The Synthesis of Two Monosubstituted *meso*-Tetraphenylporphine Sulfonates

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This paper describes the synthesis and characterization of two novel *meso*-tetrakis(4-sulfophenyl)-21*H*,-23*H*-porphine ($TPPS_4$) derivatives in which one of the phenyl rings is substituted with an anticancer agent. Several advantages of monosubstitution are pointed out: the higher efficiency of synthetic steps involving the derivatization of one, rather than several, functional group per porphyrin molecule, and the greater solubility and ease of purification of monosubstituted tetraphenylporphines. The new compounds have 5-fluorouracil and *cis* dichloroethylenediamineplatinum (*cis*-platinum) substituted in the *meta* positions of one of the phenyl rings in $TPPS_4$. The palladium analog of the *cis*-platinum dervative which contains two Pd(II) atoms per molecule - one coordinated with the ethylenediamine moiety, and the other coordinated at the center of the porphyrin ring, was also prepared.

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Introduction.

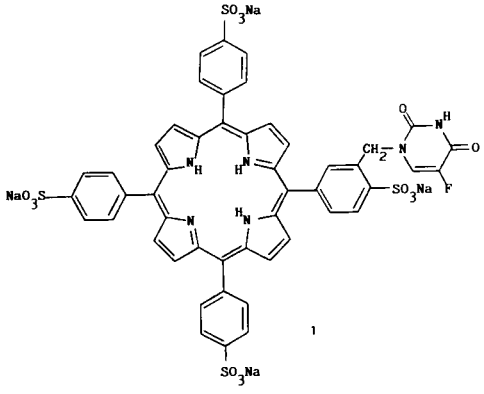
Since the observation in 1924 [1] that some natural porphyrins cause red fluorescence in tumors but not in other tissues of experimental animals, many reports on porphyrins as tumor-localizing agents have appeared [2]. A synthetic porphyrin, *meso*-tetrakis(4-sulfophenyl)-21*H*,-23*H*-porphine ($TPPS_4$), reported by J. Winkelman [3] in 1967, was found to accumulate in the cancerous tissue of rats having Walker 25 carcinosarcoma at a concentration over 50 times that of hematoporphyrin. Tsutsui and coworkers [4] studied the interactions of highly purified $TPPS_4$ with normal and tumor tissue and suggested that this compound could be a potential tumor localizing agent. Shih [5] reported the synthesis of unsymmetrically functionalized derivatives of tetraphenylphorphine as tumor localizing alkylating agents.

This report describes the synthesis of two derivatives of $TPPS_4$ containing the well-known chemotherapeutic drugs, 5-fluorouracil [6,7] and dichloroethylenediamine platinum(II) or palladium(II) complexes [8,9] substituted at the *meta* position of one of the phenyl rings of $TPPS_4$. The 5-fluorouracil group is attached to the tetraphenylporphyrin through a methylene group, whereas the ethylenediamine platinum(II) and palladium(II) complexes are chemically linked through their amino nitrogen atoms (see **1** and **2**). In both compounds the sulfonic acid groups are substituted at the *para* positions of the peripheral phenyl groups. These groups apparently have the function of imparting tumor-binding ability and water solubility.

Results and Discussion.

Synthesis of a Mono-5-fluorouracil Derivative.

Initially efforts were directed toward the preparation of 5-(α-bromo-*m*-tolyl)-10,15,20-triphenylporphyrin, which would provide the active benzylbromo group for attachment of 5-fluorouracil to the porphyrin ring. However, both cyclocondensation of α-bromo-*m*-tolualdehyde and pyrrole, and bromination of 5-(3-tolyl)-10,15,20-triphenylporphyrin were unsuccessful. In the former reaction, large amounts of unseparable tar were formed. In the latter case, the β-pyrrole protons were substituted by the alkylation reagents instead of the methyl groups in the periphe-



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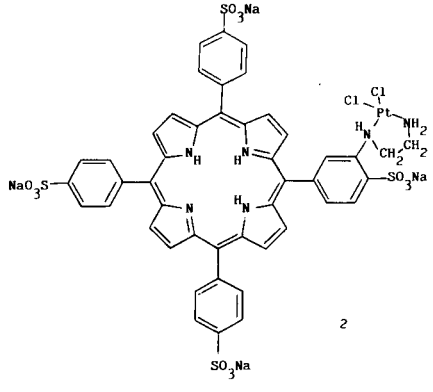

