ester. After removal of hydrogen chloride and excess alcohol, the crude ester was heated with 70 mg. of urea and 3.6 ml. of sodium ethylate solution (1.73 *N*) at 80° for twenty-two hours. The product was isolated by ether extraction of the acidified water solution, and after recrystallization from 5 to 6 ml. of water (the hot solution was decolorized with 10 mg. of purified norit), there was obtained 139 mg. (38% yield) of dry, white crystals. The melting point was 235.5–236.8° (corr.) (Dox and Bywater[2] give m. p. 230–231°). In a 23-g. mouse, an intravenous dose of 800 mg. per kg. (as sodium salt in 1.3 cc.) produced no observable effect for at least an hour after the injection. As expected, this confirmed the finding of Dox and Bywater.[2]

Anal. Calcd. for $C_8H_{12}O_3N_2$: N, 15.21. Found: N, 15.03.

Summary

Pure *t*-butylmalonic acid has been obtained in moderately good yield from *t*-butylacetic acid. That the *t*-butyl group is present in the malonic acid has been shown by conversion of the latter to known derivatives of *t*-butylacetic acid. Two derivatives of *t*-butylmalonic acid have been characterized.

NASHVILLE, TENNESSEE RECEIVED JANUARY 9, 1939

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE DEPARTMENT OF PHARMACOLOGY, COLLEGE OF MEDICINE, OF NEW YORK UNIVERSITY]

Piperidinium Analogs of Choline and its Homologs. Onium Compounds. XX[1]

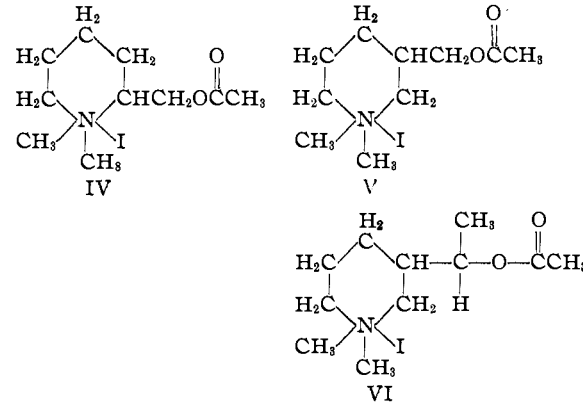
BY R. R. RENSHAW, M. ZIFF, B. BRODIE AND N. KORNBLUM[2]

The pronounced parasympathetic activity of arecoline and several derivatives of nicotinic and nipecotic acids[3–5] has suggested the preparation of heterocyclic derivatives analogous to acetylcholine and its homologs for investigation of their effects on the autonomic nervous system. In previous publications, the synthesis[6,7] and pharmacological effects[3,8] of a number of quaternary heterocyclic ethers and esters have been described. Compounds of this type, unsubstituted on the cyclic carbon atoms, have acted on the autonomic nervous system, producing an acetylcholine effect, a nicotine effect or both.

In continuation of this investigation, the preparation of ethers and esters of the choline type, substituted on the cyclic carbon atoms was begun.[7] In this paper, the preparation and brief description of the physiological properties of piperidinium salts of the choline ester type are given. These compounds contain the methylated quaternary nitrogen present in choline; the carbon chain of the latter compound is contained partly in the heterocyclic ring and partly in carbinol groups substituted in the ring.

Ethyl picolinate[9] and ethyl nicotinate[10] were reduced, using sodium and alcohol, to α-piperidylcarbinol (I) and β-piperidylcarbinol (II), respectively, by the method previously applied by Sandborn and Marvel[11] to the synthesis of the β-carbinol. The α-carbinol, a new compound, was obtained in 29% yield. Sodium and alcohol reduction, rather than the high pressure catalytic reduction methods developed by Adkins and co-workers, was used because the latter have reported alkylation of the ring nitrogen atom, undesirable in this case.[12] β-Piperidylmethylcarbinol (III) was prepared by the catalytic reduction of β-acetylpyridine according to the method of

CHART I



(1) This paper is being published, following the death of Professor Renshaw, by his collaborators. Paper XIX, THIS JOURNAL, **60**, 1765 (1938).

(2) Present address: Department of Chemistry, University of Illinois, Urbana, Ill.

(3) Hunt and Renshaw, *J. Pharmacol.*, **35**, 75 (1929).

(4) Loewy and Wolffenstein, *Therap. Gegenwart.*, **61**, 287 (1920).

(5) Haramaki, *Biochem. Z.*, **130**, 267 (1922).

(6) Renshaw and Shand, THIS JOURNAL, **54**, 1474 (1932).

(7) Renshaw and Conn, *ibid.*, **59**, 297 (1937).

(8) Hunt and Renshaw, *J. Pharmacol.*, **37**, 177 (1929).

(9) Camps, *Arch. Pharm.*, **240**, 346 (1903).

(10) LaForge, THIS JOURNAL, **50**, 2479 (1928).

(11) Sandborn and Marvel, *ibid.*, **50** 565 (1928).

