ing properties: 2,3-dimethylheptene-2, b. p. 136.2–136.8° (743 mm.); n_D^{20} 1.4233, d_4^{20} 0.742; 2,3-dimethylheptene-3, b. p. 138.4–138.8° (740.5 mm.), n_D^{20} 1.4250, d_4^{20} 0.747.

Similarly 325 g. of the mixture of olefins from *n*-amylmethylisopropylcarbinol was distilled in 34 fractions of which the chief ones were 1–8, 72 g., b. p. 157.6° (731 mm.) to 160.2° (737.5 mm.), n_D^{20} 1.4280 to 1.4282; and 14–18, 45 g., b. p. 161.0° (739 mm.) to 161.8° (739.6 mm.), n_D^{20} 1.4289 to 1.4292. The lower boiling olefin was taken as the octene-2 derivative. The middle fractions gave the following properties: 2,3-dimethyloctene-2, b. p. 158.4–158.8° (733 mm.), n_D^{20} 1.4280; 2,3-dimethyloctene-3, b. p. 161.2–161.4° (739 mm.), n_D^{20} 1.4290.

Summary

1. Aliphatic alcohols containing tertiary hydroxyl and tertiary hydrogen on adjacent carbon atoms have been prepared and dehydrated. In each case a pair of olefins was formed. These were identified by ozonolysis.

2. The new tertiary alcohols prepared and studied were 2,3-dimethylhexanol-3, 2,3-dimethylheptanol-3 and 2,3-dimethyloctanol-3.

3. These alcohols were converted to the corresponding tertiary chlorides, 3-chloro-2,3-dimethyl-hexane, -heptane and -octane.

4. The four olefins, 2,3-dimethylheptene-2 and -3 and 2,3-dimethyloctene-2 and -3 have been prepared and studied.

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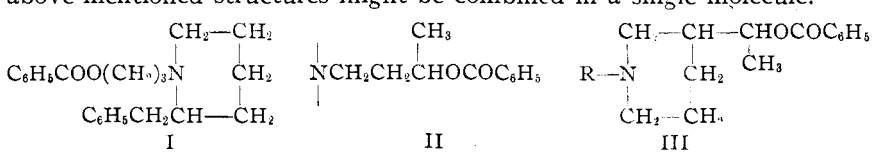
Piperidine Derivatives. XII. Local Anesthetics Derived from Reduction Products of Beta-Acetylpyridine

BY FRANK M. STRONG AND S. M. MCELVAIN

Two constructions that markedly enhance the action of the aminoalkyl benzoate type of local anesthetics on mucous surfaces have been shown to be (a) the phenylalkyl group attached to nitrogen[1] (preferably the nitrogen atom of the piperidine ring) and (b) a substituent methyl group in the alkylene group that joins the nitrogen atom to the benzoyloxy group.[2] These two types of structure are illustrated by I and II. It was the purpose of the work reported in the present paper to prepare and submit for pharmacological study a series of compounds of type III in which the two above-mentioned structures might be combined in a single molecule.

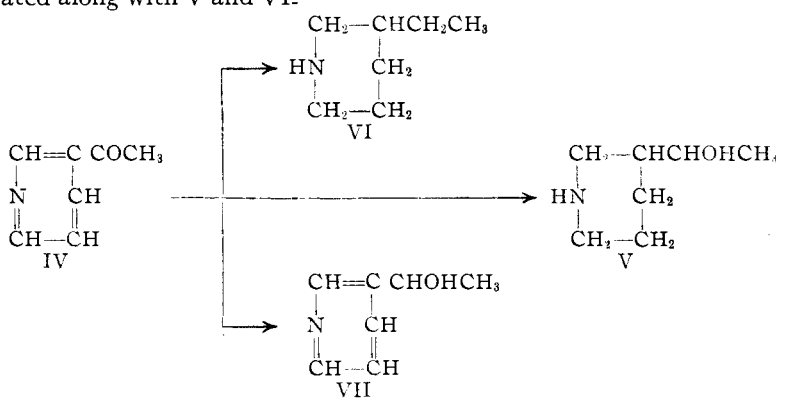


I II III

(1) (a) Bailey and McElvain, THIS JOURNAL, **52**, 1639 (1930); (b) Bolyard and McElvain, *ibid.*, **51**, 927 (1929).

(2) Thayer and McElvain, *ibid.*, **50**, 3354 (1928).

