In the case of the isomeric *p*-dimethylaminocyclohexyl compounds, the pure nitro esters were reduced in the usual way; the mixed *cis*- and *trans*-*p*-dimethylaminocyclohexyl *p*-nitrobenzoate hydrochlorides also were reduced in absolute alcohol and the isomeric amines separated by crystallization from absolute alcohol. The less soluble isomer is the higher melting (268–269°) and is probably the *trans* form; it corresponds to the nitro compound, which melts at 250–252°. The more soluble isomer was the lower melting (226–228°) and is probably the *cis* form; it corresponds to the nitro compound, which melts at 233–234°.

Summary

1. Various cyclic alkamine esters of *p*-aminobenzoic acid have been prepared. These were formed by condensing *p*-nitrobenzoyl chloride with the proper amino alcohol, followed by reduction.

2. The amino alcohols were prepared by reduction of the proper aminophenols or, in one case, by the condensation of diethylamine with *o*-chlorocyclohexanol.

3. A brief description of the relative physiological action is given.

URBANA, ILLINOIS

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

PIPERIDYL AND SUBSTITUTED PIPERIDYL ALKYL PARA-AMINOBENZOATES. III

BY O. A. BARNES[1] WITH ROGER ADAMS

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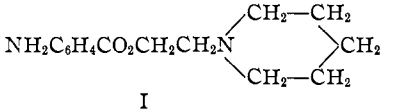
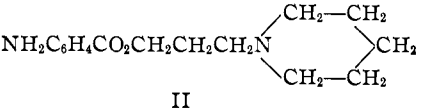
In the previous paper of this series,[2] certain cyclic alkyl amino esters of *p*-aminobenzoic acids were described. This communication describes the anesthetics I, II, III and IV formed by the condensation of β-bromoethyl *p*-nitrobenzoate and γ-bromopropyl *p*-nitrobenzoate with piperidine and methyl hexahydronicotinate (β-carbomethoxypiperidine), and subsequent reduction of the nitro groups to the corresponding amines.



I



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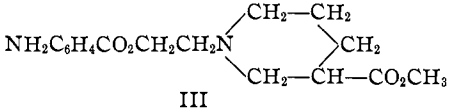
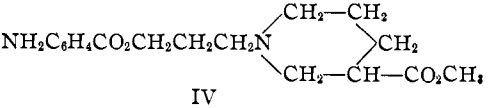


III



IV

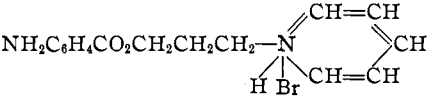
[1] This communication is an abstract of a thesis submitted by O. A. Barnes in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Heckel with Adams, THIS JOURNAL, **49**, 1303 (1927).

Thus, a comparison of such cyclic groups on the nitrogen atom with two alkyl groups on the nitrogen atom is possible. The general effect of the presence of the carbomethoxy group may also be observed and is of particular interest because this is a group present in cocaine and holds the same relative position to the nitrogen atom in cocaine as in the synthetic compounds.

The bromo alkyl *p*-nitrobenzoates were prepared by the condensation of sodium *p*-nitrobenzoate with excess of ethylene bromide or trimethylene bromide in the presence of diethylamine as a catalyst. The β-carbomethoxypiperidine was formed by reduction of methyl nicotinate hydrochloride with platinum-oxide platinum black and hydrogen. The condensation of the amines with the halogen esters took place readily and the catalytic reduction of the nitro esters to the final anesthetics by means of hydrogen and platinum-oxide platinum black followed with great ease.

The *p*-aminobenzoyl-γ-hydroxypropylpyridonium bromide was also prepared in order to determine whether any anesthetic value would exist at all when the piperidine nucleus was replaced by the pyridine nucleus.



The anesthetic index[3] toward goldfish for the piperidylethyl was approximately eight times that of procaine; of the piperidylpropyl sixteen times. The corresponding compounds not containing the *p*-amino group were much less effective, although here also the propyl derivative was several times as effective as the ethyl. The presence of the carbomethoxy groups in the piperidine nucleus greatly diminished the anesthetic effect so that the γ-(β-carbomethoxypiperidyl)-propyl compound was only slightly more anesthetic than procaine, and the ethyl derivative somewhat less.

