cyclohexane solution. In the same solvent the parent ketone, actual molecular weight 126.2, had the experimentally determined molecular weight 216.1 at 0.164 molar concentration.

Thus cycloöctanone itself is associated to a considerable extent in cyclohexane, as is cyclohexanone. The bromo derivative in the eight-membered ring on the other hand is not appreciably associated under these conditions.

Spectra.—The infrared spectra were obtained using a Beckman IR-4 spectrophotometer with a scanning speed of 0.02 μ/min. The ultraviolet spectra were obtained with a Beckman DU spectrophotometer with a Spectracord attachment. The observed infrared carbonyl spectra are plotted in Fig. 1. The frequency data are listed in Table V.

TABLE V

INFRARED CARBONYL SPECTRUM OF 2-BROMOCYCLOÖCTANONE

Solvent	ν, cm.$^{-1}$	$\Delta\nu^a$
Heptane	..	..
CCl_4	1708	6
	1715	13
$CHCl_3$	1702	12
	1712	22
C_6H_6	1705	5
	1714	14
Dioxane	1706	6
	1716	16
Me_2SO	1704	10
	1712	18

^{a} $\Delta\nu = \nu_{\text{bromoketone}} - \nu_{\text{ketone}}$.

The ultraviolet data are summarized in Table VI.

TABLE VI

ULTRAVIOLET SPECTRUM OF 2-BROMOCYCLOÖCTANONE

Solvent	$\lambda_{\max}$	ϵ	$\Delta\lambda_{\max}{}^a$	$\Delta\epsilon^b$
Heptane	313	104	22	86
CCl_4	313	106	18	88
EtOH (95%)	307	94	23	78
Me_2SO	300	85	18	58

^{a} $\Delta\lambda_{\max} = \lambda_{\max}$ (bromoketone) $- \lambda_{\max}$ (ketone). ^{b} $\Delta\epsilon = \epsilon_{\text{bromoketone}} - \epsilon_{\text{ketone}}$.

Dipole Moment.—The moment of 2-bromocycloöctanone in benzene solution was determined at 25°. The data were treated by the method of Halverstadt and Kumler[17] as described previously.[2] The molar refractivity was calculated from standard values of atomic refractivities[18] and had the value 44.720 cc. Atomic polarization was neglected. The data are summarized in Table VII.

TABLE VII

DIPOLE MOMENT DATA FOR 2-BROMOCYCLOÖCTANONE IN BENZENE

N_2	d	ϵ
0.0115006	0.882019	2.4524
.0068663	.878154	2.3792
.0043590	.875971	2.3399
.0022661	.874115	2.3071
.0012920	.873236	2.2906
.0007668	.872784	2.2833
.0000000	.872143	2.2723

$\alpha = 15.729$, $\beta = 0.850538$, $P_{2\infty} = 275.626$ cc., $\epsilon_1 = 2.2713$, $d_1 = 0.872202$, $\mu = 3.36$ D.

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[17] I. F. Halverstadt and W. D. Kumler, THIS JOURNAL, **64**, 2988 (1942).

[18] J. A. Leermakers and A. Weissberger in H. Gilman, "Organic Chemistry," Vol. II, second edition, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 1751.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Electrophilic Substitution at Saturated Carbon. I. Survey of Reactions Available for Stereochemical Study[1]

BY DONALD J. CRAM, ALBERT LANGEMANN, JANET ALLINGER AND KARL R. KOPECKY

RECEIVED JANUARY 2, 1959

A survey of reactions available for studies of the steric course of electrophilic substitution at saturated carbon has been made. These reactions all involve heterolytic cleavage of carbon–carbon bonds, with carbonyl or alkenyl leaving groups, and proton-donating solvents (secondary amines) as electrophiles. The reactions are all base-catalyzed, and in part are the reverse of ordinary nucleophilic addition reactions of organometallic reagents to unsaturated carbon. These transformations all gave 2-phenylbutane as product, and a rough order of reactivity was established as the character of the leaving group was varied. *For eleven different leaving groups, predominating retention of configuration at the seat of substitution accompanied by varying amounts of racemization was the observed steric course.*

In contrast to nucleophilic substitution (SN), electrophilic substitution (SE) at saturated carbon has been relatively little studied, particularly with respect to steric course. Similarly, although the stereochemical capabilities of carbonium ions have been extensively investigated, the stereochemical fate of carbanions has never been subjected to systematic scrutiny. The studies that have been made of the steric path of electrophilic substitution at saturated carbon have all involved reactions of organometallic reagents. Thus optically active alkyl halides have been converted to organometallic compounds which have been either protonated or added to double bonds. In all cases the over-all steric result for both transformations has been racemization.[2] Similar experiments applied to diastereomeric halides led to mixtures of acids whose composition was independent of the configuration of the starting halide.[3]

A number of articles have appeared in the literature in which authentic stereospecific electrophilic substitutions at saturated carbon are reported. Letsinger[4] observed that when (−)-2-iodoöctane

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[1] This work was supported in part by a generous grant from the Upjohn Co. and in part by the Office of Ordnance Research, U. S. Army.

[2] (a) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); (b) A. M. Schwartz and J. R. Johnson, THIS JOURNAL, **53**, 1063 (1931); (c) C. W. Porter, *ibid.*, **57**, 1436 (1935); (d) S. Tarbell and M. Weiss, *ibid.*, **61**, 1203 (1939); (e) H. Hart, *ibid.*, **78**, 2691 (1956).

[3] (a) G. Roberts and C. W. Shoppee, *J. Chem. Soc.*, 3418 (1954); (b) H. L. Goering and F. H. McCarron, THIS JOURNAL, **80**, 2287 (1958). See M. Mousseron and R. Jacquier, *Bull. soc. chim. France*, C80 (1951).

[4] R. L. Letsinger, THIS JOURNAL, **72**, 4842 (1950).

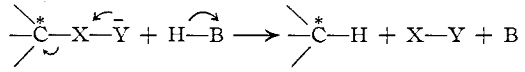
was metalated with *sec*-butyllithium and the product was carbonated (both operations were carried out at −70°), the 2-methyloctanoic acid produced was 20% optically pure, and the two reactions (metalation and carbonation) had occurred with predominating overall retention of configuration. Nesmeyanov and co-workers[5] mercurated an optically active diastereomer of menthyl 2-bromopropionate, converted this alkylmercuric halide to the dialkylmercury compound, and transformed the substance back to the alkylmercuric halide in stereospecific reactions. Cram, *et al.*,[6] reported that electrophilic substitution that accompanies reverse condensation reactions can occur with from 93% predominating retention to 50% predominating inversion. Winstein and co-workers[7] observed better than 99% retention of configuration in the reaction of *cis*-2-methoxycyclohexylneophylmercury with radioactive mercuric chloride to give radioactive *cis*-2-methoxycyclohexylmercuric chloride.

Another indication that electrophilic substitution at saturated carbon *can occur* with retention is found in the fact that a bromine atom at the bridgehead of triptycene can be replaced by lithium, and the triptycyllithium formed can be carbonated.[8] Likewise, 4-camphenylmercury derivatives readily undergo electrophilic substitution reactions.[9] In these transformations a tetrahedral configuration must have been maintained at the seat of substitution.

A body of evidence supports the hypothesis that ordinary trisubstituted carbanions are unable to maintain their configurations either because they undergo multiple or equilibrating inversions, or because they flatten out due to distribution of their charge into adjacent unsaturated centers.[10] However, evidence that *olefinic carbanions* can maintain their configurations is found in the fact that haloalkenes can be metalated and the product carbonated with predominant over-all retention of configuration.[11]

This paper is the first in a series which are concerned with the mechanism and stereochemistry of electrophilic substitution at saturated carbon.[12] The material of the first six papers is somewhat integrated, and is organized as follows. This paper is concerned with a survey of systems that might lend themselves to an examination of the steric course of electrophilic substitution. Paper II reports the effects of medium and the nature of the leaving group on the stereochemistry of the reaction. In the third paper, the configurational relationships between starting materials and product are demonstrated, and the effects of variation of temperature and of substituents at the seat of substitution are examined. Paper IV is concerned with the competition between radical and anionic cleavage reaction that are observed in a number of systems. In paper V, evidence is gathered that carbanions are intermediates in these types of electrophilic substitution reactions. In paper VI, a general mechanism of electrophilic substitution reaction at saturated carbon is elaborated. Tables, compounds and runs are numbered consecutively throughout the first six papers of this series.

Most of the reactions studied in this series can be generally formulated with X–Y as the leaving group, in which X is usually carbon but occasionally oxygen, and Y is usually oxygen but in a few cases carbon. The electrophile is in most cases, B–H, where B is oxygen or nitrogen. Most of the transformations can also be regarded as the reverse of ordinary nucleophilic addition reactions to unsaturated carbon such as the reverse Grignard, aldol, Claisen, Michael, etc., or as elimination reactions in which attention is focused on the fate of the leaving group.



Systems of this type offer certain advantages over those in which metal is the leaving group. (1) The starting materials and products are stable compounds, whose configurations can be related to one another by conventional means. (2) These systems allow the electrophilic substitution reaction itself to be isolated and studied. In stereochemical studies which involve breaking carbon–metal bonds, the metalation, possible exchange reactions, and the electrophilic substitution reactions have been separated only when mercury is the metal, and only then in systems containing more than one asymmetric carbon atom.[5,7,12a] (3) The reactions studied in these papers occur in a variety of solvents, at many temperatures, and are subject to mechanistic scrutiny involving rates, stereochemistry, isotope effects, tracer experiments, medium and constitutional effects. Because of the extreme reactivity of most organometallic compounds, the mechanisms of their reactions are very difficult to study.

This paper reports the results of a survey of reactions in which the leaving group is varied, and the stereochemical path can be fol-

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(5) A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubnaya, *Doklady Akad. Nauk, U.S.S.R.*, **88**, 479 (1953).

(6) D. J. Cram, J. Allinger and A. Langemann, *Chemistry & Industry*, 919 (1955).

(7) S. Winstein, T. G. Traylor and C. S. Garner, THIS JOURNAL, **77**, 3741 (1955).

(8) G. Wittig and U. Schoellkopf, *Tetrahedron*, **3**, 91 (1958).

(9) S. Winstein and T. G. Traylor, THIS JOURNAL, **78**, 2597 (1956).

