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Novel Rearrangements of α-N-Alkylamido-substituted Sulfides and Sulfones

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The present paper describes novel rearrangements of α-N-alkylamido-substituted sulfides and sulfones promoted by strong bases such as NaH, lithium diisopropylamide and butyllithium, where the alkyl group linked to the sulfur migrates to the amide carbonyl carbon to give the corresponding ketones. The reactions are established as intramolecular rearrangements, and the mechanism is discussed.

Keywords——alkyl (N-alkylamido)methyl sulfide; alkyl (N-alkylamido)methyl sulfone; alkyl α-(N-alkylamido)benzyl sulfide; intramolecular rearrangement; sodium hydride; lithium diisopropylamide; butyllithium

Our previous communication[1] describes a novel rearrangement of alkyl (N-alkylamido)-methyl sulfides promoted by strong bases such as sodium hydride, lithium diisopropylamide (LDA) and butyllithium (BuLi), where the alkyl group linked to the sulfur migrates to the amide carbonyl carbon to give the corresponding ketones, as illustrated in the following equation.

$$R^1SCH_2N\begin{matrix}R^3\\ \diagdown COR^2\end{matrix} \longrightarrow R^1COR^2 + (CH_2{=}NR^3) + (S)$$

We now wish to report the details of our work in this area together with results on a similar mode of rearrangement recently found with the sulfone analogs.

Series of alkyl (N-alkylamido)methyl sulfides (**1a—j**) and sulfones (**2a—f**) were prepared from alkyl (N-alkylamino)methyl sulfide hydrochlorides[2] by acylation with acyl halide and

Table I. Efficiencies of Several Bases

Substrate: $C_6H_5CH_2SCH_2N\begin{matrix}CH_3\\ \diagdown COC_6H_5\end{matrix}$ (**1a**) and $C_6H_5CH_2SO_2CH_2N\begin{matrix}CH_3\\ \diagdown COC_6H_5\end{matrix}$ (**2a**)

Substrate	Base	Molar equiv. of base	Solvent	Temp.	Time (h)	Yield (%)[a] of $C_6H_5CH_2COC_6H_5$
1a	NaH	2	THF	Reflux	48	41
1a	NaH	3	THF	Reflux	23	48
1a	LDA	2	THF	Reflux	9	40
1a	LDA	3	THF	Reflux	5	48
1a	BuLi	3	THF	r.t.	2	37[b]
1a	*tert*-BuLi	3	THF	r.t.	3.5	52
1a	PhLi	3	Ether	r.t.	4	0[c]
2a	NaH	3	THF	Reflux	11	31
2a	LDA	3	THF	Reflux	3.5	31
2a	*tert*-BuOK	3	THF	Reflux	5	9
2a	BuLi	3	THF	r.t.	8	30
2a	*tert*-BuLi	3	THF	Reflux	6.5	5
2a	PhLi	3	Ether	Reflux	10	30

a) Based on the product actually isolated.
b) $C_6H_5COCH_2(CH_2)_2CH_3$ was obtained as a by-product in 41% yield.
c) $C_6H_5COC_6H_5$ was obtained in 66% yield.

triethylamine in chloroform and by oxidation of the resultant sulfides with potassium permanganate in acetic acid, both in fairly good yields.

We found that both the sulfides and sulfones underwent rearrangement to give the corresponding ketones. Control experiments included an examination of the efficiencies of several bases, *i.e.*, NaH, LDA, BuLi, *tert*-butyllithium (*t*-BuLi), phenyllithium (PhLi) and potassium *tert*-butoxide (*t*-BuOK), for the reactions of benzyl (N-methylbenzamido)methyl sulfide (**1a**) and sulfone (**2a**), selected as representative compounds. The results are summarized in Table I. The bases NaH, LDA and BuLi are effective for both reactions of **1a** and **2a**, giving deoxybenzoin in 30—40% yield.

