tained in 86% crude yield.[21] After crystallization from chloroform–pentane, treatment of a chloroform solution of **7a** with 2 equiv of 10 N HCl gave **7b** HCl, isolable by filtration in 92% yield after precipitation from methanol–ether. In analogy to the conversion **3c** → **3d**, treatment of tetrapeptide analogue **7b** with aqueous dimethyl sulfide containing $Pb(NO_3)_2$ gave **7c** in ~40% yield. The identity of the synthetic and authentic materials verifies the structural assignment for this component of bleomycin.[8,22]

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(11) Bleomycin is both acid and base sensitive and contains a bithiazole moiety that poisons hydrogenation catalysts. Additionally, the presence of highly polar or nucleophilic substituents on each of the naturally occurring bleomycins precludes the use of the analogue of **3a** with "preformed" C-terminal substituents.
(12) E.g., dissolution of the *N*-acetyl derivative of **2** [R = $NH(CH_2)_3Br$] in neat 1,4-diaminopropane effected conversion into the intended product [**2**, R = $NH(CH_2)_3NH(CH_2)_3NH_2$] in quantitative yield within 5 min, as judged by TLC and NMR analyses.
(13) Umezawa, H. *Lloydia* **1977,** *40,* 67.
(14) Conversion of the crystalline *N*-trifluoroacetyl derivative into the corresponding acid chloride [$SOCl_2$, $(C_2H_5)_3N$, CH_2Cl_2, 25 °C, 18 h], followed by treatment with 3-bromopropylamine hydrochloride [$(C_2H_5)_3N$, $(CH_3)_2N(C_6H_4N)$, CH_2Cl_2, 25 °C, 2 h], afforded the fully blocked bithiazole derivative as colorless needles in 99% yield, mp 151–152 °C after crystallization from ethanol–water. This compound could be stored at room temperature for extended periods of time without decomposition. The structures of all new synthetic intermediates were verified by appropriate spectral measurements and by elemental analysis.
(15) The deblocking was effected in 95% (spectrophotometric) yield; as anticipated, the deblocked compound could not be isolated as the free base owing to its ready polymerization. However, solutions of the free base having concentrations of <0.4 M were sufficiently stable for routine manipulations.
(16) Prepared from *N*-(*o*-nitrophenylsulfenyl)threonine (Zervas, L.; Borovas, D.; Gazis, E. *J. Am. Chem. Soc.* **1963,** *85,* 3660) by treatment (CH_3CN, 0 °C) with equal amounts of *N,N'*-dicyclohexylcarbodiimide and 2,4-dinitrophenol. Crystallization (ethyl acetate–pentane) afforded the ester in 92% yield, mp 125.5–128 °C.
(17) Authentic tripeptide S was obtained by treatment of bleomycin A_2 with 12 N HCl at 25 °C for 7 days (Umezawa, H. *Pure Appl. Chem.* **1971,** *28,* 665), followed by chromatography on Sephadex C-25. The synthetic and authentic samples had the same mobilities on Sephadex C-25 and on paper and thin layer chromatograms using five different solvent systems. Their ultraviolet and ^1H and ^{13}C NMR spectra were also identical.
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(20) Workup of the hydrolyzed mixture of lactams (Dowex 50, H^+ form, elution with water and then with 2.9% aqueous NH_4OH) afforded a mixture of 2*R*,3*S*,4*R* and 2*S*,3*S*,4*R* amino acids in 77% yield, from which **6** could be obtained in nearly theoretical yield.
(21) Workup involved extraction of the reaction mixture with cold aqueous Na_2CO_3, concentration of the dried organic phase to a small volume, and precipitation of the product with excess pentane.
(22) Tetrapeptide S was obtained by treatment of bleomycin A_2 with 6 equiv of *N*-bromosuccinimide (Muraoka, Y.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot. (Tokyo)* **1972,** *25,* 185). The isolated peptide was purified by chromatography on Sephadex C-25 and shown to have the same chromatographic properties as the synthetic material on this support and also when analyzed by TLC and paper chromatography in several solvent systems, as well as the same properties by ultraviolet and ^1H and ^{13}C NMR spectroscopy.
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Ammoximation: Direct Synthesis of Oximes from Ammonia, Oxygen, and Ketones

