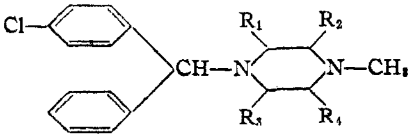
TABLE III

1-(p-CHLOROBENZHYDRYL)-4-METHYLPIPERAZINES,



No.	R₁	R₂	R₃	R₄	B.p. °C.	B.p. Mm.	Yield, %	Formula	Analyses, %[15] Calcd. C	Calcd. H	Found C	Found H	Picrate[a] M.p.,[b] °C.	Picrate[a] Calcd. N, %	Picrate[a] Found N, %
III	H	CH_3	H	H	152–153	0.3	73	$C_{19}H_{23}ClN_2$	72.48	7.36	72.56	7.08	196–197	14.50	14.38
IV	H	CH_3	CH_3	H	150–160	1	19	$C_{20}H_{25}ClN_2$	73.04	7.66	73.26	7.12	181–182	12.55	12.36
V	H	CH_3	H	CH_3	177–178	1.4	57	$C_{20}H_{25}ClN_2$	73.04	7.66	73.12	7.36	214–215	14.24	14.14
VI	H	H	$CH_2CH_2CH_2CH_2$		193–197	0.6	57	$C_{22}H_{27}ClN_2$	74.45	7.67	75.17[c]	7.74	263	13.78	13.79

[a] All formed dipicrate salts except IV which formed a monopicrate. [b] These compounds melted with decomposition. [c] An attempt was made to improve this analysis by purification of the base through its dipicrate.

ether was refluxed and stirred in a dry nitrogen atmosphere for 1.5 hours. Then a solution of 2.1 g. (0.0164 mole) of 1,2-dimethyl-3-ketopiperazine in 150 cc. of dry ether was added over a period of 15 minutes. After the reaction mixture was stirred and heated for 4.5 hours more, 8 cc. of water was added to destroy the excess lithium aluminum hydride. The inorganic salts were removed by filtration, and the filtrate was distilled. The product boiled at 151–152° at 753 mm.; yield 0.9 g. (48%).

1-(p-Chlorobenzhydryl)-4-methylpiperazines.—The previously described method[2a] for p-chlorobenzhydrylation was used to prepare these compounds. This procedure involves heating equimolar amounts of the N-methylpiperazine, p-chlorobenzhydryl chloride, and anhydrous sodium carbonate in refluxing xylene for 32–64 hours, extracting the product from the xylene with 6 *N* hydrochloric acid, basifying the aqueous solution, and collecting the product with ether. These compounds are listed in Table III. They were all high boiling, viscous liquids which were difficult to purify by distillation. Since the hydrochloride salts were hygroscopic, picrates were used to characterize the bases.[16]

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[16] Solutions were prepared for pharmacological testing by neutralizing the bases with dilute hydrochloric acid.

NORTH CHICAGO, ILLINOIS

RECEIVED JULY 27, 1951

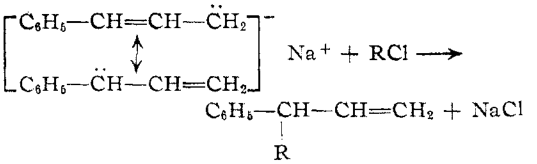
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Allylic Rearrangements. XXXIII. The Reaction of Sodium Allylbenzene with Allylic Halides and Methyl Bromide

BY WILLIAM G. YOUNG, MILTON KOSMIN,[1] R. Y. MIXER[2] AND TOD W. CAMPBELL[3]

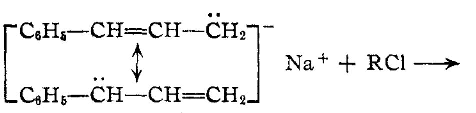
The reactions of sodium allylbenzene with allyl bromide, α- and γ-methylallyl chlorides and methyl bromide have been studied in liquid ammonia to determine whether both the primary and secondary carbon atoms of the allylbenzene carbanion are involved in the displacement reaction. It was found that the carbanion attached predominately as the secondary isomer to give the product ($C_6H_5CHRCH{=}CH_2$) but in all cases some of the primary displacement product ($C_6H_5CH{=}CHCH_2R$) was present. It has been shown that both the α- and γ-methylallyl groups retained their configuration during the displacement reaction thus eliminating the possibility of the abnormal bimolecular displacement reaction (S_N2'). In the reaction with methyl bromide it was shown that the product composition varied with the order of addition of methyl bromide *vs.* sodium allylbenzene.

