STUDIES ON THE CHEMISTRY OF NEW CYCLIC STRUCTURES AND SYNTHETIC APPLICATION

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Chapter 1

INTRODUCTION AND GENERAL SUMMARY

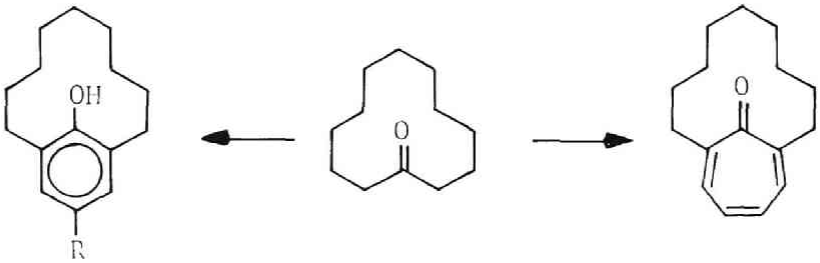
Modern organic chemistry involves several aspects of new developments resulting in remarkable achievements. At the outset of the present investigation two facets gained the author's attention.

One is the large and medium ring chemistry based on the cyclic oligomers of 1,3-butadiene,[1] *viz.*, 1,5-cyclooctadiene and 1,5,9-cyclododecatriene, which have become commercially available since early 1960's owing to the invention of G. Wilke.[2] Thus, the synthetic potentiality has become open to explore novel cyclic structures by means of the 8- and 12-membered ring compounds.

The other one is concerned with the synthetic application of the reactive species[3] including carbenes,[4] nitrenes[5] and nitrenium ions[6] as well as photo-excited molecules.[7] The generally short-lived, highly reactive intermediates often give such products which are not accessible by conventional methods. This is ascribed to the fact that the excessive energy of the reactive species is easily stored as the molecular strain of the products,[8] which serve, therefore, as versatile synthetic intermediates again. In this sense, the author was interested in the chemistry of aziridines,[9] nitrogen-containing three-membered (smallest) ring compounds, being obtained by the nitrene-addition to olefins.

This thesis deals with some aspects of the chemistry of large and medium ring compounds in the first three chapters, while the novel synthetic reactions of aziridine derivatives constitute the successive four chapters.

From the synthetic viewpoint, we may point out that constructing the desired medium and large ring structures can be performed much easily by modification of the existing cyclic systems rather than by cyclization of open chain materials.[10] This is mainly ascribed to the entropy factor of the cyclization reactions. Starting from cyclododecanone, the present author prepared a novel phenol (1), whose 2,6-positions were bridged[11] by a nonamethylene chain. What he wanted to know was the possible effect of the bridging[12] upon the structure and reactivity of the phenol. Nmr spectra have indicated that the aliphatic chain resides on the one side of the phenol ring. Accordingly, the phenolic hydroxyl group is "intermediately hindered." The postulated geometry was supported by observing the behavior of the hydroxyl group upon treatment with various electrophiles. The bridging effect is also evidenced by the regioselective Reimer-Tiemann reaction occurring exclusively on the bridgehead carbon of the phenol.



1 R = H, Me

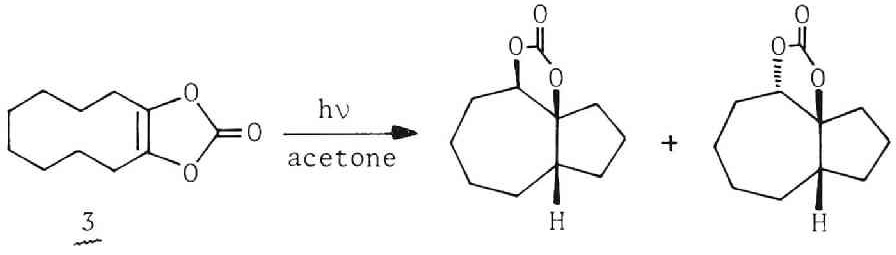
2

The chemistry of phanes[11,13] is now being extended to heterophanes[14] and even to bridged nonbenzenoid aromatics.[15] Thus, the above methodology is applied to the first synthesis of 2,7-nonamethylenetropone (2) from cyclododecanone. The ring current effect was not observed in the nmr spectra of the tropone, but the one of

the corresponding hydroxytropylium ion showed the aromatic character of the seven membered ring clearly. Details are described in Chapter 2.

During the past two decades organic chemists acquired much information of the photochemical behavior of a variety of compounds.[7] Especially, the photochemistry of olefins has provided numerous successes in modern organic syntheses.[16] Irradiation of cyclic olefins larger than eight-membered ring in the presence of sensitizers merely results in the cis⇌trans equilibrium,[17] whereas photoproducts of *cis*-cycloheptene and *cis*-cyclohexene are explained by assuming transient formation of reactive *trans*-olefins. In contrast, cyclopentenes and cyclobutenes undergo hydrogen abstraction only.

Photochemistry of vinylene carbonates,[20] or 1,3-dioxolen-2-one, is a useful tool in organic synthesis. The author discovered that the sensitized irradiation of 3 and 4 brought about the indicated cyclization occurring regioselectively to afford bicyclo-[n.3.0]alkane-1,2-diol derivatives. The transannular hydrogen shift should produce a biradical intermediate, whose recombination must account for the observed bicyclic products. Acyclic vinylene



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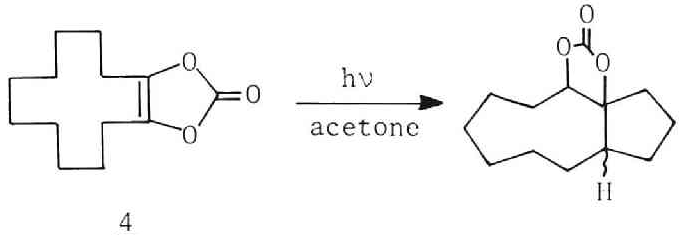

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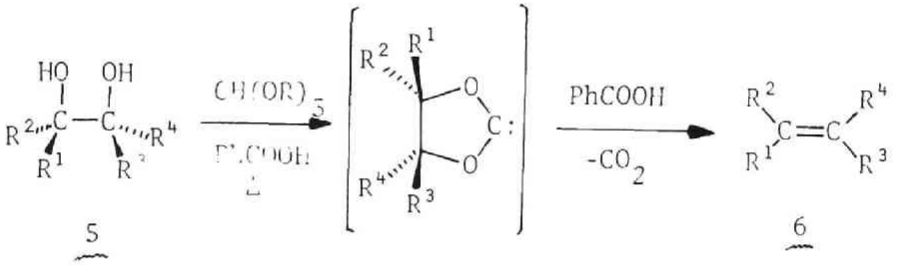
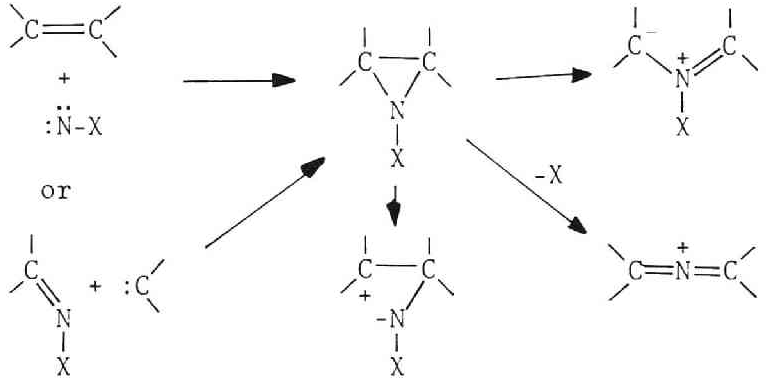
carbonates experience the reduction of the carbon-carbon double bond upon irradiation which is attributed to the biradical intermediates also. The unique photochemical behavior discussed in the latter half of Chapter 3 is ascribed to the excitation of the oxolenone ring. The former half of the Chapter is devoted to a general method of preparing this hetero ring from acyloins which are tautomeric with enediols.[21] The present photocyclization reaction does have a feature which is common to such synthetically important reactions[22] as Hofmann-Loeffler-Freytag reaction, C-H insertion of carbenes and nitrenes, Barton reaction, Remote Oxidation,[23] and so on. Namely, a combination of the regioselective intramolecular hydrogen abstraction and the subsequent C-C bond formation is the key process providing the otherwise inactive methylene group with the ability of C-C bond formation.[24]

In Chapter 4 a stereospecific transformation of diols 5 to olefins 6 is described. Among several methods of olefin synthesis the deoxygenation of pinacols has proved to be conveniently applied to tetrasubstituted ethylene synthesis.[25] For this purpose the one discovered by Eastwood[26] has been found to be facile, effective, and useful preparatively. The process probably involves the formation of 2-ethoxy-1,3-dioxolane intermediates. Benzoic acid promotes the elimination of ethanol from the C-2 of the dioxolane to give a carbene intermediate which decomposes to carbon dioxide



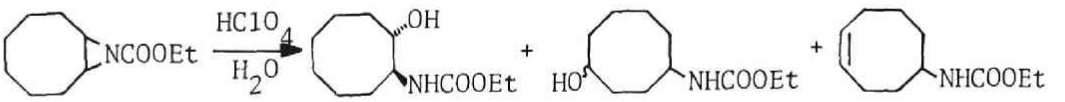
and olefin with retention of the skeletal geometry. By means of the present procedure *trans*-cyclooctene, *cis*-cyclodecene, and an artificial estrogen, stilbestrol, have been prepared.

The following four chapters are mainly concerned with the synthetic applications of aziridines,[9] or ethylenimines, having in common a nitrogen containing three-membered ring. The compounds are formally the adducts of nitrenes with olefins or of carbenes with imines. Each of them involves high strain energy (*ca.* 14 kcal/mol)[27] and therefore the remarkable reactivity. A *priori* we expect two modes of reactions initiated by heterolytic fission of either C-N bond or C-C bond. In the C-N bond cleavage we have to consider both the regioselectivity of ring fission and the stereochemistry of the reacting ring carbon (inversion or retention). Heterolysis of C-C bond proceeds stereospecifically and provides an azomethine ylide,[28] a kind of 1,3-dipole, which undergoes cycloaddition on several olefins to yield new heterocycles.[29] Alternative C-C bond cleavage involves an oxidative procedure which leaves positive charge on nitrogen[6] and opens the aziridine ring to afford 2-azaallenyl cation.



As is seen in the above paragraph the transannular reaction is one of effective methods in the synthesis and is often encountered with the reactions of medium ring compounds.[30] In order to obtain

the information on the transannular hydride shift in the solvolysis,[31] the aziridine 7 was exposed to aqueous perchloric acid. The transannular products were obtained as major ones along with a *trans*-2-amino alcohol. In contrast, the aziridine 8 gave a *trans*-2-amino alcohol derivative almost exclusively. These transformations are described in Chapter 5.



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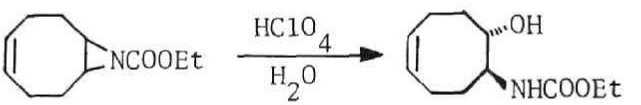

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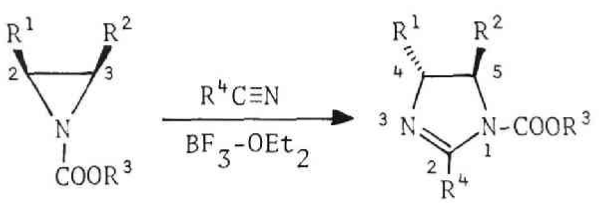
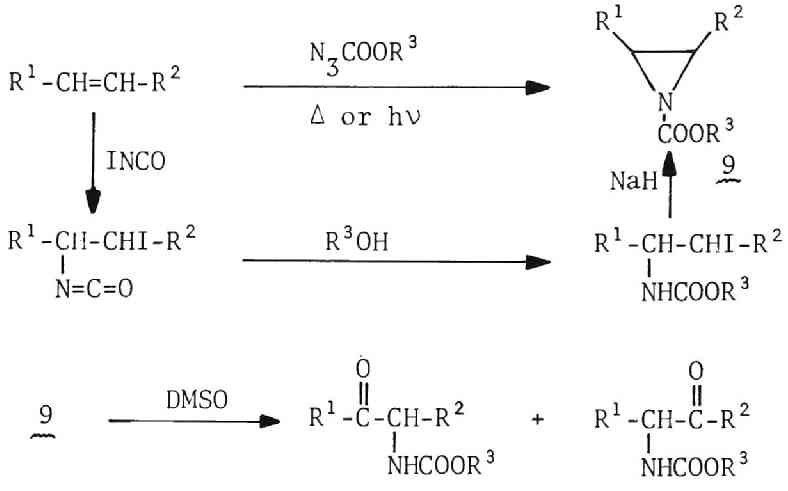
Chapter 6 deals with a novel synthesis of 1-alkoxycarbonyl-2-imidazolines (10) by means of the acid-catalyzed reaction of N-alkoxycarbonylaziridines (9) in nitriles. Boron trifluoride-etherate was found to be an effective catalyst. The resultant imidazolines are formally the cycloadducts of nitriles to aziridines. The nitrile addition was found to proceed under S_N2 type C(2)-N bond cleavage (inversion at C(2) of 9) and C(4)-N bond formation of 10. This was evidenced by the stereochemistry of *vic*-diamine derivatives obtained by the hydrolysis of 10.



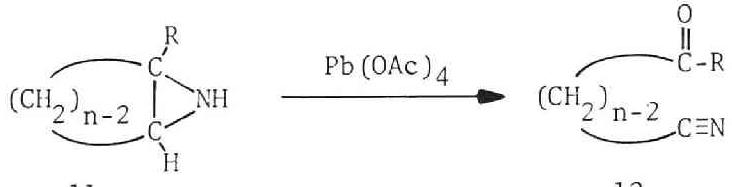
9 10

Synthesis and oxidative ring-opening of the N-ethoxycarbonyl-aziridines (9) are described in Chapter 7. The aziridines are easily accessible (a) by the decomposition of ethyl azidoformate in olefins[5] or alternatively (b) by the treatment of olefin with iodine isocyanate,[32] the successive alcoholysis and base-catalyzed cyclization. The oxidation of thus obtained aziridines with dimethyl sulfoxide has now been found to afford α-alkoxycarbonyl-amino ketones in preparative yields. The possible mechanism of this new reaction of aziridines will be discussed below.



The final Chapter is a contribution to the nitrenium ion chemistry. Nitrogen reactive species of general concern are nitrenes, nitrogen radicals and nitrenium ions.[3,5] The species are often involved in the oxidation of amines with metals in higher valency.[33] Both *cis*- and *trans*-2-phenylcyclopropylamines were oxidized with lead tetraacetate to give *trans*-cinnamaldehyde as the only product, while oxidation of 1-phenylcyclopropylamine resulted in the formation of benzonitrile and ethylene. In contrast, however, oxidation of 2-phenylaziridine resulted in the formation of benzaldehyde. These are all best explained by assuming nitrenium ion species. Extention of the oxidation to 2,3-poly-

methylene bridged aziridines 11 afforded ω-cyano carbonyl compounds 12 in good yields. The unprecedented one-step transformation provides a useful route to the aliphatic compounds which carries a cyano group at one terminal and a carbonyl moiety at an appropriate remote position. Synthesis of the starting aziridines from cycloalkanone oximes is also described.



11 12

n = 8, 11, 12

In brief, the present author has contributed to the following three points:

(1) A novel phenol bridged at 2,6-positions by nonamethylene chain is synthesized and its structure and reactions are studied. The bridge is proved to reside on the one side of the aromatic plane, which is covered by the lipophilic aliphatic chain. In contrast the other side is hydrophilic thanks to the π-electron cloud of the benzene ring and the phenolic hydroxyl group. Accordingly the phenol is a novel kind of surfactant. In a similar way [9](2,7)troponophane is synthesized for the first time, the diamagnetic ring current effect of its hydroxytropylium ion being observed.

(2) A new route to oxolenones is explored. Irradiation of this kind of carbonates derived from ten- and twelve-membered cyclic acyloins provides bicyclic compounds. Remarkably the otherwise inactive polymethylene chain is regioselectively attacked by the olefinic carbons of the oxolenone ring. A useful procedure for converting vicinal diols into olefins has been explored, in which 2-ethoxy-1,3-dioxolanes are key intermediates.

(3) A convenient synthesis of aziridines is established and the reactions are studied with emphasis on transannular reaction and stereochemistry. The investigations result in the discovery of new synthesis of 2-amino alcohols, 2-imidazolines, 1,2-diamines, and α-alkoxycarbonylamino ketones. Remarkably, $RCO(CH_2)_nC{\equiv}N$ type compounds have been obtained from 2,3-polymethyleneaziridines with R group on C(2) by means of new oxidation with lead tetraacetate.

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Chapter 2

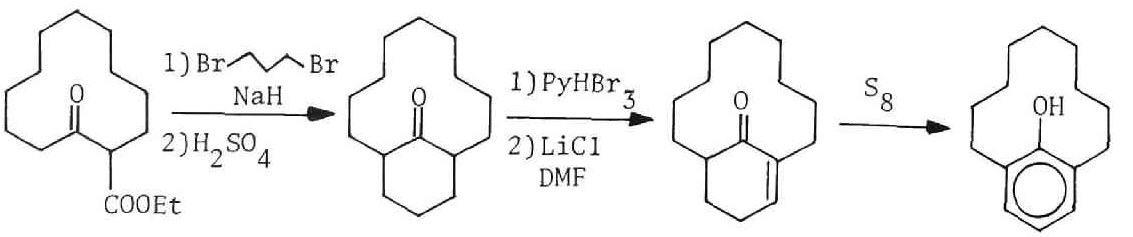
NONAMETHYLENE-BRIDGED PHENOLS AND TROPONES

Abstract---Novel phenols (4 and 6) having the hydroxyl group surrounded by nonamethylene chain are prepared from cyclododecanone. 2,7-Nonamethylene bridged tropone (11) also is obtained by stepwise bromination-dehydrobromination of bicyclo[9.4.1]hexadecan-16-one (7). The aliphatic chain of these phanes is proved to reside on the one side of the respective aromatic ring. Spectroscopic studies indicate that the phenol 6 belongs to "intermediately hindered" phenol. The reactivity of the hindered hydroxyl group and of the strained benzene ring are examined with respect to 6, which is susceptible to methylation and acetylation but not to isopropylation. 12-Methyl[9]metacyclophane (15) is obtained by mesylation of 6, followed by the reduction of the resulting sulfonate. The constraint caused in the conjugate base of 6 by the nonamethylene bridge possibly is responsible for the selectivity in the dichlorocarbene addition giving 16 exclusively. Reaction of 6 with monochlorocarbene affords bridged tropylidene 24 which is easily thermolysed to 3,4-bridged toluene 25 under ring-contraction.

Cyclophanes[1] or bridged aromatics[2] are fascinating compounds owing to their unique physical and chemical properties. The territory of "phanes"[3] now includes heterophanes[4] and bridged non-benzenoid aromatics.[5] Twenty-five years ago Prelog *et al.* examined the effect of the size of the bridge on the UV absorptions of 2,6-polymethylene-4-nitrophenol[6a] and on the reduction potential of 2,6-polymethylenebenzoquinones.[6b] These studies were solely devoted to the static character of the bridged phenols. Recent theoretical and methodological development prompted us to investigate dynamic aspects of the chemistry of bridged phenols. This chapter describes the synthesis of 2,6-nonamethylenephenols and 2,7-nonamethylene bridged tropone.[7] Furthermore the reactivity of these strained systems is discussed.

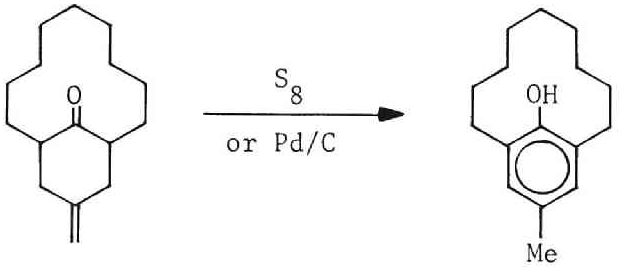
15-Hydroxy[9]metacyclophane (4)

Alkylation of 2-ethoxycarbonylcyclododecaone (1)[8] with 1,3-dibromopropane, followed by hydrolysis and decarboxylation, afforded the bicyclic ketone 2. Bromination with pyridinium hydrobromide perbromide ($PyHBr_3$) and subsequent dehydrobromination (LiCl-DMF) gave the bicyclic enone 3. Dehydrogenative aromatization of 3 was accomplished by heating with sulfur to afford 15-hydroxy[9]metacyclophane (4). 12-Methyl substituted derivative 6 was obtained from the enone 5 by simple dehydrogenation with sulfur or palladium on charcoal. Both 4 and 6 gave no coloration with ferric chloride.



1 2 3 4

This negative phenol test[9] as well as the IR spectrum of 6 shown in Fig 1 suggests that the steric hindrance of the hydroxyl group of 6 is intermediate between 2,6-xylenol and 2,6-di-*tert*-butyl-*p*-cresol (20). The bathochromic absorption of (λ_{max} (EtOH) 286 nm (log ε 3.28)) compared with those of 2,4,6-trialkylphenol (λ_{max} 275-278 nm)[10] should be ascribed to the constraint by the nonamethylene chain bridging the 2- and 6-position of the phenol. UV absorptions in alkaline ethanol are shown in Fig 2 which indicates that as much as 0.5 M sodium hydroxide concentration is required for the extensive ionization of the phenol 6. The difference of the absorption wave length between the phenolic and phenolate forms is 23 nm. These facts also support that 6 should be regarded as a partially hindered phenol according to the definition of Coggeshall *et al.*[10]



5 6

The PMR spectra of 6 as well as 4 are shown in Fig 3. Non-equivalence of the benzylic protons indicates that the nonamethylene chain resides only on the one side of the aromatic ring. This conformation appeared to be maintained up to 196° because the non-equivalence of the benzylic protons remained unchanged. As molecular models suggest, multiplet at δ 0.4-0.5 (2 H) supposedly is ascribed to one of methylene hydrogens on C(4) and C(6). PMR

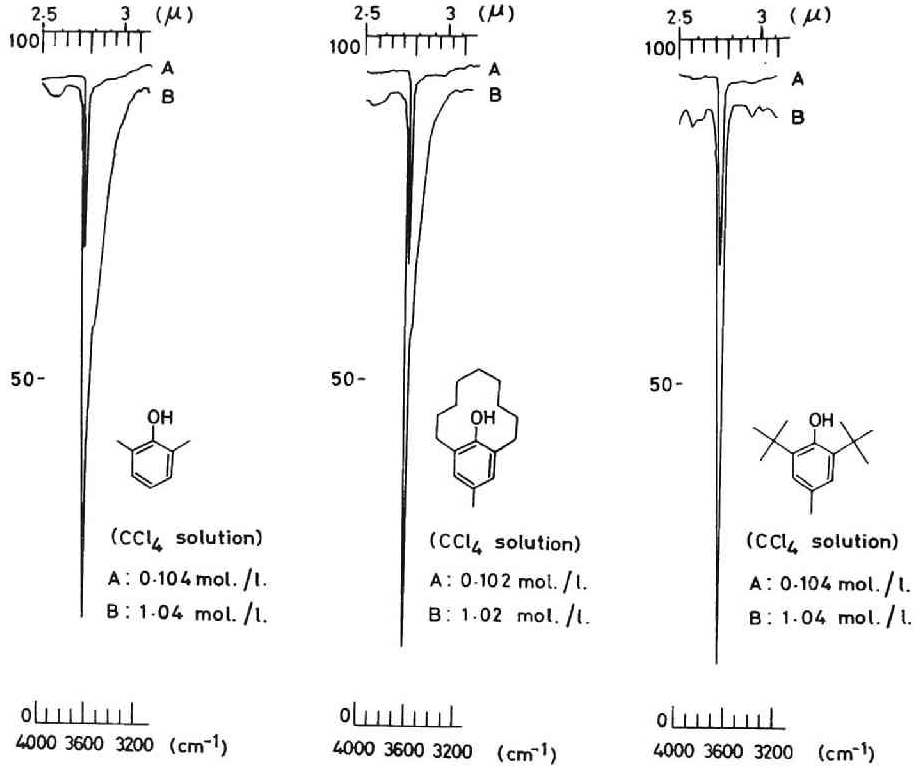


Fig 1 IR spectra of 2,6-xylenol, 6, and 20.

