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

CYCLIC ALKAMINE ESTERS OF PARA-AMINOBENZOIC ACID. II

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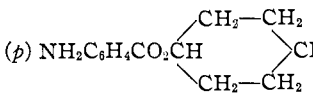
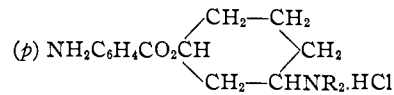
In a recent paper the relation between physical properties, physiological action and chemical constitution of various simple alkyl *p*-aminobenzoates was discussed.[2] Extensive work has now been completed on various anesthetics of the procaine (β-diethylamino-*p*-aminobenzoyl ethanol hydrochloride) type, where the amino alcohol which forms the ester of the *p*-aminobenzoic acid has been modified in regard to the groups attached to the nitrogen atom and in regard to the linkages between the oxygen and nitrogen atoms. This first paper describes a group of anesthetics containing cyclic structures between the oxygen and nitrogen atoms in the amino alcohol which are represented by the Formulas I, II and III.

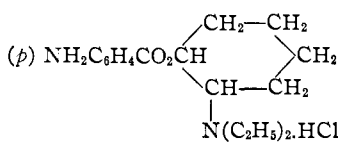


cis and *trans*

I



II



trans

III

These have been prepared in the obvious way by the condensation of *p*-nitrobenzoyl chloride with the proper amino alcohol followed by catalytic reduction to the corresponding aminobenzoyl derivatives.

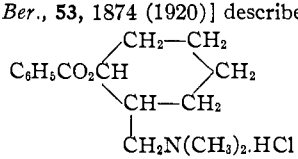
An *o*-diethylaminocyclohexyl *p*-aminobenzoate hydrochloride isomeric with III has been described by Osterberg and Kendall[3] and represents with but one exception[4] the only anesthetic with a hydrocarbon ring structure between the oxygen and nitrogen atoms which has previously been described. They employed the same general procedure for making the

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

[2] Adams, Rideal, Burnett, Jenkins and Dreger, THIS JOURNAL, **48**, 1758 (1926).

[3] Osterberg and Kendall, *ibid.*, **43**, 1370 (1921).

[4] Mannich and Braun [*Ber.*, **53**, 1874 (1920)] described the compound



and report it as an anesthetic.

intermediate amino alcohol as that used in this investigation, namely, addition of hypochlorous acid to cyclohexene, and condensation of the chlorohydrin produced with diethylamine. However, they used the action of carbon dioxide upon bleaching powder to prepare the hypochlorous acid for addition to the cyclohexene, whereas in this investigation the method of Detoeuf[5] was used, the action of chlorine upon urea and subsequent hydrolysis with dil. acetic acid. The constants of the intermediates and anesthetics made from the *o*-chlorocyclohexanol produced by the latter process are compared with the isomeric substances described by Osterberg and Kendall in Table I.

TABLE I

COMPARISON OF CONSTANTS OF *cis* AND *trans* ISOMERS

	(*cis*) Osterberg and Kendall, m. p., °C.	(*trans*) Heckel and Adams, m. p., °C.
o-Diethylaminocyclohexanol hydrochloride	160	170.5–171.5
o-Diethylaminocyclohexyl *p*-nitrobenzoate hydrochloride	175	192–194
o-Diethylaminocyclohexyl *p*-aminobenzoate hydrochloride	163	220–221

Since the new products are all higher melting, it is probable that they represent the *trans* modification. Moreover, Godchot[6] showed that Detoeuf's procedure gave an *o*-chlorocylcohexanol that hydrolyzed to a resolvable and therefore to the *trans* cyclohexanediol.

The *m*- and *p*-dialkyl aminocyclohexanols necessary for the other anesthetics were prepared by the catalytic reduction of the proper aminophenols.[7]

The comparison of the *cis*- and *trans*-4-dimethylaminocyclohexyl derivatives is of interest because they represent a pair of geometric isomers, very few of which pairs have been studied previously.

Gottlieb[8] has reported tropacocaine (benzoyl pseudotropine) to be more effective than its isomeride benzoyl tropeine, though Morgenroth[9] had previously reported essentially the same anesthetic value for the two compounds.