The compounds were only weakly anesthetic toward mucous membrane, the carbomethoxy derivatives being much inferior to the others.

The *p*-aminobenzoyl-hydroxypropylpyridonium bromide showed no anesthetic properties.

Experimental Part

Hexahydronicotinic Acid Hydrochloride.[4]—A solution of 50 cc. of 1% aqueous gum arabic solution, 15 cc. of a 10% chloroplatinic acid solution and an inoculating platinum solution (made by heating 5 cc. of 10% chloroplatinic acid solution with 0.1 g. of hydrazine hydrochloride and then adding 2 to 3 drops of a 40% potassium hydroxide solution) was shaken up with hydrogen in order to form colloidal platinum. To this

[3] Ref. 2, footnote 16.

[4] The preparation of hexahydronicotinic acid and methyl hexahydronicotinate, as described in this communication, was carried out previous to the method described by McElvain with Adams (Ref. 5). The latter procedure is the more convenient one,

was now added a solution of 30 g. of nicotinic acid hydrochloride[5] in 250 cc. of water. The apparatus[5] was evacuated and hydrogen passed into the reaction mixture under a pressure of 1.5 to 3 atm. (10 hours required).

The reduction mixture was poured into an equal volume of hot acetone and the platinum which precipitated was filtered. The clear solution was then evaporated in a vacuum at about 20 mm. pressure, keeping the temperature of the oil-bath used for heating at all times below 50°. If higher temperatures were used, the hexahydronicotinic acid hydrochloride invariably decomposed somewhat and turned dark. The residue, after evaporation, was crystallized from hot *n*-butyl alcohol or absolute ethyl alcohol, from which it gave a white, crystalline product; m. p., 239–240°. Freudenberg[6] found 240–241°. The yield amounted to 36 g. (90%).

It was found that nicotinic acid dissolved in water did not reduce under similar treatment and proceeded only slowly if dissolved in acetic or hydrochloric acid. To give the best results, the hydrochloride of the nicotinic acid must be prepared and then dissolved in water and hydrogen added. An excess of hydrochloric acid seemed to slow up the reduction, at least of the product used in this investigation.

Methyl Hexahydronicotinate.[4]—A solution of 30 g. of methyl nicotinate in 100 cc. of absolute alcohol was made. To this were added 25 cc. of glacial acetic acid (without which the reduction is exceedingly slow) and 0.5 g. of platinum oxide. The mixture was then hydrogenated in the usual way, at 1.5 to 3 atm. (about 12 hours required). The solution was shaken with air in order to coagulate the platinum, the platinum filtered and the alcohol evaporated under diminished pressure, using an oil-bath with a temperature which did not rise above 50°. A dark brown oil remained which was made slightly alkaline with well-cooled 40% potassium hydroxide solution, and the free base was extracted with ether. The ether solution was dried over solid potassium hydroxide and the hydrochloride of methyl hexahydronicotinate precipitated by passing in dry hydrogen chloride. The product was practically pure and melted at 130.5–131°. Freudenberg[6] found 131–132°. The yield of product was 30 g., or 77%.

Methyl nicotinate cannot be reduced in the presence of aqueous hydrochloric acid without considerable hydrolysis taking place.

β-Bromo-ethyl *p*-Nitrobenzoate, $NO_2C_6H_4CO_2CH_2CH_2Br$.—In a 3-liter round-bottomed flask fitted with a mechanical stirrer and a reflux condenser, 300 g. (1 mole) of finely powdered, thoroughly dried potassium *p*-nitrobenzoate, 1300 g. (4 moles) of ethylene dibromide and 2 cc. of diethylamine were mixed. The mixture was heated in an oil-bath held at 95–98° for 12 hours, vigorous stirring being carried on continuously. At the end of this time a small amount (2 g.) of solid, anhydrous potassium carbonate was added and the reaction mixture filtered with suction while hot to remove the potassium bromide and any potassium *p*-nitrobenzoate which had not reacted. The filtrate was distilled in a vacuum, first heating in an oil-bath and using a water pump until the excess of ethylene dibromide was removed, and then an oil pump in order to obtain a better vacuum for the distillation of the β-bromo-ethyl *p*-nitrobenzoate. In order to get the best results, the vacuum should be 5 mm. or below, under which conditions the product distilled readily, yielding a yellowish oil which solidified, on cooling, to a crystalline mass; m. p., 52–53°. Adams and Kamm[7] found 51–52°.

