Beckmann Rearrangement and Fission of 2-Arylcyclohexanone Oxime Tosylates. Trapping of Carbonium Ion Intermediates as Pyridinium Cations[1]

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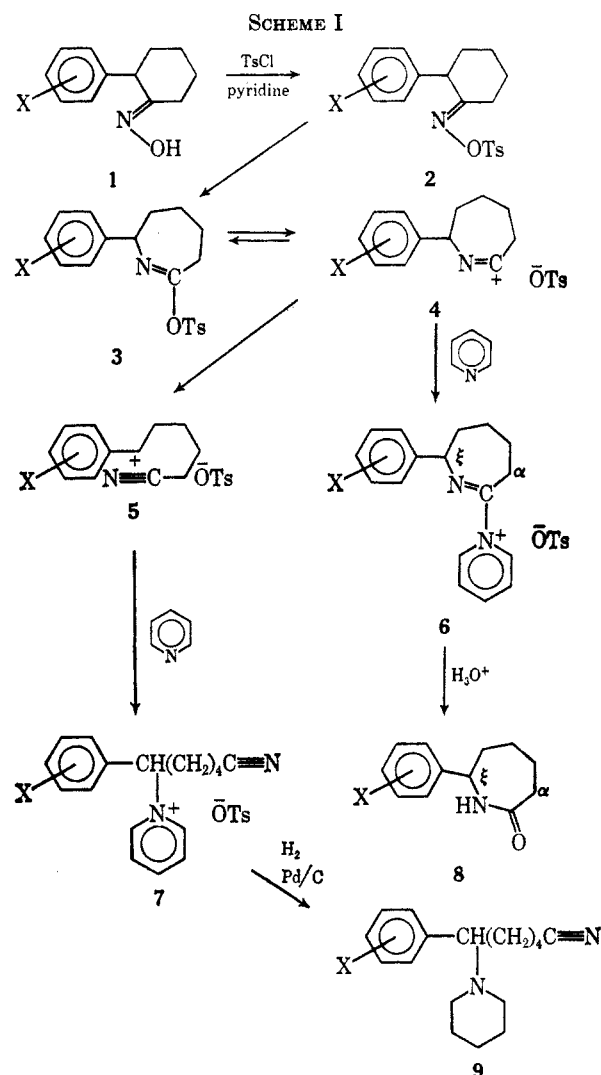*College of Pharmacy, University of Washington, Seattle, Washington 98105*

Reaction of *anti*-2-*o*-tolyl-, 2-*p*-tolyl- and 2-(*p*-chlorophenyl)cyclohexanone oximes 1 with tosyl chloride in pyridine at room temperature gave pyridinium salts 6 and 7, products of the iminyl carbonium ion 4 and of the fission carbonium ion 5, respectively. The results support a mechanism involving a rate-determining rearrangement step of oxime tosylate 2 to iminol tosylate 3, or some intermediate closely related to it, followed by a fast ionization and a partitioning of the resulting carbonium ion 4 to the corresponding pyridinium cation 6 and pyridinium cation 7 of the fission reaction. The rearrangement of the oxime tosylate was slowest with *p*-chloro compound 1c and this compound yielded the smallest amount of fission reaction pyridinium salt 7c.

In an attempt to isolate 2-*o*-tolylcyclohexanone oxime tosylate 2a oxime 1a was treated with tosyl chloride in dry pyridine at room temperature and after a few hours the mixture was poured into about eight times its volume of water. Extraction of the aqueous mixture with ethyl ether and benzene yielded very little organic material besides pyridine. Acidification of the aqueous layer caused cloudiness and extraction with ether yielded lactam 8a in about 40% yield. The high partitioning in water, prior to acidification, indicated that in our reaction the intermediate leading directly to the lactam was not iminol tosylate 3a. A more careful investigation of the reaction with the aid of nuclear magnetic resonance (nmr) showed that prior to acidic hydrolysis the main products were pyridinium salts 6a (product of the carbonium ion 4a) and pyridinium salt 7a (product of the fission reaction leading to carbonium ion 5a). Proof of structure for 6a rests on nmr and solubility data, but 7a was characterized from its hydrogenation product 9a in addition to spectroscopic data. The reaction in pyridine at room temperature was quite fast. It appeared to reach completion in less than 20 min as no subsequent change was noticeable in the nmr spectrum upon standing for 36 hr, with the possible exception of a slight increase in the ratio of 7a to 6a. Similar results were obtained with *p*-methyl isomer 1b. With *p*-chloro oxime 1c the disappearance of the oxime (or more probably the oxime tosylate) was somewhat slower, the ratio of pyridinium salt 6c to 7c was larger, and the yield of the lactam was slightly larger than with the tolyl compounds.

