[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Preparation of Aminobenzoic Acid Esters of Substituted Monoalkylamino Alcohols[1]

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In previous papers, the preparation[2] and the pharmacological properties[3] of two new series of anesthetic compounds were described.

The result of the pharmacological work on these compounds suggested the investigation of the properties of a series of esters in which the side chain was limited to two carbon atoms, one carbon atom carrying two alkyl substituents, thus forming a branched side chain.

The preparation of a series of β-alkylamino-α,α-dimethylethanols, $HOC(CH_3)_2CH_2NHR$, where R represents an alkyl group, was therefore undertaken.

The preparation of these amino alcohols required the use of β-chloro-α,α-dimethylethanol which was synthesized according to the methods of Krassuski[4] and Michael and Leighton,[5] using the addition of hypochlorous acid to isobutylene.

The β-chloro-α,α-dimethylethanol together with an excess of a primary amine in a suitable solvent was refluxed for several hours and then carefully fractionated. The average yield of β-alkylamino-α,α-dimethylethanol was 52%.

The *p*-nitrobenzoic acid esters of the amino alcohols were obtained through the condensation of the amino alcohols with *p*-nitrobenzoyl chloride in an aqueous alkaline medium. The temperature of this reaction must be maintained between 30 to 40° for optimum yields. The nitro esters are all yellow solids.

These nitro esters were reduced with tin and hydrochloric acid to the anesthetic amino bases.

The hydrochlorides of the higher members of the series of the amino bases were in all cases very viscous yellow oils; the sulfates, on the other hand, were all white crystalline solids.

Two members of another series of amino alcohols were prepared utilizing the reaction between a Grignard reagent and a chloro ester[6] or a chloro ketone.[7,8] With ethylmagnesium iodide there is obtained β-chloro-α,α-diethylethanol which on reacting with *n*-butyl- and *i*-butylamines yields the corresponding amino alcohols.

When methylmagnesium iodide is used, these two methods of preparation serve as alternative methods for making β-chloro-α,α-dimethylethanol.

Experimental

β-Ethylamino-α,α-dimethylethanol, $HOC(CH_3)_2CH_2NHC_2H_5$.—In a 250-cc. pressure bottle was placed 31.4 g. (0.23 mole) of a 33% aqueous solution of monoethylamine and 100 cc. of water. To this was added 20 g. (0.18 mole) of β-chloro-α,α-dimethylethanol, the bottle immediately stoppered and shaken occasionally during the next twenty-four hours. The reaction mixture was treated with solid sodium hydroxide and cooled, the upper layer extracted with ether, the ether layer separated and dried over anhydrous sodium sulfate. The ether was evaporated and the residue distilled. Two fractionations of the distillate gave 12 g. (56%) of a water-white liquid with a slight ammoniacal odor, boiling at 152–153°.

Preparation of the Other Members of this Series.—The preparations of the β-methyl- and β-ethylamino-α,α-dimethylethanols were carried out as described above. The higher members of this series of amino alcohols, namely, the β-*n*-propyl-, β-*i*-propyl-, β-*n*-butyl-, β-*i*-butyl-, β-*n*-amyl- and β-*i*-amylamino-α,α-dimethylethanols were prepared in a slightly different manner. 95% ethyl alcohol was used as a solvent for the reactants and the mixtures refluxed from three to twenty-four hours. The reaction mixture was acidified with concentrated hydrochloric acid and vacuum distilled almost to dryness. To the cold residue in the flask was added cold 30% sodium hydroxide solution and the same procedure used for the purification.

In Table I are summarized the physical constants of this series of amino alcohols, the molecular refraction (using Eisenlohr's[9] atomic refraction values) and the analyses of the picrates. The picrates were crystallized from either benzene or xylene.

The nitro esters are prepared by condensing the amino alcohols with *p*-nitrobenzoyl chloride as follows:

β-*i*-Butylamino-α-dimethylethyl *p*-Nitrobenzoate, (iso)-$C_4H_9NHCH_2C(CH_3)_2COOC_6H_4NO_2$.—To 10 g. (0.039 mole) of β-isobutylamino-α,α-dimethylethanol and 5 g. of sodium hydroxide in 250 cc. of water was added with stirring 13 g. (0.07 mole) of powdered *p*-nitrobenzoyl chloride in one amount. The temperature of the reaction was controlled so that it did not go above 40°. An oil was soon formed which finally solidified after one-half

(1) Submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, June, 1936, by William F. Ringk.

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(4) K. Krassuski, *J. prakt. Chem.*, [2] **75**, 241 (1907).

(5) A. Michael and V. L. Leighton, *Ber.*, **39**, 2157 (1906); *J. prakt. Chem.*, [2] **64**, 103 (1901).

(6) E. Susskind, *Ber.*, **39**, 225 (1906)

(7) Tiffeneau, *Compt. rend.*, **134**, 775 (1902).

(8) Henry, *ibid.*, **142**, 131, 494 (1906); *Rec. trav. chim.*, **26**, 149 (1906).

(9) Eisenlohr, *Z. physik. Chem.*, **75**, 585 (1910); **83**, 429 (1914).

