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Preparation and Reactions of α-Lithiobutanesultams

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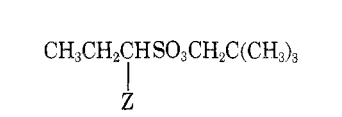
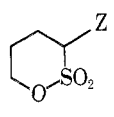
Metalations of *N*-methyl- and *N*-phenylbutanesultam were conveniently effected by means of *n*-butyllithium in THF–hexane at 25° to give α-lithio salts which were condensed with representative electrophiles to afford α-substituted derivatives in good to excellent yields. The electrophiles studied included benzyl chloride, various aldehydes and ketones, methyl benzoate, and benzonitrile. Several reactions with lithio-*N*-methylbutanesultam did not proceed in a predictable manner. Thus, this salt with benzonitrile and chalcone surprisingly afforded a primary enamine and an aminosultone, respectively, rather than the expected ketosultams. Also, this salt and aldehydes gave analytically pure β-hydroxysultams with melting point ranges of up to 30°. Metalation of *N*-methylbutanesultam was also effected by sodium amide in liquid ammonia.

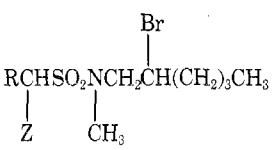
It has long been known that hydrogen atoms α to sulfonyl-containing functional groups are sufficiently acidic that they can be ionized by basic reagents to afford the corresponding carbanionic derivatives. For example, sulfonate esters like **1** have been converted to anions like **1′** by alkali metal amides in ammonia.[2] Similarly, sultones like **2** have been metalated by *n*-butyllithium in THF–hexane at −78° to give α-lithio salts like **2′**.[3] Various sulfonamides have likewise been metalated. Thus, bromosulfonamides **3** give sultams **4** via **3′** upon treatment with *n*-butyllithium in THF–hexane at −70°.[4] Sulfonamide **5** has even been *gem*-dimetalated by this same base at 25° to give **5″**.[5]



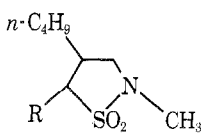
1, Z = H
1′, Z = K



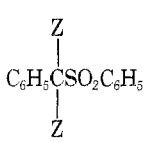
2, Z = H
2′, Z = Li



3, Z = H; R = H or CH_3
3′, Z = Li; R = H or CH_3



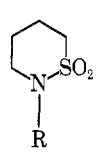
4
(R = H or CH_3)



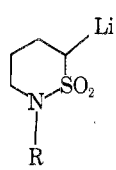
5, Z = H
5″, Z = Li

In contrast, there appear to be no reports of metalation of α hydrogens of sultams. This is somewhat surprising not only because of the above work on open-chain sulfonamides but also because sultams are more resistant to ring opening then are sultones. In light of the latter, in fact, sultams should be capable of being metalated at temperatures more convenient than those necessary for metalation of sultones. Moreover, once formed, α-lithiosultams should be more stable than α-lithiosultones. That such is the case is illustrated in this paper, which describes successful metalations of *N*-methyl- and *N*-phenylbutanesultam and subsequent reactions of the resulting carbanions with electrophiles.

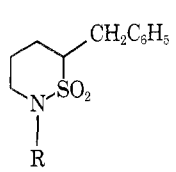
First, *N*-methylbutanesultam (**6**) was converted to its α-lithio salt (**6′**) at 25° by *n*-butyllithium in THF–hexane in only 10 min as evidenced by deuteration with deuterium oxide to give **6**-α-*d*, in a yield of 95–100%. Anion **6′** was also alkylated by benzyl chloride to afford the corresponding alkyl derivative **8** in a yield of 65%. Likewise, anion **7′** was prepared from *N*-phenylbutanesultam (**7**) and *n*-butyllithium. Alkylation of **7′** by benzyl chloride gave **9** in a yield of 70%.