The results are consistent with the sequence of events outlined in Scheme I. Scheme I is also consistent with reported information on the Beckmann rearrangement and fission (or fragmentation) reactions of ketoxime tosylates,[2-6] but to our knowledge this is the first report of the "trapping" of the carbonium ion intermediates of types 4 and 5.

There are many reports of reactions of arylsulfonyl esters of oximes in pyridine,[2,5,6] but in most cases the work-up did not provide for the detection and isolation

SCHEME I

a, X = *o*-CH₃
b, X = *p*-CH₃
c, X = *p*-Cl

(1) This investigation was supported in part by Research Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service.

(2) K. Morita and Z. Suzuki, *J. Org. Chem.*, **31**, 233 (1966).

(3) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965).

(4) C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, **47**, 1003 (1964).

(5) P. A. S. Smith in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 483 (and references therein).

(6) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

of the pyridinium salts of the fragmentation reactions. The spontaneous rearrangement of benzenesulfonate esters of ketoximes to iminol esters has been shown by Kuhara and coworkers,[7] as far back as 1914. Recently, Grob and coworkers[4] have concluded that the rate-determining step of the rearrangement of oxime tosylates in 80% ethanol involves the isomerization to

(7) M. Kuhara, K. Matsumiya, and N. Matsunami, *Mem. Coll. Sci., Univ. Kyoto*, **1**, 105 (1914), from ref 5. The original work was not consulted.

an iminol tosylate which then ionizes to a nitrilium cation,[8] the common intermediate of rearrangement and fission products. They showed that the reaction rates reflect migratory aptitudes and that fission reactions occur after the rate-determining migration step. It follows that the extent of fragmentation, under a given condition, will depend on the energy of activation for the formation of the fission carbonium ion, which in turn can be related to the stability of this carbonium ion. The results of Morita and Suzuki[2] are in agreement with this.

Our own results support the conclusions of Grob and coworkers. A mechanism for the formation of carbonium ions **4** and **5** is depicted in Scheme II but our results do not establish whether the formation of **4** must pass through **3** or whether it could come directly from an intermediate of the nature of **11**, closely related to the transition state.

SCHEME II

2 →

δ^{-}OTs
10

11

3 ⇌ 4 → 5
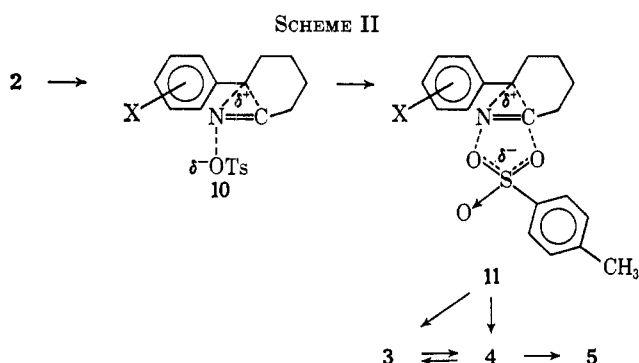
For the nmr investigation the reactions were carried out at concentrations of about 12–16% of the oxime in dry pyridine using either 1 mol or 1.1 mol equiv of *p*-toluenesulfonyl chloride (tosyl chloride). The nmr interpretation was strengthened by also carrying out the reaction on the tri- and tetradeuterated oximes **1a**-d_3 and **1a**-d_4.