TABLE I

β-ALKYLAMINO-α,α-DIMETHYLETHANOLS ($RHNCH_2C(CH_3)_2OH$)

Alkyl group	B. p., °C.	Sp. gr.	$n^{20}D$	M. p. of picrates, °C.	M_R Calcd.	M_R Found	Formula	Analyses of picrates Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Methyl	142–143	0.8875^{23}	1.4338	137–138	30.361	30.212	$C_{11}H_{16}O_8N_4$	39.76	39.87	4.82	4.84
Ethyl	152–153	$.8777^{19}$	1.4344	132–133	34.979	34.742	$C_{12}H_{18}O_8N_4$	41.62	41.81	5.20	5.41
n-Propyl	169–171	$.8646^{19}$	1.4335	128–129	39.597	39.417	$C_{13}H_{20}O_8N_4$	43.33	43.18	5.56	5.69
i-Propyl	158–160	$.8528^{19}$	1.4288	166–167	39.597	39.586	$C_{13}H_{20}O_8N_4$	43.33	43.22	5.56	5.54
n-Butyl	186–187	$.8586^{20}$	1.4362	121.5–122.5	44.215	44.175	$C_{14}H_{22}O_8N_4$	44.92	45.01	5.88	5.97
i-Butyl	180–181	$.8490^{20}$	1.4309	138–139	44.215	44.201	$C_{14}H_{22}O_8N_4$	44.92	44.68	5.88	6.22
n-Amyl	205–208	$.8543^{20}$	1.4388	109–110	48.833	48.933	$C_{15}H_{24}O_8N_4$	46.39	46.53	6.19	6.29
i-Amyl	202–204	$.8580^{19}$	1.4380	145–146	48.833	48.645	$C_{15}H_{24}O_8N_4$	46.39	46.56	6.19	6.45
β-Alkylamino-α,α-diethylethanols ($RHNCH_2C(C_2H_5)_2OH$)											
n-Butyl	216–220	0.8629^{26}	1.4433 at 23 °C.	127–128	53.451	53.182	$C_{16}H_{26}O_8N_4$	47.76	47.87	6.47	6.68
i-Butyl	214–216	$.8621^{26}$	1.4410	130.5–131.5	53.451	52.973	$C_{16}H_{26}O_8N_4$	47.76	47.91	6.47	6.70

TABLE II

β-ALKYLAMINO-α-DIMETHYLETHYL *p*-NITRO- AND *p*-AMINOBENZOATES

Alkyl group	Nitro esters, m. p., °C.	Amino esters, m. p., °C.	Amino ester sulfates m. p., °C.	Formula	Analyses of sulfates Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
n-Propyl-	108–109	123–124	138–140 150–153	$C_{28}H_{46}O_8N_4S$	56.19	56.37	7.69	7.94	9.36	9.16
n-Butyl-	87–88	116–119	$1H_2O$ Cryst.	$C_{30}H_{52}O_9N_4S$	55.91	56.14	8.07	8.43	8.37	8.19
i-Butyl-	130–131	83.5–84.5	142–143 158.5–159.5	$C_{30}H_{50}O_8N_4S$	57.51	57.39	7.99	8.39	8.95	8.81
n-Amyl-	107–109	93–95	Anhyd. 163–166 $1H_2O$	$C_{32}H_{54}O_8N_4S$	58.72	58.77	8.26	8.23	8.56	8.46
i-Amyl-	112–113	Oil	146–148	$C_{32}H_{54}O_8N_4S$	58.72	57.81	8.26	9.02	8.56	7.82
β-Alkylamino-α-diethylethyl *p*-Nitro- and *p*-Aminobenzoates										
i-Butyl-	.....	122–123	131–133	$C_{34}H_{62}O_8N_4S$	59.46	59.63	9.04	9.29	8.16	8.03

hour of stirring. The solid nitro ester was filtered off and washed with water until free of alkali. The nitro ester was recrystallized from benzene, m. p. 130–131°. The solid nitro ester was then reduced with tin and hydrochloric acid in the usual manner.

All of the esters were made similarly. In Table II are given the constants of the nitro and amino esters, as well as the analyses of the amino ester sulfates.

Pharmacology.—A preliminary pharmacological investigation of the sulfates of the β-*n*-propyl-, β-*n*-butyl, β-*i*-butyl-, and β-*n*-amyl-amino-α-dimethylethyl *p*-aminobenzoates was carried out. As a result of this investigation it was found that this series of anesthetics apparently was too toxic for injection purposes. However, the β-*n*-amyl derivative showed surface anesthetic activity to a high degree and was therefore tested further.[10]

Table III summarizes the toxicity tests of the sulfate of β-*n*-amylamino-α-dimethylethyl *p*-amino benzoate (abbreviated to *n*-amyl sulfate), Cocaine and Butyn.

In an anesthetized dog, *n*-amyl sulfate causes a slight reduction in blood pressure and a slight increase in pulse rate upon intravenous injection of a 1% solution. The intravenous toxicity for dogs is 20 mg./kg.

