Aromatic Substitution and Addition Reactions of 1*H*-Cyclobuta[*de*]naphthalenes

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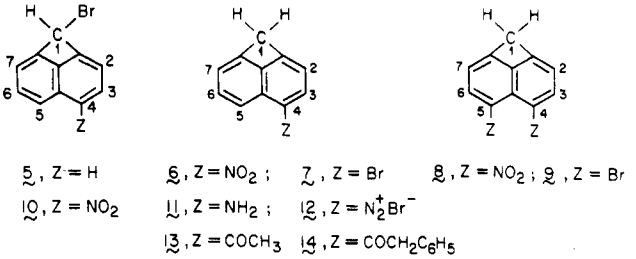
Nitration of 1*H*-cyclobuta[*de*]naphthalene (**1**) with nitric in sulfuric and acetic acids or with acetyl nitrate yields 4-nitro-1*H*-cyclobuta[*de*]naphthalene (**6**) and 4,5-dinitro-1*H*-cyclobuta[*de*]naphthalene (**8**). Similarly, 1-bromo-1*H*-cyclobuta[*de*]naphthalene (**5**) nitrates to 1-bromo-4-nitro-1*H*-cyclobuta[*de*]naphthalene (**10**). Reaction of **1** and bromine in the presence of ferric bromide gives 4-bromo-1*H*-cyclobuta[*de*]naphthalene (**7**) and 4,5-dibromo-1*H*-cyclobuta[*de*]naphthalene (**9**). Reduction of **6** with aluminum amalgam in protic environments or by hydrogenation over palladium results in 4-amino-1*H*-cyclobuta[*de*]naphthalene (**11**), diazotization of which with nitrous and hydrobromic acids yields 1*H*-cyclobuta[*de*]naphthalene-4-diazonium bromide (**12**) and then **7** upon reaction with cuprous bromide. 4-Acetyl-1*H*-cyclobuta[*de*]naphthalene (**13**) and 4-(phenylacetyl)-1*H*-cyclobuta[*de*]naphthalene (**14**) are formed efficiently by Friedel–Crafts acylations of **1** with acetyl chloride and with phenylacetyl chloride. The present study thus reveals that (1) electrophilic substitution of **1** occurs regiospecifically at its C_4 position and (2) **1** does not undergo ring opening of its cyclobuta moiety during the above reactions. The rates of electrophilic bromination and acetylation of **1** relative to naphthalene (**18**), acenaphthene (**19**), and 2,3-dihydro-1*H*-phenalene (**20**) are **19** > **20** > **1** > **18**; nitration of **1** also occurs more rapidly than that of **18**. *n*-Butyllithium effects conversion of **7** to 4-lithio-1*H*-cyclobuta[*de*]naphthalene (**24**) which isomerizes slowly to 1-lithio-1*H*-cyclobuta[*de*]naphthalene (**25**). Addition of bromine to **1** takes place upon photolysis to give a tetrabromide assigned as 1aα,2β,3β,4α-tetrabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**30**). 2,4-Dibromo-1*H*-cyclobuta[*de*]naphthalene (**35**) is formed by dehydrobromination of **30** with DBU; Red-Al effects conversion of **30** to **1**. Photobromination of **5** results in benzenoid addition to yield two pentabromides provisionally assigned as 1,1aα,2β,3α,4α-pentabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**37**, major) and 1,1aα,2β,3β,4α-pentabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**38**, minor). Reactions of **37** and **38** with Red-Al result in regeneration of **5**.

1*H*-Cyclobuta[*de*]naphthalene (**1**) and many of its 1*H* derivatives have been prepared.[1a–k] The behavior previously investigated for this highly strained peri-bridged system has concentrated on its four-membered ring unit. Thus, 1*H*-cyclobuta[*de*]naphthalen-1-yl derivatives undergo nucleophilic displacement without rupture of their cyclobuta moieties and 1*H*-cyclobuta[*de*]naphthalen-1-yl cations, carbanions, and free-radicals may be used in synthesis with maintenance of their cyclobutyl structures.[1a,b,f,g] Of note is that **1** undergoes rapid silver ion catalyzed ring opening in acetic acid to yield 1-naphthylmethyl acetate (**4**, eq 1).[1g] There is thus concern that aromatic substitution of **1** and its derivatives will be complicated in strongly acidic environments by ipso-ring-rupture reactions of their cyclobuta groups (eq 1). The behavior of **1** and 1-bromo-1*H*-cyclobuta[*de*]-naphthalene (**5**) with electrophilic reagents capable of aromatic substitution and the chemistry of the products produced therein are now described. Study has also been made of bromination reactions that result in additions to benzenoid units in **1** and **5**.

Reactions of **1** with nitric acid in sulfuric acid–acetic acid at ~25 °C or with acetyl nitrate at 0 °C give 4-nitro-1*H*-cyclobuta[*de*]naphthalene (**6**, 85%) and 4,5-dinitro-1*H*-cyclobuta[*de*]naphthalene (**8**). With nitric acid in sulfuric acid at 30 °C **6** nitrates efficiently to **8** (89%). Also bridged bromide **5**[1a–c] and nitric acid in acetic anhydride at 0 °C yield 1-bromo-4-nitro-1*H*-cyclobuta[*de*]naphthalene (**10**, 67%). Rupture of the cyclobuta units in **1**, **5**, **6**, **8**, and **10** thus does not occur and nitration other than at C_4 in **1** and **5** and at C_5 in **6** was not observed. The structure of **6** is established from its combustion analysis, exact mass, IR absorption, 12-line ^{1}H NMR spectrum, and ^{1}H NMR at δ 4.73 for *peri*-methano bridging (CH_2). Dinitro compound **8**, a symmetrical product, is assigned from analytical and spectral data, from its seven-line ^{13}C NMR and its two aromatic ^{1}H NMR doublets (δ 7.39 for H at C_2 and C_7 and 8.83 for H at C_3 and C_6). Elemental analyses and spectroscopic methods reveal the structure of **10** as indicated.



5, Z = H; **6**, Z = NO_2; **7**, Z = Br; **8**, Z = NO_2; **9**, Z = Br; **10**, Z = NO_2; **11**, Z = NH_2; **12**, Z = $N_2^+Br^-$; **13**, Z = $COCH_3$; **14**, Z = $COCH_2C_6H_5$

Electrophilic bromination of **1** was then investigated. Indeed, reaction of **1** and bromine as catalyzed by ferric bromide at 0 °C gives 4-bromo-1*H*-cyclobuta[*de*]-naphthalene (**7**, 94%). The structure of **7** is confirmed upon its conversion by bromine and ferric bromide at 0 °C to 4,5-dibromo-1*H*-cyclobuta[*de*]naphthalene (**9**, 89%). Synthesis of **7** was also accomplished from 4-amino-1*H*-cyclobuta[*de*]naphthalene (**11**) as prepared by reduction of **6** with aluminum amalgam in ethyl ether–ethanol–water or hydrogenation over palladium on carbon at 25–30 °C.[2] Diazotization of **11** with nitrous and hydrobromic acids at 0 °C and then heating 1*H*-cyclobuta[*de*]naphthalene-4-diazonium bromide (**12**) with cuprous bromide yield **7**.[3]

(1) (a) Bailey, R. J.; Shechter, H. *J. Am. Chem. Soc.* **1974**, *96*, 8116. (b) Gessner, M.; Card, P. J., Shechter, H. *Ibid.* **1977**, *99*, 2371. (c) Becker, J.; Wentrup, C. *Chem. Commun.* **1980**, 190. (d) Engler, T. A.; Shechter, H. *Tetrahedron Lett.* **1982**, 2715. (e) Yang, L. S.; Engler, T. A.; Shechter, H. *J. Chem. Soc., Chem. Commun.* **1983**, 866. (f) Bailey, R. J.; Card, P. J.; Shechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6096. (g) Card, P. J.; Friedli, F. E.; Shechter, H. *Ibid.* **1983**, *105*, 6104. (h) Chapman, O. L. *Chem. Eng. News* **1978**, *56* (38), 17. (i) Chapman, O. L. *Pure Appl. Chem.* **1979**, *51*, 331. (j) Hayes, R. A.; Hess, T. C.; McMahon, R. J.; Chapman, O. L. *J. Am. Chem. Soc.* **1983**, *105*, 7786. (k) A portion of the present results has been communicated by: Friedli, F. E.; Shechter, H. *Tetrahedron Lett.* **1985**, 1157.

