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Electrophilic Substitution at Saturated Carbon. XIX. Nitrogen as Leaving Group from an Alkyl Diimide[1]

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The stereochemistry of the SEl reaction has been examined with nitrogen as leaving group, proton donors as electrophiles, and the 2-phenyl-2-butyl anion as an intermediate. Optically active 2-phenyl-2-butylhydrazine ((+)-I) was prepared and converted to its (+)-*p*-toluenesulfonamide derivative, whose nuclear magnetic resonance spectrum was consistent only with structure (+)-II. Hydrogenolysis of (+)-I gave (+)-2-phenyl-2-butylamine whose configuration and maximum rotation were determined, thereby establishing the configurations and maximum rotations of (+)-I and (+)-II. Oxidation of (+)-I or heating of (+)-II in the absence of base in a variety of solvents gave racemic 2-phenylbutane. Addition of base to each reaction resulted in production of 2-phenylbutane (configuration and maximum rotation are known) with a stereochemical course that varied between extremes of 92% net retention and 33% net inversion, depending on base concentration and solvent. Except in water, a base concentration was easily attainable where an increase in base concentration did not increase stereospecificity. Above this threshold concentration, retention decreased regularly with increase in dielectric constant of the solvent. Above this threshold base concentration (all solvents except water), potassium periodate oxidation of (+)-I and cleavage of (+)-II gave the same stereochemical results. In water, 0.3 *N* in potassium hydroxide, cleavage of (+)-II went with 5% net inversion whereas oxidation of (+)-I with either bromine or potassium periodate gave 32% net inversion. In 9.7 *N* aqueous potassium hydroxide, cleavage of (+)-II gave 70% net retention and oxidation of (+)-I with bromine gave 77% net retention, whereas oxidation of (+)-I with potassium periodate gave 12% net inversion. Mechanistic conclusions are: (1) The same intermediate, RN=NH, is produced in all reactions except some of those in water. (2) This intermediate partitions between a base-catalyzed anionic elimination reaction to give 2-phenylbutane somewhat stereospecifically, and a non-stereospecific homolytic reaction to give the same substance. The homolytic reaction can be avoided in all solvents except water. (3) Generation of a proton donor at the front of the carbanion by reaction of base with RN=NH provides for the retention mechanism, whereas back-side proton participation (solvation by hydrogen bonding) in carbanion formation from $RN{=}\bar{N}$ accounts for the inversion mechanism. (4) In water at low base concentration, $RN{=}\bar{N}$ is produced from (+)-II, and net inversion results. At high base concentration, (+)-I with bromine gives $RNH\bar{N}Br$ and (+)-II gives $RNH\bar{N}SO_2C_6H_4CH_3$, each of which produce $R\overset{+}{N}H{=}\bar{N}$. This intermediate provides 2-phenylbutane with net retention of configuration.

Carbonium ions, radicals and carbenes formed by loss of a molecule of nitrogen from either compounds or ions have in many instances exhibited behavior different from that of the corresponding species generated through use of other leaving groups. This investigation deals with the stereochemical capabilities of the 2-phenyl-2-butyl anion generated with molecular nitrogen as leaving group, and proton donors as electrophiles.

In previous studies of the stereochemical capabilities of the 2-phenyl-2-butyl anion, carbon,[3] oxygen[4] and hydrogen[5] have been involved as leaving groups and proton and deuteron donors as electrophiles. These SEl reactions occur with as high as 99% net retention, 60% net inversion and 100% racemization, depending on the character of the solvent and cations of the basic catalyst involved. Representative reactions are formulated in Chart I.

At the outset, study of nitrogen as leaving group seemed feasible since the latter stages of the Wolff–Kishner reaction probably involve loss of nitrogen from RN_2^- to give a carbanion, which subsequently captures a proton from solvent.[6] The possibility of breaking into the late stages of a Wolff–Kishner reduction from a starting material other than a hydrazone was suggested by two analogies. In the McFadyen–Stevens reaction,[7] an arenesulfonhydrazide is treated

CHART I

Different leaving groups in E_1 reaction, $\overset{*}{R}{=}C_6H_5{}^*C(CH_3)(C_2H_5)$

Carbon

$$\overset{*}{R}\!-\!\overset{\bar{O}}{\underset{|}{C}}(CH_3)_2\overset{\overset{+}{M}}{\curvearrowright} \longrightarrow \overset{*}{R}^- \xrightarrow{HB} \overset{*}{R}\!-\!H$$

Oxygen

$$\overset{*}{R}\!-\!O\!-\!\overset{H}{\underset{|}{C}}HC_6H_5\overset{\bar{B}}{\curvearrowright} \longrightarrow \overset{*}{R}^- \xrightarrow{HB} \overset{*}{R}\!-\!H$$

Hydrogen

$$\overset{*}{R}\!-\!H\overset{\bar{B}}{\curvearrowright} \longrightarrow \overset{*}{R}^- \xrightarrow{DB} \overset{*}{R}\!-\!D$$

Nitrogen

$$\overset{*}{R}\!-\!N{=}N\!-\!H\overset{\bar{B}}{\curvearrowright} \longrightarrow \overset{*}{R}^- \xrightarrow{HB} \overset{*}{R}\!-\!H$$

with base to give ultimately an aldehyde, nitrogen serving as leaving group.[7] Treatment of sulfonamides

$$ArC(=O)\!-\!\overset{H}{N}\!-\!NH\!-\!SO_2Ar\overset{\bar{B}}{\curvearrowright} \longrightarrow ArC(=O)\!-\!N{=}N\!-\!H\overset{\bar{B}}{\curvearrowright} \longrightarrow ArC(=O)^- \xrightarrow{HB} ArCH(=O)$$

$$Ar\!-\!\overset{H}{N}\!-\!NH\!-\!SO_2Ar\overset{\bar{B}}{\curvearrowright} \longrightarrow Ar\!-\!N{=}N\!-\!H\overset{\bar{B}}{\curvearrowright} \longrightarrow Ar^- \xrightarrow{HB} ArH$$

of arylhydrazine with base has in some cases provided the aromatic hydrocarbon.[8] Another approach was suggested by the fact that arylhydrazines can be readily oxidized to give aromatic hydrocarbons.[9]

$$ArNHNH_2 + [O] \longrightarrow Ar\!-\!N{=}N\!-\!H \longrightarrow Ar^- \xrightarrow{H-B} ArH$$

(1) The authors are grateful for a National Science Foundation Grant used in support of this work.

(2) Eastman Kodak Predoctoral Fellow, 1961–1962.

(3) (a) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, *J. Am. Chem. Soc.*, **81**, 5774 (1959); (b) D. J. Cram and W. D. Nielsen, *ibid.*, **83**, 2174 (1961).

(4) D. J. Cram, C. A. Kingsbury and A. Langemann, *ibid.*, **81**, 5785 (1959).

(5) D. J. Cram, C. A. Kingsbury and B. Rickborn, *ibid.*, **83**, 3688 (1961).

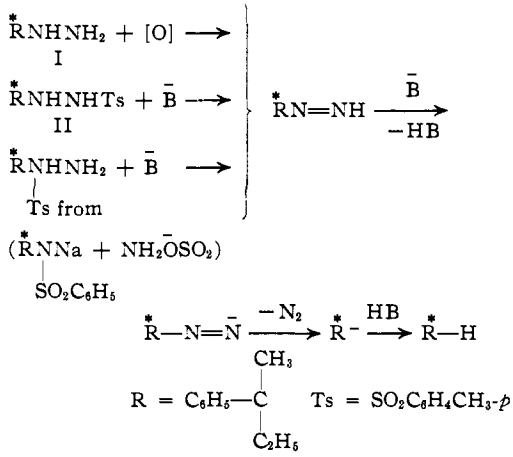
(6) The first suggestion of such a mechanism (of which the authors are aware) was made by W. Seibert, *Ber.*, **80**, 494 (1947); **81**, 266 (1948). The mechanism has been studied by H. H. Symant, H. F. Harnsberger, T. J. Butler and W. P. Barie, *J. Am. Chem. Soc.*, **74**, 2724 (1952).

(7) J. S. McFadyen and T. J. Stevens, *J. Chem. Soc.*, 584 (1936).

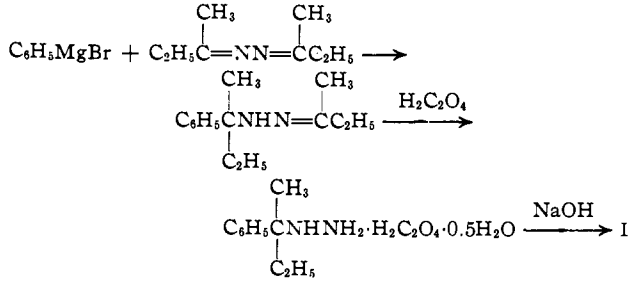
(8) *E.g.*, R. Escales, *Ber.*, **18**, 893 (1885).

(9) *E.g.*, L. Kalb and O. Gross, *ibid.*, **59**, 727 (1926).

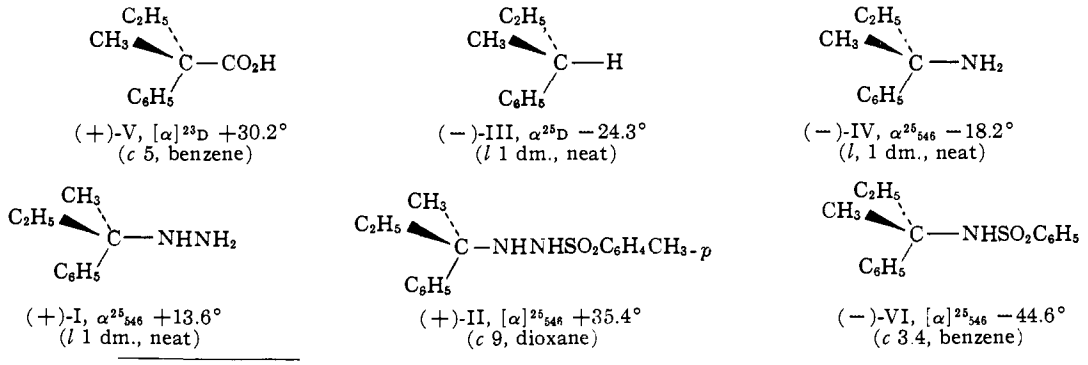
Accordingly, optically active 2-phenyl-2-butylhydrazine (I) was prepared and found to undergo oxidative cleavage to give 2-phenylbutane (III). Likewise, the *p*-toluenesulfonyl derivative II was found to cleave in base to give III. While this work was in progress, others[10] reported that the *p*-bromobenzenesulfonamide of 2-phenyl-2-butylamine when treated in base with hydroxylamine-O-sulfonic acid gave 2-phenylbutane, presumably by way of the desired alkyldiimide intermediate. Our investigation was then broadened to include this reaction applied to optically active starting materials.



