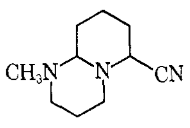
stituting *N*-methylpropane-1,3-diamine for 3-aminopropanol in the synthesis of **1**. The diamine was sufficiently stable in neutral or basic, aqueous solution to be readily isolated but no crystalline salts could be prepared.



**5**

These reactions are further examples of intramolecular Mannich reactions some of which have been described by Leonard[6] and elegantly exploited by Wenkert[7] in the synthesis of alkaloids. The successive generation of two imine (or iminium) groups by reaction of a primary amine with a dialdehyde in the presence of a nucleophile appears to provide a versatile synthetic tool which has yet to be widely used. Tricyclic products[8] have already been reported from this type of reaction and Lichtenthaler reports[9] an analogous reaction of glutaraldehyde, nitromethane, and benzylamine to give a cyclohexane derivative.

### Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian HA-100 nmr spectrometer.

**6-Cyano-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (1).**—A solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to pH 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added at 20° causing some turbidity. 3-Aminopropanol (20 g, 0.267 mol) was then added dropwise. During the addition, the temperature rose to 38° and was accompanied by a temporary rise in pH to 8 followed by a decrease to pH 7. After standing for 4 hr, the pale yellow solution was extracted with five 25-ml portions of methylene chloride. The combined extracts were dried ($Na_2SO_4$), concentrated, and distilled, giving 32.4 g (78%) of the product **1**: bp 128–130° (0.5 mm); ir (film) 2941, 2857, 2739 (CH), 2222 ($C\equiv N$), 1265, 1258, 1142, 1123, 1092, 1069, 1061 (OCN);[10] nmr ($CDCl_3$) $\delta$ 1.3–2.2 (m, 9), 2.6–3.25 (m, 2), 3.4–4.1 ppm (m, 4). Treatment of **1** with anhydrous hydrogen chloride in ether and recrystallization from ether gave the hydrochloride: mp 145–146°; ir (KBr) 2958, 2915, 2739 (CH), 2500 (broad, NH, obscuring $C\equiv N$), 1298, 1156, 1096, 1070 $cm^{-1}$ (COC).[10]

*Anal.* Calcd for $C_9H_{15}N_2OCl$: C, 53.33; H, 7.46; N, 13.82. Found: C, 53.15; H, 7.52; N, 14.02.

**6-Ethylthio-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (3).**—A 50% aqueous solution of glutaraldehyde (255 g, 1.3 mol) was added with stirring to a mixture of ethanethiol (78.9 g, 1.27 mol), methanol (90 ml), and water (300 ml) at 0°. 3-Aminopropanol (90 g, 1.2 mol) was added dropwise with stirring during which time the temperature rose to 32° and the mixture became heterogeneous and bright yellow. After stirring overnight, the mixture was basified (NaOH) and extracted with six 100-ml portions of methylene chloride. The dried ($Na_2SO_4$) extract was filtered through activated charcoal and concentrated to give a clear orange oil (211.9 g, 88% based on 3-aminopropanol), ir (film) 2941, 2857, 2732 (CH), 1312, 1273, 1149, 1126, 1098 $cm^{-1}$ (COC).[10]

*Anal.* Calcd for $C_{10}H_{19}NOS$: C, 59.67; H, 9.52; N, 6.96. Found: C, 60.00; H, 9.43; N, 6.68.

Attempted distillation of the product from a Woods metal bath at 155° gave a small amount of yellow liquid (crude **4**): bp 62–66° (1.75 mm); ir (film) 1630 ($C=C$), 1200–1100 $cm^{-1}$ (COC).[10]

**6-Cyano-1-methyl-1,2,3,4,7,8,9,9a-octahydro-6*H*-pyrido[1,2-*a*]-pyrimidine (5).**—The pH of a solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added, followed by the dropwise addition of 24.2 g (0.275 mol) of *N*-methyl-1,3-propanediamine. The diamine caused an exothermic reaction to 55° and an increase in pH which was controlled by dropwise addition of 85% phosphoric acid.

After the addition was complete, the heterogeneous mixture was allowed to stand for 4 hr, basified with 40% sodium hydroxide solution, and extracted with three 100-ml portions of ether. The dried ($Na_2SO_4$) extracts were concentrated and distilled giving 10 g of **5** (20.2%): bp 136–137° (2.5 mm); ir (film) 2941, 2857, 2793, 2710, 2577 (CH), 2222 $cm^{-1}$ ($C\equiv N$).