(2) (a) Amine **11** is a liquid which darkens rapidly on exposure to air. Reaction of **11** with phenyl isothiocyanate gives the solid derivative, 1-(1*H*-cyclobuta[*de*]naphthalen-4-yl)-3-phenylthiourea (62%), see Experimental. (b) Reduction of **6** with tin and hydrochloric acid at 0 °C yields **11** (13%) along with much amorphous material.

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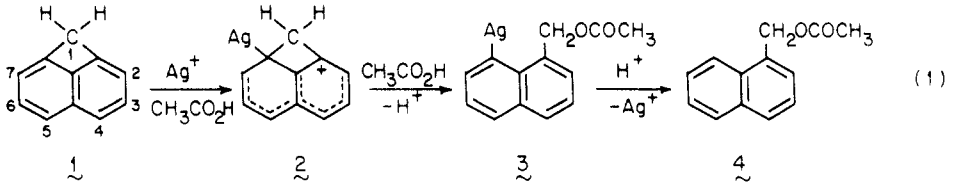


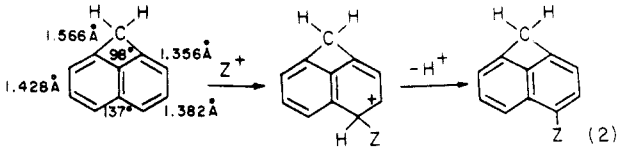
(1)

1 2 3 4

Demonstration that the nitro group in **6** can be reduced to its amine **11** without rupture of the cyclobuta moiety and that diazonium salt **12** can be used conventionally are of obvious synthesis value.

Friedel–Crafts acylations of **1** also occur without ring rupture. Thus **1** reacts with acetyl chloride and with phenylacetyl chloride in the presence of aluminum chloride at 25 °C in methylene chloride to give 4-acetyl-1*H*-cyclobuta[*de*]naphthalene (**13**, 61%) and 4-(phenylacetyl)-1*H*-cyclobuta[*de*]naphthalene (**14**, 87%). Attempts to diacetylate **1** with acetyl chloride/aluminum chloride in refluxing 1,2-dichloroethane failed.

The present study thus reveals that **1** does not ring open during reactions with nitric and sulfuric acids, bromine and ferric bromide, and acid chlorides with aluminum chloride. Further, electrophilic substitution of **1** (illustrated in detail as **15**)[4] occurs regiospecifically at the 4-position as in eq 2. This latter result contrasts sharply with electrophilic

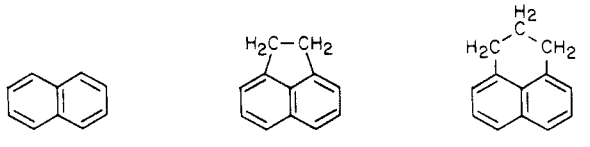


(2)

15 16 17

bromination and nitration of 1,8-dimethylnaphthalene and many other naphthalene derivatives in which substantial substitution occurs at C_2.[5] X-ray analysis of **1** (see **15**) gives insight into the highly directed electrophilic substitution reactions of the hydrocarbon at its C_4 (and C_5) position.[4] Bridging the peri positions of naphthalene with a single carbon atom moiety and maintenance of the planar ring systems lead to severe compression in the front end and to bond lengthening and angle widening in the rear end of **15** (eq 2).[4] The aromatic bonds at C_2 in **15** are thus relatively short and strong whereas those at C_4 are longer, relatively weak, and thus more susceptible to electrophilic attack (eq 2).[1b,2] The facts that nitration of **6** and bromination of **7** give **8** and **9** exclusively whereas 5-bromoacenaphthene brominates and nitrates principally to 3-substituted derivatives[5] and bromination of 4-bromo-1,8-dimethylnaphthalene results primarily in 2,4-dibromo-1,8-dimethylnaphthalene[5] illustrate vividly the effects of bond-length and bond-angle distortion on the substitution reactions of 1*H*-cyclobuta[*de*]naphthalenes.

The rates of electrophilic bromination and acetylation of **1** relative to naphthalene (**18**), acenaphthene (**19**), and 2,3-dihydro-1*H*-phenalene (**20**) were then determined.



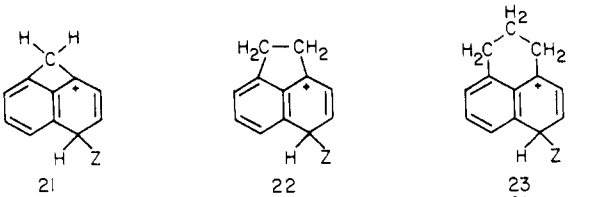
18 19 20

Table I. Relative Rates of Electrophilic Substitution of 1 and 18–20

hydrocarbons compared	relative rates: bromination[a] (0 °C)	acetylation[b] (25 °C)	nitration[b] (0 °C)
1/18[c]	110.0[c]	8.2[c]	3.5[c]
19/1	12.8	4.2	
20/1	6.1	2.6	

[a] Values determined by GC analysis. [b] Values determined by ^1H NMR methods. [c] Corrected values on the basis that 18 has twice as many ortho positions as does 1.

Mixtures of **1** (10 equiv) with **18**, **19**, and **20** (10 equiv) were thus reacted with 1 equiv of the electrophilic reagent (Br_2 and Fe in CCl_4 at 0 °C; CH_3COCl and $AlCl_3$ in CH_2Cl_2 at 25 °C) and the products from each competitive experiment were analyzed by ^1H NMR or GC methods. The results, as summarized in Table I, reveal that the reactivities for these aromatic substitutions are **19** > **20** > **1** > **18**.[6] Further, acetyl nitrate (1 equiv) in acetic anhydride effects nitration of **1** (10 equiv) faster than **18** (10 equiv) at 0 °C. The greater reactivity of **1** than of **18** presumably stems from electron donation of the *peri*-methano bridge and the strain release upon attack on **15** as in eq 2. The observations that **19** and **20** substitute more rapidly than **1** may be rationalized on the basis of greater electron release by the longer and more electron-donating connecting bridges in **19** and **20**. That the order of reactivity is **19** > **20** > **1** raises the question that substitution is affected significantly by ring-size factors in cationoidal transition states resembling **21**–**23**. Five-membered rings can more easily



21 22 23

accommodate a developing carbonium ion center than a six-membered ring and much more readily than a four-membered ring.[7]

Study of the utility of bromide **7** in synthesis has been initiated. Of initial interest is that **7** is readily converted to lithium (**24**) and Grignard (**26**) reagents which react with acetyl chloride and with acetaldehyde. These experiments result, however, in useless mixtures containing many components. A question then raised is that the initially formed organometallic reagents are undergoing structural change. A study of deuterium quenching of the products of reaction of **7** with *n*-butyllithium reveals conversion of **24** to **25** (eq 3). As summarized in Table II, formation of 4-deuterio-1*H*-cyclobuta[*de*]naphthalene (**28**), 1-deuterio-1*H*-cyclobuta[*de*]naphthalene (**29**), and **1** are explainable by time-dependent proton transfer from the bridging carbon (C_1) to the C_4 position of the organolithium reagent

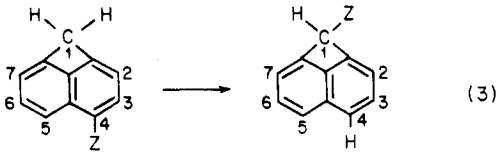
(3) The yield of **7** is only 11%. Study of the optimum conditions for effecting diazotization and displacement of **11** has not been made.

