The Beckmann Fragmentation of an α-Methioxyketoxime[1]

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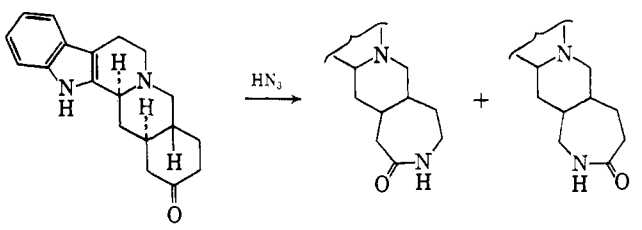
Abstract: A general procedure for the conversion of α-methylene ketones to α-methioxy ketones is exemplified by the preparation of 2-methioxy-7-methoxytetralone-1 (**4**). The steric influence of the α-methioxy function is assessed. Submission of **5**, the oxime of **4**, to the conditions of the Beckmann rearrangement causes fragmentation to a mixture of 3-aryl-*trans*- and -*cis*-1-methioxypropenes (**6** and **7**). The use of a new reagent, 2-chloro-1,1,2-trifluorotriethylamine, to bring about the Beckmann rearrangement under unusually mild conditions is reported. The over-all result of this sequence is a novel cleavage of the bond between a carbonyl and an adjacent methylene such that the termini of the cleaved bond are left in different oxidation states to permit separate modification. The possible intermediacy of a 1,2-thiazetine ring (*e.g.*, as in **29**) in the fragmentation reaction is defended.

The cleavage of a single bond between a carbonyl and an adjacent methylene is an important synthetic and degradative tool and many methods of accomplishing this operation are known, ranging in subtlety and general usefulness from direct Cr(VI) or permanganate oxidation to a diacid, to the unsymmetrical cleavages effected by the Baeyer–Villiger oxidation and the Beckmann and Schmidt rearrangements. The principles which govern (or fail to govern) the choice of which of the two bonds to the carbonyl carbon is cleaved are well understood, *viz.*, the favored direction of enolization, or steric hindrance, or the relative stability of two carbonium ions, etc. In a selected case, however, even this broad armamentarium may fail to contain a suitable weapon; thus, in the instance of our synthesis of corynantheine[4] from yohimbone (**1**), there appeared to be no suitable oxidant which would preferentially attack near the carbonyl rather than near the strongly nucleophilic tetrahydro-β-carboline system. The brief action of hydrazoic acid on yohimbone in concentrated sulfuric acid led, for example, to a pair of "unopenable" lactams, so that not only was there no



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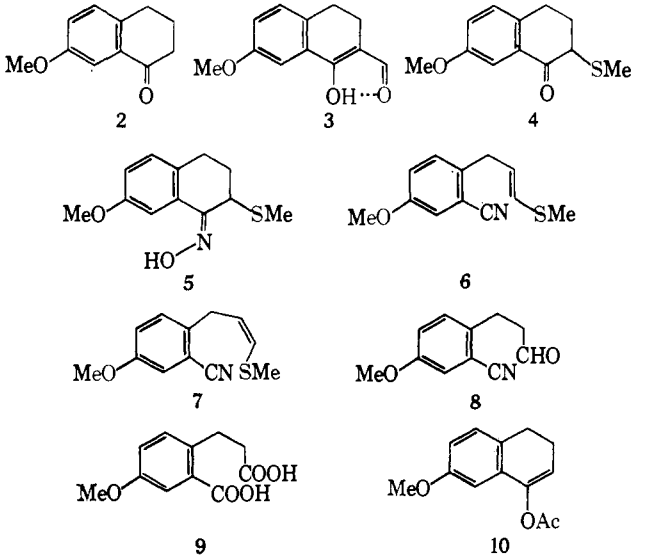
control over which bond was cleaved, but the cleavage, in a practical sense, did not occur.[5]

The potential utility of a Beckmann fragmentation was clearly indicated by the valuable article in which Hill[6] summarized the different functions which favor fragmentation over rearrangement.[7] He demonstrated the general utility of an alkoxy function α to a ketone and suggested that in principle the same effect—stabilization of a carbonium ion by an α-electron-supplying atom—could be afforded by sulfur. We now believe the mechanism of the cleavage governed by sulfur to be different (see the Discussion) from that governed by oxygen or nitrogen. The use of an alkoxy function in yohimbone seemed difficult to achieve; considering some observations of Smiles,[4] however, we deemed possible the introduction of a thioether grouping.

We undertook a model series of reactions to demonstrate the utility of the operation as a whole: the oxidation of a methylene adjacent to carbonyl by appropriately bound sulfur, and the subsequent use of the sulfur atom to direct a Beckmann fragmentation and provide an unsymmetrical cleavage in which the termini of the cleaved bond were left in different oxidation states and could be separately modified. We present the model series here, and the application of it to a total synthesis of natural corynantheine in the accompanying article.

Claisen ester condensation[8] of 7-methoxytetralone (**2**, Chart I) with ethyl formate provided the 2-formyl-

Chart I



(1) A preliminary account of this work has appeared: R. L. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, 87, 3284 (1965). It is taken in part from the Ph.D. Dissertation (1967) of P. W. S. presented to the University of Rochester.