*Anal.* Calcd for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 66.99; H, 9.39; N, 23.17.

A further 5.1 g, bp 137–143° (2.5 mm), of material with a virtually identical ir spectrum was collected bringing the total yield to 30.5%.

**6-Cyano-3,4,6,7,9,9a-hexahydro-2*H*-1,4-thiazino[3,4-*b*][1,3]-oxazine (2).**—Thiodiacetaldehyde tetraethylacetal[5] (50 g, 0.188 mol) was stirred with 250 ml of water containing 5 ml of concentrated hydrochloric acid at 55°. The mixture became homogeneous in 10 min and was stirred for a further 50 min. After cooling to 0°, a solution of 18.8 g (0.29 mol) of potassium cyanide in 50 ml of water at 0° was added, the pH being kept below 7.5 by concurrent addition of cold 50% aqueous phosphoric acid (30 ml). A flocculent white precipitate remained suspended in the mixture. 3-Aminopropanol (14.1 g, 0.188 mol) dissolved in 25 ml of water was then added, the pH again being maintained between 6.5 and 8 by the addition of 50% aqueous phosphoric acid (10 ml required). The temperature was allowed to rise to 25° during the addition and the precipitate virtually dissolved leaving a pale yellow solution. The mixture was allowed to stand overnight and was then basified and extracted with three 75-ml portions of methylene chloride. The dried ($MgSO_4$) extract was concentrated to give 21.4 g of a yellow oil which crystallized on standing. Recrystallization from ethanol gave 15.6 g (45%) of crude product, mp 116–119°, which on further recrystallization gave pure **2**, mp 126–127°. The mother liquors smelled strongly of hydrogen cyanide: ir (KBr) 2980, 2898, 2857, 2777, 2739, 2666 (CH), 2257 ($C\equiv N$), 1282, 1257, 1234, 1219, 1206, 1183, 1145, 1111, 1003, 1070 $cm^{-1}$ (COC);[10] nmr ($CDCl_3$) $\delta$ 1.6 (m, 1), 2.1 (m, 1), 2.6–3.3 (m, 6), 3.6 (m, 1), 4.1 (m, 3).

*Anal.* Calcd for $C_8H_{12}N_2OS$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.00; H, 6.53; N, 14.99.

**Registry No.**—**1**, 19791-32-3; **1** hydrochloride, 26693-23-2; **2**, 15311-74-7; **3**, 26731-49-7; **4**, 26693-20-9; **5**, 26693-21-0.

**Acknowledgments.**—The author wishes to thank the following: Professors H. O. House and H. H. Wasserman for helpful discussions; Mr. C. B. Strow and Mr. H. L. Joyce and their colleagues for the nmr and ir spectra.

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[6] N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, **82**, 5148 (1960).

[7] E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

[8] R. M. Sheeley and H. S. Broadbent, *Diss. Abstr.*, **25**, 1583 (1964).

[9] F. W. Lichtenthaler, T. Nakagawa, and A. El-Scherbiney, *Angew. Chem., Int. Ed. Engl.*, **6**, 568 (1967).

[10] E. D. Bergmann and A. Kaluszyner, *Recl. Trav. Chim. Pays-Bas*, **78**, 315 (1959). See also Z. Eckstein, A. Sacha, and T. Urbanski, *Tetrahedron*, **16**, 30 (1961).

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## Ring Strain Effects on Aromatic Reactivity. A Molecular Orbital Treatment

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*Received June 29, 1970*

The first theoretical discussion of the reduced reactivity of the $\alpha$ position of strained benzocycloalkenes was advanced by Mills and Nixon[1] over 40 years ago.

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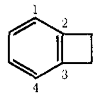
[1] W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930).