6, R = CH_3
7, R = C_6H_5

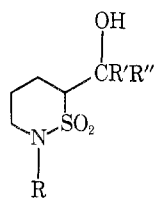


6′, R = CH_3
7′, R = C_6H_5



8, R = CH_3
9, R = C_6H_5

Next, anions **6′** and **7′** were condensed with various aldehydes and ketones to afford β-hydroxysultams. Thus, treatment of **6′** with benzophenone, benzaldehyde, and anisaldehyde gave **10**, **11**, and **12** in yields of 91, 80, and 86%, respectively. Similar condensations of **7′** with these same compounds afforded **13**, **14**, and **15** in yields of 86, 63, and 78%, respectively.

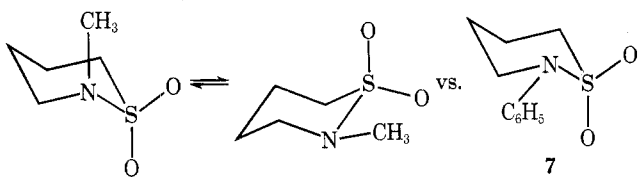


10, R = CH_3; R′ = R″ = C_6H_5
11, R = CH_3; R′ = C_6H_5; R″ = H
12, R = CH_3; R′ = *p*-$CH_3OC_6H_4$; R″ = H
13, R = R′ = R″ = C_6H_5
14, R = R′ = C_6H_5; R″ = H
15, R = C_6H_5; R′ = *p*-$CH_3OC_6H_4$; R″ = H

Incidentally, an attempt was made to prepare anions **6′** and **7′** by the interaction of the sultams and sodium amide in liquid ammonia. In the case of **6**, anion **6′** (M = Na) was

indeed formed, since addition of benzophenone gave adduct **10** in a yield of 66%. On the other hand, either **7** was not converted to **7′** (M = Na) or the latter salt was insoluble in the liquid ammonia, since addition of the ketone gave no **13**; instead, only starting materials were recovered.

The above alcohols derived from the parent sultams and benzaldehyde and anisaldehyde were particularly interesting because although those from **6** (**11** and **12**) were analytically pure, they had melting ranges of 15 and 30°, respectively. In contrast, those from **7** (**14** and **15**) exhibited sharp melting points. Moreover, the NMR spectra of these compounds indicated that the hydroxyl protons of **11** and **12** resided in at least four different environments while those of the *N*-phenyl derivatives (**14** and **15**) resided in only two different environments. The above data lead one to suggest that internal hydrogen bonding must be of major importance in this series of compounds. To visualize this, the possible conformations of **6** and **7** were examined using space-filling models. Thus, the *N*-methyl group of sultam **6** can reside in either an axial or an equatorial position (eq 1). In contrast, the more bulky *N*-phenyl group of sultam **7** can reside only in an equatorial position.



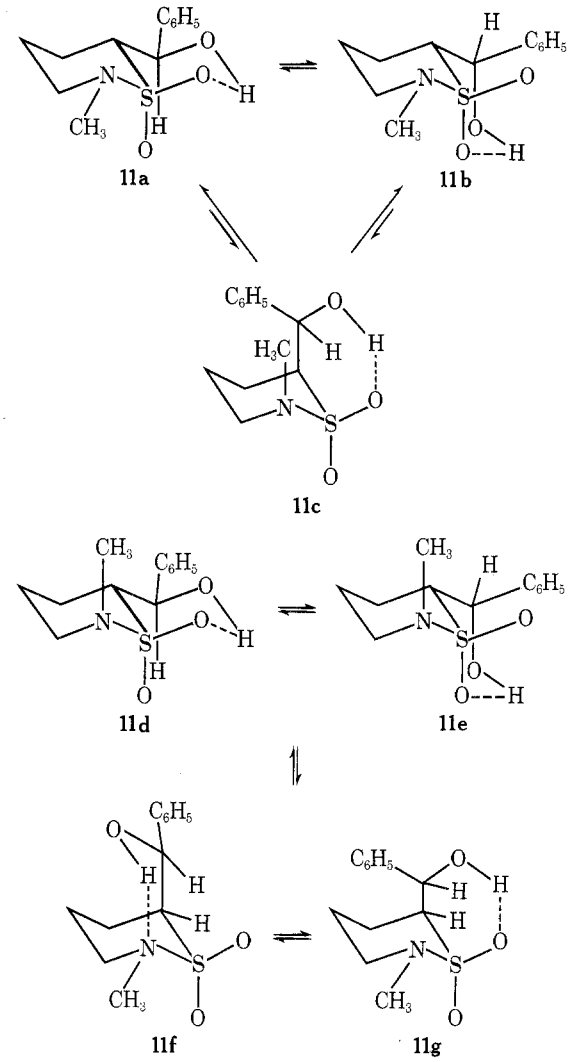
(1)

