Table I
Yield of Asp and Glu Diesters Prepared by the Copper-Catalyzed Hydrolysis of Corresponding Diesters

Ester	Crude yield,[a] mol %	Yield of recrystd ester, mol %	Mp, °C	Lit. mp, °C	Registry no.
Glu (OBzl)	95	74	169–170	169–170[b]	1676-73-9
Glu (OBzl-*p*-Cl)	93	54[c]	169–170	176[d]	20806-20-6
Glu (OBzl-*p*-NO_2)	87	54[c]	158–159[e]	171–172[f]	3940-62-3
Glu (OMe)	99		180[d]	182[d,g]	1499-55-4
Glu (OEt)	96		192–194	194[g]	1119-33-1
Asp (OBzl)	98	67	220–222	221[h]	2177-63-1
Asp (OBzl-*p*-Cl)	98	83	208–210	208[h]	14335-22-9
Asp (OBzl-*p*-NO_2)	97	88	193–195	189–190[f]	3940-63-4
Asp (OMe)	98		188–190[i]	191–193[g,i]	2177-62-0

[a] Measured by TLC of an aliquot of the reaction mixture. [b] J. Noguchi, *Chem. Abstr.*, 59, 10238 (1963). [c] The reduced yield of these esters is possibly due to their very low solubility in all common solvents. [d] M.-H. Loucheux and M. J. Parrod, *C. R. Acad. Sci., Ser. C*, 267, 614 (1968). [e] It has been observed that this compound may show more than one distinct melting point, presumably because of the existence of several crystalline forms. [f] Reference 6. [g] Reference 1, p 929. [h] M. Hashimoto and J. Aritomi, *Bull. Chem. Soc. Jpn.*, 39, 2707 (1966). [i] As hydrochloride.

Table II
Rate Constants for the Cu(II)-Catalyzed Hydrolysis of Glutamic Acid Diesters

Diester	Rate[a], min^{-1}	Registry no.
Glu (OBzl-*p*-NO_2)$_2$	0.54	47662-90-8
Glu (OBzl)$_2$	0.54	2768-50-5
Glu (OBzl-*p*-Cl)$_2$	0.14	56437-39-9
Glu (OMe)$_2$	0.070	6525-53-7
Glu (OEt)$_2$	0.067	16450-41-2
Glu (OEt 2-Cl)$_2$	0.050	56437-40-2

[a] pH 8, 32°.

were visualized with ninhydrin and the ninhydrin color eluted with ethanol and measured at 250 nm. The rates of the reaction are given in Table II.

The rates are consistent with the mechanism proposed, in that the ethyl ester reacts more slowly and the benzyl ester more rapidly than the methyl ester. Esters substituted with chlorine, however, react more slowly than do unsubstituted esters, in spite of the electron-withdrawing nature of the chlorine moiety. This anomaly is probably due to the large volume occupied by a chlorine atom, as reactions of amino acid copper complexes appear to be very susceptible to steric hindrance.[12]

Registry No.—Dibenzyl aspartate, 2791-79-9; *p*-chlorodibenzyl aspartate, 56437-41-3; *p*-nitrodibenzyl aspartate, 47636-64-6; dimethyl aspartate, 6384-18-5.

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Simple, Novel Deaminations. VII.[1,2] The High-Yield Conversion of Primary and Secondary Carbinamines to Alcohol and Formate Esters via Nucleophilic Substitution of Protonated Sulfonimide Derivatives

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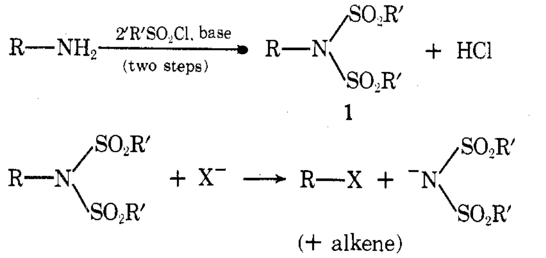
The conversion of the aliphatic primary amino group to the primary hydroxyl group has been, historically, relatively difficult to achieve. Until now the apparent best yielding procedures (25–90%) involve the pyrolysis of *N*-nitrosoamides[4] or the treatment of arylalkyl triazenes with carboxylic acids.[5] Both of these methods exclusively produce esters as the carbon–oxygen product. To obtain the alcohol, a subsequent ester hydrolysis is obligatory. Moreover skeletal rearrangements are common, although in nonpolar solvents the occurrence of this problem is reduced, presumably because the mechanism in nonpolar solvents is usually S_N2.[4–6]

