curred between the first and second hours of reaction.[20] The methanolic solution, with 2 mL of methanol as a rinse, was treated with 10 mL of 6 N hydrochloric acid, diluted with 55 mL of water, and extracted three times with chloroform. The chloroform solution was shaken with 10% sodium hydroxide solution, washed with water and brine, and dried to give 508 mg of a clear oil which crystallized on standing: VPC analysis (OV-17, 215 °C) indicated 97% conversion; IR (KBr) 3.23–3.78, 6.72, 6.81, 6.92, 7.02, 7.18, 7.76, 7.98, 8.78, and 8.83 μm; NMR ($CDCl_3$) δ 7.11 (s, aromatic) and 1.90–3.70 (m, alkyl), with δ 7.20–7.33 (m, aromatic of **7a**) and 6.92 (S, **HC=CH** of **7a**) [comparison of the integrations in the δ 6.9–7.4 region indicated 94% reduction]; MS *m/e* (rel intensity) 289 (22, M^+), 58 (100).

2-Fluoro-10,11-dihydro-11-[(β-(methylamino)ethyl)-thio]dibenz[*b,f*]oxepin (8b). To 0.50 g (0.0017 mol) of 2-fluoro-11-[(β-(methylamino)ethyl)thio]dibenz[*b,f*]oxepin (**8a**)[21] in 16 mL of methanol at room temperature was added 1.59 g (0.066 mol) of magnesium shavings. The reaction was stirred at room temperature for 2 h, and complete conversion was indicated by TLC (25% methanol–benzene, silica gel; R_f of **8a** 0.35; R_f of **8b** 0.22). The methanolic solution was decanted from any undissolved magnesium, treated with 36 mL of 6 N hydrochloric acid, and extracted with chloroform. The chloroform solution was shaken consecutively with 10% sodium hydroxide solution, water, and brine and dried to give an oil. The oil was triturated with hot pentane, and the pentane was evaporated to give 0.43 g (85% of theory) of **8b**. An ethereal solution of **8b** was treated with ethereal maleic acid, and the resulting salt was washed with ether to give 0.47 g (67% of theory overall) of a white powder: mp 115.5–117.5 °C; IR (KBr) 2.75–3.10, 3.10–4.20, 5.90, 6.38, 6.78, 7.25, 7.40, 8.00, 8.17, and 8.40 μm; NMR ($CDCl_3$) δ 13.5–8.0.(m, 2 H, CO_2**H**), 7.45–6.60 (m, 7 H, aromatic), 6.28 (s, 2 H, olefinic of maleic acid), 4.63–4.30 (m, 1 H, $SCHCH_2$), and 3.90–2.40 (m, 10 H, $ArCH_2CH + S(CH_2)_2NHCH_3$); MS (chemical ionization) *m/e* (rel intensity) 304 (29.4, MH^+).[22]

Registry No. **1a**, 103-30-0; **1b**, 103-29-7; **2**, 645-49-8; **3a**, 530-48-3; **3b**, 612-00-0; **4a**, 256-96-2; **4b**, 494-19-9; **5a**, 948-65-2; **6a**, 85-01-8; **6b**, 776-35-2; **7a**, 129-03-3; **7b**, 50603-12-8; **8a**, 71316-84-2; **8b**, 71316-85-3; **8b** maleate, 71316-86-4; magnesium, 7439-95-4.

(20) An induction period for reductions with magnesium in alcohols has been reported previously: M. Sclar and M. Kilpatrick, *J. Am. Chem. Soc.*, **59**, 584 (1937); also see ref 14a,d.

(21) The synthesis, properties, and pharmacological activity of **8a**, **8b**, and related compounds are the topic of a future publication.

(22) We wish to thank Mr. Marc N. Agnew for spectroscopic determinations and Eve Memoli for assistance in preparation of this manuscript.

