commercially. Triformylmethane was prepared by a described method[1,2] with use of the modified procedure given below. ^1H and ^{13}C NMR spectra were measured on a Varian XL-200 FT-NMR spectrometer.

Triformylmethane. To a solution of bromoacetic acid (34.74 g, 0.25 mol) in 100 mL of dimethylformamide was added $POCl_3$ (82 mL, 0.875 mol) at 15–18 °C during 2 h. After standing for 1 h the reaction mixture was heated at 75 °C for 2 h and then at 90 °C for 10 h. The reaction mixture was cooled and worked up at −25 °C by adding ethanol (100 mL) followed by water (200 mL) and 70% $HClO_4$ (50 mL). After the mixture was stirred for 2 h at −20 °C, the precipitate formed was separated by succion, washed with ethanol, followed by ethanol saturated with SO_2, and dried in vacuo. The crude diperchlorate[2] $C_{10}H_{21}Cl_2N_3O_8$ (382.2), obtained in about 55–65% yield, could be crystallized from acetonitrile (mp 224 °C), but for further procedure this purification was not necessary. The diperchlorate (3.82 g, 0.01 mol) was treated in 2 mL of CH_3OH with 4 N $NaOH/CH_3OH$ in two successive portions; the first one (5 mL) dissolved the diperchlorate, and the second one (3 mL) precipitated the sodium salt of triformylmethane. This was separated by succion and washed with a small portion of CH_3OH. The sodium salt was stirred for 1 h with a mixture of dichloromethane (15 mL), water (1 mL), and concentrated HCl (1 mL). The organic layer was separated, the aqueous layer was extracted twice with dichloromethane (8 mL), and the combined extracts were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed with use of a small distillation column, and the residue was sublimed in vacuo. Yield 0.8 g (80%), mp 101–103 °C (ref 1).

2,6,9-Trioxabicyclo[3.3.1]nona-3,7-diene-4,8-dicarbaldehyde. A mixture of triformylmethane (0.5 g, 0.005 mol), dry ether (20 mL), and thionyl chloride (3.65 mL, 0.05 mol) was stirred overnight, the ether and the excess thionyl chloride were removed in vacuo, and the residue was purified by sublimation (130 °C, 26 Pa) and crystallization from 1,2-dichloroethane: yield 0.27 g (60%); mp 180 °C; MS, e/z (percent) 182 (M^+, 17.5), 154 (31), 72 (29), 71 (28), 55 (82), 53 (44), 29 (100), 27 (40); UV (CH_3CN) λ_{max} 230 nm, ϵ 3.9×10^4; IR (KBr disk, selected bands): 3067 (m), 3050 (w), 3019 (m) (ν_{C-H} of CH=C), 2853 (m), 2754 (vw), 2740 (vw) (ν_{C-H} of CH=O), 1661 (s), 1681 (s) ($\nu_{C=O}$), 1631 (vs) ($\nu_{C=C}$), 1245 (vs) (ν_{ring}), 987 (s), 930 (s), 895 (s), 860 (s); ^1H NMR (a) in $CDCl_3$ δ 6.32 (s, OCHO), 7.61 (s, CH=), 9.34 (s, CH=O); (b) +Eu[tfc]$_3$ (L/S $\approx$ 0.5) δ 6.95 and 6.96 (s, OCHO), 7.92 and 7.96 (s, NCH=), 9.98 and 10.02 (s, CH=O).

Registry No. 1, 18655-47-5; 1·Na^+, 79341-66-5; 2, 116149-13-4; 3, 116149-12-3; $(Me_2N^+{=}CH)_2C{=}CHNMe_2{\cdot}2ClO_4^-$, 2009-81-6; bromoacetic acid, 79-08-3.

Conversion of Isocyanates to Nitro Compounds with Dimethyldioxirane in Wet Acetone

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The standard reaction sequence for transformation of a carboxylic acid into a nitro group is lengthy: acid–acylazide→isocyanate→carbamate→amine→nitro. It occurred to us that this "classical" route would be much simplified if a reagent could be found for direct oxidation of the intermediate isocyanate to the desired nitro compound. This would also obviate the necessity of working with the free amine, an important advantage as this electron-rich group is often a point of weakness in strained molecules, triggering the breakdown of the skeleton. Conveniently, the advent of azidotrimethylsilane has made isocyanates exceptionally easy to prepare *and* isolate.[1]

Table I. Oxidation of Isocyanates with Dimethyldioxirane[a]

	no water added		15% H_2O added		15% H_2O with $PhCH_2NMe_3OH$	
isocyanate	time	yield, %	time	yield[c], %	time	yield,[c] %
phenyl	no reaction		30 min	95 (65)[b]		
cubane-1,4-di	no reaction		1 h	85[b]		
n-butyl			24 h	34	1 h	89
cyclohexyl			24 h	16	3 h	94
tert-butyl			24 h	<5	8 h	83

[a] Reaction conditions: 0.08 M dimethyldioxirane in acetone solution; room temperature; dark. [b] Isolated yield. [c] By calibrated GLC analysis.

