was used for preparation of the standard solutions. As little as 1% deuterated material could be detected, although the relative error at very low deuterium concentration was larger than that at higher concentrations, where the estimated absolute error was ±1%. To ensure reproducibility, for every analysis, it was necessary to run undeuterated 2-phenylbutane to obtain the base line, then the unknown, then a 2-phenylbutane-2-*d* standard, and finally the undeuterated material again to recheck the base line. The general method was checked against the combustion analysis–falling drop method with the product of run 10 (Table II). Both methods gave exactly the same value.

Cleavages of (+)-2,3-Diphenyl-3-methyl-2-pentanol.—The starting material was prepared as before[3a] from (−)-1,2-diphenyl-2-methyl-1-butanone which had $\alpha^{27}D$ − 68.91°, *l* 1 dm., neat. The alcohol employed had $\alpha^{27}D$ + 17.5° (*c*, 71 in benzene). The cleavages were carried out in sealed tubes under nitrogen, and in solvents flushed with nitrogen. The runs were made and the products isolated and analyzed by the methods described in ref. 3.

CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

Electrophilic Substitution at Saturated Carbon. X. Steric Course in Systems that Contain an Internal Electrophile[1]

BY DONALD J. CRAM, LYLE K. GASTON[2] AND HERB. JÄGER

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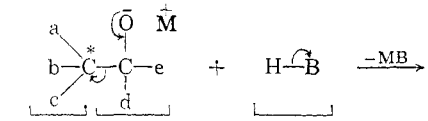
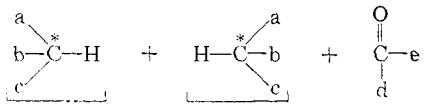
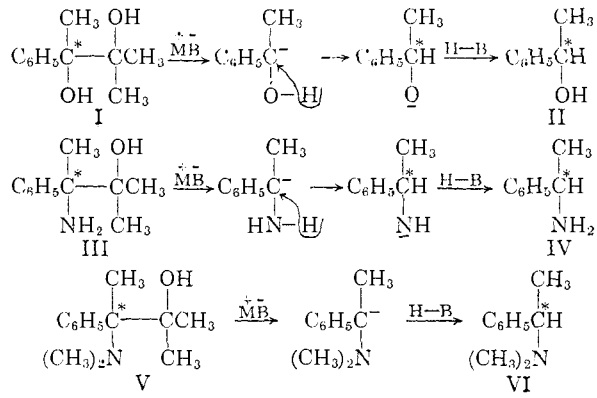
Three systems have been prepared in an optically pure state, and submitted to the base-catalyzed cleavage reaction in which acetone served as leaving group, and proton-donors as electrophiles in an S_Ei reaction. Thus (+)-2-methyl-3-phenyl-2,3-butanediol produced optically active 1-phenylethanol; (−)-3-amino-2-methyl-3-phenyl-2-butanol gave active 1-phenylethylamine, and (−)-3-dimethylamino-2-methyl-3-phenyl-2-butanol gave active 1-dimethylaminophenylethane. The configurations of starting materials and products were established by independent means. The first two systems produced carbanions which contained an internal proton source (hydroxyl or amino group), whereas the last did not. The steric courses of the reactions varied between extremes of 98% net retention and 34% net inversion, depending on the availability of internal protons, the solvent, the cation of the base and the temperature. The results are interpreted by a mechanistic scheme in which intermediate carbanions in asymmetric environments partition between products of retained and inverted configurations, depending on the detailed structure of the solvent-leaving group envelope.

The use of reactions of the type formulated for the study of the steric course and mechanism of electrophilic substitution at saturated carbon has been described in the first set of papers of this series.[3] The steric course of the reaction was found to vary between extremes of 99% net retention to 100% racemization to 64% net inversion as solvent, substituents, cations of the base and temperature were changed. In all systems, a, b and c were alkyl, phenyl, hydrogen or methoxyl groups,





none of which could act as a proton source for the carbanion intermediate involved in the reaction. This paper involves a study of the cleavage of the three systems formulated, two of which (I and III) are capable of producing carbanions which could in principle go to product by internal proton transfer. The third (V) contains no internal proton source, and provides a basis of comparison for the other two.



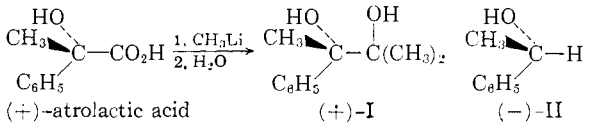
Configurations of Starting Materials and Products.—Conclusions drawn about the steric course of these cleavage reactions are directly dependent on prior knowledge of the relative configurations and maximum rotations of starting materials and products. The absolute configurations and maximum rotations of atrolactic acid and 1-phenylethanol have been previously established and reviewed.[4] Since (+)-I was prepared directly from 97% optically pure (+)-atrolactic acid without involvement of the asymmetric center, the relative configurations and maximum rotations of I and II become known.

(1) This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this Fund.

(2) Dow Chemical predoctoral fellow, 1956–1957.

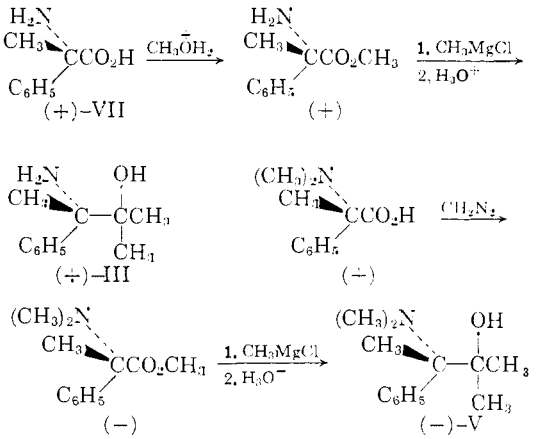
(3) (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 5740 (1959); (b) D. J. Cram, A. Langemann and F. Hauck, *ibid.*, **81**, 5750 (1959); (c) D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959); (d) D. J. Cram, A. Langemann, W. Lwowski and K. R. Kopecky, *ibid.*, **81**, 5760 (1959); (e) D. J. Cram, F. Hauck, K. R. Kopecky and W. D. Nielsen, *ibid.*, **81**, 5767 (1959); (f) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, *ibid.*, **81**, 5774 (1959).