Structural limitations on the starting sulfides and sulfones were then investigated. In the preparation of these substrates, acylation of $[R^1SCH_2\overset{+}{N}H_2R^3]Cl^-$, where $R^3=CH_3$, failed in introduction of some varied R^1 because of the poor stability of $R^1SCH_2NHR^3$ freed in the course of the acylation. When $C_6H_5CH_2$ was selected as R^3, N-acyl analogs with various R^1 could be obtained easily. Substrates, R^1S (or SO_2)$CH_2N\langle^{CH_2C_6H_5}_{COR^2}$ (**1b—h** and **2b—f**) with various R^1 and R^2 were subjected to the base-aided reaction and the results are summarized in Table II. The reaction of the sulfides was most accelerated by the use of a substrate, **1f**, possessing *p*-chlorophenyl groups ($R^1=p$-$ClC_6H_4CH_2$ and $R^2=p$-ClC_6H_4). As shown in the runs with **1h** and **2e**, when $R^2=n$-C_3H_7 the reactions of the sulfides and sulfones gave C_3H_7-$COCH_2C_6H_5$ in very poor or zero yields. Both the reactions are therefore restricted, in the main, to the use of substrates possessing an aromatic N-acyl group. The sulfide and sulfone reactions are distinguished from each other in the case of $R^1=n$-C_3H_7, where, in spite of the failure of ketone formation in the reaction of **1g**, the reactions with **2c**, **2d** and **2f** occurred to similar extents.

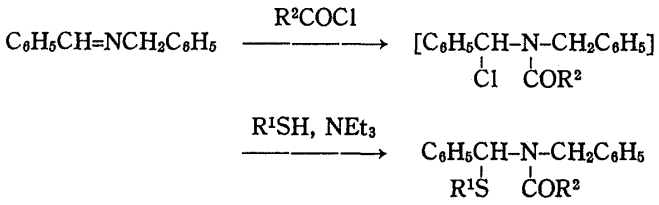
The reaction was extensively investigated with benzylidene analogs, alkyl α-(N-benzylamido)benzyl sulfides (**3a—g**), which were first synthesized by the reaction of N-(α-chlorobenzyl)-N-benzylamides, formed *in situ* from N-benzylidenebenzylamine and acyl chloride,

TABLE II. $R^1SCH_2N\langle^{CH_2C_6H_5}_{COR^2}$ (**1b—h**) or $R^1SO_2CH_2N\langle^{CH_2C_6H_5}_{COR^2}$ (**2b—f**) $\xrightarrow[\text{in THF}]{\text{NaH or LDA}}$ R^1COR^2

Compd. No.	R^1	R^2	Base[a]	Temp.	Time (h)	Yield (%)[b] of R^1COR^2
1b	$C_6H_5CH_2$	C_6H_5	NaH	Reflux	48	58
1c	$C_6H_5CH_2$	p-$CH_3OC_6H_4$	NaH	Reflux	47	22
1d	$C_6H_5CH_2$	p-ClC_6H_4	NaH	Reflux	13	55
1e	p-$ClC_6H_4CH_2$	C_6H_5	NaH	Reflux	14	61
1f	p-$ClC_6H_4CH_2$	p-ClC_6H_4	NaH	Reflux	11	70
1f	p-$ClC_6H_4CH_2$	p-ClC_6H_4	LDA	r.t.	5	68
1g	n-C_3H_7	p-ClC_6H_4	NaH	Reflux	72	0[c]
1h	$C_6H_5CH_2$	n-C_3H_7	NaH	Reflux	90	0[c]
1h	$C_6H_5CH_2$	n-C_3H_7	LDA	r.t.	8.5	12
2b	$C_6H_5CH_2$	C_6H_5	NaH	Reflux	9	12
2b	$C_6H_5CH_2$	C_6H_5	LDA	Reflux	5	18
2c	n-C_3H_7	C_6H_5	NaH	Reflux	15	43
2c	n-C_3H_7	C_6H_5	LDA	r.t.	17	32
2d	n-C_3H_7	p-ClC_6H_4	NaH	Reflux	5	33
2e	$C_6H_5CH_2$	n-C_3H_7	NaH	Reflux	3	Trace
2e	$C_6H_5CH_2$	n-C_3H_7	LDA	r.t.	2	5
2f	n-C_3H_7	p-$CH_3OC_6H_4$	NaH	Reflux	3.5	26

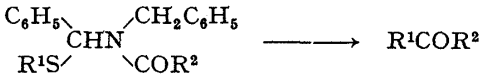
a) Molar ratio: base/substrate=3.
b) Based on the product isolated.
c) Recovery of the substrate.

with alkanethiol in the presence of triethylamine. This reaction was carried out by a procedure similar to the previously reported synthesis[3] of N-alkyl-N-(α-methoxybenzyl)-acetamide.