(10) (a) L. Ramberg and A. Mellander, *Arkiv. Kemi, Mineral Geol.*, **11B**, 31 (1934); (b) L. Ramberg and I. Hedlung, *ibid.*, **11B**, 41 (1934); (c) C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 773 (1934); (d) P. D. Bartlett and C. H. Stauffer, THIS JOURNAL, **57**, 2580 (1935); (e) S. K. Hsii and C. L. Wilson, *J. Chem. Soc.*, 623 (1936); (f) S. K. Hsii, C. K. Ingold and C. L. Wilson, *ibid.*, 78 (1938); (g) J. Kenyon and D. P. Young, *ibid.*, 216 (1940); (h) H. Heintzeler, *Ann.*, **569**, 7 (1950); (i) K. Ziegler and H. Wenz, *Ber.*, **83**, 359 (1950); (j) H. M. Walborsky and F. M. Hornyak, THIS JOURNAL, **77**, 6026 (1955). Claims for production of carbanions that have retained their configuration [R. Kuhn and H. Albrecht, *Ber.*, **60**, 1297 (1927), R. L. Shriner and J. H. Young, THIS JOURNAL, **52**, 3332 (1930), and E. S. Wallis and F. H. Adams, *ibid.*, **55**, 3838 (1933)] have been demonstrated [N. Kornblum, J. T. Patton and J. B. Woodman, *ibid.*, **70**, 746 (1948), and G. Wittig, F. Vidal and E. Bohnert, *Ber.*, **83**, 359 (1950)] to be without foundation.

(11) (a) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957); (b) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2078 (1951); (c) D. Y. Curtin and E. E. Harris, THIS JOURNAL, **73**, 4519 (1951); (d) A. S. Dreiding and R. J. Pratt, *ibid.*, **76**, 1902 (1954).

(12) Reference 6 contains a preliminary announcement of results.

(12a) NOTE ADDED IN PROOF.—Recent communications reported the resolution of *sec*-butylmercuric bromide [H. B. Charman, E. D. Hughes and C. K. Ingold, *Chem. and Ind.*, 1517 (1958), and F. R. Jensen, L. D. Whipple, D. K. Wedegaertner and J. A. Landgrebe THIS JOURNAL, **81**, 1262 (1959)] and Jensen, *et al.*, brominated the compound stereospecifically to give 2-bromobutane.

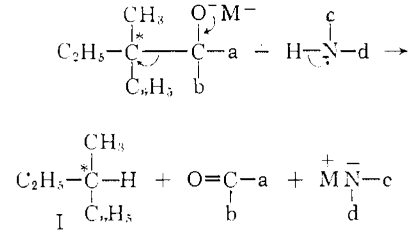
TABLE I

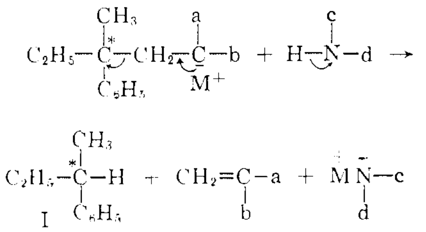
ELECTROPHILIC SUBSTITUTION AT SATURATED CARBON WITH AROMATIC AMINES AS SOLVENTS AND NUCLEOPHILES

	Starting material			Base				2-Phenylbutane					
Run	Nature	Concn., *M*	Solvent	Nature	Concn., *M*	T., °C.	Tm., hr.	Yld., %	$n^{25}\text{D}$ [a]	$\alpha^{25}\text{D}$ [b]	Opt. purity,[c] %	Predom. steric course	Opt. stable in run [d]
1	(−)-III	0.565	$C_6H_6NHCH_3$	$C_6H_5NKCH_3$	1.13	145	24	54	1.4877	+ 1.46°	6	Ret.	No
2	(+)-IV	0.550	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	0.82	134	9	4	1.4891	+ 3.2	13	Ret.	No
3	(−)-V	1.03	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	1.03	102	2.3	10	1.4877	+15.1	63	Ret.	Yes
4	(−)-VI	0.53	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	0.53	210	0.33	85	1.4878	−14.8	61	Ret.	No
5	(−)-VI	.86	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	.72	210	.33	39	1.4877	−17.1	70	Ret.	No
6	(−)-VI	.50	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	.50	210	.15	80	1.4879	−11.5	47	Ret.	No
7	(+)-VII	1.09	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	1.09	204	5	37	1.4878	− 6.5	27	Ret.	No
8	(+)-VII	0.76	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	0.75	210	0.17	45	1.4879	−12.2	50	Ret.	No
9	(+)-VIII	.20	$C_6H_5NH_2$	C_6H_5NHK	.40	72	0.5	55	1.4878	−14.07	58	Ret.	Yes
10	(−)-IX	.47	$C_6H_4(CH_2)_3NH$ [e]	$C_6H_4(CH_2)_3NK$ [f]	.17	240	9	10	1.4876	+ 0.26	1	Ret.	No
11	(−)-IX	1.07	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	1.07	72	0.5	41	1.4878	+21.7	89	Ret.	Yes
12	(−)-X	0.20	$C_6H_5NH_2$	C_6H_5NHK	0.20	188	24	80	1.4876	+20.1	83	Ret.	Yes
13	(+)-XI	.92	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	.92	72	0.5	35	1.4872	+17.1	71	Ret.	Yes
14	(−)-XII	.13	$C_6H_5NHCH_3$	$C_6H_5NKCH_3$	.14	210	17	10	1.4863	+ 3.39	14	Ret.	No
15	(+)-XIII	.31	$C_6H_4(CH_2)_3NH$ [e]	$C_6H_4(CH_2)_3NK$ [f]	.34	240	22	46	1.4876	+ 0.42	2	Ret.	No

[a] Pure 2-phenylbutane has $n^{25}\text{D}$ 1.4878. [b] *l* 1 dm., neat. [c] Optically pure 2-phenylbutane has $\alpha^{25}\text{D}$ ±24.3°, *l* 1 dm., neat. [d] See Experimental for control runs. [e] Tetrahydroquinoline. [f] Potassium tetrahydroquinolide.

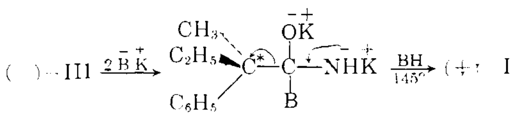
lowed. The carbon which undergoes substitution carries phenyl, methyl and ethyl substituents, the electrophile is a proton donated by solvent (secondary amines), and the product is 2-phenylbutane (I). Most of the reactions correspond to one or the other of the sequences formulated.

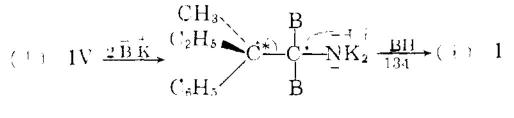




Starting Materials.—All of the starting materials for this study were prepared as shown in Chart I from the optically active isomers of 2-methyl-2-phenylbutanoic acid[13] (II), whose absolute configuration has been assigned.[14] The absolute configuration of 2-phenylbutane (I) has also been established,[15] and therefore the relative configurations of starting materials and products of the substitution reactions are known. An additional advantage of the systems employed is the fact that 2-phenylbutane (I) is a readily purified liquid, possesses characteristic physical properties (infrared, gas chromatographic behavior, index of refraction and pleasant odor), and when optically pure possesses a high rotation ($\alpha^{23}\text{D}$ + or −24.3°, *l* 1 dm., neat).

Substitution with Carbon–Oxygen or Carbon–Nitrogen Leaving Groups.—Attempts to decarboxylate optically pure (−)-2-methyl-2-phenylbutanoic acid with base failed under conditions which would not completely racemize the product (I). Amide III[13] and nitrile IV[14] of this acid underwent cleavage reactions (runs 1 and 2 of Table I) to give (+)-2-phenylbutane of 6 and 13% optical purity, respectively. These reactions were conducted in N-methylaniline as solvent and at temperatures at which the product partially racemized once formed (see Experimental). The fact that more than one mole of base (potassium N-methylanilide) was needed to cause reaction indicates that dianionic intermediates are involved, as are indicated in the formulation.





In the same solvent and base, optically pure (−)-1,2-diphenyl-2-methyl-1-butanone[14] [(−)-V] gave (+) - I of 63% optical purity under conditions that this product was optically stable (run 3).[16] The alcohol derived from this ketone was also produced [(+)-1,2-diphenyl-2-methyl-1-butanol or (+)-VI], as well as a low yield of benzanilide. Isolation of the last product indicates that the

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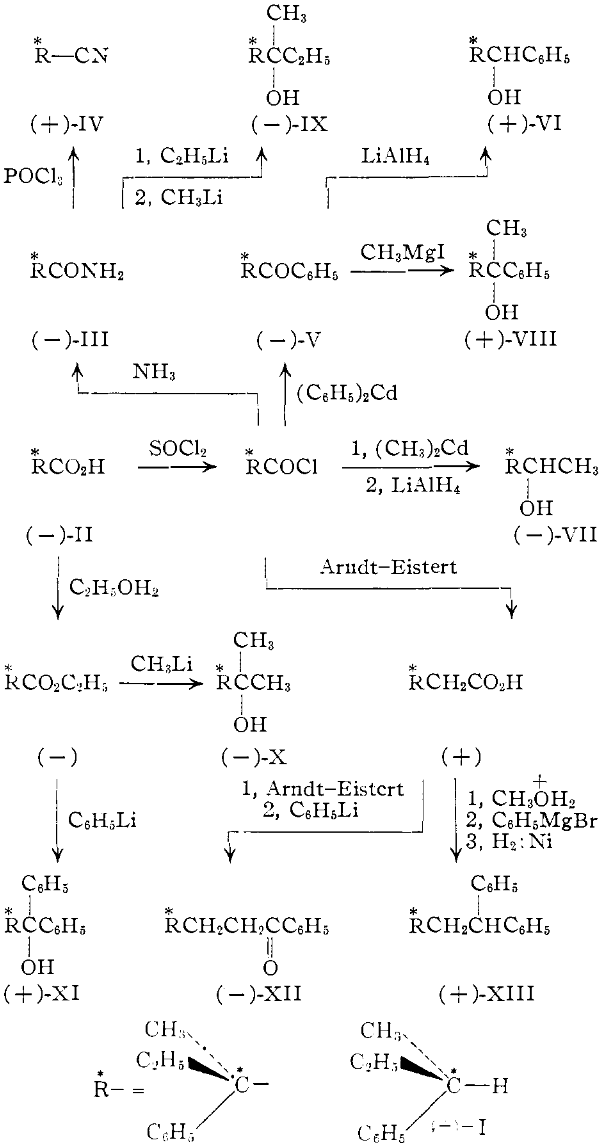
(13) D. J. Cram and J. D. Knight, THIS JOURNAL, **74**, 5835 (1952).

