Strained Heterocyclic Systems. IV. 1,2-Dihydrocyclobuta[b]quinoline and Derivatives[1]

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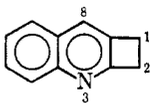
The title compound (1) and its 8-carboxy derivatives were prepared and characterized. One of the noteworthy fragmentations in the mass spectrum of 1 was the generation of 2,3-quinolyne. Spectral comparisons of the 8-carboxy derivatives with model compounds indicated that the four-membered ring exerted no steric hindrance toward the adjacent substituents. Hydrogen exchange studies of 1 reflected the strain in the fused ring system; its N-oxide underwent facile exchange.

1,2-Dihydrocyclobuta[b]quinoline (1) has recently



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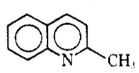
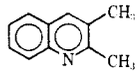
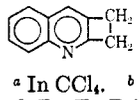
been reported in connection with ultraviolet[3] and basicity[4] studies of substituted quinolines. The present paper extends our studies of 1 and reports the preparation and characterization of the N-oxide and 8-carboxy derivatives.

The base-catalyzed condensation of *o*-aminobenzaldehyde with cyclobutanone afforded 59% of 1 under optimum conditions for this Friedländer reaction. Under conditions of acid catalysis,[5] the same product was obtained in 25% yield. During the latter stages of our work, the first synthesis of 1 was reported. Wilk, *et al.*,[3] prepared the compound in 6% yield from a sealed tube reaction of anthranil with cyclobutanone.

1,2-Dihydrocyclobuta[b]quinoline was characterized by its mass and proton magnetic resonance spectra. The nmr pattern was an A_2B_2 system with multiplets centered at δ 3.13 and 3.53, which were attributed to the C-1 and C-2 methylene groups, respectively. The assignment of the lower field signal to the protons closer to nitrogen was based on the chemical shift data in Table I. The progression to larger ^{13}C–H coupling constants in the series 2-methyl- and 2,3-dimethylquinoline and 1 parallels the analogous data reported for the benzylic protons of toluene (122 Hz),[6] *o*-xylene (128, 126 Hz),[6,7] and benzocyclobutene (138 Hz).[7] Such changes in $J(^{13}C–H)$ undoubtedly reflect the increase in strain going from adjacent methyl groups to the fused cyclobutene moiety. These data can also be expressed as per cent s character of the benzylic-type C–H bonds.

TABLE I

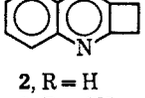
NMR SPECTRAL DATA FOR ALKYL GROUPS OF SUBSTITUTED QUINOLINES

Compound	Chemical shifts,[a] δ, ppm	$J(^{13}C–H)$,[b] Hz	C–H bond s-char.,[c] %
	2.68[d] 2.67	126.8[e] 126 ± 0.5	25.2
	2.37 2.59	130 ± 1	26.0
	3.13[f] 3.53[f]	139 ± 1	27.8

[a] In CCl_4. [b] In $DCCl_3$. [c] Defined as $0.20\,J(^{13}C–H)$: N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 1471 (1959). [d] R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966). [e] K. Tori and T. Nakagawa, *J. Phys. Chem.*, **68**, 3163 (1964). [f] Center of multiplet.

The mass spectrum of 1 contained an M − 28 peak,[4] which was consistent with the generation of 2,3-quinolyne. It was important to verify such a fragmentation, since the similarities between hetaryne formation *via* pyrolysis and electron impact have been noted in other systems.[8] Accordingly, 1 was studied under high resolution conditions. Doublets were observed at *m/e* 129, 128, and 127 (*cf.* Experimental Section for composition and relative abundance). The most interesting of these was the pair at *m/e* 127, which corresponded to C_9H_5N (**b**) and $C_{10}H_7$ (**c**). Identification of the appropriate metastable transitions established the precursors of these species; the fragmentation pattern of 1 is shown in Figure 1. The generation of 2,3-quinolyne (**b**) by loss of ethylene directly from the molecular ion was thus confirmed. This same species has recently been invoked in the pyrolysis of quinoline-2,3-carboxylic anhydride.[9] There is ample precedent for ring enlargement to an azatropylium ion accompanied by consecutive losses of H and HCN,[10] which is the route to **c**.

In the course of this investigation other routes to the ring system of 1 were explored. These studies led to several derivatives of 1. The Pfitzinger reaction of isatin with cyclobutanone afforded 1,2-dihydrocyclobuta[b]quinoline-8-carboxylic acid (2), which was con-



2, R = H
3, R = CH_3

(1) Paper III: J. H. Markgraf, W. P. Homan, R. J. Katt, and W. L. Scott, *J. Heterocycl. Chem.*, **6**, 135 (1969).