Now, the addition of an aldehyde α to the sulfonyl group gives an alcoholic proton which can form six-membered rings through internal hydrogen bonding with either of the sulfonyl oxygens or with the sulfonamide nitrogen. Using compound **11** as an example, the possible hydrogen-bonded forms are illustrated as **11a–g** along with the possibilities for equilibrium which exist among these different forms (Scheme I). In addition, the carbinol carbon and the α carbon of the ring are chiral, thus affording 14 possible hydrogen bonded conformations for **11**. Therefore, it is not surprising that the analytically pure sample had a wide melting point range and a rather complex NMR spectrum. Compound **12**, derived from **6′** and anisaldehyde, should be similar.

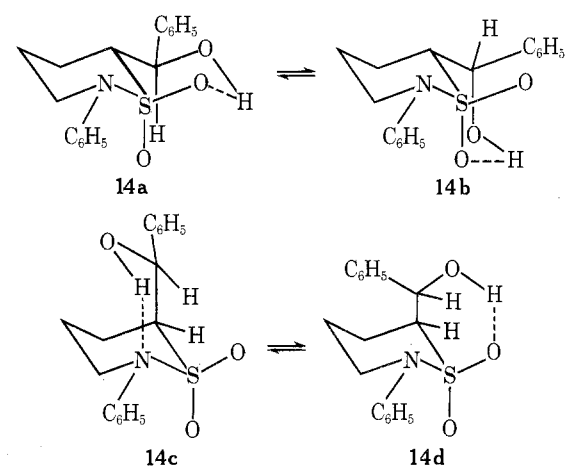
Likewise, the hydrogen-bonded isomers of **14**, derived from **7′** and benzaldehyde, are illustrated as **14a–d** (Scheme II). When the chiral carbinol carbon and the α carbon of the ring are included, there are eight internally hydrogen bonded isomers that could be present. However, since **14** has a sharp melting point, either this reaction occurs stereospecifically or the above isomers are physically nearly identical. Hydroxysultam **15**, derived from **7′** and anisaldehyde, is similar.

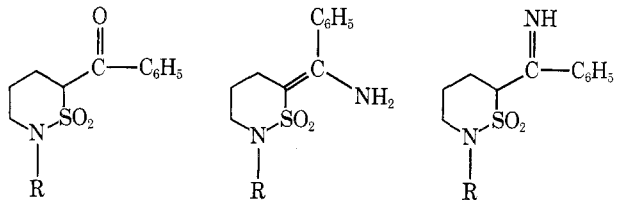
Next, **6′** and **7′** were condensed with methyl benzoate to give ketones **16** and **17** in yields of 84 and 69%, respectively. As is usual in the reaction of carbanions with esters,[6] a 2:1 ratio of lithiosultams to methyl benzoate was employed to maximize the yields of ketones. Lithio salts **6′** and **7′** were also condensed with benzonitrile to give enamine **18** and ketone **17** in yields of 79 and 64%, respectively. The condensations of **6′** and **7′** with benzonitrile are interesting for two reasons. First, under the same hydrolysis conditions, the intermediate nitrogen-containing compound from **7′** and the nitrile, either **19** or **21**, is converted to ketone while, in contrast, **18** is stable to such treatment. Second, **18** constitutes a rare example of a primary enamine.[7] Examination of space-filling models suggests why the above is realized. In essence, the primary enamine **18** is stable because of more favorable hydrogen bonding of the amino hydrogen atoms with the sulfonyl oxygen atoms through a six-membered ring than can be realized in the imine **20**. On the other hand, models of **19** indicate that in order to have hydrogen bonding as in **18**, sufficient steric interaction is present that rotation of the *N*-phenyl group is restricted. Thus, such hydrogen bonding is presumably absent and **19** or **21** are hydrolyzed to ketone **17**.

