reaction solvent under nitrogen, and dissolved with the aid of heat where necessary. When potassium was dissolved in diethylene glycol, the mixture had to be swirled to prevent local heating. Potassium could not be dissolved directly in ethylene glycol without explosion. Dry potassium *t*-butoxide was first prepared, added to ethylene glycol, and the *t*-butyl alcohol was distilled from the mixture along with some of the ethylene glycol. When potassium was dissolved in methanol or ethanol, the mixtures were cooled with Dry Ice to control the reactions.

The reactions carried out below or at the boiling point of the reaction medium were run in open systems under a nitrogen atmosphere. Runs made above the boiling points of the medium and at 150° or below were carried out in heavy-walled pressure bottles (100-ml. capacity). Above this temperature, heavy-walled sealed tubes were used. Wood metal-baths heated electrically were employed. The isolation procedure is illustrated as follows:

Run 37.—In 10 ml. of nitrogen-saturated monomethyl ether of ethylene glycol was dissolved 0.254 g. (6.50 mmoles) of freshly cut oil-free potassium. When solution was complete, 1.087 g. (5.64 mmoles) of (−)-2,3-dimethyl-3-phenyl-2-pentanol was added in enough additional solvent to give a total volume of 55 ml. The mixture was maintained in a bath at 202° for 24 hours under a slight nitrogen pressure acting through a spiral condenser. The mixture was cooled, diluted with 2 volumes of water, and extracted 3 times with pentane. The combined extracts were washed 3 times with water, dried, evaporated to a small volume through a two-foot Vigreux column, and the residue was adsorbed on 70 g. of activity I alumina.[12] The desired product (2-phenylbutane) was eluted with pentane, and the solvent was evaporated through a two-foot Vigreux column to an oil. This material was twice distilled through a micro-Claisen still at 40 mm. pressure to give 0.628 g. (83%) of 2-phenylbutane, $n^{25}\text{D}$ 1.4875, $\alpha^{26}\text{D}$ +3.93° (*l* 1 dm., neat). This material possessed an infrared spectrum superimposable on that of authentic 2-phenylbutane.

The product of runs 16, 18, 19, 20 and 33 also possessed infrared spectra identical to that of authentic 2-phenylbutane. From the chromatogram of the product from run 16 was eluted with ether a colorless liquid (0.316 g. from 1.0 g. of starting [(−)-IX], $\alpha^{25}\text{D}$ −7.17 (*l* 1 dm., neat)). The infrared spectrum of this material showed the presence of starting material and ketones (1650 cm.$^{-1}$ in infrared and $\lambda_{\max}$ 242 mμ in ultraviolet spectra). When treated with 2,4-dinitrophenylhydrazine in ethanol and hydrochloric acid, 30 mg. of a red derivative was isolated, m.p. 125–129°. This material was not characterized further, but seemed to be a mixture of derivatives of unsaturated ketones (infrared and ultraviolet spectra).

Optically pure starting material was isolated from runs 31, 32, 33, 38 and 49. Acetophenone, characterized as its 2,4-dinitrophenylhydrazone, was isolated from run 40.

Control Runs.—As a control on runs which involved potassium glycoxide as base and 2-phenylbutane as product, the following run was made. A 1 *M* solution of potassium diethylene glycoxide in diethylene glycol was prepared, and 50 ml. of this solution was refluxed at 244° for 24 hours with 0.300 g. of 2-phenylbutane, $n^{25}\text{D}$ 1.4878, $\alpha^{26}\text{D}$ −12.4° (*l* 1 dm., neat). Starting material (0.210 g.) was recovered in the usual way, $n^{25}\text{D}$ 1.4876, $\alpha^{25}\text{D}$ −12.4° (*l* 1 dm., neat).

As a control for those runs in which potassium *t*-butoxide was employed and 2-phenylbutane was product, the following experiment was carried out. To a 0.8 molar solution of potassium *t*-butoxide in *t*-butyl alcohol (10 ml.) was added 0.35 g. of 2-phenylbutane, $n^{25}\text{D}$ 1.4878, $\alpha^{25}\text{D}$ +16.30° (*l* 1 dm., neat). The solution was sealed in a heavy-walled tube and heated to 200° for 20 hours. Recovery of 2-phenylbutane in the usual way gave 0.25 g. of material, $n^{25}\text{D}$ 1.4878, $\alpha^{25}\text{D}$ +15.49° (*l* 1 dm., neat). In this treatment, 2-phenylbutane was 5% racemized. All of the runs of Table I that involve potassium *t*-butoxide as base were run at temperatures of 150° or less, and at lower base concentrations.

As a control for run 23, under the condition of the experiment, optically active 2-phenylbutane was found to racemize 4%. A procedure similar to those reported above was employed.

LOS ANGELES 24, CALIF.

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

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

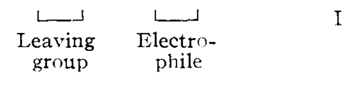
Electrophilic Substitution at Saturated Carbon. III. Effect of Solvent Composition on Reaction Path[1]

BY DONALD J. CRAM, KARL R. KOPECKY, FRED HAUCK AND ALBERT LANGEMANN

RECEIVED JANUARY 2, 1959

The stereochemistry of the base-catalyzed cleavage reactions of three tertiary alcohols (VIII, IX and XIV) and two ketones (V and XV) have been studied. In dioxane with about 5% diethylene or ethylene glycol as a proton source (electrophile), the three alcohols cleave to give *electrophilic substitution at saturated carbon which occurs with from 69 to 95% predominating retention of configuration. In diethylene glycol, these alcohols cleave with from 41 to 58% predominating inversion.* In all three systems, as the amount of glycol in dioxane is increased, the steric course undergoes a smooth transition from predominant retention to predominant inversion of configuration. In cleavages of the three tertiary alcohols in dioxane with 1% *t*-butyl alcohol as the proton source, electrophilic substitution occurs with from 84 to 96% predominating retention of configuration. Ketones V and XV cleave in dioxane with 1% *t*-butyl alcohol as proton source with 74 and 61% predominating retention, respectively, and in diethylene glycol with 38 and 17% predominating inversion, respectively. The stereospecificity of the reactions of XIV in dioxane and of VIII in diethylene glycol were found to decrease with increasing temperature. In the intermediate solvent, methanol, alcohol IX gave product with 25% predominating inversion at 180°, and with 9% predominating inversion at 210°.

