Synthesis of Adamantanoid Ketones from Bridgehead Alcohols by the Hypoiodite Thermolysis–Cyclization Sequence[1]

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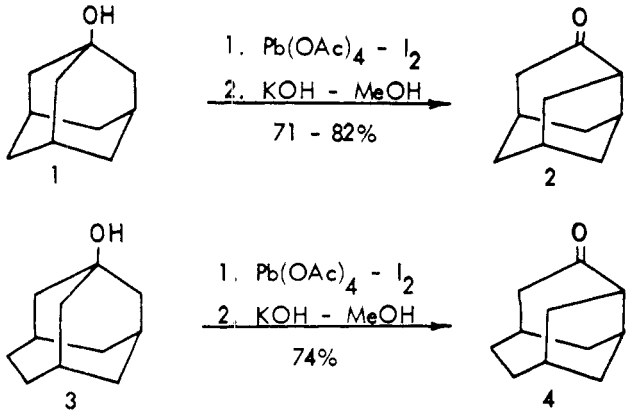
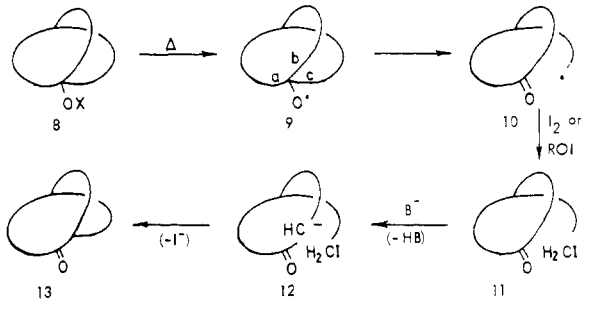
Thermolysis of tertiary polycyclic hypoiodites followed by base-promoted C-alkylation of the resulting iodo ketones appears to be an excellent synthetic route to a number of adamantanoid ketones. The hypoiodites can be prepared readily from the corresponding alcohols by the action of $Pb(OAc)_4$ and iodine and thermolyzed in a single operation. 6-Protoadamantanol yielded 70% of a 3:2 mixture of 4-homobrendan-4-one (tricyclo-[5.2.1.$0^{3,8}$]decan-4-one) and 2-homobrendan-2′-one (tricyclo[5.2.1.$0^{4,8}$]decan-3-one); 3-noradamantanol produced 30% of a 2:1 mixture of tricyclo[3.3.1.$0^{2,7}$]nonan-3-one and 1-hydroxy-2-oxaadamantane, while 4-homoisotwistan-3-ol gave exclusively the elimination product, 8-methylenebicyclo[4.4.0]decan-2-one. This route has been successfully used also in the preparation of protoadamantan-4-one,[5] 10-homoprotoadamantan-4-one (tricyclo[4.3.2.$0^{3,8}$]undecan-4-one)[6] and 4-homoprotoadamantan-4-one (tricyclo[5.3.1.$0^{3,9}$]undecan-4-one).[7] The direction of α-CC bond scission in the thermolysis of polycyclic hypoiodites appears to be controlled by the relative thermodynamic stabilities of the intermediary carbonylalkyl free radicals. In most cases this can be approximated simply by combination of the relative strain energies of the corresponding hydrocarbons and the relative stabilities of the free-radical centers. The course of intramolecular C-alkylation of polycyclic ketones is controlled by the balance of at least three factors: preferential enolization, the size of the smallest ring to be formed, and the degree of distortion of the preferred collinear arrangement of the enolate α-carbon atom and the carbon–leaving group bond.

Thermolysis of polycyclic hypohalites attracted our attention as a potentially general synthetic route to adamantanoid ketones. While thermolytic cleavage of long-chain aliphatic hypohalites yields mainly δ-halo alcohols,[2,3] short-chain, aliphatic and cyclic, tertiary hypohalites produce substantial amounts of the α-CC bond scission products: ketones and halides.[2-4] Polycyclic hypohalites will give halo ketones, which can be cyclized to polycyclic ketones by base-promoted C-alkylation. Hypoiodites appear to be particularly convenient, since they can be prepared readily from alcohols by the action of lead tetraacetate and iodine and thermolyzed in a single operation.[3]

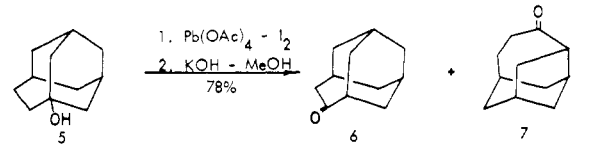
Thermolysis of 1-adamantyl hypoiodite (prepared in situ from 1-adamantanol, 1), followed by intramolecular, base-promoted, C-alkylation of the resulting bicyclic iodo ketone, afforded 71–82% of protoadamantan-4-one (**2**).[5]



Scheme I



1-Homoadamantanol (**3**) produced 74% of 10-homoprotoadamantan-4-one (**4**),[6] while 3-homoadamantanol (**5**) yielded 78% of a 3:2 mixture of homoadamantan-4-one (**6**) and 4-homoprotoadamantan-4-one (**7**).[7] The procedure is simple and the yields are good. However, the product structure frequently could not be easily predicted.



The most plausible mechanism[1,5a] (Scheme I) involves formation of the hypoiodite (**8**, X = I) in situ from the alcohol (**8**, X = H), followed by homolytic cleavage of the O–I bond and rearrangement of the resulting alkoxy radical (**9**) by scission of one α-CC bond (a, b, or c) to give the carbonylalkyl radical **10** and the corresponding iodo ketone (**11**). Intramolecular, base-promoted, C-alkylation of the iodo ketone produces the rearranged polycyclic ketone (**13**) via the enolate (**12**). Since two α-carbonyl methylene groups in the iodo ketone are activated, two isomeric polycyclic ketones could be formed from each iodo ketone. Consequently, the structure of the polycyclic ketone will depend on both the direction of CC bond scission in the alkoxy radical **9** and the course of intramolecular C-alkylation of the substituted ketone **11**. While the former

(1) Preliminary accounts of a portion of this work were presented at the 6th Meeting of Chemists of Croatia, February 1979, Zagreb, Yugoslavia, and were published recently: Z. Majerski and J. Janjatović, *Tetrahedron Lett.*, 3977 (1979).

(2) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593 (1963).

(3) J. Kalvoda and K. Heusler, *Synthesis*, 501 (1971), and references therein.

(4) J. W. Wilt and J. M. Hill, *J. Org. Chem.*, **26**, 3523 (1961); T. L. Cairns and B. E. Englund, *ibid.*, **21**, 140 (1956); D. B. Deney and W. F. Beach, *ibid.*, **24**, 108 (1959); F. D. Green, *J. Am. Chem. Soc.*, **81**, 2688 (1959).

(5) (a) R. M. Black and G. B. Gill, *J. Chem. Soc. D*, 972 (1970); (b) W. H. W. Lunn, *J. Chem. Soc. C*, 2124 (1970); (c) V. Boido and O. E. Edwards, *Can. J. Chem.*, **49**, 2664 (1971); (d) D. Lenoir, *Synth. Commun.*, 103 (1979); (e) Z. Majerski and Z. Hameršak, *Org. Synth.* **59**, 147 (1979).

(6) Z. Majerski, Z. Hameršak, and D. Škare, *Tetrahedron Lett.*, 3943 (1977).

