STEREOCHEMISTRY OF ELECTROREDUCTIONS OF BROMOCYCLOPROPANES

1-ASYMMETRIC ELECTROCHEMICAL SYNTHESIS BY REDUCTION AT A MERCURY CATHODE IN THE PRESENCE OF ADSORBED ALKALOÏDS†

R. Hazard, S. Jaouannet and A. Tallec*

Laboratoire d'Electrochimie, Université de Rennes 1, (ERA CNRS No. 896), Campus de Beaulieu,
35042 Rennes Cédex, France

Abstract—The electrochemical behaviours of 1-bromo-2,2-diphenylcyclopropane carboxylic acid, its methyl ester and 1,1-dibromo-2,2-diphenylcyclopropane are investigated in the presence of strongly adsorbed alkaloïds: yohimbine, emetine, brucine, strychnine and methylstrychninium cations. The polarographic study evidences the existence of interactions between the alkyl bromides and nitrogen cations; these interactions make easier the 2e cleavage of the carbon–halogen bond. Whatever the alkaloïd used, rather poor optical yields are obtained after electroreduction of monobromo compounds. On the contrary, notably optically active products are obtained from the dibromide derivative, but only when the inductor can act as a protonating species; 45% optical yield can be achieved in the presence of emetine. The mechanism of asymmetric electrochemical synthesis is interpreted in terms of (i) preferential presentation of one of the two stereotopic faces of the substrate at the mercury cathode, made chiral by the adsorption of the alkaloïd and (ii) protonation by the acidic form of the inductor of the carbanion resulting from a 2e reduction.

In the past few years, many attempts have been made to perform asymmetric synthesis, by electrochemical reduction at a mercury cathode, in the presence of a chiral alkaloïd acting as an inductor I.* The alkaloïd itself may constitute the supporting electrolyte; this method has been worked up in aqueous medium by Horner *et al.*[1] and in non-aqueous medium by Van Tilborg and Smit.[2] The reduction of alkyl phenyl ketones[1b] and schiff bases[1d] in aquoalcoholic media in the presence of various substituted ephedrins or desoxyephedrins have evidenced a specificity of the substrate-inductor couple. A study of the variations of the optical yield with different experimental factors has also been performed.[1c,1d] When strongly adsorbed, only small quantities of alkaloïds are required and this method has been worked up here. A recall of the main results obtained by this way is presented below before giving the reasons we had to apply it to the electrochemical reduction of some bromocyclopropanes.

ATTEMPTS OF ASYMMETRIC ELECTROREDUCTION ON MERCURY IN THE PRESENCE OF ADSORBED ALKALOÏDS

The pioneer work was made by Grimshaw and coworkers[3] who reduced 4-methylcoumarin at pH 5 to 6. Beside an inactive hydrodimer, optically active 3,4-dihydro-4-methylcoumarin was obtained when the inductor was sparteine ($\rho_R = 17\%$), narcotine ($\rho_R = -15\%$), emetine, yohimbine or codeine ($\rho_R = 12\%$); but brucine did not give rise to any induction.‡

Kariv, Terni and Gileadi[4] have performed the electrochemical reduction of acetophenone in the presence of quinine or quinidine. The optical yield of the alcohol can reach 15% but an inactive pinacol is also formed.

In our laboratory, Jubault, Raoult and Peltier[5] have first studied the electroreduction of phenylglyoxylic acid in the presence of various alkaloïds. The 2e reduction of the substrate leads quantitatively to mandelic acid. The best inductors are strychnine or brucine ($\rho_R = 20\%$), while sparteine and narcotine give $\rho_R = 0\%$. The study was then extended to the production of phenylglycine by electroreduction of the parent oximes and phenylhydrazone.[6]

Finally, Kopilov, Kariv and Miller[7] have tested the influence of the same alkaloïds in the reduction of acetylpyridines. A mixture of inactive pinacol and active alcohol is formed; when strychnine is the inductor, the optical yields are 47.5% and 40% in the case of 2-acetylpyridine and the 4-acetyl isomer respectively. On the other hand, there is no induction for 3-acetylpyridine.

Analysis of the results

The studies summarized above have demonstrated that, when used in small amount, the inductor has to be strongly adsorbed on mercury. The classification of the main quoted alkaloïds is the following in decreasing adsorption order[5] Yohimbine > Narcotine > Strychnine > Brucine > Emetine > Sparteine. However, there is no relation between the optical yield and the rate of adsorption of the inductor; thus, sparteine, the less adsorbed one, gives the best result in the case of 4-methylcoumarin.[3] Moreover, adsorption of the alkaloïd is a necessary but not a sufficient condition to observe induction; for instance, $\rho_R = 0\%$ is found for the reduction of phenylglyoxylic acid in the presence of narcotine[5] or for the reduction of 4-methylcoumarin in the presence of brucine.[3] So, a specificity of the substrate-inductor couple appears.[5]

---

†A preliminary report of this work was published in *Tetrahedron Letters*, 1105 (1979).

‡The optical yield ρ_R in the R enantiomer is given by $\rho_R = \dfrac{[R]-[S]}{[R]+[S]} = \dfrac{[\alpha]}{[\alpha_0]}$. $[\alpha]$ represents the specific rotatory power of the enantiomeric mixture and $[\alpha_0]$ the one of the pure R enantiomer. A negative value means that the S enantiomer is preferentially formed.

Finally, it is now well established that induction takes place at the interface or close by the cathode. One can then understand why a good optical yield is obtained with a small inductor concentration: it is the quantity available at the electrode which must be taken in account.

Factors affecting the optical yield

The study of the variations of the optical yield with the electrolysis conditions was successively investigated in our laboratory[5] and by Kopilov, Kariv and Miller.[7] The two main factors are the pH of the supporting-electrolyte and the working potential.

pH *of the supporting-electrolyte.* When the substrate is a ketone or an oxime, the optical yield is maximum for a pH value near 4.5, whatever the alkaloïd. A change in the acidity may interfere by different ways; either modification of the nature of the diffusing species and therefore its presentation at the cathode[8] or modification of the inductor which is protonated (I^*H^+) in acidic medium. In this respect, it seems that better optical yields are achieved when the alkaloïd is a cationic entity; however, some attempts performed in the presence of methylstrychninium cations gave only very low optical yields.[6,7] It is worth remembering that the protonation rate of the final carbanion depends on the medium acidity.

