[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

The Stereochemistry of the SN2′ Reaction. II[1]

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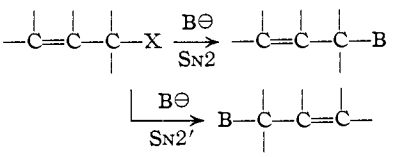
Bimolecular displacement reactions with rearrangement (SN2′) take place in allylic systems so that the entering substituent comes in *cis* to the departing group. This has been demonstrated by studying the products and the kinetics of the reaction of *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates with piperidine and malonic ester anion.

Introduction

Unsaturated systems bearing a displaceable group, X, in an allylic position may undergo bimolecular substitution without rearrangement (SN2) or with rearrangement (SN2′)

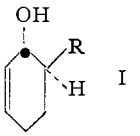


At the time this investigation was begun, only two convincing examples of the SN2′ mechanism were available, the displacement of α-ethylallyl chloride with malonate ion[2] and that of α-methylallyl chloride with diethylamine.[3] Actually, we have pointed out elsewhere that the long known reactions of the halocodides can only be interpreted satisfactorily if these substances are assumed to undergo displacement by the SN2′ mechanism.[4] More recently, a number of other examples of the reaction have been brought to light.[5–8]

The general conclusion which emerges from the available data is that the SN2′ reaction does not normally compete with the SN2 displacement. This has been shown especially clearly in the work of England,[5,7] using the reaction of radioactive bromide ion on α- and γ-methylallyl bromide. Nevertheless, the SN2′ reaction may be made the predominant or exclusive one by interfering with the normal SN2 process, either sterically or electrically, or both.[6]

Although the SN2′ process is thus well documented, there remains the problem of the intimate mechanism of the reaction, and in particular the question of the spatial relationship of the entering and departing groups, and it is with this aspect that this paper is concerned.

For the purpose at hand, it appeared that the *trans*-6-alkyl-2-cyclohexen-1-ols described in the preceding paper[9] would be substances of choice, since in these compounds (I) the SN2 reaction is hindered by the presence of the R group at the back



I

side of the hydroxyl group. Additionally, the R group serves the purpose of establishing the orientation of the displacing entity in an SN2′ reaction: entry *cis* or *trans* to the displaced hydroxyl resulting in *trans*- or *cis*-4-alkyl-2-cyclohexen-1-yl derivatives, respectively.

Results

The first problem which had to be solved was the transformation of the hydroxyl group in I into a displaceable substituent. *p*-Toluenesulfonic acid esters were initially considered, but proved impossible to obtain. Reaction with *p*-toluenesulfonyl chloride in pyridine at temperatures varying from −45 to +5°[10] led only to dehydration or unchanged starting materials, depending on the reaction time.

The procedure of Hahn and Walters,[11] addition of powdered potassium hydroxide to a solution of I and *p*-toluenesulfonyl chloride in ether at 0°, gave again olefin or starting materials. Similar results were obtained with the non-cyclic α-methylallyl alcohol, although the primary γ-methylallyl isomer gave excellent yields of tosylate by this method.

Equally unsuccessful was the method of Roberts and Chambers[12] which involved transformation of the alcohol into its salt with sodium hydride in ether, followed by refluxing with *p*-toluenesulfonyl chloride until completion of the reaction. Dehydration was again the sole result, as in a variant utilizing the lithium salt prepared in ether with *n*-butyllithium.

A final attempt was made to obtain the *p*-toluenesulfonates by the oxidation of the readily prepared *p*-toluenesulfinates with hydrogen peroxide.[13] Again the products were olefins.

We then turned to the possibility of using carboxylic ester derivatives of I, as the feasibility of displacement reactions with carboxylic esters has been demonstrated in some simple cases.[14] It is

(1) Part I, G. Stork and W. N. White, THIS JOURNAL, **78**, 4604 (1956).

(1a) Public Health Service Predoctoral Fellow, 1951-1953.

(2) R. E. Kepner, S. Winstein and W. G. Young, THIS JOURNAL, **71**, 115 (1949).

(3) W. G. Young, I. D. Webb and H. L. Goering, *ibid.*, **73**, 1076 (1951).

(4) G. Stork in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, 1952, p. 185. A full consideration of this matter is deferred until the following paper.

(5) B. D. England and E. D. Hughes, *Nature*, **168**, 1002 (1951).

(6) P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 3325 3331, 3628 (1952).

(7) B. D. England, *ibid.*, 1615 (1955).

(8) W. G. Young, R. A. Clement and Chin-Hua Shih, THIS JOURNAL, **77**, 3061 (1955).

(9) G. Stork and W. N. White, *ibid.*, **78**, 4604 (1956).

(10) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(11) F. L. Hahn and H. Walters, *Ber.*, **54**, 1531 (1921).

(12) J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 5034 (1951).

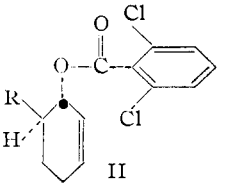
(13) *Cf.* R. M. Hann, *ibid.*, **57**, 2166 (1935).

(14) R. Willstätter and W. Kahn, *Ber.*, **35**, 2757 (1902); L. P. Hammett and H. L. Pfluger, THIS JOURNAL, **55**, 4079 (1933); J. F. Bunnett, M. M. Robison and F. C. Pennington, *ibid.*, **72**, 2378 (1950).

evident that to be serviceable the esters should be hindered toward attack by nucleophilic reagents at the ester carbonyl, and they should be derived from strong acids to facilitate their release as carboxylate ions in the displacement reactions. It was felt that benzoic esters substituted in positions 2 and 6 with halogen might be suitable for our purpose.

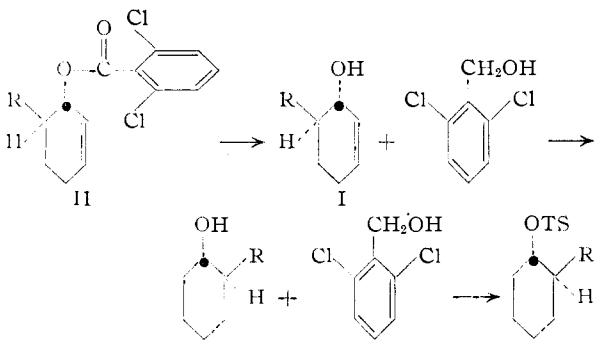
Attempts to prepare esters of I by reaction with 2,4,6-tribromobenzoyl chloride in pyridine solution were unsuccessful, the products after addition of water being unchanged I and tribromobenzoic anhydride. It was anticipated that better results might be obtained with a benzoyl chloride substituted in positions 2 and 6 by the smaller chlorine atoms. For this purpose 2,6-dichlorobenzoyl chloride was prepared by hydrolysis of commercially available 2,6-dichlorobenzal chloride to the aldehyde,[15] followed by oxidation with potassium permanganate to the acid which was then transformed into the known acid chloride[16] with thionyl chloride.

The alcohols I were successfully transformed into the 2,6-dichlorobenzoates II by heating with 2,6-dichlorobenzoyl chloride in pyridine for 2 hr. on the steam-bath. Unreacted acid chloride was converted to the amide by passing anhydrous ammonia into the reaction mixture, and the mixture of ester, amide and unreacted alcohol was washed with petroleum ether through a column of alumina. Under these conditions the amide and alcohol remained on the column and pure esters were isolated in 70–80% yields. The 2,6-dichlorobenzoates of α- and γ-methylallyl alcohol and of 2-cyclohexen-1-ol were liquids which were purified by distillation, while the esters II (R = methyl, isopropyl, *t*-butyl) were solids and were recrystallized from petroleum ether.



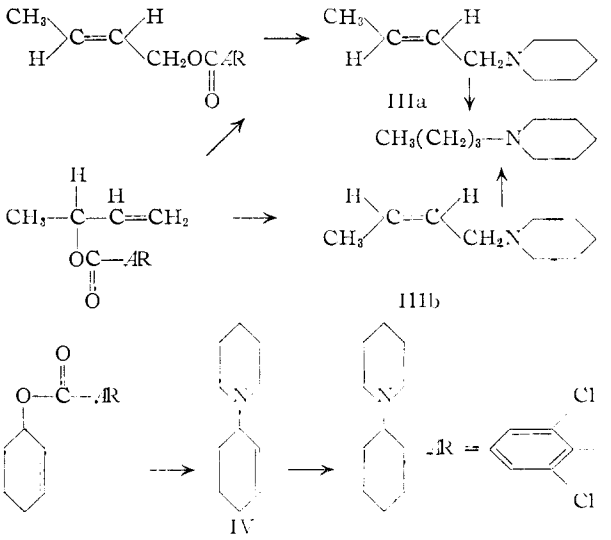
II

It was necessary to show that no rearrangement attended the rather drastic esterification reaction. This was done by reduction of each dichlorobenzoate II with lithium aluminum hydride to give a mixture of I and 2,6-dichlorobenzyl alcohol which was hydrogenated catalytically to a mixture of the benzyl alcohol and alkylcyclohexanol. The latter was proved to be the expected *trans*-2-alkylcyclohexanol by conversion to its crystalline *p*-toluenesulfonate, obtained pure in 80–95% yield after one recrystallization from petroleum ether, and comparison with the *p*-toluenesulfonate of the proper authentic *trans*-2-alkylcyclohexanol.[17]



II I

The feasibility of displacement reactions on allylic 2,6-dichlorobenzoates was established by studying the reaction of piperidine with the 2,6-dichlorobenzoates of γ- and α-methylallyl alcohol and of cyclohexenol. From the γ-methylallyl ester and piperidine, at 130° for 24 hours, an 80% yield of unsaturated amine IIIa was obtained which was reduced in 85% yield to N-butylpiperidine. Under the same conditions the α-methylallyl isomer gave 71% of a mixture of *trans*-(IIIa) and *cis*-(IIIb) unsaturated amines, reduced in 82% yield to N-butylpiperidine. Finally, the ester of 2-cyclohexen-1-ol gave 75% of allylic amine IV which was reduced to N-cyclohexylpiperidine. These reactions are[18]



IIIa IIIb IV

The results just described demonstrate the possibility of displacement reactions on II and, in the case of the methylallyl esters, they parallel the results of Young, Webb and Goering with the methylallyl chlorides and dimethylamine.[3]

When the *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates were treated with piperidine under similar conditions, unsaturated amines V were obtained in 60–73% yields. These were hydrogenated over platinum to give substituted piperidines which were shown to be N-(*trans*-4-alkylcyclohexyl)-piperidines (VI) by mixed melting point comparisons of the picrates, picrolonates and methiodides with those of the independently synthesized derivatives of the authentic amines.[19]

(15) *Cf.* A. Oppenheim, *Ber.*, **2**, 212 (1869).

