5 mmol of IMgBHT in CH_2Cl_2 as in the preparation of **1g**. The methylene chloride solution was refluxed for 30 min and worked up as outlined for **1g** to yield **2f**, (163 mg, 54%), **2g** (35 mg) and unreacted **2e** (48 mg). Data for **2f**: mp 142-145 °C; the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **2e** and **2g**, except that the singlet at δ 4.10 due to the protons of the glycol link is broadened; electronic spectrum, λ_{max} (ε) 667 (58900), 610 (9350), 534 (7230), 505 (8230), 438 sh (51100), 413 (87600) nm.

Bis(chlorophyllide *b*) Ethylene Glycol Diester (3g). The preparation was performed in a glovebox filled with dry nitrogen. A Grignard reagent was prepared from Mg (24 mg, 1.0 mmol), CH_3I (62 μL, 1.0 mmol), and dry ether (2 mL). A solution of BHT in dry thiophene (15 mL) was deoxygenated by bubbling with 99.999% argon. The solution of BHT was stirred vigorously and protected from light. The Grignard reagent solution was pipetted all at once into the BHT solution, and the resulting solution was allowed to react for 15 min. A solution of lithium 2,2,6,6-tetramethylpiperidide, prepared by dissolving the corresponding amine (85 μL, 0.5 mmol) in ether (1 mL) followed by careful addition of *n*-BuLi (0.25 mL of a 1.6 M solution in hexane (0.4 mmol)), was syringed into the reaction mixture. After 5 min of stirring, a solution of **3e** (125 mg, 0.101 mmol) in dry thiophene (25 mL) which had been previously deoxygenated with argon was pipetted into the reagent solution. The reaction proceeded for 30 min at ambient temperature. The resulting yellow-green solution was poured in pH 4.5 phosphate buffer (250 mL). Extraction of the mixture with $CHCl_3$, followed by washing of the extract three times with additional buffer, drying over anhydrous Na_2SO_4, and evaporation of the solvent, yielded a green product. This material was chromatographed on an 8 cm × 30 cm column of powdered confectioner's sugar (elution with 10% acetone in CCl_4). The fast-moving brown band of unreacted starting material was followed by a brownish green band and finally a green band. Following elution from the column, the brownish green and green fractions were each washed with water to remove the dissolved sugar and dried over anhydrous Na_2SO_4. Evaporation of the solvents and precipitation from CH_2Cl_2-hexane yielded green diester (**3g**) (74 mg; 58%; mp 173-176 °C) and brownish green chlorophyllide *b*-pheophorbide *b* ethylene glycol diester (**3f**) (22 mg; 17%; mp 160-164 °C).

Data for **3g**: ^1H NMR (benzene-d_6/5% pyridine-d_5) δ 1.49 (t, J = 7.5 Hz, 4b-H), 1.60 (d, J = 7.5 Hz, 8a-H), 2.25 (m, 7a-H), 2.50 (m, 7b-H), 3.20 (s, 1-CH_3), 3.52 (s, 5-CH_3), 3.80 (q, J = 7.5 Hz, 4a-H), 3.95 (s, 10b-CH_3), 4.20 (m, 7- or 8-H), 4.20 (s, glycol H), 4.35 (m, 7- or 8-H), 6.12 (s, 10-H), 6.18 (m, 2b-H), 7.92 (m, 2a-H), 8.50 (s, δ-H), 9.31 (s, β-H), 10.52 (s, α-H), 11.10 (s, 3a-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ε) 642 (66400), 594 (11000), 434 (194000) nm.

Data for **3f**: the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **3e** and **3g**, except that the singlet at δ 4.23 is broadened; electronic spectrum (benzene/5% pyridine), λ_{max} (ε) 650 (45400), 600 (10000), 553 (9500), 530 (14200), 436 (168000) nm.

Bis(bacteriochlorophyllide *a*) Ethylene Glycol Diester (4g). The preparation of diester **4g** was carried out by treating diester **4e** (62 mg, 0.05 mmol) with IMgBHT (1 mmol) and LiTMP (0.5 mmol) in dry thiophene (50 mL), utilizing the same procedures employed for the preparation of **3g** (yield of bluish diester **4g**, 28 mg; 44%) and purple-red bacteriochlorophyllide *a*-bacteriopheophorbide *a* ethylene glycol diester (**4f**) (10 mg; 16%).

Data for **4g**: mp 167-172 °C; ^1H NMR (benzene-d_6/5% pyridine-d_5) δ 0.62 (t, J = 8 Hz, 4b-CH_3), 1.28 (d, J = 7 Hz, 8a-CH_3), 1.54 (d, J = 7 Hz, 3a-CH_3), 1.8-2.4 (m, 7a,7b-H), 2.79 (s, 2b-CH_3), 3.16 (s, 1-CH_3), 3.32 (m, 4a-H), 3.40 (s, 5,10b-CH_3), 3.95 (m, 3,4,7,8-H), 4.00 (s, glycol H), 6.30 (s, 10-H), 8.22 (s, δ-H), 8.36 (s, β-H), 9.59 (s, α-H); electronic spectrum (in benzene/5% pyridine), λ_{max} (ε) 774 (94100), 720 sh (12200), 576 (21600), 535 sh (3760), 390 (53600), 359 (79100) nm.

Data for **4f**: mp 155-159 °C; the ^1H NMR (benzene-d_6/5% pyridine-d_5) spectrum is a superposition of those reported for **4e** and **4g**, except that the singlet at δ 4.04 due to the protons of the glycol link is broadened; electronic spectrum (benzene/5% pyridine), λ_{max} (ε) 775 (94100), 747 (49100), 720 (12000), 675 (6900), 576 (12200), 527 (21000), 490 (4000), 390 (54000), 360 (160000) nm.