(12) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

TABLE I

N-DIMETHYL-HYDROXYALKYL-PIPERIDINIUM IODIDES

Compound	Appearance	M. p., °C.[a]	Formula	Analyses, % halogen Calcd.	Found	
α-Hydroxymethyl iodide	Fine tan granules	275–280 (dec.)[b]	$C_8H_{18}NOI$	46.81	46.50	46.98
α-Hydroxymethyl chloride	Chalky white granules	288 (dec.)[b]	$C_8H_{18}NOCl$	19.73	19.67	19.51
β-Hydroxymethyl iodide	Tan platelets	140.5–142[c]	$C_8H_{18}NOI$	46.81	46.65	46.50
β-Hydroxymethyl chloride	Chalky white granules	231–232 (dec.)[b]	$C_8H_{18}NOCl$	19.73	19.64	19.47
3-(α-Hydroxyethyl) iodide[d]	Tan needles	Sinters 132[c]				
		Melts 137–139.5[c]	$C_9H_{20}NOI$	44.49	44.19	44.20

[a] The compounds decomposing above 200° turned brown before decomposition. [b] Uncorrected. [c] Corrected. [d] Diastereoisomeric mixture.

TABLE II

N-DIMETHYL-ACETOXYALKYL-PIPERIDINIUM IODIDES

Compound	Appearance	M. p., °C. (corr.)	Formula	Analyses, % I— Calcd.	Found	
α-Acetoxymethyl	Tan plates	126.5–128.5	$C_{10}H_{20}NO_2I$	40.53	40.51	40.59
β-Acetoxymethyl	Thin tan plates	134–135	$C_{10}H_{20}NO_2I$	40.53	40.55	40.45
3-(α-Acetoxyethyl)	Tan granules	165–170[a]	$C_{11}H_{22}NO_2I$	38.78	38.82	38.83

[a] Diastereoisomeric mixture.

Strong and McElvain.[13] The three piperidylcarbinols (I), (II) and (III) were transformed to the quaternary esters (IV), (V) and (VI), respectively (see Chart I), through formation of the corresponding piperidinium iodides by treatment with methyl iodide and subsequent acetylation. Compound IV is analogous to acetylcholine, V is analogous to acetyl-γ-homocholine and VI is analogous to acetyl-γ-methyl-γ-homocholine.

In continuation of this problem, a series of pyrrolidinium salts of similar structure is being prepared and investigated.

Experimental Part

α-Piperidylcarbinol (I).—This was prepared from ethyl picolinate by the method of Sandborn and Marvel for the β-carbinol.[11] Color changes similar to those observed in the preparation of the β-carbinol appeared. The compound was obtained in 29% yield as a pale yellow oil, the color of which deepened on standing, boiling from 80–83° at 1 mm. and at 221° with decomposition at atmospheric pressure (Émich micro boiling point).

Anal. Calcd. for $C_6H_{13}NO$: N, 12.15; neut. equiv., 115. Found: N, 11.85; neut. equiv., 115, 114.

A yellow picrate of I was obtained by adding an ethereal picric acid solution to an ether solution of the carbinol; m. p. 128–129.5° (uncorr.).

Anal. Calcd. for $C_{12}H_{16}N_4O_8$: N, 16.28. Found: N, 16.22.

N-Dimethyl-α-hydroxymethyl-piperidinium Iodide and N-Dimethyl-β-hydroxymethyl-piperidinium Iodide.—The secondary base (1 mole), dissolved in anhydrous ethanol, was refluxed with 1.5 moles of methyl iodide in the presence of excess barium hydroxide for two hours. After decantation from the barium hydroxide, hydrogen chloride gas was passed into the solution to remove the dissolved barium hydroxide, and the resultant barium chloride was filtered. The alcohol solutions were concentrated in a vacuum desiccator, and the piperidinium iodides precipitated by the addition of an excess of carefully dried absolute ethyl ether. The products were recrystallized from anhydrous isopropyl alcohol. The beta compound could also be recrystallized from ethyl alcohol–ethyl acetate mixtures. The yield of crude product was in each case 62–67%, and after recrystallization 50%. Their properties are described in Table I. The piperidinium iodides were shaken with silver chloride and transformed to the corresponding chlorides by the method of Jones and Major.[14] The chlorides showed solubilities similar to those of the iodides. Their properties are also described in Table I.

N-Dimethyl-3-(α-hydroxyethyl)-piperidinium Iodide.—This compound was prepared as above except that the filtrate after removal of barium chloride was evaporated to dryness in a vacuum desiccator and the resulting dark red crystalline residue was recrystallized from ethyl alcohol–ethyl acetate. After three such recrystallizations, the yield was 20%. The properties are described in Table I.

