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

Neighboring Carbon and Hydrogen. XVII. The Pinacol Rearrangement. Solvolysis of 2-Methoxy-2-phenylethyl and Related Halides[1,2]

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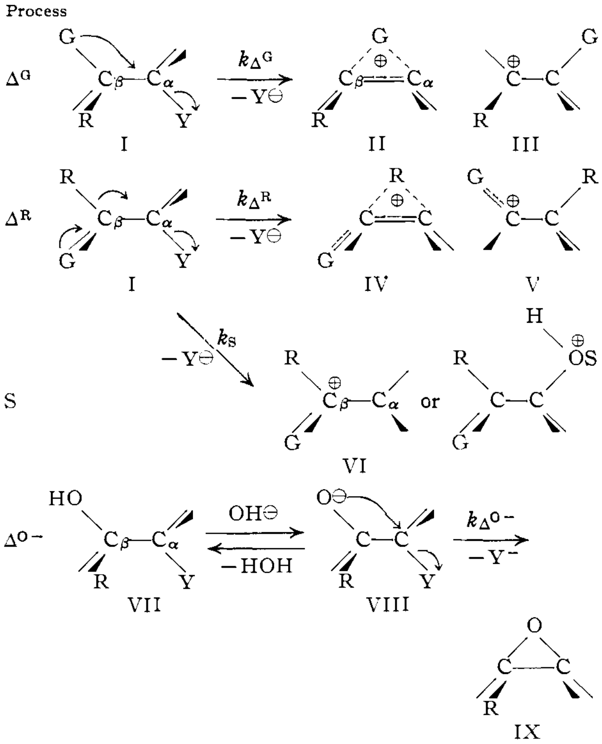
Reactions of substances capable of undergoing rearrangement of the general pinacol type may be discussed on the basis of the competing rate-determining processes: Δ^G, involving functional group participation; Δ^R, involving carbon or hydrogen participation; Δ^{O^-}, involving alkoxide ion group participation; S, solvolysis without anchimeric assistance. Structurally rearranged or unrearranged substitution product, acetal or ketal, aldehyde or ketone and oxide all may arise from one or more of the different type rate-determining processes. The competition between the competing processes may be discussed in terms of the relative driving forces. L_R, associated with carbon or hydrogen participation, will tend to follow the sequence of G groups: HO, CH_3O > F > Cl > Br > I. L_G, associated with participation of G will tend to follow the sequence: RS > I > Br > OR > Cl. Thus the ratio of carbon to functional group participation tends to follow the sequence: HO, CH_3O > Cl > Br > I. 2-Methoxy- and hydroxy-2-phenylethyl iodide give phenylacetaldehyde or its methyl acetal in various treatments with silver ion in aqueous dioxane or dry methanol under conditions toward which conceivable intermediates are stable. The S and Δ^{OR} processes fail to compete appreciably with Δ^{Ph} in these cases. On the other hand, 2-hydroxy- or methoxy-1-phenylethyl halides give rise predominantly to unrearranged substitution products, namely, styrene glycol and its mono- and dimethyl ethers, along with some products of hydrogen migration. The results show that Δ^{OR} is again unimportant; however, now S predominates.

The problem of understanding the reactions of substances capable of undergoing rearrangement of the general pinacol type is complex. Since the substances I possess a functional group G in addition to the departing group Y, several possible rate-determining processes[2,3] compete. These may be classified as follows: (i) Δ^G; rate constant k_{Δ^G}; ionization to intermediates II or III with anchimeric[4] assistance[5] due to G. (ii) Δ^R; rate constant k_{Δ^R}; ionization to intermediates[6,7] IV or V, assisted by participation of carbon or hydrogen.[2,3,8,9] (iii) S; rate constant k_S; solvolysis without anchimeric assistance. This process may or may not involve an important intermediate VI.[10] Most often the neighboring functional group is hydroxyl (VII), so that proper conditions of pH may favor a process, Δ^{O^-}, involving participation of the alcoholate ion group[5] (VII → VIII → IX).[11]



Instead of intervening in the rate-determining step, either or both of the neighboring groups G[5] and R[3,8] may intervene at a stage subsequent to formation of the intermediate VI.

With regard to stereochemistry, the situation is similar to that in the Wagner–Meerwein phenomenon.[3,6,8] For example, at C_α the displacement of Y by participating R in the Δ^R process involves inversion[8,9] of C_α. Definite evidence of anchimeric assistance by R constitutes evidence that involve-

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(1) Abstracted from part of Ph.D. Thesis of L. L. Ingraham, U.C.L.A., 1949.

(2) Much of the material of this article was presented in summary: (a) before the Organic Division of the American Chemical Society, St. Louis, Mo., Sept., 1948; (b) at the Eleventh National Organic Symposium, Madison, Wisc., June 21, 1949, page 65 of abstracts; (c) at the Symposium on Molecular Rearrangements and the Walden Inversion, Montpellier, France, April 26, 1950.

(3) S. Winstein, *Bull. soc. chim.*, [5] **18**, C55 (1951).

(4) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, THIS JOURNAL, **75**, 147 (1953).

(5) S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

(6) The questions regarding intermediates in the pinacol rearrangement are analogous to those in the Wagner-Meerwein rearrangement; S. Winstein and B. Morse, THIS JOURNAL, **74**, 1133 (1952).

(7) (a) Watson, *Ann. Repts.*, 197 (1939), 120 (1941); (b) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, 1949, p. 215; (c) I. Elphimoff-Felkin and B. Tchoubar, *Bull. soc. chim.*, **55**, 57 (1951); (d) E. R. Alexander and D. C. Dittmer, THIS JOURNAL, **73**, 1665 (1951); (e) J. F. Lane and D. R. Walters, *ibid.*, **73**, 4234 (1951); (f) R. F. Brown, J. B. Nordmann and M. Madoff, *ibid.*, **74**, 432 (1952).

