Articles

Substituent Effects on Regioselectivities in Elimination Reactions of Bridgehead-Substituted 7,8-Dichlorodibenzobicyclo[2.2.2]octadienes

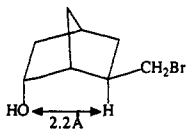
David F. Schuck, Duyen T. Bach, Ken H. Chow, Robert W. Sullivan, Michael Linhares, and Edward J. Grubbs*

Department of Chemistry, San Diego State University, San Diego, California 92182

Received June 28, 1990

The syntheses and dehydrochlorinations of a number of bridgehead-substituted 7,8-dichlorodibenzobicyclo-[2.2.2]octadienes are described. The bridgehead substituents (and corresponding substrates) include $(CH_2)_2CO_2H$ (**14b**), $(CH_2)_3OCH_3$ (**16**), CH_2OCH_3 (**17**), $(CH_2)_3OH$ (**12**), $(CH_2)_2OH$ (**20**), and CH_2OH (**22**). Base-induced dehydrochlorinations of **14b** yield predominantly vinyl chloride resulting from base attack on H at C-8 (remote from the carboxylate anion) similar to observations in previous related studies. Dehydrochlorinations of **16** and **17** yielded the isomeric vinyl chlorides with almost complete loss of regioselectivity. Dehydrochlorinations of **12** and **20** (and to a lesser extent with **22**) proceeded with high regioselectivity opposite to that observed for **14b**. These results suggest the intervention of intramolecular base-induced eliminations from **12** and **20** and to a lesser degree with **22**.

Intramolecular nucleophilic displacement reactions have been exhaustively studied in a wide variety of systems. By contrast, relatively few cases of intramolecular base-induced elimination (IBIE) have been reported. Grob and co-workers observed IBIE from anions of 3-chloro-3-methylbutanethiol and 3-chloro-2,2,3-trimethylbutanethiol.[1] For these substrates 6-membered ring transition states are operative. Thus, linear S···H···C geometries are not required. More recently Menger[2] has investigated IBIE requirements in bicyclic systems possessing a phenoxide or alkoxide oxygen rigidly located near a potentially removable "β" proton. IBIE was detected in reactions of conjugate bases of **1** and **2** (the latter involving an intramolecularly assisted enolization), but not in **3**. Again, the



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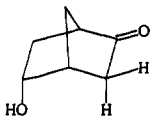

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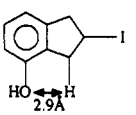

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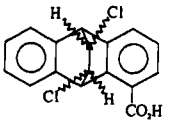
nonlinear O···H···C geometries presented no insurmountable barrier to IBIE as long as the O···H distance was not too great. Related studies by Illuminati[3] and Cort[4] have been directed toward an understanding of the effects of transition-state ring sizes on competing IBIE and intramolecular substitutions.

In previous studies of elimination reactions we determined the regioselectivities in dehydrochlorinations of a number of 7,8-dichlorodibenzobicyclo[2.2.2]octadienes possessing a carboxylate group on the aromatic ring (substrates **4**) or extending from C-9 of the anthracene precursor (substrates **5**).[5,6] The major factor controlling



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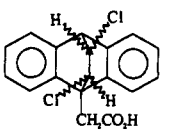

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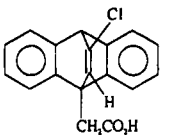
the regioselectivities in vinyl chloride formation was shown to be transition-state charge–charge repulsion between attacking base (*t*-BuO) and the carboxylate anion. For example, the cis and trans dichloro acids **5** when treated with KO*t*Bu in *t*-BuOH containing 18-crown-6 ether generated **6** and **7** in ratios of 98/2 and 95/5, respectively.



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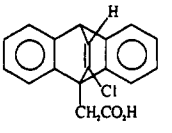

7

Suitable controls[6] provided evidence that steric effects were not significant factors. In an attempt to promote an IBIE, *trans*-**5** was treated with slightly less than 1 equiv of KO*t*Bu in *t*-BuOH containing 18-crown-6. Following a 72-h heating period at 80 °C, 87% of **5** was recovered and no vinyl chloride was detected.[6] Had the carboxylate served as an intramolecular base, the only sterically accessible transition state would have led solely to **7**. The absence of any intramolecular elimination suggests that the carboxylate anion is too weak a base under these conditions since C···H···O linear proton transfer is not a requirement in the IBIE examples cited above.

