It was precipitated by dilute hydrochloric acid, redissolved in dilute potassium hydroxide solution, reprecipitated by hydrochloric acid, washed repeatedly with dilute hydrochloric acid, dried, dissolved in alcohol (to a deep red solution) and precipitated by the addition of ether as a microcrystalline greenish-black, solid. It was somewhat hygroscopic and still impure.

Anal. Calcd. for $C_{40}H_{32}O_8S_4$: C, 62.5; H, 4.2. Found: C, 60.88; H, 4.50.

6-Retenethioindigo (IX).—When 1 g. of the crude thioindoxyl (VIII) was suspended in 100 cc. of a 5% sodium hydroxide solution, it oxidized almost immediately to the thionindigo. The mixture was boiled for ten minutes, cooled, the amorphous greenish-black precipitate removed and dried at room temperature. It was insoluble in the usual neutral organic solvents or in dilute mineral acids. In chloroform, glacial acetic acid or nitrobenzene, it dissolved slightly to a reddish solution, from which it was reprecipitated as a reddish-black amorphous solid by the addition of alcohol. Its purification was exceedingly troublesome. It was dissolved in a large volume of chloroform, precipitated by the addition of alcohol, washed on the filter with dilute hydrochloric acid, water, alcohol, and finally ether. This procedure was repeated thrice, and the product was then ashless when burned, but still very impure.

It dissolved with difficulty in an alkaline sodium hydrosulfite solution to a brownish vat which dyed cotton a bluish-green.

6-Retothiophene-3-indole-indigo (XI).—A solution of 0.6 g. of the crude thioindoxyl (VIII), 0.5 g. of isatin and 20 cc. of boiling glacial acetic acid, was allowed to cool to room temperature. Ten drops of concentrated hydrochloric acid were added and the mixture was heated for a few minutes. Addition of water precipitated the dye completely. It was filtered out, washed with water, then with alcohol and dried, when it appeared as a dark red amorphous powder, which could not be crystallized from any of the solvents tried.

Like analogous compounds in the simple indigo series,[9,10] it retained the solvent very tenaciously, and at higher temperatures (120° and above) evolved acetic acid vigorously. In alkaline sodium hydrosulfite, it formed a yellowish vat which dyed cotton reddish shades.

Thioindogenides (X) were prepared from the crude thioindoxyl and various aldehydes, essentially as described above for the isatin condensation product (XI), and proved equally difficult of purification. They were dark amorphous solids, which formed yellowish vats with alkaline hydrosulfite solution and dyed cotton the following shades: benzaldehyde, yellow; *p*-hydroxybenzaldehyde, orange; and *p*-dimethylaminobenzaldehyde, reddish.

Summary

6-(or B-)Retenesulfonic acid has been converted into its sulfonchloride, the corresponding thioretenol, retyl disulfoxide, disulfide, thioglycolic acid, thioindoxyl, and certain derivatives of these, some of which possess tinctorial properties.

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

The Local Anesthetic Action of Dialkylaminoethoxyethyl *p*-Aminobenzoates

BY LEONE A. RUBERG AND R. L. SHRINER

The structural variations which have been made in compounds of the novocaine type (formula I) have had for their purpose the securing of a molecule which would possess low toxicity, high anesthetizing power, and no irritation. A study of local anesthetic action of *p*-aminobenzoates of the type of formula II showed that introduction of the

I (*p*) $H_2NC_6H_4COO(CH_2)_nNR_2$

II (*p*) $H_2NC_6H_4COO(CH_2CH_2O)_nCH_2CH_2N(C_2H_5)_2$

III (*p*) $H_2NC_6H_4COOCH_2CH_2OCH_2CH_2NR_2$

ether linkage in the side chain conferred on the molecule the ability to cause surface anesthesia as well as injection anesthesia.[1] It was also established that the compound where $n = 1$ possessed pharmacological properties superior to those of compounds where $n = 0$, 2, 3 or 4. The present work had for its purpose the preparation of compounds of structure III which contain only one ether linkage, but in which the R groups were varied from methyl to butyl in order to determine how the alkyl groups attached to the nitrogen influenced the pharmacological action of this series of esters.

