Examination of the Mother Liquors

The mother liquors obtained in the recrystallizations of the above-mentioned mixture of sterols from wheat bran were saved and examined separately. The middle fractions yielded 10 g. of material that showed a rotation in chloroform of +10.41°. From the mother liquors of the first fractions we isolated 16.7 g. of substance having a levorotation of —30.9°. This latter material was fractionated as follows. It was dissolved in 900 cc. of boiling alcohol and as the solution cooled 13.5 g. of crystals separated. The substance was again recrystallized from 900 cc. of alcohol, yielding 10 g. of crystals. The mother liquors were concentrated and the material that separated as the solution cooled was recrystallized several times from alcohol, yielding 4.7 g. of colorless, plate-shaped crystals; $[\alpha]_D^{20}$ in chloroform —33.46°. This bottom fraction represents therefore nearly pure sitosterol.

Summary

The phytosterols occurring in wheat endosperm have been examined. Wheat endosperm contains at least two different sterols, namely, ordinary sitosterol, $C_{27}H_{45}OH$, and dihydrositosterol, $C_{27}H_{47}OH$, m. p. 144–145°; $[\alpha]_D^{20}$, +25.82°. The dihydrositosterol from wheat bran appears to be identical with the saturated sterol that occurs in corn endosperm. The substance exists throughout the wheat endosperm but the bran is particularly rich in this sterol.

GENEVA, NEW YORK

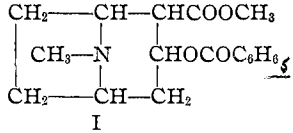
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

PIPERIDINE DERIVATIVES. A CYCLIC AND AN OPEN-CHAIN COMPOUND RELATED IN STRUCTURE TO COCAINE

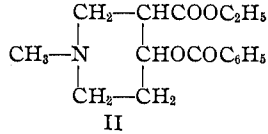
BY S. M. MCELVAIN

RECEIVED APRIL 29, 1924 PUBLISHED JULY 7, 1924

The piperidine nucleus occurs in many of the alkaloids, either as the single nucleus or in a bicyclic system. Such a bicyclic system is the basic structure upon which the molecule of cocaine is built. Since the functional groups of the cocaine molecule (I) are attached to the piperidine nucleus, piperidine derivatives of that general structure should be of interest. This communication, in part, describes the synthesis of a compound, 1-methyl-3-carbo-ethoxy-4-piperidyl benzoate (II), which has the same structure as the piperidine portion of the cocaine molecule.



I



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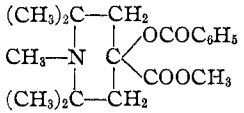

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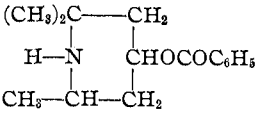
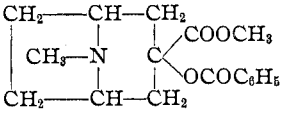
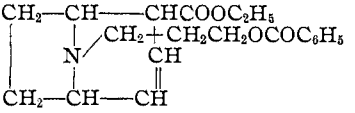


IV

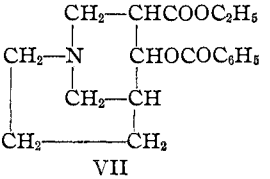
The synthetic substitutes for cocaine which have been prepared are for the most part relatively simple in their structure, and do not contain an alicyclic ring. The piperidine derivatives which have appeared in this connection are α-eucaine (III) and β-eucaine (IV). Their structures resemble the piperidine portion of the cocaine molecule fairly closely, but when the effect of modifications of the structure of cocaine as represented in α-cocaine[1] (V), eccaine[2] (VI), and ethyl benzoyl-isogranatoline-carboxylate[3] (VII) are considered, the eucaines may not represent the ideal arrangement of the functional groups about the piperidine nucleus.



V



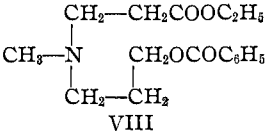
VI



VII

α-Cocaine has no anesthetic action. Eccaine is much more powerful and considerably less toxic than cocaine. Ethyl benzoyl-isogranatoline-carboxylate has a higher toxicity and much less anesthetic action than cocaine. From the standpoint of the piperidine derivatives, 1-methyl-3-carbo-ethoxy-4-piperidyl benzoate represents a return to the structure of the natural alkaloid.