(2) (a) To whom correspondence should be addressed; (b) based in part on the honors theses, Williams College, of W. L. Scott, 1967, and R. N. Shefrin, 1968.

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(8) (a) R. F. C. Brown, W. D. Crow, and R. K. Solly, *Chem. Ind.* (London), 343 (1966); (b) M. P. Cava, M. J. Mitchell, D. C. DeJongh, and R. Y. Van Fossen, *Tetrahedron Lett.*, 2947 (1966).

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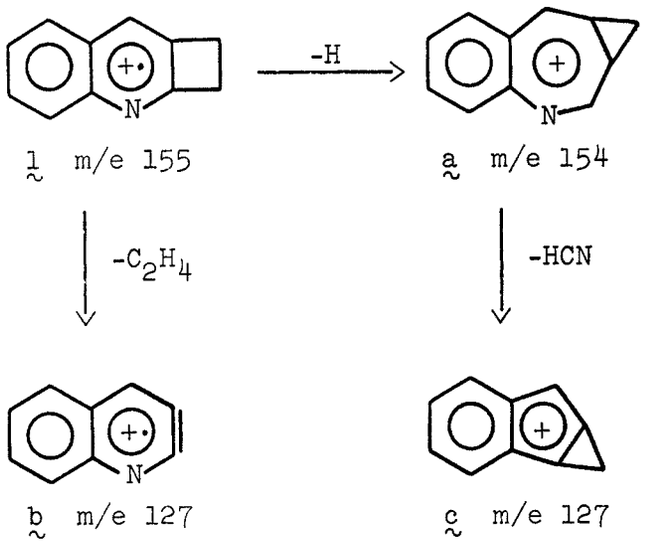
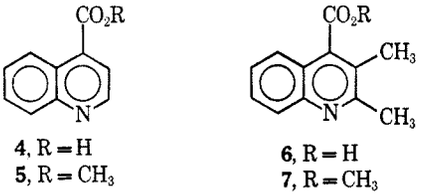


Figure 1.—Mass spectral fragmentation of 1,2-dihydrocyclobuta[*b*]quinoline (**1**). All species shown were mass measured. Appropriate metastables were observed for all pathways depicted.

verted into the methyl ester (**3**). Repeated efforts to effect decarboxylation of **2** to **1** were without success. This result was unexpected, since the facile decarboxylations of analogous cinchoninic acids containing 5–19-membered rings have been reported.[11] Thus the strained, four-membered ring is responsible for the alteration of chemical reactivity. Another example of such influence was observed in the inability to achieve aromatization of 1,2,2a,3-tetrahydrocyclobuta[*b*]quinoxaline.[1]

Possession of compounds **2** and **3** prompted a spectroscopic comparison with the same derivatives of quinoline- and 2,3-dimethylquinoline-4-carboxylic acids. It was anticipated that this series of compounds would



4, R = H
5, R = CH_3
6, R = H
7, R = CH_3

exhibit differences in the coplanarity of the 8-carboxy substituent. A similar effect was reported for an analogous series of 1-nitronaphthalene derivatives.[12] That the C-1 methylene group of **2** did not sterically hinder the coplanarity of the carboxy substituent was supported by the lower carbonyl frequencies of **2** and **4** compared with that of **6**. This same phenomenon also was reflected in the ultraviolet spectra of the corresponding methyl esters. The "abnormality" of the spectrum of **7** compared with those of **3** and **5** was consistent with steric interference by the C-3 methyl group of **7**.

Peracid oxidation of **1** afforded the previously unknown N-oxide (**8**). The conversion of **1** into **8** sufficiently altered the acidity of the hydrogens at C-2 to permit deuterium exchange. The structural assignment of the product thus obtained, 1,2-dihydrocyclobuta[*b*]quinoline-2d_2 3-oxide (**9**), was based on its nmr spectrum which contained only a singlet at δ 3.22 in the aliphatic region. Both the number and location of the deuterium atoms were thus determined by the absence of a peak at δ 3.60, the absence of splitting of the C-1 methylene signal, and the integration. That no exchange occurred at C-1 was consistent with the relative rates of exchange of the isomeric 2-methyl- and 3-methylquinoline N-oxides.[13] Under the same conditions, which corresponded to one half-life for the exchange of 2-methylquinoline,[14] **1** underwent no exchange. It is reasonable to assume that the carbon skeleton of **1** is coplanar,[15] which implies that a carbanion at C-2 can overlap the π system of the heteroaromatic mucleus. Thus the diminished reactivity of **1** relative to 2-methylquinoline reflects the unfavorable ring strain in the former system.[16] The facile exchange of **8** is in accord with the known influence of N-oxides[14] and may be attributed principally to changes in the inductive effect of the heteroatom.[17]