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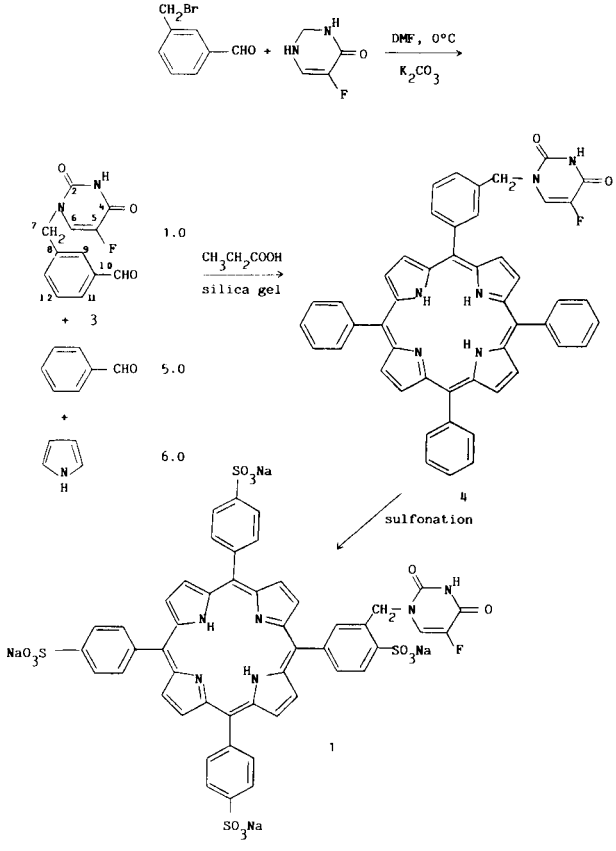
ral phenyl rings. These results led to the design of the present scheme (Scheme I), involving the use of 5-fluorouracil to react with the highly reactive α-bromo-*m*-tolualdehyde to give α-(N^1-5-fluorouracilo)-*m*-tolualdehyde **3**, which, together with benzaldehyde, was then reacted with pyrrole to form the porphyrin derivative.

Scheme I

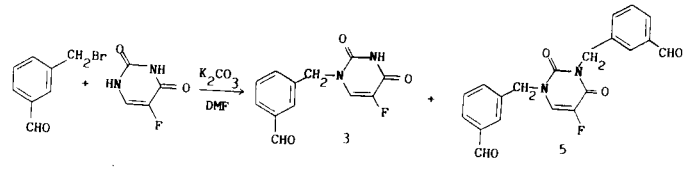
Reaction Route for the Synthesis of Mono-5FU-TPPS$_4$



The mono-5-fluorouracil-substituted tetraphenylporphyrin was prepared by a mixed-aldehyde synthesis followed by chromatographic separation [10,11]. With a 5:1 molar ratio of the aldehydes and three successive column purifications, a fairly good yield - 10% based on the α-(N^1-5-fluorouracilo)-*m*-tolualdehyde, **3** - was obtained. The 5-fluorouracil group was substituted on the *meta* position of the peripheral phenyl ring, and the four sulfonyl groups were substituted at the *para* positions, to form the water soluble porphyrin, **1**.

Due in part to the formation of N^1,N^3-bis(*m*-formylbenzyl)-5-fluorouracil, **5**, the yield of the N^1-substituted 5-fluorouracil, **3**, was only 24%. Further lowering the reaction temperature to −10° did not improve the yield. It could probably be improved by using the Hg salt of uracil to react at lower temperature [12].

Baker and Jackson [13] reported that the direct alkylation of 5-fluorouracil with benzyl chloride gives the 1-substituted compound. The position of alkylation of 5-fluorouracil is normally followed by determination of the bathochromic ultraviolet spectral shift from neutral to basic solution. The anion of a 1-substituted uracil shows no appreciable shift from the neutral species, whereas a 3-substituted uracil does show a shift to longer wavelength when converted to its anion (usually about 20 nm). The α-5-fluorouracilo-substituted tolualdehyde obtained in this research shows no appreciable shift from neutral to basic solution (see Experimental) indicating that it is the N^1-substituted compound **3**. The C-13 nmr data of this product is also consistent with the published work for 5-fluorouracil [14].