Unfortunately, little has been reported about the oxidation of isocyanates.[2]

We undertook a brief survey of the reactions of cyclohexyl isocyanate with common oxidizing agents. Ozone did not react with the isocyanate under a variety of conditions. Oxidation with potassium permanganate or with *m*-chloroperbenzoic acid gave complex mixtures of products, but these contained little or no nitrocyclohexane. Oxidation of cyclohexyl isocyanate with ruthenium tetroxide in carbon tetrachloride did give a 1:1 mixture of nitrocyclohexane and cyclohexanone. In all probability this oxidation proceeds via cyclohexanone oxime and requires the presence of hydrogen α to the isocyanate. Although certainly this reagent qualifies for further consideration, in the case of real interest to us, the oxidation of 1,4-diisocyanatocubane, the reaction with ruthenium dioxide took an obscure course and destroyed the ring system entirely.[3] After this failure, we turned to dimethyldioxirane, an oxidizing agent of extraordinary properties.[4]

Dimethyldioxirane was prepared by reaction of OXONE (DuPont trademark), $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, with buffered aqueous acetone, fairly much following the procedure described by Murray and Jeyaraman.[5a] The dimethyldioxirane was entrained along with other volatiles in a room temperature nitrogen stream; subsequent condensation gave a wet acetone solution about 0.1 M in oxidant.

Our results for the oxidation of some representative isocyanates with dimethyldioxirane in acetone are summarized in Table I. Primary, secondary, and tertiary aliphatic isocyanates, as well as phenyl isocyanate, are all cleanly converted to the corresponding nitro compounds in good yield. Water is an essential ingredient; oxidation does not occur (the isocyanate can be recovered unchanged) if the dimethyldioxirane/acetone solution is dried before use over 4A molecular sieves. On the other hand, if water is purposely added, the conversions occur quickly at rates roughly dependent on the obvious steric factors. Thus, it is clear that the electron-poor isocyanate itself is not directly oxidized, but rather is hydrolyzed first to the carbamic acid. This appears to be the rate-limiting step, for the overall rate of oxidation is increased dramatically, as shown in the table, if a catalytic amount of benzyltrimethylammonium hydroxide is added to the reaction so-

(1) (a) Kricheldorf, H. R. *Synthesis* **1972**, 551. (b) Washburne, S. S.; Peterson, W. R. *Synth. Commun.* **1972**, *2*, 227. (c) MacMillan, J. H.; Washburne, S. S. *J. Org. Chem.* **1973**, *38*, 2982.

(2) Becker, J. Y.; Zinger, B. *J. Am. Chem. Soc.* **1982**, *104*, 2327.

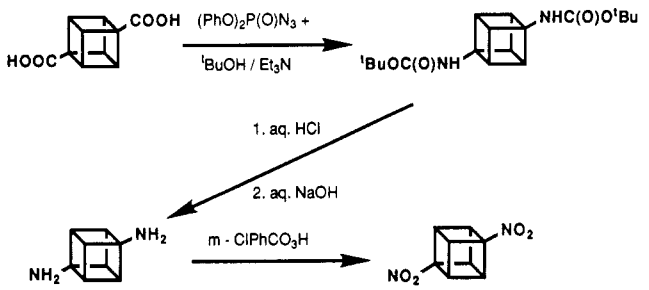
(3) This is not due to any fundamental instability of the cubane sytem to the oxidant.

(4) (a) Edwards, J. O.; Pater, R. H.; Curci, R.; DiFuria, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699 and references therein. (c) Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746 and earlier parts.