(4) Gessner, M.; M.S. Thesis, The Ohio State University, Columbus, Ohio, 1977.

(5) Lewis, I. K.; Topsom, R. D.; Vaughan, J.; Wright, G. J. *J. Org. Chem.* **1968**, *33*, 1497.

(6) That **19** undergoes electrophilic aromatic substitution faster than **20** has been previously observed.[5]

(7) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.



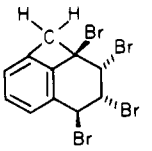
(3)

24 , Z = Li
26 , Z = MgBr

25 , Z = Li
27 , Z = MgBr

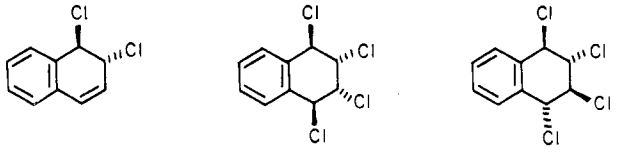
24 initially generated.[8] It is to be expected that 25, a conjugated lithio carbanionic base, is more stable than 24 and, along with the kinetic acidity of hydrogen on the methano bridge of 25, the driving forces for the isomerizations of eq 3 are obvious.[8]

N-Bromosuccinimide as initiated by benzoyl peroxide in refluxing carbon tetrachloride effects bromination of methano hydrogen in 1 to yield 5.[1g] Since 19, fluorene,[9] methyl- and dimethylnaphthalenes,[10] and acenaphthalene[11] photobrominate at their α C–H positions, the photolytic behavior of bromine and 1 was examined. Irradiation (100-W bulb) of bromine in carbon tetrachloride results, however, in addition to 1 to give the single derivative, tetrabromo product 30, assigned as 1aα,2β,3β,4α-tetra-



30

bromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene. Under identical conditions naphthalene (18) yields a 1,2,3,4-tetrabromo adduct[12] and photochlorination of 18 results in 1α,2β-dichloro-1,2-dihydronaphthalene (31),

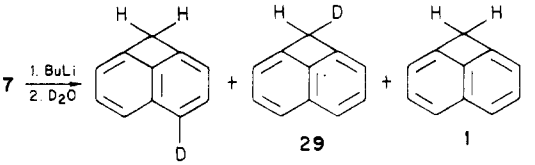


31 32 33

1α,2β,3β,4α-tetrachloro-1,2,3,4-tetrahydronaphthalene (32, major), and 1α,2β,3α,4β-tetrachloro-1,2,3,4-tetrahydronaphthalene (33, minor).[13]

The structure assigned 30 has its bromines in a trans-cis-trans relationship, is the supposed product of trans addition of bromine at $C_{3,4}$ and then $C_{1a,2}$, and, as a result of the constraints of its cyclobuta unit and the severe twisting of its cyclohexane ring, allows minimal steric interaction of its halogen atoms. The stereochemistry assigned 30 has an experimental basis from its ^{1}H NMR in the 4–5.5 δ region. The bridge protons at C_1 in 30, though not identical, appear as a broad singlet as peak 1 in Figure

Table II. Position of Deuterium Label upon Quenching 4-Lithio-1*H*-cyclobuta[*de*]naphthalene (24) with D_2O after Various Time Intervals



28 29 1

time, min[a]	percentage of each component[b] 28	29	1
2	91	9	0
10	80	15	5
20	65	26	9
30	54	35	11

[a] Time elapsed before deuteration of 24 after preparation from 7 at −78 °C. [b] Values obtained by ^{1}H NMR and MS analyses.

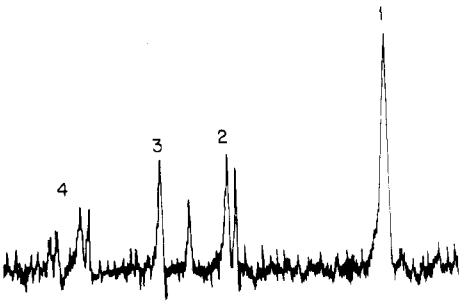
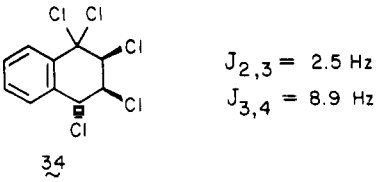


Figure 1. Partial ^{1}H NMR ($CDCl_3$) of tetrabromide 30.

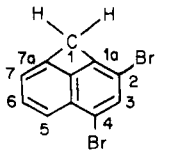
1. The low coupling constant (2.5 Hz) of doublet 2 in Figure 1 indicates a dihedral angle near 90° and a cis configuration in 30. Doublet 3 with its large coupling constant (9 Hz) comes from a large dihedral angle (150–180°) and presumably a trans diaxial arrangement of hydrogens. Doublet 2 apparently arises from hydrogen on C_2 cis to hydrogen on C_3. Doublet 3 then originates from the proton on C_4 which is trans to that on C_3. Further, the NMR values and the trans-cis-trans assignments of the bromine atoms in 30 correlate beautifully with that of pentachloride 34 as obtained from photochlorination of 1-chloronaphthalene.[13a]



34

$J_{2,3}$ = 2.5 Hz
$J_{3,4}$ = 8.9 Hz

Tetrabromide 30 is of value in synthesis in that it is dehydrobrominated by 1,5-diazabicyclo[5.4.0]undec-2-ene (DBU) to 2,4-dibromo-1*H*-cyclobuta[*de*]naphthalene (35, 74%), the first 1*H*-cyclobuta[*de*]naphthalene with an ortho



35

substituent. The detailed mechanisms of the base-catalyzed eliminations of 30 to 35 have not been established. Spectral absorbances, exact mass, and elemental analyses lend credence to the structure proposed. The most im-

(8) (a) Deuterium exchange for hydrogen on C_1 occurs readily in 1.[1f] (b) The kinetic acidities of the following hydrocarbons are: fluorene > diphenylmethane > acenaphthene > 1.[1f]

(9) Sampey, J. R.; Reid, E. E. *J. Am. Chem. Soc.* **1947**, *69*, 234.

(10) Storms, P. W.; Miller, G. B. *J. Org. Chem.* **1966**, *31*, 2705.