With these observations in mind, we set about to prepare analogues of **5** bearing the OH group in place of CO_2H and

(1) Grob, C. A.; Schmitz, B.; Sutter, A.; Weber, A. H. *Tetrahedron Lett.* **1975**, 3551.
(2) (a) Menger, F. M. *Tetrahedron* **1983**, *39*, 1031. (b) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996.
(3) Illuminati, G.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1974**, *39*, 2598.
(4) Cort, A. D.; Mandolini, L.; Masci, B. *Ibid.* **1983**, *48*, 3979.
(5) Grubbs, E. J.; Schmidt, S. P.; Wang, C. T.; Goodrow, M. H.; Lewis, R. M.; Deardurff, L. A.; Coffey, Jr., D. *J. Am. Chem. Soc.* **1983**, *105*, 4115.
(6) Grubbs, E. J.; Schmidt, S. P.; Wang, C. T.; Chen, Z.; Hamed, A. A.; Soliman, E-S. A.; Nuñez, P.; Goodrow, M. H.; Lewis, R. M.; Deardurff, L. A.; Coffey, Jr., D. *J. Org. Chem.* **1985**, *50*, 2886.

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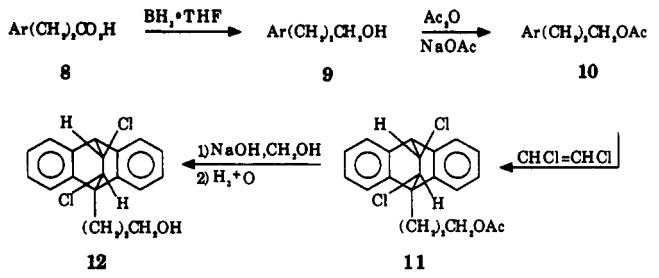
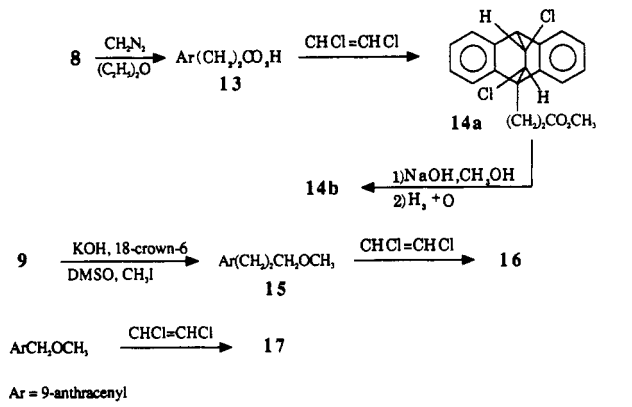
Scheme I



Ar = 9-anthracenyl

Scheme II

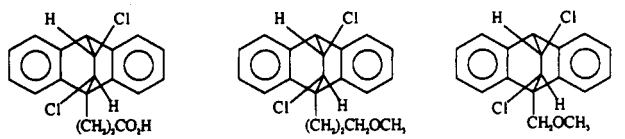


Ar = 9-anthracenyl

with varying numbers of carbons linking the bridgehead position to the potential base site. Herein we report preparations of **12**, **20**, and **22** and their dehydrochlorinations.

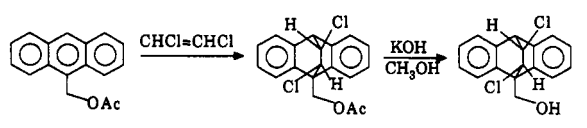
Results and Discussion

The synthesis of **12** is illustrated in Scheme I. The alcohol protection–deprotection sequence was required because useful yields of cycloaddition were not possible employing the alcohol **9** directly.[7] For purposes of comparison, the acid **14b** and the methyl ethers **16** and **17** were also prepared. The routes to these cycloadducts are illustrated in Scheme II.



14b **16** **17**

The synthesis of **20**, the lower homologue of **12**, is outlined in Scheme III. In an analogous way homologue **22** was prepared by a cycloaddition (dichloroethene) of the acetate derived from 9-anthracenemethanol followed by hydrolysis.



(7) This must clearly be a rough estimate partly because of uncertainties in the conformation of the three-carbon unit extending from the bridgehead carbon. For this calculation, the propanoic acid moiety was assumed to be fully extended with the two β hydrogens of this unit flanking the bicyclic C-1 to C-7 bond. The same charge distributions obtained in the studies involving 4[5,6] were used in this estimate.

(8) A similar problem has prevented us from effecting cycloadditions of dichloroethene with anthracene-derived substrates bearing a carboxylic acid OH.

