unit is 9.1 Å.[2] The prism may also be surrounded by pyramidal faces of various forms, as is usually the case, having various areas per atom. These crystal magnitudes should be compared with the cross-sectional areas of methyl stearate, 26.6 Å.[2], and of glycol dipalmitate, 48 Å.[2], or even, to take an extreme case, with the cross-sectional area of a "close packed" hydrocarbon chain which is 20.5 Å.[2] as given by Adam.[8] Adam also states that X-ray studies on long chain compounds have shown that when chains are packed side by side in the crystal, the cross section perpendicular to the chain is 18.4 Å.[2] with an error of 0.5% only. These magnitudes show that the cross-sectional area of the adsorbed molecules is considerably greater than the area of the structural unit in the crystal. It must be assumed, then, that the specific surface of the crystal as determined by adsorption is some function of the area of the adsorbed molecule rather than some function of the crystal structure. The function of the adsorbed molecule which has been assumed in the calculations in this article is that the area occupied by the adsorbed molecule is the same on the crystal surface as it is on a surface of 0.1 *N* hydrochloric acid.

(8) Adam, "The Physics and Chemistry of Surfaces," Oxford Press, 1930.

Summary

The adsorption of certain one, two, and three chain aliphatic compounds on various zinc oxide pigments has been investigated.

The glycol dipalmitate molecule covers twice as large an area as the methyl stearate molecule does.

The specific surfaces of the pigments calculated from these adsorption measurements agree closely with the surfaces calculated by the photomicrographic method.

The films are monomolecular or some multiple thereof in thickness.

BETHLEHEM, PENNA. RECEIVED DECEMBER 22, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE CITY COLLEGE, COLLEGE OF THE CITY OF NEW YORK]

Alkanolamines. VI. Physiologically Active Compounds. I. The Preparation of Substituted Anilino Alcohols

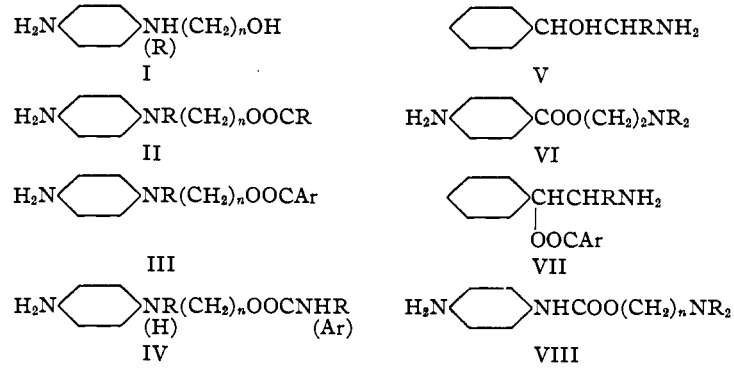
BY CHESTER B. KREMER

Introduction

The establishment of diethylaminoethyl *p*-aminobenzoate as a practical local anesthetic by Einhorn[1] in 1909 has been followed by a vast amount of research dealing with analogous compounds. While many analogs, varying mainly in the nature of alkyl groups on the tertiary nitrogen and in the kind and position of substituted groups on the benzene ring, have been synthesized, comparatively few compounds with dissimilar substituents on the nitrogen have been reported as local anesthetics. This is probably due to the difficulty of preparing the secondary amines involved in the reactions as ordinarily carried out.

Through a type reaction developed in these Laboratories, it is possible to prepare a series of new compounds containing dissimilar substituents on the tertiary nitrogen: one aryl, the other alkyl in nature. These compounds are isomers and analogs of well-known anesthetics and pressors. Their general structure is given in I, II, III and IV of Chart I. Type II is seen to be isomeric with the procaine type, VI, while compounds represented by III are analogs.

CHART I



"Alkadrins,"[2] V, which are known to exhibit pressor action and the type I compounds bear a

(1) Einhorn, *Ann.*, **376**, 162 (1909).

