Sultones as Reagents for Derivatizing Aliphatic Amines in Qualitative Organic Analysis

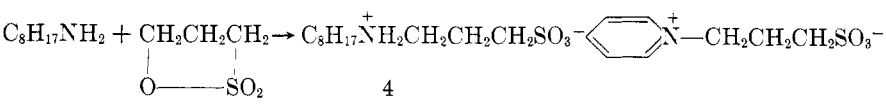
SIR: The primary aim of this investigation was to find a reagent that would be specific for two types of aliphatic amines: those having long chains and hindered amines. It was also desirable for the reagent to react with all classes of amines sufficiently rapidly so that the derivatives could be made in one laboratory period; adduct formation was especially desirable. Furthermore, the reagent had to be specific in the time selected—i.e., it had to react more rapidly with the amine than with the solvents employed.

A preliminary study of possible reagents such as isocyanates and isothiocyanates having large ballast groups (*2*); silicon tetraisothiocyanate (*7*); 2,4-dinitrobenzene–sulfenyl chloride (*6*); di-*O*-*p*-toluyltartaric acid (*5*); and sultones (*1*, *3*, *4*, *8*) led to the selection of the latter as the most suitable. Furthermore, sultones are inexpensive and readily available.

The sultones examined were propane, 2,4-butane; and 1,1,3-trimethylpropane.

The last of these was excluded at once because of the time required (14 to 20 hours) to prepare an adduct. Propane sultone best met the above requirements and it was selected as the most useful. The derivatives formed with long chain (above C_{10}) amines showed shrinkage and did not give sharp melting points in capillary tubes; the use of a melting point block obviated most of this difficulty. With these amines, the use of 2,4-butane sultone is preferable (it allows the derivative to crystallize better). With few exceptions, primary amines gave satisfactory solid derivatives with these sultones. A limited number of secondary amines likewise gave good derivatives, but only two tertiary amines (one of which was the hindered 2,4,6-trimethylpyridine) were successfully derivatized.

The adducts of all except the heterocyclic amines are named following the "a" system for simplicity and uniformity; thus, they are 4- (or 5-) azoniaalkane-1 (or -2) sulfonates. For example, the adduct (I) from octylamine and propane sultone with 12 atoms in the chain becomes 4-azoniadodecane - 1 - sulfonate. Heterocyclic amines in which the nitrogen atom is a ring member are named as -inium-1-sulfonates; pyridine and propane sultone give 3(1-pyridinium)propane-1-sulfonate (II) (*1*).



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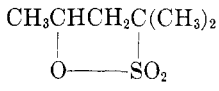
In the procedures selected, the adducts are formed in dry methanol in yields of 35 (short chain) to 70% (long and branched chains) in 2 hours at room temperature; in 1 hour the yields are slightly less (Table I). Under these conditions, interaction of the reagent and solvent is negligible. The minimum amount of an amine that can be identified was not determined, but the smallest weight of amine used in the adopted procedure was 1.5 grams (butyl). Aromatic amines or those containing aromatic groups reacted more slowly (3 to 4 days) and were reluctant to crystallize (up to 1 month); refluxing for 2 hours was advisable.

Reagents. Most of the amines used were Eastman chemicals; nonylamine came from Aldrich. The C_{12}



amine was a cut (b.p., 85–93° C./0.7 mm.) from Duomeen 12D. The C_{14} amine as Duomeen 14D, was used as received or as a middle cut from a redistillation (b.p., 129°/0.7 mm.); either seemed to be homogeneous by gas chromatography. *t*-Butyl- (b.p., 45–6° C.; n_D^{25}, 1.39) and *t*-octylamines were obtained from Rohm & Haas, and propyl and tripropyl sultones from Shell Chemical Co. The boiling points given are those of redistilled portions. If the amine were colored or wet it was dried over pellets of potassium hydroxide and/or redistilled.

Procedure. To a sample of 0.02 mole of amine in 10 ml. of absolute methanol was added 0.02 mole of the sultone, and the mixture was allowed to stand at room temperature for 2 hours; some of the adduct separated occasionally, but in each instance 5 to 10 ml. of dry ether was added before filtration. The solid was collected on a filter and air-dried unless hygroscopic. For purification, the product was recrystallized from 20 ml. of hot absolute ethanol, with 5 ml. of dry ether added to the cooled solution. Hydroxyamines required up to 10 recrystallizations to reach analytical purity.