(4) D. J. Cram and K. R. Kopecky, *ibid.*, **81**, 2748 (1959).



(+)-atrolactic acid (+)-I (−)-II

The configuration of optically pure amine IV is known,[5] and the configuration and rotation of VI is established by its preparation from IV. Both amino alcohols III and V were prepared from optically pure 2-amino-2-phenylpropanoic acid (VII) by the sequence shown. Although the absolute configuration of acid VII has not been established by chemical interconversions, use of Freudenberg's displacement rule[6] as applied to the series of compounds related to acid VII and to atrolactic acid strongly supports the configurational assignment made in Table I. Many of the compounds have been interrelated by syntheses, as is evident from the formulations. The fact that Freudenberg's displacement rule cannot be applied with



(+)-VII (+) (+)-III (−) (−)-V

complete internal consistency probably reflects the conformational complexity of some of the compounds involved, as well as the fact that the rotations were taken under a variety of conditions (some in solution, some homogeneous). The rotational correlations of Table I taken in conjunction with the correlation between the results of cleavage (see Discussion) of V and of 3-methoxy-2,3-diphenyl-2-butanol[3c] leave little doubt about the configurations of III and V.

Results

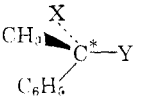
Table II summarizes the results of the cleavage reactions. All three cleavage products, 1-phenylethanol (II), 1-phenylethylamine (IV) and 1-dimethylaminophenylethane (VI) are possibly subject to ordinary base-catalyzed racemization which involves repeated proton abstraction from the asymmetric carbon atom. Besides this reaction path, II and IV might also racemize by base-catalyzed reversible oxidation–reduction with acetone (leaving group) or its condensation products as oxidant. Control runs (see Experimental) demonstrated that except for runs 2 and 4, product once formed racemized a maximum of 3%. When submitted to the conditions of runs 2 and 4, optically active 1-phenylethanol was essentially completely racemized. When the conditions of run 2 were employed (*t*-butyl alcohol–potassium *t*-butoxide, 141° for 5 hours) except that the solution was 0.22 molar in hydrazine, the product was 50% optically pure (run 3). A control run established that no racemization of the product once formed had occurred. This experiment strongly suggests that the hydrazine as a strong reducing agent reacted with any carbonyl compound in the mixture and eliminated the reversible oxidation–reduction–racemization reaction.

Attempts to find a temperature at which glycol I could be cleaved in dimethyl sulfoxide without subsequent racemization of the product failed. Unlike all other systems, glycol I required a temperature of 100° before reaction occurred at a reasonable rate (run 2). Thus amino alcohols III and V reacted at 25°, as did 2,3-dimethyl-3-phenyl-2-pentanol, 2,3-diphenyl-3-methyl-2-pentanol and 1,2-diphenyl-3-methoxy-2-butanol[3f] in this solvent–base system. The unique feature of the less reactive system is the presence of a hydroxyl group beta to the alkoxide group which initiates reaction. The ability of this group to hydrogen-bond with the negatively charged oxygen probably stabilizes the alkoxide, and thus at least partially cancels the strongly activating effect of dimethyl sulfoxide as solvent.[3f]

In runs 1, 3 and 5–8, the steric course of the reaction of glycol I was examined successfully in *t*-butyl alcohol and ethylene glycol, solvents which with

TABLE I

CONFIGURATION 2-AMINO-2-PHENYLPROPANOIC ACID AND RELATED COMPOUNDS THROUGH USE OF FREUDENBERG'S DISPLACEMENT RULE



X	Y	CO_2H	CO_2CH_3	$C(OH)(CH_3)_2$	H
OH	M_D	+ 62°[a]	+ 56°[b]	+ 38°[c,d]	− 54°[d,e]
	ΔM_D	0	− 6	− 24°	−116°
NH_2	M_D	+116°[f]	+ 13°[c,d]	+ 63°[c,d]	− 46°[c,g]
	ΔM_D	0	−103	− 53°	−162°
OCH_3	M_D	+ 94°[c,h]	−100°[i]	.....	−174°[i]
	ΔM_D	0	−192°	.....	−268°
$N(CH_3)_2$	M_D	+179°[c,d]	− 78°[c,d]	− 77°[c,d]	− 95°[c,d]
	ΔM_D	0	−257°	−256°	−274°

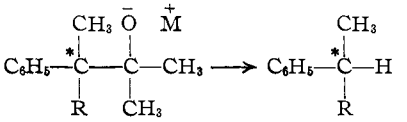
[a] Ref. 4, $[\alpha]^{28}D$ + 37.3° (ethanol, *c* 3.4). [b] A. McKenzie and A. Ritchie, *Ber.*, **70B**, 23 (1937); $[\alpha]^{18}D$ + 31.1° (neat); this value is calculated from data of this reference and that of footnote *i*. [c] See Experimental. [d] In cases where the rotation was taken neat, and no density determined, the *density is presumed to be unity;* this procedure is valid only for use in connection with Freudenberg's displacement rule. [e] E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939), and ref. 3c; $\alpha^{25}D$ − 44.2° (neat, *l* 1 dm.). [f] Ref. 13; $[\alpha]^{18}D$ +70° (*c* 2, H_2O). [g] Ref. 5; $\alpha^{26}D$ + 37.9° (neat, *l* 1 dm.). [h] Ref. 4, $\alpha^{24}D$ − 52.2° (neat, *l* 1 dm.). [i] K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933); $[\alpha]^{20}_{5780}$ + 51.6° (neat); unfortunately, the rotation is not available at λ = D. Any error introduced by use of $[\alpha]_{5780}$ instead of $[\alpha]D$ should be small since the methyl ester of atrolactic acid itself changes only from + 32.1 to + 37.4° as λ is changed from 5791 to 5461 Å. [j] Ref. 3c, and K. Mislow, *J. Am. Chem. Soc.*, **73**, 4043 (1951); with $\alpha^{25}D$ from ref. 3c and $\alpha^{25}D$ from Mislow, $[\alpha]^{25}D$ 129° (neat).

