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New Aspects of Intramolecular Hydrogen Transfer in Some Ortho-Substituted Aryl Radicals

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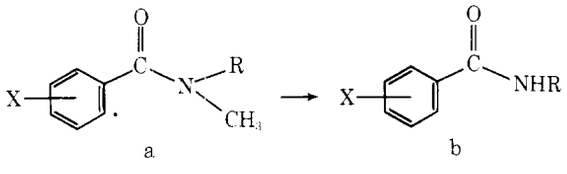
Received November 3, 1977

Intramolecular 1,5-, 1,6-, and 1,7-hydrogen transfers are observed when *o*-di-*n*-propylaminosulfonylbenzenediazonium tetrafluoroborate (**1a**) is decomposed in the system: $CuBr_2$–Me_2SO. The reaction competes with the "Sandmeyer-like" aryl bromide formation. The extent of competition is shown, by study of lower homologues, to reflect steric effects which are also evident from a comparison of the similar dediazoniation of *o*-di-*n*-propylamino- and *o*-dimethylaminocarbonylbenzenediazonium ions, **8a** and **8c**, respectively. The stereochemical argument is amplified by the failure of *o*-*n*- and -isopropoxycarbonylbenzenediazonium salts to undergo hydrogen transfer. A large solvent effect is also evident; the substitution of acetone for Me_2SO in decomposition of **8c** decreases hydrogen transfer from near 90 to about 15%, with a corresponding increase in bromoarene formation. The ultimate products of hydrogen transfer are identified and rationalized.

The demethylation of *o*-(dimethylaminocarbonyl)aryl or (*N*-aryl-*N*-methylaminocarbonyl)aryl diazonium salts by intramolecular 1,5-hydrogen transfer in homolytic fashion (Scheme I) was probably first recognized in 1954.[1] Despite extensive study of its mechanism,[2] there are still many unanswered questions which merit further work.[2b,c] It is, however, already apparent that the manner and the medium in which the radical a (Scheme I) is generated play an important role in product determination,[3a] and that when R is a substituted aryl, steric influences have been recognized.[1,3b,c]

In connection with a synthetic project, we happened upon a related reaction which also involved radical transfer, but to a propyl group of a dipropyl sulfonamide (Figure 1). Astonishingly, attack occurred at the α, β, and γ positions! The 6-, 7-, and 8-membered cyclic transition states that were required for this reactivity suggested that there were steric and other influences not previously recognized in this type of process. We have, accordingly, briefly examined some of them. Our experimental method comprised adding a dimethylsulfoxide (Me_2SO) solution of the *o*-diazonium tetrafluoroborates to $CuBr_2$ in Me_2SO, a system which is reported to give bromoaromatics in high yield,[4,5] our original goal. The use of $CuBr_2$–Me_2SO ensured a homolytic reaction, and the high concentration could also be expected to minimize rearrangement of the alkyl radicals[6] prior to oxidation and termination in products. Since this system had not previously been used to generate the analogous carboxamide radicals, we examined two of these, and, for reasons which will become clear, we also studied the behavior of two esters.

Scheme I

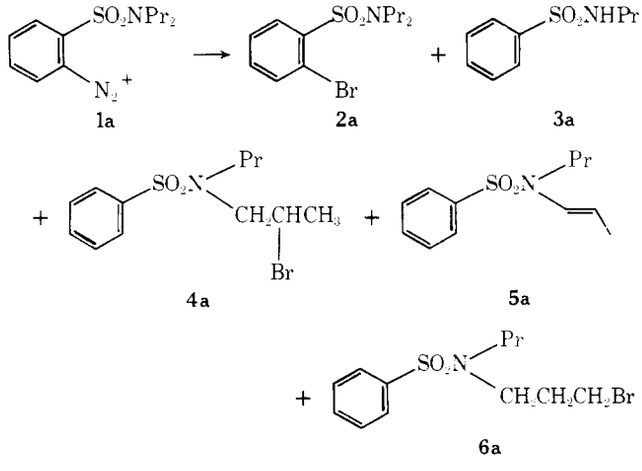


a b

Results

The instantaneous decomposition of *o*-(dialkylaminosulfonyl)benzenediazonium tetrafluoroborates **1** in $CuBr_2$–dry Me_2SO at room temperature furnished *o*-bromobenzenesulfonamides **2** from a Sandmeyer-like[7a] reaction, along with products resulting from transfer of the initially generated aryl radical site to the alkyl side chain.[7b] These latter products included monoalkyl sulfonamides, bromoalkyl sulfonamides, and alkenylalkyl sulfonamides (Scheme II), reflecting hy-

Scheme II



1a 2a 3a 4a 5a 6a

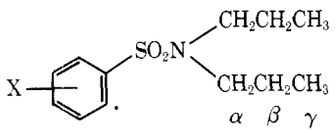


Figure 1.