(2) Hartung, Munch and Crossley, THIS JOURNAL, **57**, 1091 (1935).

close relationship to each other. The benzoic esters of the "alkadrins," VII, combine both pressor and anesthetic action.[3] Closely related to these are the type III compounds, which also possess potential pressor and anesthetic nuclei.

Substances represented by type IV are urethans and have their parallel in local anesthetics with the *p*-aminophenyl urethans,[4] VIII.

Discussion

It is the purpose of this introductory paper to deal specifically with the preparation of substituted anilino alcohols containing a secondary nitrogen atom; which together with those alcohols containing a tertiary nitrogen (to be described in the succeeding paper of this series) constitute the parent compounds from which the actual anesthetics are synthesized. The preparation, properties and physiological activities of the latter will be described at a later date. Some of the type III compounds which have been physiologically tested show strong anesthetizing ability. They possess, however, the disadvantages inherent in derivatives of the *p*-phenylenediamine type, *i. e.*, instability and irritability. These factors though have been found to be variable. A few of these substances have been synthesized previously by a different method.[5]

The anilino alcohols are prepared by condensing *o*- or *p*-nitrochlorobenzene with the appropriate amino alcohol in the presence of or without the presence of anhydrous sodium carbonate, or other neutralizing substance. Some of the amino alcohols employed were synthesized through the corresponding bromoalkylphthalimides. The time required for completion of the reaction decreased as the length of the carbon chain constituting the amino alcohol increased. For the lower members of the series, approximately six to eight hours were required, while the more complex alcohols took only from two to four hours.

The nitroanilino preparations varied in color from reddish-orange to yellow. They were reduced to the amino derivatives either by the use of tin and concentrated hydrochloric acid or with sodium hydrosulfite in a weakly alkaline solution. All the reduced products were white, altering more or less rapidly on standing. Some of the free bases were so unstable that they could only be isolated as the hydrochlorides.

One of the reduced compounds, 2-(*o*-aminoanilino)-ethanol, produced intense irritation of the nasal mucosa. A crystal of the substance if crushed between the fingers and inhaled would produce sneezing spells of many minutes duration. This property was not lost even after conversion of the free base into its hydrochloride.

In the reduction of 3-(*o*-nitroanilino)-2-methylpropanol-2 with tin and hydrochloric acid, a peculiar reaction was observed. Whereas only clear, colorless solutions had been obtained in all other instances, in this case there was formed in addition a heavy, viscous oil of intensely disagreeable odor. It is possible that this substance is produced through a ring closure reaction. There is also the possibility of hydramine cleavage occurring. The oil exhibits interesting properties and will be investigated further.

Along with the nitroanilino compounds obtained in the primary reaction, there were also isolated a number of reduction products. The reducing ability of the amino alcohols employed has been reported earlier.[6] Practically no reduction occurred with the butanolamines or pentanolamines. The reduced products were mainly *o*- or *p*-chloroaniline, although in several cases appreciable amounts of azo material were isolated.

Experimental

Preparation of Bromoalkylphthalimides

These were prepared through the Gabriel synthesis[7] with certain modifications. Trimethylene and pentamethylene bromides were made according to directions given in "Organic Syntheses."[8]

γ-Bromopropylphthalimide.—Four hundred and eighty-five grams of trimethylene bromide and 150 g. of potassium phthalimide were refluxed with mechanical stirring on an oil-bath at 190–200° for twelve hours. The excess bromide was distilled off under reduced pressure (the bromide comes over at 80–85° under a pressure of approximately 40 mm.) and the solid residue, consisting of bromopropylphthalimide, a small amount of diphthalimido propane and potassium bromide was extracted with 300 cc. of absolute ethyl alcohol. A second extraction with 200 cc. of the alcohol materially increases the final yield. On cooling, the alcohol solution deposits a crystalline mass which is filtered off and dried. The dried material was refluxed with 600 cc. of carbon disulfide and the insoluble diphthalimidopropane filtered off. The carbon disulfide was distilled off under reduced pressure, leaving a residue of very light tan crystals of bromopropyl phthalimide, m. p. 72–73°.

