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

GAMMA-PYRROLIDINO- AND GAMMA-PYRROLINOPROPYL BENZOATES[1]

BY LESLIE H. ANDREWS AND S. M. MCELVAIN

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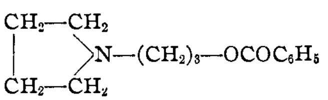
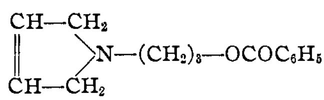
In a previous communication[2] the preparation of a number of substituted piperidino-alkyl benzoates was described. A preliminary pharmacological report on these substances indicated that they possessed local anesthetic action, the compounds in which a methyl group was substituted in the piperidine nucleus being the most efficient pharmacologically. The original purpose of the work which is reported in this paper was to prepare and submit for pharmacological study a corresponding series of compounds containing the pyrrolidine nucleus instead of the piperidine nucleus. However, on account of certain difficulties that are mentioned below, the substituted pyrrolidino-alkyl benzoates have not been prepared as yet, but two new substances, γ-pyrrolidinopropyl benzoate (I) and γ-pyrrolinopropyl benzoate (II) have been prepared and tested pharmacologically. It was thought that the latter compound would be particularly interesting as it would indicate the relative merits of an unsaturated structure in the production of local anesthesia.



I



II

These compounds were prepared by the condensation of γ-chloropropyl benzoate with the secondary amines, pyrrolidine and pyrroline, both of which were obtained by the reduction of pyrrole. Pyrrolidine was prepared by the catalytic reduction of pyrrole with Adams' platinum-oxide platinum black catalyst and pyrroline by the procedure of Knorr and Rabe,[3] which utilized zinc and hydrochloric acid as the reducing agent.

All attempts to reduce catalytically methyl and carbethoxy substituted pyrroles to the corresponding pyrrolidines were unsuccessful. While a small amount of reduction took place initially, the catalyst was soon poisoned and the reduction stopped. The catalyst could not be reactivated to any appreciable extent by shaking with oxygen. McCay and Schmidt[4] have reported a similar unsuccessful attempt to reduce the amide of pyr-

[1] This paper is taken from the thesis submitted by Leslie H. Andrews to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Master of Arts.

[2] McElvain, THIS JOURNAL, **49**, 2835 (1927).

[3] Knorr and Rabe, *Ber.*, **34**, 3491 (1901).

[4] McCay and Schmidt, THIS JOURNAL, **48**, 1933 (1926).

role-carboxylic acid. On account of the negative results obtained in these experiments, the work on the preparation of the substituted pyrrolidinoalkyl benzoates was abandoned for the present.

Pyrrolidine condensed very smoothly with γ-chloropropyl benzoate and the resulting γ-pyrrolidinopropyl benzoate was isolated as the hydrochloride, which melted at 125–126°. In the case of the pyrrolino compound, however, considerable difficulty was experienced in obtaining a pure hydrochloride. It was quite difficult to separate and crystallize this hydrochloride from a reddish oil that accompanied it. It was finally purified and found to melt at 136–138°.

Experimental

Pyrrole.—This compound was prepared by a procedure developed by Katherine Bolliger[5] which is as follows. In a twelve-inch evaporating dish 630 g. (3 moles) of mucic acid was treated with an excess of ammonium hydroxide (about 900 cc., sp. gr. 0.9) and quickly stirred to a smooth paste. It was then evaporated to dryness on a steam cone. The ammonium mucate thus formed was powdered, treated with 250–400 cc. of glycerol, allowed to stand for several hours and then distilled from a 5-liter flask. Distillation was continued until no more oily drops came over. At this point the residue in the flask foamed considerably. The upper layer of the distillate was separated in a separatory funnel and steam distilled until all of the oily, insoluble liquid had passed over. The distillate was washed with water, dried over solid sodium hydroxide and redistilled. It boiled at 128–132°. The yield varied from 80–100 g. (40–50%).

The pyrrole so obtained could not be reduced catalytically, but when it was distilled from over sodium in an atmosphere of hydrogen according to the procedure of Willstätter and Hatt,[6] a water-white product with an odor suggestive of chloroform was obtained. There was hardly any loss of pyrrole in this distillation from sodium and the product so obtained yielded to catalytic reduction.