In previous papers in this series,[1–3,7,8] it has been found that various sulfonimide activating groups (1), analogous to various sulfonate ester activating groups in the alcohol series, are readily susceptible to nucleophilic substitution (Scheme I). These processes occur with ease, most probably because sulfonimide anions are weak bases compared to NH_2^- anions, and consequently sulfonimide anions are relatively good leaving groups. For example, in these and other laboratories, primary and secondary carbinamines have been converted, usually in high yields, to alkyl halides,[2,3,8,9] to alkenes,[1–3,7–9] to ketones,[1] and to alkanes[12] and other functional groups.[2,3,8,9,11,13]

Results

However, all our attempts to convert these activated sulfonimide derivatives (1) to alcohols via the use of the hydroxide anion as a nucleophile have been essentially unsuc-

Scheme I



where R = various primary or secondary alkyl groups
R′ = p-$CH_3C_6H_4$, C_6H_5, p-BrC_6H_4, p- and m-$NO_2C_6H_4$, and CF_3
X = Cl^-, Br^-, I^-, SH^-, N_3^- and aniline

cessful, presumably owing to the highly preferential saponification at the sulfur–nitrogen bond. If, however, conditions could be designed to increase the susceptibility of the C–N bond to nucleophilic cleavage and/or to decrease the susceptibility of the S–N bond to saponification, then the conversion of the C–N bond to the C–O bond may be easily achieved. Such conditions are apparently obtained when various sulfonimides (**2**, **4–8**) are heated at 50–130° with ca. 58% aqueous hydrogen iodide in dimethylformamide (DMF); under these conditions, the already good sulfonimide leaving group is apparently further activated by protonation.[14a] For example, when *N*-*n*-hexyl-*N*,*N*-di(*p*-toluene)sulfonimide (**2**) is treated with a two- to threefold molar excess of 58% aqueous HI in DMF for 94 hr at 125°, a 98% conversion of the C–N bond to the C–O bond is indicated by the isolation and characterization of 1-hexanol (60.3%), 1-hexyl formate (37.6%), and the di(*p*-toluene)sulfonimide leaving group (**3**) in 99% yield.

Results under various conditions are summarized in Table I. These results indicate that the method worked essentially as well for a typical secondary carbinamine as for a typical primary carbinamine. Not surprisingly, however, activated cyclohexylamines (**7** and **8**) gave only cyclohexene. Under analogous conditions similar results were obtained when known iodocyclohexane or known cyclohexanol were substituted for sulfonimide-containing cyclohexyl substrates. In fact, cyclohexyl substrate **8** has been shown to undergo thermal elimination (in up to 70% yield by gas chromatography) simply by refluxing in DMF without added nucleophiles or acid.

The experimental procedures involved in characterizing and isolating the products of these deaminations are simple. In particular, a very efficient procedure for preparing sulfonimides has been developed in our laboratories,[2,3,8,9] and all the acid-induced runs on these substrates were clean and efficient. Most important, all of the runs proceeded to give 90–98% yields of products *without any observed skeletal rearrangement.*

The products were qualitatively and quantitatively analyzed with the aid of GLC, ir, and NMR, as well as by comparison with known synthetic or commercial standards. The alcohols were further characterized via their 3,5-dinitrobenzoate ester derivatives. The protonated sulfonimide leaving groups were isolated as crystalline compounds and identified by comparison of various physical properties with those of known materials synthesized by other means. Since the yields of the protonated sulfonimide leaving group in these runs were in the order of ~99%, the present-

Table I
Products[a] from Reaction of Various *N*-Alkyl-*N*,*N*-disulfonimides with Aqueous HI in DMF

