Preparation of 2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane and Its Carbamates with Electron-Donor Moieties

Epifanio Torres and Charles A. Panetta*

Department of Chemistry, The University of Mississippi, University, Mississippi 38677

Robert M. Metzger

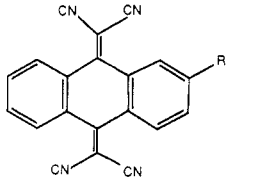
Department of Chemistry, The University of Alabama, University, Alabama 35486

Received January 20, 1987

11,11,12,12-Tetracyanoanthraquinodimethane (TCNAQ, 1) has recently been made readily available via a $TiCl_4$-mediated Knoevenagel condensation of 9,10-anthraquinone and malononitrile in pyridine.[1,2] The reasonably high electron affinity of TCNAQ suggested the incorporation of its structure into D-σ-A-type products.[3] The latter, which have electron-donor and -acceptor moieties covalently bonded together through a nonconjugated bridge of C/N/O atoms, have been proposed as possible candidates for prototype organic molecular rectifiers.[4] All D-σ-A products reported to date have been synthesized by using 5-bromo-2-(2-hydroxyethoxy)-7,7,8,8-tetracyanoquinodimethane (**9**) as the acceptor component and were only partially crystalline, at best. Since the preparation of **9** is tedious (eight steps), inefficient (less than 13% overall yield), and hazardous (cyanogen chloride required), our efforts have been directed toward obtaining an equally effective but more accessible hydroxyl-functionalized acceptor component. We report here the preparation of the title compound, **2**, in 42% yield from readily available starting materials and two new D-σ-A compounds, **3** and **4**, each obtained in the form of black crystals. These should allow the first X-ray diffraction analyses of authentic D-σ-A materials.

2-(Hydroxymethyl)anthraquinone[5] (**7**) was prepared by the chlorination of **5** followed by hydrolysis. The overall yield was 70%. The hydroxyl group was then protected as the *tert*-butyldiphenylsilyl ether **8**. Conversion of **8** to a tetracyanoanthraquinodimethane derivative, using the malononitrile and titanium tetrachloride/pyridine procedure,[1,2] failed after several attempts. The preparation of **2** was achieved when the *unprotected* hydroxy anthraquinone **7** was treated with β-alanine *in addition* to the above reagents, conditions that were not successful on the tetracyanation of **8**. Even though β-alanine was not used or required in the published[1,2] preparation of **1**, it was essential in the synthesis of **2**: its absence resulted in no **2** being formed.

The cyclic voltammogram of **2** was run by Dr. Charles Hussey of The University of Mississippi. It appeared to be very similar to that[6] of its parent, **1**, which showed a two-electron reduction resulting from coproportionation of a one-electron species: 2 $HOCH_2TCNAQ\bullet \rightleftharpoons HOCH_2TCNAQ$ **2** + $HOCH_2TCNAQ^-$. The $K_{eq} = \sim 0.6$.