(5) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939).

(6) W. F. Klyne, "Progress in Stereochemistry," Butterworths Scientific Publications, London, England, 1954, p. 206.

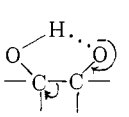
TABLE II

CLEAVAGE OF 0.2 *M* SOLUTIONS OF GLYCOL AND AMINO ALCOHOLS IN 0.2 *M* SOLUTIONS OF BASE



Run	R	Solvent	Base	T., °C.	Time, hr.	Yld., %	$n^{25}D$ [a]	Product: $\alpha^{22-26}D$ [b]	Product: Opt. purity [c]	Predom. steric course [d]
1	OH	$(CH_3)_3COH$	$(CH_3)_3COK$	130	4	1	1.5221	+23.9°	54	Ret.
2	OH	$(CH_3)_3COH$	$(CH_3)_3COK$	141	5	11	1.5239	+ 3.8	9	Ret.[e]
3	OH	$(CH_3)_3COH$[f]	$(CH_3)_3COK$	141	5	3	1.5232	+22.1	50	Ret.
4	OH	$(CH_3)_2SO$[g]	$(CH_3)_3COK$	100	2.5	50	1.5244	0.00	0	Rac.[h]
5	OH	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	210	64	10	1.5215	+18.1	41	Ret.
6	OH	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	245	32	16	1.5220	+15.0	34	Ret.
7	OH	$HOCH_2CH_2OH$	$HOCH_2CH_2OLi$	210	64	3	1.5234	+12.2	28	Ret.
8	OH	$HOCH_2CH_2OH$	$HOCH_2CH_2OLi$	245	40	13	1.5244	+10.2	23	Ret.
9	NH_2	$(CH_3)_3COH$	$(CH_3)_3COK$	142	3.5	51	1.5241	− 5.65	15	Inv.
10	NH_2	$(CH_3)_3COH$	$(CH_3)_3COK$	167	2.3	78	1.5236	+ 0.68	2	Ret.
11	NH_2	$(CH_3)_3COH$	$(CH_3)_3COK$	193	0.4	86	1.5240	+ 6.04	16	Ret.
12	NH_2	$(CH_3)_3COH$	$(CH_3)_3COLi$	193	1800	57	1.5242	+21.46	57	Ret.
13	NH_2	$(CH_3)_2SO$	$(CH_3)_3COK$	25	66	89	1.5206	+ 0.16	0	Rac.
14	$N(CH_3)_2$	$(CH_3)_3COH$	$(CH_3)_3COK$	110	20	44	1.5005	−62.14	98	Ret.
15	$N(CH_3)_2$	$(CH_3)_3COH$	$(CH_3)_3COH$	142	30	39	1.5004	−59.24	93	Ret.
16	$N(CH_3)_2$	$(CH_3)_3COH$	$(CH_3)_4NOH$	110	20	12	1.5013	− 3.57	6	Ret.
17	$N(CH_3)_2$	$(CH_3)_2SO$	$(CH_3)_3COK$	25	60	95	1.4997	− 0.58	1	Ret.
18	$N(CH_3)_2$	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	193	20	56	1.5016	+21.40	34	Inv.

[a] For pure 1-phenylethanol, $n^{25}D$ 1.5251; 1-phenylethylamine, $n^{25}D$ 1.5242; 1-dimethylaminophenylethane, $n^{25}D$ 1.5009. [b] Neat, and corrected to l = 1 dm.; in some cases l = 0.5 and 0.25 dm. for the actual observed rotation. [c] For optically pure 1-phenylethanol, $\alpha^{25}D$ ±44.2° (l 1 dm., neat); 1-phenylethylamine, $\alpha^{26}D$ ±37.66° (l 1 dm., neat); 1-dimethylaminophenylethane, $\alpha^{25}D$ ±63.25° (l 1 dm., neat). [d] Control runs established that except in runs 2 and 4, the product once formed could have racemized less than 3% (see Experimental). [e] Control run showed over 99% racemization under experimental conditions. [f] Solution was 0.22 *M* in hydrazine. [g] Solution was 0.20 *M* in *t*-butyl alcohol. [h] Control run showed 100% racemization under reaction conditions; reaction failed to occur under more mild conditions. The base, $(CH_3)_4NOH \cdot 2H_2O \cdot 0.30(CH_3)_3N$, at an initial concentration of 0.58 *M* was used; final concentration was much lower due to the reaction of the quaternary ammonium with hydroxide ion.



ordinary systems gave high retention and inversion, respectively. Runs 9–13 involved amino-alcohol III as starting material and *t*-butyl alcohol and dimethyl sulfoxide as solvent. With other systems,[3f] this latter solvent gave racemization as the steric course for the reaction. Attempts to apply ethylene glycol as solvent to reactions of amino-alcohol III gave product in which the primary amino group had been alkylated by the solvent. In runs 14 to 18, the steric course of cleavage of *t*-amino alcohol V was successfully examined in all three solvents.