(16) J. B. Cohen and S. H. C. Briggs, *J. Chem. Soc.*, **83**, 1213 (1903).

(17) The success of this method depends upon the fact that under the conditions used the 2,6-dichlorobenzyl *p*-toluenesulfonate forms a quaternary salt and is not isolated.

(18) The isolation and characterization of the unsaturated and saturated amines are described fully in the Experimental section.

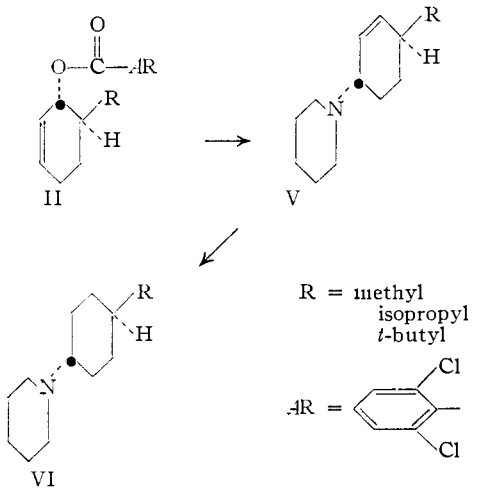
(19) Authentic N-(*trans*-4-alkylcyclohexyl)-piperidines were prepared from the *p*-toluenesulfonates of pure *cis*-4-alkylcyclohexanols by displacement with piperidine. These authentic substances are described in the Experimental section.

The melting points of the picrates of the N-(*cis*-4-alkylcyclohexyl)-piperidines[20] were different from those of the corresponding *trans* substances and depressed their melting points. Furthermore, the infrared spectra of the hydrogenated amines from the displacement reactions were identical with the spectra of the corresponding authentic N-(*trans*-4-alkylcyclohexyl)-piperidines and different from those of the *cis* isomers.

The homogeneity of the amines obtained by hydrogenation—and hence of the unsaturated amine precursors—is demonstrated by the fact that their crude picrates, obtained in 85% yields, melted within 4° and their crude methiodides (90% yield) within 3° of the melting points of the pure derivatives.

That the unsaturated amines were allylic amines, as required, was confirmed by hydrogenation of their quaternary methiodides. This led to hydrogenolysis with the formation of the corresponding alkylcyclohexane, as expected from the work of Howton.[21]

Finally, it was shown that the unreacted esters recovered from the displacement reactions were identical with the starting II. These were also recovered pure and in high yield after heating for a day in *m*-xylene at 130° in the presence or absence of dimethylaniline. Rearrangement of the ester prior to displacement is therefore ruled out and the reaction may be represented as



The material balances, determined as described in the Experimental section, are shown in Table I in percentage of product based on the weight of allylic 2,6-dichlorobenzoate used.

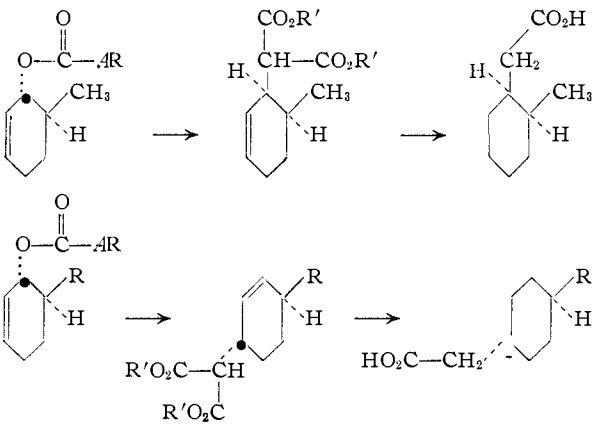
The same displacement reactions were carried out in *m*-xylene solution by heating at 130° for 75 hr. Under these conditions the reactions did not proceed to completion, but the amines isolated were identical with those obtained without solvent, and by the same tests as used previously were shown to be at least 80–90% pure. Again, the recovered esters were unchanged II.

Displacement reactions were now studied with the dichlorobenzoates and malonic ester ion; the *trans* 6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates (II) were dissolved in solutions of sodium di-*n*-butylmalonate in *n*-butyl alcohol. The solutions were refluxed 3 days and the resulting malonic ester was hydrogenated in methanol solution over platinum. Except in the case of II, R = methyl, the hydrogenation was very difficult and required repeated addition of fresh catalyst. Hydrolysis and decarboxylation of the hydrogenated malonic esters gave alkylcyclohexylacetic acids which were purified by distillation and compared with authentic alkylcyclohexylacetic acids of known configuration[22] by melting points and mixed melting points of the acids themselves (if solid), of the benzylamine salts and of the amides. These comparisons demonstrated that when R in formula II is methyl direct displacement with inversion (SN2) occurred, but with R = isopropyl or *t*-butyl the products were those of rearrangement, *trans*-4-alkyl-2-cyclohexen-1-ylmalonic esters.[23]

The purity of the crude *trans*-4-alkylcyclohexylacetic acids obtained when the alkyl group was isopropyl or *t*-butyl was estimated to be 70–80% and 80–90%, respectively, by comparison with the melting points of the pure acids. The *cis*-2-methylcyclohexylacetic acid was at least 80–90% pure, on the basis of the yield of its pure benzylamine salt. The relatively impure product when the alkyl group was isopropyl may be due to some SN2 displacement or to incomplete hydrogenation of the unsaturated malonic ester.

The possibility that the cyclohexenyl dichlorobenzoates rearranged before displacement was again ruled out by showing that the pure esters could be recovered in about 80% yield after heating for 75 hr. at 104.7 ± 0.10° in dry *n*-butyl alcohol.

We may now represent the malonic ester displacements as



(20) Authentic N-(*cis*-4-alkylcyclohexyl)-piperidines were prepared from pure *trans*-4-alkylcyclohexanol *p*-toluenesulfonates and piperidine as described in the Experimental section.

(21) D. R. Howton, THIS JOURNAL, **69**, 2555 (1947).

(22) The authentic *trans*-4-alkylcyclohexylacetic acids were prepared from the *p*-toluenesulfonates of pure *cis*-4-alkylcyclohexanols and the *cis*-2-methylcyclohexylacetic acid from the *p*-toluenesulfonate of pure *trans*-2-methylcyclohexanol. Full details will be found in the Experimental section.

(23) We would like to draw attention here to a point of considerable synthetic importance: the displacements with malonic ester result in the formation of carbon-carbon bonds of predictable stereochemistry by displacement of the 2,6-dichlorobenzoates of allylic alcohols of known configuration. This result is important since we have shown that the ordinarily serviceable toluenesulfonates are not in general obtainable in such cases.

TABLE I

THE REACTION OF ALLYLIC 2,6-DICHLOROBENZOATES WITH PIPERIDINE

2,6-Dichlorobenzoate	Amine	Acid[a]	Recovd. ester II	1,3-$C_6H_4Cl_2$
γ-Methylallyl	79	85	4	4
α-Methylallyl	71	78	8	6
2-Cyclohexen-1-yl	75	64	19	8
6-Methyl-2-cyclohexen-1-yl	63	49	32	7
6-Isopropyl-2-cyclohexen-1-yl	73	64	20	5
6-*t*-Butyl-2-cyclohexen-1-yl	60	58	34	3

[a] 2,6-Dichlorobenzoic acid.

Kinetic Results

A. Displacement with Piperidine.—The kinetics of the reaction were studied by heating at 129.5 ± 0.1°, for varying lengths of time, mixtures of the proper *trans*-6-alkyl-2-cyclohexen-1-yl 2,5-dichlorobenzoate (II) and piperidine in *m*-xylene solution. The tertiary amine present after reaction was determined by treating the total mixture with an excess of acetic anhydride to acetylate the secondary amine. The unacetylated tertiary amine was determined by titration with perchloric acid in glacial acetic acid, using a very sensitive titrimeter and quinhydrone and calomel electrodes to determine the end-point. The tertiary amine was determined rather than the 2,6-dichlorobenzoic acid liberated during the reactions since this acid was shown to undergo some decarboxylation under the conditions of the reactions.

The rate constants were calculated from the results by using the usual expressions

$$k_1 = \frac{1}{t} \ln \frac{a}{a - x}; \quad k_2 = \frac{1}{t(b - a)} \ln \frac{a(b - x)}{b(a - x)}$$

in which k_1 is the specific first-order rate constant in reciprocal hours, k_2 is the specific second-order rate constant in liters per mole hours, t is the time in hours, a is the concentration of ester in moles per liter, b is the concentration of piperidine in moles per liter and x is the concentration of tertiary amine at time t in moles per liter. A typical determination gave results as in Table II, and the values of k_1 and k_2 are shown in Table III.

