[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WISCONSIN]

CATALYTIC REDUCTION OF 1-PHENYL- AND 1-BENZYL-4-PIPERIDONES¹

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In an attempt to reduce the ketone group of 1-phenyl- and 1-benzyl-3-carbethoxy-4-piperidone, Thayer and McElvain² found that reduction of the aryl nucleus took place simultaneously and from the former compound 1-cyclohexyl-3-carbethoxy-4-piperidyl p-aminobenzoate hydrochloride was isolated but from the benzyl derivative no definite product could be obtained. Recently the preparation of a series of 1-alkyl-4-piperidyl benzoates was reported,³ and it was pointed out that the catalytic reduction of the 1-alkyl-4-piperidones (I) took place much more readily than the reduction of the corresponding 3-carbethoxy-4-piperidones (II).



It, therefore, seemed desirable to prepare 1-phenyl- and 1-benzyl-4-piperidones and ascertain if possible their behavior on reduction.

These two piperidones were prepared from the corresponding 1-phenyland 1-benzyl-3-carbethoxy-4-piperidones² by identically the same procedure used in the preparation of the 1-alkyl-4-piperidones.³ The hydrochlorides of the piperidones were subjected to catalytic reduction using Adams' platinum-oxide-platinum-black catalyst.

In the reduction of 1-phenyl-4-piperidone hydrochloride it was observed that if the reduction were stopped when enough hydrogen was absorbed to reduce the ketone group to a secondary alcohol, no definite crystalline product could be obtained after acylation with benzoyl chloride. If the reduction were allowed to proceed until no more hydrogen was absorbed, no difficulty was encountered in preparing a crystalline hydrochloride of the benzoate. The amount of hydrogen absorbed in this case was sufficient to form 1-cyclohexyl-4-hydroxypiperidine. In the reduction of 1-benzyl-4-piperidone hydrochloride, the absorption of hydrogen stopped after a period of twelve hours and the amount absorbed was sufficient only to reduce the ketone group to a secondary alcohol.

The 1-cyclohexyl- and the 1-benzyl-4-hydroxypiperidines were not isolated as such but were acylated with benzovl chloride and the resulting

¹ This work was carried out at the suggestion of Professor S. M. McElvain of the Department of Organic Chemistry, University of Wisconsin.

² Thayer and McElvain, THIS JOURNAL, 49, 2862 (1927).

⁸ Bolyard and McElvain, *ibid.*, **51**, 922 (1929).

benzoates crystallized as the hydrochlorides. In order to obtain additional information concerning local anesthetics of this type, these benzoates have been submitted for pharmacological study.

Experimental

1-Phenyl-4-piperidone Hydrochloride.—To 0.1 mole of 1-phenyl-3-carbethoxy-4piperidone hydrochloride was added 120 cc. of 20% hydrochloric acid, and the resulting solution refluxed for one hour. At the end of this time no coloration was produced in ferric chloride solution by a drop of the reaction solution. The latter was then evaporated to dryness under diminished pressure and the residue was decomposed with concentrated sodium hydroxide. The free piperidone base was extracted with three 75-cc. portions of ether and the combined extract dried over anhydrous sodium sulfate for twenty-four hours. The hydrochloride was than precipitated with dry hydrogen chloride and recrystallized from an acetone—ether mixture. The yield was 78% of the theoretical of a product melting at 145–147°.

Anal. Calcd. for C₁₁H₁₄NOCl: Cl, 16.76. Found: Cl, 16.75, 16.76.

1-Benzyl-4-piperidone Hydrochloride.—This piperidone was prepared by exactly the same procedure used for 1-phenyl-4-piperidone hydrochloride. An 87% yield of the hydrochloride was obtained which melted at $159-161^{\circ}$.

Anal. Caled. for C₁₂H₁₆NOC1: Cl, 15.71. Found: Cl, 15.57, 15.53.

Both of these piperidone hydrochlorides when crystallized from an alcohol-ether mixture gave chlorine analyses considerably lower than the calculated value, but when crystallized from an acetone-ether mixture the analyses checked with the calculated values. This behavior indicates that the hydrochlorides from the alcohol-ether solvent contained alcohol of crystallization. All attempts, however, to remove such alcohol by drying at atmospheric pressure or under diminished pressure were unsuccessful. The analyses were not changed by this treatment.