(5) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. See also (b) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

0022-3263/88/1953-5353$01.50/0

Scheme I



lution. The actual oxidation might begin on the carbamic acid *or* this intermediate might instead undergo decarboxylation to the amine, which is then oxidized. It is easy to decide in favor of the latter path as amines are easily oxidized to nitro compounds by dimethyldioxirane[6] whereas carbamates are not. We have found, for example, that 4-methylaminocubane is oxidized to 4-methylnitrocubane in excellent yield by dimethyldioxirane in acetone quickly at room temperature, but its carbamate derivative, 4-methyl(*tert*-butoxycarbonyl)aminocubane, is recovered unchanged after similar exposure to excess dimethyldioxirane in acetone at room temperature for 24 h.[7]

The synthetic merit of this new procedure for the preparation of nitro compounds from carboxylic acids can be seen clearly in the important case of conversion of 1,4-dicarboxycubane to 1,4-dinitrocubane. We had earlier prepared this high-energy cubane in 18% overall yield from the diacid by the routine illustrated in Scheme I.[8]

The major difficulty in this procedure is the low yield in the peracid oxidation, a matter which gets much worse on "scale-up" to even the 100-mg level. The new route is outlined in Scheme II.

1,4-Diisocyanatocubane was prepared by thermal rearrangement (refluxing chloroform) of the corresponding acyl azide, obtained first in the same pot by reaction of the acid chloride with excess azidotrimethylsilane. As chlorotrimethylsilane (TMSCl), the cognate of the acyl azide, reacts with both it and the diisocyanate at the temperature needed to rearrange the acyl azide, the starting reactants were used neat to achieve a good rate of formation of the azide *at room temperature*. Prior to the thermolysis, the reaction mixture was diluted substantially to depress the second-order reactions of TMSCl with the azide and isocyanate. For the same purpose much of the TMSCl was removed by distillation at the beginning of the thermolysis. With such attention to experimental detail, the diisocyanate was obtained reproducibly in 78% yield overall from the 1,4-diacid. Oxidation of the diisocyanate with 0.07 M dimethyldioxirane in 15 vol % aqueous acetone solution was complete within 1 h at room temperature and gave an 85% yield of pure, crystalline 1,4-dinitrocubane. The overall yield of the sequence in Scheme II is 66%, nearly four times that of Scheme I.

As good as this procedure is, we note that it does not satisfy our original concept–*direct* oxidation of the isocyanate group to the nitro group without passing through the amine. We encourage others to join us in a search for this potentially valuable procedure.

In the course of this work, it was determined that dimethyldioxirane not only oxidizes 1,4-diaminocubane in excellent yield[9] but works as well, indeed better, on the corresponding amine hydrochloride salt.[10] This is exceptionally convenient, as it avoids both the necessity of isolating the sensitive free amine and the problems[9] caused by reactions of it with the intermediates (the hydroxylamine and the nitroso compound) formed during the overall conversion. No doubt, the oxidation of the amine hydrochloride occurs via the small amount of free base in equilibrium with the salt, a testimony to the exceptional oxidizing abilities of dimethyldioxirane. Unfortunately, there is a practical limitation to the use of dimethyldioxirane: at present it is not feasible to prepare in the laboratory more than about 20 mmol of dimethyldioxirane in a single run. Even this requires use of a 5-L flask. In situ oxidations might prove more efficient and useful in some cases, but it would be best for ease of workup, particularly with water soluble products, if a method could be found to produce large quantities of "distilled" dimethyldioxirane/acetone. We look forward to learning of developments that permit scale-up in the preparation of this very important oxidant.

Experimental Section

Proton (500 MHz) and carbon (100 MHz) NMR spectra of $CDCl_3$ solutions containing Me_4Si as internal standard were taken in FT mode. Infrared spectra were recorded with a Nicolet SX-20 FT-IR system with digital resolution of 1 cm^{-1}. Quantitative chromatography was performed on a Hewlett-Packard 5880 equipped with a flame-ionization detector using a 10 m × 0.53 mm i.d. widebore capillary column with a 1.8-μm film of 50% cyanopropylmethyl-/50% phenylmethylpolysiloxane or a 1-μm film of polydimethylsiloxane. *All reactions were carried out behind a heavy shield.*