The requisite dialkylaminoethoxyethanols were prepared by the reaction between secondary amines and ethylene oxide. The reaction

$$R_2NH + \underset{\diagdown O \diagup}{CH_2—CH_2} \longrightarrow R_2NCH_2CH_2OH$$

$$R_2NCH_2CH_2OH + \underset{\diagdown O \diagup}{CH_2—CH_2} \longrightarrow R_2NCH_2CH_2OCH_2CH_2OH$$

requires two moles of ethylene oxide, but the products consist of a mixture of the compounds[2] re-

(1) Horne and Shriner, *J. Pharmacol.*, **48**, 371 (1933).

(2) Horne and Shriner, THIS JOURNAL, **54**, 2925 (1932); Headlee, Collett and Lazzell, *ibid.*, **55**, 1066 (1933).

sulting from the combination of the secondary amine with one to *n* moles of ethylene oxide. Fractional distillation was used to separate the chain polymers. By treating the dialkylaminoethanol with more ethylene oxide, additional amounts of the desired alcohol could be obtained, but the yields were not high, and decreased as the size of the R group increased. In the case of the amyl amines sufficient amounts of the aminoethoxyethanols could not be obtained in the pure state for the preparation of their *p*-aminobenzoates.

Treatment of the dialkylaminoethoxyethanols with *p*-nitrobenzoyl chloride gave the *p*-nitrobenzoates which were reduced catalytically to the *p*-aminobenzoates.

Experimental Part

β-(Dialkylamino)-ethoxyethanols.—Ethylene oxide was passed into a warm solution of 50 g. of the secondary amine in 50 g. of methanol at such a rate that the temperature did not rise above 60°. After the absorption of about 30% in excess of the theoretical amount for two moles of ethylene oxide, the reaction mixture was fractionated *in vacuo*, using a carborundum packed column. The low-boiling fractions were again treated with ethylene oxide and again fractionated. Three to four fractionations were necessary to secure separations.

Dimethylaminoethoxyethanol.—Fractionation of the reaction mixture from dimethylamine and ethylene oxide gave a colorless liquid boiling at 78–79° (3.5 mm.). This fraction contained only 7.2% nitrogen, whereas the calculated value was 10.52. It appeared to be a constant-boiling mixture of the desired compound with the reaction product obtained by the action of ethylene oxide with the methanol. For purification this fraction was dissolved in absolute ether and saturated with hydrogen chloride. The hydrochloride precipitated and was recrystallized from an alcohol–absolute ether mixture. It melted at 104–105.5°.

Anal. Calcd. for $C_6H_{16}NO_2Cl$: Cl, 20.95. Found: Cl, 20.80.

The yield of this amino alcohol was only 16%, which is less than that obtained by Fourneau and Ribas[3] who prepared it in 75% yields by heating a benzene solution of dimethylamine and β-chloroethoxyethanol in a sealed tube at 120°. The low yield by the above procedure is due to the volatilization of a considerable part of the dimethylamine as well as the formation of higher chain polymers.

Diethylaminoethoxyethanol.—This compound was obtained by direct fractionation of the reaction mixture from diethylamine and ethylene oxide as previously described.[2]

Di-(*n*-propyl)-aminoethoxyethanol.—This amino alcohol was obtained in 51% yield by the above general procedure. It boiled at 102–103° (2.5 mm.); d^{20}_{20} 0.9298; $n^{20}D$ 1.448.

Anal. Calcd. for $C_{10}H_{23}O_2N$: N, 7.40. Found: N, 7.20.

(3) Fourneau and Ribas, *Bull. soc. chim.*, [4] **41**, 1046 (1927).