(14) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954). Further evidence for the correctness of this assignment will be found in paper III of this series; D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 5754 (1959).

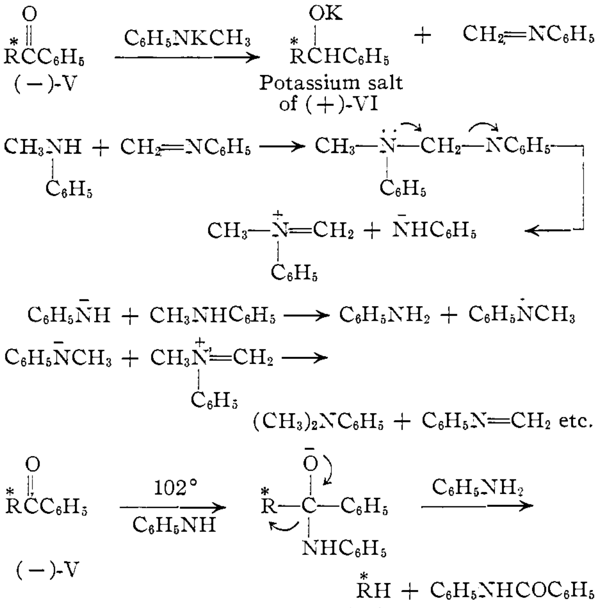
(15) D. J. Cram, *ibid.*, **74**, 2149 (1952).

(16) The cleavage of ketones with sodamide to give an amide and a hydrocarbon is a general reaction, which has been reviewed by F. W. Bergstrom and W. C. Fernelius, *Chem. Revs.*, **20**, 450 (1937).

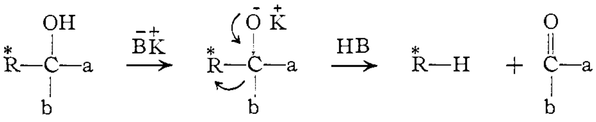
CHART I



ketone rather than the alcohol produced from it underwent cleavage, and that potassium anilide rather than potassium N-methylanilide was the base involved in this cleavage. Possibly N-methylaniline underwent a base-catalyzed disproportionation reaction of the type indicated to give dimethylaniline and aniline.

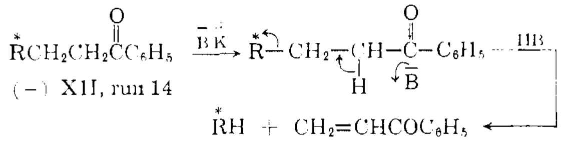


The six alcohols, (−)-VI, (+)-VII, (+)-VIII, (−)-IX, (−)-X and (+)-XI, when heated in aniline solutions of potassium anilide or N-methylaniline solutions of potassium N-methylanilide (runs 4–13) underwent cleavage reactions[17] to give 2-phenylbutane which varied between 27 and 89% optical purity depending on the nature of the leaving group and temperature of the reaction. With VI, VII, VIII and IX, mixtures of diastereomeric alcohols were employed which were configurationally homogeneous at the carbon atom undergoing electrophilic substitution. The results are formulated.[18] Control experiments (see Experimental) indicate that the product once formed maintained its optical integrity in runs 9, 11, 12 and 13, but that some racemization occurred in the other runs. Therefore the values of optical purity of the product in runs 4–8 and 10 are minimal.



(+)-VI: a = H, b = C_6H_5	(+)-I, 70% optically pure (run 5)
(−)-VII: a = H, b = CH_3	(+)-I, 50% optically pure (run 8)
(+)-VIII: a = CH_3, b = C_6H_5	(+)-I, 58% optically pure (run 9)
(−)-IX: a = CH_3, b = C_2H_5	(+)-I, 89% optically pure (run 11)
(−)-X: a = b = CH_3	(+)-I, 83% optically pure (run 12)
(+)-XI: a = b = C_6H_5	(+)-I, 71% optically pure (run 13)

Substitution with Carbon–Carbon Leaving Groups.—Ketone (−)-XII was found to undergo a reverse Michael reaction under conditions (N-methylaniline, potassium N-methylanilide at 210°) in which the 2-phenylbutane once produced racemized somewhat (run 14). Unfortunately the reaction did not occur under milder conditions.



(+) I (14% optically pure)

Hydrocarbon (+)-XIII was found to cleave only in a solution of potassium tetrahydroquinolide in tetrahydroquinoline at 240° (run 15). Under these conditions, optically active 2-phenylbutane was

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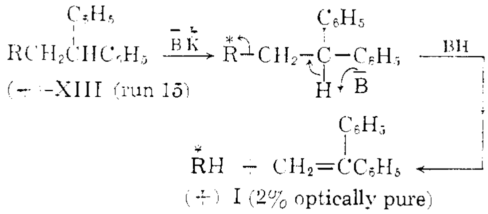
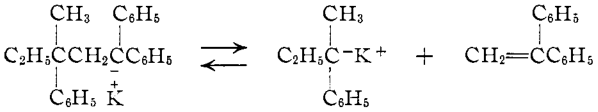
[17] Reactions of this type have been observed previously: (a) L. Ellison and J. Kenyon, *J. Chem. Soc.*, 779 (1954); (b) J. L. Greene and H. D. Zook, This Journal, **80**, 3629 (1958).

[18] Actually (−)-VI and (+)-VII were employed as starting materials and (−)-I was the product. The enantiomeric series is formulated here to simplify the presentation.

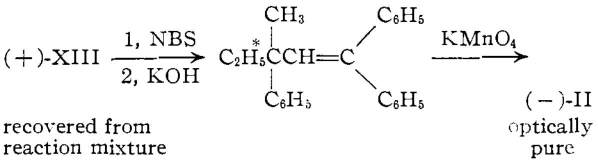
found to racemize very rapidly, and so the value of 2% optical purity for the product of the cleavage reaction is much lower than that of the hydrocarbon initially produced. This is further demonstrated by the fact that when alcohol (−)-IX was cleaved under the same conditions as hydrocarbon (+)-XIII, the 2-phenylbutane was only 1% optically pure. Under milder conditions alcohol (−)-IX gave product which was 89% optically pure (run 10).



A small amount of starting material mixed with α-phenylstyrene was recovered from the reaction mixture of run 15. Since 2-phenyl-2-propylpotassium has been found to add to α-phenylstyrene,[19] it seemed possible that the starting material might have racemized through the reversible reaction formulated.[20] Therefore, the recovered hydrocarbon mixture was degraded to (−)-II, which was

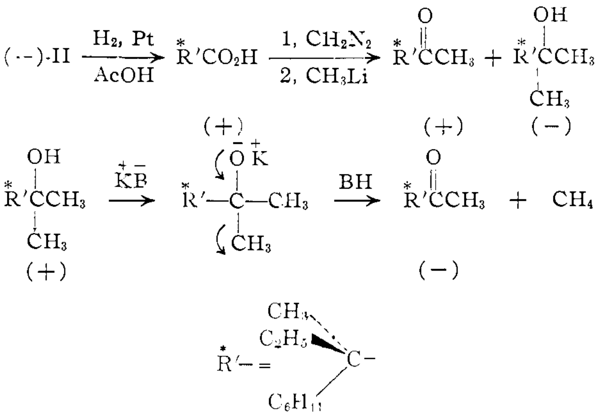


optically pure. Thus the reversible reaction if it occurs does not racemize the starting material. This result also demonstrates that the Arndt–Eistert homologation reaction occurs with complete retention of configuration of the migrating group.



In a second cleavage experiment, (+)-XIII was heated with potassium diphenylamide in diphenylamine at 270°. Although good yields of 2-phenylbutane and α-phenylstyrene were obtained, the former compound was completely racemic, probably due to the action of the strong base at the high temperature.

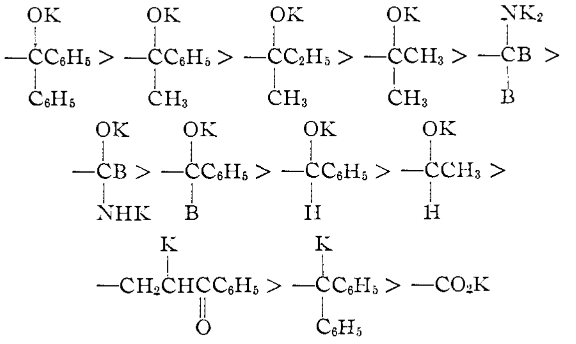
Cleavages of Other Systems.—An attempt was made to examine the stereochemistry of electrophilic substitution at a carbon atom which carried methyl, ethyl and cyclohexyl substituents. Such a system seemed particularly attractive since the absolute configuration of 2-cyclohexylbutane (the anticipated product) is known,[21] and the configuration of 2-cyclohexyl-2-methylbutanoic acid could be easily established by its synthesis from optically active II. Accordingly, (+)-2-cyclohexyl-2-methylbutanoic acid was prepared and converted to (+)-3-cyclohexyl-3-methyl-2-pentanone and (−)-3-cyclohexyl-2,3-dimethyl-2-pentanol. Attempts to decarboxylate the acid with sodamide and with potassium tetrahydroquinolide in tetrahydroquinoline at 240° failed. The alcohol did cleave under the latter conditions, but the products were (+)-3-cyclohexyl-3-methyl-2-pentanone and presumably methane. The fact that the methyl rather than the 2-cyclohexylbutyl group was expelled indicates that the cleavage reaction was not radical in type, since primary radicals are much less stable than tertiary radicals.[22] An anionic mechanism is consistent with the results since primary anions are more stable than tertiary anions.[23]



Discussion

Variation of Reactivity with Changes of Leaving Group.—By comparison of the temperatures required for reaction, the various starting materials can be arranged with some reservations in a rough reactivity order. Since the seat of electrophilic substitution, the electrophile, the solvent and base remained constant in these transformations, this order is associated with the reactivity of the leaving group. The order indicated seems to apply.

This order is of only limited use in discussing the course of the reactions because of ambiguity associated with the acid–base reaction which must precede cleavage of the carbon–carbon bond. With



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[19] K. Ziegler and K. Bahr, *Ber.*, **61**, 253 (1928).

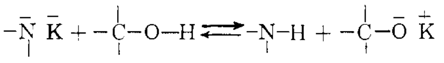
[20] H. Hart [This Journal, **78**, 2691 (1956)] found that 2-phenyl-2-pentylpotassium adds more rapidly to an ethylene molecule than it abstracts a proton from 2-phenylpentane. However, the product of addition abstracts a proton more readily from 2-phenylpentane than it adds to a second molecule of ethylene.