Liebermann and Limpach[10] demonstrated that the mandelic and tropic acid esters of pseudotropine were inactive as anesthetics, though the isomerides homatropine and atropine were very active. Similar results were observed by Harries,[11] who showed that the mandelyl ester of the

[5] Detoeuf, *Bull. soc. chim.*, [4] **31**, 177 (1922).

[6] Godchot, *Compt. rend.*, **176**, 448 (1923). See also Boeseken, Derx and Van Loon, *Rec. trav. chim.*, [4] **3**, 318, 333 (1922).

[7] Heckel with Adams, THIS JOURNAL, **47**, 1712 (1925).

[8] Gottlieb, *Arch. exptl. Path. Pharmakol.*, **97**, 113 (1923).

[9] Morgenroth, *Ber. pharm. Ges.*, **29**, 233 (1919).

[10] Liebermann and Limpach, *Ber.*, **25**, 927 (1892).

[11] Harries, *Ber.*, **29**, 2731 (1896); *Ann.*, **296**, 328 (1897).

labile form of N-methylvinyldiacetone-alkamine was active, but the isomeric ester of the stable form was inactive.

King[12] compared the benzoyl esters of the two vinyldiacetone-alkamines. On the rabbit's cornea the alpha form (β-eucaine) and the beta form (iso-β-eucaine) were equally active, while on the sciatic nerve the alpha form was more effective. The beta form was twice as toxic as the alpha.

Traube[13] prepared the benzoyl esters of α,α,β-trimethyl-α,α-diethyl-γ-ketopiperidine, but merely reported that both were anesthetics without giving any comparative values.

Finally, Gottlieb[8] showed that *dl*-pseudococaine was a more effective anesthetic than *dl*-cocaine but had approximately the same toxicity; Poulson[14] reported *d*-pseudococaine as much more effective than *l*-cocaine.

The higher-melting (probably *trans*) *p*-dimethylaminocyclohexyl *p*-aminobenzoate hydrochloride was practically twice as anesthetic to goldfish[2] in concentrations from 0.012 to 0.005 *M* as the lower-melting (probably *cis*) isomer. Toward the rabbit's cornea, equimolar concentrations showed very little difference between the isomers, in regard to length of anesthesia.[15] On the other hand, the "anesthetic index"[16] for the higher-melting form is about twice that of the lower-melting form.

All the compounds were effective anesthetics both on mucous membrane and by injection. The *trans*-4-dimethylamino derivative gave, in a concentration equivalent to a 2% cocaine hydrochloride solution, mucous membrane anesthesia slightly greater than a 2% cocaine hydrochoride solution. The other compounds were less effective.

Toward goldfish in equimolar concentrations the order of anesthesia was as follows: 3-diethylaminocyclohexyl > 3-dimethylaminocyclohexyl > 4-dimethylaminocyclohexyl (*trans*) > 4-dimethylaminocyclohexyl (*cis*) > 2-diethylaminocyclohexyl (*trans*).

A more detailed discussion of physical constants and physiological action will be given in a later paper.

Experimental Part

trans-o-**Diethylaminocyclohexanol.**—Cyclohexene was converted to *o*-chlorocyclohexanol by the method of Detoeuf.[5] A mixture of 1 molecular equivalent of chlorohydrin and 2 molecular equivalents of diethylamine in butyl alcohol solution was

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

[13] Traube, *Ber.*, **51**, 777 (1918).

[14] Poulson, *Arch. exptl. Path. Pharmakol.*, **27**, 301 (1890).

[15] The experiments were kindly made by Dr. H. McGuigan of the University of Illinois Medical School.

[16] These experiments were made in the Chemical Laboratory of the University of Illinois by E. E. Dreger, following the procedure suggested by Sollman [*J. Pharmacol.*, **7**, 67 (1918)]. The "anesthetic index" is the value obtained by dividing the minimum effective concentration of novocaine, which causes complete anesthesia for ten minutes, by the minimum effective concentration of the other anesthetics.

heated under pressure at 150° for several hours, according to the method described by Osterberg and Kendall.[8] A yield of amino alcohol was obtained equal to the weight of the chlorohydrin used. It boiled at 106–106.5°, at 17 mm. and at 225°, at 740 mm.; d_{25}^{25}, 0.9280; n_D^{24}, 1.4659. The hydrochloride, after purification from a mixture of ethyl acetate and absolute alcohol, melted at 170.5–171.5°.