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(3) Du Pont Fellow, summer 1963.

(4) R. L. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, 90, 4917 (1968).

(5) P. D. Pächt and R. L. Autrey, unpublished observations.

(6) R. K. Hill, *J. Org. Chem.*, 27, 29 (1962).

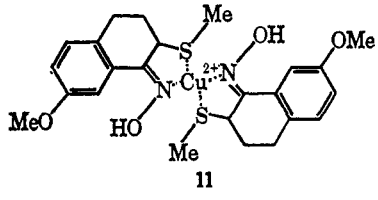
(7) For a recent summary with many key references and emphasis on the mechanistic aspects of the twin paths, rearrangement or fragmentation, for the Beckmann reaction, see C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, 47, 1003 (1964).

(8) *E.g.*, H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 9.

tetralone **3**, in which the carbon bearing two carbonyl groups was suitably acidified for the subsequent displacement on methyl thiotosylate. Purification of the β-ketoaldehyde entailed losses and was unnecessary; it was best used directly in the next operation for optimum over-all yield.

A mechanism for the condensation between the carbanion of the formyltetralone **3** and methyl thiotosylate is suggested in the accompanying article. It is worthy of note that in this condensation, we take advantage of a facet of the behavior of sulfur which is not analogous to that of oxygen—sulfur may expand its octet to accommodate the nucleophile. This accommodation may be as important in influencing the structure of the product as the difference in acid strength of the two possible leaving groups toluenesulfinate and thioltoluenesulfonate. In contrast, nucleophilic attack on methyl tosylate is at carbon and the excellent leaving group toluenesulfonate is displaced.

Oximation of the methioxy ketone required relatively harsh conditions, as we anticipated from the degree of steric hindrance near the carbonyl group. The *anti* oxime[9] was the only isomer detected. In principle, the correct assignment of its structure posed a problem, for Grob's demonstration[10] that the fragmentation governed by nitrogen is not stereospecific could be extrapolated to mean that, not having both oxime isomers for rate comparison, we could not use the observation of fragmentation to assign structure. Of the various criteria for stereochemistry applied by Fischer and Grob,[11] the infrared and ultraviolet spectroscopy were inapplicable to our case. The infrared spectrum in the hydroxyl region of an oxime *syn* to sulfur might even in the most favorable case show no intramolecular hydrogen bonding, since that bond is so weak. A comparison of the ultraviolet spectra (see Experimental Section) of the methioxyoxime **5** and the oxime of **2** led to the wrong conclusion, presumably because the model was inexact. The convincing criterion was the observation of the formation of a chelate, presumed to be **11**, on the addition of dilute ethanolic cupric nitrate



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to an ethanol solution of the oxime **5**. A mixture of the two almost colorless solutions gave an immediate chartreuse coloration. Using a Cary spectrophotometer and 0.02 *M* solutions, we observed no change in the visible spectrum of cupric ion in the presence of the oxime of **2**; whereas in the presence of oxime **5**, the extinction at 400 nm increased substantially and at 800 nm it increased appreciably. At these low concentrations, the solution required some 48 hr before the extinctions ceased to increase.

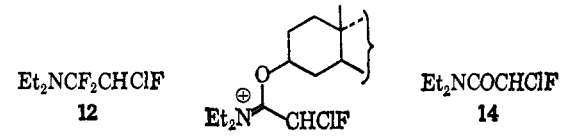
(9) There is good reason to apply system, rather than custom, to the naming of oxime stereoisomers. The CIP priority rules afford a suitable basis: R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(10) H. P. Fischer, C. A. Grob, and E. Renk, *Helv. Chim. Acta*, **45**, 2539 (1962).

(11) H. P. Fischer and C. A. Grob, *ibid.*, **45**, 2528 (1962).

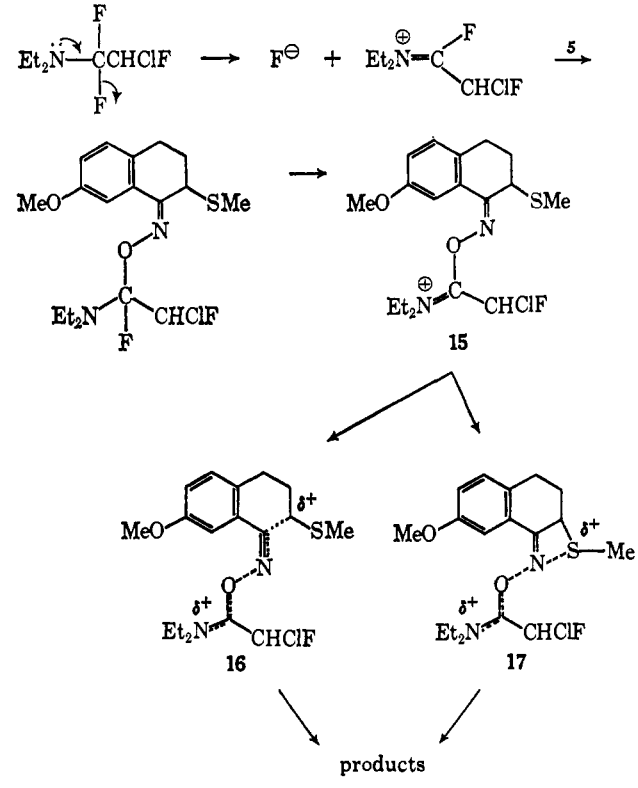
The fragmentation of methioxyoxime **5** was studied under a variety of conditions. The traditional use of tosyl chloride in pyridine required that the pyridine be boiled to effect reaction. The enol thioether products **6** and **7** were difficult to obtain pure from the very dark crude product, and were always accompanied by starting oxime. Use of methanesulfonyl chloride allowed us to conduct the reaction at a somewhat lower temperature and eliminated the return of starting material. However, the best yield of pure product was obtained when we employed a reagent not previously used to effect the Beckmann reaction, namely, 2-chloro-1,1,2-trifluorotriethylamine (**12**).