Methylpyrroles.—The α- and β-methylpyrroles were prepared by a modification of the procedure of Oddo and Mameli.[7] To 17 g. (0.7 mole) of magnesium turnings and 200 cc. of dry ether, a solution of 76 g. (0.7 mole) of ethyl bromide in 100 cc. of ether was added. After the Grignard reagent had formed, a solution of 33.5 g. (0.5 mole) of pyrrole in 100 cc. of ether was added slowly and with constant stirring. The reaction was quite vigorous and had to be carefully regulated. After all of the pyrrole solution had been added the mixture was refluxed for thirty minutes and then a solution of 63 g. (0.5 mole) of dimethyl sulfate in 100 cc. of ether was slowly added. The mixture was then refluxed for one hour, after which it was cooled by an ice and salt mixture. Cold water was then added with stirring until the white salt which formed was completely dissolved. The water and ether layers were separated and the aqueous layer was extracted with an equal volume of ether. The ether was distilled off from the combined ether extracts and the residue steam distilled. The pyrrole layer was separated from the water and the latter extracted with ether. The ethereal extract and the pyrrole layer were mixed and the resulting solution dried with anhydrous sodium sulfate, after which the ether was removed by distillation and the basic residue fractionated. There were obtained 13 g. of unchanged pyrrole (b. p. 125–132°) and 19.5 g. of a fraction that boiled at 132–155°, which consisted of a mixture of α- and β-methylpyrrole. This

[5] Katherine Bolliger, University of Wisconsin "Thesis," 1926.

[6] Willstätter and Hatt, *Ber.*, **45**, 1471 (1912).

[7] Oddo and Mameli, *Gazz. chim. ital.*, **43**, 504 (1913).

fraction was distilled twice over sodium in an atmosphere of hydrogen before it was further used.

α-Carbethoxypyrrole.—This ester was prepared by the procedure of Oddo[8] from pyrryl magnesium bromide and ethyl chlorocarbonate. Although Oddo reported yields of 85–90% of this ester, it was not possible to obtain over 20% yields of the ester that boiled at 130–138° (20 mm.) in this work. On cooling the ester solidified and the solid ester melted at 36–38°.

Pyrrolidine.—A solution of 18 g. of pyrrole (which had been twice distilled from sodium) in 60 cc. of glacial acetic was shaken with hydrogen in the presence of 0.5 g. of Adams' platinum-oxide platinum black catalyst. The absorption of hydrogen was at all times quite slow and would periodically stop, but by shaking the reduction mixture with oxygen the catalyst could be reactivated and the reduction caused to proceed. After forty-five hours an additional 0.3 g. of catalyst was added. After 96–100 hours of shaking the theoretical amount of hydrogen had been absorbed. The platinum was allowed to settle and the dark-colored solution decanted. The acid was neutralized under a reflux with a concentrated solution of sodium hydroxide and then an excess of the alkali added. The alkaline solution was then steam distilled until the distillate no longer gave an acid reaction to litmus paper. The distillate (about 1 liter) was acidified with hydrochloric acid and evaporated to dryness on a steam cone. A dark red, gummy residue remained. This residue was treated with 40% sodium hydroxide and extracted with ether. The ether solution was dried with anhydrous sodium sulfate and then distilled. There was obtained 12 g. of pyrrolidine (63% of the theoretical) boiling at 85–88°. A crystalline hydrochloride of pyrrolidine could not be obtained.

Willstätter and Hatt[6] reduced pyrrole catalytically in glacial acetic acid solution and stated that the solution became deeply colored during the reduction. Hess[9] described the reduction of pyrrole under similar conditions stating that the coloration was coexistent with inhibitory effect and was careful to exclude oxygen from the catalyst, in which cases there was no coloration of the solution. Later, Willstätter and Waldschmidt[10] found that frequent shaking of the catalyst with oxygen is absolutely essential in the reduction of pyrrole. With this latter finding the results of the present work are in agreement, for it was only by frequent shaking with oxygen that the reduction could be caused to proceed.

Pyrroline (Dihydropyrrole).—Ciamician and Dennstedt[11] report the reduction of pyrrole to pyrroline using zinc and acetic acid as the reducing agent. Knorr and Rabe[3] report a similar reduction of pyrrole with zinc and hydrochloric acid at a temperature sufficiently low to prevent the resinification of the pyrrole by the strong mineral acid. Both procedures were tried in this work and it was found that the procedure of Knorr and Rabe gave the better results. Ciamician and Dennstedt report yields of 20% of the theoretical by their method, but it has been possible in this work to obtain 56% yields of pyrroline using a modified Knorr and Rabe procedure, which is as follows.

[8] Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909); *ibid.*, **42**, II, 244 (1912).

[9] Hess, *Ber.*, **46**, 3120 (1913).

[10] Willstätter and Waldschmidt, *ibid.*, **54**, 113 (1921).

[11] Ciamician and Dennstedt, *ibid.*, **15**, 1831 (1882); *ibid.*, **16**, 1536 (1883).