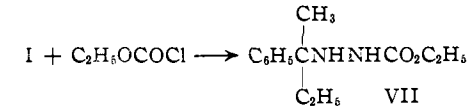
Preparation and Configurations of Starting Materials.—The preparation of 2-phenyl-2-butylhydrazine[11] (I) was patterned after that reported for 2-phenyl-2-propylhydrazine[12] (see formulas). Compound I was stored as its oxalate salt, since the material as the free base was subject to air oxidation. Resolution of I was accomplished through fractional crystallization of its dibenzoyl *d*-tartrate salt.



The maximum rotation and configuration of the isomers of I were demonstrated as follows. Material of rotation α^{25}_{546} +11.8° (*l* 1 dm., neat) was hydrogenolyzed in acetic acid with a platinum catalyst to give (+)-2-phenyl-2-butylamine ((+)-IV), α^{25}_{546} +15.8° (*l* 1 dm., neat). Application of the Curtius rearrangement to optically pure (+)-2-methyl-2-phenylbutanoic acid[13] ((+)-V) gave (−)-2-phenyl-2-butylamine, α^{25}_{546} −18.2° (*l* 1 dm., neat). Since the configurations and maximum rotations of (±)-V and of (±)-2-phenylbutane have been unequivocally established,[13b] these transformations establish the configurations and maximum rotations of (±)-I and (±)-IV. Sulfonamide (+)-II, $[\alpha]^{24}_{546}$ +32.6° (*c* 9, dioxane), m.p. 112–112.2°, was prepared from (+)-I, α^{25}_{546} +12.8° (*l* 1 dm., neat). Repeated recrystallization of grossly optically impure (−)-II gave material of maximum rotation, m.p. 112.5–113°, $[\alpha]^{25}_{546}$ −35.4° (*c* 9, dioxane). The benzenesulfonamide derivative of (−)-IV (α^{26}_{546} −18.2, *l* 1 dm., neat) was prepared ((−)-VI), $[\alpha]^{26}_{546}$ −44.57° (*c* 3.4, benzene). These interconversions establish the configurations and maximum rotations of the isomers of II and VI. The formulas below summarize the relationships.



For purposes of nuclear magnetic resonance (n.m.r.) spectral comparisons, N-carbethoxy-N′-(2-phenyl-2-butyl)-hydrazide (VII) was prepared from I. The n.m.r. spectrum of II was taken in dioxane and that of VII in carbon tetrachloride, and the presence in each spectrum of two different single hydrogen absorption bands (intensity equal to one hydrogen each) in the N–H region indicates that one hydrogen is attached to each of the two nitrogens. The amide hydrogen of II absorbed at 3.50 τ, and that of VII at 4.1 ± 0.1 τ. The amine hydrogen of II absorbed at 5.43 τ, and that of VII at 6.2 ± 0.15 τ.[14] These results indicated that both the sulfonation and carbethoxylation occurred on the least substituted nitrogen of I, probably for steric reasons.



Steric Course of Cleavage Reactions.—In all cleavage reactions of (+)-I and (+)-II, only partially optically active materials were used. The base, (+)-I, isolated by hydrolysis of the tartrate salt, was found to contain small amounts of a foreign substance which greatly affected the optical rotation. These could be eliminated by converting the material to the oxalate salt, recrystallizing that material, and regenerating (+)-I. Material of at least 15% optical purity was employed. Grossly optically impure (+)-II was recrystallized from ether–pentane until 20–40% optical purity was obtained. Benzenesulfonamide of optically pure amine (−)-IV was employed in the reductive cleavage of that

(10) A. Nickon and A. Sinz, *J. Am. Chem. Soc.*, **82**, 753 (1960).

(11) The authors are indebted to Dr. Walter Lwowski who first carried out this synthesis.

(12) C. C. Overberger and A. V. Di Giulio, *J. Am. Chem. Soc.*, **80**, 6562 (1958).

(13) (a) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952); (b) D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959).

(14) Compare with data of N. F. Chamberlain, *Anal. Chem.*, **31**, 56 (1959).

TABLE I

EFFECT OF BASE CONCENTRATION ON CLEAVAGE OF 0.073 *M* SOLUTIONS OF SULFONAMIDE (+)-II[a]

Run	Solvent	Base: Nature	Base: Concn., *M*	*T*, °C.	Time, hr.	2-Phenyl butane[b]: Yield, %	2-Phenyl butane[b]: $n^{25}D$	Net steric[c] course
1[d,e]	$(CH_3)_3COH$	None	0.000	100	2	38	1.4881	100% rac.
2[d,f]	$(CH_3)_3COH$	$(CH_3)_3COK$	.052	100	2	40	1.4880	46% ret.
3[d,g]	$(CH_3)_3COH$	$(CH_3)_3COK$	.088	100	2	77	1.4880	80% ret.
4[d]	$(CH_3)_3COH$	$(CH_3)_3COK$	.370	100	2	38	1.4877	78% ret.
5	*n*-C_4H_9OH	*n*-C_4H_9OK	.085	100	2	77	1.4880	65% ret.
6	*n*-C_4H_9OH	*n*-C_4H_9OK	.300	100	2	72	1.4880	68% ret.
7	C_2H_5OH	C_2H_5OK	.085	100	2	80	1.4880	50% ret.
8	C_2H_5OH	C_2H_5OK	.370	100	2	58	1.4876	60% ret.
9	C_2H_5OH	C_2H_5OK	.600	100	2	73	1.4880	60% ret.
10	CH_3OH	CH_3OK	.088	100	2	66	1.4870	33% ret.
11	CH_3OH	CH_3OK	.30	100	2	73	1.4876	44% ret.
12	CH_3OH	CH_3OK	.60	100	2	71	1.4880	45% ret.
13	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	.085	100	2	21	1.4879	15% ret.
14	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	.300	100	2	48	1.4881	25% ret.
15	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	.600	100	2	49	1.4890	30% ret.
16	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	1.00	100	2	48	1.4890	37% ret.
17	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	0.085	25	72	32	1.4886	49% ret.
18	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	0.340	25	72	52	1.4888	48% ret.
19[h]	H_2O	None	0.000	100	2	45	1.4864	100% rac.
20	H_2O	HOK	0.110	100	2	40	1.4880	1% inv.
21	H_2O	HOK	1.05	100	2	58	1.4886	10% inv.
22	H_2O	HOK	2.00	100	2	60	1.4873	2% ret.
23	H_2O	HOK	3.40	100	2	60	1.4875	40% ret.
24[i]	H_2O	HOK	9.70	100	2	27	1.4885	70% ret.
25[i]	H_2O	HOK	13.0	100	2	43	1.4883	73% ret.
26[j,k]	$O(CH_2CH_2)_2O$	None	0.000	75	40	37	1.4893	100% rac
27	$O(CH_2CH_2)_2O$	$(CH_3)_3COK$	.220	75	100	79	1.4884	74% ret.
28[k,h]	$(CH_3)_2SO$	None	.000	75	4.5	31	1.4890	100% rac.
29[l]	$(CH_3)_2SO$	$(CH_3)_3COK$	.087	75	4.5	37	1.4882	44% ret.

[a] Optical purity was between 20 and 40%. [b] Rotations taken neat, *l* 1 dm.; pure material, $n^{22}D$ 1.4878; purity checked with vapor phase chromatography. [c] Calculated taking into account optical purity of starting material. [d] 5 mole % water. [e] Final *p*H, 2. [f] Final *p*H, 4.5. [g] Final *p*H, 11. [h] Trace of *cis*-2-phenyl-2-butene present in product. [i] Solid potassium *p*-toluenesulfinate isolated. [j] Final *p*H, 4; trace of *cis*-2-phenyl-2-butene; small amount of *p*-tolyl-*p*-toluenethiosulfonate isolated. [k] Small amount of *p*-tolyl *p*-toluenethiosulfonate isolated. [l] Product isolated actually indicated 37% net retention; rate data (ref. 5) for racemization of 2-phenylbutane under conditions of the experiment were used to correct this value.

compound. The oxidation and cleavage runs involved standard extraction and chromatographic techniques for isolation of 2-phenylbutane. The purity of the material was established through its index of refraction and by vapor phase chromatography. The few runs in which 2-phenylalkenes were detected are marked with footnotes in the tables. Olefin was observed only in those runs conducted in the absence of base. From the rate constants for racemization of 2-phenylbutane[5] it was concluded that this product once formed maintained its optical integrity except in some of the runs in dimethyl sulfoxide. In those cases, a small correction was applied to the results for the small amount of racemization that occurred once the product had formed. In a number of cleavages of sulfonamide (+)-II, the presence of the *p*-toluenesulfinate anion in the product was demonstrated through its oxidation with chlorine gas to *p*-toluenesulfonyl chloride, which was identified.

In cleavages of sulfonamide (+)-II, the stereospecificity of the reaction varied with base concentration at low base concentration. In all solvents except water, base concentrations were easily attained above which no change in stereospecificity was observed. This same was true for ethylene glycol only at 25°, but not at 100°. In the absence of base in all solvents tried, reaction occurred to give only racemic 2-phenylbutane. The results are set forth in Table I. In runs conducted in dioxane (26) and in dimethyl sulfoxide (28), *p*-tolyl *p*-toluenethiosulfonate was isolated.[15] Cleavages at greater than 0.088 *M* base concentration in dimethyl sulfoxide resulted in substantially decreased stereospecificity due to racemization of the 2-phenylbutane once formed.

In another series of cleavages of (+)-II, the effect of composition of water–organic solvent mixtures was determined. Table II records the results. In all runs in media 50 mole % in water or less, enough base was undoubtedly present to suppress the competing non-base catalyzed non-stereospecific reaction. As the mixtures became progressively rich in water, the non-stereospecific reaction was undoubtedly present, so the true stereospecificity of the base-catalyzed reaction was probably higher than was observed.

In a third set of experiments, the effect of substituting tetramethylammonium hydroxide for potassium alkoxides was assessed. The results are recorded in Table III. In all of these runs, the base concentration was high enough to suppress the competing non-base catalyzed non-stereospecific reaction.

In an attempt to learn about the nature of the non-base catalyzed non-stereospecific reaction, a run was made in which a free radical chain reaction inhibitor (benzoquinone) was present. In a second run, a radical reaction initiator (benzoyl peroxide) was added, and in a third run, the starting material concentration was reduced 7-fold. Each run was compared with one made under the same conditions except for the special feature. Ethylene glycol at 100° was chosen as the reaction medium. In this solvent at this temperature, the base concentration can be made great enough not to change much during a run (the reaction generates acid), and yet at a concentration at which the

(15) R. Otto and O. V. Gruber [*Ann.*, **145**, 13 (1868)] reported that *p*-toluenesulfinic acid is converted to *p*-tolyl *p*-toluenethiosulfonate in hot aqueous solution.