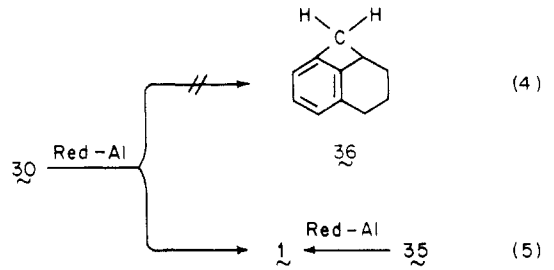
(11) (a) Petrenko, G. P.; Murugova, A. A.; Usschenko, V. G. *J. Org. Chem. U.S.S.R.* **1969**, 1968. (b) Dashevskii, M. M.; Petrenko, G. P. *Zh. Obshch. Khim.* **1955**, *25*, 1378.

(12) Sampey, J. R.; Cox, J. M.; King, A. B. *J. Am. Chem. Soc.* **1949**, *71*, 3697.

(13) (a) Burton, G. W.; de la Mare, P. B. D.; Wade, M. J. *J. Chem. Soc. Perkin Trans. 2* **1974**, 1908. (b) Burton, G. W.; de la Mare, P. B. D.; Barnett, J.; Bedford, K. R.; Nicholson, S.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1908. (c) Bedford, K. R.; Burton, G. W.; de la Mare, P. B. D.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 459. (d) Bedford, K. R.; de la Mare, P. B. D.; Burton, G. W. *Tetrahedron Lett.* **1973**, 3205.

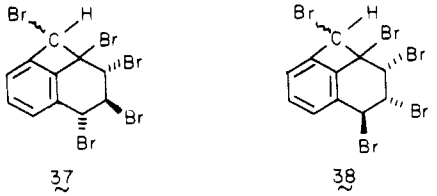
portant feature allowing the assignment as **35** rather than as the 2,3- or the 3,4-dibromide is the *isolated* aromatic NMR *singlet* at δ 7.20 for hydrogen at C_3. Additional supporting ^1H NMR data ($CDCl_3$) for **35** are δ 4.63 (s, 2 H, H on C_1), 6.98–7.07 (d of d, 1 H, H on C_7), and 7.38–7.46 (m, 2 H, H at C_5 and C_6).

Tetrabromide **30** is the first example of a new polycyclic system. In an effort to prepare the parent hydrocarbon, 1*H*-cyclobuta[*de*]-1,2,3,4-tetrahydronaphthalene (**36**, eq 4),



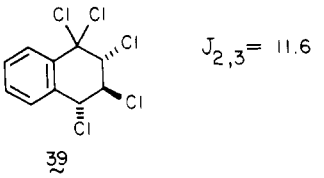
reduction of **30** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) was attempted. Formed, however, is the familiar parent hydrocarbon **1** (eq 5) in near-quantitative yield. Apparently attack on carbon with displacements of bromine in **30** are quite slow and thus Red-Al effects debromination of **30**[14] or/and double dehydrobromination to **35** which is then reduced to **1** (eq 5). Indeed, Red-Al does convert **35** to **1** efficiently (eq 5).

Photobromination (100-W bulb) was extended to **5** as with **1**. Addition to a benzenoid unit in **5** occurs to give two pentabromides provisionally assigned by ^1H NMR as 1,1aα,2β,3α,4β-pentabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**37**) and 1,1aα,2β,3β,4α-pentabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**38**) in a ratio of 4:1 (see Experimental Section). Bromine at C_1 in **5** thus has a significant effect on the mode of addition of bromine to cyclobuta[*de*]naphthalenes. As yet the stereochemistries of bromine on C_1 in **37** and **38** are not known.



Minor isomer **38** exhibits a ^1H NMR splitting pattern (Figure 2) identical with that of tetrabromide **30**. Doublet 1 (J = 2.5 Hz) represents the hydrogen on C_2 and doublet 2 (J = 8 Hz) is from the proton on C_4, both of which are coupled to doublet of doublets 3 arising from hydrogen on C_3. The proton on the bridging methylene group (C_1) gives a sharp singlet 4 (δ 5.80) as expected. On the basis of the above data the stereochemistry of the four cyclohexyl bromines in **38** is assumed to be identical with that in **30**.

Major isomer **37** displays a different ^1H NMR pattern with larger coupling constants (Figure 3) than does **38**. Hydrogen on C_3 is exhibited as doublet of doublets 2 coupled to doublets 1 (11.5 Hz) and 3 (5 Hz). Singlet 4 represents the bridge proton on C_1. Hydrogens on C_2 and C_4 are assignable to doublets 1 and 3 because for **30** and **38** the resonances for hydrogen on C_4 are shifted downfield from that at C_2. Definite assignments of doublets **1** and **3** are not yet possible. However, from the coupling constants doublet 1 might result from a trans and probably diaxial interaction whereas doublet 3 could come from trans stereochemistry not quite axial because of the severe twist of the cyclohexyl ring. The trans-trans-trans stereochemistry proposed for **37** therefore does fit the spectral data presently obtained. Further, **37** is similar in structure and the coupling constants for its hydrogens at C_2 and C_3 correlate with that of **39**.[13a] It is quite clear, however, that



the structure of **37** should be established without question by more direct methods.

Finally, reaction of the 4:1 mixture of **37** and **38** with zinc in ethyl ether containing a trace of acetic acid results in regeneration of **5** (~90%) along with reduction to **1**. This experiment reveals again the ability of a tetrabromo adduct of a 1*H*-cyclobuta[*de*]naphthalene to undergo efficient debromination to its bridged parent.

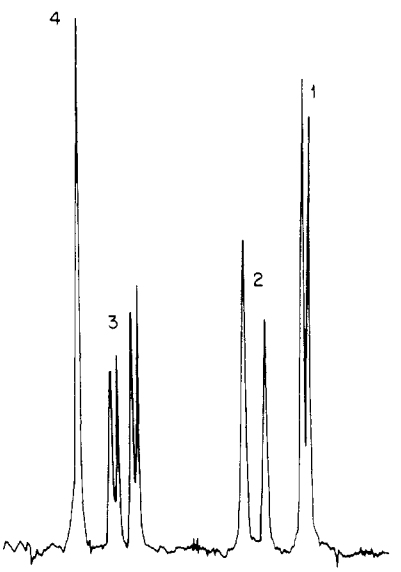


Figure 2. Partial ^1H NMR ($CDCl_3$) of pentabromide **38**.

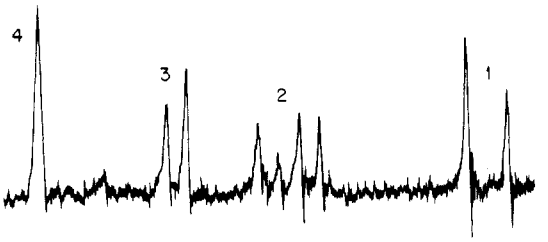


Figure 3. Partial ^1H NMR ($CDCl_3$) of pentabromide **37**.

Experimental Section

Nitration of 1*H*-Cyclobuta[*de*]naphthalene (1) with Nitric/Sulfuric Acids. A mixture of nitric acid (0.30 g of 70% HNO_3, 3.0 mmol) and concentrated sulfuric acid (0.5 mL) was added in 3 min to **1** (0.140 g, 1.0 mmol) in glacial acetic acid (2 mL) at 0 °C. The mixture was stirred 3 min, poured onto ice, neutralized with sodium bicarbonate, and extracted with ethyl ether. The ethereal layer was dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel gave the following compounds.

(1) 4-Nitro-1*H*-cyclobuta[*de*]naphthalene (**6**, 75 mg, 41%): a yellow solid; mp 124–125 °C; IR (KBr, cm^{-1}) 1505, 1300 (NO_2),

(14) For debromination of **30** to **1** by Red-Al, attack of sodium bis(2-methoxyethoxy)aluminum hydride on positive bromine with formation of sodium bis(2-methoxyethoxy)aluminum, hydrogen bromide and sodium bromide would have to occur.

