[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

LOCAL ANESTHETICS IN THE PYRROLE SERIES. I[1,2]

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The pyrrole or modified pyrrole nucleus is found in a number of naturally occurring compounds—hemoglobin, chlorophyll, proteins, bile and urinary pigments and certain alkaloids. Because of the presence of this nucleus in so many normal physiological products, we decided to introduce it into certain synthetic drugs by the substitution of this group for other cyclic radicals such as phenyl.[3]

Investigations in the chemistry of pyrrole compounds have been retarded by the high cost of pyrrole in this country and by the fact that practical laboratory methods have not been developed for the preparation of relatively large amounts of the simpler pyrrole derivatives.

Recently[4] it was found possible in this Laboratory to prepare pyrrole in fairly large quantities at moderate expense. We began, then, a detailed study of the preparation of pyrrole-carboxylic acids from pyrrole itself[5] and during the investigation of pyrrole-2-carboxylic acid the discovery was made that the ethyl ester of this substance possesses decided local anesthetic action when placed on the tip of the tongue. Although local anesthetic action is a property common to many esters of aromatic acids, especially those of aminobenzoic acids, this type of action, with one exception, has not been noticed hitherto in the case of the esters of the

[1] This paper represents the first part of a dissertation to be submitted to the Graduate School by Mr. Blake in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] We wish to take this opportunity to acknowledge our indebtedness to Frederick Stearns and Company who have made this investigation possible by the grant of a fellowship.

[3] In a few instances comparisons have been made between pyrrole, thiophene and furan compounds and the corresponding benzene derivatives. Because of the close chemical relationship between thiophene and benzene it is not surprising that a number of thiophene derivatives resemble their benzene analogs in taste and odor (Cohn, "Die organischen Geschmacksstoffe," Siemenroth, Berlin, **1914**, p. 78). Steinkopf and Ohse have prepared several synthetic drugs in which the thienyl group has been used in place of phenyl. Thiophene-cocaine hydrochloride [*Ann.*, **437**, 14 (1924)] and the thiophene analogs of eucaine-A and stovaine [*ibid.*, **448**, 205 (1926)] all proved to be strong anesthetics. Diethylamino-ethyl-2-thiophene-carboxylate and diethylamino-ethyl-2-furan-carboxylate [Gilman and Pickens, THIS JOURNAL, **47**, 252 (1925)] were found to be poor local anesthetics compared to procaine.

[4] Blicke and Powers, *Ind. Eng. Chem.*, **19**, 1334 (1927).

[5] A number of substituted pyrrole-carboxylic acids have been prepared from aliphatic compounds by ring closure. However, in many instances the yields obtained by this process are poor; furthermore, the method is applicable only for the preparation of certain definite types of pyrrole derivatives.

simpler pyrrole-carboxylic acids. Gilman and Pickens[6] prepared the diethylamino-ethyl ester of pyrrole-2-carboxylic acid and according to Kamm[7] this substance is about one-third as active as procaine.

In addition to the ethyl ester[8] of pyrrole-2-carboxylic acid, we investigated the action of the methyl,[8,9] propyl,[10] *iso*propyl,[10] butyl,[10] *iso*butyl[10] and *iso*-amyl[10] homologs. It seemed from the rough test on the tip of the tongue that the propyl ester possessed the most decided action. The phenyl ester also possessed some activity. Preliminary pharmacological tests[11] indicate that the ethyl ester is a compound of comparatively low toxicity.

The ethyl esters of pyrrole-1-carboxylic acid, 2-methylpyrrole-3-carboxylic acid[12] and of 2,4-dimethylpyrrole-3-carboxylic acid[13] possessed marked action, but the ethyl esters of the following acids were inactive: 2,5-dimethylpyrrole-3-carboxylic acid,[14] 2,5-diphenyl-pyrrole-3-carboxylic acid,[15] 1,2,5-triphenylpyrrole-3-carboxylic acid,[15] 1,5-diphenyl-2-methylpyrrole-3-carboxylic acid,[16] 1-phenyl-2,5-dimethylpyrrole-3-carboxylic acid,[17] 3-phenyl-5-methylpyrrole-4-carboxylic acid,[18] 2,4-dimethylpyrrole-3,5-dicarboxylic acid,[18] 2,5-dimethylpyrrole-3,4-dicarboxylic acid,[19] 2-pyrrolidone-5-carboxylic acid[20] and 3,4,5-tribromopyrrole-2-carboxylic acid.

