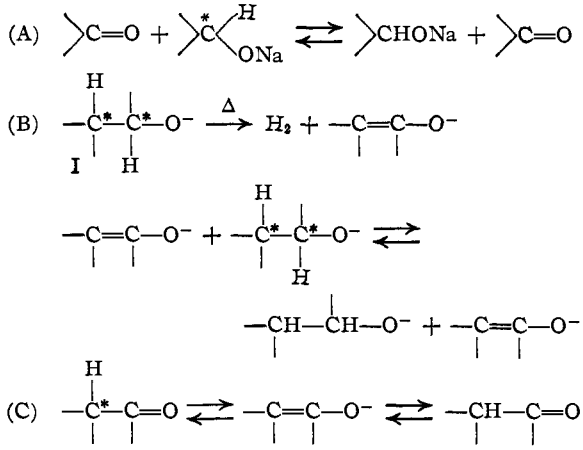
[CONTRIBUTION FROM THE CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

Stereochemical Equilibration of Alcohols[1]

BY W. VON E. DOERING AND T. C. ASCHNER

From many examples in the literature,[2,3,4] it is apparent that alcohols of the general structure I may be brought to stereochemical equilibrium[5] by treatment with alkoxide ion. Both Wagner-Jauregg[2] and Hückel[3] have suggested that the equilibration is initiated by the dehydrogenation of sodium alcoholate to aldehyde or ketone which then takes part in a Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation. Wagner-Jauregg has formulated



the reaction in general terms (A) and has left an explanation of the stereochemical equilibration of alcohols of type I to the more specific suggestions of Hückel (B) although, as has been pointed out,[4] recognition of the inevitable enolization of the carbonyl compounds related to alcohols of type I suffices to accommodate the stereochemical equilibration of the latter (C).

Doering, Cortes and Knox[4] have presented considerable evidence in support of the modified mechanism (A and C) but have been unable to demonstrate (in the case of quinine) the striking consequence of the mechanism, that optically active alcohols should not be racemized in the complete absence of oxidants. In the present work, it is shown that the racemization of (−)-phenylmethylcarbinol by potassium *t*-butoxide at 100° can be completely inhibited by excluding oxygen, potassium peroxides and carbonyl compounds, and that, under otherwise non-racemizing conditions, the addition of the rapid oxidation–reduction system,[6] fluorenone (3 mole %)–fluorenol (6 mole %), causes 56% racemization. In another example, (−)-2-methylbutanol-1, stable to boiling for twenty hours with 5 mole % of sodium, is racemized in a few hours by adding 5 mole % of benzophenone.[7] Similarly with aluminum isopropoxide as catalyst, no racemization occurs until an oxidant, benzophenone, is added.

These experiments establish with considerable certainty that the presence of carbonyl compound is a necessary condition for effecting the stereochemical equilibration of alcohols of type I and can be interpreted to mean that a reversible oxidation–reduction process is the essential mechanism of the equilibration. The further conclusion can be drawn that no initiating carbonyl compound is formed by the elimination of hydrogen gas as proposed by both Wagner-Jauregg and Hückel, at least not at the comparatively low temperature of these equilibrations, although at higher temperatures where alkoxide ion is known to decompose to hydrogen,[8] dehydrogenation may serve as a way of introducing initiating carbonyl compound.

The unique structural consequence of mechanism B, that it should be impossible stereochemically to equilibrate those secondary alcohols in which lack of α-hydrogen prohibits dehydrogenation to a related enolate ion, has been given temporary confirmation in the negative observation that α- and β-fenchol cannot be epimerized, even under conditions drastic enough to form the corresponding ketone, fenchone.[9] Contrarywise it has now been established that both α- and β-fenchol can be epimerized when the rapid oxidation–reduction system, fluorenol–fluorenone, is added. Coupled with the ability of non-enolizable ketones such as benzophenone and fluorenone to initiate stereochemical equilibration, the successful epimerization of the fenchols invalidates direct dehydrogenation to an enolate ion as the mechanism of the effectual oxidation–reduction process. Hückel's mechanism (B) is presumably generally incorrect in that it limits the reaction to alcohol–carbonyl systems having alpha hydrogen.

(1) This work, taken from a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University, was presented at the 112th meeting of the American Chemical Society, September 7, 1947, New York, N. Y., by T. C. Aschner, present address, Smith, Kline and French Laboratories, Philadelphia, Pa.

(2) Wagner-Jauregg in Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, pp. 866–867.

(3) Hückel, "Theoretische Grundlagen der organischen Chemie," Akademische Verlagsgesellschaft, Leipzig, 2nd ed., 1934, Vol. I, pp. 286–288.

(4) Doering, Cortes and Knox, THIS JOURNAL, **69**, 1700 (1947).