Working potential. The working potential E fundamentally influences the optical yields when electrolysis are carried out in a weakly acidic medium (buffered aqueous acetic acid). In the presence of strychnine, the optical yields obtained when phenylglyoxylic acid[5] or 2 and 4-acetylpyridines[7] are reduced, decrease as E becomes more negative. In the case of phenylglyoxylic acid oximes, the yield ρ_R in R-phenylglycine, preferentially formed at low negative potentials, decreases as the absolute value of E increases and is zero when $E = -1.2$ V SCE. At more negative values, the S-enantiomer is preferentially obtained.[9]

The same phenomenon has been observed when these oximes are reduced in the presence of various inductors;[6] the optical yields always cancels for a working potential lying between -1.1 and -1.3 V SCE. In this precise case, it seems that the working potential exerts its influence at the level of the final carbanion. It has been suggested that this latter species can invert under the electrical field existing near the cathode;[9] inversion would be the faster as the working potential is made more cathodic.

Interpretations

If one excludes the mechanism proposed by Grimshaw[3] (hydrogen transfer between two interpretations are presently forwarded in order to propose an explanation for asymmetric induction produced by electrochemical reduction.

For Peltier and coworkers[5,6] the presentation of the substrate S, in relation with the adsorbed inductor I^*, plays a fundamental part. An adduct SI^* would be formed and interactions would subsist until the final carbanion is protonated. This hypothesis, previously formulated by Horner[1] when an alkaloïd salt is used as the supporting electrolyte can be schemed as follow:

$$S + I^*_{ads} \rightleftarrows SI^* \xrightarrow[\text{(n-1)}H^+]{ne} \text{\textbackslash}\bar{C}I^* \xrightarrow{H^+} P^* + I^*$$
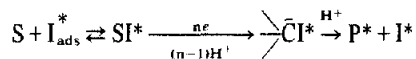
Among the arguments pleading in its favour, one can quote the observation by the means of polarography of interactions between inductor and substrate;[10] as a result, half-wave potentials are shifted.

According to Kopilov, Kariv and Miller,[7] it is the selective protonation, near the cathode, of one face of the final carbanion by the acidic form of the alcaloïd I^*H^- which brings the induction

$$S \xrightarrow[\text{(n-1)}H^+]{ne} \text{\textbackslash}C^- \xrightarrow{I^*H^+} I^* + P^*.$$
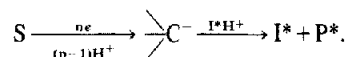
This hypothesis is based on two observations. On one hand, methylstrychninium ions give a zero optical yield, whereas strychnine, in the same experimental conditions, provokes an induction. Thus it seems that asymmetric synthesis can only be achieved when the inductor is able to act as a proton-donating species. On the other hand, 3-acetylpyridine always gives $\rho_R = 0$ while a high optical yield is obtained in the case of 2 or 4-acetyl isomer. The above authors claim that the carbanion must be conjugated and able to assume a nearly planar configuration before undergoing a stereoselective protonation.

CHOICE OF THE SUBSTRATES

Though the last hypothesis is not able to explain the obtainment of a high optical yield in the reduction of 4-methylcoumarin (the final carbanion is not conjugated), it is for the moment rather difficult to discriminate between the two recalled interpretations. Moreover all the work realized in this field involves compounds in which the prochiral carbon atom is sp^2 hybridized.

These considerations prompt us to investigate starting materials whose prochiral carbon is sp^3 hybridized. Such a study may also bring new informations about the mechanism of asymmetric synthesis produced by an electrochemical way.

For different reasons, bromocyclopropanes were selected:

(1) The mechanism of the electrochemical reduction of halogeno compounds is well known[11] and can be represented by the following scheme:

$$RX + e \rightarrow R^{\cdot} + X^-$$

$$R^{\cdot} + e \rightarrow R^-$$

$$R^- + H^+ \rightarrow RH.$$
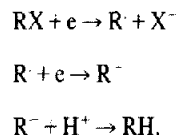
The ease of reduction increases in the order $Cl < Br < I$. In aqueous medium, the polarographic wave of chloro derivatives can be masked by the reduction of the supporting electrolyte; for example, it is the case for 1,1-dichloro 2,2-diphenylcyclopropane. When iodo derivatives are involved,[12] it is often difficult to avoid the formation of organomercuric compounds from the intermediate radical. Therefore we have focused our attention on the reduction of bromo derivatives: the intermediate neutral radical is then more easily reduced than the starting material and the carbanion is very rapidly formed at the cathode interface.

(2) The stereochemistry of electrochemical reduction of alkyl halides has received a great deal of attention.[11,13] Concerning the presentation of the molecule at the cathode, the most widely accepted view is a perpendicular attack of the C–X bond, the halogen being in direct interaction with mercury because of specific adsorption. In this respect, interesting results were obtained from *gem*-dihalogenocyclopropanes,[14,15] whose

2e reduction involves substitution of one halogen by an hydrogen atom; when the two halogens have the same number, the one which occupies the less hindered position is preferentially abstracted.

(3) The cyclopropyl carbanion inverts very slowly;[16] but the presence of an unsaturated group on the negatively charged carbon (conjugated carbanion) increases the inversion rate.[17,18] This fact was put forward in order to explain why a preferential retention of configuration occurs when optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane is reduced,[12,19] while inversion is observed during the reduction of 1-bromo-2,2-diphenyl-cyclopropane carboxylic methyl ester.[19]†

(4) Polarographic studies have evidenced the existence of interactions between halogeno compounds and quaternary ammonium salts.[21,22] Since the used inductors

---

†Recent experiments we have performed on the same compounds show that this explanation does not provide a general answer since the stereochemical result depends on the electrolysis conditions.[20]

‡In this scheme and the following ones, we suppose that the mercury cathode lies parallel under the ring.

are alkaloïds, such interactions seem propitious to asymmetric synthesis.