The previous papers[2] in this series report the results of a survey of cleavage reactions and of solvent–electrophile systems suitable for determining the stereochemistry and mechanism of electrophilic substitution at saturated carbon. Eleven compounds which correspond to the general structure formulated (the leaving group, C–Y, was varied) were found to cleave to give 2-phenylbutane (I). The steric courses of the reactions were found to correlate with the dielectric constants and with the concentration of proton donors in the medium.



$$\mathrm{C_2H_6\overset{*}{C}(CH_3)(C_6H_5)-C-\bar{Y}} + \mathrm{H-B} \longrightarrow \mathrm{C_2H_5\overset{*}{C}(CH_3)(C_6H_5)-H} + \mathrm{C{=}Y} + \mathrm{B}$$

I

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

[2] (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, THIS JOURNAL, **81**, 5740 (1959); (b) D. J. Cram, A. Langemann and F. Hauck, *ibid.*, **81**, 5750 (1959).

The present paper[3] is concerned with the steric course of electrophilic substitution in the cleavage reactions of compounds V, VIII, IX, XIV and XV, three of which (V, VIII and IX) give 2-phenylbutane (I) and two (XIV and XV) give 1-methoxy-1-phenylethane (XVI) as product. The objectives of this work were to determine the effect of the following factors on the steric course of electrophilic substitution: (1) solvent, (2) acidity of proton-source (electrophile), (3) substituents attached to carbon undergoing substitution, (4) temperature.

Configurations of Starting Materials and Products.—Any conclusions about the steric course of the cleavage reactions depend on prior knowledge of the configurations of starting materials and products. The absolute configuration of 2-phenylbutane (I) has been firmly established,[4] and the configuration of 2-methyl-2-phenylbutanoic acid (II) was assigned[4a] through the use of the reactions summarized in Chart I.[5] Since compounds (−)-V, (+)-VIII and (−)-IX were all prepared from (−)-II (see Chart I), their configurations relative to that of 2-phenylbutane have been assigned.[2a,6]

The absolute configuration of 1-methoxy-1-phenylethane (XVI) has been unequivocally demonstrated.[7] Although the rotation of optically pure XVI has been calculated,[7b] optically pure material has never been prepared. Therefore optically pure (−)-α-phenylethanol[8] was converted to (−)-XVI, which had a rotation, α^{25}D α−120.2° (*l* 1 dm., neat), a value which agrees well with the calculated value of α^{25}D +120.1° for the enantiomer (see Chart II).

CHART I

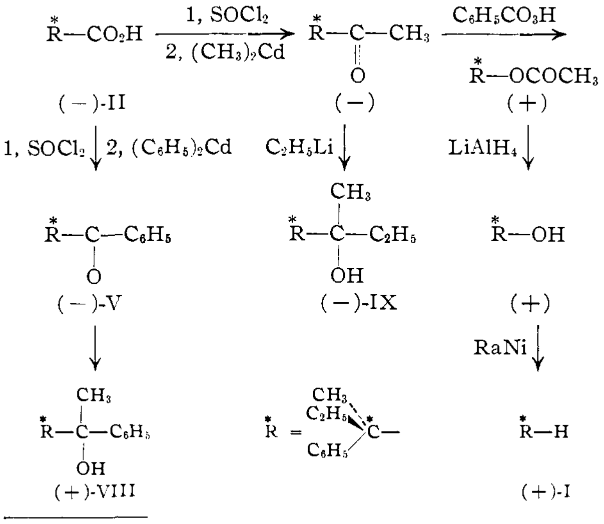
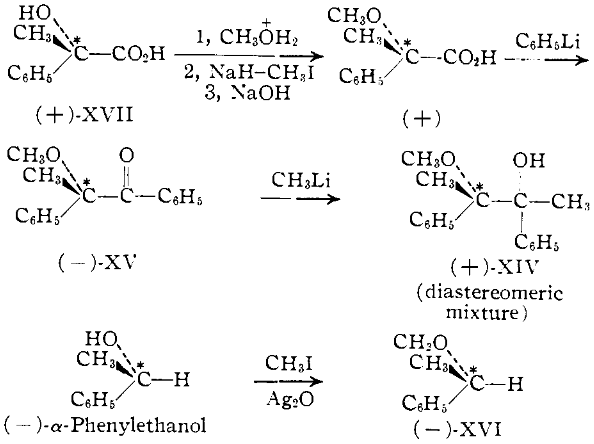
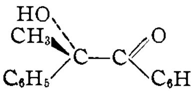


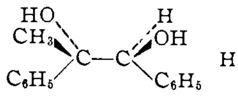
CHART II

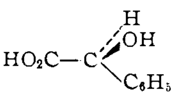


Compounds XIV and XV were prepared[9] from optically pure atrolactic acid (XVII) by the sequence outlined in Chart II. A number of different lines of evidence which depend either on comparisons of physical properties or asymmetric induction studies all point to absolute configuration, (+)-XVII, for atrolactic acid.[10] Thus the absolute configurations of XIV and XV are assigned (see Chart II).

The only direct evidence bearing on the assignment of configuration to atrolactic acid which has been gained through direct chemical interconversions rests on reactions which relate the configurations of compounds XVII through XX. Brewster[10] unequivocally related (−)-XX to (+)-XIX, and McKenzie and Ritchie,[11] (+)-XVII to (−)-XVIII. The link between (−)-XVIII and (−)-XIX *tentatively proposed* by the latter authors[11] was based on a negative sign of rotation of an oil obtained by catalytic hydrogenation of (−)-XVIII. This oil was not demonstrated to be free of negatively-rotating starting material,[12] which possesses a high rotation, and which might have been responsible for the negative sign of rotation. The situation was further confused by the fact that the oil was a mixture of diastereomers.


(−)-XVIII


(−)-XIX (*threo* isomer)


(+)-XX

This ambiguity has now been removed by reducing (−)-XVIII[9] with sodium borohydride to a crystalline compound whose melting point is the same as that of (+)-XIX, and whose rotation is equal in magnitude but opposite in sign to that of (+)-XIX. Clearly the crystalline compound is (−)-XIX, and for the first time the configurations of atrolactic and mandelic acids have been chemically related. Thus the *absolute configurations* of atrolactic acid and therefore of numerous related

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(3) Tables, compounds and runs are numbered consecutively throughout the first six papers of this series.