Facile Synthesis of 3β-Hydroxy-5α-cholest-8(14)-en-15-one 3-Acetate

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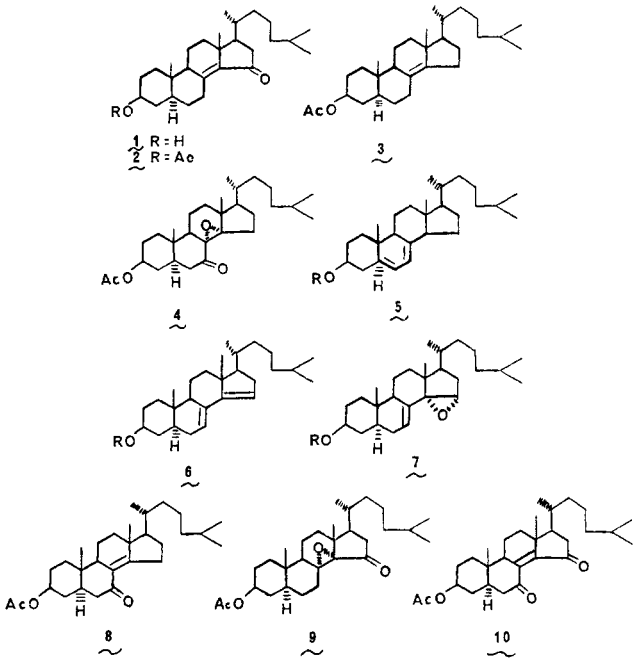
Cholesterol biosynthesis, a process common to nearly all mammalian cells because of the necessity of this sterol in membrane structure, is dependent on the rate-limiting enzyme HMG CoA reductase.[1] Recent investigations have revealed the ability of various oxygenated sterols to suppress the activity of this enzyme in a wide variety of cell systems.[2] Included in this study was the series of 15-oxygenated sterols[3] of previous interest for their role as intermediates in the biosynthesis of cholesterol.[4] In this series the ability of 3β-hydroxy-5α-cholest-8(14)-en-15-one (**1**) to lower serum cholesterol levels in vivo was particularly noteworthy[5] since it represents the first example of such an effect by this type of inhibitor of sterol biosynthesis.

Our desire to study the unique biological activity of **1** in various assays prompted an investigation into its synthesis. Past work on the chromic acid oxidation of 5α-cholest-8(14)-en-3β-ol 3-acetate (**3**) by Wintersteiner and Moore had produced the desired compound directly as its acetate ester **2**, but only in low (6–10%) yield.[6] The



major product of this reaction was the 7-keto-8(14)-epoxide **4** obtained in 16–25% yield along with other components. More recent preparation of **1** had utilized acid-catalyzed isomerization of 7-dehydrocholesterol ester (**5**; R = benzoate) to the 7,14-dienol ester **6** (R = benzoate) which, when treated with peracids, provided the 14-epoxide **7**. Acid hydrolysis then gave the desired 15-keto compound. Since the isomerization reaction is not particularly clean[7,8] and the subsequent reactions produced the desired product in only modest overall yield (ca. 25%),[7] we investigated alternate routes.[18]

A direct oxidation of the readily accessible olefin **3** was appealing, and therefore a study of this approach using some of the more recently developed oxidizing agents was pursued. Initially, **3**, prepared from 7-dehydrocholesterol

(1) HMG CoA reductase: β-hydroxy-β-methylglutaryl coenzyme A reductase. For a review on the role of this enzyme in the feedback regulation of cholesterol biosynthesis, see M. D. Siperstein, *Curr. Top. Cell Regul.*, **2**, 65 (1970).

(2) M. S. Brown and J. L. Goldstein, *J. Biol. Chem.*, **249**, 7306 (1974); A. A. Kandutsch and H. W. Chen, *ibid.*, **249**, 6057 (1974); J. J. Bell, T. E. Sargent and J. A. Watson, *ibid.*, **251**, 1745 (1976).

(3) G. J. Schroepfer, Jr., E. J. Parish, H. W. Chen, and A. A. Kandutsch, *J. Biol. Chem.*, **252**, 8975 (1977).

(4) S. Huntoon and G. J. Schroepfer, Jr., *Biochem. Biophys. Res. Commun.*, **40**, 476 (1970); S. Huntoon, B. Fourcans, B. N. Lutsky, E. J. Parish, H. Emery, F. F. Knapp, Jr., and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **253**, 775 (1978).