(5) Finally, optically active gem-diphenylcyclopropanes have high specific rotatory powers$[\alpha_0]_D$ as shown by Walborsky.[16,23,24] Thus, a good precision is attained in the evaluation of optical yield.
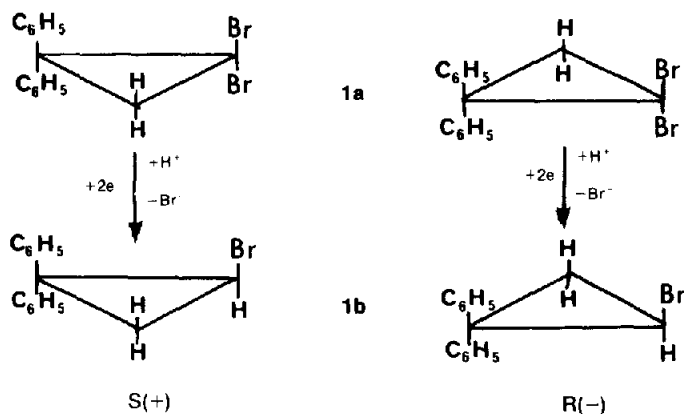
Taking in account all these considerations, the study of judiciously selected bromocyclopropanes must allow ascertaining at what stage of the reduction does the induction occur. If the presentation of the molecule at the electrode is determinating, it should be possible to perform asymmetric syntheses with valuable optical yield by reduction of 1,1-dibromo-2,2-diphenylcyclopropane (compound 1a); according to the nature of the inductor, one of the halogen must preferentially approach the cathode, the two faces of the ring being enantiotopics (scheme 1).‡

On the contrary, reduction of 1-bromo-2,2-diphenyl-cyclopropane carboxylic acid (compound 2a) or its methyl ester (compound 3a) give rise to a racemic carbanion (scheme 2). The latter being conjugated induction if observed can only occur at the protonation step.
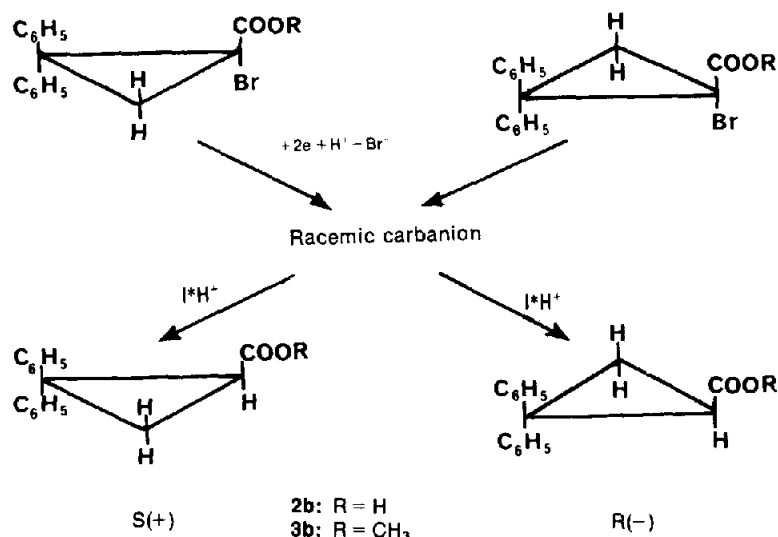
We report here the results of our investigations on

Scheme 1.

2a: R = H
3a: R = CH₃

2b: R = H
3b: R = CH₃

Scheme 2.

these three compounds. Concerning the inductors, only strongly adsorbed alkaloïds were used; among them, narcotine and sparteine always give very low optical yields; so we have retained for systematic studies: emetine, yohimbine, brucine, strychnine and methyl-trychninium cations; these latter, symbolized by I*Me$^+$, are put in the solution as iodide.[7]

POLAROGRAPHY

The title compounds are hardly soluble in water and so the reductions are performed in a mixture of aqueous supporting electrolyte and ethanol in 1-1 volume ratio in the case of the acid 2a and the ester 3a and in a medium which contains 75 per cent of alcohol in the case of *gem*-dibromide 1a.

We shall analyse the results obtained without and with inductors present in different media before discussing the influence of ammonium cations on the polarographic behaviours of the substrates.

1. *Compounds* 1a *and* 3a (*Table* 1 *and* 2; *fig.* 1a *and* b)

(a) Without inductor, these compounds give a 2e wave the $E_{1/2}$ of which is not depending on the acidity when the supporting electrolyte is a Britton Robinson buffer (B.R.) or an acetic buffer. The reduction wave is observed since pH = 2 for the ester 3a but only when pH $\geq$ 4 for the dibromide 1a. When the supporting electrolyte contains NH_4^+ ions, reduction is easier. The effect is more important for 1a ($\Delta E_{1/2} = 0.11$ V) than for 3a ($\Delta E_{1/2} = 0.05$ V). Since there is no chemical reaction preceeding the electronic transfer, the influence of NH_4^+ must not be ascribed to their proton-donating ability.

(b) In the presence of methylstrychninium ions (I*Me$^+$), half-wave potentials measured in B.R. or acetic buffers are less cathodic : $\Delta E_{1/2}$ is 0.19 V for 1a and 0.12 V for 3a. Though present at small concentration (2.10^{-5} M), I*Me$^+$ shows a larger influence than NH_4^+ ions at the concentration of 0.5 M; for the dibromide 1a, the results observed in ammonium acetate or in am-

Table 1. $E_{1/2}$ (V SCE) for $5.10^{-4}M$ 1,1-dibromo-2,2-diphenylcyclopropane 1a. Aqueous supporting electrolyte + ethanol (1:3v./v.)