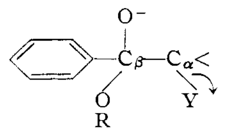
(8) S. Winstein, *et al.*, *ibid.*, **74**, 1113 (1952).

(9) (a) P. D. Bartlett and I. Pockel, *ibid.*, **59**, 820 (1937); Suter and Lutz, *ibid.*, **60**, 1360 (1938).

(10) S. Winstein, E. Grunwald and H. Walter Jones, *ibid.*, **73**, 2700 (1951).

(11) For the competition between oxygen and carbon participation in reactions of halomagnesium derivatives of halohydrins, see T. A. Geissman and R. I. Akawie, THIS JOURNAL, **73**, 1993 (1951).

More complex sets of competing possible participations may occur, for example between phenyl, OR, and O^- in a structure of the type (a).



(a)

E.g., see L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 178; C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 618 (1952).

ment of R with C_α is concerted with ionization of Y, and this demands inversion at C_α. While concertedness demands stereospecificity at C_α, considerable stereospecificity at C_α is not synonymous with concertedness, although this often has been assumed. Considerable stereospecificity at C_α is possible in rearrangement through open ion VI as a result of ionization of predominantly one conformational form of the original molecule I and the subsequent behavior[3,5,6] of the intermediate or intermediates VI as regards rotation about the C_β–C_α bond and shift of R. For example, before any rotation occurs about the C_β–C_α bond in VI, only the group R, originally *trans* to Y in I, is stereoelectronically favorably situated for migration.

The possible final products of reactions initiated by Δ^G, Δ^R, S and Δ^{O^-} processes are varied, even under so-called irreversible conditions. Structurally unrearranged substitution product conceivably may arise from Δ^G, Δ^R and S. Rearranged substitution product may arise from Δ^G and S; an acetal or ketal type of product may arise from Δ^R and S. Oxides may arise from Δ^{OH}, Δ^{O^-} and S. The usual type of pinacol rearrangement product, an aldehyde or ketone, may arise from Δ^R, S and Δ^G. While all the above types of products are observed, the detailed mechanisms of their formation are almost invariably not clear.

The competition between the Δ^R, Δ^G and S rate-determining processes may be discussed in terms of the relative driving forces,[3,5,12] L_R and L_G, ex-

$$L_R = RT \ln (k_{\Delta^R}/k_C) \qquad (1)$$

$$L_G = RT \ln (k_{\Delta^G}/k_C) \qquad (2)$$

$$\frac{k_{\Delta^R} + k_{\Delta^G}}{k_S} = \frac{(k_{\Delta^R} + k_{\Delta^G})/k_C}{(k_S/k_C)} \qquad (3)$$

pressed by equations 1 and 2, and the factor k_S/k_C, used in equation 3. The constant k_C is the pertinent ionization rate corresponding to no anchimeric assistance and no assistance from covalent solvation of C_α by a solvent molecule in the transition state.[10] The competition between Δ^R and Δ^G is determined by the difference between L_R and L_G since

$$L_R - L_G = RT \ln (k_{\Delta^R}/k_{\Delta^G})$$

To a first approximation, neglecting steric and related effects, L_G and L_R will be affected similarly, but not quantitatively identically, by additional substitution, these values decreasing with additional α-methyl or phenyl substitution and increasing with similar β-substitution.[5,8]

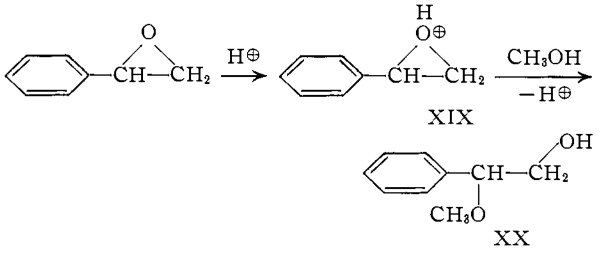
In Δ^G, G is the participating group, R assisting in the role of a β-substituent. In Δ^R, R is the participating group and G assists as a β-substituent. The competition between Δ^G and Δ^R depends on both R and G.

Keeping R fixed and varying G, one can anticipate that L_R will fall off in the order HO, CH_3O > F > Cl > Br > I, to the extent the tautomeric effect[13] of G is at work in the transition state. In Δ^G, anchimeric electron release by G follows a different order,[5,14] so that L_G will tend to decrease in the order[5] RS > I > Br > OR > Cl. This will tend to make $k_{\Delta^R}/k_{\Delta^G}$ follow the order HO, CH_3O > Cl > Br > I and CH_3O > CH_3S. Thus among different G groups, RO tends to favor carbon participation, and therefore pinacol rearrangement, while CH_3S, I and Br tend to favor functional group participation.

In seeking orientation on the competition between Δ^R, Δ^G and S, where G is OH or OCH_3, discussed in this and other papers in this series, we studied some reactions of 2-phenyl-2-methoxy or hydroxyethyl iodide. These materials possess the simplest structure containing both a β-OR and β-phenyl. With this structure, the S process can be expected[10] to lead to simple substitution products, making for a relatively simple connection between the Δ^R, Δ^G, S competition and the nature of the products. A few reactions have been studied also with the isomeric 1-phenyl-2-hydroxyethyl iodide. While treatment of 2-phenyl-2-hydroxy- and methoxyethyl iodides already had been reported to give rise to phenylacetaldehyde,[15] our aim was to obtain information on the nature of the direct products under conditions where the aldehyde could not arise from possible intermediates. For example, with the 2-phenyl-2-methoxyethyl iodide, Tiffeneau[15] ascribed the failure to isolate methoxystyrene to hydrolysis of this vinyl ether by the liberated nitric acid.