[21] D. J. Cram and J. Tadanier, *ibid.*, **81**, 2737 (1959).

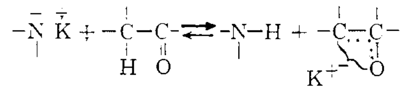
[22] In paper IV of this series [*ibid.*, **81**, 5760 (1959)], it is demonstrated that base-catalyzed cleavage of 1,1-diphenyl-2-cyclohexyl-2-methyl-1-butanol produces 2-cyclohexylbutyl radicals and diphenyl ketone radical anions in the initial stage.

[23] A. A. Morton, *Chem. Revs.*, **35**, 1 (1941).

the six alcohols, this equilibrium was probable relatively unimportant since the bases employed are much stronger than the alkoxide formed.[23] Since the rate of proton transfer was undoubtedly rapid, the order of reactivity shown above is associated with the cleavage, and not with the initial acid–base reaction. Similarly, since ketone XII must be a stronger acid than methylaniline (an estimated 9 powers of 10),[23] the same kind of considerations apply to its reaction as to the alcohols.

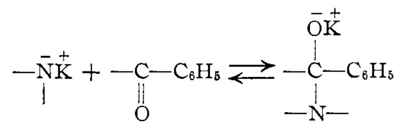


$$-\underset{|}{\bar{N}}\,\overset{+}{K} + -\underset{|}{\overset{|}{C}}-O-H \rightleftarrows -\underset{|}{N}-H + -\underset{|}{\overset{|}{C}}-\bar{O}\,\overset{+}{K}$$



$$-\underset{|}{\bar{N}}\,\overset{+}{K} + -\underset{H}{\overset{|}{C}}-\underset{O}{\underset{\|}{C}}- \rightleftarrows -\underset{|}{N}-H + -\overset{|}{C}\overset{\cdot\cdot}{=}\overset{|}{C}- \quad \overset{+}{K}\;\bar{O}$$

The rate of reaction of V (1,2-diphenyl-2-methyl-1-butanone) probably is also mainly associated with the rate of cleavage of the carbon–carbon bond, since the initial reaction of base with ketone is undoubtedly rapid, and the position of the equilibrium not unfavorable to the conjugate base of the ketone.



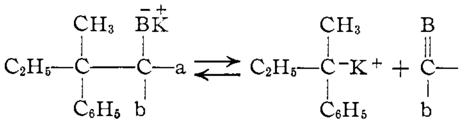
$$-\underset{|}{\overset{-\,+}{N}}K + -\underset{O}{\underset{\|}{C}}-C_6H_5 \rightleftarrows -\underset{-N-}{\underset{|}{\overset{\overset{-\,+}{OK}}{\overset{|}{C}}}}-C_6H_5$$

Since dianions are involved in the deamidation and decyanation reactions, it is not clear whether formation of the dianion or the cleavage reaction is rate determining. Similarly, in the reaction of hydrocarbon XIII, since N-methylaniline is a much stronger acid than XIII, it is possible that proton removal from the latter is the rate-determining stage.

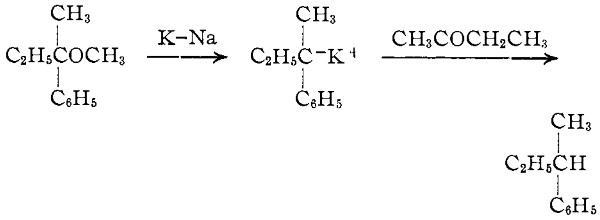
In spite of these ambiguities, a few generalizations can be made. Clearly, the reactions which initially produce ketones occur faster than those which give amides, which are faster than those which give aldehydes (initially), which are faster than that which gives the α,β-unsaturated ketone (initially). Thus as groups are successively substituted for hydrogen on the leaving carbon atom, the cleavage reaction occurs more readily. This order correlates with the relative strain of the starting states due to non-bonded steric interactions. The higher the strain, the faster the reaction. Phenyl substituents attached to the leaving group undoubtedly stabilize negative charge in the transition state of the cleavage reaction much more than alkyl groups or hydrogen atoms.

Steric Course of Electrophilic Substitution at Saturated Carbon.—The general pattern of results clearly indicates that under the conditions of these experiments, the electrophilic substitution reaction occurs with predominating retention of configuration accompanied by varying amounts of racemization. Only the cleavages of the tertiary alcohols were run under conditions in which the 2-phenylbutane once formed was completely optically stable, and these reactions gave the highest stereospecificity. Those reactions conducted under the most drastic conditions of base strength and temperature gave the lowest stereospecificity, at least partly because the product racemized somewhat after it was formed. Unfortunately the results cannot be corrected for this, since the actual reaction conditions can be only approximated in control runs. In some of the systems studied, the basic strength of the medium changed as the run proceeded, since the products contained protons more acidic than that of methylaniline. For instance, acetaldehyde or its condensation product produced from alcohol VII probably consumed base. In other cleavages (*e.g.*, of alcohol VI) in which less than a mole of base per mole of alcohol was used, the alkoxide initially formed was not a strong enough base to racemize the 2-phenylbutane formed. However, as this salt was consumed, potassium N-methylanilide was again formed, since the benzaldehyde formed (or its condensation products) does not contain any acidic protons.

Another possible mode of production of racemic 2-phenylbutane was through racemization of the starting material by a reversible addition–elimination reaction in which the 2-phenylbutylpotassium racemized. This possibility was set aside only in the cleavage of XIII by isolation of optically pure starting material before it was completely consumed. However, it seems improbable that a reversible reaction of this sort occurs, at least in the cleavage of alcohols VIII, IX and X, since 2-phenyl-2-butylpotassium was found to abstract a proton from 2-butanone instead of adding to the carbonyl group to give 3,4-dimethyl-4-phenyl-3-hexanol (IX).



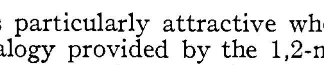
$$C_2H_5-\underset{\underset{C_6H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{b}{|}}{\overset{\overset{\overset{-\,+}{BK}}{|}}{C}}-a \rightleftarrows C_2H_5-\underset{\underset{C_6H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}{}^-K^+ + \underset{\underset{b}{|}}{\overset{\overset{B}{\|}}{C}}-a$$



$$C_2H_5\underset{\underset{C_6H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}OCH_3 \xrightarrow{K-Na} C_2H_5\underset{\underset{C_6H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}{}^-K^+ \xrightarrow{CH_3COCH_2CH_3} C_2H_5\underset{\underset{C_6H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}H$$

This reaction suggests the possibility that in some of the cleavage reactions, an internal proton is utilized in a cyclic mechanism which accounts for the product in which substitution has occurred with retention of configuration. Such an explanation appears particularly attractive when coupled with the analogy provided by the 1,2-nucleophilic rearrangements. In these reactions, the migrating group, when asymmetric, completely maintains its configuration, and the bonding electrons stay with the migrating group.[24] These rearrangements can

Cleavage by S_{Ei} Reaction Path



$$-\overset{*}{C}-\overset{\overset{\bar{O}}{|}}{A}\underset{H}{\overset{}{}}\!\!\!=\!B \longrightarrow -\overset{*}{C}-H + \bar{O}-A=B$$

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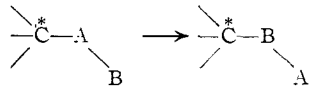
[24] See D. J. Cram in M. S. Newman's Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 251–254, for discussion and references.

also be considered as S_{Ei} reactions, in which B (migration terminus) is the electrophile and A (migration origin) is the leaving group.

1,2-Rearrangement, or S$_{Ei}$ Reaction



A cyclic mechanism for that part of the cleavage reactions which gives retention is possible only with alcohols VII, X, amide III, nitrile IV and ketone V (benzanilide could have provided the proton). In systems VI, XI, XII and XIII, no internal proton was available, and therefore the proton *must have come from solvent in these cases.* Further discussion of the mechanism of these reactions is deferred to later papers of this series.

Experimental

(–)-N-Phenyl-2-methyl-2-phenylbutanoic Amide.—Optically pure (–)-2-methyl-2-phenylbutanoic acid[13] was converted to the acid chloride,[13] 3.3 g. (0.017 mole) of which was mixed with 3.7 g. (0.040 mole) of aniline in 40 ml. of benzene. After standing for one hour at 25°, the mixture was shaken with ether and water, the organic phase was washed with dilute hydrochloric acid and with water. The solution was dried, evaporated, and the residue was crystallized from methanol–water to give 4.0 g. (94% yield) of colorless needles, m.p. 73–74°, $[\alpha]^{25}_{D}$ –25.53° (*c* 5 in benzene).

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56. Found: C, 80.76; H, 7.40.

An attempt to cleave this compound to 2-phenylbutane gave only hydrolysis product. To a solution of potassium N-methylanilide in N-methylaniline (0.31 g. of potassium and 7.3 ml. of aniline) was added 1.00 g. of N-phenyl-2-methyl-2-phenylbutanoic amide, and the mixture was heated to 125° for 24 hours. From this mixture 32% of the starting material was recovered (m.p. 73–74°) along with a small amount of (–)-2-methyl-2-phenylbutanoic acid. No 2-phenyl-butane was found.

(+)-2-Methyl-1,1,2-triphenyl-1-butanol [(+)-XI].—A solution of 50.0 g. (0.281 mole) of (-)-2-methyl-2-phenylbutanoic acid,[13] $[\alpha]^{25}_{D}$ –29.7° (*c* 4.3 in benzene), in 200 ml. of dry ethanol and 20 ml. of concentrated sulfuric acid was held at reflux temperature for 12 hours. The excess ethanol was evaporated under reduced pressure, and the residue was shaken with water and ether. The ether layer was washed with water, dried, and the solvent was evaporated. The residue was distilled to give 55.2 g. (95% yield) of (-)-ethyl 2-methyl-2-phenylbutanoate, b.p. 97–98° (3 mm.), n^{25}_{D} 1.4919, α^{30}_{D} –10.2° (*l* 1 dm.).