The synthesis of this type of compound was accomplished by first alkylating and then benzoylating 3-piperidylmethylcarbinol (V) which was obtained by the reduction of β-acetylpyridine (IV). This reduction was carried out catalytically with both Adams platinum oxide catalyst and a nickel catalyst and also by sodium in alcohol. Each of these reduction procedures gave a mixture of the diastereoisomeric carbinols (V) together with a relatively large amount of 3-ethylpiperidine (VI). Since the reduction with the platinum catalyst seemed to be most satisfactory from the standpoint of control and yield of the desired product, the results obtained by this method will be outlined briefly. When the ketone (IV) was reduced in dilute hydrochloric acid solution with the platinum catalyst and the reduction stopped after 4 moles of hydrogen had been absorbed, a small amount of the partially reduced product, β-pyridylmethylcarbinol VII was isolated along with V and VI.



If, however, the reduction were allowed to proceed until no more hydrogen was absorbed, only V and VI were isolated. The yields of these latter products were 38–52% and 30–38%, respectively. In aqueous solution containing no hydrochloric acid the ketone IV absorbed only one mole of hydrogen and from this reduction the carbinol VII was isolated in 85% yield. Apparently the formation of a small amount of the more basic piperidine compound destroyed the activity of the catalyst, because the addition of hydrochloric acid to the solution after the one mole of hydrogen had been absorbed allowed the reduction to continue to completion. The reduction of VII either with platinum or nickel catalysts produced both V and VI in the relative amounts mentioned above.[3] Reduction of either this carbinol or β-acetylpyridine by sodium and alcohol produced even higher ratios of ethylpiperidine.

(3) This fact is in accord with the observations of Adkins and co-workers in this Laboratory that a carbinol group attached to an unsaturated carbon atom is converted to a methylene group by catalytic reduction with nickel. Also there is an apparent correlation between the behavior of β-acetylpyridine and β-benzoylpyridine on reduction with platinum. In the reduction of the three benzoylpyridines it was only in the case of the β-compound that a low yield of the phenylpiperidylcarbinol was obtained [Crook and McElvain, THIS JOURNAL, **52**, 4011 (1930)].

The mixture of the isomeric 3-piperidylmethylcarbinols (V) which was obtained consisted of approximately 20% of a higher melting (103–104°) compound and 80% of a lower melting (58–61°) compound. In spite of this adverse ratio the higher melting compound was used in the subsequent experiments because lower solubility caused it to be much more susceptible to purification. The relationship between these two compounds was established by analysis and acetyl value.[4] Attempts to convert the lower melting isomer into the higher melting one as was done in the case of the 2-piperidylphenylcarbinols[4] were unsuccessful.

A number of N-alkyl and N-phenylalkyl derivatives of the higher melting 3-piperidylmethylcarbinol were prepared and benzoylated and the desired anesthetics (type III) obtained as the hydrochlorides without any particular difficulty. The N-benzoyloxypropyl derivative of ethylpiperidine was prepared for comparison with previously prepared alkylpiperidinopropyl benzoates. Also the β-pyridylmethylcarbinol (VII) was converted into the benzoate and *p*-aminobenzoate, both of which, as will be seen from the pharmacological data, were found to possess very unusual physiological properties.

Experimental

Ethyl Nicotinoacetate Hydrochloride.—The free base of this compound has been prepared, but not isolated or purified, by Hurd.[5] The following procedure was used in the present work. A mixture of 151 g. (1 mole) of ethyl nicotinate, 167 g. (1.9 moles) of ethyl acetate and 104 g. (1.55 moles) of sodium ethoxide was allowed to stand at room temperature for about one hour with occasional shaking. The mixture became quite warm and assumed a deep reddish brown color. It was then refluxed five to six hours, cooled and diluted with an equal volume of water. The unreacted esters were extracted with ether and the remaining aqueous solution acidified with concentrated hydrochloric acid and then made slightly alkaline with sodium carbonate solution. The oily layer of ethyl nicotinoacetate and acetoacetic ester was separated and the aqueous layer extracted twice with ether. These ether extracts were combined with the keto ester layer and, after drying with anhydrous potassium carbonate, saturated with dry hydrogen chloride. The precipitated ethyl nicotinoacetate hydrochloride after recrystallization from an alcohol–ether mixture melted at 156–157.5°. The yield was 115–161 g. (50–70%). Calcd. for $C_{10}H_{12}O_3NCl$: Cl, 15.44. Found: Cl, 15.39.