Acknowledgment. The authors thank Benjamin Cope for purifying the pheophytins, Ursula Smith for growing the *R. sphaeroides*, and both Martin Studier and Randall Winans for obtaining the time-of-flight mass spectra. This research was supported by the Office of Basic Energy Sciences of the Department of Energy.

Registry No. 1b, 603-17-8; **1c**, 15664-29-6; **1d**, 61774-49-0; **1e**, 73197-83-8; **1f**, 73193-00-7; **1g**, 61823-38-9; **2b**, 14409-87-1; **2c**, 24533-72-0; **2d**, 60485-35-0; **2e**, 73178-45-7; **2f**, 73192-99-1; **2g**, 67582-80-3; **3b**, 3147-18-0; **3c**, 20239-99-0; **3d**, 73178-46-8; **3e**, 73178-47-9; **3f**, 73192-97-9; **3g**, 73192-98-0; **4a**, 17499-98-8; **4c**, 73178-48-0; **4d**, 73178-49-1; **4e**, 63727-22-0; **4f**, 73197-84-9; **4g**, 63594-63-8.

Reactions of 1,5-Dichloroanthraquinone with Nucleophiles

Edward H. Ruediger, Magdy L. Kaldas, Sham S. Gandhi, Cristi Fedryna, and Martin S. Gibson*

Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada

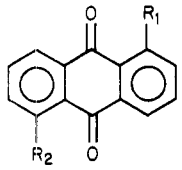
Received February 11, 1980

Reactions of 1,5-dichloroanthraquinone (**1**) with various nucleophiles were examined to evaluate possibilities for selective substitution. 1-Amino-5-chloroanthraquinone was obtained from **1** by reaction with (a) sodium azide in dimethyl sulfoxide and (b) ammonia in the presence of potassium fluoride, but **1** with potassamide in ammonia gave 3-chlorobenzoic acid. Conditions were found for preferential substitution in reactions of **1** with (c) 4-toluidine, (d) hexamethylphosphoric triamide, and (e) *N*-methylformamide. Reagent e is preferred for making 1-chloro-5-(methylamino)anthraquinone, though this compound predominates in mixtures produced when d is used. Potassium hydroxide in 2-ethoxyethanol converts **1** to the corresponding mono- and diethers of 1,5-dihydroxyanthraquinone, while sodium hydrosulfide and **1** give bis(5-chloroanthraquinonyl) sulfide.

1,5-Dichloroanthraquinone (**1**) offers a number of possibilities as a starting material for the synthesis of more complex molecules because of the juxtaposition of the chlorine atoms and the carbonyl groups of the central ring. A key to developing such syntheses lies in differential nucleophilic substitution of the chlorine atoms in **1**. We now report the outcome of a number of experiments to this end.

We first examined reactions of **1** with a number of nitrogen nucleophiles. In some instances, differential displacement was readily achieved. For example, **1** reacted readily with sodium azide in boiling dimethyl sulfoxide

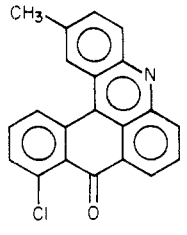
0022-3263/80/1945-1974$01.00/0



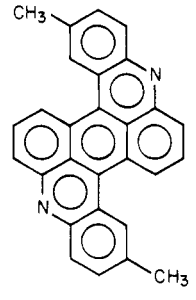
1, $R_1 = R_2 = Cl$
2, $R_1 = NH_2$; $R_2 = Cl$
3, $R_1 = NHC_6H_4CH_3$; $R_2 = Cl$
4, $R_1 = R_2 = NHC_6H_4CH_3$
7, $R_1 = NHCH_3$; $R_2 = Cl$
8, $R_1 = R_2 = NHCH_3$
9, $R_1 = N(CH_3)_2$; $R_2 = Cl$
10, $R_1 = NHCH_3$; $R_2 = N(CH_3)_2$
11, $R_1 = NH_2$; $R_2 = OH$
12, $R_1 = R_2 = OCH_2CH_2OC_2H_5$
13, $R_1 = OCH_2CH_2OC_2H_5$; $R_2 = OH$
14, $R_1 = OH$; $R_2 = Cl$

(Me_2SO) to give **2**. This reaction presumably leads to 1-azido-5-chloroanthraquinone and is followed by loss of nitrogen and formation and subsequent hydrolysis of an intermediate sulfilimine. The same amine **2** was also readily prepared by reaction of **1** with ammonia in Me_2SO, with potassium fluoride added as a strong hydrogen bonding agent.[1] By contrast, potassamide in ammonia cleaved **1** to 3-chlorobenzoic acid, an interesting if not particularly useful result.[2] Such a reaction is not likely to be general for simpler substituted anthraquinones. We had earlier noted that 1-chloroanthraquinone gave primarily 1- and 2-aminoanthraquinones on treatment with potassamide in ammonia; incidentally, 1-chlorofluorenone gave mainly 1-aminofluorenone, with minimal cleavage to 3-chlorobiphenyl-2′-carboxylic acid, under similar conditions.

More commonly, mono- and disubstitution are noted in reactions of **1** with nitrogen nucleophiles, and the problem becomes one of separation and purification of products. When refluxed with 4-toluidine, **1** was converted to **3** and **4**. These products were separated chromatographically and converted, by cyclodehydration with 70% sulfuric acid, to the complex acridines **5** and **6**, respectively.