γ-Bromopropyl *p*-Nitrobenzoate, $NO_2C_6H_4CO_2CH_2CH_2CH_2Br$.—The same procedure was used for making this substance that was used for the β-bromo-ethyl *p*-nitrobenzoate. The temperature of the oil-bath for heating was maintained at 105–107° for 12 hours. It was also important in the preparation of this substance, to use

[5] McElvain with Adams, THIS JOURNAL, **45**, 2738 (1923).

[6] Freudenberg, *Ber.*, **51**, 1679 (1918).

[7] Adams and Kamm, *C. A.*, **12**, 1469 (1918).

a very low vacuum in distilling the ester, if a good yield was to be obtained and considerable decomposition avoided. The product was a light yellow oil, b. p. 187–188° at 6 mm., which solidified on cooling to a crystalline mass; yield, about 75%. Upon recrystallization from ethyl alcohol, a product melting at 39–40° was obtained.

Anal. Subs., 0.2000: AgBr, 0.1292. Calcd. for $C_{10}H_{10}O_4BrN$: Br, 27.8. Found: 27.5.

Considerable care had to be used in the distillation of this substance after the excess of trimethylene bromide was removed; the temperature of the bath was increased very gradually. There was always a residue consisting of the ester obtained from the condensation of 2 moles of potassium *p*-nitrobenzoate and trimethylene bromide.

β-Hydroxy-ethyl-(β-carbomethoxy)-pyridonium Chloride, *m*-$CH_3CO_2C_5H_4N(Cl)$-CH_2CH_2OH.—A mixture of 3 g. of ethylene chlorohydrin and 5 g. of methyl nicotinate was placed in a 100cc. round-bottomed flask and heated for one hour in an oil-bath maintained at a temperature of 120°. If higher temperatures were used the product became highly colored. Upon cooling, a thick mass resulted which was reddish-brown in color. This mass was readily soluble in absolute alcohol, and by addition of ether the product precipitated as an oil. It could also be obtained as an oil from hot *n*-butyl alcohol.

β-(β-Carbomethoxypiperidyl)-ethyl *p*-Nitrobenzoate Hydrochloride.—A solution of 20 g. of methyl nicotinate in 50 cc. of absolute alcohol was treated with 15 cc. of glacial acetic acid and 0.3 g. of platinum oxide and reduced as previously described. The mixture was shaken with air, the platinum filtered and the filtrate evaporated in a vacuum, not allowing the bath to rise above 50°. To the residue in the distilling flask was added 40 g. of β-bromo-ethyl *p*-nitrobenzoate; the apparatus was again evacuated to about 15 mm. and the flask immediately immersed in an oil-bath at 105–110° and maintained for one hour at that temperature. A vigorous reaction took place at the beginning. About 10 cc. of acetic acid distilled during the heating, and toward the end of the heating, the residue in the flask generally solidified to a light colored mass. The product was cooled and treated with an excess of well-cooled 40% potassium hydroxide solution, extracted with ether and dried over solid potassium hydroxide. From the ether, by addition of dry hydrogen chloride, a precipitate of β-(β-carbomethoxypiperidyl)-ethyl *p*-nitrobenzoate hydrochloride formed. The product was crystallized from *n*-butyl alcohol or from ethyl alcohol. It formed crystals melting at 197–198°; yield, about 22 g., or 41%.

Anal. Subs., 0.5000: 12.9 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 27.6 cc. (27°, 750 mm.). Calcd. for $C_{16}H_{21}O_6N_2Cl$: Cl, 9.53; N, 7.52. Found: Cl, 9.56; N, 7.60.