TABLE II

DISPLACEMENT OF II, R = ISOPROPYL, WITH PIPERIDINE

$a = 0.4206$, $b = 1.5713$

Hour	$k_1 \times 10^3$	$k_2 \times 10^3$	Hour	$k_1 \times 10^3$	$k_2 \times 10^3$
14.50	2.28	1.46	64.50	2.25	1.46
20.75	2.26	1.45	73.00	2.31	1.50
39.75	2.26	1.46	86.00	2.21	1.44
51.75	2.22	1.43	106.75	2.23	1.46

TABLE III

RATE CONSTANTS FOR THE DISPLACEMENT OF II WITH PIPERIDINE

	$k_1 \times 10^3$	$k_2 \times 10^3$	a	b
II, R = methyl	1.57 ± 0.03	0.624 ± 0.01	0.3515	2.5355
II, R = isopropyl	2.25 ± .03	1.46 ± .01	.4206	1.5713
	2.31 ± .01	1.38 ± .01	.2286	1.6718
	2.35 ± .02	1.44 ± .01	.0925	1.5368
II, R = *t*-butyl	5.43 ± .04	3.48 ± .01	.1023	1.5767
	5.55 ± .11	3.45 ± .02	.4158	1.6546
	6.36 ± .06	3.50 ± .03	.2227	1.8318

An inspection of the results makes it clear that the above data are not sufficient to tell whether the reaction is first or second order, especially as k_1 did not show much drift in the course of any one determination.

The order was then determined with respect to each reactant by the differential method of van't Hoff.[24] If the concentration of one of the reactants, say a, is held constant and the other is varied, then $-(\mathrm{d}(b)/\mathrm{d}t)_1 = k(a)^m(b)_1^n$ and $-(\mathrm{d}(b)/\mathrm{d}t)_2 = k(a)^m(b)_2^n$. This gives $(\mathrm{d}(b)/\mathrm{d}t)_1/(\mathrm{d}(b)/\mathrm{d}t)_2 = (b)_1^n/b_2^n$. If $\mathrm{d}(b)/\mathrm{d}t$ is set equal to the finite increment $\Delta(b)/\Delta t$, then it is possible to evaluate the order n with respect to b. If $\Delta(b)$ is small the error will not be large. Thus, $\Delta(b)_1/\Delta t_1/\Delta(b)_2/\Delta t_2 = (b)_1^n/(b)_2^n$, and if conditions are chosen so that $\Delta t_1 = \Delta t_2$ and $(b)_2 = 2(b)_1$ then $\Delta(b)_1/\Delta(b)_2 = {}^1/_2{}^n$ and $n = (\log \Delta(b)_2/\Delta(b)_1)/\log 2$. The order m with respect to a may be found similarly: $m = (\log \Delta(a)_3/\Delta(a_1))/\log 2$. The values of m and n thus obtained are shown in Table IV.

TABLE IV

	m	n
II, R = methyl	1.15	1.03
II, R = isopropyl	1.12	1.01
II, R = *t*-butyl	1.07	0.96

These results demonstrate the second-order nature of the reaction between piperidine and the 6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates.

B. Displacement with Malonate Ion.—The kinetics of this reaction were studied by heating a mixture of *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate and sodium di-*n*-butylmalonate in *n*-butyl alcohol at 104.7 ± 0.1° for varying lengths of time. The unreacted sodium malonic ester was determined by titration with perchloric acid solution using *m*-cresol purple as indicator. The rate constants were determined as discussed above and the results are shown in Table V, together with the order in dichlorobenzoate (m) and malonic ester anion (n).

TABLE V

DISPLACEMENTS WITH MALONIC ESTER ANION ON II

	$k_1 \times 10^2$	$k_2 \times 10^2$	m	n
II, R = methyl	1.91 ± 0.15	3.51 ± 0.06	1.05	0.93
II, R = isopropyl	4.46 ± .41	8.41 ± .13	1.08	.88
II, R = *t*-butyl	6.62 ± .51	12.9 ± .03	0.93	.95

In this case there was considerable drift in the first-order rate constants. The order in dichlorobenzoate and malonic ester anion was nevertheless determined and confirmed the bimolecular nature of the reaction.

The rate of solvolysis of the 6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates in dry *n*-butyl alcohol was determined by heating the esters for varying periods of time at 104.7 ± 0.1°. The results are shown in Table VI.

TABLE VI

RATES OF SOLVOLYSIS OF 6-ALKYL-2-CYCLOHEXEN-1-YL 2,6-DICHLOROBENZOATES

	$k_1 \times 10^3$
II, R = methyl	0.854 ± 0.20
II, R = isopropyl	1.71 ± .08
II, R = *t*-butyl	2.51 ± .09

(24) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N.Y., 1950, p. 14.

Discussion

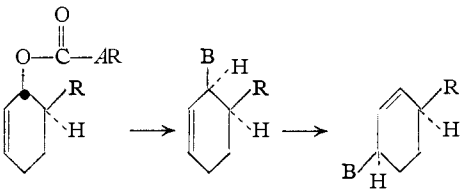
The results obtained in the displacement reactions with piperidine and malonic ester anion on *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates demonstrate unambiguously that all these displacements follow second-order kinetics, and the reactions which lead to rearrangement are therefore SN2′.

The possibility of rearrangement of the initial dichlorobenzoates is ruled out because recovered unreacted esters were identical with the starting materials and experiments in which the dichlorobenzoates were heated under the same conditions as in the actual displacements, but leaving out the displacing agent, led again to almost complete recovery of the starting dichlorobenzoates.

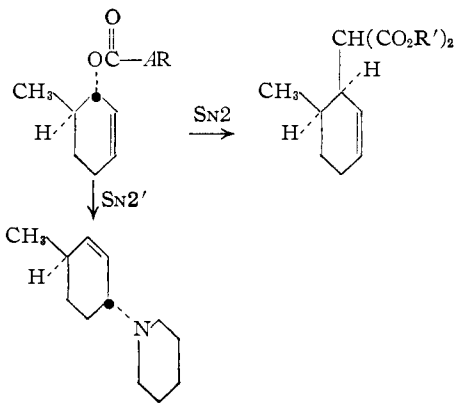
The possibility of a rate-determining ionization of the dichlorobenzoates, followed by fast reaction with the displacing anion, is ruled out because even in the favorable case of *n*-butyl alcohol solvent, the rate of first-order solvolysis is such that only 3–4% of the reaction could possibly follow this course.

The possibility of *trans* SN2′ attack followed by rearrangement, which is barely conceivable in the case of displacement by piperidine, is ruled out by the use of malonic ester anion. In the latter case the rearrangement would involve the breaking of a carbon–carbon bond and need not be considered.

Finally, the use of a cyclic system allows ruling out initial slow SN2 displacement followed by a fast rearrangement of the product (SN1′) as this would lead to *cis*-4-alkylcyclohexyl derivatives

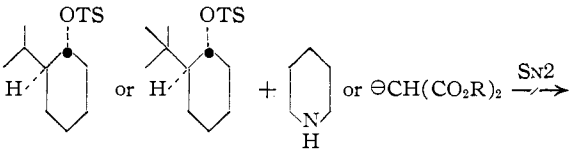


In the case of the displacements with piperidine, all three *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates gave exclusively SN2′ products. Even a 6-methyl group *trans* to the dichlorobenzoate hindered approach leading to SN2 reaction enough that the sole product was that of rearrangement. On the other hand, and very significantly, the methyl group was not enough to prevent normal SN2 displacement with malonic ester anion

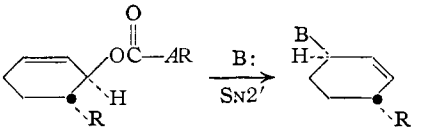


This cannot be the result of smaller steric interference to the approach of the bulkier malonic ester anion and is good evidence for a special advantage of piperidine. This could be attributed to two causes: the neutral piperidine might be expected to be better able to approach the *p*-electron system of the allylic double bond than the negatively charged malonic ester ion; and there will be coulombic repulsion in the transition state, in the latter case, between the entering anion and departing dichlorobenzoate ion. Secondly, hydrogen bonding as postulated by Young, *et al.*,[3] will help the SN2′ reaction with the secondary amine molecule while it is, of course, impossible with the malonic ester anion.

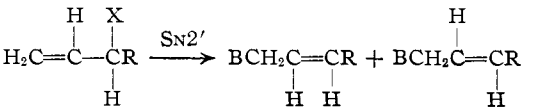
With a *trans*-6-isopropyl group the result with malonic ester anion is changed over to SN2′, although our results do not exclude a very small amount of SN2 reaction in this case. The effectiveness of the isopropyl and *t*-butyl groups *trans* to the displaceable group on the adjacent carbon is well illustrated by the fact that no displacement could be achieved with *trans*-2-isopropyl- or *trans*-2-*t*-butyl-cyclohexanyl *p*-toluenesulfonate and either piperidine or malonic ester anion



In all cases in which SN2′ reaction was observed in this work the displacing group entered the molecule *cis* to the departing substituent

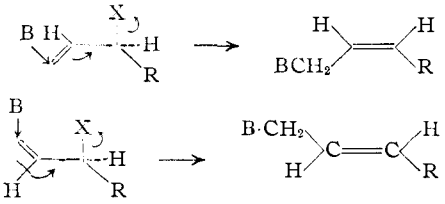


We would like to draw attention here to an interesting point of stereochemistry. We have pointed out that displacement with piperidine on α-methylallyl alcohol 2,6-dichlorobenzoate gives both *cis*- and *trans*-N-(γ-methylallyl)-piperidine (IIIa and IIIb). Similarly, Young, Webb and Goering[3] obtained both *cis*- and *trans*-N-(γ-methylallyl)-dimethylamine from the action of α-methylallyl chloride on dimethylamine. Again de la Mare and Vernon obtained *cis* and *trans* products from the SN2′ displacement of thiophenolate ion on 3,3-dichloro-1-propene.[6] In all these cases we have the results



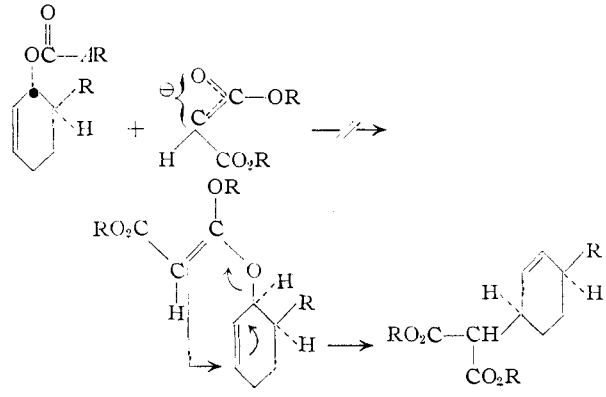
Some confusion[25] has resulted from the juxtaposition of these facts with our demonstration of the *cis* stereochemistry *of the entering and departing groups*. This stereochemistry for the SN2′ reaction is, of course, compatible with the results in acyclic cases, as is easily seen from the formulation

(25) J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1956, p. 129.