Mannich and co-workers[21] found, unexpectedly, that β-N-piperidinoethyl phenyl ketone, $C_6H_5COCH_2CH_2NC_5H_{10}$, a substance obtained readily from acetophenone, piperidine hydrochloride and paraformaldehyde, possesses local anesthetic action. Furthermore, the benzoyl derivative of the corresponding secondary carbinol, $C_6H_5CH(OCOC_6H_5)CH_2CH_2NC_5H_{10}$, was shown to be a strong anesthetic. We prepared the above ketone by another process, a method which indicates definitely the structure of the substance, namely, by the action of β-bromopropiophenone on piperidine

[6] Gilman and Pickens, THIS JOURNAL, **47**, 245 (1925).

[7] Kamm, *ibid.*, **47**, 252 (1925).

[8] (a) Ciamician and Silber, *Ber.*, **17**, 1152 (1884); (b) Oddo, *Gazz. chim. ital.*, I, **39**, 658 (1909).

[9] Oddo and Moschini, *Gazz. chim. ital.*, II, **42**, 252 (1912).

[10] This ester has been prepared from pyrrylmagnesium bromide and the alkyl chloroformic ester by Oddo and Moschini, *Gazz. chim. ital.*, II, **42**, 253 (1912).

[11] Conducted in the Laboratories of Frederick Stearns and Company.

[12] Benary, *Ber.*, **44**, 495 (1911).

[13] Knorr and Lange, *ibid.*, **35**, 3007 (1902).

[14] Hantzsch, *ibid.*, **23**, 1475 (1890).

[15] Kapf and Paal, *ibid.*, **21**, 3060 (1888).

[16] Lederer and Paal, *ibid.*, **18**, 2595 (1885).

[17] Feist, *ibid.*, **35**, 1546 (1902).

[18] Knorr, *Ann.*, **236**, 318 (1886).

[19] Knorr, *Ber.*, **18**, 302 (1885).

[20] Haitinger, *Monatsh.*, **3**, 228 (1882); Abderhalden and Kautzsch, *Z. physiol. Chem.*, **78**, 115 (1912).

[21] Mannich and Lammering, *Ber.*, **55**, 3515 (1922); German Patent, 379,950; *Friedländer*, **14**, 1247; Mannich and Curtas, *Arch. Pharm.*, **264**, 750 (1926).

$$C_6H_5COCH_2CH_2Br + 2HNC_5H_{10} \longrightarrow C_6H_5COCH_2CH_2NC_5H_{10} + HNC_5H_{10}\cdot HBr$$

From bromo-acetophenone and piperidine we obtained N-piperidinomethyl phenyl ketone, $C_6H_5COCH_2NC_5H_{10}$, the lower homolog of the above ketone. This latter compound, as well as the benzoate of the corresponding secondary alcohol, $C_6H_5CH(OCOC_6H_5)CH_2NC_5H_{10}$, was found to possess anesthetic activity.

2-Acetylpyrrole, piperidine hydrochloride and paraformaldehyde react readily to form a substance which possesses marked anesthetic action. Based on analogy the compound should have the structure $C_4H_4NCOCH_2CH_2NC_5H_{10}$. Unfortunately, we were unable to obtain this material in crystalline condition.

Experimental Part

Pyrrole.—We wish to add the following notes to the information published previously[4] concerning the preparation of pyrrole.

For the preparation of ammonium mucate on a large scale about three and one-half times the amount of ammonia water (technical) required theoretically was added to mucic acid which had been put into a large crock. The mixture was stirred thoroughly from time to time. After several weeks, through evaporation of the water, the ammonium salt was obtained in the form of a thick paste. The latter was transferred to galvanized iron trays and allowed to dry thoroughly. The material was then milled to a flour-like powder.

It was found advantageous to replace the metal coil condenser by two ordinary glass bulb condensers.

As soon as the mixture of pyrrole, water and ammonium carbonate begins to distil from the apparatus at a fairly rapid rate, the Fletcher burner should be replaced by a micro burner. If the bottom of the apparatus is heated too strongly at this stage of the operation the reaction mixture invariably foams over into the condenser.