Rearrangement of 2-Phenyl-2-methoxy- and Hydroxyethyl Iodides.—Treatment of 2-phenyl-2-methoxyethyl iodide (X) with silver nitrate in aqueous dioxane in the presence of sodium bicarbonate gave phenylacetaldehyde (XIV) in good yield, if one allows for the well-known difficulty of handling this aldehyde. Control experiments were performed on both α-methoxystyrene and β-methoxystyrene, both of which proved to be very stable to the whole set of reaction conditions.

Both glycol monomethyl ethers XX and XXI were prepared for use in control experiments. The primary alcohol XX was easily available from methanolic acid-catalyzed opening of styrene oxide, which proceeds very predominantly in this direction. The isomeric monomethyl ether XXI was prepared in quantity by the methoxide ion-catalyzed opening of styrene oxide with methanol. A mixture of the two isomeric monomethyl ethers XX and XXI, predominantly the secondary alcohol XXI, is produced, from which the primary alcohol XX can be removed by treatment with phthalic anhydride. Both of the monomethyl ethers XX and XXI were completely stable to the reaction conditions and this could not account for formation of any of the phenylacetaldehyde.



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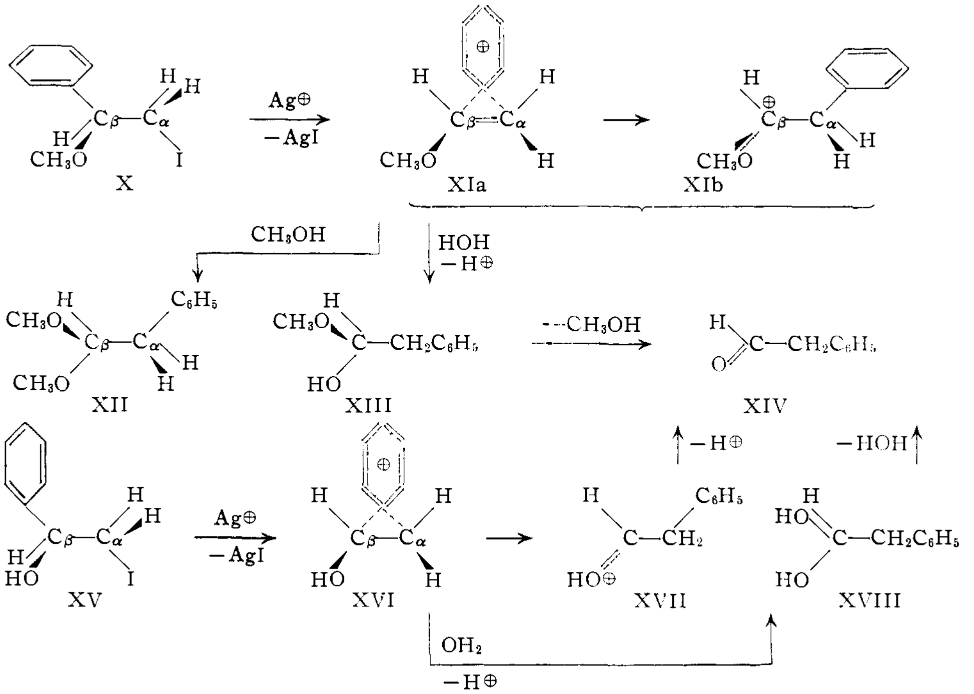
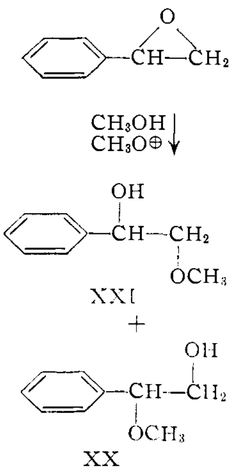
(12) S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, **70**, 821 (1948).

(13) C. K. Ingold, *Chem. Reviews*, **15**, 225 (1934).

(14) G. Baddeley, *J. Chem. Soc.*, 663 (1950).

(15) M. Tiffeneau, *Compt. rend.*, **145**, 811 (1901).





When the treatment of the 2-phenyl-2-methoxyethyl iodide (X) with silver ion was performed in methanol, using silver oxide, a material was obtained in good yield, whose properties were close to those of phenylacetaldehyde dimethyl acetal (XII) and styrene glycol dimethyl ether (XXV). The refractive index of the material was identical with that of the acetal XII, and its behavior toward hydrolytic conditions proved it to be virtually quantitatively acetal. A quantitative analytical scheme, based on the weight of phenylacetaldehyde dinitrophenylhydrazone obtained from an aliquot sample, gave a figure of 96% acetal in the material. In this analytical scheme, the dinitrophenylhydrazone was obtained quantitatively from the acetal XII and from β-methoxystyrene, but the yield was 0% from glycol monomethyl ether XX and less than 2% from glycol dimethyl ether XXV.

When styrene iodohydrin (XV) was treated with silver nitrate in aqueous dioxane, a 52% yield of phenylacetaldehyde was obtained as the sodium bisulfite addition compound. No discernible amounts of styrene oxide or glycol were obtained. A control experiment on styrene glycol showed it survived the reaction conditions and therefore could not be an intermediate. A control experiment on the stability of styrene oxide toward the conditions for formation of the bisulfite addition compound showed it to be stable. Therefore, styrene oxide cannot be an intermediate, since, if it survived the reaction conditions, it should have been isolated, and, if it did not survive the reaction conditions, it should have given styrene glycol.

