chem. Soc.*, **76**, 3649 (1954).(4) A. W. Hofmann, *Ber.*, **14**, 659 (1881).(5) L. Senfters and J. Tafel, *ibid.*, **27**, 2309 (1894).(6) F. G. Bordwell and R. J. Kern, *J. Am. Chem. Soc.*, **77**, 1141 (1955), footnote 14.(7) J. Weinstock and F. G. Bordwell, *ibid.*, **77**, 6706 (1955).(8) S. J. Cristol and F. R. Stermitz, *ibid.*, **82**, 4692 (1960).(9) J. Weinstock, R. G. Pearson and F. G. Bordwell, *ibid.*, **76**, 4748 (1954).(10) F. G. Bordwell and M. L. Peterson, *ibid.*, **77**, 1145 (1955).

Purification of the olefin fraction afforded pure 1-phenylcyclohexene-3,3,6,6- d_4 (in 81–91% yield) which analyzed for 3.86 atoms of deuterium per molecule by falling drop analysis; mass spectrographic analysis of this olefin showed it to consist of less than 1% dideuterated species, 4.8% trideuterated species and 94.3% tetradeuterated species. It may therefore be concluded that the thermal degradation of V proceeds with direct loss of the *cis*-C₂-hydrogen atom during the elimination reaction and that the possibility of formation and subsequent isomerization of 3-phenylcyclohexene has been excluded.

It appears that a combination of steric and electronic effects are required to favor this *cis* E2 elimination. In order for a *trans*- β -elimination to occur, both the phenyl and trimethylammonium groups would be required to assume axial conformations, a factor which should considerably heighten the energy of the transition state for normal elimination. The presence of the phenyl group increases the acidity of the *cis*- β -hydrogen atom. However, that the electronic effect of the phenyl group cannot be the sole factor is shown by the Hofmann elimination of *erythro*- and *threo*-1,2-diphenylpropylamine.¹³ Both isomers were studied separately and found to undergo stereospecific *trans* elimination. Similarly, steric effects alone will not account for this reversal of the usual mechanism, for the decomposition of menthyl-trimethylammonium hydroxide leads to a predominance of 2-menthene.¹⁴

Experimental¹⁵

2,5-Dihydrothiophene-2,2,5,5- d_4 -1,1-dioxide.—A mixture of 100 g. of 2,5-dihydrothiophene-1,1-dioxide and 1.0 g. of anhydrous potassium carbonate was dissolved in a mixed solvent of 50 ml. of anhydrous dioxane and 100 g. of deuterium oxide. The solution was kept at room temperature for 48 hours, and the solvent was then removed by freeze drying. This equilibration procedure was repeated five times, the solution being filtered prior to the final freeze drying. The white powdery residue was recrystallized from 2.4 parts of 2:1 tetrahydrofuran-pentane; m.p. 66.8–67.3°; deuterium analysis: 3.99 atoms of deuterium per molecule.

Anal. Calcd. for C₄H₂D₄SO₂: C, 39.32; S, 26.24. Found: C, 39.32; S, 26.32.

Butadiene-1,1,4,4- d_4 .—2,5-Dihydrothiophene-2,2,5,5- d_4 -1,1-dioxide was thermally decomposed by a procedure similar to that of Grummitt, Ardis and Fick¹⁶ for the undeuterated compound. A 39.1-g. sample of the sulfone was placed in a round-bottomed flask fitted with a nitrogen inlet and connected in series through two absorption traps containing 200 ml. of 10% aqueous sodium hydroxide solution and a Drierite tube to a gas collecting vessel cooled in liquid nitrogen. Nitrogen was slowly passed through the system and the sulfone was heated. Decomposition occurred at 130–162° over a period of approximately 1 hour.

(13) D. J. Cram, F. D. Greene and C. H. Depuy, *J. Am. Chem. Soc.*, **78**, 790 (1956).

(14) A. C. Cope and E. Acton, *ibid.*, **80**, 355 (1958). The actual composition of the olefin obtained from this reaction (86% 2-menthene and 14% 3-menthene) suggests that some *cis* elimination may occur in this system.