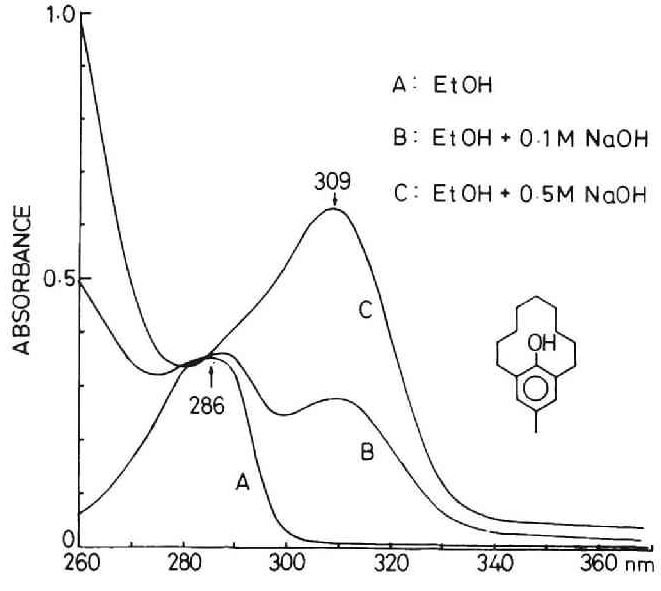


Fig 2 UV spectra of 6 in alkaline ethanol solution.
(A: EtOH, B: 0.1 M NaOH/EtOH, C: 0.5 M NaOH/EtOH)

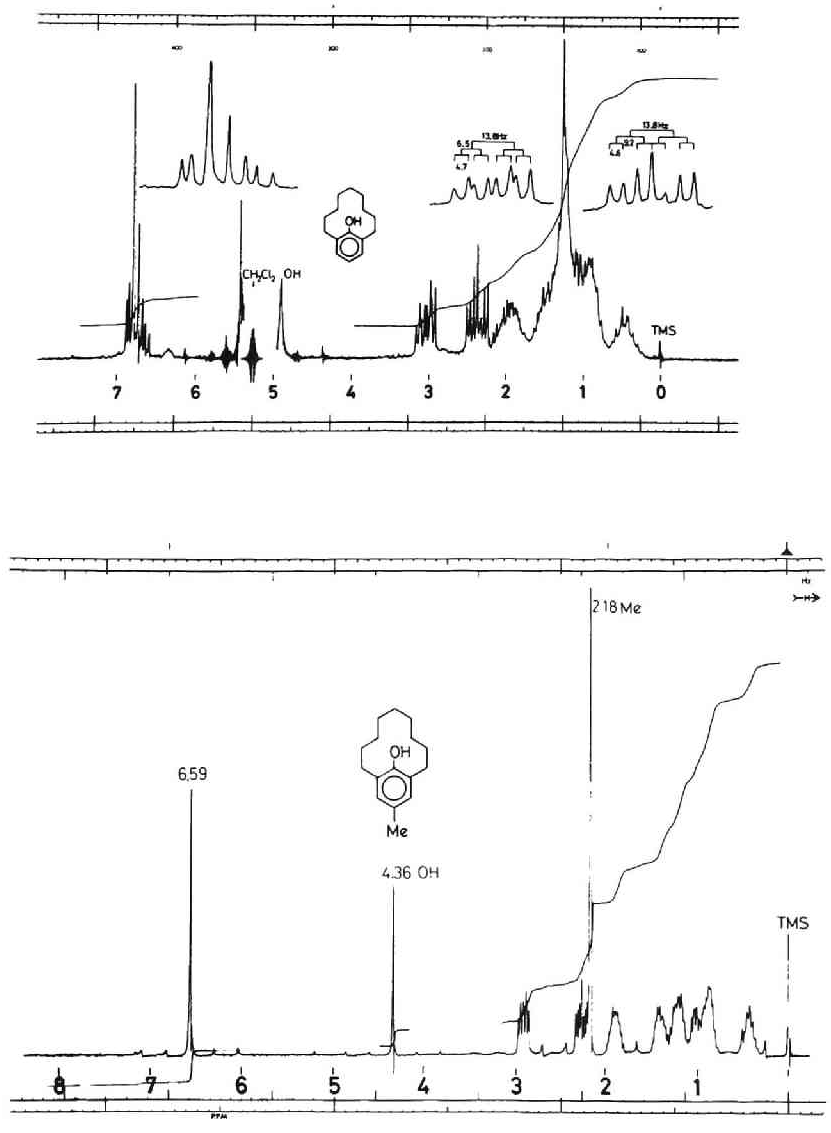
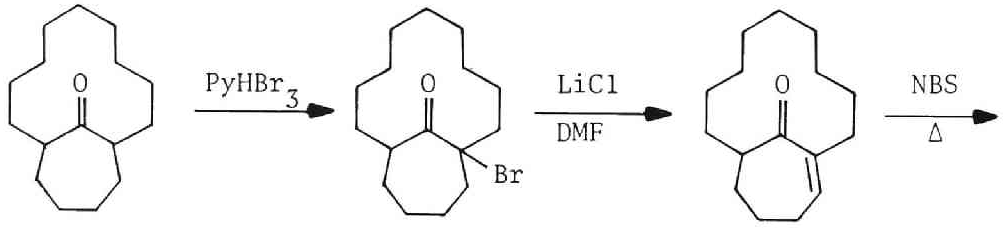


Fig 3 PMR of 4 (upper, 100 MHz, CCl_4, TMS, CH_2Cl_2 standard, r.t.) and 6 (below, 220 MHz, CCl_4, TMS, r.t.).

study using a shift reagent was attempted. Addition of 0.1 equivalent of $Eu(fod)_3$ to 6 in carbon tetrachloride caused a slight down-field shift of the polymethylene signals (0.17 ppm for benzylic and 0.09 ppm for average methylenes). The saturation was observed already at molar ratio of as much as 0.3. The non-linear relationship between the chemical shift change and the amount of $Eu(fod)_3$ suggests that the coordination of the oxygen atom in 6 to Eu is hindered by the nonamethylene chain.

2,7-Nonamethylene Bridged Tropone (11)

While bridged benzotropones have been recorded by Heilbronner *et al.*[11] and recently by American[12] and French[13] chemists, the bridged tropone itself has been unknown. In continuation of our investigation on bridged aromatics, we have synthesized 2,7-nonamethylene bridged tropone and examined its spectroscopic characteristics.



7 8 9

10 11 12

Bromination of bicyclo[9.4.1]hexadecan-16-one (7)[14] with $PyHBr_3$ gave the monobromo ketone 8. Dehydrobromination (LiCl in DMF) afforded the enone 9. Allylic bromination (NBS) gave the unstable dienone 10 which rapidly polymerized on standing at room temperature. The dienone 10 was immediately subjected to the subsequent bromination ($PyHBr_3$) and neutralization (sodium bicarbonate) to yield 2,7-nonamethylenetropone (11).[15a] IR and UV spectra (Experimental) of the compound were consistent with those reported on 2,7-dialkyltropones.[15b] PMR spectra of 11 shown in Fig 4 indicate the non-equivalence of the two benzylic protons. This implies that the nonamethylene chain is fixed to the one side of the tropone ring. Apparent ring current effect of tropone ring was not observed.[16] In contrast, addition of a little more than one equivalent of trifluoroacetic acid caused down-field shift of the olefinic (0.92 ppm) and benzylic (0.12-0.41 ppm) protons, owing to the formation of the tropylium cation (12). The diamagnetic ring current of the tropylium cation was evidenced by the splitting of the polymethylene signals and by the new peaks appearing at δ 0.75 and 0.93 ppm. The diamagnetic ring current was also observed in the ^{13}C-NMR (CMR) spectra of 11 summarized in Table 1. Upon addition of CF_3COOH peaks at 26.452 and 26.634 ppm shifted to higher field (*ca.* 0.12-0.30 ppm) inspite of the resulting positive charge[17] of the tropylium cation.

Reaction of 6 with Electrophiles

Since the phenol 6 is more easily prepared than 4, the reactivity of the hydroxyl group surrounded by nonamethylene chain was examined with respect to 6. Treatment of 6 with sodium hydride and then with methyl iodide provided the methyl ether 13, while the reaction with isopropyl bromide failed. The more bulky isopropyl group cannot approach the phenoxy anion sheltered by the nonamethylene chain. Meanwhile, acetylation of 6 was accomplished with acetic anhydride-pyridine.

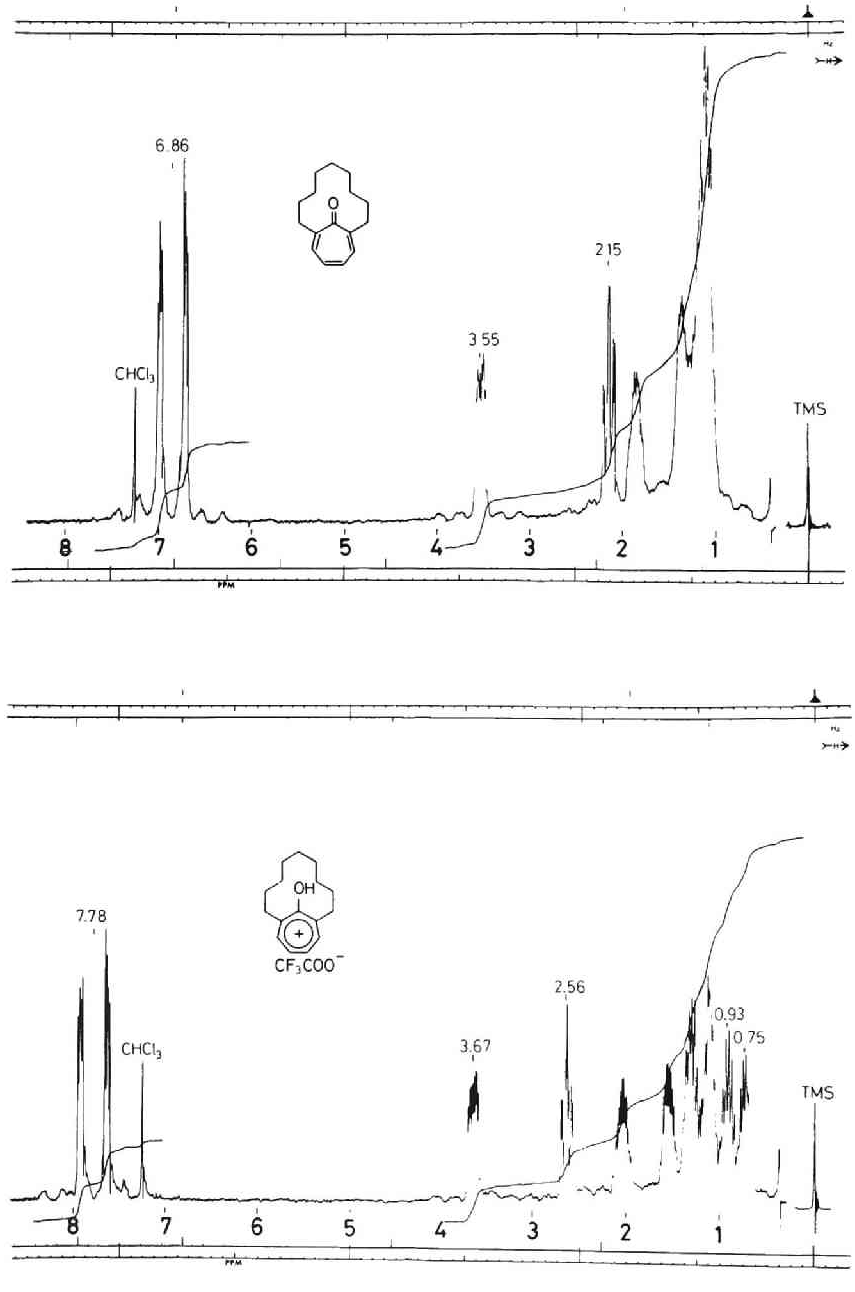
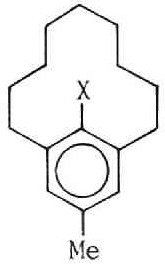


Fig 4 PMR of 11 (upper) and 12 (below) (220 MHz, $CDCl_3$, TMS, r.t.).

Mesylation of 6 by means of sodium hydride and methanesulfonyl chloride, followed by reduction of the resulting sulfonate with sodium metal in liquid ammonia, yielded 12-methyl[9]metacyclophane (15) along with the recovered phenol 6. The PMR spectrum (Experimental) clearly shows that the nonamethylene chain is swinging up and down the aromatic ring. The motion of the chain does not seem to be frozen even at -112°.[18]



13: X = OMe
14: X = OAc
15: X = H

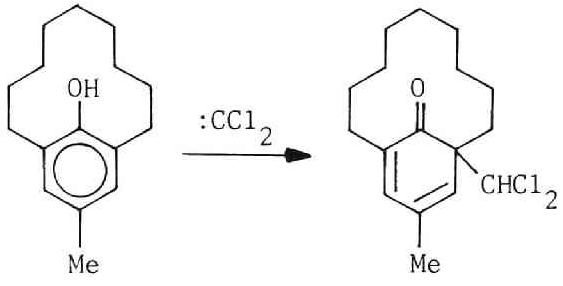
Table 1. CMR of 11 ($CDCl_3$, TMS standard, taken by Mr. Hirose, JEOL Co.).

Peak No.	Chemical shift (ppm)	Height	Chemical shift (ppm) (CF_3COOH)	Height
1	23.297	3764	23.479	3543
2	23.600	6268	23.661	5621
3	26.452	6867	26.331	10576
4	26.634	8307		
5	36.705	6578	37.252	4275
6	130.746	7164	134.143	5237
7	132.809	6210	138.269	4027
8	150.100	2535	151.192	2149
9	188.808	1189	189.233	788

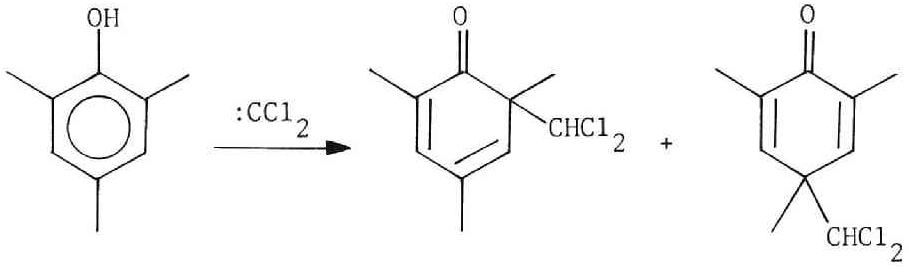
Reaction of 6 with Halocarbenes

Reactivity of the bridged phenol in the Reimer-Tiemann reaction deserves to be examined because the bridging effect and the accompanying strain should affect the reaction course. Dichlorocarbene generated by use of the phase-transfer technique[19] reacted with 6 to yield the dienone 16, whereas the less hindered phenol 17 gave a mixture (4:1) of 18 and 19. The more hindered phenol 20 afforded cross-conjugated cyclohexadienone 21 exclusively, probably because the *ortho* positions are sterically hindered by the two *tert*-butyl groups. The fact that the bridged phenol 6 yielded only 16 may be ascribed to the constraint by the nonamethylene chain. The strained system[20] prefers sp^3 bridgehead carbon rather than the planar sp^2 carbon. Thus the reaction proceeded between 22 and dichlorocarbene to yield only 16.

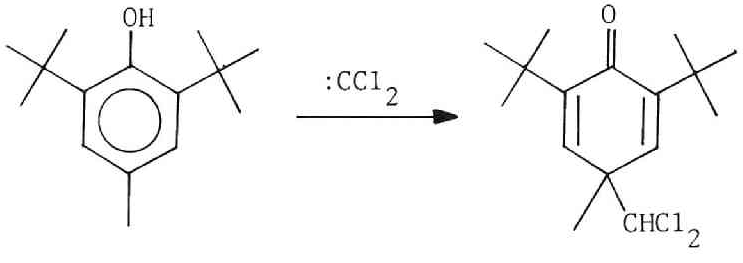
The reaction of monochlorocarbene[21] with the bridged phenol was studied to obtain the ring-expanded bridged tropone 23. The phenol 6 in dichloromethane was treated with three equivalents of n-butyllithium, giving hydroxytropylidene (24). Gas-chromatographic separation (190-200°) of crude 24 caused the decomposition of the compound and the isolated product proved to be *ortho*-bridged toluene 25. Supposedly the thermal fragmentation[22] is especially facilitated by the constraint of the nonamethylene chain. The reaction path was attested by the reaction of the bridged tropone 11 with n-butyllithium, followed by the thermolysis, affording benzocycloundecene (27), whereas the more hindered phenol 20 gave the ring-expanded tropone 28. The subsequent nucleophilic addition of n-butyllithium to the carbonyl group of 28 is possibly prevented by the neighboring *tert*-butyl groups.[23]



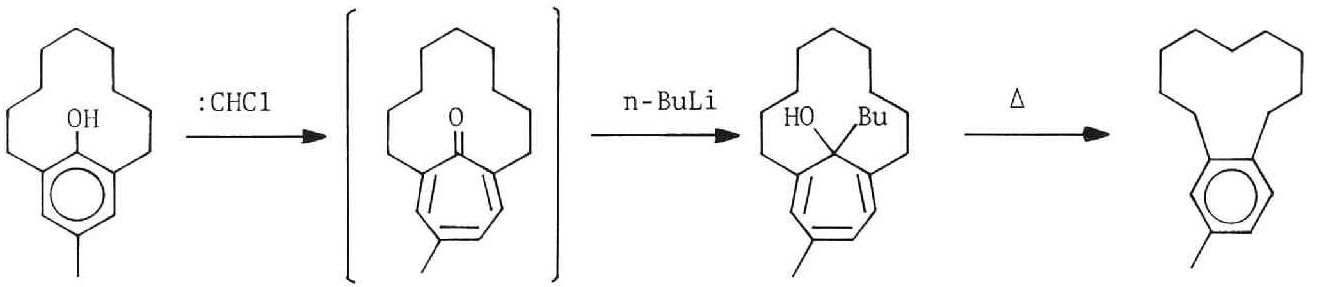
6 16 22



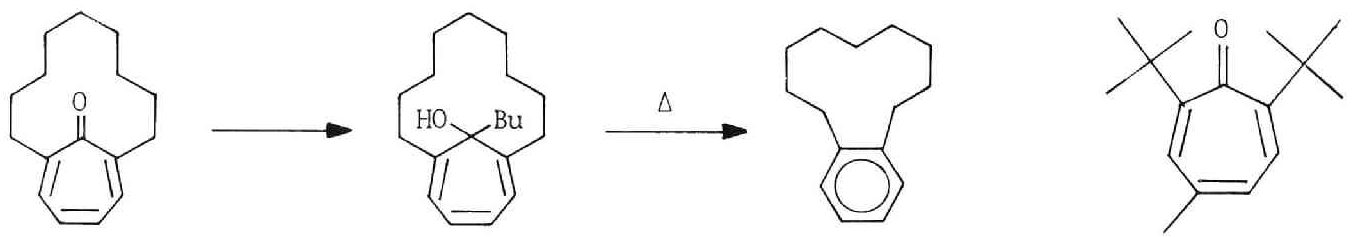
17 18 19



20 21



6 23 24 25



11 26 27 28

Experimental

Following instrumentation and abbreviations are pertinent to the all experimental parts of this Thesis. PMR spectra were taken on a JEOL C-60-H (60 MHz), on a Varian EM 360 (60 MHz), on a Varian HA-100D (100 MHz), or on a Varian HR-220 spectrometer (220 MHz) in carbon tetrachloride or deuteriochloroform solution. The chemical shifts are recorded in δ values relative to tetramethylsilane as an internal standard. The data are given in the order of multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = unresolved multiplet), integration, and assignment. IR spectra were recorded on a Shimadzu IR-27-G spectrometer, UV spectra on a Shimadzu MPS-50L spectromer, and MS spectra on a Hitachi RMU-6L machine (80 eV). Microanalyses were performed at the Elemental Analyses Center of Kyoto University or at the Department of Industrial Chemistry by Mrs. K. Fujimoto. All the temperatures are uncorrected.

Bicyclo[9.3.1]pentadecan-15-one (2). A mixture of xylene (28 ml) and 2-ethoxycarbonylcyclododecanone (1) (12.7 g, 50 mmol) was added dropwise to the suspension of sodium hydride (2.40 g, 100 mmol) in xylene mixture (10 ml) at room temperature (*ca.* 45 min). After stirring was continued for an hour trimethylene dibromide (10.0 g, 50 mmol) was added rapidly and the reaction mixture was heated at 85-92° for 22 hr. Work-up gave a viscous oil (9.10 g), which was dissolved in a mixture of acetic acid (100 ml), water (40 ml) and concentrated sulfuric acid (30 ml). Heating the solvent to reflux for 15 hr, the subsequent work-up and fractional

distillation at 103-105°/0.1 mm gave cis and trans mixture of 2 (3.76 g, 34%), which solidified on standing, mp 58-60° (methanol). IR (Nujol): 1710, 1122, 1060, 740, 725 cm^{-1}; PMR (CCl_4): δ 0.5-3.1 (m); MS: *m/e* 222 (M^+).

Found: C, 81.1; H, 12.0. Calcd for $C_{15}H_{26}O$: C, 81.0; H, 11.8%.

Bicyclo[9.3.1]-$\Delta^{1(14)}$-pentadecen-15-one (3). Pyridinium hydrobromide perbromide (775 mg, 2.4 mmol) was added to the ketone 2 (538 mg, 2.4 mmol) in acetic acid (4 ml) at 50° under a nitrogen atmosphere. The reaction mixture was heated at 70° for 20 hr. Another crop of $PyHBr_3$ (500 mg) was added and the heating was continued for 2 days. Water was then added and the mixture was extracted with n-hexane. Evaporation of the solvent gave crystallines (710 mg). Recrystallization from methanol gave 1-bromobicyclo[9.3.1]pentadecan-15-one (340 mg, 47%).

This compound was obtained by an alternative method. Bromine (2.1 g, 0.7 ml, 13 mmol) was added to the solution of the bicyclic ketone 2 (2.22 g, 10 mmol) in acetic acid (6 ml) at room temperature. After the addition was complete the mixture was heated at 70° for 24 hr. Work-up gave a pale yellow oil (*ca.* 2.8 g) which solidified. Recrystallization from methanol afforded pale yellow needles (1.01 g, 34% yield), mp 84.0-84.5°. IR (Nujol): 1725 cm^{-1}; PMR ($CDCl_3$): δ 0.5-3.1 (m); MS: *m/e* 300 (M^+), 302 ($M^+ + 2$).

Found: C, 59.6; H, 8.5. Calcd for $C_{15}H_{25}BrO$: C, 59.8; H, 8.4%.

The crystalline bicyclic bromoketone (1.00 g, 3.3 mmol) was heated with lithium chloride (200 mg, 4.7 mmol) in DMF (12 ml) for 4.5 hr at 93°. Work-up afforded an oil (660 mg, 88%) which was practically pure by GLC assay. Distillation at 120-125° (bath temperature)/0.1 mm, followed by recrystallization from ethanol, gave an analytical sample, mp 67-68°. IR (neat): 1674, 783, 734 cm^{-1}; PMR (CCl_4): δ 1.0-3.0 (m, 23 H, methylenes and methine), 6.2-6.4 (m, 1 H, -CH=); MS: *m/e* 220 (M^+).

Found: C, 81.6; H, 10.8. Calcd for $C_{15}H_{24}O$: C, 81.8; H, 11.0%.

15-Hydroxy[9]metacyclophane (4). The bicyclic enone 3 (186 mg, 0.85 mmol) was heated under a nitrogen atmosphere with sulfur (28.6 mg, 0.89 mmol) at 160-200° for 30 min. Extraction with ether and the subsequent purification by preparative TLC (PLC) (silica gel, n-hexane elution, R_f 0.1-0.2) afforded the bridged phenol 4 (91 mg, 49% yield), bp 130-140° (bath temperature)/0.07 mm. IR (CCl_4): 3650, 3040, 1588, 1190 cm^{-1}; IR (neat): 3570, 3040, 1590, 1190, 770, 745 cm^{-1}; MS: *m/e* (relative abundance) 218 (M^+, 82), 161 (28), 147 (33), 121 (61), 120 (100), 107 (53), 91 (46).

Found: *m/e* 218.1664 (M^+). Calcd for $C_{15}H_{22}O$: *m/e* 218.1671.