Attempts to synthesize the corresponding sulfones by oxidation encountered difficulties, because of lability of the benzylidene compounds to oxidation.

The benzylidene compounds, **3a—g**, were subjected to the reaction using LDA as a base. The results are summarized in Table III. As can be seen, in general, rather higher reactivity of the benzylidene analogs relative to that of the methylene analogs was observed.

TABLE III. 

3a—g

Compd. No.	R^1	R^2	Base[a]	Temp.	Time (h)	Yield (%)[b] of R^1COR^2
3a	$C_6H_5CH_2$	C_6H_5	LDA	r.t.	23	51
3b	*p*-$ClC_6H_4CH_2$	C_6H_5	LDA	0	4	78
3c	$C_6H_5CH_2$	*p*-ClC_6H_4	LDA	r.t.	4	70
3d	*p*-$ClC_6H_4CH_2$	*p*-ClC_6H_4	LDA	0	2	85
3e	*p*-$CH_3C_6H_4CH_2$	C_6H_5	LDA	r.t.	3	83
3f	*n*-C_3H_7	C_6H_5	LDA	r.t.	20	Trace
3g	$C_6H_5CH_2$	C_2H_5	LDA	r.t.	24	Trace

a) Molar ratio: base/substrate=3.
b) Based on the product isolated.

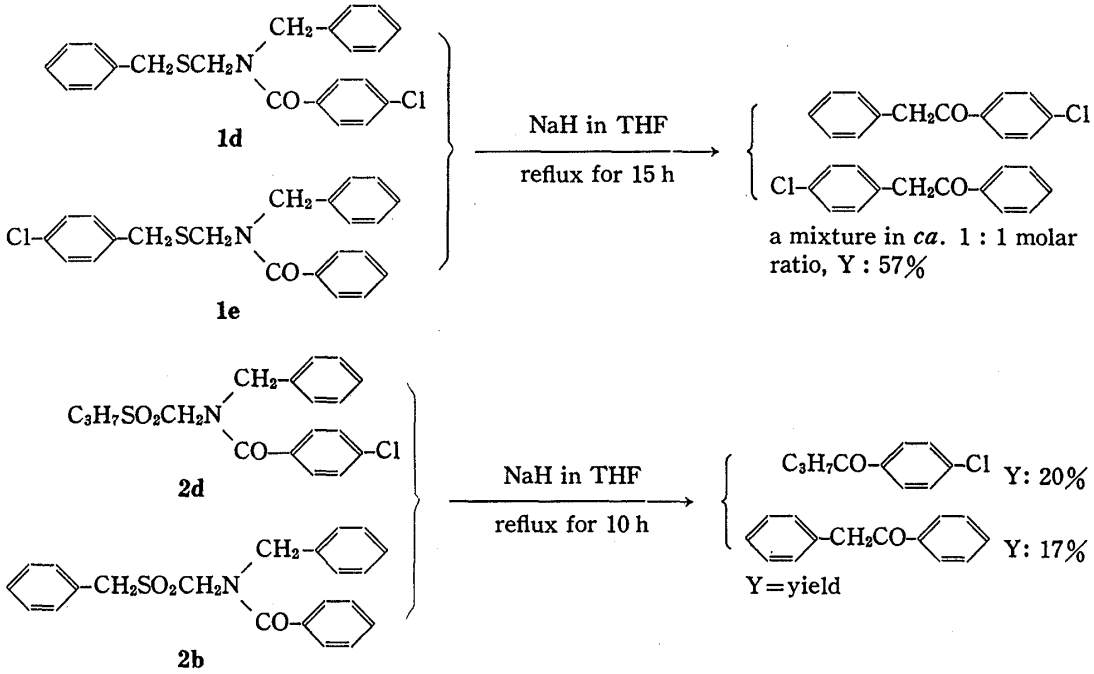
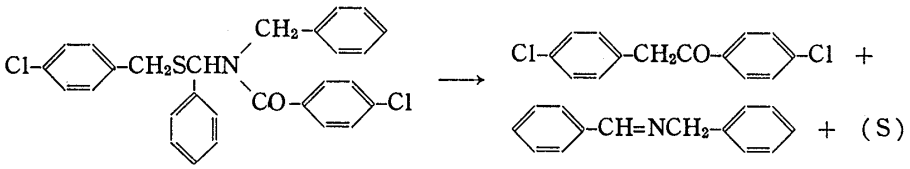