This amine has previously been used to convert sterols to fluoro steroids of inverted configuration,[12] a suggested intermediate being the imonium ether **13** and the driving force for the reaction being the formation of amide **14**. Since it has been shown in the ster-



oid work that the reaction is frequently fast at room temperature, and our application required brief heating of the reaction mixture to 70°, we believe that the intermediate **15** was rapidly formed as illustrated in Scheme I and that the slow step involved the formation

Scheme I



of transition state **16** or **17** in which charge is dispersed. We suspect that this reaction led more smoothly to clean products because the fragmentation

(12) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

of oxime sulfonate esters requires charge separation in the transition state, rather than charge dispersal.

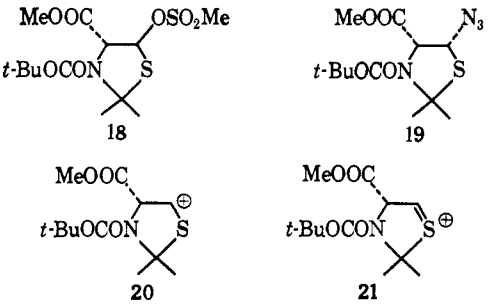
Apart from speculation and despite the difficulty of handling chlorotrifluorotriethylamine, the yield of cleaved products **6** and **7** was higher and they were more readily purified than was true for fragmentations conducted by the other means that we tried. The fragmentations gave approximately 1:1 mixtures of the *cis* (**7**) and *trans* (**6**) olefins, the composition of the mixtures being readily ascertained from the integral values for the two methioxy singlets at 2.18 and 2.27 ppm. The two olefins proved rather unstable in air, and did not survive attempts to separate them, nor were they successfully oxidized to sulfones.

For proof of structure and proof of the originally desired utility of the sequence to provide a bond cleavage with termini in different oxidation states (already true in the enol thioethers, of course) the olefin mixture was hydrolyzed to the cyanoaldehyde **8**. In contrast to the ready hydrolysis of enol ethers, the hydrolysis of enol thioethers requires vigorous conditions. No odor of methanethiol was detected above a solution of the enol thioethers and 1.7 *M* perchloric acid in 50% ethanol at room temperature, but hydrolysis occurred when the solution was heated to 70° for 30 min. The yield of product was only 50% and it was accompanied by polymeric material which we believe resulted from aldol condensation of the liberated aldehyde **8**.

Discussion of the Fragmentation. The mechanism of the fragmentation governed by sulfur is of interest. It was suggested by Hill[6] that the mechanisms for all fragmentations are similar in that any substituent on the carbon atom α to the oxime which stabilizes a carbonium ion at that site favors fragmentation. Among stabilizing substituents he included the thioether function, citing work of Barltrop and Morgan[13] as an example. The stabilization of an α carbonium ion by sulfur must be by resonance electron donation to give a p,p π bond, *viz.*

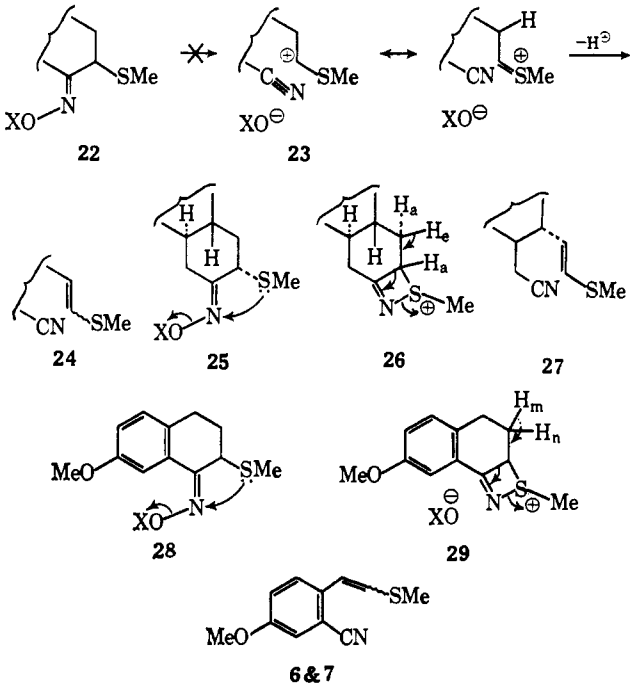
$$MeS\overset{\oplus}{\cdots}CR_2 \longleftrightarrow Me\overset{\oplus}{S}{=}CR_2$$