1a-d_3 **1a**-d_4
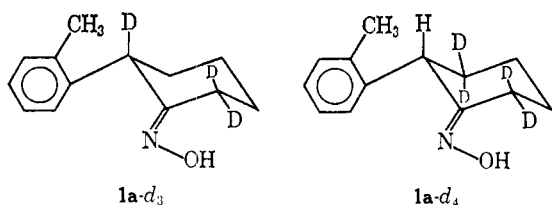
Spectrum A, Figure 1, is the 60-MHz nmr spectrum of the reaction mixture in pyridine of 2-*o*-tolylcyclohexanone oxime **1a** with 1.1 mol equiv of tosyl chloride after standing for 36 hr. The spectrum indicates a mixture of pyridinium salts **6a** and **7a** in a ratio of about 3:2, respectively. The signals at τ 7.80, 7.63, and 7.53 are attributed to the aromatic methyl groups of the tosylate ion, and the pyridinium cations **6a** and **7a**, respectively. The broad signals at τ 6.32 and 4.69 (ratio of 2:1) are attributed to the α-methylene and ϵ-methine hydrogens, respectively, of **6a**. The methylene signal at τ 6.32 and the aromatic methyl signal at τ 7.63 integrate to a ratio of approximately 2:3. The signal at τ 0.15 (downfield from the signals of the pyr-
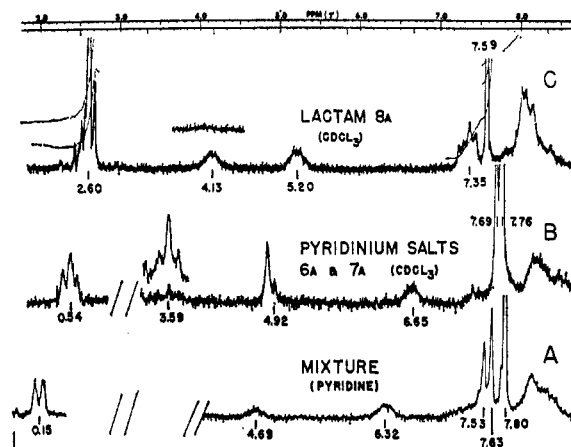

Figure 1.—60-MHz nmr spectra of reaction mixture of **1a** with tosyl chloride in pyridine (A); mixture of pyridinium salts **6a** and **7a** in chloroform-*d* (B); and lactam **8a** in chloroform-*d* (C); all with TMS as internal standard.

idine) is attributed to the combined α hydrogens of pyridinium cations **6a** and **7a**. This signal integrates to an approximate ratio of 2:6 to the combined signals of all aromatic methyl groups. The chemical shift of this signal is sensitive to moisture. Addition of 5 drops of D_2O causes an upfield shift of 0.3–0.4 ppm. The addition of D_2O also caused the aromatic methyl signals at τ 7.53 and 7.63 to overlap at 7.57. The addition of D_2O also caused a small triplet (separation of about 7 Hz) to appear at τ 3.58. This signal is attributed to the methine hydrogen of **7a**, hidden under the signals of the pyridine prior to addition of D_2O. The signal at τ 0.15 is very indicative of the presence of salts **7a** and **6a** because this signal is not seen with *p*-toluenesulfonic acid nor tosyl chloride in pyridine but such a signal is seen with benzylpyridinium bromide. Additional proof is obtained from the spectra of the following work-up products.

The reaction mixture giving spectrum A was mixed with an equal volume of water and the mixture extracted successively with ethyl ether and benzene, removing most of the pyridine. The remaining aqueous layer was extracted several times with chloroform, the chloroform layer washed with water, the chloroform removed at room temperature, and an nmr spectrum of the resulting material was determined in chloroform-*d*, spectrum B. The combined signals of the α hydrogens of pyridinium salts **6a** and **7a** are still in the ratio of 2:6 in relation to the combined aromatic methyl hydrogens, which includes the tosyl group. The signal of the methine hydrogen of **7a** gives the expected triplet at τ 3.59.[9] The signals of the ϵ and α hydrogens of **6a** are at τ 4.92 and 6.65, respectively. The signal at τ 4.92 is partially overlapped with the signal of hydrogen from moisture (shown by addition of D_2O). Salt **7a** was isolated by acid hydrolysis of either the original reaction mixture, or the mixture giving spectrum B, using about 15% *p*-toluenesulfonic acid. In both cases the resulting lactam **8a** was extracted with ether or benzene and **7a** was obtained by extraction of the aqueous layer with chloroform or dichloromethane. Any remaining pyridine was azeotroped at room tem-

(8) The cation is really a resonance hybrid between the nitrilium ion and iminyl carbonium ion structures. In cyclic structures where linearity of the nitrilium structure is prevented the ion will have a greater degree of carbonium ion character.