Regarding the mechanisms of the above described conversions of 2-phenyl-2-methoxyethyl iodide (X) and styrene iodohydrin (XV), it is quite clear that the S and Δ^{OR} processes fail to compete appreciably with the Δ^{Ph} process.[16] For structures as unsubstituted as the one in X and XV, the S process would lead to unrearranged substitution product. These would be glycol monomethyl ether (XX) or dimethyl ether (XXV) from X in water or methanol, respectively, and styrene glycol from XV in water. Judging from the behavior of the conjugate acid of styrene oxide (XIX), the Δ^{OR} process, which produces the same or analogous intermediates, would give rise to rearranged monomethyl ether XXI or dimethyl ether XXV from X in water and methanol, respectively, and to oxide or glycol from XV in water. None of these materials is produced in appreciable amount.

The silver ion-assisted ionization of 2-phenyl-2-methoxyethyl iodide (X), with phenyl participation, gives rise to the phenyl-bridged intermediate XIa. This may well open to the relatively stable intermediate XIb, with a methoxyl group on the electron-deficient carbon atom, before reaction with methanol[17] or water. In any case, reaction with methanol gives acetal XII and reaction with water gives hemiacetal XIII and finally aldehyde[18] XIV. Analogously, ionization of styrene iodohydrin (XV) gives rise to the phenyl-bridged intermediate XVI. It is attractive to formulate XVI opening to XVII, the conjugate acid of the aldehyde XIV. However, it is conceivable that XVI reacts with water to give the hydrated aldehyde XVIII, which then collapses to aldehyde.[19]

It is striking how sharply the very high ratio of Δ^R to Δ^{OR} processes with the 2-phenyl-2-methoxyethyl system differs from that in aliphatic analogs,

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[16] Δ^{OR} denotes Δ^G, specialized for methoxyl or hydroxyl as the participating group G. Δ^{Ph} is Δ^R, R being phenyl (Ph).

[17] This consideration would be serious for stereochemistry of substitution at Cβ.

[18] R–O cleavage in the RO group has been suggested[7c] for similar cases of aldehyde formation. However, the formation of acetal and aldehyde as formulated here is in line with the chemistry of formation and hydrolysis of acetals. See remarks: S. Winstein, *Bull. soc. chim.*, **55**, 60 (1951); C. Prevost, *ibid.*, **55**, 51 (1951).

[19] These two routes would give contrasting amounts of inclusion, in the final aldehyde, of O^{18} from O^{18}-labeled water.

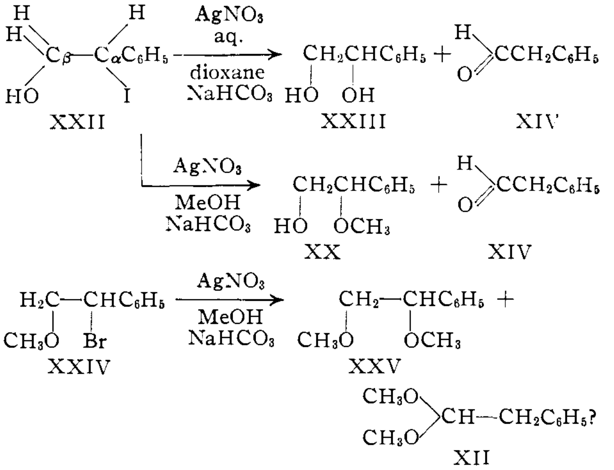
for example, the 2-methyl-2-methoxy-1-propyl system.[20] With the latter system, Δ^{OR} predominates by far over Δ^R. This difference is mainly due to the difference in R, this being phenyl in the first case and methyl in the second, but a more quantitative discussion is deferred until more quantitative data are presented.

Solvolysis–Rearrangement of 2-Methoxy- or Hydroxy-1-phenylethyl Halides.—For contrast with 2-phenyl-2-hydroxyethyl iodide, 1-phenyl-2-hydroxyethyl iodide (XXII), with an α- instead of a β-phenyl group, also was treated with silver nitrate.

On treatment with silver nitrate in aqueous dioxane, under conditions which permitted survival and high recovery of styrene oxide, 1-phenyl-2-hydroxyethyl iodide (XXII) gave rise to styrene glycol (XXIII) and phenylacetaldehyde (XIV) in the ratio of *ca.* 2:1. Similarly, the same reaction in methanol as a solvent gave rise to glycol monomethyl ether (XX) and aldehyde. The glycol monomethyl ether was quite pure primary alcohol XX, giving directly the proper pure 3,5-dinitrobenzoate derivative.

An impure sample of 1-phenyl-2-methoxyethyl bromide (XXIV), prepared by treatment of the corresponding glycol monomethyl ether (XXI) with phosphorus tribromide, was treated with silver nitrate in methanol. The product consisted, for the most part, of the dimethyl ether of styrene glycol (XXV). The product contained *ca.* 20% of materials giving phenylacetaldehyde on hydrolysis. Probably phenylacetaldehyde acetal (XII) was among them, but β-methoxystyrene was probably an impurity in the original bromide and thus also present in the final product.

With the α-phenylalkyl halides XXII and XXIV, the competition between rate-determining processes S, Δ^{OR} and Δ^H needs to be considered. It is quite clear that Δ^{OR} is unimportant here. Also, it is clear that S now predominates, giving rise to the simple substitution products XXIII, XX and XXV. The ratio of S to Δ^H must be at least 2, but it may be very large, since hydrogen shift may occur in the intermediate from the S process. Thus aldehyde may result from the S process and does not require the Δ^H process for its formation.



Experimental Part

All melting points are corrected.