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 237B, calibrated with a polystyrene film. Nmr spectra were determined on Varian A-60 and HA-100 instruments; $J(^{13}C-H)$ data were obtained with a time-averaging computer (Varian C-1024) and electronic counter (Hewlett-Packard 5245L). Chemical shifts are expressed in parts per million downfield from a tetramethylsilane internal standard. Ultraviolet spectra were recorded on a Beckman spectrophotometer, Model DK-2A. Mass spectra were acquired at the American Cyanamid Co. (Stamford, Conn.) by Mr. T. A. Mead with a CEC spectrometer, Model 21-110B; samples were directly inserted into the ion source (100–120°) *via* a probe, ionizing voltage 70 eV (20 μA). Substances were chromatographed on alumina (neutral, activity I) and eluded with chloroform. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

1,2-Dihydrocyclobuta[*b*]quinoline (**1**).—A solution of freshly prepared *o*-aminobenzaldehyde[18] (0.50 g, 4.1 mmol), cyclobutanone (0.24 g, 3.4 mmol), and 33% aqueous KOH (2 ml) in 10 ml of 95% EtOH was allowed to stand 3 days at room temperature, brought rapidly to boiling, diluted with H_2O (20 ml), and treated with charcoal; the filtrate was then chilled to give 0.31 g (59%) of **1**, mp 94–96°. The product was chromatographed to give 0.27 g of **1**: mp 96.8–97.4°, picrate mp 236–237° [lit.[3] mp 95.5°, picrate mp 236°]; uv max (H_2O) 304 mμ (ϵ 5800), 310 (5500), 317 (7400); ir (KBr) 1588, 1384, 906, 786, 760, 738 cm^{-1}; nmr (CCl_4) δ 3.13 (m, 2), 3.53 (m, 2), 7.25–8.1 (m, 5); mass spectrum *m/e* (rel intensity) 155 (100), 154 (68), 140 (11) [$C_{10}H_8N$], 129 (7) [$C_{10}H_9$–C_9H_7N, 1:7], 128 (10) [$C_{10}H_8$–C_9H_6N, 2:1], 127 (13) [$C_{10}H_7$–C_9H_5N, 3.3:1], 115 (9) [C_9H_7], 114 (9) [C_9H_6], 113 (5), 89 (6), 77 (10), 75 (7), 74 (5), 64 (6), 63 (12), 51 (7), 50 (6).[19] With the same work-up method, the above

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(19) Additional high resolution mass spectra of **1** were obtained at the University of California, Berkeley, on a CEC 2-110B instrument purchased with funds from the National Science Foundation (Grant GP-5323).

procedure represented the optimal conditions derived from variations in reactant ratios (1:1 to 1:1.2 equiv), time (3 hr to 5 days), temperature (ambient and reflux), and catalyst (33% aqueous KOH and Triton B were equally effective). Yields of 55% were obtained routinely in reactions on a ten-fold scale.

Under conditions of acid catalysis (0.01 mole scale, "method A," 6-hr reflux)[5a] **1** was obtained in 25% yield.

2,3-Dimethylquinoline.—A solution of *o*-aminobenzaldehyde (1.0 g, 8.2 mmol), 2-butanone (0.59 g, 8.2 mmol), and 33% aqueous KOH (5 ml) in 20 ml of 95% EtOH was refluxed 1 hr, neutralized with acetic acid, concentrated on a rotary evaporator, and extracted with Et_2O. The residue from the extract was chromatographed to give 0.75 g (58%) of product: mp 68.2–69.0° [lit.[20] mp 68–69°]; ir (KBr) 1495, 1418, 1002, 786, 762, 756 cm^{-1}; nmr (CCl_4) δ 2.37 (s, 3), 2.59 (s, 3), 7.2–8.0 (m, 5). The nmr spectrum established the absence of any 2-ethylquinoline.

1,2-Dihydrocyclobuta[*b*]quinoline-8-carboxylic Acid (2).—The condensation of isatin (2.1 g, 0.014 mol) and cyclobutanone (1.0 g, 0.014 mol) with 33% aqueous KOH (5.6 ml) in 11 ml of 95% EtOH by the method of Borsche[11a] gave 0.57 g (20%) of **2**: mp 281–282° dec (EtOH), S-benzylthiuronium salt, mp 162.5–163.5°; ir (KBr) 1698 cm^{-1}; mass spectrum (160°) *m/e* (rel intensity) 199 (100), 171 (6), 170 (26), 154 (26), 153 (7), 143 (17), 142 (14), 128 (7), 127 (10), 115 (5).