Scheme I



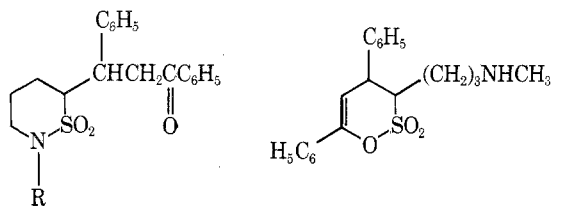
Scheme II





16, R = CH_3 18, R = CH_3 20, R = CH_3
17, R = C_6H_5 19, R = C_6H_5 21, R = C_6H_5

Finally, 6′ and 7′ were treated with α,β-unsaturated ketones to give products arising from 1,4-conjugate additions. However, drastically different results were obtained depending upon the N substituent of the sultam and the structure of the carbonyl compound. Thus, 7′ was condensed with chalcone to give the expected ketosultam **22** in a yield of 88%. Surprisingly, similar reaction of 6′ with this ketone gave the aminosultone **23** in a yield of 36%. Presum-

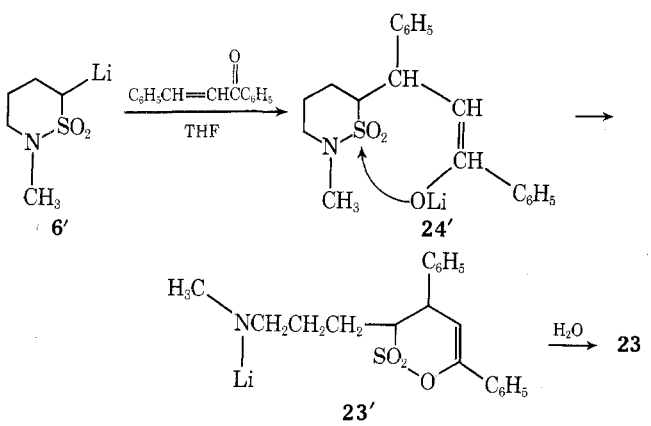


22, R = C_6H_5
25, R = CH_3

23

ably, the latter condensation proceeded via the intermediacy of 1,4-adduct **24**, which underwent ring opening and reclosure as indicated in Scheme III. Formation of **23** instead

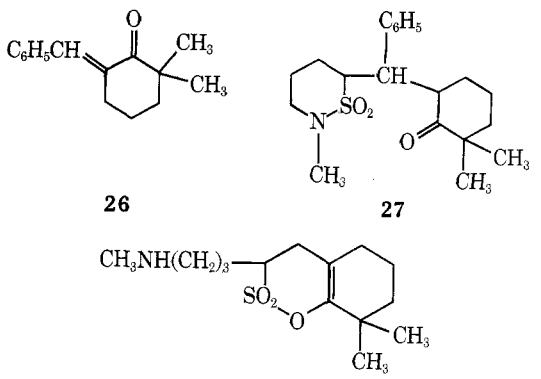
Scheme III



of the expected **25** is surprising in light of the fact that the proposed nucleophilic attack by the alkoxide ion of **24** leads to the more strongly basic nitrogen anion of **23′** (Scheme III). Previous workers investigating the interaction of certain sulfonamides with various alkoxides to give sulfonate esters and substituted amines reported that much more vigorous conditions were required to effect their transformations than were used in the current study.[8]

In an attempt to find another example of the above rearrangement, 6′ was condensed with 2,2-dimethyl-6-benzylidenecyclohexanone (**26**). The product obtained, though, was the ketosultam **27** in a yield of 70%, not the anticipated aminosultone **28**. Presumably, potential steric constraint in **28** was sufficient to preclude its formation.

