Their action as topical anesthetics is shown in Table II.

However, such data alone does not necessarily give a true idea of relative anesthetic usefulness. The compounds have been subject to extensive pharmacologic investigation the results of which will be published elsewhere.

Several members of a similar series of esters have been prepared from β-(2-piperidyl)-propanol, γ-(2-piperidyl)-propanol, and (2-piperidyl)-isopropanol. The last two alcohols are prepared readily from the corresponding pyridine compounds, which, in turn, are easily prepared in 40% yields by treating lithium picolyl with ethylene oxide, and with acetaldehyde, respectively. This will be the subject of a future communication.

## Summary

A series of substituted benzoic esters of β-(2-piperidyl)-ethanol hydrochloride has been prepared and their local anesthetic properties determined.

NEWARK, N. J. RECEIVED APRIL 17, 1939

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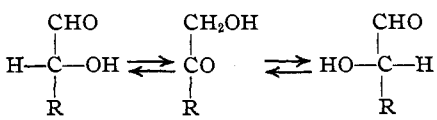
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY AND FROM THE CHEMICAL LABORATORY OF MCGILL UNIVERSITY]

# The Rearrangement of α-Hydroxy Carbonyl Compounds

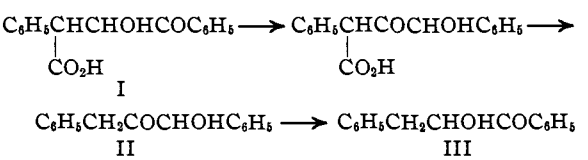
BY PHILIP G. STEVENS

The first case of the rearrangement of α-hydroxy carbonyl compounds was that studied by Lobry de Bruyn,[1] wherein glucose, fructose, and mannose were shown to be in equilibrium with one another in alkaline solutions. The essential change is a shift of the carbonyl and hydroxyl groups, presumably through a dienol intermediate

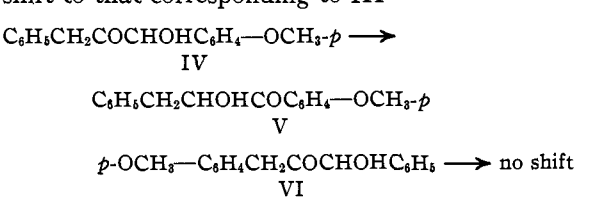


Wohl[2] found that in all probability the same equilibrium existed between certain trioses, namely, glyceric aldehyde and dihydroxyacetone, because in alkaline solutions both compounds yielded the same β-acrose. This view was supported later by Fischer's discovery[3] that glyceric aldehyde could be converted into dihydroxyacetone by mere boiling with pyridine. Still later a similar shift of the carbonyl and hydroxyl groups has been reported by Shoppee[4] with highly substituted cyclic α-hydroxy ketones.

More recently Kohler and Kimball[5] observed the same shift in alkaline media with derivatives of diphenylpropane. Thus α-phenyl-β-hydroxy-β-benzoylpropionic acid I with alkalies lost carbon dioxide spontaneously, forming α-hydroxy-dibenzyl ketone II; and this in turn could be converted to its isomer α-hydroxy-benzylacetophenone III. The conversion of II into III convinced them that the mechanism of the formation of II from I involved a similar shift



Later Kohler and Leers[6] found the same shift in the *p*-methoxy substituted series. The position of the substitute was, however, of importance, for while both mono-*p*-methoxy-substituted acids formed hydroxy ketones corresponding to II, only one of these would undergo further shift to that corresponding to III



Although neither III, V, nor VI was altered by further treatment with alkalies, Kohler and Kimball believed that an equilibrium existed between the two isomers, but offered no evidence as proof, for in no case was the shift —$CH_2$—CHOH—CO— → $CH_2$—CO—CHOH— observed.

This paper deals with the observation of such a reverse shift with the *p*-chloro analog of IV

(1) Lobry de Bruyn, *Ber.*, **28**, 3078 (1895).
(2) Wohl, *Ber.*, **33**, 3095 (1900).
(3) Fischer, *ibid.*, **60**, 479 (1927).
(4) Shoppee, *J. Chem. Soc.*, 1662 (1928).
(5) Kohler and Kimball, THIS JOURNAL, **56**, 729 (1934).
(6) Kohler and Leers, *ibid.*, **56**, 981 (1934).