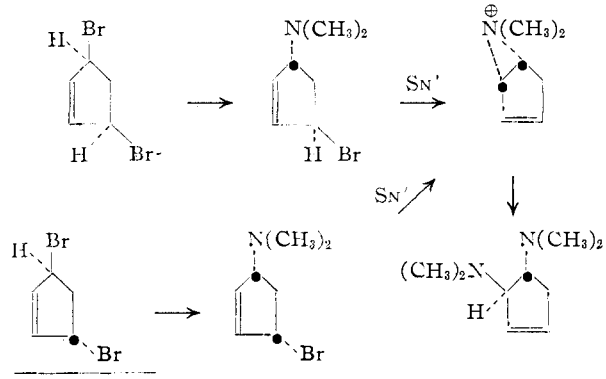
The *cis* and *trans* products result from two different conformations of the transition state, but *both of them are formed through cis entry of the displacing group.*

It is worth drawing attention to the fact that our results with malonic ester anion cannot be interpreted on the basis of the suggestion of Dewar[26,27] that apparent SN2′ reactions with malonic ester anion might be the result of slow SN2 O-alkylation, followed by fast Claisen type rearrangement of the intermediate; such a path would have led in our cases to *cis*-4-alkylcyclohexylmalonic esters and this is contrary to fact.



The preferred *cis* stereochemistry of departing and entering group which has thus been demonstrated is in keeping with the subsequently demonstrated *cis* stereochemistry in E-2′ reactions.[28]

In an interesting paper, Cope, *et al.*,[29] showed that the reaction of either *cis*- or *trans*-3,5-dibromocyclopentene with dimethylamine gives *trans*-1,2-bis-(dimethylamino)-3-cyclopentene, a result which was explained as (SN′ being the symbol for the internal SN2′ type reaction)



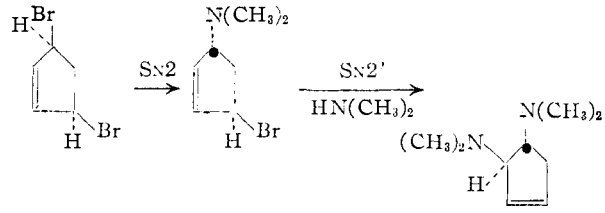
(26) M. J. S. Dewar, *Bull. soc. chim.*, **18**, C43 (1951).

(27) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, Eng., 1953, p. 592.

(28) S. J. Cristol, W. Barasch and C. H. Tieman, THIS JOURNAL, **77**, 583 (1955).

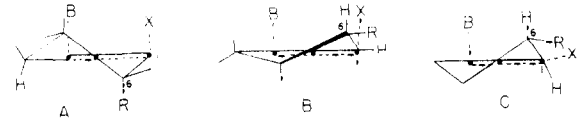
(29) A. C. Cope, L. L. Estes, Jr., J. R. Emery and A. C. Haven, Jr., *ibid.*, **73**, 1199 (1951).

This would imply SN′ reaction either *cis* or *trans*. A more likely explanation on the basis of the foregoing discussion would be that the *cis*-dibromo compound gives the final product by the route



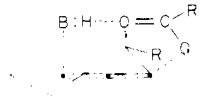
The demonstrated stereochemistry of the SN2′ reaction justifies the theoretical assumptions of Young, Webb and Goering[3] regarding the probable geometry of the transition state in SN2′ reactions, but our results with malonic ester anion make it necessary to modify the previous view that with negatively charged nucleophilic reagents SN2 attack seems to be the general rule.[3] This need not always be the case, depending on the steric situation.

A final aspect of the reaction will now be discussed. Of the three possible transition states, A, B and C, it would seem that B or C must be the favored situation as the substituent R is axial in



A and one might expect a decrease in rate in going from R = methyl to R = *t*-butyl, whereas there is actually a *very slight increase, with piperidine as well as with malonic ester anion.* Actually, B, although a half boat, is better than this implies because the opposition between the hydrogen on C_6 and the dichlorobenzoate group (X) on C_1 gets relieved as the C–X bond becomes stretched and the opposition between the alkyl group (R) on C_6 and the hydrogen on C_1 becomes less as the latter rotates upward during the transformation of C_1 from a tetrahedral to a trigonal configuration. It is nevertheless difficult to see why conformation B should not become of higher energy as the size of R increases.

In situation C the angle of the C–X bond with the ring is somewhat less favorable for the elimination process, but this may be compensated by the fact that the ring is in the lowest energy conformation. It should be noted that since the cases under discussion involve a group X, which is a carboxylic ester, hydrogen bonding (*e.g.* with piperidine) is still possible even in conformation C



It is further in favor of C that the C–X bond is somewhat more axial than an ordinary equatorial bond ("quasi equatorial") because of its allylic

situation.[30] Finally, C is undoubtedly favored by electrostatic repulsion in those cases in which the entering group bears a negative charge (*e.g.*, malonic ester anion).[31]

Experimental

2,6-Dichlorobenzaldehyde.—Commercial 2,6-dichlorobenzal chloride (498 g.) was stirred during 90 minutes into 750 cc. of 95% sulfuric acid maintained at 90–95°. After stirring for an additional hour at that temperature, hydrogen chloride evolution ceased and the mixture was cooled and poured on 3 kg. of ice. The solid was filtered off, crushed, washed with water, dried in air and crystallized from ligroin to give 353 g. (93%) of the white, crystalline aldehyde, m.p. 69.0–70.0° (lit.[32] m.p. 71°).

2,6-Dichlorobenzoic Acid.—To a stirred mixture of 353 g. of 2,6-dichlorobenzaldehyde and 1.5 l. of water, kept at 70°, was added 605 g. of solid potassium permanganate at such a rate as to maintain refluxing. The addition required 2 hr., and after its completion (persistence of purple color) the mixture was stirred 0.5 hr. longer. Ice-cold 50% sulfuric acid (800 cc.) was added, followed by enough saturated sodium bisulfite solution to dissolve the manganese dioxide. The mixture was cooled to 10° and filtered. The precipitate was washed with water and dissolved in 800 cc. of 10% sodium hydroxide solution. This solution was extracted with ether several times. The aqueous layer was boiled to expel the ether, acidified with concd. hydrochloric acid and cooled to 10°. The precipitate was filtered off, washed with water, dried in air and crystallized from ethanol to give 245 g. (64%) of white, crystalline 2,6-dichlorobenzoic acid, m.p. 141.2–142.0° (lit.[33] m.p. 143–144°).

2,6-Dichlorobenzoyl Chloride.—The acid chloride was prepared by refluxing 222 g. of 2,6-dichlorobenzoic acid and 250 cc. of thionyl chloride for 2 hr. Distillation of the residue after removal of the excess thionyl chloride at atmospheric pressure gave 94% of colorless, slightly lachrymatory liquid, b.p. 110.5–111.5° (7.5 mm.) (reported[16] b.p. 142–143°(21 mm.)). This was further characterized by its amide, prepared by passing ammonia gas into an ether solution of the acid chloride. Crystallization from benzene gave the pure amide, m.p. 200.1–201.2° (reported m.p.[16] 202°).

2,6-Dichlorobenzoates of Allylic Alcohols.—2,6-Dichlorobenzoyl chloride (2.40 g.) was swirled into a solution of 0.01 mole of alcohol in 5.0 cc. of dry pyridine. The mixture was warmed on a hot-plate until all was liquid and was then heated on the steam-bath for 2.5 hr. Ammonia gas was passed rapidly through the dark mixture for 10 minutes, with external cooling. The mixture was then poured into 75 cc. of cold 5% hydrochloric acid solution and was extracted with ether. The ether solution was washed with 5% hydrochloric acid solution, water and 10% bicarbonate solution. After drying over potassium carbonate and evaporation of the ether, 50 cc. of 30–60° petroleum ether was swirled into the warm residue which was allowed to stand for 2 hr. The precipitated amide was removed by filtering through Celite, the filtrate was evaporated and the residue was dissolved in 5 cc. of petroleum ether and chromatographed on a 1.5 × 15 cm. column of alumina. The desired ester was eluted by washing the column with 750 cc. of petroleum ether. The petroleum ether solution was evaporated and the residue was distilled or recrystallized from petroleum ether to give the products shown in the following tables.

Proof of Structure of the Dichlorobenzoates from *trans*-6-Alkyl-2-cyclohexen-1-ols.—The following sequence was used to demonstrate that no rearrangement had taken place on formation of the dichlorobenzoates. A solution of 0.005 mole of the allylic ester in 10 cc. of dry ether was added during 10 minutes to a suspension of 0.50 g. of lithium aluminum hydride in 20 cc. of dry ether. The mixture was refluxed for 1 hr. and the excess hydride was decomposed by the cautious addition of methanol. The ether solution was shaken with 50 cc. of 5% hydrochloric acid solution, dried over potassium carbonate and evaporated. The residue was dissolved in 20 cc. of methanol and was hydrogenated at 25° and 1 atmosphere in the presence of 0.10 g. of prereduced platinum oxide. After 1 hr., hydrogen uptake had completely ceased and the solution was filtered through Celite and evaporated. Water (50 cc.) was added to the residue and the mixture was extracted three times with ether. The ether solution was dried over potassium carbonate and evaporated. A solution of 0.01 mole of *p*-toluenesulfonyl chloride in 7 cc. of pyridine was added to the residue and the resulting solution was kept 1 hr. at 25° and 12 hr. at 10°. It was poured into 50 cc. of 5% hydrochloric acid solution and extracted with ether. The ether solution was washed with water, with sodium bicarbonate solution and was dried over potassium carbonate and evaporated. The residue was crystallized once from 30–60° petroleum ether.