It was quite necessary that during this last reaction the flask be heated suddenly. If β-bromo-ethyl *p*-nitrobenzoate was heated gradually with the methyl hexahydronicotinate, a much smaller yield resulted, since such conditions presumably favored a partial conversion of the acetate of methyl hexahydronicotinate to the corresponding acid amide.

It was found that methyl nicotinate could not be reduced in alcohol solution with hydrochloric acid since this invariably caused considerable hydrolysis of the ester. Acetic acid, moreover, was more desirable since the secondary condensation could be carried out directly in the presence of acetic acid, whereas such was not the case with hydrochloric acid.

β-(β-Carbomethoxypiperidyl)ethyl *p*-Aminobenzoate Hydrochloride, III.—A solution was made of 20 g. of β-(β-carbomethoxypiperidyl)-ethyl *p*-nitrobenzoate hydrochloride in 400 cc. of hot, absolute ethyl alcohol. Without cooling, the solution was

reduced, using 0.3 g. of platinum oxide as a catalyst (1.25 hours). After shaking with air and filtering the platinum, the alcohol was evaporated under diminished pressure, the temperature of the oil-bath being maintained below 45°. It is advisable to pass a slow current of hydrogen through the flask while evaporating, in order to prevent any possible oxidation. The hydrochloride seemed to be perfectly stable when dry but changed to a reddish-brown color in solution, or when moistened. On the other hand, the reddish solution immediately became colorless upon shaking with hydrogen and a little platinum.

The hydrochloride was crystallized best by dissolving in a very small amount of absolute methyl alcohol, cooling, filtering and washing first with cold, absolute methyl alcohol and then with ether. Deep coloration was likely to take place during this procedure provided the solution was not handled in an atmosphere of carbon dioxide. The product thus obtained was practically white; m. p., 186–188°; yield, about 16 g., or 74%. The product was soluble in water, giving a solution neutral to litmus.

Anal. Subs., 0.5000: 14.0 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 30.2 cc. (27°, 750 mm.). Calcd. for $C_{16}H_{23}O_4N_2Cl$: Cl, 10.37; N, 8.17. Found: Cl, 10.42; N, 8.32.

γ-(β-Carbomethoxypiperidyl)-propyl *p*-Nitrobenzoate Hydrochloride.—This substance was made in a manner analogous to the β-(β-carbomethoxypiperidyl)-ethyl *p*-nitrobenzoate hydrochloride compound. It was advisable, however, to carry out the condensation of the methyl hexahydronicotinate with γ-bromopropyl *p*-nitrobenzoate at a little lower temperature, 100–105°. Of the hydrobromide which was thus obtained, a small portion, after recrystallization from acetone, melted at 204–205°. The remainder, however, was treated with alkali, extracted with ether, dried and reprecipitated as the hydrochloride. This was then recrystallized from hot *n*-butyl alcohol, giving a colorless compound; m. p., 207–208°; yield, about 43%.

Anal. Subs., 0.5000: 12.5 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 27.0 cc. (25°, 751 mm.). Calcd. for $C_{17}H_{23}O_6N_2Cl$: Cl, 9.18; N, 7.24. Found: Cl, 9.31; N, 7.44.

γ-(β-Carbomethoxypiperidyl)-propyl *p*-Aminobenzoate Hydrochloride, IV.—Twenty g. of the γ-(β-carbomethoxypiperidyl)-propyl *p*-nitrobenzoate hydrochloride was reduced in 400 cc. of absolute ethyl alcohol with 0.3 g. of platinum black (1.25 hours). The same precautions were used in the isolation and purification as described under the corresponding ethyl compound; yield, 80–90%. For purification, it was crystallized from absolute methyl alcohol, from which it formed white crystals; m. p., 195–196°.

Anal. Subs., 0.5000: 13.5 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 27.1 cc. (26°, 750 mm.). Calcd. for $C_{17}H_{25}O_4N_2Cl$: Cl, 9.95; N, 7.85. Found: Cl, 10.06; N, 7.48.

Crystallization from the higher-boiling alcohols was not satisfactory and invariably caused the material to become colored.