It seemed advisable to make a comparison between the piperidine derivative and the open-chain compound, γ-(methyl-β-carbo-ethoxy-ethyl)-aminopropyl benzoate (VIII).



VIII

As may be seen, in this molecule the piperidine ring has been opened between the carbon atoms which carry the substituent groups. Such a

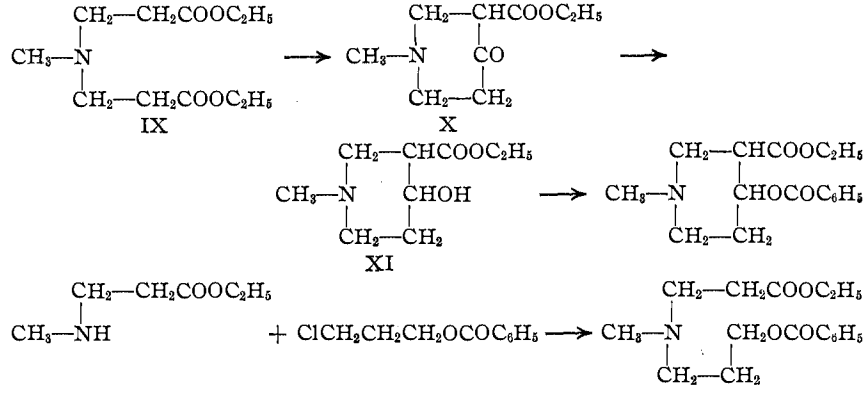
[1] Willstätter, *Ber.*, **29**, 2216 (1896).

[2] von Braun, *Ber.*, **51**, 235 (1918).

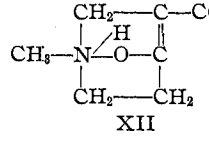
[3] McElvain and Adams, THIS JOURNAL, **45**, 2738 (1923).

comparison, it was thought, might give some indication of the relative anesthetic action of cyclic and open-chain compounds.

The synthesis of these two substances has involved well-known reactions, and may be represented by the following scheme,



In the case of the piperidine derivative, the intermediate compounds are of some interest. The condensation of β,β'-dicarbo-ethoxy-diethyl-methylamine (IX) into 1-methyl-3-carbo-ethoxy-4-piperidone (X) was effected with sodium in xylene. The reaction runs with remarkable smoothness, with yields of 55–60% of those calculated. This is a much higher yield than has ever been reported from a condensation of this type. Ruzicka[4] has used the same reaction in the synthesis of 4-piperidones. He made no attempt to isolate the keto ester, and obtained a maximum yield of 25% of the ketone. The keto ester has the general properties which have been described[5] for ethyl isogranatonine-carboxylate. It gives a deep reddish-violet color with ferric chloride; it may be distilled with no appreciable isomerization; on standing it slowly passes into an isomeric form which is probably an inner salt (XII).



The reduction of the keto ester and the benzoylation of the resulting hydroxy ester followed the same procedure as that used for the isogranatonine derivatives.[3]

The author is indebted to Mr. Henry L. Schmitz of the Department of Pharmacology of the University of Wisconsin for the pharmacological tests. 1-Methyl-3-carbo-ethoxy-4-piperidyl benzoate hydrochloride is equally toxic with cocaine hydrochloride but less efficient in producing

[4] Ruzicka and others, *Helv. Chim. Acta*, **3**, 817 (1920); **5**, 717 (1922).

[5] Ref. 3, p. 2740.

anesthesia. A 2% solution applied to the rabbit's cornea for one minute produces anesthesia lasting an average of six minutes, whereas the same concentration of cocaine hydrochloride produces anesthesia of twenty-eight minutes' average duration. γ-(Methyl-β-carbo-ethoxy-ethyl)amino-propyl benzoate hydrochloride is only about one-third as toxic as the piperidine derivative, but is less efficient in producing anesthesia. A 2% solution applied to the rabbit's cornea for one minute produced only partial anesthesia in one case and no anesthesia at all in two other experiments.

The difference in anesthetic action and toxicity of the cyclic and open-chain compound may be attributed to one or both of two causes. The first is one of structure, that is, one is cyclic and the other is not. The second cause is that the cyclic compound contains two points of asymmetry, while the open-chain compound contains none. It has recently been pointed out by King,[6] in connection with the stereo-isomerism and local anesthetic action of β-eucaine, that compounds of similar structure have the same type of action, but differ in the quantity of action which they show. This difference in action is probably due to the preference of the asymmetric cells of the body for one form rather than its optical isomer. Upon this basis it is probable that an increase in the number of points of asymmetry in a compound would increase the quantity of its action. The investigation of cyclic and open-chain compounds of this type will be continued in the hope of arriving at some conclusions as to the relation of structure to therapeutic action.