Sir:

Ketoximes have been prepared by a reaction according to the equation

$$NH_3 + {}^1/_2O_2 + \text{ketone} \rightarrow \text{ketoxime} + H_2O \qquad (1)$$

The further oxidation of a mixture of NH_3 and an olefin (propylene) or an aldehyde (acrolein) to form a nitrile (acrylonitrile) is termed ammoxidation. The present process referring to the synthesis of ketoximes as described by equation 1 is termed ammoximation. It is well known that cyclohexanone oxime can be rearranged to caprolactam in high yields in the vapor phase over aluminosilicate catalysts.[1] Therefore, a direct synthesis of caprolactam could be envisioned for converting cyclohexanone, NH_3, and air directly into caprolactam by placing a reactor for the vapor-phase rearrangement of the oxime directly after the ammoximation reactor.

Oximes are normally prepared by reaction of ketones with hydroxylamine. The source of NH_2OH is the oxidation of NH_3 to NO (or NO_2) followed by reduction with H_2 or SO_2.[2] The formation of NH_2OH from NH_3 and O_2 has been reported.[3,4] The reactants were passed over a Pt catalyst at low pressures and high temperatures (>800 °C). Small amounts of NH_2OH and N_2O were found as the major products collected in a (liquid air) cold trap. While NH_2OH is thermally unstable,[5-7] it was felt that scavenging the NH_2OH or its precursors with ketones to form the more stable oximes would be a much more favorable process. However, we have not yet been able to identify NH_2OH as an intermediate in reaction 1. It is also known that oximes can be prepared from ketones, NH_3, and H_2O_2 or organic peroxides.[8] However, the present synthesis is thought not to involve peroxides since addition to the feed of a variety of peroxides or of radical inhibitors[9] did not influence the ammoximation reaction.

Vapor-phase reactions[10] were conducted in a borosilicate glass tube of ~14-mm o.d. containing a glass frit or plug of glass wool to hold the catalyst in place. The reactor was inside an electrically heated tube furnace, with concurrent, down-flow

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feed of reactants. The preparation of oximes of dialkyl, cycloalkyl, and alkaryl ketones was found to be operable in the temperature range 60–300 °C.

As a specific example, NH_3-O_2–cyclohexanone were passed over a catalyst of 0.8 g of Porasil A, 80–100 mesh (Waters Associates, Framingham, Mass.). This material is a very pure, porous, amorphous silica gel in the form of silica beads, described by the manufacturer as having a pore diameter of 10.0 nm and a surface area of 350–500 m^2/g. The cyclohexanone was vaporized in a saturator at a rate of ~0.65 cm^3 (as vapor)/min into a gas stream of N_2 (37 cm^3/min) to which NH_3 (12.0 cm/min) and O_2 gas (1.0 cm^3/min) were then added.[11] The catalyst temperature was maintained at 194 °C.

Initially, there was a lag in the production of cyclohexanone oxime, after which a selectivity (to oxime)[12] of 51%, at 54% conversion of the ketone, was obtained (i.e., a yield of oxime of 28% of theory based on the cyclohexanone employed). Other than unreacted ketone, the oxime is the only product which emerges from the reactor. There is no combustion of the ketone. The byproduct(s) remains on the catalyst as an intractable residue(s). The formation of the oxime was confirmed by GLC, GC/MS, and the specific, spectrophotometric analysis employing *p*-nitrobenzaldehyde as the indicating reagent.

Reaction 1 has been observed for a wide variety of ketones. Ketones which can be used must, of course, be reasonably stable at the reaction conditions of temperature, time, and catalyst. Ketones which have been demonstrated to give the corresponding oxime include acetone, 3-pentanone, cyclohexanone, 2-methylcyclohexanone, and acetophenone.