(4) D. J. Cram, THIS JOURNAL, **74**, 2149 (1952).

(4a) NOTE ADDED IN PROOF.—W. A. Bonner and T. W. Greenlee [THIS JOURNAL, **81**, 3336 (1959)] on the basis of rotational correlations have recently made the same configurational assignments. These authors report that when treated with Raney nickel (−)-2-methyl-2-phenyl-1-butanol (made from (−)-2-methyl-2-phenylbutanoic acid) gave (+)-2-phenylbutane. Contrary to the claims of these authors, their data demonstrate that this reaction occurred with predominating *retention* (rather than *inversion*) of configuration.

(5) D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954).

(6) In ref. 5, (+)-II was converted to (−)-I, rather than (−)-II to (+)-I, as is indicated in Chart I. The principles involved are not altered by this change, which is made for purposes of clarity.

(7) (a) K. Mislow, THIS JOURNAL, **73**, 3954 (1951); (b) **73**, 4043 (1951).

(8) E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939).

(9) D. J. Cram and K. R. Kopecky, THIS JOURNAL, **81**, 2748 (1959).

(10) J. Brewster, *ibid.*, **78**, 4061 (1956); the evidence is summarized in this reference.

(11) A. McKenzie and A. Ritchie, *Ber.*, **70**, 23 (1937).

(12) The amount of hydrogen consumed was not reported.

TABLE V

RESULTS OF CLEAVAGE REACTIONS

Run	Starting material Compound	Starting material Molality	Solvent, mole % Dioxane	Solvent, mole % Dieth. glyc.	Base Nature	Base Molality	Temp., °C.	Time, hr.	Product Nature	Product Yld., %	Product $\alpha^{24-29}{}_{D}$[a]	Product % opt. purity[b]	Predom. steric course
50	(+)-VIII	0.08	95	5	KODG[c]	0.08	150	83	(+)-I	71	+19.0°	78	Ret.
51	(+)-VIII	.09	75	25	KODG[c]	.10	150	83	(+)-I	28	+ 6.37	26	Ret.
52	(+)-VIII	.08	66	34	KODG[c]	.08	150	92	(−)-I	29	− 0.78	3	Inv.
53	(+)-VIII	.09	51	49	KODG[c]	.09	150	83	(−)-I	66	− 7.56	31	Inv.
54	(+)-VIII	.09	28	72	KODG[c]	.09	150	92	(−)-I	59	−12.3	51	Inv.
55	(+)-VIII	.08	0	100	KODG[c]	.10	150	94	(−)-I	50	−14.6	60	Inv.
56	(−)-IX	.71	94	6[d]	KOEG[e]	.71	200	36	(+)-I	82	+23.1	95	Ret.
57	(−)-IX	.80	75	25[d]	KOEG[e]	.80	200	36	(+)-I	78	+18.8	77	Ret.
58	(−)-IX	.87	50	50[d]	KOEG[e]	.87	200	36	(+)-I	84	+ 1.44	6	Ret.
59	(−)-IX	.90	24	76[d]	KOEG[e]	.90	200	36	(−)-I	94	− 5.95	25	Inv.
60	(−)-IX	1.0	0	100[d]	KOEG[e]	1.0	200	24	(−)-I	42	−12.43	51	Inv.
61	(+)-XIV	0.18	96	4	KODG[c]	.19	180	95	(−)-XVI	72	−83.2	69	Ret.
62	(+)-XIV	.18	75	25	KODG[c]	.19	180	95	(−)-XVI	35	−42.4	35	Ret.
63	(+)-XIV	.18	52	48	KODG[c]	.19	180	95	(+)-XVI	34	+ 1.70	1	Inv.
64	(+)-XIV	.18	38	62	KODG[c]	.19	180	95	(+)-XVI	12	+28.4	23	Inv.
65	(+)-XIV	.18	27	73	KODG[c]	.19	180	95	(+)-XVI	36	+31.6	26	Inv.
66	(+)-XIV	.18	0	100	KODG[c]	.19	180	95	(+)-XVI	15	+48.4	41	Inv.
67	(+)-VIII	.11	100	0	KO*t*Bu[f]	.09	150	49	(+)-I	85	+23.0	95	Ret.
68	(−)-IX	.09	100	0	KO*t*Bu[f]	.13	125	26	(+)-I	80	+32.2	96	Ret.
69	(+)-XIV	.11	100	0	KO*t*Bu[f]	.18	125	24	(−)-XVI	27	−100.8	84	Ret.
70	(−)-V	.10	100	0	KO*t*Bu[f]	.10	150	74	(+)-I	64	+17.8	74	Ret.
71	(−)-V	.11	0	100	KODG[c]	.11	210	50	(−)-I	38	− 9.14	38	Inv.
72	(−)-XV	.17	100	0	KO*t*Bu[f]	.18	165	44	(−)-XVI	10	−73.5	61	Ret.
73	(−)-XV	.12	0	100	KODG[c]	.07	220	72	(+)-XVI	3	−20.6	17	Inv.

[a] *l* 1 dm., neat. [b] Calculated on the basis of ±24.3° (*l* 1 dm., neat) for optically pure I [see D. J. Cram, THIS JOURNAL, **74**, 5518 (1952)] and α_D ±120.2° (*l* 1 dm., neat) for optically pure XVI. [c] Potassium diethylene glycoxide. [d] Ethylene glycol, *not* diethylene glycol. [e] Potassium ethylene glycoside. [f] Potassium *t*-butoxide.

compounds (*e.g.*, XIV and XV) are now established beyond any reasonable doubt.

Strong independent evidence for the correctness of assignment of configuration to 2-methyl-2-phenylbutanoic acid and related compounds (see Chart I) is found in the completely similar behavior of V, VIII and IX, and of XIV and XV in the cleavage reactions, which are described in the next section. Taken together, the evidence for the absolute configuration of 2-methyl-2-phenylbutanoic acid (II) is overwhelming.