In regard to the cyclocondensation reaction used to form the porphyrin, both 3:1 and 5:1 molar ratios of benzaldehyde to α-(N^1-5-fluorouracilo)-*m*-tolualdehyde mixture were tried. The latter was found to be superior for the preparation of mono-5FU-TPP, while the former is suitable for the preparation of both mono- and di-substituted porphyrins. A typical tlc plate which was developed with chloroform-methanol (v/v = 95:5) is shown in Figure 1a. The relative Rf values are TPP, 0.98; mono-5FU-TPP, 0.49; *trans*-di-5FU-TPP, 0.28; *cis*-di-5FU-TPP, 0.21, tri-5FU-TPP, 0.12. All these porphyrins were identified by mass spectroscopy.

When the mono- and di-5FU-TPP mixture was dissolved in a small amount of chloroform, glistening purple crystalline material was filtered out and was found to dissolve readily in benzene. The tlc plate obtained from the benzene solution is shown in Figure 1c, and that of the chloroform filtrate is illustrated by Figure 1b. This separation of the two products is due to the fact that the symmetric *trans*-di-5FU-TPP is less soluble in the more polar solvent

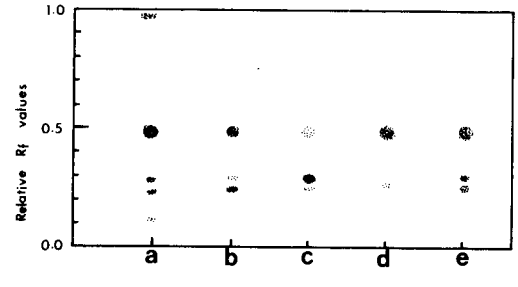


Figure 1. Several tlc plates of mono- and di-5FU-TPP mixtures. (developed by chloroform-methanol, v/v = 95:5)

chloroform. The mono- and di-5FU-TPP mixture was extracted with ethyl ether, and the tlc plates of the insoluble material and the ether solution are shown in Figures 1e and 1d, showing that the mono-5FU-TPP is more soluble in ether. All three porphyrins are moderately soluble in methanol, so that they cannot be recrystallized from chloroform-methanol as is done with most porphyrins. A methylene chloride-cyclohexane mixture was found to be a good solvent for recrystallization of the mono-5FU-TPP.

The 5-fluorouracil group was found to remain intact during sulfonation and the sulfonyl groups are substituted at the *para* positions of the phenyl groups, thus forming a very water-soluble porphyrin. Its Rf value was found to be 0.9, developed in methanol. It may be purified free from inorganic salts with a silica gel column. This compound was characterized and its structure identified by ir, nmr, and uv-visible spectra, and elemental analysis.

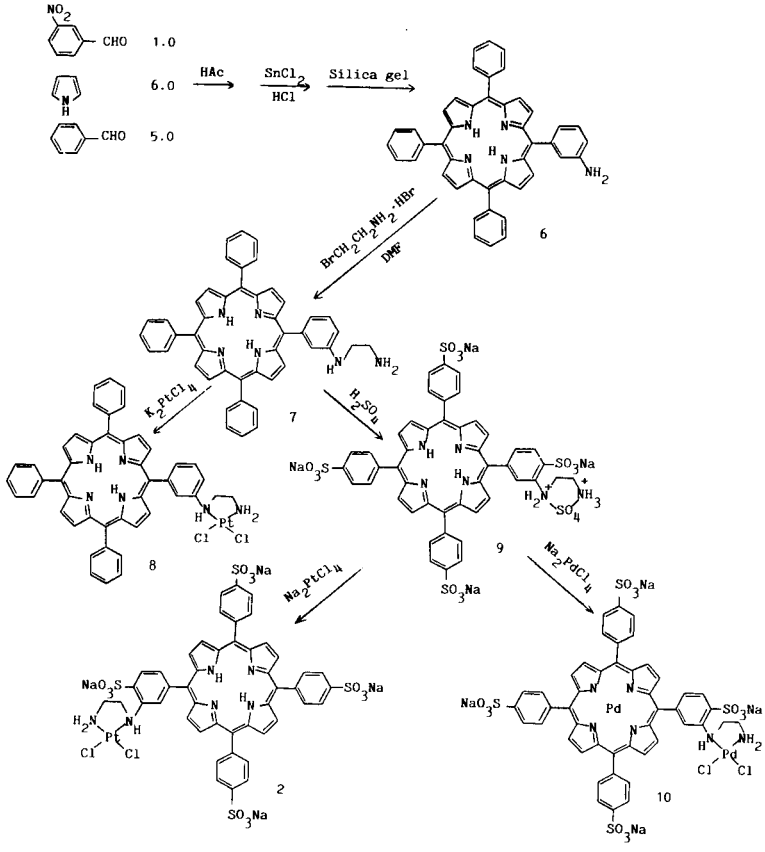
Synthesis of "*cis*-Platinum" Derivatives.