Dimethyldioxirane.[5a] A 5-L, five-necked, round-bottomed flask was fitted with a substantial mechanical stirrer, an air-cooled Allihn condenser loosely packed with glass wool, a solids addition funnel, a 500-mL liquids addition funnel, and a gas inlet adapter with long stem extending down into the reaction mixture. The air condenser was connected laterally via a glass tube to a dry ice cold finger condenser fitted with a 500-mL receiver. Dry ice/ethanol was used to cool this condenser and its receiver. The exit of the dry ice condenser was attached in series to two 11 in. × 1.25 in. o.d. traps, each cooled with liquid nitrogen/ethanol slush baths, and an oil bubbler. The apparatus was flushed with nitrogen before cooling the traps. The nitrogen flow was continued gently (!) throughout the reaction to entrain the product.[11] Acetone (Aldrich ACS, 150 mL, 2.0 mol), distilled water (240 mL), and sodium bicarbonate (430 g) were put into the reaction vessel and vigorously stirred. OXONE ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, Aldrich, 900 g) was added from the solids funnel as acetone (300 mL) in water (480 mL) was added over 2 h from the other. The reaction mixture began to froth, but this could be controlled easily by reducing the rate of OXONE addition. A yellow solution of dimethyldioxirane in acetone distilled into the cooled receiver. A soft vacuum (50–100 Torr) was applied after the last trap instead of the bubbler during the latter two-thirds of the reaction. About 200 mL of a solution of dimethyldioxirane in acetone containing 1–2% water was collected in the receiver. Repeat runs were made without dissembling the apparatus after cleaning the generator flask with generous flushes of water and emptying the traps. The dimethyldioxirane solution, which can be dried if desired over 4A molecular sieves, was stored in the freezer (−15 °C) and titrated just before use. One-milliliter aliquots were analyzed by measuring the conversion of thioanisole (23.5 μL) in acetone (1.0 mL) to methyl phenyl sulfoxide by GLC on a glass $^1/_4$ in. × 6 ft, 2%

(6) Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335.

(7) The carbamate was taken as a model for the carbamic acid as the acid decarboxylates too easily to use. In the hydrolysis of phenyl isocyanate in 15 vol % aqueous acetone there is no detectable (by ^1H NMR) buildup of any carbamic acid, although the amine can be seen to form rapidly.

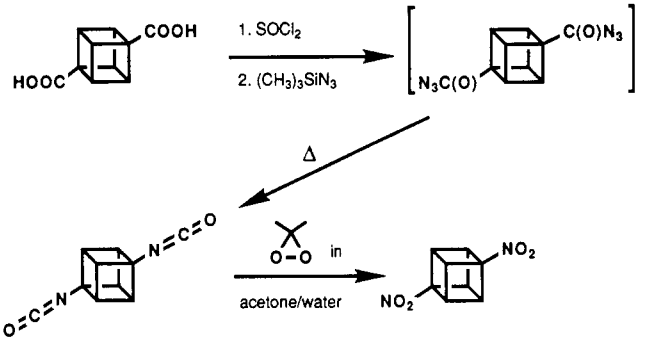
(8) Eaton, P. E.; Ravi Shankar, B. K.; Price, G. D.; Pluth, J. J.; Gilbert, E. E.; Alster, J.; Sandus, O. *J. Org. Chem.* **1984**, *25*, 185.

(9) Murray, R. W.; Rajadhyaksha, S. N., University of Missouri—St. Louis, private communication.

(10) Farina, G.; Pramod, K., this laboratory, unpublished observation.

(11) Murray[5a] used helium; Adam[5b] used argon; we detect no significant difference when nitrogen is used as the carrier gas.

Scheme II



OV-225 on 80–100 mesh Chromosorb G-HP column at 100 °C. The concentration was usually between 0.07 and 0.12 M.

1,4-Diisocyanatocubane. *A heavy shield must be used. Solutions of cubane-1,4-bis(acyl azide) have not caused problems, but the crystalline compound detonates if touched. Great care should be exercised.* A mixture of 1,4-dicarboxycubane (2.30 g, 12.0 mmol) and 25 g of thionyl chloride (freshly distilled from triphenyl phosphite) was stirred at reflux under nitrogen for 3 h. Most of the excess thionyl chloride was recovered by distillation.[12] Approximately 15 mL of carbon tetrachloride (dried over 4A molecular sieves) was added and distilled; this operation was repeated. Azidotrimethylsilane (Aldrich, 6.50 mL, 49.0 mmol) was added, and the mixture was stirred at room temperature under nitrogen for 2 h (no longer!).[13] (The disappearance of the diacid chloride resonance at δ 4.45 and the appearance of the diacylazide peak at δ 4.27 ppm were followed by ^{1}H NMR analysis of diluted aliquots.) Approximately 80 mL of ethanol-free chloroform was added, and half of it was slowly distilled. Another 40 mL of the ethanol-free chloroform was added, and again half of the solution was distilled. The solvent and excess azidosilane were removed in vacuo. The residual yellow solid was sublimed (oil bath at 70–110 °C/0.3 Torr) to give 1.74 g (78%) of snow-white 1,4-diisocyanatocubane: mp 113–115 °C; ^{1}H NMR δ 3.98 (s, 6 H); ^{13}C NMR δ 124.1, 66.8, 49.7; IR (CCl_4) ν 3005, 2256, 1258, 1093 cm^{-1}. The material is sensitive to moisture but can be stored cold under nitrogen without deterioration for at least 1 month.