The reaction of allylic halides with sodium allylbenzene (γ-phenylpropenyl sodium) in liquid ammonia has been described by Levy and Cope.[4] Since these workers were primarily interested in the preparation of the secondary-type of reaction product (resulting from reaction I), no special effort was made to isolate other products which

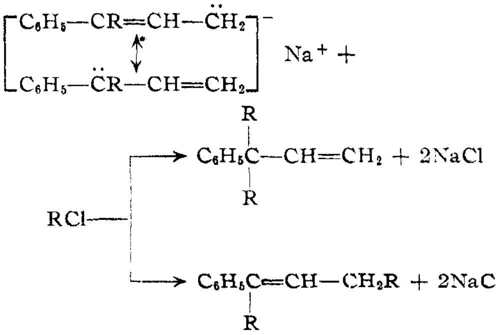


$$\left[\begin{array}{c} C_6H_5{-}CH{=}CH{-}\ddot{C}H_2 \\ \updownarrow \\ C_6H_5{-}\ddot{C}H{-}CH{=}CH_2 \end{array}\right]^- Na^+ + RCl \longrightarrow C_6H_5{-}\underset{\displaystyle R}{\underset{|}{C}H}{-}CH{=}CH_2 + NaCl \quad (I)$$

might have been formed in low yields. These other products could arise as a result of attack by the primary carbon atom of the allylbenzene carbanion (reaction II), and by the reaction of the halide with a new carbanion formed by acid–base interchange between sodium allylbenzene and the hydrocarbon formed in reaction (I) (see reactions III and IV). These other products might be expected since Campbell and Young[5] have shown that the reaction



$$\left[\begin{array}{c} C_6H_5{-}CH{=}CH{-}\ddot{C}H_2 \\ \updownarrow \\ C_6H_5{-}\ddot{C}H{-}CH{=}CH_2 \end{array}\right]^- Na^+ + RCl \longrightarrow C_6H_5{-}CH{=}CH{-}CH_2R + NaCl \quad (II)$$



$$\left[\begin{array}{c} C_6H_5{-}CR{=}CH{-}\ddot{C}H_2 \\ \updownarrow \\ C_6H_5{-}\ddot{C}R{-}CH{=}CH_2 \end{array}\right]^- Na^+ + RCl \longrightarrow \begin{cases} C_6H_5\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}{-}CH{=}CH_2 + 2NaCl & (III) \\ C_6H_5\underset{\displaystyle R}{\underset{|}{C}}{=}CH{-}CH_2R + 2NaCl & (IV) \end{cases}$$

of sodamide with either allyl- or propenylbenzene in liquid ammonia gives the same resonating carbanion system and that the reaction of this system

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[1] Monsanto Chemical Co., Dayton, Ohio.

[2] Standard Oil Co. of California Fellow, 1950–1952.

[3] Western Regional Research Laboratory, Albany, California.

[4] H. Levy and A. C. Cope, THIS JOURNAL, **66**, 1684 (1944).

[5] T. W. Campbell and W. G. Young, *ibid.*, **69**, 688 (1947).

with proton donating substances gives mixtures in which the primary-type of reaction product ($C_6H_5CH{=}CH{-}CH_2R$) predominates. Later they[6] demonstrated that the reaction of this carbanion system with carbon dioxide and acetone gave mixtures of reaction products with the secondary-type predominating while with benzophenone only the primary-type of reaction product was found. Recently it has been shown[7] that the displacement of halogen from substituted haloacetic acids using sodium allylbenzene gave mixtures ranging from 57 to 93% of the primary-type reaction product.

The present work was directed toward a careful study of the reaction of sodium allylbenzene with three allylic halides (allyl bromide, α-methylallyl chloride and γ-methylallyl chloride) and methyl bromide to determine the extent to which the primary-type of reaction (reaction II) actually occurs.

Three independent methods were used to analyze the products resulting from the reaction of sodium allylbenzene with the allylic halides. A portion of the product was fractionally distilled at reduced pressure and the analysis based on the refractive indexes of the various cuts. Another portion of the reaction product was hydrogenated and then carefully fractionated with the analysis based on the refractive indexes of the distillate. The purpose of this procedure was to eliminate the possible thermal rearrangement of the olefins during the distillation. The ultraviolet absorption spectra were obtained on still another portion of the reaction mixture and compared with the spectra of the corresponding pure compounds. A comparison of the composition of the reaction mixtures as determined by each of the three methods is given in Table I.