Aqueous supporting electrolyte		$2.10^{-5}\underline{M}$ INDUCTOR					
		—	Strychnine	Methyl-strychninium	Brucine	Emetine	Yohimbine
Britton Robinson Buffer	pH = 4	- 1.46	- 1.25	- 1.27	- 1.32	- 1.05	- 1.34
	pH = 6	- 1.46	- 1.26	- 1.27	- 1.32	- 1.10	- 1.40
	pH = 8	- 1.46	- 1.42	- 1.27	- 1.38	- 1.28	- 1.45
	pH = 10	- 1.46	- 1.45	- 1.27	- 1.46	- 1.41	- 1.45
0.5 $\underline{M}$ Buffered aqueous acetic acid (pH = 4.7)		—	- 1.24	- 1.27	- 1.29	- 1.07	- 1.36
0.5 $\underline{M}$ Ammonium acetate (pH = 6.7)		- 1.35	- 1.22	- 1.24	- 1.26	- 1.08	- 1.34
0.5 $\underline{M}$ Ammoniacal buffer (pH = 9.8)		- 1.35	- 1.30	- 1.25	- 1.27	- 1.17	- 1.34

Table 2. $E_{1/2}$ (V SCE) for $5.10^{-4}M$ 1-bromo-1-carbomethoxy-2,2-diphenylcyclopropane 3a. Aqueous supporting electrolyte + ethanol (1:1 v./v.)

| Aqueous supporting electrolyte		$2.10^{-5}\underline{M}$ INDUCTOR					
		—	Strychnine	Methyl-strychninium	Brucine	Emetine	Yohimbine
Britton Robinson Buffer	pH = 2	- 1.06	- 0.96	- 0.94	- 0.84	- 0.87	- 0.95
	pH = 4	- 1.06	- 0.96	- 0.94	- 0.90	- 0.87	- 0.95
	pH = 6	- 1.06	- 0.96	- 0.94	- 0.90	- 0.90	- 0.97
	pH = 8	- 1.06	- 1.02	- 0.94	- 0.98	- 1.00	- 1.03
	pH = 10	- 1.06	- 1.05	- 0.94	- 1.06	- 1.06	- 1.06
0.1 $\underline{N}$ H_2SO_4 (pH = 1)		—	- 0.84	- 0.94	- 0.86	- 0.87	- 0.92
0.5 $\underline{M}$ Buffered aqueous chloroacetic acid (pH = 2.6)		—	- 0.96	- 0.94	- 0.93	- 0.90	- 0.95
0.5 $\underline{M}$ Buffered aqueous acetic acid (pH = 4.7)		- 1.06	- 0.96	- 0.94	- 0.93	- 0.90	- 0.95
0.5 $\underline{M}$ Ammonium acetate (pH = 6.7)		- 1.01	- 0.96	- 0.94	- 0.93	- 0.90	- 0.97
0.5 $\underline{M}$ Ammoniacal buffer (pH = 9.8)		- 1.01	- 1.00	- 0.94	- 1.00	- 1.00	- 1.00
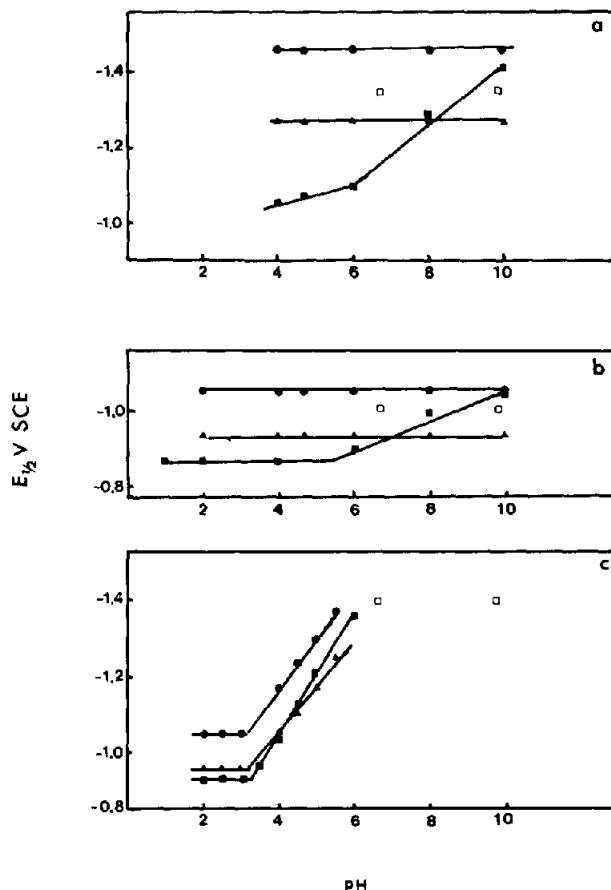
Fig. 1 Half wave potential as a function of pH for the studied compounds a: compound 1a; b: compound 3a; c: compound 2a. ●, Britton Robinson buffers, buffered acetic or chloroacetic acids; □, Ammonium acetate or ammoniacal buffer; ▲, Britton Robinson buffer + 2.10⁻⁵M I*Me⁺; ■, Britton Robinson buffer + 2.10⁻⁵M emetine.

moniacal buffer show that the effects of these cations are partly cumulative.

(c) In the presence of inductors of the I* type, there is also, in strongly acidic medium, a shift of $E_{1/2}$ towards more anodic values. This shift depends on the nature of the inductor (emetine is the most efficient one) and on the nature of the substrate: for the compound 1a, strychnine provokes a larger effect than brucine but the reverse is true for the ester 3a. As the pH is raised, the influence of the inductor decreases progressively in B.R. buffer (Fig. 1a and 1b).

When NH_4^+ ions are present, the analysis of the results is critical. If ammonium acetate is the supporting electrolyte, all the inductors, but yohimbine in the case of 1a, cause a proper shift of potential. In ammoniacal buffer, a notable shift of $E_{1/2}$ is only observed for 1a with emetine, strychnine or brucine.

Compound 2a (Table 3. Fig. 1c)

(a) Without inductor, a 2e wave is observed for pH ≥ 2. Its height decreases for pH ≥ 5 and then the reduction wave rapidly merged with that of the supporting electrolyte discharge when the latter is B.R. buffer. Variations of $E_{1/2}$ as a function of the pH of the aqueous supporting electrolyte are drawn on Fig. 1c; from the

*In B.R. buffer, when the inductor is strychnine, a parasite wave appears, whose nature has been already discussed.[6]

results observed in B.R. buffer, one can conclude than the pK_a of the bromoacid 1a is about 3.2. The values of $E_{1/2}$ measured in ammonium acetate and in the ammoniacal buffer are nearly equal and the height of the wave is maximum. It is then the carboxylate anion which is directly reduced at the mercury drop.

(b) In the presence of I*Me⁺, when the supporting electrolyte is a B.R. buffer, a constant shift of $E_{1/2}$ is observed ($\Delta E_{1/2} = 0.12 \pm 0.02$ V); on the other hand, when NH_4^+ ions are present, methylstrychninium cations do not exert any influence.

