THE ASYMMETRIC BROMINATION OF ALKENES IN THE PRESENCE OF CINCHONA ALKALOIDS*

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Abstract—The bromination of several acyclic and cyclic alkenes in the presence of *Cinchona* alkaloids produces optically active dibromides. The influence of the configuration of the alkaloid and of the structure of the alkene on the stereochemical results of the reaction has been investigated. The possible mechanism of the asymmetric bromination, and its use as a method for determining the absolute configuration of vicinal dibromides are discussed.

THE work described is concerned with a new method for the preparation of optically active vicinal dibromides, based on the reaction of alkenes with bromine in the presence of asymmetric organic bases. This is an example of the type of asymmetric kinetic transformations,¹ in which symmetric reactants lead to partially resolved asymmetric products in the presence of an asymmetric catalyst. Previously described cases include the synthesis of active cyanohydrins catalysed by cellulose,² cyclodextrine,³ alkaloids,⁴ or that of esters from disubstituted ketenes and alcohols in the presence of alkaloids.⁵

It has been found that several olefins give dibromides showing low but definite optical rotations if they are treated with bromine in the presence of *Cinchona* bases. Tables 1 and 2 summarize the results of such asymmetric brominations for some simple aliphatic and cycloaliphatic alkenes. All the non-aromatic mono- and 1,2-disubstituted ethylenes that were tested gave dibromides exhibiting rotations which were well outside possible experimental errors, while 1,1-disubstituted, trisubstituted, as well as aryl or hydroxymethyl substituted compounds produced inactive dibromides. The observed optical rotations are not due to impurities, as shown by gas chromatographic analysis and by the fact that the rotation values do not change after repeated distillations.

When the alkenes are asymmetric, as in the case of 4-methyl-1-hexene, 4-methyland 4-t-butylcyclohexene, mixtures of diastereoisomeric dibromides are formed.

* Dedicated to Prof. Remo de Fazi on his 75th birthday. Part of this work was presented at the XIXth International Congress of Pure and Applied Chemistry. London, July (1963).

¹ E. L. Eliel, Stereochemistry of Carbon Compounds p. 65. McGraw-Hill, New York (1962).

² G. Bredig and F. Gerstner, *Biochem. Z.* 250, 414 (1932); G. Bredig F. Gerstner and H. Lang, *Ibid.* 282, 88 (1935).

⁸ F. Cramer and W. Dietsche, Chem. Ber. 92, 1739 (1959).

⁴⁴ G. Bredig and P. S. Fiske, *Biochem. Z.* **46**, 7 (1912); ^b V. Prelog and M. Wilhelm, *Helv. Chim. Acta* **37**, 1634 (1954).

⁵ H. Pracejus, *Liebigs Ann.* 634, 9 (1960); H. Pracejus and H. Mätje, J. Prakt. Chem. [4] 24, 195 (1964).

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This is particularly evident in the case of 4-t-butylcyclohexene (Ia + Ib) which, when brominated in the presence of cinchonine, gives a levorotatory product, which on distillation yields fractions with different specific rotations. IR analysis shows that they consist of mixtures containing different amounts of the *trans* dibromides II and III.⁶ The fact that all fractions are levorotatory indicates that the amount of IIa must be different from that of IIb, and that of IIIa different from that of IIIb, with the (-)-enantiomers predominating over the (+) ones.





The bromination of norbornene (IV) in the presence of cinchonine gives a mixture of the three products V, VI and VII, which have been previously reported for the reaction of IV with bromine and pyridine.⁷ Fractional distillation allows separation of pure 3-bromonortricyclene (V), which is dextrorotatory, from slightly levorotatory mixtures of the dibromides (VI and VII).

Cyclohexene and cyclopentene, which are easily obtained pure and do not pose problems with *cis-trans* isomerism and give higher-rotating dibromides than the acyclic olefins, were used for a more detailed investigation of the asymmetric brominations. Table 3 shows that optical yields are not affected too much by wide changes in the ratios of olefin to alkaloid, particularly in the case of cyclohexene.

Table 4 summarizes the results which were obtained in the brominations of cyclohexene in the presence of different asymmetric bases. *Cinchona* bases appear to be much more effective than other types of alkaloids: thus, nicotine and ephedrine

⁶ E. L. Eliel and R. G. Haber, J. Org. Chem. 24, 143 (1959).