TABLE II

EFFECT OF COMPOSITION OF WATER–ORGANIC SOLVENT MIXTURES ON STERIC COURSE OF CLEAVAGE OF (+)-II[a] AT 0.073 *M* CONCENTRATION AT 100°

Run	Mole % water	Org. solvent	Base: Nature	Base: Concn., *M*	Time, hr.	2-Phenylbutane[b]: Yield, %	2-Phenylbutane[b]: $n^{25}D$[c]	Net steric course[d]
30	0	$(CH_3)_3COH$	$(CH_3)_3COK$	0.30	2	83	1.4878	80% ret.
31	3	$(CH_3)_3COH$	$(CH_3)_3COK$	.39	2	79	1.4880	85% ret.
32	5	$(CH_3)_3COH$	$(CH_3)_3COK$	.37	2	38	1.4877	78% ret.
33	10	$(CH_3)_3COH$	$(CH_3)_3COK$	.085	2	65	1.4878	79% ret.
34	85	$(CH_3)_3COH$	HOK	.085	2	64	1.4874	50% ret.
35	95	$(CH_3)_3COH$	HOK	.085	2	27	1.4878	5% inv.
36	100	None	HOK	.110	2	40	1.4880	1% inv.
37	95	CH_3OH	HOK	.085	2	27	1.4878	7% inv.
38	95	$HOCH_2CH_2OH$	HOK	.085	2	27	1.4873	8% inv.
39[e]	0	$(CH_3)_2SO$	$(CH_3)_3COK$	.087	4.5	37	1.4882	44% ret.[f]
40	45	$(CH_3)_2SO$	HOK	.085	2	55	1.4880	42% ret.
41	50	$(CH_3)_2SO$	HOK	.085	2	34	1.4864	40% ret.
42	55	$(CH_3)_2SO$	HOK	.085	2	49	1.4872	37% ret.
43	75	$(CH_3)_2SO$	HOK	.085	2	69	1.4880	25% ret.
44	90	$(CH_3)_2SO$	HOK	.085	2	54	1.4879	5% ret.
45	95	$(CH_3)_2SO$	HOK	.085	2	39	1.4881	2% inv.

[a] Optical purity was between 20 and 35%. [b] Rotations taken neat, *l* 1 dm.; purity checked with vapor phase analysis. [c] Pure material, $n^{25}D$ 1.4878. [d] Calculated taking into account lack of optical purity of starting material. [e] Run at 75°. [f] Value corrected for 7% racemization of product once formed.

TABLE III

EFFECT OF NATURE OF CATION OF BASIC CATALYST ON STERIC COURSE OF CLEAVAGE OF (+)-II[a]

Run	Concn. st. mat., *M*	Solvent	Base: Nature	Base: Concn., *M*	*T*, °C.	Time, hr.	2-Phenylbutane[b]: Yield, %	2-Phenylbutane[b]: $n^{25}D$[c]	Net steric course[d]
46	0.090	$(CH_3)_3COH$–0.32 *M* H_2O	$(CH_3)_3COK$	0.16	52.5	100	78	1.4875	92% ret.
47	.096	$(CH_3)_3COH$–0.32 *M* H_2O	$(CH_3)_4NOH$	.16	52.5	100	59	1.4885	60% ret.
48	.073	$(CH_3)_3COH$ dry	$(CH_3)_3COK$	.33	52.5	20	83	1.4873	80% ret.
49	.073	$(CH_3)_3COH$ dry[e]	$(CH_3)_4NOH$	.33	52.5	20	74	1.4876	52% ret.
50	.073	$HOCH_2CH_2OH$–0.68 *M* H_2O	$HOCH_2CH_2OK$	.34	25	72	52	1.4888	48% ret.
51	.100	$HOCH_2CH_2OH$–0.68 *M* H_2O	$(CH_3)_4NOH$	.34	25	50	55	1.4870	46% ret.
52	.066	$O(CH_2CH_2)_2O$–0.32 *M* H_2O	$(CH_3)_3COK$	.20	75	40	77	1.4880	68% ret.
53	.066	$O(CH_2CH_2)_2O$–0.32 *M* H_2O	$(CH_3)_4NOH$	.16	75	40	62	1.4883	39% ret.
54	.074	$(CH_3)_2SO$ dry	$(CH_3)_3COK$	.088	52.5	90	51	1.4875	45% ret.[e]
55	.075	$(CH_3)_2SO$ dry[f]	$(CH_3)_4NOH$[g]	.110	52.5	92	42	1.4876	42% ret.

[a] Optical purity varied between 20 and 40%. [b] Rotations taken neat, *l* 1 dm.; purity checked with vapor phase analysis. [c] Pure material, $n^{25}D$ 1.4878. [d] Calculated taking into account lack of optical purity of starting material. [e] Dry to Karl Fischer reagent. [f] Corrected for small amount of racemization of product once formed. [g] Concn. of base at end of run, 0.025 *M*.

TABLE IV

ATTEMPTS TO DETECT RADICAL CHAIN REACTIONS IN THE CLEAVAGE OF (+)-II[a] IN ETHYLENE GLYCOL–ETHYLENE GLYCOXIDE AT 100°

Run	Concn. st. mat., *M*	Base concn., *M*	Time, hr.	2-Phenylbutane[b]: Yield, %	2-Phenylbutane[b]: $n^{25}D$[c]	Net steric course[d]
56	0.073	0.085	2	21	1.4879	15% ret.
57	.010	.10	2	58	1.4878	24% ret.
58	.073	.60	2	49	1.4880	30% ret.
59[e]	.073	.60	2	62	1.4882	32% ret.
60	.074	.30	2	48	1.4881	25% ret.
61[f]	.074	.30	2	55	1.4878	27% ret.

[a] Optical purity 20–33%. [b] Rotations taken neat, $l = 1$ dm.; purity checked with vapor phase analysis. [c] Pure material, $n^{25}D$ 1.4878. [d] Calculated taking into account lack of optical purity of starting material. [e] Medium of run was 4.5×10^{-4} *M* in benzoyl peroxide. [f] Medium of run was 2.1×10^{-3} *M* in benzoquinone.

non-base catalyzed non-stereospecific reaction competes with the partially stereospecific transformation. Table IV records the results.

A large number of oxidizing agents were examined with respect to their ability to convert hydrazine I to 2-phenylbutane (III) in a variety of solvents. Aside from oxygen, which largely produced olefin, many different oxidizing agents gave the conversion, but potassium periodate was found to be the most practical over the solvent range. The halogens were the next best, but care had to be taken not to halogenate the product once formed. The susceptibility of ethylene glycol to oxidation itself prevented use of this solvent for the reaction. The results are found in Table V.

Three runs were made with the 3 different starting materials ((+)-I, (+)-II and (−)-VI) under experimental conditions as close to one another as possible. Selection of media was dictated by the fact that only 10% by weight of ethanol in water as medium provided a sufficient yield of material to be practical. Table VI records the results. Run 77 involved the reaction of huge amounts of hydroxylamine-O-sulfonic acid with the benzenesulfonamide of 2-phenyl-2-butylamine ((−)-VI). Most of the reagent was decomposed by the base to give sodium sulfate and hydroxylamine, so the concentration of base, of reagent and of hydroxylamine were changing throughout the run.[16] The effect of base concentration change on the steric course of cleavages of (+)-II in water was demonstrated to be large (Table I), so run 77 was made at an initial concentration of base at 3.0 *M* and very low substrate concentration (0.050 *M*) so that even though a 50-fold excess of hydroxylamine-O-sulfonic acid had to be added, the base concentration remained substantial and averaged 1.66 *M*. Runs 74–76 were made at an initial concentration of 1.66 *M*. Presence of hydroxylamine in the mixture had a pronounced effect on the stereochemistry

(16) The authors are indebted to Dr. Graham R. Knox for carrying out run 77, and converting (+)-V to (−)-IV.

TABLE V

OXIDATIVE CLEAVAGES OF (+)-I[a] AT 100°

Run	St. mat. concn., M	Solvent	Base: Nature	Base: Concn., M	Oxidizing agent: Nature	Oxidizing agent: Concn., M	Time, hr.	2-Phenylbutane[b]: Yield, %	2-Phenylbutane[b]: $n^{25}D$[c]	Net steric course[d]
62	0.081	$(CH_3)_3COH$	None	0.00	KIO_4[e]	0.081	48	13[f]	1.4871	100% rac.
63	.081	$(CH_3)_3COH$	$(CH_3)_3COK$	.30	KIO_4[e]	.081	48	28	1.4882	80% ret.
64	.079	$(CH_3)_3COH$	$(CH_3)_3COK$	.30	I_2	.083	14	27	1.4868	77% ret.
65	.079	C_2H_5OH	C_2H_5OK	.30	KIO_4[e]	.079	48	63	1.4890	55% ret.
66	.079	CH_3OH	CH_3OK	.30	KIO_4[e]	.079	48	57	1.4883	42% ret.
67	.079	H_2O	None	.00	KIO_4[e]	.079	2	28	1.4877	100% rac.
68	.079	H_2O	HOK	.012	KIO_4[e]	.079	2	46	1.4872	30% inv.
69	.079	H_2O	HOK	.30	KIO_4[e]	.079	2	68	1.4874	32% inv.
70	.048	H_2O	HOK	.30	Br_2	.05	2	40	1.4880	33% inv.
71	.079	H_2O	HOK	9.70	KIO_4[e]	.079	2	32	1.4879	12% inv.
72	.048	H_2O	HOK	9.70	Br_2	.05	2	31	1.4877	77% ret.
73	.079	$(CH_3)_2SO$	$(CH_3)_3COK$	0.127	KIO_4[e]	.079	2	24	1.4878	39% ret.[g]

[a] Optical purity 15% except in run 72 where 5% material was used; smallest observed rotation for either starting material or product was 0.66°. [b] Rotations taken neat, l 1 dm.; purity checked with vapor phase analysis. [c] Pure material, $n^{25}D$ 1.4878. [d] Calculated taking into account lack of optical purity of starting material. [e] Potassium periodate is soluble in water but not the organic solvents. [f] A mixture of 2-phenylbutane and 2-phenylbutenes was produced. [g] Corrected from observed 37% retention because of racemization of product after its formation.

