marily in a marked increase in toxicity with only a minor increase in activity. In the case of the diphenyl sulfide ester the toxicity is likewise greater than that of its dibenzothiophene analog, although in this instance the anesthetic potency is substantially enhanced both as to duration and quality.

None of these compounds had a mydriatic action in the concentrations used, whereas they all caused more or less irritation of the cornea and conjunctiva, the extent of the damage depending on the concentration. The pathological changes were conjunctivitis, chemosis, opacity of the cornea and intense secretion with consequent ectropion.

Effect on Blood Pressure and Respiration.—The action on blood pressure and respiration was determined for compounds no. 1, 8 and 12 by intravenous injection of 5 mg./kg. in dogs anesthetized with ether or without anesthesia. All three drugs caused depression of respiration and a sharp fall in blood pressure, the latter effect being only slightly diminished by the addition of epinephrine.

Action on Human Skin.—The anesthetic action of five of these compounds was further examined by means of wheal experiments on human skin under aseptic conditions. The solutions were prepared so as to contain 0.9% sodium chloride and a concentration of epinephrine of 1:250,000. Two-tenths cc. of this solution was used for intracutaneous injection. The duration, quality of anesthesia and side effects were observed and compared with procaine.

The same relative order of activity as was observed in the corneal studies is maintained in this instance. The unusual duration of compound 8 is worthy of note. As might have been predicted from the experiments on the rabbit cornea each of the compounds thus examined was more or less irritating and painful on injection.

The irritating effects of the entire group of compounds appear to be inherent to the nucleus involved, since meticulous purification, variation of the substituent groups and changing the method of synthesis does not materially alter the situation.

Acknowledgment.—The authors wish to express their appreciation to Mr. John W. Cusic for assistance with some of the experimental work.

Summary

The investigation of a series of alkylaminoalkyl esters of carbazole-, dibenzofuran- and dibenzothiophenecarboxylic acids led to some powerful local anesthetics. The best one of the series is β-diethylaminoethyl 5-ethylcarbazole-3-carboxylate hydrochloride (no. 8), which is more than thrice as potent as cocaine and only one-fifth as toxic. The activity of these compounds appears to be predominantly a function of the position of the carboxyl group rather than other structural variations. Opening of the carbon–carbon bridge in the dibenzofuran and dibenzothiophene derivatives does not improve the therapeutic efficiency. All of these compounds were more or less irritating to the rabbit's eye and to human skin, so that they cannot be regarded as useful anesthetics.

CHICAGO, ILLINOIS
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CALCO CHEMICAL DIVISION, AMERICAN CYANAMID CO.]

Sulfanilamide Derivatives. VI. Substituted N^1-Aliphatic Sulfanilamides[1]

BY M. L. CROSSLEY, E. H. NORTHEY AND M. E. HULTQUIST

A number of N^1-alkyl and hydroxyalkylsulfanilamides have been prepared by Kharasch, Mietzsch, Fourneau, Bauer and others.[2,3,4,5] As part of our program on N^1-substituted sulfanilamides, we have independently synthesized many of the derivatives reported by these authors, as well as a number of others which have not hitherto been published to our knowledge. The latter are sulfanilyl derivatives of aliphatic amines, amino-alcohols, diamino-alcohols, and amino-acids. Closely allied derivatives of morpholine and difurfurylamine are included.

The syntheses of these derivatives followed the

(1) Presented in part before the Division of Medicinal Chemistry, A. C. S., September, 1939.

(2) M. S. Kharasch and O. Reinmuth, U. S. Patents 2,097,414, and 2,097,415, October 26, 1937.

(3) F. Mietzsch and J. Klarer, U. S. Patent 2,085,037, June 29, 1937.

(4) E. Fourneau, J. and Mme. J. Trefouel, F. Nitti and D. Bovet, *Compt. rend. soc. biol.*, **122**, 258 (1936).

(5) S. M. Rosenthal, H. Bauer and S. E. Branham, *Public Health Reports, U. S. Treas. Dept.*, **52**, 662 (1937).