(5) (a) D. L. Raulston, C. O. Mishaw, E. J. Parish, and G. J. Schroepfer, Jr., *Biochem. Biophys. Res. Commun.*, **71**, 984 (1976); (b) G. J. Schroepfer, Jr., D. Monger, A. S. Taylor, J. S. Chamberlain, E. J. Parish, A. Kisic, and A. A. Kandutsch, *ibid.*, **78**, 1227 (1977); (c) A. Kisic, D. Monger, E. J. Parish, S. Satterfield, D. L. Raulston, and G. J. Schroepfer, Jr., *Artery (Lenoidas, Mich.)*, **3**, 421 (1977).

(6) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **65**, 1513 (1943).

(7) J. C. Knight, P. D. Klein, and P. A. Syczepanik, *J. Biol. Chem.*, **241**, 1502 (1966); E. J. Parish, T. E. Spike, and G. J. Schroepfer, Jr., *Chem. Phys. Lipids*, **18**, 233 (1977).

(8) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

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(5; R = H) via catalytic hydrogenation with concomitant isomerization of the 7 double bond to the 8(14)-position and subsequent acetylation (85% yield for the overall transformation), was treated with Collins reagent.[9] While this oxidant produced the desired acetate **2** consistently in ca. 16% yield by using a 20:1 ratio of complex to substrate at room temperature in 4–6 h, a number of other products were also formed. The epoxide **4**, characterized by its conversion to the conjugated ketone **8** by previously described methods,[10] was the accompanying major component of the mixture. While the yield of **2** was modest, its ease of isolation via chromatography and the expediency of the route prompted additional work.

A more recently developed chromium trioxide complex with 3,5-dimethylpyrazole as the complexing ligand was also evaluated.[11,12] The results with this oxidant were most gratifying. The major product from oxidation of **3** with 20 equiv of reagent at −20 to −30 °C in ca. $^1/_2$ h reaction time was **2**, obtained in yields up to 32% after chromatography. The major contaminant of the oxidation was again **4**, isolated in ca. 8% yield. We found the procedure of Salmond et al.[12] for formation of the complex and workup to be preferable over that described earlier.[11] There was no evidence of acetate hydrolysis during the workup.

It is interesting to note that each of our allylic oxidation reactions produced the 7-keto-8(14)-epoxide **4** as the principal byproduct whereas the isomeric 15-keto analogue **9** was not isolated. If present, it was formed to a much lesser extent.[13] This observed difference in the formation of **4** and **9** apparently is not due to differences in the reactivity of **8** and **2** to the initial oxidizing reagent. When **8** was subjected to the chromium trioxide/3,5-dimethylpyrazole complex under the conditions described above, no evidence for the formation of **4** was observed. After an extended reaction time (2 h) we observed the formation of the diketone **10** and an unidentified oxidation product[15] as the major components of the reaction mixture. This suggests that a 1,4 conjugate addition of the complex to the enone **8** is ostensibly not the mode of formation of the epoxides[16] even though this enone system has been shown to readily undergo 1,4 conjugate addition with diethylaluminum cyanide.[17]

In summary, the process herein reported is the first example of the use of a direct allylic oxidation method for the preparation of a 8(14)-en-15-one sterol in sufficient yield to be synthetically useful. Moreover, it is a facile method for obtaining the biologically interesting 15-keto sterol **1** and provides an attractive alternative to previously reported methods.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were taken on a Varian A-60A or T-60 spectrometer using Me_4Si as an internal standard, UV spectra were obtained on a Beckman DK-2A, and optical rotations were taken on a Perkin-Elmer Model 141 by the group of Mr. A. J. Damascus. Mass spectra were obtained on an AEI-MS-30 double-beam mass spectrometer by Dr. J. Hribar and associates. Microanalyses were performed by the group of Mr. E. Zielinski. Hydrogenations were carried out by Mr. M. Scaros and associates.

5α-Cholest-8(14)-en-3β-ol 3-Acetate (3). To 14.5 g (0.0378 mol) of 7-dehydrocholesterol in 580 mL of ethyl acetate and 11.6 mL of acetic acid was added 1.8 g of 5% palladium-on-carbon catalyst in a 2 L Parr shaker bottle. After 1 equiv of hydrogen had been consumed over a 6-h period at room temperature and atmospheric pressure, the catalyst was removed by filtration. Solvent removal from the filtrate left a solid residue which was taken up into 100 mL of pyridine and 50 mL of acetic anhydride. After the mixture was allowed to stand overnight at room temperature, water was added, and the precipitate which formed upon continued stirring was collected. Recrystallization from methanol/ether gave 13.7 g (85%) of **3** in two crops: mp 77–78 °C (lit.[14] 76–77 °C); $[\alpha]_D$ +8.7° (lit.[14] +9.3°).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.34; H, 11.31.