(5) The term "stereochemical equilibration" is defined to embrace racemization, partial racemization, epimerization, and *cis-trans* interconversion, the specific process depending on the detailed structure of the alcohol under consideration.

(6) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

(7) In the absence of consciously added oxidant, Stevens [*ibid.*, **54**, 3732 (1932)] has observed a much slower rate of racemization.

(8) Hückel cites the Guerbet reaction and the inversion of *cis-cis*-α-decalol [Hückel and Naab, *Ber.*, **64**, 2137 (1931)]. Compare footnote 18 of ref. 4.

(9) Hückel, Kindler and Wolowski, *ibid.*, **77**, 220 (1944).

The failure to epimerize the fenchols in the presence of fenchone and the vain attempt to effect the partial racemization of quinine in the presence of quininone[4] clearly indicate that excessively slow rates of oxidation–reduction may conspire to make the necessary presence of carbonyl compound an insufficient condition for stereochemical equilibration. In these, as well as in less extreme cases, the stereochemical equilibration can be catalyzed by adding a much more rapid oxidation–reduction system.[6] For example, in the very slowly reacting fenchol–fenchone sys-

$$\text{Fenchone}^* + \text{Fenchol} \underset{\longleftarrow}{\overset{\longrightarrow}{(1)}} \text{Fenchol}^* + \text{Fenchone}$$

$$\text{Fluorenol}^* + \text{Fluorenone} \underset{\longleftarrow}{\overset{\longrightarrow}{(2)}} \text{Fluorenone}^* + \text{Fluorenol}$$

$$\text{Fluorenol} + \text{Fenchone} \underset{\longleftarrow}{\overset{\longrightarrow}{(3)}} \text{Fluorenone} + \text{Fenchol}$$

tem (1), the addition of fluorenol and fluorenone, which interact very rapidly (2), introduces a cross reaction (3) of intermediate rate that results in the more rapid establishment of equilibrium (1).[10]

Experimental[11]

Racemization of Phenylmethylcarbinol.—(−)-Phenylmethylcarbinol, $[\alpha]^{27}D$ −50.6° (c = 3, toluene), b.p. 86.5–87.5° (8 mm.), was obtained by resolution of the acid phthalate according to Downer and Kenyon.[12] Decomposition of the active acid phthalate and distillation of the active alcohol were carried out under nitrogen. The racemizations were effected in thiophene-free toluene which had been distilled repeatedly from sodium under nitrogen. Potassium *t*-butylate was prepared by dissolving freshly cut and carefully washed potassium in *t*-butyl alcohol in a nitrogen atmosphere. *t*-Butyl alcohol was purified by refluxing over potassium permanganate and twice distilling from sodium under nitrogen. Preliminary experiments, carried out in the simple apparatus customarily used to avoid contact with air, led to considerable and unpreventable racemization even in the absence of added oxidant. The more complicated apparatus shown in Fig. 1 prevented contamination by oxidants when employed according to the following procedure: After the system had been flushed with nitrogen, 10 cc. of toluene from flask A, containing purified toluene and 1 g. of sodium, was distilled under nitrogen into D. The remaining system was closed at G and E, D was detached and potassium, freshly cut and weighed under toluene, was quickly dropped into D which was then reattached to G and flushed with nitrogen through L, F and E. L and I were closed, G was opened and toluene was forced through E into F by nitrogen pressure. Five drops of *t*-butyl alcohol was added through B to A and was distilled with 10 cc. of toluene into D. All liquid was forced out of D into F as before and the surface of the potassium was further cleaned by rinsing with two additional 10-cc. portions of toluene distilled from A; *t*-butyl alcohol (3.0 g.) was added through B to A and was distilled into D with 10 cc. of toluene. Still under positive nitrogen pressure, D was heated in an oil-bath until all the potassium had reacted. A weighed amount of (−)-phenylmethylcarbinol was added through H to D and the volume in D was adjusted to 30 cc. by distilling additional toluene from A. All reagents added through H or B were forced into the system by applying excess nitrogen pressure. Finally D was heated in an oil-bath at 99–100°. In experiments 1 and 4, fluorenol and fluorenone in toluene were added to D through H prior to the final heating. After being cooled, the reaction mixture was forced into the cleaned flask F, and neutralized under nitrogen with dilute hydrochloric acid added through J. Phenylmethylcarbinol was isolated from reactions 1 to 3 by fractionation of the washed reaction mixtures through a 10-cm. Vigreux column, the specific rotation of the main fraction b.p. 203–204° (760 mm.), being determined at 27° (c = 3, toluene). Partly racemized phenylmethylcarbinol from reaction 4 was separated from non-alcoholic impurities by conversion to the acid phthalate. Treatment of alkali-insoluble compounds extracted from the alkaline solution of the acid phthalate with 2,4-dinitrophenylhydrazine, yielded only 0.04 g. of acetophenone-2,4-dinitrophenylhydrazone. The results of these experiments are compiled in Table I.