Experimental Part

β, β'-Dicarbo-ethoxy-diethyl-methylamine (IX).—A solution of 25 g. (1 molecular equivalent) of methylamine hydrochloride and 135 g. (2 equivalents) of ethyl β-bromo-propionate in 400 cc. of 95% alcohol was treated with 240 g. of silver oxide. The mixture was shaken intermittently until it had cooled and the liquid above the precipitated silver halide gave no test for bromides. The silver halide was then filtered off and washed with 100 cc. of 95% alcohol. The alcohol was distilled from the filtrate and the remaining oil dissolved in 500 cc. of ether. A small layer of quaternary compound which appeared was removed. The ether was distilled and the resulting amino ester distilled in a vacuum; b. p., 136–138° (4 mm.); d_{20}^{20}, 1.0190; n_D^{20}, 1.4411; yield, 56 g., or 65%. Practically none of the secondary amino ester was formed.

Analyses. Subs., 0.5192, 0.5032: 38.63, 37.90 cc. of 0.0586 *N* HCl. Calc. for $C_{11}H_{21}O_4N$: N, 6.06. Found: 6.10, 6.18.

1-Methyl-3-carbo-ethoxy-4-piperidone Hydrochloride.—A mixture of 3.5 g. of sodium and 40 g. of xylene was placed in a 300cc. flask fitted with a ground-glass reflux condenser. The sodium was finely powdered by first heating the xylene to boiling and then shaking it vigorously while it cooled. After the xylene had cooled somewhat, 35 g. of β,β'-dicarbo-ethoxy-diethyl-methylamine was added and the mixture heated in an oil-bath. When the temperature of the bath reached 70–80° a vigorous reaction set in, and sufficient heat was evolved to cause the contents of the flask to boil. After this re-

[6] King, *J. Chem. Soc.*, **125**, 41 (1924).

action had subsided the temperature of the bath was raised to 150–160° and the liquid in the flask was boiled for 15 minutes. The flask was then cooled and the contents were dissolved in about 150 cc. of ice water. The xylene layer was separated and the aqueous portion extracted with ether in order to remove any unchanged ester. After this extraction the aqueous portion was acidified to congo red with hydrochloric acid, care being taken not to let the temperature of the solution rise above 10°. The solution was then made alkaline with solid potassium carbonate, and extracted with ether until the ether extracts gave practically no coloration with ferric chloride. These ether extracts were combined and concentrated to a volume of about 200 cc. Dry hydrogen chloride was then passed into the ether solution in order to precipitate the hydrochloride of the amine. It came down as a white crystalline precipitate which, after the ether was decanted, was crystallized from a mixture of alcohol and ether; yield, 19 g., or 57%. This product was dried at 75° (2 mm.) for two hours. When heated slowly it melted sharply at 128–129°, but when placed in a hot bath (115–120°) it melted over a considerable range (118–125°). This behavior was probably due to the presence of stereo-isomeric forms.

Analyses. Subs., 0.2010, 0.2010: AgCl, 0.1298, 0.1291. Calc. for $C_9H_{16}O_3NCl$: Cl, 16.03. Found: 15.96, 15.90.

1-Methyl-3-carbo-ethoxy-4-piperidone (X).—A mixture of 9 g. of 1-methyl-3-carbo-ethoxy-4-piperidone hydrochloride and 25 cc. of saturated potassium carbonate solution was extracted twice with 25cc. portions of ether. The ether layer was separated and the ether evaporated. The remaining oil was distilled in a vacuum; b. p., 114–116° (4 mm.); d_{20}^{20}, 1.0660; n_D^{20}, 1.4802; yield, 6 g., or 80%. There was practically no isomerization during the distillation as shown by the fact that 6 g. of pure ester on distillation yielded 5.5 g. of distillate.

Analyses. Subs., 0.3220, 0.4407: 30.22, 42.32 cc. of 0.0586 *N* HCl. Calc. for $C_9H_{15}O_3N$: N, 7.57. Found: 7.70, 7.88.