After 200–250 cc. of pyrrole (this refers to experiments in which 5.5 pounds of ammonium mucate have been used) has been collected, the formation of pyrrole becomes so slow that it seems that the process is complete. The micro burner should now be replaced by a Fletcher burner. The distillation of pyrrole then begins again and at least 100 cc. more of pyrrole is obtained.

The crude pyrrole contains considerable ammonia and this should be removed by treatment of the material with a small amount of water.

Contrary to the statements in the literature,[22] we found that pyrrole is appreciably soluble in water and in a saturated solution of ammonium carbonate. One hundred cc. of water dissolves about 5 cc. of pyrrole at ordinary temperature. The aqueous ammonium carbonate layer obtained in the preparation of pyrrole should be extracted with ether.

To obtain pyrrole in a colorless state it should be distilled in a stream of dry nitrogen and kept in sealed ampules, under nitrogen, protected from light.

Ethyl Ester of Pyrrole-1-carboxylic Acid.[23]—This compound was prepared from

[22] Schwanert, *Ann.*, **116**, 279 (1860); Beilstein, "Handbuch der organischen Chemie," **1899**, vol. IV, p. 64.

[23] Ciamician and Dennstedt, *Ber.*, **15**, 2579 (1882); *Ann.*, **210**, 400 (1881); Tschelinseff and Maxoroff, *J. Russ. Phys.-Chem. Soc.*, **1**, 161 (1915); Tschelinseff and Maxoroff, *Ber.*, **60**, 196 (1927). The latter investigators (*ibid.*, p. 195) were able to isolate the unstable pyrrole-1-carboxylic acid and studied a number of its derivatives.

potassium pyrrole and ethyl chloroformate. The potassium pyrrole can be prepared rapidly by the use of excess pyrrole as a solvent as described in a later experiment. The potassium compound, which precipitates when the hot concentrated solution is cooled, is filtered and washed with absolute ether.

In an attempt to rearrange the ester into the ethyl ester of pyrrole-2-carboxylic acid, the material was passed through a hot combustion tube. The only products which we were able to identify were ethylene and a very small amount of pyrocoll. The ethylene was isolated as ethylene bromide; b. p. 128°.

Esters of Pyrrole-2-carboxylic Acid.—Pyrrole-2-carboxylic acid was obtained from pyrrylmagnesium bromide and carbon dioxide.[24] The dark colored acid was purified in the following manner. The substance was dissolved in somewhat more than the required amount of ammonium hydroxide. The solution was diluted and then boiled for a short time with "nuchar." The mixture was filtered and the filtrate cooled with ice. After the addition of ether the colorless solution was stirred and dilute sulfuric acid added in small amounts. The carboxylic acid was obtained from the ether solution in a practically colorless state. It was found that in some instances the acid did not dissolve readily in ether if it had been precipitated completely and then treated with a solvent.

In order to prepare the alkyl esters an excess of the alkyl halide was heated in a pressure bottle, immersed in a bath of boiling water, with the silver salt of pyrrole-2-carboxylic acid; in some instances, however, we refluxed a mixture of the alkyl bromide, the silver salt of the acid and toluene. The crude esters boiled over a considerable range of temperature and the distillate was collected in several portions. The fractions used in our tests boiled as follows: methyl ester, 220–223° (m. p. 72–73°); ethyl ester, 227–230° (m. p. 38–40°); *n*-butyl ester, 255–260° (m. p. 36–38°); *iso*butyl ester, 250–255° (m. p. 68–69°); *iso*-amyl ester, 263–267°. The barometric pressure was 740 mm.