A solution of phenyllithium was prepared from 10 g. (1.43 moles) of lithium metal and 100 g. (0.638 mole) of bromobenzene in 350 ml. of dry ether. The solution was filtered from lithium bromide and unreacted lithium, and to the filtrate held at 0° was added dropwise 54.0 g. (0.262 mole) of the above ester dissolved in 100 ml. of dry ether. No green color developed (evidence of lack of radicals). The mixture was stirred at 0° for 1 hour, and mixed with 150 g. of ice. The ether layer was washed with water, dried with potassium carbonate, and the solvent was evaporated under reduced pressure to give 115 g. of a viscous yellow liquid. This mixture was chromatographed on 3000 g. of activity III alumina[25] in pentane. Bromobenzene and biphenyl were washed from the column with 6 liters of pentane, and the desired alcohol [(+)-XI] was eluted with 8.5 liters of purified pentane–ether (10 to 1). The solvent was evaporated under reduced pressure and the residue was dissolved in 200 ml. of purified pentane. The light yellow solution was decolorized with activated charcoal, and evaporated under reduced pressure. The residual viscous liquid was rotated as a film at 70° under 1 mm. pressure to free it from pentane to give 72 g. (87% yield) of XI, n^{25}_{D} 1.6095, $[\alpha]^{23}_{D}$ +31.67° (*c* 6.4 in benzene).

Anal. Calcd. for $C_{23}H_{24}O$: C, 87.30; H, 7.65. Found: C, 87.50; H, 7.65.

3-Methyl-3-phenylpentanoic Acid.—The racemic acid was prepared from racemic 2-methyl-2-phenylbutanoic acid (II)[13] by the Arndt–Eistert synthesis as modified by Wilds.[26] The material was obtained as a pale yellow liquid, b.p. 140° (1 mm.), n^{25}_{D} 1.5197. This compound was analyzed as its methyl ester (see below). From optically pure (–)-II ($[\alpha]^{26}_{D}$ –28.9°, *c* 4.5 in benzene) was obtained, by the same procedure, a 58% yield of (+)-3-methyl-3-phenylpentanoic acid as white needles (pentane), m.p. 43–44°, $[\alpha]^{25}_{D}$ +14.6° (*c* 3.8 in chloroform).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.93; H, 8.39. Found: C, 74.80; H, 8.42.

(+)- and Racemic Methyl 3-Methyl-3-phenylpentanoate.—Both racemic and (+)-3-methyl-3-phenylpentanoic acid were esterified with methanol by the Fischer method[27] in about 90% yields. Racemic ester was distilled at a pot temperature of 150° (8 mm.), n^{25}_{D} 1.5008.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.67; H, 8.79. Found: C, 75.63; H, 9.05.

The (+)-ester had b.p. 96° (1 mm.), n^{25}_{D} 1.5018, α^{25}_{D} 12.7° (neat, *l* 1 dm.).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.67; H, 8.79. Found: C, 75.47; H, 8.81.

(+)- and Racemic 1,1,3-Triphenyl-3-methyl-1-pentanol.—To 100 ml. of an ethereal solution of phenyllithium prepared from 9.4 g. (0.06 mole) of bromobenzene and 0.84 g. (0.12 mole) of lithium was added 1.75 g. (0.01 mole) of racemic methyl 3-methyl-3-phenyl-pentanoate in 10 ml. of ether. The mixture was stirred for 24 hours at 25°, and then was mixed with water. The ether layer was washed with water, dried, and evaporated to an oil. This material was chromatographed on 150 g. of neutral, activated alumina. Benzene, bromobenzene and biphenyl were eluted with pentane, and the product was eluted with 25% ether–pentane. Evaporation of the latter eluate gave 2.3 g. (78% yield) of racemic alcohol as dense white cubes, m.p. 54.4–55.2°.

Anal. Calcd. for $C_{24}H_{26}O$: C, 87.22; H, 7.93. Found: C, 87.20; H, 7.97.

In a similar manner, (+)-alcohol was prepared in 75% yield as a viscous oil which could not be crystallized, $[\alpha]^{25}_{D}$ +29.2° (*c* 3.8 in chloroform). This oil could not be distilled without decomposition.

(+)- and Racemic 3-Methyl-1,1,3-triphenylpentane [XIII and (+)-XIII].—To a mixture of 15 g. of Raney nickel in 150 ml. of absolute ethanol was added 4.8 g. of racemic 1,1,3-triphenyl-3-methyl-1-pentanol. The resulting mixture was refluxed and stirred for 8 hours, cooled, and filtered through Celite. The nickel was washed with 200 ml. of ethanol, and the combined filtrates were evaporated under reduced pressure to an oil. This was distilled (200° pot temperature, 2 mm.) to give 3.8 g. (84% yield) of a colorless, viscous liquid, n^{25}_{D} 1.5804.

Anal. Calcd. for $C_{24}H_{26}$: C, 91.66; H, 8.33. Found: C, 91.77; H, 8.48.

By the same procedure, (+)-alcohol was converted to (+)-XIII in 92% yield, n^{25}_{D} 11.5788, $[\alpha]^{23}_{D}$ +2.61 (*c* 5.3 in chloroform).

Anal. Calcd. for $C_{24}H_{26}$: C, 91.66; H, 8.33. Found: C, 91.46; H, 8.49.

Degradation of (+)-3-Methyl-1,1,3-triphenylpentane [(+)-XIII] to (–)-2-Methyl-2-phenylbutanoic Acid [(–)-II].—A mixture of 15 ml. of dry carbon tetrachloride, 0.68 g. (0.0021 mole) of hydrocarbon (+)-XIII, 0.38 g. (0.0021 mole) of N-bromosuccinimide and a trace of benzoyl peroxide was heated to reflux. After 40 minutes the N-bromosuccinimide had been consumed, and the mixture was cooled and filtered. The filtrate was evaporated, and the red oil was chromatographed on 100 g. of neutral, activated alumina. The column was eluted with 10% ether–pentane (700 ml.), and the eluate was concentrated to a viscous oil. This oil was heated to reflux in 10 ml. of an 8% solution of potassium hydroxide in 95% ethanol for 12 hours. The solvent was then evaporated, and the residual oil was heated to 100° for one hour in 10 ml. of pyridine to which was added an excess of a basic solution of potassium permanganate.

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[25] H. Brockmann and H. Schodder, *Ber.*, **74B**, 73 (1941).

[26] A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

[27] L. F. Fieser, "Experiments in Organic Chemistry," third edition, D. C. Heath and Co., Boston, Mass., 1955, p. 78.

Methanol was added to destroy the excess permanganate, and the mixture was filtered from manganese dioxide. The filtrate was washed twice with ether, acidified, and extracted twice with pentane. The pentane was dried, and concentrated to a colorless oil which crystallized, m.p. 77–81°. This material was recrystallized from pentane to give 50 mg. (13% yield) of white needles, $[\alpha]^{27}_{D}$ −26.9° (*c* 1.6 in benzene), m.p. 84–85°, undepressed by admixture with an authentic sample of (−)-II, $[\alpha]^{27}_{D}$ −26.9° (*c* 1.7 in benzene).

(−)-**4-Methyl-4-phenylhexanoic Acid.**—The compound, (+)-3-methyl-3-phenylpentanoic acid, was homologated to (−)-4-methyl-4-phenylhexanoic acid by the same procedure used for preparing the starting acid. From 14.0 g. of optically pure (+)-3-methyl-3-phenylpentanoic acid was obtained 62. g. (43% yield) of (−)-product as a light yellow liquid, which distilled at a pot temperature of 170° (1 mm.), n^{25}_{D} 1.5160, $[\alpha]^{25}_{D}$ −50.2° (*c* 6.3 in benzene).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.70; H, 8.78. Found: C, 75.52; H, 8.67.

(−)-1,**4-Diphenyl-4-**methyl-1-**hexanone** [(−)-**XII**].—To 250 ml. of a well-stirred ethereal solution of phenyllithium (from 0.9 g. or 0.13 mole of lithium and 10 g. or 0.064 mole of bromobenzene) was added 6.0 g. (0.031 mole) of (−)-4-methyl-4-phenylhexanoic acid in 50 ml. of ether. The addition was carried out at −10°, and the resulting mixture was stirred at 0° for 3 hours, allowed to warm to room temperature, and stirred for an additional 6 hours. The mixture was shaken with water, and the ether layer was washed, dried and evaporated to an oil. From the water layer was recovered 1.4 g. of starting acid.

The oil was chromatographed on 200 g. of neutral, activated alumina. The column was washed with 1 liter of pentane, and ketone (−)-XII was eluted with 2.5 liters of 10% ether–pentane. When evaporated, this eluate gave 2.9 g. (50% yield) of (−)-XII as a liquid which distilled at a pot temperature of 200° (3 mm.), n^{25}_{D} 1.5602, α^{25}_{D} −31.2° (*l* 1 dm., neat). The infrared spectrum of this material showed strong carbonyl absorption at 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.66; H, 8.33. Found: C, 85.46; H, 8.25.

Further elution of the chromatograph column with ether gave 3.0 g. of a viscous yellow oil whose infrared spectrum showed hydroxyl absorption at 3490 cm.$^{-1}$.

Racemic 1,**3-Diphenyl-3-**methyl-1-**pentanone.**—To 7.0 g. (0.038 mole) of racemic 3-methyl-3-phenylpentanoic acid in 200 ml. of ether at 0° was added 200 ml. of a solution of phenyllithium made from 12.4 g. (0.077 mole) of bromobenzene and 1.2 g. (0.155 mole) of lithium. After addition was complete the mixture was stirred at room temperature for 4 hours. The mixture was then shaken with water, the ether layer was washed with water, dried and evaporated. The residual oil was chromatographed on 300 g. of neutral, activated alumina. The column was washed with 1.25 liters of 3% ether–pentane, and the desired ketone was eluted with 2.5 liters of 10% ether–pentane. Concentration of the eluate gave 3.4 g. (37% yield) of a pale yellow oil, b.p. 163–164° (2 mm.), n^{25}_{D} 1.5625.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.71; H, 7.94. Found: C, 85.85; H, 8.18.

Racemic 1,**3-Diphenyl-3-**methyl**pentane.**—When submitted to the modified Wolff–Kishner reduction,[28] 3.0 g. of racemic 1,3-diphenyl-3-methyl-1-pentanone gave 2.0 g. (71% yield) of 1,3-diphenyl-3-methylpentane as a mobile, colorless oil, b.p. 148° (2 mm.), n^{25}_{D} 1.5423. The characteristic odor of 2-phenylbutane was not noted at any time during the reduction.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.76; H, 9.24. Found: C, 90.52; H, 9.42

Racemic 4-Methyl-4-phenyl-2-hexanone.—The reaction of methyllithium with racemic 3-methyl-3-phenylpentanoic acid when carried out as in the preparation of 1,3-diphenyl-3-methyl-1-pentanone gave from 13.5 g. of starting acid, 10 g. of the desired product as a colorless, mobile oil, b.p. 105° (2 mm.), n^{25}_{D} 1.5086.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.10; H, 9.47. Found: C, 82.15; H, 9.64.

