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ENANTIOMERIC SELECTION VIA 1,3-ELIMINATION. A SIMULTANEOUS KINETIC RESOLUTION OF HALOHYDRINS AND EPOXIDES

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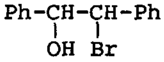
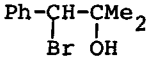
1,2-Dehydrohalogenation of β-halogenoethylsulphoxides promoted by alkaloids represents a convenient route to chiral sulphoxides.[1] Both starting material and product can be obtained partially resolved. We wish to report now that the same type of process which was applied to the sulphur compounds can be successfully used to prepare simultaneously two important classes of chiral compounds, i.e. halohydrins and epoxides.

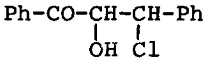
When racemic halohydrins (I)—(V) were allowed to react with an insufficient amount of (-)-quinine a 1,3-elimination took place leading to the corresponding epoxides (VI)—(X) with an enantiomeric excess in the range 12—35%.

erythro  (I)

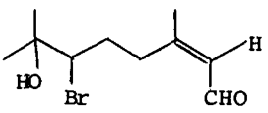
$\mathrm{Ph{-}\underset{OH}{CH}{-}\underset{Br}{CH}{-}Ph}$

 (II)

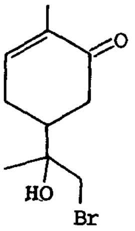
$\mathrm{Ph{-}\underset{Br}{CH}{-}\underset{OH}{C}Me_2}$

erythro  (III)

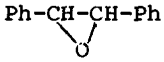
$\mathrm{Ph{-}CO{-}\underset{OH}{CH}{-}\underset{Cl}{CH}{-}Ph}$



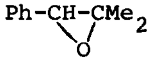
(IV)



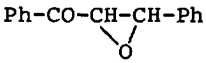
(V)

trans  (VI)

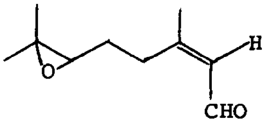
$\mathrm{Ph{-}\underbrace{CH{-}CH}_{O}{-}Ph}$

 (VII)

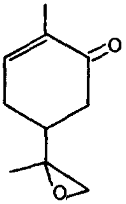
$\mathrm{Ph{-}\underbrace{CH{-}C}_{O}Me_2}$

trans  (VIII)

$\mathrm{Ph{-}CO{-}\underbrace{CH{-}CH}_{O}{-}Ph}$



(IX)

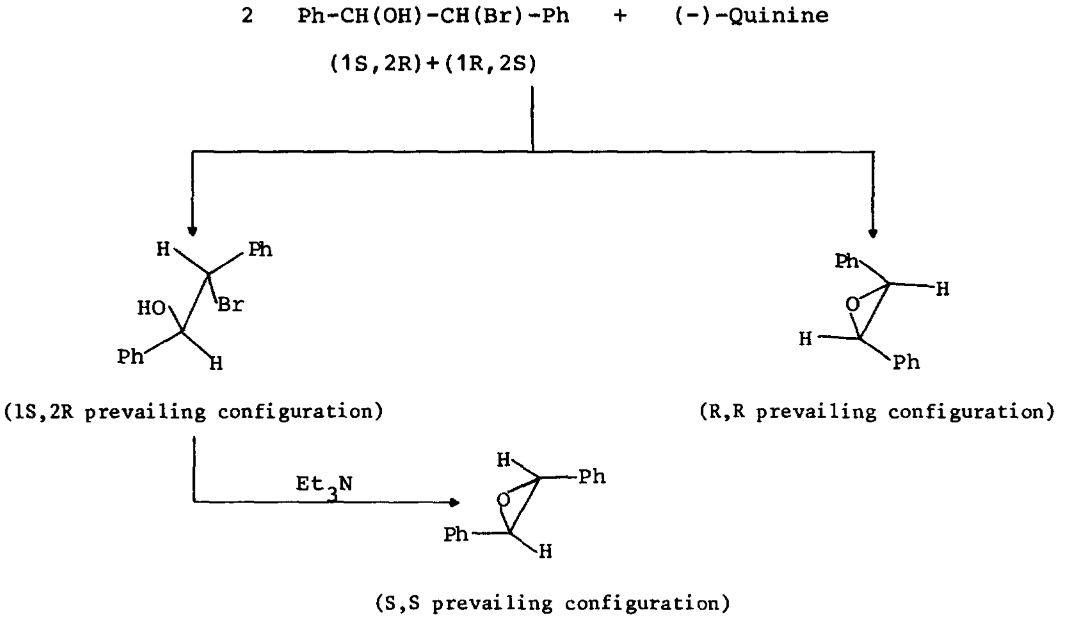


(X)

The results (see Table) can be considered satisfactory when a comparison is made with other methods which are most frequently based upon oxidation processes.[2] However, the procedure here reported offers the unique advantage that at the same time the unconverted halohydrins can be recovered easily and they are found enriched in the less reactive optical isomer.