Chart 1

Cross experiments were then carried out with a mixture of **1d** and **1e** as the sulfides and with a mixture of **2b** and **2d** as the sulfones.

As shown in Chart 1, no crossed product was detected in the two experiments by GLC analysis. The reactions of the sulfide and the sulfone are, therefore, established as intramolecular reactions.

In experiments to clarify the stoichiometric relationship of the reaction, **3d** was used as a representative substrate. Considerable amounts of N-benzylidenebenzylamine and sulfur were obtained as by-products. Therefore the reaction sequence of **3d** can be represented as follows.



3d

A possible mechanism for the reactions of the sulfides and the sulfones is shown in Chart 2. A carbanion **4** formed initially undergoes thiazolidine formation followed by breakdown to give β-ketothiolate or β-ketosulfinate (**6**) and azomethine. The intermediate **6** is then converted into the ketone enolate **7** with elimination of sulfur or sulfur dioxide.

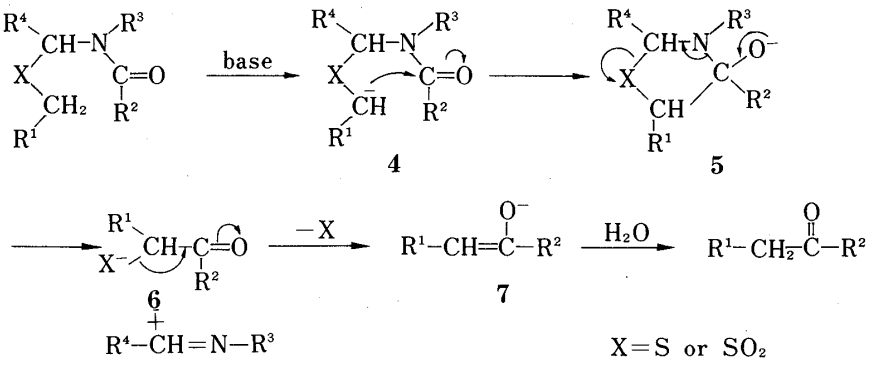
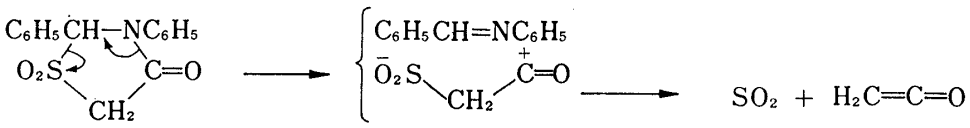


Chart 2

Such a conversion of α-ketothiolate has been reported[4] in the reaction of α-mercaptoketones induced by alkali or sodium ethoxide. A thiazoline derivative related to the intermediate **5**, where $X=SO_2$, has been reported[5] as a reaction product of Schiff's base, ketene and sulfur dioxide. This compound was reported to decompose into the starting materials when heated. This reaction, which can be represented as follows, provides support for the above mechanism for the reaction of the sulfones.



The formation of *p*-chlorophenylpropyl ketone from **2d** in contrast to the case of **1g** (see Table II) can be explained by the above mechanism as the result of easier formation of the carbanion at the α-carbon to the sulfonyl group than at the carbon adjacent to sulfide sulfur.