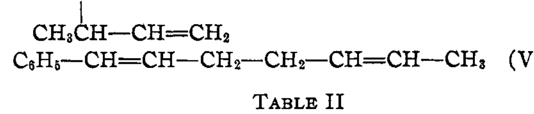
TABLE I

TOTAL YIELD AND COMPOSITION OF PRODUCTS FROM THE REACTION OF SODIUM ALLYLBENZENE WITH ALLYLIC HALIDES

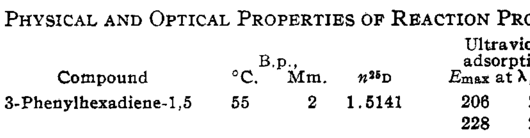
Method of analysis	Total yield, %	Primary-type product, % $C_6H_5CH{=}CHCH_2$—$RCH{=}CHCHR'$	Secondary-type product, % $C_6H_5CHCH{=}CH_2$—$R'CHCH{=}CHR$
Allyl bromide (R = R′ = H)			
Fractionation	72	7	93
Hydrogenation + fractionation	67	9	91
UV absorption spectra	. .	13	87
α-Methylallyl chloride (R = H, R′ = CH_3)			
Fractionation	86	5	95
Hydrogenation + fractionation	86	2	98
UV absorption spectra	. .	9	91
γ-Methylallyl chloride (R = CH_3, R′ = H)			
Fractionation	86	14	86
Hydrogenation + fractionation	71	13	87
UV absorption spectra	. .	17	83

It was interesting to note that in the reactions of the sodium allylbenzene with α- and γ-methylallyl chlorides, there was no evidence that an allylic rearrangement of either the α- or the γ-methylallyl fragment had occurred during the displacement of the chloride. Thus maintenance of integrity of the methylallyl moiety in the product precludes any abnormal displacement (S_N2') on the methylallyl chlorides or ionization of the allylic halide prior to reaction.

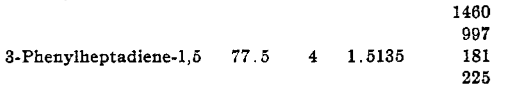
In the preparation of purified samples of the various products from the reactions for physical properties and ultraviolet absorption spectra, it was found very difficult to purify the small quantities of high-boiling primary-type reaction products. As a result, these products were formed by thermal isomerization (reactions VI, VII, VIII) of the secondary-type products based on the findings of Levy and Cope.[4,8] The physical and optical properties of the products (both types) are contained in Table II. In the present work we have confirmed the observations of Levy and Cope that the secondary-type reaction product predominates in the reaction of sodium allylbenzene with allylic halides.



$$C_6H_5{-}\underset{CH_2-CH=CH_2}{\underset{|}{C}H}{-}CH{=}CH_2 \longrightarrow C_6H_5{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2 \quad (VI)$$



$$C_6H_5{-}\underset{CH_2-CH=CH-CH_3}{\underset{|}{C}H}{-}CH{=}CH_2 \longrightarrow C_6H_5{-}CH{=}CH{-}CH_2{-}\underset{CH_3}{\underset{|}{C}H}{-}CH{=}CH_2 \quad (VII)$$



$$C_6H_5{-}\underset{CH_3CH-CH=CH_2}{\underset{|}{C}H}{-}CH{=}CH_2 \longrightarrow C_6H_5{-}CH{=}CH{-}CH_2{-}CH_2{-}CH{=}CH{-}CH_3 \quad (VIII)$$

TABLE II

PHYSICAL AND OPTICAL PROPERTIES OF REACTION PRODUCTS

Compound	B.p., °C.	B.p., Mm.	$n^{25}D$	Ultraviolet adsorption E_{max}	at λ, mμ
3-Phenylhexadiene-1,5	55	2	1.5141	206	253.5
				228	258.5
1-Phenylhexadiene-1,5	83.5	3	1.5421	19900	250
				1460	283.5
				997	292.5
3-Phenylheptadiene-1,5	77.5	4	1.5135	181	248
				225	253.5
				251	258.5
1-Phenylheptadiene-1,5	119.5	8	1.5407	19000	250.5
				1426	284
				. . .	293
3-Methyl-4-phenylhexadiene-1,5	96.5	16	1.5122	240	253.5
				255	259
4-Methyl-1-phenylhexadiene-1,5	110	10	1.5336	19400	251
				1500	284
				. . .	293

The displacement reaction of sodium allylbenzene on methyl bromide was studied in an effort to determine the amount and nature of the products and if the order of addition of the reactants had any effect on the course of the reaction. The reaction was carried out by two methods: in the first method (A), the sodium allylbenzene in liquid ammonia was added to a fourteen-mole excess of liquid methyl bromide; and in the other (B), the

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(6) T. W. Campbell and W. G. Young, THIS JOURNAL, **69**, 3066 (1947).