This ester after several weeks showed a considerable amount of isomerization. Since the resulting product showed the solubility behavior of a quaternary compound, it was probably an inner salt (XII).

1-Methyl-3-carbo-ethoxy-4-hydroxypiperidine (XI).—A solution of 15 g. of 1-methyl-3-carbo-ethoxy-4-piperidone hydrochloride in 75 cc. of absolute alcohol was shaken with platinum oxide catalyst[7] and hydrogen under pressure in a manner analogous to that described for the reduction of ethyl isogranatonine-carboxylate hydrochloride. About 2 g. of catalyst and 50 hours of shaking were required to reduce the keto ester sufficiently to give a negative ferric chloride test. After the catalyst was filtered off the alcohol was distilled under diminished pressure. The remaining hydrochloride was amorphous, and all attempts made to recrystallize it were unsuccessful. The free base was liberated into ether with 40% sodium hydroxide solution and, after the removal of the ether, was distilled in a vacuum. It was obtained as a very thick, colorless oil that boiled at 122–124° (4 mm.); d_{20}^{20}, 1.0879; n_D^{20}, 1.4742; yield, 10 g., or 79%.

Analyses. Subs., 0.3572, 0.3840: 33.20, 35.15 cc. of 0.0586 *N* HCl. Calc. for $C_9H_{17}O_3N$: N, 7.48. Found: 7.62, 7.50.

1-Methyl-3-carbo-ethoxy-4-piperidyl Benzoate Hydrochloride (II).—The alcoholic solution from the catalytic reduction of the keto ester, representing 10 g. of 1-methyl-3-carbo-ethoxy-4-hydroxypiperidone hydrochloride, was evaporated under diminished pressure until no more alcohol remained. The resulting hydrochloride was a semisolid, amorphous mass. To this residue 20 cc. of benzoyl chloride was added

[7] Adams and others, THIS JOURNAL, **44**, 1397 (1922); **45**, 1071 (1923); **45**, 2171 (1923).

and the mixture heated in an oil-bath at 140–150° until the evolution of hydrogen chloride ceased. After the solution had cooled, it was diluted with 100 cc. of anhydrous ether, and the liquid portion decanted from the precipitated benzoyl derivative. This light brown, gummy precipitate was washed with another 100cc. portion of anhydrous ether, and then recrystallized from a mixture of alcohol and ether. After three recrystallizations the product melted at 181–183°; yield, 9 g., or 61%.

Analyses. Subs., 0.1002, 0.1006: AgCl, 0.0435, 0.0444. Calc. for $C_{16}H_{22}O_4NCl$: Cl, 10.84. Found: 10.72, 10.91.

Ethyl β-Methylaminopropionate.—To 100 g. of β-bromopropionic acid was added a solution of 55 g. of sodium bicarbonate in 200 cc. of water. After complete solution had taken place, a solution of 118 g. of methylamine in 500 cc. of water was added. It was found necessary to cool the resulting solution somewhat as the reaction proceeded, in order to prevent the loss of methylamine. The mixture was then allowed to stand at room temperature for three days. After this time the solution was concentrated by distillation to about 300 cc. and made acid to congo red with hydrochloric acid. The resulting acid solution was evaporated to complete dryness under diminished pressure and the residue treated with 500 cc. of 95% alcohol. The inorganic salt was filtered off and the alcoholic filtrate evaporated to dryness under diminished pressure. The yellowish-brown residue was esterified by boiling for 12 hours with 1 liter of a 6% solution of hydrogen chloride in absolute alcohol. The alcohol was then removed under diminished pressure until about 200 cc. of solution remained. This solution was cooled to between —10° and 0°, covered with 300 cc. of ether, and cold 50% potassium hydroxide solution added, while the mixture was kept constantly cooled until the aqueous layer was distinctly alkaline. The ether layer was separated and the aqueous portion extracted with two successive 300cc. portions of ether. The ether extracts were combined and after the removal of the ether the remaining esters were fractionated in a vacuum. After two fractionations there was obtained 32 g., a yield of 37%, of ethyl β-methylaminopropionate which boiled at 59–61° (4 mm.); d_{20}^{20}, 1.0082; n_D^{20}, 1.4443; and 8 g., or a yield of 11%, of β,β′-dicarbo-ethoxy-diethyl-methylamine (IX) that boiled at 125–140° (4 mm.).