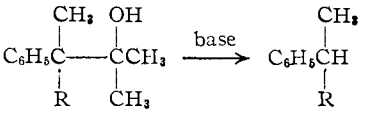
Discussion

Comparison of Steric Path for Reaction of *t*-Amino-alcohol V with that of Other Systems without Internal Proton Donors.—The steric course of electrophilic substitution that accompanies cleavage of the *t*-amino alcohol V appears to be dependent on the character of the solvent in a way very similar to that observed for a number of systems studied previously.[3] These systems gave as products either 2-phenylbutane or 1-methoxyphenylethane. Acetone, acetophenone, methyl ethyl ketone or benzophenone served as leaving groups. Table III contains a sample comparison between the behavior of *t*-amino alcohol V and 2,3-dimethyl-3-phenyl-2-pentanol. In *t*-butyl alcohol both systems give high net retention, in dimethyl sulfoxide almost complete racemization, and in ethylene glycol a moderate amount of net inversion. These results leave little doubt about either the correctness of the configurational assignment to V (and therefore to III), or about the question of whether V cleaves by mechanistic paths[3f] similar to those utilized by systems previously studied. As would be expected, the greater steric compression in V as compared to 2,3-dimethyl-3-phenyl-2-pentanol is reflected in the lower temperature required for reactions of the former compound. Correlations of this type have been made previously.[3a,3d]

Other similarities between the behavior of V and other systems not containing nitrogen are evident in the data. In run 16, substitution of quaternary ammonium hydroxide for the potassium *t*-butoxide used in run 14 (*t*-butyl alcohol was solvent) reduced the stereospecificity from 98% to 6% net retention. A similar effect was noted in the cleavage of 2,3-diphenyl-3-methyl-2-pentanol in *t*-butyl alcohol (runs 183 and 184).[3f] Substitution of benzyltrimethylammonium hydroxide for potassium *t*-butoxide changed the steric course from 84% retention to 1% inversion. In run 15, lithium *t*-butoxide was substituted for the potassium *t*-butoxide used in run 14, both runs being conducted in *t*-butyl alcohol. The result was a reduction of the stereospecificity from 98 to 93% net retention. An inverse change in steric result was previously

TABLE III

COMPARISON OF DEPENDENCIES ON SOLVENT OF STERIC COURSE OF CLEAVAGE OF 3-DIMETHYLAMINO-2-METHYL-3-PHENYL-2-BUTANOL AND 2,3-DIMETHYL-3-PHENYL-2-PENTANOL

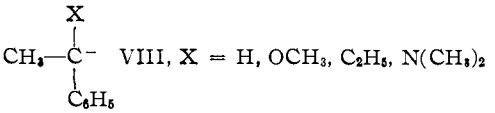


Run	Ref.	R	Solvent	Base	T., °C.	Net steric course
14	..[a]	$N(CH_3)_2$	$(CH_3)_3COH$	$(CH_3)_3COK$	110	98% Ret.
35	3b	C_2H_5	$(CH_3)_3COH$	$(CH_3)_3COK$	150	90% Ret.
17	..[a]	$N(CH_3)_2$	$(CH_3)_2SO$	$(CH_3)_3COK$	25	1% Ret.
163	3f	C_2H_5	$(CH_3)_2SO$	$(CH_3)_3COK$	25	100% Rac.
18	..[a]	$N(CH_3)_2$	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	193	34% Inv.
38	3b	C_2H_5	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	210	52% Inv.

[a] Table II of this paper.

observed to accompany this same change in reaction conditions for cleavage of 3,4-dimethyl-4-phenyl-3-hexanol (see runs 122 and 123).[3e]

Four systems[3,7] have now been examined in which one group attached to the seat of electrophilic substitution has been changed. The stereochemical fate of the carbanion intermediate VII envisioned[3f] for these reactions seems to be remarkably insensitive to the character of this group. Although the electronic properties of these substituents do not differ from one another in a major way,

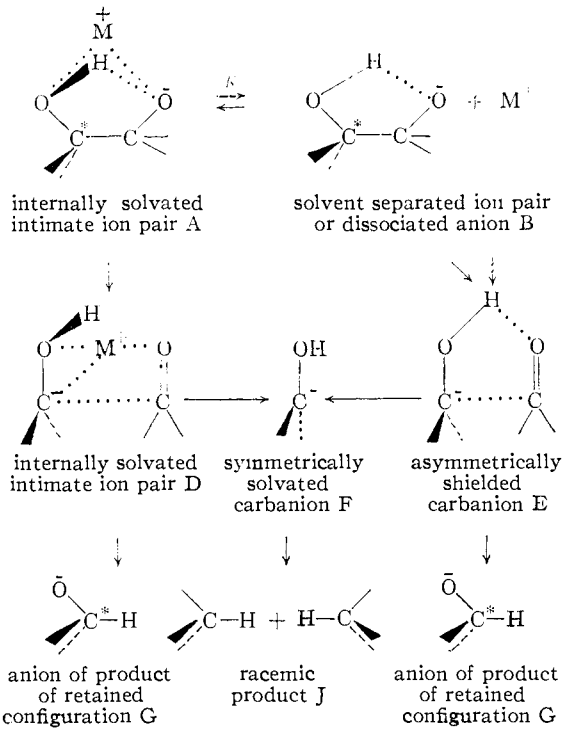


their steric requirements cover a very large range. This fact suggests that the product-controlling transition states occur before proton donors become involved at the center undergoing substitution. This conclusion supports the carbanion mechanisms developed in this series of papers.

Steric Path for Reaction of Systems that Contain Internal Proton Donors.—As expected, attachment of a proton-donating group to the seat of electrophilic substitution has a pronounced effect on the steric course of the reaction in all solvents except dimethyl sulfoxide. Mechanistic schemes similar in general outline to those developed earlier but modified in detail readily account for the observed effects.

Unlike systems examined earlier, glycol I gives net retention in both *t*-butyl alcohol and ethylene glycol as solvent. In both solvents, a lower temperature favored higher retention, and had the reactions in the two solvents been carried out at the same temperature it is probable that ethylene glycol would have provided product of as highly retained a configuration as did *t*-butyl alcohol (50% net retention).[8] In Chart I, cleavage of either the internally solvated intimate ion pair A or the more dissociated anion B provide mechanistic routes to product of retained configuration. In *t*-butyl alcohol, a relatively non-dissociating solvent, processes A → D → G and A → D → F → J account for the steric result. In ethylene glycol, a more

CHART I



dissociating solvent, processes B → E → G and B → E → F → J explain the facts. In this scheme, both intermediates D and E are predisposed to go to product of retained configuration (even if the carbanion becoms flat) because the conformation of the hydroxyl group places the proton nearer the side of, rather than the side remote from, the leaving group. To the extent that conformational equilibration of the hydroxyl group occurs, and the carbanion passes into a symmetrical environment, racemization is observed. Possibly much of the racemic product J arose by protonation of F by solvent rather than by the hydroxyl group of the benzyl anion.