Di-(*n*-butyl)-aminoethoxyethanol.—A 33% yield of this compound was obtained: b. p. 117–121° (1 mm.); d^{20}_{20} 0.9157; $n^{20}D$ 1.455.

Anal. Calcd. for $C_{12}H_{27}O_2N$: N, 6.45. Found: N, 6.11.

The dialkylaminoethoxyethanols are colorless, viscous, hygroscopic liquids which rapidly turn from yellow to amber on standing. They are easily soluble in water, benzene, acetone, and ether with the exception of the di-*n*-butyl derivative which is sparingly soluble in water.

β-(Dialkylamino)-ethoxyethyl *p*-Nitrobenzoate Monohydrochlorides.—An anhydrous benzene solution of the above aminoethoxyethanols was treated with a slight excess of *p*-nitrobenzoyl chloride and the mixture was refluxed one to nine hours as required for completion of the reaction. When the solution was cooled, the dialkylaminoethoxyethyl *p*-nitrobenzoate separated as the hydrochloride. The crude product was recrystallized several times by dissolving in the minimum amount of absolute ethyl alcohol, and by reprecipitating with absolute ether. The diethylaminoethoxyethyl *p*-nitrobenzoate could not be obtained in the pure crystalline state. The yields and analyses are given in Table I.

TABLE I

Compound	M. p., °C.	Yield, %	Analyses (Cl), % Calcd.	Found
(*p*) $O_2NC_6H_4CO_2CH_2CH_2$-$OCH_2CH_2N(CH_3)_2 \cdot HCl$	97–99	66	11.13	10.96
(*p*) $O_2NC_6H_4CO_2CH_2CH_2$-$OCH_2CH_2N(C_3H_7)_2 \cdot HCl$	106–108	67	9.47	9.45
(*p*) $O_2NC_6H_4CO_2CH_2CH_2$-$OCH_2CH_2N(C_4H_9)_2 \cdot HCl$	99–101	37	8.81	8.41

β-(Dialkylamino)-ethoxyethyl *p*-Aminobenzoate Monohydrochlorides.—The *p*-nitrobenzoate hydrochlorides were reduced with hydrogen and a platinum oxide catalyst in absolute methyl alcohol solution. The reduction required one to three hours for 3- to 5-g. portions. The platinum was filtered and the solvent was removed by distillation. After standing for twelve to forty-eight hours, the residue crystallized. The *p*-aminobenzoates of dimethyl-, diethyl-, and di-*n*-propylaminoethoxyethanol hydrochlorides were purified by dissolving in absolute alcohol and reprecipitating with absolute ether. In the case of di-*n*-butylaminoethoxyethyl *p*-aminobenzoate hydrochloride, washing with dioxane was found to be more effective in raising the melting point of the product.

The *p*-aminobenzoate hydrochlorides are insoluble in benzene, ligroin, and ether; sparingly soluble in chloroform and ethyl acetate, with little temperature coefficient; and very soluble in absolute methyl or ethyl alcohol. They are readily oxidized on exposure to air. The formulas, melting points, and analyses are given in Table II.

Pharmacological Data.—Through the courtesy of the Lilly Research Laboratories the local anesthetic action of 1% aqueous solutions of the monohydrochlorides of each of the above compounds was determined by intracutaneous injection in guinea pigs and by surface application to the rabbit's cornea. The toxicity, irritation and depressant action were also noted.

TABLE II

β-(DIALKYLAMINO)-ETHOXYETHYL *p*-AMINOBENZOATE MONO-HYDROCHLORIDES

No.	Compound	Color	M. p., °C.	Chlorine, % Calcd.	Found
A	p-$H_2NC_6H_4CO_2CH_2CH_2OCH_2CH_2N(CH_3)_2 \cdot HCl$	Greenish-yellow	150–152	12.28	12.28
B	p-$H_2NC_6H_4CO_2CH_2CH_2OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	Light yellow	150–152	11.21	11.24
C	p-$H_2NC_6H_4CO_2CH_2CH_2OCH_2CH_2N(C_3H_7)_2 \cdot HCl$	Light yellow	128.5–130	10.30	10.32
D	p-$H_2NC_6H_4CO_2CH_2CH_2OCH_2CH_2N(C_4H_9)_2 \cdot HCl$	Deep yellow	134–136	9.53	9.67

The results of the pharmacological study are summarized in Table III which also includes the data on novocaine and cocaine for comparison.