Table I. Yield of Products (%)[a] from the Decomposition of 1 in $CuBr_2$–Me_2SO

Product	1a, R = n-C_3H_7	1b, R = C_2H_5	1c, R = CH_3
o-$BrC_6H_4SO_2NR_2$ (2)	32	43	75
$C_6H_5SO_2NHR$ (3) (α-abstraction)	20	24	<2
$C_6H_5SO_2NRR'$ (4) (β-bromo)	32	10	
$C_6H_5SO_2NRR''$ (5) (enamide)	6	3	
$C_6H_5SO_2NRR'''$ (6) (γ-bromo)	7		
$C_6H_5SO_2NR_2$ (7) (reduction)	2	4	4

[a] **4a**, R′ = $CH_2CHBrCH_3$; **4b**, R′ = CH_2CH_2Br; **5a**, R″ = $CH{=}CHCH_3$; **5b**, R″ = $CH{=}CH_2$; **6a**, R‴ = $CH_2CH_2CH_2Br$. A small amount (1.5%) of $C_6H_5SO_2N(C_2H_5)CH{=}CHBr$ (**5d**) was also isolated from the reaction of **1b**. Approximately 10–12% of "dimeric" ether **3d** was formed from **1c** (see text for discussion). The yields reported were determined by preparative SiO_2 chromatography or GLC determination against standards.

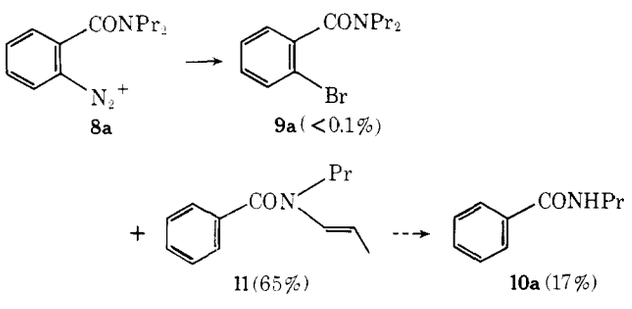
drogen abstraction from each of the aliphatic carbon atoms. A small amount of reduction product, dialkyl benzenesulfonamide **7**, was invariably reduced by what must be an intermolecular reaction. The yields of general products are summarized in Table I. Ethers were formed from two molecules, particularly in the case of **1c**, by what was probably an ionic process. Their characterization was incomplete, but nevertheless secure.

The effect of moisture on the reaction was assessed in the case of **1b**, the diethyl homologue. Both N-(β-bromovinyl)-N-ethylbenzenesulfonamide (**5d**) and N-ethyl-N-vinylbenzenesulfonamide (**5b**), minor products which formed in dry solvent, were not detected using Me_2SO containing 0.1% moisture. An experiment employing reverse addition of the reactants showed that higher bromide concentrations favored Sandmeyer product formation over hydrogen transfer.

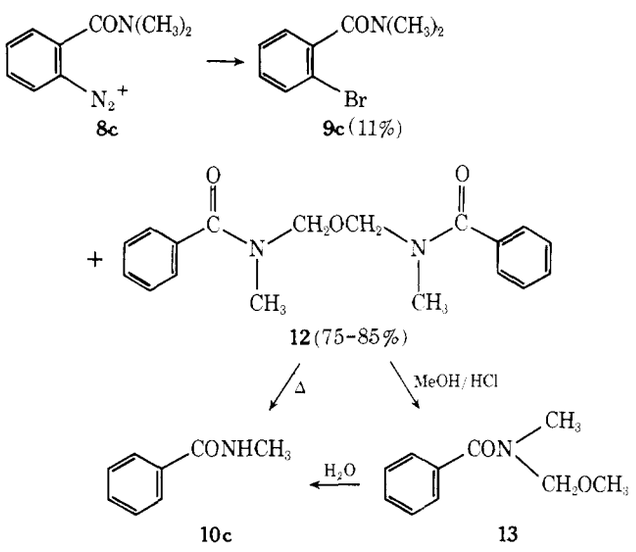
No Sandmeyer product **9a** was detected from decomposition of the dipropyl carboxamide **8a**, (Scheme III), nor was there any evidence for 1,7-hydrogen transfer. The products which were seen were (mono) N-propylbenzamide (**10a**) and the enamide **11**, products of 1,5- and 1,6-hydrogen transfers, respectively.

Dimethyl carboxamide **8c** gave, in $CuBr_2$–Me_2SO, only 11% bromide **9c** and ca. 75–85% of 2,6-dibenzoyl-2,6-diaza-4-oxaheptane (**12**), which although not obtained in pure form

Scheme III

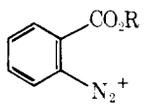


Scheme IV



was thoroughly and unambiguously identified (Scheme IV). A small and variable amount (2–10%) of N-methylbenzamide (**10c**) was detected by GLC. In contrast, decomposition of **8c** in $CuBr_2$–acetone gave 78% of Sandmeyer product and 14% of **10c**.

The diazonium salts **14a** and **14b**, prepared from n- and



14a, R = n-C_3H_7
b, R = i-C_3H_7

isopropylanthranilate, respectively, gave high yields of Sandmeyer product without any evidence for radical transfer products. The ubiquitous reduction products were observed here just as they were with the sulfonamides and carboxamides.