⁷ J. D. Roberts, E. R. Trumbull, W. Bennett and R. Armstrong, J. Amer. Chem. Soc. 72, 3116 (1950); H. Kwart and L. Kaplan, Ibid. 76, 4072 (1954).

Run No.	Alkene	Alkaloid ^a	Molar ratio alkene:alkaloid	$\alpha_{\rm D}$ (temp)
1	cis-CH ₂ CH:CHCH ₂	С	6	+0.52° (16°)
2	cis-CH ₁ CH:CHCH ₁	Brucine	4	-0·10° (18°)
3	CH, C(CH, CH, CH, CH,	С	2	0.00°
4	CH, C(CH, CH, CH, CH,	D	2	0-00°
5	CH _a :CH(CH _a) _a	С	4	+0·12° (17°)
6	CH _s CH:C(CH _s) _s	D	4	0.00°
7	CH,:CHCH,CH,CH,	С	4	+0·98° (29°)
8	CH, CHCH, CH, CH,	D	2	+1·08° (29°)
9	CH ₁ :CH(CH ₁) ₂ CH ₁	С	1.2	+1·04° (16°)
10	CH, CHCH, CH(CH,)C, H,	С	3	+0·62° (17°)
11	CH.;CH(CH.),CH.	С	2	+0·86° (17°)
12	CH.:CHCH.OH	С	5	0.00°
13	C ₆ H ₆ CH:CH ₂	С	1	0.00°

TABLE 1.	OPTICAL	ROTATIONS	OF	DIBROMIDES	FROM	ALKENES

• C = cinchonine; D = dihydrocinchonine.

TABLE 2.	OPTICAL	ROTATIONS	OF	DIBROMIDES	OBTAINED	FROM	CYCLOALKENES
		IN THE	PRE	SENCE OF CI	NCHONINE		

Run No.	Cycloalkene	Molar ratio alkene:alkaloid	α _D (temp)
14	Cyclohexene	1	-6·00° (18°)
15	1-Me-cyclohexene	3	-0·50° (17°)
16	1-Et-cyclohexene	2.5	0.00°
17	4-Me-cyclohexene	3	-2·24° (20°)
18	4-t-Bu-cyclohexene	1	-0·50°, -0·64° (19°)⁼
19	Cyclopentene	1	-7·00° (19°)
20	Norbornene	3	$-0.86^{\circ} (18^{\circ})^{\circ}; -0.16^{\circ} (16^{\circ})^{\circ}$

* Specific rotation in chf (Experimental). 3-Bromonortricyclene. * Mixture of VI and VII.

TABLE 3. DEPENDENCY OF OPTICAL YIELDS OF DIBROMIDES ON THE ALKENE: CINCHONINE RATIO.

Run No.	Alkene	Molar ratio alkene:cinchonine	α_D^{18}
21	Cyclohexene	0.6	—6·70°
22	Cyclohexene	1.0	−6 •00°
23	Cyclohexene	2.4	— 5·90 °
24	Cyclohexene	3.6	−5·70°
25	Cyclohexene	3.6	-6·40°
26	Cyclopentene	1.0	-7 ·00 °
27	Cyclopentene	4-3	— 5 ·96°
28	Cyclopentene	8.6	-4·00°

• The bromination was carried out at 0°.

Run No.	Alkaloid	Molar ratio cyclohexene:alkaloid	α _D (temp)
29	Cinchonine	1	-6·00° (18°)
30	Cinchonine · HCl	4	-0.50° (29°)
31	Cinchonine diacetate	4	-0.08° (17°)ª
32	Dihydrocinchonine	4	-5.70° (20°)
33	Cinchonidine	1	+5.30° (18°)
34	Quinidine	4	-1.00° (20°)
35	O-Benzoylcinchonine	3.5	-0.42° (20°)
36	β -Isocinchonine	3.5	-0·24° (20°)
37	Desoxydihydrocinchonine	3.5	0.00°
38	9-Chlorodesoxycinchonine	3.5	+1.08° (20°)
39	Nicotine	2.2	0.00°
40	Brucine	1	+0·16° (21°)
41	Ephedrine	1	0.00°
42	Cinchonine dibromide-Br, complex	1	-0·70° (29°)
43	Cinchonine dibromide-Br, complex ^e	1	-0.06° (29°)
44	Dihydrocinchonine-Br ₁ complex	1	-3·00° (15°)

TABLE 4. BROMINATION OF CYCLOHEXENE IN THE PRESENCE OF DIFFERENT ALKALOIDS

^e Bromination carried out in AcOH soln. ^b Bromination carried out at 0°. ^c With one mole excess bromine.