5



6

For the introduction of a methylamino group to give **7**, **1** had previously been treated with methylamine in pyridine at elevated temperature and pressure, but purification was lengthy, and yields were not specified.[3] There are indications from our own work that the product isolated as **7** was contaminated with the disubstitution product **8**. Compound **7** has also been obtained by reaction of **1** with dimethylformamide (DMF), but the reaction mixture was complex and the separation tedious.[4] Along these lines, we decided to examine the reaction of **1** with hexamethylphosphoric triamide (HMPT). This reagent has been used for introduction of dimethylamino groups into aromatic rings which are amenable to nucleophilic substitution.[5] Our expectation in this case was that, if introduced, a dimethylamino group would undergo facile demethylation to a methylamino group, as occurs in the reaction of **1** with DMF,[4] and this indeed proved to be so. Reaction of **1** with HMPT proceeded readily. Monitoring of the reaction by thin-layer chromatography showed initial formation of **9**, after which demethylation occurred to give **7**; this was followed by formation of disubstituted products. After the mixture was refluxed for 15 min, the isolated products were **7**, **9**, and **10**, with **7** predominating (34%); some of **1** was recovered. We noted that 1,8-dichloro- and 1-chloroanthraquinones behaved in the same way, but 2-chloroanthraquinone in a slower reaction gave 2-(dimethylamino)anthraquinone with little demethylation; hexaethylphosphoric triamide behaved similarly with the two monochloroanthraquinones. We envisage the facile demethylation experienced in the 1-substituted series in terms of a cyclic transition state analogous to that proposed by Lynch and Meth-Cohn to rationalize earlier results of Fokin and co-workers.[6]

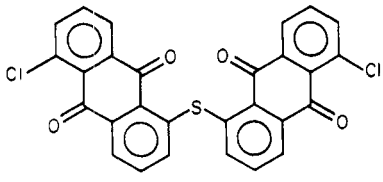
The reaction of **1** with HMPT suffered from the disadvantage of the corresponding reaction with DMF, namely, the difficulty of separation of products and their purification. A more satisfactory process involved reaction of **1** with *N*-methylformamide. This reaction, conducted in the normal way under reflux, gave a mixture of **7** and **8** which proved exceedingly difficult to separate chromatographically. However, by careful mass spectrometric monitoring of the reaction, it was possible to interrupt the reaction before detectable amounts of **8** had been formed. This permitted a straightforward chromatographic separation of **7** from **1** which could then be recycled. Pure **7** was purple and lusterless; pure **8**, obtained after extended reaction times, was purple and lustrous (as were mixtures of **7** and **8**).

We had an interest in examining the reactions of **2** and of **7** with (a) potassamide in ammonia and with (b) potassium *tert*-butoxide in *tert*-butylbenzene[7] to see whether syntheses of acridone-1-carboxylic acids (through cleavage and recyclization) might be developed, but the results were not encouraging. Compound **2** was recovered under both sets of conditions, with slight hydrolysis to **11** under the latter circumstances. Compound **7** reacted to some extent to give mixtures from which, despite initial hopes, it was only possible to isolate and identify 1-(methylamino)-anthraquinone after lengthy plate chromatography; the nature of the dechlorination process leading to this material is not clear but may have parallels in anthraquinone chemistry.[4]

We also examined the reaction of **1** with potassium hydroxide and with sodium hydrosulfide. With potassium hydroxide in Me_2SO, reaction was not specific; mono- and disubstitution products were rapidly formed (as shown by mass spectrometric monitoring) but were very difficult to separate. When the reaction was conducted in 2-ethoxyethanol as solvent, it was found possible to separate two reaction products. These were not, however, products of mono- and disubstitution but proved to be the ethers **12** and **13** of 1,5-dihydroxyanthraquinone. 1-Chloro-5-

(1) Cf. J. H. Clark and J. M. Miller, *J. Am. Chem. Soc.*, **99**, 498 (1977).
(2) M. S. Gibson and M. M. Kayser, unpublished results. Cf. J. F. Bunnett and B. F. Hrutfiord, *J. Org. Chem.*, **27**, 4152 (1962).
(3) R. H. Hall and D. H. Hey, *J. Chem. Soc.*, 736 (1948).
(4) W. M. Lord and A. T. Peters, *J. Chem. Soc. C*, 783 (1968).
(5) E. B. Pedersen, J. Perregaard, and S.-O. Lawesson, *Tetrahedron*, **29**, 4211 (1973), and references cited therein.
(6) J. Lynch and O. Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1*, 920 (1973). Cf. E. P. Fokin and V. V. Russkikh, *Zh. Org. Khim.*, **2**, 912 (1966), and previous papers.
(7) Cf. J. I. G. Cadogan, K. A. Hall, and J. T. Sharp, *J. Chem. Soc. C*, 1860 (1967).

hydroxyanthraquinone (14) was prepared from 2 by diazotization and thermal decomposition;[8] however, the yield was poor as diazotization was sluggish and incomplete, and 14 had to be separated from unchanged 2. When 14 was refluxed with potassium *tert*-butoxide in *tert*-butylbenzene, extensive resinification occurred with attendant low recovery of 14 and of its product of dechlorination, 1-hydroxyanthraquinone; no xanthone-1-carboxylic acid was obtained. Finally, 1 was refluxed with sodium hydrosulfide in benzyl alcohol; from this was isolated the sulfide 15 resulting from condensation of the first-formed 1-chloroanthraquinone-5-thiol with unchanged 1.



15

These results show that nucleophilic substitution of chlorine atoms in 1 is possible in a number of cases, but development rests upon more general procedures being found.