β-Acetylpyridine Hydrochloride.—A solution of 42 g. of ethyl nicotinoacetate in 300 cc. of 10% hydrochloric acid was refluxed for six hours. The resultant solution, which gave no coloration with ferric chloride, was evaporated to dryness on a steam-bath and the remaining residue recrystallized from alcohol. A yield of 27.5 g. (96%) of β-acetylpyridine hydrochloride, m. p. 176–177.5°, was obtained. Calcd. for C_7H_8ONCl: Cl, 22.51. Found: Cl, 22.69.

The free base boils at 90–92° (5 mm.), melts at 13–14°, and is completely soluble in cold water.

β-Pyridylmethylcarbinol, 3-Piperidylmethylcarbinol (2 Forms) and 3-Ethylpiperidine.—A solution of 25 g. of β-acetylpyridine in 150 cc. of distilled water was shaken with 0.5 g. of Adams platinum oxide catalyst until no more hydrogen was absorbed. At this point approximately one mole of hydrogen had been taken up, and if the catalyst

(4) Ref. 3, p. 4010.

(5) Hurd, THIS JOURNAL, **49**, 551 (1927).

were removed and the solution distilled, 21.5 g. (85%) of β-pyridylmethylcarbinol,[6] b. p. 123–125° (5 mm.), was obtained.

Anal. Calcd. for C_7H_9ON: C, 68.3; H, 7.32, acetyl value,[4] 1. Found: C, 68.2; H, 7.49; ac. v., 0.96. The hydrochloride of this carbinol melts at 92–93°. Calcd. for $C_7H_{10}ONCl$: Cl, 22.25. Found: Cl, 22.20.

If, however, 20 cc. of hydrochloric acid (sp. gr. 1.2) were added to the reduction mixture after the first mole of hydrogen had been absorbed and the reduction allowed to continue, the total hydrogen absorption amounted to about 10% excess of 4 moles. It was necessary toward the end of the reduction to reactivate the catalyst by shaking with oxygen. The catalyst was then filtered off and the filtrate evaporated to dryness. The residue was taken up in absolute alcohol and titrated with alcoholic potassium hydroxide using phenolphthalein as an indicator. The precipitated potassium chloride was filtered off and, after removal of the alcohol, the free bases were fractionated. Yields of 7–9 g. (30–38%) of 3-ethylpiperidine[7] b. p. 148–152°, and 10–14 g. (38–52%) of material boiling at 105–120° (3 mm.), which on cooling solidified, were obtained. This solid was extracted with 50 cc. of boiling absolute ether and the ethereal solution filtered. After three such extractions and filtrations a residue of the higher melting isomer, m. p. 103–104°, remained. The yield of this isomer amounted to 2–2.5 g. Calcd. for $C_7H_{15}ON$: C, 65.2; H, 11.70; acetyl value 2. Found: C, 64.9; H, 11.70; ac. v., 1.91. The hydrochloride of this isomer melted at 152–153°. Calcd. for $C_7H_{16}ONCl$: Cl, 21.45. Found: Cl, 21.17.

The ethereal extracts obtained above were saved and several of them worked up together. After removal of the ether by distillation, the remaining residue was distilled. It boiled at 116–119° (5 mm.) and solidified on cooling. A 16.5-g. sample recrystallized from dioxane yielded 10 g. of material, m. p. 56–60°. The melting point of this compound could be raised to 58–61° by further recrystallizations. Calcd. for $C_7H_{15}ON$: C, 65.2; H, 11.70; acetyl value, 2. Found: C, 65.1; H, 11.62; ac. v., 1.99. This isomer gave a hydrochloride which could not be caused to crystallize.

α-(1-Alkyl-3-piperidyl)-ethyl Benzoate Hydrochlorides.—These compounds were prepared by first heating 2 moles of the higher melting 3-piperidylmethylcarbinol with 1 mole of the appropriate alkyl halide in dioxane solution for a few hours on a steam-bath. After cooling, the reaction mixture was diluted with absolute ether and the precipitated carbinol hydrohalide filtered off. The solvent was removed from the filtrate by distillation and the residue warmed with a 30% excess of benzoyl chloride. The resulting reaction mixture was diluted with ether, the precipitated hydrochloride taken up in absolute alcohol and caused to crystallize by the careful addition of ether. The compounds which were prepared are summarized in Table I. The phenylbutyl derivative is omitted because no crystalline salt could be prepared from it.