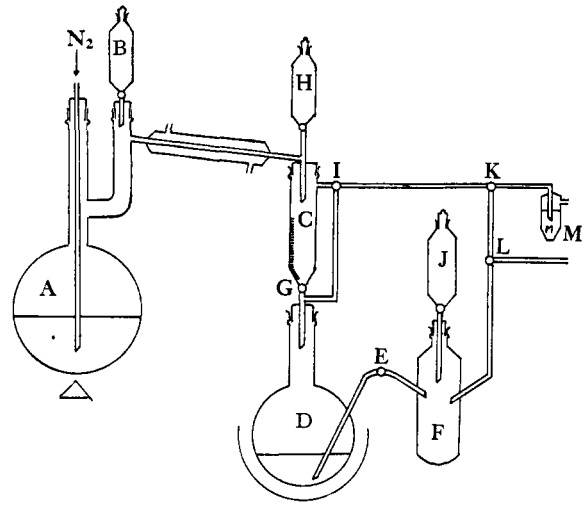


Fig. 1.

TABLE I

Expt.	Potassium in mole %	*t*-Butyl alcohol in mole %	Phenylmethylcarbinol, g.	Reaction time, hours	$[\alpha]^{27}D$ of phenylmethylcarbinol	% Racemization
1	20	100	2.0	19	−49.3°	2
2[a]	20	100	2.0	17	−27.5°	46.5
3[b]	20	100	4.0	17	−49.4°	2
4[b]				17	−22.4°	56

[a] Prior to the start of heating, 1 mole % of fluorenone and 2 mole % of fluorenol were added to the reaction mixture; [b] One-half of reaction 3 was forced into flask F after seventeen hours of heating and phenylmethylcarbinol was isolated; to the remaining reaction mixture, 3 mole % of fluorenone and 6 mole % of fluorenol were added and heating was continued seventeen hours longer (reaction 4).

Racemization of (−)-2-Methylbutanol-1.—From a commercially available fraction of fusel oil containing about 17% of (−)-2-methylbutanol-1, and about 80% of 3-methylbutanol-1, various fractions of (−)-2-methylbutanol-1 (75–100% optically active) were obtained by two fractionations (at a reflux ratio of 1:100) through a four-foot adiabatic column packed with metal helices.

From 2.2 to 8.8 g. of optically active alcohol was treated with sodium under an atmosphere of nitrogen or, in other experiments, was added to aluminum isopropoxide. The resulting alkoxide solution was then heated at 120° with or without previous addition of oxidants, for various periods of time under positive nitrogen pressure. After being cooled, the reaction mixture, made weakly acidic by adding hydrochloric acid, was extracted with 100 cc. of ether. The ether extract was washed with water, dried over

(10) It may be mentioned that the acceleration depends in no way on oxidation–reduction potentials; in fact, equilibrium concentrations could be chosen so that no concentration changes would accompany the acceleration of (1).

(11) All melting points are corrected.

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

magnesium sulfate and fractionated through a 10 cm. Vigreux column. The fraction boiling at 127–128° was collected, the specific rotation being measured in methanol at 27°. From blank runs it was established that further purification of the recovered alcohol was not necessary. The results of various experiments are compiled in Table II.

TABLE II

Catalyst in mole %	Added reagents in mole %	Reaction time, hours[a]	$[\alpha]^{27}D$ starting alcohol[b]	$[\alpha]^{27}D$ recovered alcohol	Racemization in %
5[c]	5 Fluorenone; 10 fluorenol	16	−5.3	0.0	100
5[c]		17	−5.3	−5.3	0
5[c]	5 Heptaldehyde	17	−4.3	0.0	100
5[c]		17	−4.3	−3.9	11
5[c]	5 Benzophenone	5	−3.8	−0.3	89
5[c]		20	−3.8	−3.8	0
5[d]	5 Benzophenone	4.5	−4.3	−3.4	21
5[d]		4.5	−4.3	−4.3	0
5[d]	5 Benzophenone	14	−4.3	−2.6	42
5[e]		5	−6.6	−6.6	0

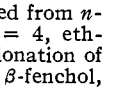
[a] Reaction temperature was 120°. [b] The specific rotations were measured in methanol (c = 3). Starting materials with identical specific rotations were obtained from the same sample. [c] Sodium. [d] Aluminum isopropoxide.