Experimental

All boiling and melting points are uncorrected. Infrared (IR) spectra were taken on a Hitachi EPI-G2 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi R-24 spectro-

meter and chemical shifts are given in ppm downfield from TMS. GLC analysis was carried out with a Hitachi 163 gas chromatograph using a column (3 mm × 1 m) packed with 10% SE-30 on Chromosorb W 80—100 mesh at a column temperature of 170°C and a flow rate of carrier gas (N_2) of 60 ml/min.

Preparation of Alkyl (N-Alkylamido)methyl Sulfides (1a—j) (see Table IV): General Procedure——Acyl chloride (0.5 mol) and then triethylamine (1.1 mol) were added to a suspension of alkyl (N-alkylamino)-

TABLE IV. Preparation of $R^1SCH_2N(R^3)COR^2$ (1a—j)

Compd. No.	Yield (%)	mp (°C) (Recry. solv.) bp (°C) (mmHg)	IR ν_{max}^{KBr} (cm^{-1}) –CON<	NMR[a] δ (in $CDCl_3$) $-SCH_2N<$	Formula	Analysis (%) Calcd (Found) C	H	N
1a	76	164—165 (0.25)	1632[b]	4.45(s)	$C_{16}H_{17}NOS$	70.80 (71.09)	6.33 (6.35)	5.16 (5.18)
1b	72	64—66 (EtOH)	1638	4.65(s)	$C_{22}H_{21}NOS$	76.03 (75.97)	6.10 (6.08)	4.03 (4.00)
1c	81	69—70 (EtOH)	1638	4.72(s)	$C_{23}H_{23}NO_2S$	73.17 (73.47)	6.15 (6.13)	3.71 (3.70)
1d	71	77—78 (EtOH)	1640	4.68(s)	$C_{22}H_{20}ClNOS$	69.17 (69.09)	5.29 (5.31)	3.67 (3.67)
1e	74	52—53 (Petr. ether)	1638	4.68(s)	$C_{22}H_{20}ClNOS$	69.17 (69.19)	5.29 (5.36)	3.67 (3.66)
1f	78	62—63 (EtOH)	1642	4.64(s)	$C_{22}H_{19}Cl_2NOS$	63.44 (63.25)	4.61 (4.58)	3.36 (3.28)
1g	80	43—44 (*n*-Hexane)	1630	4.76(s)	$C_{18}H_{20}ClNOS$	64.73 (65.04)	6.05 (5.88)	4.20 (4.50)
1h	61	183—184 (0.01)	1651[b]	4.43(s)	$C_{19}H_{23}NOS$	72.79 (73.11)	7.41 (7.38)	4.47 (4.56)
1i[c]	70	46—48 (Petr. ether)	1622	4.83(s)	$C_{18}H_{21}NOS$	72.24 (71.93)	7.02 (7.03)	4.68 (4.64)
1j[c]	95	193—194 (0.18)	1630[b]	4.80(s)	$C_{19}H_{23}NO_2S$	69.26 (69.40)	7.05 (6.91)	4.25 (4.33)

a) s: singlet.
b) Liquid film.
c) **1i**: R^1=*n*-C_3H_7, R^2=C_6H_5. **1j**: R^1=*n*-C_3H_7, R^2=*p*-$CH_3OC_6H_4$. These compounds, **1i** and **1j**, were used only for preparation of the corresponding sulfones, **2c** and **2f**.

TABLE V. Preparation of $R^1SO_2CH_2N(R^3)COR^2$ (2a—f)

Compd. No.	Yield (%)	mp (°C) (Recry. solv.)	IR ν_{max}^{KBr} (cm^{-1}) –CON<	$-SO_2-$	NMR[a] δ (in $CDCl_3$) $-SO_2CH_2N<$	Formula	Analysis (%) Calcd (Found) C	H	N
2a	85	133—134 (EtOH)	1625	1122, 1304	4.75(s)	$C_{16}H_{17}NO_3S$	63.44 (63.52)	5.66 (5.74)	4.62 (4.56)
2b	65	118—119 (Benzene)	1622	1115, 1310	4.85(s)	$C_{22}H_{21}NO_3S$	69.62 (69.93)	5.59 (5.63)	3.69 (3.79)
2c	75	73—74 (iso-Pr_2O)	1643	1114, 1303	4.91(s)	$C_{18}H_{21}NO_3S$	65.26 (65.57)	6.34 (6.50)	4.23 (4.26)
2d	91	86—87 (EtOH)	1641	1117, 1290	4.86(s)	$C_{18}H_{20}ClNO_3S$	59.07 (58.98)	5.52 (5.37)	3.83 (3.80)
2e	80	102—103 (MeOH)	1658	1135, 1281	4.80(s)	$C_{19}H_{23}NO_3S$	66.05 (66.01)	6.72 (6.60)	4.06 (4.08)
2f	71	Liquid	1640[b]	1122, 1313	4.90(s)	$C_{19}H_{23}NO_4S$	63.12 (63.10)	6.43 (6.41)	3.88 (3.66)