β-Hydroxy-ethylpyridonium Chloride,[8] $C_6H_5N(Cl)CH_2CH_2OH$.—A mixture of 80 g. (1 mole) of pyridine (b. p., 113–115°) and 81 g. (1 mole) of ethylene chlorohydrin was heated in a 200cc. round-bottomed flask, to which a reflux condenser was attached, for one hour in an oil-bath held at 132–135°. At the end of this time the reaction mixture was poured while hot into a beaker and the reaction flask rinsed out with absolute ethyl alcohol. The crude material thus obtained was dissolved in 200–300 cc. of hot absolute alcohol, filtered and absolute ether added until a precipitate just failed to appear. Upon cooling, practically a quantitative yield of product crystallized in

[8] (a) Roithner, *Monatsh.*, **15**, 668 (1894). (b) Litterscherd, *Arch. Pharm.*, **240**, 78 (1902).

snow-white flakes; m. p., 124–125°. The product was very deliquescent, however, and particular care had to be taken to keep moisture away.

N-(β-Hydroxy-ethyl)-piperidine.[9]—Fifty g. of β-hydroxy-ethyl pyridonium chloride was dissolved in 300 cc. of water and reduced with hydrogen under 1.5 to 3 atm. pressure, using as a catalyst colloidal platinum made by shaking with hydrogen 50 cc. of a 1% gum arabic solution, 15 cc. of a 10% chloroplatinic acid solution and an inoculating platinum solution (made by heating 5 cc. of 10% chloroplatinic acid solution with 0.1 g. of hydrazine hydrochloride and then adding 2 to 3 drops of a 40% potassium hydroxide solution). The reduction was complete at the end of about 11 hours. At this time it was treated with an equal volume of hot acetone, filtered to remove the platinum and evaporated under diminished pressure below 50°. The solid residue was made alkaline with 40% potassium hydroxide solution, extracted with ether and dried over solid potassium hydroxide. By distillation of the solvent, then vacuum distillation of the residue, the free base[9] was obtained, b. p., 89–91°, at 20 mm. (Ladenburg,[10] b. p., 199°); n_D^{25}, 1.4749; d_{25}^{25}, 0.9732.

The hydrochloride of N-(β-hydroxy-ethyl)-piperidine was made by passing dry hydrogen chloride into an anhydrous ether solution of the base; m. p., 122–124°. It was somewhat hygroscopic.

Anal. Subs., 0.4000: 22.8 cc. of 0.1050 *N* $AgNO_3$. Calcd. for $C_7H_{16}ONCl$: Cl, 21.48. Found: 21.23.

γ-(Hydroxypropylpyridonium Chloride).—The product was made in exactly the same way as β-hydroxy-ethylpyridonium chloride, using 140 g. of trimethylene chlorohydrin and 117 g. of pyridine. Instead of obtaining a white, crystalline solid by the addition of dry ether to the absolute ethyl alcohol solution, a yellowish oil formed. This was shaken several times with absolute ether and then dried in a vacuum desiccator over sulfuric acid; yield, 220 g., or 85%.

N-γ-Hydroxy-ethylpiperidine.—A solution was made of 150 g. of γ-hydroxypropylpyridonium chloride in 250 cc. of hot 95% ethyl alcohol and reduced under a pressure of 1.5 to 3 atm., using 0.5 g. of platinum oxide as a catalyst. The reduction was complete at the end of about eight hours. After shaking with air, the platinum was filtered off and the filtrate evaporated under diminished pressure, holding the oil-bath under a temperature of 50°. The white, crystalline residue was made alkaline with 40% potassium hydroxide solution, extracted with ether and the ether solution dried over solid potassium hydroxide. After removal of the ether, the free base boiled at 108–109°, at 20–21 mm.; n_D^{25}, 1.4742; d_{25}^{25}, 0.9529; yield, 108 g., or 87%.

By dissolving in dry ether and passing in dry hydrogen chloride, a white, crystalline solid was produced which, after washing with ether and drying over sulfuric acid, melted at 139–141°. The salt was somewhat hygroscopic.

Anal. Subs., 0.4000: 21.1 cc. of 0.1050 *N* $AgNO_3$. Calcd. for $C_8H_{18}ONCl$: Cl, 19.78. Found: 19.68.