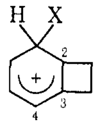
Their model, along with others presented recently, has proven to be inaccurate.[2] Recently, two generalizations have been put forth to explain the observed reactivity. Vaughan[3] has offered a bond order argument. He points out that in the Wheland intermediate for α substitution, the bond common to both rings has $^2/_3$ double bond character, while for β substitution it has only $^1/_3$ double bond character. This tends to decrease the bond length for α substitution but increase it for β substitution. Accordingly, he argues that as strain is increased in the fused ring, the transition state for α attack will be destabilized relative to the transition state for β attack. Streitwieser[4] has offered an explanation based on a rehybridization–polarization argument. In this model, it is suggested that the ring juncture carbons will have to rehybridize to accommodate the small bond angles of the strained ring. Thus, the σ bonds in the strained ring will have increased p character and the remaining σ bonds to the aromatic carbons α to the fused ring will have more s character. This increase in orbital electronegativity results in a polarization of σ electrons away from the α carbons. The net result is a decrease in reactivity of the α position toward electrophiles. In addition, the observed increase in acidity of the α protons with increased strain is explained.[4,5] Markgraf's[6] observation of reduced basicity of the lone pair of electrons of a nitrogen α to a strained ring is also explained.

We have demonstrated that Streitwieser's model can also be used to explain changes in half-wave reduction potentials[7,8] and changes in spin densities[9,10] of aromatic radical anions. We have been able to correlate this data within the Hückel framework by making the α carbons more electronegative with increased strain and the ring juncture carbons more electropositive. In this paper, we would like to point out that use of simple perturbation theory[11] within the Hückel framework plus the parameters derived from the epr and polarographic data can explain the observed decrease in reactivity of the α position of benzocyclobutene.

The energy of the neutral molecule in simple perturbation theory is equal to that of the unperturbed molecule, benzene, plus the change in energy due to changes in coulomb integrals of the atomic orbitals.[12] The energies of the Wheland intermediates for α and β substitution are equal to the unperturbed pentadienyl cation, $E^+$, plus the energy changes caused by the changes in coulomb integrals of the atomic orbitals.[13]



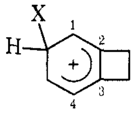
$$\alpha_1 = \alpha_4 = \alpha_0 + h_1\beta$$
$$\alpha_2 = \alpha_3 = \alpha_0 + h_2\beta$$
$$E^0 = E_{\text{benzene}} + h_1\beta + h_2\beta + h_3\beta + h_4\beta$$
$$E^0 = E_{\text{benzene}} + 2h_1\beta + 2h_2\beta$$



I

$$E^{\text{I}} = E^+ + \tfrac{2}{3}h_2\beta + h_3\beta + \tfrac{2}{3}h_4\beta$$
$$h_1 = h_4 \text{ and } h_2 = h_3$$
$$E^{\text{I}} = E^+ + \tfrac{2}{3}h_2\beta + h_2\beta + \tfrac{2}{3}h_1\beta$$
$$E^{\text{I}} = E^+ + \tfrac{2}{3}h_1\beta + \tfrac{5}{3}h_2\beta$$

The energy of activation for α and β attack can then be approximated by substracting the energy of the neutral molecule from that of each of the Wheland intermediates. In order to explain the observed preference of β attack, it follows that $\Delta E_{\text{I}} > \Delta E_{\text{II}}$; if we ignore common terms



II

$$E^{\text{II}} = E^+ + \tfrac{2}{3}h_1\beta + h_2\beta + \tfrac{2}{3}h_3\beta + h_4\beta$$
$$h_1 = h_4 \text{ and } h_2 = h_3$$
$$E^{\text{II}} = E^+ + \tfrac{2}{3}h_2\beta + h_2\beta + \tfrac{2}{3}h_2\beta + h_1\beta$$
$$E^{\text{II}} = E^+ + \tfrac{5}{3}h_1\beta + \tfrac{5}{3}h_2\beta$$

$\Delta E$ for α attack

$$\Delta E_{\text{I}} = E^{\text{I}} - E^0 = E^+ - E_{\text{benzene}} - {}^4/_3h_1\beta - {}^1/_3h_2\beta$$

$\Delta E$ for β attack

$$\Delta E_{\text{II}} = E^{\text{II}} - E^0 = E^+ - E_{\text{benzene}} - {}^1/_3h_1\beta - {}^1/_3h_2\beta$$

the inequality shown below must hold. This demonstrates that $h_1$ must be positive and greater than zero.

$$(4h_1 + h_2) > (h_1 + h_2)$$

Thus the carbon atoms α to the strained, fused ring have become more electronegative with respect to the π electrons; this is implied by Streitwieser's Model[4] and has been demonstrated by our epr and polarographic studies.[7-10] The parameters for naphtho[*b*]cyclobutene[8] derived from polarographic studies were $h_1 = 0.1$ and $h_2 = -0.3$. If one used these parameters in conjunction with the expressions derived above for the energies of activation and a value of −18 kcal/mol for β,[14] one predicts that β substitution will occur approximately 50:1 over α substitution. In addition, the simple theory predicts that electrophilic substitution at the β position will occur faster than electrophilic substitution of benzene while substitution at the α position will occur almost at the same rate as benzene. Recently,

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(2) J. B. F. Lloyd and P. A. Ongley, *Tetrahedron*, **20**, 2185 (1964).