(7) T. W. Campbell and W. G. Young, *ibid.*, **71**, 296 (1949).

(8) A. C. Cope, K. E. Hoyle and D. Heyl, *ibid.*, **63**, 1843 (1941).

methyl bromide was added dropwise to the solution of sodium allylbenzene in liquid ammonia until an equivalent amount had been added.

The separation of the reaction products was carried out by fractional distillation and the identity of the various products was established by comparison of boiling range, refractive index and ultraviolet absorption spectra. The results of these analyses are given in Table III.

TABLE III

TOTAL YIELD AND PRODUCT COMPOSITION FROM REACTION OF SODIUM ALLYLBENZENE WITH METHYL BROMIDE

Method	A	B
Yield of methylated products, %	70	42
Composition		
3-Phenyl-1-butene, %	91.5	38
cis-1-Phenyl-1-butene, %	8.5	12
trans-1-Phenyl-1-butene, %		14
3-Methyl-3-phenyl-1-butene, %		36
Dimer, %	14	16
Total yield, %	84	58

It is interesting to note that only upon the addition of sodium allylbenzene to the methyl bromide (method A), that is, where the methyl bromide is always in excess, does a reasonably clear-cut reaction take place. Where the sodium allylbenzene is in excess, mono- and disubstitution products of allylbenzene result in approximately equal amounts. The bottoms from both methods were found to be made up of the same material, a dimer of allylbenzene.

Thus when the sodium allylbenzene is in excess, the unreacted material has an opportunity for an acid–base exchange with a product molecule (*i.e.*, 3-phenyl-1-butene) to form a new sodium salt which in turn can react with methyl bromide to form 3-methyl-3-phenyl-1-butene. However, when the methyl bromide is in large excess, this exchange has little chance to occur.

When two moles of sodamide were used per mole of allylbenzene and to this was added two moles of methyl bromide, two products resulted, α,α-dimethyl allylbenzene and α,γ-dimethylallylbenzene, presumably through reaction V.

Experimental[9]

Reaction of Sodium Allylbenzene with Allylic Halides.—The method described by Levy and Cope[4] was used. The sodium allylbenzene solution was added to the solution of allylic halide in liquid ammonia. The reaction mixture from 0.5 mole of sodium allylbenzene and 0.508 mole of allylic halide was treated with 150 ml. of ether and the excess sodamide neutralized with ammonium chloride. After the ammonia had evaporated, water was added and the ether layer separated. The aqueous phase was extracted with ether and the ether layers were combined, washed, neutralized and dried. The ether solutions from the various reactions were handled in the following manners:

Analysis by Fractional Distillation.—After careful removal of the ether by distillation, the main product was distilled at reduced pressure in a center-rod type of column (rated at 20 theoretical plates at atmospheric pressure). The higher boiling residues, containing the primary-type of addition product, were distilled through a 12-inch Vigreux column with a heated jacket. The analyses were based on the weighted values of the refractive indexes of the cuts. The total yields ranged from 67 to 86%.

Analysis by Fractional Distillation of Hydrogenated Reaction Mixture.—After careful removal of ether, the product was diluted with 95% ethanol (100 ml. per 0.1 mole) and hydrogenated with platinum oxide catalyst in a Parr-type hydrogenation apparatus at 50 p.s.i. initial pressure and room temperature. The volume of hydrogen consumed varied from 1.99 to 2.02 moles of hydrogen per mole of product.

Fractional distillation was carried out as described above for the non-hydrogenated products. The various fractions of the phenylhexanes were converted to the diacetamido derivatives,[10] and melting points compared with derivatives from known compounds or with values from the literature. The properties of the phenylhexanes and corresponding diacetamido derivatives are given in Table IV.