2-Methoxy-2-phenylethyl Iodide.[15]—This material was prepared in 90% yield from redistilled styrene, iodine and mercuric oxide in methanol; b.p. 107–108° (5 mm.), n^{25}D 1.5793, d^{25}_4 1.5811, *MR*D 55.12 (calcd. 54.60) [reported[15] b.p. 135–138° (14 mm.), $d°$ 1.596].

α-Methoxystyrene.[15]—Twenty-three grams (1 g. atom) of sodium was dissolved in 500 ml. of methanol and 131 g. (0.50 mole) of 2-methoxy-2-phenylethyl iodide was added. The solution was refluxed for an hour, poured into 500 ml. of water and extracted with ether. The ether extract was dried over potassium carbonate, after which distillation through a 9″ centered rod column yielded 64.02 g., 95%, of product, b.p. 85–89° (20 mm.) of which 59.2 g. had b.p. 88–89° (20 mm.), n^{25}D 1.5410, n^{20}D 1.5434 [reported[21] b.p. 90.5° (18 mm.), n^{20}D 1.5422, n^{25}D 1.53997].

2-Methoxy-2-phenylethanol.—Two drops of concd. sulfuric acid was added to a solution of 89.1 g. (0.74 mole) of styrene oxide in 300 ml. of methanol. The reaction was vigorous and cooling was required. The solution was neutralized with methanolic potassium hydroxide and worked up in the conventional manner. Distillation through a 9″ centered rod column gave rise to 74.7 g., 66%, cf product, b.p. 120–123° (18 mm.), of which 70.7 g. had b.p. 122–123° (18 mm.), n^{25}D 1.5172, d^{25}_4 1.0602, *MR*D 43.44 (calcd. 43.38).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.02; H, 7.96.

The 3,5-dinitrobenzoate, prepared in the usual way and crystallized once from petroleum ether (b.p. 70–90°), had m.p. 98.0–98.5°.

Anal. Calcd. for $C_{16}H_{14}O_7N_2$: C, 55.50; H, 4.08. Found: C, 55.34; H, 4.54.

A mixture of 45 g. (0.296 mole) of 2-methoxy-2-phenylethanol, 35 g. (0.296 mole) of acetic anhydride and 100 ml. of pyridine was refluxed for an hour. Working up the reaction mixture in the usual way and distillation through a 9″ centered rod column yielded 48.8 g., 84%, of the acetate, b.p. 138–139° (20 mm.), n^{25}D 1.4928, d^{25}_4 1.0659, *MR*D 52.94 (calcd. 52.69).

Preparation of 2-Methoxy-2-phenylethyl Alcohol by Reduction of Methyl α-Methoxyphenylacetate.—Methyl α-methoxyphenylacetate,[22] b.p. 243–244° (754 mm.), 116–117° (10 mm.) (reported[22] 246°), n^{25}D 1.5110, was reduced with lithium aluminum hydride. Distillation through a 5″ Vigreux column yielded the alcohol, b.p. 120–128° (18 mm.).

The 3,5-dinitrobenzoate was difficult to purify, five crystallizations from petroleum ether (b.p. 70–90°) giving m.p. 97–98°, mixed m.p. with the material from acid-catalyzed opening of styrene oxide in methanol, 97–98°, mixed m.p. with the material from base-catalyzed opening of styrene oxide in methanol, 84–86°.

Base-catalyzed Opening of Styrene Oxide with Methanol.—A solution of 89.1 g. (0.74 mole) of styrene oxide in 300 ml. of methanol containing 0.04 mole of sodium methoxide (1 g. sodium) was refluxed for two hours and then added to an equal volume of water. The oil which separated was taken up in ether and the ether extract was dried over potassium carbonate. Distillation through a 9″ centered rod column gave rise to 85.6 g., 76%, of material, b.p. 123–129° (18 mm.). The 3,5-dinitrobenzoate, when crystallized slowly from petroleum ether (b.p. 70–90°), yielded both plates and needles which could be separated mechanically. Three repetitions of this procedure yielded needles, m.p. 117°, and plates, m.p. 98°, mixed m.p. with material from acid-catalyzed opening of styrene oxide, 98–98.5°.

A 79-g. quantity of the product of base-catalyzed opening of styrene oxide was refluxed with 75 g. of phthalic anhydride in 200 ml. of benzene for an hour. The solution was cooled and the excess phthalic anhydride was filtered out. The filtrate was washed with 6 *N* potassium hydroxide and the basic solution was acidified with 6 *N* hydrochloric acid and extracted with ether.

The benzene solution was distilled through a 9″ centered rod column giving 59.5 g., 75%, of 2-methoxy-1-phenylethanol, b.p. 126–127° (18 mm.), n^{25}D 1.5185, d^{25}_4 1.061, *MR*D 43.51 (calcd. 43.38) [reported[15b] b.p. 132° (18 mm.),

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[20] S. Winstein, C. R. Lindegren and L. L. Ingraham, THIS JOURNAL, **75**, 155 (1953).

[21] K. Auwers, *Ber.*, **44**, 3514 (1911).

[22] R. Meyer, *Ann.*, **220**, 45 (1883).

d^{0} 1.080 and[23] b.p. 128–132° (18 mm.), $n^{26}\mathrm{D}$ 1.5165, d^{25}_{25} 1.070]. The 3,5-dinitrobenzoate, prepared in the usual way, melted at 116° after one crystallization from petroleum ether (b.p. 70–90°) and 117° after two crystallizations.

Anal. Calcd. for $C_{16}H_{14}O_7N_2$: C, 55.50; H, 4.08. Found: C, 55.38; H, 4.14.