3β-Hydroxy-5α-cholest-8(14)-en-15-one 3-Acetate (2) and 5α-Cholestan-3β-ol 8α(14α)-Oxide 3-Acetate (4). In a 1-L three-necked flask equipped with a mechanical stirrer, 40.0 g (0.40 mol) of chromium trioxide, previously dried in the presence of phosphorus pentoxide in vacuo, suspended in 400 mL of methylene chloride in a nitrogen atmosphere was cooled to −20 °C. To the cooled reaction mixture was then added in one portion 38.5 g (0.40 mol) of 3,5-dimethylpyrazole. After stirring the reaction mixture at the above temperature for 15 min, 8.6 g (0.02 mol) of **3** dissolved in 100 mL of methylene chloride was added at a rate so as to maintain a temperature of ca. −20 °C. After the addition the reaction mixture was stirred for an additional 30 min at −20 °C before 250 mL of 5 N sodium hydroxide solution was added with the reaction mixture assuming a temperature of −10 °C during the addition. After the reaction mixture was stirred at −10 °C for 45 min, the two layers were separated. The aqueous phase was extracted with additional methylene chloride, and the combined extracts were washed with 1 N hydrochloric acid solution and saturated salt solution. After being dried over magnesium sulfate, the solution was treated with activated charcoal and filtered through a cake of Florex. Solvent removal in vacuo gave 7.0 g of oil. The crude oil was chromatographed by using a Waters Associates Prep LC/System 500 instrument and a Prep PAK-500 silica cartridge and eluting with 3% ethyl acetate–Skelly B. The desired material was isolated in fractions 12–20 (approximately 500 mL), affording 2.85 g (32%) of **2**: UV (MeOH) 259 nm (ε 13 300). Recrystallization from aqueous methanol gave analytically pure **2**: mp 134–135 °C (lit.[6] mp 134–135 °C); UV (MeOH) 259 nm (ε 14 100) [lit.[6] (EtOH) 259 nm (ε 12 750)]; mass spectrum, *m/e* 442 (M^+); NMR ($CDCl_3$) δ 4.15 (1 H, d of br m, 7β-H).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.48. Found: C, 78.62; H, 10.58.

Subsequent fractions afforded the 7-keto epoxide **4** in ca. 10–12% typical yield. Recrystallization from methanol/ether gave the pure compound, mp 140–141 °C (lit.[6] mp 139.5–140.5 °C).

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.04; H, 10.14.

3β-Hydroxy-5α-cholest-8(14)-en-7-one 3-Acetate (8). To 0.42 g of **4** in 5 mL of acetic acid was added 0.42 g of zinc dust, and the reaction mixture was refluxed for 45 min. The hot reaction mixture was then filtered, and upon addition of water to the filtrate a solid formed which was collected, affording 0.37 g (91%) of crude product. Recrystallization from methanol–ether gave pure **8**: mp 143–145 °C (lit.[6] mp 142.5 °C); UV (MeOH) 261 nm (ε 10 300) [lit.[10a] 261.5 nm (ε 9500)].

(9) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); W. G. Dauben, M. Lorber and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969); D. S. Fullerton and C.-M. Chen, *Synth. Commun.*, **6**, 217 (1976).

(10) (a) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953); (b) H. Heusser, G. Sausy, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 2090 (1952).

(11) E. J. Corey and G. W. J. Fleet, *Tetrahedron Lett.*, 4499 (1973).

(12) W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978).

(13) This product has been reported by Wintersteiner and Moore[6] in the chromic acid oxidations of **3**, but the isolated yield was only 2–4%.

(14) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **65**, 1507 (1943).

(15) The NMR spectrum of this component as well as thin-layer chromatography confirmed the fact that it was not the previously isolated 7-keto epoxide **4**.