Authentic *p*-toluenesulfonates were prepared for comparison by utilizing the above procedure, starting with the proper *trans*-2-alkylcyclohexanol.[34] ***trans*-2-Methylcyclohexyl *p*-toluenesulfonate** is known; it had m.p. 27–28°, as reported.[35] ***trans*-2-Isopropylcyclohexyl *p*-toluenesulfonate** had m.p. 90.2–90.7°.

Anal. Calcd. for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.75; H, 8.21.

***trans*-2-*t*-Butylcyclohexyl *p*-toluenesulfonate** had m.p. 67–68°.

Anal. Calcd. for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.98; H, 8.59.

The *p*-toluenesulfonates from the alcohols resulting from the lithium aluminum hydride reductions described above were obtained in 80–95% yields, in a state of purity. Melting points and mixed melting points served to establish identity with the proper *trans*-2-alkylcyclohexyl *p*-toluenesulfonate.

Reaction of the Allylic 2,6-Dichlorobenzoates with Piperidine in the Absence of Solvent. Structure and Stereochemistry of Products.—A solution of 0.01 mole of the proper 2,6-dichlorobenzoate in 5.00 cc. of piperidine was sealed in a tube and kept at 130° for 24 hr. The tube was cooled, opened and emptied into 30 cc. of cold 10% hydrochloric acid solution. This was extracted with ether and the ether solution was washed with 25 cc. of 5% hydrochloric acid solution, 10 cc. of water and with two 25-cc. portions of 10% sodium bicarbonate solution. All the washings were saved. The ether solution was dried over potassium carbonate and evaporated. The residue was distilled at diminished pressure from an oil-bath which was heated no higher than 100°. The distillate was *m*-dichlorobenzene, b.p. 172° (reported b.p. 172°); 4,6-dinitroderivative m.p. 103°, as reported. It was weighed and the residue after its removal was dissolved in petroleum ether and was chromatographed, as described earlier in the preparation of the pure dichlorobenzoates. The petroleum ether eluates were evaporated on the steam-bath (finally at 2 mm.) to remove all traces of solvent. The residue, which consisted of starting dichlorobenzoate as shown by m.p. and mixed m.p., was weighed.

The bicarbonate washings of the original ether solution were acidified with hydrochloric acid and extracted with

MODEL ALLYLIC 2,6-DICHLOROBENZOATES

Allyl group	Yield, %	B.p., °C.	Mm.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
γ-Methylallyl	80	142–143	5.0	53.90	53.67	4.11	4.36
α-Methylallyl	75	133–134	5.0	53.90	53.69	4.11	4.12
2-Cyclohexen-1-yl	69	163–164	1.6	57.58	57.68	4.46	4.48

TRANS-6-ALKYL-2-CYCLOHEXENYL 2,6-DICHLOROBENZOATES

Alkyl group	Yield, %	M.p., °C.	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Methyl	76	56.8–57.6	58.96	59.16	4.95	5.01
Isopropyl	75	66.5–67.2	61.35	61.56	5.75	6.00
t-Butyl	80	71.2–71.9	62.39	62.65	6.16	6.29

(30) D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry and Industry*, 21 (1954). It will be seen in the following paper (G. Stork and F. H. Clarke, THIS JOURNAL, **78**, 4619 (1956)) that SN2′ displacements take place readily in the haloiodide series in which the departing halide is fixed in a quasi equatorial confirmation.

(31) The small increase in rates as the R group becomes bulkier may be due to steric acceleration, resulting from interference between the two equatorial substituents on the allylic (dichlorobenzoate group) and homoallylic carbon (R group).

(32) Reich, *Bull. soc. chim.*, [4] **21**, 217 (1917).

(33) J. F. Norris and A. E. Bearse, THIS JOURNAL, **62**, 953 (1940).

(34) These have been described in the preceding paper; *cf.* reference 9.

(35) G. A. C. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.*, 2052 (1926).

ether. The ether solution was dried over sodium sulfate and evaporated. The residue, which m.p. and mixed m.p. proved to be 2,6-dichlorobenzoic acid, was dried and weighed.

The acid extracts of the original ether solution were made alkaline with 20% sodium hydroxide solution and were extracted several times with ether. The ether solution was dried over potassium carbonate and evaporated. The residue was fractionated and produced the unsaturated amine which was weighed and transformed into its picrate. This was recrystallized from ethanol.

A mixture of 0.005 mole of unsaturated amine, 0.05 g. of platinum oxide and 10 cc. of methanol was hydrogenated at 25° and 1 atmosphere for 2 hr., after which hydrogen uptake ceased. Filtration through Celite and evaporation left a residue of the saturated amine which was distilled and converted to several derivatives in the usual manner. Infrared spectra were also recorded.

A weighed sample of the saturated amine was treated with an amount of hot saturated picric acid in ethanol containing 300% excess of picric acid so as to form the picrate quantitatively. After cooling and standing 2 hr., the picrate was filtered off, washed with a very small amount of alcohol and dried at 55° for 24 hr. The picrate was weighed and its m.p. was recorded. Similarly, a weighed sample of the saturated amine was dissolved in a tenfold excess of methyl iodide and was kept for 2 hr. at room temperature. The mixture was then diluted with 5 cc. of petroleum ether, and the precipitate was filtered and dried at 55° for 24 hr. The methiodide was weighed and its m.p. was recorded. The material balances obtained are shown in Table I.

Identification of the Unsaturated Amines. (a) Reaction of γ-Methylallyl, α-Methylallyl and 2-Cyclohexen-1-yl 2,6-Dichlorobenzoates.—The unsaturated amine obtained from γ-methylallyl 2,6-dichlorobenzoate was *trans*-**N**-(γ-methylallyl)-**piperidine (IIIa)**, b.p. 171–173° at atmospheric pressure.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.65; H, 12.21.

The picrate had m.p. 98.5–99.5°. Hydrogenation of IIIa gave, in 85% yield, N-butylpiperidine, b.p. 171–173° at atmospheric pressure, which formed a picrate m.p. 131.5–132.5° (reported[36] 132°) alone or mixed with authentic material.

From α-**methylallyl 2,6-dichlorobenzoate** a mixture of the same *trans*-**N**-(γ-**methylallyl**)-**piperidine (IIIa)** together with its *cis* isomer IIIb was obtained, b.p. 170–173° at atmospheric pressure.

Anal. Calcd. for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.56; H, 12.24.

The mixture gave a **picrate** (mixture), m.p. 81.0–81.9°, and gave in 82% yield N-butylpiperidine, identified as its picrate, on hydrogenation.

From 2-cyclohexen-1-yl 2,6-dichlorobenzoate, N-(2-cyclohexen-1-yl)-piperidine (IV) was obtained, b.p. 227–229° at atmospheric pressure. This gave a **picrate**, m.p. 108.0–108.8°.

Anal. Calcd. for $C_{17}H_{22}O_7N_4$: C, 51.77; H, 5.62. Found: C, 52.08; H, 5.82.

Hydrogenation produced the known N-cyclohexylpiperidine, b.p. 108–112° (19 mm.) (reported[37] b.p. 106–107° (16 mm.)) in 84% yield. This was identified by its **methiodide**, m.p. 254.2–254.6° (lit.[37] m.p. 253°) alone or mixed with an authentic sample. **The picrate**, m.p. 130.5–131.3°, likewise showed no depression with that made from authentic N-cyclohexylpiperidine.

(b) **Reaction of the 2,6-Dichlorobenzoates of** *trans*-**6-Alkyl-2-cyclohexen-1-ols.**—The unsaturated amine obtained from *trans*-**6-methyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate** (II, R = methyl) was **N-(*trans* 4-methyl-2-cyclohexen-1-yl)-piperidine**, b.p. 128–129° (27 mm.).

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 11.81. Found: C, 80.26; H, 11.95.

A picrate could not be obtained crystalline. Hydrogenation of the allylic amine produced 91% yield of N-(*trans*-4-methylcyclohexyl)-piperidine, b.p. 126–127° (26 mm.).[38]

From *trans*-**6-isopropyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate** (II, R = isopropyl) **N-(*trans*-4-isopropyl-2-cyclohexen-1-yl)-piperidine**, b.p. 131–132° (10 mm.), was obtained.[34] This gave a **picrate**, m.p. 159.0–160.0°.

Anal. Calcd. for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47. Found: C, 55.40; H, 6.68.

The amine was hydrogenated to give 93% of N-(*trans*-4-isopropylcyclohexyl)-piperidine, b.p. 130–131° (9 mm.).[38]

The unsaturated amine from *trans*-6-*t*-butyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate (II, R = *t*-butyl) proved to be **N-(*trans*-4-*t*-butyl-2-cyclohexen-1-yl)-piperidine** b.p. 137–138° (8 mm.). It gave a **picrate**, m.p. 124.5–125°.

Anal. Calcd. for $C_{21}H_{30}O_7N_4$: C, 55.99; H, 6.71. Found: C, 55.78; H, 6.92.

Hydrogenation of the unsaturated amine gave 91% of N-(*trans*-4-*t*-butylcyclohexyl)-piperidine, b.p. 136–137° (7 mm.).