1600, 1575, 1460, 1435, 1405, 1180, 890, 855, 780 (Ar); ^{1}H NMR ($CDCl_3$) δ 4.73 (s, 2 H, CH_2), 7.16 (d, 1 H, J = 6 Hz, H on C_7), 7.21 (d, 1 H, J = 7 Hz, H on C_2), 7.65 (d of d, 1 H, J = 9, 6 Hz, H on C_6), 8.19 (d, 1 H, J = 9 Hz, H on C_5), 8.48 (d, 1 H, J = 7 Hz, H on C_3); UV λ (ϵ) 346 nm (5450), 254 (10600), 213 (37200); exact mass calcd 185.04766, found 185.04799. Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.78. Found: C, 70.97; H, 3.99.

(2) 4,5-Dinitro-1*H*-cyclobuta[*de*]naphthalene (8, 55 mg, 24%): a pale yellow solid; mp 166–168 °C; IR (KBr, cm^{-1}) 1510, 1315 (NO_2), 1610, 1575, 1350, 910, 845, 816, 755 (Ar); ^{1}H NMR ($CDCl_3$) δ 4.81 (2 H, CH_2), 7.39 (d, 2 H, J = 7 Hz, ortho), 8.85 (d, 2 H, J = 7 Hz, meta); C^{13} NMR ($CDCl_3$) δ 45.6 (1 C, C_1), 109.4 (1 C, C_9), 119.8 (2 C, $C_{2,7}$), 131.2 (2 C, $C_{3,6}$), 142.1 (1 C, C_8), 145.5 (2 C, $C_{4,5}$), 146.2 (2 C, $C_{1a,7a}$); UV λ (ϵ) 329 nm (6615), 238 (24500), 201 (37400); exact mass calcd 230.03273; found, 230.03223. Anal. Calcd for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.62. Found: C, 56.95; H, 2.50.

Nitration of 1 with Acetyl Nitrate. Nitric acid (70%, 700 mg, 7.5 mmol) in acetic anhydride at 0 °C was added dropwise to 1 (1.0 g, 7.1 mmol) in acetic anhydride (20 mL) at 0–5 °C. The mixture was stirred 1 h and then warmed to room temperature. Ethyl ether (300 mL) and 20% potassium hydroxide (200 mL) were added and the mixture was stirred for 2 h. The ethereal layer was separated and dried over magnesium sulfate, and the solvent was removed under reduced pressure leaving 6 (1.12 g, 85%), identical with previous material.

Nitration of 4-Nitro-1*H*-cyclobuta[*de*]naphthalene (6). Nitric acid (70%, 16 mL) in concentrated sulfuric acid (10 mL) was added to 6 (125 mg, 0.66 mmol) in acetic acid (10 mL) at room temperature. The mixture was stirred 30 min, poured into water, neutralized with sodium bicarbonate, and extracted with ether. The ethereal layer was dried ($MgSO_4$) and concentrated. After the residue in benzene had been passed through silica gel, solvent was removed leaving 8 (0.140 g, 89%), identical with an authentic sample.

Nitration of 1-Bromo-1*H*-cyclobuta[*de*]naphthalene (5). A solution of nitric acid (70%, 0.44 mL) in acetic anhydride (5 mL) was added at 0 °C to 5 (0.62 g, 2.8 mmol) in acetic anhydride (5 mL). After having been stirred 30 min, the mixture was neutralized ($NaHCO_3$) and extracted with ethyl ether. The ethereal layer was dried and concentrated to yield 1-bromo-4-nitro-1*H*-cyclobuta[*de*]naphthalene (10, 0.50 g, 67%): mp 115–117 °C; IR (KBr, cm^{-1}) 1510, 1310 (NO_2), 1430, 1340, 1150, 893, 778, 723 (Ar); NMR ($CDCl_3$) δ 6.73 (s, 1 H, bridge), 7.27 (d, 1 H, J = 8 Hz, H on C_7), 7.35 (d, 1 H, J = 7 Hz, H on C_2), 7.78 (d of d, 1 H, J = 8, 8 Hz, H on C_6), 8.28 (d, 1 H, J = 8 Hz, H on C_5), 8.50 (d, 1 H, J = 7 Hz, H on C_3); UV λ (ϵ) 347 nm (4800), 253 (9300), 224 (shoulder, 16500), 215 (21000); exact mass calcd 262.95822, found 262.95858. An analytical sample was prepared by two sublimations at 80–90 °C (0.1 mm) and recrystallization from hexane. Anal. Calcd for $C_{11}H_6BrNO_2$: C, 50.03; H, 2.29. Found: C, 49.99; H, 2.40.

4-Acetyl-1*H*-cyclobuta[*de*]naphthalene (13). Aluminum chloride (130 mg, 1 mmol) was added in 1 h to 1 (140 mg, 1.0 mmol) and acetyl chloride (78 mg, 1.0 mmol) in dichloromethane (6 mL). The mixture was stirred 8 h, poured into water, and extracted with ether. The ethereal layer was dried and concentrated under reduced pressure. After the residue had been passed through silica gel with benzene, removal of solvent yielded 13 (140 mg, 61%). An analytical sample was prepared by sublimation at 130 °C (0.1 mm): mp 39–42 °C; IR (KBr, cm^{-1}) 1665 (C=O), 1580, 1460, 1345, 1305, 1260, 952, 830, 783 (Ar); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3 H, CH_3), 4.53 (s, 2 H, CH_2), 6.89 (d, 1 H, J = 6 Hz, H on C_7), 6.99 (d, 1 H, J = 4 Hz, H on C_2), 7.39 (d of d, 1 H, J = 6, 7 Hz, H on C_6), 7.85 (d, 1 H, J = 7 Hz, H on C_5), 8.19 (d, 1 H, J = 4 Hz, H on C_3); UV λ (ϵ) 324 nm (5310), 313 (5600), 227 (23400), 208 (24100), 198 (26100); exact mass calcd for $C_{13}H_{10}O$ 182.07315, found, 182.07345. Anal. Calcd for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.43; H, 5.90.

Reaction of 13 with (2,4-dinitrophenyl)hydrazine in absolute ethanol containing hydrochloric acid gave 4-acetyl-1*H*-cyclobuta[*de*]naphthalene 2,4-dinitrophenylhydrazone (56%): mp 251–252 °C; IR (KBr, cm^{-1}) 1610, 1580, 1505, 1320, 1290, 1250, 1120, 1080, 830, 783; exact mass calcd for $C_{19}H_{14}N_4O_4$ 362.10148, found 362.10186. Anal. Calcd for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.89. Found: C, 63.22; H, 4.01.