Scheme III

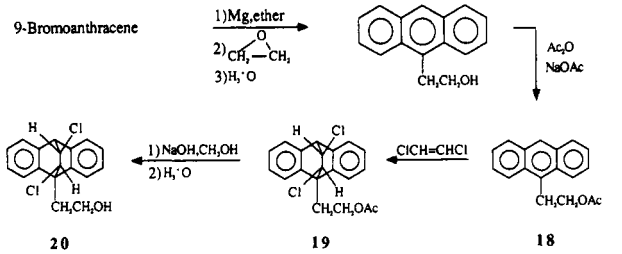
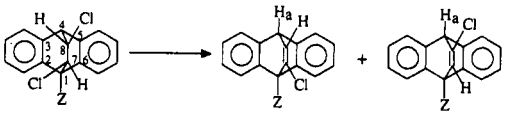


Table I. Dehydrochlorinations[a] of 12, 14b, 16, 17, 20, and 22 at 80 °C

substrate	base/solvent	product ratio (23:24)
12	KO*t*Bu[b]/*t*-BuOH, CE	88:12
12	KO*t*Bu[b]/*t*-BuOH	95:5
12	KH[c]/THF, CE	95:5
14b	KO*t*Bu[b]/*t*-BuOH, CE	10:90
14b	KO*t*Bu[b]/*t*-BuOH	15:85
14b	KH[c]/THF, CE	–
16	KO*t*Bu[b]/*t*-BuOH	23:77
16	KO*t*Bu[b]/*t*-BuOH, CE	37:63
16	KH[c]/THF, CE	–
17	KO*t*Bu[b]/*t*-BuOH, CE	57:43
17	KO*t*Bu/*t*-BuOH	46:54
20	KO*t*Bu/*t*-BuOH, CE	93:7
20	KO*t*Bu/*t*-BuOH	85:15
20	KH[c]/THF, CE	100:00
22	KO*t*Bu/*t*-BuOH, CE	84:16
22	KO*t*Bu/*t*-BuOH	88:12
22	KH[c]/THF, CE	83:17

[a] Reaction times 48–96 h. [b] Base concentration approximately 0.24 M; base:substrate ratio approximately 5:1. [c] Slightly less than 1 equiv of KH (as a 0.08 M solution in THF) per equivalent of substrate was employed.

Dehydrochlorinations of **12**, **14b**, **16**, **17**, **20**, and **22** were effected using potassium *tert*-butoxide as the added base. For **12**, **20**, and **22** eliminations were also induced by generating the conjugate base of each using potassium hydride. Yields of isolated mixtures of **23** and **24** ranged from 87 to 100% based upon unrecovered starting material. The ratios **23**:**24** were determined by area integrations for the C-4 protons, H_a. The coupling constants for **23**



and **24** (6–7 and 2 Hz, respectively) allow unambiguous isomeric assignments. In most cases, ratios were confirmed by use of capillary GC (directly where Z bears an alcohol or ether or as methyl esters where Z possesses a carboxylic acid). The results are summarized in Table I.

The regioselectivity in vinyl chloride formation observed when the carboxylic acid derivative **14b** is dehydrohalogenated with potassium *tert*-butoxide is in accord with expectations based upon our earlier studies.[5,6] An estimate for the expected ratio **24**:**23** (Z = $CH_2CH_2CO_2H$) based upon calculations described for **4** and **5** (and using the value of D_E = 13.7 obtained in that study) is 81:19.[7] Again in the bimolecular elimination the product ratio appears to be determined principally by charge–charge repulsions between the incoming base and the carboxylate anion. As previously observed for **5**, the anion from **14b** (generated with approximately 0.9 equiv of KH in THF) did not undergo dehydrohalogenation to any measurable extent. After 48 h at 80 °C reacidification led to a 99% recovery of unreacted **14b**.

Bimolecular eliminations in substrates possessing a C–O dipole extended from the bridgehead carbon were investigated. Methyl ethers **16** and **17** were employed for this purpose. As seen from Table I, essentially all regioselectivity is lost in eliminations from **17** and little remains in eliminations from **16**.[9] These data serve to establish the isomeric product distributions to be expected for bimolecular eliminations on the closely related substrates **12**, **20**, and **22**.[10]

It is thus particularly striking that a high degree of regioselectivity is observed in dehydrochlorinations of the alcohols **12** and **20**. *However, it is predominantly the H on the dichloroethano bridge nearer to the functionalized bridgehead carbon that is removed.* A similar but less dramatic reversal in elimination regioselectivity is observed from **22**.[11] These data support an interpretation based upon the involvement of the substrates' alkoxide oxygen (generated in equilibrium with *tert*-butoxide or nearly stoichiometrically from KH) acting as intramolecular bases. Such transition states appear to dominate the competitive bimolecular processes for **12** and **20** and to at least some degree to compete with the bimolecular transition states involving **22**. It will be noted that the "ring sizes" (for the intramolecular processes) including the protons undergoing transfer are 7, 6, and 5 for **12**, **20**, and **22**, respectively. It is of interest to compare the "nearest approach distances" for the alkoxide oxygens and the proton at C-7 in **12**, **20**, and **22** with the corresponding distances in the substrates studied by Menger and co-workers. For **12**, this nearest approach distance is less than 1 Å, for **20**, it is approximately 1.7 Å in a most favorable chairlike 6-membered ring conformation, and approximately 2.5 Å (without bond angle deformations) for **22**. It is noteworthy that this distance for **22** lies midway between those for the bicyclic substrates **1** and **3** (namely 2.2 and 2.9 Å) studied by Menger. As mentioned earlier, IBIE was observed for **1**, but not for **3**. Thus, 2.5 Å may be approaching the limit for which IBIE may successfully compete energetically with the bimolecular counterparts. Kinetic studies are planned to further illuminate the characteristics of these elimination transition states and will be published at a later time.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