Five hundred cc. of 20% hydrochloric acid is placed in a flask fitted with a mechanical stirrer, dropping funnel and a thermometer, cooled to 0° by means of an ice and salt mixture, and 200 g. of zinc dust is added with vigorous stirring. Fifty g. of pyrrole is then added slowly from a dropping funnel. It is important that the temperature of the liquid be kept low (0–10°) at the start, else the speed of reaction will cause the temperature to get out of control. After all of the pyrrole had been added (about one hour), 300 cc. of concentrated hydrochloric acid was added and the stirring continued for two hours longer. The temperature was kept at 15–25° during this time. The cooling bath was then removed and the mixture stirred for four and one-half hours at room temperature. The remaining zinc was then filtered off and washed with a little water. The filtrate was made sufficiently alkaline to dissolve the precipitated zinc hydroxide and then steam distilled until the distillate was no longer alkaline to litmus. The distillate was made acid with hydrochloric acid and evaporated on a steam-bath. The remaining gummy residue was treated with an excess of 40% sodium hydroxide and extracted twice with ether. This ether extract was dried with anhydrous sodium sulfate and distilled. The pyrroline fraction boiled at 89–92° and weighed 28.5 g. There was also obtained 6.5 g. of a fraction that boiled at 115–125° (20 mm.). The hydrochloride of pyrroline was obtained crystalline and melted at 162–163°.

Attempted Reduction of Methylpyrroles and α-Carbethoxypyrrole.—A solution of 8 g. of the methylpyrrole fraction, twice distilled from sodium and boiling at 132–155°, was subjected to catalytic reduction as described above in the preparation of pyrrolidine. In the first twenty minutes there was a rapid absorption of hydrogen amounting to approximately one-eighth of the theoretical amount, but after this initial absorption of hydrogen the reduction stopped and could not be induced to continue either by shaking with oxygen or by the addition of fresh catalyst. Several runs were made with samples of platinum catalyst of known catalytic activity with similar results.

α-Carbethoxypyrrole in acetic acid solution gave practically the same results as the methylpyrroles on catalytic reduction. On account of the extremely small amount of hydrogen that was absorbed, no attempt to isolate a reduction product was made in either case.

γ-Pyrrolidinopropyl Benzoate Hydrochloride.—A mixture of 20 g. (2 moles) of pyrrolidine and 28 g. (1 mole) of γ-chloropropyl benzoate was heated on a steam-bath for one and one-half hours. The reaction mixture, which had separated into two layers, was then diluted with 100 cc. of ether and the oily, insoluble layer of pyrrolidine hydrochloride separated by carefully decanting off the ether solution. The γ-pyrrolidinopropyl benzoate was precipitated from the ether solution as the hydrochloride, which was recrystallized several times from an alcohol–ether mixture. The purified product weighed 14 g. and melted at 125–126°.

Anal. Calcd.: Cl, 13.15. Found: Cl, 13.25, 13.26.

γ-Pyrrolinopropyl Benzoate Hydrochloride.—A mixture of 10 g. (2 moles) of pyrroline and 14 g. (1 mole) of γ-chloropropyl benzoate was heated on a steam-bath for half an hour. The reaction mixture was worked up as described above in the preparation of γ-pyrrolidinopropyl benzoate hydrochloride. The hydrochloride of the pyrrolino derivative so obtained was quite difficult to crystallize and was found by analysis to contain a higher percentage (15.05%) of halogen than its formula required, which fact indicated that some pyrroline hydrochloride was mixed with it. Accordingly it was found advisable to shake the crude pyrrolinopropyl benzoate hydrochloride with 10% sodium hydroxide and benzoyl chloride. After this procedure the tertiary amine was reprecipitated from ether as the hydrochloride, which was recrystallized twice from an alcohol–ether mixture and twice from acetone. The product so obtained weighed 3.5 g. and melted at 136–138°.

Anal. Calcd.: 13.25. Found: Cl, 13.58, 13.58.

The melting point of a mixture of the pyrrolidino and pyrrolino derivatives was depressed to 75° and it was completely molten at 120°. The latter compound when shaken with dilute potassium permanganate solution caused immediate decolorization, while the former reacted very slowly with this reagent.

Pharmacological Report

γ-Pyrrolidinopropyl benzoate hydrochloride (I) and γ-pyrrolinopropyl benzoate hydrochloride (II) are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Indianapolis, Indiana. A preliminary report of this work, given in the table below, includes subcutaneous and intravenous toxicity determinations and measurements of the duration of anesthesia produced by the application of a 2% solution of the anesthetic to the rabbit's cornea. The corresponding values for γ-piperidinopropyl benzoate hydrochloride (III), cocaine and procaine taken from another paper[12] are included for comparison.