$C_6H_5CH_2CHOHCOC_6H_4Cl\text{-}p \longrightarrow$
VII
$C_6H_5CH_2COCHOHC_6H_4Cl\text{-}p$
VIII

Henze[7] likewise observed a reverse shift in a similar system in the presence of sodium ethylate, but did not report the existence of an equilibrium between the two substances

$CH_3COCH_2CHOHCOC_6H_5 \longrightarrow$
$CH_3COCH_2COCHOHC_6H_5$

If these intramolecular shifts are to be classed with that of Lobry de Bruyn, it is essential to establish the existence of an equilibrium in alkaline media between the two isomeric hydroxy ketones. This it has been possible to do in the case of VII and VIII, for each has been transformed into the other by means of weak alkali. The reaction should then be written VII $\rightleftarrows$ VIII.

It is quite likely then that all α-hydroxy carbonyl compounds are in equilibrium with their dismutation isomers, and that the failure to observe this equilibrium may be due merely to the position of the equilibrium being almost entirely on one side or the other—or due to the unfavorable physical or chemical properties of one of the isomers, making its isolation difficult.

The establishment of this equilibrium lends support to the new mechanism recently advanced by Hibbert[8] for the formation of lignin from guaiacol and pyruvic aldehyde. This system is closely related to that reported in this paper, and hence it is quite probable that an equilibrium actually exists

$CH_3COCHO + C_6H_4(OH)(OCH_3) \longrightarrow$
$CH_3COCHOHC_6H_3(OH\text{-}p)(OCH_3\text{-}m) \rightleftarrows$
$CH_3CHOHCOC_6H_3(OH\text{-}p)(OCH_3\text{-}m) \longrightarrow$ lignin

The mechanism of the interconversion of these hydroxy carbonyl compounds very probably involves a dienol intermediate. This is consistent with the existence of an equilibrium, since alkaline media favor enolization. Acid media being proton donors likewise favor enolization, and should also cause an equilibrium to be established. Favorsky[9] has shown already that similar interconversions occur under the influence of acids, and hence it is probable that here, too, an equilibrium exists between the two isomeric substances.

In the work here, it unfortunately was impossible to determine the position of the equilibrium between VII and VIII, because of the unstable character of both isomers, as well as the unfavorable physical properties of one of them, VII.

The sensitive character of VIII for example was shown by its behavior with strong alkalies, whereby large amounts of oxidation and reduction products appeared. These would be expected if a dienol intermediate were formed, since dienols are peculiarly active hydrogen donors.[10] The following scheme, in part suggested earlier by Kohler and Kimball, indicates a possible course of the reaction with strong alkalies

$C_6H_5CH_2COCHOHC_6H_4Cl\text{-}p \rightleftarrows (C_6H_5CH_2C(OH)=CC_6H_4Cl\text{-}p) \rightleftarrows C_6H_5CH_2CHOHCOC_6H_4Cl\text{-}p$
VIII VII

Oxidation and reduction

$(C_6H_5CH_2COCOC_6H_4Cl\text{-}p) + (C_6H_5CH_2CH_2COC_6H_4Cl\text{-}p)$ not isolated

Cleavage: $p\text{-}ClC_6H_4CO_2H$

Benzilic acid rearrangement: $C_6H_5CH_2C(OH)(C_6H_4Cl\text{-}p)(CO_2H)$

This work was done under the direction of Professor Kohler, in partial fulfilment for the degree of Doctor of Philosophy, Harvard University, 1929. Some time before his death, Professor Kohler kindly gave the author permission to publish the work independently.

## Experimental Part

**α-Hydroxy-*p*-chlorobenzyl Benzyl Ketone, VIII.**—This α-hydroxy ketone was prepared both from α-phenyl-

(7) Henze, *Z. physiol. Chem.*, **232**, 117 (1935).
(8) Hibbert, THIS JOURNAL, **61**, 725 (1939).
(9) Favorsky, *Bull. soc. chim.*, **39**, 215 (1925).
(10) Szent-Györgyi, *Ber.*, **72A**, 53 (1939); compare Fuson and Corse, THIS JOURNAL, **61**, 975 (1939).

β-hydroxy-*p*-chlorobenzoylpropionic acid, previously reported by Kohler and Shohan,[11] and by synthesis from *p*-chlorobenzaldehyde cyanhydrin and benzylmagnesium chloride. The ketone crystallized from 95% alcohol as needles, melting at 125.5–126°.

*Anal.* Calcd. for $C_{15}H_{13}O_2Cl$: C, 69.1; H, 5.0. Found: C, 69.0; H, 5.0.

