Table I. Yields of Products Obtained from Azoxy Compounds and N-Oxides

reactant	product	% yield[a] $Mo(CO)_6/Al_2O_3$	% yield[a] $Fe_3(CO)_{12}/Al_2O_3$
azoxybenzene	azobenzene	28	61
4,4'-azoxyanisole	4,4'-azoanisole	34	68
4,4'-azoxyphenetole	4,4'-azophenetole	15	59
quinoline N-oxide	quinoline	41	79
4-picoline N-oxide	4-picoline	32	86
nicotinamide N-oxide	nicotinamide	71	

[a] Yields are of isolated, pure materials. Products were identified by comparison of physical properties with those for authentic materials.

synthetically useful conversion.

After molybdenum hexacarbonyl had been adsorbed on alumina by heating for 1 h at 105 °C, it was treated with an azoxy compound or heterocyclic N-oxide overnight in refluxing 1,2-dimethoxyethane. Simple workup gave the deoxygenated products in 15–71% yields (Table I).

Significantly higher product yields were realized with triiron dodecacarbonyl on alumina (Table I). Furthermore, these reactions were effected at room temperature.

The nature of the species produced by the adsorption of $Mo(CO)_6$ on alumina depends, among other factors, on the temperatures at which the adsorbent was dried and the metal carbonyl was deposited on the oxide.[8] Good evidence has been obtained for the intermediacy of the hydridoundecacarbonyltriferrate anion with $Fe_3(CO)_{12}$ and alumina.[9]

The product yields obtained by using triiron dodecacarbonyl on alumina are both lower, or in some cases higher, than that for iron pentacarbonyl in butyl ether. However, the latter process requires much more drastic conditions [140 °C, 17–24 h].[10] The above-described method is also competitive with, or superior to, the use of other reagents for effecting the same transformations.[11,12] For example, the recently reported[11] deoxygenation of pyridine N-oxides by trimethyl(ethyl)amine sulfur dioxide complexes occurs in refluxing dioxane (~100 °C) [for 4-picoline N-oxide—the only case for direct comparison—the yield of deoxygenated material is lower (70–75%) than that realized with $Fe_3(CO)_{12}/Al_2O_3$].

Experimental Section

General Procedure for Reaction of Azoxybenzenes and N-Oxides with $Mo(CO)_6/Al_2O_3$. After being dried overnight at 350 °C, alumina (30 g, Fisher A-540, 80–200 mesh) was suspended in dry, degassed hexane (150 mL) containing $Mo(CO)_6$ (2.64 g, 10.0 mmol) (nitrogen atmosphere). The hexane was removed by rotary evaporation, and the $Mo(CO)_6/Al_2O_3$ was heated for 1 h at 105 °C. The N-oxide or azoxy compound (3.0 mmol) was added to the cooled solid, along with 1,2-dimethoxyethane (60 mL), and the reaction mixture was stirred at reflux overnight. The mixture was cooled and filtered, the solid was treated with ether or methylene chloride, and the ether was added to the filtrate. Concentration of the filtrate gave the crude product, which was purified by chromatographic techniques (Florisil, silica gel).

General Procedure for Reaction of Azoxybenzenes and N-Oxides with $Fe_3(CO)_{12}/Al_2O_3$. Alumina (20 g, Biorad AG 7, 100–200 mesh) was dried at 150 °C (4–5 mmHg). Triiron dodecacarbonyl (2.0 mmol) in anhydrous hexane (60 mL) was added to the cooled alumina and the mixture was stirred for 2 h at room temperature (nitrogen atmosphere). The azoxy compound or N-oxide (2–4 mmol) was added, either as such or in benzene (10 mL), and the reaction mixture was stirred overnight at room temperature. Workup was effected as described for $Mo(CO)_6/Al_2O_3$.

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Registry No. Azoxybenzene, 495-48-7; azobenzene, 103-33-3; 4,4'-azoxyanisole, 1562-94-3; 4,4'-azoanisole, 501-58-6; 4,4'-azoxyphenetole, 4792-83-0; 4,4'-azophenetole, 588-52-3; quinoline N-oxide, 1613-37-2; quinoline, 91-22-5; 4-picoline N-oxide, 1003-67-4; 4-picoline, 108-89-4; nicotinamide N-oxide, 1986-81-8; nicotinamide, 98-92-0; $Mo(CO)_6$, 13939-06-5; $Fe_3(CO)_{12}$, 17685-52-8.