(15) Melting points are corrected and boiling points are uncorrected. All deuterium analyses indicating the number of atoms of deuterium per molecule were determined by the falling drop method; these analyses were performed by Mr. Josef Nemeth, Urbana, Ill. Mass spectrographic analyses were determined with a C.E.C. type 21-103C instrument with a heated inlet system. We are indebted to Drs. K. Biemann and J. Seibl for these analyses.

(16) O. G. Grummitt, A. E. Ardis and J. Fick, *J. Am. Chem. Soc.*, **72**, 5167 (1950).

The trap was connected through the drying tube to a small tared steel cylinder and the system was evacuated to 1 mm. The cylinder was cooled in liquid nitrogen and the trap containing the butadiene was allowed to warm to room temperature. The yield of butadiene-1,1,4,4- d_4 was 16.5 g. (88%); deuterium analysis: 95.5% tetradeuterated species and 4.5% trideuterated species.

***trans*-4-Nitro-5-phenylcyclohexene-3,3,6,6- d_4 (I).**—Butadiene-1,1,4,4- d_4 (16.5 g., 0.28 mole), β -nitrostyrene (26.8 g., 0.18 mole) and 35 ml. of toluene were heated in a glass-lined bomb at 150° for 5 hours. The crystalline product was separated from the residual liquid by suction filtration. Additional product was obtained by evaporation of the solvent and fractional recrystallization from pentane. A final recrystallization from methanol yielded 15.5 g. (42%) of product, m.p. 104.8–105.5°; deuterium analysis: 3.93 atoms of deuterium per molecule.

***trans*-1-Nitro-2-phenylcyclohexane-3,3,6,6- d_4 (II).**—Diborane, generated by the dropwise addition of a solution of 2.85 g. of sodium borohydride in 60 ml. of diglyme to a solution of 14.2 g. of boron trifluoride etherate in 20 ml. of diglyme, was slowly passed into a solution of 49.0 g. of *trans*-4-nitro-5-phenylcyclohexene-3,3,6,6- d_4 in 400 ml. of diglyme. The diborane was generated over a period of 3 hours. Nitrogen was slowly passed through the system for 2 hours. The mixture was stirred for 18 hours, treated with 60 ml. of glacial acetic acid and stirred for an additional 72 hours. The mixture was poured into 750 ml. of ether; the ethereal solution was extracted four times with 200-ml. portions of water, twice with 200-ml. portions of 10% aqueous sodium bicarbonate and once with 100 ml. of water. The organic layer was dried over sodium sulfate and concentrated on a rotary evaporator to give an oily residue. The residue was extracted with four 200-ml. portions of boiling hexane. Evaporation of the hexane extracts and recrystallization from methanol yielded 5.14 g. (10%) of product, m.p. 120.1–121.4°; deuterium analysis: 4.00 atoms of deuterium per molecule.

***trans*-1-Amino-2-phenylcyclohexane-3,3,6,6- d_4 (III).**—*trans*-1-Nitro-2-phenylcyclohexane-3,3,6,6- d_4 (5.06 g., 0.0242 mole) was dissolved in 45 ml. of 95% ethanol and added to a solution of 45.4 g. of stannous chloride dihydrate in 30 ml. of concentrated hydrochloric acid. The solution was heated under gentle reflux for 8 hours. Evaporation of the solvent under reduced pressure left a white solid residue which was mixed with 250 ml. of saturated aqueous potassium carbonate. The aqueous mixture was extracted four times with 100-ml. portions of ether. The extracts were combined and dried over potassium carbonate. Evaporation of the solvent gave 2.31 g. (53%) of product, m.p. 53.0–56.4°. Recrystallization from pentane raised the melting point to 57.9–59.1°; deuterium analysis: 3.83 atoms of deuterium per molecule; 1% dideuterated species, 6% trideuterated species, 93% tetradeuterated species and less than 1% pentadeuterated species.