Cleavage Reactions.—A series of cleavage reactions of alcohols (+)-VIII and (+)-XIV were carried out in mixtures of dioxane and diethylene glycol, and in pure diethylene glycol. The basic catalyst was in all cases potassium diethylene glycoxide. These runs were homogeneous (see Table V). A similar series of reactions was applied to alcohol (−)-IX (Table V) in mixtures of dioxane, ethylene glycol and potassium glycoxide. Unfortunately runs 58, 59 and 60 were heterogeneous. In Fig. 1 is plotted the steric results of these reactions against the mole fraction of glycol in dioxane.

Alcohols (−)-IX and (+)-XIV were also cleaved (runs 68 and 69, respectively) in dioxane with potassium *t*-butoxide as base. Ketones (−)-V and (−)-XV were cleaved in diethylene glycol with potassium diethylene glycoxide as base (runs 71 and 73, respectively), and in dioxane with potassium *t*-butoxide as base (runs 70 and 72, respectively). These runs were homogeneous.

Table VI records the results of a study of the effect of temperature on the stereospecificity of the electrophilic substitution reaction in retention, intermediate and inversion solvents. Compounds (+)-VIII, (−)-IX and (+)-XIV were employed.

Under the conditions of the experiments of Tables V and VI, optically active 2-phenylbutane (I) and 1-methoxy-1-phenylethane (XVI) were shown to be optically stable.

Discussion

Medium and Substituent Effects in Electrophilic Substitution.—The results of the experiments described in Table V provide another demonstration[2b] that electrophilic substitution at saturated carbon can occur with either predominating retention or inversion. Figure 1 indicates how the steric course and stereospecificity change with solvent composition as the proportions of dioxane and glycol are varied. With three different systems, [(+)-VIII, (−)-IX and (+)-XIV], predominating *retention* (69 to 95%) *is observed when the solvent is largely dioxane, and predominating inversion* (41 to 60%) *when the solvent is mainly diethylene glycol or ethylene glycol.* In (+)-VIII and (+)-XIV, the leaving group is the same, and the systems differ only with respect to one of the substituents (C_2H_5 or CH_3O) attached to carbon undergoing substitution. In (+)-VIII and (−)-IX, the leaving groups are different and the seats of substitution the same. With all three tertiary alcohols, a smooth transition from predominant retention to inversion is observed as the solvent is enriched in glycol. The curves for (+)-VIII and (+)-XIV even resemble one another in shape. The curve for (−)-IX is somewhat different, possibly because some of the reactions were not homogeneous, or

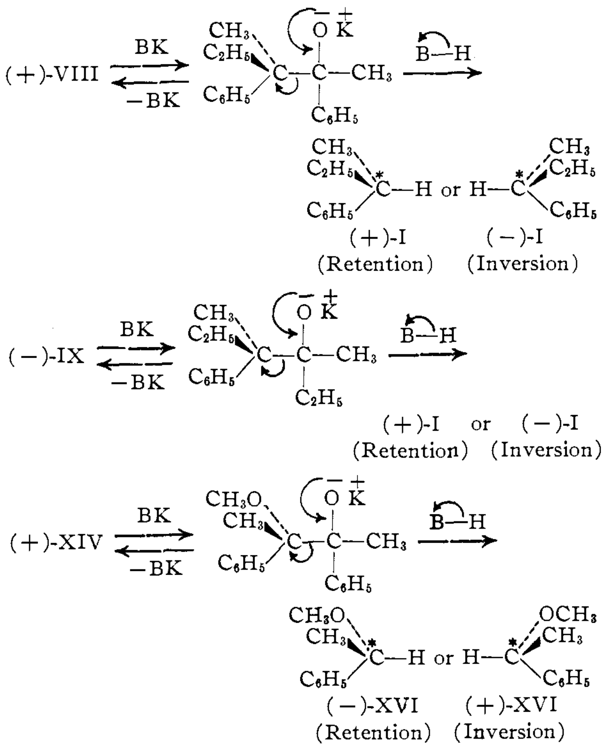
TABLE VI

EFFECT OF TEMPERATURE ON STEREOSPECIFICITY OF ELECTROPHILIC SUBSTITUTION REACTION

	Starting mat.			Base				Product					
Run	Compound	Mol.	Solvent	Nature	Mol.	Time, hr.	Temp., °C.	Nature	Yld., %	$n^{25}D$ [a]	$\alpha^{25}D$ [b]	% opt. purity [c]	Predom. steric course
74	(+)-XIV	0.16	$O(CH_2CH_2)_2O$	$KOC(CH_3)_3$	0.1	44	100	XVI	56	1.4884	−114°	95	Ret.
75	(+)-XIV	.16	$O(CH_2CH_2)_2O$	$KOC(CH_3)_3$	.1	24	125	XVI	27	1.4887	−101	84	Ret.
76	(+)-XIV	.16	$O(CH_2CH_2)_2O$	$KOC(CH_3)_3$	.1	20	150	XVI	25	1.4881	−93	77	Ret.
77	(+)-XIV	.16	$O(CH_2CH_2)_2O$	$KOC(CH_3)_3$	.1	20	180	XVI	72	1.4892	−83	69	Ret.
78	(+)-VIII	.08	$O(CH_2CH_2OH)_2$	$KO(CH_2CH_2O)_2H$	.1	94	150	I	50	1.4878	−14.7	60	Inv.
79	(+)-VIII	.09	$O(CH_2CH_2OH)_2$	$KO(CH_2CH_2O)_2H$	.1	50	180	I	68	1.4876	−13.1	54	Inv.
80	(−)-IX	.20	CH_3OH	$KOCH_3$	2.0	96	180	I	4	1.4876	− 6.0	25	Inv.
81	(−)-IX	.20	CH_3OH	$KOCH_3$	0.4	27	210	I	51	1.4876	− 2.2	9	Inv.

[a] $n^{25}D$ 1.4878 for pure 2-phenylbutane and $n^{25}D$ 1.4882 for pure 1-methoxy-1-phenylethane. [b] l 1 dm., neat. [c] For 2-phenylbutane, $\alpha^{25}D$ ±24.3° (neat, l 1 dm.) and for 1-methoxy-1-phenylethane, $\alpha^{25}D$ ±120° (neat, l 1 dm.).

because ethylene glycol rather than diethylene glycol was employed.



