TABLE I

N-ALKYLSACCHARIN DERIVATIVES

RX	Yield, %[a]	M.p., °C.[b]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Methyl iodide	94	131–132(132)[c]							
Ethyl bromide	70	93.5–94.5(94)							
n-Butyl chloride	52	39–40(38)							
s-Butyl chloride[d]	13	80–81(81)							
n-Heptyl iodide	40	37.5–38.5	$C_{14}H_{19}NO_3S$	59.75	59.52	6.80	6.71	4.98	4.79
n-Decyl bromide	59[h]	35–36	$C_{17}H_{25}NO_3S$	63.12	62.91	7.79	7.86	4.33	4.14
n-Undecyl bromide	16[h]	38.5–39.5	$C_{18}H_{27}NO_3S$	64.05	63.99	8.07	8.25	4.15	4.14
n-Dodecyl bromide	64	48–50(51)[e]							
n-Tetradecyl bromide	94	52.5–54.5	$C_{21}H_{33}NO_3S$	66.46	66.56	8.76	8.75	3.69	3.59
n-Hexadecyl bromide	90	63–65	$C_{23}H_{37}NO_3S$	67.80	67.66	9.15	9.15	3.43	3.47
n-Octadecyl bromide	86	68–71	$C_{25}H_{41}NO_3S$	68.95	69.21	9.49	9.56	3.21	3.12
β-Phenylethyl bromide	68	138–139[f]	$C_{15}H_{13}NO_3S$	62.72	62.66	4.56	4.65	4.87	4.93
Allyl chloride	66	89–90(94)[e]							
Benzyl chloride	92	110–111(111)							
o-Chlorobenzyl chloride	94	166–167	$C_{14}H_{10}ClNO_3S$	54.63	54.39	3.28	3.17	4.55	4.64
p-Chlorobenzyl chloride	95	157–159[g]	$C_{14}H_{10}ClNO_3S$	54.63	54.82	3.28	3.22	4.55	4.52

[a] Yields indicated are based on the crude product obtained unless otherwise stated. [b] Melting point of analytical sample; analytical samples were recrystallized three to six times from isopropyl alcohol unless otherwise stated. [c] Melting points in parentheses are those reported by Merritt, *et al.* (ref. 3) unless otherwise stated. [d] It had been reported (ref. 3) that a derivative could not be obtained with *s*-butyl chloride in accordance with the procedure given, although the bromide and iodide did furnish derivatives. [e] As reported by H. W. Arnold and N. E. Searle, U. S. Patent 2,462,835; *C. A.*, **43**, 4421 (1949). [f] Recrystallized from a mixture of petroleum ether (b.p. 30–50°) and acetone. [g] Recrystallized from a mixture of petroleum ether (b.p. 30–50°) and ethyl acetate. [h] Yield of once recrystallized material.

to vary from 6 to 35% for methyl, ethyl, *n*-butyl, allyl and benzyl derivatives when Butyl Carbitol was the solvent. Our yields for the preparation of the same derivatives varied from 52–94% (Table I). The saccharin derivative from *s*-butyl chloride had not been obtained using Butyl Carbitol as a solvent,[3] but it is easily prepared by the use of dimethylformamide.

An increase in the yield of N-alkylsaccharin derivatives was noticed by Merritt, *et al.*,[3] when potassium iodide was used in the reaction of sodium saccharin with alkyl chlorides. In our work sodium iodide also was found to bring about increased yields for all reactions involving alkyl chlorides.

The reaction is usually complete after 30 minutes when carried out at temperatures of from 90–150°. Derivatives could not be obtained from *t*-butyl bromide, cyclohexyl iodide, *p*-nitrobromobenzene, or N-bromosuccinimide. Isoamyl bromide, *n*-hexyl bromide, *n*-octyl bromide, and *n*-nonyl bromide give derivatives which did not crystallize from isopropyl alcohol. Longer chain halides gave saccharin derivatives which were difficult to purify. The clean, rapid reactions experienced with dimethylformamide do, however, make it possible to work with lower melting point derivatives with a minimum of difficulty. All derivatives prepared along with pertinent information have been recorded in Table I.