(8) Kazusaka, A.; Howe, R. F. *J. Mol. Catal.* **1980**, *9*, 183.
(9) Hugues, F.; Smith, A. K.; Ben Taarit, Y.; Basset, J. M.; Commereuc, D.; Chauvin, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 68.
(10) Alper, H.; Edward, J. T. *Can. J. Chem.* **1970**, *48*, 1543.
(11) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *Synthesis* **1980**, 660 and references cited therein.
(12) Olsen, H.; Snyder, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 285.

Formation of Macrocyclic Lactones in Microemulsions[1a]

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Detergentless microemulsions have been identified and structurally characterized through the use of conductivity, ultracentrifugation, light scattering, and nuclear magnetic resonance.[2-5] Detergentless systems thus far reported consist of a dispersion of water droplets (~100-Å diameter) in a hydrocarbon continuum. They differ from conventional microemulsions in that they form in the absence of long-chain surfactants and by virtue of the fact that they contain up to 30% of the aqueous, dispersed phase.

Microemulsions would appear to be excellent media for facilitating chemical reactions. The presence of both polar and nonpolar phases allows the dissolution of a wide variety of chemical reagents while the very large interfacial area enhances the probability of a reagent encounter, measurably accelerating the rate of reaction compared to a normal two-phase system. A further control on the rate of reaction can be introduced through the utilization of surfactants with different charges on the head groups[6] though an advantage of employing detergentless microemulsions for chemical reactions is that purification is

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(2) Smith, G. D.; Donelan, C. E.; Barden, R. E. *J. Colloid Interface Sci.* **1977**, *60*, 448.
(3) Barden, R. E.; Holt, S. L. "Micellization, Solubilization, and Microemulsions"; K. Mittal, Ed.; Plenum Press: New York, 1979; p 707.
(4) Keiser, B. A.; Varie, D.; Barden, R. E.; Holt, S. L. *J. Phys. Chem.* **1979**, *83*, 1267.
(5) Lund, G.; Holt, S. L. *J. Am. Oil Chem. Soc.* **1980**, 264.
(6) Keiser, B. A.; Holt, S. L.; Barden, R. E. *J. Colloid Interface Sci.* **1980**, *73*, 290.

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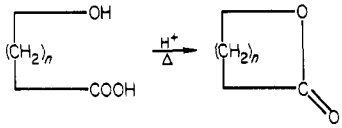
Table I

acid	matl recovd, wt % lactone	2-propyl ester	polymers	acid
12-hydroxyoctadecanoic	18	35	20	20
15-hydroxypentadecanoic	20	40	20	15
16-hydroxyhexadecanoic	23	40	20	10
11-bromoundecanoic	25	-	18	45
15-bromopentadecanoic	22	-	15	50

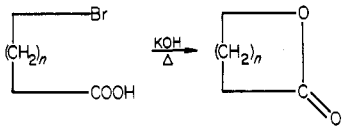
simplified. In micellar or phase-transfer catalysis a surfactant, crown ether, alkylammonium halide, or other nonvolatile reagent is introduced. In detergentless microemulsions we need contend only with water, a low molecular weight hydrocarbon, and 2-propanol, all easily separated from the products. The potential of microemulsions as media for synthesis is clearly evident.

Studies of the metalation of prophyrins[6] and the bas-catalyzed hydrolysis of esters[7] have demonstrated the effect of microemulsification on both reaction rate and pathway. We report here the first attempt to utilize microemulsions as a medium for chemical synthesis.