When the foregoing procedure did not give a solid adduct, changes in solvent were made. A 2:1 mixture of ether and acetonitrile or nitromethane was used advantageously in a few instances. After being refluxed for 1 hour most of the solvent was distilled, and ethyl acetate was used for crystallization; the ester, finally diluted by ether, was also employed to initially separate the adducts. In this way, the adducts from propane sultone and piperidine, morpholine, di-*n*-heptylamine, di-*n*-octylamine, and di-*n*-undecylamine (with 2,4-butane sultone) and 2,4,6-trimethylpyridine were prepared. The adduct from triethylamine and propane sultone resulted after 2 hours' refluxing of a benzene solution; recrystallization occurred first from ethyl acetate and then from absolute alcohol.

Table I. Yield in Grams of Derivatives with Propane Sultone

Amine	Temp.	In time, hours 1	2
n-Butyl	Room	2.4	3
Isobutyl	Room	1.4	1.8
Pentyl	B. P.	1.7	2.3

The adducts that have melting points above 200° C. have a tendency to shrink in a capillary tube before they melt. A glassy brown solid is then usually formed. The point at which this separates from the wall of the tube and forms a pool at the bottom is taken as the melting point. This behavior accounts for the apparent discrepancy in the recorded melting point of the adduct from dodecylamine, which in a patent (*1*) is given as 215° C., whereas we found it to be 279–80° C. The lower limit for a primary amine appears to be C_4. The adducts and their properties are shown in Table II.

In spite of numerous attempts with varying conditions and solvents, pure adducts were not readily obtainable with many secondary, tertiary, and polyamines. Water-soluble sticky gums or oils were formed in a few minutes; if an apparent solid did result, the adhering gum could not be removed completely, nor the crude material recrystallized except in a few instances. The use of ethyl acetate was sometimes helpful, but even with its aid the resulting solid was not analytically pure. Such failures were encountered with allylamine, di-*n*-butylamine, diisopentylamine; δ-aminobutylmethyldiethoxysilane; 1,6-diaminohexane; triethylenetetramine; ethyl carbamate; ethyl anthranilate; and pyrrole.

Adducts from 1,1,3-trimethylpropane sultone were obtained in very

small amounts after mixtures of the sultone (3.3 grams) and *t*-butylamine (1.5 grams) or *t*-octylamine (2.5 grams) in dry methanol (15 ml.) were refluxed for 14 and 20 hours, respectively. The melting points of the crude products were 206–7° and 165–6° C.; these products were not purified because of lack of material.

Three new salts of di-*O*-*p*-toluoyltartaric acid were prepared following Kidd's procedure (*5*) from *t*-butyl, dodecyl, and tetradecylamines. 4-Chlorophenyl dodecyl thiourea was obtained by refluxing, for 15 minutes, a mixture of *p*-chlorophenylisothiocyanate and dodecylamine in 95% alcohol; the thiourea crystallized after water was