(7) Z. Hameršak, D. Škare, and Z. Majerski, *J. Chem. Soc., Chem. Commun.*, 478 (1977).

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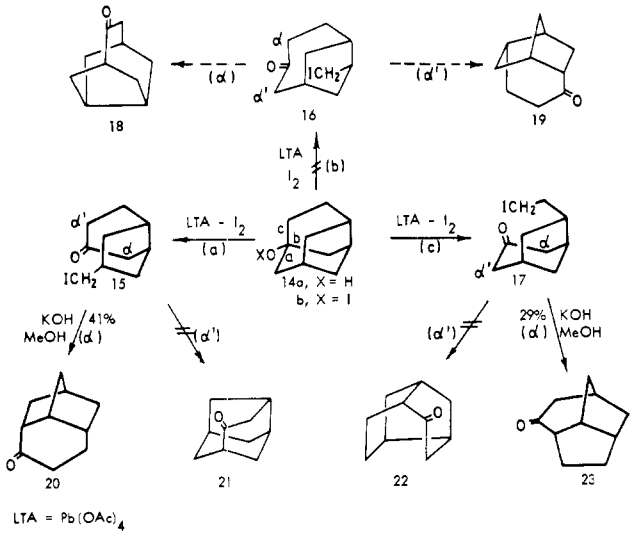
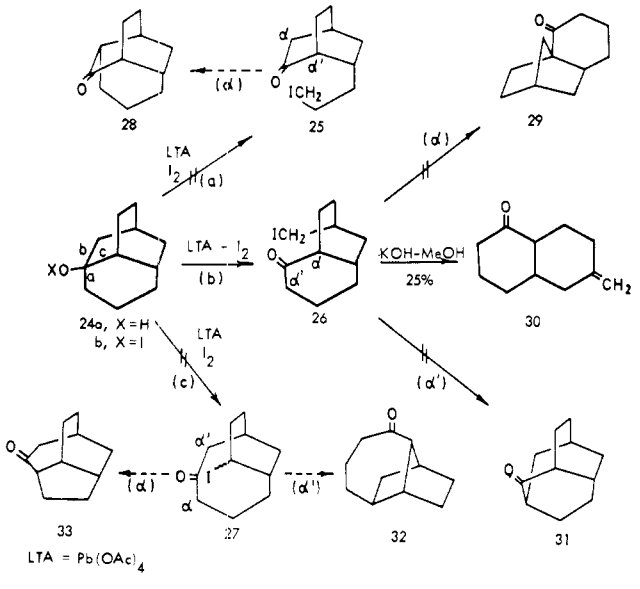
Scheme II



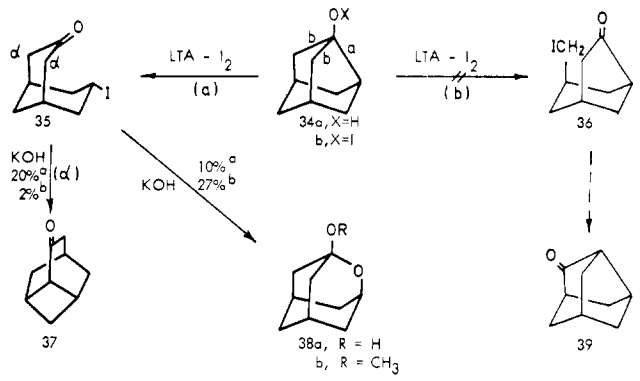
Scheme III



of these two reactions has been little studied, particularly with polycyclic systems, the latter has been widely used in synthetic chemistry and extensively studied recently by House[8] and Baldwin[9] using relatively simple systems. However, the intramolecular C-alkylations of bicyclic and polycyclic ketones appear to be more complex, and their course cannot be easily predicted. Most of the substrates studied so far could cyclize via just one carbanion center to yield one product.[10]

In this work we have studied thermolytic α-CC bond scission in bridgehead polycyclic hypoiodites and intramolecular, base-promoted, C-alkylation of the resulting

Scheme IV[a,b]



[a] LTA = $Pb(OAc)_4$. [b] (a) KOH in 70% aqueous dioxane; (b) KOH in methanol.

iodo ketones, in order to discover the main factors which direct the course of these two reactions. As the starting materials were used 6-protoadamantanol[11] (**14a**), 4-homoisotwistan-3-ol[12] (**24a**), and 3-noradamantanol (**34a**).

Unlike the systems studied previously,[5-7] all three α-CC bonds in **14** and **24** (Schemes II and III) are nonequivalent ($a \neq b \neq c$). Consequently, three isomeric iodo ketones, **15–17**, could be formed through the CC bond scission of **14** (Scheme II). The intramolecular C-alkylation of **15–17** could theoretically produce six ketones, **18–23**. Analogously, **24** (Scheme III) could give three iodo ketones, **25–27**, and five ketones, **28**, **29**, and **31–33**. Since the enolization toward the α' bridgehead carbon atom in iodo ketone **25** is highly unfavored, only one ketone (**28**) may reasonably be expected to arise from **25**. 3-Noradamantyl hypoiodite (**34b**, Scheme IV) could theoretically yield secondary iodo ketone **35** and primary iodo ketone **36**. The two α-carbonyl methylene groups in **35** are equivalent, while the enolization toward the α bridgehead carbon atom in **36** is forbidden. Consequently, the intramolecular C-alkylation of **35** and **36** could be expected to produce just two ketones, **37** and **39**, respectively.

Results

Hypoiodites **14b**, **24b**, and **34b** were prepared and thermolized in a single operation by treatment of the corresponding alcohols (**14a**,[11] **24a**,[12] and **34a**) with lead tetraacetate and iodine in a dry benzene solution at 60–70 °C. The solid materials were removed, and the filtrate was concentrated to give the crude iodo ketone(s), which was treated with methanolic KOH. The resulting product(s) was purified by column chromatography.

Thermolysis of 6-protoadamantyl hypoiodite (**14b**, Scheme II) produced an approximately 3:2 mixture (by ^1H NMR) of two iodo ketones, which yielded a 3:2 mixture of two ketones by intramolecular C-alkylation in methanolic KOH. The ketones were separated on a 10% charcoal–silica gel column by using a 0–5% ethyl acetate–cyclohexane mixture as eluent.[13] The spectral data of both products were in accord with those of all six proposed structures, **18–23**. For assignment of the correct structures to the products, they were reduced to the parent hydrocarbons by the Wolff–Kishner reaction. The major product (41%) was identified as 4-homobrendan-4-one[14]

(8) H. O. House, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.*, **43**, 700 (1978); H. O. House, T. S. B. Sayer, and C.-C. Yau, *ibid.*, **43**, 2153 (1978).

(9) J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 233 (1977); J. E. Baldwin, *ibid.*, 734 (1976).

(10) H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **84**, 3412 (1962); H. W. Whitlock, Jr., and M. W. Siefken, *ibid.*, **90**, 4929 (1968); K. A. Adachi, K. Naemura, and M. Nakazaki, *Tetrahedron Lett.*, 5467 (1968); J. E. McMurray, *J. Am. Chem. Soc.*, **99**, 6821 (1968); E. Piers, R. W. Britton, and W. de Waal, *J. Chem. Soc. D*, 1067 (1969); E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.*, **93**, 5113 (1971); K. J. Schmelzl and R. N. Mirrington, *Tetrahedron Lett.*, 3219 (1970); *J. Org. Chem.*, **37**, 2877 (1972); S. A. Monti and S.-S. Yuan, *ibid.*, **36**, 3350 (1971); S. A. Monti and J. H. Harlless, *J. Am. Chem. Soc.*, **99**, 2690 (1977); S. D. Larsen and S. A. Monti, *ibid.*, **99**, 8015 (1977).