TABLE VI

COMPARISON OF THE STEREOCHEMICAL COURSE OF CONVERSION OF (+)-I, (+)-II AND (−)-VI TO 2-PHENYLBUTANE IN 10% ETHANOL–90% WATER (BY WEIGHT) 1.66 M IN SODIUM HYDROXIDE[a] SATURATED IN SODIUM SULFATE AT 100°

Run	Starting material: Nature	Starting material: Concn., M	Starting material: % Opt. pur.	Init. concn., M NH_2OH	Time, hr.	2-Phenylbutane[b]: Yield, %	2-Phenylbutane[b]: $n^{25}D$[c]	Net steric course[d]
74	(+)-I	0.03	15	1.11	1	10	1.4890	26 ± 6% ret.[e]
75	(+)-I	.03	15	None	1	59	1.4883	2% inv.
76	(+)-II	.03	28	1.11	1	83	1.4876	37% ret.
77	(−)-VI	.05	100	None	3	10	...	32% ret.

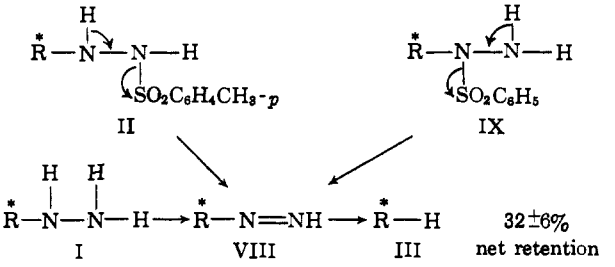
[a] Initial concentration of base in runs 74–76, and average concentration in run 77; initial concentration of base in run 77 was 3.0. [b] Purity checked by vapor phase analysis. [c] Pure material, $n^{25}D$ 1.4878. [d] Calculated taking into consideration optical purity of starting material. [e] Product had to be diluted with racemic 2-phenylbutane for rotation determination, reducing observed rotation to a value which gave this probable error. [f] Not taken due to insufficient sample.

of the oxidative cleavage of (+)-I (compare runs 74 and 75). The average concentration of hydroxylamine in run 77 was selected for runs 74 and 76 which involved (+)-I and (+)-II as starting materials. The yield of III was very low in run 74 because the oxidizing agent reacted with hydroxylamine at least as fast as with hydrazine (+)-I. Sodium sulfate (1.1 M) was also added to each of these runs to approximate further the conditions of run 77. Considering the difficulties in duplicating the conditions for production of 2-phenylbutane from (+)-I, (+)-II and (−)-VI, the results of runs 74, 76 and 77 are within experimental error of one another.

Discussion

The results of the three reactions for breaking a carbon–nitrogen and making a carbon–hydrogen bond indicate that several mechanisms are available for both the bond-breaking and bond-making processes, some of which are stereospecific and some non-stereospecific. In the first parts of this section, the evidence for and characteristics of these mechanisms are discussed. In the later sections, the effects of solvent, cation of the base and oxidizing agent on the stereochemical capabilities of carbanions are rationalized.

Generation of Alkyldiimide as a Reaction Intermediate.—Evidence for the generation of 2-phenyl-2-butyl diimide (VIII) as an intermediate in the conversions of I, II and VI to 2-phenylbutane rests on two bases: (1) Although I, II and VI all have widely different structures, they all produce 2-phenylbutane and nitrogen. With amide VI as starting material, compound IX is undoubtedly an intermediate,[10] IX being a position isomer of II except for the p-methyl group of II. Production of diimide VIII from II and IX involves elimination reactions which differ only in their direction. Such reactions are undoubtedly base catalyzed (E_2 reaction), or in the absence of base might be solvolytic (E_1 reaction). Oxidation of I to VIII would involve removal of one mole of hydrogen from I by the oxidizing agent. (2) The data of Table VI indicate that I, II and VI give 2-phenylbutane with the same stereochemical course within experimental error (32 ± 6% net retention). This result provides strong evidence that at least one intermediate is common to all 3 reactions, and this intermediate partitioned between racemic and active product.



More detailed and therefore more convincing evidence is found in the data collated in Table VII. In 7 sets of experiments over the whole range of solvents (5 in number), in the presence and absence of base, and with 3 different oxidizing agents, the steric courses of the reaction are essentially independent of which starting material was employed.[17] The stereochemical results vary in these experiments from 100% racemization to 78% net retention of configuration. The formation of alkyl diimide resembles the formation of diimide itself as a reaction intermediate by

(17) An exception to this generalization is found with water as medium and with an intermediate amount of base present. This exception is discussed in a later section.

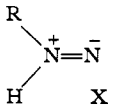
TABLE VII

IDENTITY OF RESULTS OBTAINED IN CLEAVAGE OF (+)-II AND OXIDATION OF (+)-I AS OXIDIZING AGENT, SOLVENT AND BASE CONCENTRATION ARE VARIED

Run	Substrate	Oxid. agent	Solvent	Base concn., M	Net steric course
62	(+)-I	KIO_4	$(CH_3)_3COH$	None	100% rac.
1	(+)-II	..	$(CH_3)_3COH$	None	100% rac.
63	(+)-I	KIO_4	$(CH_3)_3COH$	0.30	80% ret.
64	(+)-I	I_2	$(CH_3)_3COH$	.30	77% ret.
4	(+)-II	..	$(CH_3)_3COH$	.37	78% ret.
65	(+)-I	KIO_4	C_2H_5OH	.30	55% ret.
8	(+)-II	..	C_2H_5OH	.37	60% ret.
66	(+)-I	KIO_4	CH_3OH	.30	42% ret.
11	(+)-II	..	CH_3OH	.30	44% ret.
67	(+)-I	KIO_4	H_2O	None	100% rac.
19	(+)-II	..	H_2O	None	100% rac.
72	(+)-I	Br_2	H_2O	9.7	77% ret.
24	(+)-II	..	H_2O	9.7	70% ret.
73	(+)-I	KIO_4	$(CH_3)_2SO$	0.127	39% ret.
29	(+)-II	..	$(CH_3)_2SO$	0.087	44% ret.

oxidizing hydrazine,[18a,18b,18c] and through elimination reactions.[18a,18d]

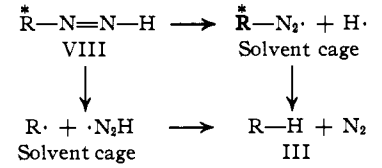
The possibility exists that the intermediate produced possesses not structure VIII but azamine structure[19] X. Although it is possible that X could be produced from II by a 1,1-elimination reaction, or from I by a 1,1-oxidation, IX could give X only by migration of either a hydrogen or the 2-phenyl-2-butyl group from one nitrogen to the other. Since X would undoubtedly be of higher energy than VIII, such a migration is highly unlikely, as is structure X for the intermediate produced by I, II and IX in the runs of Tables VI and VII.



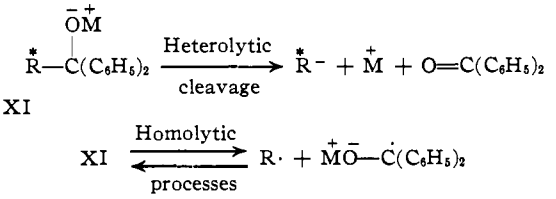
Disposal of Alkyldiimide as a Reaction Intermediate. —The dependence of the stereochemical outcome of the oxidation of (+)-I and cleavage of (+)-II on base concentration in all solvents tried[7] indicates that the 2-phenyl-2-butyl diimide of these reactions can be disposed of by two independent competing reactions. One of these is base-catalyzed and partially stereospecific in nature, and the other is not base-catalyzed and is non-stereospecific. In the absence of base, both (+)-I and (+)-II produce completely racemic 2-phenylbutane in all solvents tried. For (+)-I, *tert*-butyl alcohol (run 62) and water (run 67) were employed, and for (+)-II, *tert*-butyl alcohol (run 1), water (run 19), dioxane (run 26) and dimethyl sulfoxide (run 28) gave this result. On the other hand, in all solvents tried except water and ethylene glycol at 100° a base concentration was easily reached above which no change in stereospecificity could be observed in cleavage of (+)-II by further increases in base concentration. Solvents *tert*-butyl alcohol (runs 1–4), ethanol (runs 7–9), methanol (runs 10–12) and ethylene glycol at 25° (runs 17 and 18) employed for the cleavage of (+)-II exhibited this property. Thus conditions were found which isolated the non-base-catalyzed non-stereospecific mechanism for (+)-I and (+)-II, and which isolated the base-catalyzed partially stereospecific mechanism for (+)-II. The fact that the same steric course was observed in oxidation of (+)-I as in cleavage of (+)-II, once this threshold base concentration was reached, demonstrates that the base-catalyzed partially stereospecific mechanism for (+)-I was also isolated.

Non-base-catalyzed Reaction of Alkyl Diimide VIII. —The non-base catalyzed reaction has the following characteristics: (1) It produces 2-phenylbutane non-stereospecifically. (2) The reaction is inhibited only slightly by a 7-fold dilution of substrate (runs 56 and 57), is not catalyzed by benzoyl peroxide (runs 58 and 59), and is not inhibited by benzoquinone (runs 60 and 61, all of Table IV). Clearly a radical chain reaction is eliminated. (3) The reaction can be suppressed by increasing base concentration in ethylene glycol at 25° (runs 17 and 18) but not at 100° (runs 13–16). Thus the reaction increases in rate faster with increase in temperature than the competing base-catalyzed reaction. (4) The rate of the reaction is less affected by increased polarity of the solvent than the base-catalyzed reaction, as shown by the fact that in water and ethylene glycol at 100° increased base concentration does not suppress the reaction (runs 19–25) but does in the less polar solvents. (5) Small amounts of 2-phenylbutenes accompany the production of 2-phenylbutane in the absence of base (runs 1, 19, 26, 28, 62, 67). (6) No 3,4-dimethyl-3,4-diphenylhexane (dimer of 2-phenyl-2-butyl radical) could be detected in any of the runs.

These facts are compatible with only two mechanisms for the non-base-catalyzed reaction. The first involves a homolytic cleavage of either the carbon–nitrogen or nitrogen–hydrogen bond followed by disproportionation of the radical pair formed within the solvent cage.



Some analogies for this type of scheme are found in the pyrolytic decomposition of dialkyldiazo compounds.[20] Olefin could be produced by a side reaction in which 2-phenyl-2-butylhydrazine is protonated and undergoes an E_1 reaction to give a mixture of 2-phenylbutenes. That such a reaction occurs has been demonstrated.[21] Formation of the 2-phenyl-2-butyl radical was demonstrated to occur competitively with heterolytic base-catalyzed cleavage of XI.[22] In solvents such as dioxane or *tert*-butyl alcohol, the radical produced 3,4-dimethyl-3,4-diphenylhexane, but in basic ethylene glycol it largely went to 2-phenylbutane.[22]



The second possible mechanism is acid catalyzed and involves initial formation of the 2-phenyl-2-butyl

(18) (a) S. Hunig, H. R. Müller and W. Thier, *Tetrahedron Letters*, **No. 11**, 353 (1961); (b) E. J. Corey, W. L. Mock and D. J. Pasto, *ibid.*, **No. 11**, 347 (1961); (c) F. Aylward and M. Savistovska, *Chem. Ind.* (London), 404, 433 (1961); (d) E. E. van Tamelen, R. S. Dewey and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3725 (1961).