(16) Epoxide formation is then mostly likely a result of direct oxidation of the olefin. Since only **4** is observed and not **9** suggests that attack of the complex occurs at the double bond from the less hindered α face of the molecule producing a 14α adduct which then leads to the 7-keto epoxide **4**. Analogous attack at the C-8 would give an unfavorable 8α adduct, necessitating a much higher energy ring C boat conformation.

(17) M. Anastasia, A. Fiecchi, G. Cighetti, and G. Galli, *J. Chem. Soc., Perkin Trans. 1*, 700 (1977).

(18) After this manuscript was being prepared for publication we became aware of a new synthesis of the title compound. M. Anastasia, A. Fiecchi and A. Scala, *J. Chem. Soc., Perkin Trans. 1*, 1821 (1979).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.48. Found: C, 78.68; H, 10.62.

Oxidation of 8 with Chromium Trioxide/3,5-Dimethylpyrazole. To 15 mmol of chromium trioxide/3,5-dimethylpyrazole complex in 25 mL of methylene chloride formed as above at −20 °C was added 0.33 g (0.00075 mol) of **8** in 3 mL of methylene chloride. The reaction mixture was stirred at −20 °C for 2 h before addition of 50 mL of 5 N sodium hydroxide solution. After being stirred for 30 min, the layers were separated and worked up as above to give 0.29 g of dark oil. Thin-layer chromatography on POLYGRAM Sil G/uv plates (Macherey-Nagel and Co.) with 25% ethyl acetate/toluene as the eluant showed two new major components more polar than the starting material, neither of which corresponded to **4**. Low-pressure chromatography over Woelm silica with 5% ethyl acetate/toluene as the eluant gave 34 mg of the less polar component which was not characterized further. The more polar major component (54 mg) proved to be the 7,15-diketone **10**: mp 139–141 °C; UV (MeOH) 259 nm (ϵ 10 400); mass spectrum, *m/e* 456 (M^+).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.41; H, 9.72.

Registry No. **2**, 34495-42-6; **3**, 6562-21-6; **4**, 16780-48-6; **5** (R = H), 434-16-2; **8**, 21152-11-4; **10**, 71369-91-0.

Transannular Carbene Insertion Reactions in the Bicyclo[4.2.1]nonane System

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The study of the conformations of medium ring compounds has raised much interest in the field of NMR spectroscopy[1,2] and chemical reactivity.[1,3] From the conformational point of view, the seven- and eight-membered rings are complex substrates, because of the multiplicity of the conformations which can be involved.[1,4a] The introduction of linkages between two nonvicinal carbons in such rings gives rise to bicyclic derivatives in which the medium ring freedom degree is decreased. The purpose of this paper is to show the particular interest of such substrates in the study of: the proximity of transannular carbons in bridged molecules such as bicyclo[4.2.1]nonanes or bicyclo[3.2.1]octanes; and the structural features of carbene insertion reactions, which has been the subject of current interest and which appears as being a

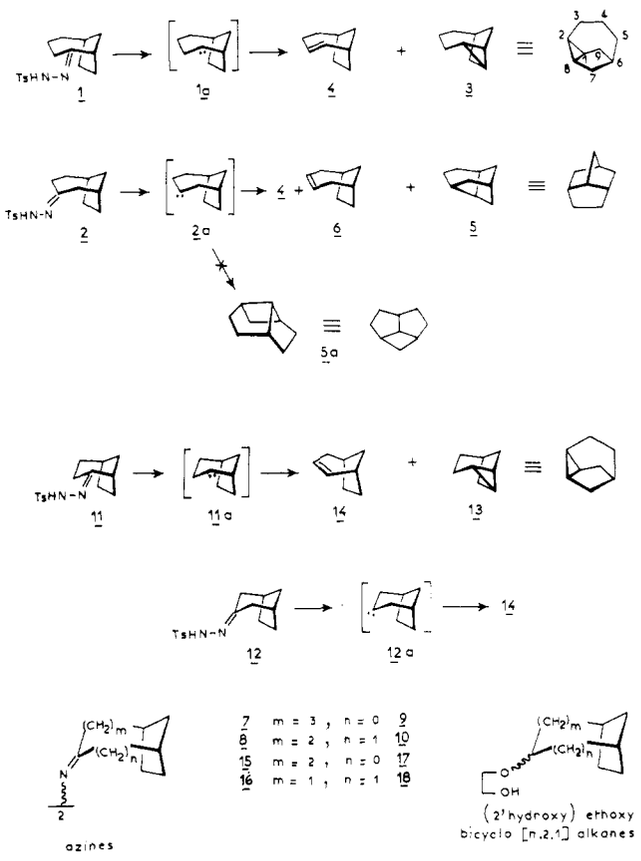

Figure 1.