The observation that lower retention accompanied a change of base from potassium to lithium ethylene glycoxide (compare runs 5 and 6 with 7 and 8, respectively) demonstrates that even in ethylene glycol, the reacting species is not entirely dissociated anion. With the lithium alkoxide, probably some product arose by cleavage of A, and

(7) D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2178 (1961).

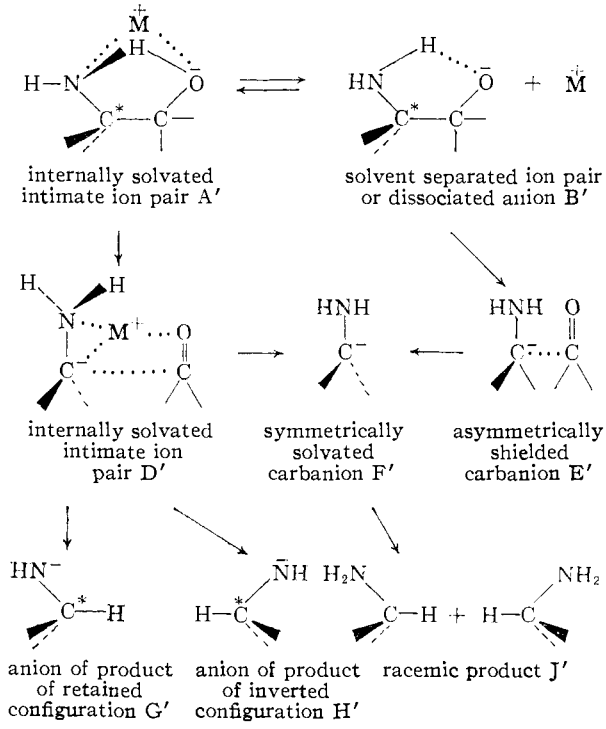
(8) With conventional systems, low temperature favored higher retention in *t*-butyl alcohol, and higher inversion in ethylene glycol or diethylene glycol (ref. 3c).

intermediate D partitioned more favorably to give F than did intermediate E.

Comparison of the results of runs 9–12 with those of runs 1–3 indicates that important differences exist between an amino and a hydroxyl group as an internal proton source. Cleavage of amino alcohol III in *t*-butyl alcohol with potassium *t*-butoxide as base gave results that varied between 16% net retention at 193° (run 11) and 15% net inversion at 142° (run 9). When lithium *t*-butoxide was substituted for potassium *t*-butoxide (193°), net retention increased to 57% (run 12). With glycol I, only net retention was observed in *t*-butyl alcohol.

Chart II provides an explanation for these results as follows. In *t*-butyl alcohol, a non-dissociating solvent, A′ is presumed to be the species that cleaves. The internally solvated intimate ion pair produced (D′) is envisioned as partitioning directly between product of retained and inverted configuration (G′ and H′, respectively), and between a symmetrically solvated carbanion (F′) which gives racemic product J′. In this scheme, G′ and H′ arise only by internal proton transfer from nitrogen to carbon, whereas formation of J might also involve proton transfer from solvent. *Internal protons are available on both the side of, and the side remote from, the leaving group in intermediate D′ of Chart II.* Which one is utilized would be

CHART II



expected to be highly sensitive to subtle changes in conformation, which would vary both with temperature and the character of the metal cation. The fact that the net steric direction of the reaction can be altered simply by a change in temperature is strong evidence that some of the racemic material arises through mutual cancellation of two opposing stereospecific processes such as D′ → G′ and D′ → H′.[9]

When cleaved in dimethyl sulfoxide as solvent, amino alcohol III gave completely racemic material (run 13). Dimethyl sulfoxide, although polar enough to be a good dissociating solvent, is itself not a proton donor. This result is interpreted in terms of sequence B′ → E′ → F′ → J′ of Chart II. Possibly an internal proton source was not used prior to step F′ → J′ because of the unusual affinity of the sulfoxide group for hydrogen bonds. The low acidity of the amino group, particularly in dimethyl sulfoxide, might increase the life time of the carbanion to allow it to pass into a symmetrical environment. This same steric result was observed for the cleavage of several other systems in dimethyl sulfoxide,[3f] although none of these involved potential internal proton sources.

Experimental

Racemic and (+)-2-Methyl-3-phenyl-2,3-butanediol (I).—From 360 g. of atrolactic acid was obtained 33.2 g. of optically pure (+)-atrolactic acid,[10] m.p. 114–116° $[\alpha]^{23}D$ +37.9° (*c* 3.6, ethanol), and 66.2 g. of 97% pure acid, m.p. 113–115°, $[\alpha]^{25}D$ + 36.9° (*c* 3.3, ethanol).

A solution of methyllithium in 2700 ml. of ether was prepared from 24 g. of lithium (3.45 g. atoms) and 240 g. of methyl iodide. The resulting mixture was filtered under nitrogen, and to the stirred filtrate at 0° was cautiously added 27 g. (0.16 mole) of racemic atrolactic acid dissolved in 500 ml. of dry ether. The resulting mixture was refluxed for 2 hours, and cautiously mixed with water. The ether layer was washed with water, dried and evaporated. The resulting oil only partially crystallized, and so it was again treated with a large excess of methyllithium in ether, this time at −15°. After this second treatment, the oil crystallized completely, and the solid was recrystallized from ether–pentane twice to give racemic diol, wt. 16.7 g., m.p. 83–84°, lit.[11] m.p. 83.5–84.5°.

Optically active diol was prepared by the same procedure. From 30 g. of 97% optically pure (+)-atrolactic acid (see above) was obtained 21.4 g. of (+)-diol, m.p. 60.6–61.6°, $[\alpha]^{25}D$ + 20.34° (*c* 3.2, ethanol).