because the inductive effect of the sulfur substituent will be electron withdrawing and destabilizing. The contention[15] that electron pair release from sulfur into a p,p π bond is facile is supported neither by theoretical calculation[16] nor by evidence. Thus, the pK_a of 4-methioxybenzoic acid is not significantly different from that of benzoic acid;[17] the hydrolysis of thioenol ethers requires vigorous conditions—boiling in 0.5 *M* acid[14] or 1.7 *M* acid at 70°—as opposed to the extraordinary ease of hydrolysis of enol ethers.[18] Most striking in support of our analysis is the stereochemical integrity maintained in the transformation of methanesulfonate **18** to azide **19** by the action of sodium azide in dimethylformamide solution. In discussing the reaction, Woodward[19] excludes the possibility of the intermediacy of carbonium ion **20** on the grounds that the canonical form **21** would be of relatively high energy.



Reviewing these facts, we find it reasonable to conclude that the fragmentation governed by sulfur does not proceed *via* the carbonium ion **23** but that sulfur is otherwise involved. We suggest that the involvement may be as depicted in Scheme II.

Scheme II



(13) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 4486 (1960). As we have previously commented,[1] these authors claim to have observed the usual Beckmann rearrangement, rather than a fragmentation. While there is some possibility of differing interpretation of their experimental evidence, we believe that their observations are more consistent with their own than with Hill's interpretation. A key point making Hill's interpretation possible is the requirement that *o*-nitrophenyl isopropenyl sulfide be hydrolyzed by dilute ice-cold hydrochloric acid. Our experience and that of Djerassi[14] is that enol thioethers require relatively drastic acid conditions for hydrolysis.

(14) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 73, 1528 (1951).

(15) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1964, Chapters 1 and 2. These authors advance strongly the hypothesis that such electron pair release is important. The experimental evidence that they cite is equivocal, however, in that some phenomena (SN1 and SN2 reactions of α-chloro sulfides, for example) show a marked effect (orders of magnitude smaller than that for α-chloro ethers, however) while others (acidities of carboxylic acids, phenols, anilinium ions) show only a small effect opposite in sense to that required. Our conclusion is not that the support of an adjacent carbonium ion by sulfur is nonexistent, but that it is unimportant in influencing the fragmentation.

(16) H. Krebs, "Grundzüge der anorganischen Kristallchemie," Enke, Stüttgart, 1968, p 69. We thank Professor Krebs for making the results of his calculations available to us prior to their publication.

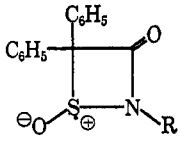
(17) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, 74, 1058 (1952).

(18) Conditions (0.03 *M* aqueous alcoholic hydrogen chloride at 40° for 4 hr) which left unchanged a tertiary, benzylic hydroxyl system but cleaved an enol methyl ether are described by M. M. Shemyakin, M. N. Kolosov, Yu. A. Arbuzov, M. G. Karapetyan, E. S. Chaman, and A. A. Onishchenko, *Zh. Obshch. Khim.*, 29, 1831 (1959).

(19) R. B. Woodward, "Les Prix Nobel," The Nobel Foundation, 1966, p 192.

An electron pair on sulfur displaces the leaving group on the oxime nitrogen by SN2 attack to form a substituted 1,2-thiazetine ring. Loss of a proton β to the sulfur leads to product. Favorable aspects of this suggestion are (1) the avoidance of a stabilized carbonium ion α to sulfur; (2) a relatively strain-free four-membered intermediate; (3) accommodation of the stereochemical results in the two synthetic sequences; and (4) accommodation of the observation[20] of fragmentation in only one of a stereoisomeric pair of oximes α to sulfur, whereas both members of such pairs α to nitrogen fragment.

The thiazetine ring does not appear to be known, but apart from the difference in stability of an imine *vs.* an olefin, it should be more stable than cyclobutene. Thus, the bond angles at sulfur are normally near 90°;[22] the smaller angles and longer bonds to sulfur are both conducive to lower strain than in cyclobutene. Finally there is the existence and ready formation of compound **30**,[23] which has a number of structural factors in common with the postulated intermediate thiazetines **26** and **29**, sulfonium bonded to nitrogen having double-bond character to carbon, all in a four-membered ring.