For the elimination reactions, all preparations of alkoxide base solutions (as well as KH use) and mixing of reactants were performed in a dry box under a nitrogen atmosphere. The elimination reactions were then conducted in degassed and sealed tubes. The *trans*-1,2-dichloroethene was obtained from Aldrich Chemical Co. and used without additional purification.

3-(9-Anthracenyl)propanoic Acid (8). This starting acid was prepared using the procedure reported by Daub and Doyle.[12] By using twice recrystallized anthrone, freshly distilled acrylonitrile, and potassium *tert*-butoxide prepared directly from dry *tert*-butyl alcohol and potassium, the crude acid (mp 189–192 °C) was obtained in 56% yield. Recrystallization from glacial acetic acid afforded **8** as yellow prisms: mp 192–194 °C (lit.[12] mp 191–192 °C); ^{1}H NMR ($CDCl_3$) δ 7.1–8.3 (m, 9 H), 3.8–4.0 (m, 2 H), 2.6–2.9 (m, 2 H); IR (KBr) 3600–3300 (OH), 1700 cm^{-1} (C=O).

Methyl 3-(9-Anthracenyl)propanoate (13). The acid **8** was esterified with ethereal diazomethane. The pure ester was obtained in 73% yield following recrystallization from methanol: mp 72–73 °C (lit.[13] mp 75–76 °C); ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 9 H), 3.8 (m, 2 H), 3.6 (s, 3 H), 2.6 (m, 2 H); IR (KBr) 1730 cm^{-1} (C=O).

Methyl 3-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)propanoate (14a). A mixture of 0.500 g (1.90 mmol) of **13**, 3.0 mL (39 mmol) of *trans*-1,2-dichloroethene, and 0.038 g (0.18 mmol) of 2,6-di-*tert*-butylphenol in 5.0 mL of benzene was degassed and sealed in a reaction tube. The tube was heated in a steel bomb (charged with benzene) at 180 °C for 48 h. The cooled reaction mixture was removed from the tube with ether. The resulting mixture was concentrated and crystallized by addition of a mixture of petroleum ether and benzene. The crude product was recrystallized from the same solvent mixture, affording 0.43 g (63%) of a white solid: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 8 H), 4.4 (m, 2 H), 4.0 (d, 1 H), 3.8 (s, 3 H), 2.9 (br s, 4 H); mass spectrum, *m/z* 360 (M^+, 100), 362 (M^+ + 2, 69); IR (KBr) 1730 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{18}Cl_2O_2$: C, 66.49; H, 5.02. Found: C, 66.64; H, 4.96.

3-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)propanoic Acid (14b). A 1.46-g (4.06-mmol) sample of **14a** was mixed with 90 mL of 1.8 M methanolic sodium hydroxide. The mixture was boiled for 6 h. The resulting solution was acidified and extracted with ether. The extract was dried and concentrated, leaving 0.98 g (70%) of a yellow powder, mp 190–191 °C, which was recrystallized from chloroform (60% recovery) affording the acid as colorless crystals: mp 206–208 °C; ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ 7.1–7.6 (m, 8 H), 4.58 (d, 1 H, *J* = 2.9 Hz), 4.39 (t, 1 H, *J* = 2.9 Hz), 4.15 (d, 1 H, *J* = 2.9 Hz), 2.92 (m, 4 H); IR (KBr) 3400 cm^{-1} (br OH), 1700 cm^{-1} (C=O); mass spectrum, *m/z* 346 (M^+, 100), 348 (M^+ + 2, 66). Anal. Calcd for $C_{19}H_{16}Cl_2O_2$: C, 65.72; H, 4.64; Cl, 20.42. Found: C, 65.76; H, 4.65; Cl, 19.83.

3-(9-Anthracenyl)-1-propanol (9). To 0.730 g (2.92 mmol) of **8** in 15 mL of dry THF was added four 5.5-mL portions of diborane (0.5 M BH_3·THF complex). The four diborane additions were carried out over a 3-day period at room temperature. The reaction mixture was then quenched with water and extracted with aqueous sodium carbonate. The remaining THF–water mixture was extracted with ether. The extract was dried and concentrated to a yellow oil, and cold hexane was added. Vigorous agitation of the mixture induced crystallization, affording 0.58 g (84%) of the crude alcohol, mp 82–90 °C. Recrystallization of the crude alcohol from a mixture of ether and hexane (slow evaporation) gave the pure alcohol with 90% recovery: mp 99–100 °C (lit.[14] mp 97.5–98.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.2–8.2 (m, 9 H), 3.6 (m, 3 H), 2.0 (m, 2 H), 1.5 (m, 2 H); IR (KBr) 2900–3700 cm^{-1} (O–H).

