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]

Acknowledgments. I express my gratitude to Messrs. B. DeRites, W. Gates, R. Leming, and P. Zambri for their technical assistance, as well as to my colleagues, Mr. E. Carlson and Drs. I. Mador, A. K. Price, W. C. Conner, B. Turnham, and R. Tang, for many valuable discussions. We are indebted to invaluable comments from Professors M. Dewar and J. Brauman.

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(9) Private communication with Dr. B. Turnham, Allied Chemical Corp. Addition of 4 wt % cumene hydroperoxide, 1% *tert*-butyl hydroperoxide, or 0.5% diazobutylnitrile to the cyclohexanone did not substantially alter the selectivity to the oxime. (For these experiments, the cyclohexanone mixtures were added dropwise directly above the catalyst onto a bed of quartz chips maintained at 195 °C.)
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(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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John N. Armor
Allied Chemical Corporation, Chemical Research Center
Morristown, New Jersey 07960

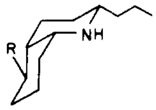
Received November 5, 1979

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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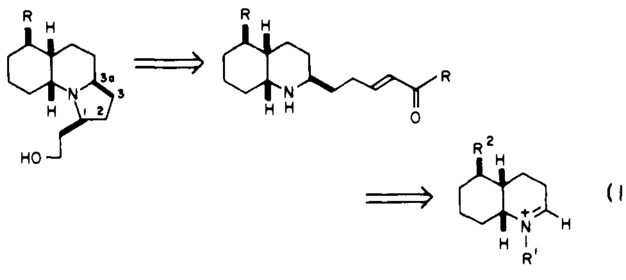
Gephyrotoxin is structurally related to the dendrobatid alkaloid pumiliotoxin C (**4**).[2,3] The disubstituted *cis*-decahydroquinoline ring is common to both alkaloids, but the relative and absolute stereochemistry of the side chains α to nitrogen differ, with the orientation found in gephyrotoxin being the more formidable synthetic challenge. As a result of interesting neurological activity in this series,[2,4] and the extreme scarcity of natural material, we have initiated a program to develop chemical syntheses of these substances. Herein is described a stereoselective total synthesis of (±)-perhydrogephyrotoxin (**3**).[5]

Our operating strategy (eq 1) rested on the assumption that the desired cis orientation of the pyrrolidine ring, with respect to the bridgehead hydrogens, could be obtained by addition of the elements of this ring to a *cis*-octahydroquinoline such as **5**. We envisioned that **5** would be available by the dienamide Diels–Alder approach we had previously developed for the total synthesis of (±)-pumiliotoxin C.[6] To our surprise, initial attempts to reduce this scheme to practice were thwarted by the unexpected preference of organolithium and Grignard reagents to add to iminium ion **5** (R^2 = Me; R^1 = CH_2Ph) from the more sterically congested, concave α face.[7] We reasoned[7] that this undesired stereochemical outcome reflected the interplay of strong stereoelectronic control in the addition step[8] and the importance of $A^{(1,2)}$ interactions[9] in this system. The formation of the C_3–C_{3a} bond by a reaction which would have different stereoelectronic constraints appeared to offer a possible solution to this problem, and we therefore pursued the approach detailed in which this bond is formed by a 2-azonia-[3,3]-sigmatropic rearrangement.[10,11]

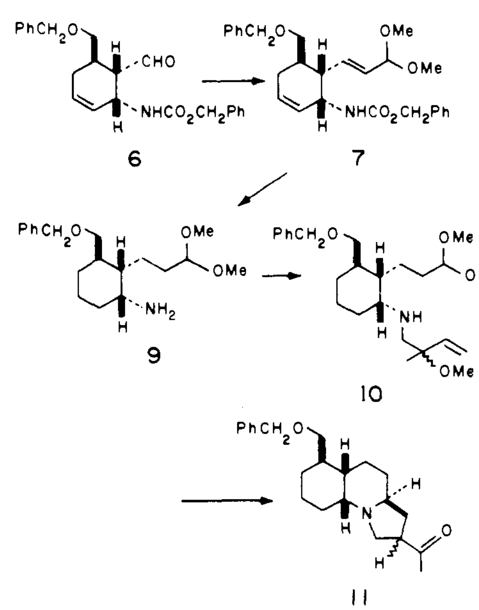


(1)