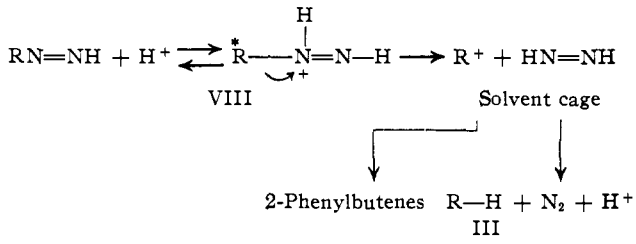
(19) (a) J. Kenner and E. C. Knight, *Ber.*, **69**, 341 (1936); (b) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957); (c) P. Carter and T. S. Stevens, *J. Chem. Soc.*, 1743 (1961).

(20) (a) C. G. Overberger, N. P. Marullo and H. G. Hiskey, *J. Am. Chem. Soc.*, **83**, 1374 (1961), and previous papers; (b) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 511.

(21) D. J. Cram and M. V. Sahyun, *J. Am. Chem. Soc.*, in press.

(22) D. J. Cram, A. Langemann, W. Lwowski and K. R. Kopecky, *ibid.*, **81**, 5760 (1959).

cation and diimide, which disproportionate in the solvent cage to produce largely 2-phenylbutane and nitrogen. In a side reaction, the carbonium ion could lose a proton to give the 2-phenyl-2-butenes. In an attempt to detect the presence of diimide in the reaction

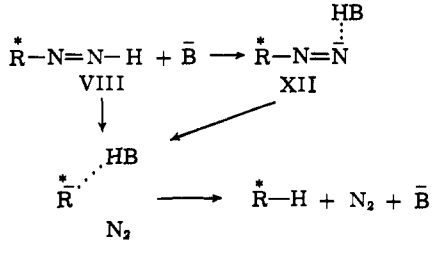


mixture, a run was made in the presence of cyclohexene, which is known to be reduced by diimide.[18] No cyclohexane was detected in the product by vapor phase chromatographic analysis. If diimide is produced, it must be consumed before leaving the solvent cage.

Of the two general schemes, the radical mechanisms are preferred, since the carbonium ion mechanism should result in retention of configuration (S_Ni reaction).

Base-catalyzed Reaction of Alkyl Diimide VIII.— The base-catalyzed reaction of alkyl diimide VIII exhibits a stereospecificity and even a steric direction which is dependent on solvent type. Clearly the 2-phenyl-2-butyl anion is an intermediate in this reaction, and as with carbon,[3] hydrogen[5] and oxygen[4] as leaving groups, the stereochemical fate of the carbanion depends on the detailed structure of its immediate environment.

The 2-phenyl-2-butyl anion could be generated either directly from VIII in a one-stage process, or VIII could go to its anion XII by proton loss, and lose nitrogen in a second stage. If the latter mechanism applied, the life of XII would probably be extremely short, possibly short enough in some media so that the mole of proton donor generated by proton abstraction could still be hydrogen-bonded to RN_2^- when the carbon–nitrogen bond broke.



The data of Table VIII show a distinct correlation between the stereochemistry of the base-catalyzed reaction and the dielectric constant of the solvent. These are runs in which the competing non-base-catalyzed reaction has been either suppressed or nearly so (runs 27, 16 and 29). The concentration of proton donors and acidity of the solvent seem to play a very small role. Even changes from hydroxylic to non-hydroxylic solvents seem to have only a minor effect on the stereochemistry. Thus dioxane and *tert*-butyl alcohol give similar results, as do methanol and dimethyl sulfoxide. Only water gives net inversion, and then only under certain circumstances (see later section).

The data of Table III demonstrate that in the non-dissociating solvents dioxane (runs 52 and 53) and *tert*-butyl alcohol (runs 46–49), substitution of tetramethylammonium hydroxide for potassium alkoxide (or hydroxide) as base reduced the stereospecificity by only about a third. In the dissociating solvents ethylene glycol (runs 50 and 51) and dimethyl sulfoxide (runs 54 and 55), a similar substitution of a quaternary ammonium base for alkoxide made no detectable difference in the stereochemistry of the reaction. Thus in the non-dissociating solvents, the base as an ion-pair is probably the active species, the cation of which plays a minor role in the stereochemical reaction course. In the dissociating solvents, the free anion seems to be the catalytic species.

TABLE VIII

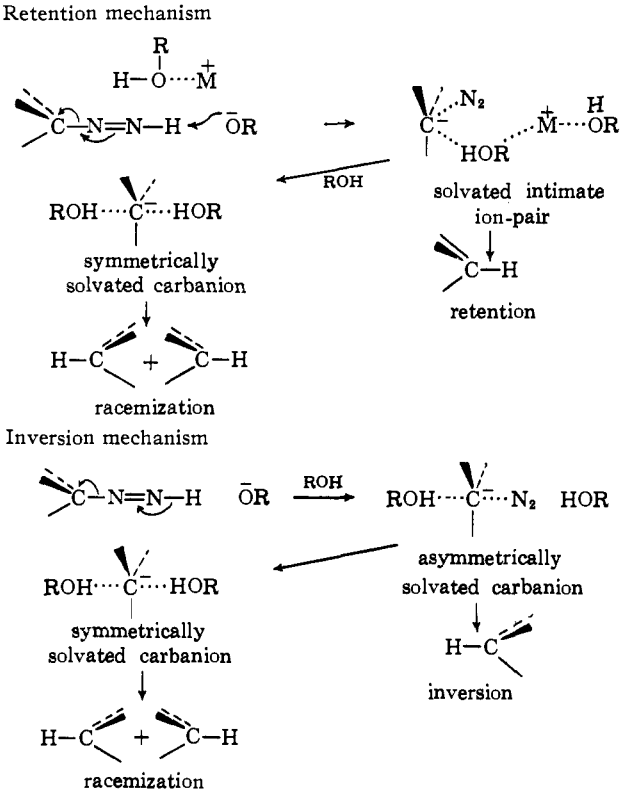
CORRELATION BETWEEN STEREOCHEMISTRY AND DIELECTRIC CONSTANT OF SOLVENT

Run	Solvent	$\epsilon^{°C.}$	Steric course
27	$O(CH_2CH_2)_2O$	2.2^{25}	74% ret.
4	$(CH_3)_3COH$	11^{19}	78% ret.
6	*n*-C_4H_9OH	18^{25}	68% ret.
8	C_2H_5OH	27^{20}	60% ret.
11	CH_3OH	34^{18}	44% ret.
16	$HOCH_2CH_2OH$	35^{20}	37% ret.
29	$(CH_3)_2SO$	49^{20}	44% ret.
69	H_2O	80^{20}	32% inv.

These results indicate that nitrogen is similar in certain respects to carbon[3] and hydrogen[5] as leaving groups. All three substrate types in hydroxylic solvents exhibit a correlation of stereochemical course with solvent dielectric constant, net retention being associated with solvents of low, and net inversion with solvents of high dielectric constant. However, nitrogen as leaving group is different from the others in three respects: (1) The retention–inversion scale is condensed and shifted toward retention. (2) Dimethyl sulfoxide is a retention rather than a racemization solvent. (3) Substitution of quaternary ammonium for an alkali metal cation in a retention solvent does not produce racemic product. These differences correlate with the fact that in the base-catalyzed reaction of VIII, a proton donor is generated on the leaving-group side of the carbanion. In proton-donating solvents of low dielectric constant or in non-proton donating solvents, the carbanion captures the proton before the species diffuse apart, and net retention results. As the hydroxylic solvents become more acidic and of higher dielectric constant, solvent begins to participate from the side remote from the leaving group in the breaking of the carbon–nitrogen bond. A carbanion hydrogen-bonded from the back side is produced and collapses to give inverted product. These two processes not only compete with one another, but also with a third in which the carbanion becomes symmetrically solvated, and produces racemic material. This explanation of the results applies more simply to a mechanism in which the carbon–nitrogen and nitrogen–hydrogen bonds of VIII are broken in the same transition state, but can also be easily adapted to the two-stage process. The hypothesis is summarized in Chart II.

Superimposed on the above scheme is the solvent-orienting ability of the potassium ion in solvents in which the catalyst is an ion-pair. Substitution of the quaternary ammonium cation for the potassium ion reduces retention because the former cannot coordinate with solvent, and hold proton donors at the front of the carbanion. The addition of small amounts of water to the *tert*-butyl alcohol enhances retention with both types of bases (compare runs 46 and 48, and runs 47 and 49 of Table III). This is interpreted as the result of water solvation of ion pairs, which are the active basic catalyst. The environment at the front of the carbanion is accordingly enriched with proton-donating water molecules.

CHART II



Special Case of Water as Solvent.—Some of the generalizations made in the preceding sections for organic solvents do not apply in all cases to water as solvent. The relevant results are listed in Table IX. One striking anomaly is the fact that in water, the steric course depends on whether alkylhydrazine (+)-I or its sulfonamide derivative (+)-II is the starting material. Although (+)-I at low base concentration gives 32–33% net inversion with either potassium periodate or bromine as oxidizing agent, under the same conditions cleavage of (+)-II gives only 5% net inversion. A second example is the production of 70–77% retention with (+)-II or with (+)-I and bromine at a very high base concentration, but under the same conditions (+)-I with potassium periodate gives 12% inversion. These results clearly demonstrate that in water at least two different base-catalyzed stereospecific reactions are involved. A possible interpretation is given below.

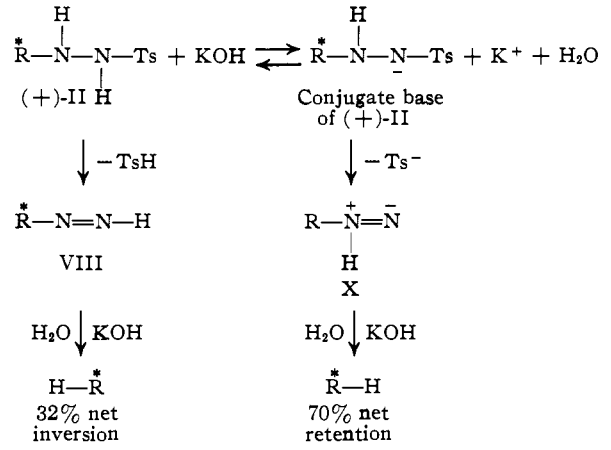
TABLE IX

SPECIAL CASE OF WATER AS SOLVENT

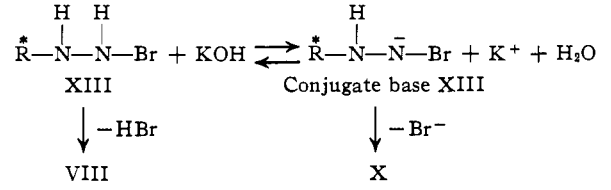
Run	Substrate	Oxid. agent	Base concn., *M*	Net steric course
69	(+)-I	KIO_4	0.30	32% inv.
70	(+)-I	Br_2	.30	33% inv.
20–21	(+)-II	None	.30	5% inv.[a]
71	(+)-I	KIO_4	9.70	12% inv.
72	(+)-I	Br_2	9.70	77% ret.
24	(+)-II	None	9.70	70% ret.