3-(9-Anthracenyl)propyl Ethanoate (10). A mixture of 0.400 g (1.69 mmol) of the alcohol **9**, 6.5 mL (66 mmol) of acetic anhydride, and 0.25 g (3.0 mmol) of anhydrous sodium acetate was stirred for 3 h at 35 °C. The mixture (including a white precipitate) was poured into 50 mL of ice water and was extracted with ether. The ether extract was then washed with aqueous sodium hydroxide (10%) and then with water. The dried ether layer was concentrated, leaving 0.70 g (92%) of the crude acetate, mp 109–111 °C. The crude product was recrystallized from ethanol (75% recovery) affording the pure acetate **10**: mp 112–113 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 7.3–8.5 (m, 9 H), 4.24 (t, 2 H), 3.77 (m, 2 H), 2.1 (m, 2 H), 2.08 (s, 3 H); IR (KBr) 1726 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.25; H, 6.58.

3-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)propyl Ethanoate (11). Sealed, degassed tubes containing a total of 1.56 g (5.61 mmol) of **10**, 7.8 mL (101 mmol) of *trans*-1,2-dichloroethene, 114 mg (0.54 mmol) of 2,6-di-*tert*-butylphenol, and 15 mL of benzene were heated in a steel bomb. The bomb (also

(9) The source of this small regioselectivity is unknown, but is probably the result of a minor steric effect difference in the two competing transition states.

(10) In the case of bimolecular eliminations involving collisions between pairs of conjugate bases of **12**, **20**, or **22**, modest to large regioselectivities favoring isomers of general structure **24** would be expected on the basis of electrostatic charge–charge repulsive interactions.

(11) In dehydrochlorinations of **20** and **22** the larger *tert*-butoxide/substrate ratio used with **12** led to complex reaction mixtures. By reducing the base/substrate ratio to 1.4–1.5, the eliminations proceeded cleanly again to the mixture of vinyl chlorides. At present the structures of the byproducts formed at higher base/substrate ratios remain unknown.

(12) Daub, G. H.; Doyle, W. C. *J. Am. Chem. Soc* **1952**, *74*, 449.

(13) Cook, J. W.; Ludwiezak, R. S.; Schoental, R. *J. Chem. Soc.* **1950**, 1112.

(14) Stewart, F. H. C. *Aust. J. Chem.* **1960**, *13*, 478.

charged with benzene) was heated at 180 °C for 62 h. The reaction mixtures were combined and concentrated. The residue was chromatographed on a column of Florisil. The crude product [1.3 g (62%), mp 130–133 °C] eluted with 25% ether in hexane. This was recrystallized from a petroleum ether/benzene mixture, affording 0.90 g of a white solid: mp 134–135 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 7.3 (m, 8 H), 4.57 (d, 1 H), 4.41 (t, 1 H), 4.36 (t, 3 H), 2.64 (m, 4 H), 2.10 (s, 3 H); IR (KBr) 1736 cm^{-1} (C=O). Anal. Calcd for $C_{21}H_{20}Cl_2O_2$: C, 67.21; H, 5.37. Found: C, 67.44; H, 5.19.

3-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)-1-propanol (12). A 0.940-g (2.51-mmol) sample of 11 was added to 60 mL of 1.9 M methanolic sodium hydroxide. The mixture was heated at 35 °C for 4 h, diluted with water, and extracted with ether. The dried extract was concentrated under reduced pressure. The resulting oil was triturated with cold hexane. Following vigorous agitation of the mixture the alcohol crystallized, affording 0.84 g (83%) of the desired product, mp 110–111 °C. An analytical sample (mp 111–112 °C) was obtained by recrystallization from ether/hexane: ^{1}H NMR [$(CD_3)_2CO$] δ 7.3 (m, 8 H), 4.56 (d, 1 H, J = 2.9 Hz), 4.41 (t, 1 H, J = 2.9 Hz), 4.13 (d, 1 H, J = 2.9 Hz), 3.92 (m, 4 H), 2.66 (m, 2 H); IR (KBr) 2900 cm^{-1} (br, O–H). Anal. Calcd for $C_{19}H_{18}O_2Cl_2$: C, 68.48; H, 5.44. Found: C, 68.42; H, 5.55.