β-Piperidylethyl *p*-Nitrobenzoate Hydrochloride.—In a 250cc. round-bottomed flask fitted with a reflux condenser, a solution of 20 g. (1 mole) of β-hydroxy-ethylpiperidine dissolved in 50 cc. of benzene was slowly added to a solution of 29 g. (1 mole) of *p*-nitrobenzoyl chloride in 100 cc. of benzene. The reaction was vigorous, and a white precipitate separated almost immediately. The mixture, however, was heated for two hours to complete the reaction. An equal volume of ether was then added and the

[9] Since the completion of the work, this substance has been made several times and it has been found more convenient to reduce the β-hydroxy-ethylpyridonium chloride with hydrogen and platinum-oxide platinum black.

[10] Ladenburg, *Ber.*, **14**, 1877 (1881).

precipitate filtered and washed with ether. The product thus obtained was recrystallized from *n*-butyl alcohol. It could also be recrystallized from acetone. When pure it melted at 203–204°; yield, about 45 g., or 92%.

Anal. Subs., 0.5000: 15.2 cc. of 0.1050 *N* $AgNO_3$. Calcd. for $C_{14}H_{19}O_4N_2Cl$: Cl, 11.28. Found: 11.32.

The free base of this substance had already been prepared; m. p., 61–62°.[11]

β-Piperidylethyl *p*-Aminobenzoate Hydrochloride, I.—A solution of 60 g. of β-piperidylethyl *p*-nitrobenzoate hydrochloride was made in 300 cc. of warm 95% ethyl alcohol. This was reduced, using 1.5 to 3 atm. pressure and 0.2 g. of platinum oxide. The reduction was exceedingly rapid and was complete inside of an hour. The mixture was shaken with air in the usual way, and the platinum filtered, the filtrate evaporated under diminished pressure below 50° and the product crystallized from hot methyl alcohol; m. p., 213–214°; yield, 40 g., or 73%. Einhorn reports a melting point of 213°.

Anal. Subs., 0.5000: 16.7 cc. of 0.1050 *N* $AgNO_3$. Calcd. for $C_{14}H_{21}O_2N_2Cl$: Cl, 12.47. Found: 12.43.

γ-Piperidylpropyl *p*-Nitrobenzoate Hydrochloride.—In a 500cc. round-bottomed flask fitted with a reflux condenser, a solution of 65 g. of N-γ-hydroxypropylpiperidine in 100 cc. of benzene was slowly added to a solution of 87 g. of *p*-nitrobenzoyl chloride in 150 cc. of benzene. The reaction took place immediately and a large amount of heat was given off. The reaction mixture was heated for two hours to be sure of completion, an equal volume of dry ether was added, and the crystals were filtered. The product was recrystallized from *n*-butyl alcohol; yield, 115 g., or 75%; m. p., 206–208°.

Anal. Subs., 0.5000: 14.65 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 30.4 cc. (25°, 748 mm.). Calcd. for $C_{15}H_{21}O_4N_2Cl$: Cl, 10.80; N, 8.52. Found: Cl, 10.92; N, 8.37.

This substance was also produced by condensing γ-bromopropyl *p*-nitrobenzoate with piperidine, but the yields were not nearly so satisfactory as those obtained from the method just described. A solution of 59 g. of γ-bromopropyl *p*-nitrobenzoate in 50 cc. of xylene was refluxed for 12 hours with 35 g. of piperidine. At the end of this time, the piperidine hydrobromide which separated was filtered and the xylene solution concentrated under diminished pressure. Twice the volume of dry ether was then added and the hydrochloride was precipitated by passing in dry hydrogen chloride; yield, less than 50%.

γ-Piperidylpropyl *p*-Aminobenzoate Hydrochloride, II.—This compound was best obtained by dissolving 100 g. of the nitro ester hydrochloride in 400 cc. of hot alcohol and reducing at 1.5 to 3 atm. pressure, using 0.2 g. of platinum oxide as a catalyst. The reaction was completed within two hours. After filtering off the platinum and evaporating the solvent under diminished pressure, 65 g. of product was obtained (71.4%). It was best crystallized from a mixture of absolute methyl and ethyl alcohol, and melted when pure at 214–215°.