Epimerization of α- and β-Fenchol.—α-Fenchol was prepared from purified d-fenchone by reduction with sodium and amyl alcohol[13]; m.p. 43.6–44.5°, $[\alpha]^{27}D$ −12.7° (c = 3, 95% ethanol); acid phthalate, m.p. 145–146°, $[\alpha]^{27}D$ + 20.2° (c = 5, methanol). β-Fenchol was prepared by catalytic reduction of d-fenchone with copper chromite catalyst in ethanol at 100 atmospheres and 110°.[14] The alcohol was isolated from the reduction mixture via the acid phthalate (twice crystallized from n-hexane), m.p. 151–151.6° $[\alpha]^{22}D$ + 11.7° (c = 4, ethanol), which yielded upon hydrolysis and fractionation of the hydrolysate in a molecular still, 94.4% pure β-fenchol, $[\alpha]^{27}D$ −21.8° (c = 4, ethanol).

A mixture of 7.7 g. of β-fenchol (0.05 mole), 9.1 g. of fluorenol (0.05 mole) and 0.91 g. of fluorenone (0.005 mole) in 38 cc. of t-butyl alcohol containing 0.12 g. of sodium (0.005 mole) was heated in a bomb-tube under nitrogen for seventy hours at 165°. The high-boiling fraction [7 g., b.p. 83–86° (20 mm.)] of the neutralized reaction mixture was heated twenty-five hours with 7.0 g. of phthalic anhydride in 8.5 g. of pyridine at 100° to give 9.6 g. of crude fenchyl acid phthalate, which was crystallized from glacial acetic acid. The first crop (4.8 g., m.p. 139–141°, $[\alpha]^{27}D$ +17.2°) yielded after two recrystallizations from the same solvent, 3.0 g. of α-fenchyl acid phthalate, m.p. 145–145.6°, $[\alpha]^{27}D$ +20.8° (c = 3, ethanol); the second crop (3.0 g., m.p. 138–143.5°, $[\alpha]^{27}D$ + 14.1°) yielded after three recrystallizations from glacial acetic acid an additional 0.48 g., m.p. 143–145.2°, $[\alpha]^{27}D$ + 19.1°. Hydrolysis and sublimation of the combined samples of α-fenchyl acid phthalate yielded 1.1 g. of α-fenchol, $[\alpha]^{27}D$ −12.2° (c = 4, ethanol), m.p. 43.5–44.6°, mixed m.p. 43.5–44.5°. The combined acid phthalate mother liquors yielded after three recrystallizations from n-hexane 3.0 g. of solid, m.p. 148–149.5°, $[\alpha]^{27}D$ + 13.8° (c = 3, ethanol), from which 1.1 g. of β-fenchol was recovered upon hydrolysis, $[\alpha]^{27}D$ −19.0° (c = 3, ethanol).

A mixture of 6.1 g. of α-fenchol (0.04 mole), 7.3 g. of fluorenol (0.04 mole) and 0.75 g. of fluorenone (0.004 mole) in 30 g. of butyl alcohol containing 0.09 g. of sodium (0.004 mole) was heated in a bomb-tube under nitrogen for thirty-five hours at 160–180°. After removal of solvent from the neutralized reaction mixture, fenchol was co-distilled with 12 cc. of decalin from the residue of fluorenol and fluorenone. From the distillate, b.p. 118–119° (100 mm.), fenchol (3.6 g., $[\alpha]^{22}D$ −14.9°) was separated by conversion to the acid phthalate, extraction of neutral impurities, hydrolysis, steam distillation and fractionation. Upon redistillation through a molecular still, some α-fenchol crystallized on the cold finger and the distillate was thus further enriched in β-fenchol[15], $[\alpha]^{27}D$ −15.7° (c = 2, ethanol).

Summary

From the fact that (−)-phenylmethylcarbinol and (−)-2-methylbutanol-1 are not racemized by alkoxide ion in the complete absence of oxidants but are racemized in the presence of ketones, it is concluded that the stereochemical equilibration of alcohols  is accomplished through an oxidation–reduction mechanism. α- and β-fenchols, thought previously to be unepimerizable because of lack of α-hydrogen, have now been epimerized.

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(13) Gardner, *J. Chem. Soc.*, **73**, 276 (1898).

(14) We are grateful to Dr. H. R. Snyder for suggesting and carrying out, in the laboratories of the University of Illinois, the reduction of d-fenchone with copper chromite catalyst, when Raney nickel failed.

(15) In agreement with Hückel's findings,[9] we were unable to isolate pure β-fenchol from the mixture which contained a substantial excess of α-fenchol. However, the change in specific rotation from −12.7° to −15.7° can only be assigned to the formation of β-fenchol, since the likely optically active contaminant, fenchone ($[\alpha]^{27}D$ +62°), would have changed the rotation in the opposite direction.