(11) A. Karim and M. A. McKervey, *J. Chem. Soc., Perkin Trans. 1*, 2475 (1974).

(12) K. Aigami, Y. Inamoto, N. Takaishi, Y. Fujikura, A. Takatsuki, and G. Tamura, *J. Med. Chem.*, **19**, 536 (1976).

(13) The separation on silica gel alone and alumina as well as by preparative GLC (DEGS, FFAP, Carbowax 20M, OV-210, QF-1) was less satisfactory.

(**20**, tricyclo[5.2.1.$0^{3,8}$]decan-4-one) by comparing the ^{13}C NMR, ^{1}H NMR, IR, and mass spectra as well as GLC retention time of its parent hydrocarbon, 4-homobrendane,[15] with those of an authentic sample.[16] The ^{13}C NMR spectrum of the hydrocarbon derived from the minor product (29%) showed 10 signals. Such a spectrum can correspond only to structures **21** and **23**.[17] However, the ^{13}C NMR, ^{1}H NMR, IR, and mass spectra of the minor product and its parent hydrocarbon were entirely different from those of authentic samples of protoadamantan-5-one[18] (**21**) and protoadamantane, respectively. Consequently, structure **23** (2-homobrendan-2′-one;[14,19] tricyclo-[5.2.1.$0^{4,8}$]decan-3-one) was assigned to the minor product.

Thermolysis of 4-homoisotwist-3-yl hypoiodite (**24b**, Scheme III) followed by methanolic KOH treatment of the resulting iodo ketone yielded 25% of a single, oily product. The spectral data of this product and the mode of formation indicated that it was 8-methylenebicyclo[4.4.0]-decan-2-one (**30**): ^{13}C NMR δ 211.6 (C=O), 147.2 (C=), 108.0 (H_2C=), 54.4, 45.9, 42.4, 41.7, 33.7, 32.9, 26.4, 26.3; ^{1}H NMR δ 4.6 (s, H_2C=), 1.0–2.6 (m, 14 H); IR 3060 (H_2C=), 1720 (C=O), 1645 (C=C), 885 (H_2C=) cm^{-1}; mass spectrum, *m/e* 164 (M^+, 100%).

3-Noradamantyl hypoiodite (**34b**, Scheme IV) produced almost quantitatively 7-*exo*-iodobicyclo[3.3.1]nonan-3-one[20] (**35**). Crude iodo ketone **35** was cyclized by treatment with sodium hydride in dry tetrahydrofuran and potassium hydroxide in both aqueous dioxane and methanol. The treatment with sodium hydride yielded 17% (based on **34a**) of tricyclo[3.3.1.$0^{2,7}$]nonan-3-one (**37**) as the only definable product. Ketone **37** was identified by the mass spectrum [*m/e* 136 (M^+)], ^{13}C NMR spectrum [δ 213.4 (s, 1 C, C=O), 47.9 (d, 1 C), 47.6 (t, 1 C), 38.5 (t, 1 C) 34.9 (d, 2 C), 34.1 (t, 2 C), 28.4 (d, 1 C)], and IR spectrum [1705, 1725 cm^{-1}, (C=O)]. The physical and spectral properties of the parent hydrocarbon, obtained by the Wolff–Kishner reductioin of ketone **37**, agree well with those reported[22] recently for this compound. The reaction of iodo ketone **35** with potassium hydroxide in 70% aqueous dioxane produced 30% of a 2:1 mixture of **37** and an alcohol. The spectral data of the alcohol revealed that it was 1-hydroxy-2-oxaadamantane (**38a**): ^{13}C NMR δ 94.0 (s, 1 C), 71.9 (d, 1 C), 41.8 (t, 2 C), 34.7 (t, 2 C), 34.6 (t, 1 C), 29.2 (d, 2 C); ^{1}H NMR δ 4.3 (s, 1 H), 3.7 (s, 1 H), 1.5–2.5 (m, 12 H); IR 3280 (OH), 1180 (CO) cm^{-1}; mass spectrum, *m/e* 154 (M^+, 57%). The treatment of iodo ketone **35** with methanolic KOH yielded 29% of a 7:93 mixture of ketone **37** and 1-methoxy-2-oxaadamantane (**38b**; see Experimental Section).

Discussion

Hypoiodite Thermolysis. Thermolytic cleavage of the α-CC bond in polycyclic bridgehead hypoiodites appears to be a selective process. Thermolysis of 6-protoadamantyl hypoiodite (**14b**, Scheme II) proceeds through scission of bonds a and c, rather than b, producing iodo ketones **15** and **17**, while iodo ketone **16** is not formed. It should be noted that all three iodo ketones **15**–**17** are primary with respect to the iodine atom and are formed through the primary carbonylalkyl radicals. 4-Homoisotwist-3-yl hypoiodite (**24b**, Scheme III) produces primary iodo ketone **26** by cleavage of bond b, rather than iodo ketones **25** (primary) and **27** (secondary) by cleavage of bonds a and c, respectively. Thermolysis of 3-noradamantyl hypoiodite (**34b**, Scheme IV) yields secondary iodo ketone **35** through scission of bond a but not primary iodo ketone **36** by cleavage of bond b.

The direction of α-CC bond cleavage in simple tertiary alkoxy radicals is known to depend on the relative stability of the resulting alkyl free radicals.[2] Secondary alkyl radicals are generally more stable than primary ones. However, in the case of polycyclic systems the change in the total strain energy of the system on going from the alkoxy radical to the carbonylalkyl radical should also influence the CC bond cleavage process.

The relative strain energies of the carbonylalkyl free radicals and the corresponding iodo ketones may be assumed to roughly parallel the relative strain energies of the hydrocarbons from which they are derived. Thermolysis of hypoiodite **14b** produces iodo ketones **15** and **17** rather than iodo ketone **16** (Scheme II). The calculated strain energy of the hydrocarbon corresponding to **16** (bicyclo[4.2.1]nonane, 20.95 kcal/mol)[23] is twice the strain energy of the hydrocarbons related to **15** and **17** (bicyclo[4.3.0]nonane, 9.86 kcal/mol; bicyclo[3.2.1]octane, 12.06 kcal/mol).[23] Hypoiodite **24b** (Scheme III) yields exclusively primary iodo ketone **26**, although formation of secondary iodo ketone **27** would involve a secondary free-radical intermediate. Iodo ketone **26** is derived from the thermodynamically more stable hydrocarbon *cis*-bicyclo[4.4.0]decane (strain energy 4.65 kcal/mol)[23] than are both "competitive" iodo ketones **25** and **27** (bicyclo-[2.2.2]octane, 12.95 kcal/mol; bicyclo[5.3.1]undecane, >15 kcal/mol).[23,24] The large difference between the strain energy of the *cis*-bicyclo[4.4.0]decane system and the bicyclo[5.3.1]undecane system prevails over the difference in stabilities between the secondary and the primary free radical. Thermolysis of hypoiodite **34b** (Scheme IV) will produce secondary iodo ketone **35** rather than the primary isomer **36**. Strain energies of the hydrocarbons corresponding to **35** and **36** differ by only 2.5 kcal/mol (bicyclo[3.3.1]nonane, 9.59 kcal/mol; bicyclo[3.2.1]octane, 12.06 kcal/mol),[23] but **35** is derived from a secondary carbonylalkyl radical and **36** from a generally less stable, primary, free radical.