Anal. Subs., 0.5000: 16 cc. of 0.1050 *N* $AgNO_3$. Subs., 0.4000: N_2, 33.8 cc. (25°, 748 mm.). Calcd. for $C_{15}H_{23}O_2N_2Cl$: Cl, 11.89; N, 9.38. Found: Cl, 11.92; N, 9.31.

The above substance was also made by the reduction of the nitro compound with iron and hydrochloric acid. A colored product, however, was invariably obtained. The color could be removed by distilling the free base with a little zinc dust, under which conditions a colorless distillate, b. p. 212–213° at 7–8 mm., was obtained which solidified

[11] *Friedländer*, **8**, 993 (1905–1907). Einhorn, *Ann.*, **371**, 139 (1909).

on cooling, and after recrystallization from absolute ethyl alcohol melted at 192–193°. The hydrochloride was made by neutralizing the base in alcohol with alcoholic hydrochloric acid and evaporating until crystallization took place.

β-Piperidylethyl Benzoate Hydrochloride, $C_6H_5CO_2CH_2CH_2NC_5H_{10}$.—This product was made from benzoyl chloride and β-hydroxy-ethylpiperidine in exactly the same manner as the corresponding *p*-nitro compound. The substance was purified by crystallization from acetone from which it formed white crystals; m. p., 179–181°; previously reported,[8b,12] 175–176°. The yield was practically quantitative.

Anal. Subs., 0.4000: 86.7 cc. of 0.0171 *N* $AgNO_3$. Calcd. for $C_{14}H_{20}O_2NCl$: Cl, 13.17. Found: 13.22.

γ-Piperidylpropyl Benzoate Hydrochloride, $C_6H_5CO_2CH_2CH_2CH_2NC_5H_{10}$.—This substance was made in exactly the same way as that just mentioned, from benzoyl chloride and γ-hydroxypropylpiperidine. It was purified by crystallization from acetone or *n*-butyl alcohol, after which it formed white crystals; m. p., 191–193°. Brill[13] found 192°. It was produced in quantitative yields.

Anal. Subs., 0.4000: 84.1 cc. of 0.0171 *N* $AgNO_3$. Calcd. for $C_{15}H_{22}O_2NCl$: Cl, 12.52. Found: 12.76.

γ-*p*-Nitrobenzoyl-hydroxypropylpyridonium Bromide, $NO_2C_6H_4CO_2CH_2CH_2CH_2NC_5H_5$.—Sixteen g. (1 mole) of pyridine and 57 g. (1 mole) of γ-bromopropyl *p*-nitrobenzoate were mixed in a round-bottomed flask fitted with a condenser. The mixture was heated for one hour in an oil-bath held at about 130°, after which it was poured while hot into a beaker and rinsed out with 200 cc. of absolute alcohol. The reaction mixture was then heated to boiling with the alcohol, filtered, and the filtrate treated while still hot with absolute ether until a precipitate just failed to appear. Upon cooling, a white precipitate separated which was washed with a mixture of ether and alcohol and finally with a little ether. It was purified by recrystallization from absolute ethyl alcohol; yield, about 85%; m. p., 191–193°, with decomposition.

Anal. Subs., 0.5000: 80.1 cc. of 0.0171 *N* $AgNO_3$. Calcd. for $C_{15}H_{15}O_4N_2Br$: Br, 21.80. Found: 21.92.

γ-*p*-Aminobenzoyl-γ-hydroxypropylpyridonium Bromide.—A solution of 10 g. of the nitro compound just mentioned was made in 20 cc. of water, and 50 g. of iron powder was added. The reduction took place readily and the temperature was not allowed to rise above 60°. After the initial reaction had taken place, the mixture was heated on a water-bath at 60° for about half an hour. It was now filtered with suction and washed several times with a little hot water. The filtrate was evaporated to dryness on a steam-bath and the residue was recrystallized from absolute alcohol; yield, 4 g., or 45%. When pure, the substance was practically colorless; m. p., 114–115°.