The exo-methylene ketone 5. To a mixture of cyclododecanone (18.2 g, 0.1 mol) and sodium hydride (2.4 g, 0.1 mol) suspended in benzene (30 ml) 3-chloro-2-chloromethylpropene (12.5 g, 0.1 mol) was added all at once and the mixture was heated to boil for 3 days. Addition of water (100 ml), followed by extraction with n-hexane and subsequent work-up, gave the ketone 5 (8.2 g, 34%), bp 125-130°/2 mm, mp 53-58° (methanol) (perhaps a mixture of cis and trans isomers). IR (Nujol): 3080, 1710, 1652, 890, 740 cm^{-1}; NMR (CCl_4): δ 0.6-2.9 (m, 24 H, methylenes and methines), 4.7-4.9 (m, 2 H, $=CH_2$); MS: *m/e* 234 (M^+).

Found: C, 81.9; H, 11.2. Calcd for $C_{16}H_{26}O$: C, 82.0; H, 11.2%.

15-Hydroxy-12-methyl[9]metacyclophane (6). The ketone 5 (2.75 g, 11.8 mmol) was heated under a nitrogen atmosphere with sulfur (0.400 g, 12.5 mmol) at 200-220° for 4.5 hr. The organic substances were taken into ether and distilled at 145-149°/0.5 mm, affording the crystalline bridged *p*-crseol 6 (1.39 g, 51%), mp 82-

83° (n-hexane). IR (KBr): 3495, 3005, 1605, 1193, 836, 752, 722 cm^{-1}; IR (Nujol): 3475, 1191, 760 cm^{-1}; MS: *m/e* (relative abundance) 232 (M^+, 100), 161 (20), 147 (16), 135 (44), 134 (63), 121 (53), 91 (45).

Found: C, 82.6; H, 10.4. Calcd for $C_{16}H_{24}O$: C, 82.7; H, 10.4%.

1-Bromobicyclo[9.4.1]hexadecan-16-one (8). The bicyclic ketone 7 (664 mg, 2.81 mmol) was admixed with acetic acid (7 ml) and $PyHBr_3$ (1.02 g, 3.20 mmol) and the mixture was heated under a nitrogen atmosphere at 60° for 44 Hr. When the mixture was cooled in an ice bath, white needles (715 mg, 81%) of 8 were obtained, mp 156-157° (acetic acid). IR (Nujol): 1710 cm^{-1}; PMR ($CDCl_3$): δ 0.7-3.3 (m); MS: *m/e* 314 (M^+), 316 (M^++2).

Found: C, 60.9; H, 8.7. Calcd for $C_{16}H_{27}BrO$: C, 61.0; H, 8.6%.

Bicyclo[9.4.1]-$\Delta^{1(15)}$-hexadecen-16-one (9). A mixture of the bromo ketone 8 (823 mg, 2.61 mmol), lithium chloride (150 mg, 3.53 mmol), and DMF (11 ml) was heated at 130-140° for 13 hr. Work-up yielded an oil (571 mg, 94%), bp 120-130° (bath temperature)/0.08 mm. IR (neat): 1683, 1632 cm^{-1}; PMR (CCl_4): δ 0.8-3.2 (m, 25 H, methylenes and methines), 6.0-6.4 (AB quartet, J = 4.8, 9.0 Hz, 1 H, -CH=); MS: *m/e* 234 (M^+).

Found: C, 81.9; H, 11.2. Calcd for $C_{16}H_{26}O$: C, 82.0; H, 11.2%.

2,7-Nonamethylenetropone (11). A solution of the enone 9 (1.55 g, 6.64 mmol), NBS (1.55 g, 8.71 mmol), and a small amount (*ca.* 10 mg) of benzoyl peroxide in carbon tetrachloride (20 ml) was heated under a nitrogen atmosphere at 85° for 6 hr. After cooling in an ice bath the precipitates were filtered off, and the

solution was concentrated *in vacuo* by warming at 40° for 20 min. The residue was mixed with $PyHBr_3$ (2.30 g, 7.19 mmol) in acetic acid (30 ml) and heated under a nitrogen atmosphere for 1 hr at 90-95°. Neutralization of the reaction mixture with aqueous sodium bicarbonate, followed by extraction with benzene and the subsequent PLC purification (silica gel, benzene/n-hexane 1:1 elution, R_f 0.4-0.6), afforded an oily bridged tropone (11) (535 mg, 35%). Distillation at 150-180°/0.2 mm, followed by recrystallization from n-hexane, yielded an analytical sample, mp 60-64.5°. IR (KBr): 1620, 1575, 1515, 1070, 790, 730 cm^{-1}; IR (neat): 1675, 1624, 1588, 1515, 1075, 795, 738 cm^{-1}; MS: *m/e* (relative abundance) 230 (M^+, 85), 173 (48), 159 (86), 147 (100), 145 (81), 134 (96), 120 (79), 107 (86), 105 (61), 91 (83); UV (EtOH): λ_{max} (log ε) 239 (4.31), 314 (3.78).

Found: C, 83.3; H, 9.8. Calcd for $C_{16}H_{22}O$: C, 83.4; H, 9.6%.

Methyl ether of the bridged phenol 6. To a suspension of sodium hydride (25 mg, 1.0 mmol) in tetrahydrofuran (THF) the phenol 6 (232 mg, 1.0 mmol) in THF was added drop by drop. After 1 hr methyl iodide (0.2 ml) was added at room temperature and the mixture was heated at 76° for 4 hr. Usual work-up and distillation at 120-125° (bath temperature)/2 mm gave 13 (212 mg, 86%), which solidified on standing, mp 61-62° (n-hexane). IR (neat): 1218, 1022 cm^{-1}; PMR (CCl_4): δ 0.2-3.4 (m + s (δ 2.23), 21 H, methylenes and methyl), 3.63 (s, 3 H, MeO-), 6.70 (s, 2 H, aromatic); MS: *m/e* 246 (M^+).

Found: C, 82.9; H, 10.5. Calcd for $C_{16}H_{26}O$: C, 82.9; H, 10.6%.

Acetate of 6. A mixture of the phenol 6 (260 mg, 1.14 mmol) and pyridine (3.5 ml) was added to sodium hydride (55 mg, 2.3 mmol). The resulting solution was stirred for 1 hr, treated with acetic anhydride (0.2 ml) and then heated to reflux for 2 hr. Usual work-up yielded a solid 14 (213 mg, 71%), mp 85.5-86.5° (methanol).

IR (Nujol): 1763, 1220, 1185, 905 cm^{-1}; PMR (CCl_4): δ 0.2-3.0 (m + two s (δ 2.20, 2.26), 24 H, methylenes and methyls), 6.71 (s, 2 H, aromatic); MS: *m/e* 274 (M^+).

Found: C, 79.0; H, 9.6. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6%.

12-Methyl[9]metacyclophane (15). The phenol 6 (232 mg, 1.0 mmol) in THF (1 ml) was treated with sodium hydride (50 mg, 2.0 mmol) suspended in THF (1 ml). Methanesulfonyl chloride (150 mg, 1.3 mmol) was then added at room temperature and the mixture was worked up after 13 hr. The crude sulfonate (380 mg) was dissolved in THF (5 ml) and liquid ammonia (50 ml), and sodium metal (100 mg, 4.0 mol) was added at -78°. The solution was gradually warmed up to room temperature until most of ammonia was evaporated. Usual work-up and the subsequent purification of the product on PLC (silica gel, n-hexane elution, R_f 0.45) gave 12-methyl[9]metacyclophane (15) (90 mg, 75% yield based on the consumed 6) along with the recovered phenol (R_f 0.15, 103 mg, 44%). The physical properties of 15 are as follows: bp 115-120°/0.06 mm; IR (neat): 3030, 1606, 838, 705 cm^{-1}; PMR (CCl_4): δ 0.5-2.3 (m, 14 H, methylenes), 2.30 (s, 3 H, Me), 2.65 (t, 4 H, benzylic methylenes), 6.68 (s, 2 H, C(11)-H and C(13)-H), 6.94 (s,1 H, C(15)-H); MS: *m/e* (relative abundance) 216 (M^+, 95), 201 (15), 173 (24), 159 (34), 145 (100), 131 (47), 120 (59), 119 (58), 118 (57), 105 (99), 91 (46).

Found: C, 88.8; H, 11.1. Calcd for $C_{16}H_{24}$: C, 88.8; H, 11.2%.

Reaction of 6 with dichlorocarbene. To a mixture of the bridged phenol 6 (223 mg, 1 mmol), Cetrimide (36 mg, 0.1 mmol) and chloroform (0.40 ml, 5 mmol) 50% aq sodium hydroxide (200 mg of sodium hydroxide and 0.2 ml of water) was added dropwise (*ca.* 13 min) under a nitrogen atmosphere and vigorous stirring at 50°. Stirring was continued for 4 hr (50-55°). The mixture was neutralized with dil hydrochloric acid and extracted with ether.

Work-up afforded the cyclohexadienone 16 (240 mg, 76%), which was gas-chromatographically pure. Analytical sample was obtained by PLC (alumina, n-hexane elution, R_f 0.45-0.5) followed by recrystallization from ethanol, mp 127-129°. IR (KBr): 3040, 1655 (sh), 1646, 1228, 814, 770, 748, 720 cm^{-1}; PMR (CCl_4): δ 0.8-3.3 (m + d (δ 1.98, J = 1.2 Hz), 21 H, methylenes and methyl), 6.07 (s,1 H, $-CHCl_2$), 6.37 (m, 1 H, -CH=), 6.69 (m, 1 H, -CH=); MS: *m/e* 314 (M^+), 316 ($M^+ + 2$), 318 ($M^+ + 4$); UV (EtOH): λ_{max} (log ε) 317 (3.35).

Found: C, 64.7; H, 7.6. Calcd for $C_{17}H_{24}Cl_2O$: C, 64.8; H, 7.7%.

Reaction of the hindered phenol 20 with dichlorocarbene. The phenol 20 (220 mg, 1 mmol) was treated with chloroform (0.4 ml, 5 mmol), 50% aq sodium hydroxide (0.25 ml, 5 mmol) and Cetrimide (4 mg, 0.01 mmol) as described above. Work-up, followed by PLC purification (silica gel, n-hexane elution, R_f 0.35-0.55), afforded white needles (235 mg, 78%) of 21, mp 83-84° (ethanol). IR (Nujol): 1665, 1646, 1249, 928, 902, 880, 769, 731 cm^{-1}; PMR (CCl_4): δ 1.24 (s, 18 H, *t*-Bu), 1.40 (s, 3 H, Me), 5.54 (s, 1 H, $CHCl_2$), 6.44 (s, 2 H, -CH=); MS: *m/e* 302 (M^+), 304 ($M^+ + 2$), 306 ($M^+ + 4$).

Found: C, 63.4; H, 8.0. Calcd for $C_{16}H_{24}Cl_2O$: C, 63.4; H, 8.0%.

Reaction of mesitol (17) with dichlorocarbene. Mesitol (545 mg, 4 mmol) was subjected to the dichlorocarbene reaction described as above. Work-up and the separation of the products by PLC (silica gel, n-hexane elution) gave the cyclohexadienone 18 (236 mg, 59%, R_f 0.4-0.55) and the cross-conjugated cyclohexadienone 19 (67 mg, 17%, R_f 0.15-0.25).[24] IR (neat) of 18: 1670 (sh), 1650, 1234, 889, 829, 786, 742 cm^{-1}; PMR (CCl_4) of 18: δ 1.24 (s, 3 H, Me), 1.87 (s, 3 H, Me), 2.02 (d, J = 2.1 Hz, 3 H, Me), 5.94 (s, 1 H, $CHCl_2$), 6.14 (s, 1 H, -CH=), 6.65 (s, 1 H, -CH=). IR (neat) of 19: 1670, 1638, 1210, 905, 778, 757 cm^{-1}; PMR (CCl_4)

of 19: δ 1.38 (s, 3 H, Me), 1.92 (s, 6 H, Me), 5.58 (s, 1 H, $CHCl_2$), 6.58 (s, 2 H, -CH=).

Reaction of 6 with monochlorocarbene. n-Butyllithium (3 mmol) in n-hexane was added dropwise (10 min) to the dichloromethane (4 ml) solution of the phenol 6 (232 mg, 1.0 mmol) at room temperature under a nitrogen atmosphere. Stirring was continued for 5 hr. Work-up followed by PLC purification (silica gel, benzene/n-hexane 1:1 elution) yielded the recovered phenol 6 (91 mg, 39%, R_f 0.50-0.65) and the bridged hydroxytropylidene 24 (100 mg, 55% based on the consumed phenol, R_f 0.70-0.85), bp 145-150° (bath temperature)/0.1 mm. IR (neat): 3640, 1684, 1630, 1210, 1128, 850, 810 cm^{-1}; PMR (CCl_4): δ 0.5-3.0 (m + s (δ 1.96), 31 H, methylenes, methyl and OH), 5.4-5.8 (ABM pattern, J_{AB} = 6.9 Hz, 3 H, -CH=); MS: *m/e* (relative abundance) 302 (M^+, trace), 245 (M^+ - Bu, 57), 105 (100). Since the isolation of 24 in completely pure state failed due to the instability to heat or to a trace of acid, satisfactory elemental analysis of the compound was not obtained.

Thermolysis of 24. This was performed on a JEOL JGC 1100 (helium gas, 0.55 kg/cm^2, injection temperature 290°, detector temperature 145°, column (High Vacuum Silicone SE 30, 25%, 1 m) temperature 190°) gas-chromatograph, and the product 25 was collected, bp 110-115° (bath temperature)/2 mm. IR (neat): 3050, 3010, 1611, 1500, 1348, 878, 810 cm^{-1}; PMR (CCl_4): δ 0.7-2.2 (m, 14 H, methylenes), 1.35 (s, 3 H, Me), 2.66 (t, J = 6.4 Hz, 4 H, benzylic), 6.7-7.0 (m, ABM pattern, J_{AB} = 7.9 Hz, 3 H, aromatic); MS: *m/e* (relative abundance) 216 (M^+, 63), 145 (52), 119 (100), 118 (53), 105 (40).

Found: C, 89.1; H, 11.4. Calcd for $C_{16}H_{24}$: C, 88.8; H, 11.2%.

The collection of the more volatile component (C_5) was futile.

Benzocycloundecene (27). The bridged tropone 11 (230 mg,

1 mmol) was treated with n-butyllithium (1.5 mmol). Work-up gave a bridged hydroxytropylidene 26. IR (neat): 3640, 3550, 3040, 1645, 1130, 748 cm^{-1}; PMR (CCl_4): δ 0.6-3.2 (m, 18 H, methylenes and OH), 5.7-6.3 (m, A_2B_2 pattern, 4 H, -CH=); MS: *m/e* 288 (M^+).

Found: *m/e* 288.2457 (M^+). Calcd for $C_{20}H_{32}O$: *m/e* 288.2453.

The hydroxytropylidene 26 was thermolyzed as above. An oily product 27 (26%) was collected, bp 115-120° (bath temperature)/3 mm. IR (neat): 3070, 3020, 1493, 750 cm^{-1}; PMR (CCl_4): δ 0.6-1.9 (m, 14 H, methylenes), 2.56 (t, J = 6.0 Hz, 4 H, benzylic), 6.72 (br s, 4 H, aromatic); MS: *m/e* (relative abundance) 202 (M^+, 72), 131 (63), 118 (54), 105 (100), 104 (91), 91 (49).

Found: *m/e* 202.1737 (M^+). Calcd for $C_{15}H_{22}$: *m/e* 202.1722.

2,7-Di-tert-butyl-4-methyltropone (28). This was obtained by the reaction of 2,6-di-*tert*-butyl-4-methylphenol (110 mg, 0.5 mmol), n-butyllithium (1.5 mmol) and dichloromethane (2 ml) at -78°. Work-up and the subsequent PLC purification yielded 28 (45 mg, 39% yield) along with an unidentified product (39 mg). IR (neat) of 28: 3010, 1635, 1615, 1483, 1377, 1363, 1261, 872, 839, 820 cm^{-1}; PMR (CCl_4): δ 1.31 (s, 18 H, *t*-Bu), 2.18 (s, 3 H, Me), 4.2-4.8 (m, ABM pattern, J_{AB} = 6.4 Hz, 3 H, =CH-); MS: *m/e* 232 (M^+).

Found: C, 82.5; H, 10.5. Calcd for $C_{16}H_{24}O$: C, 82.7; H, 10.4%.

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Chapter 3

PHOTOCHEMISTY OF 4,5-DISUBSTITUTED 1,3-DIOXOLEN-2-ONES

Abstract---Benzene-sensitized photoreaction of 4,5-dipropyl (2a) and 4,5-tetramethylene-1,3-dioxolen-2-one (2b) in isopropyl alcohol gives the reduction products, *cis*- (5) and *trans*-4,5-disubstituted 1,3-dioxolan-2-one (6). The irradiation of octa- (2d) and deca-methylene-bridged vinylene carbonate (2e) results in transannular hydrogen atom transfer from a methylene group to the olefinic bond and the subsequent recombination affording tricyclic products, 9, 10, and 19. Examination of the stereochemistry of the products has indicated the participation of a biradical intermediate.

1,3-Dioxolen-2-ones (vinylene carbonates) are useful synthetic intermediates.[1] Recent reports deal with the photochemical dimerization[2] as well as cycloaddition reaction to olefins[3] and acetylenes.[4] We first wanted to obtain a general method of the preparation of 4,5-disubstituted derivatives and then proceeded to examine the photochemical behavior[5] of the derivatives.

Preparation of 4,5-disubstituted 1,3-dioxolen-2-ones

The known route to vinylene carbonates is consisted of chlorination of ethylene carbonates and subsequent dehydrochlorination.[6] Vinylene carbonates are carbonic acid esters of ene-diols which are tautomeric with acyloins.[7] Treatment of an acyloin 1 with phosgene in the presence of pyridine afforded monochlorinated ethylene carbonate 3. Direct distillation of 3 caused thermal dehydrochlorination to give a crude vinylene carbonate 2 (Scheme 1). As the NMR spectrum showed contamination by exocyclic isomer(s), the crude carbonate 2 was converted to a pure form by heating the mixture dissolved in xylene with *p*-toluenesulfonic acid. The resulting 2 showed satisfactory NMR signals (no olefinic protons).

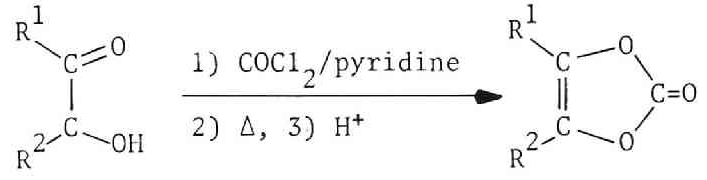
The carbonate 2d was prepared also by ethoxycarbonylation of sebacoin (1d) with ethyl chloroformate, followed by treatment with *p*-toluenesulfonic acid in boiling xylene (Scheme 2).

Photoreduction

UV irradiation of 2a in isopropyl alcohol containing benzene sensitizer afforded *cis*-4,5-dipropyl-1,3-dioxolan-2-one (5a) and its *trans* isomer (6a) along with two dimers of 2a and acetone pinacol. The ratio of 5a/6a was determined by gas-chromatography (GLC) to be 8:92 (Scheme 3). The structures of the products were established by comparison with authentic samples prepared by esterification of *meso*- and *dl*-4,5-octanediol[8] with phosgene.

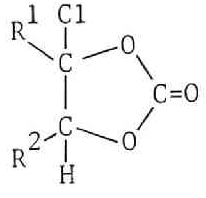
On the other hand, UV irradiation of 2a in acetone gave two kinds of dimers exclusively. The stereochemistry of the dimers

Scheme 1



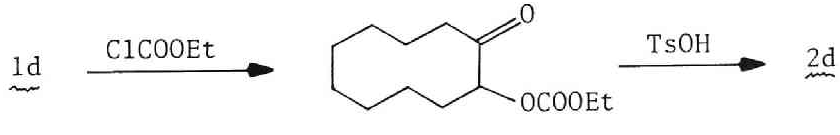
1 2

a: $R^1 = R^2 = Pr$
b: $R^1 = R^2 = -(CH_2)_4-$
c: $R^1 = R^2 = -(CH_2)_6-$
d: $R^1 = R^2 = -(CH_2)_8-$
e: $R^1 = R^2 = -(CH_2)_{10}-$
f: $R^1 = R^2 = Ph$



3

Scheme 2

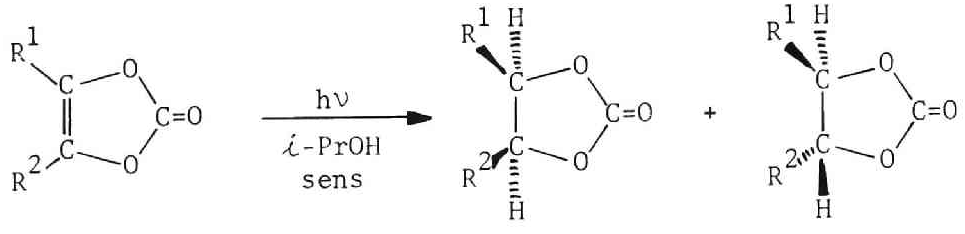


was not examined.

Tetramethylene derivative 2b gave saturated products 5b and 6b (19% yield, 89:11) upon irradiation in isopropyl alcohol-benzene. In the absence of hydrogen donors, 2b resisted the photoreaction.

The hexamethylene derivative 2c behaved differently and gave only a dimer upon irradiation both in acetone and in isopropyl alcohol-benzene.

Scheme 3



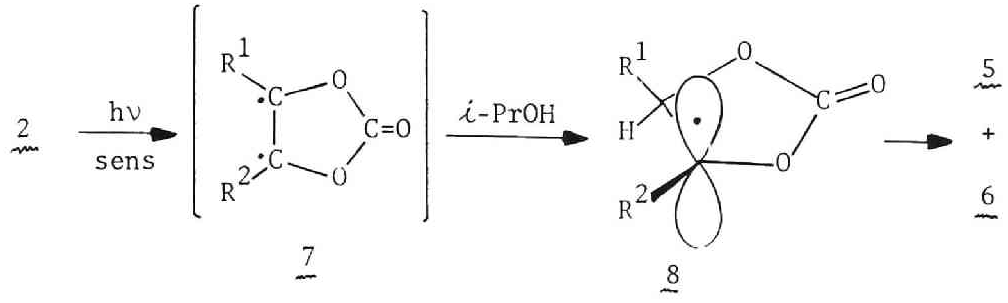
2 5 6

a: $R^1 = R^2 = Pr$
b: $R^1 = R^2 = -(CH_2)_4-$

Since the photoreaction of 2 required the presence of triplet sensitizers[2] such as acetone and benzene, the reaction must involve the triplet state of the olefinic functional group as a biradical. The photochemical behavior of the ene-diol carbonate moiety of 2 may be understood on the same line as the photoreduction of cyclopentenes.[9] The triplet state 7 abstracts a hydrogen atom from isopropyl alcohol to produce the radical 8 stablized by the adjacent oxygen atom. This yields then a mixture of ethylene carbonate isomers (5 and 6) in which the thermodynamically more

stable one predominates (Scheme 4).

Scheme 4

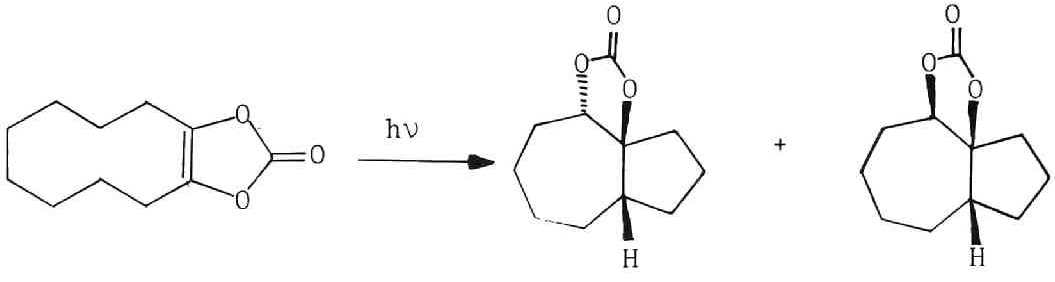


Intramolecular Hydrogen Abstraction

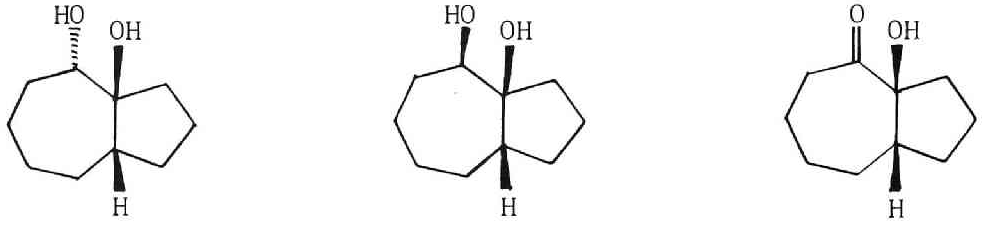
Irradiation of 2d in acetone gave no dimers but a mixture of novel tricyclic stereoisomers 9 and 10 in a 71% yield. As the separation of the two isomers failed, the mixture was hydrolyzed to the vicinal diols 11 and 12 (Scheme 5). The ratio of 11/12 was determined by GLC as 85:15. Separation of the two diols was accomplished by preparative thin layer chromatography (PLC).