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03; neut equiv, 199.2. Found: C, 72.43; H, 4.63; N, 6.80; neut equiv, 198.5.

Attempts to decarboxylate **2** with copper powder[21] or with copper chromite in quinoline[22] afforded only recovered starting material.

Esterification of **2** with diazomethane gave methyl 1,2-dihydrocyclobuta[*b*]quinoline-8-carboxylate (**3**): mp 108–109°; uv max (95% EtOH) 246 mμ (ϵ 17,200), 251 (16,500), 325 (7200); nmr (CCl_4) δ 3.33 (m, 2), 3.52 (m, 2), 3.93 (s, 3), 7.4–9.0 (m, 4); mass spectrum *m/e* (rel intensity) 213 (100), 198 (15), 183 (9), 182 (6), 170 (6), 155 (6), 154 (17), 153 (6), 127 (7).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.30; H, 5.19; N, 6.52.

Methyl Quinoline-4-carboxylate (5).—Quinoline-4-carboxylic acid [**4**, ir (KBr) 1692 cm^{-1}] was esterified by treatment with thionyl chloride followed by triethylamine and methanol to give **5**: bp 141–143° (4 mm) [lit. bp[23] 88–94° (0.1 mm)]; uv max (95% EtOH) 238 mμ (ϵ 20,100), 315 (4600); nmr (CCl_4) δ 3.93 (s, 3).

Methyl 2,3-Dimethylquinoline-4-carboxylate (7).—Condensation of isatin with 2-butanone by the method of Buu-Hoi and Royer[24] gave 2,3-dimethylquinoline-4-carboxylic acid (**6**): mp 320° dec [lit.[24] mp >310°]; ir (KBr) 1724 cm^{-1}. Esterification with diazomethane followed by chromatography gave **7**: mp 120.2–122.2° [lit.[25] mp 120–121°]; uv max (95% EtOH) 230 mμ (sh, ϵ 27,600), 235 (28,800), 306 (4300), 319 (4900); nmr (CCl_4) δ 2.36 (s, 3), 2.68 (s, 3), 4.02 (s, 3), 7.4–9.0 (m, 4); mass spectrum *m/e* (rel intensity) 215 (100), 200 (15), 184 (34), 183 (38), 157 (9), 156 (48), 155 (35), 154 (9), 115 (23), 114 (6), 89 (7).

1,2-Dihydrocyclobuta[*b*]quinoline 3-Oxide (8).—An ice-cold solution of **1** (0.20 g, 1.3 mmol) in $HCCl_3$ (2 ml) was treated with *m*-chloroperbenzoic acid (0.31 g, 1.4 mmol, 80% assay) in $HCCl_3$ (3.5 ml), refrigerated overnight, washed twice with 1 *N* NaOH, dried, and evaporated to dryness to give 0.18 g (84%) of product (mp 172.5–175° dec) which after recrystallization from ethyl acetate gave **8**: mp 177–179° dec; uv max (CH_3OH) 238 mμ (ϵ 66,400), 314 (10,900), 327 (9700); nmr ($DCCl_3$) δ 3.22 (m, 2), 3.60 (m, 2), 7.2–8.9 (m, 5); mass spectrum *m/e* 171 (molecular ion).

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.20; H, 5.39; N, 8.06.

1,2-Dihydrocyclobuta[*b*]quinoline-2d_2 3-Oxide.—To a solution prepared from sodium (25 mg) and EtOD (2.5 ml) was added **8** (0.10 g, 0.58 mmol); the mixture was refluxed under N_2 for 1 hr, neutralized with AcOH, concentrated at reduced pressure, and diluted with H_2O to give 29 mg (29%) of product: mp 175–176.5° dec; ir (KBr) 2235 cm^{-1}; nmr ($DCCl_3$) δ 3.22 (s, 2), 7.2–8.9 (m, 5); mass spectrum *m/e* 173 (molecular ion).

Registry No.—**1**, 13353-49-6; **2**, 13848-02-7; **3**, 21691-02-1; **8**, 21691-04-3; **9**, 21691-05-4; 2-methylquinoline, 91-63-4; 2,3-dimethylquinoline, 1721-89-7; **2** (S-benzylthiuronium salt), 21691-01-0.

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