

[CONTRIBUTION FROM THE BIOMEDICAL RESEARCH GROUP OF LOS ALAMOS SCIENTIFIC LABORATORY AND THE CHEMISTRY DEPARTMENTS OF NORTHWESTERN UNIVERSITY AND ILLINOIS INSTITUTE OF TECHNOLOGY]

Reactions of 1,2-Epoxydes with Salts of Organic Bases. II. Cyclohexene Oxide^{1,2}

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trans-2-Hydroxycyclohexyl quaternary salts of pyridine, 3-picoline and isoquinoline were prepared from cyclohexene oxide and from *trans*-2-hydroxycyclohexyl *p*-toluenesulfonate. The very poor yield of quaternary salt from the reaction of cyclohexene oxide with pyridinium iodide has suggested a general mechanistic scheme involving cyclohexenoxonium ion and cyclohexene halohydrin. The quaternary iodides have been hydrogenated to the corresponding tertiary amines. Configurations have been established as *trans* through preparation of authentic 1-(*cis*- and *trans*-2-hydroxycyclohexyl)-piperidines.

It has been demonstrated that styrene oxide reacts with strong acid salts of heterocyclic tertiary amines to give isomeric 2-hydroxyphenethyl quaternary salts.³ Plausible intermediates accounting for these products are the styrenoxonium ion and the "halohydrins" formed from it by reaction with the anion of the acid used.

This reaction has now been extended to cyclohexene oxide, allowing a study where interest is centered on the geometrical configuration of the products instead of positional isomerism as in the case of styrene oxide.

Cyclohexene oxide (I) reacts with perchloric acid salts (IIa) of pyridine, 3-picoline and isoquinoline to give *trans*-2-hydroxycyclohexyl quaternary perchlorates (IIIa) in quantitative yields. Treatment with sodium iodide in acetone easily converted the perchlorate salts to the corresponding iodides (IIIc). Pyridinium *p*-toluenesulfonate and I gave a quaternary salt which was transformed to 1-(*trans*-2-hydroxycyclohexyl)-pyridinium iodide.

The *p*-toluenesulfonate salts of this series (IIIb) were also prepared from the reaction of the corresponding amine base with *trans*-2-hydroxycyclohexyl *p*-toluenesulfonate (IVb).⁴ The stereochemical result strongly suggests that the reaction proceeds through the cyclohexenoxonium ion.⁵

In a striking departure from the previously reported behavior of styrene oxide in this reaction,³ I and pyridinium iodide gave only 10% of the quaternary iodide, along with a large amount of cyclohexanone. A similar product mixture was obtained by heating *trans*-2-iodocyclohexanol (IVc)⁶ with pyridine, a very different result from that arrived at by the use of IVb.

All the reactions presented may be considered to fit into the scheme shown in Fig. 1 wherein a competition reaction is set up between the amine and the anion for the cyclohexenoxonium ion. The first path yields a *trans*-2-hydroxycyclohexyl quaternary salt (III) and the second a *trans*-2-substituted cyclohexanol (IV) where the substituent is the anion of the acid used. This latter path may be reversible or the generalized halohydrin (IV) may enter into an elimination reaction to give cyclohexanone.

(1) Work done in part under the auspices of the U. S. Atomic Energy Commission.

(2) Supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service.

(3) L. C. King, N. Berst and F. N. Hayes, *THIS JOURNAL*, **71**, 3498 (1949).

(4) R. Criegee and H. Stanger, *Ber.*, **69**, 2754 (1936).

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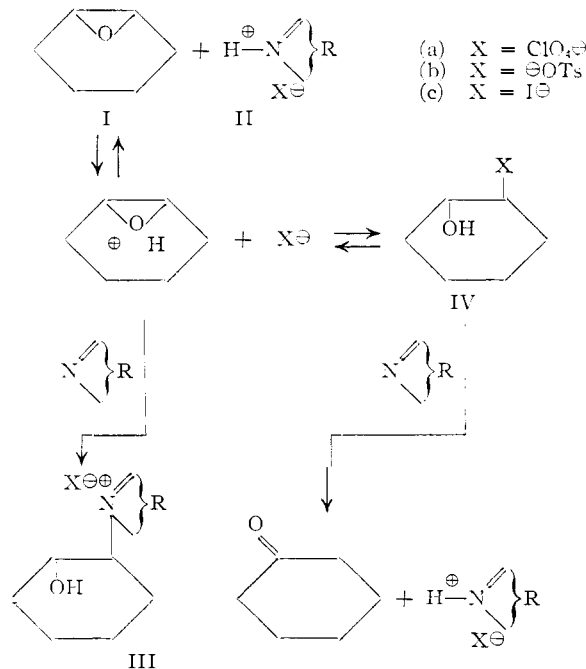


Fig. 1.