[a] Value interpolated from values of runs 20 and 21.

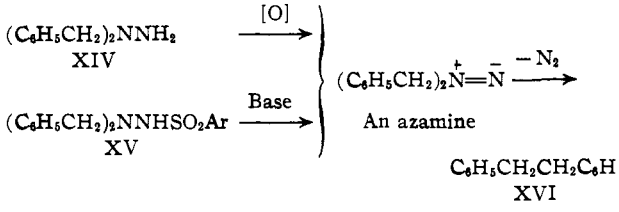
In oxidation of (+)-I in runs 69 and 70 at low base concentrations, alkyl diimide VIII is an intermediate in a medium which exhibits inversion properties (32–33%) because of its high dissociating and solvating ability. In water, (+)-II produces both alkyl diimide VIII by a 1,2-elimination and azamine X by a 1,1-elimination reaction. The former goes to product with 32% net inversion, the latter to product with 70–77% net retention. Proton abstraction from azamine X by base places a proton donor much closer to the front face of the carbanion than in proton abstraction from VIII, and therefore X would be expected to be more disposed toward a retention result. In basic solution, (+)-II is in equilibrium with its anion, and high concentrations of base shift the equilibrium toward its conjugate base. Since (+)-II is the starting material for VIII, and the conjugate base of (+)-II the starting material for X, high base concentration should favor X as an intermediate, and retention as the steric course, as is observed. The increase in inversion for (+)-II at low base concentration as base is increased is due to the suppression of the non-base catalyzed, non-stereospecific reaction. Bromine compound XIII is probably



the initial product of the reaction between (+)-I and bromine. Compound XIII is also undoubtedly



in equilibrium with its conjugate base, but possesses a lower equilibrium constant than II. Hence at 0.3 *M* base (run 70), only VIII is produced and 33% net inversion is observed. At 9.7 *M* base, only X is produced and 77% net retention results. Some analogy for the postulated 1,1-elimination reaction of II is found in the transformations[19] of XIV and XV to XVI, presumably through azamine intermediates.



Another interesting property of water as solvent for the cleavage of (+)-II is the fact that at about 0.1 *M* base, addition of 5 mole % of four widely different organic solvents increased net inversion from 1% to from 2 to 8% (see Table X). These results could well be due to a solvent effect which leaves the rate of the non-base catalyzed non-stereospecific reaction unchanged but which slightly promotes the rate of the base-catalyzed elimination reaction. Addition of more organic solvent as in run 34 (15 mole % *tert*-butyl alcohol) dramatically changes the steric result to 50% retention. Apparently the inversion mechanism is dependent on a not too serious disruption of the structure of liquid water.

TABLE X

EFFECT OF ADDED MATERIALS TO 0.1 *M* SOLUTIONS OF WATER IN CLEAVAGE OF (+)-II

Run	Added mat. Nature	Added mat. Mole %	Net steric course
36	None	..	1% inv.
37	CH_3OH	5	7% inv.
38	$HOCH_2CH_2OH$	5	8% inv.
45	$(CH_3)_2SO$	5	2% inv.
35	$(CH_3)_3COH$	5	5% inv.
34	$(CH_3)_3COH$	15	50% ret.

Experimental

2-Phenyl-2-butylhydrazine Oxalate.[11]—Methyl ethyl ketazine[23] was prepared in 43% yield, b.p. 62–64° at 15 mm., $n^{25}D$ 1.4538; reported[23] b.p. 72° at 12 mm., $n^{26.6}D$ 1.4516. A solution of phenylmagnesium bromide was prepared from 340 g. of bromobenzene and 56 g. of magnesium in 940 ml. of dry ether under nitrogen. The ketazine, 140 g., was dissolved in 940 ml. of dry ether and was added dropwise with stirring to the Grignard reagent. The resulting mixture was stirred under reflux for 5 days, cooled to 5°, and added to 400 g. of ammonium chloride suspended in ice. The organic layer was separated, and the aqueous layer was extracted 3 times with 200-ml. portions of ether. The combined organic layers were washed with water saturated with sodium bicarbonate, dried and evaporated. Distillation of the residue gave 107 g. (49%) of methyl ethyl ketone N'-2-phenyl-2-butylhydrazone, b.p. 100–115° at 3 mm. The infrared spectrum of the compound gave a weak C=N band at 1620 cm.$^{-1}$, comparable to that reported for diethyl ketone N'-3-phenyl-3-pentylhydrazone.[12] The hydrazone, 16 g., was added to 24 g. of oxalic acid hydrate (m.p. 101°) dissolved in a mixture of 80 ml. of absolute ethanol, 80 ml. of ether and 1 ml. of water. A white granular solid separated from the mixture held at 25° for 36 hr. A second crop was obtained by adding more ether to the filtrates. The two crops, wt. 10.6 g. (57%), were combined and recrystallized from hot ethanol–ether and then from hot ethanol; m.p. 131–132°.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.74; H, 7.14; N, 11.02. Found: C, 55.60; H, 7.13; N, 11.06.

In a second preparation of this material a 64% yield was obtained, m.p. 92–94°. After the substance had been recrystallized twice from hot ethanol and had been dried at 65° at 2 mm., it exhibited m.p. 109–110°, and analyzed as a half hydrate.

Anal. Calcd. for $C_{12}H_{18}O_4N_2 \cdot 0.5H_2O$: C, 54.76; H, 7.22; N, 10.62. Found: C, 54.76; H, 7.32; N, 10.57.

2-Phenyl-2-butylhydrazine (I).[11]—The above oxalate salt, 17.0 g., was dissolved in a solution of 10 g. of potassium hydroxide in 120 ml. of water. The mixture was extracted 3 times with 100-ml. portions of ether, the combined ether extracts were dried with anhydrous sodium carbonate (a necessary drying agent), the ether was evaporated and the product (I) was distilled under a nitrogen atmosphere; 9.3 g. (84%), b.p. 81–84° at 0.4 mm., $n^{26}D$ 1.5308.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.94; H, 10.11; N, 17.33.

In a second preparation, the material exhibited $n^{25}D$ 1.5354.

Hydrazine I reduced Fehling solution slowly at 25°. When exposed to air, it developed bubbles and slowly decomposed, but could be stored for long periods of time under nitrogen at −80°.

Resolution of 2-Phenyl-2-butylhydrazine (I).—Dibenzoyl-*d*-tartartic acid hydrate was prepared as previously[24]; m.p. 84–87°, $[\alpha]^{25}D$ −111° (*c* 1.1, ethanol); reported m.p. 88–89°,[24,25] $[\alpha]^{27}D$ −112.5° (*c* 1.1, ethanol).[25] The hydrate, 20.6 g., was dissolved in a mixture of 150 ml. of absolute ethanol and 50 ml. of distilled water, and 9.0 g. of alkylhydrazine I was added. The resulting mixture was stirred and allowed to stand for 5 days at 0–5°. The salt that separated was collected; wt. 17 g. (57%), m.p. 140–145°, $[\alpha]^{25}D$ −74.1° (*c* 1, ethanol). A small sample was converted to its free base (see below for procedure), $n^{25}D$ 1.5356, α^{25}_{546} +0.77° (*l* 1 dm., neat). The tartrate salt was recrystallized 5 times from 3:1 ethanol–water to give 3.8 g. of salt, which was converted to (+)-I as follows. The tartrate salt was dissolved in 20 ml. of 10% aqueous potassium hydroxide and extracted with three 20-ml. portions of ether. The combined ether extracts were dried with anhydrous sodium carbonate, the ether was evaporated, and the product was distilled under a nitrogen atmosphere, 0.51 g. (84%), $n^{25}D$ 1.5358, α^{25}_{546} +1.82° (*l* 1 dm., neat).

In an attempt to reach optical purity, tartrate salt (20 g.) was dissolved in 4 l. of boiling water, and allowed to crystallize slowly to give 13 g. of material. This process was repeated 3 times to give 3.3 g. of salt as fine needles. This material was converted to the free base, 0.65 g., $n^{25}D$ 1.5354, α^{26}_{546} +11.8° (*l* 1 dm., neat). Subsequent experiments demonstrated this material to be only 87.5% optically pure.

Purification of Optically Active 2-Phenyl-2-butylhydrazine ((+)-I) for Oxidative-cleavage Reactions.—Hydrazine (+)-I prepared by the above method gave a spurious rotation due to the presence of an optically active impurity which lowered the rotation. This impurity was removed as follows. Partially optically active (+)-I, α^{25}_{546} +1.98 ± 0.05° (*l* 1 dm., neat), 14 g., was added to 11 g. of oxalic acid hydrate dissolved in a mixture of 42 ml. of absolute ethanol and 42 ml. of dry ether. The resulting solid, 21.4 g. (98%), was recrystallized from hot ethanol to give 18.5 g., m.p. 113–114°. Conversion of 16.5 g. of this material to its free base ((+)-I) gave 6.8 g. (49% over-all) of recovered material, α^{25}_{546} +2.07 ± 0.05° (*l* 1 dm., neat).

(+)-1-(2-Phenyl-2-butyl)-2-*p*-toluenesulfonhydrazide ((+)-II).—To 0.50 g. of (+)-2-phenyl-2-butylhydrazine, α^{26}_{546} +12.8° (*l* 1 dm., neat), 93% optically pure, in 10 ml. of dry pyridine at 0° was added slowly with stirring 0.60 g. of *p*-toluenesulfonyl chloride in 5 ml. of dry pyridine. The resulting mixture was warmed to 25° and added to 3 *N* hydrochloric acid. The solid that separated was collected and dissolved in ether. The ether solution was washed 3 times with a saturated solution of sodium bicarbonate in water, decolorized with charcoal, dried, and the solvent was evaporated until white crystals appeared. Pentane was added, and the white needles were collected; wt. 0.57 g. (56%). The material was recrystallized from 1:1 ether–pentane; wt. 0.49 g., m.p. 112–112.2°, $[\alpha]^{25}_{546}$ +39.4° (*c* 5.13, dioxane), $[\alpha]^{25}_{546}$ +35.6° (*c* 7.3, dioxane), $[\alpha]^{26}_{546}$ +32.6° (*c* 9, dioxane).