In conclusion, the direction of α-CC bond scission in thermolysis of polycyclic hypoiodites appears to be controlled by the relative thermodynamic stabilities of the intermediary carbonylalkyl free radicals. In most cases this can be approximated simply by combination of the relative

(14) For the semitrivial nomenclature used see: Z. Majerski, S. Djigaš, and V. Vinković, *J. Org. Chem.*, **44**, 4064 (1979).

(15) N. Takaishi, Y. Fujikura, Y. Inamoto, and K. Aigami, *J. Org. Chem.*, **42**, 1737 (1977).

(16) We thank Dr. Bernard Boyer for providing a sample of 4-homobrendan-4′-one, which was reduced to 4-homobrendane.

(17) The ^{13}C NMR spectra of the hydrocarbons corresponding to ketones **18**, **19**, and **22** would show 4, 6, and 6 signals, respectively.

(18) M. Fărcasiu, D. Fărcasiu, J. Slutsky, and P. v. R. Schleyer, *Tetrahedron Lett.*, 4059 (1974).

(19) Derivatives of 2-homobrendane were prepared recently also by: F. J. Jäggi, P. Buchs, and C. Ganter, *Helv. Chim. Acta*, **63**, 872 (1980); A. de Meijere, O. Schallner, C. Weitemeyer, and W. Spielmann, *Chem. Ber.*, **112**, 908 (1979); H. Bos, G. Ellen, G. W. Klumpp, and J. J. Vrielink, *Tetrahedron Lett.*, 5203 (1973); P. v. R. Schleyer, private communication.

(20) Orientation of the 7-iodo substituent was assigned to be exo by comparison of the ^{13}C chemical shifts determined for **35** and the estimated chemical shifts for the exo and endo isomer. The latter were calculated by addition of the chemical shifts of bicyclo[3.3.1]nonan-3-one and those of *cis*- and *trans*-1-iodo-4-*tert*-butylcyclohexane,[21] respectively. Formation of the exo rather than endo isomer may be explained by the preferential attack of iodine on the intermediary 3-oxobicyclo[3.3.1]-non-7-yl radical (in the double chair conformation) from the sterically less hindered exo side.

(21) H.-J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978); also private communication.

(22) R. K. Murray, Jr., and D. L. Goff, *J. Org. Chem.*, **43**, 3844 (1978).

(23) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).

(24) The strain energy of bicyclo[5.3.1]undecane can reasonably be assumed to be higher than that of cyclodecane, from which it can be formally derived by a methylene bridge addition.

strain energies of the corresponding hydrocarbons and the relative stabilities of the free-radical centers.

Intramolecular C-Alkylation. Recently House[8] pointed out that intramolecular, base-promoted, C-alkylation of ketones requires collinear arrangement of the enolate α-carbon atom and the carbon–leaving group bond in the transition state. This arrangement can be attained without excessive distortion of the normal carbon bond angles when the number of the carbon atoms in the endocyclic ketone to be formed is six or larger. However, substantial distortion of the normal carbon bond angles is required to attain the transition state leading to five- or four-membered endocyclic ketones. In these cases, cyclic ethers (O-alkylation products) will be formed rather than ketones.[8]

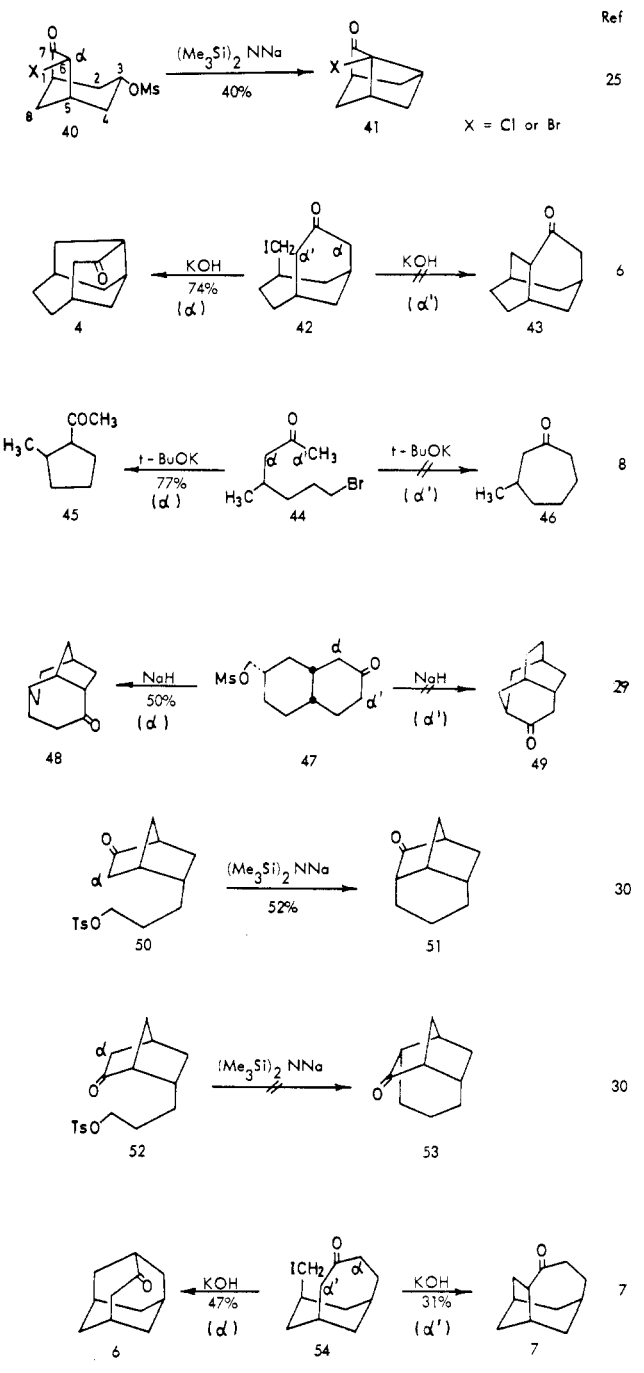
Intramolecular C-alkylation of polycyclic ketones appears to be considerably more complex compared with that of acyclic analogues. Treatment of mesyloxy ketone **40** (Scheme V) with a strong base yielded 40% of tricyclic ketone **41** by formation of the C_3–C_6 bond,[25] i.e., by cyclization of a *five-membered endocyclic ketone ring* (C_1-$C_2C_3C_6C_7$) and a four-membered exocyclic ketone ring ($C_3C_4C_5C_6$), respectively. Owing to the specific skeleton geometry of **40**, its enolate α-carbon atom and the C–OMs bond can rather easily achieve a nearly collinear arrangement.