Discussion

As stated in the introductory section, 1,5-intramolecular hydrogen abstractions have previously been observed with some o-carboxamide radicals. The formation of **4**, **5**, and **6** (Table I) constitutes, to the best of our knowledge, the first authentic examples of 1,6- and 1,7-hydrogen abstractions by an aryl radical.[8]

Some of the studies by Cohen et al., utilizing isotopically labeled **8c** showed that the radical transfer step was exceedingly rapid[9] in terms of conformational motion of some of the involved atoms, and we have no reason not to extrapolate their conclusions, at least qualitatively, to our system. This being so, one can make a case that the ratios of α-, β-, and γ-abstraction products obtained from **1a** represent, roughly, the conformational preferences of **1a**. Conformational preferences were previously invoked in explaining the anomalously low reactivity in some intermolecular hydrogen transfers to aryl and other radicals.[10] The rate at which hydrogen atoms are transferred to such a hot aryl radical site[9] largely precludes attainment of conformational equilibrium during the fleeting existence of the radical per se.

Sulfonamides. It is clear from the yields shown in Table I that the hydrogen transfer products dominate the reaction of **1a** and that the Sandmeyer bromoarene **2c** prevails with the much less encumbered dimethyl homologue. The diethyl case, starting with **1b**, occupies an intermediate position. The yield of bromide **2b** from it, 43%, may be compared with the sum of **2a** (32%) and **6a** (7%), the latter coming from a γ-car-

Table II. Effect of Reaction Conditions on the Decomposition of 1b

Product	Conditions[a,b] A	B	C
2b	54.8	62.8	34.2
3b	26.8	27.8	32.0
4b	12.2	9.3	16.9
5b	4.8	0	14.8
5d	1.5	0	2.2

[a] Standard conditions described in the Experimental Section (A); used undried Me_2SO (B); inverse addition of reactants (C). [b] Values are given in GLC area (%).

bon transfer process not available to **1b**. On the other hand, when considering the minimally crowded dimethyl homologue **1c**, even the α-carbon hydrogen transfer diminishes in importance compared to the Sandmeyer path, accentuating a picture of steric obstruction to the approach of Br^- with **1a** and **1b**. A preparatively useful yield (60%) of analytically pure **2c** may, in fact, be obtained by one crystallization of its total reaction mixture.

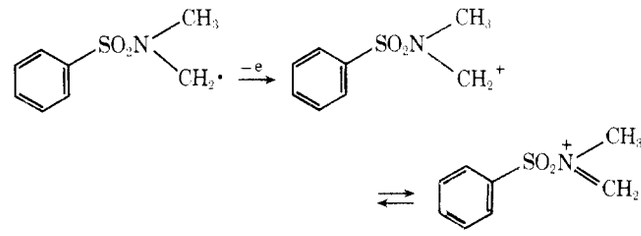
Hydrogen transfer in the case of **1c** gave not the simple demethylation product **3c**, but $C_6H_4SO_2N(CH_3)$-$CH_2OCH_2N(CH_3)O_2SC_6H_5$ (**3d**) which was readily converted to **3c** during chromatography. Its formation may be rationalized in the same way as **12**, an entirely analogous product from the corresponding carboxamide, which is discussed below in the section in carboxamides.

It is quite reasonable that both fundamental reaction routes (i.e., leading to Sandmeyer or hydrogen transfer products) compete from the same initial aryl radical and not from some other unidentified reactive species. Support for this view comes from an experiment in which the product ratio was altered by reversing the order of reactant addition. In that case, $CuBr_2$–Me_2SO solution was added slowly to **1b** in Me_2SO, limiting the concentration of Br^- in the system. The yield of bromoarene **2b** dropped from 43 to 27%, while the yields of **3b**, **4b**, and **5b** increased accordingly, as measured by GLC area ratios (Table II). The increase in **5b** was the greatest of the three, further suggesting a role for Br^- concentration in determining the product split from the β-alkyl radical. We believe that enamides **5a** and **5b** arise from a β-carbon radical by oxidative elimination either with or without the intermediacy of an organocopper species,[6,11] although their formation from an α-carbon radical similarly cannot be strictly ruled out by our data. The ease with which the latter should and does suffer either dealkylation or ether formation (see below) with the dimethyl homologue, and even more evidently with the carboxamide **8c**, suggests these latter processes are the most important outlets for α-carbon radicals. Their resonance-enhanced stability resulting from the adjacent nitrogen[10] would also favor continued oxidation by the reagent to α-carbenium ions like that postulated in anodic oxidations of dimethyl benzamide,[12] as suggested in Scheme V.

Dehydrobromination of bromoalkylamides **4a** and **4b** to the enamides **5a** and **5b** is unlikely in view of the demonstrated stability of the former to GLC and silica gel chromatography. Vinyl derivative **5b**, however, is susceptible to hydrolysis, and is not recovered from silica gel chromatography in benzene–methanol. Moreover, it is not even detected when the dediazoniation of **1b** is performed in Me_2SO containing as little as 0.1% water (Table II).

Bromovinyl sulfonamide **5d** is an unusual product, owing its identification to the power of modern spectroscopic tools. Its obviously arises from a double oxidation. We did not find double oxidation products from other substrates, and we offer

Scheme V



no insight into its formation. It was only a minor product, ca. 1.5%; however, its formation was reproducible.

In summary, the major features of the reactions of sulfonamides **1a–c** can be related to previous studies of **8c** in different media, but modified by sensible steric arguments.

How does **8c** itself behave in the same medium, and what are the differences which are introduced in a larger homologue?