4-(1-Phenylacetyl)-1*H*-cyclobuta[*de*]naphthalene (14). After having been stirred 8 h, the mixture from phenylacetyl chloride (250 mg, 1.6 mmol), 1 (200 mg, 1.5 mmol), and aluminum chloride (220 mg, 1.6 mmol) in methylene chloride (15 mL) was poured into water and extracted with dichloromethane. The organic phase was dried, concentrated, passed through silica gel with benzene, and concentrated to 14 (320 mg, 87%). An analytical sample was prepared by recrystallization from hexane and sublimation at 80–100 °C (0.1 mm): mp 91.5–93.5 °C; IR (KBr, cm^{-1}) 1660 (C=O), 1460, 1300, 1230, 1130, 9795, 835, 788, 705; ^{1}H NMR ($CDCl_3$) δ 4.23 (s, 2 H, CH_2 next to C=O), 4.57 (s, 2 H, CH_2 bridge), 7.18 (br s, 5 H, C_6H_5), 6.98 (d, 1 H, J = 7 Hz, H on C_7), 7.03 (d, 1 H, J = 7 Hz, H on C_2), 7.47 (d of d, 1 H, J = 7, 7 Hz, H on C_6), 8.06 (d, 1 H, J = 7 Hz, H on C_5), 8.29 (d, 1 H, J = 7 Hz, H on C_3); UV λ (ϵ) 318 nm (7800), 242 (22750), 227 (29500), 211 (32000); exact mass calcd for $C_{19}H_{14}O$ 258.10445, found 258.10499. Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.04; H, 5.55.

Reaction of 1 and Bromine as Catalyzed by Ferric Bromide. Bromine (400 mg, 2.5 mmol) in carbon tetrachloride (10 mL) was added slowly in the dark at 0 °C to 1 (350 mg, 2.5 mmol), powdered iron (20 mg), and carbon tetrachloride (10 mL). After having been stirred 4 h at room temperature and hexane (100 mL) had been added, the mixture was filtered through silica gel. The solvent was removed under reduced pressure to leave 4-bromo-1*H*-cyclobuta[*de*]naphthalene (7) as a pale yellow oil (520 mg, 94%). Distillation (105–120 °C; 0.1 mm) yielded pure 7: mp 21–23 °C; IR (KBr, cm^{-1}) 3090, 2960, 1460, 1430, 1405, 1315, 1180, 1000, 820, 775, 750; NMR ($CDCl_3$) δ 4.50 (s, 2 H, CH_2), 6.7–7.55 (m, 5 H, Ar); UV λ (ϵ) 320 nm (430), 316 (602), 300 (3, 150), 289 (5280), 281 (5125), 227 (55330); exact mass calcd for $C_{11}H_7Br$ 217.9732, found 217.9737. Anal. Calcd for $C_{11}H_7Br$: C, 60.30; H, 3.22. Found: C, 59.78; H, 3.44.

4-Bromo-1*H*-cyclobuta[*de*]naphthalene Picrate. Picric acid (110 mg, 0.48 mmol) in hot ethanol (2 mL) was mixed with 7 (100 mg, 0.46 mmol) in hot ethanol (2 mL). The mixture cooled slowly to room temperature and the yellow crystals that formed were washed with cold ethanol. Recrystallization from ethanol gave an analytical sample of 4-bromo-1*H*-cyclobuta[*de*]-naphthalene picrate: mp 107–108 °C. Anal. Calcd for $C_{17}H_{10}BrN_3O_7$: C, 45.56; H, 2.25. Found: C, 45.59; H, 2.33.

4,5-Dibromo-1*H*-cyclobuta[*de*]naphthalene (9). Bromine (160 mg, 1 mmol) in carbon tetrachloride (10 mL) was added slowly at 0 °C to a mixture of 7 (220 mg, 1 mmol), carbon tetrachloride (5 mL), and powdered iron (20 mg). After the reaction mixture has been stirred 1 h at room temperature, diluted with hexane, and filtered, the solvent was removed under reduced pressure. The white crystalline residue (265 mg, 89%) was identified as 9: mp 142–144 °C; IR (KBr, cm^{-1}) 3040, 2990, 1470, 1425, 1300, 1120, 1040, 860, 830; NMR ($CDCl_3$) δ 4.39 (s, 2 H, CH_2), 6.82 (d, 2 H, J = 7 Hz, ortho), 7.59 (d, 2 H, J = 7 Hz, meta); ^{13}C NMR ($CDCl_3$) δ 44.2 (1 C, C_1), 113.5 (2 C, $C_{4,5}$), 119.8 (2 C, $C_{2,7}$), 123.5 (1 C, C_9), 136.3 (2 C, $C_{3,6}$), 140.4 (2 C, $C_{1a,7a}$), 146.2 (1 C, C_8); UV λ (ϵ) 328 nm (1400), 317 (4000), 303 (6450), 292 (5650), 232 (32000); exact mass calcd for $C_{11}H_6Br_2$ 395.8837, found 395.8841. Anal. Calcd for $C_{11}H_6Br_2$: C, 44.34; H, 2.03. Found: C, 44.51; H, 2.19.

4-Amino-1*H*-cyclobuta[*de*]naphthalene (11). Procedure 1: Ethyl ether (125 mL), ethanol (40 mL), and water (25 mL) were added to 6 (600 mg, 3.2 mmol) in a flask equipped with a nitrogen inlet, a glass stopper, and a condenser connected to a nitrogen outlet. Activated aluminum strips were prepared by cutting aluminum foil into strips and dipping them successively (15-s each) into aqueous sodium hydroxide (10%), water, ethanol, ethyl ether, aqueous mercuric chloride (2%), water, ethanol, and ethyl ether. The aluminum strips (1.5 g) upon activation were quickly inserted into the reduction mixture. There was noticeable evolution of hydrogen upon introduction (1 h) of the metal strips. The mixture was filtered through Celite with ethyl ether and concentrated. After water had been added, the product was extracted with chloroform, and the organic layer was dried and concentrated. The residue was chromatographed on silica gel eluting with hexane/benzene to yield 11 (470 mg, 77%): bp 130–135 °C (0.15 mm); IR (KBr, cm^{-1}) 3450, 3360 (NH_2), 3040, 2960, 2920, 1675, 1610, 1490, 1450, 1325, 1275, 820, 780, 750; ^{1}H NMR ($CDCl_3$) δ 4.64 (s, 2 H, CH_2), 4.87 (br s, 2 H, NH_2), 6.53–7.60

(m, 5 H, Ar); exact mass calcd for $C_{11}H_9N$ 155.073 49, found 155.073 58.

Procedure 2: A mixture of **6** (185 mg, 1 mmol), methanol (50 mL), and palladium on carbon (5%, 10 mg) was hydrogenated in a Parr apparatus at 1.5 atm for 30 min. Ethyl ether was added and the mixture was then filtered and concentrated under reduced pressure. Chromatography on silica gel eluting with hexane/benzene yielded (1) **6** (66 mg, 36%), identical with initial **6**, and (2) **11** (86 mg, 55%), identical with previous **11**.

1-(1*H*-Cyclobuta[*de*]naphthalen-4-yl)-3-phenylthiourea. A solution of **11** (155 mg, 1 mmol) and phenyl isothiocyanate (135 mg, 1 mmol) in methanol (6 mL) was stirred 2 h at room temperature. The solid formed was recrystallized from ethanol and identified as 1-(1*H*-cyclobuta[*de*]naphthalen-4-yl)-3-phenylthiourea (180 mg, 62%): mp 184–187 °C; exact mass calcd for $C_{18}H_{14}N_2S$ 290.0879, found 290.0885. Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65. Found: C, 74.65; H, 4.50; N, 9.35.

Conversion of 11 to 7. Nitrous acid, prepared by adding hydrobromic acid (48%, 2 mL) slowly to sodium nitrite (140 mg, 2 mmol) in water (5 mL), was added dropwise to a solution of **11** (250 mg, 1.6 mmol) in hydrobromic acid (48%, 1 mL) at 0 °C. After the mixture had been stirred 15 min, copper(I) bromide (0.5 g) was added. The mixture was refluxed 30 min, poured into water, neutralized with sodium bicarbonate, and extracted with ethyl ether. The ethereal layer, on drying ($MgSO_4$), concentration, and chromatography on silica gel and eluting with hexane yielded **7** (38 mg, 11 %), identical with that prepared by monobromination of **1** as previously described. The amorphous reaction product was not identified further.