Experimental[10]

Preparation of N-Alkylsaccharin Derivatives. Procedure A. N-*n*-Decylsaccharin.—Sodium saccharin (11.0 g., 0.046 mole) was added to a solution of 5.0 g. (0.023 mole) of *n*-decyl bromide in 50 ml. of dimethylformamide contained in a round-bottomed flask fitted with a reflux condenser. The mixture was heated on a steam-bath for 30 minutes with occasional shaking. The mixture was diluted with water and extracted with several portions of chloroform. Evaporation of the chloroform, after drying over anhydrous sodium sulfate, produced a residue which was crystallized from isopropyl alcohol.

Procedure B. N-*o*-Chlorophenylsaccharin.—Fifteen grams (0.062 mole) of sodium saccharin and 9.3 g. (0.062 mole) of sodium iodide were added to a solution of 5.0 g. (0.031 mole) of *o*-chlorobenzyl chloride in 50 ml. of dimethylformamide. The mixture was heated on a steam-bath for 30 minutes.

Upon dilution with water a light yellow, crystalline product separated. The mixture was extracted with several portions of chloroform. The combined extracts were washed with sodium bisulfite to remove iodine, once with water, and then dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the chloroform was recrystallized from isopropyl alcohol.

The less reactive, normal and branched chained alkyl chlorides were found to give best yields when the reaction was carried out at 150°.

Acknowledgment.—The authors wish to express appreciation for suggestions offered by Dr. Gardner W. Stacy during a portion of this work. Appreciation is also extended to the Du Pont Co. for a generous quantity of dimethylformamide.

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(10) All melting points are corrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tennessee.

The Synthesis of N,N-Bis-(β-diethylaminoethyl)-amine and Some N-Substituted Alkanesulfonamides

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RECEIVED JUNE 26, 1953

A new and potentially useful amine intermediate, N,N-bis-(β-diethylaminoethyl)-amine, has been synthesized. The synthesis of this compound has led to the preparation of certain N-substituted alkanesulfonamides. In addition to sulfonamides that incorporate the above amine moiety, a number of other N-substituted alkanesulfonamides

TABLE I

N-SUBSTITUTED ALKANESULFONAMIDES

	Name	Yield, %	M.p.,[a,b] °C.	B.p.,[a] °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd.	Found
1	N,N-Bis-(β-diethylaminoethyl)-ethanesulfonamide	46		154–156	<1			S, 10.42	10.00
2	N,N-Bis-(β-diethylaminoethyl)-ethanesulfonamide dihydrochloride	65[c]	193–195					Cl, 18.66	18.68
3	N,N-Bis-(β-diethylaminoethyl)-methanesulfonamide	64		145–147	<1			S, 10.92	10.86
4	N,N-Bis-(β-diethylaminoethyl)-methanesulfonamide dihydrochloride	72[d]	215–217					Cl, 19.35	19.18
5	N-β-Diethylaminoethylethanesulfonamide	81[f]		140–145	1	1.4664	1.087	S, 15.38	15.42
6	N-β-Diethylaminoethylmethanesulfonamide	68[f]		135–140	1	1.4664	1.064	S, 16.50	16.52
7	N,N-Diethylethanesulfonamide	65		100–102	1–2	1.4485	1.087	S, 19.41	19.29
8	N,N-Diethylmethanesulfonamide	66		95–100	1–2	1.4467	1.118	S, 21.20	21.15
9	Ethanesulfonylpyrrolidine	59		113–116	1–2	1.4764	1.196	S, 19.64	19.66
10	Methanesulfonylpyrrolidine	74[e]	69–70					N, 9.39	9.05

[a] Temperatures are uncorrected. [b] Determined with Fisher–Johns apparatus. [c] Colorless prisms from MeOH–abs. Et_2O. [d] Colorless granules from MeOH–abs. Et_2O. [e] Colorless stubby needles from abs. Et_2O. [f] Amber-green.

have been prepared by treating an appropriate primary or secondary amine with an alkanesulfonyl chloride.