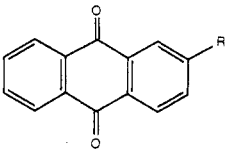


1 R = -H

2 R = -CH_2OH

3 R = -CH_2OCNH (1-pyrenyl)

4 R = -CH_2OCNH (p-NMe_2-phenyl)

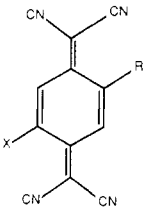


5 R = -CH_3

6 R = -CH_2Cl

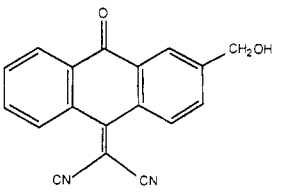
7 R = -CH_2OH

8 R = -$CH_2OSi(C_6H_5)_2$-t-bu



9 X = -Br

R = -OCH_2CH_2OH



10

Two new and crystalline D-σ-A products (**3**, **4**) were prepared by the treatment of **2** with 1-pyrenyl isocyanate and *p*-(*N*,*N*,-dimethylamino)phenyl isocyanate. Work is in progress on the X-ray diffraction determination of the solid-state conformations of **3** and **4**.[7] The latter crystallizes in the space group $P\bar{1}$, with unit cell constants a = 8.748 (4) Å, b = 10.989 (3) Å, c = 13.541 (8) Å, α = 90.67 (4)°, β = 99.15 (4)°, γ = 98.62 (4)°, Z = 2 for $C_{30}H_{20}N_6O_2$; 1932 unique X-ray reflections were collected on a ENRAF-Nonius CAD-4F diffractometer, and the structure was solved by direct methods and was refined to R = 12.7%. Figure 1 is an ORTEP plot of the molecule (50% probability ellipsoids); the molecule has an extended but bent geometry: the TCNAQ moiety is folded along the C4–C11 axis, with a dihedral angle of 37.3° between the two least-squares outer six-membered rings; the dihedral angle between the phenyl ring and the central ring of TCNAQ is 37.2°. This property is important to the proper alignment of the molecules in thin films, which is necessary in order to evaluate possible rectification properties.

Experimental Section

Melting points were run on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Beckman Acculab 3. E. Merck silica gel (9385) was used in column chromatography. Cyclic voltammograms were obtained by using an Amel Model 551 potentiostat programmed by a Parc 175 universal programmer. Elemental analyses were performed by Mic Anal., P.O. Box 41838, Tucson, AZ 85717.

2-(Chloromethyl)anthraquinone (6). The published procedure[5] for the chlorination of **5** was modified only slightly to afford a 79% yield of **6**: mp 164–165 °C (lit. mp 165–166 °C).

2-(Hydroxymethyl)anthraquinone (7). The published procedure[5] for the hydrolysis of **6** was repeated exactly to obtain an 88% yield of **7**: mp 193–194 °C (lit. mp 192–193 °C).

2-[((*tert*-Butyldiphenylsilyl)oxy)methyl]anthraquinone (8). *tert*-Butyldiphenylchlorosilane (1.47 g, 5.3 mmol) was added to 1.0 g (4.2 mmol) of **7**, 0.71 g (10.0 mmol) of imidazole, and 2.0 mL of dry DMF under an inert atmosphere (glovebox). The reaction mixture was then stirred at 55 °C in the dark under an Ar atmosphere for 48 h. It was poured into ice–water, and the

(1) Aumuller, A.; Hunig, S. *Liebigs Ann. Chem.* **1984**, 618.
(2) Ong, B. S.; Keoshkerian, B. *J. Org. Chem.* **1984**, *49*, 5002.
(3) Panetta, C. A.; Baghdadchi, J.; Metzger, R. M. *Mol. Cryst. Liq. Cryst.* **1984**, *107*, 103. Metzger, R. M.; Panetta, C. A.; Heimer, N. E.; Bhatti, A. M.; Torres, E.; Blackburn, G. F.; Tripathy, S. K.; Samuelson, L. A. *J. Mol. Electron.*, in press.
(4) Aviram, A.; Ratner, M. A. *Chem. Phys. Lett.* **1974**, *29*, 277; *IBM Reserach Report* RC 5419 (No. 23668) May 5, 1975. Aviram, A.; Freiser, M. J.; Seiden, P. E.; Young, W. R. *U.S. Pat.* 3953874, *1976*.
(5) Aldrich Chemical Company. Literature preparation: Lin, T.-S.; Teicher, B. A.; Sartorelli, A. C. *J. Med. Chem.* **1980**, *23*, 1237.
(6) Kini, A. M.; Cowan, D. O.; Gerson, F.; Mockel, R. *J. Am. Chem. Soc.* **1985**, *107*, 556.

(7) To be published elsewhere.