a) s: singlet.
b) Liquid film.

TABLE VI. Preparation of $R^1SCHN(C_6H_5)COR^2$ (R^3) (3a—g)

Compd. No.	Yield (%)	mp (°C) (Recry. solvt.)	IR ν_{max}^{KBr} (cm^{-1}) –CON<	NMR[a] δ (in $CDCl_3$) –CH_2S–	NMR[a] δ (in $CDCl_3$) –CH_2N<	Formula	Analysis (%) Calcd (Found) C	H	N
3a	62	96—97 (EtOH)	1632	3.62(s)	4.92(d) 4.47(d)	$C_{28}H_{25}NOS$	79.40 (79.29	5.95 5.91	3.31 3.33)
3b	70	83—84 (EtOH)	1630	3.49(br)	4.84(d) 4.39(d)	$C_{28}H_{24}ClNOS$	73.43 (73.27	5.28 5.33	3.06 2.95)
3c	60	85—86 (EtOH)	1640	3.49(br)	4.78(d) 4.33(d)	$C_{28}H_{24}ClNOS$	73.43 (73.32	5.28 5.30	3.06 3.10)
3d	78	95—96 (EtOH)	1636	3.54(br)	4.83(d) 4.40(d)	$C_{28}H_{23}Cl_2NOS$	68.29 (68.38	4.71 4.64	2.84 2.93)
3e	62	87—88 (EtOH)	1640	3.53(br)	4.84(d) 4.41(d)	$C_{29}H_{27}NOS$	79.60 (79.87	6.23 6.23	3.20 3.36)
3f	85	Liquid	1638[b]	2.46(br)	4.72(d) 4.38(d)	$C_{24}H_{25}NOS$	76.76 (76.92	6.71 6.58	3.73 3.76)
3g	71	Liquid	1650[b]	3.72(s)	4.58(d) 3.94(d)	$C_{24}H_{25}NOS$	76.76 (76.84	6.71 6.64	3.73 3.80)

a) s=singlet, d=doublet, br=broad singlet.
b) Liquid film.

methyl sulfide hydrochloride[2] (0.5 mol) in 1000 ml of chloroform with stirring. During this period the temperature was kept at 0°C. Stirring was continued for 2 h at 0°C and for 2 h at room temperature, then the reaction mixture was concentrated and the resulting residue was extracted with benzene. The benzene layer was washed with water and dried over $MgSO_4$. Removal of the solvent gave a crystalline residue which was washed with petr. ether. Recrystallization from an appropriate solvent gave the pure product (**1a—j**). The products **1a**, **1h** and **1j** were purified by distillation under reduced pressure.

Preparation of Alkyl (N-Alkylamido)methyl Sulfones (2a—f) (see Table V): General Procedure——Alkyl (N-alkylamido)methyl sulfide (0.5 mol) was dissolved in 720 ml of acetic acid, then potassium permanganate (0.6 mol) was added gradually to the solution. After the mixture had been stirred for 15 h at room temperature, an aqueous solution of Na_2SO_3 was added until the color of MnO_4^- was quenched. The crystals that deposited were collected by filtration and dried. The filtrate was evaporated to dryness under reduced pressure. The residue was extracted with benzene and the benzene solution was washed with aq. $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent gave an additional crop of the product. The combined crystals were recrystallized from an appropriate solvent. The product **2f** was purified by column chromatography on silica-gel with benzene.