N-Dimethyl-α-acetoxymethyl-piperidinium Iodide (IV), N-Dimethyl-β-acetoxymethyl-piperidinuim Iodide (V) and N-Dimethyl-3-(α-acetoxyethyl)-piperidinium Iodide (V) I.—One gram of piperidinium carbinol iodide was heated in a sealed tube in 10 g. of acetic anhydride at 100° for ten hours. The esters were precipitated by addition of excess absolute ether as yellow oils, which crystallized on standing. They were purified by boneblacking in anhydrous ethanol and precipitation from the latter solvent several times by addition of dry ether. These compounds are described in Table II. Attempted acetylation of the β-hydroxymethyl-piperidinium chloride yielded a crystalline product which was too hygroscopic to characterize.

Physiological Activity

The activity of the compounds in lowering the blood pressure of the cat on intravenous administration was measured. The dimethyl-piperidin-

(13) Strong and McElvain, THIS JOURNAL, **55**, 818 (1933).

(14) Jones and Major, *ibid.*, **52**, 307 (1930).

ium-carbinol iodides were relatively inactive in doses of 1 mg., but acetylation increased their activity considerably. This is analogous to the increase in activity obtained on acetylation of choline.[15] Compound V was the most active ester, being about one-tenth as active as acetylcholine when administered in a dose of 0.01 mg. Compound IV was about one-thirtieth as active as acetylcholine, and VI produced only a slight fall in does of 0.01 mg. Since IV is the analog of acetylcholine, while V is analogous to the less active acetyl-γ-homocholine, it was surprising to observe that V was more active than IV. The relative inactivity of VI as compared to V as a result of the introduction of a methyl group was also unexpected. It seems necessary, therefore, to consider the effect of the ring carbon atoms as substituents on the physiological moiety in interpreting the observed physiological data.

Since Hunt has shown arecoline to be one-fiftieth to one-hundredth as active as acetylcholine,[16] the beta ester is evidently distinctly more active than arecoline in its effect upon blood pressure. This is in line with the evidence that the choline ester type is more active than the betaine ester type. A more detailed report of the pharmacological data will be published elsewhere.

The authors wish to acknowledge the help of Dr. Daniel Green, who collaborated in the physiological experiments.

(15) Hunt and Taveau, *Hyg. Lab. Bull.*, No. 73, 68 (1911).

Summary

The preparation of α-piperidylcarbinol and a group of quaternary piperidinium salts of α-piperidylcarbinol, β-piperidylcarbinol and β-piperidylmethylcarbinol, analogous to simple choline esters is described. Their pharmacological activity is discussed briefly.

(16) Hunt and Renshaw, *J. Pharmacol.*, **29**, 17 (1926).

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RECEIVED JANUARY 7, 1939

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

Reaction of Paraffins with Hexahydroaromatic Hydrocarbons in the Presence of Aluminum Halides[1]

BY HERMAN PINES, ARISTID V. GROSSE AND V. N. IPATIEFF

It has been shown previously that aromatic hydrocarbons are destructively alkylated by paraffins in the presence of metal halide (aluminum chloride, zirconium chloride) or phosphoric acid catalysts[2-4]; the reaction proceeded according to the following scheme (Ar = aryl group)

$$C_{(m+n)}H_{2(m+n)+2} + ArH \longrightarrow ArC_nH_{2n+1} + C_mH_{2m+2} \quad (I)$$

A similar reaction has now been observed to take place when hexahydroaromatic hydrocarbons such as cyclohexane or methylcyclohexane are reacted with paraffins in the presence of aluminum bromide or chloride. It was found that the destructive alkylation of naphthenes proceeds readily with *2,2,3- and 2,2,4-trimethylpentane* and *3,4-dimethylhexane*, whereas *n-octane* and *2,2,3-trimethylbutane* do not destructively alkylate cyclohexane under similar conditions. The destructive alkylation of cyclohexane and methylcyclohexane by paraffins was made at temperatures ranging from 50 to 80°; the use of higher temperatures was not desirable since at such temperatures the naphthenes themselves decompose, and this phenomenon would complicate the study of the reaction products. The main reaction proceeds analogously to the equation written above, with the substitution of the hexahydroaromatic for the aromatic hydrocarbon. For example, the reaction of 2,2,4-trimethylpentane and cyclohexane yields *i*-butane and methylated cyclohexanes, the latter being formed by isomerization[5] of *t*-butylcyclohexane.

The structure of the alkylated cyclohexanes was determined by converting them to the corresponding aromatic hydrocarbons by dehydrogenation over platinized aluminum oxide. The aromatic hydrocarbons were identified through the bromo or nitro derivatives. It was found that the al-

(1) Presented at the meeting of the Division of Organic Chemistry of the American Chemical Society at Rochester, N. Y., September 6–10, 1937.

(2) Grosse and Ipatieff, THIS JOURNAL, **57**, 2415 (1935).

(3) Grosse, Mavity and Ipatieff, *J. Org. Chem.*, **3**, 137, 448 (1938).

(4) Ipatieff, Komarewsky and Pines, THIS JOURNAL, **58**, 918 (1936). Ipatieff, "Catalytic Reaction under High Pressures and Temperatures," The Macmillan Co., New York, N. Y., 1936.

(5) V. Grignard and Stratford, *Compt. rend.*, **178**, 2149; *Bull. soc. chim.*, [4] **35**, 931 (1924).