The structure and stereochemistry of 11 and 12 were established as follows. Since the oxidation of 11 and 12 by N-bromosuccinimide (NBS)[12] gave the same ketol 13, the diols should have the same ring system and ring fusion. The absorption of 13 at 1700 cm^{-1} implied that the ring including the carbonyl group was medium-sized. Glycol cleavage of 11 and 12 with periodate-permanganate[13] afforded ε-(2-ketocyclopentyl)valeric acid (14).[14] Hence both 11 and 12 were established to have a bicyclo[5.3.0]decane structure. The *cis*-ring fusion of the photoproducts was determined by the fact that half-tosylation of the mixture of 11 and 12, followed by reduction with lithium aluminum hydride or sodium borohydride,

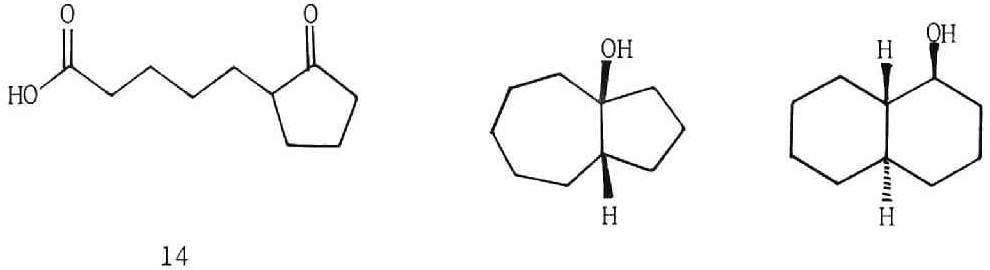
Scheme 5



2d 9 10



11 12 13



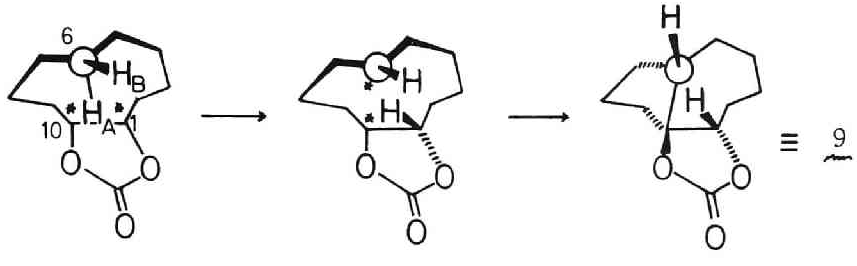
14 15 16

afforded *cis*-bicyclo[5.3.0]decan-1-ol (15) along with *trans*,*trans*-α-decalol (16).[15] The formation of the latter can be ascribed to the base-catalyzed rearrangement of the half-tosylate,[16] followed by the reduction of the resulting *trans*-α-decalone. In fact, treatment of the half-tosylate of 11 and 12 with sodium methoxide in methanol afforded *trans*-α-decalone.

Reduction of 13 with sodium bis(2-methoxyethoxy)aluminum hydride (VSH) yielded 11 almost exclusively. On the basis of Cram's rule[17] the *trans*-configuration of the vicinal hydroxyl groups of 11 was established and consequently 12 turned out to be its *cis*-diol isomer. Thus 11 and 12 were concluded to be *cis*-bicyclo[5.3.0]decane-*trans*-1,2-diol and its *cis*-diol isomer, respectively. The transannular photoreaction of 2d proceeded even in isopropyl alcohol upon benzene sensitization and neither reduction products nor dimers were detected among the products.

Inspection of Dreiding models of 2d suggests that the hydrogen atom on the C(6) in the excited state[18] resides closest to the C(1) (17) and the abstraction of H_A by C(1) radical should occur *via* a seven-membered cyclic transition state. Subsequent recombination[19] of the resulting biradical 18 may account for the preference for 9.

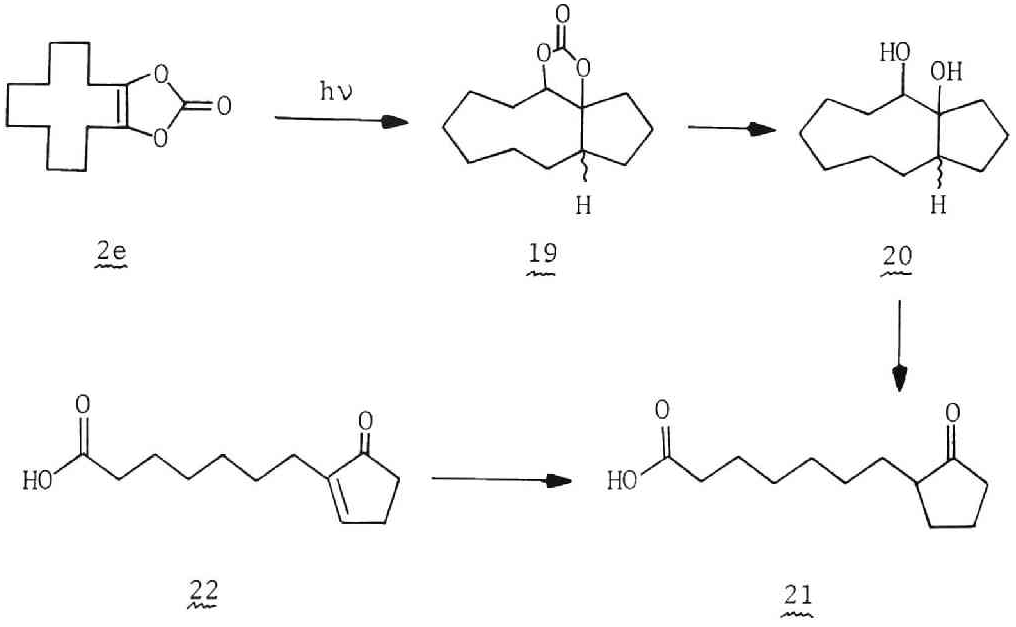
Scheme 6



17 18

Decamethylene derivative 2e proved to be rather less reactive than 2d. Irradiation of an acetone solution of 2e yielded 19 in a 49% yield along with the recovery of 2e (21%) (Scheme 7). The presence of the stereoisomers was not excluded, as no satisfactory separation of the isomers was accomplished. Alkaline hydrolysis gave the vicinal diol 20, which was subjected to the Rudloff oxidation to afford 7-(2-ketocyclopentyl)heptanoic acid (21). IR bands of the keto acid appeared at 1737, 1708 cm^{-1} characteristic of a five-membered ketone and a carboxylic acid, respectively. An authentic sample of 21 was obtained by hydrogenation of the unsaturated derivative 22.[20] Consequently, the structure of 19 was established as bicyclo[7.3.0]dodecane-1,2-diol. The stereochemistry of the vicinal hydroxyl groups and the mode of the ring fusion were not examined.

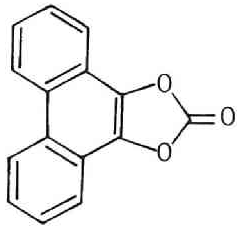
Scheme 7



2e 19 20

22 21

The diphenylvinylene carbonate 2f was recovered unchanged upon irradiation in cyclohexane, whereas the photoreaction of 2f in the presence of iodine gave a phenanthrene derivative 23 in a 77% yield.



23

Experimental

Preparation of 2. General Procedure. To a solution of an acyloin (50 mmol) in benzene (60 ml) and pyridine (90 ml) a mixture of 30% toluene solution (55 g) of phosgene (167 mmol) and benzene (80 ml) was added drop by drop at 0° and the mixture was stirred overnight. After dilution with n-hexane (300 ml) the precipitated pyridinium chloride was filtered off. The filtrate was washed twice with water (100 ml) and dried over anhydrous potassium carbonate. Evaporation of the solvent *in vacuo* and distillation gave a mixture of 2 and its isomer(s). The distillate was dissolved in xylene mixture (*ca.* 80 ml) and the solution was heated to reflux for 24 hr in the presence of *p*-toluenesulfonic acid (*ca.* 1 g). Neutralization with pyridine, filtration and distillation gave 2. Yields and physical properties are summarized in Table 1.

4,5-Diphenyl-1,3-dioxolen-2-one (2f). This was prepared

Table 1 Physical Properties of 1,3-Dioxolen-2-ones (2)

Compound	Yield (%)	Bp (°)/mm [Mp] (Solv)	IR[a] (cm^{-1})	NMR[b] (δ)
2a[c]	69	90-93/4	1830, 1200, 1030	1.97 (t, 6 H, CH_3-), 1.62 (sextet, 4 H, CH_2), 2.37 (t, 4 H, CH_2C=)
2b[d]	34	120-125/21	1820, 1750, 1200 940	1.0-2.1 (m, 4 H), 2.1-2.7 (m, 4 H)
2c[e]	56	94-106/2	1820, 1730, 1710 1130, 1040	1.0-2.3 (m, 12 H, methylenes), 2.55 (t, 4 H, CH_2C=)
2d[f]	80 67[h]	[44-45] (n-hexane)	1830, 1730, 1184 1170, 1130, 1010[g]	0.9-1.9 (m, 12 H, methylenes), 2.45 (t, 4 H, CH_2C=)
2e[i]	50	[53.5-54] (n-hexane)	1825, 1728, 1215 1142[g]	1.1-2.0 (m, 16 H, methylenes), 2.35 (t, 4 H, CH_2C=)

[a] Neat unless otherwise stated.

[b] Determined in carbon tetrachloride at 24°, 60 MHz.

[c] Found: C, 63.3; H, 8.3. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.3%. MS: *m/e* (relative abundance) 170 (M^+, 18), 141 (43), 83 (47), 71 (33), 69 (34), 55 (100), 44 (70).

Footnotes of Table 1, continued.

[d] Found: C, 60.2; H, 6.0. Calcd for $C_7H_8O_3$: C, 60.0; H, 5.8%. MS: *m/e* (relative abundance) 140 (M^+, 54), 112 (13), 95 (14), 68 (100), 67 (80), 55 (98).

[e] Found: C, 64.4; H, 7.2. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.2%. MS: *m/e* (relative abundance) 168 (M^+, 29), 95 (26), 81 (48), 68 (61), 67 (88), 55 (100).

[f] Found: C, 67.6; H, 8.2. Calcd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2%. MS: *m/e* (relative abundance) 196 (M^+, 34), 137 (3), 123 (10), 109 (20), 97 (34), 95 (40), 81 (60), 67 (78), 55 (100), 41 (88).

[g] Nujol mull.

[h] Prepared by ethoxycarbonylation of sebacoin, followed by acid-treatment, *vide infra*.

[i] Found: C, 69.4; H, 9.0. Calcd for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0%. MS: *m/e* (relative abundance) 224 (M^+, 20), 151 (2), 137 (6), 123 (8), 111 (14), 109 (14), 98 (44), 95 (30), 81 (40), 67 (48), 55 (100).

similarly as described above. Distillation at 140-150°/0.15 mm gave 2f in a 61% yield which crystallized, mp 71-73° (lit.,[7] 74-76° (n-hexane)). IR (KBr): 1820, 1695, 1208, 1068, 995, 727, 692 cm^{-1}. MS: *m/e* (relative abundance) 238 (M^+, 3), 165 (13), 152 (5), 105 (100), 77 (64).

4,5-Octamethylene-1,3-dioxolen-2-one (2d). An Alternate Procedure. Ethyl chloroformate (6 ml, 63 mmol) was added drop by drop to a solution of sebacoin (5.10 g, 30 mmol) in pyridine (30 ml) at room temperature and stirring was continued for 1 hr. The mixture was diluted with n-hexane (100 ml) and the precipitated pyridinium chloride was filtered off. The solvents were evaporated *in vacuo* to yield ethyl 2-ketocyclodecyl carbonate quantitatively. IR (neat): 1750, 1728, 1260, 1010 cm^{-1}.

The unsymmetrical carbonate was directly mixed with *p*-toluenesulfonic acid (0.59 g, 3.4 mmol) in xylene (150 ml) and the whole was heated to reflux. After one day *p*-toluenesulfonic acid (1.18 g, 6.8 mmol) was added and the heating was continued for another day. The acid was neutralized with pyridine and the precipitated salts were filtered off. Evaporation and distillation gave 2d (3.97 g, 67%), bp 123-126°/3 mm. The oil solidified and recrystallized from n-hexane (see Table 1).

UV irradiation of 2a in acetone. A solution of 2a (1.14 g, 67 mmol) in acetone (50 ml) was placed in a quartz tube and irradiated with a 200 W high-pressure mercury lamp externally for 62 hr. Evaporation of excess acetone *in vacuo* gave a crude solid (*ca.* 1.5 g), which was recrystallized from n-hexane/ether/ethyl acetate to yield a dimer (0.05 g), mp 225-226°. IR (Nujol): 1810, 1100, 1035 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.3 (m). MS: *m/e* (relative abundance) 171 (16), 170 ($M^+/2$, 100), 141 (30), 83 (18), 71 (25), 69 (8), 55 (22), 43 (66).

Found: C, 63.6; H, 8.3. Calcd for $C_{18}H_{28}O_6$: C, 63.5; H, 8.3%.

The mother liquid was subjected to chromatography on a silica gel column. Elution with benzene gave another crop of the crystalline dimer (0.18 g, totally 20% yield). Further elution gave an oily dimer (0.87 g, 76%), bp 100-110° (bath temperature)/0.2 mm. IR (neat): 1810, 1212, 1131, 1032 cm^{-1}. NMR (CCl_4): δ 0.8-2.3 (m). MS: *m/e* (relative abundance) 170 ($M^+/2$, 28), 169 (11), 141 (21), 83 (20), 71 (59), 55 (43), 43 (100).

Found: C, 63.5; H, 8.8. Calcd for $C_{18}H_{28}O_6$: C, 63.5; H, 8.3%.

UV irradiation of 2a in isopropyl alcohol-benzene. A mixture of 2a (1.12 g, 66 mmol), isopropyl alcohol (50 ml) and benzene (1 ml) was irradiated as described above for five days. Evaporation and distillation at 120-140°/20 mm gave acetone pinacol (0.4 g). Further distillation (110°/0.8 mm) gave a mixture of 5a and 6a (0.22 g, 19%). GLC (High Vacuum Silicone Grease on Celite 545, 10%, 2 m) of the mixture revealed that the ratio 5a/6a was 8:92. Each component was separated by preparative GLC (Silicone SE 30 on Chromosorb W, 30%, 1 m), whose mass and infrared spectra and retention time on GLC were identical with those of the respective authentic sample (*vide infra*).

cis-4,5-Dipropyl-1,3-dioxolan-2-one (5a). Pyridine (2 ml) was added drop by drop at 0° to a mixture of *meso*-4,5-octanediol (0.30 g, 2 mmol), benzene (10 ml) and 30% phosgene solution in toluene (1.5 g). Stirring was continued overnight. Work-up gave 5a quantitatively, bp 85-90° (bath temperature)/3 mm. IR (neat): 1810, 1095, 1030 cm^{-1}. NMR (CCl_4): δ 0.8-2.1 (m, peak at δ 1.03 and 1.65, 14 H, methyls and methylenes), 3.7-4.5 (m, 2 H, CH-O). MS: *m/e* (relative abundance) 129 (M^+-43, 3), 128 (M^+-44, 1), 98 (4), 86 (9), 85 (11), 71 (16), 67 (26), 57 (68), 56 (61), 55 (53), 43 (84), 41 (100).

Found: C, 62.9; H, 9.4. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4%.

trans-4,5-Dipropyl-1,3-dioxolan-2-one (6a). This was prepared similarly as above from *dl*-4,5-octanediol and formed an oil, bp 105-110° (bath temperature)/3 mm. IR (neat): 1802, 1180, 1030 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.2 (m, peak at δ 0.95 and 1.55, 14 H, methyls and methylenes), 4.5-5.0 (m, 2 H, CH-O). MS: *m/e* (relative abundance) 129 (4), 128 (3), 99 (5), 86 (10), 85 (12), 71 (28), 67 (36), 57 (78), 43 (100), 41 (98).

Found: C, 62.9; H, 9.4. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4%.

UV irradiation of 2b in isopropyl alcohol-benzene. A mixture of 2b (0.42 g, 3 mmol), isopropyl alcohol (15 ml) and benzene (0.5 ml) was irradiated for 5 days. GLC of the mixture showed the presence of 5b and 6b along with the recovered 2b. Separation of 5b and 6b was performed by preparative GLC. IR and mass spectra and retention times on GLC of both products were identical with those of the authentic samples. Yield of 5b and 6b was estimated by GLC to be 13% and the ratio 5b/6b was determined to be 89:11.

cis- and trans-4,5-Tetramethylene-1,3-dioxolan-2-one (5b and 6b).[21] These were prepared from *cis-* and *trans*-cyclohexane-1,2-diol similarly as described in the preparation of 5a and 6a. The *cis* isomer 5b exhibited IR (neat): 1800, 1205, 1162, 1135, 1030 cm^{-1}. NMR ($CDCl_3$): δ 1.2-2.2 (m, 8 H, methylenes), 4.5-5.0 (m, 2 H, methines). The *trans* isomer 6b exhibited IR (Nujol): 1795, 1190, 1150, 1100, 1058, 1040 cm^{-1}. NMR ($CDCl_3$): δ 1.0-2.5 (m, 8 H, methylenes), 3.8-4.3 (m, 2 H, methines).

UV irradiation of 2c. Irradiation of 2c (1.40 g, 8.3 mmol) in acetone for 6 days, concentration and chromatography on a silica gel column gave crystals (0.62 g, 44%), mp 268° (acetonitrile-ethyl acetate 1:1). IR (Nujol): 1805, 1190, 1050 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.8 (m, peak at δ 1.45, methylenes). MS: *m/e* (relative abundance) 168 ($M^+/2$, 61), 140 (9), 129 (14), 95 (35),

84 (62), 67 (48), 59 (76), 55 (89), 43 (100), 41 (73).

Found: C, 64.1; H, 7.1, MW (cryoscopic method) 325. Calcd for $C_{18}H_{24}O_6$: C, 64.3; H, 7.2%, MW 336.

Irradiation of 2c (1.01 g, 6 mmol) in isopropyl alcohol (18 ml) and benzene (1 ml) for 4 days, followed by separation of the products by chromatography on a silica gel column gave the dimer in a 45% yield.

UV irradiation of 2d. An acetone solution (30 ml) of 2d (1.00 g, 5.1 mmol) was irradiated for one day, concentrated and subjected to chromatography on a silica gel column. Elution with benzene gave the recovered 2d (0.03 g) and an inseparable mixture of 9 and 10 (0.71 g, 71%), bp 130-135°/3 mm. IR (neat): 1800, 1175, 1160, 1028 cm^{-1}. NMR (CCl_4): δ 0.8-2.5 (m, peak at δ 1.80, 15 H, methylenes and methine), 4.2-4.8 (m, 1 H, CH-O). MS: *m/e* (relative abundance) 196 (M^+, 8), 152 (17), 124 (24), 110 (28), 109 (26), 97 (49), 95 (40), 84 (92), 81 (67), 67 (85), 55 (98), 41 (100).

Found: C, 67.2; H, 8.0. Calcd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2%.

Hydrolysis of 9 and 10. A mixture of 9 and 10 (1.33 g, 6.8 mmol) was added to a solution of potassium hydroxide (1.5 g) dissolved in water (40 ml) and ethanol (40 ml). The whole was stirred for 6.5 hr at room temperature. Ethanol was evaporated *in vacuo* and the residue was extracted with chloroform. Evaporation of the solvent and purification of the residue by chromatography on a silica gel column gave a mixture of 11 and 12 (0.83 g, 72%). Recrystallization of the mixture gave 11, mp 82-83° (acetone). IR (Nujol): 3400, 1065, 1010, 910 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.3 (m, peak at δ 1.65, 15 H, methylenes and methine), 2.43 (s, 2 H, OH), 3.2-3.8 (m, 1 H, CH-O). MS: *m/e* (relative abundance) 170 (M^+, 6), 152 (9), 123 (15), 111 (17), 97 (100), 84 (66), 67 (29), 55 (41).

Found: C, 70.5; H, 10.6. Calcd for $C_{10}H_{18}O_2$: C, 70.5;

H, 10.7%.

PLC of the mother liquid gave 12, bp 100-105°/0.15 mm. IR (neat): 3480, 1085, 1035, 920 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.4 (m, 15 H, methylenes and methine), 2.55 (s, 2 H, OH), 3.0-3.7 (m, 1 H, CH-O). MS: *m/e* (relative abundance) 170 (M^+, 12), 152 (12), 123 (15), 111 (34), 97 (100), 84 (70), 67 (33), 55 (50).

Found: C, 70.5; H, 10.7. Calcd for $C_{10}H_{18}O_2$: C, 70.5; H, 10.7%.

Oxidation of 11 with NBS. A mixture of 11 (0.14 g, 0.8 mmol), acetone (10 ml), water (1 ml), NBS (0.20 g, 1.1 mmol) and acetic acid (5 drops) was stirred overnight at room temperature. Work-up and purification by PLC gave the ketol 13 (0.07 g, 50%), bp 100° (bath temperature)/3 mm. IR (neat): 3460, 1700, 1137 cm^{-1}. NMR ($CDCl_3$): δ 0.8-2.7 (m, peak at δ 1.75 and 2.25, methylenes and methine), 2.78 (s, 1 H, OH). MS: *m/e* (relative abundance) 168 (M^+, 25), 150 (11), 124 (26), 111 (100), 98 (68), 97 (67), 83 (39), 78 (40), 55 (50).

Found: C, 71.0; H, 9.6. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6%.

Oxidation of 12 with NBS. This was performed as described above. IR and mass spectra and retention time on GLC were identical with those obtained by oxidation of 11.

Reduction of 13 with VSH. Benzene solution of VSH (72 wt%, 0.5 ml) was added drop by drop to 13 (0.02 g, 0.12 mmol) in benzene (10 ml), and stirred overnight. Work-up gave diol (0.03 g, quantitative). IR spectrum and retention time on GLC were identical with those of 11.

Periodate-permanganate Oxidation of 11 and 12. To a mixture of 11 and 12 (0.36 g, 2.1 mmol), *t*-butyl alcohol (30 ml), potassium carbonate (0.10 g) and water (20 ml) was added an aqueous solution (50 ml) of sodium metaperiodate (2.60 g), potassium permanganate

(0.05 g) and potassium carbonate (0.10 g) at room temperature and the mixture was stirred for 3 hr. Extraction with chloroform and concentration gave the crude keto acid 14 (0.29 g, 78%). IR (neat): 3600-2400, 1735, 1710, 1200, 1155 cm^{-1}. MS: *m/e* (relative abundance) 184 (M^+, 4), 129 (14), 97 (16), 84 (100), 69 (24), 55 (50), 41 (58). The oxime melted at 121-124° (lit., [14] 124-125.5°). The semicarbazone melted at 192-193° (lit., [14] 195-196°).

Conversion of 11 and 12 to 15 and 16. A mixture of 11 and 12 (0.10 g, 0.6 mmol) and *p*-toluenesulfonyl chloride (0.12 g, 0.6 mmol) was treated with pyridine (5 ml) at room temperature and stirring was continued overnight. Work-up gave the half-tosylate of 11 and 12 (0.15 g). IR (neat): 3420, 1170, 890 cm^{-1}.