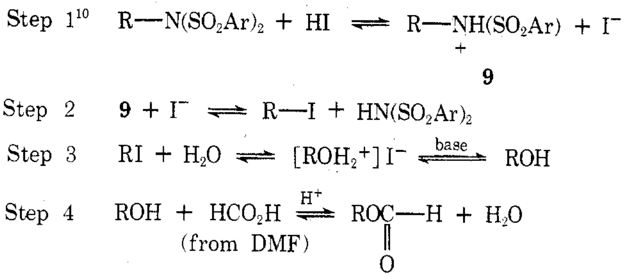
Compd	Structure[b]	Conditions [c]	Products[d] (% yield)[e]
2	*n*-Hexyl-*N*(Ts)$_2$ mp 114.9–115.2°	DMF, 125° 94 hr	1-Hexanol (60.3) 1-Hexyl formate (37.6) 3 (99.0)
4	*n*-Hexyl-*N*(Bs)$_2$ mp 99.8–100.0°	DMF, 130° 72 hr	1-Hexanol (55.5) 1-Hexyl formate (35.6) (Bs)$_2$NH (97.7)
5	*n*-Hexyl-*N*(Ns)$_2$ mp 132.8–133.1°	DMF, 100° 47 hr	1-Hexanol (57.5) 1-Hexyl formate (38.6) (Ns)$_2$NH (99.6)
	(1-Iodohexane)[f]	DMF, reflux 96 hr	1-Hexanol (50.4) 1-Hexyl formate (35.0)
6	*dl*-2-Heptyl-*N*(Ns)$_2$ mp 129.0–131.0°	DMF, 50° 24 hr	2-Heptanol (8.0)[g] 2-Heptyl formate (89.6) (Ns)$_2$NH (98.0)
7	Cyclohexyl-*N*(Bs)$_2$ mp 189.0–190.0°	DMF, 100° 46 hr	Cyclohexene (73.7)[h] (Bs)$_2$NH (98.2)
8	Cyclohexyl-*N*(Ns)$_2$ mp 193.0–195.0°	DMF, 85° 48 hr	Cyclohexene (90.2)[h] (Ns)$_2$NH (98.6)

[a] All products were isolated directly, independently separated, and fully characterized. [b] The synthesis, purification, structural assignments, and further physical data for each of these starting materials are thoroughly outlined in ref 3. Abbreviations: Ts = *p*-toluenesulfonyl, Bs = *p*-bromobenzenesulfonyl, and Ns = *p*-nitrobenzenesulfonyl. [c] Solvent, temperature (°C), and reaction time. Reaction times were extended in order to maximize yields; it is likely that shorter times in some instances could produce similar yields. [d] All volatile products were characterized by ir, proton NMR, and GLC behavior in comparison with known synthetic or commercial standards. The alcohols were additionally converted into their 3,5-dinitrobenzoate esters. The protonated leaving group, 3, and its analogs, were fully characterized as noted in ref 3. [e] Numbers listed indicate *mole* percentages of each compound based on the disulfonimide as limiting reagent; i.e., the sum of the percent yield for alcohol and ester is a direct measure of the total C–N to C–O conversion. Each reaction was run at least in duplicate and the yields noted are easily reproducible. In the cases of alcohol–ester mixtures, quantitative analysis was performed by the internal standard GLC method (cf. Experimental Section) on the in-hand, isolated, two-component mixture. [f] Known, control reaction; no evidence of iodoalkane at end of reaction period. [g] Trace amounts of *cis*- and *trans*-2-heptene also noted in this run. The 2-heptenes (with the trans isomer predominating) are artifactual side products derived presumably from the initially produced substitution products. Under kinetically controlled conditions, the olefins(s) can be noted to accumulate later in the reaction period; the amount of olefinic product, which can be significant at elevated temperatures, can be controlled and essentially eliminated by lower temperatures and shorter reaction times. [h] No substitution products elicited by GLC. See also discussion in text.

ly reported reaction may also be considered to be an excellent procedure for making sulfonimides. No previously reported procedures give such good yields of these sulfonimides.[14b] For a complete detailed listing of physical properties, melting points, literature citations, etc., see ref 3, Table V.

A hypothetical mechanism for the reaction is given in Scheme II. A detailed discussion of the mechanism of this reaction will be presented in a later paper.