TABLE I

α-(1-ALKYL-3-PIPERIDYL)-ETHYL BENZOATE HYDROCHLORIDES

Compound Type III R is	Formula	M. p., °C.	Analyses, Cl, % Calcd.	Found
Benzyl	$C_{21}H_{26}O_2NCl$	199–200	9.86	9.88
β-Phenylethyl	$C_{22}H_{28}O_2NCl$	196–198	9.49	9.52
γ-Phenylpropyl	$C_{23}H_{30}O_2NCl$	158–159	9.16	9.14
ε-Phenylamyl	$C_{25}H_{34}O_2NCl$	141–142	8.55	8.65
n-Hexyl	$C_{20}H_{32}O_2NCl$	142–144	10.04	10.07

(6) This compound has been imperfectly described by Hardy and Calmels, *Bull. soc. chim.*, **48**, 230 (1887).

(7) The hydrochloride melted at 140–141°; *cf.* Günther, *Ber.*, **31**, 2140 (1898). The acetyl value[4] of the free base was 1.03.

γ-(3-Ethylpiperidino)-propyl Benzoate Hydrochloride.—This compound was prepared from 3-ethylpiperidine and chloropropyl benzoate by a procedure previously described.[8] It melted at 164–165°. Calcd. for $C_{17}H_{26}O_2NCl$: Cl, 11.38. Found: Cl, 11.33.

The Hydrochloride of α-(β-Pyridyl)-ethyl Benzoate and *p*-Nitrobenzoate.—β-Pyridylmethylcarbinol was benzoylated by mixing with a slight excess of benzoyl chloride and allowing to stand at room temperature. The reaction mixture became very hot and darkened considerably. On cooling it solidified. The resultant mass was recrystallized from an alcohol–ether mixture. The yield of α-(β-pyridyl)-ethyl benzoate hydrochloride, m. p. 175–176°, was 85% of the theoretical. Calcd. for $C_{14}H_{14}O_2NCl$: Cl, 13.47. Found: Cl, 13.40.

The *p*-nitrobenzoate hydrochloride was prepared by heating the carbinol with *p*-nitrobenzoyl chloride in benzene solution for four to five hours. The precipitated hydrochloride after recrystallization from alcohol melted at 199–200°. Calcd. for $C_{14}H_{13}O_4N_2Cl$: Cl, 11.50. Found: Cl, 11.37.

α-(β-Pyridyl)-ethyl *p*-Aminobenzoate.—The catalytic reduction of the above *p*-nitrobenzoate was unsuccessful, presumably on account of simultaneous reduction of the pyridine ring. However, it was readily reduced to the *p*-aminobenzoate in 75% yields by iron powder and dilute hydrochloric acid. No crystalline salt of this compound could be obtained so it was purified by distillation and recrystallization. It boiled at 227–230° (4 mm) and, after recrystallization of the distillate from dilute alcohol, it melted at 100–101°. Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.4; H, 5.82; N, 11.57. Found: C, 69.7; H, 5.73; N, 11.38.

Pharmacological Report

The local anesthetics prepared in the course of this work are being studied pharmacologically by Dr. K. K. Chen and Mr. Charles L. Rose of The Lilly Research Laboratories, Indianapolis, Indiana. A preliminary report on the pharmacological properties of these compounds is summarized in Table II.

The durations of anesthesia were determined in the usual way by application of a 1% solution of the anesthetic to a rabbit's cornea. Toxicities are reported as subcutaneous to white mice and intravenous to white rats.

TABLE II

PHARMACOLOGICAL DATA

Compound	Av. duration of corneal anesthesia, Min.	% sol'n.	Subcutaneous toxicity (mg./kg.) M. L. D.	Intravenous toxicity (mg./kg.) M. L. D.
Benzyl	68	1	200	10
β-Phenylethyl	40	1	1000	35
γ-Phenylpropyl	83	1	1000	45
γ-Phenylamyl	180	1	..	40
n-Hexyl	72	1	1000	32
VIII	15	1	1000	30
IX	43	1	1000	100
X	0	1	..	110
Cocaine	29	2	150	17.5
Procaine	0	2	1000	40

(8) McElvain, THIS JOURNAL, **49**, 2837 (1927).

The benzoates of α-(1-alkyl-3-piperidyl)-ethyl alcohols are designated in Table II by the substituent alkyl groups as in Table I. γ-(3-Ethylpiperidino)-propyl benzoate, α-(β-pyridyl)-ethyl benzoate and α-(β-pyridyl)-ethyl *p*-aminobenzoate are designated by the numerals VIII, IX and X, respectively. Since the latter compound was furnished as the free base, it was put into solution by titration with one equivalent of hydrochloric acid. Cocaine and procaine are included in the table for comparison.