Reduction of the half-tosylate with lithium aluminum hydride[22] or sodium borohydride[23] was performed according to the reported procedure. GLC assay of the mixture revealed the presence of 15 as well as 16, which was separated by preparative GLC. The alcohol 16 showed IR (neat): 3380, 1140, 1035, 1015 cm^{-1}. MS: *m/e* (relative abundance) 154 (M^+, 7), 136 (100), 121 (35), 111 (33), 95 (55), 94 (58), 81 (50), 67 (83), 55 (60), 41 (73).

Separation of 15 was unsuccessful but its formation was proven by comparing the retention times on two different GLC columns (Dowfax 9N9, 10%, 2 m, and High Vacuum Silicone Grease, 10%, 2 m) with those of the authentic sample[24] which was prepared by hydroboration[25] of $\Delta^{1(7)}$-bicyclo[5.3.0]decene.[26] The alcohol 15 thus obtained showed IR (neat): 3360, 1010 cm^{-1}. MS: *m/e* (relative abundance) 154 (M^+, 2), 136 (43), 121 (32), 97 (50), 95 (59), 81 (60), 67 (88), 55 (80), 41 (100).

UV irradiation of 2e. Irradiation of 2e (4.29 g, 19 mmol) in acetone (60 ml) for 11 days and chromatography on a silica gel column gave 2e (0.90 g, 21%) (elution with n-hexane/benzene 1:1). Further elution with n-hexane/benzene 1:3 gave 14 (2.12 g, 49%).

IR (neat): 1800, 1255, 1039 cm^{-1}. NMR (CCl_4): δ 1.2-2.8 (m, peak at δ 1.63, 19 H, methylenes and methine), 4.0-4.7 (m, 1 H, CH-O). MS: *m/e* (relative abundance) 224 (M^+, 9), 180 (3), 151 (6), 137 (6), 123 (14), 111 (24), 98 (66), 84 (52), 81 (49), 67 (63), 55 (100).

Found: C, 69.5; H, 9.0. Calcd for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0%.

Hydrolysis of 19. A mixture of 19 (2.12 g, 9.4 mmol), potassium hydroxide (2 g), water (40 ml) and ethanol (60 ml) was stirred overnight. Work-up gave crude 20 (1.28 g, 69%). Recrystallization from n-hexane gave white needles, mp 90.4-91.6°. IR (Nujol): 3360, 1094, 1015 cm^{-1}. NMR (CCl_4): δ 0.7-2.7 (m, 19 H, methylenes and methine), 3.2-4.0 (m, 3 H, CH-O and OH). MS: *m/e* (relative abundance) 198 (M^+, 10), 180 (4), 139 (12), 125 (27), 111 (19), 97 (93), 84 (100), 67 (57), 55 (90).

Found: C, 72.7; H, 11.3. Calcd for $C_{12}H_{22}O_2$: C, 72.7; H, 11.2%.

Oxidation of 20. This was performed similarly as described in the oxidation of 11 and 12 and afforded 21 in an 86% yield. IR (neat): 3700-2300, 1737, 1708, 1410, 1250, 1200- 1155 cm^{-1}. MS: *m/e* (relative abundance) 212 (M^+, 2), 163 (4), 123 (5), 109 (5), 97 (14), 84 (100), 83 (20), 69 (15), 55 (30). The semicarbazone melted at 169-171°.

Hydrogenation of 22. A mixture of 22 (0.13 g, 0.62 mmol) and Raney's Nickel (*ca.* 0.1 g) in ethanol (10 ml) was stirred under a hydrogen atmosphere for a day. Filtration of the catalyst and concentration gave 21 quantitatively. The semicarbazone melted at 170-172°.

UV irradiation of 2f. A solution of 2f (2.5 g, 10.5 mmol) and iodine (0.2 g) in cyclohexane (75 ml) was irradiated for 7 days. The precipitates of 23 (1.92 g, 77%) were collected by filtration and recrystallized from benzene to afford needles,

mp 178-179°. IR (KBr): 1840, 1805, 1622, 1605, 1120, 1045, 1024, 910, 740, 712 cm^{-1}. NMR ($CDCl_3$): δ 7.5-8.2 (m, 6 H), 8.4-8.9 (m, 2 H). MS: *m/e* (relative abundance) 236 (M^+, 80), 180 (44), 164 (100), 152 (28), UV (n-hexane): λ_{max} (log ε) 248 (5.72), 255 (5.82), 269 (4.95), 280 (4.67), 292 (4.86), 305 (5.12).

Found: C, 76.1; H, 3.2. Calcd for $C_{15}H_8O_3$: C, 76.3; H, 3.4%.

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Chapter 4

A FACILE, STEREOSPECIFIC PREPARATION OF OLEFINS FROM PINACOLS

Abstract---The present chapter deals with the experimental details in the preparation of alkylsubstituted stilbenes and cyclic olefins in an extention of the method first described by Eastwood *et al.* For example, *erythro*-isomer of acetophenone pinacol, heated with an excess of ethyl orthoformate and a catalytic amount of benzoic acid at 100° for 2 hr and subsequently at 170-190° for 2 hr, is converted to (Z)2,3-diphenyl-2-butene stereospecifically (83% yield). The *threo*-isomer of the pinacol is transformed to the (E) isomer quantitatively. The sequence is shown to be a beneficial route to stilbestrol. This method is also applicable to the preparation of *trans*-4,4'-dimethoxystilbene, *trans*-cyclooctene as well as *cis*-cyclodecene.

Considerable attention has been focused on stereospecific or stereoselective olefin syntheses.[1] Among them deoxygenation of pinacols constitutes a convenient route to olefins, especially symmetric ones.[2] Desulfurization of thioncarbonates of pinacols with phosphite[3] is well known, but the method requires not easily available thiocarbonyldiimidazole as well as higher reaction temperature. Reaction of benzaldehyde acetal of pinacols with n-butyllithium[4] proceeds at low temperature and has been successfully applied to the preparation of *trans*-cyclooctene, but the attempt to prepare stilbene from dihydrobenzoin has been reported to be unfruitful. In contrast, the third method discovered by Eastwood *et al.*[5] has proven to be quite useful in preparation of alkylsubstituted stilbenes and cyclic olefins. The present note describes experimental details in these new applications.

A mixture of the pinacol 1b, for example, excess of ethyl orthoformate, and catalytic amount of benzoic acid was heated at 100° for 2 hr and subsequently at 170-190° for 2 hr to afford stereospecifically the olefin 2b in good yield. The results are summarized in Table 1, which shows that the sequence provides a beneficial route to stilbestrol.[6] Since the pure *threo* diols, 1d and 1f, were unaccessible, a mixture of diastereomers was subjected to the reaction in the case of 1d. The yields of the *trans*-olefins, 2d and 2f, were improved by isomerization of the corresponding *cis*-olefins (2c and 2e).

The method was further found to be applicable to the preparation of *trans*-cyclooctene. *trans*-Cyclooctane-1,2-diol (1g) was subjected to the reaction sequence and the product was immediately distilled off to afford the *trans*-olefin 2g almost quantitatively. Redistillation gave gas-chromatographically pure sample in a 53% yield. The transformation 1g→2g by means of N,N-dimethylformamide diethyl acetal could not be attained, since the resulting 2g reacts with the accompanying acetic acid to afford cyclooctyl acetate.[8] *cis*-Cyclodecene (2h) was also obtained in a 67% yield

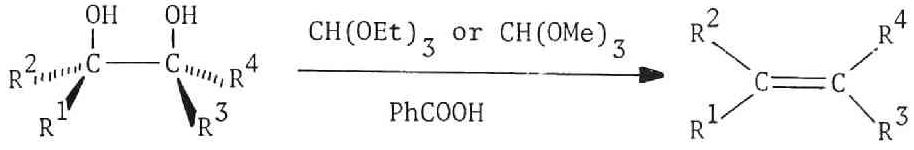

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Table 1 Yields of Olefins from Pinacols.

	Pinacol	Olefin	Y(%)
a: $R^1 = R^3 = Ph$, $R^2 = R^4 = Me$	1a	2a	100
b: $R^1 = R^4 = Ph$, $R^2 = R^3 = Me$	1b	2b	83
c: $R^1 = R^3 = p\text{-}MeOC_6H_4$, $R^2 = R^4 = Et$	1c	2c	86
d: $R^1 = R^4 = p\text{-}MeOC_6H_4$, $R^2 = R^3 = Et$	1d (+ 1c)[a]	2d	37[b]
e: $R^1 = R^3 = p\text{-}MeOC_6H_4$, $R^2 = R^4 = H$	1e	2e	c
f: $R^1 = R^4 = p\text{-}MeOC_6H_4$, $R^2 = R^3 = H$	1e	2f	36
g: $R^1,R^4 = -(CH_2)_6-$, $R^2 = R^3 = H$	1g	2g	53
h: $R^1,R^3 = -(CH_2)_8-$, $R^2 = R^4 = H$	1h	2h	67

[a] A mixture of stereoisomers obtained by pinacolic reduction.

[b] The yield based on *p*-methoxypropiophenone.

[c] Not isolated. See Experimental.

from 1h[7] stereospecifically.

Experimental[9]

Preparation of trans-2,3-Diphenyl-2-butene (2b). A mixture of *dl*-2,3-diphenylbutane-2,3-diol (1b, 642 mg, 2.65 mmol), ethyl orthoformate (600 mg, 5.6 mmol) and benzoic acid (20 mg, 0.16 mmol) was stirred at 100° for 2 hr. Evaporation of the produced ethanol and the excess orthoformate *in vacuo* (300 mg) was added and the mixture was heated at 170-190° for 2 hr, during which evolution of carbon dioxide and refluxing of ethanol were observed. After cooling, dichloromethane (20 ml) was added, and the solution was washed with saturated sodium bicarbonate (four 5 ml portions) and dried with anhydrous potassium carbonate. Concentration gave crystalline 2b (593 mg). Recrystallization from methanol afforded analytically pure sample (460 mg), mp 103-104° (lit.,[10] 106°). NMR (CCl_4): δ 1.85 (s, 6 H) and 7.15 (s, 10 H). MS: *m/e* 208 (M^+, 100%).

cis-2,3-Diphenyl-2-butene (2a). This olefin (402 mg) was obtained from 1a (484 mg). NMR (CCl_4): δ 2.10 (s, 6 H) and 6.85 (s, 10 H).

cis-3,4-Di-p-methoxyphenyl-3-hexene (2e). Heating of 1c (660 mg, 2 mmol), ethyl orthoformate (300 mg), and benzoic acid (50 mg) at 170° for 1 hr and the subsequent work-up gave 2c (510 mg), bp 190° (bath temperature)/4 mm. NMR (CCl_4): δ 0.90 (t, 6 H), 2.44 (q, 4 H), 3.52 (s, 6 H), 6.40 (d, J = 8.4 Hz, 4 H), and 6.68 (d, J = 8.4 Hz, 4 H). MS: *m/e* 296 (M^+, 100%).

trans-3,4-Di-p-methoxyphenyl-3-hexene (2d). Isomer mixture of pinacol 1c and 1d obtained by the reduction[6] of p-methoxypropiophenone (2.80 g, 17 mmol) was heated at 170-180° for 2 hr with ethyl orthoformate (4 ml), and benzoic acid (0.5 g). Addition of n-hexane precipitated unchanged 1c (230 mg). Concentration of the filtrate and recrystallization of the residue (1.8 g) gave 2d (640 mg), mp 118-120° (lit.,[6] 124°). The mother liquor was concentrated (*ca.* 1.0 g), dissolved in chloroform (10 ml) and iodine (0.5 g). The solution was heated under reflux for 3.5 hr, washed thoroughly with aqueous sodium bisulfite, then with water, and dried (sodium sulfate). Concentration of the solution, followed by recrystallization of the residue, gave additional 2d (420 mg). Totally 1.06 g of 2d was obtained. NMR (CCl_4): δ 0.75 (t, 6 H), 2.09 (q, 4 H), 3.74 (s, 6 H), 6.72 (d, J = 8.4 Hz, 4 H), and 6.98 (d, J = 8.4 Hz, 4 H). MS: *m/e* 296 (M^+, 100%).

trans-p,p'-Dimethoxystilbene (2f). Heating of hydroanisoin (1e) (822 mg, 3 mmol) with ethyl orthoformate (900 mg) for 1 hr at 170-180°, followed by evaporation of the excess orthoformate and ethanol *in vacuo*, gave an oil (2e) (1.2 g). The oil was heated with iodine (0.50 g) in chloroform (10 ml) under reflux for 3 hr. Work-up and recrystallization (n-hexane/acetone) afforded colorless needles (260 mg), mp 216-218° (lit.,[11] 214-215°).

trans-Cyclooctene (2g). *trans*-Cyclooctane-1,2-diol (1g) (385 mg, 2.7 mmol), methyl orthoformate (0.5 ml) and benzoic acid (20 mg) were heated at 90-100° for 2 hr. Methanol and excess orthoformate were evaporated under reduced pressure. Benzoic acid (50 mg) was added and the mixture was heated at 160-170°. The produced olefin was distilled with accompanying carbon dioxide and methanol. The distillate was taken in dichloromethane, washed with aqueous sodium bicarbonate and dried (sodium sulfate). Concentration gave crude 2g quantitatively. Distillation at 90-100° (bath

temperature)/95 mm gave 2g (155 mg). IR (neat): 3020, 1650, and 982 cm^{-1}. Gas-chromatographic analysis (High Vacuum Silicone Grease, 10% on Celite 545, 2 m, 60°) showed a single peak.

cis-Cyclodecene (2h). *cis*-Cyclodecane-1,2-diol (1h) (860 mg, 5 mmol), methyl orthoformate (1.0 ml), and benzoic acid (50 mg) were heated at 90-100° for 2 hr. After concentration *in vacuo* benzoic acid (100 mg) was added and the mixture was heated at 160-170° for 1 hr. Work-up gave 2h (465 mg), bp 120-130° (bath temperature)/106 mm. IR (neat)[12]: 706 cm^{-1}.

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Chapter 5

THE ACID-CATALYZED RING-OPENING OF CYCLOOCTENIMINE DERIVATIVES

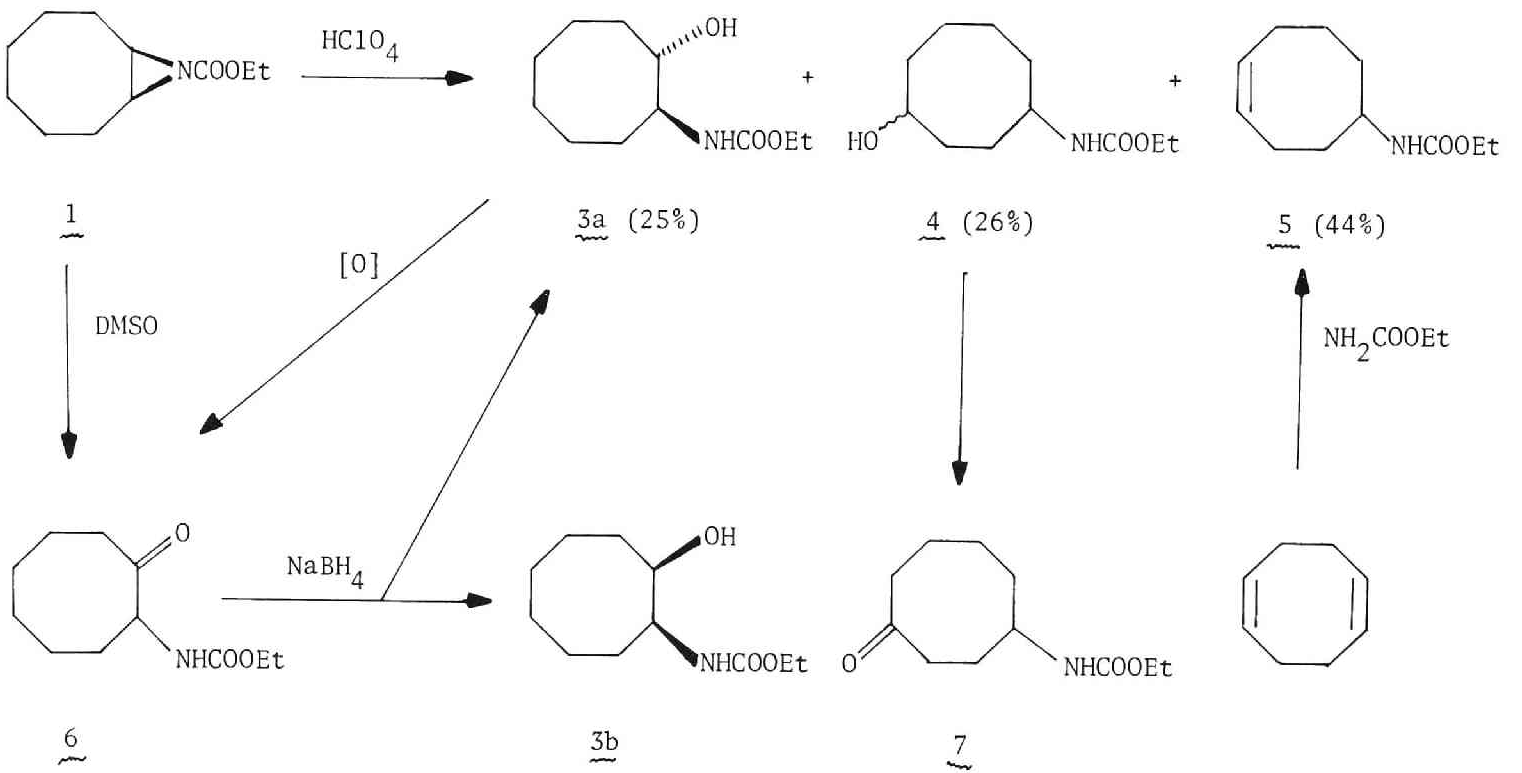
Abstract---The acid-catalyzed ring-opening of 9-ethoxycarbonyl-9-azabicyclo[6.1.0]nonane (1) gives a normal adduct along with remarkable amount of transannular products (4 and 5). Solvolysis of 9-ethoxycarbonyl-9-azabicyclo[6.1.0]-4-nonene affords a *trans*-1,2-adduct as a major product.

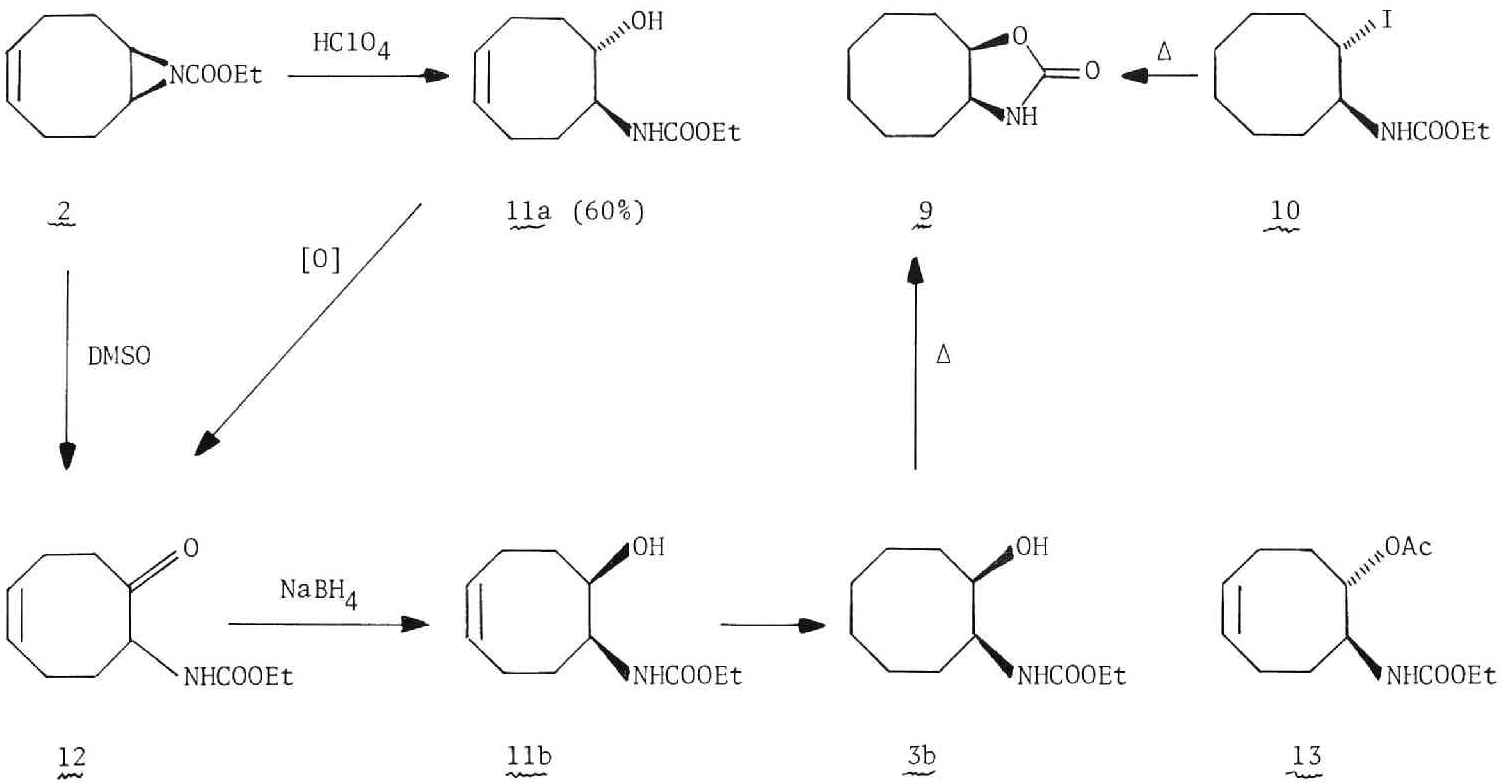
While the ring opening of cyclooctene oxide is well known,[1] treatment of cyclooctenimine with perchloric acid results in recovery of the starting material.[2] We wish to report the acid-catalyzed aziridine ring cleavage of 9-ethoxycarbonyl-9-azabicyclo-[6.1.0]nonane (1) and -4-nonene (2).

The reaction of 1 with perchloric acid gave ethyl *trans*-2-hydroxycyclooctane-1-carbamate (3a) along with two transannular products, 4 and 5. The structure of 3a was determined on the basis of spectral data and the following chemical correlation. Oxidation of 3a with chromic acid gave the corresponding ketone 6 which was identical with the product prepared by the DMSO-oxidation of aziridine 1.[3] The *trans*-configuration of 3a was determined by hydrolysis which gave *trans*-2-aminocyclooctanol described previously. Sodium borohydride reduction of 6 afforded 3a as well as the *cis*-isomer (3b) whose configuration was established by conversion to *cis*-2-aminocyclooctanol. Heating 3b at 170° under reduced pressure afforded *cis*-4,5-hexamethylene-2-oxazolidone (9). The same compound was obtained by thermolysis of *trans*-β-iodocarbamate (10). The formation of 2-oxazolidones from N-alkoxycarbonyl-β-amino alcohols has not been reported previously.

The transannular product 4 was oxidized to the corresponding ketone (7) which exhibited an IR band at 1705 cm^{-1} characteristic of a medium-sized cyclic ketone. The elemental analysis and spectral data indicated that 4 was the isomer of 3a and 3b. The structure of 4 was tentatively assigned to be ethyl 4-hydroxycyclooctane-1-carbamate on the analogy of the formation of cyclooctane-1,4-diol in the solvolysis of cyclooctene oxide.[1] The olefinic product 5 was identical with the authentic ethyl 4-cyclooctene-1-carbamate prepared by the acid-catalyzed addition of urethane to 1,5-cyclooctadiene.[3]

The acid-catalyzed cleavage of 2 in aqueous phase gave ethyl *trans*-8-hydroxy-4-cyclooctene-1-carbamate (11a), together with a


NCOOEt
HClO4
OH
NHCOOEt
+
HO
NHCOOEt
+
NHCOOEt
1
3a (25%)
4 (26%)
5 (44%)
[O]
DMSO
NH2COOEt
O
NaBH4
OH
NHCOOEt
O
NHCOOEt
6
3b
7


NCOOEt
$HClO_4$
OH
NHCOOEt
O
NH
O
Δ
I
NHCOOEt
2
11a (60%)
9
10
[O]
DMSO
Δ
O
NHCOOEt
$NaBH_4$
OH
NHCOOEt
OH
NHCOOEt
OAc
NHCOOEt
12
11b
3b
13

small amount of transannular by-products whose structures have not been determined. The *trans*-configuration of 11a was established by the fact that 11a absorbed one molar equivalent of hydrogen to afford 3a. Chromic acid oxidation of 11a yielded the corresponding ketone 12 which was also prepared by the DMSO-oxidation of 2.[3] Reduction of 12 with sodium borohydride afforded ethyl *cis*-8-hydroxy-4-cyclooctene-1-carbamate (11b) exclusively, whose catalytic hydrogenation gave 3b. The difference between 6 and 12 in borohydride reduction should be ascribed to the rigidity[4] of the ring of 12 as compared with the one of 6. Ethyl *trans*-8-acetoxy-4-cyclooctene-1-carbamate (13) was obtained by the treatment of 2 with dry acetic acid along with several bicyclic minor products.