Anal. Subs., 0.5060: 24.38 cc. of 0.0995 *N* $AgNO_3$. Calcd. for $C_{10}H_{21}ON.HCl$: Cl, 17.08. Found: 17.01.

This amino alcohol corresponds to the one described by Brunel,[17] prepared from diethylamine and cyclohexene oxide.

trans-o-**Diethylaminocyclohexyl *p*-Nitrobenzoate Hydrochloride.**—One molecular equivalent of *o*-diethylaminohexanol and 2 molecular equivalents of *p*-nitrobenzoyl chloride were heated together for an hour until evolution of hydrogen chloride ceased. The crude ester was treated with dry ether, filtered, and recrystallized from a mixture of ethyl acetate and butyl alcohol; m. p., 192–194°.

Anal. Subs., 0.4999: 11.61 cc. of 0.1160 *N* $AgNO_3$. Calcd. for $C_{17}H_{24}O_4N_2.HCl$: Cl, 9.94. Found: 9.55.

Dialkyl Aminocyclohexyl *p*-Aminobenzoate Hydrochloride.—The *o*-, *m*- and *p*-dialkyl aminocyclohexyl *p*-aminobenzoate hydrochlorides were prepared by the catalytic reduction of the corresponding nitro compounds.[18] These were dissolved in absolute ethyl or butyl alcohol and reduced with hydrogen under 3–3.5 atm. pressure in the presence of platinum-oxide platinum black[19] (0.2 g. per 0.1 mole of nitro compound in 100–150 cc. of solvent). Upon filtration of the catalyst and evaporation of the solvent, practically pure amine hydrochloride resulted.

TABLE II

AMINE HYDROCHLORIDES

Dialkyl aminocyclohexyl *p*-aminobenzoate hydrochloride	Reduction solvent	Solvent for recrystn.	M. p., °C.	Analysis Subs.	$AgNO_3$, cc.	Cl, % Calcd.	Found
trans-o-Diethylamino ($C_{17}H_{26}O_2N_2.HCl$)	abs. C_2H_5OH	abs. C_2H_5OH + $CH_3CO_2C_2H_5$	220–221	0.5102	15.70 (0.0995 *N*)	10.85	10.86
m-Dimethylamino ($C_{15}H_{22}O_2N_2.HCl$)	C_4H_9OH	C_4H_9OH	184–185	.5002	14.38 (0.1160 *N*)	11.87	11.82
m-Diethylamino ($C_{17}H_{26}O_2N_2.HCl$)	abs. C_2H_5OH	abs. C_2H_5OH + $CH_3CO_2C_2H_5$	184–186	.5031	15.36 (0.0995 *N*)	10.85	10.78
p-Dimethylamino (*cis*?) ($C_{15}H_{22}O_2N_2.HCl$)	abs. C_2H_5OH	abs. C_2H_5OH	226–228	.2412	6.84 (0.1160 *N*)	11.87	11.67
p-Dimethylamino (*trans*?)	abs. C_2H_5OH	abs. C_2H_5OH	268–269	.2417	7.03 (0.1160 *N*)	11.87	11.96

[17] Brunel, *Ann. chim. phys.*, [8] **6**, 252 (1905).

[18] Adams, Cohen and Rees, THIS JOURNAL, **49**, 1093 (1927).

[19] Adams and Shriner, *ibid.*, **45**, 2171 (1923).

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

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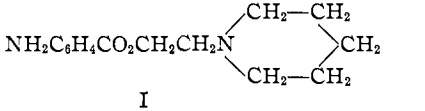
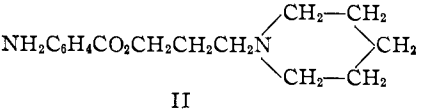
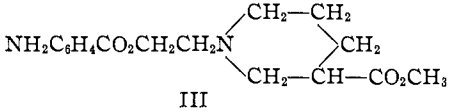
In the previous paper of this series,[2] certain cyclic alkyl amino esters of *p*-aminobenzoic acids were described. This communication describes the anesthetics I, II, III and IV formed by the condensation of β-bromoethyl *p*-nitrobenzoate and γ-bromopropyl *p*-nitrobenzoate with piperidine and methyl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



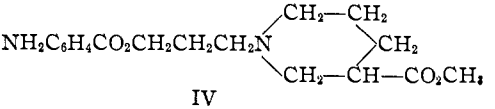
I



II



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).