Repeated recrystallization of the above diol resulted in very slow enrichment of the first crops in racemic material. These experiments indicate that the above diol is 95–96% optically pure.

Resolution of 2-Formylamino-2-phenylpropanoic Acid.—Racemic starting material was prepared by formylation of 2-amino-2-phenylpropanoic acid as follows.[12] A solution of amino acid in 98% formic acid (100 g. in 228 ml.) was heated at 60° for 15 minutes. Acetic anhydride, 175 ml., was added dropwise at such a rate as to maintain a temperature of 60–62°.[13] Water, 36 ml., was then added cautiously. The resulting solution was cooled, the solid collected, washed with water and dried. The desired formamido acid amounted to 97 g. (83%), m.p. 176–177° (lit.[14] 178–179°). This material was resolved[14] through its quinine and cinchonine salts to give a 23% yield of (+)-isomer, $[\alpha]^{25}D$ +90.4° (*c* 3.3, ethanol) [lit.[14] $[\alpha]^{16}D$ +91.9° (*c* 3.2, ethanol)], m.p. 193–194° dec., and an 18% yield of (−)-isomer, $[\alpha]^{26}D$ −89.3° (*c* 3.4, ethanol) [lit.[14] $[\alpha]^{17}D$ −91.6° (*c* 3.7, ethanol)], m.p, 193–194° dec.

(+)- and (−)-2-Amino-2-phenylpropanoic Acid.—Hydrolysis of the two formamido acids with aqueous hydro-

(9) In an earlier study the cleavage of 2,3-diphenyl-3-methyl-2-pentanol in an appropriate mixture of dioxane–diethylene glycol was found to change steric direction as the temperature was varied. However, in that system both A and B were presumed to cleave, the former to give net retention and the latter net inversion [see D. J. Cram and W. D. Nielsen, *J. Am. Chem. Soc.*, **83**, 2174 (1961)].

(10) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910).

(11) R. Roger, *ibid.*, **127**, 518 (1925).

(12) R. E. Sleiger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 88.

(13) V. du Vigneaud, R. Dorfmann and H. S. Loring, *J. Biol. Chem.*, **98**, 577 (1932).

(14) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **101**, 390 (1912).

bromic acid[14] gave a 64% yield of (+)-isomer, $[\alpha]^{26}D$ + 70.3° (*c* 2.0, water), m.p. 295° dec.; lit.[14] $[\alpha]^{18}D$ +70.0° (*c* 2.0, water), m.p. 295° dec. An 80% yield of (−)-isomer was obtained, $[\alpha]^{26}D$ −72.0° (*c* 2.0, water), lit.[14] $[\alpha]^{18}D$ − 69.5° (*c* 1.8, water).

Racemic and (+)-Ethyl 2-Amino-2-phenylpropionate.—Racemic amino acid, 49.5 g., was suspended in 400 ml. of absolute ethanol. The solvent was saturated with dry hydrogen chloride, and the mixture refluxed for 1 hour. Benzene, 100 ml., was added, and the solution was slowly distilled until a temperature of 78° was reached. The solution was cooled, and shaken with a mixture of ether and cold saturated aqueous sodium bicarbonate solution. The aqueous layer was brought to a *p*H of 13 with sodium hydroxide, and again extracted with ether. The combined ether extracts were dried, evaporated, and the residual oil was distilled, b.p. 144–146° (22 mm.), wt. 38.9 g. (67%), $n^{25}D$ 1.5092.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.31; H, 7.97.

Optically pure (+)-amino acid was esterified by the same method in 57% yield, $n^{25}D$ 1.5089, $\alpha^{24}D$ +12.14° (neat, *l* 1 dm.).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.10; H, 7.99.

(−)-Methyl 2-Amino-2-phenylpropionate.—A suspension of 1.1 g. of optically pure (−)-amino acid was suspended in 12 ml. of dry methanol, and the mixture was saturated with dry hydrogen chloride at 60°. After refluxing for 12 hours, the reaction mixture was poured into 100 ml. of 4 *N* potassium hydroxide solution at 0°, and the resulting solution was extracted with ether. The ether was dried, evaporated, and the resulting oil was twice flash distilled (bath temperature 160°, pressure 18 mm.) to give 0.52 g. of product, $n^{25}D$ 1.5204, $\alpha^{26}D$ −7.10° (neat, *l* 1 dm.).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 66.92; H, 7.24.

Racemic, (+)- and (−)-3-Amino-2-methyl-3-phenyl-2-butanol (III).—Ethyl 2-aminopropionate, 10.0 g., was added to a Grignard reagent prepared from 31.6 g. of methyl iodide, 5.15 g. of magnesium and 200 ml. of ether. After addition was complete, the solution was refluxed for 14 hours, and then a saturated aqueous solution of ammonium chloride was added until the complex dissolved. The layers were separated, 5 g. of potassium hydroxide was added to the aqueous layer, and the aqueous solution was extracted with ether. The combined ether layers were washed with aqueous sodium bicarbonate solution, dried and evaporated. The resulting oil was crystallized and recrystallized from pentane to give 6.0 g. (65%) of racemic III, m.p. 52–53.5°.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.99; H, 9.58.

With an identical procedure, (−)-III was prepared from (−)-methyl ester in 36% yield, b.p. 95° (1.5 mm.), $n^{25}D$ 1.5378, $\alpha^{24}D$ + 34.94° (*l* 1 dm., neat).

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.48; H, 9.96.

Similarly, (+)-III was made from (+)-methyl ester in 35% yield, b.p. 82° (0.7 mm.), $n^{25}D$ 1.5372, $\alpha^{25}D$ − 35.01° (neat, *l* 1 dm.).

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.80; H, 9.28.

Racemic and (+)-2-Dimethylamino-2-phenylpropanoic Acid.—Racemic 2-aminopropanoic acid (10.0 g.) was added to 28 g. of formic acid and 12 ml. of 36% formalin. The resulting solution was heated at 100° for 5 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in absolute ethanol. Solvent was evaporated to the cloud point, and 8.6 g. (73%) of *t*-amino acid separated, m.p. 232–233° dec.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.16; H, 7.59.