Iodo ketones **15** and **17**, formed by thermolysis of 6-protoadamantyl hypoiodite (**14b**, Scheme II), yielded exclusively ketones **20** and **23**, respectively. Both iodo ketones **15** and **17** can achieve collinear arrangement of the C–I bond with either of the two enolate α-carbon atoms (α or α').[26] However, formations of ketones **20** and **23** involve cyclization of the five-membered exocyclic (and the eight-membered endocyclic) ketone rings, while formations of ketones **21** and **22** would involve cyclization of the six-membered exocyclic (and the seven-membered endocyclic) ketone rings. Iodo ketone **42** (obtained from 1-homoadamantanol) cyclized readily by methanolic KOH to give ketone **4** rather than isomer **43**[6] (Scheme V). Again, formation of the five-membered exocyclic (and the eight-membered endocyclic) ketone ring is preferred to cyclization of the six-membered exocyclic (and the seven-membered endocyclic) ketone ring. The five- and six-membered exocyclic ketone rings are the smallest rings which could be formed by these cyclizations. It appears that, when a nearly collinear arrangement of the carbon–leaving group bond can be achieved with either of the two enolate α-carbon atoms, the five-membered ring will be formed rather than the six-membered one. This is in good agreement with the rates of the base-promoted cyclizations of ω-halogenoalkylmalonic esters to the cycloalkane-1,1-dicarboxylates.[27] The relative rates of closure of the four-, five-, and six-membered rings were found to be 1:6500:5, respectively. A similar rate ratio was obtained for lactonization of ω-bromoalkanoate anions.[28] These rate ratios were interpreted in terms of the balance between the enthalpy and entropy of activation for the ring closure.

Intramolecular C-alkylations of ketones leading to five- and six-membered exocyclic ketone rings appear to be favored over seven-membered-ring closures. Bromo ketone **44** yielded five-membered exocyclic ketone **45** rather than seven-membered endocyclic ketone **46**[8] (Scheme V). Analogously, mesyloxy ketone **47** gave ketone **48** by formation of the five-membered exocyclic ketone ring rather than isomer **49**,[29] which would be formed by cyclization of the seven-membered endocyclic ketone ring (Scheme V). Both tosyloxy ketones **50** and **52** can easily attain collinear arrangement of the enolate α-carbon and the C–OTs bond, but only isomer **50** cyclized to give tricyclic ketone **51**[30] (Scheme V). Formation of **51** involves cyclization of the six-membered exocyclic (and the eight-membered endocyclic) ketone ring, while formation of **53** would involve cyclization of the seven-membered exocyclic (and the seven-membered endocyclic) ketone ring.

However, iodo ketone **54** (obtained from 3-homoadamantanol) gave a mixture of ketones **6** and **7**[7] (Scheme V). The former isomer arose by cyclization of the six-

Scheme V

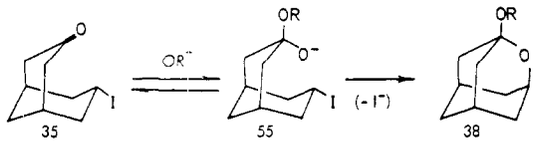


(25) J. M. Harless and S. A. Monti, *J. Am. Chem. Soc.*, **96**, 4714 (1974).
(26) The collinear arrangement involving the enolate α'-carbon atoms can be achieved even easier than with the α-carbons. Nevertheless, ketones **20** and **23** are formed rather than **21** and **22**.
(27) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).
(28) L. Mandolini, *J. Am. Chem. Soc.*, **100**, 550 (1978).
(29) N. Takaishi, Y. Inamoto, Y. Fujikura, and K. Aigami, *J. Org. Chem.*, **44**, 650 (1979).
(30) J. G. Henkel and L. A. Spurlock, *J. Am. Chem. Soc.* **95**, 8339 (1973).

membered exocyclic (and the seven-membered endocyclic) ketone ring and the latter one by cyclization of the five-membered exocyclic (and the eight-membered endocyclic) ketone ring. This may be interpreted in terms of the "less strained" transition state leading to the thermodynamically more stable skeleton **6**.[31] The course of intramolecular C-alkylation of a polycyclic ketone should depend on the relative free energies of activation for the competitive cyclizations (α and α') of the ketone molecule rather than just on those for the corresponding ring closures. However, when both possible products are about equally strained and the entropy changes are not significantly different, the product ratio will depend on the size of the rings to be formed, provided that collinear arrangement of the carbon–leaving group bond can be achieved with both enolate α-carbon atoms. This is correct only if neither of the two possible directions of enolization (α and α') is preferred.

Enolization of a polycyclic ketone toward a bridgehead α-carbon to give a strained olefinic structure should be disfavored. In addition, secondary carbanions are generally more stable than tertiary ones. This may explain why iodo ketone **26** (Scheme III) in methanolic KOH eliminates HI to give methylene ketone **30** rather than cyclizes to ketones **29** and/or **31**. Enolization of **26** toward the α bridgehead carbon atom leading to **29** is disfavored, while the intramolecular C-alkylation of **26** at methylene position α' leading to **31** would require an unfavorable seven-membered-ring closure. Consequently, formation of either **29** or **31** cannot successfully compete with elimination to yield **30**.

Cyclization of iodo ketone **35** (Scheme IV) by potassium hydroxide in aqueous dioxane and methanol yielded 1-hydroxy-2-oxaadamantane (**38**, R = H) and 1-methoxy-2-oxaadamantane (**38**, R = CH_3), respectively, in addition to the expected tricyclic ketone **37**. Ketone **37** arose by cyclization of the six-membered endocyclic and the four-membered exocyclic ketone ring. The 1-substituted 2-oxaadamantanes (**38**) are probably formed by addition of the hydroxide and methoxyde ion, respectively, to the carbonyl group in iodo ketone **35** followed by O-alkylation of the intermediary hemiketal anion **55**. Owing to their



35 55 38

specific geometry, 3,7-disubstituted bicyclo[3.3.1]nonanes are particularly prone to cyclization to adamantanes.[32] The intramolecular C-alkylation of **35** leading to ketone **37** involves an unfavored four-membered-ring closure. In addition, a collinear arrangement of the enolate α-carbon atom and the C–I bond can be attained only with some distortion of the normal carbon bond angles. Consequently, the O-alkylation process, in this case, can successfully compete with the C-alkylation. The C-/O-cycloalkylation ratio is considerably larger in aqueous dioxane than in methanol. This may be explained by the greater nucleophilicity of the methoxide ion, which attacks the carbonyl group in **35** more readily than the hydroxide ion. The equilibrium between iodo ketone **35** and hemiketal anion **55** should be shifted toward the hemiketal anion more in methanolic KOH than in the aqueous dioxane–KOH solution.

We may conclude that the course of intramolecular C-alkylation of polycyclic ketones is controlled by the balance of at least three factors: preferential enolization, the size of the smallest ring to be formed, and the degree of distortion of collinear arrangement of the enolate α-carbon atom and the carbon–leaving group bond.

Experimental Section

^{13}C NMR spectra were taken on a JEOL FX-100 or a Varian XL-100 spectrometer, ^1H NMR spectra were obtained on a Varian EM-360 spectrometer, IR spectra were recorded with a Perkin-Elmer 297 spectrophotometer, and mass spectra were taken on a Varian CH-7 mass spectrometer. GLC analyses were carried out on a Varian Aerograph 940 gas chromatograph. Melting points were determined in sealed capillary tubes completely immersed in oil by using a Thiele apparatus and are uncorrected. Lead tetraacetate was freshly prepared according to a literature procedure[33] or recrystallized from glacial acetic acid and dried prior to use for at least 12 h over KOH and P_2O_5 in an evacuated desiccator which was protected from direct light. The drying agent employed was magnesium sulfate unless otherwise specified.

