absence of oxygen and peroxides to give 2,2-dibromobutane.

2. Under the influence of peroxide catalysis racemic 2,3-dibromobutane is obtained. This product is most easily obtained by retarding the normal reaction through dilution with an inert solvent.

CHICAGO, ILLINOIS RECEIVED APRIL 20, 1939

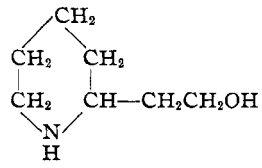
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE MALTBIE CHEMICAL CO.]

Local Anesthetics from β-(2-Piperidyl)-ethanol

BY L. A. WALTER AND RUSSEL J. FOSBINDER

The recent publication of Tullock and MacElvain[1] on anesthetics derived from α-picoline prompts submission of the following paper.

A series of substituted benzoic esters of β-



(2-piperidyl)-ethanol was prepared by refluxing one equivalent of the hydrochloride of the amino alcohol with one equivalent of acid chloride in dry chloroform. The amino ester hydrochlorides were purified by crystallization from absolute alcohol or from absolute alcohol–ether mixture. The N-phenylurethan and the cinnamate were prepared similarly from phenyl isocyanate and cinnamoyl chloride, respectively. The hydrochlorides of the nitro esters were reduced to the amino compounds with platinum and hydrogen in glacial acetic acid.

Pure β-(2-pyridyl)-ethanol is best prepared by heating α-picoline with twice its weight of 40% formaldehyde in a sealed tube at 120° for sixteen to twenty hours. The mixture is then fractionally distilled at a pressure sufficiently reduced so that the temperature of the mixture never rises above 130°. The yields are only 15 to 20% but the product is not contaminated with the β-(2-pyridyl)-allyl alcohol which is formed by dehydration of β-(2-pyridyl)-propylene glycol at higher temperatures. Some of the latter compound is formed from two moles of formaldehyde and one of picoline even at 120°.

The pyridyl alcohol was reduced to the piperidyl alcohol with sodium and absolute alcohol.[2]

The properties of the compounds are recorded in the following table. They are all nicely crystalline and non-hygroscopic without exception.

TABLE I

	β-(2-Piperidyl)-ethanol ester hydrochloride	Formula	M. p., °C., corr.	Analyses, %Cl Calcd.	Found
I	Benzoate	$C_{14}H_{20}O_2NCl$	189–191[a]	13.14	13.08
II	*p*-Nitrobenzoate	$C_{14}H_{19}O_4N_2Cl$	209–210	11.26	11.15
III	*m*-Nitrobenzoate	$C_{14}H_{19}O_4N_2Cl$	170–172	11.26	10.96
IV	*o*-Nitrobenzoate	$C_{14}H_{19}O_4N_2Cl$	148–150	11.26	11.46
V	*p*-Aminobenzoate	$C_{14}H_{21}O_2N_2Cl$	249–251	12.44	12.20
VI	*m*-Aminobenzoate	$C_{14}H_{21}O_2N_2Cl$	177–180	12.44	12.28
VII	*o*-Aminobenzoate	$C_{14}H_{21}O_2N_2Cl$	209–211	12.44	12.30
VIII	*p*-Ethoxy, *m*-nitrobenzoate	$C_{16}H_{23}O_5N_2Cl$	150–155	9.87	10.21
IX	*p*-Ethoxy, *m*-aminobenzoate	$C_{16}H_{25}O_3N_2Cl$	173–175	10.78	10.61
X	*p*-Ethoxybenzoate	$C_{16}H_{24}O_3NCl$	146–148	11.29	11.44
XI	Cinnamate	$C_{16}H_{22}O_2NCl$	180–182	11.98	11.95
XII	N-Phenylurethan	$C_{14}H_{21}O_2N_2Cl$	200–202	12.44	12.54

[a] Ladenburg, *Ann.*, **301**, 124 (1898), gives m. p. 182–183°.

TABLE II

Compound	Duration of anesthesia rabbit cornea, min., 2% solution	Subcutaneous toxicity to mice M. L. D. 50% mg./kg.
I	6	85
V	47	20
VI	27	87
VII	100	23
IX	10	..
X	15	..
XI	0	..
XII	9	40
Cocaine	56	10

(1) Tullock and MacElvain, THIS JOURNAL, **61**, 961 (1939).

(2) Marvel and Shelton, *ibid.*, **51**, 915 (1929).

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.

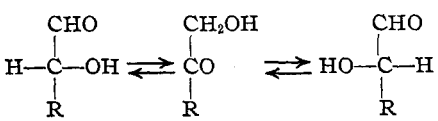
NEWARK, N. J. RECEIVED APRIL 17, 1939

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

The Rearrangement of α-Hydroxy Carbonyl Compounds

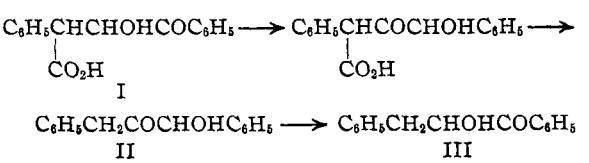
BY PHILIP G. STEVENS

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

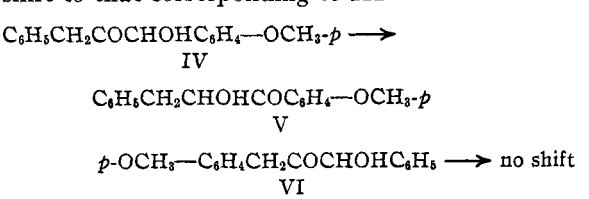


Wohl[2] found that in all probability the same equilibrium existed between certain trioses, namely, glyceric aldehyde and dihydroxyacetone, because in alkaline solutions both compounds yielded the same β-acrose. This view was supported later by Fischer's discovery[3] that glyceric aldehyde could be converted 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).