produce no optical activity in the dibromides, brucine only a very low one. Salt formation drastically reduces the asymmetric catalyst activity of cinchonine, as shown by the run with the monohydrochloride and by that carried out in acetic acid. The results obtained with different Cinchona bases and with their transformation products indicate that the configurations at C-8 and C-9 in the alkaloid⁸ are of fundamental importance in determining configuration of the enantiomeric dibromide formed in larger amount. Thus, cinchonine (VIII) which under the conditions of the reaction is rapidly brominated in the vinyl side-chain and probably exerts its asymmetric influence in the form of the 10,11-dibromo derivative, and 10,11-dihydrocinchonine (IX) produce (-)-dibromocyclohexanes with similar specific rotations. Quinidine (X) which has the same configuration as cinchonine, also gives the (-)-dibromide, but with much lower optical yield, a fact which is not easy to understand, as one would expect only a small influence on the mechanism of optical activation from a methoxy group, which is far from the chiral atoms. Large differences between the asymmetric catalytic activity of 6'-methoxylated and non-methoxylated Cinchona bases had been observed also by Prelog and Wilhelm^{4b} in the asymmetric cyanohydrin synthesis.

Cinchonidine (XI), which is enantiomeric to cinchonine at C-8 and C-9, gives, as expected, an excess of the (+)-dibromide. 9-Chlordesoxycinchonine (XII), which is probably enantiomeric to cinchonine at C-9,⁴⁰ but has the same configuration at C-8, also gives a dextrorotatory dibromocyclohexane, while dihydrodesoxycinchonine (XIII), in which the chiral centre at C-9 is no longer present, is completely inactive as an asymmetric catalyst: C-9, therefore, seems to play a more important role than

⁸ R. H. F. Manske and H. L. Holmes, *The Alkaloid* Vol. III, p. 24. Academic Press, New York (1953).



C-8, in the mechanism of optical activation. β -Isocinchonine (XIV), in which the geometry of the molecule is altered by the formation of an oxygen bridge, and cinchonine benzoate (XV) are much less active than cinchonine as asymmetric catalysts.

In the only run made with chlorine instead of bromine, cyclohexene and cinchonine gave a dichloride of very low optical activity.

It is not possible to estimate the optical yields achieved in the asymmetric brominations, as no data are available on the specific rotations of vicinal dibromides. Only for *trans*-1,2-dibromocyclohexane Applequist and Werner⁹ report a calculated value of specific rotation; if one accepts this rather uncertain value, the product of highest rotation we have obtained should correspond to about 5.5% optical purity.

The mechanism of the formation of the active bromides must involve the alkaloid in the transition state of the bromination, or its action on an intermediate, or on the final product of the bromination. There are some references in the literature to partial resolutions of racemic halides by preferential interaction of one enantiomer

[•] D. E. Applequist and N. D. Werner, J. Org. Chem. 28, 48 (1963).

with an alkaloid: thus, Lucas and Gould obtained optically active 3-chloro-2butanol¹⁰ and 2,3-dibromobutane¹¹ by leaving the racemates in contact with brucine; more recently a similar resolution was achieved with *trans*-2-chlorocyclohexanol,¹² but, while in the first case the optical activation was attributed to preferential quaternarization of one enantiomer, in the latter case it was explained with a preferential adsorption, without reaction. In our case, however, we can rule out bromination to racemic dibromide, followed by preferential reaction or adsorption of one enantiomer, as the cause of optical activation. Completely inactive *trans*-1,2-dibromocyclohexane was recovered after contact with cinchonine or brucine; similarly, no activation was observed when (\pm) -2,3-dibromobutane was left in contact with cinchonine. Furthermore, brucine, which gave good results in the partial resolution of the latter



dibromide by Lucas' method, led only to a very small optical activity when used as an asymmetric catalyst for the bromination of *cis*-2-butene by our method. While these facts do away with the hypothesis of preferential quaternarization of one of the two enantiomers, after a normal bromination step, they do not rule out completely the preferential capture of one of the enantiomeric forms of an asymmetric cationic intermediate of the bromination. This intermediate could not be a bromonium ion, as such a species would be asymmetric for *cis*-2-butene, cyclohexene, etc., nor a classical carbonium ion, but could be a carbonium ion with hindered rotation, such as shown in scheme I. However, this mechanism does not appear to be likely, as a competition between Br^- and the highly hindered quinuclidine nitrogen should favour the former by several orders of magnitude. Furthermore, the optical yield for such a mechanism would be expected to depend much more than observed on the alkaloid:olefin ratio.