The results of the reaction of cyclohexene oxide with pyridinium iodide are quite reasonable on this basis since iodide is at the same time the most nucleophilic and the least easily displaced of the three anions used. This allows *trans*-2-iodocyclohexanol to be formed rapidly and almost irreversibly, subsequently giving rise to cyclohexanone. In the reaction of the pyridinium *p*-toluenesulfonate, any *trans*-2-hydroxycyclohexyl *p*-toluenesulfonate formed will react with pyridine, as separately demonstrated, to give the quaternary salt.

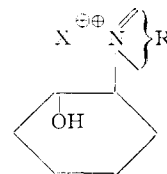
The *trans*-2-hydroxycyclohexyl iodide salts of pyridine, 3-picoline and isoquinoline were hydrogenated over platinum and then treated with base to yield the corresponding free tertiary amines. The isoquinolinium salt gave a 1,2,3,4-tetrahydroisoquinoline. The piperidine compound was identical in properties to the 1-(*trans*-2-hydroxycyclohexyl)-piperidine first reported by Kusner.^{7,8}

In order to place on a more firm foundation the assignment of *trans* configuration to this series of compounds, both *cis* and *trans*-2-hydroxycyclohexylpiperidines were prepared by a new method. Pentamethylene iodide was allowed to react with

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(8) F. N. Hayes, H. K. Suzuki and D. E. Peterson, *THIS JOURNAL*, **72**, 4524 (1950).

TABLE I



	X ⁻	Yield, %	M. p., °C.	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
Pyridine	ClO ₄	100 ^a	122	C ₁₁ H ₁₆ ClNO ₅	47.57	47.57	5.81	5.68
Pyridine	OTs	100 ^b , 98 ^b	174-175	C ₁₃ H ₂₃ NO ₄ S	61.87	61.69	6.63	6.59
Pyridine	I	10 ^a , 71 ^c , 80 ^d	154	C ₁₁ H ₁₅ INO	43.29	43.26	5.28	5.40
3-Picoline	ClO ₄	100 ^d	99-100	C ₁₂ H ₁₅ ClNO ₅	49.40	49.62	6.22	6.32
3-Picoline	OTs	88 ^b	153	C ₁₃ H ₂₃ NO ₄ S	62.78	62.40	6.93	6.90
3-Picoline	I	71 ^c	144-145	C ₁₂ H ₁₈ INO	45.15	45.51	5.68	5.58
Isoquinoline	ClO ₄	..	^e
Isoquinoline	OTs	91 ^b	195-196	C ₂₂ H ₂₄ NO ₄ S	66.14	66.11	6.31	6.35
Isoquinoline	I	77 ^{c,f}	171-172	C ₁₅ H ₁₃ INO	50.71	50.69	5.11	5.15
Piperidine (<i>cis</i>)	g	52 ^b	89-90	C ₁₁ H ₂₁ NO	72.08	72.39	11.55	11.54
Piperidine (<i>trans</i>)	g	58 ^b	34-35
Piperidine (<i>trans</i>)	g	76 ^j	34-35
3-Pipecoline	g	62 ^j	(^b ₂ 102-103)	C ₁₂ H ₂₃ NO	73.04	72.97	11.75	11.90
1,2,3,4-Tetrahydroisoquinoline	g	61 ^j	46-48	C ₁₅ H ₂₁ NO	77.88	78.10	9.15	9.10

^a Directly from I. ^b Directly from IVb. ^c Metathetically from the perchlorate. ^d Metathetically from the *p*-toluenesulfonate. ^e Obtained as an oil which would not crystallize. ^f Calculated for over-all reaction from I. ^g Free tertiary amine. ^h From *cis*-2-aminocyclohexanol. ⁱ From *trans*-2-aminocyclohexanol. ^j From corresponding quaternary salt.

cis-⁹ and *trans*-2-aminocyclohexanol¹⁰ in a procedure patterned after that described by Luft.¹¹ The resulting piperidines were quite different and the lower melting *trans* compound was identical with the three preparations of 1-(*trans*-2-hydroxycyclohexyl)-piperidine referred to previously.