Table II. Properties of Adducts

Amine used	Azonia No.	Alkane with substituent	Sulfonate No.	M.P., °C.	Formula	Analysis Calculated, % C	H	S	Found, % C	H	S
n-Butyl	4	Octane	1	156 –7	$C_7H_{17}NO_3S$	43.1	8.7	16.4	43.4	8.8	16.7
n-Pentyl	4	Nonane	1	203 –4 (d.)	$C_8H_{19}NO_3S$	45.9	9.1	15.3	45.8	8.9	15.3
n-Hexyl	4	Decane	1	209 –10 (d.)	$C_9H_{21}NO_3S$	48.6	9.4	14.4	48.6	9.4	14.4
n-Heptyl	4	Undecane	1	254 –5 (d.)	$C_{10}H_{23}NO_3S$	50.7	9.7	13.5	50.6	9.5	13.5
n-Octyl	4	Dodecane	1	262 –3 (d.)	$C_{11}H_{25}NO_3S$	52.6	9.9	12.7	52.5	9.9	13.0
n-Nonyl	4	Tridecane	1	265.5–6.5	$C_{12}H_{27}NO_3S$	54.3	10.2	12.1	54.0	10.2	12.4
n-Decyl	4	Tetradecane	1	277 –8	$C_{13}H_{29}NO_3S$	55.9	10.4	11.5	56.1	10.5	11.4
n-Undecyl	4	Pentadecane	1	269 –70	$C_{14}H_{31}NO_3S$	57.4	10.6	10.9	57.3	10.3	10.9
n-Undecyl[a]	5	Hexadecane	2	174 –5	$C_{15}H_{33}NO_3S$	58.7	10.7	10.4	59.0	11.0	10.5
n-Dodecyl[b]	4	Hexadecane	1	279 –80	$C_{15}H_{33}NO_3S$	58.7	10.7	10.4	58.3	10.6	10.6
n-Dodecyl[a,b]	5	Heptadecane	2	167	$C_{16}H_{35}NO_3S$	59.8	10.9	10.0	59.5	10.7	9.8
n-Tetradecyl[a,c]	4	Octadecane	1	268 –9 (d.)	$C_{17}H_{37}NO_3S$	61.0	11.0	9.6	61.2	11.2	9.8
n-Tetradecyl	4	Octadecane	1	270 –1 (d.)	$C_{17}H_{37}NO_3S$	61.0	11.0	9.6	61.0	10.8	9.4
n-Tetradecyl[a,c,e]	5	Nonadecane	2	165 –6	$C_{18}H_{39}NO_3S$	61.9	11.2	9.2	61.8	11.2	9.4
n-Tetradecyl[a,d,e]	5	Nonadecane	2	161 –2	$C_{18}H_{39}NO_3S$	61.9	11.2	9.2	61.6	11.0	9.5
n-Hexadecyl	4	Eicosane	1	296 –7	$C_{19}H_{41}NO_3S$	62.8	11.3	8.8	62.4	11.3	9.1
n-Hexadecyl[a]	5	Heneicosane	2	228 –9	$C_{20}H_{43}NO_3S$	63.7	11.4	8.5	63.4	11.4	8.6
n-Octadecyl[a,c]	5	Tricosane	2	241 –2	$C_{22}H_{47}NO_3S$	65.2	11.6	7.9	65.5	11.8	7.8
Isobutyl	4	6-Methylheptane	1	263 –4 (d.)	$C_7H_{17}NO_3S$	43.1	8.7	16.4	42.9	8.9	16.3
Isopentyl	4	7-Methyloctane	1	257 –8	$C_8H_{19}NO_3S$	46.0	9.1	15.6	46.1	9.1	15.7
1-Methylheptyl	4	5-Methylundecane	1	276 –7	$C_{11}H_{25}NO_3S$	52.6	9.9	12.7	52.7	10.1	13.0
2-Ethylhexyl	4	6-Ethyldecane	1	187 –8	$C_{11}H_{25}NO_3S$	52.6	9.9	12.7	52.5	9.8	12.7
sec-Butyl	4	5-Methylheptane	1	251 –2	$C_7H_{17}NO_3S$	43.1	8.7	16.4	43.0	8.6	16.7
Cyclohexyl	4	4-Cyclohexylbutane	1	330 –1	$C_9H_{19}NO_3S$	48.9	8.6	14.5	49.2	8.6	14.8
t-Butyl	4	5,5-Dimethylhexane	1	322 –3	$C_7H_{17}NO_3S$	43.1	8.7	16.4	43.1	8.5	16.4
t-Butyl[a]	5	6,6-Dimethylheptane	2	324 –5	$C_8H_{19}NO_3S$	45.9	9.1	15.3	45.7	8.9	15.5
t-Octyl	4	5,5,7,7-Tetramethyloctane	1	280.5–1.5[f]	$C_{11}H_{25}NO_3S$	52.6	9.9	12.7	52.5	9.9	12.7
t-Octyl[a]	5	6,6,8,8-Tetramethylnonane	2	279 –80[f]	$C_{12}H_{27}NO_3S$	54.4	10.2	12.1	54.2	10 2	12.1
Benzyl	4	5-Phenylpentane	1	241 –2	$C_{10}H_{15}NO_3S$	52.4	6.6	14.0	52.2	6.3	14.3
Benzylmethyl	3	2-Phenylhexane	6	232 –3	$C_{11}H_{17}NO_3S$	54.4	7.0	13.2	54.3	7.1	13.3
β-Phenethyl	4	6-Phenylhexane	1	224 –5	$C_{11}H_{17}NO_3S$	54.4	7.0	13.2	54.2	6.8	13.4
Methyl anthranilate	4	*o*-Carbomethoxyphenylbutane	1	237 –8	$C_{11}H_{15}NO_5S$	48.4	5.5	11.8	48.2	5.4	12.0
3-Methoxypropyl	4	Methoxyheptane	1	165 –6	$C_7H_{17}NO_4S$	39.8	8.1	15.2	39.6	8.2	15.1
Ethanolamine	4	6-Hydroxyhexane	1	175 –6	$C_5H_{13}NO_4S$	32.8	7.1	17.5	32.6	7.0	17.7
6-Hydroxy-6-methylheptyl-2	4	5,9-Dimethyl-9-hydroxydecane	1	166.5–7.5	$C_{11}H_{25}NO_4S$	49.4	9.4	12.0	49.2	9.4	12.1
1-Amino-2,3-propanediol	4	6,7-Dihydroxyheptane	1	180 –1	$C_6H_{16}NO_5S$	33.6	7.5	15.0	33.9	7.4	15.2
2-Aminomethyltetrahydropyran	4	5-(2-Tetrahydropyranyl)-pentane	1	185 –6	$C_9H_{19}NO_4S$	45.6	8.0	13.5	45.9	8.0	13.7
Diethyl	4	4-Ethylhexane	1	144 –5	$C_7H_{17}NO_3S$	43.1	8.7	16.4	42.8	8.8	16.5
Di-*n*-heptyl	4	4-Heptylundecane	1	119 –20	$C_{17}H_{37}NO_3S$	60.9	11.0	9.6	60.7	11.0	9.5
Di-*n*-octyl	4	4-Octyldodecane	1	133 –4	$C_{19}H_{41}NO_3S$	62.8	11.3	8.8	63.0	11.2	8.8
Di-*n*-undecyl[a]	5	5-Undecylhexadecane	2	136 –7	$C_{26}H_{55}NO_3S$	68.5	11.6	6.9	68.6	12.6	7.1
Triethyl	4	4,4-Diethylhexane	1	293.5–4.5	$C_9H_{21}NO_3S$	48.6	9.4	14.4	48.4	9.7	14.1
Pyrrolidine		3-(1-Pyrrolidinium) propane	1	199 –200	$C_7H_{15}NO_3S$	42.7	7.9	16.6	43.0	7.7	16.5
Morpholine		3-(4-Morpholinium) propane	1	283.5–4.5	$C_7H_{15}NO_4S$	40.2	7.2	15.3	40.4	7.2	15.0
2,4,6-Trimethylpyridine		3-(2,4,6-Trimethyl-1-pyridinium)propane	1	277 –8	$C_{11}H_{17}NO_3S$	54.2	7 0	13.2	54.0	7.2	13.0
Piperidine		3-(1-Piperidino)propane	1	257 –8	$C_8H_{17}NO_3S$	46.4	8.2	15.5	46.2	8.0	15.4