TABLE I

Name	Crystallized from	Crystalline form	Melting range, °C.	Calcd. mol. wt.	Assay by $NaNO_2$ Calcd.	Found
N^1-*n*-Octylsulfanilamide	Alcohol	Long prisms	114–119.5	284.4	N, 9.86	9.87
N^1-*n*-Dodecylsulfanilamide	Toluene	Leaves	118–124	340.5	N, 8.23	8.40
N^1-*n*-Octadecylsulfanilamide	60% alc.	Leaves	127–130	456.7	N, 6.13	6.06
N^1-(9-Octadecenyl)-sulfanilamide	60% alc.	Needles	118–122.5	454.7	N, 6.16	6.22
1,2-*bis*-Sulfanilamidoethane	H_2O as Na salt	Crystalline powder	229.4–231.2	370.2	99.9	
1,2-*bis*(N^4-Sulfanilylsulfanilamido)-ethane	60% acetone	Prisms	>118 dec.	680.8	100.6	
N^1,N^1-*bis*(2-Sulfanilamidoethyl)-sulfanilamide trihydrochloride	Water	Crystalline powder	241.5–244	678.1	99.4	
N^1-Methyl-N^1-2-hydroxyethyl sulfanilamide	Water	Prisms	124.5–126.3	230.2	100.2	
2-Methyl-2-sulfanilamido-1-propanol	95% alc.	Prisms	154–155.8	242.3	99.6	
2-Methyl-2-sulfanilamido-1,3-propanediol	95% alc.	Prisms	131.8–134.0	260.3	100.3	
1,3-*bis*-Sulfanilamido-2-propanol	50% alc.	Fine needles	184.2–186.5	400.3	100.0	
N^1-2-Hydroxyethyl-N^1-(2-sulfanilamidoethyl)-sulfanilamide	50% alc.	Short prisms	163.0–164.5	414.5	100.3	
N^1,N^1-Difurfurylsulfanilamide	95% alc.	Needles	134.0–136.5	334.38	99.0	
N-(2-Sulfanilamidoethyl)-morpholine	20% alc.	Needles	98–100.4	285.3	100.1	
Ethyl N-sulfanilylglycinate	30% alc.	Needles	90.4–92.0	258.2	100.3	
Di-*n*-butyl-N-sulfanilylglutamate hydrochloride	Dioxane–ether	Crystalline powder	138.4–141.6	451.0	100.2	
2-Sulfanilamidoethyl dodecanoate	60% alc.	Prisms	63.4–64.8	398.5	100.3	

general procedure used previously[6] except in the case of the amino-acid ester derivatives. The N-sulfanilylamino acids were first prepared.[7] These were then esterified by boiling with the corresponding alcohol in the presence of hydrogen chloride. Di-*n*-butyl-N-sulfanilylglutamate was difficult to crystallize, so was isolated and recrystallized as the hydrochloride.

Pharmacology.—The long chain N^1-alkylsulfanilamides were prepared with the object of obtaining lipoid solubility. The promising pharmacological properties of N^1-dodecanoylsulfanilamide[8] made the investigation of other lipoid soluble derivatives of particular interest. The available results indicate that the long chain N^1-alkylsulfanilamides are decidedly inferior to the corresponding N^1-acylsulfanilamides on experimental streptococcal infections in mice.

The derivatives of amino-alcohols, amino-acid esters and morpholine appeared to be almost inactive while the difurfurylamine derivative was toxic. The esters were also inactive.

The pharmacological work was done under the direction of D. R. Climenko and will be reported elsewhere.

Experimental

2-Sulfanilamidoethyl Dodecanoate.—4-Nitrobenzenesulfonyl chloride was heated with excess aqueous 2-hydroxyethylamine and the product recrystallized from 50% alcohol giving N-2-hydroxyethyl-4-nitrobenzenesulfonamide, m. p. 126–127°; 41 g. (0.166 mole) of this was dissolved in 40 cc. of pyridine at 80° and 40 g. of dodecanoyl chloride was added gradually at 90–100°. The temperature was maintained for twenty min., then the hot mixture was poured into 500 cc. of water. The product was recrystallized from 80% alcohol, giving 78.4 g. of yellow crystals of 4-nitrobenzenesulfonamidoethyl dodecanoate, m. p. 72.0–73.5°. The nitro group was reduced by adding a solution of the compound in 100 cc. of toluene to a hot mixture of 60 g. of iron powder, 200 cc. of water, and 4 cc. of hydrochloric acid, then boiling for fifteen hours under agitation. The mixture was neutralized to *p*H 8, filtered, and the cake washed with hot toluene. The toluene layer was dried over calcium chloride and distilled under reduced pressure. The residue was taken up in 60% alcohol and recrystallized three times, using activated charcoal.

Intermediates for this series were obtained as follows: "Lorolamine" from E. I. du Pont de Nemours & Company was fractionated giving *n*-octylamine, b. p. 183–188° (770 mm.), and *n*-dodecylamine, 135.5–138.5° (15 mm.), setting point 26.5°. *n*-Octadecylamine and 9-octadecenylamine were obtained from Armour & Company, and were used without purification. β-Hydroxyethylamine, ethylenediamine, diethylenetriamine and N-(β-hydroxyethyl)-ethylenediamine were obtained from Carbide & Carbon Chemical Corp. and were used without purification. Difurfurylamine was obtained from the B. F. Goodrich Tire & Rubber Company. 2-Methyl-2-amino-1-propanol and 2-methyl-2-amino-1,3-propanediol were obtained from Commercial Solvents Corp. 1,3-Diamino-2-propanol was obtained from Eastman Kodak Company. 4′-(2′-Aminoethyl)-morpholine was synthesized from ethylenediamine and *bis*-β-chloroethyl ether.[9]

Summary

1. Eighteen new sulfanilamide derivatives are reported. These are sulfanilyl derivatives of aliphatic amines, polyamines, amino alcohols, diamino alcohols and aminoacid esters. Closely allied derivatives of morpholine and difurfurylamine are included.