3-(9-Anthracenyl)-1-methoxypropane (15). The reaction was adapted from a procedure described by Johnstone.[15] A mixture of 0.365 g (6.36 mmol) of ground KOH and 1.68 g (6.54 mmol) of 18-crown-6 ether in 4 mL of dimethyl sulfoxide was stirred for 5 min. To this reaction mixture were added 0.384 g (1.63 mmol) of 3-(9-anthracenyl)-1-propanol and 0.50 mL (8.0 mmol) of methyl iodide. After 3 h an additional 0.50 mL of methyl iodide was added. The mixture was stirred for 3 h and then poured into 10 mL of water. The white precipitate was extracted with ether. The ether extract was washed with an aqueous solution of potassium iodide (150 mg of KI/150 mL of H_2O) and then with water. The ether in the dried extract was allowed to evaporate with periodic additions of small amounts of cold hexane. The product crystallized in this way, affording 0.265 g (66%) of the desired methyl ether: mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.35–8.45 (m, 9 H), 3.75 (t, 2 H), 3.51 (t, 2 H), 3.44 (s, 3 H), 2.13 (m, 2 H); IR (KBr) 1116 cm^{-1} (C–O–C). Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.22; H, 7.36.

3-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)-1-methoxypropane (16). Sealed, degassed tubes containing 1.00 g (4.00 mmol) of **15**, 0.076 g (0.36 mmol) of 2,6-di-*tert*-butylphenol, 5.6 mL (72 mmol) of *trans*-1,2-dichloroethene, and 10 mL of benzene were heated at 180 °C for 48 h in a steel bomb charged with benzene. The reaction mixture was diluted with dichloromethane and chromatographed on Florisil. The adduct eluted with approximately 10% ether in hexane as a yellow oil which slowly crystallized leaving 0.54 g (38%) of **16**, mp 95–97 °C. This was further purified by chromatography (Florisil) and recrystallization from aqueous ethanol, affording 0.300 g (56% recovery) of pure **16**: mp 99–100 °C; ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ 7.3 (m, 8 H), 4.56 (d, 1 H, J = 2.9 Hz), 4.40 (t, 1 H, J = 2.9 Hz), 4.13 (d, 1 H, J = 2.9 Hz), 3.69 (m, 2 H), 3.42 (s, 3 H), 2.64 (m, 2 H), 2.05 (m, 2 H). Anal. Calcd for $C_{20}H_{20}Cl_2O$: C, 69.17; H, 5.80. Found: C, 68.95; H, 6.00.

2-(9-Anthracenyl)ethyl Ethanoate (18). A mixture of 2.06 g (9.28 mmol) of 2-(9-anthracenyl)ethanol,[16] 1.37 g (16.5 mmol) of anhydrous sodium acetate, and 36 mL (360 mmol) of acetic anhydride was stirred at 35 °C for 3 h. The workup was carried out as for **10**, affording the crude acetate which was recrystallized from methanol, affording 1.66 g (68%) of **18**: mp 91–94 °C; ^{1}H NMR ($CDCl_3$) δ 8.36 (m, 3 H), 8.02 (m, 2 H), 7.51 (m, 4 H), 4.47 (t, 2 H), 3.98 (t, 2 H), 2.07 (s, 3 H); IR (KBr) 1735 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.83; H, 6.10.

2-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)ethyl Ethanoate (19). Sealed, degassed tubes containing 1.49 g (5.61 mmol) of **18**, 0.114 mg (0.54 mmol) of 2,6-di-*tert*-butylphenol, 7.80 mL (101 mmol) of *trans*-1,2-dichloroethene, and 15 mL of benzene were heated in a steel bomb charged with benzene at 180 °C for 62 h. The reaction mixtures were combined and concentrated. The dark brown, crude product was chromatographed on silica gel, from which crude **19** eluted with 25% ether in hexane. This was recrystallized from 1:1 benzene/petroleum ether, affording 0.523 g (26%) of pure **19**: mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.64 (m, 8 H), 4.76 (t, 1 H), 4.32 (m, 3 H), 3.99 (d, 1 H), 2.90 (m, 2 H), 2.18 (s, 3 H); IR (KBr) 1735 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{18}Cl_2O_2$: C, 66.49; H, 5.02; Cl, 19.63. Found: C, 66.72; H, 5.10; Cl, 19.93.

2-(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)-ethanol (20). The bridged acetate **19** [0.206 g (0.571 mmol)] was hydrolyzed with methanolic sodium hydroxide as described for the preparation of **12**. The crude alcohol was recrystallized from 1:1 ether/hexane, affording 0.110 g (60%) of **20**: mp 151–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.01–7.31 (m, 8 H), 3.8–4.3 (m, 4 H), 2.6–3.0 (m, 2 H), 1.4–1.8 (m, 2 H). Anal. Calcd for $C_{18}H_{16}Cl_2O$: C, 67.72; H, 5.05; Cl, 22.21. Found: C, 67.67; H, 5.04; Cl, 22.01.