TABLE III

PHARMACOLOGICAL ACTION OF DIALKYLAMINOETHOXYETHYL *p*-AMINOBENZOATE MONO-HYDROCHLORIDES

Compound (see Table II)	Toxicity (intravenous mice) mg./kg.	Anesthesia (min.) Intracutaneous guinea pig	Rabbit cornea	Irritation Rabbit eye	Rabbit skin
A	55	13	None	None	None
B	55	31	20	None	None
C	25	26	16	None	None
D	10	40	43	None	Mild
Novocaine	40	24	None	None	None
Cocaine	17.5	41	20	None	None

Examination of the toxicity column in the above table shows that increasing the size of the alkyl group attached to nitrogen causes an increase in toxicity. This effect parallels that observed for novocaine analogs (formula I).[4] Anesthetic action also increased as the size of the alkyl group increased, although the increase is not a regular one. It is interesting that the dimethyl derivative did not cause topical anesthesia. The present data do not show the optimum size of the alkyl group since none of the compounds with groups larger than butyl could be obtained.

Summary

The monohydrochlorides of dialkylaminoethoxyethyl *p*-aminobenzoates of the general formula $(p)H_2NC_6H_4COOCH_2CH_2OCH_2CH_2NR_2$ have been prepared in which the R group has been varied from methyl to *n*-butyl. The toxicity and local anesthetic action of these compounds increased as the size of the alkyl group was increased.

(4) Schmitz and Loevenhart, *J. Pharm. Exp. Therap.*, **24**, 159 (1924).

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[CONTRIBUTION NO. 127 FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, RESEARCH LABORATORY OF ORGANIC CHEMISTRY]

Pyrylium Derivatives by the Condensation of Saturated Ketones

BY TENNEY L. DAVIS AND CATHERINE BATES ARMSTRONG

In the preparation of *sym*-trianisylbenzene by the condensation of *p*-methoxyacetophenone under the influence of a mixture of concentrated sulfuric acid and potassium pyrosulfate by the method of Odell and Hines[1] we have found that about 11% of the material is converted into the desired product and another 11% of it into a bright scarlet crystalline material readily soluble in water to yield a strongly fluorescent solution. Colored material of similar appearance but of undetermined composition has been reported by Schneider and Seebach[2] as formed in condensations leading, under the influence of a sulfoacetic acid reagent, to *sym*-trianisylbenzene. We find that the colored salt is 2,4,6-trianisylpyrylium acid sulfate, a salt of the same base which Dilthey[3] prepared in the form of the chloride–ferric chloride double salt by the reaction of anisal-*p*-methoxyacetophenone with *p*-methoxyacetophenone in the presence of ferric chloride and acetic anhydride. Our substance yields a picrate and a chloroplatinate identical with those prepared from the salt produced by Dilthey's method.

When a pyrylium derivative is prepared by Dilthey's method, the product contains all of the carbon atoms which were present in the reagents; the ferric chloride acting as an oxidizing agent removes only hydrogen atoms. But when three molecules of *p*-methoxyacetophenone react to form one molecule of the pyrylium salt, one methyl group is lost. Since analysis does not distinguish sharply between a simple trianisylpyrylium salt and one which contains an additional methyl

(1) Odell and Hines, THIS JOURNAL, **35**, 82 (1913).

(2) Schneider and Seebach, *Ber.*, **54**, 2298 (1921).

(3) Dilthey, *J. prakt. Chem.*, **94**, 53 (1916); **95**, 116 (1917).