The overall synthetic route is shown in Scheme II. In a previous paper [11], the synthesis of 5-(3-nitrophenyl)-10,15,20-triphenylporphyrin (mono-*m*-nitroTPP) and 5-(3-aminophenyl)-10,15,20-triphenylporphyrin (mono-*m*-aminoTPP) were reported. The use of monoaminoporphyrin was found to be advantageous in that the buildup of substituents at the amino group is simpler and gives rise to reaction products of higher purity, than is the case for tetra-amino and other more highly substituted TPP's.

Wright [15] prepared a series of substituted *N*-phenylethylenediamines by reaction of bromoethylamine hydrobromide with substituted anilines in about 60% yield. Two equivalents of aniline were employed, one equivalent of which served as the acid-removing reagent. To conserve the valuable porphyrin derivative, several inexpensive bases such as sodium carbonate, sodium bicarbonate and pyridine were employed to remove the hydrogen bromide formed in the alkylation of **6**, but none proved to be successful. Because it was necessary in any case to recover unreacted mono-*m*-aminoTPP, excess porphyrin itself was finally used as the acid-removing agent. Dimethylformamide was selected as a good solvent in place of toluene, which was used in the Wright alkylation procedure [15]. Under these conditions, the reaction was carried out at 150° for 6 hours to give a 55% yield. The presence of the

Scheme II

Reaction Route for the Synthesis of
Mono-(*m*-$NH_2CH_2CH_2NH$)-$TPPS_4$ and Its Pt(II) and Pd(II) Complexes



ethylenediamine substituent was verified by ir, nmr and C-13 nmr.

Most of the platinum complexes reported have been prepared in water or acetone because the potassium tetrachloroplatinate(II) usually employed for this reaction is insoluble in most organic solvents. However, the mono-ethylenediamine porphyrin **7** does not dissolve in water or acetone. Dioxane was found to be the solvent of choice, and an 80% yield of the platinum-porphyrin complex **8** was obtained. Because the platinum-porphyrin complex **8** has nearly the same ir spectrum, visible spectrum and C-13 nmr spectrum as its precursor porphyrin, mono-ethylenediamine-porphyrin **7**, it was verified mainly by elemental analysis. However, the Rf values of the ethylenediamine porphyrin and its platinum complex are quite different. The visible spectrum of the platinum complex is still the same as those of the other three kinds of porphyrins prepared, nitro-, amino-, 2-aminoethylamino-substituted porphyrins. This fact provides evidence that the product does not contain platinum coordinated at the center of the porphyrin ring.

The sulfonation and purification of ethylenediamine porphyrin **7** was successfully accomplished in a manner similar to the procedure employed for sulfonation of mono-5FU-TPP **4**, except that a 3:1 v/v mixture of methanol and water was used as eluant in column purification to remove inorganic impurities.

Synthesis of the Pd(II) Analog.

Palladium(II), with a coordinate covalent radius smaller than that of platinum(II), was found to more strongly combine with the center of the porphyrin ring that with the ethylenediamine residue, contrary to the behavior described above for the Pt(II) analog. Thus only the complex, **10**, with a 2:1 ratio of Pd(II) to mono-($NH_2CH_2CH_2NH$)-$TPPS_4$ **9** was prepared. Elemental analysis shows that the atomic ratio to be N:S:Pd = 6:4:2, as expected. This complex has a red brown color; the 518 nm peak of mono-($NH_2CH_2CH_2NH$)-$TPPS_4$ **9** is shifted to 527 nm and the other three peaks of the parent ligand vanish in the visible spectra of the Pd complex, as would be expected if one of the two Pd atoms goes to the center of the porphyrin ring [16].

EXPERIMENTAL

Measurements.