The most logical explanation for the formation of optically active dibromides appears to be that an asymmetric bromine-alkaloid complex is the actual brominating agent and that preferential formation of one enantiomer is determined by the tendency

- ¹⁰ H. J. Lucas and C. W. Gould, J. Amer. Chem. Soc. 63, 2541 (1941).
- ¹¹ H. J. Lucas and C. W. Gould, J. Amer. Chem. Soc. 64, 601 (1942).
- ¹³ F. J. Zeelen, M. E. Kronenberg and E. Havinga, Rec. Rrav. Chim. 77, 674 (1958).

to minimize repulsive non-bonded interactions between the substituents on the alkene and those on the alkaloid during the transfer of the halogen from nitrogen to carbon. Cinchona bases, as in general tertiary amines, form 1:1 complexes with bromine;¹³ although it is not known which of the two nitrogen atoms of the alkaloid is involved, it appears likely that the bromine is attached to the quinuclidine nitrogen, as the quinoline one appears to be too far from the chiral atoms to justify an asymmetric effect in the brominations. The brominating action of the amine-bromine complexes is well known, and Acheson *et al*¹⁴ assume that the catalytic action of pyridine in brominations is due to the formation of N-bromopyridinium bromide, which acts as a donor of Br⁺. Asymmetric cationic intermediates were also proposed to explain the asymmetric synthesis of esters from ketenes and alcohols in the presence of alkaloids.⁵ We resist the temptation of trying to give any exact representation of the asymmetric transition state of the reaction: there are too many uncertainties and variables to be considered, such as the structure of the bromine-alkaloid complex, its



preferred conformation, the relative orientations of the complex and the alkene during the halogen transfer step, etc., so that in such cases precise graphic schemes are often pure speculation and may justify almost any stereochemical result.¹⁶ Anyway, it is quite plausible that a relatively rigid, hindered and highly asymmetric system, such as that of *Cinchona* bases, poses some limitations to the way in which the alkene can approach it at such a distance as to allow the transfer of Br⁺, and that one of the orientations which leads to the formation of one of the enantiomeric dibromides, for instance of the (R)-form (XVIa), be favoured over those leading to the (S)-form (XVIb), or vice-versa.

- ¹³ J. Buraczewski and M. Dziurzynski, Chem. Zentr. II, 2083 (1909).
- ¹⁴ R. M. Acheson, F. G. Hoult and K. A. Barnard, J. Chem. Soc. 4142 (1954).
- ¹⁶ For instance, C. W. Bird [*Tetrahedron* 18, 1 (1962)] tried to explain the differences in the rates of esterification of enantiomeric alcohols with acyl chlorides in the presence of brucine or cinchonine on the basis of a model considering the presumable preferred conformation of the acylammonium cation and the attack of the alcohol from the least hindered side; unfortunately, the wrong absolute configurations were attributed in the paper to several aliphatic carbinols, so that the actual experimental results reported in it are just the opposite of what would be expected on the basis of the model proposed by the author.

The failure of trisubstituted and aryl-substituted alkenes to give optically active dibromides may be ascribed to a steric hindrance to the approach at such a distance as to allow direct transfer of Br^+ from nitrogen to carbon, or to a lack of stereo-specificity because of stabilization of the carbonium ion. The fact that the use of preformed alkaloid-bromine complexes gave poorer results, than the addition of bromine to the alkene-base mixture, particularly in the case of cinchonine (Table 4), may be due to the very low solubility of such complexes, and does not necessarily disprove the mechanism we suggest. An alternative mechanism based on the assumption of the reaction of bromine with an alkaloid-alkene complex cannot be ruled out completely, but appears very unlikely.

One of the uses of the present method of "asymmetric synthesis" could be in the determination of the absolute configurations of dibromides. Although some care must be exercised in generalizing methods of configurational assignment of this type, particularly in cases involving low optical yields,¹⁶ it appears likely that, at least in homologous series and under identical reaction conditions, the enantiomeric dibromides formed in excess have the same configuration. This hypothesis is supported by the observation that all the dibromides obtained in the presence of cinchonine from aliphatic olefins were dextrorotatory, while those formed from cycloalkenes were levorotatory. Unfortunately, definite data on absolute configurations of such compounds are lacking. However, on the basis of calculations by Brewster's method,¹⁷ and in accordance with the data of Applequist,⁹ there can be little doubt that (—)-*trans*-1,2-dibromocyclohexane, and very probably (—)-*trans*-1,2-dibromocyclopentane, have the (R:R)-configuration XVII and XVIII.