During a Wolff–Kishner reduction of this ketone, no odor of 2-phenylbutane was evident.

(+)-**3-Methyl-3-phenyl-2-pentanol** [(+)-**VII**].—A solution of 0.90 g. (0.0051 mole) of optically pure (+)-3-methyl-3-phenyl-2-pentanone,[14] $[\alpha]^{25}_{D}$ +69.1° (*l* 1 dm., neat), n^{25}_{D} 1.5080, in anhydrous ether was reduced in the usual way with lithium aluminum hydride (0.292 g., or 0.0077 mole). The product was isolated as a crude oil, chromatographed on activity III[25] alumina, and distilled to give 0.78 g. (86% yield) of (+)-VII, n^{25}_{D} 1.5189, d^{25}_{4} 0.9866, $[\alpha]^{25}_{D}$ +9.10° (*l* 1 dm., neat).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 10.39.

Racemic and (−)-**2,3-Dimethyl-3-phenyl-2-pentanol** [(−)-**X**].—Methyllithium was prepared from 213 g. (1.5 moles) of methyl iodide and excess lithium cut into small pieces from ribbon in 1.5 liters of dry ether. The reagent was filtered under nitrogen pressure through glass wool and was cooled to −10° and stirred while 35 g. (0.184 mole) of racemic methyl 2-methyl-2-phenylbutanoate was added dissolved in 200 ml. of dry ether. The mixture was slowly allowed to come to room temperature. Excess reagent was destroyed with water, the organic layer was washed with water, with sodium sulfite solution, sodium carbonate solution and again with water. The solution was dried, evaporated, and fractionally distilled in a center-rod column at 1 mm. pressure. The early fractions consisted largely of 3-methyl-3-phenyl-2-butanone, and the later fractions of X (shown by infrared). One of the late fractions (1.5 g.) was chromatographed on 150 g. of activity I neutral alumina.[25] Ketone was washed from the column with 10% ether in pentane, and X with ether; wt. 0.92 g., b.p. 106° at 4 mm., n^{25}_{D} 1.5187, colorless oil.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.08; H, 10.41.

The same procedure was applied to preparation of (−)-X. From 65 g. of (−)-methyl 2-phenyl-2-phenylbutanoate (see below for preparation) and methyllithium (from 425 g. of methyl iodide) was obtained a mixture of ketone and alcohol which was subjected to the same procedure for two additional cycles. The final product was chromatographed as before to give 48 g. of (−)-X, α^{27}_{D} −2.03° (*l* 1 dm., neat), n^{25}_{D} 1.5199.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.02; H, 10.27.

(−)-**Methyl 2-Methyl-2-phenylbutanoate.**—A solution of 65 g. of optically pure 2-methyl-2-phenylbutanoic acid,[13] $[\alpha]^{25}_{D}$ −30.2° (*c* 5.8 in benzene) in 300 ml. of dry ether was prepared, and a solution of excess diazomethane in dry ether was added dropwise. The excess diazomethane was decomposed with formic acid, and the resulting ether solution was washed with water and dilute sodium bicarbonate solution. The solution was dried, evaporated, and the residual oil was distilled to give 69 g. of (−)-ester, b.p. 120–121° (14 mm.), n^{25}_{D} 1.5003, α^{26}_{D} −19.23° (*l* 1 dm., neat).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.94; H, 8.38. Found: C, 74.82; H, 8.20.

Racemic ester was prepared the same way.

(+)-**2,3-Diphenyl-3-methyl-2-pentanol** [(+)-**VIII**].—Methyl-lithium was prepared from 35.5 g. (0.25 mole) of methyl iodide and 4.5 g. (0.65 mole) of freshly cut lithium ribbon in 400 ml. of ether. The reagent was filtered through glass wool under nitrogen pressure into a second flask and cooled in an ice–salt-bath. To this clear solution (at 0°) was added dropwise with stirring, a solution of 12 g. (0.050 mole) of (−)-1,2-diphenyl-2-methyl-1-butanone (α^{27}_{D} −68.9°, *l* 1 dm., neat)[14] in 100 ml. of ether. The mixture was stirred at 0° for 2 hours, and treated with water cautiously at 0°. The layers were separated, and the organic layer was washed with water, sodium bisulfite, sodium carbonate solution and again with water. The solution was dried, and the solvent was evaporated in vacuum, and finally the ether was removed by twice adding pure pentane and evaporating in vacuum. The residue was chromatographed on 400 g. of activity I alumina.[25] The column was washed with pentane, and the desired alcohol was eluted with 1 to 3 pentane–ether to give 9.3 g. of product. This material could not be distilled without decomposition, and was freed of solvent by heating to 35° for 24 hours at 0.1 mm. pressure. This material gave n^{25}_{D} 1.5696, $[\alpha]^{26}_{D}$ +17.5° (*c* 71 in benzene).

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.82; H, 8.92.

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[28] Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(+)-2-Cyclohexyl-2-methylbutanoic Acid.—A mixture of 4.0 g. of optically pure (−)-2-methyl-2-phenylbutanoic acid [(−)-II], 50 ml. of glacial acetic acid and 0.1 g. of platinum oxide was shaken in a hydrogen atmosphere until 98.5% of theory of hydrogen was absorbed. The mixture was filtered, the solvent was evaporated, and the residue was crystallized from pentane to give 3.5 g. (85% yield) of (+)-acid, m.p. 38–39°. $[\alpha]^{22}_{\mathrm{D}}$ +21.1° (*c* 5.77 in benzene).

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.72; H, 10.91. Found: C, 71.76; H, 11.08.

This acid in ether was treated with excess diazomethane, and the resulting solution was treated with excess acetic acid. The mixture was washed with dilute sodium carbonate solution, dried and evaporated to an oil which was distilled to give (+)-methyl 2-cyclohexyl-2-methylbutanoate in 90% yield, b.p. 104° (9 mm.), n^{25}_{D} 1.4574, α^{24}_{D} +12.1° (*l* 1 dm., neat).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.67; H, 11.19. Found: C, 72.90; H, 10.97.

(+)-3-Cyclohexyl-3-methyl-2-pentanone and (−)-3-Cyclohexyl-2,3-dimethyl-2-pentanol.—To 300 ml. of a stirred ethereal solution of methyllithium prepared from 0.07 mole of iodomethane and 0.14 mole of lithium (held at −10°) was added 2.6 g. (0.013 mole) of optically pure (+)-methyl 2-cyclohexyl-2-methylbutanoate in 30 ml. of ether. The mixture was stirred at −10° for 1 hour and allowed to stand at 0° for 12 hours. The reaction mixture was shaken with water (methane was evolved), and the organic layer was washed with sodium bisulfite solution, dried and concentrated. The residual oil was chromatographed on 150 g. of neutral, activated alumina. The column was washed with 500 ml. of pentane, and (+)-3-cyclohexyl-3-methyl-2-pentanone was eluted with 1 liter of 10% ether–pentane. The eluate was evaporated, and the residual oil was distilled at 1 mm. to give 2.0 g. of (+)-ketone as a colorless oil, n^{25}_{D} 1.4673, α^{25}_{D} +14.1° (neat, *l* 1 dm.). This material showed no absorption in the infrared at 3100–3500 cm.$^{-1}$, but gave a strong band at 1690 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{22}O$: C, 79.12; H, 12.09. Found: C, 79.18; H, 11.98.

Further elution of the above chromatograph column with 500 ml. of ether gave 0.5 g. of (−)-3-cyclohexyl-2,3-dimethyl-2-pentanol which was combined with material prepared as follows. The above reaction was repeated at −30° with 10 g. of (+)-ester as starting material. The product was recycled three times, the reaction with methyllithium being carried out at −30° in each cycle. From the final product was obtained 1.0 g. of (+)-ketone and 3.5 g. of (−)-alcohol as an oil from the chromatogram. This material was rapidly distilled through a short-path still which had been soaked in dilute ammonia solution and dried. The distillation was carried out at 1 mm. and a pot temperature of 125°. The alcohol product was an oil, n^{25}_{D} 1.4848, α^{24}_{D} −4.2° (*l* 1 dm., neat).

Anal. Calcd. for $C_{13}H_{26}O$: C, 78.76; H, 13.13. Found: C, 78.64; H, 13.18.

Attempt to Decarboxylate 2-Methyl-2-phenylbutanoic Acid (II).—A solution of 5 g. of acid II in 10 ml. of ethanol was titrated to the phenolphthalein end-point with an ethanolic solution of sodium ethoxide. The solvent was evaporated, and the sodium salt was heated for 12 hours at 250° in tetrahydroquinoline. Only starting material was isolated from the reaction mixture, and no odor of 2-phenylbutane was evident at any time.

Purification of N-Methylaniline.—Methylaniline was dried by refluxing with potassium metal for 30 minutes, and the solvent was distilled from the metal through a short fractionating column. A middle cut was taken, b.p. 194° (760 mm.), n^{25}_{D} 1.5685. A similar procedure was applied to the purification of tetrahydroquinoline and aniline.

Deamidation of (−)-3-Methyl-3-phenylbutanoic Amide [(−)-III].—Potassium metal (0.44 g. of 0.0113 mole) was dissolved in dry N-methylaniline (9.0 ml. or 0.0829 mole) under a dry nitrogen atmosphere at 200°. The mixture was cooled, and 1.00 g. (0.00565 mole) of optically pure (−)-III,[13] $[\alpha]^{25}_{\mathrm{D}}$ −18.3° (*c* 4.0 in benzene) was added. The resulting solution was held at 145° bath temperature (under dry nitrogen) for 24 hours, cooled and shaken with 15 ml. of purified pentane and 25 ml. of 6 *N* hydrochloric acid. The aqueous layer was washed twice more with purified pentane, the organic layers were combined and washed with water and dilute sodium carbonate solution. The pentane solution was dried, evaporated through a 40-cm. Vigreux column, and the residual oil was twice distilled in a micro-still at 20 mm. pressure to give 0.41 g. of 2-phenylbutane (run 1).

When the above reaction was carried out at 200°, and nitrogen was bubbled through the solution to sweep out the 2-phenylbutane, the reaction was over in 15 minutes. Product was isolated in 56% yield, n^{25}_{D} 1.4877, α^{24}_{D} 0.00 (*l* 1 dm., neat).