Apparently, the acid-catalyzed aziridine ring-cleavage is favored by the presence of alkoxycarbonyl group on the nitrogen. Initial protonation on carbonyl oxygen[5] would account for this rather unusual activation. Formation of the transannular products may be explained by intramolecular hydride shift analogously to the solvolysis of cyclooctene oxide.[1] The normal addition products 3a and 11a have trans configuration, where the so-called "borderline" S_N2 mechanism should be involved in a stereochemical sense. The preference of 1,2-addition in the solvolysis of 2 compared with that of 1 is attributable to the rigidity of the system which interferes with the expected participation of the olefinic moiety in the solvolytic transition state.

Experimental

Acid-catalyzed Hydrolysis of 1. A solution of aziridine 1[3] (1.27 g, 65 mmol) in ether (12 ml) was added dropwise for 5 min at room temperature to a mixture of water (0.80 g), ether (15 ml) and 60% perchloric acid (0.30 g). After stirring for 6.5 hr, the reaction mixture was neutralized with aqueous sodium bicarbonate, extracted with ether and dried over sodium sulfate. Concentration and separation through a silica gel column (benzene/ether 4:1 as a solvent) afforded ethyl 4-cyclooctene-1-carbamate (5) (0.56 g, 44%), which was identical with the authentic sample.[3]

Subsequent elution with ether gave ethyl *trans*-2-hydroxycyclooctane-1-carbamate (3a) (0.35 g, 25%), bp 140-145°/0.05 mm, mp 42-43° (n-hexane/acetone). IR (neat): 3450-3300 (broad), 1690, 1535, 1300, 1250-1235, 1090, 1035 cm^{-1}. NMR (CCl_4): δ 5.7-5.3 (broad, 1 H, NH), 4.09 (q, 2 H, OCH_2CH_2), 4.0-3.3 (m, 3 H, methines and OH), 2.4-1.0 (m, 12 H, methylenes), 1.28 (t, 3 H, OCH_2CH_3).

Found: C, 61.4; H, 10.0; N, 6.8. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

The third eluent was ethyl 4-hydroxycyclooctane-1-carbamate (4) (0.36 g, 26%) bp 150-155°/0.05 mm. IR (neat): 3450-3330 (broad), 1685, 1530, 1300, 1235, 1090, 1059, 1028 cm^{-1}. NMR (CCl_4): δ 6.0-5.3 (broad, 1 H, NH), 4.3-3.4 (m + q, 5 H, methines, OH and OCH_2CH_3), 2.5-1.3 (m, 12 H, methylenes), 1.25 (t, 3 H, OCH_2CH_3).

Found: C, 61.4; H, 10.0; N, 6.5. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

Oxidation of 4. The compound 4 (0.12 g, 0.56 mmol) was oxidized by the Brown procedure.[7] Preparative thin-layer chromatography (TLC) of the crude product afforded ethyl 4-cyclooctane-1-carbamate (7), bp 110-115°/0.5 mm. IR (neat): 3350, 1705, 1675, 1530, 1380, 1340, 1225, 1040 cm^{-1}. NMR (CCl_4): δ 4.87 (s, 1 H, NH),

4.14 (q, 2 H, OCH_2CH_3), 3.9-3.4 (m, 1 H, methine), 2.7-1.0 (t + m, 15 H, OCH_2CH_3 (δ 1.30) and methylenes).

Found: C, 62.5; H, 9.1; N, 6.6. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

Oxidation of 3a. The compound 3a (0.12 g, 0.56 mmol) was oxidized by the Brown procedure[7] to give ethyl 2-oxocyclooctane-1-carbamate (6), whose IR and NMR spectra were completely identical with those of the sample prepared by the DMSO-oxidation of 1.[3]

Reduction of 6 with sodium borohydride. Sodium borohydride (0.10 g) was added in one portion to a solution of 6 (0.15 g, 0.70 mmol) in methanol at 0°. After stirring for 4 hr, the suspension was acidified to pH 4 by dilute hydrochloric acid, poured into water, extracted with ether and dried. Concentration and separation by preparative TLC afforded 3a (0.025 g, 17%) as well as ethyl *cis*-2-hydroxycyclooctane-1-carbamate (3b) (0.040 g, 26%), bp 160°/1 mm. IR (neat): 3450-3350 (broad), 1685, 1520-1510, 1310, 1248, 1107, 1090, 1060, 1035 cm^{-1}. NMR (CCl_4): δ 5.7-5.2 (broad, 1 H, NH), 4.2-3.5 (m + q, 4 H, methines and OCH_2CH_3), 3.4-3.0 (broad, 1 H, OH), 2.0-1.0 (m + t, 13 H, methylenes and OCH_2CH_3 (δ 1.20)).

Found: C, 61.3: H, 9.9; N, 6.2. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

Hydrolysis of 3a. A mixture of 3a (0.26 g, 1.2 mmol), sodium hydroxide (1.5 g), methanol (10 ml) and water (10 ml) was refluxed under nitrogen atmosphere for 25 hr. Usual work-up gave *trans*-2-aminocyclooctanol (0.18 g) quantitatively, mp 72.6-73° (lit.,[8] mp 73-74°).

Hydrolysis of 3b. This was performed by mixing 3b (0.050 g, 0.23 mmol) with methanolic sodium hydroxide to yield *cis*-2-aminocyclooctanol (0.030 g, 90%) as a solid, whose IR spectrum was identical with that of the sample prepared from the oxazolidone (9).

cis-4,5-Hexamethylene-2-oxazolidone (9). A solution of β-iodocarbamate 10[3] (5.0 g, 15 mmol) in xylene (40 ml) was heated for 20 hr. Concentration and recrystallization gave the oxazolidone (9) (2.57 g) quantitatively, mp 106.5-107.5° (acetone). IR (Nujol): 3260, 3170, 1745, 1725, 1260, 1235, 1090, 1080, 1042, 974 cm^{-1}. NMR (CCl_4): δ 7.4-7.1 (broad, 1 H, NH), 4.8-4.2 (m, 1 H, CH-O), 4.1-3.5 (m, 1 H, CH-N), 2.4-1.0 (m, 12 H, methylenes).

Found: C, 63.7; H, 9.1; N, 8.2. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3%.

The same oxazolidone (9) was obtained by distillation of 3b at 170°/1.5 mm.

Hydrolysis of 9. The oxazolidone 9 (1.69 g, 10 mmol) was hydrolyzed in alcoholic potash, affording *cis*-2-aminocyclooctanol (1.40 g, 98%), mp 45-47° (n-hexane/benzene) (lit.,[8] mp 52-54°).

Acid-catalyzed hydrolysis of 2. Aziridine 2[3] (4.68 g, 24 mmol) was treated with perchloric acid as described above. Recrystallization of the crude solid (5.6 g) gave ethyl *trans*-8-hydroxy-4-cyclooctene-1-carbamate (11a) (2.38 g), mp 98.8-99.5° (ethyl acetate/n-hexane). IR (Nujol): 3420, 3290, 3090, 3040, 1690, 1550, 1260, 1239, 1154, 1130, 1060, 1042 cm^{-1}. NMR ($CDCl_3$): δ 5.8-5.5 (m, 2 H, olefinic), 5.4-5.0 (broad, 1 H, NH), 4.3-3.5 (m + q, 4 H, methines and OCH_2CH_3), 2.80 (s, 1 H, OH), 2.7-1.3 (m, 8 H, methylenes), 1.26 (t, 3 H, OCH_2CH_3).

Found: C, 61.7; H, 9.0; N, 6.5. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

The mother liquor was submitted to chromatography on silica gel. Elution with benzene/ether 3:1 gave an isomerization product (0.68 g, 15%), bp 100-110°/0.04 mm. IR (neat): 3320, 1690, 1525, 1230, 1080, 1045 cm^{-1}. NMR (CCl_4): δ 5.9-5.2 (m, 4 H, olefinic and NH), 4.07 (q, 2 H, OCH_2CH_3), 2.7-1.3 (m, 8 H, methylenes), 1.23 (t, 3 H, OCH_2CH_3). MS: *m/e* 195 (M^+). The compound was tentatively

assigned as ethyl 1,5-cyclooctadiene-1-carbamate.

Found: C, 67.4; H, 8.8; N, 7.0. Calcd for $C_{11}H_{17}NO_3$: C, 67.7; H, 8.8; N, 7.2%.

Further elution with benzene/ether 1:1 gave additional 11a (0.70 g, totally 3.08 g, 60%). The third component was an oil (0.24 g, 5%), bp 120-130°/0.05 mm. IR (neat): 3450-3330, 1688, 1535, 1288, 1240, 1098, 1070, 1046 cm^{-1}. NMR (CCl_4): δ 5.7-5.4 (broad, 1 H, NH), 4.9-4.5 (m, 1 H, methine), 4.3-3.5 (m + q, methine and OCH_2CH_3), 2.93 (s 1 H, OH), 2.6-0.8 (m + t, 13 H, methylenes and OCH_2CH_3). MS: *m/e* 213 (M^+). The compound was tentatively assigned as ethyl 6-hydroxybicyclo[3.3.0]octane-2-carbamate, since the corresponding ketone obtained by its oxidation exhibited an IR band at 1735 cm^{-1} characteristic of a five-membered cyclic ketone.

Oxidation of 11a. Chromic acid oxidation[7] of 11a (0.43 g, 2.0 mmol) gave an oil (0.37 g, 88%), which was identical with the sample of 12 prepared by the DMSO-oxidation of 2.

Sodium Borohydride Reduction of 12. The α-ethoxycarbonylamino-ketone 12 (0.75 g, 3.5 mmol) and subsequent chromatography on silica gel column gave ethyl *cis*-8-hydroxy-4-cyclooctene-1-carbamate (11b) (0.63 g, 83%), mp 93.5-94.5° (acetone). IR (Nujol): 3420, 3280, 1690, 1550, 1255, 1235, 1060, 1040 cm^{-1}. NMR ($CDCl_3$): δ 5.8-5.4 (m, 3 H, olefinic and NH), 4.3-3.6 (m + q, 5 H, OH, methines and OCH_2CH_3), 2.9-1.5 (m, 8 H, methylenes), 1.26 (t, 3 H, OCH_2CH_3).

Found: C, 61.8; H, 9.1; N, 6.4. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

Hydrogenation of 11a. A mixture of 11a (0.50 g, 2.4 mmol), Raney's nickel (*ca.* 0.3 g) and ethanol (10 ml) was stirred under hydrogen atmosphere at room temperature until one molar hydrogen was absorbed (*ca.* 24 hr). The catalyst was filtered off, washed exclusively with ether and the combined washings were evaporated

in vacuo, yielding 3a as an oil (0.51 g, quantitatively).

Hydrogenation of 11b. The compound 11b (0.26 g, 1.2 mmol) was hydrogenated as above giving 3b (0.23 g, 90%) as a colorless oil, which was identical with the sample obtained by reduction of 6.

Solvolysis of 2 in acetic acid. A solution of 2 (1.56 g, 8 mmol) in glacial acetic acid (5 ml) was added dropwise under a nitrogen atmosphere to a mixture of acetic acid (8 ml), acetic anhydride (3 drops) and BF_3-etherate (10 drops) at 50-55°. After stirring for 3 hr and usual work-up, chromatography on silica gel gave the isomerization product (0.22 g, 14%) which was identical with the one obtained by the hydrolysis of 2.

The second eluent was ethyl *trans*-8-acetoxy-4-cyclooctene-1-carbamate (13) (0.92 g, 45%), bp 110-120°/0.05 mm. IR (neat): 3350, 1724, 1700, 1530-1510, 1230, 1050, 1032 cm^{-1}. NMR (CCl_4): δ 5.8-5.5 (m, 2 H, olefinic), 5.1-4.5 (m, 2 H, methine and NH), 4.3-3.7 (m + q, 3 H, methine and OCH_2CH_3), 2.5-1.4 (m + s, 11H, methylenes and MeCOO (δ 2.00)), 1.22 (t, 3 H, OCH_2CH_3).

Found: C, 60.9; H, 8.3; N, 5.5. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5%.

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Chapter 6

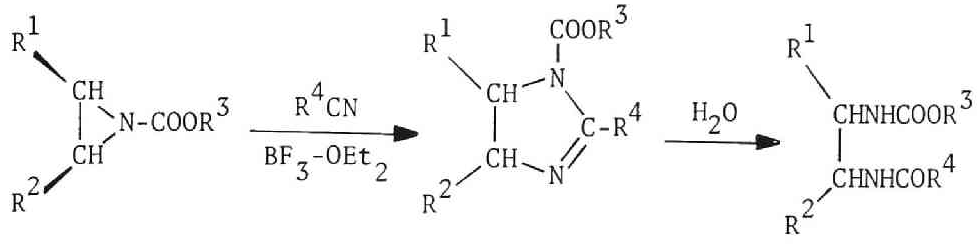
REACTION OF N-ALKOXYCARBONYLAZIRIDINES WITH NITRILES

Abstract---Acid-catalyzed reaction of acetonitrile or benzonitrile with N-alkoxycarbonylaziridines, 1a and 1b is found to yield the corresponding 1-alkoxycarbonyl-2-imidazolines, 2ax, 2ay, and 2bx. The imidazolines obtained by the reaction of N-ethoxycarbonyl-2,3-tetramethyleneaziridine (1c) with acetonitrile or benzonitrile are labile and readily be hydrolyzed to afford *trans*-cyclohexane-1,2-diamine derivatives (3cx or 3cy). The nitrile-addition supposedly proceeds S_N2 type C-N bond cleavage and C-N bond formation.

N-Alkoxycarbonylaziridines are readily accessible by the addition of alkoxycarbonylnitrenes to olefins[1] or by the addition of iodine isocyanate to olefins and the subsequent alcoholysis and base-treatment.[2] They react with nucleophiles in the presence of an acid catalyst.[3,4] This article describes an acid catalyzed reaction of N-alkoxycarbonylaziridines with nitriles, thus providing a new route to 2-imidazolines.

The reaction of 1-methoxycarbonyl-2-phenylaziridine (1a)[2] with acetonitrile and a catalytic amount of boron trifluoride etherate at a reflux temperature gave 1-methoxycarbonyl-2-methyl-4-phenyl-2-imidazoline (2ax) in 82% yield. The structure was elucidated as follows. IR absorptions of 2ax at 1740 cm^{-1} and 1630 cm^{-1} are due to an N-methoxycarbonyl and an imino group respectively. The NMR signal (see Table 2) at δ 2.30 is due to the methyl proton on C-2. The aziridine 1a also reacted with benzonitrile at 100°, affording 2ay as a sole product.

The aziridine 2b having an attached eight-membered ring reacted with acetonitrile to give 2bx and no accompanying transannular products were detected. The purification of the product 2by resulting from the reaction of 2b and benzonitrile was unsuccessful. The imidazolines 2cx and 2cy, which were obtained by the reactions of 2c with acetonitrile and with benzonitrile, were unstable to moisture and the isolation could not be accomplished. However the spectral data (see Table 2) suggested the formation of 2cx and 2cy. Distillation or chromatographic purification of 2cx resulted in hydrolysis to give N-acetyl-N'-ethoxycarbonylcyclohexane-1,2-diamine (3cx). Similarly column chromatography of 2cy afforded bisamide 3cy. The configuration of the two amino groups was proved to be trans by the following sequence. Hydrolysis of the crude 2cx with concentrated hydrochloric acid, followed by sulfonylation with benzenesulfonyl chloride, yielded *trans*-N,N'-bisbenzenesulfonylcyclohexane-1,2-diamine.[5] Thus the attack of



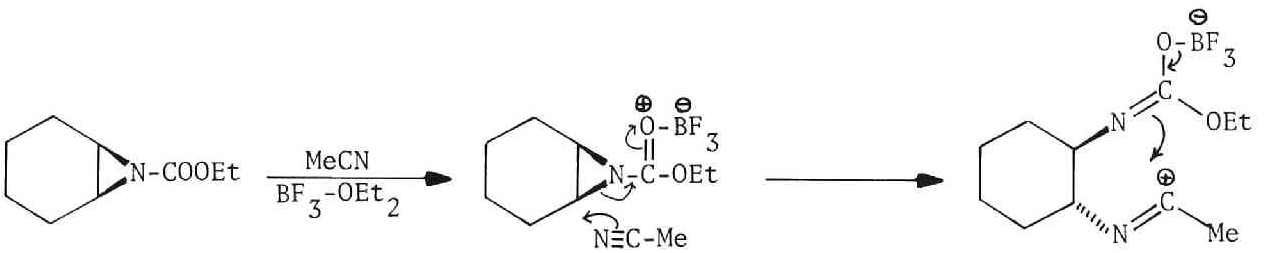
1 2 3

a: R^1 = H, R^2 = Ph, R^3 = Me
b: R^1,R^2 = -(CH_2CH_2CH=$CHCH_2CH_2$)-, R^3 = Et
c: R^1,R^2 = $(CH_2)_4$-, R^3 = Et
x: R^4 = Me
y: R^4 = Ph

Table 1 Reaction of 1 with nitriles

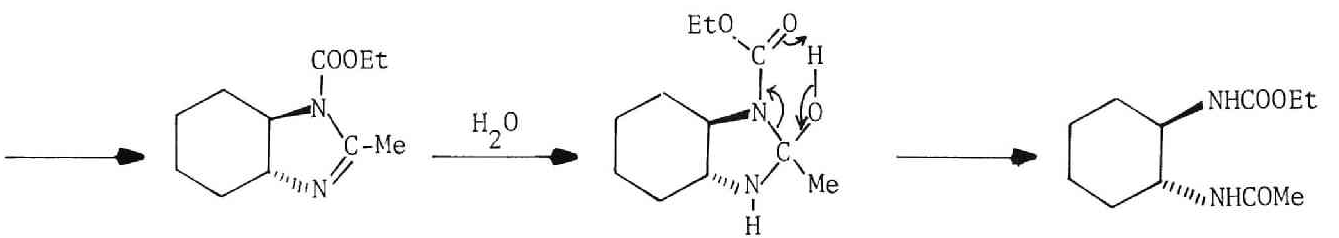
Aziridine	Nitrile	Product	Reaction Time (hr)	Reaction Temp (°)	Yield (%)
1a	MeCN	2ax	4	81	82
1a	PhCN	2ay	4	100	56
1b	MeCN	2bx	8	81	67
1c	MeCN	3cx	6	81	45
1c	PhCN	3cy	6	100	50

Scheme



1c

4



2cx

5

3cx

the nitrile to the aziridine ring occurred in a trans fashion.[6] The mechanism of the reaction can be interpreted as shown in the scheme. Since the presence of a Lewis acid is necessary, direct nucleophilic attack by nitriles is excluded. Boron trifluoride coordinates to the oxygen atom of 1c, whereas acetonitrile attacks the aziridine ring to afford a zwitter ion 4, which subsequently cyclizes to 2cx. The stereochemistry clearly indicates an S_N2 type reaction path.[3,4] Formation of bisamide 3cx can be understood in terms of the intermediacy of 2-hydroxyimidazolidine 5 which isomerizes to 3cx *via* a six-membered cyclic array.

Since aziridines have been reported to react with nitriles only in the form of the unstable aziridinium salts,[7] the present reaction[8] constitutes one of useful tools in organic syntheses to prepare 2-imidazolines and 1,2-diamines.[9]

Experimental

Reaction of Aziridines with Acetonitrile. A Typical Procedure. To a mixture of boiling acetonitrile (15 ml) and boron trifluoride etherate (0.02 ml) aziridine 1a (0.040 g, 2.3 mmol) was added drop by drop under a nitrogen atmosphere and refluxing was continued for 4 hr. After cooling, the acid was neutralized with solid anhydrous sodium carbonate and the solution was concentrated *in vacuo*. The product was purified by preparative thin layer chromatography on alumina (elution with dichloromethane). Table 2 lists the physical properties of the products.

Hydrolysis of 2cx. A mixture of 2cx (200 mg) and conc HCl (2 ml) was heated at 120° in a sealed tube for 12 hr. After cooling HCl was removed *in vacuo*, and the residue was treated with

Table 2 Physical Properties of the New Compounds.

Compound	bp (°/mm) [mp (°)]	IR (cm^{-1})[a]	NMR (δ)[b]
2ax[c]	140/0.08	1740, 1630, 760 700	2.30 (s, 3 H, CH_3), 3.35 (d, J = 9.6 Hz, 1 H, CH), 3.58 (s, 3 H, CH_3), 3.90 (d, J = 9.3 Hz, 1 H, CH) 4.84 (d-d, 1 H, CH), 7.07 (s, 5 H, Ph)
2ay[d]	170/0.08 (bath temp)	1720, 1630	3.65 (s, 3 H, CH_3), 3.95 (d, J = 8.0 Hz, 1 H, CH), 4.35 (d, J = 9.6 Hz, 1 H, CH), 5.25 (d-d, J = 8.0, 9.6 Hz, 1 H, CH), 7.30 (s, 10 H, Ph).
2bx[e]	160/0.09	1725, 1660, 1650	0.8-2.5 (m, 8 H, methylenes), 1.30 (t, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 3.7-4.2 (m, 2 H, methines), 4.26 (q, 2 H, CH_2), 5.5-5.8 (m, 2 H, CH=CH).
2cx[f]	--------	1720, 1620	1.0-2.2 (m, 8 H, methylenes), 1.35 (t, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.5-3.3 (m, 2 H, methines), 4.25 (q, 2 H, CH_2)
2cy[f]	--------	1715, 1615	1.0-2.2 (m, 8 H, methylenes), 0.95 (t, 3 H, CH_3), 2.60 (m, 1 H, CH), 3.29 (m, 1 H, CH), 3.87 (q, 2 H, CH_2), 7.30 (m, 5 H, Ph)

Table 2, continued.

3cx[g]	[134-135][j]	3300, 3250, 1690 1640, 1540[h]	1.20 (t, 3 H, CH_3), 1.1-2.7 (m, 8 H, methylenes), 1.80 (s, 3 H, CH_3), 3.2-3.8 (m, 2 H, methines), 4.08 (q, 2 H, CH_2), 5.1 (broad s, 1 H, NH), 6.3 (broad s, 1 H, NH)
3cy[i]	[175-176][j]	3350, 3300, 1690 1640, 1550[h]	1.20 (t, 3 H, CH_3), 0.7-3.0 (m, 8 H, methylenes), 3.2-4.5 (m, 2 H, methines), 4.10 (q, 2 H, CH_2), 5.2 (broad s, 1 H, NH), 7.2 (broad s, 1 H, NH), 7.7 (s, 5 H, Ph)

Footnotes of Table 2

[a] Neat liq film unless otherwise stated.

[b] Recorded in deuteriochloroform solution.

[c] MS: *m/e* (relative abundance) 218 (M^+, 42), 141 (100), 140 (58), 90 (51). Found: C, 66.1; H, 6.6; N, 12.3. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5; N, 12.8%.

Footnotes of Table 2, continued.

[d] MS: *m/e* (relative abundance) 280 (M^+, 17), 193 (100), 90 (21), 77 (12).
Found: C, 72.5; H, 5.8; N, 10.0. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.8; H, 5.8; N, 10.0%.

[e] MS: *m/e* (relative abundance) 236 (M^+, 43), 198 (77), 197 (78), 95 (77), 42 (100).
Found: C, 66.1; H, 8.6; N, 11.9. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.9%.

[f] Not isolated in a pure form.

[g] MS: *m/e* (relative abundance) 228 (M^+, 2), 169 (36), 140 (40), 112 (42), 111 (40), 97 (50), 57 (50), 44 (100).
Found: C, 57.9; H, 8.9; N, 12.2. $C_{11}H_{20}N_2O_3$: C, 57.9; H, 8.8; N, 12.3%.

[h] KBr.