With the same procedure, (+)-2-aminopropanoic acid was converted to (+)-*t*-amino acids, m.p. 252° dec., $[\alpha]^{26}D$ + 93.0° (*c* 2.0, water).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.50; H, 7.86.

Racemic and (+)-Methyl 2-Dimethylamino-2-phenylpropanoate.—Solid racemic 2-dimethylamino-2-phenylpropanoic acid (9.73 g.) was added to an ethereal solution of distilled diazomethane prepared from 61.8 g. of nitrosomethylurea. Excess diazomethane was decomposed with formic acid. The ether was dried, evaporated and the resulting material was distilled, b.p. 104–107° (4 mm.), wt. 6.8 g. (65%), $n^{25}D$ 1.5098.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.78; H, 8.34.

By the same procedure, from 3.3 g. of optically pure (+)-amino acid was obtained 2.67 g. (75%) of methyl ester, b.p. 106–107° (6 mm.), $n^{25}D$ 1.5099, $\alpha^{25}D$ − 37.55° (*l* dm., neat).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 69.54; H, 8.27. Found: C, 69.73; H, 8.38.

Racemic and (−)-3-Dimethylamino-2-methyl-3-phenyl-2-butanol (V).—A Grignard reagent was prepared from 1.17 g. of magnesium and excess methyl chloride in 150 ml. of dry ether. The excess halide was removed by distilling 50 ml. of ether. The resulting solution was cooled to −40°, and 4.0 g. of racemic methyl 2-dimethylamino-2-phenylpropanoate dissolved in 25 ml. of dry ether was added. The solution was stirred for 1 hour at −40° and then for 14 hours at 25°. The reaction mixture was cooled to 0°, and an aqueous saturated solution of ammonium chloride was added. This mixture was added to alkaline (NaOH) ice water and extracted exhaustively with ether. The extract was dried, evaporated, and the residue was distilled to give 2.1 g. (53%) of racemic V, b.p. 94–96° (1.5 mm.), $n^{25}D$ 1.5271.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21. Found: C, 75.23; H, 10.23.

From 3.9 g. of optically pure (−)-amino ester was prepared by the above procedure an 87% yield of (−)-V, m.p. 40.6–41.6° (pentane–ether), $[\alpha]^{23}D$ −37.4° (*c* 3.0, $CHCl_3$).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21. Found: C, 75.40; H, 9.94.

Racemic and (+)-1-Dimethylamino-1-phenylethane (VI).—A mixture of 10.0 g. of 1-phenylethylamine, 40 ml. of formic acid and 17 ml. of 37% formalin was refluxed for 2 hours, poured into water and made alkaline with potassium hydroxide. The mixture was extracted with ether, the ether extract was dried, evaporated, and the residue was chromatographed on 70 g. of neutral, activity I alumina[15] with pentane as eluant. The first liter of eluent was evaporated, and the residue distilled, b.p. 183°, to give 5.25 (43%) of VI, $n^{25}D$ 1.5007.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.40; H, 10.26.

Optically pure (+)-1-phenylethylamine was prepared, $\alpha^{26}D$ +37.7° (*l* 1 dm., neat), $n^{25}D$ 1.5242, b.p. 185–187°; lit.[16] $\alpha^{28}D$ +37.9° (*l* 1 dm., neat). This material was methylated by the above procedure to give in 57% yield (+)-VI, $n^{25}D$ 1.5009, $\alpha^{25}D$ +63.65° (*l* 1 dm., neat).

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.58; H, 10.35.

General Notes on the Cleavage Reactions.—Ethylene glycol was purified by reaction with sodium under an atmosphere of nitrogen. After the mixture had refluxed for several hours, the solvent was distilled at 20 mm. under nitrogen. The distillate was passed through a column of Linde Molecular Sieves No. 4A, and finally distilled from fresh Molecular Sieves under nitrogen. The *t*-butyl alcohol was purified by reflux and distillation under nitrogen from potassium metal. Any remaining oxygen in the solvent was removed prior to use by alternately freezing it under vacuum and melting it under oxygen-free nitrogen. Dimethyl sulfoxide was purified by careful distillation at 10 mm. of pressure. The distillate was treated with Molecular Sieves No. 4A for 2 days, and distilled at 2 mm. from fresh Molecular Sieves under a nitrogen atmosphere. Prior to use, the solvent was flushed with oxygen-free nitrogen. Tetramethylammonium hydroxide, 10% aqueous solution, was dried by lyophilization. The solid obtained was powdered and heated to 50° for 3 days at 0.5 mm. Since some of the hydrated forms were almost liquids, the material had to be powdered frequently. When dried to

(14) H. Brockmann and H. Schodder, *Ber.*, **74B**, 73 (1941).

(15) H. W. Ingersoll in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

TABLE IV

CONTROL RUNS FOR CLEAVAGE REACTIONS

Run nos. reactions controlled[a]	Substrate	Solvent	Base	Time, hr.	T, °C.	% recov.	α^{24-26} [b]	% rac.
9, 10, 14, 15, 16	(+)-IV$_1$	$(CH_3)_3COH$	$(CH_3)_3COK$	2.33	167	84	+36.09°	3
11 + 12[j]	(+)-IV$_1$	$(CH_3)_3COH$	$(CH_3)_3COK$	0.4	193	71	+36.06	2
13	(+)-IV$_1$	$(CH_3)_2SO$	$(CH_3)_3COK$	25	61	62	+36.4	0.5
18	(+)-VI$_1$	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	20	193	70	+63.43	0.2
17	(+)-VI$_1$	$(CH_3)_2SO$	$(CH_3)_3COK$	61	25	84	+61.4	3
1 + 3	(+)-II$_1$	$(CH_3)_3COH_1$	$(CH_3)_3COK$	5	141	65	+ 7.64	0
2	(+)-II$_1$	$(CH_3)_3COH$	$(CH_3)_3COK$	5	141	25	+ 0.04	99
4	(+)-II$_1$	$(CH_3)_2SO$	$(CH_3)_3COK$	2.5	100	75	+ 0.01	100
5,7	(+)-II$_1$	$HOCH_2CH_2OH$	$HOCH_2CH_2OK$	64	210	65	+ 7.80	0
6, 8	(+)-II'	$HOCH_1CH_2OH$	$HOCH_2CH_2OK$	32	245	65	+7.70	0