Anal. Calcd. for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.97. Found: C, 64.09; H, 7.13.

Racemic material, prepared similarly, exhibited m.p. 101.5–102°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.97; N, 8.80. Found: C, 64.03; H, 6.67; N, 8.64.

(−)-1-(2-Phenyl-2-butyl)-2-*p*-toluenesulfonhydrazide ((−)-II).—Grossly optically impure (−)-I, α^{26}_{546} −0.75° (*l* 1 dm., neat) was converted to its toluenesulfonhydrazide, which was recrystallized from ether–pentane until the rotation stopped changing. The initial rotation was $[\alpha]^{25}_{546}$ −5.3° (*c* 8.5, dioxane); after 4 recrystallizations, $[\alpha]^{25}_{546}$ −36.3° (*c* 8, dioxane). Two more recrystallizations gave $[\alpha]^{25}_{546}$ −35.4° (*c* 9, dioxane), m.p. 112.5–113°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.97. Found: C, 63.84; H, 7.11.

N-Carbethoxy-N'-(2-phenyl-2-butyl)-hydrazine (VII).—To 2.0 g. of 2-phenyl-2-butylhydrazine in 6 ml. of pyridine at 0° was slowly added 1.3 g. of ethyl chloroformate in 15 ml. of dry ether. The reaction was exothermic. The mixture was allowed to come to 25°, and was added to 100 ml. of 1.5 *N* hydrochloric acid at 0°. The mixture was extracted 3 times with 50-ml. portions of ether, the combined ether extracts were washed with a saturated solution of sodium bicarbonate in water, and dried over anhydrous sodium carbonate. Evaporation of the ether and distillation of the residual oil under a nitrogen atmosphere (b.p. 118–126° at 0.25 mm.) gave 1.0 g. (35%) of VII, $n^{24}D$ 1.5174. An infrared spectrum of this material in chloroform exhibited bands at 3400 and 3340 cm.$^{-1}$, attributed to the N–H stretching of hydrazide and hydrazine moieties, respectively.[26]

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.97; H, 8.80; N, 12.07.

Hydrogenolysis of (+)-2-Phenyl-2-butylhydrazine ((+)-I) to (+)-2-Phenyl-2-butylamine ((+)-IV).—Platinum oxide hydrate, 0.046 g., was reduced with hydrogen in 5 ml. of pure glacial acetic acid. To this mixture under a hydrogen atmosphere at atmospheric pressure was added 0.85 g. of (+)-I, α^{26}_{546} +11.8° (*l* 1 dm., neat), dissolved in 10 ml. of glacial acetic acid. The calculated amount of hydrogen, 135 ml., was absorbed over a period of 6 hr. The mixture was filtered, and the filtrate was shaken with an excess of dilute potassium hydroxide in water and ether at 0°. The aqueous layer was extracted with two additional 50-ml. portions of ether. The combined ether layers were dried, filtered and evaporated to give a residue. This material was distilled at 2 mm. under nitrogen to give 0.56 g. of amine (+)-IV. After a second distillation the colorless oil exhibited $n^{25}D$ 1.5124, α^{26}_{546} +15.8° (*l* 1 dm., neat).

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.47; H, 10.13. Found: C, 80.65; H, 10.25.

Conversion of (+)-2-Methyl-2-phenylbutanoic Acid ((+)-V) to (−)-2-Phenyl-2-butylamine ((−)-IV).[16]—A solution of 8.9 g. of (+)-V, $[\alpha]^{26}D$ +30.1° (*c* 5, benzene)[13] in 15 ml. of reagent grade thionyl chloride and 50 ml. of anhydrous ether was allowed to stand at 25° for 18 hr., and was then held at reflux for 1 hr.

(23) I. Heilbron's, "Dictionary of Organic Compounds," Eyre and Spottiswoods, London, England, 1953, Vol. 3, p. 387.

(24) C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, **55**, 2605 (1933).

(25) G. Losse, *Ber.*, **87**, 1279 (1954).

(26) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 178 and 215.

The solvent and excess reagent were evaporated under reduced pressure, and the residue was distilled through a 6 in. Vigreux column to provide the desired acid chloride; 8 g. (82%), b.p. 91° at 2 mm. This material and 2.8 g. of activated sodium azide[27] in 25 ml. of dry xylene was heated slowly to 80° with vigorous stirring. When a steady gas evolution commenced, 2.8 g. of additional activated sodium azide was added and stirring was continued for 3 hr. The temperature was then raised to 180° for 1 hr. The mixture was then cooled, filtered, evaporated to 35 ml. and stirred for 18 hr. with 15 ml. of concd. hydrochloric acid. The crystalline amine hydrochloride that separated was collected, washed with ether, and added to a dilute solution of aqueous potassium hydroxide. The mixture was extracted 3 times with 50-ml. portions of ether, and the combined extracts were dried and evaporated to an oil under reduced pressure in the absence of air. The residue was distilled to give 4.0 g. (66%) of (−)-2-phenyl-2-butylamine ((−)-IV), b.p. 50–52° at 2 mm., $n^{25}D$ 1.5148, α^{27}_{546} −18.2° (*l* 1 dm., neat).

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.47; H, 10.13; N, 9.40. Found: C, 80.16; H, 10.37; N, 9.68.

(−)-2-Phenyl-2-butylamine((−)-IV) N-Benzenesulfonamide ((−)-VI).[16]—The procedure for the conversion of (+)-I to (+)-II was used (see above). From (−)-IV, α^{26}_{546} −18.2° (*l* 1 dm., neat), and benzenesulfonyl chloride in pyridine at −10° was obtained a 90% yield of product. An analytical sample of (−)-VI was obtained by repeated precipitations of the material from hot 10% sodium hydroxide solution with acid, followed by a recrystallization from ethanol; m.p. 108.8–109.6°, $[\alpha]^{27}_{546}$ −44.57° (*c* 3.4, benzene).

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62. Found: C, 66.65; H, 6.58.

Purification of Solvents.—The alcohols used as solvents were all distilled from their sodium or potassium salts onto Linde Molecular Sieves 4A, 14 by 30 mesh. Baker Analyzed dimethyl sulfoxide was passed through Molecular Sieves, distilled in an efficient column under reduced pressure, and stored over Molecular Sieves. Dioxane was purified as before.[28] Pure pentane (Phillips Petroleum Co.) was fractionally distilled through a 4-ft. helix-packed column before use. Distilled water was boiled before use.

Cleavage Reactions.—With the exception of run 57 (high dilution experiment) and runs 74–77, all of the reactions were carried out in heavy-walled pressure bottles of 150-ml. capacity. All solvents and pressure bottles were flushed with dry, oxygen-free nitrogen (passed over hot copper) before use. Constant temperature baths of 52.5 ± 0.1°, 75.6 ± 0.1° and 100 ± 2° were used for all reactions at elevated temperatures. Only partially optically active starting materials (−)- and (+)-I and (+)-II were used because of the difficulty in obtaining material of greater than 20–25% optical purity. Since II was completely soluble only in dioxane and dimethyl sulfoxide, all cleavage reactions of (+)-II were heterogeneous except those made in these solvents, or in these solvents mixed with minor amounts of other solvents. All oxidative cleavages of I were homogeneous with respect to I and bromine or iodine, but heterogeneous with respect to potassium periodate. The product of every run was analyzed on a 30% pimelonitrile column at 90° and 108°. Only 2-phenylbutane was detected except where noted. The results are found in Tables I–VI. Representative procedures as well as exceptional ones are recorded below.

Run 31.—A solution (0.30 *M*) of potassium *tert*-butoxide in pure *tert*-butyl alcohol was prepared from 0.473 g. of potassium metal and 40 ml. of solvent under pure dry nitrogen. Optically active (+)-II, 0.690 g., $[\alpha]^{25}_{546}$ +11.5 ± 0.15° (*c* 9.15 in dioxane), was placed in the pressure bottle, and 30 ml. of the basic solution added. The mixture was saturated with oxygen-free, dry nitrogen, the bottle was sealed, and immersed in a 100 ± 2° constant temperature oil-bath for 2 hr. The bottle was cooled, and the contents were shaken with 50 ml. of pure pentane and 50 ml. of water. The aqueous layer was extracted twice more with pentane, the combined pentane layers were washed with water, dried, and evaporated through a Vigreux column. The residual oil was chromatographed on 50 g. of activity I alumina[29] with pure pentane as solvent. The first 150 ml. of column eluant was evaporated through a Vigreux column, and the residual oil was distilled at atmospheric pressure to give 0.243 g. (83%) of 2-phenylbutane, $n^{25}D$ 1.4878, $\alpha^{26}D$ + 6.36° (*l* 1 dm., neat), 80% net retention.

The aqueous extract on layer was acidified with hydrochloric acid and treated with gaseous chlorine. The dense white precipitate was filtered and air-dried; m.p. 66–67°, m.m.p. with authentic *p*-toluenesulfonyl chloride, 67–68°. A similar treatment of *p*-toluenesulfonic acid gave no product.

Run 54.—A 0.088 *M* potassium *tert*-butoxide (freshly sublimed) solution in dimethyl sulfoxide was prepared from the alkoxide (0.395 g.) and 40 ml. of solvent. The run was made in the ordinary way except that before the 2-phenylbutane (III) was submitted to chromatography, 5% of the starting material separated and was collected. Compound III was produced with 37% net retention, which was corrected to 44% net retention from use of the following data.

The final base concentration from run 54 proved to be 0.010 *M*. A control run was made with optically active 2-phenylbutane under the exact conditions of the above experiment, and the average base concentration of 0.031 *M* base. The material was racemized 23%. From these data, it is estimated that in run 54, III once formed racemized enough to reduce the retention by 7%.

Run 63.—A 0.30 *M* potassium *tert*-butoxide solution in *tert*-butyl alcohol was prepared as before. A mixture of 30 ml. of this solution and 0.560 g. of potassium periodate was placed in a 150-ml. heavy-walled bottle, and the solution and bottle were flushed with pure nitrogen. Hydrazine (+)-I, 0.400 g., was suspended in a platinum bucket over the mixture, the bottle was sealed and placed in an oil-bath at 100 ± 2°. The hydrazine was tipped into the reaction mixture. Potassium iodate separated when the reaction mixture was cooled for product isolation. Product was isolated as in run 31.

Run 77.—A solution of 1.156 g. of (−)-VI, $[\alpha]^{26}_{546}$ −44.57° (*c* 3.4, benzene), in 10 ml. of ethanol was heated to reflux. A solution of 10 g. of sodium hydroxide in 70 ml. of water was added. Freshly prepared hydroxylamine-O-sulfonic acid,[30] 22.6 g., was added to the solution at such a rate that gentle reflux was maintained. The mixture was cooled, diluted with an equal volume of water, and the starting material that separated was collected (0.67 g.). This material was recycled twice through the reaction procedure. The product (III) from the three cycles was isolated in the same work-up, which resembled that of run 31.