Carboxamides. We expected and found steric influences based on the differing bond lengths and angles of the >C=O vs. $>SO_2$ bridging groups. The absence of radical attack upon the γ-methyl group of the dipropyl carboxamide **8a** (cf. 7% with **1a**) and the lack of Sandmeyer product from the same substrate (cf. 32% with **1a**, 11% with **8c**) are clear examples (Scheme III). Polar effect differences of the aryl radical[13] cannot be responsible for the latter; the two-carbon insulator eliminates any explanation based upon differences in nitrogen basicity[10] in the former.[14] Despite the fact that 1,5-hydrogen abstractions are generally favored over 1,6 abstractions on steric grounds, **8a** shows a reversal in preference of ca. 4:1. This reversal in preference strengthens the case for conformational control in this fast reaction.

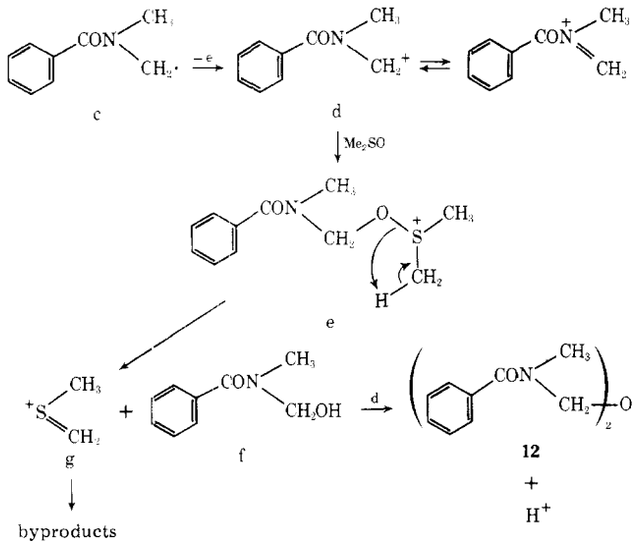
Incidentially, if we reject the hypothesis that the enamides result from β-carbon attack, and are another product of initial α-carbon attack, then we would have, in the case of **8a**, a *regiospecific* reaction at the α-carbon site. This seems very unlikely in view of the many observations reported above.

Other aspects of the carboxamide reactions deserve mention. We suggest that the total lack of a β-bromoalkyl product analogous to **4a** reflects greater electron density at the nitrogen atom which can stabilize transition to an enamide more readily than can the nitrogen in sulfonamide **1a**.

The 11% yield of Sandmeyer product **9c** in Me_2SO contrasts with the decomposition of the same substrate in chloride-containing aqueous media.[2a] In that case, 44.6% of *o*-(*N*,*N*-dimethyl)chlorobenzamide was formed. We suspect that the solvent plays a more important role than the different nucleophile, especially since decomposition of **8c** in acetone–$CuBr_2$ yields 77.5% of **9c**. Zollinger's group, in studying the effect of solvents on dediazoniation, invoked charge transfer complex formation with Me_2SO in a pre-rate-determining step of the decomposition of the *p*-nitrobenzenediazonium ion.[15] On the other hand, Sandmeyer reaction in Me_2SO to form aryl chlorides is inferior to the similar aryl bromide synthesis.[4]

Formation of the "dimeric" product (**12**, Scheme IV) from decomposition of **8c** merits comments, too. Initial examination of the reaction by GLC showed a small amount of **9c** and **10c** as the only volatile compounds, contrasting with TLC evidence of a major product different from those two. Preparative chromatography was accompanied by decomposition, as were initial attempts at mass spectroscopy. NMR spectra of the total reaction mixture suggested that this major product contained singlet aromatic, methyl, and methylene protons in integrated ratios of 5:3:2.[16a] The aliphatic groupings were broad, but they sharpened on heating,[16b] suggesting the well-known phenomenon attributed to restricted rotation of an *N*,*N*-dialkyl amide. Decomposition of **12** became evident at 80 °C, and after carrying it to its completion the resulting

Scheme VI



product could be clearly identified at **10c.** Particularly diagnostic for such a dealkylation process is the appearance of the lower field ortho aromatic protons, signifying allowed coplanarity of the ring and carbonyl moieties.

At the same time, solvolysis of a sample in methanol–HCl was followed by GC–MS, and formation of **10c** was shown to arise through the intermediacy of **13.** Structure **12** was thus supported by this chemistry and the ^1H and ^{13}C NMR chemical shifts for its methylene group. Further reinforcement then came from mass spectroscopy (chemical ionization); a strong M + 1 ion (*m/e* 313) was formed with isobutane as the reactant gas. Indeed, even a mass spectrum (field desorption) was eventually obtained showing M^+ 312. As noted above, structures similar to **12** have been formed by anodic oxidation of *N,N*-dialkyl amides.[12]

The involvement of Me_2SO in homolytic dediazoniation has recently been demonstrated by the inclusion of an ^{18}O label from the solvent into the product.[15] A similar occurrence could explain the presence of the ether oxygen in **12,** although an ionic pathway may be more likely in view of the enhanced stability of a carbenium ion intermediate. We have adapted the ideas of Ross[12] and Zollinger[15] in describing a plausible sequence to **12** (Scheme VI). The attack of Me_2SO on carbenium ion d to give e may be followed by bond reorganization as pictured, or stepwise, to give alcohol f and the methylenesulfonium ion g. The former, alcohol f, could be expected to yield **12** in reaction with another ion d upon loss of a proton.