All of the sultam derivatives reported above are new. Their structures were supported by elemental analyses and by ir and NMR spectroscopy. The above condensations should be capable of being extended to other sultams as well as other electrophiles. Of particular interest would be



26 27

28

a systematic study of other α,β-unsaturated carbonyl compounds to ascertain if the scope of the rearrangement of alkoxysultams to aminosultones could be broadened.

Experimental Section

Infrared spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrometer. NMR spectra were obtained on a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. *n*-Butyllithium in hexane was purchased from Apache Chemical Co., Rockford, Ill. Tetrahydrofuran was dried by distillation from calcium hydride and stored over sodium wire under an atmosphere of helium. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of Starting Materials. 4-Chlorobutanesulfonyl chloride was prepared by the method of Williams.[9] *N*-Methyl-4-chlorobutanesulfonamide was prepared using an adaptation of the method of Bliss and coworkers.[10] *N*-Methylbutanesultam (**6**) was prepared by cyclization of *N*-methyl-4-chlorobutanesulfonamide using potassium hydroxide according to the method of Bliss and coworkers.[10] *N*-Phenylbutanesultam was prepared from 4-chlorobutanesulfonyl chloride, aniline, and sodium carbonate as previously described.[11] 2,2-Dimethyl-6-benzylidenecyclohexanone (**26**) was prepared as described by Johnson.[12]

Preparation of the Lithium Salts of *N*-Methyl- and *N*-Phenylbutanesultams. To a 100-ml three-necked flask equipped with a septum, a magnetic stirrer, and a reflux condenser under a helium atmosphere were added 2.85 g (0.02 mol) of *N*-methylbutanesultam (**6**) and 25 ml of anhydrous THF followed by 12.8 ml (0.02 mol) of 15% *n*-butyllithium in hexane. The resulting pale yellow solution was stirred for 10 min, then treated with an appropriate electrophile as outlined in Table I. Lithio-*N*-phenylbutanesultam was similarly prepared using 3.15 g (0.015 mol) of sultam **7** in 50 ml of anhydrous THF and 9.6 ml (0.015 mol) of 15% *n*-butyllithium in hexane. The resulting white suspension was stirred for 10 min, then treated with an appropriate electrophile as outlined in Table I. The condensations were performed at 25°.

Condensations of Lithio Salts 6′ and 7′ with Electrophiles. Since the results of the condensations of 6′ and 7′ with electrophiles are summarized in Table I, and since conditions are standard for each class of electrophile, only one specific example will be presented below for alkyl halides, aldehydes and ketones, esters, benzonitrile, and α,β-unsaturated ketones, respectively.

A. Preparation of 2*H*-2-Phenyl-6-benzyltetrahydro-1,2-thiazine 1,1-Dioxide (9). Alkylation. To a suspension of 0.015 mol of lithio-*N*-phenylbutanesultam (7′) was added dropwise 1.90 g (0.015 mol) of benzyl chloride in 20 ml of THF. The mixture was stirred for 1 hr, neutralized by the addition of wet THF, and filtered, and the solvent was removed under vacuum to give a yellow tar. This tar was allowed to stand overnight in 25 ml of ethyl ether and the crystals that formed were filtered and recrystallized from benzene to give 3.15 g (70%) of **9**, mp 97–99°.