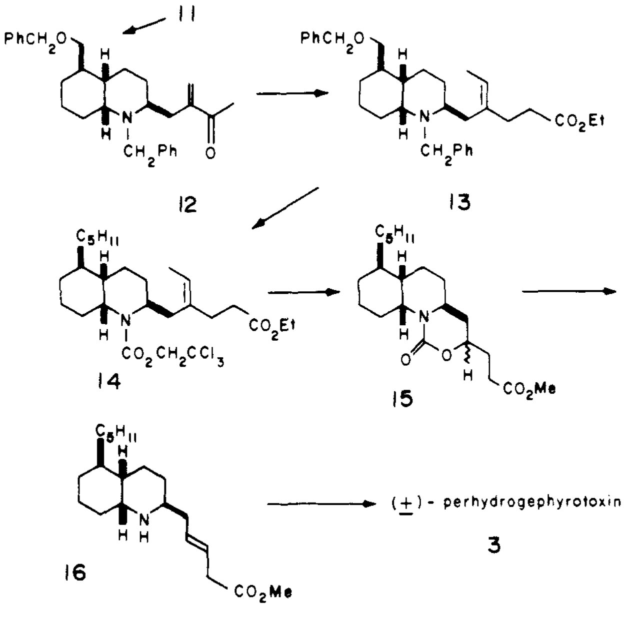
5

Cycloaddition of benzyl *trans*-1,3-butadiene-1-carbamate[12] with *trans*-4-benzyloxy-2-butenal[13,14] at 110 °C gave the *endo*-**6**[15] and exo cycloadducts in a ratio of 10:1. Olefination of this mixture with formylmethylenetriphenylphosphorane[16] in refluxing THF, followed by acetalization with methanol (pyridinium *p*-toluenesulfonate[17] catalyst), afforded isomerically pure **7**[15] (mp 74 °C) in 47% overall yield.[18] The stereochemistry of the major cycloadduct **6** was confirmed by converting it, along previously established lines,[6] into *cis*-decahydroquinoline **8**. Hydrogenation (1 atm, Pd/C) of **7** in methanol proceeded smoothly with the uptake of 3 equiv of H_2 to give amine acetal **9**[15] in 95% yield. Reductive amination by sequential treatment with 2-methoxy-2-methyl-3-butenal[10a] and sodium borohydride afforded homoallylic amine **10**[15] (a 1:1 mixture of diastereomers) in 92% yield. To our delight, when **10** was heated[10] (for 6 h at 80 °C) in benzene with 0.90 equiv of *p*-toluenesulfonic acid monohydrate, followed by extraction with 10% NaOH and chromatographic purification on silica gel, perhydropyrrolo[1,2-*a*]quinoline (**11**)[15,19] was obtained in 79% yield as an ~3:2 mixture of acetyl epimers. Our expectation that sigmatropic rearrangement would occur stereoselectively across the convex face of iminium ion **5** (R^2 = CH_2OCH_2Ph; R^1 = $CH_2CCH_3(OMe)CH{=}CH_2$) was justified as a careful examination of chromatography fractions failed to reveal other isomers. The sequence of Scheme I thus provides a particularly efficient (32% overall yield from benzyl *trans*-1,3-butadiene-1-carbamate) method for constructing the perhydropyrrolo[1,2-*a*]quinoline ring system of **11** and demonstrates the application of directed 2-azonia-[3,3]-sigmatropic rearrangements[10] for indolizidine annulation.