It is more difficult to apply Brewster's method to the acyclic dibromides, because of the uncertainty about contributions of the different conformations. It is however possible to assume on reasonable grounds that the dextrorotatory dibromides should

¹⁸ See, for instance: K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, J. Amer. Chem. Soc. 87, 1958 (1965); K. Mislow, M. M. Green and M. Raban, Ibid. 67, 2761 (1965). It must also be kept in mind that in some cases changes in temperature can influence not only the optical yield, but may even produce inversion in the sign of rotation of the mixture of enantiomers obtained; such cases were observed by Pracejus (Ref. 5) for reactions of methyl phenyl ketene with alcohols in the presence of alkaloids.

¹⁷ J. H. Brewster, J. Amer. Chem. Soc. 81, 5475, 5483, 5493 (1959).

belong to the (R) or (R:R) series. Taking for instance the case of (R:R)-2,3dibromobutane, one can calculate the following molar rotations for the three staggered conformations: XIXa -545° , XIXb $+230^{\circ}$, XIXc $+310^{\circ}$.¹⁸ According to Brewster's selection rules, XIXa should be the only conformer to be considered, but it is known from NMR data¹⁹ that actually XIXc is the most populated conformation, the relative values being about 60% XIXc, 20% XIXa and 20% XIXb. It can therefore be expected that (R:R)-2,3-dibromobutane has a molar rotation in the order of $+110^{\circ}$; even if the latter value is only a very rough estimate, there can be little doubt about the fact that the compound should be dextrorotatory. Similar considerations, which assume a predominance of conformations with *trans* bromine atoms, even if with less quantitative foundation, because of lack of data on conformational contributions, make it plausible that also the other dextrorotatory dibromides in Table 1 belong to the (R) series. In support of this hypothesis is the fact that for the dichlorides XX and XXI the (R) forms are known to be dextrorotatory.²⁰

CH ₂ Cl	CH3
CHCI	 CHCl
 CH3	 CHCl
-	 СН"
XX	XXI

It can be concluded, although definite data are still needed, that at least in the case of simple cyclic and acyclic olefins, bromination in the presence of cinchonine very probably gives an excess of the (R) or (R:R)-enantiomer (XXII and XXIII).



EXPERIMENTAL

Optical rotations—partly with a Hilger visual polarimeter, and partly with a Perkin-Elmer photoelectric polarimeter, Mod. 141; unless stated otherwise, the values given are observed rotations for neat liquids in a 1-dm tube and are accurate within $\pm 0.02^{\circ}$. GLC—Perkin-Elmer Mod. 116E vapor fractometer using 2-m columns containing Apiezon "L" grease, with a flame-ionization detector. IR spectra—Perkin-Elmer Infracord, Mod. 137.

¹⁸ Calculations were based on the empirical equation given by Brewster (Ref. 17): $[M]_D = +$ or

 $-160\sqrt{R_A \times R_B}$ for each gauche interaction. For instance, in the case of conformation XIXa:

$$[\mathbf{M}]_{\mathbf{D}} = 160(\mathbf{C}\cdot\mathbf{C} - \mathbf{B}\mathbf{r}\cdot\mathbf{B}\mathbf{r} + 2\mathbf{H}\cdot\mathbf{B}\mathbf{r} - 2\mathbf{C}\cdot\mathbf{H})$$

 $= 160(2.59 - 8.74 + 2\sqrt{8.74 \times 1.03} - 2\sqrt{2.59 \times 1.03}) = -545^{\circ}.$

¹⁹ A. A. Bothner-By and C. Naar-Colin, J. Amer. Chem. Soc. 84, 743 (1962); F. A. L. Anet, Ibid. 84, 747 (1962).

²⁰ W. Fickett, H. K. Garner and H. J. Lucas, J. Amer. Chem. Soc. 73, 5063 (1951).