[a] From butane-2,4-sultone. [b] Armeen 12D, b.p. 85–93° C./0.7 mm. [c] Eastman grade. [d] Armeen 14D, b.p. 129° C./0.7 mm. [e] Homogeneous by v.p.c. [f] Mixture m.p., 260–4° C.

Table III. Properties of Other New Adducts

Amine used	With	M.P., °C.	Formula	C	H	N	C	H	N
t-Butyl-	Kidd's acid (*5*)	200	$C_{28}H_{40}N_2O_8$	63.3	7.5	5.3	63.3	7.3	5.1
Dodecyl-	Kidd's acid (*5*)	187	$C_{44}H_{72}N_2O_8$	69.8	9.6	3.7	69.4	9.3	3.6
Tetradecyl-	Kidd's acid (*5*)	187	$C_{48}H_{80}N_2O_8$	70.9	9.8	3.5	70.7	9.6	3.4
Dodecyl-	4-ClC_6H_4NCS	84	$C_{19}H_{31}ClN_2S$	64.3	8.7	10.0[a]	64.5	8.9	10.1[a]

[a] % Chlorine

added to incipient cloudiness. It was recrystallized from alcohol. The properties of these salts, obtained during the preliminary screening with other reagents, are listed in Table III.

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Use of Tetrachlorophthalimide for Identification of Alkyl Halides and Alkyl Sulfonates

SIR: The use of tetrachlorophthalimide for the identification of many types of aliphatic halogen compounds by heating in the absence of a solvent was described in an earlier paper (*2*). The long heating period and the use of sealed tubes in some instances may have detracted to a certain extent from its many advantages. The current availability of ionizing solvents, such as dimethylformamide and dimethyl sulfoxide, and of the tetrabromo- and tetraiodophthalic anhydrides led us to re-examine this useful reaction.