Since the same type of proton source (glycol) was involved in all these runs, the steric direction of the substitution seems to be mainly associated with the medium. It is also clear from the patterns of yield data that *large differences* in rate are not observed with changes in media from dioxane to glycol. Higher temperatures were required to cleave system IX than the other two.

In the cleavages of the three tertiary alcohols in dioxane with 1% *t*-butyl alcohol as proton source, the reactions occurred with from 84 to 96% predominating retention. Table VII compares the steric results of these three runs with those for the same systems in the same solvent (dioxane) in which the electrophile was about 1% of glycol. The latter values are obtained by extrapolating the curves of Fig. 1 to 1% glycol. For cleavage of a given system, the *steric result varies in only a minor way as the acidity of the proton source is changed* from that of glycol to that of *t*-butyl alcohol, even though in some cases the temperatures of the runs compared are different.

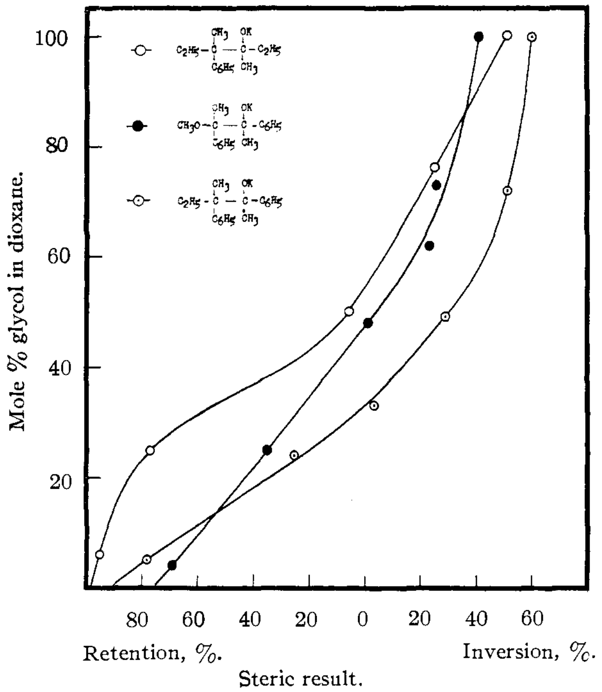


Fig. 1.—Stereochemical course of electrophilic substitution in cleavage reactions: curve ⊙, cleavage of 0.09 molar solution of (+)-3-methyl-2,3-diphenyl-2-pentanol [(+)-VIII] at 150° in diethylene glycol–dioxane mixtures about 0.09 molar in potassium diethylene glycoxide; curve O, cleavage of 0.9 molar solutions of (−)-3,4-dimethyl-4-phenyl-3-hexanol [(−)-IX] at 200° in ethylene glycol–dioxane mixtures about 0.9 molar in potassium ethylene glycoxide; curve ●, cleavage of 0.18 molar solutions of (+)-2,3-diphenyl-3-methoxy-2-butanol [(+)-XIV] at 180° in diethylene glycol–dioxane mixtures 0.19 molar in potassium diethyl glycoxide.

In ketones (−)-V and (−)-XV the leaving groups are the same, and the seat of substitution differs only in the character of one substituent (C_2H_5 or CH_3O). The results of their cleavages (Table VIII) parallel those obtained with the corresponding alcohols. In dioxane, retention is observed, and in diethylene glycol inversion is the steric result. When the leaving group is changed from

TABLE VII

EFFECT OF ACIDITY AND CONCENTRATION OF ELECTROPHILE ON STERIC PATH OF ELECTROPHILIC SUBSTITUTION IN DIOXANE

Source of data	System cleaved	Electrophile Nature	Electrophile N	Temp., °C.	Retention (net), %	
Run 67[a]	(+)-VIII	$(CH_3)_3COH$	13	150	95	values compared
Curve ⊙[b]	(+)-VIII	$O(CH_2CH_2OH)_2$	0.4	150	91	
Run 68[a]	(−)-IX	$(CH_3)_3COH$	13	125	96	values compared
Curve ○[b]	(−)-IX	$HOCH_2CH_2OH$	0.6	200	97	
Run 69[a]	(+)-XIV	$(CH_3)_3COH$	13	125	84	values compared
Curve ●[b]	(+)-XIV	$O(CH_2CH_2OH)_2$	0.4	180	75	

[a] See Table V. [b] Values obtained from extrapolating the curves of Fig. 1 to 1 mole % glycol concentration.

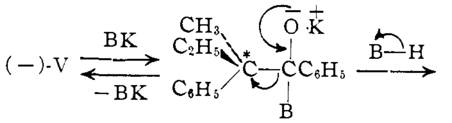
TABLE VIII

EFFECT OF LEAVING GROUP AND SOLVENT ON STERIC PATH OF ELECTROPHILIC SUBSTITUTION

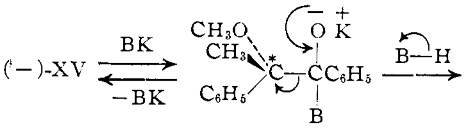
Run[a]	System cleaved	Solvent	Temp., °C.	Steric result	
67	(+)-VIII	Dioxane[b]	150	95% retention	values compared
70	(−)-V	Dioxane[b]	150	74% retention	
55	(+)-VIII	$O(CH_2CH_2OH)_2$	150	60% inversion	values compared
71	(−)-V	$O(CH_2CH_2OH)_2$	210	38% inversion	
69	(+)-XIV	Dioxane[b]	125	84% retention	values compared
72	(−)-XV	Dioxane[b]	165	61% retention	
66	(+)-XIV	$O(CH_2CH_2OH)_2$	180	41% inversion	values compared
73	(−)-XV	$O(CH_2CH_2OH)_2$	220	17% inversion	

[a] See Table V for details. [b] $(CH_3)_3COH$ is proton source.

that of tertiary alcohol to that of ketone, the stereospecificity decreases in both retention and inversion solvents, although in most cases the higher temperature required for ketonic cleavage might have been partially responsible for the decrease.



(+)-I or (−)-I
(Retention) (Inversion)



(−)-XVI or (+)-XVI
(Retention) (Inversion)

Furthermore, when the carbon that undergoes substitution carries a methoxyl instead of an ethyl group, a decrease in stereospecificity is observed in both the retention and inversion solvents, and with both types of leaving groups.