Discussion of the Pharmacological Data

It is seen from the above data that the phenyl alkyl substituents in this type of structure produce anesthetics of relatively high potency. It should be noted, however, that the highest value is obtained with the phenylamyl derivative, a fact which fails to agree with the previous observation[1a] that maximum anesthetic effects were produced when the phenyl radical was attached to the nitrogen atom by less than five carbon atoms. Also a comparison of the anesthetic activity of the phenylethyl derivative in the above table with 1-phenylethyl-4-piperidyl benzoate[1b] indicates that the substituent methyl group in the carbon chain between the nitrogen atom and the benzoyloxy group decreases rather than increases the anesthetic activity of the compound.

The 3-ethylpiperidinopropyl benzoate (VIII) shows approximately the same order of pharmacological activity as the corresponding methylpiperidino compounds.[8]

The anesthetics derived from β-pyridylmethylcarbinol (IX and X) show the most unusual and unexpected pharmacological behavior. It is seen that the benzoate (IX) produces considerably longer anesthesia in 1% solution than does cocaine in 2% solution. At the same time its toxicity is exceedingly low, being less than half of that of procaine. However, this compound produced considerable irritation of the rabbit's eye, presumably on account of the acidity of the salt of such a weak base. It was for this reason that the corresponding *p*-aminobenzoate (X) was prepared and used as a monohydrochloride. This change in structure did not decrease the irritating qualities of the compound but it did completely destroy its anesthetic action on mucous surfaces. The *p*-aminobenzoate did, however, produce considerable anesthetic effect when injected intracutaneously. Its most surprising property was the extremely low intravenous toxicity, which was found to be even less than that of the benzoate. The pharmacological behavior of this compound is completely out of line with past observations.[9] These have definitely pointed to the generalization that *p*-aminobenzoates produce at least as much anesthetic effect as the corresponding benzoates and are generally considerably more toxic.

(9) In agreement with this behavior, however, is the recorded experiment [Ehrlich and Einhorn, *Ber.*, **27**, 1870 (1894)] that the introduction of an amino group into the benzoyl radical of cocaine causes inactivation.

Summary

The following reduction products have been isolated from the catalytic reduction of β-acetylpyridine: ethylpiperidine, two diastereoisomeric forms of 3-piperidylmethylcarbinol and β-pyridylmethylcarbinol.

A group of new local anesthetics has been prepared from these reduction products. The data which are presented show that these anesthetics, particularly those derived from β-pyridylcarbinol, possess unusual and interesting pharmacological properties.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF SWARTHMORE COLLEGE]

Organic Selenium Compounds. II. A New Type of Aromatic Selenium Halide

BY DUNCAN G. FOSTER

Introduction

There are, at the present time, four types of organic selenium halides described in the literature: (1) RSeX, in which R is aromatic; (2) $RR'SeX_2$, in which R and R′ are either di-aryl or alkyl-aryl; (3) R_3SeX, in which R is aryl only; and (4) $RSeX_3$. The only reported case of this last type is Shaw and Reid's ethyl selenium tribromide, $C_2H_5SeBr_3$,[1] no aromatic compounds of this type and no analogous compounds in which X is another halogen than bromine having been prepared. This list does not include halogen acid addition compounds, such as $RSeO_2H \cdot HCl$, but only true halides.

In the course of an investigation of the reactions of the first three types of halides mentioned, to be reported in a later paper, the formation of phenyl selenium tribromide, the first example of an aromatic compound of the last-mentioned class, has been observed, the analogous phenyl selenium trichloride, $C_6H_5SeCl_3$, has also been prepared, and an unsuccessful attempt made to prepare phenyl selenium triiodide, which is too unstable to exist under ordinary conditions. The various synthetic methods employed with these compounds and some of their reactions indicate that they are halogen salts of a selenonium base, $C_6H_5Se(OH)_3$, the ortho form of ordinary benzene seleninic acid, C_6H_5SeOOH.

Outline and Discussion of the Present Investigation

(1) **Phenyl selenium tribromide,** $C_6H_5SeBr_3$, was first observed as a by-product formed during the preparation of phenyl ethyl selenium dibromide, $(C_6H_5)(C_2H_5)SeBr_2$, from phenyl ethyl selenide, $(C_6H_5)Se(C_2H_5)$

(1) Shaw and Reid, THIS JOURNAL, **48**, 525 (1926).