reaction particularly well adapted to the study of transannular reactions. These reactions have been extensively studied in medium ring compounds,[5] but much less in bridged substrates involving seven- or eight-membered rings.[6]

Tosylhydrazones were used as starting materials, since it is possible, by submitting them to different experimental conditions, to induce carbanionic, carbenic, or cationic reactions.[7c,d] Tosylhydrazones **1**, **2**, **11**, and **12** have been prepared from bicyclo[4.2.1]nonan-2- and -3-ones and bicyclo[3.2.1]octan-2- and -3-ones by standard procedures. They were reacted under conditions recorded in Tables I and II, which also report the yield of the different products obtained.

When carbanionic conditions are used (alkyllithium in aprotic solvents)[7cd,9] olefins are the exclusive reaction products as expected.

It has been shown previously, that in the presence of excess sodium methoxide in aprotic solvent (diglyme) tosylhydrazones lead to free carbenes.[7,8] The carbene **1a** yielded a mixture of tricyclo[4.2.1.$0^{2,8}$]nonane (**3**) and bicyclo[4.2.1]non-2-ene (**4**) in the ratio 1:0.85, while **2a** gave

(1) For reviews, see J. Dale in "Structure et propriétés moléculaires", Vol. VII, Masson et Cie, Ed., Paris, 1970, p 221; J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 911 (1975).

(2) F. A. L. Anet and T. N. Rawdah, *J. Am. Chem. Soc.*, **100**, 7810, 7167 (1978); F. A. L. Anet and V. J. Basus, *ibid.*, **95**, 4424, (1973); F. A. L. Anet, A. K. Cheng, and J. Krane, *ibid.*, **95**, 7877, (1973); S. H. Grover, D. H. Marr, J. B. Stothers, and C. T. Tan, *Can. J. Chem.*, **53**, 1351 (1975).

(3) J. Sicher, *Angew. Chem., Int. Ed. Engl.*, **11**, 200, (1971); J. Casanova and B. Waegell, *Tetrahedron*, **31**, 1035, (1975).

(4) (a) J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036, 7043 (1967); N. L. Allinger, M. T. Tribble, M. A. Miller, and J. D. Wertz, *ibid.*, **93**, 1637 (1971). (b) Of course it would be interesting to have some information on the conformations of the carbenes (**1a** and **11a**) themselves. Only closely related analogues such as the corresponding ketones are available, but in the latter case, there are no marked differences between the most stable conformations of the cyclooctane and cyclooctanone: N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972); F. A. L. Anet, M. St. Jacques, P. M. Henrichs, A. K. Cheng, J. Krane, and L. Wong, *ibid.*, **30**, 1629, (1974).

(5) (a) A. C. Cope, M. M. Martin, and M. A. McKervey, *Q. Rev., Chem. Soc.*, **20**, 119 (1966); (b) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **83**, 3159, (1961); (c) J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 598 (1975).

(6) L. A. Paquette, G. V. Meehan, and J. J. Marshall, *J. Am. Chem. Soc.*, **91**, 6779, (1969); M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 2565, (1969); T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Am. Chem. Soc.*, **91**, 212, (1969); M. S. Baird, P. Sadler, J. Hatem, J. P. Zahra, and B. Waegell, *J. Chem. Soc., Chem. Commun.*, 452 (1979).

(7) For reviews, see: (a) W. Kirmse, "Carbene Chemistry", Academic Press, New York, 1971; (b) W. J. Baron, M. R. Decamp, M. E. Hendrick, M. Jones, Jr., R. H. Levin, and M. B. Sohn in "Carbenes", M. Jones and R. A. Moss, Ed., Wiley-Interscience, New York, 1973; (c) J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 922 (1975); (d) R. H. Shapiro, *Org. React.*, 405 (1975).

(8) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).

(9) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).

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