ε-Bromopentylphthalimide.—Two hundred and fifty grams of pentamethylene bromide and 60 g. of potassium

(3) Hartung, Munch and Kester, THIS JOURNAL, **54**, 1526 (1932).
(4) Horne, Cox and Shriner, *ibid.*, **55**, 3435 (1933).
(5) Von Braun and Kirschbaum, *Ber.*, **52B**, 2011 (1919).
(6) Kremer and Kress, THIS JOURNAL, **60**, 1031 (1938).
(7) Gabriel, *Ber.*, **21**, 2671 (1888).
(8) "Organic Syntheses," Coll. Vol. I, 1932, pp. 28, 419.

TABLE I

NITROANILINO ALKANOLS

Compound	Yield, %	Cryst. from	M. p., °C.[a]	Mol. formula	Nitrogen, % Calcd.	Found
2-(*o*-Nitroanilino)-ethanol	60	Chlorobenzene	76–76.5	$C_8H_{10}O_3N_2$	15.38	15.46
2-(*p*-Nitroanilino)-ethanol	20	Chlorobenzene	110–110.5	$C_8H_{10}O_3N_2$	15.38	15.64
3-(*o*-Nitroanilino)-propanol-1	80	Benzene	60.5–61	$C_9H_{12}O_3N_2$	14.28	14.22
3-(*p*-Nitroanilino)-propanol-1	80	Benzene	74–74.5	$C_9H_{12}O_3N_2$	14.28	14.23
3-(*o*-Nitroanilino)-propanol-2	55	Water	67.5–68.5	$C_9H_{12}O_3N_2$	14.28	14.19
3-(*p*-Nitroanilino)-propanol-2	20	Benzene	85.5–86	$C_9H_{12}O_3N_2$	14.28	14.38
3-(*o*-Nitroanilino)-2-methyl-propanol-2	90	Benzene	80–80.5	$C_{10}H_{14}O_3N_2$	13.33	13.48
3-(*p*-Nitroanilino)-2-methyl-propanol-2	85	Benzene	114–114.5	$C_{10}H_{14}O_3N_2$	13.33	13.38
5-(*o*-Nitroanilino)-pentanol-1	90	...	B. p. 200–201° (1 mm.)	$C_{11}H_{16}O_3N_2$	12.49	12.65

[a] All melting points are corrected.

phthalimide were treated as described above. An alternate method for removing the excess bromide is to steam distil the reaction mixture. This is preferable to distillation under reduced pressure as it is difficult to remove the bromide completely by vacuum distillation. The heavy oil resulting is taken up in ether (ethyl), the solution filtered and dried over anhydrous sodium sulfate. The ether is distilled off, leaving a heavy red-brown oil which solidifies on standing to a tan crystalline mass; yield about 75%.

Preparation of Amino Alcohols

The 2-hydroxy-2-methylpropylamine was obtained from the Shell Development Company.

The 2-hydroxypropylamine was purchased from Eastman Kodak Company.

3-Hydroxypropylamine and 5-hydroxypentylamine were obtained by hydrolysis of the corresponding Gabriel compounds. With slight modifications, the procedure is that developed by Putokhin.[9]

3-Hydroxypropylamine.—Eighty grams of γ-bromopropylphthalimide is added to 500 cc. of a 20% potassium hydroxide solution and the mixture refluxed for one hour. The solution is then distilled using a Widmer fractionating column and the first 300 cc. of distillate discarded. The column is removed and distillation continued to dryness. The residue is treated with 50 cc. of water and distilled again to dryness. This is repeated a second time. Approximately 300 cc. of the joint distillates is then fractionated using the Widmer column. When the temperature rises to about 180°, the column is removed and the amino alcohol is then distilled over between 185–186°; yield about 85%.