The reaction we have chosen to investigate is the synthesis of macrocyclic lactones. The two most direct routes are the intramolecular esterification of ω-hydroxyalkanoic acids[8] and cyclization of the potassium salts of ω-bromoalkanoic acids[9] (eq 1 and 2). In both reactions a compe-



(1)



(2)

titive pathway yields polymeric material, and, as a consequence, it is usually necessary to use either high dilutions ($\sim 5 \times 10^{-4}$ M) of ω-hydroxy acid in the presence of a 10–40-fold excess of *p*-toluenesulfonic acid[8] or slow addition (e.g., 7×10^{-3} mol/day/L of solvent[9]) of the bromo acid to a solvent containing excess potassium carbonate. These limitations lead to extended reaction times of up to 16 days.[10] Because of their ability to partition reactants, detergentless microemulsions can be expected to offer a solvent system in which high dilution, long reaction times, and presence of excess catalyst may be avoided. [Our reaction conditions for the formation of the lactones using *p*-toluenesulfonic acid employ concentrations of hydroxy acid which were 10 times those used in earlier work with "catalyst" ratios reduced from 40/1 (reactant/catalyst) to approximately 1/1.]

The results in Table I show that the amount of polymer formation is exceedingly low considering the concentrations used. (If the reaction is carried out in a mixture of water and IPA, approximately equal quantities of polymer and isopropyl ester, but no detectable lactone, are found.) This supports the premise that the reacting species are highly dispersed in the water droplets. The principal drawback to use of this technique for forming macrocyclic lactones from the hydroxyalkanoic acid is the competing reaction which produces the isopropyl ester. One can see, however, that the ring closure proceeds in significant yield in spite of the large amount of isopropyl alcohol present. (When the ω-bromo acid was used, dropwise addition of the reactant was not employed. As a consequence, the concentration of reactant was far in excess of that obtained in earlier experiments—yet the yield of polymer was small and the yield of lactone notable, on the basis of the amount of starting material recovered.) The primary barrier to high yield appears to be the limit placed on reaction temperatures by the lower boiling temperatures of the microemulsions.

We are presently investigating reactions that proceed at ambient temperature for which microemulsions are the reaction medium of choice.

Experimental Section

Reagents. 12-Hydroxyoctadecanoic acid (P&B), 15-hydroxypentadecanoic acid (Columbia Organics), 16-hydroxyhexadecanoic acid (Columbia Organics), and 11-bromoundecanoic acid (Fluka) were commercial samples and were used as received. 15-Bromopentadecanoic aicd [mp 67–68 °C (lit.[11] mp 66 °C)] was prepared by refluxing 15-pentadecanolide (Columbia Organics) in an acetic acid–hydrobromic acid mixture and isolating the product by standard methods.

General Method for Preparation of Lactones from Hydroxy Acids. In a 500-mL, round-bottom, three-necked flask fitted with a condenser was placed a microemulsion consisting of 9.2 mL of H_2O, 84.1 mL of 2-propanol, and 101.3 mL of toluene. This microemulsion was made 8×10^{-3} M in *p*-toluenesulfonic acid (Fischer). To the above solution was added an equal volume of a microemulsion of identical composition and 1×10^{-2} M in hydroxy acid over a period of 2 h. After the addition was completed, the resulting mixture was heated at 65 °C for 12 h. Removal of the solvent under vacuum afforded a light yellow solid which was triturated with pentane (3 × 100 mL) and filtered. The pentane solution was extracted with water (25-mL portions) until the water layer was no longer acidic, after which the pentane solution was dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum afforded a light yellow solid. This solid was subjected to preparative layer chromatography or column chromatography with silica gel as solid support and hexane–ether (5:1) as eluent to afford pure lactone and 2-propyl esters which were identified by melting point, TLC, NMR, IR, and saponification.

General Method for Preparation of Lactones from ω-Bromo Acids. In a 250-mL, round-bottom flask fitted with a condenser was placed a microemulsion of the same composition as used in the above procedure. This solution was made 3×10^{-3} M in bromo acid after which an equivalent amount of KOH was added to generate the potassium salt. This solution was then heated at 65 °C for 1 day. After removal of the solvent the residue was treated with pentane (2 × 100 mL), and any insoluble (potassium salt) material was removed by filtration. The pentane solution was evaporated, and the resulting residue was subjected to preparative layer or column chromatography to afford pure lactone, which was identified as before.