Dimethylformamide greatly reduces the time required for a Gabriel synthesis (*3–5, 8, 12*). This advance has been confirmed in this paper; derivatives for the purposes of identification can now be prepared in 1 hour or less. Furthermore, most of the now commonly available long chain aliphatic halides have been converted to suitable reference compounds. Only one halogen of α, ω-dihalides reacts under the conditions adopted; this is a well known characteristic of the Gabriel synthesis. Bifunctional halogen compounds such as chloroacetamide, ethyl chloroacetoacetate, and others have been successfully derivatized.

When 2-chloroethyl *p*-toluenesulfonate was employed, only the sulfonate group reacted, resulting in a 2-chloroethyl imide. The reaction showed that the halogen was less active in the alkylation and also indicated that derivatives from esters of sulfonic acids could be readily prepared. The rate of reaction of sulfonic acid esters in dimethylformamide is surprisingly rapid; furthermore, pressure is not required because the lower members—e.g., methyl methanesulfonate—are not nearly so volatile as the corresponding halides. These observations suggest a useful laboratory synthetic route for conversion of a primary alcohol, via the ester, to a primary amine using phthalimide itself.

Dimethyl sulfoxide was examined for 1 hour at each of two temperatures. At 95° C. (steam bath) the reaction took place smoothly, but at the boiling point there was considerable decomposition with production of much color. The yields of derivatives were good in both instances. However, the possibility of side reactions with dimethyl sulfoxide (*6, 11*) makes dimethylformamide the preferable solvent until dimethyl sulfoxide has been shown not to interfere. The marked advantage of using dimethyl sulfoxide at the lower temperature is the fact that such low boiling halides as methyl iodide and ethyl bromide can now be easily converted to imides without the use of a sealed tube.

Because *N*, *N'*-bisphthalimidoalkanes are not produced, even as contaminants in the Gabriel reaction, and because sulfonate esters react more readily than halides with the reagent (potassium tetrachlorophthalimide), bissulfonates (*1*) should form such bisalkanes more easily. However, up to now, analytically pure bis compounds have not been obtained; the main contaminant, tetrachlorophthalimide, persists throughout numerous recrystallizations of the scale employed for making identifications.

To learn the effect of change of halogen upon the melting point of derivatives, tetrabromo- and tetraiodophthalimides were examined in three instances. The melting point was raised 30° to 36° C. for each change (Table I). A slight spread was observed with long chain derivatives of the tetrabromoimide. A greatly decreased solubility and apparent evidence of decomposition led to the exclusion of a further study of iodo derivatives. However, in view of the large number of tetrachloroimides already described, the general use of the chlorinated reagent has been retained; the brominated derivative might be useful in a few instances, such as with the long chain halides.

Table I. Melting Points in °C. of Derivatives from Different Haloimides

Substituent	Cl_4	Br_4	I_4
$-(CH_2)_3CN$	194	230–2	264–7 (d)
$-C_{14}H_{29}$	130	167	201 (d)
$-C_{16}H_{33}$ (*1*)	129–30	163–4	197 (d)

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Reagents. The three tetrahalophthalimides were obtained by the previously described procedure (*1*) or by the use of formamide (*9, 10*). The second was preferable for the bromo and iodo imides; iodine vapor was noticed if overheating occurred (*9*). The potassium derivative of the iodinated imide was best prepared by the addition of methanolic potassium hydroxide to a dimethylformamide solution of the imide. All the bromo and iodo imides were recrystallized from dimethylformamide. The alkyl halides and sulfonates used were Eastman chemicals, or were prepared by standard procedures. With the higher alkyl *p*-toluene-sulfonates, the crude ester remaining after evaporation of the solvent from the ether extract (*7*) was used directly—undecyl *p*-toluenesulfonate, f.p., 30° to 32° C. A specimen of dodecenyl chloride from Rohm and Haas was used—b.p., 108° C./3 mm., n_D^{25} = 1.4617. Bismethanesulfonates are described in a patent (*1*).

Preparation of Derivatives. AT THE BOILING POINT. The potassium tetrahaloimide, 0.009 mole; a slight molar excess of halogen compound or sulfonate; and 15 ml. of dimethylformamide or dimethyl sulfoxide were thoroughly mixed and refluxed for 1 hour. When the sulfonate esters in dimethylformamide were employed, the temperature began to rise rapidly at 80° to 90° C., and the appearance of the suspended solid changed (gelatinous) by 130° C. The mixture was then quenched with 50 to 70 ml. of water to precipitate the product, which was extracted with 50 to 75 ml. of acetone or 25 to 50 ml. of chloroform. Chloroform, however, did not dissolve the