Scheme II



Step 1[10] $R{-}N(SO_2Ar)_2 + HI \rightleftharpoons \underset{\mathbf{9}}{R{-}\underset{+}{N}H(SO_2Ar)} + I^-$

Step 2 $\mathbf{9} + I^- \rightleftharpoons R{-}I + HN(SO_2Ar)_2$

Step 3 $RI + H_2O \rightleftharpoons [ROH_2{}^+]\,I^- \overset{\text{base}}{\rightleftharpoons} ROH$

Step 4 $ROH + \underset{\text{(from DMF)}}{HCO_2H} \overset{H^+}{\rightleftharpoons} RO\underset{\underset{O}{\|}}{C}{-}H + H_2O$

Experimental Section

Materials. All chemicals used in these preparations were reagent grade or better. The DMF was spectrophotometric grade (Fisher Scientific Co.) and the *o*-dichlorobenzene was Aldrich reagent grade.

Instrumentation. Melting points, ir, proton NMR, and analytical gas–liquid partition chromatography (GLC) were performed on instruments described in Part V in this series.[3] The reaction mixtures were routinely examined for homogeneity, maximum number of products, or diagnostic experiments (such as GLC of known mixtures, peak enhancement experiments, temperature programming, etc.) on various columns of varying polarity which included 10% QF-1 and 10% Carbowax 20M on 60/80 mesh Chromosorb W, and 10% SE-30, 5 and 10% DEGS, and 10% FFAP on 80/100 Chromosorb W. (All solid supports were acid washed, DMCS treated.) The quantitative analysis of the liquid mixtures was performed on an F & M Scientific Hewlett-Packard Model 407 high-efficiency gas chromatograph using the 10% Carbowax 20M column (6 ft × 0.125 in.), a column temperature of 95°, and helium as the carrier gas. These conditions were used for both the standardizations and the unknown determinations. Response factors for the 1-hexanol and 1-hexyl formate vs. the internal standard, *o*-dichlorobenzene, were obtained from the least-square slopes of the plots of known weight ratios vs. area ratios. GLC peak areas in this study were estimated by chromatographing, cutting out the peaks directly, and weighing in triplicate, and the average value was taken for each solution. The response factors were validated for the concentration range normally encountered.

For quantitative purposes commercial reagent grade 1-hexanol and 1-hexyl formate (both of which had several unidentified impurities by analytical GLC) were both preparatively chromatographed on a Hewlett-Packard 776 Prepmaster Jr. instrument using an 80 × 0.75 in. 20% Carbowax 20M column at 85°. The analytically pure samples thus obtained were then used to obtain the response factor vs. the internal standard as noted above. With the aid of these factors, quantitative analytical GLC was used to determine the compositions of the mixtures noted in Table I.

Deaminations in DMF with Aqueous Hydriodic Acid (Methods). The results of all trials are recorded in Table I. All experiments were similarly conducted, and only samples will be presented in detail. It should be noted that all isolations of liquids included bulb-to-bulb distillations. It was essential for maximum efficiency (and yield) in these distillations to wrap the glass tubing between the bulbs with a 4 ft × 0.75 in. heating tape (Glas-Col), and to maintain magnetic stirring of the reaction mixture after one freeze–evacuation (to ca. <0.1 mmHg)–thaw cycle.

The *N*-alkyl-*N,N*-di(sulfonimides) (**2, 4–8**) were prepared and identified by the procedures previously described in Part V in this series.[3]

Deamination of 2 with Aqueous HI in DMF. 2 (40.96 g, 0.10 mol), mp 114.9–115.2°, was dissolved in 100 ml of DMF and 43.88 g (0.20 mol) of 58.3% HI added. The mixture was heated to ca. 125° for 94 hr under reflux. The reaction mixture was then bulb-to-bulb distilled; the distillate was mixed with 50 ml of water and extracted with ten 20-ml portions of diethyl ether. The combined ether extracts were then washed with two 50-ml portions of water and dried (Na_2SO_4). The ether was distilled off and nitrogen was passed over the remaining water-white liquid for 10 min. This residue was then washed with 2 × 10 ml of water and dried over type 4A molecular sieves. The product obtained, a mixture of 1-hexanol and 1-hexyl formate, totaled 11.06 g. Quantitative GLC determination of the product mixture yielded 4.90 g of 1-hexyl formate (37.6 mol%) and 6.16 g of 1-hexanol (60.3 mol%). In addition, similar mixtures from other runs of this preparation were separated and independently isolated by preparative GLC. Both products thus derived were identical with known standards in ir, proton NMR, and analytical GLC retention behavior. The 1-hexanol was also characterized by its 3,5-dinitrobenzoate ester derivative (mp 58.0°, lit.[15] mp 58.4°). This derivative had an ir, melting point, and mixture melting point identical with those of the 3,5-dinitrobenzoate of known 1-hexanol.