The methiodides of the *unsaturated* amines above took up almost 2 moles of hydrogen when reduced in methanol with platinum oxide at 25° and 1 atmosphere yielding 61–85% yields of methylcyclohexane,[39] isopropylcyclohexane and *t*-butylcyclohexane, b.p., respectively, 100–101° (reported[40] 100.0–100.2°), 153–154° (reported[41] 154.7°) and 165–166° (reported[42] 166–167°) at atmospheric pressure.

Reaction of the *trans*-**6-Alkyl-2-cyclohexen-1-yl 2,6-Dichlorobenzoates in Xylene Solution.**—A solution of 0.01 mole of *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate and 0.03 mole of piperidine was made up to 20 cc. with *m*-xylene and sealed in a tube. The tube was kept at 130° for 100 hr., cooled and opened. The contents were worked up as described previously but, except in the case of the 6-methyl compound, structure was established before hydrogenation by comparison of the unsaturated amine picrate with the derivative previously prepared and characterized. The same compounds were obtained as in the experiments without solvent, but the recovered starting dichlorobenzoate amounted to 75, 71 and 54%, respectively, in the case of the 6-methyl, 6-isopropyl and 6-*t*-butyl compounds, and the conversion to unsaturated amines was consequently only 15, 20 and 35%, respectively.

***trans*-4-Alkylcyclohexanols.**—Pure *trans*-4-alkylcyclohexanols were prepared from the known 4-methyl-, 4-isopropyl- and 4-*t*-butylcyclohexanones, themselves produced by dichromate–sulfuric acid oxidation of the cyclohexanol mixtures obtained by Raney nickel reduction of the appropriate phenols. Reduction with sodium in moist ether and purification was carried out as described in the preceding paper for the similar *trans*-2-alkylcyclohexanols.[9] The alcohols were converted into their *p*-toluenesulfonates by the method described under "Proof of Structure of the Dichlorobenzoates." Thus obtained were:

***trans*-4-Methylcyclohexanol**, b.p. 100.5–101.0° (56 mm.) (reported[35] b.p. 174° at atm. press.); hydrogen phthalate, m.p. 118–119° (reported[35] 120°); ***p*-toluenesulfonate** (94% yield), m.p. 70.8–71.8° (reported[35] m.p. 71–72°).

***trans*-4-Isopropylcyclohexanol**, b.p. 210–211° (atm. press.) (reported[43] b.p. 212 at atm. press.); 3,5-dinitrobenzoate, m.p. 123.0–123.7° (reported[44] m.p. 124.5°); ***p*-toluenesulfonate** (94% yield), m.p. 35.5–36.5°.

Anal. Calcd. for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.96; H, 7.86.

***trans*-4-*t*-Butylcyclohexanol**, b.p. 127.5–128.5° (28 mm.), m.p. 80.0–80.5° (reported[45] m.p. 80.5°); **3,5-dinitrobenzoate**, m.p. 158.0–158.5° (from benzene).

Anal. Calcd. for $C_{17}H_{22}O_6N_2$: C, 58.27; H, 6.33. Found: C, 58.40; H, 6.15.

The hydrogen phthalate had m.p. 141.0–142.0° (from

(36) J. von Braun, *Ber.*, **40**, 3914 (1907).

(37) C. Mannich and H. Davidson, *ibid.*, **69**, 2106 (1936).

(38) The picrates, picrolonates, methiodides and (in the case of the *t*-butyl compound) styphnate of the reduced amines did not depress the melting points of the corresponding derivatives of the same m.p. from the appropriate *authentic* N-(*trans* 4-alkylcyclohexyl)-piperidine. The preparation of the authentic reference compounds is described later in this paper.

(39) The low yield (61%) of methylcyclohexane was due to the difficulty of separating it from methanol.

(40) R. Adams and J. R. Marshall, THIS JOURNAL, **50**, 1970 (1928).

(41) J. Timmermans, *Bull. soc. chim. Belg.*, **36**, 503 (1927).

(42) Halse, *J. prakt. Chem.*, [2] **92**, 41 (1915).

(43) G. Vavon and A. Callier, *Bull. soc. chim.*, [4] **41**, 677 (1927).

(44) R. G. Cooke, D. T. C. Gillespie and A. K. Macbeth, *J. Chem. Soc.*, 518 (1939).

(45) G. Vavon and M. Barbier, *Bull. soc. chim.*, [4] **49**, 567 (1931).

cyclohexane) and the *p*-**toluenesulfonate** (95% yield) showed m.p. 87.5–88.3°.

Anal. Calcd. for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 66.08; H, 8.58.

N-(*cis*-4-Alkylcyclohexyl)-piperidines.—These reference compounds were prepared from the *trans*-4-alkylcyclohexyl *p*-toluenesulfonates described above: A solution of 0.015 mole of the sulfonate in 10.0 cc. of piperidine was kept 12 hr. at 25° and at 85° for another 12 hr. The solution was then poured into 50 cc. of cold 10% hydrochloric acid and the solution was extracted with ether. The ether layer was discarded and the aqueous layer was made alkaline with 50 cc. of 25% sodium hydroxide solution. The resulting mixture was extracted several times with ether, the ether solution was dried over potassium carbonate and was fractionated. In this way **N-(*cis*-4-methylcyclohexyl)-piperidine** was obtained in 51% yield, b.p. 125–126° (25 mm.).

Anal. Calcd. for $C_{12}H_{23}N$: C, 52.67; H, 6.39. Found: C, 52.86; H, 6.53.

The picrate had m.p. 130.5–131°.

N-(*cis*-4-Isopropylcyclohexyl)-piperidine was obtained in 38% yield, b.p. 126–127° (10 mm.).

Anal. Calcd. for $C_{14}H_{27}N$: C, 54.78; H, 6.90. Found: C, 54.92; H, 7.05.

The picrate had m.p. 144.8–145.5°.

N-(*cis*-4-*t*-Butylcyclohexyl)-piperidine was formed in 41% yield, b.p. 128–129° (8 mm.).

Anal. Calcd. for $C_{15}H_{29}N$: C, 55.74; H, 7.13. Found: C, 55.98; H, 7.24.

The picrate had m.p. 135.2–136°.

***cis*-4-Alkylcyclohexanols.**—These could be prepared from the required 4-alkylcyclohexanones by catalytic hydrogenation with platinum oxide in acetic acid solution containing some concd. hydrochloric acid, following the method used by Anziani and Cornubert for 2-methylcyclohexanone.[46] The method produced mixtures in all cases—including 2-methylcyclohexanone—and many recrystallizations of a suitable solid ester were necessary before pure material could be obtained in low yields. The pure alcohols were much more easily obtained by acetolysis of the *p*-toluenesulfonates of the *trans*-4-alkylcyclohexanols which have been described above. The method has been used previously by Gough, Hunter and Kenyon to prepare *cis*-4-methylcyclohexanol.[35] A solution of 0.10 mole of the *p*-toluenesulfonate of the appropriate *trans*-4-alkylcyclohexanol in 100 cc. of glacial acetic acid containing 25 g. of anhydrous potassium acetate was kept at 40° for 10 hr. and at 90° for 20 hr. It was cooled and poured into 1750 cc. of cold 10% sodium hydroxide solution, and the mixture was extracted with ether. The ether solution was fractionated after drying over potassium carbonate and the isolated acetates were hydrolyzed with base. Solid alcohols were recrystallized from 30–60° petroleum ether.

***cis*-4-Methylcyclohexanol** was thus obtained by hydrolysis of the **acetate**, b.p. 183–184° at atm. press., as reported.[35] The acetate was formed in 21% yield together with 62% 4-methylcyclohexene, b.p. 101–102° at atm. press. The alcohol obtained from the acetate was purified by conversion to its *p*-**nitrobenzoate** (80% yield), m.p. 93.5–94.5° (from ligroin) (reported[47] m.p. 96°). Hydrolysis gave the pure **alcohol**, b.p. 96.5–97.0° (56 mm.) (reported[35] b.p. 174° at atm. press.); *p*-**toluenesulfonate** (89% yield), m.p. 72.0–72.8°.

Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 62.65; H, 7.51. Found: C, 62.85; H, 7.63.

***cis*-4-Isopropylcyclohexanol** was obtained from its **acetate**, b.p. 221–222° (20 mm.), which was formed in 20% yield together with 52% of 4-isopropylcyclohexene, b.p. 153–154° (760 mm.). The alcohol was purified *via* its **hydrogen phthalate** (84% yield), m.p. 130.5–131.2° (from cyclohexane) (reported[44] m.p. 130°). Hydrolysis gave the pure **alcohol**, b.p. 87–88° (10 mm.), m.p. 37–38.1° (reported[44] m.p. 34.4°); *p*-**toluenesulfonate** (95% yield), m.p. 54–55°.

Anal. Calcd. for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 64.64; H, 8.27.

***cis*-4-*t*-Butylcyclohexanol** was obtained by hydrolysis of the **acetate**, b.p. 228–230° (25 mm.), which was formed in 25% yield together with 69% of 4-*t*-butylcyclohexene, b.p. 162–163° (760 mm.). The alcohol was purified through its *p*-nitrobenzoate (82% yield), m.p. 130.2–131.0° (from cyclohexane).

Anal. Calcd. for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.59. Found: C, 66.99; H, 7.63.

Regeneration gave the pure **alcohol**, b.p. 133–134° (32 mm.), m.p. 82–82.5° (reported[43] m.p. 83.5°); *p*-**toluenesulfonate** (87% yield), m.p. 77.5–78.5°.

Anal. Calcd. for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.79; H, 8.32.

N-(*trans*-4-Alkylcyclohexyl)-piperidines.—These were prepared, exactly as with the *cis* analogs, from *cis* 4-alkylcyclohexanols. The derivatives were crystallized from alcohol, except the methiodides which were crystallized from either isopropyl alcohol or *t*-butyl alcohol.

N-(*trans*-4-Methylcyclohexyl)-piperidine was obtained in 39% yield, b.p. 126–127° (25 mm.).