Preparation and Thermolysis of 6-Protoadamantyl Hypoiodite (14b). A mixture of 6-protoadamantanol[11,34] (**14a**; 1.06 g, 7 mmol), dry $Pb(OAc)_4$ (7.5 g, 17 mmol), and iodine (3.8 g, 15 mmol) was vigorously stirred in 60 mL of dry benzene at 75 °C for 5 min and at 70 °C for an additional 2 h. The reaction mixture was then allowed to cool, and the inorganic salts were removed by filtration and washed with ether. The filtrate was washed successively with a saturated aqueous solution of $Na_2S_2O_3$ (150 mL), water (150 mL), and a saturated aqueous solution of $NaHCO_3$ (100 mL) and dried. Evaporation of the solvent without heating yielded 1.8 g of an oily mixture of products, the spectral data of which indicated the presence of two iodo ketones in a ratio of 3:2: ^1H NMR ($CDCl_3$) δ 3.2 and 3.1 (d + t,[35] 4 H), 1.5–2.7 (m, 26 H); ^{13}C NMR (C_6D_6) 20 signals, δ 209.7 and 210.5 (C=O); IR (film) 1720 cm^{-1} (C=O). The iodo ketones are thermally unstable and were used without purification in the next step within 30 min.

Cyclization of 6-Protoadamantyl Hypoiodite (14b) in Methanolic KOH. The mixture of crude iodo ketones (1.8 g) obtained from **14b** was dissolved in methanol (50 mL), KOH (1.8 g, 32 mmol) was added, and the resulting solution was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into ice–water (200 mL), and the resulting mixture was extracted with ether (3 × 50 mL). The combined extracts were dried. Removal of the solvent left a crude mixture of 4-homobrendan-4-one (**20**) and 2-homobrendan-2′-one (**23**), which was purified on a neutral alumina (activity III) column by using pentane as eluent. The overall yield of the pure ketones (≥96% by GLC; DEGS, 150 °C) was 730 mg (70% based on **14a**). Ketones **20** and **23** were separated by 2 or 3 successive column chromatographies on a 10% charcoal–silica gel column with a 0–5% ethyl acetate–cyclohexane mixture as eluent. For **20**: mp 81–83 °C; ^{13}C NMR ($CDCl_3$) δ 215.4, 50.3, 46.9, 41.4, 37.9, 35.7, 33.8, 33.3, 31.3, 27.7; ^1H NMR ($CDCl_3$) δ 0.8–3.0 (m); IR (neat) 2950 (s), 2870 (m), 1700 (s), 1455 (m), 1290 (m), 1250 (m), 1240 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 150 (M^+, 72), 108 (27), 96 (69), 79 (69), 66 (100). For **23**: mp 121–124 °C; ^{13}C NMR ($CDCl_3$) δ 217.2, 56.1, 49.1, 46.1, 41.6, 41.3, 34.6, 33.9, 33.6, 32.6; ^1H NMR ($CDCl_3$) δ 1.0–2.8 (m); IR (neat) 2940 (s), 2860 (m), 1695 (s), 1450 (m), 1350 (m), 1220 (m), 1110 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 150 (M^+, 100), 107 (88), 95 (60), 79 (90), 67 (91). The ketones were reduced[36] to the parent hydrocarbons by the Wolff–Kishner reaction. The ^{13}C NMR, ^1H NMR, IR, and

(31) E. Osawa, K. Aigami, N. Takaishi, Y. Inamoto, Y. Fujikura, Z. Majerski, P. v. R. Schleyer, E. M. Engler, and M. Färcasiu, *J. Am. Chem. Soc.*, **99**, 5361 (1977).

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(34) ^{13}C NMR ($CDCl_3$) δ 71.4, 48.2, 41.2, 41.0, 36.6, 36.5, 36.0, 35.0, 33.4, 24.2; IR (KBr) 3300 (s), 2930 (s), 2860 (m), 1070 (m) cm^{-1}. The ^1H NMR and mass spectral data agree with those previously reported.[11]

(35) Relative intensity 3:2.

(36) S. H. Liggero, Z. Majerski, P. v. R. Schleyer, A. P. Wolf, C. S. Redvanly, H. Wynberg, J. A. Boerma, and J. Strating, *J. Labelled Compd.*, **7**, 3 (1971).

mass spectral data of 4-homobrendane (derived from **20**) agree well with those reported[15] previously for this compound. However, the melting point of 4-homobrendane, prepared from **20** as well as from 4-homobrendan-4'-one,[16] was determined to be 106–108 °C rather than 65–67 °C as given in ref 15. The physical and spectral data of 2-homobrendane (derived from **23**) are as follows: mp 133–135 °C; ^{13}C NMR (C_6D_6) δ 46.5, 42.8, 41.4, 38.0, 34.1, 33.5, 33.2, 32.9, 30.6, 23.3; ^{1}H NMR (C_6D_6) δ 0.9–2.6 (m); IR (KBr) 2930 (s), 2860 (m), 1470 (w), 1455 (w) cm^{-1}; mass spectrum, *m/e* (relative intensity) 136 (M^+, 27), 95 (30), 94 (27), 85 (60), 71 (83), 57 (100).

4-Homoisotwist-3-yl hypoiodite (24b) was prepared and thermolyzed at 65 °C (5 min at 70 °C) by following the procedure described for 6-protoadamantyl hypoiodite (**14b**). From 500 mg (3 mmol) of 4-homoisotwistan-3-ol (**24a**) was obtained 820 mg of crude iodo ketone **26**.

Reaction of 4-Homoisotwist-3-yl Hypoiodite (24b) with Methanolic KOH. A solution of crude iodo ketone **26** (820 mg) and KOH (820 mg, 14.6 mmol) in methanol (90 mL) was refluxed overnight, allowed to cool down, and poured into ice–water (200 mL). The product was extracted with pentane (3 × 70 mL). The combined extracts were dried. The solvent was evaporated, and the crude product was purified on a neutral alumina (activity II/III) column with pentane–methylene chloride as eluent to give 136 mg (29% based on **24a**) of 8-methylenebicyclo[4.4.0]decan-2-one (**30**): ≥96% pure (by GLC; Carbowax 20M, 150 °C); ^{13}C NMR ($CDCl_3$), see text; ^{1}H NMR ($CDCl_3$), see text; IR (film) 3060 (w), 2920 (s), 1720 (s), 1645 (w), 1445 (w), 885 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 164 (M^+, 100), 149 (19), 97 (85), 93 (48), 81 (48), 80 (48), 79 (56).

3-Noradamantanol (34a) was prepared in 47% overall yield by starting from 2-methyl-2-adamantanol[37] via 7-chlorobicyclo-[3.3.1]non-3-yl methyl ketone and 3-noradamantyl methyl ketone;[5a] the latter was converted to 3-noradamantanol by the Baeyer–Villiger oxidation followed by $LiAlH_4$ reduction.[38]

7-Chlorobicyclo[3.3.1]non-3-yl Methyl Ketone.[39] To a 10% aqueous solution of technical grade NaOCl (56 mL) stirred at 0 °C was added a cold solution of 2-methyl-2-adamantanol[37] (3.4 g, 20.6 mmol) in CCl_4 (14 mL) followed by addition of cold glacial acetic acid (3.5 mL). The reaction mixture was vigorously stirred at 0 °C for 2.5 h. The layers were separated, and the aqueous one was extracted with CCl_4 (2 × 20 mL). The combined extracts were washed with a 3% aqueous solution of $NaHCO_3$ and dried. Half of the solvent was evaporated, and the concentrated solution was refluxed for 7 h. Removal of the solvent left 4.0 g (97%) of oily, light yellow 7-chlorobicyclo[3.3.1]non-3-yl methyl ketone, the spectral data of which agree well with those reported[5a] previously. The crude ketone was used, without purification, for the preparation of 3-noradamantyl methyl ketone.