[i] MS: *m/e* (relative abundance) 290 (M^+, 8), 169 (34), 105 (100), 77 (48).
Found: C, 66.5; H, 7.9, N, 9.7. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.2; H, 7.6; N, 9.7%.

[j] Recrystallized for n-hexane/ethyl acetate 1:1.

10% sodium hydroxide aq solution (5 ml) and benzenesulfonyl chloride (0.5 ml). After stirring at room temperature overnight, work-up gave colorless needles, mp 151-152° (benzene). An authentic sample prepared according to the reported procedure[5] melted at 150-152°. NMR and IR spectra of both were completely identical.

References and Footnotes

(1) W. Lwowski, "Nitrenes," John Wiley and Sons, New York, 1970.

(2) S. Fujita, T. Hiyama, and H. Nozaki, *Tetrahedron*, 26, 4347 (1970).

(3) H. Nozaki, Y. Okuyama, and S. Fujita, *Can. J. Chem.*, 46, 3333 (1968).

(4) S. Fujita, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Japan*, 43, 3239 (1970).

(5) The trans isomer is recorded to melt at 154-155°, while the cis isomer melts at 165-166°. See, A. T. Nielsen, *J. Org. Chem.*, 27, 1998 (1962).

(6) Acid-catalyzed hydration of aziridine is reported to yield *trans*-2-amino alcohols exclusively. As to the stereochemistry of the ring opening of the aziridines, see ref 2.

(7) E. Pfeil and U. Harder, *Angew. Chem. Int. Ed.*, 4, 518 (1965); D. R. Crist and N. J. Leonard, *Ibid.*, 8, 962 (1969); N. J. Leonard, D. B. Dixon, and T. R. Keenan, *J. Org. Chem.*, 35, 3488 (1970); N. J. Leonard and D. B. Dixon, *Ibid.*, 35, 3483 (1970).

(8) Acid-catalyzed reactions of epoxides with nitriles have been recorded to afford 2-oxazolidinium salts or 2-amino alcohols. See, N. J. Leonard and B. Zwanenburg, *J. Amer. Chem. Soc.*, 89, 4456 (1967); S. Julia and G. Bourgery, *Compt. Rend.*, 264 (C) 333 (1967). Episulfides also react with nitriles to provide

2-thiazolines. See, G. K. Helmkamp, D. J. Pettitt, J. R. Lowell, Jr., W. R. Mabey, and R. G. Wolcott, *J. Amer. Chem. Soc.*, 88, 1030 (1966).

(9) An alternative route to 1,2-diamines involves the reaction of sodium azide with aziridines followed by hydrogenolysis. See the reference in the footnote 5.

Chapter 7

OXIDATIVE RING-OPENING OF 1-ALKOXYCARBONYLAZIRIDINES

Abstract---The title reaction furnishes a practical preparation of α-alkoxycarbonylamino ketones from nitrene adducts of the corresponding olefins. The aziridines are alternatively accessible *via* addition of iodine isocyanate, alcoholysis and elimination of hydrogen iodide. DMSO-cleavage of *cis* and *trans* isomers of 1-ethoxycarbonyl-2-methyl-3-phenylaziridine proceeds regioselectively: the *cis* isomer reacts at 1,2-bond and 1,3-bond in a ratio of 1:1, whereas the *trans* isomer at 1,3-bond almost exclusively. The 1,3-bond cleavage is predominant under acidic conditions for both isomers. Under neutral conditions, the cleavage proceeds *via* an S_N2 type transition state.

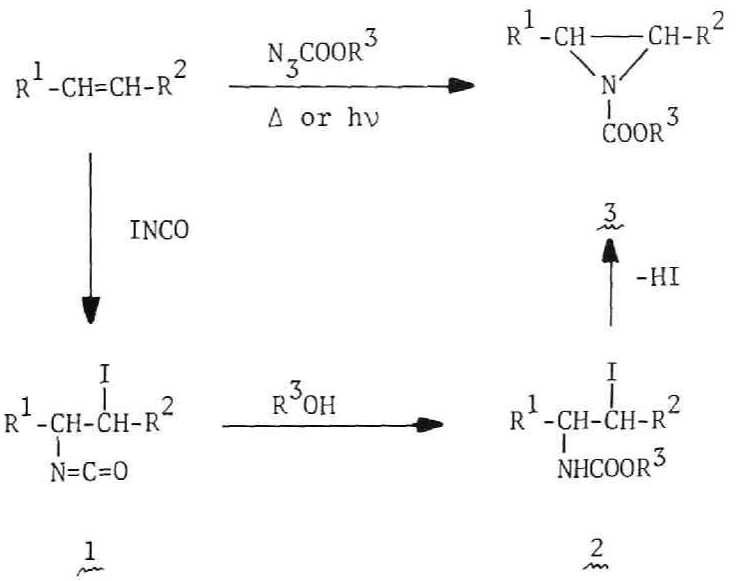
The recorded reaction of 1-aroylaziridines with dimethyl sulfoxide (DMSO)[1] is of interest as a possible means of obtaining α-acylamino ketones, but the required aziridines are not easily accessible. The present paper deals with an extention of the oxidative ring-opening to more readily available 1-alkoxycarbonyl-aziridines (3), which have been shown to give rise to α-alkoxy-carbonylamino ketones (4,5) in preparative yields. Hitherto unknown regioselectivity of this reaction has been disclosed with respect to the *cis* and *trans* isomers of 1-ethoxycarbonyl-2-methyl-3-phenylaziridine (3a). The mechanistic aspect of the reaction has been studied and it has been shown that the cleavage involves an S_N2 attack of DMSO on the ring carbon.[2]

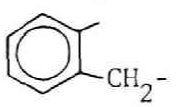
α-Alkoxycarbonylamino Ketones.

The aziridines (3) have been prepared (a) by stereospecific addition of alkoxycarbonylnitrene to olefins[3,4] or alternatively (b) by the addition of iodine isocyanate[5] to olefins, alcoholysis and the final ring closure.[4] DMSO-oxidation was carried out analogously on 1-aroylaziridines[1] by heating DMSO solutions of aziridines to afford good yields of the desired ketones (4,5). Under such neutral conditions, no transannular products were obtained in the oxidation of the aziridine (3b) derived from *cis*-cyclooctene. In contrast, however, heating in the presence of boron trifluoride-etherate gave a transannular product 8 together with 4b. Compound 8 was identical with the authentic sample prepared by the addition of urethane to 1,5-cyclooctadiene. The reaction would probably proceed *via* 6, 7 and/or 9.[6] Physical properties and analyses of the compounds obtained in the present preparation are listed in Table 1.

Regioselectivity of the Oxidation.

Heating of the *trans* isomer of 3a in DMSO afforded 4a and a small amount of 5a in a ratio given in Table 2, which contains



a: R^1 = Ph, R^2 = Me, R^3 = Et (*cis* and *trans*)
b: R^1,R^2 = $-(CH_2)_6-$, R^3 = Et
c: R^1 = Ph, R^2 = H, R^3 = Me
d: R^1,R^2 =  , R^3 = Et
e: R^1,R^2 = $-(CH_2)_4-$, R^3 = Et
f: R^1,R^2 = $-(CH_2CH_2CH=)_2$, R^3 = Et

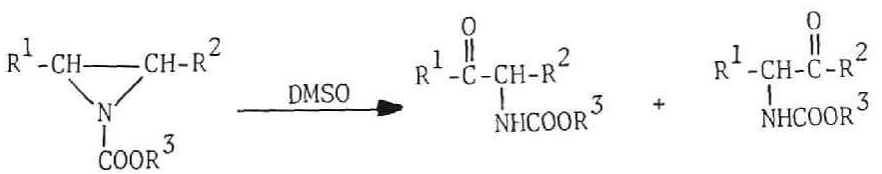


Table 1 Physical Properties of New Compounds Obtained.[a]

Compd	Yield (%)	bp (°/mm) [mp (°)]	IR (cm^{-1})[b]	NMR (δ ppm)[c]
2b[d]	58	[78.5-78.9] (EtOH)	3330, 1685, 1550 1375, 1270, 1245 1090, 1038[e]	5.4-5.0 (broad, 1 H), 4.5-3.8 (m + q, 4 H) 2.3-1.6 (m, 12 H), 1.25 (t, 3 H)
2c[f]	72	[101.6-102.2]	3260, 1688, 1552 1280, 1267, 1043 700[e]	7.35 (s, 5 H), 5.6-5.2 (broad, 1 H), 5.0-4.7 (m, 1 H), 3.70 (s, 3 H), 3.52 (d, J = 6 Hz, 2 H)
3b[h]	56[i] 47[j]	103-110/0-07	1720, 1470, 1370 1294, 1278, 1227 1100	4.05 (q, 2 H), 2.4-0.9 (m + t (δ 1.25), 17 H)
3c[k]	68	90-93/0.08	1725, 1445, 1320 1305, 1280, 1230 1200, 760, 700	7.18 (s, 5 H), 3.63 (s, 3 H), 3.37 (q, 1 H) 2.55 (d, J = 6 Hz, 1 H), 2.13 (d, J = 3.6 Hz, 1 H)
3d[l]	45	100-105/0.05	1720, 1475, 1370 1305, 1260, 1175 1015, 795, 760, 725	7.5-7.0 (m, 4 H), 3.9-2.7 (m + q, 6 H) 0.85 (t, 3 H)
3f[m]	65[i]	64/0.06	1720, 1445, 1370 1295 1230, 1090 1020	5.9-5.3 (m, 2 H), 6.06 (q, 2 H), 2.6-1.7 (m, 10 H), 1.28 (t, 3 H)

Table 1, continued

4a[n]	o	120/0.04	3350, 1720, 1688 1500-1530 (broad) 1450, 1225, 1095 1065, 970, 700	8.1-7.9 (m, 2 H), 7.6-7.4 (m, 3 H), 5.90 (d, 1 H), 5.25 (quintet, 1 H), 4.06 (q, 2 H), 1.38 (d, 3 H), 1.22 (t, 3 H)
5a[p]	o	[84.8-85.8] (n-hexane/ AcOEt)	3340, 1710, 1495 1230, 1165, 1055 700[e]	7.28 (s, 5 H), 6.2-5.9 (broad, 1 H), 5.25 (d, 1 H), 3.97 (q, 2 H), 2.05 (s, 3 H), 1.18 (t, 3 H)
4b[q]	45	110-120/0.05	3340, 1722, 1703 1500-1530 (broad) 1370, 1330, 1250 1195, 1086, 1042	5.8-5.5 (broad, 1 H), 4.5-3.8 (m + q, 3 H) 3.0-1.5 (m, 12 H), 1.25 (t, 3 H)
4c[r]	66	[97.4-97.8] (AcOEt)	3340, 1726, 1698 1550, 1220, 1040 690[e]	8.1-7.9 (m, 2 H), 7.7-7.4 (m, 3 H), 6.0-5.6 (broad, 1 H), 4.70 (d, J = 5.4 Hz, 2 H), 3.74 (s, 3 H)[g]
4f[s]	58	120-130/0.15	3340, 1720, 1705 1520, 1370, 1300 1250, 1095, 1060 1035, 740	6.0-5.3 (m, 3 H), 4.6-3.7 (m + q, 3 H), 3.0-1.2 (m, 8 H), 1.20 (t, 3 H)

Footnotes for Table 1

[a] For the *trans* and *cis* isomers of 3a, see ref 4.

[b] Neat unless otherwise stated.

[c] Determined in CCl_4 at 24°, 60 MHz unless otherwise stated.

[d] Found: C, 40.8; H, 6.1; N, 4.4. Calcd for $C_{11}H_{20}INO_2$: C, 40.6; H, 6.2; N, 4.3%.

[e] Nujol.

[f] Found: C, 39.7; H, 3.9; N, 4.8. Calcd for $C_{10}H_{12}INO_2$: C, 39.4; H, 4.0; N, 4.6%.

[g] Determined in $CDCl_3$

[h] Found: C, 67.0; H, 9.8; N, 7.1. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1%.

[i] Prepared by method (a).

[j] Prepared by method (b).

[k] Found: C, 67.6; H, 6.2; N, 7.7. Calcd for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9%.

[l] Found: C, 71.7; H, 6.7; N, 6.7. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9%.

[m] Found: C, 67.4; H, 8.8; N, 7.0. Calcd for $C_{11}H_{17}NO_2$: C, 67.7; H, 8.8; N, 7.2%.

[n] Found: C, 65.4; H, 7.1; N, 6.1. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3%.

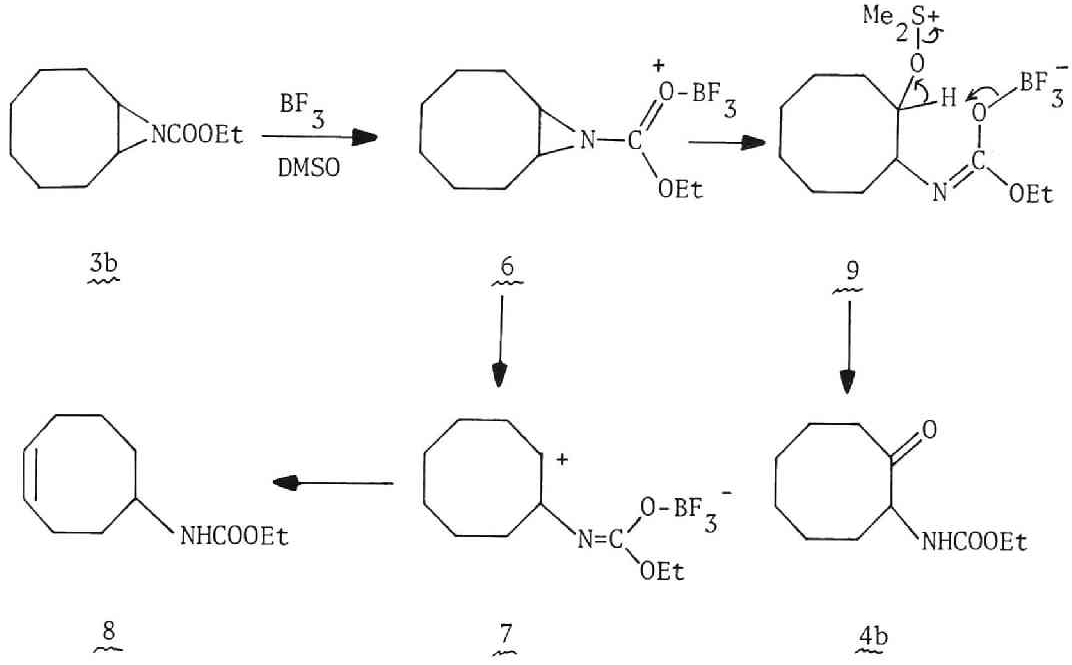
[o] The product ratio of 4a/5a is given in Table 2.

[p] Found: C, 65.2; H, 6.8; N, 6.3. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3%.

[q] Found: C, 62.0; H, 9.0; N, 6.5. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

[r] Found: C, 62.3; H, 5.6; N, 7.2. Calcd for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7; N, 7.3%.

[s] Found: C, 62.9; H, 8.4; N, 6.6. Calcd for $C_{11}H_{17}NO_3$: C, 62.5; H, 8.1; N, 6.6%.



product ratios obtained under various conditions and in the presence of other sulfoxides.

Remarkably, the *cis* isomer of 3a reacted more sluggishly than the *trans* isomer and gave considerable amounts of the regioisomer 5a. The *trans* isomer also afforded increased amounts of 5a in the presence of bulky sulfoxides. This is explained by assuming an S_N2 type transition state (10) between *cis*-3a and 4a. The non-bonded interaction between methyl and phenyl groups in the *cis* isomer inhibits the delocalization of developing plus charge on C(3),[7] which is incidentally more crowded than C(2). Such an effect is absent in the *trans* isomer of 3a, which gives 4a predominantly.

Table 2 Oxidative Cleavage of 3a with Sulfoxides.

Substrate	Sulfoxide	Temp (°)	Total Yield[a] (%)	Product distribution[a] 4a (%)	5a (%)
trans-3a	DMSO[b,c]	120	82	93	7
trans-3a	DMSO[b]	120	78	97	3
trans-3a	DMSO[d]	120	96	100	0
trans-3a	DMSO[d]	120	63	91	9
trans-3a	*i*-PrSOMe[b]	120	62	87	13
cis-3a	DMSO[b,c]	140	56	40	60
cis-3a	DMSO[b]	140	58	54	46
cis-3a	DMSO[d]	120	95	100	0
cis-3a	PhSOMe[b]	140	22	51	49
cis-3a	*i*-PrSOMe[b]	140	e	e	e

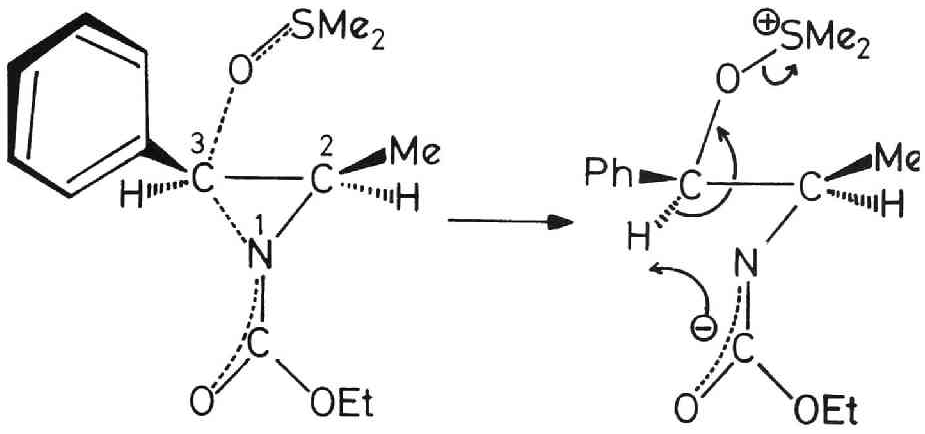
[a] Estimated by GLC (High Vacuum Silicone Grease 30% on Celite 545, 200° or Versamide 900 10% on Celite 545, 184°) using 4,5-decamethylene-1,3-dioxolen-2-one as an internal standard. Unless otherwise stated, they were determined directly on crude mixtures. The reaction was continued 24 hr in each case.

[b] The reaction was performed in a vessel previously washed with aq sodium hydroxide and water.

[c] The total yield and product distribution were determined after single distillation.

[d] The reaction was performed in a vessel previously washed with sulfuric acid and water.

[e] No oxidation products were detected by GLC.



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In the presence of less than a trace of acid, the exclusive product obtained in improved yields was 4a for both isomers. This would be ascribed to S_N1 type bond cleavage affording the benzylic cation, which is then transformed to 5a.[8] These explanations are consistent with transannular results of the ring opening of 3b as described above.

Experimental

Sulfoxides used were heated under reflux over calcium hydride, distilled and stored over molecular sieves. The physical properties and analyses of new compounds are collected in Table 1.

Ethyl trans-2-iodocyclooctane-1-carbamate (2b). Iodine (19 g, 75 mmol) was added at 0° in one portion to a mixture of cyclooctene (8.25 g, 75 mmol), silver cyanate (15 g, 100 mmol) and dry ether (110 ml). Stirring was continued for 7 hr at 0°, then for 4 hr at room temperature. After filtration of the precipitated silver iodide, ethanol (100 ml) containing a small amount of sodium ethoxide (100 mg) was added to the filtrate, which was allowed to stand in the dark for 3 days. The solvent was evaporated *in vacuo* and the residue was poured onto ice-water containing sodium sulfite (5 g), extracted with ether and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a crude solid. Recrystallization afforded 2b (14.0 g).

9-Ethoxycarbonyl-9-azabicyclo[6.1.0]nonane (3b). A mixture of ethyl azidoformate (5.0 g) and cyclooctene (70 ml) in a quartz tube was irradiated with a 200 W high pressure mercury arc until nitrogen evolution had ceased (*ca.* 40 hr). Distillation *in vacuo* gave 3b as a colorless oil (4.8 g).

The aziridine 3b was also obtained by dehydriodination of 2b.

Methyl 2-iodo-1-phenylethane-1-carbamate (2c). This was prepared from styrene (7.8 g, 75 mmol) by the method similar to the one reported.[5]

1-Methoxycarbonyl-2-phenylaziridine (3c). A solution of iodocarbamate (2c) (6.08 g, 20 mmol) in dry benzene (60 ml) was added dropwise to sodium hydride (2.2 g) suspended in dry benzene (30 ml) during 1 hr under a nitrogen atmosphere at 55-60°. After an additional stirring for 3 hr at 55-60°, insoluble materials were filtered off, washed with dry ether and the combined filtrates were carefully concentrated below 40°. Immediate distillation yielded 3c as a colorless oil (2.4 g).

N-Ethoxycarbonyl-1,2-iminoindene (3d). This aziridine was prepared by dehydriodination of ethyl *trans*-2-iodoindan-1-carbamate[5] (2.2 g) as described above. The aziridine (0.61 g) is thermally very unstable and was contaminated by a small amount of an isomerized product. The analytical sample was obtained by chromatography on alumina (elution with n-hexane/benzene 1:3).

9-Ethoxycarbonyl-9-azabicyclo[6.1.0]non-4-ene (3f). A mixture of 1,5-cyclooctadiene (70 ml) and ethyl azidoformate (5.0 g) was irradiated for 40 hr just as described above. Distillation yielded aziridine (3f).

Oxidation of Aziridines with Sulfoxides. General Procedure. A solution of aziridine in dry sulfoxide was heated at 120° under a nitrogen atmosphere for 24 hr. After cooling, the mixture was poured into aq sodium chloride, extracted four times with ether and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and careful distillation afforded the corresponding α-alkoxycarbonyl-amino ketone.

Oxidation of 1-Ethoxycarbonyl-2-methyl-3-phenylaziridine (3a). The *trans*-isomer[4] of 3a (1.64 g, 80 mmol) was oxidized with DMSO. Distillation and subsequent preparative GLC gave N-ethoxycarbonyl-α-aminopropiophenone (4a) and ethyl 1-phenylpropan-2-one-1-carbamate (5a). The former was identical with the authentic sample described below.

The *cis*-isomer[4] of 3a (0.25 g, 2 mmol) was oxidized with DMSO as described above. Distillation gave a mixture of 4a and 5a.

The product distributions were determined by GLC as shown in Table 2, which also summarizes the results of oxidation with sulfoxide under various conditions.

Ethyl Cyclooctane-2-one-1-carbamate (4b). The carbamate (0.58 g) was obtained by DMSO-oxidation of 3b (1.18 g, 6 mmol).

Methyl N-Phenacylcarbamate (4c). Aziridine (3c, 0.50 g, 3 mmol) was oxidized with DMSO. Distillation and recrystallization gave 4c (0.36 g) as colorless plates. GLC analysis of the crude product showed no contamination by other products.

Ethyl Cyclohexan-2-one-1-carbamate (4e). Aziridine[9] (3e) (1.71 g, 10 mmol) was oxidized with DMSO to afford 4e as a colorless oil (1.21 g, 65%) whose spectral data were identical with an authentic sample.[10]

Ethyl Cyclooct-5-en-2-one-1-carbamate (4f). Aziridine (3f) (1.06 g, 53 mmol) was oxidized with DMSO. Distillation and following chromatography on silica gel afforded the corresponding amino ketone 4f (0.66 g).

Isomerization of N-Ethoxycarbonyl-1,2-iminoindene (3d) in DMSO. A solution of 3d (0.40 g, 2 mmol) in dry DMSO (5 ml) was heated at 120° under a nitrogen atmosphere for 24 hr. After usual work-up, chromatographic separation on silica gel afforded 2-ethoxycarbonylaminoindene (11) (0.19 g, 48%), mp 149-150° (acetone). IR (Nujol): 3330, 1702, 1550, 1308, 1240, 1055, 832, 747, 714 cm^{-1}; NMR ($CDCl_3$): δ 7.5-6.7 (m, 5 H), 6.50 (s, 1 H), 4.24 (q, 2 H), 3.63 (s, 2 H), 1.32 (t, 3 H). MS: *m/e* 203 (M^+).

Found: C, 71.0; H, 6.3; N, 6.9. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9%.

N-Ethoxycarbonyl-α-aminopropiophenone (4a). A mixture of sodium dichromate dihydrate (0.6 g, 2 mmol), conc sulfuric acid (1.5 ml) and water (15 ml) was added dropwise at 20° to a solution of N-ethoxycarbonyl-ψ-norephedrine (1.12 g, 5 mmol)[4] in ether (30 ml). After usual work-up, distillation *in vacuo* gave 4a as a colorless oil (1.0 g, 89%). The spectral data are given in Table 1.