(c) In the presence of the other inductors, when pH < pK_a, the positive shift of $E_{1/2}$ is again constant for a given alkaloïd, excepted in the case of brucine; for higher pH values in the B.R. buffer,* the effect of the inductor progressively ceases. However, the wave height remains constant as long as it is observable.

In ammonium acetate, all the inductors but yohimbine, give again a small shift of $E_{1/2}$; in ammoniacal buffer, only brucine exerts an own influence.

Discussion

Our results corroborate and complete two kinds of observations.

Interactions which make easier the reduction of the carbon halogen bond take place between an alkyl bromide and an ammonium cation.[21,22] To our knowledge, these property has not been pointed out for NH_4^+ ions. In the

Table 3. $E_{1/2}$ (V SCE) for $5.10^{-4}M$ 1-bromo-1-carboxy-2,2-diphenylcyclopropane 2a. Aqueous supporting electrolyte + ethanol (1:1 v./v.)

Aqueous supporting electrolyte		$2.10^{-5}M$ INDUCTOR					
		—	Strychnine	Methyl-strychninium	Brucine	Emetine	Yohimbine
Britton Robinson Buffer	pH = 2	- 1.06	- 0.94	- 0.96	- 0.92	- 0.93	- 1.00
	pH = 3	- 1.06	- 0.94	- 0.96	- 0.97	- 0.93	- 1.00
	pH = 4	- 1.17	- 1.05	- 1.05	- 1.04	- 1.04	- 1.09
	pH = 5	- 1.30	- 1.16	- 1.17	- 1.21	- 1.17	- 1.23
	pH = 6	—	- 1.37	—	- 1.36	- 1.33	—
H_2SO_4 N	pH = 0	—	- 0.92	- 0.95	- 0.92	- 0.92	- 1.00
0.5 M Buffered aqueous acetic acid	(pH = 4.7)	- 1.28	- 1.20	- 1.15	- 1.20	- 1.14	- 1.19
0.5 M Ammonium acetate	(pH = 6.7)	- 1.40	- 1.35	- 1.39	- 1.36	- 1.36	- 1.40
0.5 M Ammoniacal buffer	(pH = 9.8)	- 1.40	- 1.40	- 1.40	- 1.36	- 1.39	- 1.40

experiments quoted above, these cations are present in high concentration so it is difficult to ascertain whether their action is achieved in the bulk of the solution or in the reaction layer surrounding the cathode. On the other hand, methylstrychninium ions and $I*H^+$ cations probably operate at the surface of the mercury since small concentrations of these adsorbed alkaloïds are efficient. In B.R. buffer, it is noteworthy that the effect of the $I*$ type inductors cancels for pH values closed to 8, which is near by the pK_a values for the acids $I*H^+$ (respectively 7.4, 8.0 and 8.2 for strychnine, brucine and emetine).

For Mairanovsky[21,25] the formation of a "positive charged physical complex" between the substrate and a quaternary ammonium cation is responsible for the shift of $E_{1/2}$ towards positive values. In our opinion, the word "complex" is not suitable because it implies a coordination bond which cannot exist in the present case. Probably a Van der Walls' interaction is established between the dipolar substrate and the cationic charge; the result is an exalted polarisation of the carbon halogen bond. Such an interpretation was recently put forward by Peltier et al.[26] concerning the reduction of oximes and ketones.

The study of the acid 2a shows that $I*H^+$ cations are able to act as preprotonating species for the carboxylate anion since the wave height, when it is kinetically controlled, is increased when these ions are present. The same observation was previously made for the reduction of phenylglyoxylic acid oximes.[26]

It is worth reporting another ascertainment: emetine, strychnine and brucine exert an own influence in an ammoniacal buffer; then it seems that they can be adsorbed as protonated species though pH be higher than

the pK_a for the $I*H^+/I*$ couple. We think that ammonium ions favour the protonation of the inductor according to a kinetic process in which $I*H^+$ ions are consumed.

PREPARATIVE ELECTROLYSES

Reduction of the dibromide derivative 1a

Preparative electrolyses were carried out with a $10^{-4}M$ concentration of the different alkaloïds. Results are collected in Table 4. The following comments can be made. Optical yields varying from 8 to 42% are achieved with $I*$ inductors whereas methylstrychninium ions give only rise to a very slight induction.†

Emetine, strychnine and brucine preferentially lead to the R-enantiomer. The optical yield dows not depend on the working potential nor the pH of the supporting electrolyte when the inductor is emetine. On the other hand, when reductions are performed in the presence of strychnine or brucine, for a given pH value the optical yield increases when the potential is made more negative; for a given working potential, it is always higher in acetic buffer than in ammoniacal buffer.

With yohimbine, the S-enantiomer is preferentially formed but only if the electrolyses are conducted in an acetic buffer. Since the shift of $E_{1/2}$ induced by this alkaloïd is not important, the number of experiments is limited; however, the cathodic potential does not seem to affect the optical yield.

In Table 5 are given the results observed for various concentrations of the alkaloïds. It appears that the optical yield is maximum for an inductor concentration lying from 10^{-4} to $5 \times 10^{-4}M$.‡ These results confirm that induction is a surface phenomenon since the alkaloïds are efficient at low concentrations. As already pointed out[5] a decrease in temperature enhances the inductor adsorption and improves the optical yield; for a reduction at -1.4 V in acetic buffer, with $10^{-4}M$ emetine but at 5°C, the optical yield is $p_R = 45\%$.

Some conclusions which would be useful to discuss the mechanism of asymmetric induction can be stated.

Obtention of a high optical yield is related to the existence of marked interactions between the prochiral substrate and the alkaloid. If the intensity of these

---

†We have controlled that iodide anions brought in the solution at the same time than $I*Me^+$ cations have no influence on the optical yield. An experiment performed in acetic buffer at $E = -1.4$ V, in the presence of $10^{-4}M$ strychnine and $10^{-4}M$ potassium iodide gives $[\alpha]_D = -45.0°$.

‡In the ammoniacal buffer, we were not able to conduct experiments for concentrations of emetine higher than $2.10^{-4}M$. The $E_{1/2}$ of the dibromide is then shifted towards cathodic values and the polarographic waves merge with the hydrogen discharge.