Saponification of the acid phthalate fraction and distillation of the product through a 9″ centered rod column yielded 8.7 g., 11%, of alcohol, b.p. 122–126° (18 mm.), $n^{25}\mathrm{D}$ 1.5177.

Reaction of 2-Methoxy-2-phenylethyl Iodide with Aqueous Silver Nitrate.—Ninety-five grams (0.55 mole) of silver nitrate in 250 ml. of water was added dropwise with stirring to a mixture of 131 g. (0.50 mole) of 2-methoxy-2-phenylethyl iodide, 250 ml. of dioxane and 30 g. (0.30 mole) of calcium carbonate. The reaction mixture was steam distilled. The distillate was extracted with ether and the ether extract was dried over magnesium sulfate. Distillation through a 9″ centered rod column gave 32.8 g., 55%, of product, b.p. 90–92° (20 mm.), $n^{25}\mathrm{D}$ 1.5238, semicarbazone, m.p. 156°, mixed m.p. with phenylacetaldehyde semicarbazone, 156°. The refractive index increased rapidly with time, reaching the value 1.5318 in two weeks (reported[23] $n^{25}\mathrm{D}$ 1.5242).

When the reaction mixture was not steam distilled, 20–30% yields of phenylacetaldehyde, b.p. 73–75° (10 mm.), were obtained together with large amounts of the viscous yellow high-boiling oil typical for reactions involving phenylacetaldehyde.

In a control experiment, 0.50 mole of nitric acid in 250 ml. of water was added dropwise with stirring to a mixture of 38 g. (0.25 mole) of 2-methoxy-1-phenylethanol, 250 ml. of dioxane, 117.5 g. (0.50 mole) of silver iodide and 30 g. (0.30 mole) of calcium carbonate. The reaction mixture was filtered and the filtrate was continuously extracted with ether. The ether extract was dried over potassium carbonate after which distillation through a 9″ centered rod column gave 32.1 g., 84%, of recovered alcohol, b.p. 125–128° (18 mm.), $n^{25}\mathrm{D}$ 1.5184.

A similar experiment with 76.1 g. (0.50 mole) of 2-methoxy-2-phenylethanol yielded 66.6 g., 87.5%, of recovered alcohol, b.p. 123–125° (20 mm.), $n^{25}\mathrm{D}$ 1.5178. Similarly, from 67 g. (0.50 mole) of α-methoxystyrene was recovered 59.5 g., 89%, of material, b.p. 86–94° (20 mm.), *ca.* 90%, b.p. 89–90° (20 mm.), $n^{25}\mathrm{D}$ 1.5413.

A similar control experiment was performed on 30 g. (0.306 mole) of β-methoxystyrene[24] which had been made available to us by Dr. T. L. Jacobs and Mr. Willard Scott. There was recovered 18.3 g., 61%, of material, b.p. 109–112° (30 mm.), $n^{20}\mathrm{D}$ 1.5655 (reported[21] $n^{20}\mathrm{D}$ 1.5639).

Dimethyl Acetal of Phenylacetaldehyde.[25]—This material was prepared in the usual way in 70% yield, b.p. 107–108° (20 mm.), $n^{20}\mathrm{D}$ 1.4941, $n^{25}\mathrm{D}$ 1.4922, d^{25}_{4} 1.005 [reported d^{18}_{4} 1.0042, b.p. 219–221° (754 mm.),[25] b.p. 95.5–96° (10 mm.)[26]].

Analysis for Phenylacetaldehyde-forming Materials.—Analysis for phenylacetaldehyde produced under mild hydrolysis conditions was based on precipitation of the 2,4-dinitrophenylhydrazone. A 0.2–0.4-g. sample of material to be analyzed was added to 50 ml. of a solution prepared by dissolving 2 g. of 2,4-dinitrophenylhydrazine in 15 ml. of concd. sulfuric acid and diluting with 200 ml. of ethanol. After the sample was stirred well with the 2,4-dinitrophenylhydrazine solution, it was allowed to stand overnight. The solution was then filtered onto a weighed filter paper and 20 ml. of petroleum ether (b.p. 30–60°) and 100 ml. of water was added to the filtrate. This gave another precipitate which was filtered onto the first. The precipitate was dried in a vacuum desiccator for a day and then weighed. By this procedure, 2-methoxy-2-phenylethanol assayed 0%, phenylacetaldehyde dimethyl acetal 103% and β-methoxystyrene 99%.

Reaction of 2-Methoxy-2-phenylethyl Iodide with Silver Oxide in Methanol.—A solution of 131 g. (0.50 mole) of 2-methoxy-2-phenylethyl iodide in 500 ml. of methanol was refluxed with stirring with 88 g. (0.38 mole) of silver oxide for two hours. Working up in the conventional manner yielded 23.5 g., 18% of unreacted starting material, b.p. 140–141° (20 mm.), $n^{25}\mathrm{D}$ 1.5790, and 47.5 g., 57%, of product, b.p. 106–112° (20 mm.). Redistillation of the latter material yielded a product, b.p. 107.0–107.5° (20 mm.), $n^{20}\mathrm{D}$ 1.4943, $n^{25}\mathrm{D}$ 1.4922. Steam distillation of a sample of this material from 1 *N* sulfuric acid and conversion of the product to a semicarbazone yielded a derivative, m.p. 156°, mixed m.p. with the semicarbazone of phenylacetaldehyde, 156°. The dinitrophenylhydrazine analytical method gave an analysis of 96% acetal.

When phenylacetaldehyde was subjected to the above reaction conditions, only the typical polymeric material was obtained.

