Summary.

Ethyl cyclohexane-1,1-dicarboxylate was prepared by condensation of 1,5-dibromopentane with ethyl malonate. This condenses with urea and with guanidine to form derivatives of cyclohexane-1,5-*spiro*-pyrimidine. The cyclohexane-*spiro*-pyrimidines are very similar in properties to the corresponding cyclobutane-*spiro*-pyrimidines described in our previous paper.

DETROIT, MICHIGAN.

[CONTRIBUTION FROM THE MAYO FOUNDATION CLINIC.]

THE ORTHO-DIETHYLAMINO-CYCLOHEXANOL ESTER OF PARA-AMINOBENZOIC ACID.

BY A. E. OSTERBERG AND E. C. KENDALL.

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Amino alcohol esters of aromatic acids are known to possess physiological properties, chief among which is that of producing local anesthesia. The anesthetic effect of the diethylamino ethyl ester of *p*-aminobenzoic acid, (procaine), is ascribed in part to the linkage, $-O-\overset{H_2}{C}-\overset{H_2}{C}-N$ = [1], the maximum being produced when the oxygen is bound directly to the carbonyl of an aromatic acid.

Cyclohexanol resembles more definitely an aliphatic alcohol than an aromatic phenol. Similarly the properties of *o*-amino-cyclohexanol are those of an aliphatic amino alcohol. In discussing the properties of this substance with Professor Julius Steiglitz he suggested the possibility of its use in the preparation of esters of the above type.

With the idea of maintaining those linkages to which physiological action is ascribed but at the same time materially enhancing its molecular weight we have prepared a homolog of procaine, the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid. The physiological properties of this compound together with those of derivatives of this ester containing substituents in the cyclohexane ring are being studied and will be reported elsewhere. This report concerns only the synthesis of the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid.

Preparation of *o*-Diethylamino-cyclohexanol.

Fifty-four g. of *o*-chloro-cyclohexanol is treated with twice the theoretical amount of diethylamine at 150° in a sealed tube for several hours. To the reaction product is added 25 g. of sodium carbonate and a small amount of water, and the excess of diethylamine and water boiled off. The residue is extracted with absolute alcohol. After removal of the

[1] O. Kamm, THIS JOURNAL, **42**, 1030–3 (1920).

alcohol the *o*-diethylamino-cyclohexanol is dissolved in dil. hydrochloric acid and distilled with steam to remove any unchanged *o*-chloro-cyclohexanol. The residue is then made strongly alkaline and again is distilled with steam. The amine separates in the distillate as a clear oil. It is removed by ether extraction, dried, and fractionated *in vacuo*. The fraction boiling at 100° to 150° at 10 mm. is redistilled in atmospheric pressure. B. p., 224° at 730 mm.

The hydrochloride, formed from the amine in ether and hydrogen chloride, melts at 160°.

Subs., 0.2518: Cl, 0.0428. Subs., 0.2040: N, 0.0143. Calc. for $C_{10}H_{22}ONCl$: N, 6.75; Cl, 17.07. Found: N, 7.00; Cl, 17.01.

o-Diethylamino-cyclohexanol Ester of *p*-Nitrobenzoic Acid.

Seventeen g. of *o*-diethylamino-cyclohexanol is added gradually to a solution of 20 g. of *p*-nitrobenzoyl chloride in absolute ether. The reaction proceeds easily but the mixture is allowed to stand for a few hours to insure completion.

The hydrochloride of the *o*-diethylamino-cyclohexanol ester of *p*-nitrobenzoic acid separates as a pasty mass, and is filtered off. The yield corresponds to 80% of the calculated amount. The hydrochloride melts at 175°.

Subs., 0.3550: Cl, 0.0345. Subs., 0.1810: N, 0.0140. Calc. for $C_{17}H_{25}O_4N_2Cl$: N, 7.85; Cl, 9.94. Found: N, 7.73; Cl, 9.72.

o-Diethylamino-cyclohexanol Ester of *p*-Aminobenzoic Acid.

Excess tin is added to a suspension of the hydrochloride of the *o*-diethylcyclohexanol ester of *p*-nitrobenzoic acid in strong hydrochloric acid. During the reduction the temperature is maintained at about 35° until the reaction is complete. The solution is then diluted and the tin removed with hydrogen sulfide.

Excess sodium hydroxide is added to the clear filtrate and the resulting oil extracted with ether. The ether solution is dried and the ether removed by distillation.

The residue of the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid crystallizes slowly and is obtained as wide plates; m. p. 72° with preliminary softening.

Subs., 0.1512: N, 0.0147. Calc. for $C_{17}H_{26}O_2N_2$: N, 9.65. Found: 9.72.

The monohydrochloride melts at 163°.

Summary.

A homolog of procaine, the *o*-diethylamino-cyclohexanol ester of *p*-aminobenzoic acid has been prepared.

The physiological action of this substance and derivatives containing substituents in the cyclohexane ring are being studied.

ROCHESTER, MINN.