3-Noradamantyl methyl ketone was prepared by following the reported procedure.[5a] Purification of the crude ketone on a neutral alumina (activity III) column with pentane–ether as eluent afforded 85% of 3-noradamantyl methyl ketone: ≥98% pure by GLC; QF-1, 150 °C; ^{1}H NMR ($CDCl_3$) δ 1.5–2.8 (complex m, sharp signal at δ 2.1); IR (film) 2920 (s), 2860 (m), 1695 (s), 1355 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 164 (M^+, 65), 149 (59), 121 (100), 93 (43), 79 (87), 43 (88).

3-Noradamantyl Acetate. To a stirred mixture of 3-noradamantyl methyl ketone (3.0 g, 18.3 mmol), dry, well-ground Na_2HPO_4 (12 g, 84 mmol), and CH_2Cl_2 (14 mL) was added dropwise a solution of peroxytrifluoroacetic acid in CH_2Cl_2 [prepared from 4.5 mL (32.2 mmol) of trifluoroacetic anhydride and 2.0 mL of 80% H_2O_2 in 4.5 mL of CH_2Cl_2 at 0 °C[40]]. The reaction is exothermic. After the addition of peroxytrifluoroacetic acid, the reaction mixture was cooled in an ice–water bath. The solid materials were removed by filtration, and the filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and dried. Evaporation of the solvent yielded 2.2 g (67%) of crude 3-noradamantyl acetate (≥92% pure by GLC; QF-1, 135 °C), which was purified on a neutral alumina (activity II) column with a 2–5% ethyl acetate–pentane mixture as eluent: ^{1}H NMR ($CDCl_3$) δ 1.3–2.6 (complex m, sharp signal at δ 2.0); IR (film) 2930 (s), 2870 (m), 1740 (s), 1365 (m), 1265 (m), 1230 (s) cm^{-1}; mass spectrum, *m/e* (relative intensity) 180 (M^+, 1.5), 138 (72), 95 (100), 80 (16), 79 (9).

3-Noradamantanol (34a). 3-Noradamantyl acetate (3.0 g, 16.7 mmol) was reduced with $LiAlH_4$ (0.9 g, 23 mmol) in dry ether (80 mL), yielding 85% (1.96 g) of 3-noradamantanol (**34a**): ≥99% pure (by GLC; QF-1, 135 °C); mp 233–235 °C; ^{13}C NMR ($CDCl_3$) δ 84.7 (s, 1 C), 51.2 (t, 2 C), 44.2 (d, 1 C), 43.6 (t, 2 C), 37.9 (d, 2 C), 34.3 (t, 1 C); ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m); IR (KBr) 3260 (s), 2920 (s), 1320 (m), 1150 (w), 1120 (w), 1050 (w) cm^{-1}; mass spectrum, *m/e* (relative intensity) 138 (M^+, 58), 95 (100), 80 (73), 79 (73), 77 (56), 67 (48).

3-Noradamantyl hypoiodite (34b) was prepared and thermolyzed at 60 °C (5 min at 65 °C) by following the procedure described for 6-protoadamantyl hypoiodite (**14b**). From 550 mg (4 mmol) of 3-noradamantanol (**34a**) was obtained 1 g (95%) of crude, solid, iodo ketone **35**: ^{13}C NMR ($CDCl_3$) δ 211.5 (s, 1 C), 46.7 (t, 2 C), 46.1 (t, 2 C), 33.9 (d, 2 C), 31.6 (t, 1 C), 21.1 (d, 1 C); ^{1}H NMR ($CDCl_3$) δ 3.9–4.6 (m, 1 H), 1.8–2.6 (m, 12 H); IR (KBr) 2940 (m), 2920 (s), 2900 (m), 1680 (s), 1335 (m), 1205 (m), 1075 (m), 745 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 264 (M^+, 2), 137 (100), 105 (21), 89 (31), 77 (56).

Tricyclo[3.3.1.0^{2,7}]nonan-3-one (37). A solution of crude iodo ketone **35** (264 mg, 1.0 mmol) in dry THF (2.5 mL) was added dropwise to a suspension of NaH (120 mg, 5 mmol) in dry THF (2.5 mL) and the mixture stirred at room temperature. The reaction mixture was stirred for an additional 20 min at 37–40 °C and then cooled. Ether (5 mL) was added followed by a slow and careful addition of water (5 mL) at 0 °C. The layers were separated and the aqueous one was extracted with ether (2 × 5 mL). The combined ether extracts were dried. Evaporation of the solvent yielded crude ketone **37**, which was purified on a neutral alumina (activity II) column with pentane as eluent followed by sublimation in vacuo. Ketone **37** (≥97% pure by GLC; DEGS, 125 °C) was obtained in 17% yield: 23.6 mg; mp 97–99 °C; ^{13}C NMR ($CDCl_3$), see text; ^{1}H NMR ($CDCl_3$) δ 1.1–3.0 (m); IR (KBr) 2950 (s), 2860 (m), 1725 (s), 1705 (s), 1220 (m), 1085 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 136 (M^+, 65), 95 (58), 92 (60), 79 (57), 68 (100), 67 (79), 58 (51). Ketone **37** was reduced by the Wolff–Kishner reaction[36] to yield 53% of the parent hydrocarbon, tricyclo[3.3.1.0^{2,7}]nonane (mp 137–139 °C), the spectral data of which agree well with those reported[22] previously.

Cyclization of Iodo Ketone 35 in Methanolic KOH. A solution of crude iodo ketone **35** (1.0 g, 3.8 mmol) and KOH (1.0 g, 18 mmol) in methanol (30 mL) was stirred and refluxed for 2 h, cooled to room temperature, and poured into ice–water (100 mL). The resulting mixture was extracted with ether (3 × 30 mL). The combined extracts were dried. The solvent was evaporated, and the crude product mixture was purified on a neutral alumina (activity IV) column with pentane–ether as eluent to give 200 mg (30%) of a mixture which contained 93% of 1-methoxy-2-oxaadamantane (**38b**) and 7% of tricyclo[3.3.1.0^{2,7}]nonan-3-one (**37**) by GLC (DEGS, 140 °C; SE-30, 110 °C; OV-101, 120 °C). Pure **38b** (≥98% by GLC; DEGS, 140 °C) was obtained by column chromatography using a neutral alumina (activity II) column with pentane–ether as eluent: ^{13}C NMR ($CDCl_3$) δ 95.9 (s, 1 C), 71.6 (d, 1 C), 48.2 (q, 1 C), 38.9 (t, 2 C), 35.1 (t, 1 C), 35.0 (t, 2 C), 29.2 (d, 2 C); ^{1}H NMR ($CDCl_3$) δ 4.2 (s, 1 H), 3.4 (s, 3 H), 1.5–2.4 (m, 12 H); IR (film) 2940 (s), 2860 (m), 1200 (s), 1150 (m), 1090 (m), 1010 (m), 995 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 168 (M^+, 57), 136 (14), 111 (46), 100 (100), 94 (68), 79 (54), 67 (54).