Starting materials

Alkenes. The following commercial products were redistilled, if necessary, to obtain at least 99% purity (checked by gas-chromatography): cis-2-butene, 2-methyl-2-butene, 3-methyl-1-butene 2-methyl-1-butene, 1-hexene, 1-decene, styrene and norbornene. 4-Methyl-1-hexene was kindly supplied by Prof. L. Lardicci. Cyclohexene,³¹ cyclopentene,³² 1-methylcyclohexene,³⁴ 4-methylcyclohexene,³⁴ and 4-t-butylcyclohexene³⁵ were prepared by literature methods shortly before use, to avoid formation of peroxides.

Alkaloids. Cinchonine, cinchonidine, quinidine, nicotine, brucine, and ephedrine were commercial products of controlled purity. O-benzoylcinchonine,³⁰ 10,11-dihydrocinchonine,³⁷ β -isocinchonine,³⁸ 9-chlorodesoxycinchonine,³⁹ and 10,11-dihydrodesoxycinchonine³⁰ were prepared by known methods.

	Fou	ind	Literature		
Alkene	b.p./mm	$n_{\rm D}$ (temp)	b.p./mm	$n_{\rm D}$ (temp)	
cis-2-Butene	90–92°/90	1.5122 (25°)	75·6–75·8°/50	1.5125 (25°)°	
1-Pentene	76-77°/22	1.5050 (24°)	81·6-82·0°/27	1.5063 (20°)*	
2-Methyl-1-butene	69-70°/21		60-62°/15°		
3-Methyl-1-butene	71°/ 24	1·5085 (25°)	61-62°/12	1.5093 (20°) ^d	
2-Methyl-2-butene	63-65°/25	_	70°/30•		
1-Hexene	93-94°/22	1·5030 (16°)	89-90°/18	1.5024 (20°)/	
4-Methyl-1-hexene	94°/12	1·4977 (22°)	94·7-95·7°/11	1.4980 (20°) ^a	
1-Decene	147-147·5°/14	1·4899 (25°)	145–160°/15	1.4891 (24°)*	
Styrene	m.p. 74–76°	_	m.p. 74–75°'		
Allyl alcohol	118°/19	1·5532 (25°)	110–112°/15	1·5577 (25°)'	
Cyclopentene	77°/18	1·5510 (16°)	72·4–72·6°/15	1·5460 (24°)*	
Cyclohexene	102-103°/14	1.5504 (25°)	99-103°/16	1.5521 (24°) ²	
1-Methylcyclohexene	104-105°/16	1.5421 (25°)	100-102°/12m		
1-Ethylcyclohexene	117·5°/16	1.5435 (20°)	120°/20*	-	
4-Methylcyclohexene	105–107°/17	1.5379 (24°)	107-108°/15°		

TABLE 5. B.PS AND REFRACTIVE INDEXES OF DIBROMIDES

⁶ W. G. Young, R. T. Dillon and H. J. Lucas, J. Amer. Chem. Soc. 51, 2528 (1929); ⁶ M. L. Shevrill, M. E. Smith and D. D. Thompson, *Ibid.* 56, 611 (1934); ⁶ W. L. Evers, H. S. Rothrock, H. M. Woodburn, E. E. Stahly and F. C. Whitmore, *Ibid.* 55, 1136 (1933); ⁴ L. Kutscherow, Chem. Centr. I, 753 (1914); ⁶ C. Harries, Liebigs Ann. 383, 175 (1911); ⁷ C. G. Schmitt and C. E. Boord, J. Amer. Chem. Soc. 54, 751 (1932); ⁶ F. J. Soday and C. E. Boord, *Ibid.* 55, 3293 (1933); ^{*} T. H. Vaughn, *Ibid.* 56, 2064 (1934); ⁴ J. Read and W. G. Reid, J. Chem. Soc. 1487 (1928); ⁴ H. S. Gilchrist and C. B. Purves, *Ibid* 127, 2735 (1925); J. C. Phillip, *Ibid* 101, 1866 (1912); ^{*} P. I. Abell and C. Chiao, J. Amer. Chem. Soc. 82, 3610 (1960); [†] H. R. Snyder and L. A. Brooks, Org. Syntheses coll. Vol. II, 171 (1943); M. W. Lister, J. Amer. Chem. Soc. 63, 143 (1941); ^m N. Zelinsky and A. Gorsky, Ber. Dtsch. Chem. Ges. 41, 2630 (1908); ^m M. Mousseron, R. Jacquier, A. Fontaine and R. Zagdoun, Bull. Soc. Chim. Fr. 1246 (1954); ^o N. Zelinsky and A. Gorsky, Ber. Dtsch. Chem. Ges. 41, 2479 (1908).