The proton nmr spectra were recorded on a EM-390 spectrometer and the C-13 nmr spectra on a Varian XL-200 spectrometer operating at 200 Hz. Unless otherwise specified, the solvent employed was deuteriochloroform with tetramethylsilane as standard. The chemical shifts are given in ppm relative to tetramethylsilane and the coupling constants are in Hz. The uv-visible spectra of methylene chloride solutions were obtained with a Cary 14 recording spectrophotometer. The infrared spectra were obtained in potassium bromide pellets with a Sargent-Welch Model 3-2000 infrared spectrophotometer. The mass spectra were measured with a Californium-252 Plasma Desportion Mass Spectrometer.

The C,H,N,S analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The Pt analysis was carried out in the Chemistry Department of Texas A & M University with an Inductively-Coupled Plasma Emission Spectrometer Model No. 34000 manufactured by Applied Research Laboratory.

Separation.

The chromatographic separation described below was carried out by the dry-column procedure with silica gel 40 (70-230 mesh ASTM) purchased from MC/B Manufacturing Chemists, Inc. (EM Reagent). Tlc was done on commercially prepared silica gel 60 F-254 purchased from Merck (layer thickness 0.2 mm).

Materials.

All solvents and reagents were purchased commercially and used as supplied except as follows: pyrrole was distilled before use; dimethylformamide was dried with 4A molecular sieves and distilled, *p*-dioxane was dried over potassium hydroxide and distilled from sodium; benzene was dried over activated 4A molecular sieves.

5-(α-(*N*¹-Fluorouracilo)-4-sulfo-3-tolyl)-10,15,20-tris(*p*-sulfophenyl)porphyrin Tetrasodium Salt **1**.

Baker's [17] procedure for the preparation of a different isomer was used to convert α-bromo-*m*-toluonitrile by Stephen's reaction [18] to α-bromo-*m*-tolualdehyde. The product was recrystallized from petroleum ether (bp range 30-60°), yield 52%, mp 47-48°; pmr: δ 10 (s, 1H, CHO), 7.5-7.9 (m, 4H, Ph), 4.5 (s, 2H, $-CH_2-$), ir: λ C=O at 1700 cm^{-1}. The synthon α-(N'-5-fluorouracilo)-*m*-tolualdehyde, **3**, was then prepared by the addition of α-bromo-*m*-tolualdehyde (4 g, 20 mmoles) to a suspension of powdered 5-fluorouracil (2.7 g, 20 mmoles) and anhydrous potassium carbonate (1.4 g, 20 mmoles) in dimethylformamide (40 ml). The reaction mixture was vigorously stirred at 0° for 7 hours. The solvent (dimethylformamide) and water were removed by vacuum distillation at about 60°, 1-2 mm Hg, and the residue was extracted with boiling chloroform. The extract was filtered through a hot funnel and when cooled to room temperature, was placed in a refrigerator overnight. 1.18 g of white crystalline material was obtained, yield, 24%, mp 204-205°; uv (0.1 *M* hydrochloric acid): 255 nm; (0.1 *M* sodium hydroxide) 250 nm; pmr (acetone-d_6): δ 9.5 (s, 1H, CHO), 7.1-7.5 (m, 5H, Ph and 6-H of 5FU), 4.5 (s, 2H, CH_2); C-13 nmr (acetone-d_6): (see **3** in Scheme I for numbering system) C-2, 150.3; C-4, 157.7; J-CF, 26.9; C-5, 140.9; J-CF, 251.7; C-6, 129.8; J-CF, 33.9; C7, 51.6; C-14, 193; C-9,11,12,13, 129.2, 129.6, 130.2, 134.4; ms: m^-/e 129.00 (100), $5FU^-$, 247.04 (65.8), $(M-H)^-$; m^+/e 129.66 (3.6), 5FU, 249.09 (3.5), (M + H), 119.03 (20.4), $(M-5FU)^+$, 293.00 (49.6), $(M+2Na-H)^+$. To obtain the insoluble immediate precursor 5-(α-(*N*¹-5-fluorouracilo)-3-tolyl]-10,15,20-triphenyl)porphyrin (mono-5FU-TPP), **4**, benzaldehyde (2.46 g, 23 mmoles) and α-(*N*¹-5-fluorouracilo)-*m*-tolualdehyde (1.16 g, 4.6 mmoles) were dissolved in 37 ml of propionic acid. The mixture was heated to 125° (oil bath temperature), and 1.85 g of pyrrole (27.6 mmoles) was added as rapidly as possible without causing excess evolution of heat. The resulting dark brown solution was heated at this temperature for 25 minutes, then quickly cooled to 20° and allowed to stand overnight. The reaction mixture was vacuum distilled nearly to dryness. The residue was washed with methanol-water (v/v 1:1) and pure methanol, then vacuum dried. About 5 g of black residue was obtained. This material was separated and purified chromatographically with silica gel columns three times, with a solution of chloroform-benzene (v/v 3:1) as eluant. The product (mono-5FU-TPP) was detected with a tlc plate and had an Rf value 0.5 (developed by chloroform-methanol 95:5), 0.355 g of pure product was obtained, yield 10%. When the reaction mixture had a molar ratio of 3:1:4 for benzaldehyde:α-(*N*¹-5-fluorouracilo)-*m*-tolualdehyde:-pyrrole, the yield of mono-5FU-TPP was about 5%. Under these conditions some of the *trans*-di-5FU-TPP(5,15-bis[α-(*N*¹-5-fluorouracilo)-3-tolyl]-10,20-diphenylporphyrin) and *cis*-di-5FU-TPP(5,10-bis[α-(*N*¹-5-fluorouracilo)-3-tolyl]-15,20-diphenylporphyrin) were also collected. Mono-5FU-