The solid residue left behind in the bulb-to-bulb distillation was recrystallized from 1500 ml of benzene, yielding 29.67 g of **3**, mp 168–169° (lit.[3] mp 168–169°). Concentration of the mother liquor yielded 2.53 g more of **3**, mp 168–169°. Thus a total yield of protonated leaving group of 32.20 g (99.0%) was obtained. Isolated **3** also had an ir and proton NMR identical with those of known **3**.

Disulfonimides **4** and **5** were similarly deaminated, worked up, the resultant products GLC analyzed, and the results noted in Table I.

Deamination of 7 with HI in DMF. 7 (13.43 g, 0.025 mol), mp 189–190°, was dissolved in 40 ml of DMF, 10.97 g (0.050 mol) of 58.3% HI was added, and the mixture was heated at ca. 100° for 46 hr under reflux. After bulb-to-bulb distillation, the distillate was fractionally distilled to yield 1.51 g (73.7 mol%) of cyclohexene, bp 82–83°, which was homogeneous to GLC. The product had an ir spectrum (neat) which was identical with that of an authentic sample of freshly distilled cyclohexene. The protonated leaving group was recrystallized from 100 ml of 4:1 (v:v) water–acetone, yielding 9.25 g of di(*p*-bromobenzene)sulfonimide, mp 232–233° (lit.[3] mp 232–233°). Concentration of the mother liquor gave 2.03 g more, mp 232–233°. Thus a total yield of 11.28 g (98.2%) was isolated. As in the above preparation, the isolated protonated leaving group had ir and proton NMR identical with those of known material synthesized by literature methods (for citations see ref 3).

Cyclohexyl substrate **8** was similarly treated and analyzed.

The HI runs on the *dl*-2-heptyl substrate (**6**) were performed and analyzed analogously. The 3,5-dinitrobenzoate ester of the product 2-heptanol had mp 49.0–50.5° (lit.[16] mp 48.5–50°); the ir spectrum (CCl_4), melting point and mixture melting point of known 2-heptyl 3,5-dinitrobenzoate and the derivatized reaction product were identical. Known 2-heptyl formate was made by the method of Staab[17] using *N*-formyl imidazolide. This product was used for the internal standard GLC analysis, and was identical in all respects (ir, NMR, and analytical GLC behavior) with the ester product formed in the reaction.

In an identical run on the 2-heptyl substrate, the product mixture after ethereal extraction was further diluted and then refluxed overnight with a 3 molar excess of freshly opened $LiAlH_4$. Work-up included decomposition of the excess hydride with very dilute aqueous H_2SO_4, filtration, washing, drying (4A molecular sieves), and removal of the ether. These procedures provided an essentially pure (only a trace of unreduced 2-heptyl formate was elicited by GLC) 2-heptanol in 94.7% yield (based on **6**), which was identical in all respects with known material.

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Registry No.—**2**, 24332-41-0; **3**, 3695-00-9; **4**, 52374-06-8; **5**, 24332-42-1; **6**, 52374-08-0; **7**, 52374-15-9; **8**, 24332-44-3; 1-hexanol, 111-27-3; 1-hexyl formate, 629-33-4; $(Bs)_2NH$, 1156-18-9; $(Ns)_2NH$, 4009-06-7; 2-heptanol, 543-49-7; 2-heptyl formate, 56282-06-5; cyclohexene, 110-83-8.

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A Novel Method for Sulfinylation Reaction of Lithioamines Using Sulfur Dioxide

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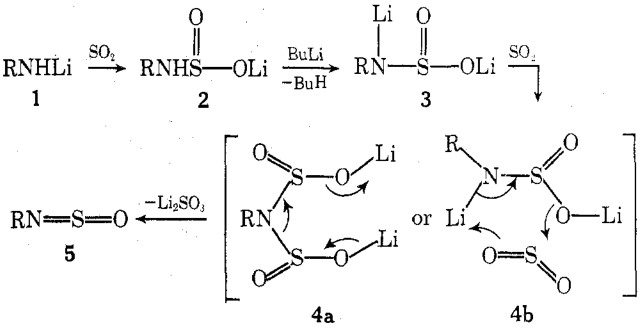
Thionyl chloride is usually used as a sulfinylating reagent of amines or amides in the presence of base such as pyridine or trimethylsilyl amide.[1-9] In connection with a utilization of sulfur dioxide, we have found a novel and direct sulfinylation reaction of lithioamines with sulfur dioxide to afford *N*-sulfinylamines.