- ²¹ A. I. Vogel, *Textbook of Practical Organic Chemistry* (3rd Edition) p. 243. Longmans, London (1956).
- ²² C. Harries and L. Tank, Ber. Dtsch. Chem. Ges. 41, 1701 (1908).
- ³³ G. Ohloff, Liebigs Ann. 627, 79 (1959).
- ³⁴ C. Harries, Liebigs Ann. 395, 253 (1913).
- ¹⁵ S. Winstein and N. J. Holness, J. Amer. Chem. Soc. 77, 5562 (1955).
- ¹⁶ E. Leger, Bull. soc. chim. Fr. [3] 9, 714 (1893).
- ²⁷ A. Skita and H. H. Franck, Ber. Dtsch. Chem. Ges. 44, 2862 (1911).
- ¹⁸ O. Hesse, Liebigs Ann. 260, 213 (1890).
- ¹⁹ P. Rabe, Liebigs Ann. 373, 85 (1910).
- ³⁰ C. Schoepf and E. Schmidt, Liebigs. Ann. 465, 117 (1928).

General method for "asymmetric brominations". To a solution of the alkene and of the alkaloid in a volume of chloroform corresponding to 100 times the wt of alkaloid, was added slowly, with stirring, a 10% soln of purified³¹ Br_a in chf; the volume used corresponded to an equimolar quantity of Br_a with respect to the alkene, plus a 10% excess, and, in the case of cinchonine, cinchonidine, quinidine, cinchonine benzoate and 9-chlorodesoxycinchonine, plus an equimolar quantity with respect to the alkaloid, to compensate for addition to the vinyl double bond. Unless stated otherwise the additions were carried out at room temp. After the end of the addition, which took 10 to 30 min depending on the scale of the run, the soln was filtered, washed with 2N H₂SO₄, NaHSO₄ and Na₂CO₅ solns and dried over MgSO₄; if the soln was colored it was treated once or twice with charcoal and evaporated. Yields of crude dibromides were in the 80–90% range. The crude bromo derivatives were distilled under red. press., and the distillate checked by gas-phase chromatography; if more than traces of impurities were present, which happened only occasionally, distillation was repeated once or twice. Runs were conducted on a scale ranging from 10 to 100 mmole of olefin. Results are summarized in Tables 1, 2, 3 and 4; physical properties of the dibromides are given in Table 5.

Special cases

Run No. 10 (Table 2). The 1,2-dibromo-4-methylhexane obtained in this run gave a single GLC peak on a normal 2-m column, but showed two partly overlapping peaks on a 50-m Golay column containing Apiezon L. They were evidently due to the two possible diastereoisomeric forms of the dibromide.

Run No. 23 (*Table* 3). The dibromocyclohexane obtained in this run was distilled 3 times with no change in the optical rotation; also different fractions of every distillation had the same rotations: α^{19} (1 dm): at 578 m μ -5.90°, at 546 m μ -6.72°, at 436 m μ -12.02°, at 365 m μ -19.95°.

Reactions with preformed alkaloid-bromine complex

Runs No. 42, 43 and 44 (*Table* 4). Cinchonine (3.6 g, 12.2 mmoles) was dissolved in 140 ml chf on a steam bath, the soln was cooled and treated dropwise, with stirring, with 31.3 ml of 12.5% Br in chf (24.5 mmoles). An orange precipitate was formed. After 15 min, 1 g (24.5 mmoles) cyclohexene in 20 ml chf was added slowly; the precipitate dissolved. Stirring was continued for 30 min, and after 2 hr the soln was washed with 2N Na₂CO₂ and 2N H₂SO₄. Evaporation of the chf left a residue of 2.50 g which was distilled: b.p. 108°/23 mm, α_{D}^{55} –0.70°.

A similar reaction, using 12.2 mmoles each of dihydrocinchonine, Br and cyclohexene, gave a dibromocyclohexane $\alpha_{15}^{16} - 3.00^{\circ}$ (run No. 44, Table 4).

Another run (No. 43, Table 4) conducted under similar conditions but with a large amount of Br (37 mmole), gave a dibromocyclohexane, $\alpha_D^{se} = -0.06^\circ$.