Table 4. Observed values of optical yields after preparative electrolysis of 3.4 10⁻³M solutions of compound 1a in aqueous supporting electrolyte + ethanol (1:3 v./v.) with 10⁻⁴M concentration of the inductors

Supporting electrolyte	Working potential E (V SCE)	Strychnine		Méthylstrychninium		Brucine		Emetine		Yohimbine	
		$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R
0.5 M Buffered aqueous acetic acid	- 1.2							- 85.6	+ 42.1		
	- 1.3	- 34.3	+ 16.9			- 51.4	+ 25.3	- 80.4	+ 39.6	+ 17.1	- 8.4
	- 1.4	- 45.0	+ 28.1	+ 3.2	- 1.5	- 56.8	+ 28	- 80.4	+ 39.6	+ 16.1	- 7.9
	- 1.5	- 62.1	+ 30.6			- 64.3	+ 31.7	- 81.4	+ 40.1		
0.5 M Ammoniacal buffer	- 1.1							- 81.4	+ 40.1		
	- 1.2	- 25.7	+ 12.6			- 24.1	+ 11.9	- 77.1	+ 38		
	- 1.3	- 39.6	+ 19.5	+ 3.2	- 1.5	- 42.9	+ 21.1	- 81.4	+ 40.1	0	0
	- 1.4	- 46.0	+ 22.7			- 46.1	+ 22.7	- 78.2	+ 38.5	0	0
	- 1.5										

Table 5. Observed values of optical yield after preparative electrolysis of 3.4 10⁻³M solutions of compound 1a in aqueous supporting electrolyte + ethanol (1:3 v./v.) as a function of the concentration of the inductor

Concentration of the inductor	0.5 M Buffered acetic acid						0.5 M Ammoniacal buffer			
	Strychnine working potential = - 1.4 V SCE		Emetine working potential = - 1.4 V SCE		Yohimbine working potential = - 1.5 V SCE		Strychnine working potential = - 1.4 V SCE		Emetine working potential = - 1.2 V SCE	
	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R
5.10⁻⁵	- 39.6	+ 19.5	- 78.2	+ 38.5	+ 17.4	- 8.6	- 33.5	+ 16.5	- 66.4	+ 32.7
10⁻⁴	- 45.0	+ 22.2	- 80.4	+ 39.6	+ 16.1	- 7.9	- 39.6	+ 19.5	- 77.1	+ 38
2.10⁻⁴	- 57.8	+ 28.5	- 81.4	+ 40.1	+ 32.1	- 15.8	- 45.0	+ 22.2	- 77.1	+ 38
5.10⁻⁴	- 54.6	+ 26.9	- 90.0	+ 44.3	+ 33.2	- 16.3	- 43.0	+ 21.2		
10⁻³	- 53.6	+ 26.4	- 85.7	+ 42.2	+ 21.4	- 10.5	- 42.3	+ 20.1		

interactions decreases (as it occurs for brucine or strychnine in ammoniacal buffer), the optical yield decreases. It cancels when there is no longer interaction (this happens for yohimbine in ammoniacal buffer).

Nevertheless, occurence of interactions is not a sufficient condition since methylstrychninium cations induce nothing but a very low optical yield. We can conclude that a good induction is only attained if the adsorbed inductor exists as a protonated species I^*H^-. In that respect, the following experiment proves a contrario that strychnine is adsorbed as I^*H^+ in the ammoniacal buffer: the o.y. is only 2% when the reduction is carried out at -1.4 V in the presence of strychnine in a medium of pH $= 10$ which does not contain ammonium cations.

From another point of view, our results show that interpretation of the influence of the working potential may be ambiguous. In the studied case, the final carbanion is not conjugated; however, ρ varies as a function of the working potential when the inductor is strychnine or brucine but only little effect of this variable is observed with emetine. This suggests that adsorption of some alkaloïds may be altered by variations of the cathodic potentials.

Reduction of compounds 2a and 3a

The optical yield obtained by electrochemical reductions of the acid 2a (Table 6) and the parent ester 3a (Table 7), in the presence of a $10^{-4}M$ inductor, are clearly smaller than those reached in the case of the dibromide derivative 1a.

Emetine usually gives the best results but there is now preferential formation of the *S*-enantiomer. Yohimbine leads to a small excess of the *R*-enantiomer, even in ammoniacal buffer when starting from the ester. With strychnine or brucine, the sign of the rotatory power of the reduction product depends upon the pH of the supporting electrolyte. Concerning the acid, one could think that the nature of diffusing species is decisive since ρ_R is negative for pH $<$ pK$_a$ (diffusion of the molecular acid) and positive for pH $>$ pK$_a$ (diffusion of the carboxylate anion). Nevertheless this hypothesis is not consistent with the results observed for the ester in the presence of brucine: reductions in acetic and ammoniacal buffers also lead to opposite signs for ρ_R.

In a few cases optical yields achieved in the presence of I^*Me^+ cations are comparable in absolute value with those reached with strychnine. But in the medium where the two inductors produce a measurable induction, the sign of ρ_R is systematically different.

A circumstantial analysis of the above results would be uncertain because optical yields are too small and the variations from one experiment to another are generally of the magnitude of experimental error. However, one fact must be underlined: taking only into account a small but non-negligible induction, it appears that I^*Me^+ may be as an efficient inductor as I^*H^+ in the asymmetric electroreduction of monobromocyclopropanes.

MECHANISM OF ASYMMETRIC ELECTROCHEMICAL SYNTHESIS

The results of the present work allow us to rationalize the mechanism of electrochemical asymmetric synthesis.

A high optical yield cannot be reached if a racemic carbanion is formed at the cathode. The stereoselective protonation of such a species by an acidic inductor results only in a poor induction as shown by reductions of monobrominated derivatives. Moreover, the fact that

I^*Me^+ cations also induce small optical yields suggests that another mechanism is then possible. A diastereoselective interaction may take place between the carbanion and the inductor:

$$\left(\underset{/}{\overset{\backslash}{>}}C^-\right)_{\pm} + I^*Me^+ \rightleftarrows \left(\underset{/}{\overset{\backslash}{>}}C, IMe\right)^*.$$
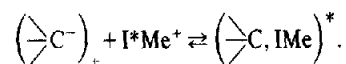
The stabilities of the two epimeric ion pairs are very low but sufficiently different to account for the obtainment of a small optical yield after protonation.