TPP, visible spectra: 648, 588, 548, 514, 480, 418 nm; pmr: δ 8.8-8.9 (s, d, 8H, β-pyrrole), 8.2-8.3 (m, 8H, *o*-Ph), 7.7-7.9 (m, 12H, *m*-Ph, *p*-Ph, 6-H of 5FU), 5.1 (s, 2H, $-CH_2-$); ms: m^-/e 129.01 (100), $5FU^-$, 756.56 (2.0) $(M-H)^-$; m^+/e: 628.26 (22), (M-5FU), 757.30 (100), M^+, 1513.16 (0.77), $2M^+$; Di-5FU-TPP; ms: m^-/e 128.59 (100), $5FU^-$; m^+/e 757.04 (100) mono-5FU-TPP$^+$, 899.15 (48.9), di-5FU-TPP$^+$, 1042.04 (8.1), tri-5FU-TPP$^+$. Purified **4** was then used in the sulfonation reaction. A 230 mg sample of mono-5FU-TPP was mixed with 5 ml of concentrated sulfuric acid, the mixture was heated on a steam bath for 12 hours, and then was allowed to stand at room temperature for 24 hours. The dark green reaction mixture was carefully diluted to 100 ml with water. 7.0 g of Calcium oxide was added slowly with stirring until the solution changed to a permanent dark purple color. Calcium sulfate was filtered off and washed with a minimum quantity of hot water until the calcium sulfate cake became nearly white. The filtrate and washings were combined and concentrated to about 10 ml on a steam bath. Enough sodium carbonate solution was added to the hot solution to completely precipitate the calcium carbonate, which was removed by filtration and washed with water. The combined filtrate and washings were concentrated again. Small quantities of 90% ethanol were periodically added to the filtrate, which was further concentrated on a steam bath. The saturated solution was cooled to room temperature and the product was crystallized, with cooling, and with coprecipitation of a considerable amount of calcium carbonate and sodium carbonate. It was filtered and dried, then loaded on 4 g of dry silica gel. The loaded silica gel was placed on the top of 8 g of silica gel in a column of 10/100 mm and eluted with methanol. About 50 ml of eluant was collected, which contained a component of Rf 0.9 (developed by methanol). After concentration and the addition of small amounts of ether, the product precipitated. It was recrystallized from water and acetone, and dried at 80° for one hour. The water content in this compound was determined by heating it under vacuum at 140° to constant weight. The product was found to contain 12 water molecules. 160 mg of this pure porphyrin was obtained, yield 38%.

Visible spectra (methanol): 414, 514(I), 550(II), 592(III), 646(IV) nm (relative intensity I > II > III > IV) (For comparison, $TPPS_4$ in methanol: 410, 514, 548, 590, 656 nm). The uv spectrum shows a peak at 286 nm for the 5FU group. The ir spectra show four strong bands at 1230, 1200, 1120 and 1040 cm^{-1} due to sulfonic acid (salt) [19,20] absorptions in addition to 1680, 1600, 1560-1530 cm^{-1} (uracil) [14] vibrations.

Anal. Calcd. for $C_{49}H_{29}N_6FO_{14}S_4Na_4 \cdot 12H_2O$: N, 6.08; S, 9.28. Found: N, 6.07; S, 9.48.