Relatively few N-substituted alkanesulfonamides have been reported.[1–4] Several of the compounds we prepared, [N,N-bis-(β-diethylaminoethyl)-methanesulfonamide, N,N-bis-(β-diethylaminoethyl)-ethanesulfonamide, N,N-diethylmethanesulfonamide and N-β-diethylaminoethylethanesulfonamide], were described in the above references. A portion of our work was concomitant with the published studies. Our work corroborates the properties reported for these compounds and they are included in this note to confirm the published work. These and other N-substituted alkanesulfonamides that we have synthesized and their properties are presented in Table I.

Although Bovet[3] reported that N,N-bis-(β-diethylaminoethyl)-ethanesulfonamide is effective in the treatment of experimental traumatic shock produced by an adaptation of the Noble–Collip drum technique,[5] the N,N-bis-(β-diethylaminoethyl)-ethanesulfonamide and all of the other N-substituted alkanesulfonamides prepared by us were found to have poor activity when tested in a similar manner.[6]

It was also of interest to determine whether these sulfonamides possessed any bacteriostatic or bactericidal properties. Experiments in which *E. coli*, *S. aureus*, *S. typhosa*, *Ps. aeruginosa* and *S. fecalis* were employed as test organisms, showed that these compounds were ineffective.[7] In another study, an attempt was made to see whether these compounds would attach themselves to the mucous membranes of the respiratory tract and effectively inhibit hemolytic *Streptococci*.[8] The results were negative.

(1) O. Eisleb (to I. G. Farbenind A.G.) German Patent 735,866, April 22, 1943; *C. A.*, **38**, 4101 (1944).

(2) C. S. Marvel, M. D. Helfrick and J. P. Belsley, THIS JOURNAL, **51**, 1272 (1929).

(3) D. Bovet and J. Fournel, *Proc. Soc. Exp. Biol. Med.*, **74**, 421 (1950).

(4) R. M. Jacob, G. Bo and J. G. Robert, U. S. Patent 2,553,093, May 15, 1951; *C. A.*, **46**, 522[h] (1952).

(5) D. Bovet, S. Courvoisier, R. Ducrot and R. Jacob, *Compt. rend.*, **227**, 1423 (1948).

(6) J. A. Wells, Dept. of Pharmacology, Northwestern University Medical School, private communication.

(7) M. Usdin, J. McLallen, R. Lamey and O. Boening, Microbiology Department, Baxter Laboratories, unpublished study.

Experimental

β-Diethylaminoethylbromide hydrobromide (I) was prepared according to a method described by Cortese[9] for the preparation of β-aminoethylbromide hydrobromide. The melting point of the compound corresponded to that given by Amundsen and Krantz, 208–209°.[10]

N,N-Bis-(β-diethylaminoethyl)-amine (II) was obtained by treating I with β-diethylaminoethylamine according to a method described by O'Gee and Woodburn,[11] for the preparation of N-alkylethylenediamines. Attempts to purify the free base by distillation over a narrow boiling range were unsuccessful. Analysis for nitrogen and determination of neutral equivalent gave values which were not in agreement with calculated ones. Consequently, the free base was purified by conversion to its trihydrochloride salt. In detail, the procedure employed is as follows: A solution of 20.0 g. (0.08 mole) of I in 100 ml. of water was added rapidly with stirring to 46.4 g. of β-diethylaminoethylamine (0.40 mole) in 125 ml. of water. Stirring was continued for 30 minutes after the addition, following which the clear, colorless solution was heated at the boiling point for 12 hours. The solution was then cooled and solid sodium hydroxide pellets were added until two phases appeared and the reaction mixture was distinctly alkaline. The organic phase was separated and the aqueous phase was extracted with generous portions of ether. The ether extracts and organic phase were combined and dried over anhydrous potassium carbonate. The carbonate was collected on a filter, and the ether was removed from the amber colored solution at atmospheric pressure through a 10-cm. Vigreux column. From the oily residue there was obtained 28.0 g. of unreacted β-diethylaminoethylamine, b.p. 65–67° (40 mm.), and 11.7 g. of an amber colored liquid, b.p. 70–105° (1 mm.) (II).