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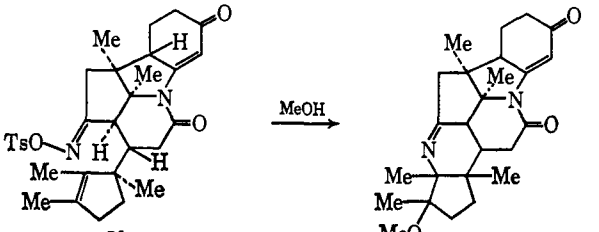
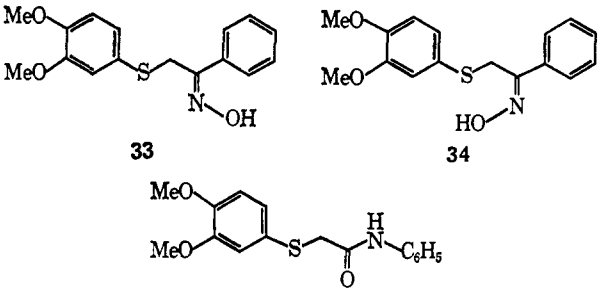
The postulated formation of the ring by direct SN2 displacement is not the usual course for substitution at a trigonal atom, but the more common mode, addition followed by elimination, is stereochemically implausible, because the same constraints that destabilize a 1,10-octalin with the 9-hydrogen in a position pseudo-equatorial to the ring to which the double bond is *exo* operate strongly to destabilize a [4.2.0] bicyclooct-8-ene with the 6-hydrogen similarly pseudo-equatorial to the six-membered ring. The argument applies *a fortiori* to the extent that the reaction partakes of SN1 character. Our observation that the reaction is much faster in the instance of the probable imonium ion fragmentation (*cf.* **15** to **17**, in which bond breaking is surely advanced over bond making at the oxime nitrogen) is reinforcing.

Apart from the three-membered ring intermediate[24] in the Beckmann rearrangement itself, there appears to be no clearly demonstrated example[25] in the literature of a substitution at oxime nitrogen such as we invoke. However, some work of Wagner-Jauregg[26] has been interpreted as ring formation by carbon–carbon double bond participation at oxime nitrogen in the ring-forming step. And a facet of the unpublished research aimed at a corrin synthesis contains an example (**31** → **32**) in which, in a fused ring system, an appositely placed double bond participates in displacement at an oxime tosylate of appropriate stereochemistry with formation of a new, heterocyclic ring.[27]



31 **32**

It is significant that, in the instance of the two stereoisomeric oximes **33** and **34**, Vinkler and Autheried found that, on treatment with benzenesulfonyl chloride in pyridine or phosphorus pentachloride in ether, only the *anti* oxime **33** gave benzonitrile by fragmentation; the *syn* oxime **34** gave dimethoxyphenylthioglycolic acid anilide (**35**).[21] *anti*-Oxime fragmentation driven



33 **34**

35

by an electron pair from a β-amino nitrogen is three to four orders of magnitude faster than the comparable *syn*-oxime fragmentation.[10] One may argue therefore that in the case of a β-thioether function, *syn*-oxime fragmentation does not occur simply because it is not competitive in rate with the ordinary rearrangement. We prefer to believe, however, that it does not compete because a front-side displacement would be required to form the four-membered ring, and we construe its failure to occur in support of our mechanistic rationale.

The last point to demonstrate is the consistency of our formulation with the stereochemical results in the fragmentations of α-methioxyyohimban-17-one oxime (**25**) and 2-methioxy-7-methoxytetral-1-one oxime (**28**). In the former case the fragmentation appears stereospecific: we obtained only the *trans*-substituted olefin **27**.[4] In the latter case the olefin mixture was 52% *trans*. The stereospecific example is readily explained by our formulation: the ring system is locked into a single conformation by the 15,20-*trans* ring junction (see **25a**) and the methioxy group is equatorial.[4] The half-flip required to place the methioxy group axial to add to the carbon–nitrogen double bond in the more

(20) The earliest authentic example we have found of a Beckmann fragmentation governed by an α-thioether is that of Vinkler and Autheried.[21]

(21) E. Vinkler and K. Autheried, *Acta Univ. Szeged. Acta Phys. Chem.*, 2, 50 (1948).

(22) For example, in thiophene-2-carboxylic acid the CSC angle is 92°: M. Nardelli, G. Fava, and G. Giraldi, *Acta Cryst.*, **15**, 737 (1962).

(23) H. Beecken and F. Korte, *Tetrahedron*, **18**, 1527 (1962).

(24) R. Huisgen, J. Witte, and I. Ugi, *Ber.*, 90, 1844 (1957), and other articles in this series.

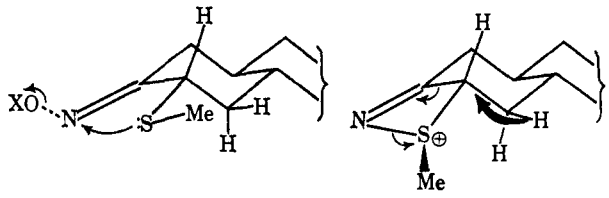
(25) It is appropriate to note that H. O. House and W. F. Berkowitz [*J. Org. Chem.*, 28, 2271 (1963)], in a study of the stereochemistry of the Neber rearrangement, have suggested that their data do not completely exclude a displacement mechanism, as in i, but they strongly and reasonably, favor a vinyl nitrene intermediate, as in ii.

i ii

(26) J. Meinwald, *Proc. Chem. Soc.*, 286 (1958); see also T. Wagner-Jauregg and M. Roth, *Helv. Chim. Acta*, **45**, 771 (1962).