Analyses. Subs., 0.3685, 0.3014: 48.60, 40.05 cc. of 0.0586 *N* HCl. Calc. for $C_6H_{13}O_2N$: N, 10.68. Found: 10.82, 10.91.

β-Methylaminopropionic acid has been prepared by Gansser[8] by heating in a sealed tube β-iodopropionic acid with a 33% solution of methylamine in water. He has described the ethyl ester as boiling at 58° (8 mm.); d_5, 0.9669. The method described here was considered much more suitable for the preparation of the ester in quantity.

γ-(Methyl β-Carbo-ethoxy-ethyl)aminopropyl Alcohol.—A mixture of 15 g. of ethyl β-methylaminopropionate and 4.5 g. of trimethylene chlorohydrin was heated in an oil-bath at 140–150° for one hour. At the end of this time two layers had separated. The top layer was dissolved in 50 cc. of ether and separated from the lower hydrochloride layer by decantation. The ether was distilled and the remaining tertiary amine distilled in a vacuum; b. p., 123–125° (2 mm.); d_{20}^{20}, 1.0190; n_D^{20}, 1.4450; yield, 8 g., or 79%.

Analyses. Subs., 0.3240, 0.2821: 29.90, 26.19 cc. of 0.0586 *N* HCl. Calc. for $C_9H_{19}O_3N$: N, 7.40. Found: 7.56, 7.60.

γ-(Methyl β-Carbo-ethoxy-ethyl)aminopropyl Benzoate Hydrochloride (VIII).—The attempts to prepare this compound by the benzoylation of γ-(methyl β-carbo-ethoxy-ethyl)aminopropyl alcohol were unsuccessful, inasmuch as it was impossible to obtain a crystalline product from the reaction mixture. It was best prepared according to the

[8] Gansser, *Z. physiol. Chem.*, **61**, 42 (1909).

following procedure. A mixture of 10 g. of ethyl β-methylaminopropionate and 8 g. of γ-chloropropyl benzoate was heated for one hour in an oil-bath at 140–150°. The mixture was allowed to cool and the upper layer of tertiary amine dissolved in 100 cc. of absolute ether. The ether layer was separated from the lower hydrochloride layer by decantation. The tertiary amine was precipitated as the hydrochloride from the ether solution with hydrogen chloride. The ether was poured off and the hydrochloride recrystallized twice from a mixture of alcohol and ether. It melted at 103–105°; yield, 6 g.

Analyses. Subs., 0.2068, 0.2144: AgCl, 0.0880, 0.0920. Calc. for $C_{16}H_{24}O_4NCl$: Cl, 10.77. Found: 10.52, 10.63.

Summary

1. The synthesis of some 1,3,4-trisubstituted piperidines has been effected and their properties have been reported.

2. 1-Methyl-3-carbo-ethoxy-4-piperidyl benzoate is of particular interest in that it has the structure of the piperidine portion of the cocaine molecule. It is equally as toxic as cocaine and less efficient in producing anesthesia.

3. The open-chain compound, γ-(methyl β-carbo-ethoxy-ethyl)amino-propyl benzoate, which represents the structure of the piperidine portion of the cocaine molecule with the ring opened between the carbons carrying the substituent groups, has been prepared. It has about one-third the toxicity of cocaine, but produces practically no anesthesia when applied to the rabbit's cornea.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE ADDITION OF METHYL HYPOBROMITE TO CERTAIN ETHYLENE DERIVATIVES

BY JAMES B. CONANT AND ERNEST L. JACKSON

RECEIVED MAY 1, 1924 PUBLISHED JULY 7, 1924

As a result of several investigations of the last few years,[1] a very satisfactory method has been developed for adding hypochlorous and hypobromous acids to ethylene and ethylene derivatives. This method consists in rapidly stirring the organic compound with water into which a current of chlorine or bromine vapor is passed; the hypohalogen acid formed by the reaction of the halogen with the water rapidly adds to the double linkage of the unsaturated compound and forms the chloro- or bromohydrin. In connection with an attempt to synthesize certain substituted ethylene oxides, we tried to utilize this method for the preparation of bromohydrins from certain unsaturated compounds of high molecular weight which were practically insoluble in water. Probably because of the sparing solubility no satisfactory results could be obtained and we

[1] Read and Williams, *J. Chem. Soc.*, **111**, 240 (1917); **117**, 359 (1920). Read and Hook, *ibid.*, **117**, 1214 (1920). Gomberg, THIS JOURNAL, **41**, 1414 (1919).