Anal. Calcd. for $C_{12}H_{23}N$: C, 52.67; H, 6.39. Found: C, 52.92; H, 6.61.

Picrate, m.p. 153.3–154.3°; **picrolonate**, 188.5–188.9°; **methiodide**, m.p. 239.4–239.7°.

N-(*trans*-4-Isopropylcyclohexyl)-piperidine obtained in 34% yield had b.p. 135–137° (11 mm.).

Anal. Calcd. for $C_{14}H_{27}N$: C, 54.78; H, 6.90. Found: C, 55.01; H, 7.18.

Picrate, m.p. 123.5–124.2°; **picrolonate**, m.p. 174.7–175.1°; **methiodide**, m.p. 250.2–250.4°.

N-(*trans*-4-*t*-Butylcyclohexyl)-piperidine was formed in 43% yield and had b.p. 136–137° (7 mm.).

Anal. Calcd. for $C_{15}H_{29}N$: C, 55.74; H, 7.13. Found: C, 55.94; H, 7.34.

Picrate, m.p. 166.5–167.5°; **picrolonate**, m.p. 199.4–199.9°; **methiodide**, m.p. 253.0–253.2°.

Displacement of 6-Alkyl-2-cyclohexenyl 2,6-Dichlorobenzoates with Malonic Ester Anion. (a) Procedure.—Di-*n*-butyl malonate was prepared by the esterification of cyanoacetic acid with *n*-butyl alcohol–sulfuric acid, b.p. 122.9–123° (9 mm.) (reported[48] b.p. 140° (18 mm.)). The malonic ester (4.34 g.) was added dropwise to a solution of 0.46 g. of sodium in 10 cc. of dry *n*-butyl alcohol, and 0.01 mole of pure *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate was added to the mixture which was then refluxed for 75 hr. with exclusion of moisture. The mixture was cooled and poured into 50 cc. of 5% hydrochloric acid solution. The ether extract of the separated oil was washed with water and sodium bicarbonate solution (acidification of the bicarbonate extracts gave 2,6-dichlorobenzoic acid). The ether solution was dried over potassium carbonate and the solvent was removed, finally at 85° and 20 mm. pressure.

The residue was dissolved in 10 cc. of methanol and was hydrogenated at atmospheric pressure and room temperature by adding 0.10 g. of platinum oxide catalyst to the hydrogenation mixture every hour for 6 hr. By this method quantitative hydrogen uptake was achieved. The catalyst was removed by filtration through Celite and the filtrate was diluted to 30 cc. with methanol and refluxed for 2 hr. with a solution of 7.5 g. of potassium hydroxide in 10 cc. of water. Water was then added to the solution and distilled off over a 2-hr. period. The residue was cooled and acidified with 50 cc. of cold 15% hydrochloric acid solution, and the mixture was extracted several times with ether. The ether solutions were combined and dried over sodium sulfate. The ether was evaporated and the solid residue was heated in an oil-bath at 180–200° for 2 hr. to effect the decarboxylation of the malonic acid. The residue was then distilled to give the pure alkylcyclohexylacetic acid.[49]

(b) Characterization of Products.—From *trans*-6-methyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate the product proved to be *cis*-2-methylcyclohexylacetic acid, b.p. 108–110° (3 mm.), formed in 64% yield.

From *trans*-6-isopropyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate, *trans*-4-isopropylcyclohexylacetic acid was ob-

(46) P. Anziani and R. Cornubert, *Bull. soc. chim.*, [5] **12**, 359 (1945).

(47) L. M. Jackman, A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 1717 (1949).

(48) C. Contzen-Crowet, *Bull. soc. chim. Belg.*, **35**, 192 (1926).

(49) The acid was converted to its crystalline amide and to its benzylamine salt, and identity was established by comparison with the proper derivatives of the authentic *cis*- and *trans*-acid. The synthesis of the authentic acids is described later in this paper.

tained in 76% yield, b.p. 131–133° (3.5 mm.), m.p. 77–78°.

From *trans*-6-*t*-butyl-2-cyclohexen-1-yl 2,6-dichlorobenzoate the product, formed in 83% yield, was *trans*-4-*t*-butylcyclohexylacetic acid, b.p. 137–139° (3.5 mm.), m.p. 94.8–95.5°.

Stability of *trans*-6-Alkyl-2-cyclohexen-1-yl 2,6-Dichlorobenzoates in *n*-Butyl Alcohol.—Small weighed samples (0.2 g.) of the cyclohexenyl esters were dissolved in 2.0 cc. of dry *n*-butyl alcohol and sealed in tubes. The tubes were kept at 104.7 ± 0.1° for 25 and 75 hr. The contents were then poured into 30 cc. of 10% sodium bicarbonate solution and the mixture was extracted with ether. The ether solution was dried over potassium carbonate and evaporated, the last traces of *n*-butyl alcohol being removed by keeping at 80° and 2 mm. pressure for an hour. The remaining solid was crystallized once from petroleum ether (20–40°) at Dry Ice temperature. In all cases pure starting ester was recovered in yields from 78 to 92%.

Authentic Alkylcyclohexylacetic Acids.—To a solution of 1.15 g. of sodium in 25 cc. of absolute ethanol was added dropwise, with swirling, 8.0 g. of diethyl malonate. Pure alkylcyclohexyl *p*-toluenesulfonate (0.02 mole) was dissolved in this solution and the entire mass was heated on the steam-bath for 2 hr. The mixture was poured into 100 cc. of 10% hydrochloric acid solution. The oily ester was extracted with ether and the ether extract was washed with water and sodium bicarbonate solution. The extract was dried over potassium carbonate and evaporated. The residue was distilled giving the pure cyclohexylmalonate which was then hydrolyzed by refluxing 0.01 mole in a solution of 7.5 g. of potassium hydroxide, 20 cc. of ethanol and 10 cc. of water for 90 minutes and continuing as described earlier with the malonates derived from the cyclohexenyl dichlorobenzoates. When the distilled acid was a solid it was further purified by crystallization from petroleum ether, b.p. 30–60°. Benzylamine salts and amides were prepared in the usual fashion.

trans-2-Methylcyclohexyl *p*-toluenesulfonate gave the *cis*-malonic ester, b.p. 116–118° (3.5 mm.) (14% yield), from which ***cis* 2-methylcyclohexylacetic acid**, b.p. 116–118° (4.0 mm.), was obtained in 74% yield. Its **amide**[50] had m.p. 152.9–153.6°, and the **benzylamine salt** had m.p. 116.7–117.2° (from ligroin).

Anal. Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57. Found: C, 72.81; H, 10.07.

cis-2-Methylcyclohexyl *p*-toluenesulfonate produced in 23% yield the *trans*-malonic ester, b.p. 116–118° (3.5 mm.), hydrolyzed to ***trans*-2-methylcyclohexylacetic acid** in 80% yield, b.p. 116–118° (4 mm.); **amide**,[50] m.p. 172.1–173°; **benzylamine salt**, m.p. 92.5–93.1° (from petroleum ether).

Anal. Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57. Found: C, 72.90; H, 9.76.

trans-4-Methylcyclohexyl *p*-toluenesulfonate afforded a 44% yield of the *cis*-malonic ester, b.p. 126–128° (4.0 mm.), hydrolyzed to ***cis*-4-methylcyclohexylacetic acid** in 82% yield, b.p. 107–109° (3.5 mm.), m.p. 42–43°; **amide**,[50] m.p. 145–145.5°; **benzylamine salt**, m.p. 106–106.8° (from ligroin).

Anal. Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; N, 9.57. Found: C, 72.45; H, 9.99.

cis-4-Methylcyclohexyl *p*-toluenesulfonate yielded 55% of the *trans*-malonic ester, b.p. 126–128° (4 mm.), hydrolyzed to ***trans*-4-methylcyclohexylacetic acid** in 82% yield, b.p. 106–108° (3.5 mm.), m.p. 71.5–72.5°; **amide**,[50] m.p. 161–161.8°; **benzylamine salt**, m.p. 100.8–101.4° (from cyclohexane).

Anal. Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57. Found: C, 72.90; H, 9.66.

trans-4-Isopropylcyclohexyl *p*-toluenesulfonate furnished 49% of the *cis*-malonic ester, b.p. 147–149° (4 mm.), hydrolyzed to ***cis*-4-isopropylcyclohexylacetic acid** in 83% yield, b.p. 140–142° (4.8 mm.), m.p. 39–40°; **amide**,[50] m.p. 169.2–170°; **benzylamine salt**, m.p. 101–101.6° (from cyclohexane).

Anal. Calcd. for $C_{18}H_{29}O_2N$: C, 74.18; H, 10.03. Found: C, 74.04; H, 10.01.

cis-4-Isopropylcyclohexyl *p*-toluenesulfonate formed 58% of the *trans*-malonic ester, b.p. 151–153° (4 mm.), hydrolyzed to ***trans*-4-isopropylcyclohexylacetic acid** in 92% yield, b.p. 131–133° (3.5 mm.), m.p. 77.5–78.2°; **amide**,[50] m.p. 200–200.2°; **benzylamine salt**, m.p. 145.9–146.5° (from cyclohexane).

Anal. Calcd. for $C_{18}H_{29}O_2N$: C, 74.18; H, 10.03. Found: C, 74.36; H, 10.06.

trans-4-*t*-Butylcyclohexyl *p*-toluenesulfonate generated a 38% yield of the *cis*-malonic ester, b.p. 147–149° (3.5 mm.), hydrolyzed to ***cis*-4-*t*-butylcyclohexylacetic acid** in 76% yield, b.p. 143–145° (4 mm.), m.p. 98–98.8°; **amide**,[50] m.p. 209.5–210°; **benzylamine salt**, m.p. 144.2–144.8° (from benzene).