5 - Hydroxypentylamine.—ε - Bromopentylphthalimide when treated as described above for the propyl compound results in the corresponding amino alcohol. The yield was somewhat lower, the best run approximating 60%. The alcohol boils at 270–271°.

Preparation of the Substituted Anilino Alkanols

Condensations in the Presence of Sodium Carbonate.—The general procedure was to reflux, with stirring, molar quantities of the chloronitrobenzene and the amino alcohol in the presence of two moles of anhydrous sodium carbonate. Heating was carried out for a period of approximately six to eight hours after which the reaction mixture was steam distilled to remove reduction products and unreacted chloronitrobenzene. With the exception of the pentanol derivative, the anilino alkanols settled out as oils in the distillation flask and on cooling, solidified. The solid product was then recrystallized from the appropriate solvent as given in Table I. Condensations with 5-hydroxypentylamine required a much shorter period of heating, averaging about three hours. If the period of heating was much extended, tars were the main products.

Condensations without Added Alkali.—These were carried out practically as described above, with the exception that two moles of the amino alcohol were refluxed with one mole of the chloronitrobenzene.

Reductions with Tin and Hydrochloric Acid.—The nitro compound was dissolved in concentrated hydrochloric acid and excess mossy tin added. The mixture was refluxed for one hour, the excess tin removed, the solution made strongly alkaline with sodium hydroxide and then filtered. The filtrate was extracted with ether (ethyl) and the solid residue, with hot benzene. Evaporation of the solvents left residues of the white reduction product which were combined and recrystallized. Several of the reduced para compounds were too unstable to be isolated as free bases.

In the reduction of 3-(*o*-nitroanilino)-2-methylpropanol-2, unexpected results were obtained. Five grams of this compound was treated with tin and hydrochloric acid and refluxed for one hour. A dark viscous oil separated out. This was separated from the water layer and the latter, after the usual treatment to rid of tin, was extracted with ether (ethyl). Upon evaporation of the ether, a white crystalline solid remained which melted at 98–99°. Calculated % N for 3-(*o*-aminoanilino)-2-methylpropanol-2, 15.54; N found, 24.84. It is obvious that the product obtained is not the expected compound.

Reduction with Sodium Hydrosulfite.—Approximately 1.5 g. of the nitro compound was suspended in 20 g. of water and a pellet of potassium hydroxide added. The mixture was heated to boiling and powdered sodium hydrosulfite added in small portions until the solution became permanently decolorized. Upon cooling, the reduced product separates out. The amino anilino compounds are given in Table II.

Preparation of the Hydrochlorides

With Anhydrous Hydrogen Chloride in Ether.—The procedure followed depended upon whether the amino anilino compound was stable or not. If the free base was stable, it was dissolved in dry ether and the hydrochloride

(9) Putokhin, *Trans. Inst. Pure Chem. Reagents (Moscow)*, No. 6, 10–21 (1927); through *C. A.* **23**, 2938 (1929).

TABLE II

AMINOANILINO ALKANOLS

Compound	Yield, %	Cryst. from	M. p., °C.[a]	Mol. formula	Nitrogen, % Calcd.	Found
2-(*o*-Aminoanilino)-ethanol	90	Benzene	106–106.5	$C_8H_{12}ON_2$	18.42	18.28
2-(*o*-Aminoanilino)-ethanol·HCl	45	Abs. ethanol	144.5–145.5	$C_8H_{14}ON_2Cl$	14.85	14.69
2-(*p*-Aminoanilino)-ethanol·HCl	10	Abs. ethanol	198–199(d)	$C_8H_{14}ON_2Cl$	14.85	14.67
3-(*o*-Aminoanilino)-propanol-1	80	Benzene	65.5–66	$C_9H_{14}ON_2$	16.85	16.74
3-(*o*-Aminoanilino)-propanol-1·HCl	40	Abs. ethanol	146.5–147	$C_9H_{16}ON_2Cl$	13.82	13.94
3-(*o*-Aminoanilino)-propanol-2	60	Benzene	85.5–86.5	$C_9H_{14}ON_2$	16.85	16.60
3-(*p*-Aminoanilino)-2-methyl-propanol-2	60	Benzene	107.5–108	$C_{10}H_{16}ON_2$	15.54	15.63
5-(*o*-Aminoanilino)-pentanol-1	80		[b]	$C_{11}H_{18}ON_2$	14.42	