Reaction of 2-Iodo-1-phenylethanol with Silver Nitrate.—In an experiment kindly performed by Richard Heck, a solution of 45 g. of silver nitrate in 100 ml. of water was added over a period of 10 minutes to a stirred solution of 60 g. of styrene iodohydrin[27] in a mixture of 100 ml. of water and 250 ml. of purified dioxane. After 15 minutes stirring, the mixture was filtered and the organic material was extracted with petroleum ether. The extracts were washed with water and then extracted with two 100-ml. portions of water containing 40 g. of sodium metabisulfite. The precipitate was filtered and washed with water and petroleum ether. The yield of phenylacetaldehyde bisulfite addition compound was 28 g., 52%.

The remaining petroleum ether solution was concentrated to 2 g. of a red oil which decomposed on attempted vacuum distillation.

The original aqueous dioxane solution was neutralized with sodium bicarbonate and continuously extracted with chloroform for 30 hours. Evaporation of the extracts yielded 2 g. of an oil which did not crystallize when seeded with styrene glycol.

In a control experiment on styrene oxide, a solution of 20 g. of styrene oxide, $n^{25}\mathrm{D}$ 1.5316, in 100 ml. of petroleum ether was shaken for 15 minutes with a solution of 40 g. of sodium metabisulfite in 100 ml. of water. Working up the material, 19.5 g., 97.5%, of styrene oxide, b.p. 83–84° (18 mm.), $n^{25}\mathrm{D}$ 1.5318, was recovered.

In a control experiment on styrene glycol, a solution of 22.5 g. of silver nitrate and 8.5 ml. of concd. nitric acid was added dropwise over a period of 5 minutes to a stirred solution of 16.5 g. of styrene glycol and 22.5 g. of potassium iodide in 125 ml. of dioxane plus 75 ml. of water. After 10 minutes stirring, the filtered solution was extracted with two portions of petroleum ether. The extract was treated with 20 ml. of a saturated sodium bisulfite solution but no precipitate formed.

Continuous extraction of the original aqueous dioxane solution for 30 hours yielded an oil which crystallized on cooling. Recrystallization gave 13.3 g., 80.6%, of recovered glycol, m.p. 65–67°.

The Reaction of 2-Hydroxy-1-phenylethyl Iodide with Silver Ion in Water.—2-Hydroxy-1-phenylethyl iodide, m.p. 78.5–79°, was prepared in 80% yield by the method of Golumbic and Cottle.[27] Forty-five grams (0.266 mole) of silver nitrate in 100 ml. of water was added dropwise with stirring to a mixture of 60 g. (0.242 mole) of 2-hydroxy-1-phenylethyl iodide, 41 g. (0.484 mole) of sodium bicarbonate, 150 ml. of water and 250 ml. of dioxane. Stirring was continued for about 10 minutes after all the silver nitrate had been added. The solids were filtered out and the filtrate was extracted with 3 100-ml. portions of petroleum ether (b.p. 30–60°). The petroleum ether extract was dried over magnesium sulfate. Distillation through a 9″ centered rod column gave 2.95 g. of a material, b.p. 88–90° (20 mm.), $n^{25}\mathrm{D}$ 1.5250, semicarbazone, m.p. 156° undepressed on mixing with phenylacetaldehyde semicarbazone, together with 5.00 g. of polymeric material (27% including polymer).

The aqueous solution was continuously extracted with chloroform. Evaporation of the chloroform and crystallization from benzene–ligroin (b.p. 30–60°) mixture gave 15.2 g., 45.5%, of styrene glycol, m.p. 53–57°, m.p. 66–67° after recrystallization (reported[28] m.p. 67–68°).

Styrene oxide was subjected to the above reaction conditions. Five-tenths mole of nitric acid in 100 ml. of water was added dropwise with stirring to 60 g. (0.50 mole) of styrene oxide, 250 ml. of dioxane, 117.5 g. (0.50 mole) of silver iodide, 84 g. (1 mole) of sodium bicarbonate, 8.5 g. (0.50 mole) of silver nitrate and 150 ml. of water. The solids were filtered out and the filtrate was extracted with

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[23] W. S. Emerson, THIS JOURNAL, **67**, 516 (1945).

[24] T. L. Jacobs and W. R. Scott, Jr., *ibid.*, **75**, 5500 (1953).

[25] E. Fischer and E. Hoffa, *Ber.*, **31**, 1989 (1898).

[26] F. Sigmund, *Monatsh.*, **49**, 271 (1928).

[27] C. Golumbic and D. L. Cottle, THIS JOURNAL, **61**, 996 (1939).

[28] Th. Zincke, *Ann.*, **216**, 286 (1883).

ether. The ether extract was dried over potassium carbonate. Distillation through a 9" centered rod column gave 54.9 g., 91.5%, of recovered oxide, b.p. 100–102° (40 mm.), $n^{25}\text{D}$ 1.5313.

Treatment of 2-Iodo-2-phenylethanol with Silver Ion in Methanol.—A solution of 102 g. (0.60 mole) of silver nitrate in 5 l. of methanol was added dropwise with stirring to 125 g. (0.50 mole) of iodohydrin and 50 g. (0.60 mole) of sodium bicarbonate in 1 liter of methanol. The reaction mixture was filtered and the filtrate was concentrated and then added to a liter of water saturated with salt. The mixture was extracted with five 100-ml. portions of ether and the ether extract was dried over magnesium sulfate. Distillation through a 9" centered rod column yielded 17.55 g., 59.5%, of 2-methoxy-2-phenylethanol, b.p. 120–125° (18 mm.), plus 7.5 g. of polymer which would correspond to 25% of phenylacetaldehyde. The carbinol fraction yielded a 3,5-dinitrobenzoate, m.p. 98.0–98.5°, mixed m.p. with authentic material 98.0–98.5°, mixed m.p. with isomeric material 85–89°.