Scheme I



Scheme II



After problems were encountered with several more direct approaches, tricyclic ketone **11** was successfully converted into (±)-perhydrogephyrotoxin by the sequence shown in Scheme II. Reaction of **11** with benzyl bromide in refluxing $CHCl_3$, followed by treatment with 2% NaOH, afforded isomerically pure enone **12**[15] (70% yield). Reduction ($NaBH_4$) of **12**, followed by ortho ester Claisen rearrangement,[20] gave **13**[15] in 79% yield. Selective O-debenzylation was accomplished by treatment of **13** at room temperature with excess ethanethiol in the presence of boron trifluoride etherate,[21] and the *n*-pentyl side chain was elaborated by treating the derived tosylate with 3 equiv of lithium dibutyl cuprate in ether at −20 °C. Chloroformate debenzylation then gave **14**[15] in 78% overall yield from **13**. Without purification of intermediates, **14** was converted into carbamate ester **15**[15] in 70% yield by sequential treatment with (i) O_3, (ii) $NaBH_4$, (iii) LiOH, (iv) NaH, and (v) CH_2N_2. Ester **15** was transformed to the α,β-unsaturated ester by selenoxide elimination,[22] and vinylogous reductive elimination was accomplished by subsequent treatment at 95

°C with zinc and acetic acid to afford **16** in ~70% yield. Without purification, amine ester **16** was treated with a catalytic amount of NaOMe in refluxing methanol, followed by reduction with $LiAlH_4$, to give (±)-perhydrogephyrotoxin **3** and its C_1 epimer in a ratio of ~8:1 (50% yield). Pure (±)-perhydrogephyrotoxin[23] was obtained by silica gel chromatography and was identical (TLC, capillary GLC, ^1H NMR, ^{13}C NMR, solution IR, EI, and CI mass spectra) with an authentic sample prepared by hydrogenation[2] of gephyrotoxin.[24]

Efforts aimed at converting intermediates such as **13** to gephyrotoxin, as well as developing a more concise method for elaborating the hydroxyethyl-substituted pyrrolidine ring, are being actively pursued and will be reported in due course.

Acknowledgment. Support from the National Institutes of Health (NS-12389) and the Camille and Henry Dreyfus Foundation (teacher-scholar award to L.E.O.) is gratefully acknowledged. NMR and mass spectra were determined with spectrometers purchased with the assistance of NSF instrumentation grants.

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(19) IR (film) 2930, 2860, 2790, 2720, 1710, 1450, 1360, 1100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, major epimer) 7.3 (broad s, C_6H_5), 4.51 (s, OCH_2Ph), 3.50 (d, $J = 7.3$ Hz, $CHCH_2O$), 2.16 ppm (s, CH_3CO); ^{13}C NMR (22.6 MHz, $CDCl_3$, major epimer) 208.6, 138.5, 128.0, 127.3, 127.2, 72.8, 72.1, 53.9, 53.5, 50.4, 48.2, 39.5, 37.0, 33.1, 31.4, 28.7, 25.7, 22.8, 20.3, 17.6 ppm. The minor isomer showed characteristic ^{13}C NMR absorptions at 54.6, 53.1, and 17.9 ppm.
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(23) ^1H NMR (90 MHz, $CDCl_3$) 4.0 (dt, $J = 11, 2$ Hz), 3.7 (m), 3.2 ppm (m); ^{13}C NMR (C_6D_6) 60.1, 56.8, 56.3, 51.1, 41.8, 40.5, 33.4 (two carbons), 32.9, 32.0, 31.6, 28.6, 27.2, 27.1, 25.9, 23.5, 21.1, 17.3, 14.8 ppm; IR ($CHCl_3$) 3250 (br), 2930, 2860, 1465, 1380, 1100, 1040 cm^{-1}; mass spectrum (CI, isobutane) m/z (rel intensity) 294 (100), 276 (5), 248 (40), 222 (4).
(24) We are indebted to Dr. John Daly for providing us with a sample of natural gephyrotoxin and for initially arousing our interest in this problem.