Modest amounts of such an ether **3d** arose also from **1c,** as indicated by ^{13}C NMR spectra and solvolytic enhancement of the yield of **3c.** Formation of its higher homolgue from **1b** could also be supported from the ^{13}C NMR spectra of the total reaction.

Our last argument for steric effects rests on the failure of the ester analogues **14a** and **14b** to yield radical transfer products. No electronic reasons preclude hydrogen abstraction from the side chain; in fact, an adjacent oxygen increases reactivity at C_α, compared to a hydrocarbon, albeit not as much as does an adjacent nitrogen.[10] Beyond the α position, all electronic distinctions between the esters and amides should vanish. Even though rotation may occur freely in the alkoxycarbonyl moiety, we suggest that because of the diazo function, there is little concentration, if any, of a conformer having alkyl hydrogens near the proradical site. In the rapid reaction which occurs, hydrogen transfer cannot compete with attack by bromide.

Experimental Section[17]

Starting materials were made from the corresponding *o*-nitro acid chlorides followed by catalytic reduction over PtO_2 in alcohol. The only aniline not previously reported was ***N,N*-di-*n*-propyl-2-aminobenzenesulfonamide,** bp 148–150 °C (0.1 mm). Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.22; H, 7.86; N, 10.93. Found: C, 56.22; H, 7.76; N, 10.76.

Me_2SO (J. T. Baker) was dried over molecular sieves before use, except as noted. All other reagents and solvents were reagent grade and were used as received.

Diazonium salts were made according to the general procedure reported here for **1a.** A solution of 5.3 g (20.7 mmol) of *N,N*-di-*n*-propyl-2-aminobenzenesulfonamide in 10 mL of isopropyl alcohol and 4 mL of 48% HBF_4 (28 mmol) was cooled and stirred at 0–5 °C while adding 3.1 mL (23 mmol) of isoamyl nitrite. When crystallization was essentially complete, generally 10–40 min, 100 mL of ether was added, and the crystalline salt was collected and washed with ether. After drying in vacuo at ~23 °C, the salt weighed 6.9 g (19.4 mmol, 94%).

All yields were uniformly high. The ^1H NMR spectra (Me_2SO-d_6) were as expected; decomposition in the solvent *without* catalyst was shown to occur, but at an inconsequential rate compared to the catalyzed reactions (see below).

Dediazoniations were performed according to the general procedure, except as noted, reported here for **1b.** A solution of 190 mg (0.58 mmol) of **1b** in 0.5 mL of Me_2SO was added dropwise with stirring to 2.5 mL of Me_2SO containing 420 mg of $CuBr_2$ at 17–23 °C. Gas evolution was apparent and instantaneous. After 8–10 min, the mixture was diluted with methylene chloride, poured into ice and water, and worked up in the usual way.

Products. In each case the crude product mixture from a decomposition was studied by NMR spectroscopy, GLC, TLC, and sometimes GC–MS. Most yields reported in the text, tables, and Experimental Section were obtained either from silica gel chromatography on preparative plates or from GLC. They are accurate to ca. 3%. Some (e.g., the ethers) are obviously approximations. The individual sections below describe in brief the examination of each product mixture and the characterization for each product which was identified.

Dipropyl Sulfonamide 1a. Preparative plate chromatography (95:5 hexane–ethyl acetate) of 205 mg of mixture gave four bands, which are described in order of increasing polarity.

Band A: 10.2 mg of **5a;** mass spectrum, *m/e* 239 (M^+, 25), 210 (30), 198 (15), 141 (75), 77 (85), 70 (100); the ^1H NMR ($CDCl_3$) spectrum showed vinylic protons at δ 4.9 (m) and 6.5 (d).

Band B: 142 mg; contained nearly equal amounts of **2a** and **4a** and ~3% of **7a.** Rechromatography (benzene) allowed separation of the major constituents. **2a:** mass spectrum, *m/e* 321 (M^+), 319 (4), 292, 290 (100), 250, 248 (13), 221, 219 (63), 157, 155 (78). **4a:** mass spectrum, *m/e* 321 (M^+), 319 (0.4), 292, 290 (4), 240 (3), 212 (100), 170 (15), 141 (58), 77 (69); the ^1H NMR ($CDCl_3$) spectrum showed a methyl doublet at δ 1.75 and a methine multiplet at δ 4.35; the ^{13}C NMR ($CDCl_3$) spectrum showed the methine carbon at δ_c 46.75.

The small amount of **7a** was identified by GC comparison (mixed injection) with an authentic sample; GC–MS, *m/e* 241 (M^+).

Band C: 16.5 mg of **6a;** mass spectrum, *m/e* 321 (M^+), 319 (3), 292, 290 (55), 212 (82), 141 (100), 77 (64); the ^1H NMR ($CDCl_3$) spectrum showed a triplet at δ 3.40 for $-CH_2Br$; the ^{13}C NMR spectrum ($CDCl_3$) showed this carbon at δ_c 30.42.

Band D: 26.8 mg of **3a;** identified by GC comparison (mixed injection) with an authentic sample. Mass spectrum, *m/e* 199 (M^+, 5), 170 (53), 141(59), 77 (100).