(27) R. B. Woodward, private communication.

usual, addition–elimination sequence for substitution at a trigonal atom makes it quite remote from the reaction site; and, were it formed, the resulting intermediate would be highly strained. The formation of intermediate **26** (*cf.* **26a**) and its subsequent decom-



25a **26a**

position in accord with stereoelectronic principles, however, accounts for the observed stereochemistry of the olefin; electron demand at sulfur requires the breaking of the nitrogen–sulfur bond; a (nearly) concerted loss of a proton would require that the equatorial hydrogen at C-19 be lost since its bond is *anti*-coplanar to the broken ring bond. The result is a C-18–C-19 *trans* olefin, as found. If, with the aid of molecular models, one studies the same argument in the tetralone sequence (*cf.* **28** → **6** + **7** in Scheme II), several points of interest emerge. The initial formation of the four-membered ring seems more difficult, and the resulting intermediate, with four trigonal atoms in the thiazabicyclooctene system, is much less strongly constrained to a single conformation. Moreover, neither hydrogen β to sulfur can achieve a conformation such that its bond is *anti*-coplanar to the relevant ring bond; and the loss of hydrogen to give a *trans* olefin appears only slightly favored over the other. The predictions that one would make from models, using our hypothesis, are the results we have found: the reaction appears to require more vigorous conditions, and there is no significant preference for *trans* olefin over *cis*.

Experimental Section

General. Melting points were determined with Anschütz thermometers in a modified Hershberg melting point apparatus; those marked (vacuum) were taken in capillaries sealed under pressure of a few micrometers. Infrared spectra were measured on a Perkin-Elmer Model 421 spectrometer; nmr spectra were observed in deuteriochloroform solution, on a Varian A-60 instrument; ultraviolet spectra were measured with a Cary 11 spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

7-Methoxytetralone-1 (2). Friedel–Crafts acylation of anisole by succinic anhydride on a 2.5-mol scale gave 93% of 3-(*p*-anisoyl)-propionic acid, mp 147.1–147.5°. Clemmensen reduction of that acid gave 4-(*p*-anisyl)butyric acid: 91% yield of distilled acid; mp 58.0–60.0° Friedel–Crafts cyclization[28] on a 1-mol scale gave the tetralone: 83% yield of distilled ketone; mp 59.8–62.2°. The oxime had the following characteristics: mp 87.5–88.2°; $\lambda\lambda_{max}^{EtOH}$ nm (ϵ), 255 (8980), 306.5 (3480). In the presence of 0.5 mol (1.0 equiv) of Cu^{2+}: ϵ_{400} 4.6, ϵ_{500} 1.6, ϵ_{800} 14.

2-Formyl-7-methoxytetralone-1 (3). Freshly prepared sodium methoxide (from 4.6 g of sodium) was dried 1 hr at 160° (1 mm), covered by 300 ml of THF, cooled to 0°, and purged by nitrogen. To the mixture was added ethyl formate (16.7 g, freshly distilled from phosphorus pentoxide), then 7-methoxytetralone (20.51 g). The mixture was stirred 2 hr at room temperature; the yellow sodium salt was filtered, washed with THF, and dissolved in water. The solution was acidified with dilute hydrochloric acid to pH 2 and extracted with ether. The dried ether extract yielded 19.27 g (79.8%) of formyltetralone as a pale yellow oil which solidified on standing at 0°. The solid was recrystallized from benzene–petroleum ether (bp 30–60°) to afford pale yellow crystals, mp 31.2–32.0° (vacuum); lit.[29] oily.

The semicarbazone, from aqueous ethanol, had mp 199.7–200.6° dec (vacuum); lit.[29] mp 210°. Isoxazole, colorless plates from petroleum ether had mp 75.0–76.5°.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.55; N, 6.89.

2-Methioxy-7-methoxytetralone-1 (4). In a dry flask there were placed 20.0 g of freshly fused potassium acetate, 13.62 g of methyl thiotosylate, and a slurry of 14.05 g of formyltetralone **3** in 250 ml of absolute ethanol. Under nitrogen, the mixture was boiled under reflux for 4 hr; it became homogeneous. It was cooled, concentrated *in vacuo* to 90 ml, diluted with 20 ml of water, and refrigerated. The crystals were filtered and washed with water, yield 15.20 g (94.8%). Recrystallization from 75% ethanol gave the analytical sample: mp 70.0–70.6° (vacuum).

Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42. Found: C, 64.64; H, 6.49; S, 14.36. δ^{CCl_4} 2.08 (S*Me*), 3.75 (O*Me*)

2-Methioxy-7-methoxytetralone-1 *anti*-Oxime (5). Under nitrogen, 4.29 g of ketone, 3.5 g of hydroxylamine hydrochloride, 8 g of sodium hydroxide and 100 ml of 95% ethanol were combined and boiled under reflux for 2 hr. The oxime (2.80 g, 64%) was isolated by ether extraction and recrystallized from ethyl acetate. The analytical sample, from ethyl acetate, was colorless microcrystals, mp 107.9–108.8° (vacuum); δ^{CCl_4} 2.0–3.5 (multiplet, 4.07 H, methylenes), 2.09 (sharp singlet, 3.00 H, S*Me*), 3.75 (sharp singlet, 3.00 H, O*Me*), 4.76 (triplet, J = 3.2 cps, 0.98 H, *H*CSMe), 6.75–7.25 (multiplet, 2.08 H, *H*'s at C-5,6), 7.31 (doublet of doublets, J's = 2.8 and 0.5 cps, 0.99 H, at C-8), 9.10 ppm (broadened singlet, shifts upfield on dilution, 0.92 H, =NO*H*); $\lambda\lambda_{max}^{EtOH}$ nm (ϵ), 257 (9350), 308 (3400). In the presence of 0.5 mol (1.0 equiv) Cu^{2+} (based on chelate molecular weight): ϵ_{400} 92, ϵ_{500} 25, ϵ_{800} 20.

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 61.21; H, 6.50; N, 6.10; S, 13.38.

3-(2-Cyano-4-methoxyphenyl)-1-methioxypropenes-1 (6 and 7). Method A. To a solution of 250 mg of oxime **5** in 5 ml of dioxane (freshly distilled from sodium) was added 400 mg of chlorotrifluorotriethylamine (**12**). Under nitrogen the solution was heated to 70° in 18 min, quickly cooled in ice and kept at 0° for 0.5 hr, diluted with water, and extracted with ether. The ether extract was washed with water, then brine, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to leave 381 mg of red oil. The oil was chromatographed on 20 g of activity I Woelm acidic alumina; elution with 25:1 benzene–ether gave 105 mg (45.5% yield, 63.2% conversion) of yellow semisolid product; elution with 150:1 ether–methanol returned 70 mg of oxime in reusable condition.

The enol thioether was unstable in air and was best carried on at once after chromatography. An analytical sample was prepared by rechromatography: $\lambda\lambda^{neat}$ 4.48 (–CN), 6.20 (C=C), 10.31 and 10.73 μm (*trans*-disubstituted olefin); δ^{CCl_4} 2.18 and 2.27 (sharp singlets, 1.57 and 1.38 *H*, S*Me*), 3.52 (broadened doublet, 1.88 *H*, methylene), 3.77 (sharp singlet, 2.88 *H*, O*Me*), 5.1–6.3 (complex, 1.89 *H*, vinyl), 6.8–7.4 ppm (complex, 3.16 *H*, aromatic).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.44; H, 6.05; N, 6.25; S, 14.24.

Method B. Under nitrogen in 25 ml of pyridine there were placed 519 mg of oxime **5** and 376 mg of methanesulfonyl chloride. The solution was heated and stirred at 85° for 4 hr, cooled, and filtered from pyridine hydrochloride. The filtrate was partitioned between ether and water, and the dried ether layer was evaporated *in vacuo*. Chromatography of the dark, oily product gave 281 mg (56.5%) of palely colored oil suitable for further use.

3-(2-Cyano-4-methoxyphenyl)propanal (8). To a solution of 232 mg of enol thioethers **6** and **7** in 10 ml of 95% ethanol was added 10 ml of 28% perchloric acid. The solution was boiled gently for 0.5 hr, cooled, and neutralized by the addition of solid sodium bicarbonate. The filtered solution was concentrated *in vacuo* to an aqueous emulsion which was extracted with ether. The dried ether yielded 127 mg of aldehyde **8**: $\lambda\lambda^{CCl_4}$ 4.48 (–CN), 5.77 (–CHO), bands at 10.31 and 10.73 μm absent; δ^{CCl_4} 3.76 (O*Me*) and 9.76 ppm (C*H*O).

For analysis, a 2,4-dinitrophenylhydrazone was prepared, then recrystallized from ethyl acetate, then dioxane–water, to give orange crystals, mp 197–198.5°.

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Anal. Calcd for $C_{17}H_{15}N_5O_5$: C, 55.29; H, 4.09; N, 18.96. Found: C, 55.56; H, 4.19; N, 18.89.

3-(2-Carboxy-4-methoxyphenyl)propionic Acid (9). Method A. The cyanoaldehyde **8** (0.50 g) was oxidized in acetone solution by Jones' reagent and the product was obtained in ether, then extracted into sodium carbonate solution. This solution was acidified and the product was extracted into ether which was washed, dried, and evaporated to leave 80 mg of nitrile acid: $\lambda\lambda^{KBr}$ 2.8–4.0 (–COOH), 4.48 (–CN), 5.80 μm (–COOH).