Determination of the Rates of Electrophilic Substitution of 1 Relative to Naphthalene (18), Acenaphthene (19), and 2,3-Dihydro-1*H*-phenalene (20). Standard mixtures of **1** (1.4 g, 10 mmol) were prepared with naphthalene (**18**, 10 mmol), acenaphthene (**19**, 10 mmol), and 2,3-dihydro-1*H*-phenalene (**20**, 10 mmol). Each competitive experiment—acetylation, bromination, and nitration—was conducted twice on each sample mixture.

Authentic Products. 1-Bromonaphthalene, 2-bromoacenaphthene, 6-bromo-1*H*-2,3-dihydrophenalene, 1- and 2-acetylnaphthalenes, 5-acetylacenaphthene, and 6-acetyl-1*H*-2,3-dihydrophenalene were prepared by standard procedures or were purchased, purified, and, along with **6**, **7**, and **13**, used for comparison and for analysis of the products from the studies of the relative rates of electrophilic substitutions of **1** and **18–20**.

Acetylations. Aluminum chloride (132 mg, 1 mmol) was added slowly to each standard mixture and acetyl chloride (70 mg, 1 mmol) was stirred in methylene chloride (50 mL) at room temperature. After 10 h each solution was poured into water and extracted with methylene chloride. Each organic extract was dried, concentrated, and chromatographed on silica gel with hexane. The ketone fraction was analyzed by ^1H NMR.

Brominations. Bromine (180 mg, 1 mmol) in carbon tetrachloride (10 mL) was added slowly in the dark to a standard hydrocarbon mixture and iron filings in carbon tetrachloride (40 mL). After having been stirred 6 h, the solution was filtered, concentrated in vacuo, and analyzed by GLC.

Nitration. Acetyl nitrate (prepared from acetic anhydride (10 mL) and 70% nitric acid (90 mg, 1 mmol)) was added slowly to a standard hydrocarbon mixture stirred in acetic anhydride (50 mL) at 0 °C. The solution was stirred 1 h, poured into aqueous sodium hydroxide, stirred 15 min, and extracted with ethyl ether. The ethereal layer was dried, concentrated, and passed through silica gel with hexane. The nitro compounds produced were analyzed by ^1H NMR.

Results. The product ratios from the various experiments were determined, averaged, and summarized in Table I. The ratios of **1** and **18** were adjusted on the basis that **18** has four active positions for electrophilic substitution while **1** has only two. The products from each experiment were isolated and compared with authentic samples and the yields determined. The yields for the various brominations were ~90%, for Friedel–Crafts acetylations 75%, and for nitrations ~85%. For all brominations and nitrations, only "para" substituted compounds were isolable. For the Friedel–Crafts acetylations with **18–20**, *para*-substitution products were major; ~10–15% ortho substitutions also occurred.

Studies of Deuteration of 4-Lithio-1*H*-cyclobuta[*de*]naphthalene (24). Various samples of **24** (110 mg, 0.5 mmol) were dissolved in dry tetrahydrofuran (20 mL) and *n*-butyllithium (0.55 mmol) was added at −78 °C under nitrogen. Deuterium oxide (2 mL) was added to these samples at selected time intervals. After the mixtures had warmed to room temperature, the organic layer was separated and dried with magnesium sulfate, and the solvent was removed under reduced pressure. The products, deuterated samples of **1**, were analyzed by NMR and mass spectroscopy (see Table II for a summary of results).

Photolytic Bromination of 1. Under the light of a 100-W bulb, bromine (180 mg, 1 mmol) in carbon tetrachloride (20 mL) was added slowly to stirred **1** (140 mg, 1 mmol) in carbon tetrachloride (20 mL). After the mixture had been irradiated further, removal of the solvent under reduced pressure and chromatography on silica gel eluting with hexane yielded (1) **1** (50 mg, 36 %), identical with initial **1**, and (2) 1aα,2,3,4α-tetrabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalene (**30**, 180 mg, 39%): mp 119–121 °C; IR (KBr, cm^{-1}) 1390, 1320, 1255, 1210, 1660, 1130, 1110, 952, 925, 895, 780, 732, 724, 700; ^1H NMR ($CDCl_3$) δ 4.10 (br s, 2 H, CH_2), 4.76 (d, 1 H, J = 2.5 Hz, H on C_2), 5.03 (d, 1 H, J = 9 Hz, H on C_4), 5.42 (d of d, 1 H, J = 2.5, 9 Hz, H on C_3), 6.9–7.6 (m, 3 H, Ar); exact mass calcd for $C_{11}H_8Br_4$ 455.7362, found 455.7371. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75. Found: C, 28.84; H, 1.88.

Reaction of 30 with Red-Al. Red-Al (10 mL, a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene) was added slowly to **30** (360 mg, 0.8 mmol) in dry ethyl ether (100 mL). Excess hydride was decomposed with ethyl acetate and water. The organic layer was then dried with magnesium sulfate and the solvent removed under reduced pressure to leave **1** (100 mg, 90%), identical with an authentic sample.

2,4-Dibromo-1*H*-cyclobuta[*de*]naphthalene (35). A mixture of 1,5-diazabicyclo[5.4.0]undec-5-ene (250 mg, 1.6 mmol) and **30** (230 mg, 0.5 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature 1 h, poured into pentane (200 mL), and passed through silica gel. Removal of the solvent left **35** as a white solid (110 mg, 75%). An analytical sample was sublimed at 80 °C (0.1 mm) and recrystallized from hexane: mp 61–63 °C; IR (KBr, cm^{-1}) 1390, 1280, 1070, 1000, 855, 845, 770, 754; ^1H NMR ($CDCl_3$) δ 4.63 (s, 2 H, CH_2), 7.02 (d of d, 1 H, J = 4, 4 Hz, ortho H), 7.20 (s, 1 H, H on C_3), 7.38–7.46 (m, 2 H, meta and para H); UV λ (ϵ) 326 nm (350), 292 (5245), 282 (5290), 235 (31 000); exact mass calcd for $C_{11}H_6Br_2$ 295.8837, found 295.8844. Anal. Calcd for $C_{11}H_6Br_2$: C, 44.34; H, 2.03. Found: C, 44.25; H, 2.19.

Reduction of 35 with Red-Al. A mixture of **35** (150 mg, 0.5 mmol), Red-Al (10 mL, a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene, and dry ethyl ether (100 mL) was refluxed under nitrogen for 30 h. After the excess hydride had been decomposed with ethyl acetate and water, the organic layer was separated, dried, and concentrated to yield **1** (60 mg, 85%) as the only product.