B. Preparation of 2*H*-2-Methyl-6-(diphenylhydroxymethyl)tetrahydro-1,2-thiazine 1,1-Dioxide (10). Condensation with Benzophenone. To a solution of 0.025 mol of lithio-*N*-methylbutanesultam (6′) was added dropwise a solution of 4.56 g (0.025 mol) of benzophenone in 20 ml of THF. The resulting suspension was stirred for 30 min, neutralized with wet THF, filtered, and concentrated under vacuum to afford a yellow solid. Recrystallization of the solid from toluene gave 7.54 g (91%) of **10**, mp 182–185°.

C. Preparation of 6-(2*H*-2-Phenyltetrahydro-1,2-thiazine 1,1-Dioxide) Phenyl Ketone (17). Acylation. To 0.03 mol of 7′ in 50 ml of THF was added dropwise 2.04 g (0.015 mol) of methyl

Table I
Products Derived from Condensation of Lithiosultams with Electrophiles[a]

Sultam	Coreagent	Product	Yield, %	Mp, °C	Recrystn solvent	Nmr, δ[b]
6	Benzyl chloride	8	65	61–63[c]		1.55 (m, 4, CH_2), 2.62 (s, 3, CH_3), 2.80 (m, 5, CH, CH_2), 7.04 (s, 5, ArH)
	Benzophenone	10	91	182–185	Toluene	1.67 (m, 2, CH_2), 2.00 (m, 2, CH_2), 2.83 (s, 3, CH_3), 3.30 (m, 2, CH_2), 4.11 (m, 1, CH), 4.64 (s, 1, OH), 7.50 (m, 10, ArH)
	Benzaldehyde	11	80	91–108	1:2 petroleum ether–benzene	1.80 (m, 4, CH_2), 2.95 (s, 3, CH_3), 3.30 (m, 3, CH, CH_2), 3.46 (d, 1, OH), 5.82 (s, 1, CH), 7.48 (s, 5, ArH)
	Anisaldehyde	12	86	115–145	Benzene	1.40 (m, 4, CH_2), 2.68 (s, 3, CH_3), 3.10 (m, 3, CH, CH_2), 3.40 (d, 1, CH), 3.75 (s, 3, OCH_3), 5.30 (m, 1, OH), 6.95 (q, 4, ArH)
	Methyl benzoate	16	84	135–137	Ethanol	1.83 (m, 2, CH_2), 2.36 (m, 2, CH_2), 2.97 (s, 3, CH_3), 3.44 (m, 2, CH_2), 5.00 (q, 1, CH), 7.80 (m, 5, ArH)
	Benzonitrile	18	79	140–142	Ethanol	1.60 (m, 2, CH_2), 2.68 (t, 2, CH_2), 3.05 (s, 3, CH_3), 3.65 (t, 2, CH_2), 5.45 (s, 2, NH), 7.66 (s, 5, ArH)
	Chalcone	23	36	186–188	2:1 Ethanol–benzene	1.95[d] (m, 2, CH_2), 2.41 (m, 3, CH, CH_2), 3.01 (s, 3, CH_3), 3.45 (m, 3, CH, CH_2), 4.64 (m, 2, NH_2^+), 6.90 (s, 1, vinyl CH), 7.20 (m, 10, ArH)
	26	27	70	164–167	Ethanol	0.90 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.60 (m, 10, CH_2), 2.55 (s, 3, NCH_3), 3.15 (m, 4, CH, CH_2), 3.80 (m, 1, CH), 7.20 (m, 5, ArH)
7	Benzyl chloride	9	70	97–99	Benzene	2.11 (m, 4, CH_2), 3.02 (m, 1, CH), 3.68 (m, 4, CH_2), 7.50 (s, 5, ArH), 7.58 (s, 5, ArH)
	Benzophenone	13	86	170–172	Benzene	1.91 (m, 2, CH_2), 2.10 (m, 2, CH_2), 4.00 (m, 3, CH, CH_2), 4.91 (s, 1,OH), 7.32 (m, 15, ArH)
	Benzaldehyde	14	63	145–147	Ethanol	2.10 (m, 4, CH_2), 3.58 (m, 1, OH), 3.82 (m, 3, CH, CH_2), 5.90 (s, 1, CH), 7.62 (d, 10, ArH)
	Anisaldehyde	15	78	135–137	Ethanol	1.97 (d, 4, CH_2), 3.70 (m, 4, CH, OH, CH_2), 4.02 (s, 3, CH_3), 5.40 (d, 1, CH), 7.35 (q, 4, ArH), 7.58 (s, 5, ArH)
	Methyl benzoate	17	69	151–153	Ethanol	2.10 (m, 4, CH_2), 3.77 (m, 2, CH_2), 5.11 (q, 1, CH), 7.35 (m, 8, ArH), 8.00 (m, 2, ArH)
	Benzonitrile	17	64	151–153	Ethanol	
	Chalcone	22	88	164–166	Ethanol	1.78 (m, 2, CH_2), 2.21 (m, 2, CH_2), 3.40 (m, 2, CH_2), 4.00 (m, 4, CH, CH_2), 7.30 (m, 13, ArH), 8.00 (m, 2, ArH)