According to Ciamician and Silber[8a] bromination of the methyl ester of pyrrole-2-carboxylic acid yields a tribromo derivative. We brominated the ethyl ester in the presence of water according to the method described by the above-mentioned investigators. A tribromo substitution product was formed which, after recrystallization from acetic acid and then from alcohol, melted at 195–196°. *Anal.* Calcd. for $C_7H_6O_2NBr$: Br, 63.79. Found: Br, 63.75. The following preparative method was found to be much more satisfactory. To 1.4 g. of the ester, dissolved in 5 cc. of acetic acid, there was added slowly, with cooling, 1.6 cc. (3 molecular equivalents) of bromine dissolved in 5 cc. of acetic acid. The bromine was decolorized almost instantly with the evolution of hydrogen bromide and the greater part of the bromo ester separated from the solution. The product was recrystallized twice from acetic acid and then from alcohol; m. p. 195–196°. The compound dissolves in warm, aqueous sodium hydroxide. Upon acidification of the solution a gelatinous precipitate was obtained. The latter melted at 195° after recrystallization from acetic acid. In view of the fact that the compound can be recovered unchanged from an alkaline solution and that the methyl ester of tribromopyrrole-2-carboxylic acid yields a tribromopyrrole-2-carboxylic acid upon hydrolysis,[8a] it seems certain that the bromine atoms in the bromo esters occupy the nuclear positions 3, 4 and 5.

The phenyl ester was obtained in the following manner. The acid chloride[9] obtained from 3 g. of pyrrole-2-carboxylic acid was dissolved in ether and heated for two hours on a steam-bath with sodium phenolate which had been prepared from 2.5 g. of phenol, 0.62 g. of sodium and 70 cc. of absolute ether. The mixture was treated

[24] Oddo, *Gazz. chim. ital.*, I, **39**, 649 (1909); I, **44**, 482 (1914); *Ber.*, **43**, 1012 (1910); McCay and Schmidt, THIS JOURNAL, **48**, 1935 (1926).

with dilute sodium hydroxide, then with water, and the ether layer dried over fused sodium sulfate. After removal of the ether a dark colored, oily residue was obtained. The material was dissolved in hot petroleum ether (30–60°). When the solution was cooled crystals were obtained which melted at 44–45°. The yield was 2.8 g.

Anal. Subs., 0.2350; CO_2, 0.6089; H_2O, 0.1035. Calcd. for $C_{11}H_9O_2N$: C, 70.56; H, 4.85. Found: C, 70.66; H, 4.93.

β-*n*-Piperidino-ethyl Phenyl Ketone.—β-Bromopropionic acid was mixed with three times the calculated amount of thionyl chloride. After two days the excess thionyl chloride was removed under diminished pressure. The acid chloride of β-bromopropionic acid was then distilled; b. p. 69–71° under 23 mm. pressure.[25]

Thirty grams of the acid chloride (0.17 mole) was dissolved in 150 cc. of dry benzene and 28 g. of aluminum chloride (0.21 mole) was added in small portions.[26] After twenty-four hours the reaction mixture was decomposed with ice and hydrochloric acid. Upon removal of the excess benzene under diminished pressure the residue became crystalline. The β-bromopropiophenone melted at 59–60° after recrystallization from alcohol. The yield was 29 g. or 80% of the calculated amount. The halogen is removed rapidly from the bromo ketone when the latter is heated with alcoholic sodium hydroxide.

Anal. Calcd. for C_9H_9OBr: Br, 37.51. Found: Br, 37.62.

Ten cc. of piperidine (0.1 mole) dissolved in 50 cc. of absolute ether was added slowly to 10.6 g. (0.05 mole) of β-bromopropiophenone, dissolved in 70 cc. of the same solvent. Eight and one-tenth grams of piperidine hydrobromide precipitated immediately. The calculated amount of piperidine hydrobromide is 8.2 g. After removal of the piperidine salt the ether layer was washed with water and then dried thoroughly with fused sodium sulfate. The solution was filtered and then treated with dry hydrogen chloride. There precipitated 8.3 g. of the hydrochloride of β-*n*-piperidino-ethyl phenyl ketone. The calculated yield of the hydrochloride is 12.6 g. The salt melted at 187–188°.[27] The melting point was unchanged after recrystallization from ethyl acetate to which a few drops of alcohol had been added. We prepared the ketone hydrochloride by the method of Mannich and Lammering;[27] the material melted at 182–183°.