Photolytic Bromination of 1-Bromo-1*H*-cyclobuta[*de*]naphthalene (5). Bromine (800 mg, 5 mmol) in carbon tetrachloride (20 mL) was added to **5** (1.1 g, 5 mmol) in carbon tetrachloride (40 mL) under the light of a 100-W bulb. Irradiation, concentration, and chromatography on silica gel (hexane as eluent) gave (1) **5** (510 mg, 46% recovery) and (2) 1,1a,2,3,4-pentabromo-1a,2,3,4-tetrahydro-1*H*-cyclobuta[*de*]naphthalenes (**37** and **38**, 980 mg, 36%), two stereoisomers in the ratio of 4:1 partially separated by fractional recrystallization: mp (mixture) 144–146 °C; IR (mixture, KBr, cm^{-1}) 1460, 1390, 1160, 985, 890, 880, 850, 810, 785, 730; ^1H NMR (**37**, major isomer) ($CDCl_3$) δ 4.15 (d, 1 H, J = 11.5 Hz, H on C_2), 5.49 (d, 1 H, J = 5 Hz, H on C_4), 6.10 (s, 1 H, H on C_1), 7.05–7.7 (m, 3 H, Ar); ^1H NMR (**38**, minor isomer) ($CDCl_3$) δ 4.82 (d, 1 H, J = 2.5 Hz, H on C_2), 5.05 (d, 1 H, J = 8 Hz, H on C_4), 5.59 (d of d, 1 H, J = 2.5, 8 Hz, H on C_3), 5.80 (s, 1 H, H on C_1), 7.1–7.7 (m, 3 H, Ar); exact mass (mixture) calcd for $C_{11}H_7Br_5$ 533.6467, found 533.6479. Anal. (mixture) Calcd for $C_{11}H_7Br_5$: C, 24.53; H, 1.31. Found: C, 24.50; H, 1.48.

Reaction of Pentabromides 37 and 38 with Zinc. Zinc dust (65 mg, 1 mmol) was added to pentabromides **37** and **38** (300 mg, 0.56 mmol) in glacial acetic acid (2 mL) and ethyl ether (10 mL). The mixture was stirred 12 h at room temperature, ethyl ether was added, and the solution was filtered. After removal of solvent, ^1H NMR analysis of the residue (105 mg) revealed the products

to be **5** (79%) and **1** (12%).

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Registry No. **1**, 24973-91-9; **5**, 54125-11-0; **6**, 97383-48-7; **7**, 97383-27-2; **7**·picrate, 99018-28-7; **8**, 97383-25-0; **9**, 97383-26-1; **10**, 99018-23-2; **11**, 97383-28-3; **13**, 97383-30-7; **13** DNP, 99018-27-6; **14**, 99018-24-3; **18**, 91-20-3; **19**, 83-32-9; **20**, 479-58-3; **24**, 99018-25-4; **30**, 97383-31-8; **35**, 97383-32-9; **37**, 99018-26-5; DBU, 6674-22-2; 1-(1*H*-cyclobuta[*de*]naphthalen-4-yl)-3-phenylthiourea, 99018-29-8.

Oxidative Cleavage and Cyclization of Disulfide Carboxylic Acids and Alcohols by Aqueous Iodine: A Facile Route to Five-Membered Ring Sultines

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The kinetics and mechanism of the oxidative cleavage by aqueous iodine of disulfide carboxylic acids and alcohols are presented. There is evidence for intramolecular interaction of the oxygen nucleophiles. The sole product of the iodine oxidation of 3,3′-dithiodipropanol is the sultine 1,2-oxathiolane 2-oxide, which is formed after the rate-determining step, apparently via rapid cyclization of the sulfenyl iodide. The anchimeric assistance provided by the neighboring carboxylate group in the reaction of 3,3′-dithiodipropanoic acid is responsible for the pH profile of the rate of oxidative cleavage. At a given pH, the rate law for the reaction is $-d[RSSR]/dt = k_I[I_3^-][RSSR](0.0905[I^-]^{-1} + 0.0019[I^-]^{-2})$. The inverse second term in iodide ion has not been observed previously in kinetic studies of disulfide reactions and is interpreted as evidence for a disulfide–iodonium complex.

Electrophilic cleavage of alkyl disulfides is facilitated by neighboring nucleophiles.[1] This facilitation may account for instances of unusually reactive disulfides in multifunctional macromolecules, such as proteins. When iodine is used as the electrophile the initially formed cyclic intermediates may be further oxidized to sulfinic and sulfonic acids. When the neighboring nucleophile is a primary amine group, unusually stable cyclic sulfinamides are generated.[1]

The kinetic study of the aqueous iodine oxidation of the amino acid cystine had been reported in the pioneering study by Shinohara and Kilpatrick.[2] Although cystine has a neighboring carboxylate group properly placed to interact with the cleaving disulfide group, the rate of cleavage is slow, and the kinetics are consistent with a mechanism in which the carboxylate group is not involved. Cleavage occurs by attack of iodide ion on a disulfide–iodine complex. However, amino acids are difficult to study because of their limited solubility in aqueous solutions and variation in overall charge. In addition, the carboxylate anion of amino acids may have reduced nucleophilicity relative to an isolated carboxylate anion due to the positive charge on the α-amino group over the pH range from 2 to 10. Therefore we decided to look for anchimeric assistance by the carboxylate group in the simplest compound with proximate disulfide and carboxylic acid groups, 3,3′-dithiodipropanoic acid. The disulfide alcohols 3,3′-dithiodipropanol and 4,4′-dithiodibutanol were also examined to see whether the weakly nucleophilic hydroxyl group would also participate in the cleavage reaction.

Experimental Section

Equipment. The equipment used has been listed in previous publications[1] except for the following. The mass spectra were determined on a V.G. Analytical high-resolution mass spectrometer with a 1250 data system. The infrared spectra were obtained from Sirius 100 and Perkin-Elmer 180 IR spectrometers.

Kinetics. The procedures and equipment have been described previously.[3]

3,3′-Dithiodipropanoic Acid. 3,3′-Dithiodipropanoic acid was obtained from Aldrich Chemical Co. and was purified by recrystallization from ethanol.

3,3′-Dithiodipropanol.[4] Thioacetamide (11.95 g, 0.159 mol) was dissolved in water containing 17.84 g (0.318 mol) of KOH. After the addition of 5.10 g (0.159 mol) of sulfur and 10.06 g (0.106 mol) of 3-chloro-1-propanol the reaction mixture was heated at 50–60 °C for 3 h. A black solid material was centrifuged out, and the remaining clear liquid was continuously extracted with ether for 24 h. The mixture was dried over $MgSO_4$, and the solvent was removed by rotary evaporation, leaving a clear viscous liquid. Vacuum distillation yielded three fractions with bp in the range 137–145 °C (0.15 torr) [lit. 160 °C (0.15 torr)]. The first and third fractions were found to contain thiols by the nitroprusside test. The middle fraction was purified further by column chromatography on Merck silica gel with 5% EtOH in $CHCl_3$. After removal of the solvent, 2.77 g of purified product was obtained: TLC (on Merck silica gel plates) R_f 0.13 (5% EtOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.7 (t, 2), 2.7 (t, 2), 1.9 (m, 2). Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39.53; H, 7.74. Found: C, 39.38; H, 7.90.

1,2-Oxathiolane 2-Oxide from 3,3′-Dithiodipropanol. The disulfide (0.102 g, 5.63×10^{-4} mol) was dissolved in 10 mL of water, and the mixture was attached to an autotitrator which contained 2 M KOH. The end point was set for pH 7. The iodine (1.7×10^{-3} mol) in 3.2 mL of aqueous KI was added gradually over 4 h at ambient temperature, and the solution was allowed to stand overnight. The solution was freeze-dried, and the residue was extracted with CH_2Cl_2 in a Soxhlet extractor for 8 h. The CH_2Cl_2 was removed by slow distillation to give 0.44 g of a colorless liquid, identified as 1,2-oxathiolane 1-oxide:[5] ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 1), 4.40 (m, 1), 3.05 (t, 2), 2.35 (m, 2); FT IR (neat) 1448, 1415,

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