(9) The spectrum of benzylpyridinium bromide in chloroform-*d* gives a complex doublet at τ 0.40 for the α-pyridinium hydrogens and a singlet at τ 3.72 for the methylene hydrogens.

perature with 2,2,4-trimethylpentane on a rotary evaporator. The nmr spectrum of **7a** in chloroform-d lacks the peaks at τ 6.65 and 4.92, seen in spectrum B, but gives a doublet for the pyridinium α hydrogen at τ 0.72 and a triplet for the methine hydrogen at τ 3.67 in the ratio of 2:1 (the positions of these two signals vary with presence of moisture) and singlets of equal intensities at τ 7.69 and 7.80 for the aromatic methyl groups of the **7a** cation and the tosylate anion, respectively. Salt **7a** is somewhat hydroscopic and was not analyzed but an elementary analysis was obtained on its hydrogenation product **9a**. The ir spectra of **7a** and **9a** exhibit a C≡N stretching band at 2240 cm⁻¹.

Spectrum C is that of the lactam **8a** measured in chloroform-d. The signals at τ 4.13, 5.20, 7.35, and 7.59 integrate for one, one, two, and three hydrogens, respectively, and are assigned to the NH, the benzylic ϵ-methine hydrogen, the α-methylene hydrogens, and the aromatic methyl hydrogens in that order. The signal at τ 4.13 disappears upon exchange with D$_2$O (upper curve). The assignment of structure **8a** is unambiguous[10] and is further substantiated by the spectra of the lactams obtained from the deuterated oximes **1a**-d_3 and **1a**-d_4. The structure of lactam **8a** establishes the structure of the starting oxime as having the *anti* configuration.[10] The same is true for **1b** and **1c**.

In the reactions with the deuterated oximes the acid hydrolysis was carried out without removal of the pyridine. Deuterated lactams **8a** and deuterated pyridinium salts **7a** were isolated for nmr analysis. With **1a**-d_3 the nmr spectrum of the reaction mixture differed from spectrum A only in the absence of the signals at τ 4.69 and 6.32 and in the absence of appearance of the triplet around τ 3.58 upon addition of D$_2$O. The spectrum of salt **7a** lacked the triplet seen at τ 3.67, attributed to the methine hydrogen in the spectrum of nondeuterated **7a**. The spectrum of the lactam differed from spectrum C in the absence of signals at τ 5.20 and 7.35. With tetradeuterated oxime **1a**-d_4 the spectrum of the reaction mixture lacked the signal at τ 6.32 and the signal at 4.69 was now a sharper singlet. This is as expected for **6a** having deuterium on the α and δ carbons. Addition of D$_2$O caused a singlet to appear in the vicinity of τ 3.58. The spectrum of the moist pyridinium tosylate salt **7a**-d_4, measured in chloroform-d, gave a doublet (2 H) at τ 0.75, a sharp singlet (1 H) at 3.70, a complex pattern for the remaining aromatic hydrogens (11 H), two singlets (3 H each) at 7.70 and 7.80, and a broad signal of four hydrogens at about τ 8.5. The data are consistent with structure **7a** having deuterium on C-2 and C-5 of the chain. The most significant differences in the spectrum of the tetradeuterated lactam were the absence of the signal at τ 7.35 in C and a sharpening of the signals at 5.20.

2-p-Tolylcyclohexanone oxime **1b** gave results very similar to those of the *ortho* isomer but there was a partial overlap of the signals of the aromatic methyl groups of **6b**, **7b**, and the tosyl group for the reaction mixture in pyridine.