**Action of Alkalies on the α-Hydroxy Ketone, VIII.**—In contrast to the α-hydroxy ketones II and IV, this ketone yielded with strong alkalies non-crystallizing oils, from which only secondary products could be isolated, namely, *p*-chlorobenzoic acid, and α-hydroxy-α-*p*-chlorophenyl-β-phenylpropionic acid. These acids result from cleavage and benzilic acid rearrangement respectively, of the intermediate α-diketone, formed presumably from the dienol intermediate by intermolecular oxidation and reduction. The latter acid crystallized from ether and ligroin, and melted at 201–202° with decomposition.

*Anal.* Calcd. for $C_{15}H_{13}O_3Cl$: C, 65.1; H, 4.7. Found: C, 64.9; H, 4.9.

It was further identified by synthesis from α-phenyl-α'-*p*-chlorobenzoylethylene oxide by means of alkalies according to the method of Bodforss[12] and Jörlander,[13,14] and also by oxidation with sodium dichromate in acetic acid to *p*-chlorodesoxybenzoin. This ketone crystallized from ligroin as plates melting at 104.5–105.2°.

*Anal.* Calcd. for $C_{14}H_{11}OCl$: C, 72.9; H, 4.8. Found: C, 73.2; H, 4.7.

This difference in reaction between these α-hydroxy ketones is probably due to the much greater solubility of the isomeric ketone VII. It was only by using weak alkalies that it was possible to isolate VII, and then only with difficulty and in very poor yields. Five grams of VIII was dissolved in 75 cc. of hot 95% alcohol; 50 cc. of water was added, and an excess of solid sodium carbonate. The solution turned orange at once. After thirty minutes of boiling, the solution was made faintly acid, and then evaporated to one-half its volume. On cooling 2.7 g. of VIII precipitated unchanged. The filtrate was evaporated further until it become cloudy, and was then allowed to stand overnight. The oil which had precipitated was now extracted with chloroform and ligroin mixture. More water was then added, precipitating more oil (about 0.2 g.). This finally crystallized on standing for four days at 0°, and melted at 39–42°. A mixed melting point with the isomeric ketone VII, m. p. 43–44°, was 41–44°.

**Benzyl-*p*-chloroacetophenone.**—This saturated ketone, prepared easily by reduction of benzal-*p*-chloroacetophenone with Adams platinum oxide catalyst in methyl alcohol solution, crystallized from ligroin as plates, melting at 75–76°.

*Anal.* Calcd. for $C_{15}H_{13}OCl$: C, 73.2; H, 5.3. Found: C, 72.5; H, 5.0.

**Benzyl-α-bromo-*p*-chloroacetophenone.**—The ketone brominated easily in chloroform solution, yielding a crystalline α-bromo ketone, melting at 92–93°.

*Anal.* Calcd. for $C_{15}H_{12}OClBr$: C, 55.6; H, 3.7. Found: C, 55.6; H, 3.9.

**Benzyl-α-hydroxy-*p*-chloroacetophenone, VII.**—Seventeen grams of the bromo ketone was dissolved in 500 cc. of hot 95% alcohol, and water was added until the boiling solution just remained clear. Then 4.2 g. of sodium bicarbonate was added, and the mixture boiled for 40 minutes. The solution became yellowish. On cooling, 3.3 g. of the bromide precipitated unchanged, and was filtered out. The filtrate was poured into water, extracted with ether, and dried. Addition of ligroin deposited an oil which slowly crystallized at −10–15°. Thus 3.7 g. of the hydroxy ketone was obtained, which after several recrystallizations from chloroform and ligroin melted at 43–44°. The ketone was very soluble in all solvents save ligroin and water, and is far more soluble than its isomer VIII.

*Anal.* Calcd. for $C_{15}H_{13}O_2Cl$: C, 69.1; H, 5.0. Found: C, 69.0; H, 5.3.

**Action of Alkalies on the α-Hydroxy Ketone, VII.**—One-fifth gram of VII was dissolved in 10 cc. of 95% alcohol. An excess of sodium carbonate was now added, and the mixture boiled for one hour. The solution was then neutralized, and the volume reduced to 5 cc. On cooling, the isomeric α-hydroxy ketone VIII crystallized out pure, melting at 125–126°, and identified by comparison with an authentic sample.

## Summary

1. Two isomeric α-hydroxy ketones, derived from *sym*-diphenylpropane, have been shown to be in equilibrium in alkaline solution.

2. The presence of this equilibrium lends support to Hibbert's theory of lignin formation.

CAMBRIDGE, MASSACHUSETTS
MONTREAL, CANADA RECEIVED APRIL 3, 1939

(11) Kohler and Shohan, THIS JOURNAL, **48**, 2425 (1926).
(12) Bodforss, *Ber.*, **49**, 2795 (1916).
(13) Jörlander, *ibid.*, **50**, 406 (1917).
(14) Ref. 5, p. 731.