2. The available pharmacological results in-

(6) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938); see also for nomenclature.

(7) Hultquist, U. S. Patent 2,142,847, January 3, 1939.

(8) Crossley, Northey and Hultquist, THIS JOURNAL, **61**, 2950 (1939).

(9) Hultquist and Northey, *ibid.*, **62**, 447 (1940).

dicate that these compounds as a class are less effective than sulfanilamide against infections by beta hemolytic streptococci in mice.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY AND UNIVERSAL OIL PRODUCTS COMPANY]

The Electrolysis of Some Higher Aliphatic Organomagnesium Halides in Ethyl Ether

BY WARD V. EVANS, DAVID BRAITHWAITE AND EDMUND FIELD

The electrolysis studies of the simple organomagnesium halides have been completed.[1] These studies indicated that the main course of the reaction was the liberation of the organic free radical, which then reacted by disproportionation to give the corresponding saturated and unsaturated hydrocarbons. In the electrolysis of *n*-propylmagnesium halide in ethyl ether[1d] it was found, however, that there was a marked tendency for the liberated free radical to combine to give the coupled product *n*-hexane. The isopropylmagnesium halide, on the other hand, showed very little or no tendency to couple upon electrolysis.

The present work is a continuation of this problem, electrolyzing some higher organomagnesium halides in ethyl ether, and attempting thereby to further our knowledge of the coupling tendency. To accomplish this the four isomeric butyl compounds were studied, as well as the *n*-hexyl compound.

Experimental

The same apparatus that has previously been described was used,[1b] and platinum electrodes were employed throughout the investigation.

***n*-Butylmagnesium Bromide.**—In this electrolysis the solution conducted the electric current so readily that even at 0.4 to 0.5 ampere there was not sufficient heat generated to cause the solvent to reflux. Since refluxing was the sole means of agitation, there was no great amount of disturbance in this electrolysis, and consequently the magnesium plated out and often bridged the gap between the electrodes. For the most part this was avoided by shaking the cell, but it undoubtedly accounts for the low efficiency found.

It was noted, however, that gas was liberated when the gap between the electrodes had nearly been closed, whereas otherwise no gas was liberated. Samples of this gas at different current densities were taken, and the analyses, made by the absorption method, are shown in Table I. Change in current density had no effect on the composition of the gas over a small range.

A quantity of 0.72 mole of Grignard reagent was decomposed during the electrolysis, and the efficiency was approximately 65% based on the number of coulombs passed through the solution. On the basis of the amount of octane isolated experimentally, approximately 85% of the butyl radicals liberated coupled. Because of loss in isolating and purifying the octane, the actual amount of coupling must be approximately 100%.

Isobutylmagnesium Bromide.—As in the case of *n*-butylmagnesium bromide, no gas was liberated except when magnesium nearly bridged the gap between the electrodes. There was not sufficient gas to fractionate, and all that could be done with this small amount of gas was to determine that the saturated hydrocarbon gas in the mixture was essentially C_4.

A 500-cc. sample of the original organomagnesium halide (1.36 *N*) was hydrolyzed and analyzed. About 5 cc. of diisobutyl was found, indicating a slight coupling during the formation of the Grignard reagent.

The efficiency of this electrolysis was found to be about 83% based on the number of coulombs passed through the solution. After electrolysis, 500 cc. (0.6 *N*) was hydrolyzed and analyzed. No alcohols were found, but approximately 35 cc. of diisobutyl was present. During the electrolysis 0.78 equivalent of Grignard compound was decomposed. Therefore, on the basis of the amount of diisobutyl found, approximately 96% of the liberated isobutyl free radical coupled.

***s*-Butylmagnesium Bromide.**—No gas was liberated during this electrolysis.

A 500-cc. sample (1.35 *N*) of the original Grignard was hydrolyzed and analyzed before electrolysis. A 2-cc. portion of this solution was identified as the coupled product, 3,4-dimethylhexane.

On the basis of the amount of 3,4-dimethylhexane found on analyzing the solution after electrolysis, about 43% of the liberated free radical coupled. This would appear to be a poor yield of the coupled product, but considerable difficulty was encountered in the isolation of the product.

No alcohols were found.

On a second electrolysis of *s*-butylmagnesium bromide, the solution was prepared 0.588 *N* and 825 cc. electrolyzed until 0.165 equivalent had been decomposed. On the basis of the amount of coupled product isolated from the original solution and the electrolyzed solution, coupling took place to about 49%. In this experiment an external heater was used to keep the solution in the vicinity of the electrodes refluxing vigorously. This heater accomplished two things. It stopped the magnesium from bridging

(1) (a) Evans and Field, THIS JOURNAL, 58, 720 (1936); (b) Evans and Field, *ibid.*, 58, 2284 (1936); (c) Evans and Lee, *ibid.*, 56 654 (1934); (d) Evans and Braithwaite, *ibid.*, 61, 898 (1939).