With equal molar quantity of 2-(p-chlorophenyl)-cyclohexanone oxime **1c** and tosyl chloride the nmr spectrum measured at 30 min of reaction time had two

tosyl methyl signals of almost identical intensities, τ 7.70 and 7.78. After 6.5 hr of total reaction time only one methyl signal was present at τ 7.78. Otherwise the spectrum was quite similar to spectrum A, Figure 1, showing a complex doublet at τ 0.0, and signals in ratio of 1:2 at τ 4.77 and 6.34, respectively. Integration indicated a higher proportion of **6c** compared to **7c** than with the tolyl compounds. The signals at τ 7.70 and 7.78, at 30-min reaction time, are attributed to the aromatic methyl hydrogens of oxime tosylate **2c** and the tosylate anions of **6c** and **7c**. This implies that the rearrangement of **2c** is slower than **2a** and **2b**. This is consistent with the expected lower migratory aptitude of the p-chlorobenzyl than methylbenzyl groups. The larger proportion of pyridinium salt **6c** (and subsequent higher yield of the lactam **8c**) is also consistent with the expected lower stability of the carbonium ion **5c** compared to **5a** and **5b**.

Experimental Section

Melting points were determined on a Kofler micro hot stage melting point apparatus. The nmr spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

anti-2-**Arylcyclohexanone oximes** (**1a**, **1b**, and **1c**) were prepared from the known 2-o-tolyl-, 2-p-tolyl-, and 2-(p-chlorophenyl)cyclohexanones[11] by a method similar to that of Drefahl and Martin.[12] The preparation of 2-o-tolylcyclohexanone oxime **1a** is described as a general example. To a mixture of 9.60 g (0.051 mol) of 2-o-tolylcyclohexanone and 7.20 g (0.103 mol) of hydroxylamine hydrochloride in 210 ml of methanol was added a solution of 7.70 g (0.058 mol) of potassium carbonate in 105 ml of water. The mixture was refluxed for 1.5 hr and cooled in ice; 100 ml of ice-cold water was added. The resulting precipitate was collected by suction filtration, washed with two 20-ml portions of water, and recrystallized from 95% ethanol, giving a total recovery of 9.5 g (91%): mp 197–198°; 2-p-tolylcyclohexanone oxime **1b** (90%), mp 183–184°; 2-(p-chlorophenyl)cyclohexanone oxime **1c** (84%), mp 186–187°.

Anal. Calcd for C₁₃H₁₇NO: C, 76.81; H, 8.43; N, 6.89. Found for **1a**: C, 76.77; H, 8.39; N, 6.81. Found for **1b**: C, 76.60; H, 8.57; N, 6.72.

Anal. Calcd for C₁₂H₁₄ClNO: C, 64.43; H, 6.31; N, 6.26. Found for **1c**: C, 64.65; H, 6.44; N, 6.03.

ϵ-**Aryl**-ϵ-**caprolactams** (**8a**, **8b**, and **8c**).—The method described for ϵ-o-tolyl-ϵ-caprolactam **8a** was used as a general method for obtaining the lactams but variations in work-up procedures were used for nmr studies of the pyridinium salts **6** and **7** as described in the text.

To a solution of 2.032 g (0.010 mol) of **1a** in 10 ml of anhydrous, freshly distilled, pyridine was added a solution of 2.10 g (0.011 mol) of p-toluenesulfonyl chloride in 3 ml of anhydrous pyridine. A yellow color developed. The mixture was cooled intermittently in ice to prevent the temperature from rising above 24° and was then allowed to stand at room temperature for about 36 hr. The yellow solution was poured into 50 ml of 10% HCl[13] and the mixture extracted successively with three portions of ethyl ether and benzene. The combined extracts were washed with 5% sodium bicarbonate, followed by water, filtered through anhydrous sodium sulfate, and dried further over Drierite. Evaporation of the solvent gave 980 mg of yellowish solid which was treated with decolorizing carbon in 2-propanol and recrystallized from 2-propanol, yielding 790 mg (39%) of colorless crystalline material, mp 109–115°. The compound undergoes crystal modification in the region of the melting point. Crystals are seen to melt, resolidify, and remelt at higher temperature.