Experimental Section

Mass spectra were determined with an AEI MS-30 double-beam spectrometer; *m/e* values are quoted for the lowest isotopic species, and relative intensities are noted in parentheses. ^{1}H NMR spectra were obtained on a Bruker WP-60FT spectrometer (60 MHz; tetramethylsilane as internal standard).

Commercial samples of 1 contained trichloroanthraquinone(s) (*m/e* 310, M^+) and were crystallized before use. HMPT was stored over 13X molecular sieves.

1-Amino-5-chloroanthraquinone (2). A. Sodium azide (7.0 g, 0.11 mol), dissolved in water (25 mL), was added during 5 min to a warm solution of 1 (10.0 g, 0.036 mol) in Me_2SO (100 mL). The mixture was refluxed for 30 min, was allowed to cool, and was then poured into water (600 mL). The next day, the chocolate-brown solid (9.4 g) was filtered off, dried, and extracted (Soxhlet) with chloroform; the insoluble carbonaceous residue (3.1 g) was discarded. The chloroform solution was evaporated, and the residue was chromatographed on silica gel (benzene/petroleum ether) to yield 1 (0.43 g, 4%), followed by 2, which crystallized from aqueous acetic acid as brick-red needles (3.01 g, 33%): mp 204–208 °C (lit.[9] mp 210 °C); mass spectrum, *m/e* 257 (M^+, 100), 229 (M – CO, 25), 223 (38), 201 (M – 2 CO, 13), 195 (8), 173 (5), 166 (17), 166 (17), 139 (25).

B. Ammonia was slowly bubbled through a stirred solution of 1 (2.0 g) and anhydrous potassium fluoride (5.0 g) in Me_2SO (50 mL) at 90–100 °C for 2 h. When cool, the mixture was poured into water (400 mL) and acidified (H_2SO_4). The red-brown solid (1.9 g) was filtered off, dried, and chromatographed to yield 1 (0.15 g, 8%) and 2 (0.65 g, 35%).

Virtually no reaction was observed in the absence of potassium fluoride.

1- and 2-Aminoanthraquinones.[17] A solution of 1-chloroanthraquinone (5.0 g) in dry tetrahydrofuran (200 mL) was added to a stirred solution of potassamide (from 5.0 g of potassium) in liquid ammonia (350 mL). After 4 h, ammonium chloride (5.0 g) was added, and ammonia was allowed to evaporate overnight. Water (200 mL) was added, and organic products were extracted with chloroform, a small amount of insoluble material being retained. The chloroform solution was washed, dried ($MgSO_4$), and evaporated. Chromatography of the dark red residue (neutral alumina, chloroform) gave in turn 1-chloroanthraquinone (0.56 g, 11%; identical with the starting material), 1-aminoanthraquinone (2.05 g, 45%) as red needles [mp 253–254 °C (from ethanol) (lit.[10] mp 253–254 °C)], and 2-aminoanthraquinone (1.21 g, 26%) as orange-red needles [mp 308–310 °C (from ethanol) (lit.[10] mp 303–306 °C)]; the aminoanthraquinones were identified by R_f and correlation of IR, UV, and mass spectra. The insoluble material from the original extraction, when submitted to sublimation at 190 °C (0.3 mm), gave a sublimate (0.8 g) which contained 1- and 2-aminoanthraquinones.

1-Chlorofluorenone (2.0 g), similarly treated, gave 1-aminofluorenone (0.47 g, 25%; identical with an authentic sample)[11] together with unreacted 1-chlorofluorenone (0.61 g, 31%); basic aqueous washings from the extraction were acidified and evaporated to yield inorganic salts contaminated with trace amounts of a cleavage product of 1-chlorofluorenone which is considered to be 3-chlorobiphenyl-2′-carboxylic acid: mass spectrum, *m/e* (relative intensity) 232 (M^+, 90), 152 (100).

1-Chloro-5-(4-methylphenyl)- and 1,5-Bis(4-methylphenyl)aminoanthraquinones (3) and (4). Compound 1 (5.0 g) was refluxed in 4-toluidine (20 g) for 15 min. When cool, the mixture was digested with ethanol (50 mL), and the red-black solid (4.7 g) was filtered off. Chromatography (silica gel, benzene) gave 4 (0.25 g, 3.3%) as black needles with a golden luster: mp 301–305 °C (from pyridine); mass spectrum, *m/e* (relative intensity) 418 (M^+, 100), 417 (M – H, 8); ^{1}H NMR (Me_2SO-d_6) δ 8.1 (br s, 2 H), 7.7–7.3 (m, 6 H), 7.2 (s, 8 H), 2.4 (s, 6 H); trace impurity $C_{28}H_{21}ClN_2O_2$, *m/e* 452 (M^+).

Anal. Calcd for $C_{28}H_{22}N_2O_2$: mol wt 418.1681. Found: mol wt (mass spectrometry) 418.1517.

Continued elution gave a purple-red solid. This was rechromatographed (toluene) to yield a further sample (0.1 g, 1.3%) of 4, followed by 3 which crystallized from ethanol as dark red needles (2.3 g, 37%): mp 165–166 °C; mass spectrum, *m/e* (relative intensity) 347 (M^+, 100), 332 (M – CH_3, 3), 254 (4), 241 (M – $NHC_6H_4CH_3$, 5), 240 (4), 173.5 (M^{2+}, 10), 166 [(M – CH_3)$^{2+}$, 8]; ^{1}H NMR ($CDCl_3$) δ 8.2 (br s, 1 H), 7.7–7.3 (m, 6 H), 7.2 (s, 4 H), 2.4 (s, 3 H).

Anal. Calcd for $C_{21}H_{14}ClNO_2$: C, 72.5; H, 4.1; N, 4.0; mol wt 347.0713. Found: C, 71.8; H, 4.0; N, 3.7; mol wt (mass spectrometry) 347.0585.