Preparation of Alkyl α-(N-Alkylamido)benzyl Sulfides (3a—g) (see Table VI): General Procedure——A solution of N-benzylidenebenzylamine (0.5 mol) in 200 ml of THF was added dropwise to a solution of acyl chloride (0.5 mol) in 300 ml of THF with cooling. The solution was stirred for 1 h at room temperature, then a solution of triethylamine (0.55 mol) in 50 ml of THF was added at 0°C, followed by a solution of alkanethiol (0.5 mol) in 150 ml of THF. The mixture was stirred for 2 h at room temperature. The deposited triethylamine hydrochloride was filtered off and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was dissolved in 500 ml of benzene and the solution was washed with water and dried over $MgSO_4$. Removal of the solvent gave a crystalline residue, which was washed with petr. ether and recrystallized from ethanol. Products **3f** and **3g** were purified by column chromatography on silica gel with benzene.

Rearrangement of Alkyl (N-Alkylamido)methyl Sulfides (1a—h) (see Tables I and II): General Procedure——A mixture of alkyl (N-alkylamido)methyl sulfide (0.03 mol) and a base (0.09 or 0.06 mol of NaH, LDA, BuLi, *t*-BuLi, PhLi or *t*-BuOK) in 60 ml of THF or ether was stirred at room temperature or under reflux for the period given in Table I or II. The reaction was quenched by addition of water, and CO_2 gas was bubbled through the mixture with cooling. The reaction mixture was concentrated under reduced pressure and the residue was extracted with benzene. The benzene solution was washed with 5% HCl and aq. $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized or distilled under reduced pressure to give the corresponding ketone. The ketones obtained gave satisfactory IR spectra and elemental analyses.

Rearrangement of Alkyl (N-Alkylamido)methyl Sulfones (2a—f) (see Tables I and II)——The procedure described above was repeated using 0.03 mol of alkyl (N-alkylamido)methyl sulfone and 0.09 mol of a base

to afford the corresponding ketone.

Rearrangement of Alkyl α-(N-Alkylamido)benzyl Sulfides (3a—g) (see Table III): General Procedure——Alkyl α-(N-alkylamido)benzyl sulfide (0.02 mol) was added to a solution of LDA (0.06 mol) in 60 ml of THF at −70°C with stirring. Stirring was continued for several hours at 0°C or at room temperature, then the reaction was quenched by addition of water and CO_2 gas was bubbled through the mixture with cooling. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in benzene. Insoluble material was filtered off and the filtrate was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed over silica gel with benzene and AcOEt–benzene as eluents to give the corresponding ketone and Schiff's base. In the run with **3d**, careful chromatography gave sulfur as a first fraction.

Cross Experiments as Evidence for an Intramolecular Mechanism——A mixture of *p*-chlorobenzyl (N-benzylbenzamido)methyl sulfide (**1e**) (13.4 g, 0.035 mol), benzyl (N-benzyl-*p*-chlorobenzamido)methyl sulfide (**1d**) (13.4 g, 0.035 mol) and 0.21 molar equiv. of NaH in 140 ml of THF was stirred under reflux for 15 h. After addition of water, CO_2 gas was bubbled through the mixture with cooling. The mixture was concentrated under reduced pressure and the resulting residue was extracted with benzene. The benzene solution was washed with 10% HCl and aq. $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, a volatile ketone fraction, bp 100—150°C (0.07 mmHg), was collected by distillation under reduced pressure. GLC analysis showed the distillate to be composed of 4-chlorodeoxybenzoin and 4′-chlorodeoxybenzoin. Deoxybenzoin and 4,4′-dichlorodeoxybenzoin were not detected. 4-Chlorodeoxybenzoin and 4′-chlorodeoxybenzoin were actually isolated by column chromatography on silica gel with benzene.

The same procedure as described above was repeated using benzyl (N-benzylbenzamido)methyl sulfone (**2b**) and *n*-propyl (N-benzyl-*p*-chlorobenzamido)methyl sulfone (**2d**) to afford only deoxybenzoin and *p*-chlorobutyrophenone.

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References and Notes

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