Registry No. 12-Hydroxyoctadecanoic acid, 106-14-9; 15-hydroxypentadecanoic acid, 4617-33-8; 16-hydroxyhexadecanoic acid, 506-13-8; 11-bromoundecanoic acid, 2834-05-1; 15-bromopentadecanoic acid, 56523-59-2; potassium 11-bromoundecanoate, 77172-44-2; potassium 15-bromopentadecanoate, 77172-45-3; 12-hydroxyoctadecanoic acid lactone, 673-02-9; 15-hydroxypentadecanoic acid lactone, 106-02-5; 16-hydroxyhexadecanoic acid lactone, 109-29-5; 11-bromoundecanoic acid lactone, 1725-03-7; isopropyl 12-hydroxyoctadecanoate, 74819-91-3; isopropyl 15-hydroxypentadecanoate, 77172-46-4; isopropyl 16-hydroxypentadecanoate,

(7) Borys, N. F.; Holt, S. L.; Barden, R. E. *J. Colloid Interface Sci.* **1979**, *71*, 526.
(8) Stoll, M.; Rouve, A. *Helv. Chim. Acta* **1934**, *17*, 1283.
(9) Hunsdiecker, H.; Eclbach, H. *Chem. Ber.* **1947**, *80*, 129.
(10) Stoll, M.; Gardner, R. E. *Helv. Chim. Acta* **1934**, *17*, 1609.
(11) Hunsdiecker, H.; Hunsdiecker, C. *Chem. Ber.* **1942**, *75*, 291.

77172-47-5; 12-hydroxyoctadecanoic acid polymer, 27924-99-8; 15-hydroxypentadecanoic acid polymer, 37453-68-2; 16-hydroxyhexadecanoic acid polymer, 30792-74-6; 11-bromoundecanoic acid polymer, 77172-42-0; 15-bromopentadecanoic acid polymer, 77172-43-1; 12-hydroxyoctadecanoic acid repeating unit, 27941-02-2; 15-hydroxypentadecanoic acid repeating unit, 73207-55-3; 16-hydroxyhexadecanoic acid repeating unit, 32239-70-6; 11-bromoundecanoic acid repeating unit, 25735-90-4.

Reaction of Halomethyl Ketones with Thiols and Selenols: Substitution vs. Reduction[1,2]

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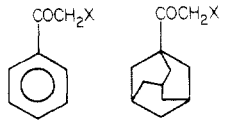
This report describes the novel reduction of iodomethyl ketones to methyl ketones by thiols and selenols in high yield under extremely mild conditions.

In connection with a major ongoing program on semisynthetic anthracycline analogues, we were interested in preparing some 14-thia analogues of adriamycin and of *N*-(trifluoroacetyl)adriamycin-14-valerate (AD 32), a clinically promising adriamycin analogue,[3,4] for antitumor and structure–activity evaluation. Our initial synthetic approach involved reaction of 14-iodo-*N*-(trifluoroacetyl)-daunorubicin (1, X = I), a readily available intermediate in our laboratory, with alkane- and arenethiols, with the expectation of **2** (Scheme I), from which the corresponding free amino compounds could be achieved by alkaline hydrolysis of the trifluoroacetamide. However, treatment of 1 (X = I) with various short- or long-chain alkanethiols, or with benzenethiol, in anhydrous ethanol at room temperature in the presence of K_2CO_3 in each instance resulted in a rapid reaction and the exclusive formation of *N*-(trifluoroacetyl)daunorubicin (**3**), a known and well-characterized compound; with *n*-dodecanethiol, the concomitant formation of di-*n*-dodecyl disulfide was verified by vapor-phase chromatography. In contrast, when the corresponding 14-bromo compound, 1 (X = Br), was treated with thiols under identical conditions, nucleophilic displacement of the halide occurred, with the formation of the desired 14-thia derivatives, **2**.[2]

Unaware of a precedent for the iodomethyl ketone reduction, we investigated several model compounds to explore the generality of the reaction. Thus, α-chloroacetophenone and α-bromoacetophenone reacted normally with *n*-dodecanethiol and benzenethiol to give the corresponding sulfides **4** (X = $SCH_2(CH_2)_{10}CH_3$, SC_6H_5), whereas α-iodoacetophenone prepared by halide exchange from **4** (X = Cl) under the same conditions afforded exclusively acetophenone and the companion disulfide. Similarly with 1-adamantyl halomethyl ketones **5** (X = Br) gave exclusively substitution, whereas **5** (X = I) underwent reduction.