Cyclization of 3. Compound 3 (2.0 g) was heated with 70% sulfuric acid (50 mL) at 160–180 °C for 1 h. When cool, the mixture was poured into water, and the chocolate-brown solid (1.92 g) was filtered off. Chromatography (silica gel, benzene) gave 5 (1.1 g, 58%) which crystallized from ethanol as golden brown needles: mp 218–221 °C; mass spectrum, *m/e* (relative intensity) 329 (M^+, 100), 301 (M – CO, 5), 295 (39), 266 (11), 265 (14), 264 (16), 164.5 (M^{2+}, 8), 132.5 (39); ^{1}H NMR ($CDCl_3$) δ 8.5–7.3 (m, 9 H), 2.6 (s, 3 H).

Anal. Calcd for $C_{21}H_{12}ClNO$: C, 76.5; H, 3.7; Cl, 10.8; N, 4.3. Found: C, 76.3; H, 3.7; Cl, 10.4; N, 4.3.

Attempted cleavage[12] of 5 with potassium *tert*-butoxide/1,2-dimethoxyethane/water (1 h, reflux) gave a complex mixture which apparently contained none of the anticipated acridinecarboxylic acid (mass spectrum).

Cyclization of 4. Compound 4 (0.5 g) was refluxed for 30 min in 70% sulfuric acid (30 mL). When cool, the blue solution was poured into water (300 mL) and neutralized with aqueous sodium hydroxide solution. Isolated by extraction with chloroform, 6 (0.4 g, 83%) separated from ethanol as purple-red crystals: mp >320 °C; mass spectrum, *m/e* (relative intensity) 382 (M^+, 100), 367 (M – CH_3, 9), 191 (M^{2+}, 13), 179.5 [(M – CH_3)$^{2+}$, 6]; ^{1}H NMR ($CDCl_3$) δ 8.4–7.7 (m, 10 H), 7.3 (s, 2 H), 2.6 (s, 6 H).

Reactions of Chloro- and Dichloroanthraquinones with HMPT. The chloroanthraquinone (2.42 g, 0.01 mol) or dichloroanthraquinone (2.76 g, 0.01 mol) was refluxed in HMPT (20 mL) for 15 min (45 min for 2-chloroanthraquinone). When cool, the reaction mixture was poured into water (150 mL), and the resulting precipitate was filtered off and dried. This was separated chromatographically (silica gel, benzene) to give the compounds noted.

(a) From 1,5-Dichloroanthraquinone. The dark red crude product (2.81 g) gave 1 [0.1 g (4%) (R_f and mass spectrum)], 7 [0.92 g (34%); blood-red needles; mp 198–200 °C (from ethanol)

(8) A. Green, *J. Chem. Soc.*, 2203 (1926).
(9) L. Gatterman, *Justus Liebigs Ann. Chem.*, **393**, 169 (1912).
(10) R. C. Weast, "Handbook of Chemistry and Physics", 57th ed., Chemical Rubber Co., Cleveland, OH, 1977.
(11) F. Bell and J. A. Gibson, *J. Chem. Soc.*, 3560 (1955).
(12) D. G. Davies and P. Hodge, *J. Chem. Soc. C*, 3158 (1971).

(lit.[4] mp 196–197 °C); mass spectrum, *m/e* (relative intensity) 271 (M^+, 100); ^1H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.3–7.0 (6 H, m), 3.0 (3 H, d, J = 5.1 Hz); ($CDCl_3$ + D_2O) δ 9.5 (br s 1 H), 8.3–7.0 (6 H, m), 3.0 (3 H, skewed d)], **9** [40 mg (1.4%); brick-red needles; mp 153–155 °C (from ethanol) (lit.[4] mp 144–145 °C); mass spectrum, *m/e* (relative intensity) 285 (M^+, 73), 270 (100); ^1H NMR ($CDCl_3$) δ 8.2–7.1 (6 H, m), 3.0 (6 H, s)], and slightly impure **10** [58 mg (2%); dark red solid; mp 90–96 °C, mass spectrum, *m/e* (relative intensity) 280 (M^+, 35), 78 (100); ^1H NMR ($CDCl_3$) δ 9.6 (br s, 1 H, removed on D_2O exchange), 8.2–6.9 (6 H, m), 3.0 (br s, 9H)].

(b) From 1-Chloroanthraquinone. The dark red crude product (2.32 g) gave 1-chloroanthraquinone [0.22 g (9%); mp 158–160 °C (melting point, R_f, and mass spectrum)], 1-methylaminoanthraquinone [0.70 g (30%); red microcrystals with a golden luster; mp 172–173 °C (from ethanol) (lit.[13] 167, 170 °C); mass spectrum, *m/e* (relative intensity) 237 (M^+ 100); ^1H NMR ($CDCl_3$) δ 9.5 (br s, 1 H), 8.5–6.8 (7 H, m), 3.0 (3 H, d, J = 4.9 Hz); ($CDCl_3$ + D_2O) δ 8.5–6.8 (7 H, m), 3.0 (3 H, s)], and 1-(dimethylamino)anthraquinone [50 mg (2%); dark red prisms; mp 139–140 °C (from ethanol) (lit.[14] mp 140–141 °C); mass spectrum, *m/e* (relative intensity) 251 (M^+, 82), 234 (100); ^1H NMR ($CDCl_3$) δ 8.3–7.2 (7 H, m), 3.0 (6 H, s)].