(3) J. Vaughan and G. J. Wright, *J. Org. Chem.*, **33**, 2580 (1968); J. Vaughan, J. Welch, and G. J. Wright, *Tetrahedron*, **21**, 1665 (1965).

(4) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

(5) R. A. Finnegan, *J. Org. Chem.*, **30**, 1333 (1965).

(6) J. H. Markgraf and R. J. Katt, *Tetrahedron Lett.*, 6067 (1968); J. H. Markgraf and W. L. Scott, *Chem. Commun.*, 296 (1967).

(7) R. D. Rieke, W. E. Rich, and T. H. Ridgway, *Tetrahedron Lett.*, 4381 (1969).

(8) R. D. Rieke, W. E. Rich, and T. H. Ridgway, *J. Amer. Chem. Soc.*, in press.

(9) R. D. Rieke, C. F. Meares, and L. I. Rieke, *Tetrahedron Lett.*, 5275 (1968).

(10) R. D. Rieke and W. E. Rich, *J. Amer. Chem. Soc.*, **92**, 7349 (1970).

(11) N. V. Riggs, "Quantum Chemistry," Macmillan, New York, N. Y., 1969, p 184.

(12) In simple perturbation theory, the change in total π energy of a molecule caused by a change of one or more coulomb integrals is given by the product of the total electron density at a particular atom (i) and the change in the coulomb integral for that atom, $h_i\beta$.

(13) Using the nonbonding molecular orbital of the pentadientyl system, the total π-electron densities of $^2/_3$ for positions 2, 4, and 6 are easily determined. The π-electron densities at positions 3 and 5 are found to be unity.

(14) The value of −18 kcal/mol is frequently used in simple molecular orbital theory. The basic conclusions of the paper are not dependent on the value of β and essentially the same results will be obtained if one uses one of the other values for β found in the literature.

Eaborn[15] published the relative rates of protodesilylations of a series of benzocycloalkenes. He found that in benzocyclobutene the $\beta$ position underwent protodesilylation ten times faster than the $\alpha$ position; this is remarkably close to what the simple molecular orbital calculations predict. He also found that the $\beta$ position was 154 times as reactive as benzene while the $\alpha$ position was only 16 times as reactive. Once again, these results are close to those predicted by the above treatment.

The only other strained aromatic hydrocarbon for which there is any electrophilic substitution data is naphtho[*b*]cyclobutene.[9,16] Cava has reported that upon nitration of naphtho[*b*]cyclobutene the major product isolated is the 1-nitronaphtho[*b*]cyclobutene.[16] We found that the major product upon bromination is 1-bromonaphtho[*b*]cyclobutene.[9] There are, however, no relative rate studies available for this molecule. However, if one applies the simple perturbation calculations to this molecule, one finds that using $h_1 = 0.08\beta$ and $h_2 = -0.38\beta$ will give preferred electrophilic attack $\alpha$ to the fused, four-membered ring rather than in the adjacent benzene ring. These parameters are essentially the same as those derived from the polarographic data for this molecule.

One could make the simple MO calculations agree even better with the electrophilic substitution data by arbitrarily varying the parameters. Due to the semiempirical nature of this approach, this would add nothing to the argument. The remarkable thing about this model of ring strain and the derived parameters is that they adequately describe such diverse chemical and physical properties as epr and polarographic data,[7-10] acidity and basicity,[4-6] and relative rates of electrophilic substitution.[15] Vaughan's model, on the other hand, is not based on a firm theoretical basis and is not able to explain the changes in physical properties of aromatic hydrocarbons with strain.

**Registry No.**—Benzocyclobutene, 694-87-1.

**Acknowledgment.**—Financial support of this investigation by the University of North Carolina Materials Research Center under Contract SD-100 with the Advanced Research Projects Agency is gratefully acknowledged.

[15] A. R. Bassindale, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc. B*, 12 (1969).

[16] M. P. Cava and R. L. Shirley, *J. Org. Chem.*, **26**, 2212 (1961).