On the other hand, better optical yields are attained if the substrate offers two stereotopic faces as it is the case for the dibromide derivative. According to the presentation at the cathode made chiral by the adsorption of the alkaloïd, an optically active carbanion is produced. In all probability, the interactions made evident in the polarographic study command the orientation of the depolarizer. The stronger are these interactions, the higher is the optical yield.

Finally, it is necessary for the inductor to be adsorbed as a protonated species I^*H^+. In this way, the two hypothesis recalled in the introduction of the present paper are rather complementary. But as for its reaction with the carbanion, it is much more the proton-donating ability of the acidic inductor than its chirality which is of importance. If the adsorbed alkaloïd cannot act as an acid (I^* or I^*Me^-), the carbanion undergoes protonation far from the electrode and racemisation occurs.

In this respect, it will be noted that the low optical yield attained when the dibromide derivative is reduced in the presence of I^*Me^+ cations are always of the opposite sign of those produced by strychnine in the same experimental conditions. However since these two inductors have very similar structures, they may impose the same presentation of the substrate. The following interpretation can then be put forward: with adsorbed I^*H^+ cations, protonation of the carbanion essentially occurs with retention of the configuration resulting of the preferential presentation of the substrate; this is equivalent to a protonation by the cathode. When I^*Me^+ cations are used, only a small amount of the carbanion reacts in the near vicinity of the electrode; but in this case, the proton-donor is a constituant of the supporting electrolyte and it attacks back-side from the cathode.

It follows from the above conclusions that compounds possessing a prochiral carbon which is in a sp^2 hybridization state are the most suitable substrates for asymmetric electroreduction. But the present work shows that induction can also be achieved by monocleavage at a sp^3 carbon bearing two identical leaving groups.

Table 6. Observed values of optical yields after preparative electrolysis of $3.4 \cdot 10^{-3} M$ solutions of compound 2a in aqueous supporting electrolyte + ethanol (1:1 v./v.) with $10^{-4} M$ concentration of the inductors

Supporting electrolyte	Working potential E (V SCE)	Strychnine		Méthylstrychninium		Brucine		Emetine		Yohimbine	
		$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R
1 N H₂SO₄	– 1.0 – 1.1	0	0	0	0	+ 6.9	– 3.2	0	0	0	0
0.5 M Buffered chloro-acetic acid	– 1.0 – 1.1 – 1.2	+ 4.4	– 2	– 7.5	+ 3.5	+ 15 + 11.9	– 7 – 5.6	– 4.3 – 2.0 – 5.6 – 2.6 – 11.2 – 5.2		– 3.8	+ 1.8
0.5 M Buffered acetic acid	– 1.3 – 1.4 – 1.5	– 3.8	+ 1.9	0	0	– 4.4	+ 2.2	– 8.1 – 4.0 – 7.5 – 3.8 – 8.1 – 4.0		– 4.4	+ 2.2
0.5 M Ammonium acetate	– 1.4 – 1.5 – 1.6	0	0	0	0	– 2.5	+ 1.6	+ 6.2	– 3.8	0	0

Table 7. Observed values of optical yields after preparative electrolysis of $3.4 \cdot 10^{-3} M$ solutions of compound 3a in aqueous supporting electrolyte + ethanol (1:1 v./v.) with $10^{-4} M$ concentration of the inductors

Supporting electrolyte	Working potential E (V SCE)	Strychnine		Méthylstrychninium		Brucine		Emetine		Yohimbine	
		$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R	$[\alpha]_D$	ρ_R
0.5 M Buffered acetic acid	– 1.2 – 1.3 – 1.4 – 1.5	+ 3.0	– 1.5	– 3.7	+ 1.8	+ 2.4 0	– 1.2 0	+ 13.4 – 6.6 + 15.9 – 7.8 + 15.9 – 7.8 + 13.4 – 6.6		– 4.9	+ 2.4
0.5 M Ammoniacal buffer	– 1.1 – 1.2 – 1.3 – 1.4 – 1.5	0	0	– 4.9	+ 2.4	– 5.5 – 5.5	+ 2.7 + 2.7	+ 6.1 – 3.0 + 9.8 – 4.9 + 4.9 – 2.4		– 4.9	+ 2.4

Table 8. Specific rotations for active acid **2b** and ester **3b** in the different supporting electrolytes used

Supporting electrolyte	$[\alpha]_D^{25}$ for acid **2b**	$[\alpha]_D^{25}$ for ester **3b**
1N H_2SO_4	~ 216	~ 218
0.5 M Buffered chloracetic acid	~ 215	~ 227
0.5 M Buffered acetic acid	~ 200	~ 203
0.5 M Ammonium acetate	~ 162	~ 216
0.5 M Ammoniacal buffer	~ 161	~ 200

Preparative electrolyses

The cell reported by Moinet and Peltier has been used.[27] The mercury pool area is about 33 cm^2. The speed of the stirring system was fixed to 90 rpm; the working potential is made constant by the means of a Tacussel PRT potentiostat and the amount of electricity measured with a Tacussel IG 5 coulometer. For a typical run, $3,4\,10^{-3}$ and 10^{-4} respective molar concentrations of the substrate and the inductor were worked up at room temperature in 150 ml of the catholyte. $[\alpha]_D^{25}$ for the mixture of enantiomers resulting from a 2e reduction of the starting material is determined from the difference between specific rotations measured before and after electrolysis. The optical yield ρ_R is then

$$\rho_R = \frac{[\alpha]_D^{25}}{[\alpha_0]_D^{25}}$$

$[\alpha]_D^{25}$ being the specific rotation of the pure R-enantiomer measured in the same experimental conditions.

Starting materials

1,1-dibromo-2,2-diphenylcyclopropane **1a**, 1-bromo-1-carbomethoxy-2,2-diphenylcyclopropane **3a** and the parent acid **2a** have been obtained by known procedures.[23,28] All the inductors except I*Me$^+$, I^{-7} are commercially available compounds.