1-Chloro-5-(methylamino)anthraquinone (7). Compound **1** (3.4 g) and *N*-methylformamide (20 mL) were refluxed together for 3 h. After the mixture had been allowed to stand for 12 h at room temperature, the cherry-red solid was filtered off and dried. Chromatography (Florisil, benzene/petroleum ether) gave **1** (1.70–2.0 g) as yellow needles (mp 251 °C) identical with the starting material, followed by **7** (1.2–1.5 g, 35–43%) as long dark red needles, mp 205.5–206.5 °C (from chloroform) (lit.[4] mp 196–197 °C).

1,5-Bis(methylamino)anthraquinone (8). Compound **1** (3.4 g) and *N*-methylformamide (30 mL) were refluxed together for 24 h. After the mixture had been allowed to stand for 3 h at room temperature, the solid was filtered off and dried. Crystallization from acetone gave **8** (2.1 g, 64%) as dark red prisms with a golden luster; mp 218–220 °C (lit.[4] mp 218–220 °C). A further quantity (0.8 g, 25%) was obtained by dilution of the reaction filtrate with water and chromatography of the precipitated material (Florisil, benzene/petroleum ether).

Treatment of 2 with Potassium *tert*-Butoxide. A mixture of **2** (1.05 g), potassium *tert*-butoxide (from 0.5 g of potassium), and *tert*-butylbenzene (35 mL) was refluxed for 12 h. Evaporation, acidification, and extraction with chloroform, followed by washing with aqueous sodium bicarbonate solution, gave (from the chloroform solution) unreacted **2** (0.78 g, 67%). Acidification of the bicarbonate washings and extraction with chloroform gave a solid (25 mg) which showed two spots on TLC. Plate chromatography (silica, 1:1 benzene/petroleum ether) gave two bands. Extraction of the upper orange band gave **11** (15 mg, 2%) as red needles: mp 208–209 °C (from aqueous ethanol) (lit.[15] mp 210, 216 °C); mass spectrum, *m/e* (relative intensity) 239 (M^+, 100), 238 (8), 223 (4), 211 (17), 183 (17), 154 (13), 127 (8); metastable peak observed at *m/e* 186, assigned to $M^+ \rightarrow (M - HCO)^+ + HCO'$ (m^*_{obsd} *m/e* 186; m^*_{calcd} *m/e* 186.3). The sample was identical (R_f, mass spectrum) with a sample prepared from **2** and potassium hydroxide (1 equiv) in Me_2SO (1 h, reflux).

Anal. Calcd for $C_{14}H_9NO_3$: mol wt 239.058 67. Found: mol wt (mass spectrometry) 239.080 67.

The lower violet band from the plate gave a small amount of brown high-melting solid which was not further examined.

Compound **2** was recovered (60%) from treatment with potassamide in ammonia; none of the desired acridone-1-carboxylic acid was observed.

Reaction of 7 with Potassamide. Compound **7** (1.35 g) in dry tetrahydrofuran (100 mL) was treated with potassamide (from 3.9 g of potassium) in redistilled liquid ammonia (500 mL) for 4 h in the usual way. The crude product was treated with 2 M hydrochloric acid, and the mixture was extracted with ether and separated into basic, neutral, and acidic fractions in the normal way.

The base fraction yielded a red solid (0.18 g) consisting (chromatography) of **7** and an unidentified yellow compound (30 mg). The acidic fraction gave a red solid (0.88 g) which appeared to crystallize as a single substance [0.63 g, mp 141–143 °C, red needles (from benzene)]. Careful plate chromatography (silica, 7:3 benzene/petroleum ether) of a sample (60 mg) enabled the separation of two principal bands. The upper bluish band yielded a solid (10 mg) which sublimed as magenta needles: mp 225–227 °C dec; mass spectrum, *m/e* (relative intensity) 271 (M^+, 19), 254 (10), 242 (29), 208 (100), 180 (76), 152 (43).

Anal. Calcd for $C_{15}H_{13}NO_4$: mol wt 271.0845. Found: mol wt (mass spectrometry) 271.0865.

The lower pink band gave a red solid (30 mg) which had a melting point of 172–173 °C after crystallization from benzene. This was identified as 1-(methylamino)anthraquinone by comparison with an authentic sample (melting point, R_f, and IR, ^1H NMR, and mass spectra.

Similar results were obtained from treatment of **7** with potassium *tert*-butoxide in *tert*-butylbenzene.

Reaction of 1 with Potassium Hydroxide. (a) In Me_2SO. Compound **1** (3.45 g) and potassium hydroxide (2.1 g) were refluxed in Me_2SO (50 mL) and water (10 mL) for 30 min. When cool, the mixture was diluted with water and acidified, and the precipitate (3.2 g) was filtered off. This contained 1,5-dichloro-, 1-chloro-5-hydroxy-, and 1,5-dihydroxyanthraquinones (mass spectrum), and the last two compounds could not be satisfactorily separated by chromatography.

(b) In 2-Ethoxyethanol. Compound **1** (3.45 g) and potassium hydroxide (3.5 g) were refluxed in 2-ethoxyethanol (50 mL) for 2 h. When cool, the mixture was filtered to give a pale brown solid (2.4 g) and a dark red filtrate.