Anal. Subs., 0.5000: 8.6 cc. of 0.0171 *N* $AgNO_3$. Calcd. for $C_{15}H_{17}O_2N_2Br$: Br, 23.74. Found: 23.53.

The γ-*p*-nitrobenzoyl-hydroxypropylpyridonium bromide was also reduced in ethyl alcohol solution with platinum black, according to the method already described for a number of the other products. The reduction took place rapidly. After filtering off the platinum, the solution was evaporated to dryness under diminished pressure, the residue made alkaline with 40% potassium hydroxide solution, and then extracted with ether. Upon evaporation of the ether, the free base was obtained which was taken up in alcohol and neutralized exactly with an alcoholic solution of hydrochloric acid. Upon evaporation, the hydrochloride of γ-piperidylpropyl *p*-aminobenzoate was ob-

[12] Pyman, *J. Chem. Soc.*, **93**, 1801 (1908).

[13] Brill, THIS JOURNAL, **47**, 1134 (1925).

tained in about 80% yields. The substances proved to be identical with that made by the condensation of *p*-nitrobenzoyl chloride with γ-hydroxypropylpiperidine.

Summary

1. β-Piperidylethyl and γ-piperidylpropyl *p*-aminobenzoates, β-(β-carbomethoxypiperidyl)-ethyl and γ-(β-carbomethoxypiperidyl)-propyl *p*-aminobenzoates have been prepared.

2. They are all local anesthetics, the substituted piperidyl derivatives being less effective than the unsubstituted.

3. *p*-Aminobenzoyl-γ-hydroxypropylpyridonium bromide had no anesthetic properties.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 542]

RESEARCHES ON THIAZOLES. XII. THE SYNTHESIS OF NEW ISOMERS OF DEHYDROTHIO-PARA-TOLUIDINE AND OF SOME RELATED COMPOUNDS: THE CONNECTION BETWEEN CHEMICAL CONSTITUTION AND TINCTORIAL PROPERTIES IN THE THIOFLAVINE AND CHLORAMINE YELLOW GROUPS[1]

BY MARSTON TAYLOR BOGERT AND ROGER WILLIAM ALLEN

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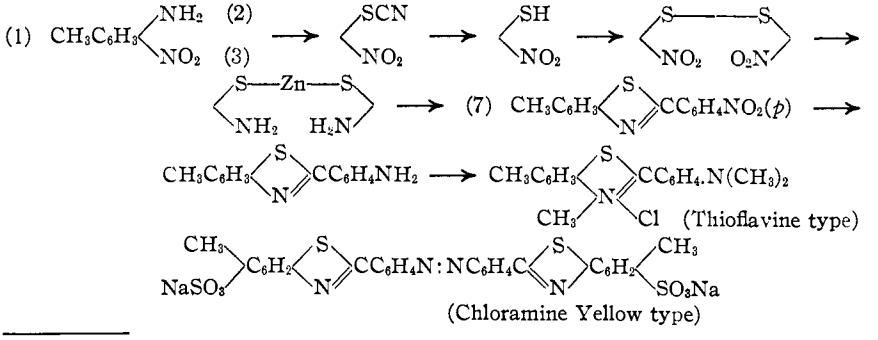
Introduction

Following up recent work from this Laboratory on dehydrothio-*p*-toluidine,[2] and on its 5-methyl isomer,[3] we have now completed the synthesis of other new isomers, carrying the methyl and amino groups in different positions. For the production of the isomer with the methyl group in Position 7, the following reactions were employed.



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[1] Presented in abstract before the Dye Division of the American Chemical Society, at the Richmond Meeting, April, 1927.

[2] (a) Bogert and Meyer, THIS JOURNAL, **44**, 1568 (1922). (b) Bogert and Snell, *Color Trade J.*, **14**, 109 (1924). (c) Bogert and Bergeim, *Proc. Nat. Acad. Sci.*, **10**, 318 (1924); (d) *Color Trade J.*, **15**, 63 (1924).

[3] Bogert and Allen, *Ind. Eng. Chem.*, **18**, 532 (1926).