The ketone was reduced to the secondary carbinol in the following manner. The hydrochloride described above was dissolved in water and the free base liberated by the addition of sodium hydroxide. Five g. of the oily base, dissolved in 50 cc. of absolute alcohol, was reduced with hydrogen in the presence of 0.35 g. of platinum oxide catalyst[28] under an initial pressure of four atmospheres. The calculated amount of hydrogen was absorbed in about twenty minutes. The carbinol was obtained in solid form after removal of the alcohol; m. p. 64–65° after recrystallization from petroleum ether (30–60°).[29] The hydrochloride precipitated immediately when hydrogen chlo-

[25] The acid chloride would probably distil without decomposition under ordinary pressure.

[26] Collet, *Bull. soc. chim.*, [3] **17,** 66 (1897), studied the interaction of a number of halogenated acid chlorides and benzene in the presence of aluminum chloride. He found that only the acyl halogen reacts readily with the benzene.

[27] Mannich and Lammering, *Ber.*, **55,** 3515 (1922), recorded the melting point as 192–193° and stated that the hydrochloride can be recrystallized from a mixture of dilute alcohol and acetone.

[28] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1928,** Vol. VIII, p. 92.

[29] Mannich and Lammering, *Ber.*, **55,** 3517 (1922), state the melting point to be 68–69°. They reduced the amino-ketone hydrochloride with hydrogen in the presence of palladium–charcoal.

ride was passed into an ether solution of the carbinol; m. p. 139–140°. Upon benzoylation of the carbinol in chloroform the benzoate described by Mannich and Lammering was obtained. Hydrolysis of the benzoate with alcoholic sodium hydroxide yielded the secondary carbinol which melted at 64–65° after recrystallization from petroleum ether.

n-Piperidinomethyl Phenyl Ketone.—To 16 g. of bromo-acetophenone[30] dissolved in 100 cc. of absolute ether there was added 16 cc. of piperidine dissolved in 50 cc. of the same solvent. The calculated amount of piperidine hydrobromide precipitated at once. The piperidino ketone was obtained in the form of an oil which exhibited marked local anesthetic action on the tongue. The hydrochloride was obtained in crystalline form from an ether solution of the ketone and hydrogen chloride. It can be recrystallized from ethyl acetate to which a few drops of alcohol have been added; m. p. 210–211°. The hydrochloride possesses anesthetic action.

In order to prepare the secondary carbinol 10.5 g. of the ketone was dissolved in 50 cc. of absolute alcohol and reduced with hydrogen in the presence of 0.5 g. of platinum oxide catalyst. The initial pressure was four atmospheres. After thirty minutes the reduction seemed to be complete. A solid material was obtained which, after recrystallization from petroleum ether, melted at 69–70°. The hydrochloride melts at 193–194°.

Anal. Subs., 0.2201: CO_2, 0.6143; H_2O, 0.1854. Calcd. for $C_{13}H_{19}OH$: C, 76.02; H, 9.33. Found: C, 76.11; H, 9.42.

The secondary carbinol was benzoylated in the following manner. One gram of the carbinol was dissolved in 25 cc. of absolute ether. The required amount of benzoyl chloride, dissolved in ether, was added. Seven-tenths of a gram of the hydrochloride of the benzoate precipitated; m. p. 193–194°. The free base was obtained in the form of an oil. The hydrochloride and the free base both possess anesthetic action. The melting point of the carbinol, obtained by hydrolysis of the benzoate, was 69–70°.

n-Piperidinomethyl 2-Pyrryl Ketone.—Twelve and one-tenth grams of piperidine hydrochloride, 30 cc. of absolute alcohol and 4.5 g. of paraformaldehyde were heated and 10.9 g. of 2-acetylpyrrole was added during the course of half an hour. An additional 3 g. of paraformaldehyde was then added and the mixture heated for fifteen minutes longer. After evaporation of the alcohol the ketone was obtained in the form of an oily hydrochloride. The latter was dissolved in water and the free base precipitated by the addition of sodium hydroxide. The oily base possessed anesthetic action.

Summary

It has been found that a number of esters of pyrrole-carboxylic acids, especially the alkyl esters of pyrrole-2-carboxylic acid, possess marked local anesthetic action on the tongue.

n-Piperidinomethyl phenyl ketone, *n*-piperidinomethyl 2-pyrryl ketone and the benzoate of *n*-piperidinomethylphenylcarbinol were found to possess local anesthetic action.

ANN ARBOR, MICHIGAN

[30] Mohlau, *Ber.*, **15**, 2465 (1882).