Under these conditions no thermal rearrangement of secondary isomers is likely as the unsaturated compounds are never heated above room temperature; hence any primary-type products that are formed are produced in the initial reaction.

Analysis by Ultraviolet Absorption Spectra.—In all studies of spectra the Beckman model DU quartz photoelectric spectrophotometer was used. The ultraviolet absorption spectra were measured for the various reaction mixtures and for pure samples of the hydrocarbons involved. The analyses were made using the molar extinction coefficients at 250 mμ, since maxima occur at this wave length for the primary-type product ($C_6H_5CH{=}CHCH_2R$), the secondary-type product ($C_6H_5CHRCH{=}CH_2$) and the reaction mixtures.

Isomerization of Secondary to Primary-type Products.—The secondary-type of products ($C_6H_5CHR{-}CH{=}CH_2$) were isomerized by sealing 15 ml. of the material in a small ampule and heating in a vapor-bath of the desired temperature (generally 175°) until the isomerization was complete (determined by small control ampules). The resultant material was then purified by fractional distillation at reduced pressure.

Reaction of Sodium Allylbenzene with Methyl Bromide Method A.—11.5 g. (0.50 mole) of sodium in 300 ml. of liquid ammonia was converted to sodamide with $FeCl_3$ and 69 g. (0.585 mole) of allylbenzene was added over a 20-minute period. The red solution of sodium allylbenzene was run into approximately 690 g. (7.3 moles) of anhydrous liquid methyl bromide in a two-liter flask with stirring. A vigorous reaction ensued. When the reaction was complete, the ammonia and excess methyl bromide were allowed to evaporate and water was added. The organic material was extracted with benzene, the benzene solution was dried, and the solvent was removed through a short column. The yield of crude material was 76.7 g. (101%). This product was very carefully distilled through an 8 mm. × 18-inch Podbielniak Heligrid column at 150 mm. pressure, boil-up rate 3 ml./min. and reflux ratios between 30 and 120 to 1. The results are given in Table III under Method A.

The main fraction of 3-phenyl-1-butene had $n^{25}D$ 1.5050. A portion of this material was passed through 28–200 mesh silica gel in an effort to further separate it from conjugated isomers and oxidized material. The resulting refractive index was 1.5048 and the ultraviolet absorption spectra showed the following maxima

Molar extinction coefficient	Wave length, mμ
295	253
296	258
171	267.5

The residue from the distillation was diluted with 250 ml. of petroleum ether and passed through 60 ml. of activated alumina. The eluate was then stripped of solvent and distilled in a Hickman Vacuum Still at 1 to 1.5 mm. pressure. The resulting distillate was a colorless, viscous liquid having $n^{25}D$ 1.5620.

Method B.—One-half mole of sodium allylbenzene in liquid ammonia was prepared as in Method A. Approximately 60 g. of methyl bromide was distilled into a dropping funnel through a silica gel tube and added to the ammonia solution until all of the red color had disappeared. This required *ca.* 27 ml. or 0.490 mole of methyl bromide. After

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[9] All melting points and boiling ranges are uncorrected except where indicated.

[10] V. H. Ipatieff and L. Schmerling, THIS JOURNAL, 59, 1056 (1937).

TABLE IV

PHYSICAL PROPERTIES OF HYDROGENATED REACTION PRODUCTS AND CORRESPONDING DIACETAMIDO DERIVATIVES

Compound	B.p., °C.	B.p., Mm.	n^{25}D	Diacetamido deriv. m.p. (cor.), °C.	Analysis of diacetamido deriv., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1-Phenylhexane	118	18	1.4839	203–204	69.53	8.75	...	69.33	8.79	...
3-Phenylhexane	83	18	1.4849	205–206	69.53	8.75	10.14	69.57	9.03	10.16
1-Phenylheptane	85	3	1.4835	196–197	70.31	9.02	9.65	69.91	9.33	9.59
3-Phenylheptane	100	18	1.4832	164–165	70.31	9.02	9.65	70.49	9.44	...
1-Phenyl-4-methylhexane	85–86	3	1.4838	197–198	70.31	9.02	9.65	70.61	9.40	9.53
3-Phenyl-4-methylhexane	95	12	1.4898	194–195	70.31	9.02	9.65	70.55	9.35	9.56

evaporation of ammonia the residue was diluted with benzene and filtered to remove the salt. The filtrate was stripped of solvent in a short column and the residue (78.6 g.) carefully distilled in the Podbielniak column under the same conditions as described under Method A. The results are given in Table III under Method B. Ultraviolet spectra were taken of several fractions to confirm the presence of conjugated olefins, *cis*- and *trans*-1-phenyl-1-butene. The refractive indexes of these fractions approach closely the most recent values[11] (n^{25}D 1.5314 and 1.5382) for these olefins.