ϵ-p-Tolyl-ϵ-lactam **8b** (47%) had mp 153–154°; mass parent ion 203.1366 (calcd 203.1309).

ϵ-(p-Chlorophenyl)-ϵ-lactam **8c** (52%) had mp 172–174°. The ir (KBr disk) of all three lactams show sharp N—H stretching at 3320 cm⁻¹ and C=O stretching at 1650 cm⁻¹.

(10) A. C. Huitric, D. B. Roll, and J. R. DeBoer, *J. Org. Chem.*, **32**, 1661 (1967).

(11) A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.*, **78**, 614 (1956).

(12) G. Drefahl and D. Martin, *Chem. Ber.*, **93**, 2497 (1960).

(13) In reactions with **1b** and **1c** corresponding lactams **8b** and **8c** precipitated out as solids at this point and were filtered off.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found for **8a**: C, 76.48; H, 8.47; N, 6.73. Found for **8b**: C, 76.73; H, 8.81; N, 6.82.

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found for **8c**: C, 64.35; H, 6.16; N, 6.17.

6-o-Tolyl-6-(1-piperidyl)hexanenitrile (9a).—A mixture of 400 mg (0.000915 mol) of 1-(1-o-tolyl-5-cyanopentyl)pyridinium *p*-toluenesulfonate (**7a**)[14] and 80 mg of 10% palladium on carbon in 20 ml of absolute ethanol was shaken for 24 hr under 30 psi of hydrogen in a Parr hydrogenator. The catalyst was removed by filtration through Celite and the solvent removed under reduced pressure on a rotary evaporator, giving 340 mg of oily material, ir 2240 cm^{-1} (C≡N). The nmr showed the absence of the pyridine ring, the replacement of the triplet of the methine benzylic hydrogen of the pyridinium salt **7a** (Figure 1) at τ 3.59 by a multiplet at τ 5.50, the increase of the integration of signals above τ 7.0 by ten hydrogens compared to **7a**, and the presence of the tosylate group. The oil was dissolved in 20 ml of chloroform, the solution washed with 10% NaOH, followed by water, and dried (Na_2SO_4). Removal of the solvent gave 220 mg of a yellow oil, ir 2240 cm^{-1} (C≡N). The major differences of the nmr compared to that of the tosylate salt was the absence of signals due to the tosylate group and an upfield shift of the signal of the methine benzylic hydrogen from τ 5.50 to 6.50. The free base was converted into the HCl salt by bubbling HCl in a hexane

(14) Pyridinium tosylate salt **7a** was obtained by chloroform extraction of the aqueous layer resulting from the lactam formation by hydrolysis of the reaction mixture with 15% *p*-toluenesulfonic acid, as explained in the text.

solution of the base, and the salt recrystallized from 2-propanol, mp 188–191°.

Anal. Calcd for $C_{18}H_{27}N_2Cl$: C, 70.45; H, 8.87; N, 9.15. Found: C, 70.37; H, 8.72; N, 9.09.

Deuterated Oximes 1a-d_3 and 1a-d_4.—The deuterated oximes were prepared from the corresponding deuterated ketones by the method described for nondeuterated **1a**.

2-o-Tolylcyclohexanone-2,6,6-d_3 was prepared by base-catalyzed deuterium exchange on 1.5 g of 2-o-tolylcyclohexanone in a mixture of 6.2 ml of anhydrous purified dioxane and 3.0 ml of D_2O with trace amount of sodium methoxide as source of base. The mixture was stirred at 90° for 2 hr, cooled, poured into 10 ml of water, extracted with ether, and dried (Na_2SO_4); the ether was removed. The process was carried out three times. After the third exchange the nmr integration indicated that the exchange was essentially complete: yield 1.3 g; mp 54.0–55.0° [lit.[11] (nondeuterated) mp 55.5–56.5°].