(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)methyl Ethanoate (21). A sample of 1-(9-anthracenyl)methyl ethanoate[17] was prepared by acetic anhydride/sodium acetate esterification of the corresponding alcohol (Aldrich). The cycloaddition of 3.00 g (12.0 mmol) of this acetate with an excess of *trans*-1,2-dichloroethene (20.9 g, 0.216 mol) in benzene was effected as described for the preparation of **11**. Following the removal of solvent and excess dichloroethene, the crude product was purified by chromatography over silica gel (CH_2Cl_2/hexane) and recrystallization from petroleum ether, affording 0.551 g (13%) of **21**: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 6.5–7.8 (m, 8 H), 5.1 (s, 1 H), 4.2 (s, 2 H), 2.0 (s, 2 H), 1.4 (s, 3 H). Anal. Calcd for $C_{19}H_{16}Cl_2O_2$: C, 65.72; H, 4.64. Found: C, 65.82; H, 4.85.

(*trans*-7,8-Dichlorodibenzobicyclo[2.2.2]octadienyl)-methanol (22). The acetate **21** (0.800 g, 2.31 mmol) was hydrolyzed in 50 mL of 2 M methanolic potassium hydroxide. The crude alcohol was recrystallized from a mixture of petroleum ether and diethyl ether, affording 0.630 g (89.6%) of white crystals: mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 6.7–7.9 (m, 8 H), 4.8 (s, 2 H), 4.3 (m, 3 H's), 1.9 (br s, 1 H). Anal. Calcd for $C_{17}H_{14}ClO$: C, 66.90; H, 4.62; Cl, 23.23. Found: C, 67.00; H, 4.76; Cl, 23.88.

1-(Methoxymethyl)-7,8-*trans*-dichlorodibenzobicyclo-[2.2.2]octadiene (17). A mixture of 1.00 g (4.50 mmol) of 9-(methoxymethyl)anthracene,[18] 5.1 g (0.053 mol) of *trans*-dichloroethene, 6 mL of benzene, and 0.05 g of 2,6-di-*tert*-butylphenol was degassed and sealed in a glass tube. The tube was heated in a steel bomb (charged with benzene) for 22 h at 175 °C. The reaction mixture was dissolved in ether, treated with activated carbon, filtered, and concentrated. The residual oil was chromatographed on silica gel. The product eluted with 95:5 hexane/dichloromethane. The light yellow product was recrystallized from ethanol, affording 0.14 g (9.5%) of **17** as white crystals: mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 6.9–7.4 (m, 8 H), 4.1–4.4 (m, 5 H), 3.5 (s, 3 H); IR (KBr) 1100 cm^{-1} (C–O–C). The mass spectrum revealed the molecular ion at m/z 318 with the expected dichloroisotopic distribution. Anal. Calcd for $C_{18}H_{16}Cl_2O$: C, 67.73; H, 5.02; Cl, 22.23. Found: C, 67.91; H, 5.06; Cl, 22.41.

Potassium *tert*-Butoxide Induced Dehydrochlorinations. The basic procedures involving use of sealed tubes has been described.[6] Typical workup procedures are given for the dehydrochlorination of **12** under two sets of conditions.

A. Dehydrochlorination of 12 with Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. The contents of a tube (initially containing 0.16 mmol of **12** and 5 mL of 0.156 M KO*t*Bu/*t*BuOH) was heated for 43 h at 80 °C. The reaction mixture was diluted with 10 mL of water. The resulting precipitate was extracted with ether. The ether solution was then washed several times with water, dried, and concentrated. Slow evaporation of an ether/hexane solution of the residue afforded a crystalline mixture of the isomeric vinyl chlorides in 87% yield, mp 110–120 °C.

B. Dehydrochlorination Using Potassium Hydride in Tetrahydrofuran. A reaction mixture of approximately 3.0 mL

(15) Johnstone, R. W.; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169.
(16) Becker, H.-D.; Hansen, L.; Andersson, K. *J. Org. Chem.* **1986**, *51*, 2956.
(17) Nakaya, T.; Tomomoto, T.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 691.
(18) Mancilla, J. M.; Nonhebel, D. C.; Rusell, J. A. *Tetrahedron* **1975**, *31*, 3097.

of 0.08 M potassium hydride/THF, 0.30 mmol of **12**, and 0.30 mmol of 18-crown-6 ether was degassed and sealed in a glass tube. The tube was heated at 80 °C for 48 h. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with water, dried, and concentrated, leaving 85 mg (98% recovery including 10% unreacted **12**) of a white solid, mp 80-95 °C.