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all the sultam derivatives. [b] The solvent was deuteriochloroform unless noted otherwise. [c] The compound was first distilled at 151–154° (2 mm) and solidified upon scratching. [d] The solvent was trifluoroacetic acid.

benzoate in 20 ml of THF. After 30 min, the mixture was neutralized and worked up as in A and B to give a yellow oil which crystallized upon standing in ether for 30 min. The product was recrystallized from ethanol to give 3.25 g (69%) of **17**, mp 151–153°.

D. Preparation of 2*H*-2-Methyl-6-(1-amino-1-phenylmethylidene)tetrahydro-1,2-thiazine 1,1-Dioxide (18). Condensation with Benzonitrile. To 0.025 mol of **6'** in 25 ml of THF was added 2.56 g (0.025 mol) of benzonitrile in 15 ml of THF. After 30 min, the mixture was worked up as above to give a tan solid that was recrystallized from ethanol to give 4.99 g (79%) of **18**, mp 140–142°.

E. Preparation of 2*H*-2-Phenyl-6-(1,3-diphenyl-3-oxo-1-propyl)tetrahydro-1,2-thiazine 1,1-Dioxide (22). Condensation with Chalcone. To 0.015 mol of **7'** in 50 ml of THF was added 3.12 g (0.015 mol) of chalcone in 20 ml of THF. After stirring for 0.5 hr, the orange mixture was worked up in the usual fashion to afford a yellow tar that was allowed to stand overnight in 25 ml of ether. The solid that formed was collected and recrystallized from ethanol to give 5.50 g (88%) of **22**, mp 164–166°.

Ionization of *N*-Methylbutanesultam by Sodium Amide in Ammonia. Condensation with Benzophenone. To a gray suspension of 0.03 mol of sodium amide in 250 ml of anhydrous liquid ammonia[13] was added 4.48 g (0.03 mol) of sultam **6** in 25 ml of THF. The mixture was stirred for 20 min, then treated dropwise with a solution of 5.46 g (0.03 mol) of benzophenone in 30 ml of THF. After 5 min, the mixture was poured into a beaker containing 1.61 g (0.03 mol) of ammonium chloride, and the ammonia and the THF were allowed to evaporate. The residual solid was dissolved in 40 ml of water and the product was extracted by benzene. Evaporation of the benzene gave a solid that was recrystallized from toluene to give 6.52 g of **10**, mp and mmp 183–195°.

A similar series of reactions involving *N*-phenylbutanesultam afforded only recovered starting materials.