The trihydrochloride salt was prepared by saturating an absolute ether solution of (II) with anhydrous hydrogen chloride in the cold. A sirup resulted which was crystallized by dissolving in hot 95% ethyl alcohol, adding acetone to turbidity and cooling; weight 9.0 g. (34.6% based on (I), m.p. 185–187°).

Anal. Calcd. for $C_{12}H_{32}N_3Cl_3$: Cl, 32.82; N, 12.95. Found: Cl, 32.42; N, 12.77.

N,N-Bis-(β-diethylaminoethyl)-alkanesulfonamides (III) were prepared by reaction of (II) with ethanesulfonyl or methanesulfonyl chloride as described in a method that has

(8) L. S. Fosdick, Dental School, Northwestern University, private communication.

(9) F. Cortese, THIS JOURNAL, **58**, 191 (1936); "Organic Syntheses," Coll. Vol. II, edited by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 91.

(10) L. H. Amundsen and K. W. Krantz, THIS JOURNAL, **63**, 305 (1941).

(11) R. C. O'Gee and H. M. Woodburn, *ibid.*, **73**, 1370 (1951).

been employed for the preparation of 1-alkylsulfonyl-4-alkylpiperazines.[12] The ethanesulfonyl chloride[13] was prepared by the method used by Hearst and Noller[14] for the preparation of methanesulfonyl chloride.

The intermediate amine free base (II) was obtained from the salt by adjusting the *p*H of an aqueous solution from 2 to 10 with potassium hydroxide and extracting with ether. The N,N-bis-(β-diethylaminoethyl)-amine distilled at 91–93° (1 mm.), yield 60%.

Anal. Calcd. for $C_{12}H_{29}N_3$: N, 19.55. Found: N, 19.37.

The alkanesulfonyl chloride (0.0081 mole) in 75 ml. of absolute ether was added to a cooled, stirred solution of II (0.0163 mole) in 75 ml. of absolute ether. The reaction mixture, containing a white sirup, was stirred for two hours and permitted to stand for 15 hours. The ether was decanted and the sirup adhering to the walls of the vessel was dissolved in 5 ml. of hot 95% ethyl alcohol. Upon the addition of excess ether, the sirup crystallized. The melting point of the solid conformed to that of N,N-bis-(β-diethylaminoethyl)-amine trihydrochloride, 185–187°.

The ether solution containing the product was evaporated to a brown oil on the steam-bath. The oil was distilled at reduced pressure to give the N,N-bis-(β-diethylaminoethyl)-alkanesulfonamide (III) (no. 1 and 3, Table I).

N-Substituted Alkanesulfonamides (No. 5–10).—These compounds were prepared by treating twice the theoretical amount of the appropriate primary or secondary amine with methane or ethanesulfonyl chloride. All compounds were oils with the exception of no. 10, which was crystallized by concentrating the ether solution after removing the insoluble primary or secondary amine salt.

Yields of compounds 5 and 6 were improved by repeated extraction of the amine salt by-products with ether.

(12) R. M. Jacob, U. S. Patent 2,507,408, May 9, 1950; *C. A.*, **44**, 7888^g (1950).

(13) A. G. Kostsova, *Zhur. Obshchei Khim. (J. Gen. Chem.)*, **18**, 729 (1948); *C. A.*, **43**, 120^e (1949).

(14) R. J. Hearst and C. R. Noller, *Org. Syntheses*, **30**, 58 (1950).

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Rates of Reaction of Diphenyldiazomethane with Aliphatic Carboxylic Acids in Ethanol[1]

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RECEIVED JULY 17, 1953

Roberts and co-workers have used the rates of the reaction of diphenyldiazomethane (DDM) with carboxylic acids in ethanol at 30° to obtain quantitative measurements of the relative polar effects of substituent groups.[2] *m*- and *p*-substituted benzoic acids in this reaction follow the Hammett equation with a rho value of +0.937.[2a] Linear free energy relationships between rates of the DDM reaction and corresponding ionization constants (in 50% vol. aq. ethanol) also have been found for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids[2e] and for cycloalkane carboxylic acids.[2d] All of these cases involve rigid structures adjacent to the carboxyl group, and, except for perhaps two members of the latter series, the substitution is carried out at centers well removed from the carboxyl group.