The enantiomeric excess (10-30%) for the halohydrins was obtained by converting them into epoxides by means of an achiral base (*e.g.* Et_3N, *t*-BuO$^-$,NaOH). The method besides giving the required information does represent a convenient route to partially resolved epoxides with the prevailing isomer having a configuration opposite to that obtained directly during the process promoted by the chiral base. The procedure adopted which permits an easy entry to *three* optical active compounds is outlined in the following Scheme for the case of *erythro* 2-bromo-1,2-diphenylethanol.

SCHEME


2 Ph-CH(OH)-CH(Br)-Ph + (-)-Quinine

(1S,2R)+(1R,2S)

(1S,2R prevailing configuration)

(R,R prevailing configuration)

(S,S prevailing configuration)

Since the reactions were allowed to reach **half** -completion similar enantiomeric enrichments would be expected for the product and the unconverted reactant.[1] The deviations from this expectation in the reported data are not large. The differences observed can be justified by taking into account experimental errors and also considering the participation of side reactions. For instance, racemization of the halohydrin (II) may occur during the main process or the work up. Furthermore, participation of 1,2-elimination was revealed for compounds (I) and (III). Actually, in the latter case 1,2-dehydrohalogenation appeared to prevail

TABLE

Reactions between (-)-quinine and various halohydrins in refluxing benzene[a].

Racemic starting materials	Recovered substrates		Products		
	$[\alpha]_D^{25}$[b]	%e.e.[c]		$[\alpha]_D^{25}$[b]	%e.e.
(I)	-10.4	20.2	(VI)	+87.1	24.4[d]
(II)	-47.1	29.0	(VII)	+13.1	35.0[e]
(III)	-10.6[f]	9.1	(VIII)	+24.5[f,g]	11.8[h]
(III)	-18.0[f]	26.0	(VIII)	— [i]	—
(IV)[j,k]	+ 4.5	—	(IX)	+ 2.5	—
(V)[j,l]	+ 0.3[m]	—	(X)	+ 2.6[m]	—

[a] Concentrations of substrates and (-)-quinine were in the range $1\cdot10^{-2}$-$1\cdot10^{-1}$M. A good balance between recovered and produced materials was obtained.

[b] Optical rotations (unless otherwise indicated) were taken in benzene (c 2).

[c] The data were calculated after transformation of the recovered halohydrins into epoxides (see text).

[d] Evaluated from the $[\alpha]_D^{25}$=+357° reported in ref.3.

[e] Evaluated by N.M.R. in presence of tris [3-(trifluoromethylhydroxymethylene)-d-camphorato]Europium(III) (see ref.4).

[f] Optical rotations were taken in CH_2Cl_2 at 578 nm.

[g] Dehydrochlorination was performed in refluxing MeCN. Low yields (20-30%) of epoxide were obtained.

[h] Calculated by comparison with the data reported in ref.2d.

[i] Epoxide was not formed (see text). The reaction was performed at 25°.

[j] The substrates were prepared from the corresponding alkenes in dioxane/water 60/40 v/v with equimolecular amount of 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (see ref.5).

[k] The reported data refer to bromohydrin obtained from citral. Neral gave similar results.

[l] Racemic carvone was the starting material for the bromohydrin synthesis.

[m] Preferential formation of diastereoisomers is possible in this case.

over ring closure and benzoic acid very likely deriving from the resulting sensitive diketone[6] was detected among the products.

Finally, the last examples of halohydrins(IV)—(V)[7] and epoxides (IX)—(X)[7] derived from natural compounds emphasize the usefulness of the double kinetic resolution here reported.

In a typical experiment 1.00 g ($3.6\cdot10^{-3}$mole) of racemic erythro 2-bromo-1,2-diphenylethanol was dissolved in 200 ml of a solution $9\cdot10^{-3}$M of (-)-quinine in benzene. After refluxing for 50 hours water was added to the reaction mixture. Extraction with ether and evaporation of the solvent yielded a residue which was separated by means of t.l.c. (preparative scale, on silica gel; petroleum ether b.p.40-70 °/ethyl ether 7:3 as eluant) to give 0.28 g of trans stilbene oxide $[\alpha]_D^{25}$=+87.1, (R,R, prevailing configuration) and 0.44 g of 2-bromo-1,2-diphenylethanol (1S,2R prevailing configuration). 0.02 g of deoxybenzoin were also isolated. The partially resolved bromohydrin when treated with an excess of Et_3N in benzene gave trans-stilbene epoxide having $[\alpha]_D^{25}$=-75.4 (S,S prevailing configuration).

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