Run 76.—A solution that was the calculated average of that used in run 77 was prepared from 8.2 g. of hydroxylamine sulfate, 7.1 g. of sodium sulfate, 14 g. of sodium hydroxide, 70 ml. of water and 10 ml. of ethanol (the sodium sulfate was incompletely dissolved). To this mixture held at reflux was added 0.690 g. of (+)-II. After 1 hr. at this temperature product was isolated and characterized as in run 77.

Runs 74 and 75.—The same procedure used in run 76 was applied in run 74 to 0.400 g. of (+)-I, except that while the solution was at reflux, 2.5 g. of potassium periodate was added in small portions. Product was isolated and characterized as in run 77. Run 75 was made identically to run 74 except that the hydroxylamine was omitted.

Runs 70 and 72.—In runs 70 and 72 in which bromine was the oxidizing agent, the maximum bromine concentration attainable was 0.05 *M*. Accordingly, (+)-I at 0.048 *M* was used. The base concentration was determined by titration with standard acid.

Runs 26 and 28.—In these runs, (+)-II was cleaved in the absence of base. Gas chromatographic analysis of the product demonstrated the presence of 0.5% of *cis*-2-phenyl-2-butene. A white solid material, m.p. 74–77°, was crystallized from the oil obtained on evaporation of the initial pentane extracts. The infrared spectrum[31] of this material was superimposable on that of pure *p*-tolyl *p*-toluenesulfonate,[15] m.p. 77°. A nuclear magnetic resonance spectrum of the material gave aromatic absorption which accounted for 57% of the hydrogen (theory 57%) and 43% was found in an aliphatic singlet peak (theory 43%).

Run 62.—The reaction was carried out in 95 mole % *tert*-butyl alcohol–5 mole % water with 2.20 g. of (+)-I. The product isolated was submitted to vapor phase chromatography against known standards[21] and was demonstrated to be 25% 2-phenylbutane, 43% *cis*-2-phenyl-2-butene, 31% 2-phenyl-1-butene and 1% *trans*-2-phenyl-2-butene. This composition resembles that observed for the solvolysis of (+)-I.[21] Hydrocarbon III was isolated by preparative v.p.c. on a 30% pimelonitrile on firebrick column, wt. 0.237 g. (13%), and was completely racemic.

Runs 47, 51 and 53.—The appropriate amounts of tetramethylammonium hydroxide dihydrate[32] were employed, and the amount of base in the solution was determined by titration of aliquots against standard acid.

Runs 49 and 55.—In these runs, tetramethylammonium hydroxide dihydrate in *tert*-butyl alcohol (run 49) or in dimethyl sulfoxide (run 55) was rid of water through use of Linde Molecular Sieves 4A, 14 by 30 mesh, until Karl Fischer reagent titration demonstrated the absence of water. An aliquot of each basic solution was titrated with standard acid.

(27) P. A. S. Smith, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 382.

(28) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 369.

(29) H. Brockman and H. Schrodder, *Ber.*, **74B**, 73 (1941).

(30) F. Sommer, O. F. Sbulz and M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).

(31) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1960, No. 15579.

(32) D. J. Cram, L. K. Gaston and H. Jager, *J. Am. Chem. Soc.*, **83**, 2183 (1961).

Runs 59 and 61.—Both runs resembled run 31 except that in 59, 0.007 g. of benzoyl peroxide was added, and in run 69, 0.010 g. of benzoquinone was employed.

Attempted Reduction of Cyclohexene.—A mixture of 25 ml. of 0.13 *M* aqueous potassium hydroxide, 0.800 g. of racemic II and 2 ml. of cyclohexene was heated to 100 ± 2° for 2 hr. in a 150-ml. heavy-walled pressure bottle. The product was isolated as in run 31 except that special care was taken to avoid loss of cyclohexene, and was submitted to gas chromatographic analysis on a 30% pimelonitrile on firebrick column at 108°. No trace of cyclohexane was observed.

Control Runs.—In previous experiments, optically active 2-phenylbutane was found not to racemize at 240° for 24 hr. in a 1 *M* solution of potassium diethylene glycoxide in diethylene glycol.[13b] This experiment controls all runs made in primary alcohols or water as solvents. Other control experiments[3a] were carried out in dioxane at 150° and in *tert*-butyl alcohol at 102° in the presence of potassium *tert*-butoxide without racemization of active III. In dimethyl sulfoxide which was 0.11 *M* in potassium *tert*-butoxide, active 2-phenylbutane racemized completely at 110° for 28 hr.[3a] A control run was conducted under the conditions of run 54. After 90 hr. at 52.5 ± 0.1°, (+)-III was 23% racemized.

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The Synthesis of Orotidine-5′ Phosphate

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The reaction of the silver salt of orotidine with methyl iodide gives orotidine methyl ester which is converted to its isopropylidine derivative and phosphorylated with the cyanoethyl phosphate–dicyclohexylcarbodiimide reagent. After removal of protecting groups the resulting orotidine-5′ phosphate is both chemically and enzymatically identical with the natural material. Attempted esterification of the nucleoside by a variety of other methods gave products in which N_3 was also methylated. Several derivatives of these N_3 methylated nucleosides are described and the rates of alkaline hydrolysis of the methyl ester groups in both the N_3-methylated and unmethylated series are described.

During the past ten years the biosynthetic pathways leading to both the purine and pyrimidine ribonucleotides have been clearly defined.[2] Information is also accumulating as to the steps involved in the conversion of ribonucleotides into the corresponding deoxyribonucleotides.[3] The involvement of orotic acid (XI) as a precursor of the pyrimidine ribonucleosides was demonstrated by Hurlbert and Potter[4] and it remained for Lieberman, Kornberg and Simms[5] to clarify this key process. The latter workers[5] showed that in yeast the first intact pyrimidine nucleoside derivative in the biosynthetic pathway was orotidine-5′ phosphate (IV), formed by the condensation of orotic acid (XI) and 5-phosphoribosyl α-1-pyrophosphate (PRPP),[6] and that IV was subsequently decarboxylated to uridine-5′ phosphate by the enzyme orotidylate decarboxylase. The same pathway also obtains in mammalian systems.[7,8]

The nucleoside orotidine (I) was originally isolated from mutants of *Neurospra crassa* which possess relatively low levels of orotidylate decarboxylase.[9] More recently it has been demonstrated in several laboratories[10–12] that this enzyme is inhibited by the nucleotide analog 6-azauridine-5′ phosphate or by large amounts of uridine-5′ phosphate[7] and that accordingly there is a build-up of orotidylic acid and its dephosphorylated derivative orotidine. We have recently had occasion to isolate relatively large amounts of orotidine from the urine of tumor-bearing subjects who have received azauridine therapy. The availability of this pure material has prompted a study of the chemistry of orotidine derivatives and in particular the first synthesis of the key biological intermediate orotidine-5′ phosphate (IV). It is of interest to note that with the exception of its naturally occurring phosphate (IV) no derivatives of orotidine have previously been described.

The most obvious key intermediate in a specific synthesis of orotidine-5′ phosphate (IV) is 2′,3′-O-isopropylidineorotidine methyl ester (III) and our first goal was the preparation of this compound. Since some difficulties were to be expected due to spontaneous hydrolysis of the isopropylidine group in compounds bearing a free carboxyl group (as in VII), it was decided first to prepare orotidine methyl ester (II) and then form the isopropylidine derivative III. The formation of II without complication, however, proved to be quite difficult. This is not unexpected in view of the confusion in the earlier literature regarding the methylation of orotic acid itself.[13] It was not possible, for example, to effect selective methylation of the free carboxyl group using diazomethane since N_3 of the pyrimidine ring was concurrently alkylated.[14] The resulting crystalline N_3-methylorotidine methyl ester (V) was isolated by chromatography on silicic acid. It was shown that the compound was an N-methyl rather than an O-methyl derivative by its stability to acid[14a] and by its hydrolysis with mild alkali to the potentially interesting antimetabolite N_3-methylorotidine (VIII) which was isolated as its crystalline cyclohexylammonium salt. It is interesting to note that some cleavage of the glycosidic bond apparently resulted during the methylation reaction since a small amount of crystalline material that was neutral and periodate negative was isolated from the reaction. This compound had the chromatographic behavior and elemental analysis expected for N_3-methylorotic acid methyl ester (X).

The reaction of crude N_3-methylorotidine methyl ester (V) with acetone containing 2,2-dimethoxypropane

(1) Syntex Institute for Molecular Biology, 3221 Porter Drive, Palo Alto, Calif.

(2) For recent reviews, see J. M. Buchanan and S. C. Hartman, in *Advan. in Enzymol.*, **21**, 199 (1959), and P. Reichard, *ibid.*, **21**, 263 (1959).

(3) See, *e.g.*, P. Reichard, *J. Biol. Chem.*, **236**, 2511 (1961), and preceding papers; S. S. Coben, H. D. Barner and J. Lichtenstein, *ibid.*, **236**, 1448 (1961).

(4) R. B. Hurlbert and V. R. Potter, *ibid.*, **209**, 1 (1954).

(5) I. Lieberman, A. Kornberg and E. S. Simms, *ibid.*, **215**, 403 (1955).

(6) A. Kornberg, I. Lieberman and E. S. Simms, *ibid.*, **215**, 389 (1955).

(7) D. G. R. Blair, J. E. Stone and V. R. Potter, *ibid.*, **235**, 2379 (1960).

(8) W. A. Creasey and R. E. Handschumacher, *ibid.*, **236**, 2058 (1961).

(9) A. M. Michelson, W. Drell and H. K. Mitchell, *Proc. Natl. Acad. Sci. U.S.*, **37**, 396 (1951).

(10) R. E. Handschumacher, *J. Biol. Chem.*, **235**, 2917 (1960).

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(12) R. E. Handschumacher, *Nature*, **182**, 1090 (1958).

(13) For a clarification of this problem, see J. J. Fox, N. Yung and I. Wempen, *Biochem. Biophys. Acta*, **23**, 295 (1957).

(14) Numerous examples of alkylations at N_3 of pyrimidine nucleosides by diazomethane are known, *e.g.*, (a) H. T. Miles, *J. Am. Chem. Soc.*, **79**, 2565 (1957); (b) W. Szer and D. Shugar, *Acta Biochem. Polon.*, **7**, 491 (1960). Since the present work was completed it has been found that Dr. R. E. Handshumacher (personal communication) has obtained crystalline II by the use of limiting amounts of diazomethane. A sample of the resulting material kindly provided by Dr. Handscbumacher was chromatographically identical with the non-crystalline product obtained from the silver salt of orotidine and methyl iodide as described later.