[a] See Table II. [b] l = 1 dm., neat. [c] $\alpha^{25}D$ +37.19° (l 1 dm., neat). [d] Unpublished work has shown that lithium t-butoxide racemizes 1-methoxy-1-phenylethane one-twenty-fifth as fast as potassium t-butoxide. [e] $\alpha^{25}D$ +63.53° (l 1 dm., neat). [f] $\alpha^{25}D$ +7.45° (l 1 dm., neat). [g] Solution was 0.22 M in dry hydrazine.

constant weight, the tetramethylammonium hydroxide contained two moles of water and 0.3 mole of trimethylamine. Potassium t-butoxide was dried by sublimation at 180–200° at 0.5 mm. Potassium in small pieces was dissolved directly in *extremely efficiently* stirred ethylene glycol under nitrogen. The temperature of the liquid was never allowed to rise above 40°, or explosion occurred. Hydrazine was prepared in anhydrous form from hydrazine hydrate by slow distillation from a mixture of hydrate and sodium hydroxide.[17] Glass tubes, 19–25 mm. outer diameter, sealed under nitrogen at −80° were used for all reactions. The tubes were never filled more than half full. Heating baths of the refluxing vapor type were employed. The following solvents were useful: toluene, o-xylene, trimethylbenzene, decalin and triethylbenzene.

Sample Procedures for Cleavage Reactions: Run 18.—A solution of 0.517 g. of (−)-dimethylamino alcohol V in 12.1 ml. of 0.206 M potassium ethylene glycoxide in ethylene glycol was flushed with nitrogen and heated in a sealed tube at 193° for 20 hours. The reaction mixture was diluted to 150 ml. with water and 50 g. of potassium hydroxide was added. The resulting solution was distilled, and the first 10 ml. of distillate was extracted with three 15-ml. portions of ether. The ether was dried and slowly evaporated through a long Vigreux column. The residue was distilled at a bath temperature of 145° (100 mm.) to give 0.210 g. (56%) of VI, $n^{25}D$ 1.5016, $\alpha^{24}D$ +21.4° (l 1 dm., neat).

Run 10.—A solution of 0.207 g. of (+)-amino alcohol III, 5.6 ml. in a 0.206 M potassium t-butoxide solution, was flushed with nitrogen and heated at 167° for 2.3 hours. The reaction mixture was diluted to 150 ml. with water, and hydrochloric acid was added until the solution was pH 3–4. The solution was distilled until a temperature of 100° was reached. The solution was cooled, 50 g. of potassium hydroxide was added, and 10 ml. of the solution distilled. The distillate was extracted three times with 10 ml. of ether, the ether extracts were combined, dried and evaporated slowly through a tall Vigreux column. The residue was distilled at a bath temperature of 142° at 100 mm., wt. 0.110 g. (78%), $n^{25}D$ 1.5236, $\alpha^{26}D$ − 0.68° (l 1 dm., neat).

(17) G. Bauer, "Handbuch der präparativen anorganischen Chemie," Stuttgart, 1951, p. 360.

Run 17.—A solution of 0.352 g. of (−)-dimethylamino alcohol V and 0.194 g. of sublimed potassium t-butoxide in 8.5 ml. of dimethyl sulfoxide was flushed with nitrogen and allowed to stand at room temperature for 60 hours. The reaction mixture was poured into 100 ml. of water, and 50 g. of potassium hydroxide was added. This solution was extracted with three 50-ml. portions of pentane. The pentane solution was dried and slowly evaporated through a tall Vigreux column. The residue was distilled, bath temperature 147° (100 mm.), to give 0.162 g (64%) of VI, $n^{25}D$ 1.4997, $\alpha^{26}D$ −0.58° (l 1 dm., neat).

Run 3.—A solution of 0.901 g. of (+)-glycol I in 25 ml. of t-butyl alcohol which was 0.20 M in potassium t-butoxide and 0.22 M in dry hydrazine was heated in a sealed tube to 141° for 5 hours. The reaction mixture was diluted with 50 ml. of ether, and washed 4 times with 15-ml. portions of water. The ether solution was dried, and slowly evaporated through a long Vigreux column (vapor phase analysis of the distillate showed absence of 1-phenylethanol). To destroy starting material (which proved difficult to separate), the residue was dissolved in 50 ml. of 0.1 N HIO_4, and allowed to stand for 2 hours. The solution was extracted 4 times with 50-ml. portions of ether, the combined extracts were washed with water, dried and evaporated through a Vigreux column. The residue was chromatographed on 30 g. of activated alumina. Acetophenone and colored material were eluted with pentane–ether (6 to 1), whereas ether eluted the desired product mixed with small amounts of impurities. The ether eluate was evaporated to a small volume, and the residue was submitted to vapor phase chromatography on a polypropylene column at 170° with nitrogen as carrier gas. Appropriate control runs indicated at what point 1-phenylethanol left the column. The product was free of acetophenone, but always had a low refractive index due to contamination with a small amount of monomerized column packing (a control run showed that the index of refraction of pure 1-phenylethanol changed from $n^{25}D$ 1.5251 to 1.5238 when passed through the column). The product was collected, wt. 0.020 g., $\alpha^{25}D$ +22.1° (l 1 dm., neat), $n^{25}D$ 1.5232.

Control Runs.—All control runs were carried out under conditions identical to those used in the cleavage reactions except that in place of starting material, the solutions were 0.2 M in optically active product and 0.2 M in acetone. The results are summarized in Table IV.