Temperature Effects on Electrophilic Substitution Reaction.—The results reported in Table VI demonstrate that in dioxane, methanol and ethylene glycol, the more stereospecific results are associated with the lower temperatures. In dioxane, when the temperature was changed from 100 to 180°, XIV gave product with a steric result which changed from 95 to 69% predominating retention. In methanol, when the temperature was changed from 180 to 210°, IX produced product with a steric result that changed from 25 to 9% predominating inversion. In diethylene glycol, a temperature change from 150 to 180° reduced the stereospecificity of the cleavage of VIII from 60 to 54% predominating inversion. Thus in extreme retention, inversion and intermediate solvents, the lower temperatures produce the more stereospecific results.

A comparison of the magnitude of the temperature effect on the inversion and retention mechanisms is interesting. In cleavage of XIV (runs 76 and 77), k_{ret}/k_{inv} changed by a factor of about 1.4 from 150 to 180° (retention solvent), whereas in cleavage of VIII (runs 78 and 79), k_{ret}/k_{inv} changed only by a factor of about 1.2 over the same temperature range (inversion solvent).

These trends can be explained in two ways. In the first of these, only two mechanisms are competing, both of which are stereospecific; one gives product of retained and the other product of inverted configuration. Racemic product then arises simply by mixing two stereospecific processes. If this explanation applies, then in a solvent such as dioxane in which the reaction goes with predominating retention, the increase in racemic product which accompanies a rise in temperature would be due to a *decrease* in the value of k_{ret}/k_{inv}. In a solvent such a diethylene glycol, which gives predominant inversion, the increase in racemic product at higher temperatures would have to be explained by an *increase* in the same ratio. If this explanation applies, this ratio would have temperature coefficients that would change signs with a change in the character of the solvent.

A more plausible explanation involves three discrete reaction paths, two of which are stereospecific which give either retained or inverted product, and one which is non-stereospecific and gives only racemic product. It is reasonable to expect this latter process to become more important at higher temperatures at the expense of the other two, and in either type of solvent.

The solvent composition that would produce racemic product in the curves of Fig. 1 are different for the cleavage of VIII, IX and XIV. For VIII at 150°, the medium would be 33 mole % glycol; for XIV at 180°, the medium would be 47 mole % glycol; and for IX at 200°, the medium would be 54 mole % glycol. Probably both the temperature differences as well as the differences in the system cleaved contribute to these effects.

The mechanistic implications of these results are further discussed in papers V[13] and VI[14] of this series.

Experimental

Conversion of (−)-1,2-Diphenyl-2-hydroxy-1-propanone [(−)-XVIII] to (−)-threo-1,2-Diphenyl-1,2-propanediol [(−)-XIX].—To a solution of 2.0 g. of optically pure (−)-XVIII prepared from (+)-XVIII[9] in 20 ml. of ethanol was added 0.5 g. of sodium borohydride. The mixture became

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[13] D. J. Cram, F. Hauck, K. R. Kopecky and W. D. Nielsen, THIS JOURNAL, **81**, 5767 (1959).

[14] D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, *ibid.*, **81**, 5774 (1959).

warm and gas was evolved. After 10 minutes gas evolution ceased, 10 ml. of water was added, and the mixture was heated to reflux. The mixture became clear, and was then cooled to 0°. The heavy oil that separated was dissolved in ether, and the solution was washed with water, dried and concentrated to an oil. This material was chromatographed on 100 g. of neutral alumina. Elution of the column with 250 ml. of ether gave 0.9 g. of a yellow, viscous oil with an unpleasant odor. The next 500 ml. of eluate was empty. Elution of the column with 250 ml. of 10% ethanol-ether also gave empty eluate. Successive fractions (of 250 ml. each) contained small amounts of eluate. Material from fractions 4 through 7 were combined and concentrated to give 0.080 g. of an oil which crystallized from carbon disulfide–pentane to give 0.045 g. of a white solid, m.p. 91–93°, α^{25}_{D} −27° (*c* 0.8 in acetone). The compound, (+)-*threo*-XIX has been reported,[15] m.p. 92–93°, $[\alpha]_{\mathrm{D}}$ +31° (*c* 1.8 in acetone).

(−)-1-Methoxy-1-phenylethane [(−)-XVI].—The compound α-phenylethanol was resolved[8] as its acid phthalate (100 g.) to give 17.2 g. of (+)-acid phthalate, m.p. 83.5–85.5°, $[\alpha]^{26}_{\mathrm{D}}$ +60.0° (*c* 5.2 in carbon disulfide) and 23 g. of (−)-acid phthalate, m.p. 83–84.5°, $[\alpha]^{26}_{\mathrm{D}}$ −62.0° (*c* 5.1 in carbon disulfide). The (−)-ester was hydrolyzed to (−)-α-phenylethanol,[8] n^{25}_{D} 1.5251, α^{25}_{D} −44.2° (*l* 1 dm., neat). When methylated,[7b] this alcohol gave material which was twice chromatographed, and twice distilled, n^{25}_{D} 1.4882, α^{25}_{D} −120.2° (*l* 1 dm., neat).

Other Starting Materials.—The preparation of (−)-V, (+)-VIII and (−)-IX have been described previously.[2a] Alcohol (+)-XIV was the mixture of diastereomers prepared by the addition of methyl-lithium to optically pure (−)-1,2-diphenyl-2-methoxy-1-propanone [(−)-XV], $[\alpha]^{25}_{\mathrm{D}}$ −25.6° (*c* 4.7 in ethanol), $[\alpha]^{25}_{\mathrm{D}}$ +4.7° (*c* 5.1 in chloroform).[9]

Purification of Solvents.—Dioxane was purified by the method of Fieser,[16] and then was distilled from lithium aluminum hydride. Ethylene glycol and *t*-butyl alcohol were fractionally distilled from their sodium salts. Diethylene glycol was passed through a 4 by 30 cm. column of Linde molecular sieves, type 4A, 14 by 30 mesh, and then distilled from its sodium salt. Philips Petroleum Co. pure grade pentane was fractionally distilled through a 2 by 85 cm. helipacked column.