***trans*-1-Dimethylamino-2-phenylcyclohexane-3,3,6,6- d_4 (IV).**—*trans*-1-Amino-2-phenylcyclohexane-3,3,6,6- d_4 (2.01 g., 0.0112 mole) was heated for 5 hours at 100° with a mixture of 3.0 g. of 98% formic acid and 3.0 g. of 40% formaldehyde. The mixture was treated with 4 ml. of concentrated hydrochloric acid and concentrated to a thick sirup under reduced pressure. The sirup was dissolved in 10 ml. of water and extracted twice with 10 ml. of pentane. The aqueous layer was made basic by the addition of 20% aqueous sodium hydroxide. The amine was extracted with four 100-ml. portions of ether and the extracts were dried over potassium hydroxide. The ether was removed under reduced pressure and the residue was distilled through a semi-micro column, yielding 1.78 g. (77%) of product, b.p. 112.5–114° (2 mm.); n_D^{20} 1.5273; deuterium analysis: 3.99 atoms of deuterium per molecule.

***trans*-2-Phenylcyclohexyl-3,3,6,6- d_4 -trimethylammonium Iodide.**—A solution of *trans*-1-dimethylamino-2-phenylcyclohexane-3,3,6,6- d_4 (1.50 g., 7.24 mmoles) in 15 ml. of ether was stirred with 1.50 ml. of methyl iodide for 3.5 hours, after which an additional 1.25 ml. of methyl iodide was added. After the solution had been stirred for 40 hours, the precipitated salt was collected by suction filtration, washed with ether and with pentane, and dried in vacuum. Recrystallization from 85:15 acetone-ethanol gave 2.34 g. (92%) of product, m.p. 231.4–232.9° dec.; deuterium analysis: 4.00 atoms of deuterium per molecule.

Decomposition of *trans*-2-Phenylcyclohexyl-3,3,6,6-*d*₄-trimethylammonium Hydroxide (V).—A solution of 1.00 g. of *trans*-2-phenylcyclohexyl-3,3,6,6-*d*₄-trimethylammonium iodide in 3.0 ml. of water and 6.0 ml. of methanol was stirred for 24 hours with freshly prepared silver oxide obtained from 0.970 g. of silver nitrate. The solution was filtered and the precipitate was washed until the filtrate was neutral. The filtrate was concentrated at 1.0 mm. at room temperature. The flask containing the quaternary base was attached to a series of two traps, the first cooled in Dry Ice-acetone, the second in liquid nitrogen. The pressure was reduced to 1 mm. and the flask was heated slowly to 60°, at which point decomposition began. The temperature was raised slowly to 80° over a period of 20 minutes. The pressure was then reduced to 0.05 mm. and the temperature was raised to 120° to distil all the olefin into the trap. The material in the Dry Ice-acetone trap was dissolved in 5 ml. of pentane. Gas chromatography of the pentane solution on 1,2,3-tris-(2-cyanoethoxy)-propane¹⁷ showed that there was no 3-phenylcyclohexene in

the solution. The pentane solution was washed with 10% hydrochloric acid¹⁸ and water and dried over Drierite. The bulk of the pentane was removed by distillation and the residue was purified by gas chromatography on Silicone oil¹⁷ to obtain 376 mg. (81%) of 1-phenylcyclohexene-3,3,6,6-*d*₄, *n*_D²⁰ 1.5651, λ_{max} 247 m μ (ϵ 11,390); deuterium analysis: 3.86 atoms of deuterium per molecule; mass spectrograph analysis: less than 1% dideuterated species, 4.8% tri-deuterated species and 94.3% tetradeuterated species.

(17) Gas chromatography columns were 8-mm. Pyrex tubes of 190-cm. length containing 30% by weight of liquid phase absorbant. The liquid phase absorbants employed were: Dow-Corning Silicone oil no. 550 on 60-80 mesh firebrick support (column temperature 170-180°) and 1,2,3-tris-(2-cyanoethoxy)-propane on 48-80 mesh firebrick support (column temperature 180°). Helium at 15 p.s.i. was the carrier gas and thermistors were employed for detecting sample peaks.