Diethyl Sulfonamide 1b. Preparative plate chromatography (99:1 benzene–methanol) of 154 mg gave the following in order of increasing polarity.

Band A: 2.9 mg (~1.5%) of *N*-(β-bromovinyl)-*N*-ethylbenzenesulfonamide (**5d**); mass spectrum, *m/e* 291 (M^+, 10), 289 (M^+, 8), 146 [$M^+ - (Br + SO_2)$, 48], 141 (23), 125 (52), 77 (100), 69 (32).

Band B: 11.3 mg, which upon reexamination by GLC was a gross mixture containing all the known products as well as some which were not identified.

Band C: 92.6 mg (52%); contained **2b** and **4b** in ca. 4.5:1 ratio, respectively. Rechromatography gave substantially pure samples of each. **2b:** mass spectrum, *m/e* 293 (M^+), 291 (10), 278 (100), 276 (97), 221 (58), 219 (56), 157 (52), 155 (53); the ^1H NMR ($CDCl_3$) spectrum showed the aromatic, methylene, and methyl protons in the ratio 4:4:6. **4b:** mass spectrum, *m/e* 293 (M^+, 5), 292 (3), 291 (M^+, 5), 290 (2), 278 (16), 276 (18), 228 (16), 212 (4), 198 (100), 141 (65), 77 (98); in the ^1H NMR ($CDCl_3$) spectrum the $BrCH_2CH_2-$ signal was found as a single line at δ 3.45.

Band D: 5.2 mg, most of which was nonvolatile. A small amount of **7b** was identified by GLC comparison with an authentic sample.

Band E: 24.8 mg (24%) of *N*-ethylbenzenesulfonamide (**3b**); identified by comparison with an authentic sample.

The enamide **5b** was clearly identified by GC–MS and ^{13}C NMR spectra of the original crude mixture (mass spectrum, *m/e* 211 (M^+, 0.2), 185 (9), 170 (31), 141 (46), 77 (100), 51 (off scale); the ^{13}C NMR spectrum showed the terminal methylene at δ_c 92.6), but it was not found after silica gel chromatography. Its yield (3%) was estimated from GLC area (%) only.

When the same reaction was repeated identically, except that undried Me_2SO was used (H_2O, 1.13 mg/mL by Fisher titration), the unsaturated compounds **5b** and **5d** were undetectable (see Table II). The inverse addition reaction, performed by slowly adding 2.5 mL of dry Me_2SO saturated with $CuBr_2$ to 190 mg of **1b** in 1 mL of dry Me_2SO, gave the full spectrum of products, but in different proportions (Table II).

Dimethyl Sulfonamide 1c. An aliquot of a preparative scale reaction mixture was crystallized from methanol to give **2c,** mp 59–61 °C, in 60% direct yield; mass spectrum, *m/e* 265 (M^+), 263 (42), 221 (18), 219 (14), 184 (13), 157 (53), 155 (55), 44 (100); ^1H NMR ($CDCl_3$) δ 2.86 (s, 6, CH_3), 7.3–8.2 (m, 4, aromatic).

Anal. Calcd for $C_8H_{10}BrNO_2S$: C, 36.37; H, 3.82; N, 5.30; Br, 30.25. Found: C, 36.71; H, 3.64; N, 5.31; Br, 30.17. Chromatography of the mother liquors (9:1 benzene–methanol) gave an additional 15% of **2c.**

Another experiment was assayed by GLC using octadecane as an internal standard. It showed yields of 71, 11, and 4.5% for **2c, 3c,** and **7c,** respectively. After warming a portion of the total reaction mixture at 60 °C in methanol and aqueous HCl for 60 h, the amount of **3c** increased. The increase was attributed to hydrolysis of $C_6H_5SO_2N(CH_3)CH_2–O–CH_2N(CH_3)SO_2C_6H_5$, evidence for which was a ^{13}C NMR signal at δ_c 74.3, which was a triplet according to an off-resonance decoupling experiment. The fact that **3c** was undetectable in the ^{13}C NMR spectrum of the reaction before hydrolysis suggests that its observation by GLC represents thermal decomposition on the column.

Dipropyl Carboxamide 8a. Distillation of a preparative-sized reaction mixture gave pure **11,** bp 132–134 °C (4 mm) [lit.[18] bp 155–159 °C (13 mm)]; mass spectrum, *m/e* 203 ($M^{+\bullet}$, 11), 188 (4), 105 (100), 77 (4); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.6 (d, 3, CH_3CH=), ~1.6 (m, 2, CH_2), 3.65 (t, 2, CH_2), 5.0 (d of q, 1, CHCH$_3$), 6.5 (brd d, 1, NCH), 7.4 (brd s, 5, aromatic).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; 6.89. Found: C, 76.61; H, 8.19; N, 6.59.