Reduced compounds

Two electron reductions of the starting materials, without the presence of any inductor, led to racemic compounds, identical to those already described.[24,29] Optically active 2,2-diphenylcyclopropane carboxylic acid **2b** and the parent ester have been resolved as described by Walborsky;[24] the absolute configuration of the levogyre enantiomer of **2b** $([\alpha]_D^{25} = -216°)$ is R.[16] We have plotted in Table 8 $[\alpha]_D^{25}$ values for $(-)R$ **2b** and **3b** measured in the different supporting electrolytes used for preparative reductions. At the present, nothing has been reported about optically active 1-bromo-2,2-diphenylcyclopropane **1b** and we failed in an attempt of stereo-specific synthesis according to the procedure used by Walborsky for 1-chloro 2,2-diphenylcyclopropane.[30]

Concerning the absolute configuration, by comparison with the parent chloro compound, we assume that the levogyre enantiomer of **1b** is R. First estimations of the specific rotations for the pure enantiomers have been obtained by Mannschreck:[31] liquid chromatography on an optically active stationary phase results in enriched samples of active **1b**; simultaneous recording of absorbance and rotatory power of the eluate led to an estimation of the optical purity and then $[\alpha_0]$. A recent improvement of the method[32] led to the value $[\alpha_0]_{365}^{31} = -724° \pm 22°$ for pure $(-)R$ enantiomer. At the same time, another sample of $(-)$ R **1b** obtained in our laboratory after repeated fractional crystallizations from water–ethanol mixtures was found to be optically pure. Its specific rotation did not vary with the supporting electrolyte and the values for $[\alpha_0]$ were $[\alpha_0]_{365}^{31} = -706°$ and $[\alpha_0]_D^{25} = -203°$; the latter has been used for calculations of ρ_R.

Acknowledgements—Acknowledgment is made to the Centre National de la Recherche Scientifique (ATP Energie et Matières premières 1979) for partial support of this work. The authors are grateful to Prof. Mannschreck, University of Regensburg, R.F.A., and his coworkers for kind assistance in the determination of the specific rotatory power of 1-bromo-2,2-diphenylcyclopropane.

REFERENCES

[1a] L. Horner and D. Degner, *Tetrahedron Lett.* 5889 (1968); [b] L. Horner and D. Degner, *Electrochim. Acta* **19**, 611 (1974); [c] D. Brown and L. Horner, *Liebigs Ann. Chem.*, **77** (1977). [d] L. Horner and D. H. Skaletz, *Ibid.* 1365 (1977).

[2] W. J. M. Van Tilborg and C. J. Smit, *Rec. Ibid. Trav. Chim.*, **97**, 89 (1978).

[3] R. N. Gourley, J. Grimshaw and P. G. Millar, *J. Chem. Soc. C* 2318 (1970).

[4] E. Kariv, H. A. Terni and E. Gileadi, *Electrochim. Acta* **18**, 433 (1973); *J. Electrochem. Soc.* **120**, 639 (1973).

[5] M. Jubault, E. Raoult and D. Peltier, *Electrochim. Acta* **19**, 865 (1974).

[6] M. Jubault, E. Raoult and D. Peltier, *Ibid.* **25**, 1359 (1980).

[7] J. Kopilov, E. Kariv and L. L. Miller, *J. Am. Chem. Soc.* **99**, 3450 (1977).

[8] R. Hazard, J. Sarrazin and A. Tallec, *Electrochim. Acta* **24**, 239 (1979).

[9] M. Jubault, E. Raoult, J. Armand and L. Boulares, *J. Chem. Soc. Chem. Comm.* 250 (1977).

[10] M. Jubault, E. Raoult and D. Peltier, *Electrochim. Acta* **21**, 407 (1976).

[11] J. Casanova and L. Eberson, *The Chemistry of the Carbon Halogen Bond* (Edited by S. Patai), Vol. 2, p. 979. Wiley, London (1973).

[12] J. L. Webb, C. K. Mann and H. M. Walborsky, *J. Am. Chem. Soc.* **92**, 2042 (1970).

[13] K. P. Butin, *Russ. Chem. Rev.* **40**, 525 (1971).

[14] A. J. Fry and R. H. Moore, *J. Org. Chem.* **33**, 1283 (1968).

[15] R. E. Erickson, R. Annino, M. D. Scanlon and G. Zon, *J. Am. Chem. Soc.* **91**, 1767 (1969).

[16] H. M. Walborsky, F. J. Impastato and A. E. Young, *Ibid.* **86**, 3283 (1964).

[17] M. Julia, S. Julia, B. Bemont and G. Tchernoff, *C.R. Acad. Sci.* **248**, 242 (1959).

[18] H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.* **78**, 872 (1956).

[19] R. Annino, R. E. Erickson, J. Michalovic and B. Mc Kay, *Ibid.* **88**, 4424 (1966).

[20] R. Hazard, S. Jaouannet and A. Tallec, *J. Electroanal. Chem.* **111**, 397 (1980).

[21] S. G. Mairanovsky, *Elektrokhimiya* **8**, 424 (1972).

[22] K. P. Butin, *Doklady Akad. Nauk SSSR* **4**, 878 (1973).

[23] H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *J. Am. Chem. Soc.* **83**, 2517 (1961).

[24] H. M. Walborsky and F. M. Hornyak, *Ibid.* **77**, 6026 (1955).

[25] S. G. Mairanovsky and F. K. Ignat'eva, *Elektrokhimiya* **14**, 876 (1978).

[26] M. Jubault, E. Raoult and D. Peltier, *Electrochim. Acta* **24**, 1219 (1979).

[27] C. Moinet and D. Peltier, *Bull. Soc. Chim. Fr.* 635 (1969).

[28] *Org. Synth.* **56**, 32 (1977).

[29] J. W. Hausser and M. J. Grubber, *J. Org. Chem.* **37**, 2650 (1972).

[30] H. M. Walborsky, L. E. Allen, H. J. Traenckner and E. J. Powers, *Ibid.* **36**, 2937 (1971).

[31] A. Mannschreck, M. Mintas, G. Becher and G. Stühler, *Angew. Chem.* **92**, 490 (1980).

[32] R. Küspert, G. Stühler, A. Mannschreck, in press.