The solid, after three crystallizations from acetone/chloroform (charcoal), gave **12** (1.7 g, 35%) as pale yellow needles: mp 132 °C; mass spectrum, *m/e* (relative intensity) 384 (M^+, 18), 339 ($M - C_2H_5O$, 37), 325 ($M - C_2H_5OCH_2$, 11), 312 ($M - C_2H_5OCH{=}CH_2$, 5), 293 (15), 266 (41), 253 (91), 240 ($M - 2C_2H_5OCH{=}CH_2$, 100), 238 (74), 224 (17), 210 (6), 208 (6), 195 (7), 184 (5), 168 (5), 150 (11), 139 (25); ^1H NMR ($CDCl_3$) δ 8.1–7.2 (m, 6 H), 4.4 (skewed t, J = 5.4 Hz, 4 H), 4.0 (skewed t, J = 5.4 Hz, 4 H), 3.7 (q, J = 7.0 Hz, 4 H), 1.3 (t, J = 7.0 Hz, 6 H).

Anal. Calcd for $C_{22}H_{24}O_8$: C, 68.7; H, 6.3. Found: C, 68.6; H, 6.2.

The reaction filtrate was diluted, filtered, and acidified (H_2SO_4), and the brown solid (0.97 g) was filtered off. Chromatography on silica gel (benzene, chloroform) gave **13** (0.7 g, 18%) as bright yellow microcrystals: mp 98–100 °C (from ethanol); mass spectrum, *m/e* (relative intensity) 312 (M^+, 5), 266 ($M - C_2H_5OH$, 25), 253 ($M - C_2H_5OCH_2$, 50), 240 ($M - C_2H_5OCH{=}CH_2$, 100), 224 (18), 212 (6), 196 (6), 184 (10), 168 (8), 155 (13), 139 (55); ^1H NMR ($CDCl_3$) δ 12.6 (s, 1 H), 8.2–7.1 (m, 6 H), 4.3 (skewed t, J = 5.4 Hz, 2 H), 3.9 (skewed t, J = 5.4 Hz, 2 H), 3.7 (q, J = 7.0 Hz, 2 H), 1.3 (t, J = 7.0 Hz, 3 H).

Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.2; H, 5.2. Found: C, 68.7; H, 5.0.

1-Chloro-5-hydroxyanthraquinone (14). Compound **2** (2.0 g) was diazotized according to the method of Green.[8] The desired phenol **14** was separated from unreacted **2** (0.9 g, 45%) by treatment of the crude reaction product with 2% sodium hydroxide solution. The red filtrate was acidified and the yellow solid filtered off. Chromatography (silica gel, benzene) gave **14** (0.4 g, 19%) as bright yellow needles: mp 222–224 °C (from ethanol) (lit.[8] mp 223–224 °C); mass spectrum, *m/e* (relative intensity) 258 (M^+, 100), 257 ($M - H$, 12), 230 ($M - CO$, 14), 224 (94), 202 ($M - 2\,CO$, 18), 196 (10), 173 (5), 168 (17), 139 ($C_{11}H_7^+$, 38); ^1H NMR ($CDCl_3$) δ 11.6 (s, 1 H), 8.4–7.3 (m, 6 H).

Treatment of 14 with Potassium *tert*-Butoxide. A mixture of **14** (0.5 g), potassium *tert*-butoxide (from 0.25 g of potassium), and *tert*-butylbenzene (25 mL) was refluxed for 12 h. The reaction produced much dark material. By chloroform extraction, acid/base fractionation, and chromatography there were obtained unreacted **14** (10 mg, 2%) and 1-hydroxyanthraquinone (20 mg, 5%): mp 181–185 °C (lit.[16] mp 193 °C); mass spectrum, *m/e*

(13) F. Ullman and O. Fodor, *Justus Liebigs Ann. Chem.*, **380**, 320 (1911).
(14) A. Allais, *Ann. Chim. (Rome)*, [12] **2**, 739 (1947).
(15) L. Wacker, *Ber. Dtsch. Chem. Ges.*, **35**, 3925 (1902).
(16) E. Laube, *Ber. Dtsch. Chem. Ges.*, **39**, 2245 (1906).

(relative intensity) 224 (M^+, 100), 223 (M - H, 30), 196 (M - CO, 12), 168 (M - 2 CO, 20), 139 (M - 2 CO - HCO, 35); metastable peak observed at m/e 171.5, assigned to $M^+ \rightarrow (M - CO)^+ + CO$ (m^*_{obsd} m/e 171.5; m^*_{calcd} m/e 171.5); metastable peak observed at m/e 144, assigned to $(M - CO)^+ \rightarrow (M - 2\,CO)^+ + CO$ (m^*_{obsd} m/e 144; m^*_{calcd} m/e 144); ^1H NMR ($CDCl_3$) δ 11.4 (s, 1 H), 8.4-7.3 (m, 7 H). The sample was identified (mass spectrum) by comparison with an authentic sample of 1-hydroxyanthraquinone.

Compound **14** was recovered (91%) from treatment with potassamide in ammonia.

Reaction of 1 with Sodium Hydrosulfide. The quinone **1** (8.28 g), sodium hydrosulfide (1.68 g), and benzyl alcohol (100 mL) were refluxed for 9 h. When the mixture was cool, the solid (7 g, impure starting material) was filtered off and discarded. The filtrate was concentrated to ca. 10 mL, acetone (30 mL) was added, and the solid was collected. Chromatography (silica gel, benzene) gave **15** (780 mg, 10%) as small orange cubes: mp 326-327 °C, mass spectrum, m/e (relative intensity) 514 (M^+, 17), 275 (33), 273 ($C_{14}H_6ClO_2S^+$, 100), 240 (14), 218 (10), 206 (12), 185 (11), 173 (13), 150 (46), 105 (38).

(17) With G. J. Chen.

Anal. Calcd for $C_{28}H_{12}Cl_2O_4S$: C, 65.4; H, 2.3; Cl, 13.6; S, 6.2. Found: C, 65.3; H, 2.4; Cl, 13.5; S, 6.3.