The nitrile acid was hydrolyzed by 24 hr boiling in 25 ml of 10% sodium hydroxide. An ether extract of the acidified reaction solution was washed, dried, filtered, and evaporated to leave a pale yellow solid, mp 193–194°. This was sublimed at 160° (1 mm), then recrystallized from acetone to give colorless, very fine crystals, mp 195.5–196.9°. The melting point was not depressed on admixture with a sample prepared as described in method B, and the infrared spectra of the two samples were identical.

Method B. 7-Methoxytetralone (2.00 g) was converted into its enol acetate by the action of isopropenyl acetate and toluenesulfonic acid. The crude product was distilled at 100° (0.1 mm) to give 0.91 g of colorless enol acetate **10**: $\lambda\lambda^{neat}$ 5.65 (carbonyl) and 12.50 μm (trisubstituted olefin).

1-Acetoxy-3,4-dihydro-7-methoxynaphthalene (**10**, 910 mg) was oxidized at 0° in acetone solution by the slow addition of 1.74 g (22% excess) of finely powdered potassium permanganate. The dark residue resulting on removal of the acetone was dissolved in 10% sulfuric acid, bleached with sodium sulfite, and extracted with ether. The ether extract was extracted with saturated sodium bicarbonate which was acidified and again extracted with ether. The dried ether solution yielded 308 mg of diacid, purified as described in method A. The analytical sample, mp 196–197°, was recrystallized from dioxane–water.

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.06; H, 5.68.

Methyl *p*-Toluenethiolsulfonate. Sodium thiotosylate (sharp decomposition at 308°, vacuum) in methanol was methylated by dimethyl sulfate. The product (51% based on starting tosyl chloride) after two recrystallizations from benzene was large, colorless prisms: mp 57.5–58.5° (lit.[30] mp 58°); δ^{CHCl_3} 2.46 (sharp singlet, C*Me*), 2.51 (sharper singlet, S*Me*), 7.55 ppm (quartet, aromatic *H*'s).

2-Chloro-1,1,2-trifluorotriethylamine (12). The addition of diethylamine to chlorotrifluoroethylene was conducted essentially as described by Yarovenko and Raksha.[31] It was distilled at 35° (11 mm) and for best results was used immediately after preparation. It deteriorated at an appreciable rate even on storage at −80°.

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(31) N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959).

The Tricyclo[4.4.0.0^{3,8}]decane to Adamantane Rearrangement

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Abstract: Synthesis of the tricyclo[4.4.0.0^{3,8}]decane ring system is detailed and its behavior in carbonium ion rearrangements is investigated. A scheme for the formalization of complex rearrangements is advanced and discussed.

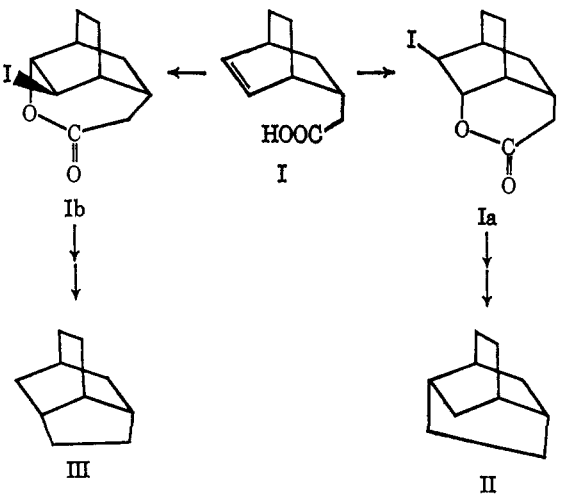
The work of Schleyer and others[1–3] over the past several years has led to the recognition that the combination of the thermodynamic stability of the adamantane carbon skeleton with the protean phenomena accompanying aluminum halide catalyzed alkane isomerizations results in the facile, often high-yield formation of adamantane and substituted adamantanes from (usually) isomeric hydrocarbons. This paper is concerned with the synthesis and chemistry of tricyclo[4.4.0.0^{3,8}]decane (twistane)[4] and its derivatives, and particularly with the systematics of their rearrangement to the adamantane carbon skeleton.

Synthesis

The synthesis of twistane and its simple functionalized derivatives is basically as communicated several years ago[5] and is detailed in the Experimental Section. Several points concerning the synthesis should be mentioned.

(1) M. Nomura, P. von R. Schleyer, and A. A. Arz, *J. Amer. Chem. Soc.*, **89**, 3657 (1967), and earlier references.
(2) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).
(3) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Org. Chem.*, **31**, 1617 (1966).
(4) The best justification of the use of short "pet" names such as twistane and protoadamantane as is done here lies in the cumbersomeness of their systematic alternatives.
(5) H. W. Whitlock, Jr., *J. Amer. Chem. Soc.*, **84**, 3412 (1962).

A possible ambiguity in the synthesis of twistane lies in the direction of iodolactonization of acid I which is formally capable of either δ lactonization (Ia) (and hence



(1)

to twistane (II)) or ω lactonization (Ib) with ultimate formation of tricyclo[4.3.1.0^{3,7}]decane (III) (eq 1). Formation of an analogous pair of isomeric iodolactones from *endo*-bicyclo[2.2.2]oct-2-ene-5-carboxylic acid has