Registry No.—**6,** 54531-78-1; **6′,** 54531-79-2; **7,** 54531-80-5; **7′,** 54531-81-6; **8,** 54531-82-7; **9,** 54531-83-8; **10,** 54531-84-9; **11,** 54531-85-0; **12,** 54531-86-1; **13,** 54531-87-2; **14,** 54531-88-3; **15,** 54531-89-4; **16,** 54531-90-7; **17,** 54531-91-8; **18,** 54531-92-9; **22,** 54531-93-0; **23,** 54531-94-1; **26,** 17622-50-3; **27,** 54531-95-2; benzyl chloride, 100-44-7; benzophenone, 119-61-9; benzaldehyde, 100-52-7; anisaldehyde, 123-11-5; methyl benzoate, 93-58-3; benzonitrile, 100-47-0; chalcone, 94-41-7.

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Notes

One-Step, High Yield Conversion of Penicillin Sulfoxides to Deacetoxycephalosporins

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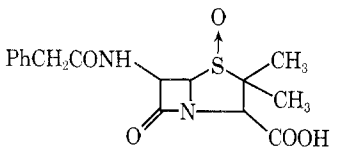
Morin and coworkers demonstrated the chemical relationship between the penicillin and cephalosporin skeleton by an unprecedented acid-catalyzed rearrangement.[1] Because of the therapeutic utility of cephalexin[2] (**2a**), a deacetoxycephalosporin, a high yield conversion of a penicillin sulfoxide to a deacetoxycephalosporanic acid would be very attractive. The known methods, of which some give yields of >80%,[3] have the disadvantage of being limited to the conversion of esters of a penicillin sulfoxide to the corresponding esters of the deacetoxycephalosporin, which requires two more reaction steps, viz., the esterification of the starting penicillin compound as well as the de-esterification of the deacetoxycephalosporin. Rearrangement of the acids gives either decarboxylated products[1] or 3-hydroxy-3-methylcepham compounds.[4] In some cases deacetoxycephalosporanic acids are also formed but the yields are low.[5]

The present paper describes a convenient and efficient method to convert penicillin sulfoxides to deacetoxycephalosporanic acids by using silyl protection.

The use of the silyl group for protection of a carboxyl group has advantages such as easy introduction and removability over the use of other protecting groups. The conversion of a penicillin sulfoxide to a deacetoxycephalosporin implies the liberation of a molecule of water. Accordingly, the known rearrangement procedures[3] fail when applied to silylated penicillin sulfoxides,[6] since silyl esters[7] are very susceptible to cleavage by water. The use of an excess of silyl compound, e.g., trimethylchlorosilane, seemed to offer the best chance of success for three reasons: the carboxyl group is protected against decarboxylation, the HCl that is



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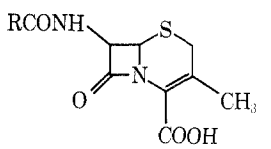
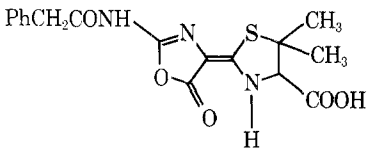


2a, R = PhCH(NH$_2$)

b, R = PhCH$_2$



3

formed catalyzes the ring enlargement reaction, and attack on the silylated carboxyl group is prevented because the excess silyl compound traps the water[8] formed during the reaction. However, when an attempt was made to rearrange benzylpenicillin sulfoxide (**1**) with a sufficiently large excess of trimethylchlorosilane to fulfil the conditions mentioned above, formation of deacetoxycephalosporanic acid could not be detected. Better results were obtained when a large excess of a rather weak base was added to the reaction mixture. In this way benzylpenicillin sulfoxide was converted in a yield of 75% to a mixture of ring-enlarged products, consisting of Δ^2- and Δ^3-benzyldeacetoxycephalosporanic acid and the decarboxylated cephalosporin (method A), from which the Δ^3 compound could be isolated in yields of up to 50%. Interesting is a side reaction, viz., the formation of the oxazolonethiazolidine compound (**3**), better known as "dehydrobenzylpenicillin".[9] The control of this product ratio was insufficient which is obviously related to the triple role played by the silyl compound and especially to the fact that the amount of HCl present during the reaction is