When the above reaction was carried out at 150° under nitrogen for 24 hours as in the original procedure except that only 0.220 g. (0.00565 mole) of potassium metal was used for 1.00 g. of (−)-III (0.00565 mole), no 2-phenylbutane was produced.

When 1.00 g. (0.00396 mole) of (−)-N-phenyl-2-methyl-2-phenyl-butanoic amide was submitted to the original procedure with 0.308 g. (0.00790 mole) of potassium used to form base, no 2-phenylbutane was produced. Starting material (0.32 g.) was recovered along with 0.03 g. of (−)-II.

Decyanation of (+)-2-Methyl-2-phenylbutanoic Nitrile [(+)-IV].—Starting nitrile was prepared by dehydration of amide (−)-III with phosphorus oxychloride to give in 97% yield (+)-IV, n^{25}_{D} 1.5033, α^{23}_{D} +6.78° (*l* 1 dm., neat). The enantiomer was similarly prepared, n^{25}_{D} 1.5033, α^{25}_{D} −6.97° (*l* 1 dm., neat).[14]

Anal. Calcd. for $C_{11}H_{13}N$: C, 82.98; H, 8.23. Found: C, 82.94; H, 8.40.

Potassium metal (0.369 g. or 0.0095 mole) in 10.5 ml. of dry N-methylaniline under an atmosphere of dry nitrogen was heated to 134° for 9 hours with 1.00 g. (0.0063 mole) of (+)-IV. The above isolation procedure gave 2-phenylbutane contaminated with starting material. The mixture was refluxed with a solution of 0.50 g. of lithium aluminum hydride in ether, and was worked up by the usual procedure. The product (2-phenylbutane) amounted to 0.032 g. (run 2).

Cleavage of (−)-1,2-Diphenyl-2-methyl-1-butanone [(−)-V].—Potassium N-methylanilide, formed from 0.214 g. (0.00535 mole) of potassium and 2 ml. of N-methylaniline (200° under dry nitrogen) was mixed at 25° with a solution of 1.27 g. (0.00535 mole) of (−)-V,[14] $[\alpha]^{26}_{\mathrm{D}}$ −65.6° (*c* 3.3 in benzene), in 1.9 ml. of N-methylaniline. The resulting mixture was heated at 102° for 2.25 hours under dry nitrogen, cooled, and shaken with a mixture of pure pentane and dilute hydrochloric acid. The pentane solution was washed with water, dried, and evaporated through a 40-cm. Vigreux column. The residue was absorbed on 40 g. of activity II alumina,[25] and the product washed through the column with 150 ml. of pentane. Solvent was evaporated through a Vigreux column, and the residue was distilled twice through a short-path still at 20 mm. pressure to give 0.070 g. of (+)-I (run 3). The infrared absorption spectrum of this material was identical to that of an authentic sample.[15]

When the chromatograph column was washed with 4-to-1 pentane–ether mixture, an oil was obtained which was distilled at a bath temperature of 170° (4 mm.) to give 0.79 g. of an oil, n^{25}_{D} 1.5708, $[\alpha]^{28}_{\mathrm{D}}$ +25.8° (*c* 10 in benzene). This material possessed an infrared absorption spectrum similar to that of a mixture of diastereomeric 1,2-diphenyl-2-methyl-1-butanols.[14] No carbonyl absorption was evident, and the physical properties are in agreement with those of the alcohols. The rotation of this mixture suggests that it consists of about 50% *erythro* and 50% *threo* material.

During the extraction of 2-phenylbutane from the water phase, a small amount of solid material formed at the interface. This material was collected and crystallized from ether–pentane at 0°, and recrystallized from absolute ethanol to give 0.04 g. of needles, m.p. 162–163.5°, m.m.p. with authentic benzanilide, 163–165°.

Cleavage of Diastereomeric Mixture of (−)-3,4-Dimethyl-4-phenyl-3-hexanol [(−)-IX]. Procedure A.—Potassium metal (0.219 g. or 0.00548 mole) was dissolved in 2 ml. of N-methylaniline at 205° (stirring) for 2.5 hours under dry nitrogen. The mixture was cooled to 72°, and a solution of 1.128 g. (0.00548 mole) of a diastereomeric mixture of (−)-IX, $[\alpha]^{25}_{\mathrm{D}}$ −11.2° (*c* 11 in benzene)[13] in 2 ml. of N-methylaniline was added. The resulting mixture was heated for 0.5 hour, cooled, and 2 ml. of 50% ethanol in N-methylaniline was added. The resulting mixture was shaken with a mixture of 40 ml. of water, 20 g. of ice, 4 ml. of concentrated hydrochloric acid and purified pentane. The pentane extract was washed with dilute acid, with water, was dried, and evaporated through a 40-cm. Vigreux column. The residue was chromatographed on activity II alumina[25] (40 g.) and the product washed through with 150 ml. of pure pentane. Pure ether washed 0.50 g. of starting material from the column. The pentane eluate was concentrated through a 40-cm. Vigreux column, and the residue was distilled three times through a short-path still at 20 mm. pressure to give 0.30 g. of (+)-I (run 11).

When the reaction was performed in the same way as above at 25°, 0.090 g. of 2-phenylbutane (13% yield) was obtained, along with 0.75 g. of starting alcohol, n^{25}D 1.5202, $[\alpha]^{25}$D −11.3° (*c* 8 in benzene).

Cleavage of (+)-2-Methyl-1,1,2-triphenyl-1-butanol [(+)-XI].—Procedure A was employed. From 1.223 g. (0.00388 mole) of (+)-XI, 0.156 g. (0.00388 mole) of potassium and 2.8 ml. of N-methylaniline was obtained 0.18 g. of (+)-2-phenylbutane (run 13). Development of the chromatograph column with 9-to-1 pentane–ether gave after recrystallization from ethanol, 0.10 g. of benzophenone, m.p. 54–56°, undepressed by admixture with an authentic sample. Elution of the column with 4-to-1 pentane–ether gave a small amount of a viscous oil, probably starting material.

Cleavage of (−)-1,2-Diphenyl-2-methyl-1-butanol [(−)-VI].—Application of procedure A to a mixture of optically pure diastereomers of (−)-VI, $[\alpha]^{27}$D −19.7° (*c* 13.2 in benzene),[14] gave only recovered starting material, $[\alpha]^{25}$D −20.9° (*c* 11.4 in benzene). When carried out by procedure A except that a temperature of 200° and a reaction time of 2 hours was employed, a 37% yield of (−)-2-phenylbutane was obtained, n^{25}D 1.4878, α^{25}D −1.22° (*l* 1 dm., neat), 5% optically pure.

Procedure B.—To minimize the amount of racemization of the 2-phenylbutane once formed, procedure A was modified as follows. About half of the amount of potassium metal was employed, and the product was swept from the reaction flask through a micro-Claisen distillation head into a Dry Ice trap by means of a wide-bore capillary tube extending to the bottom of the flask. The alcohol was added dropwise as a solution in N-methylaniline to the reaction flask held at 210°. Only the product distilled from the reaction mixture was examined. The reaction was carried out with 0.9151 g. (0.00377 mole) of (−)-VI, $[\alpha]^{22}$D −17.9° (*c* 11.7 in benzene), 0.152 g. (0.00378 mole) of potassium and 6.2 ml. of N-methylaniline. After a reaction time of 20 minutes at 210°, the distillate was treated as in procedure A to give 0.42 g. of (−)-2-phenylbutane (run 4).

In another run (5) similar to the above (210° and reaction time of 20 minutes), 0.147 g. (0.00377 mole) of potassium, 1.193 g. (0.00448 mole) of (−)-VI and 4 ml. of N-methylaniline were employed.

Procedure C.—This procedure was the same as B except that after the base was prepared, the reaction flask was cooled to 100°, the alcohol was added, the flask was rapidly heated to 210° and the product distilled with the help of nitrogen as fast as possible. The distillate and the reaction mixture were combined for the isolation procedure.

From 0.814 g. (0.00339 mole) of (−)-VI, 0.134 g. (0.00337 mole) of potassium and 6 ml. of N-methylaniline was obtained 0.36 g. of 2-phenylbutane (run 6). The reaction time at 210° was 9 minutes.

Cleavage of (+)-3-Methyl-3-phenyl-2-pentanol [(+)-VII].—Procedure A was first applied to (+)-VII (0.985 g. or 0.0055 mole), 0.222 g. (0.0055 mole) of potassium and 4.05 ml. of N-methylaniline. The reaction was carried out at 204° for 5 hours and 0.27 g. of 2-phenylbutane was produced (run 7).

When procedure C was applied to 0.942 g. (0.00528 mole) of (+)-VII, 0.209 g. (0.00522 mole) of potassium and 6 ml. of N-methyl-aniline, 0.32 g. (45% yield) of 2-phenylbutane was obtained (run 8). The reaction time was 10 minutes.

Cleavage of (−)-2,3-Dimethyl-3-phenyl-2-pentanol [(−)-X].—From 1.0 g. (0.0052 mole) of (−)-X, 0.17 g. of potassium (0.0045 g. atom), and 51 ml. of pure aniline through the use of procedure A (temperature of 188° for 24 hours) was obtained 0.557 g. (0.00415 mole) of (+)-I (run 12).

Cleavage of (+)-2,3-Diphenyl-3-methyl-2-pentanol [(+)-VIII].—From 1.0 g. (0.00394 mole) of (+)-VIII, 0.153 g. (0.00394 mole) of potassium and 18 ml. of pure aniline through the use of procedure A (temperature of 50° for 36 hours) was obtained 0.360 g. (0.00268 mole) of (+)-I (run 9).

Cleavage of (+)-3-Methyl-1,1,3-triphenylpentane [(+)-XIII].—Attempts to cleave racemic XIII at 190° for 27 hours by procedure A gave only a trace of 2-phenylbutane. Therefore procedure B was applied to 5.5 g. (0.017 mole) of (+)-XIII, 50 ml. of tetrahydroisoquinoline (purified by distillation from potassium) and 0.75 g. (0.019 mole) of potassium. After 22 hours at reflux about 5 ml. of distillate had collected in the Dry Ice trap. The still-head was flamed lightly until 5 ml. of additional solvent had distilled. From the distillate was obtained 1.07 g. of 2-phenylbutane (run 15). In a second run, the same procedure was employed except that the reaction was run for only 22 hours. The residue in the reaction flask was examined as follows. Hydrocarbon present was isolated by pentane extraction and chromatography. This material was converted to (−)-2-methyl-2-phenylbutanoic acid by the oxidative procedure recorded above to give material, m.p. 86–87°, $[\alpha]^{25}$D −27.4° (*c* 1.8 in benzene).