Cleavage Reactions.—Solutions of potassium in diethylene glycol and *t*-butyl alcohol were prepared by dissolving a weighed amount of clean metal in solvent saturated with nitrogen, the operation being carried out under nitrogen. Potassium *t*-butoxide was prepared by evaporating solutions of the salt in *t*-butyl alcohol under vacuum, adding the desired reaction solvent, and evaporating it to get rid of residual *t*-butyl alcohol. Solutions of potassium ethylene glycoxide were prepared this way since direct addition of potassium to ethylene glycol results in explosion. Desired solutions were prepared by mixing the appropriate amounts of glycol containing the base and dioxane, or by dissolving potassium *t*-butoxide in dioxane.

From 1.0 to 2.0 g. of the system to be cleaved was used in each case. Reactions conducted at temperatures below the boiling points of the solvents employed were carried out in round-bottom flasks with spiral condensers under nitrogen and immersed in a Wood metal-bath. Reactions conducted at temperatures above the boiling point of the solvents were carried out in either pressure bottles or sealed heavy-walled vials, which were immersed either in a Wood metal-bath or a constant temperature oil-bath.

The isolation procedures are illustrated in the descriptions of actual runs that were made.

Run 69.—Potassium, 0.336 g., was dissolved in 10 ml. of pure nitrogen-saturated *t*-butyl alcohol in a 200-ml. pressure bottle under dry nitrogen. After solution was complete, the excess solvent was evaporated at 80° at 10 mm., and heated for 0.5 hour to remove the last amount of solvent. Pure nitrogen-saturated dioxane (50 ml.) containing 1.22 g. of (+)-XIV was added and the bottle was loosely stoppered and heated in a Wood metal-bath at 100°. After 5 minutes the stopper was clamped on tightly and the temperature was raised to 125°, and kept there for 24 hours. The flask was then cooled, opened, and shaken with a mixture of 300 ml. of water and 100 ml. of pure pentane. The water was extracted with two 100-ml. portions of pentane. The combined pentane layers were washed with five 200-ml. portions of water. The organic solution was then dried and evaporated through a two-foot Vigreux column. The residual oil was adsorbed on 2 by 30 cm. column of neutral activity I alumina.[17] The product (XVI) was washed from the column with pure pentane, which was evaporated from eluate through a two-foot Vigreux column. The residue was distilled twice through a short-path, semi-micro Claisen head at about 70 mm. and 100° pot temperature to give 0.285 g. of XVI, n^{25}_{D} 1.4903, α^{26}_{D} −99.4° (*l* 1 dm., neat).

Since the index of refraction of this material was high, it was contaminated with olefin, which was removed by the following procedure. The material was dissolved in 20 ml. of acetone, and 2 ml. of 2% aqueous permanganate solution was added. The resulting mixture was shaken in a stoppered flask for 2 hours at room temperature. A small amount of brown precipitate was evident. The mixture was shaken with 100 ml. of pentane and 100 ml. of water. The pentane solution was washed with water four times, dried, evaporated through a two-foot Vigreux column, and the product was distilled twice as before to give 0.169 g. (27% yield) of XVI, n^{25}_{D} 1.4887, α^{25}_{D} −100.8° (*l* 1 dm., neat). The infrared spectrum of this material was superimposable on that of authentic XVI. The index of refraction of XVI from various runs ranged from 1.4880 to 1.4887 after treatments of some of the samples with permanganate to remove olefin. The rotations changed only about 1% with olefin removed. When yields were exceptionally low, the product was diluted with racemic XVI for rotations.

The above chromatograph column was eluted with one liter of 15% ether–pentane to give an oil, which was treated with excess 2,4-dinitrophenylhydrazine reagent. The orange precipitate that separated (0.3 g.) was recrystallized twice from ethanol to give the 2,4-dinitrophenylhydrazone of acetophenone, m.p. 247–249°, undepressed by admixture with an authentic sample of the derivative of acetophenone.

In many of the runs, starting material was isolated from the chromatograph column, and was found to be unchanged in physical properties (*e.g.*, rotation). In run 72, a 20% yield of benzoic acid was isolated from the original basic solution which was extracted with pentane, m.p. 121–122°, undepressed by admixture with authentic material.

Run 53.—Potassium, 0.179 g., was dissolved in 26.8 g. of pure diethylene glycol saturated with dry nitrogen. The operation was carried out under nitrogen in a heavy-walled pressure bottle. Pure dioxane (23.2 g.) saturated with nitrogen and containing 1.142 g. of (+)-VIII was added, and the resulting solution was heated to 100° for 10 minutes with the stopper loose. The stopper was then secured, and the flask was immersed in a Wood metal-bath at 150° for 83 hours. The flask was then cooled, and the contents shaken with a mixture of 200 ml. of pure pentane and 200 ml. of water. The aqueous layer was washed with 100 ml. of pure pentane, and the combined aqueous layer was washed five times with 100-ml. portions of water. The pentane solution was dried, evaporated through a two-foot Vigreux column, and the residue was chromatographed on 70 g. of activity I neutral alumina.[17] The product (I) was eluted with 300 ml. of pure pentane, which was evaporated through a two-foot Vigreux column to give an oil, which was twice distilled through a micro-Claisen still at 40 mm. and 100° pot temperature to give 0.398 g. (66% yield) of 2-phenylbutane (I), n^{25}_{D} 1.4878, α^{24}_{D} −7.56° (*l* 1 dm., neat). The infrared spectrum of this material was identical to that of authentic 2-phenylbutane.

In some runs the index of refraction and infrared spectra indicated the presence of olefin (bands at 782 cm.$^{-1}$) in the sample. This was removed by treatment of the sample with potassium permanganate as described in the procedure for run 69. This treatment usually altered the rotation about 2%, but lowered the yield from operational losses by 10 to 40%. The index of refraction of final product ran from n^{25}_{D} 1.4876 to 1.4880. In a number of cases, starting material was recovered, and was found unchanged in its physical properties.

Control Procedures.—As a control on the procedure used to remove olefin from impure samples of I or XVI, the following control was run. A sample of 0.350 g. of 2-phenylbutane, n^{25}_{D} 1.4878, α^{24}_{D} −12.3° (*l* 1 dm., neat) was subjected to the potassium permanganate treatment, and re-

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[15] R. Roger, *Biochem. Z.*, **230**, 320 (1930).

[16] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 369.