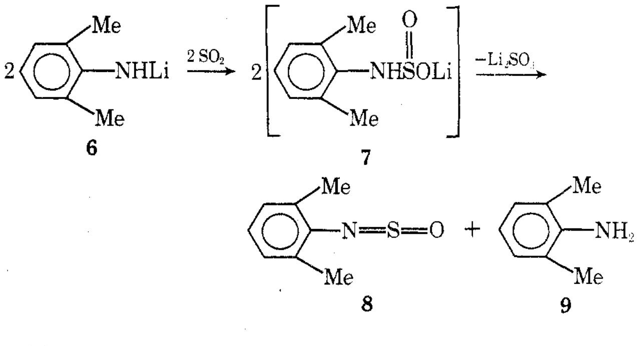
The lithioamine **1** prepared in situ from primary amine and butyllithium in tetrahydrofuran was treated with an equimolar amount of sulfur dioxide to form lithium aminosulfinate **2**. The A_2B_2 signals in the NMR spectra were shifted downfield from δ 6.07 and 6.47 for **1** to 6.39 and 6.59 for **2** ($R = p\text{-}CH_3C_6H_4$). Lithium *N*-(*p*-tolyl)aminosulfinate (**2**) was allowed to react with butyllithium to afford butane and the *N*-lithio-*N*-tolylaminosulfinate **3** ($R = p\text{-}CH_3C_6H_4$), which showed a new broad singlet at δ 6.66 in the NMR spectrum. Subsequently, introduction of a second mole of sulfur dioxide caused exothermic reaction and the characteristic bands of ν_{NSO} appeared at 1280 and 1157 cm^{-1} in the ir spectrum of the reaction mixture. After refluxing, the reaction mixture was distilled to separate *N*-sulfinyltoluidine **5** ($R = CH_3C_6H_4$).



The formation of *N*-sulfinyltoluidine by heating the intermediate **2** or **3** could not be observed even in the ir and NMR spectra of the reaction mixture, so the role of the second mole of sulfur dioxide is essential in the preparation reaction for *N*-sulfinylamine **5**. On the other hand, in the presence of the second mole of sulfur dioxide, **3** was easily decomposed to afford **5** and lithium sulfite which was detected by the $\nu_{SO_3{}^{2-}}$ bands of inorganic sulfite at 1010 and 960 cm^{-1} in the ir spectrum of solid mass in a distillation residue. Although the intermediate or transition state, **4a** or **4b**, could not be identified even by spectroscopic method such as ir or NMR, it will be postulated to explain the observed accelerating effect of the second mole of sulfur dioxide in the decomposition reaction of **3**. The same phenomena have also reported in the cases of the reaction of lithium *N*-lithiocarbamate with carbon disulfide to give isothiocyanate[10] and of the exchange reaction of heterocumulenes using organostannyl compounds.[11]

In usual cases for preparation of sulfinylamines, 2 mol each of butyllithium and sulfur dioxide per 1 mol of amine were used stepwise. The NMR data for the product mixtures indicated the complete and selective conversion of amines to sulfinylamines, but the yields shown in Table I were rather low, probably owing to hydrolysis of *N*-sulfinylamines.

The behavior of *N*-lithio-2,6-xylidine (**6**) was different from those of other *N*-lithioamines: it reacted exothermically with an equimolar amount of sulfur dioxide to afford an equimolar mixture of free xylidine and *N*-sulfinylxylidine in the absence of the second mole of sulfur dioxide, the latter being characterized by the comparisons of the ir and NMR spectra of the reaction products with those of the mixture of the authentic **8** and **9**.



The abnormal behavior of *N*-lithio-2,6-xylidine was assumed to be due to the steric effect of two *o*-methyl groups on the stability of **7** or **8**, although detailed investigations are now in progress.