The most effective catalysts appear to be porous, amorphous silicas and aluminas, especially porous, amorphous silica having a surface area in the range of 100-500 m^2/g. Trace metals are not responsible for catalysis of the reaction since the silicas contain <50 ppm of any metal. Yet, the nature of the surface is critical since reaction 1 does not proceed in the gas phase at <300 °C over quartz chips or within an empty reactor.

While the mechanism of reaction 1 is still unknown, it is not believed to involve a radical-chain process based on the results obtained upon the addition of peroxides or radical scavengers to the feed mixture.[9] There are two classes of mechanisms in which the nitrogen atoms are oxidized: (a) before bonding to carbon and (b) after bonding to carbon. Besides the possible formation of hydroxylamine-like precursors (case a), reaction 1 could also be viewed as proceeding via oxidation of the transient imine of cyclohexanone (case b). With regard to the ammoxidation process cited earlier, it is interesting to note that the traditional catalysts[13] for the ammoxidation of olefins to nitriles generally function best above 350 °C. A recent paper[14] discussed the oxidation of NH_3 in the presence of ketones (>350 °C) using bismuth–molybdenum catalysts. There the main products were nitriles of lower carbon number. We have found that the traditional ammoxidation catalysts[13] are poor catalysts for ammoximation. We can conclude that the unique reaction described by reaction 1 proceeds only if the temperature is low enough to avoid overoxidation of the oxime. Further, this unique use of silica as a selective oxidation catalyst may explain why others have not observed reaction 1 before. Currently, we believe that two parallel reaction pathways, perhaps involving different surface sites, lead to oxime and to the byproducts. It appears that one site is particularly effective toward ammoximation, while the other site is effective for the production of byproducts. Since the aldol condensation of cyclohexanone has been reported to be catalyzed by oxides, the aldolization of cyclohexanone to yield an intractable polymeric species (on reaction with NH_3) is a possible side reaction from reaction 1.[15]

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(7) While the $\Delta G°$ values for oximes are not readily available, it is expected that the difference between the ketone and oxime is more than compensated by the $\Delta G°_f$ for water of −55 kcal/mol (at 25 °C). Thus, we believe that reaction 1 lies sufficiently far to the right.
(8) E. G. E. Hawkins, *J. Chem. Soc. C*, 2671 (1969), and references therein; U.S. Patent 3 654 268 (1972).
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(10) J. Armor, U.S. Patent 4 163 756 (Aug 7, 1979).
(11) Most of our experiments were done outside the upper explosion limits for NH_3–air and for ketone–air mixtures. At <12% O_2, it has been reported that NH_3–air mixtures are not explosive.
(12) % selectivity (S) = (mol of oxime produced × 100)/mol of ketone reacted, % conversion (C) = (mol of ketone reacted × 100)/mol of ketone fed; yield = CS/100.
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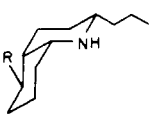
Stereoselective Total Synthesis of (±)-Perhydrogephyrotoxin. Synthetic Applications of Directed 2-Azonia-[3,3]-Sigmatropic Rearrangements

Sir:

The gephyrotoxins, a new class of skin alkaloids from poison-dart frogs of the genus *Dendrobates*, have recently been described by Daly, Witkop, and co-workers.[1,2] The parent alkaloid of this class is gephyrotoxin, which was shown by X-ray analysis[2] to have the tricyclic perhydropyrrolo[1,2-*a*]quinoline structure **1**. Also isolated from *Dendrobates histrionicus* is dihydrogephyrotoxin **2**, which, together with **1**, affords perhydrogephyrotoxin **3** upon catalytic hydrogenation.[2]



1, R = (Z)-CH=CHC≡CH
2, R = CH=CHCH=CH$_2$
3, R = $CH_2CH_2CH_2CH_3$
4, R = CH_3
8, R = CH_2OCH_2Ph

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