[a] Melting points are corrected. [b] Material decomposed on distillation. An impure fraction distilled over at 163–165° (2 mm.).

precipitated by passing in dry hydrogen chloride gas. Where the free base was unstable, the nitro compound was reduced as described and the entire alkaline mixture extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then treated with dry hydrogen chloride.

The hydrochlorides were precipitated as white crystalline products in all cases. On filtering away from the ether and exposing the compounds to air, a peculiar behavior was noted. The hydrochlorides appeared to deliquesce, at the same time undergoing an effervescent reaction with bubbles of gas being blown up from the surface. After a period of time this action ceased and the materials dried up to somewhat colored, no longer deliquescent, solids. These can be recrystallized from absolute ethanol and analyze for the monohydrochlorides.

What apparently occurs here is that the dihydrochlorides are first precipitated in the ether solution; but on exposure to air, one molecule of hydrogen chloride escapes leaving the stable monohydrochloride. The hydrochlorides are included in Table II.

Summary

A new series of N-(*o*-amino- and *p*-aminophenyl)alkanolamines has been prepared by reduction of the corresponding nitro compounds resulting from the condensation of *o*- and *p*-nitrochlorobenzene with a series of amino alcohols. These compounds and their derivatives are of interest because of possible pressor and local anesthetic action.

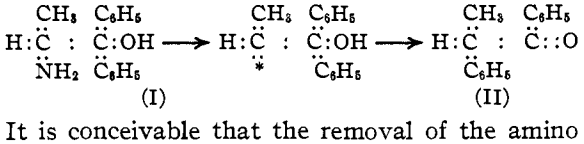
NEW YORK, N. Y. RECEIVED MARCH 8, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Common Basis of Intramolecular Rearrangements. V.[1] Inversion of Configuration in Semipinacolic Deamination. The Configurational Relationship between (+)-Alanine and (+)-Methylphenylacetic Acid

BY HERBERT I. BERNSTEIN AND FRANK C. WHITMORE

Semipinacolic deamination may take place as follows[1]



(I) (II)

It is conceivable that the removal of the amino group and the shift of phenyl may be essentially simultaneous. Evidence for this is the fact that the optically active aminoalcohol I gives the ketone II in optically active form.[2] If the indicated intermediate existed independently, the three groups around the electronically deficient carbon could occupy a single plane and racemization would seem inevitable. We decided to study this change in order to find out whether the shifting phenyl group actually takes the place of the removed amino group or takes part in a Walden inversion by approaching the back of the adjacent carbon atom, the front being considered as the corner holding the amino group. In the case of the ordinary pinacolic rearrangement the group removed is the hydroxyl group. The general case may be represented as follows: X being the group removed with a complete octet of electrons, thus leaving the carbon with only six electrons (C*). The two possible ways for a group to shift with its complete octet to the electronically deficient carbon would then be

(1) *Cf.* Whitmore, THIS JOURNAL, **54**, 3274 (1932); **60**, 2002 (1938).

(2) (a) McKenzie, Roger and Wills, *J. Chem. Soc.*, 779 (1926); (b) McKenzie and Dennler, *Ber.*, **60**, 220 (1927); (c) Roger and McKenzie, *ibid.*, **62**, 272 (1929).