Larry E. Overman,* Chikara Fukaya
Department of Chemistry, University of California
Irvine, California 92717

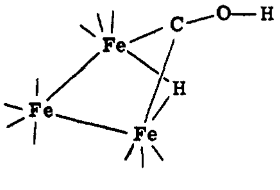
Received August 31, 1979

A New Reaction for the Conversion of Carbon Monoxide into Methane: Proton-Induced Reduction of CO in a Metal Carbonyl Cluster, $[Fe_4(CO)_{13}{}^{2-}]$

Sir:

In an attempt to better understand the heterogeneous reduction of CO[1] and possibly to develop homogeneous analogues, attention has focused on the reduction of coordinated carbon monoxide in molecular systems. The reactions available to date involve external reducing agents such as dihydrogen[2-5] or alane.[6] We report here a new route based on the protonation of a polynuclear metal carbonyl anion.

Protonation of coordinated carbon monoxide, which recently was observed in the polynuclear complexes I and II,[7,8] may be interpreted as a partial reduction of the CO ligand. This interpretation prompted us to attempt further reduction by treating metal carbonyl clusters with very strong acids. The components necessary for reduction, H^+ and electrons, may be supplied by the acid and metal atoms of the cluster, respectively. The most successful results to date have been obtained with the cluster $[Fe_4(CO)_{13}{}^{2-}]$.



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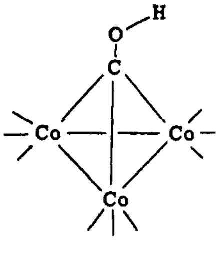

II

A substantial yield of methane was obtained when 0.11 mmol of $[PPN]_2[Fe_4(CO)_{13}]$ [PPN = μ-nitrido-bis(triphenylphosphorus)(+1)][9] was dissolved in 2.0 mL of HSO_3CF_3 and allowed to react for 3 days at room temperature on a vacuum line. Analysis of the evolved gases by a combination of selective low-temperature adsorption on silica gel, mass spectroscopy, PVT measurement, and quantitative infrared spectroscopy demonstrated the following yields of moles of gas per mole of cluster: CH_4, 0.56; H_2, 0.20; and CO, 2.2. Extraction of the acid solution with cyclohexane followed by infrared spectroscopy on the deep brown hydrocarbon layer demonstrated the presence of a metal carbonyl having bands at 2047 (s), 2029 (s), 2015 (m), 1990 (s), and 1980 (m) cm^{-1}. The 1990-cm^{-1} band is assigned to $Fe(CO)_5$; among the remaining bands, all but the lowest are in good agreement with those reported for $Fe_5(C)(CO)_{15}$.[10] In a separate run the acid layer was diluted with water and titrated with Ce^{4+}. Assuming that the sole oxidizable component is Fe^{2+}, this result indicates the production of 1.56 Fe^{2+} per cluster. (An independent qualitative colorimetric test confirmed the presence of large quantities of Fe^{2+} in the acid phase.) Based on the average oxidation state of $-1/2$ for each iron in the cluster, this yield of Fe^{2+} provides 3.9 electrons per cluster, and an additional 1.2 electrons are available assuming that the remaining iron-containing products are in the zero oxidation state. The yield of reduction products listed above would require 3.8 electrons per cluster. Thus the quantity of Fe^{2+} is of the right magnitude to account for the observed yields of CH_4 and H_2, but the exact electron balance will depend on the oxidation state of iron in the iron carbonyl products. These observations are consistent with the reaction summarized in eq 1.

$$[Fe_4(CO)_{13}{}^{2-}] + HSO_3CF_3 \rightarrow CH_4 + H_2 + CO + Fe^{2+} + H_3O^+ + SO_3CF_3{}^- + \text{iron carbonyls} \quad (1)$$

The yield of methane is sensitive to the acidity. Thus no methane is produced with a 1:1 mixture of HSO_3CF_3–H_2O.

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