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# Photocoronopilin-A, a Cleaved Pseudoguaianolide from the Photolysis of Coronopilin

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In our continuing study of the photochemical transformations of sesquiterpene lactones[1] we wish to report a $C_4$–$C_5$ cleaved photolytic product from the pseudoguaianolide coronopilin (**1**). The product, which we named photocornopilin-A,[2] was of particular interest since we had previously discovered a series of naturally occurring $C_4$–$C_5$ cleaved pseudoguaianolides, the psilostachyins, in various *Ambrosia* species.[3,4] For example, *Ambrosia psilostachya* DC. plants which occur on a chain of islands which line the Texas gulf produce only cleaved pseudoguaianolides while plants of the same species which were collected on the adjacent mainland contained only typical pseudoguaianolides including coronopilin.[5] Furthermore, the major island constituent psilostachyin-A (**2**) could be derived directly by treatment of coronopilin with peracetic acid.

A benzene solution of coronopilin (*c* 0.08) was irradiated at 253.7 nm for 2.5 hr.[6] A major photo product, photocoronopilin-A (**3**) (mp 93–97°, $C_{15}H_{20}O_4$), was isolated in about 40% yield based upon the amount of coronopilin consumed. The presence of an $\alpha,\beta'$-conjugated $\gamma$-lactone function and a hydroxyl group in the photoproduct was evident from the uv, ir, and nmr data: $\lambda_{\max}$ 211 nm ($\epsilon$ 8900); ir bands 3500–3600, 1752, 1655, and 1640 cm$^{-1}$; nmr (see Experimental Section). Moreover, the nmr data indicated that while the $C_{10}$ secondary methyl group was still present, the $C_5$ methyl group had disappeared. Acetylation of photocoronopilin-A gave an acetate whose nmr spectrum (see Experimental Section) was best interpreted on the basis of formula **4**. Accordingly, photocoronopilin-A would be represented by structure **3**.

Confirmation of structure **3** for photocoronopilin-A was provided by $CrO_3$ oxidation of photocoronopilin-A to the known anhydropsilostachyin (**5**), a substance previously prepared from psilostachyin-A (**2**).[3]

Photocoronopilin-A appears, for the following reasons, to be a 1:1 mixture of $C_4$ epimers: (1) The $C_{13}$-methylene and $C_{10}$-methyl proton signals of photocoronopilin-A are each overlapped doublets. (2) A stereospecific hemiacetal formation during photolysis does not appear to be likely.

### Experimental Section[7]

The photolytic reaction was carried out using a Rayonet reactor, Model PRP-100 equipped with ultraviolet lamps (35-W; wavelength 253.7 nm) and a quartz reactor vessel (50.8 nm internal diameter, 33-cm length). Nmr spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ using TMS as an internal reference.

**Photocoronopilin-A (3) from Coronopilin (1) (Scheme I).**—Coronopilin (**1**) (400 mg) was dissolved in 500 ml of benzene which had been preflushed by bubbling a stream of nitrogen through the solution for 2 hr. The solution was irradiated at 35° under nitrogen for 2.5 hr. The residue obtained upon evaporation of the solvent was chromatographed over a column of

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* To whom correspondence should be addressed.

[1] H. Yoshioka, T. J. Mabry, and A. Higo, *J. Amer. Chem. Soc.*, **92**, 923 (1970).

[2] The designation A is employed for the photolytic product from coronopilin since Dr. J. Kagan has informed us that he obtained this same substance along with two other compounds by the photolysis of coronopilin under conditions different from those described here.

[3] T. J. Mabry, H. E. Miller, H. B. Kagan, and W. Renold, *Tetrahedron*, **22**, 1139 (1966).

[4] For a recent review of the distribution of sesquiterpene lactones in *Ambrosia*, see T. J. Mabry in "Phytochemical Phylogeny," J. B. Harborne, Ed., Academic Press, New York, N. Y., 1970, Chapter 12, pp 269–298.

[5] H. E. Miller, T. J. Mabry, B. L. Turner, and W. W. Payne, *Amer. J. Bot.*, **55**, 316 (1968).

[6] An acetic acid solution of coronopilin did not undergo any significant photolysis under similar irradiation.

[7] Melting points are uncorrected. The analysis was determined by Dr. Alfred Bernhardt, Mikronalytisches Laboratorium, Elbach über Engelskirchen, West Germany.