Recoveries from preparative thin-layer chromatography were 65% of **11** and 17% of **10a** [mass spectrum, *m/e* 163 (M^+, 29), 105 (100), 77 (33)], which behaved identically (GLC, TLC, NMR) with an authentic sample. A trace of *N,N*-dipropylbenzamide was visible by GLC. No other products of significance were detectible by ^1H or ^{13}C NMR spectroscopy of the mixture. When the reaction was run by adding solid **8a** to the $CuBr_2$ solution, a number of other minor products were formed in addition to **10a** and **11.**

Dimethyl Carboxamide 8c. Quantitative GLC showed 2–3% of **10c** and traces of *N,N*-dimethylbenzamide, both identical with authentic samples, and an 11% yield of bromocarboxamide **9c,** identical in all respects with a sample prepared from *o*-bromobenzoyl chloride and dimethylamine: bp 144 °C (3.6 mm); mass spectrum, *m/e* 229 (M^+), 227 (23), 228, 226 (30), 185, 183 (100), 157, 155 (43), 148 (25), 76 (81), 75 (70); ^1H NMR ($CDCl_3$) δ 2.8 (s, 3, CH_3), 3.1 (s, 3, CH_3), 7.0–7.7 (m, 4, aromatic).

Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.20; H, 4.48; N, 6.03.

The ^1H NMR spectrum ($CDCl_3$) of the entire crude reaction mixture showed signals attributable to **12:** δ 2.95 (brd s, 3, CH_3), 4.65 (brd s, 2, CH_2), 7.35 (brd s, 5, aromatic); ^{13}C NMR signals for the methyl and methylene groups were broad and centered at δ_c 34 and 77, respectively; mass spectrum (chemical ionization, isobutane), *m/e* 313 ($M^+ + 1$).

A small portion of the reaction mixture containing an internal GLC standard was heated over the weekend at 60 °C in methanol containing a few drops of HCl. GLC analysis showed 85.5% of **10c** and 11% of **9c.** A sample of this hydrolysis taken after ~2 h of reaction time showed a product whose mass spectrum identified it as **13;** mass spectrum, *m/e* 179 (M^+, 12), 164 (20), 148 (4), 105 (100), 77 (35). **13** was absent at the end of the hydrolysis. Decomposition carried out in dry acetone instead of Me_2SO gave 78% of **9c** and 14% of **10c,** as measured by quantitative GLC. Bromoacetone was also formed.

Ester 14a. The product consisted of 11% *n*-propyl benzoate and 89% *n*-propyl *o*-bromobenzoate (**15a**), as measured by GLC. Authentic **15a** was prepared from the corresponding acid chloride: bp 123 °C (4 mm); mass spectrum, *m/e* 244 (M^+), 242 (7), 202, 200 (58), 185, 183 (100), 157, 155 (42), 104 (14), 76 (83), 75 (70).

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found C, 49.46; H, 4.83.

Ester 14b. GLC measured yields of 6% isopropyl benzoate and 94% isopropyl *o*-bromobenzoate (**15b**) were obtained from reaction in the usual way. Authentic **15b** was made from the corresponding acid chloride: bp 92 °C (4 mm); mass spectrum, *m/e* 244 (M^+), 242 (21), 202, 200 (42), 185, 183 (100), 157, 155 (26), 104 (11), 76 (46), 75 (39).

Acknowledgment. It is with great pleasure that we dedicate this paper to Dr. John M. Chemerda in appreciation for his stimulating, provocative, and skillful research leadership. We also acknowledge the stimulating discussion with Professor T. Cohen of the University of Pittsburgh and Drs. A. W. Douglas and R. A. Firestone of these laboratories.

Registry No.—**1a,** 65000-08-0; **1b,** 65000-09-1; **1c,** 65000-10-4; **2a,** 65000-11-5; **2b,** 65000-12-6; **2c,** 65000-13-7; **3a,** 23705-37-5; **3c,** 5183-78-8; **3c,** 65000-14-8; **4a,** 65000-15-9; **4b,** 65000-16-0; **5a,** 65000-17-1; **5b,** 65000-18-2; **5d,** 65000-19-3; **6a,** 65000-26-2; **8a,** 65000-20-6; **8c,** 22396-44-7; **9c,** 54616-47-6; **10a,** 10546-70-0; **11,** 19326-67-1; **12,** 65000-21-7; **13,** 65000-22-8; **14a,** 65000-23-9; **14b,** 65000-24-0; **15a,** 65000-25-1; **15b,** 592-47-52-8; *N,N*-dipropyl-2-aminobenzenesulfonamide, 65000-27-3; *o*-bromobenzoyl chloride, 7154-66-7; Me_2SO, 67-68-5; $CuBr_2$, 7789-45-9.

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(6) C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.,* **94,** 856–865 (1972).
(7) (a) We shall henceforth refer to this process and product without the "-like" limitation, even though the "true" Sandmeyer reaction uses Cu^I salts in aqueous media. For leading references, see "The Merck Index", 9th ed, 1976, p ONR 79. (b) Radical transfer and hydrogen transfer are synonymous in the context of this paper and will be used interchangeably.
(8) (a) A 1,6 attack may have occurred with an *N*-ethylbenzanilide;[3a,d] however, no product specifically characteristic of this process was reported. (b) Breslow and his co-workers have capitalized on steric proximity, employing hydrogen abstraction by aryl-*bound* functional groups well beyond 7-bond distances. For a leading reference, see R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kalega, *J. Am. Chem. Soc.,* **99,** 905–915 (1977).
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(14) A referee has suggested that attribution of the results with **8a** to a steric effect "ignores the real possibility that α abstraction may be far more favorable in the carboxamide than in the sulfonamide due to the greater electron donation in the former," thereby effectively eliminating competitive γ abstraction in that substrate. No doubt that is a factor, but if it was a significant or controlling one we would be hard pressed to explain why no γ (or indeed, α or β) abstraction occurs in the case of the esters **14a** and **14b.** We believe that an effect which fits *all* the experimental results, i.e., the steric effect, should not be minimized. Furthermore, we have not ignored the possible role of the greater basicity of the carboxamide N in the discussion of the enamide formation (see below in text).
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(16) (a) The NMR spectra also showed that the amount of *N*-methylbenzamide

(10c) was at the lower end of the 2–10% range observed by GLC, suggesting that some of it was a thermal product. (b) We are indebted to Mr. R. Zerfing for this experiment.