Experimental Part¹²

Reactions of Cyclohexene Oxide (I).—Equivalent quantities of I³ and the amine perchlorate (IIa) or *p*-toluenesulfonate (IIb) were dissolved in pyridine and heated on a steam-bath for an hour, after moderating the initial exothermic reaction. Treatment with dry ether gave oils which slowly crystallized. The products were recrystallized from acetone-ether.

The quaternary perchlorates (IIIa) and *p*-toluenesulfonates (IIIb) were converted to iodides (IIIc) by preparing saturated solutions in hot acetone and adding excess saturated sodium iodide in acetone. Cooling of the perchlorate solutions gave the crystalline iodides. Immediate filtration of the warm *p*-toluenesulfonate solutions is necessary in order to remove the insoluble sodium *p*-toluenesulfonate. The data for the products are listed in Table I.

Reactions of *trans*-2-Hydroxycyclohexyl *p*-Toluenesulfonate (IVb).⁴—In each case, IVb was dissolved in an excess of the base and the solution was heated on a steam-bath for 5 hr. Subsequent treatment with dry ether gave crystalline products which were recrystallized from alcohol-ether mixtures. The conversion of these to iodides, as above, gave products identical to those obtained from the perchlorate salts.

Reaction of Cyclohexene Oxide (I) with Pyridinium Iodide and *trans*-2-Iodocyclohexanol (IVc) with Pyridine.—A mixture of 10.35 g. of pyridinium iodide and 4.9 g. of cyclohex-

ene oxide (I) was heated on a steam-bath for 25 hr. The addition of dry ether threw out 11.0 g. of brown crystals, m. p. 135-200°. A Volhard iodide analysis gave 58.40% I⁻, from which yields of pyridinium iodide and 1-(*trans*-2-hydroxycyclohexyl)-pyridinium iodide were calculated to be 90 and 10%, respectively. Heating with acetone separated the product into a large insoluble fraction identified as pyridinium iodide, m. p. 175-190°, and a small soluble fraction, m. p. 152-153°, identical with 1-(*trans*-2-hydroxycyclohexyl)-pyridinium iodide. The ether solution from above was evaporated on a steam-bath and the residual liquid was treated with 10 g. of semicarbazide hydrochloride and 15 g. of sodium acetate in 50 ml. of 70% alcohol. Warming for 4 hr., followed by long cooling, gave white crystals weighing 4.4 g. (57%), m. p. 166°, corresponding to cyclohexanone semicarbazone.¹⁴

A solution of 11.5 g. of *trans*-2-iodocyclohexanol⁶ (IVc) in 10 ml. of pyridine was heated for 7 hr. and then treated with ether in the same manner as before. The iodide analysis of 58.85% corresponded to yields of 89% pyridinium iodide and 8% 1-(*trans*-2-hydroxycyclohexyl)-pyridinium iodide. The ether extracts produced 3.5 g. (45%) of cyclohexanone semicarbazone, m. p. 166°.

Hydrogenation of Quaternary Iodides.—Solutions of the salts in 50% aqueous methanol were hydrogenated at room temperature in a low-pressure apparatus using platinum oxide. Gas absorption was complete in a few hours, whereupon the catalyst was separated and the solution was evaporated to remove most of the methanol. Treatment with excess potassium hydroxide yielded an oil layer which was extracted with ether. Distillation at reduced pressures gave the desired amines (Table I).

Reaction of Aminocyclohexanols with Pentamethylene Iodide.—Equivalent quantities of the aminocyclohexanol and pentamethylene iodide along with excess anhydrous potassium carbonate were placed in acetone and the mixture was refluxed for 4 hr. with good stirring. Water was added and the resulting oil layer was extracted with ether. Distillation under reduced pressure gave the desired hydroxycyclohexylpiperidines. The products are reported in Table I.

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