2-o-Tolylcyclohexanone-3,3,6,6-d_4 was prepared by the method previously reported.[15]

Registry No.—**1a**, 19640-09-6; **1a-d_3**, 19640-10-9; **1b**, 19640-11-0; **1c**, 19640-12-1; **6a**, 19643-00-6; **7a**, 19643-01-7; **8a**, 19643-02-8; **8b**, 19643-03-9; **8c**, 19643-04-0; **9a** (HCl salt), 19643-05-1; tosyl chloride, 98-59-9.

(15) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

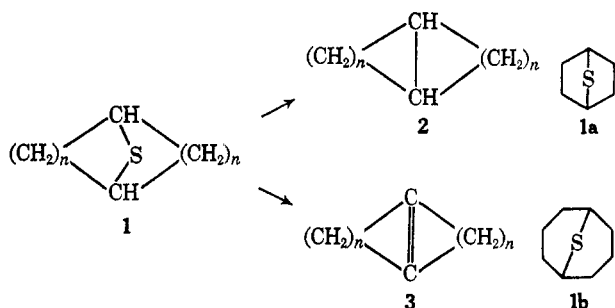# Sulfur-Bridged Carbocycles. II. Extrusion of the Sulfur Bridge[1]

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The extrusion of the sulfur bridge from 7-thiabicyclo[2.2.1]heptane (**1a**) and 9-thiabicyclo[3.3.1]nonane (**1b**) and their derivatives, a synthetically useful procedure for the controlled formation of transannular single and double bonds, is described. A novel synthesis of $\Delta^{1,5}$-bicyclo[3.3.0]octene (**8**) has been achieved through the Ramberg–Bäcklund rearrangement of 1-bromo-9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**7**). Thermal extrusion of sulfur dioxide from 7-thiabicyclo[2.2.1]heptane 7,7-dioxide (**4**) and 9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**5**) affords 1,5-hexadiene and bicyclo[3.3.0]octane (**14**), respectively, as major products. Photochemical extrusion of sulfur from **1a** and **1b** in trivalent organophosphorus solvents affords, as the major products, cyclohexene and an equimolar mixture of **14** and cyclooctene, respectively. Related studies on the photochemical extrusion of sulfur from bivalent sulfur compounds in organophosphorus solvents are also described.

We have previously described several convenient synthetic routes to two members of the class of symmetrical sulfur-bridged carbocycles represented by **1**.[1] A variety of other bicyclic and polycyclic sulfur-bridged carbocycles has recently become readily available.[2] It is apparent that, if the bridging sulfur, in any of its valence states, could be extruded from such sulfur-

bridged rings with the concomitant formation of a bond between the carbon atoms previously joined to sulfur, affording bicyclic structures **2** or **3**, an interesting synthetic method would be at hand for the controlled formation of transannular single or double bonds.[3] Extension of this procedure to the synthesis of bridgehead- and/or ring-substituted bicyclic or polycyclic structures from the appropriately substituted sulfur-bridged precursors should be possible. The general utility of the proposed synthetic procedure requires the elaboration of suitable methods for the conversion of the C–S–C linkage to a C–C single or double bond.

Advantage has been taken in these studies of several unique and characteristic properties of organically bound sulfur, including its ability to exhibit multiple valence states (thereby making available a variety of sulfur bridges), its ability to stabilize adjacent bridgehead carbanions (making bridgehead substitution possible), and the relative photochemical and thermal lability of the C–S bond.

Formation of Transannular Double Bonds. The Ramberg–Bäcklund Reaction.—In 1940, Ramberg and

(1) (a) For paper I of this series, see E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966); (b) also see E. Block, Ph.D. Thesis, Harvard University, 1967 [*Dissertation Abstr.*, **28**, 1849-B (1967)].

(2) (a) For a general survey, see ref 1b; (b) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966); (c) F. Lautenschlaeger, *ibid.*, **31**, 1679 (1966); (d) F. Lautenschlaeger, *Can. J. Chem.*, **44**, 2813 (1966); (e) P. Y. Blanc, P. Diehl, H. Fritz, and P. Schlapfer, *Experientia*, **23**, 896 (1967); (f) F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2620, 2627 (1968).

(3) For a thorough review of the subject of extrusion, see B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, New York, N. Y., 1967.