Boron Trifluoride-catalyzed Reaction of 3b in DMSO. A

solution of boron trifluoride-etherate (0.1 ml) in DMSO (5 ml) was added under a nitrogen atmosphere to the aziridine 3b (0.30 g, 1.5 mmol) and heated at 120° for 8 hr. After usual work-up, distillation and preparative TLC gave ethyl cyclooct-4-ene-1-carbamate (8) (0.14 g, 47%) and the oxidation product (4b) (0.07 g, 22%). The retention time on GLC and the IR spectrum of each compound were identical with those of the authentic sample.

Ethyl Cyclooct-4-ene-1-carbamate (8). This compound was prepared from 1,5-cyclooctadiene according to the reported method.[11] A solution of 1,5-cyclooctadiene (2.70 g, 25 mmol) in dry xylene (3 ml) was added dropwise under a nitrogen atmosphere to a mixture of urethane (2.23 g, 25 mmol), boron trifluoride-etherate (2 ml) and xylene (8 ml) during 2.5 hr at 80-90°. The mixture was heated at 100° for 22 hr. After usual work-up, chromatography on alumina and following distillation gave 8 as an oil (0.70 g, 17%), bp 100-110°/0.06 mm; IR (neat): 3340, 1690, 1525, 1225, 1096, 1045 cm^{-1}; NMR (CCl_4): δ 5.8-5.5 (m, 2 H), 5.0-4.4 (broad, 1 H), 4.04 (q, 2 H), 3.9-3.3 (m, 1 H), 2.5-1.2 (m, 8 H), 1.24 (t, 3 H).

Found: C, 67.1; H, 10.0; N, 6.9. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1%.

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(6) Direct protonation of N-acylaziridine has been reported to result in carbonyl oxygen and not nitrogen protonation. See, G. A. Olah and P. J. Szilagyi, *J. Amer. Chem. Soc.*, 91, 2949 (1969).

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(8) The acid-catalyzed ring-opening of 3a has been reported to involve the racemization of the configuration on C(3) corresponding to the S_N1 mechanism. See ref. 4.

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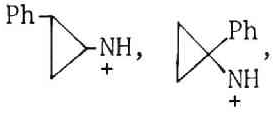
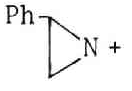
Chapter 8

OXIDATION OF CYCLOPROPYLAMINES AND AZIRIDINES WITH LEAD TETRAACETATE

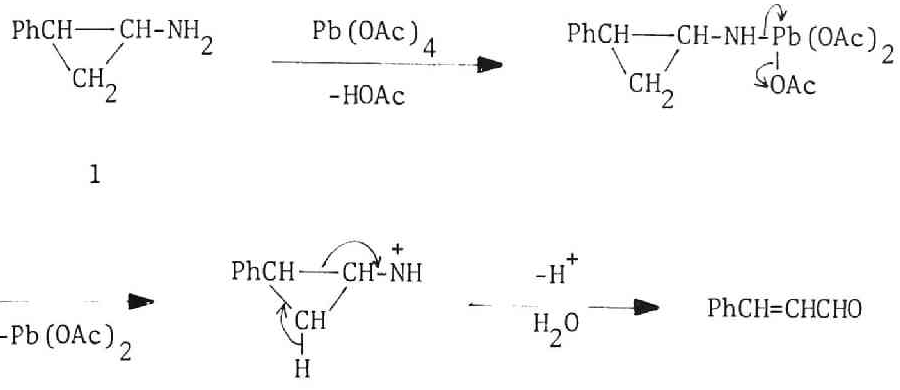
Abstract---The title reaction of 2-phenylcyclopropylamine gives cinnamaldehyde, while that of the 1-phenyl isomer produces benzonitrile and ethylene. The similar treatment of 2-phenylaziridine provides benzaldehyde as the only isolable product. These reactions are explained by assuming the common intermediacy of nitrenium ions such as  , , and  respectively. The assumption is confirmed by the oxidation of the corresponding amines with sodium hypochlorite. Extention of the reaction to 2,3-polymethyleneaziridines with R group on C(2) afforded R-CO-$(CH_2)_n$-C≡N type products (R = H, alkyl, phenyl) in preparative yields. This provides a novel method of C=C bond cleavage of cycloalkenenes.

Information on reactive metastable species has been accumulating.[1] Among them much attention has been focused on the oxidation of amines with metal salts in higher valency.[2] The species involved in the oxidation are nitrenium ions, nitrogen radicals,[3] and nitrenes.[4] We wish to report that the lead tetraacetate oxidation of cyclopropylamines and aziridines proceeds nitrenium ion intermediates.[5]

The trans isomer of 2-phenylcyclopropylamine (1) in dichloromethane was treated with equimolar lead tetraacetate at -78° to afford *trans*-cinnamaldehyde. The oxidation of the cis isomer of 1 gave the same product. The regioisomer, 1-phenylcyclopropylamine (2), reacted in a completely different way to produce benzonitrile and ethylene, the latter being ascertained by obtaining 1,2-dibromoethane.

Nitrene intermediates in these reactions are excluded on the basis of the following facts. Thermal decomposition of cyclopropyl azides results in the ring expansion to yield 1-azetines.[6] This transformation involves cyclopropylnitrene intermediates.[6c] In contrast, however, fragmentation to olefins and nitriles is observed when appropriately substituted cyclopropyl azides are decomposed.[7] The choice of either ring expansion or fragmentation seems to depend upon the substituents on the cyclopropane ring. The fragmentation is particularly favored in the one that partial positive charge being developed in the transition state resides on the remaining nitrogen upon the extrusion of nitrogen molecule.[7]

More appropriately the above oxidation can be explained by assuming the intermediacy of nitrenium ions.[8] In order to confirm this, the amines *trans*-1 and 2 were treated successively with sodium hypochlorite and with silver perchlorate. The products obtained under such nitrenium ion producing conditions[9] were the same as in the above oxidation, *i.e.*, cinnamaldehyde from *trans*-1 and benzonitrile from 2.



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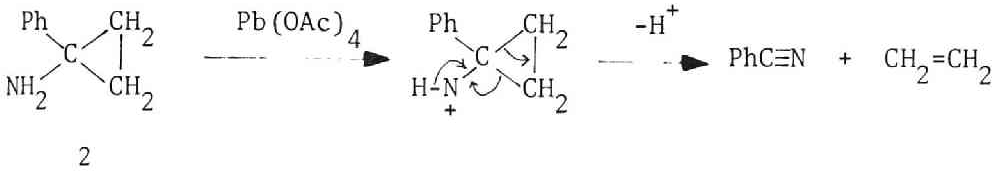

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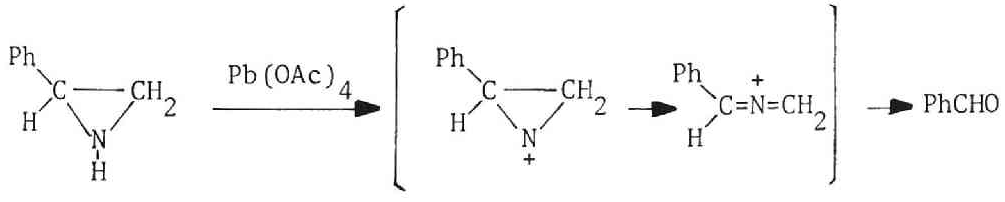
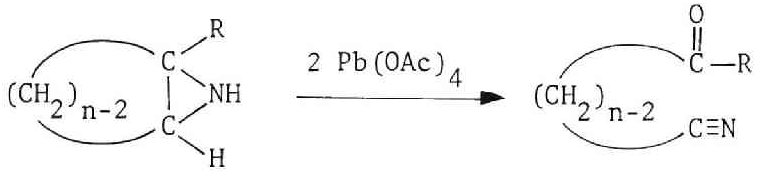
Oxidation of 2-phenylaziridine (3) gave benzaldehyde as a sole isolable product. Possibly the reaction involves nitrenium ion intermediate 4[10] and the 2-azaallenyl cation 5,[11] which is then oxygenated to benzaldehyde. With this observation in hand we examined lead tetraacetate oxidation of aziridines fused with medium and large rings.



3 4 5

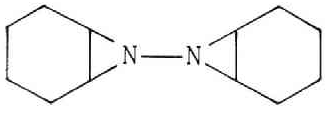
The aziridine 6a dissolved in dichloromethane was treated with lead tetraacetate under a nitrogen atmosphere at -40°. Stirring for 1 hr at -40°, warming up to room temperature during 2 hr and

work-up gave 12-cyano-2-dodecanone (7a). Best results were obtained upon the use of two molar equivalents of lead tetraacetate. The structure of the product was unambiguously confirmed by the alternative synthesis of 7a. Namely, ethyl acetoacetate was alkylated with 1,9-dibromononane and the resulting product was heated in aqueous dimethyl sulfoxide containing sodium cyanide. Both decarboxylation[12] and replacement of bromine by cyano group were attained in this single operation yielding 7a. The oxidation was extended to aziridines 6b, 6c, 8a-c, and to the nonamethylene homologue 11a. The yields as well as the physical properties of the products are listed in Table 2. In contranst to the above results, 7-azanorcarane (10c) was recovered unchanged under the typical condition, but the reaction at reflux of dichloromethane gave a product tentatively assigned as 13.



6 (n = 12), 8 (n = 8) 7 (n = 12), 9 (n = 8)
10 (n = 6), 11 (n = 11) 12 (n = 11)

a: R = Me, b: R = Ph, c: R = H



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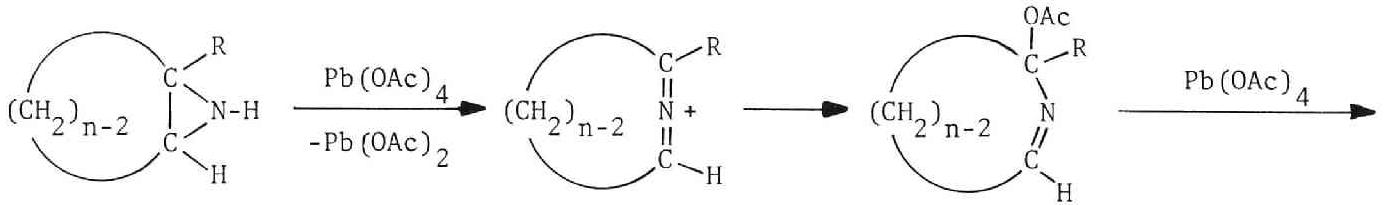
The mechanism of the novel transformation can be understood by the following scheme involving two moles of lead tetraacetate. A cyclic 2-azaallenyl cation is readily susceptible to nucleophilic attack of acetate anion to give 14. Addition of lead tetraacetate on the C=N bond in 14 followed by elimination yields 15. Facile thermal rearrangement affords a *gem*-diacetate 16, characterized by the spectrometry of the crude product (1735-1744 cm^{-1}, δ ~2.0 (singlet)). Purification upon silica gel TLC induces the hydrolysis of 16 to give the corresponding ω-cyano carbonyl compound. Obviously 10c should give a nitrenium ion which can not be isomerized to a seven-membered azaallenyl cation due to the strain. This accounts for the formation of 13.

The transformation of an olefin into an ω-cyanoaldehyde has been previously achieved by the addition of nitrosyl chloride and the following Beckmann rearrangement.[13] The present method is more generally applicable, as the 2-substituted aziridines are easily obtained from cyclic ketone oximes by means of the Neber reaction[14] proceeding in the presence of Grignard reagents or organolithiums.

Experimental

Oxidation of Amines 1, 2, and 3 with Lead Tetraacetate. A General Procedure. To a solution of lead tetraacetate (490 mg, 1.1 mmol) in dichloromethane (20 ml) an amine (1.0 mmol) dissolved in dichloromethane (5 ml) was added dropwise under a nitrogen atmosphere at -78°. The mixture was then gradually warmed up to room temperature in *ca.* 10 hr. Isolation of the product was accomplished by concentration of the reaction mixture, followed by preparative TLC. The product was identified by the comparison of

Scheme



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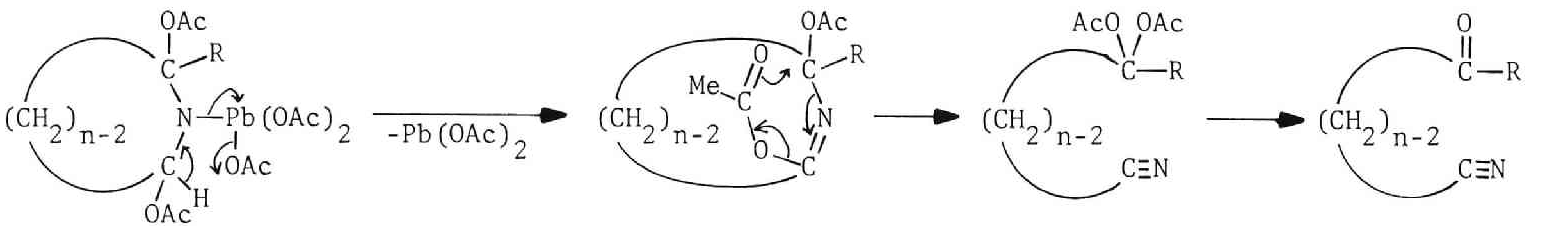

15 16

its spectral data with those of the authentic specimen. The results are summarized in Table 1. The yields were estimated either by the isolation or GLC assay as indicated.

Oxidation of Amines, trans-1 and 2, with Sodium Hypochlorite. An amine (0.6 mmol) was added to ice-cooled commercially available aqueous sodium hypochlorite (5% content, 5.2 g) at 0°. The mixture was stirred at 0° for 10 min and then at room temperature for 1 hr. Extractive work-up with ether gave a crude product which was treated with silver perchlorate (166 mg) in acetone (5 ml) for a night. The results are listed in Table 1.

Oxidation of 2,3-Polymethyleneaziridines. A Typical Procedure. Aziridine 6a (197 mg, 1.0 mmol) dissolved in dichloromethane (4 ml) was added to a solution of lead tetraacetate (1.00 g, 2.3 mmol) in dichloromethane (15 ml) under a nitrogen atmosphere at -40°. Precipitation of lead diacetate immediately occurred. The mixture was gradually warmed up to room temperature in 6 hr and then concentrated *in vacuo*. The product 7a (171 mg, 82% yield) was separated from lead diacetate by preparative TLC on silica gel (n-hexane/ether 3:1, R_f 0.4). The yields and the physical properties of the products are collected in Table 2.

1-Methyl-13-azabicyclo[10.1.0]tridecane (6a). A methylmagnesium iodide solution prepared from methyl iodide (11.4 g, 80 mmol) and magnesium (2.0 g, 82 mmol) in ether (20 ml) was diluted with toluene (20 ml) and then cyclododecanone oxime (3.94 g, 20 mmol) was added. Ether was removed by heating the mixture and the remaining toluene solution was heated to reflux overnight. The mixture was poured into ice-cooled aqueous ammonium chloride and extracted with benzene. Work-up and distillation at 89-90°/0.1 mm gave the aziridine 6a (2.19 g, 56% yield), mp 33.0-33.5° (n-hexane). IR (neat): 3250, 888 cm^{-1}, NMR (CCl_4): δ 0.9-2.4 (m + s (δ 1.17), methylenes, methyl and methine), MS: *m/e* 195 (M^+), 194 (M^+-1), 180

Table 1. Oxidation of 1, 2, and 3.

Amine	Oxidant	Product	Yield (%)
trans-1	$Pb(OAc)_4$	PhCH=CHCHO	79[a]
trans-1	NaOCl	PhCH=CHCHO	34[a]
cis-1	$Pb(OAc)_4$	PhCH=CHCHO	84[a]
2	$Pb(OAc)_4$	PhC≡N[c]	69[b]
2	NaOCl	PhC≡N	21[b]
3	$Pb(OAc)_4$	PhCHO	42[b]

[a] Isolation yield. [b] Estimated by gas-chromatographic assay. [c] The accompanying ethylene was identified as 1,2-dibromoethane.

(M^+-15).

Found: C, 79.8; H, 13.2; N, 7.4. Calcd for $C_{13}H_{25}N$: C, 79.9; H, 12.9; N, 7.2%.

1-Phenyl-13-azabicyclo[10.1.0]tridecane (6b). Cyclododecanone oxime (5.91 g, 30 mmol) and toluene (70 ml) were added to an ethereal solution of phenyllithiuml prepared from lithium dispersion (1.75 g) in ether (50 ml) and bromobenzene (18.8 g, 120 mmol)). The resulting suspension was concentrated to remove ether and heating was continued for 24 hr (bath temperature 140°). Work-up and column chromatography (silica gel, n-hexane/ether 1:1) afforded 6b (6.19 g, 80%), mp 55-56° (n-hexane). IR (Nujol): 3230, 1604, 1580, 763, 701 cm^{-1}, NMR: δ 0.5 (broad s, 1 H, NH), 0.8-2.2 (m, 21 H, methylenes and methine), 7.10 (s, 5 H, Ph). MS: *m/e* 257 (m^+), 256 (M^+-1), 148 (100%).

Found: C, 83.8; H, 10.8; N, 5.7. Calcd for $C_{18}H_{27}N$: C, 84.0; H, 10.6; N, 5.4%.

13-Azabicyclo[10.1.0]tridecane (6c). A mixture (*ca.* 1:1) of *cis*- and *trans*-cyclododecene (1.66 g, 10 mmol) was treated with silver isocyanate (2.0 g, 13 mmol) and iodine (2.54 g, 10 mmol) in tetrahydrofuran (20 ml) in a similar manner as the reported procedure[15] to obtain methyl 2-iodocyclododecanecarbamate, mp 108-109.5° (n-hexane), IR (Nujol): 3200, 1692, 1536 cm^{-1}.

Found: C, 45.9; H, 7.2; N, 3.7. Calcd for $C_{14}H_{26}INO_2$: C, 45.8; H, 7.1; N, 3.8%.

The carbamate (1.11 g, 30 mmol) was heated in methanol (40 ml) and water (8 ml) containing sodium hydroxide (2.4 g, 60 mmol) for 2 hr. Work-up followed by distillation at 120-130° (bath temperature)/0.2 mm gave the aziridine 6c (490 mg, 90% yield), mp 46.5-47.5° (n-hexane), IR (neat): 3250, 969, 874 cm^{-1}.

Found: C, 79.4; H, 12.9; N, 7.8. Calcd for $C_{12}H_{23}N$: C, 79.5; H, 12.8; N, 7.7%.

1-Methyl-9-azabicyclo[6.1.0]nonane (8a). The aziridine was obtained in 62% yield, bp 103-105°/0.1 mm. IR (neat): 3230, 1601, 1496, 931, 828, 809, 760, 742, 701 cm^{-1}, NMR (CCl_4): δ 0.7-2.7 (m, 14 H), 7.0-7.7 (m, 5 H), MS: *m/e* 201 (M^+), 200 (M^+-1).

Found: C, 83.4; H, 9.7; N, 6.7. Calcd for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.0%.

Aziridines 8c and 10c. The aziridines were prepared according to the literature.[16]

1-Methyl-12-azabicyclo[9.1.0]dodecane (11a). The aziridine was obtained by the similar method from cycloundecaone oxime in 71% yield, bp 160-165°/22 mm. IR (neat): 3250, 894 cm^{-1}, NMR: δ 0.2-0.7 (broad s, 1 H), 0.7-2.3 (m + s (δ 1.18), 22 H), MS: *m/e* 181 (M^+).

Found: C, 79.5; H, 12.8; N, 7.7. Calcd for $C_{12}H_{23}N$: C, 79.4; H, 12.9; N, 7.6%.

Table 2 Lead Tetraacetate Oxidation of Aziridines 6, 8, 10 and 11, and the Physical Properties of the Products.

Aziridine	Product	Yield(%)	bp or mp	IR(cm^{-1})[a]	NMR(δ)
6a	7a[b]	82	110°/0.09 mm (bath temp)	2260, 1713	0.9-2.0 (m, 16 H, methylenes), 1.98 (s, 3 H, Me), 2.1-2.5 (m, 4 H, CH_2CO and CH_2CN)
6b	7b[c]	85	54-55° (n-hexane)	2270, 1678 1600, 1580[d]	1.0-2.0 (m, 16 H, methylenes), 2.27 (t, J = 6 Hz, 2 H, CH_2CN), 2.90 (t, J = 6 Hz, 2 H, CH_2CO), 7.2-7.7 (m, 3 H, Ph-*m*,*p*), 7.8-8.1 (m, 2 H, Ph-*o*)
6c	7c[e]	58	2,4-DNPH[f] 91-92°	2725, 2250 1723	1.0-2.0 (m, 16 H, methylenes), 2.0-2.6 m, 4 H, CH_2CO and CH_2CN), 9.77 (t, J = 1.8 H, 1 H, CHO)
8a	9a[g]	58	120°/2.5 mm	2260, 1711	1.0-2.0 (m, 8 H, methylenes), 2.06 (s, 3 H Me), 2.2-2.6 (m, 4 H, CH_2CO and CH_2CN)
8b	9b[h]	46	41-41.5° (n-hexane)	2255, 1677 1600, 1580 742, 727 690	0.8-2.0 (m, 8 H, methylenes), 2.28 (t, J = *ca.* 6 Hz, 2 H, CH_2CN), 2.90 (t, J = 6 Hz, 2 H, CH_2CO), 7.0-7.6 (m, 3 H, Ph-*m*,*p*), 7.8-8.1 (m, 2 H, Ph-*o*)
8c	9c[i]	29	100°/0.07 mm 2,4-DNPH[j] 75-77°	2730, 2255 1722	1.0-2.0 (m, 8 H, methylenes), 2.0-2.8 (m, 4 H, CH_2CO and CH_2CN), 11.07 (t, J = 1.4 Hz, 1 H, CHO)
11a	12a[k]	82	140-145°/6 mm (bath temp)	2260, 1716	0.6-2.0 (m, 14 H, methylenes), 2.09 (s, 3 H, Me), 2.1-2.6 (m, 4 H, CH_2CN, CH_2CO)
10c	13[l]	-		955, 840, 790	0.8-2.0 (m)

Footnotes of Table 2

[a] Neat unless otherwise stated.

[b] MS: *m/e* 209 (M^+). Found: C, 74.6; H, 11.1; N, 6.7. Calcd for $C_{13}H_{23}NO$: c, 74.6; H, 11.1; N, 6.7%.

[c] MS: *m/e* 291 (M^+). Found: C, 79.9; H, 9.3; H, 9.3. Calcd for $C_{18}H_{25}NO$: C, 79.7; H, 9.3; N, 5.2%.

[d] Nujol.

[e] MS: *m/e* 195 (M^+).

[f] Lit., 90-92° (Ref 12).

[g] MS: *m/e* 153 (M^+). Found: C, 70.4; H, 10.0; N, 9.2. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1%.

[h] MS: *m/e* 215 (M^+). Found: C, 70.4; H, 10.0; N, 9.2. Calcd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5%.

[i] MS: *m/e* 139 (M^+).

[j] Lit., 76-77° (Ref 12).

[k] MS: *m/e* 195 (M^+). Found: C, 73.6; H, 11.1; N, 7.2. Calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.8; N, 7.2%.

[l] MS: *m/e* 192 (M^+).

Alternative Preparation of 12-Cyano-2-dodecanone (7a). Ethyl acetoacetate (1.30 g, 10 mmol) was added to sodium hydride (10 mmol) suspended in dimethoxyethane (20 ml). After the evolution of hydrogen gas ceased 1,9-dibromononane (2.86 g, 10 mmol) was added to the resulting pale yellow solution. Stirring at room temperature for two days, followed by chromatographic separation of the crude product, gave 12-bromo-3-ethoxycarbonyl-2-dodecanone (0.62 g, 54% yield based on the consumed dibromide). The alkylate was dissolved in 95% aqueous dimethyl sulfoxide (10 ml) containing sodium cyanide (0.50 g), and the solution was heated at 160-165° for 3 hr. Extractive work-up and the subsequent purification by preparative TLC (silica gel, ether/n-hexane 1:3, R_f 0.4-0.5) afforded 7a (0.11 g, 28% yield). All the spectral data were identical with those of the oxidation product.

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Publication List

I. Parts of the present thesis have been published in the following journals.

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Chapter 8 *Tetrahedron Letters*, 2143 (1973).
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II. Following publications are not included in this thesis.

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