Spectral Characterizations of Elimination Products. The ^{1}H NMR spectra of elimination product mixtures (**23** + **24**) show pairs of partially resolved doublets for the bridgehead protons (H_a in **23** and **24**) in the region δ 4.9-5.2. The vinyl protons lie within the aromatic regions (approximate δ 7-8). The methylene protons absorb as varying types of multiplets for products from **12** (δ 2.8-3.9), four sets of triplets for products from **20** (δ 2.9, 3.1, 4.2, 4.4), and two singlets for products from **22** (δ 4.8). In the case of vinyl chlorides from **22** the area integrations for the two singlets could be used to confirm the product isomeric distribution from analyses of the bridgehead proton absorptions.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

A Nitrone-Based Cycloaddition Approach to the Synthesis of the Glycosyl System of Nogalomycin, Menogaril, and Their Congeners

Philip DeShong,* Wei Li, John W. Kennington, Jr., and Herman L. Ammon

Department of Chemistry and Biochemistry, The University of Maryland, College Park, Maryland 20742

Joseph M. Leginus[1]

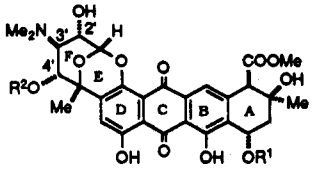
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

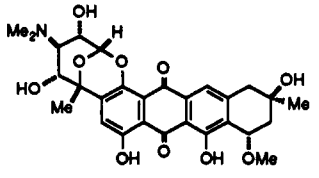
Received June 5, 1990

A series of model systems for the benzoxocin portion of nogalomycin was synthesized by cycloaddition of nitrone **8** with assorted dipolarophiles. Cycloaddition between nitrone **8** and vinyltrimethylsilane afforded isoxazolidines which were fragmented to produce either benzoxocins **21** and **23** or tricyclic isomer **27**. Tricyclic systems **23** and **27** were produced also from the adduct of nitrone **8** and allyltrimethylsilane following fragmentation and oxidative cleavage of the resulting homoallylic amine derivative. Dipolar cycloaddition between nitrone **8** and vinylene carbonate yielded two diastereomeric isoxazolidines **40** and **41**, both of which had the intact carbon skeleton of the glycosyl region of nogalomycin but which bore the incorrect relative configuration for transformation to menogaril analogue **5**.

Introduction

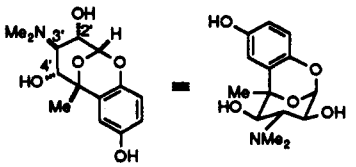
The carbon-linked glycosidic anthracyclines comprise a family of antibiotics with unique biological properties.[2] Nogalomycin (**1**), its degradation product menogaril (**4**), and decilorubicin (**2**) display potent antitumor activity, especially menogaril, which has entered phase II clinical trials. Arugomycin and viriplanin A are two additional members of this family of C-glycosidic anthracyclines whose aglycon differs from nogarol (**3**) only in the relative configuration of the hydroxyl at C-4′. Arugomycin displays antitumor activity similar to nogalomycin. Interestingly, viriplanin A does not have antitumor activity, but is highly active against Herpes simplex virus.[2]





1: Nogalomycin: R^1 = nogalose; R^2 = H
2: Decilorubicin: R^1 = rhodosamine; R^2 = L-decilonitrose-L-diginose
3: Nogarol: $R^1 = R^2$ = H

4: Menogaril



5

Several synthetic strategies for the synthesis of the benzoxocin (DEF ring) system of nogalomycin have been reported,[3] and Terashima has published a total synthesis of menogaril and several F-ring congeners.[4] As an integral portion of our studies concerning the total synthesis of amino sugars, the preparation of the carbon-linked glycosidic portion (the DEF ring) of menogaril employing a nitrone-based strategy has been developed, and a report of this preliminary study has appeared.[1,5] The original approach focused on construction of the acyclic precursor of benzoxocin **5** by a stereoselective, nitrone [3 + 2] cycloaddition as outlined in Scheme I. Cycloaddition of nitrone **8** and vinylene carbonate was anticipated to afford isoxazolidinecarbonate **7**. The stereoselectivity of this cycloaddition was anticipated to occur as indicated based upon previous studies from our laboratory (vide infra).[1,6,7]

Preparation of nitrone **8** was accomplished as outlined in Scheme II. Benzylation of 2,5-dihydroxyacetophenone (**9**) and Horner-Emmons-Wadsworth condensation of the resulting dibenzyl ether gave predominantly the *E* ester (*E*:*Z* = 8:1). The geometry of the major isomer was verified

(1) Taken in part from the Ph.D. Thesis of Joseph M. Leginus, The Pennsylvania State University, 1985.

(2) For a review of this topic see: Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1988; Vol. 2, pp 186-228.

(3) Bates, M. A.; Sammes, P. G. *J. Chem. Soc. Chem. Commun.* **1983**, 896. Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 1169. Joyce, R. P.; Parvez, M.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 4885. Bates, M. A.; Sammes, P. G.; Thomson, G. A. *J. Chem. Soc., Perkins Trans. 1* **1988**, 3037. Semmelhack, M. F.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 605.

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