In order to determine whether only polar effects of substituents determine rates of this reaction when less rigid and bulky groups are introduced adjacent to the carboxyl group, we have determined the rates of reaction of DDM in ethanol at 25° with a series of carboxylic acids, RCOOH. The spectrophotometric method of Roberts and co-workers has been used.[2,3] The second-order constants obtained are listed in Table I.

The results fit with satisfactory precision the relationship[4]

$$\log k/k_0 = \sigma^*\rho^* \qquad (1)$$

where k/k_0 is the second-order rate constant for an aliphatic acid relative to that for acetic acid; σ^* is the polar substituent constant for the group, R, relative to the CH_3 group. Values of σ^*, which were obtained principally from rates of alkaline and acidic hydrolysis of esters, RCOOG, have been listed previously[4]; ρ^* is a reaction constant measuring the relative susceptibility of the DDM reaction to polar substituents.

The value of ρ^* obtained from the present data by methods of least squares is $+1.175 \pm 0.043$. The median probable error of the fit of the data to equation 1 is 0.06 log unit. This is not an unsatisfactory fit in view of the uncertainties in the present data (see Experimental) and in the values of σ^*.[4] An appreciable number and variety of reaction series involving bulky groups adjacent to the reaction centers have previously been shown to fit eq. 1 with similar precision.[4]

TABLE I

SECOND ORDER RATE CONSTANTS k_2 FOR REACTION OF CARBOXYLIC ACIDS, RCOOH, WITH DIPHENYLDIAZOMETHANE IN ABSOLUTE ETHANOL AT 25° IN L. MOLE^{-1} MIN.$^{-1}$

Subst., R	k_2	Subst., R	k_2
$CNCH_2$	18.5	$C_6H_5CH_2$	1.47
$ClCH_2$	12.9		
$C_6H_5(OH)CH$	6.77	$C_6H_5CH_2CH_2$	1.09
$HOCH_2$	3.01	C_6H_5	0.96
$(C_6H_5)_2CH$	2.32	CH_3	.463
H	2.23	n-C_5H_{11}	.442
$ClCH_2CH_2$	2.24	t-C_4H_9	.296

Figure 1 shows a plot of $\log k_2$ *vs.* σ^*. The phenyl group provides an exception to eq. 1; the point for this group is 0.40 log unit or 500 cal./mole less than eq. 1 predicts. The deviation is in line with a specific resonance effect of the phenyl group similar to that suggested for the ionization of benzoic acid.[4]

Figure 1 illustrates that the present data require that steric effects remain constant whether R is a small group, such as H or CH_3, or a bulky one such as $(C_6H_5)_2CH$ or t-C_4H_9.[4] Thus the change in steric interaction between substituent and the carboxyl group obtained when the former groups are replaced by the latter must remain constant between the reactant and the transition states.

Judging from the number and variety of substituent groups studied, it is implied that the DDM reaction can be used as a convenient method for determining polar substituent constants for

(1) Taken from the senior thesis of Daniel J. Smith, The Pennsylvania State College, June, 1953.

(2) (a) J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2923 (1949); (b) J. D. Roberts, R. L. Webb and E. A. McElhill, *ibid.*, **72**, 408 (1950); (c) J. D. Roberts and E. A. McElhill, *ibid.*, **72**, 628 (1950); (d) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5030 (1951); (e) J. D. Roberts and W. T. Moreland, Jr., *ibid.*, **75**, 2167 (1953).

(3) (a) J. D. Roberts and W. Watanabe, *ibid.*, **72**, 4869 (1950); (b) J. D. Roberts, W. Watanabe and R. E. McMahon, *ibid.*, **73**, 760 (1951).

(4) R. W. Taft, Jr., *ibid.*, **75**, 4231 (1953).