2-Methoxy-1-phenylethyl Bromide.—To a stirred solution of 40 ml. of dimethylaniline, 30 ml. of dry ether and 76 g. (0.50 mole) of 2-methoxy-1-phenylethanol, 20 ml. (0.21 mole) of phosphorus tribromide was added dropwise while the temperature was kept below 0°. After the addition was complete, the stirring was continued for an hour and the temperature was allowed to rise to 20°. The reaction mixture was then cooled to 0° again and 20 ml. of water was added. The reaction mixture was then added to 400 ml. of water and the oil which separated was taken up with three 100-ml. portions of ether. The ether was dried over magnesium sulfate, then distilled through a 5" Vigreux column to yield 34.1 g., 32%, of impure product, b.p. 88–92° (1 mm.), $n^{25}\text{D}$ 1.5480, d^{25}_{4} 1.332, $MR\text{D}$ 51.31 (calcd. 49.57).

Treatment of 2-Methoxy-1-phenylethyl Bromide with Silver Ion in Methanol.—A solution of 62.6 g. (0.369 mole) of silver nitrate in 3.2 l. of methanol was added dropwise with stirring over a period of *ca.* half-hour to 62.2 g. (0.74 mole) of sodium bicarbonate and 72.1 g. (0.335 mole) of 2-methoxy-1-phenylethyl bromide in 1 l. of methanol. The reaction mixture was filtered and the methanol was distilled off through a 9" Vigreux column. When 1 l. of solution remained, it was added to 1 l. of a saturated salt solution and extracted with five 100-ml. portions of ether. The ether was distilled off through a 13" Vigreux column and the residue was distilled through a 9" centered rod column yielding 37.5 g., 68%, of product, b.p. 107–115° (20 mm.), $n^{25}\text{D}$ 1.5035.

Analysis of the product by the dinitrophenylhydrazine method indicated *ca.* 20 mole per cent. of material, calculated as acetal, which gives phenylacetaldehyde dinitrophenylhydrazone.

A mixture of *ca.* 35 g. of the crude product and 400 ml. of 2 *N* sulfuric acid was steam distilled and the distillate was extracted with ether. The ether extract was dried over potassium carbonate. Distillation at 20 mm. pressure through a centered rod column yielded *ca.* 15 g. of product, b.p. 107–109° (20 mm.), with 10 g., b.p. 108–109° (20 mm.), $n^{25}\text{D}$ 1.4943, presumably styrene glycol dimethyl ether.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.50. Found: C, 72.03; H, 8.39.

The dinitrophenylhydrazine analytical method indicated less than 2% of phenylacetaldehyde-forming compounds.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM HALL LABORATORY OF CHEMISTRY, WESLEYAN UNIVERSITY]

Cyanide Ion as a Catalyst for Transesterification. Non-aqueous Buffering

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It has been demonstrated that methanolic potassium cyanide, serving as a non-aqueous buffer system, effects the transesterification of several esters. The transesterification reaction has been shown to be an effective alternative to hydrolysis in a system where the hydrolytic reaction is complicated by elimination.

In the course of another investigation it was observed that when a methanolic solution of 7-ketocholesteryl acetate was refluxed with potassium cyanide, 7-ketocholesterol was isolated directly in a pure state (m.p. 170–171.5°, $\alpha^{28}\text{D}$ $-106°$) as the only solid organic product.[1]

Bergstrom and Wintersteiner[2] obtained pure 7-ketocholesterol by the hydrolysis of the acetate with potassium carbonate in 80% methanol, but they did not report the yield. Other workers[3–5] have had considerable difficulty with both yield and purity of the hydrolysis product because of accompanying elimination. Barnett,[3] when using the methanolic potassium carbonate method, obtained material melting 10° low, the impurities being of such a nature that repeated recrystallization did not raise the melting point.

In view of the normally troublesome nature of this hydrolysis it was felt that the use of alcoholic cyanide might be a somewhat general answer to the problem of concurrent elimination during hydrolysis. For this reason the reaction was studied further to determine the mechanism, generality and optimum conditions.

For the first part of this study cholesteryl acetate (I) and the base sensitive 7-ketocholesteryl acetate (II) were used. When the original conditions were varied by rendering the reaction anhydrous, no significant change in the course of the reaction was noted. This observation ruled out hydrolysis as a mechanism. The reactions were also found to take place at room temperature, in the presence or absence of water. The results are summarized in Table I.

The only significant difference between I and II was the more rapid rate of reaction of the 7-keto compound, expected on the basis of the electron withdrawing effect of the conjugated carbonyl oxygen. 7-Ketocholesterol was produced from its acetate in approximately one-third of the time necessary to transform cholesteryl acetate into the free alcohol. Additional reflux time did not induce any decomposition of the 7-ketocholesterol.

The effectiveness of a weaker base than cyanide

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(1) A reaction of zinc cyanide with certain esters, leading to the production of the free alcohol, was described by L. P. McHatton and M. J. Soulal (*Chem. & Ind.*, 1337 (1953)). Inasmuch as neither alcohol nor water was reported present in sufficient quantity to account for the observed result, the mechanism of the reaction carried out by the British workers is not the same as that proposed for the reaction described in this paper.

(2) S. Bergstrom and O. Wintersteiner, *J. Biol. Chem.*, **141**, 602 (1941).

(3) J. Barnett, *J. Chem. Soc.*, 528 (1946).

(4) J. Mauthner and W. Suida, *Monatsh.*, **17**, 579 (1896).

(5) A. Ogota and I. Kawakani, *J. Pharm. Soc. Japan*, **58**, 738 (1938).