1-Cyclohexyl-4-piperidyl Benzoate Hydrochloride.—A solution of 3.5 g. of the 1-phenyl-4-piperidone hydrochloride in 40 cc. of 95% alcohol was shaken with 0.2 g. of Adams' platinum-oxide-platinum-black catalyst and hydrogen under a pressure of 2-3 atmospheres. After sixteen hours the theoretical amount of hydrogen had been absorbed to form 1-cyclohexyl-4-hydroxypiperidine hydrochloride. The catalyst was removed from the solution and the alcohol distilled under diminished pressure. To the residue which remained was added 7 cc. of benzoyl chloride and the mixture heated in an oil-bath at 130-140° for one hour. When the benzoylation had finished, 15 cc. of absolute alcohol was added to decompose the excess benzoyl chloride. The resulting alcohol solution was diluted with 150 cc. of ether and the precipitated 1-cyclohexyl-4piperidyl benzoate hydrochloride allowed to crystallize. The product was recrystallized from an alcohol-ether mixture. A 57% yield of a product which melted at $250-252^{\circ}$ was obtained.

Anal. Calcd. for C₁₈H₂₈NO₂Cl: Cl, 10.95. Found: Cl, 10.95, 11.00.

1-Benzyl-4-piperidyl Benzoate Hydrochloride.—This compound was prepared in exactly the same way as the 1-cyclohexyl-4-piperidyl benzoate hydrochloride. In this case, however, no more hydrogen than that required for the reduction of the ketone group was absorbed. After twelve hours the reduction had stopped. A 40% yield of the 1-benzyl-4-piperidyl benzoate hydrochloride was obtained. It melted at 198–200°.

Anal. Calcd. for C19H22NO2Cl: Cl, 10.69. Found: Cl, 10.83, 10.92.

Pharmacological Report.—The 1-cyclohexyl and 1-benzyl-4-piperidyl benzoate hydrochlorides are being studied pharmacologically by Mr.

Charles L. Rose of the Lilly Research Laboratories, Indianapolis, Indiana. A preliminary report of this work is given in the following table.

		Pharm	ACOLOGIC	al Data			
	Average duration of	Subcutaneous toxicity to white mice (mg./kg.)			Intravenous toxicity to white rats (mg./kg.)		
1-Substituent	minutes	M. T. D.	M. L. D.	mice used	M. T. D.	M. L. D.	rats used
Cyclohexyl	42	300	400	11	12.5	15	8
Benzyl	19	200	3 00	9	25	30	7

It will be seen from the table that 1-cyclohexyl-4-piperidyl benzoate hydrochloride has a lower subcutaneous and a higher intravenous toxicity than the 1-benzyl-4-piperidyl benzoate hydrochloride. Neither of these products shows any unusual anesthetic properties.

Summary

1. The preparation and properties of 1-phenyl- and 1-benzyl-4-piperidones have been described.

2. The catalytic reduction of these piperidones has been studied.

3. Two local anesthetics, 1-cyclohexyl and 1-benzyl-4-piperidyl benzoate hydrochlorides, have been prepared from the reduction products.

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THERMAL DATA ON ORGANIC COMPOUNDS. VI. THE HEAT CAPACITIES, ENTROPIES AND FREE ENERGIES OF SOME SATURATED, NON-BENZENOID HYDROCARBONS¹

By George S. Parks,² Hugh M. Huffman³ and S. Benson Thomas⁴ Received August 12, 1929 Published March 6, 1930

In five earlier papers⁵ the entropies and free energies of nineteen compounds of carbon, hydrogen and oxygen were calculated from heat capacity data by means of the third law of thermodynamics. These results indicated that the entropy and free energy of an organic compound are related to its constitution in a simple additive manner. The present in-

¹ This paper contains results obtained in an investigation of the heat capacities and free energies of some typical hydrocarbon compounds, listed as Project No. 29 of the American Petroleum Institute Research. Financial assistance in this work has been received from a research fund of the American Petroleum Institute donated by The Universal Oil Products Company. This fund is being administered by the Institute with the coöperation of the Central Petroleum Committee of the National Research Council.

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⁵ Parks, THIS JOURNAL, **47**, 338 (1925); Parks and Kelley, *ibid.*, **47**, 2094 (1925); Parks and Anderson, *ibid.*, **48**, 1506 (1926); Parks and Huffman, *ibid.*, **48**, 2788 (1926); Parks, Kelley and Huffman, *ibid.*, **51**, 1800 (1929).

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