0022-3263/87/1952-2944$01.50/0

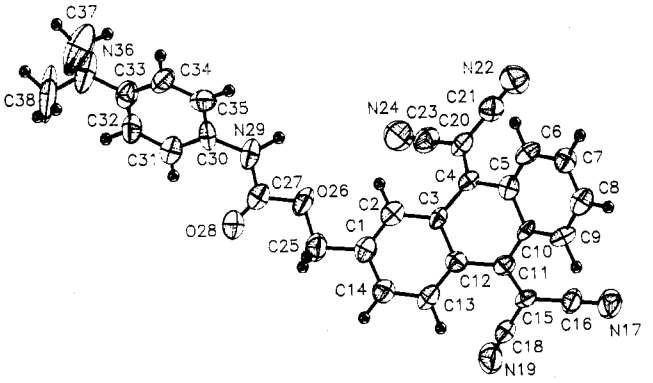


Figure 1. ORTEP plot of **4**.

pale yellow solid that separated was collected by filtration. This product, which appeared to be light-sensitive, was purified by silica gel chromatography (EtOAc/hexane, 5:95) to afford a pale yellow solid (**8**), 1.92 g (96%). This could be recrystallized from EtOAc–hexane: mp 119–120 °C; IR (KBr) 3040, 1655, 1115, 1090, 825 cm^{-1}. Anal. Calcd for $C_{31}H_{28}O_3Si$:C, 78.09; H, 5.92. Found: C, 78.14; H, 5.91.

2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (2). Two solutions were prepared in a glovebox under an atmosphere of N_2. The first was made by the addition of 4.13 g (22 mmol) of $TiCl_4$ to a solution of 1.0 g (4 mmol) of **7** in 40 mL of dry $CHCl_3$. The second solution consisted of 8.01 g (121 mmol) of malononitrile, 2.19 g (24.6 mmol) of β-alanine, 3.75 mL of pyridine, and 50 mL of dry $CHCl_3$. The second solution was added to the first in three portions, and the resultant dark mixture was then heated to the reflux temperature for 4 h under N_2. It was stored at room temperature for 16 h before being poured into ice–water. The aqueous phase was extracted with $CHCl_3$ and then with EtOAc. The organic layers were combined, dried (anhydrous $MgSO_4$), and distilled under reduced pressure to yield 9.0 g of an oily product, which contained malononitrile. Silica gel column chromatography (acetone/hexane, 20:80) separated the product, **2**, which was recrystallized from EtOAc–hexane: 0.585 g (42%); mp 256–257 °C; IR (KBr) 3510, 2220, 1560, 1045, 830, 770 cm^{-1}. Anal. Calcd for $C_{21}H_{10}N_4O$: C, 75.44; H, 3.01; N, 16.76. Found: C, 75.12; H, 2.99; N, 16.51. A cyclic voltammogram was done at a Pt disk electrode on a 7.3 mM solution of **2** in CH_3CN that was 0.1 M in tetrabutylammonium hexafluorophosphate. The reduction peak potential was −0.372 V vs. SCE at 298 K. $E_{1/2}$ estimated from the average peak potentials was −0.333 V.

In some runs, especially those where β-alanine was omitted, a faster moving material was obtained by column chromatography which was also recrystallized from EtOAc–hexane: mp 204–206 °C; IR (KBr) 3300, 2220, 1675, 1060, 775, 700 cm^{-1}. Anal. Calcd for $(C_{18}H_{10}N_2O_2)_4H_2O$: C, 74.35; H, 3.64; N, 9.63. Found: C, 74.24; H, 3.95; N, 9.29. This was assumed to be a dicyano derivative, such as **10**.

The *p*-(*N*,*N*-Dimethylamino)phenylcarbamate of 2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (4). To a solution of 117 mg (0.34 mmol) of **2** and 56 mg (0.35 mmol) of *p*-(*N*,*N*-dimethylamino)phenyl isocyanate[8] in 15 mL of dry CH_3CN was added 25 μL of dibutyltin dilaurate, and the resultant mixture was stirred at room temperature for 2.5 h and at 45 °C for 17.5 h, all under an N_2 atmosphere. The solvent was removed by distillation in vacuo, and the brown-black residue was purified by silica gel column chromatography (EtOAc/hexane, 60:40) and then by recrystallization from EtOAc to afford almost black crystals (**4**): 89 mg (51%); mp 243–245 °C; IR (KBr) 3430, 2240, 1725, 1215, 1065, 820, 770 cm^{-1}. Anal. Calcd for $C_{30}H_{20}N_6O_2$: C, 72.57; H, 4.06; N, 16.93. Found: C, 72.28; H, 3.91; N, 16.72.