Table I

Pharmacological Data

Compound	Av. dur. of anesthesia, min.	Subcutaneous toxicity to white mice (mg./kg.) M. T. D.	M. L. D.	No. of mice used	Intravenous toxicity to white rats (mg./kg.) M. T. D.	M. L. D.	No. of rats used
I	15	400	450	9	17.5	20	9
II	5	1000	1100	11	25	30	8
III	0	400	450	8	15	17.5	10
Cocaine	29	200	250	18	15	17.5	12
Procaine	0	900	1000	17	45	50	10

Discussion of Pharmacological Data

It is seen that the pyrrolidinopropyl benzoate (I) is a much more efficient anesthetic than the compound (III) that contains the piperidine nucleus instead of the pyrrolidine nucleus. This, it seems, would not have been expected, for practically all of the data which are available on the physiological behavior of various types of local anesthetic indicate that in a particular series[13] of compounds the substances of higher carbon content are more active physiologically (considering either toxicity or production of anesthesia or both) than those of lower carbon content. Compounds I and III have very similar structures, the only difference being that III contains one CH_2 grouping more in its cyclic structure than I. The effect of the double bond in II is quite marked, for when compared with I it is seen that

[12] McElvain, This Journal, **49**, 2839 (1927).

[13] For example, in the dialkylamino-alkyl-*p*-aminobenzoate series, an increase in size of the alkyl groups attached to the nitrogen atom causes an increase in both toxicity and anesthetic action [Schmitz and Loevenhart, *J. Pharm. Exptl. Ther.*, **24**, 159 (1924)], and in the 1-alkyl-3-carbethoxy-4-piperidyl benzoates and *p*-aminobenzoates an increase in the size of the alkyl group causes an increased anesthetic action with a decreased toxicity [McElvain, This Journal, **48**, 2179, 2239 (1926)].

this change in structure causes a very great lowering in the physiological activity of the compound.

Summary

1. It has been found that while pyrrole can be reduced catalytically to the tetrahydro derivative, the methyl and carbethoxy substituted pyrroles could not be similarly reduced.

2. γ-Pyrrolidinopropyl benzoate and γ-pyrrolinopropyl benzoate have been prepared and tested pharmacologically as local anesthetics. It was found that the presence of the double bond in the latter greatly reduces its anesthetic activity. The pyrrolidino derivative was shown to have greater anesthetic action than the corresponding piperidino derivative. It is pointed out that this was an unexpected relationship, since data on other series of anesthetics indicated that the reverse should be true.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOBART COLLEGE]

SOME DERIVATIVES OF TRIMETHYLETHYLSTANNANE

BY RALPH H. BULLARD AND RAYMOND A. VINGEE

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The study of the organic compounds of tin has been continued by investigating certain derivatives of trimethylethylstannane, $(CH_3)_3C_2H_5Sn$.

The hydride, dimethylethylstannane, $(CH_3)_2C_2H_5SnH$, derived from trimethylethylstannane by the substitution of a hydrogen atom for a methyl group, is of particular interest. It is oxidized by the air, being converted into the corresponding hydroxide. The reaction is represented by the equation $2(CH_3)_2C_2H_5SnH + O_2 = 2(CH_3)_2C_2H_5SnOH$. This oxidation is interesting in view of the fact that trimethylstannane, $(CH_3)_3SnH$, prepared by Kraus and Greer[1] is stable in the air, whereas triphenylstannane, $(C_6H_5)_3SnH$, prepared by Chambers and Scherer[2] oxidizes in the air to hexaphenylstanno-ethane, $(C_6H_5)_3SnSn(C_6H_5)_3$, with the formation of water.

Trimethylethylstannane, $(CH_3)_3C_2H_5Sn$.—This compound has been prepared by Cahours[3] from trimethylstannyl iodide and zinc diethyl, and also by Pope and Peachey[4] by the use of the Grignard reaction. The following method may also be used to advantage.

Trimethylstannyl bromide, $(CH_3)_3SnBr$, was dissolved in liquid ammonia and converted into the sodium salt by adding two atoms of sodium per mole of bromide. On adding ethyl bromide slowly the yellow color of the

[1] Kraus and Greer, THIS JOURNAL, **44**, 2629 (1922).

[2] Chambers and Scherer, *ibid.*, **48**, 1054 (1926).

[3] Cahours, *Ann.*, **122**, 48 (1862).

[4] Pope and Peachey, *Proc. Chem. Soc.*, **19**, 290 (1903).