A third cleavage was carried out in diphenylamine at 270° for 10 hours. From 3.0 g. (0.009 mole) of (+)-XIII, 40 ml. of diphenylamine and 0.3 g. (0.008 mole) of potassium was obtained 0.60 g. (50% yield) of 2-phenylbutane, n^{25}D 1.4878, α^{24}D +0.01° (*l* 1 dm., neat). Hydrocarbon which was isolated from the reaction flask was oxidized with potassium permanganate to give 1.0 g. of benzophenone, identified as its 2,4-dinitrophenylhydrazone, m.p. 239–241°, not depressed by admixture with an authentic sample.

As a control (−)-3,4-dimethyl-4-phenyl-3-hexanol [(−)-IX] was cleaved by procedure B except that tetrahydroquinoline was employed as solvent, the reaction was run for 9 hours at 140°. From 1.00 g. (0.0048 mole) of (−)-IX, 0.384 g. (0.0018 mole) of potassium and 9.7 g. of tetrahydroquinoline was obtained 0.12 g. of 2-phenylbutane (run 10).

Cleavage of (−)-1,4-Diphenyl-4-methyl-1-hexanone [(−)-XII].—Procedure B was applied to 2.50 g. (0.0094 mole) of (−)-XII, 70 ml. of N-methylaniline and 0.38 g. (0.0098 mole) of potassium. The reaction was run and the product distilled with dry nitrogen for 17 hours at reflux temperature. The distillate amounted to 25 ml., and yielded 0.127 g. of 2-phenylbutane (run 14).

Cleavage of (−)-3-Cyclohexyl-2,3-dimethyl-2-pentanol.—The cleavage was carried out in refluxing tetrahydroquinoline by procedure B. The reaction mixture was prepared from 0.78 g. (0.020 mole) of potassium, 50 ml. of tetrahydroquinoline and 2.4 g. (0.012 mole) of (−)-ketone, and the reaction was allowed to run for 6 days. From the 5 ml. of distillate in the Dry Ice trap was isolated a neutral, olefinic oil, 0.092 g., n^{25}D 1.4298, α^{24}D +2.93° (*l* 1 dm., neat). The infrared spectrum of this material showed strong absorption at 880 cm.$^{-1}$ and medium at 1630 cm.$^{-1}$.

From the reaction flask was isolated 0.35 g. (15% yield) of (+)-3-cyclohexyl-2,3-dimethyl-2-pentanone, n^{25}D 1.4673, α^{25}D +13.4° (*l* 1 dm., neat). The infrared spectrum of this material was superimposable on that of authentic (+)-ketone.

Control Experiments with Optically Active 2-Phenylbutane.—A mixture of (+)-2-phenylbutane, (+)-I, 0.375 g., α^{29}D +16.8° (*l* 1 dm., neat), was heated at 72° for 0.5 hour with a solution made from 0.112 g. (0.00281 mole) of potassium and 1 ml. of N-methylaniline. From this mixture, 0.20 g. of (+)-I was recovered, n^{25}D 1.4876, α^{29}D +16.8° (*l* 1 dm., neat). The above procedure was repeated except that the mixture was held at 102° for 2 hours. Recovered (+)-I had α^{27}D +16.5° (*l* 1 dm., neat), n^{25}D 1.4877. The above procedure was repeated at 140° for 24 hours (no distillation). Recovered (+)-I had α^{26}D +3.2° (*l* 1 dm., neat), n^{25}D 1.4877. The mixture was 81% racemized by this treatment.

In another experiment, 0.38 g. of (−)-I, α^{25}D −12.4° (*l* 1 dm., neat), was heated with a solution prepared from 0.8 g. of potassium (0.02 mole) and 4 ml. of N-methylaniline. The mixture was heated rapidly to 210°, held there 4 minutes, and distillation started as in procedure B. From the distillate 0.29 g. of (−)-I was recovered, n^{25}D 1.4878, α^{25}D −10.5° (*l* 1 dm., neat). The material was racemized 15% by this treatment. Repetition of the above experiment except that the mixture was heated for 30 minutes and then distilled gave results as follows. Starting material was α^{25}D +13.6° (*l* 1 dm., neat), and product had α^{23}D +4.0° (*l* 1 dm., neat), and 70% racemization had occurred. This experiment was repeated at 140° for 24 hours (no distillation). Recovered (+)-I had α^{2}D +11.2° (*l* 1 dm., neat), n^{25}D 1.4877. The mixture was 18% racemized by this treatment.

The following control in tetrahydroquinoline was performed. Potassium metal, 0.193 g. (0.00484 mole), was dissolved in 4 ml. of tetrahydroquinoline and mixed with 0.647 g. of (+)-I, α^{25}D +12.1° (l 1 dm., neat), and the resulting mixture was refluxed for 24 hours. The product isolated by the usual method contained olefin, n^{25}D 1.4889. This material was rid of olefin by treatment with 2,4-dinitrobenzenesulfenyl chloride,[15] and 0.30 g. of totally racemic I was obtained, n^{25}D 1.4879.

In a control run in N-methylaniline, the potassium was omitted. A solution of 0.35 g. of (+)-I, n^{25}D 1.4878, α^{25}D +16.3° (l 1 dm., neat) and 6 ml. of dry N-methylaniline was heated to 200° for 20 hours. The starting material was recovered in 77% yield, n^{25}D 1.4878, α^{25}D +16.29° (l 1 dm., neat).

Reaction of 2-Phenyl-2-butylpotassium with 2-Butanone.—To 600 ml. of ether under dry nitrogen was added 16 ml. of sodium-potassium alloy. Methyl 2-phenylbutyl ether[13] (26.8 g.) was added and the mixture was stirred at room temperature under nitrogen for 18 hours. The mixture was filtered under dry nitrogen, and 2-butanone (7.4 g.) was added to the filtrate until the red color had just disappeared. The ether solution was washed with water, dried, and the ether was removed. The residue was fractionally distilled to give 10 fractions. Fractions 1–5 contained some 2-butanone. Fractions 6–9, 15.2 g., b.p. 75–77° (27 mm.), n^{25}D 1.4876–1.4878, was 2-phenylbutane (74% yield).

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.60; H, 10.40.

The pot residue was crystallized from pentane to give 0.50 g. white needles, m.p. 169–170°.

Anal. Calcd. for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.15; H, 9.74. The structure of this compound was not elucidated.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

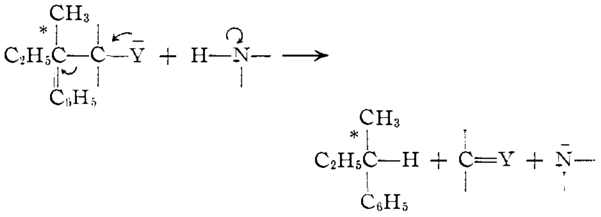
Electrophilic Substitution at Saturated Carbon. II. Retention and Inversion Reaction Paths[1]

BY DONALD J. CRAM, ALBERT LANGEMANN AND FRED HAUCK

RECEIVED JANUARY 2, 1959

The effect of solvent on the stereochemistry of electrophilic substitution at saturated carbon has been investigated. In the base-catalyzed cleavage reactions of (−)-3,4-dimethyl-4-phenyl-3-hexanol, (−)-2,3-dimethyl-3-phenyl-2-pentanol, (+)-2,3-diphenyl-3-methyl-2-pentanol, (+)-3-methyl-3-phenyl-2-pentanol and (+)-1,2-diphenyl-2-methyl-1-butanol, 2-phenylbutane is produced as the result of solvent (as an electrophile) donating a proton to negative carbon. Fourteen different solvents have been examined, and the optical purity of the 2-phenylbutane produced ranges from 96% (retention of configuration) to 51% (inversion of configuration). The steric courses of the reactions are relatively insensitive to variations in the leaving group, acidity and concentration of the nucleophile, and are controlled largely by the nature of the solvent. Solvents of low dielectric constant tend to give retention whereas solvents of high dielectric constant give inversion of configuration.

In paper I of this series[2] (which summarizes the relevant literature), eleven systems were subjected to base-catalyzed (anionic) cleavage reactions in secondary amines as solvents to give 2-phenylbutane as product. The reaction was found to occur in each case with predominant retention of configuration at C-2 of 2-phenylbutane.

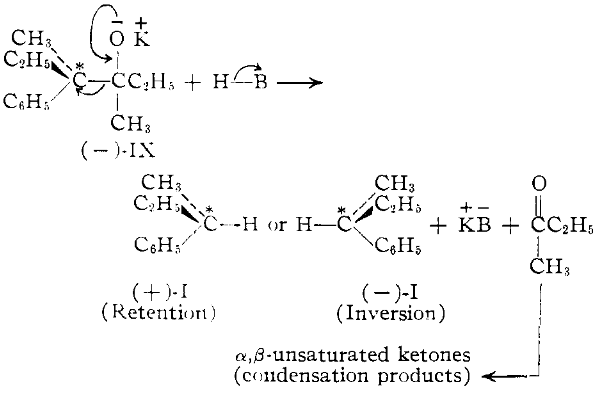


I

The present paper reports the results of a survey of sixteen solvents to assess their effect on the steric course of the cleavage of five systems of the type formulated. The relative configuration of starting materials and products have been established elsewhere.[3,4]

Results

Table II[5] records the conditions for and the results of cleavages of system IX, which is a mixture of diastereomers[6] configurationally homogeneous at the carbon atom which undergoes substitution. The 2-phenylbutane (I) produced was characterized by its refractive index in all cases, which constant is very sensitive to olefinic and other contaminants, and serves as a good criterion of purity. In representative cases, the infrared spectrum of this hydrocarbon was also compared with that of authentic I,[7] and in all cases the spectra were superimpossible. In a number of reactions carried out in tertiary alcohols or ethers as solvents, mixtures of



(−)-IX

(+)-I (Retention)

(−)-I (Inversion)

α,β-unsaturated ketones (condensation products)

α,β-unsaturated ketones were isolated which are presumably condensation products of 2-butanone produced in the cleavage reaction. In some of the runs in primary and secondary alcohols, these α,β-

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[1] This work was sponsored by the Office of Ordnance Research, U. S. Army.

[2] D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, THIS JOURNAL, **81**, 5740 (1959).

[3] D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954).

[4] D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959).

[5] Tables, compounds and runs are numbered consecutively throughout the first six papers of this series.

[6] D. J. Cram and J. D. Knight, THIS JOURNAL, **74**, 5835 (1952).

[7] D. J. Cram, *ibid.*, **74**, 2149 (1952).