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

covered; wt. 0.270 g., n^{25}D 1.4878, α^{25}D −12.3° (*l* 1 dm., neat).

As a control for those runs in which potassium *t*-butoxide was the base and 1-methoxy-1-phenylethane (XVI) was the product, the following experiment was carried out. A 0.23 molar solution of potassium *t*-butoxide in dioxane was prepared, and 25 ml. of this solution was mixed with 0.35 g. of XVI, n^{25}D 1.4882, α^{24}D +35.6° (*l* 1 dm., neat). The resulting solution was heated in a heavy-walled sealed tube to 190° for 26 hours. Recovery of XVI in the usual way gave 0.245 g. of material, n^{25}D 1.4884, α^{23}D +34.4° (*l* 1 dm., neat). Racemization occurred to the extent of 3%. The solution was twice as concentrated as any runs of this type recorded in Table V, and this control was carried out 40° higher in temperature.

As a control for those runs carried out with potassium diethylene glycoxide as base, the following experiment was carried out. A 0.11 *M* solution of potassium diethylene glycoxide in diethylene glycol was prepared, and 25 ml. was mixed with 0.25 g. of XVI, n^{25}D 1.4882, α^{24}D +35.6° (*l* 1 dm., neat). The solution was held at reflux at 245° for 16 hours, and XVI recovered in the usual way, n^{25}D 1.4888, α^{23}D +36.1° (*l* 1 dm., neat). No material racemized during this treatment.

Control runs reported previously[2b] apply to other experiments of this paper.

Los Angeles 24, Calif.

[Contribution from the Instituto de Química, Universidad Nacional Autónoma de México, and Department of Chemistry of the University of California at Los Angeles]

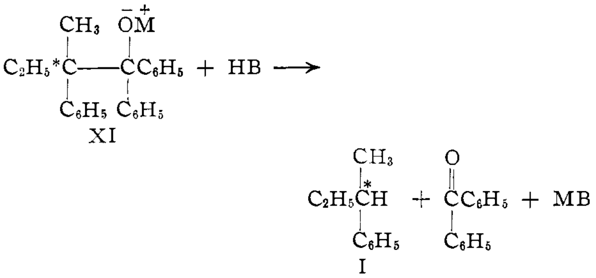
Electrophilic Substitution at Saturated Carbon. IV. Competing Radical and Anionic Cleavage Reactions[1]

By Donald J. Cram,[2] Albert Langemann, Walter Lwowski and Karl R. Kopecky

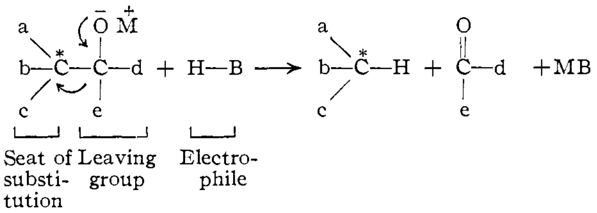
Received January 2, 1959

The base-catalyzed cleavage of optically pure (+)-2-methyl-1,1,2-triphenyl-1-butanol has been studied in a variety of solvents. The compound has been shown to undergo reversibly a homolytic cleavage reaction to give 2-phenyl-2-butyl radical and the ketyl of benzophenone (radical anion) which both dimerize. This homolytic reaction competes with a heterolytic anionic cleavage which results in 2-phenylbutane and benzophenone. The effects of solvent and metal cation on these cleavages have been examined. The radical cleavage leads only to racemic products, whereas the anionic cleavage gives from 99% retention to 36% inversion in the accompanying electrophilic substitution at saturated carbon. The base-catalyzed cleavage of racemic 1,1,2-triphenyl-2-methoxy-1-propanol was found to give products which also indicated competing homolytic and heterolytic cleavage reactions. Cleavage of (+)-2-cyclohexyl-1,2-diphenyl-2-methyl-1-butanol gave only racemic 2-cyclohexylbutane in basic ethylene glycol and in basic *t*-butyl alcohol. Evidence is presented which suggests the reaction proceeds by a radical process.

This paper is concerned with the mechanism and steric course of the base-catalyzed cleavages of (+)-2-methyl-1,1,2-triphenyl-1-butanol [(+)-XI], and of structural relatives of XI in which the substituents on the asymmetric carbon of the substances are varied. Cleavage reactions of compounds related to XI have been studied in previous papers of this series,[3] with major emphasis being placed on the factors which controlled the stereochemical course of the over-all electrophilic substitution which occurs at the benzyl carbon atom. In the past studies it seemed clear from the nature of reactants, products and conditions that the cleavage stage of these reactions involved a heterolytic and anionic process which can be generally described as in the formulation



$$C_2H_5\overset{*}{C}(CH_3)(C_6H_5)-C(\bar{O}\overset{+}{M})(C_6H_5)C_6H_5 + HB \longrightarrow C_2H_5\overset{*}{C}H(CH_3)C_6H_5 + C_6H_5C(=O)C_6H_5 + MB$$



Compound XI seemed to be a particularly good system to study for a number of reasons. (1) The cleavage reaction occurs at somewhat lower temperatures than systems in which d and e of the leaving group are other than phenyl. (2) Benzophenone is formed in this reaction in good yield, and is not subject to base-catalyzed condensation reactions which might liberate water to the medium. (3) The appearance of benzophenone might be followed spectroscopically, and kinetic measurements made. (4) Unlike systems in which d or e are methylene groups, systems with d and e as phenyl groups have no internal proton source available to the carbanion created in the reaction.

Cleavage Reactions of (+)-2-Methyl-1,1,2-triphenyl-1-butanol [(+)-XI].—Optically pure starting material (XI) was reported previously[3a] and its configuration relative to that of I established.[3a,3c] The results of cleavage reactions of this system are recorded in Table IX. In run 82 a 66% yield of 2-phenylbutane (I) was obtained, the reaction having occurred with 60% predominating retention of configuration. This run differed in a number of important respects from those carried out in the

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

[2] Visiting Professor at the Instituto de Quimica, Universidad Nacional Autónoma de México, summer of 1956.

[3] (a) D. J. Cram, A. Langemann, J. Allinger and K. R. Kopecky, This Journal, **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). Tables, compounds and runs are numbered consecutively throughout the first six papers of this series.