1,4-Dinitrocubane. 1,4-Diisocyanatocubane (1.30 g, 7.0 mmol) was added with stirring to a mixture of 1 L of 0.072 M dimethyldioxirane (72 mmol) in acetone and 175 mL of distilled water. The solution was stirred at room temperature in the dark under nitrogen for 1.5 h. (The progress of the reaction was followed by GC: $^1/_4$ in. × 6 ft glass column with 2% OV-225 on 80–100 mesh Chromosorb G-HP column; 23 mL/min flow; start at 140 °C, then 20 °C/min to 230 °C; retention times: diisocyanate, 2.4 min; dinitrocubane, 6.0 min.) The acetone was removed in vacuo (bath temperature 27 °C), leaving a white solid and some water. The solid was collected and crystallized from benzene (two crops) to give 1.15 g (85%) of snow-white 1,4-dinitrocubane: mp 260 °C dec; ^{1}H NMR δ 4.67 (s); ^{13}C NMR δ 86.3, 49.8; IR (KBr) ν 1510, 1372, 1358, 1194, 950, 811 cm^{-1}; MS (CI, isobutane), *m/e* (relative intensity) 195 (17), 118 (84), 102 (100), 90 (84).

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(12) A heating mantle should not be used; overheating and runaway reactions are possible. Use a temperature-controlled oil bath. The same recommendation applies to all work with the highly strained cubane system.

(13) If crystallization occurs, dilute immediately with chloroform.

Synthetic Approaches toward Mitomycins: Construction of *p*-Quinone Moiety on 1-Benzazocine Derivative

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Mitomycins[1] are an important class of antitumor antibiotics among which mitomycin C (MMC)[2] has been used in the treatment of various neoplastic diseases.[3] Although numerous synthetic studies[4] toward MMC have been carried out since its structural elucidation,[5] only Kishi[6] and Fukuyama[7] have achieved total syntheses of natural mitomycins.

In the course of our synthetic work related to MMC, a new reaction named criss-cross annulation was discovered[8] and applied to the synthesis of various natural products.[9] The reaction could be controlled to give benzazocine derivatives (**2**, **3**), which are key intermediates for our synthetic plan shown in Scheme I. In the present paper, we disclose the X-ray crystallographic analysis of the conformational isomers of **8A** and **8B** and an efficient synthesis of proposed MMC intermediate **12** by taking advantage of the reactivity difference of the conformers.

Hydrogenolysis of **2**[10] afforded primary amine **4** in 96% yield, which was oxidized with $Pb(OAc)_4$ (2.2 mol equiv) in CH_2Cl_2 to give *o*-quinone imide **5**. Hydrolysis of crude **5**, followed by hydrogenation gave catechol **7** in 48% overall yield. Direct ketalization[11] of **7** gave **8A** in up to 50% yield together with a significant amount of a byproduct. In an alternative preparation of **8**, catechol **7** was first converted to the corresponding benzyl ether. Under these conditions, the products were obtained as a 1:1 mixture of conformational isomers. Ketalization of this mixture under the same conditions as described above afforded smoothly the desired ketal **9** in 86% yield from **7** as a mixture of the conformers **9A** and **9B** (Scheme II). Since isomer **9A** slowly isomerized to **9B** even at room temperature, the ratio of **9A** and **9B** was different in every experiment (**9A**:**9B** = 1:3 ~1:10). Debenzylation of this mixture provided **8A** and **8B** in the same ratio as **9** in 85% yield. The conformational isomers (**8A** and **8B**) were easily separated by column chromatography.

In a previous paper,[12] the isolation of the conformational isomers of **3** (**3A**,**B**) was reported. Spectral data of **8A** and **8B** are parallel with those of **3A** and **3B**, respectively. Single X-ray crystallographic analysis[13] of **8A** and **8B** (Figure 1) showed that the conformation of both isomers is a twist-boat-chair form, in which the only difference between the structures is the stereochemistry of C-6 methyl group, which is pseudoequatorial in **8A** and pseudoaxial in **8B**. Isomerization of **8B** in benzene at reflux temperature for 42 h provided the thermodynamically more stable **8A** in 97% yield. The greater stability of **9B** is attributed to the severe steric interactions between C-7 benzyloxy and C-6 methyl groups in **9A**. Since **8A** and **8B** were not equilibrated at room temperature, debenzylation of a mixture of **9A** and **9B** afforded **8A** and **8B** in the same

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