The distillation residues were treated in the same manner as in Method A and were identical. Molecular weight determination on the dimer by bromine titration gave 231 (calculated 236). Ultraviolet absorption spectra showed the following maxima (with shoulder at 283 mμ).

Molar extinction coefficient	Wave length, mμ
5450	249
240	292.5

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.03; H, 8.54.

Dimethylation of Allylbenzene.—Fifty grams of allylbenzene (0.42 mole) was added to a solution of one mole of sodamide in 1.5 l. of liquid ammonia. Methyl bromide was distilled into the mixture until the color was completely discharged. The solvent was evaporated and organic material was taken up in benzene, the benzene solution washed with dilute sulfuric acid, dried and distilled through a column packed with platinum gauze, which had been described previously.[6] The distillation yielded 53% of α,α-dimethylallylbenzene, b.p. 188° (760 mm.), n^{25}D 1.5085, d^{20}_4 0.9039; *MR*D calcd., 48.93; found, 49.12.

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.24; H, 9.7.

A second product, b.p. 197° (760 mm.), n^{25}D 1.5252, was obtained in 3% yield. It gave on ozonization, acetophenone (identified as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 248°) and propionaldehyde (identified as its methone derivative[12]). This indicates the formation of some mixed primary–secondary-type of addition, with the formation of $C_6H_5C(CH_3)$=$CHCH_2CH_3$.

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(11) D. L. Hagmann, Ph.D. Thesis, University of California at Los Angeles, 1950.

(12) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

LOS ANGELES 24, CALIFORNIA

RECEIVED JULY 10, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Sulfonic Acid Esters of Aminoalcohols

BY ARTHUR C. COPE AND MARION BURG[1]

A number of esters of aliphatic and aromatic sulfonic acids and aminoalcohols containing secondary or tertiary amino groups have been prepared (and isolated as hydrochlorides) by reaction of the aminoalcohols, their hydrochlorides or sodium aminoalkoxides with sulfonyl chlorides at low temperatures. Chemical and pharmacological properties of the esters are reported.

Since many carboxylic acid esters of aminoalcohols have local anesthetic and other pharmacological activity, we were interested in studying sulfonic acid esters of aminoalcohols, which might differ in pharmacological properties because of their chemical dissimilarities. Sulfonic acid esters, for example, differ from carboxylic acid esters in rate and manner of hydrolysis, and are much more reactive alkylating agents.

A few sulfonic acid esters of aminoalcohols are mentioned in the patent literature, without details of methods of preparation or properties.[2] The preparation of 2-dimethylaminoethyl methanesulfonate hydrochloride from 2-dimethylaminoethanol and methanesulfonyl chloride has been reported,[3] and while our work was in progress the preparation of 1-dimethylamino-2-propyl methanesulfonate hydrochloride by a similar procedure was described.[4]

Monoalkylaminoalcohols (2-cyclohexylaminoethanol, 2-*n*-amylaminoethanol and 1-cyclohexylamino-2-propanol) were converted to the sulfonic acid ester hydrochlorides listed in Table I by first preparing their hydrochlorides to block amide formation, and then adding various aliphatic and aromatic sulfonyl chlorides in chloroform containing one to four equivalents of pyridine at 0° (Procedure A). The yields of esters obtained from the primary alcohols were much higher (29–67%) than from the secondary alcohol, 1-cyclohexylamino-2-propanol (16%). A side reaction which occurred at higher temperatures in the preparation of 2-cyclohexylaminoethyl methanesulfonate hydrochloride was a displacement of the methanesulfonate ester group by chloride, forming 2-cyclohexylaminoethyl chloride hydrochloride, in an alkylation which for convenience can be represented as

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(1) Sharp and Dohme Research Associate.

(2) The patents concerned are listed by K. H. Slotta and R. Behnisch, *Ann.*, **497**, 170 (1932).

(3) R. D. Haworth, A. H. Lamberton and D. Woodcock, *J. Chem. Soc.*, 182 (1947).

(4) N. L. Wendler and M. Tishler, THIS JOURNAL, **71**, 374 (1949).