Bromination of 4-t-butylcyclohexene (Run No. 18, Table 2). 4-t-Butylcyclohexene (65.2 mmole) was brominated with 136 mmoles Br in the presence of 65.2 mmoles cinchonine, according to the general method. The product was distilled at 13 mm to give the following fractions: I: 5.2 g, b.p. 137-140°, n_{20}^{00} 1.5273, α_{10}^{10} -0.50° (c 10, chf); II: 5.10 g, b.p. 140-141°, n_{20}^{00} 1.5272, α_{10}^{10} -0.60° (c 10, chf); III: 2.1 g, b.p. 141-145°, n_{20}^{00} 1.5272, α_{10}^{10} -0.64° (c 10, chf); III. b.p. 142°/13 mm; III, b.p. 116-124°/5 mm, n_{20}^{20} 1.5251. The IR spectra of the fractions show that they are all mixtures of 3-trans-4-cis-dibromo-t-butylcyclohexane (II) and 3-cis-4-trans-dibromo-t-butylcyclohexane (III) with an excess of the former; the amount of III increases in passing from fraction I to fraction III as shown by several characteristic bands, and particularly by one at 12.32 μ .

Bromination of nornornene (Run No. 20, Table 2). Norbornene (106 mmoles) was brominated with 141 mmoles Br in the presence of 34 mmoles cinchonine. The crude product (19.5 g) was distilled to give the following fractions: I: 0.4 g, b.p. 40-67°/18 mm; II: 5.2 g, b.p. 67-74°/17 mm, n_{b}^{34} 1.5298, α_{D}^{15} +0.62°; III: 6.6 g, b.p. 70-100°/1.5 mm, n_{D}^{25} 1.5615, α_{D}^{16} -0.16°. Redistillation of fraction III gave a product, b.p. 68-70°/17 mm, n_{D}^{35} 1.5290, α_{D}^{30} +0.86°, whose IR spectrum was identical with that of a sample of V, prepared according to Roberts *et al.*;⁷ it gave a single peak on gas-chromatography. Redistillation of fraction III at 1.4 mm gave: I: 0.9 g, b.p. 80-94°, n_{D}^{19} 1.5563, α_{D}^{16} -0.10°; II: 1.55 g, b.p. 96-98°, n_{D}^{19} 1.5623, α_{D}^{18} -0.16°, α_{436}^{436} -0.30°, α_{436}^{436} -0.46°; III: 1.45 g, b.p. 100-106°, n_{D}^{18} 1.5687, α_{D}^{16} -0.00°, α_{436}^{186} -0.18°. All three fractions were mixtures of VI and

³¹ P. Pascal, Nouveau Traite de Chimie Minerale Vol. XVI, p. 340. Masson, Paris (1960).

VII, the amount of the latter increasing in going from fraction I to III; this was desumed on the basis of the IR spectra, which are given by Kwart and Kaplan.⁷

Chlorination of cyclohexene. A soln containing 1 g ($12\cdot 2 \text{ mmoles}$) cyclohexene and 1 g ($3\cdot 4 \text{ mmoles}$) cinchonine in 120 ml chf was saturated with Cl, washed with 2N Na₂CO₃ and 2N H₂SO₄, dried and evaporated. The residue was distilled (b.p. 188–190°/760 mm) to give 0.70 g trans-1,2-dichlorocyclohexane, $\alpha_{D}^{10} - 0.28^{\circ}$.

Attempts of resolution of dibromides with alkaloids. (1) (\pm) -trans-1,2-Dibromocyclohexane (6.8 mmoles) and cinchonine (3.4 mmoles) in 160 ml chf were left at room temp for 1 hr. The soln was washed with 2N H₂SO₆, dried, evaporated and the residue distilled to give the unchanged dibromide, $[\alpha]_{10}^{10} 0.00^{\circ}$. (2) A similar test in which the same amounts of dibromide and cinchonine in 15 ml chf were left at room temp for 18 days, led to recovery of the dibromide $[\alpha]_{D} 0.00^{\circ}$. (3) A mixture of 3.4 mmoles cinchonine and 6.8 mmoles (\pm) -trans-1,2-dibromocyclohexane was left for 28 hr at room temp, then taken up in pet. ether (b.p. 40–60°) and filtered. All the cinchonine was recovered and gave a negative Beilstein test for halogen. Evaporation of the pet. ether left a residue of cyclohexane bromide, $[\alpha]_{D} 0.00^{\circ}$ (4) A similar run with 20 mmoles of the dibromide and 8 mmoles brucine also gave completely inactive dibromide. (5) Also a run with 30 mmole (\pm) -2,3-dibromobutane and 12 mmole cinchonine, conducted as in 3, led to the recovery of inactive dibromide.