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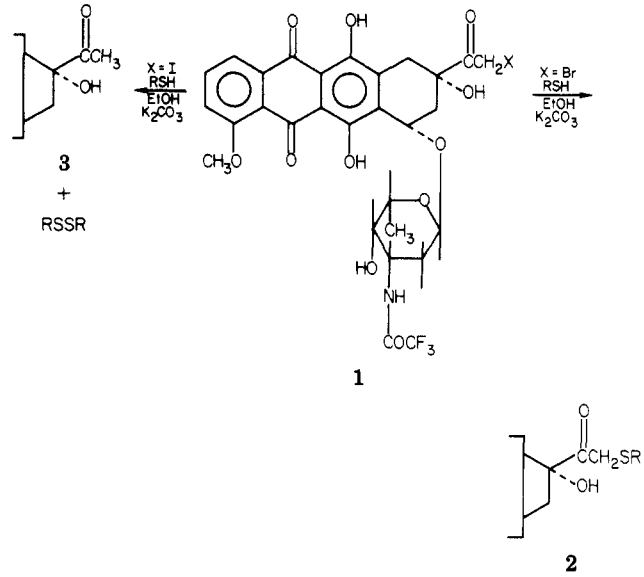
Scheme I



A similar effect was seen when a selenol was used in place of a thiol. Reaction of 1 (X = Br) with benzeneselenol under the indicated conditions afforded the hitherto unknown 14-(phenylseleno)-*N*-(trifluoroacetyl)daunorubicin, whereas with 1 (X = I) only **3** and diphenyl diselenide were formed.

The formation of methyl ketones from iodomethyl ketones by reaction with thiols is noteworthy for its ease and simplicity, mild reaction conditions, and high, often quantitative, yields. Reactions are easily monitored by thin-layer chromatography, and products, being easily separated by column chromatography from the accompanying disulfide, are obtained in high purity. As indicated by the stoichiometry, complete reaction is obtained at room temperature with a reactant ratio of 2:1 thiol–iodomethyl ketone; a lower ratio of reagents results in mixtures of disulfide, methyl ketone, and unchanged starting material.

It has been previously reported that reactions of chloro- or bromomethyl ketones with thiolate give mixtures of reduction and substitution products (together with unchanged starting material) when equimolar amounts of reactants are used; however, with excess thiolate, reactions gave predominantly reduction products.[5] In the present work, we also can find some substitution product derived from iodomethyl ketone, if the reaction is carried out at −70 °C. These observations suggest that the reactivity of the halogen of the halomethyl ketone function plays a determining role in directing the course of the reaction, reduction vs. substitution. Thus, the significance of the present report lies in the greater reactivity of iodomethyl ketones with thiols at room temperature, a fact which results in almost instantaneous reaction and high yield of reduction product.

The mechanism for the thiol reduction of halomethyl ketones remains somewhat speculative, as is also the situation for the related reduction of benzyl iodides by thiols, recently described by Hevesi.[6] Oki et al.[5] suggest that, in their examples, reduction is brought about by the action of excess thiolate on the initially formed substitution product. However, the rapidity of reaction of iodomethyl ketones, together with the fact that some of the reactions of chloromethyl and bromomethyl ketones require 30 min

(1) This work was supported by Research Grant CA 17263 from the National Cancer Institute, National Institutes of Health, Bethesda, MD.
(2) Presented in part at the 175th National Meeting, American Chemical Society, Anaheim CA, 1978, MEDI 47.
(3) M. Israel, E. J. Modest, and E. Frei III, *Cancer Res.*, 35, 365 (1975).
(4) R. H. Blum, M. B. Garnick, M. Israel, G. P. Canellos, I. C. Henderson, and E. Frei III, *Cancer Treat. Rep.*, 63, 919 (1979).
(5) M. Oki, W. Funakoshi, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, 44, 828 (1971).
(6) L. Hevesi, *Tetrahedron Lett.*, 3025 (1979).

0022-3263/81/1946-2596$01.25/0