The 1-Pyrenylcarbamate of 2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (3). Dibutyltin dilaurate (50 μL) was added to a mixture of 105 mg (0.31 mmol) of **2**, 78 mg (0.32 mmol) of 1-pyrenyl isocyanate,[8] and 10 mL of dry THF, and the result was stirred at room temperature for 15 h under an atmosphere of N_2. After removal of the solvent by distillation in vacuo, the brown oily residue was chromatographed on a silica gel column (EtOAc/hexane, 35:65), and the purified fraction was recrystallized from EtOAc/hexane, yielding dark crystals of **3**: 69 mg (28%); mp 251.5–253.0 °C; IR (KBr) 3380, 2220, 1730, 1210, 1075, 835, 780 cm^{-1}. Anal. Calcd for $C_{38}H_{19}N_5O_2$: C, 79.02; H, 3.32; N, 12.12. Found: C, 79.02; H, 3.20; N, 11.87.

(8) Prepared from the carboxylic acid via the acid chloride and the acid azide.

Acknowledgment. We gratefully acknowledge support from the National Science Foundation, Solid State Chemistry (DMR 84-17563). We thank Dr. C. Hussey of The University of Mississippi for the cyclic voltammogram of **2**.

Synthesis of Erbstatin, a Naturally Occurring Inhibitor of Tyrosine-Specific Protein Kinase

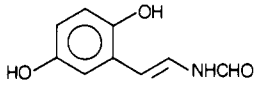
Wayne K. Anderson,* Thomas T. Dabrah, and D. Michael Houston

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260

Received July 30, 1986

Retroviral oncogenes encode a group of proteins known as transforming growth factors (TGFs) that induce a reversible malignant transformation of cells.[1] One type of TGF binds to the epidermal growth factor (EGF) receptor and activates the receptor-associated tyrosine-specific protein kinase. This leads to phosphorylation of the EGF receptor and induction of anchorage-independent cell growth. The human oncogene *erb*-B encodes an abnormal EGF receptor that cannot bind EGF but that continuously activates the protein kinase. Thus, normal growth control is lost in a cell with an aberrant EGF receptor or a cell that produces TGF and a receptor for the TGF. One possible way to control this growth is to regulate the activity of the protein kinase.

In this paper we report the synthesis of erbstatin (**1**). Erbstatin (**1**) inhibits tyrosine-specific protein kinase and inhibits the phosphorylation of the epidermal growth factor receptor.[2] Erbstatin has also been shown to inhibit the



1

growth of human epidermoid carcinoma (A-431 cells) and IMC-carcinoma cells in tissue culture.[2] The compound is an antibiotic produced by a strain of *Streptomyces* (MH435-hF3) related to *Streptomyces viridosporus* and was isolated as part of a screening program for inhibitors of tyrosine-specific protein kinase derived from the membrane fraction of human epidermoid carcinoma cell line A-431.[2,3]

The synthesis (Scheme I) begins with the treatment of the readily available 2,5-dimethoxybenzaldehyde with nitromethane in methanol–sodium hydroxide (0 → 20 °C) followed by dehydration (60 °C) in a modification of a

(1) (a) Stiles, C. D. *Cancer Res.* **1985**, *45*, 5215. (b) Brissenden, J. E.; Derynck, R.; Francke, U. *Ibid.* **1985**, *45*, 5593.
(2) Umezawa, H.; Imoto, M.; Sawa, T.; Isshiki, K.; Matsuda, N.; Uchida, T.; Iinuma, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1986**, *39*, 170.
(3) Nakamura, H.; Iitaka, Y.; Imoto, M.; Isshiki, K.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1986**, *39*, 314.

0022-3263/87/1952-2945$01.50/0