TABLE III

SUBCUTANEOUS TOXICITY

Compd.	Concn., %	Animal	No. of animals	M. L. D. mg./kg.	% died at M. L. D. indicated
n-Amyl sulfate	1	White mice	64	45	10
Cocaine	1	White mice	41	75–100	0–18
Cocaine	4	White mice	19	100–150	0–25
Butyn	1	White mice	26	25–50	0–12.5
Butyn	5	White mice	26	Approx. 50	14
n-Amyl sulfate	1	Guinea pigs	43	35–40	0–27
Intravenous Toxicity					
n-Amyl sulfate	1	White mice	9	10–15	0–100

Corneal anesthesia in the rabbit's eye, using a 1% *n*-amyl sulfate solution, a 4% cocaine solution and a 2% butyn solution produces anesthesia averaging eighty-seven, sixty-six and seventy-nine minutes, respectively, when from one to five drops of the solution are instilled into the rabbit's eyes. Immediate anesthesia was produced in all cases and no demonstrable irritations found in any treated eye. *n*-Amyl sulfate caused practically no mydriasis and no corneal erosion. Application of one drop of a 1% solution of *n*-amyl sulfate to the cornea of the rabbit's eye produces anesthesia last-

(10) We are indebted to Dr. Donald C. A. Butts of Philadelphia for the pharmacological investigation of this compound.

ing forty-three minutes while a 0.05% (1:2000) solution anesthetizes for six minutes. *n*-Amyl sulfate does not alter the intraocular tension of the rabbit's eye when used in 1% concentrations.

Summary

A series of new β-alkylamino-α,α-dimethylethanols has been prepared.

From these alcohols, as well as two β-alkylamino-α,α-diethylethanols, by combination with *p*-nitrobenzoyl chloride and reduction, there has been prepared a series of new esters.

A pharmacological study of one ester shows it to have interesting surface anesthetic properties.

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Nickel as a Catalyst for the Hydrogenation of Aromatic Halogen Compounds

BY CHARLES F. WINANS*

The catalytic hydrogenation of *o*-nitrochlorobenzene over nickel was first attempted by Sabatier and Mailhe[1] who, however, obtained aniline hydrochloride as a result of a combined hydrogenation and dehalogenation. Furthermore, Sabatier and Espel[2] found that small amounts of halogen compounds did not interfere with the vapor phase reduction of benzene provided that some nickel remained in catalytically active form after a portion had been converted to nickel halide in removing the impurity. The simultaneous hydrogenation and dehalogenation of organic compounds has been effected by several workers[3] using platinum and palladium catalysts, and certain others have effected hydrogenation without the removal of halogen. Ellis[4] describes the preparation of a reduced nickel catalyst suitable for the production of chlorinated aromatic amines from the corresponding nitro compounds. Strangely, very little has appeared in the recent literature concerning the use of nickel for the hydrogenation of halogen compounds. The present paper attempts to demonstrate that the hydrogenation of these compounds is a general reaction which is applicable in an efficient and economical process.

The success of this conversion depends upon the choice of a stable halide, the use of a temperature below that at which dehalogenation occurs, and the use of a catalyst with sufficient mass of metal. These conditions have been met in the hydrogenation of aromatic halogen compounds at temperatures below 150° with Raney[5] nickel.

The substituents reducible below 150° which may be attached to the halogenated aromatic nucleus include the olefinic, acetylenic, nitro, nitroso, cyano, oximino, azido, azo, and carbonyl groups. Anils and hydro-amides may also be treated. It has not been possible to hydrogenate chlorobenzene to chlorocyclohexane, for at the temperature required to saturate the benzenoid ring halogen was removed giving rise to benzene in small amounts. Benzyl chloride gave some diphenylethane under similar conditions. In the aliphatic series 1-chloropropene, ω-chlorostyrene, *sym*-dichloroethylene, and tetrachloroethylene resisted saturation of the olefin bond.

The accompanying table gives the names of hydrogen acceptors and reaction products with physical properties and yields for fourteen different halogen compounds illustrating the behavior of several types. Most of the products were distilled from the reaction mixture. Others were obtained in crystalline form as solid product or hydrochloride derivative. All products were identified by the formation of known characteristic derivatives or by analysis.

The relative strength of attachment of chlorine, bromine, and iodine to the aromatic nucleus was demonstrated in the reduction of the halogenated nitrobenzenes. *p*-Chloronitrobenzene gave rise to *p*-chloroaniline even at 150° in nearly quantitative yield. *p*-Bromonitrobenzene was not quite so stable, but still the predominant product was *p*-bromaniline. *o*-Iodonitrobenzene was largely dehalogenated during reduction to aniline, only a small amount of *o*-iodoaniline being isolated from

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(1) Sabatier and Mailhe, *Compt. rend.*, **138**, 245 (1904).

(2) Sabatier and Espel, *Bull. soc. chim.*, **15**, 778 (1914).

(3) For a complete résumé of the prior work in hydrogenation of organic halogen compounds, see Ellis, "Hydrogenation of Organic Substances," 3d. ed., D. Van Nostrand Co., Inc., New York, N. Y., 1930.

(4) Page 259 of Reference 3.

(5) Murray Raney, U. S. Patent 1,628,190, May 10, 1927.