Acknowledgment. We thank Mr. G. J. Chen and Mrs. M. M. Kayser for preliminary experiments, the National Research Council of Canada for financial support, and the Government of Ontario for graduate scholarships (to E. H.R.).

Registry No. **1**, 82-46-2; **2**, 117-11-3; **3**, 3098-20-2; **4**, 82-20-2; **5**, 73192-96-8; **6**, 73178-73-1; **7**, 73178-74-2; **8**, 2987-66-8; **9**, 18084-38-3; **10**, 18084-37-2; **11**, 71502-46-0; **12**, 73178-75-3; **13**, 73178-76-4; **14**, 73178-77-5; **15**, 73178-78-6; sodium azide, 26628-22-8; ammonia, 7664-41-7; 1-chloroanthraquinone, 82-44-0; potassamide, 17242-52-3; 1-aminoanthraquinone, 82-45-1; 2-aminoanthraquinone, 117-79-3; 1-chlorofluorenone, 36804-56-5; 1-aminofluorenone, 6344-62-3; 3-chlorobiphenyl-2'-carboxylic acid, 73178-79-7; 4-toluidine, 106-49-0; hexamethylphosphoric triamide, 680-31-9; 1-(methylamino)anthraquinone, 82-38-2; 1-(dimethylamino)anthraquinone, 5960-55-4; *N*-methylformamide, 123-39-7; potassium *tert*-butoxide, 865-47-4; potassium hydroxide, 1310-58-3; 1,5-dihydroxyanthraquinone, 117-12-4; 2-ethoxyethanol, 110-80-5; 1-hydroxyanthraquinone, 129-43-1; sodium hydrosulfide, 16721-80-5.

Electrochemistry of Natural Products. 7. Oxidative Decarboxylation of Some Tetrahydro-β-carbolinecarboxylic Acids[1]

James M. Bobbitt* and John P. Willis

Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06268

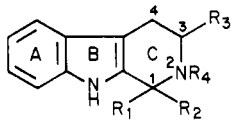
Received December 7, 1979

A series of 1,2,3,4-tetrahydro-β-carboline-1- and -3-carboxylic acids containing various substituents in positions 1, 2, and 3 were oxidized electrochemically. In general, the acids were decarboxylated, and unsaturation was introduced into the C ring. The oxidation appears to take place through the indole ring nitrogen, and possible mechanisms of the reactions are presented. Parallels between the observed reactions and early steps in indole alkaloid biosynthesis are discussed. The oxidative dimerization of tetrahydrocarbazole is reported.

In the previous paper of this series,[1a] we presented an argument in favor of the inclusion of an oxidative decarboxylation step in the early stages of isoquinoline alkaloid biosynthesis. The reaction was the decarboxylation of phenolic tetrahydroisoquinoline-1-carboxylic acids, and the oxidations were carried out electrochemically.[2] In this paper we have extended the work to the indole alkaloids, more specifically, to a study of tetrahydro-β-carboline-1- and -3-carboxylic acids.

As shown in Scheme I, several pathways may be visualized for the biosynthesis of the simple β-carboline alkaloids,[3] harman, **9**, for example.[4] There are essentially two points of variation in the possible pathways. The first depends upon whether tryptophan, **1**, or tryptamine, **2**, is involved in the ring-closure step. For many years, it was thought that only tryptamine was involved. However, the recent discovery of some alkaloids containing a 3-carboxyl group[5] means that at least some coupounds are derived directly from 1. Actually, this idea was suggested many

Table I. Tetrahydro-β-carboline Derivatives



compd	R_1	R_2	R_3	R_4
3	CH_3	CO_2H	CO_2H	H
4	CH_3	CO_2H	H	H
5	CH_3	H	CO_2H	H
6[a]	CH_3		CO_2H	
8	CH_3	H	H	H
10	CH_3	CH_2OH	CO_2H	H
11	H	CH_2OH	CO_2H	H
12	H	H	CO_2H	H
13	H	H	H	H
14	H	H	H	$COCH_3$
15	CH_3	H	H	$COCH_3$
16	CH_3	CH_3	CO_2H	H
17	H	CH_2CH_2[b]	CO_2H	CO[b]

[a] 1-Methyl-3,4-dihydro-β-carboline-3-carboxylic acid. [b] Contains a five-membered lactam ring between positions 1 and 2.

(1) (a) Part 6: J. M. Bobbitt and T. Y. Cheng, *J. Org. Chem.*, 41, 443 (1976). (b) Taken in part from the Ph.D. dissertation of J. P. W., The University of Connecticut, 1977. The work was sponsored in part by Research Grant No. CA-10494 from the Cancer Institute of the National Institutes of Health and by Grant No. GP-7601 from the National Science Foundation.

(2) J. M. Bobbitt, *Heterocycles*, 1, 181 (1973).

(3) R. H. F. Manske in "The Alkaloids", Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, 1965, p 47.

(4) (a) T. A. Geissman and D. H. G. Crout, "Organic Chemistry of Secondary Plant Metabolites", Freeman, Cooper and Co., San Francisco, 1969, p 473; (b) R. A. Abramovitch and I. D. Spencer, *Adv. Heterocycl. Chem.*, 3, 83 (1964); (c) M. Slayton and I. J. McFarlane, *Phytochemistry*, 7, 605 (1968); (d), I. A. Veliky, *ibid.*, 11, 1405 (1972).

(5) (a) R. T. Brown, C. L. Chapple, and G. K. Lee, *J. Chem. Soc., Chem. Commun.*, 1007 (1972); (b) K. L. Stuart and R. Woo-Ming, *Heterocycles*, 3, 223 (1975).

0022-3263/80/1945-1978$01.00/0