Cyclization of Iodo Ketone 35 in Aqueous Dioxane–KOH. A solution of crude iodo ketone **35** (1.0 g, 3.8 mmol) and KOH (1.0 g, 18 mmol) in 70% aqueous dioxane (30 mL) was stirred and refluxed for 1 h, cooled, and poured into ice–water (50 mL). The resulting mixture was extracted with ether (3 × 30 mL), saturated with NaCl, and extracted with CH_2Cl_2 (3 × 30 mL). The ether and CH_2Cl_2 extracts were dried separately. Evaporation of the ether left crude tricyclo[3.3.1.0^{2,7}]nonan-3-one (**37**), which contained approximately 15% of alcohol **38a** (by GLC; DEGS, 150 °C). The products were separated on a neutral alumina (activity

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(39) Cf. F. D. Greene, *J. Am. Chem. Soc.*, **81**, 2688 (1959).

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IV) column with pentane–ether–CH_2Cl_2 as eluent. Ketone **37** was purified further by column chromatography using a neutral alumina (activity I/II) column with pentane as eluent to give 109 mg (20%) of **37**: ≥99% pure (by GLC; DEGS, 140 °C); ^{13}C NMR, ^1H NMR, IR, and mass spectra of the product were identical with those of the ketone obtained by cyclization of **35** with NaH in THF. Evaporation of CH_2Cl_2 yielded crude 1-hydroxy-2-oxaadamantane (**38a**), which was combined with the alcohol obtained from the ether extracts and sublimed in vacuo to give 67 mg (10%) of **38a**: ≥97% pure (by GLC; DEGS, 150 °C); ^{13}C NMR ($CDCl_3$), see text; ^1H NMR ($CDCl_3$), see text; IR (KBr) 3280 (s), 2900 (s), 1180 (m), 980 (m), 960 (m) cm^{-1}; mass spectrum, *m/e* (relative intensity) 154 (M^+, 57), 95 (56), 94 (100), 86 (59), 79 (74), 69 (64), 67 (61).

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Registry No. 14a, 35128-58-6; **14b**, 73683-14-4; **20**, 50529-96-9; **23**, 73683-17-7; **24a**, 57234-55-6; **24b**, 74987-37-4; **26**, 74987-38-5; **30**, 74987-39-6; **34a**, 67403-70-7; **34b**, 74987-40-9; *exo*-**35**, 74998-58-6; **37**, 74987-41-0; **38a**, 2879-40-5; **38b**, 2859-74-7; 4-homobrendane, 49700-65-4; 4-homobrendan-4'-one, 50529-80-1; 2-homobrendane, 42836-61-3; 2-methyl-2-adamantanol, 702-98-7; 7-chlorobicyclo[3.3.1]non-3-yl methyl ketone, 29844-79-9; 3-noradamantyl methyl ketone, 29844-80-2; 3-noradamantyl acetate, 74987-42-1; tricyclo[3.3.1.$0^{2,7}$]-nonane, 766-67-6.

Cycloaddition Reaction of Dimethyl Acetylenedicarboxylate with 2,4,5-Triphenyl-3*H*-pyrrol-3-one 1-Oxide

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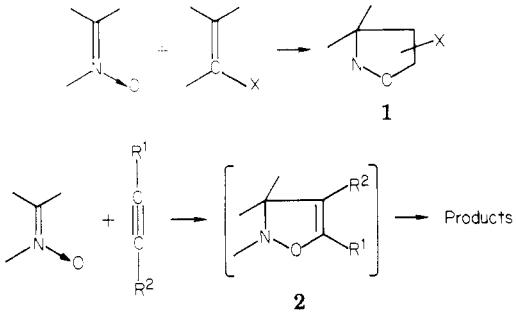
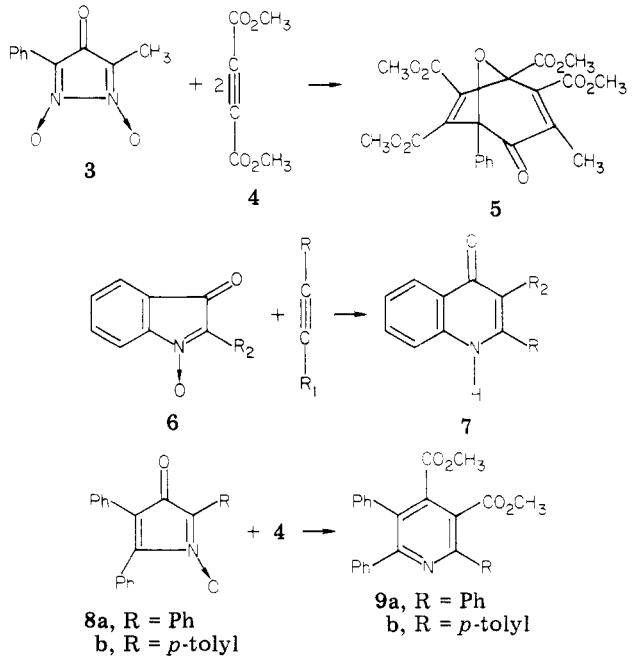
The reaction of 2,4,5-triphenyl-3*H*-pyrrol-3-one 1-oxide with dimethyl acetylenedicarboxylate gave pyridine **9a**, 4(3*H*)-pyridone **10a**, isoxazolidine **11**, and traces of pyridone **13**. Pyridone **10a** is not an intermediate in the formation of **9a**, yet on photolysis or pyrolysis above its melting point, **10a** yielded pyridine **9a**. Possible reaction mechanisms that rationalize the formation of these products are discussed.

The cycloaddition reaction of nitrones with dipolarphiles is recognized as the most versatile method for the synthesis of isoxazolidines **1**.[1] On the other hand, the corresponding reaction with acetylene derivatives usually gives products that result from the rearrangement of the expected Δ^4-isoxazoline **2**. For example, Freeman and Hoare[2] found



that the reaction of 3,4-diazacyclopentadienone 3,4-dioxide **3** with dimethyl acetylenedicarboxylate (DMAD), **4**, involved 2 mol of the latter to give the bicyclo[3.2.1] system **5**. Noland and co-workers[3] reported the ring expansion of 2-phenylisatogen **6** into 4-quinolinone derivatives **7**. Recently, Jones and Sadighi[4] described the reaction of 2,4,5-triphenyl-3*H*-pyrrol-3-one 1-oxide (**8a**) with DMAD to give pyridine **9a** as a "single product in high yield". Although each of the above *N*-oxides has a nitrone functional group, it is clear that they follow different pathways with acetylene derivatives.



As part of our interest in cycloaddition reactions,[2] we examined the reaction of **8a** with DMAD in some detail. Indeed, heating of a chloroform solution[4] of **8a** with **4** resulted in the gradual disappearance of the violet color of **8a**. Workup and separation of the components of the reaction residue gave **9a**, identical with that reported by Jones and Sadighi[4] and with that prepared by Eicher and co-workers[5] (vide infra), and **10a**, **11a/12a**, and **13a**.

The formation of pyridone **13** is analogous to that of the quinolinones reported from isatogens and acetylenes;[3]

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