(17) Boiling points and melting points are uncorrected. Elemental analyses were performed under the direction of J. P. Gilbert of these laboratories. ^{1}H NMR spectra were obtained with Jeol (USA) C-60 HL and Hitachi Perkin-Elmer R-24 spectrometers. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer. All chemical shifts are referred to tetramethylsilane. Mass spectra were obtained courtesy of Messrs. J. Smith and H. Flynn, and Patricia Cala, using LKB 9000, Varian MAT-371, and Finnegan 3200 spectrometers. For brevity, only parts of some spectra are reported. GLC analyses were performed on a Hewlett Packard 5830A gas chromatograph using thermal conductivity detection. Three columns, 6 ft × 1/8 in. stainless steel, packed with 10% SP 2401, 10% SP 2340, and 10% OV-225, all on 80–100 mesh Supelcoport, were used with He as a carrier gas. The appropriate hydrocarbon was used as an internal standard in all chromatographies used for yield calculations. The "usual workup" involved washing organic solvent solutions with water, drying over magnesium sulfate, and evaporating to dryness in vacuo.

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Preparation of 6β-Imidopenicillinate 1(*S*)-Oxides

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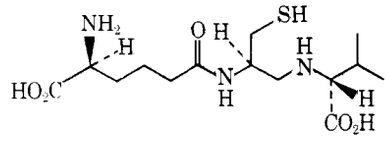
Received September 21, 1977

Examples of the as yet unknown 6β-imidopenicillinate 1(*S*)-oxides were prepared and the stereochemistry was proven unambiguously by x-ray diffraction. These substances were thermodynamically stable with respect to the corresponding 1(*R*)-oxides as shown by equilibration via thermal ring opening. The possible significance of these results with respect to the biogenetic relationships of penicillins and cephalosporins is discussed.

The biogenesis of the β-lactam antibiotics, penicillins and cephalosporins,[1] is now generally recognized to derive from Arnstein's tripeptide, L-α-aminoadipyl-L-cysteinyl-D-valine (**1**), since the bioconversion of this substance to penicillins has been reported.[2] The isolation of this substance from *Cephalosporium* sp. has also been reported.[3] The sequence of reactions involved in the conversion of **1** into penicillin N (**2**) and cephalosporin C (**3**) is still unknown; however, two suggestions have been made. Thus, in one case,[4] a priori formation of monocyclic species (**4**) is followed in a branched pathway by the formation of **2** and **3**.[5] An earlier alternative, suggested by Abraham,[6] is the bioconversion of **2** to **3**, but, until recently,[7] this scheme has had little support. The latter is attractive, since the in vitro ring expansion of penicillin sulfoxides to deacetoxycephalosporins is the basis of a commercial production of these compounds.[8] Thus, for example, refluxing methyl 6β-phenoxyacetamidopenicillinate 1(*S*)-oxide (**5**) in xylene with a trace of acid gives the deacetoxycephalosporin (**7**) by way of the sulfenic acid (**6**).[9]



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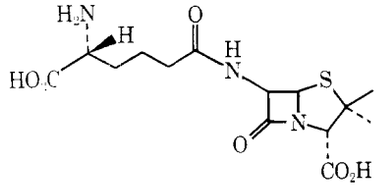

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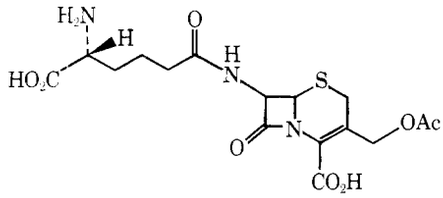

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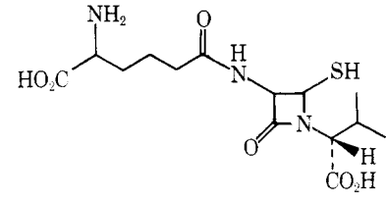

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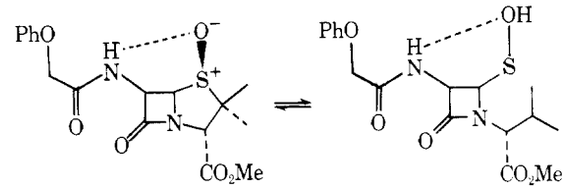
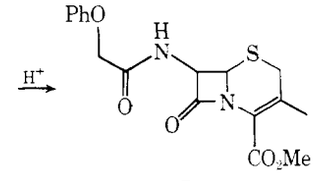


5 **6**



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An immediate objection that could be raised to this hypothesis is that the relatively high temperatures (in the region of 100 °C) required to initiate the thermal ring opening (syn elimination) of **5** to **6** would hardly be available in vivo. An

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