Anal. Calcd. for $C_{19}H_{31}O_2N$: C, 74.71; H, 10.23. Found: C, 74.72; H, 10.33.

cis-4-*t*-Butylcyclohexyl *p*-toluenesulfonate supplied a 48% yield of the *trans*-malonic ester, b.p. 150–152° (3.5 mm.), hydrolyzed to ***trans*-4-*t*-butylcyclohexylacetic acid** in 80% yield, b.p. 137–139° (3.5 mm.), m.p. 95.5–96.1°; **amide**,[50] m.p. 192.8–193.2°; **benzylamine salt**, m.p. 151.9–152.2° (from benzene).

Anal. Calcd. for $C_{19}H_{31}O_2N$: C, 74.71; H, 10.23. Found: C, 74.73; H, 10.51.

Kinetic Studies. (a) **Displacement with Piperidine.**—The *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates described earlier were recrystallized several times from petroleum ether, b.p. 30–60°, with no further change in their melting points.

Eastman Kodak Co. white label piperidine was dried over potassium hydroxide and fractionated through a 1 × 125 cm. glass-helix packed, heated column, the fraction boiling at 105.6–106.0° (lit.[51] b.p. 105.6°) being collected. This was refractionated, the same fraction again being collected.

Eastman Kodak Co. white label *m*-xylene was twice fractionated through a 1 × 125 cm. glass helix packed column, the fraction boiling at 138.7–139.1° being collected (lit.[52] b.p. 138.8–139.2°).

The dichlorobenzoate and the piperidine were weighed into a volumetric flask. The mixture was made up to volume with *m*-xylene. After the solution was well mixed, 2.00-cc. aliquots were sealed in soft glass ampoules, which were heated at 129.5 ± 0.1° for varying lengths of time. The ampoules were then crushed and the contents treated with 10 cc. of acetic anhydride for 3 hr. After addition of 25 cc. of glacial acetic acid, the mixture was titrated potentiometrically with perchloric acid in glacial acetic acid using a calomel and a quinhydrone electrode. The titrimeter used had to be extremely sensitive because of the high resistance of the cell and the buffering effect of the amide formed. The titration procedure is described more fully by Wagner, Brown and Peters.[53]

The initial concentrations of dichlorobenzoate (a) and of piperidine (b) were calculated from the weights used in making the original mixture. The value of b was checked by titration of an aliquot of the solution of amine and ester with perchloric acid in glacial acetic acid using α-naphtholbenzein as indicator. The two values agreed closely.

Calculations for k_1 and k_2 were made using the equations in the Discussion section.

The determination of the order in ester and amine by van't Hoff's method was carried out by the same procedure.

(b) **Displacement with Malonic Ester Anion.**—The allylic esters were purified as above. Di-*n*-butyl malonate, synthesized as previously mentioned, was fractionated twice through a 40-cm. Vigreux column, taking the fraction boiling at 122.9–123.0° (9.0 mm.).

Merck and Co., Inc., reagent grade *n*-butyl alcohol was dried by refluxing with sodium for 3 hr. It was then fractionated through a 40-cm. Vigreux column, taking the fraction boiling at 117.4–117.5° (lit.[54] b.p. 117.6–117.7° at 760 mm.).

Sodium *n*-butoxide was prepared by refluxing 100 cc. of dry *n*-butyl alcohol with 4.6 g. of freshly shaved sodium until solution was complete, excluding moisture. The strength of this solution was determined by titrating aliquots with standard acid.

(50) The amides were all recrystallized several times from toluene.

(51) W. H. Davies and L. L. McGee, *J. Chem. Soc.*, 678 (1950).

(52) T. W. Richards, C. L. Speyers and E. K. Carver, THIS JOURNAL, **46**, 1196 (1924).

(53) C. D. Wagner, R. H. Brown and E. D. Peters, *ibid.*, **69**, 2609 (1947).

(54) J. W. Williams and F. Daniels, *ibid.*, **46**, 903 (1924).

Sodium di-*n*-butylmalonate was obtained by adding, under anhydrous conditions, the theoretical amount of di-*n*-butyl malonate into the standardized sodium *n*-butoxide solution. This solution was prepared immediately before use.

The proper quantity of dichlorobenzoate was weighed into a volumetric flask and an aliquot of sodium di-*n*-butylmalonate was added. The mixture was made up to volume with dry *n*-butyl alcohol. The solid dichlorobenzoate was dissolved by careful warming and shaking. Aliquots of this solution were pipetted into soft glass ampoules which were then sealed and heated for the required length of time at 104.7 ± 0.1°.

After heating, the tubes were cooled and crushed under 50.00 cc. of absolute methanol. The resulting solution was titrated with standard perchloric acid using *m*-cresol purple to determine the end-point. The original concentration of dichlorobenzoate (*a*) was determined from its weight and the volume of the solution, and the original concentration of the sodium di-*n*-butylmalonate (*b*) by removing two of the soft glass ampoules from the thermostat after 5 minutes and titrating as described above (zero time was taken as being 5 minutes after the tubes were immersed in the thermostat). The determination of the order in dichlorobenzoate and malonic ester anion was carried out by the same procedure.

Rate of Solvolysis of the Dichlorobenzoates.—Weighed portions of the 2,6-dichlorobenzoates were made up to volume with dry *n*-butyl alcohol. The solid esters were dissolved by shaking and heating. Aliquots of the resulting solutions were sealed in soft glass ampoules and heated at 104.7 ± 0.1° for timed intervals. The ampoules were cooled and crushed under 50.00 cc. of absolute methanol, and the resulting solutions were titrated with standard aqueous sodium hydroxide solution using brom thymol blue to find the end-point. The rate constant, k_1, was calculated from the original concentration (*a*) of the ester derived from the weight of ester used and the volume of the solution.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

The SN2′ Reaction. III. Structure and SN2′ Reactions of the Halocodides

BY GILBERT STORK AND FRANK H. CLARKE

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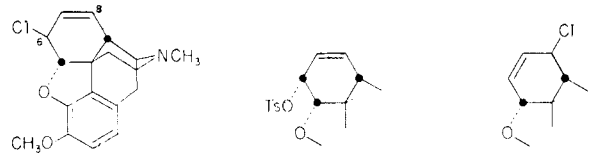
Structures previously assigned[1] to the halocodides are confirmed. The general occurrence of SN2′ displacements with these substances is corroborated by studying the kinetics of the displacement reaction of piperidine on α-chlorocodide.

Some time ago structures were advanced for the halides derived from codeine and its isomers, the so-called halocodides, and the conclusion was reached that SN2′ mechanisms are generally involved in the reactions of these substances.[1] We now wish to present the evidence which verifies our earlier postulates.

α-Chlorocodide has been shown to have its chlorine at C_6[2] and must have the stereochemistry shown in I[3] for reasons which we have discussed previously.[1] We have further confirmed this



I II III

stereochemical assignment by showing that α-chlorocodide is formed in quantitative yield from the reaction of codeine tosylate, II[4] with lithium chloride in acetone. Since α-chlorocodide is unstable and rearranges on heating to β-chlorocodide,[5] the formation of the α-isomer must be the direct product of normal bimolecular displacement with inversion (see reaction of codeine tosylate with piperidine below).

β-Chlorocodide has been postulated to be the C_8 allylic isomer of α-chlorocodide.[6] That this assignment is valid follows from the reactions of the substance[1] which require that it be either the C_6 epimer of the α-compound or a C_8 allylic isomer. Only the latter formulation is compatible with the lack of reaction with potassium iodide in methanol of β-chlorocodide, as we have now shown that codeine tosylate reacts readily with iodide ion. β-Chlorocodide is then the C_8 isomer with the hindered back side and has the structure and stereochemistry shown in III.

We have now established that bromocodide and

(1) G. Stork in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, New York, N. Y., 1952, pp. 176–189.

(2) L. F. Small, B. F. Faris and J. E. Mallonee, *J. Org. Chem.*, **5**, 334 (1940).

(3) This is based on the stereochemistry that we have considered established for morphine and codeine, ref. 1, p. 171. Our conclusions have been confirmed recently by the X-ray work of M. Mackay and D. Crowfoot Hodgkin, *J. Chem. Soc.*, 3261 (1955).

We take this opportunity to answer some remarkable assertions by Bentley, *et al.*: (a) Bentley and Thomas, *J. Chem. Soc.*, 3237 (1955), apparently do not realize that *further evidence has to be provided* when a structure is proposed which is based on mechanisms without analogy. (b) Bentley and Cardwell, *ibid.*, 3245 (1955), attribute to us the implication that ethanol is *mechanistically* required in the reduction of thebaine with sodium in liquid ammonia. We merely stated that we obtained good results *only* in the presence of alcohol. This is a statement of fact. Bentley and Cardwell go to some length to show that the alcohol may be omitted by using thebaine which has gone through an 80-mesh sieve. We prefer the simpler expedient of using ethanol. (c) Bentley and Cardwell, *ibid.*, 3252 (1955), misquote us: "This disposes of Stork's attempt . . . ("The Alkaloids" . . . Vol. II, 171)" is followed by "Stork's subsequent attempt (ref. 1, p. 190)." The fact is that the whole discussion of the relationship of the ethanamine chain and the oxide bridge is on pp. 173–174. Far from disposing of our "attempt to deduce the stereochemistry of morphine . . ." the discussion of Bentley and Cardwell does not seem compatible with the evidence. We take very strong objection to the statement that "to maintain this argument [Stork] subsequently (ref. 1, p. 191) overlooks the fact that the Hofmann degradation . . . involves a *cis* elimination . . ." Not only did we *not* overlook it, but we *took pains to emphasize it* by writing the reaction *not* as a concerted *trans* but as a non-concerted *cis*-elimination!

(4) P. Karrer and G. Widmark, *Helv. Chim. Acta*, **34**, 34 (1951); H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).

(5) L. F. Small and F. S. Palmer, *ibid.*, **61**, 2186 (1939).

(6) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II Academic Press, New York, N. Y., 1952, p. 63.