(18) Preliminary experiments showed that 3-phenylcyclohexene is not isomerized to 1-phenylcyclohexene by brief shaking of a pentane solution of the olefin with cold 10% hydrochloric acid.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

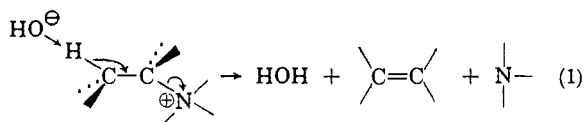
Mechanism of the Hofmann Elimination Reaction: Evidence that an Ylide Intermediate is not Involved in Simple Compounds¹

BY ARTHUR C. COPE,² NORMAN A. LEBEL,² PHYLIS T. MOORE³ AND WILLIAM R. MOORE

RECEIVED MARCH 3, 1961

The trimethylamine produced at the outset of pyrolyses of cyclohexylmethyl- β -*d*-trimethylammonium hydroxide (I) and ethyl- β -*d*-trimethylammonium hydroxide (II) has been shown to be deuterium-free. As the pyrolyses progressed, the trimethylamine evolved contained an increasing amount of deuterium as a result of isotope exchange (with the DOH formed) in the methyl groups of the quaternary ammonium hydroxides. Pyrolysis of II at *ca.* 170° while sweeping with a large excess of steam produced deuterium-free trimethylamine. The reaction of cyclohexylmethyl- β -*d*-trimethylammonium bromide and of octyl- β -*d*-trimethylammonium bromide with phenyllithium in ether resulted in the incorporation of deuterium in the trimethylamine that was formed (evidence for the ylide mechanism of this elimination, sometimes called the Wittig reaction).

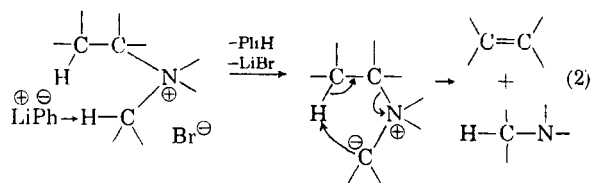
The Hofmann elimination reaction, the thermal decomposition of a quaternary ammonium hydroxide which gives an olefin and a tertiary amine, generally has been considered to be an E2 elimination.⁴ Thus the mechanism has been depicted as involving removal of a β -proton by hydroxide ion with simultaneous expulsion of the (forming) tertiary amine (eq. 1). This mechanism now has



been supported by recent studies which exclude two-step (β -carbanion) and α -elimination processes in the systems investigated.^{5,6}

Wittig and Polster found that trimethylalkylammonium bromides react with phenyllithium to give trimethylamine and an olefin, an over-all result similar to that of the Hofmann elimination.⁷ They suggested that the mechanism involved initial formation of an ylide followed by intramolecular

proton transfer from the β -carbon atom with resultant collapse to the observed products (eq. 2). This *cis*-ylide elimination requires a 5-membered cyclic transition state which closely resembles



the transition state for the thermal decomposition of an amine oxide.⁴ In view of the fact that several Hofmann eliminations are known in which there cannot be a β -proton *trans* to the ammonium group and since isotopic exchange experiments^{6,8} have established that ylides are formed under conditions similar to those employed for the Hofmann decomposition, an important question arises concerning the possibility that the Hofmann elimination, at least in part, follows the *cis*-ylide mechanism. Shiner and Smith noted that deuterium-free trimethylamine resulted from the decomposition of ethyl- β -*d*₃-trimethylammonium hydroxide in ethylene glycol at 130°. This result indicates that in this solvent the elimination does not involve ylide intermediates. However, this conclusion cannot be extended to the normal Hofmann reaction, pyrolysis of the quaternary ammonium

(1) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

(2) Postdoctoral Fellow, 1957.

(3) Postdoctoral Research Associate, 1959-1960.

(4) A. C. Cope and E. R. Trumbull in "Organic Reactions," Vol. XI, John Wiley and Sons, Inc., New York, N. Y., 1960.

(5) W. von E. Doering and H. Meislich, *J. Am. Chem. Soc.*, **74**, 2099 (1952).

(6) V. G. Shiner and M. L. Smith, *ibid.*, **80**, 4095 (1958).

(7) (a) G. Wittig and R. Polster, *Ann.*, **699**, 13 (1956). (b) G. Wittig and T. F. Burger, *ibid.*, **632**, 85 (1960).

(8) W. von E. Doering and A. K. Hofmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).