5-(3-*N*-[Dichloro-(2-aminoethylamino)platinum(II)]phenyl)-10,15,20-triphenylporphyrin **8**.

The common intermediate 5-[3-(2-aminoethylamino)phenyl]-10,15,20-triphenylporphyrin (mono-($NH_2CH_2CH_2NH$)-TPP), **7**, was prepared from the monoaminoporphyrin, **6**. A 1.3 g (1.8 mmoles) sample of **6** was dissolved in 12 ml of dimethylformamide, 0.176 g (0.86 mmole) of bromoethylamine hydrobromide was added, and the mixture was stirred at 145° for 1.5 hours, then at 150-155° for another 2 hours. The cooled reaction mixture was poured into 250 ml 3% potassium hydroxide aqueous solution and a brown precipitate resulted. After filtration, the precipitate was washed with 200 ml of 3% potassium hydroxide. The porphyrins were then dissolved in 150 ml of chloroform, washed with 3% potassium hydroxide, saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. This solution was vacuum evaporated to about 70 ml and loaded onto 30 g of silica gel, which was placed on the top of 70 g silica gel in a 45/100 mm column. The porphyrins were eluted from the column with a solvent consisting of benzene and ether at a volume ratio of four to one. The first band with Rf = 0.57 (developed by chloroform:methanol 95:5) was found to be unreacted mono-*m*-aminoTPP; the second band was an unidentified porphyrin. The third band was then eluted with about 700 ml of chloroform, ethanol and methanol in a volume ratio of 100:10:5, respectively. After removing the solvent and recrystallization from chloroform and methanol, 0.33 g of shining purple crystalline product was obtained, yield 55%; ir: 3300 cm^{-1} ($-NH_2$), 2290 cm^{-1}, 2850 cm^{-1} ($-CH_2CH_2-$); visible spectrum (chloroform): 648, 592, 553, 517, 484 nm; pmr: δ 8.8-8.9 (s, d, 8H, β-pyrrole), 8.2 (m, 6H, *o*-Ph), 7.7 (m, 9H, *m*-Ph, *p*-Ph), 7.3-7.7 (m, 3H, aminophenyl), 6.9 (d, 1H, aminophenyl), 3.2 and 3.3 (m, *ca.* 3H, ethylene), 1.7 (s, 2H, NH_2); C-13 nmr: 146 (pyrrole α), 132 (pyrrole β), 121 (porphine meso), 143 (phenyl 1), 135 (phenyl 2), 128 (phenyl 3), 129 (phenyl 4), 44 and 38 (ethylene).

To effect a conversion of **7** to **8**, 0.325 g of mono-($NH_2CH_2CH_2NH$)-TPP was dissolved in 25 ml of dioxane and 6 ml of aqueous solution which contained 41.5 mg of K_2PtCl_4 was added. The reaction mixture was heated to reflux at 100-110° in an oil bath for 2.5 hours. The cooled reaction mixture was filtered and the precipitate was washed with dioxane and ether until the washings became pale yellow. The filtrate and washings were combined and vacuum evaporated to near dryness. The residue obtained was washed with water and methanol and then vacuum dried. It was recrystallized from chloroform-methanol, 0.37 g of product was obtained, yield 80%. The Rf value of this complex on a silica gel tlc plate developed with a chloroform-methanol solution with a v/v ratio of 95:5 is nearly zero. Visible spectrum: 646, 589, 548, 480 nm; C-13 nmr: δ 146 (pyrrole α), 132 (pyrrole β), 121 (porphine meso), 142 (phenyl 1), 135 (phenyl 2), 127 (phenyl 3), 128 (phenyl 4), 44-46 (ethylene).

Anal. Calcd. for $C_{46}H_{36}Cl_2N_6Pt$ (FW 938): C, 58.85; H, 3.84; N, 8.96; Pt, 20.78. Found: C, 58.62; H, 4.00; N, 8.75; Pt, 20.09.

5-(3-*N*-[Dichloro-(2-aminoethylamino)platinum(II)]-4-sulfophenyl)-10,15,20-tris-(4-sulfophenyl)porphyrin Tetrasodium Salt **2**.

Compound **8** was sulfonated using the 5FU-$TTPS_4$ procedure except that the eluant methanol-water solution ratio was changed to 3:1 to purify the crude product on a silica gel column. The yield of 5-[3-(2-aminoethylamino)-4-sulfophenyl]-10,15,20-tris(4-sulfophenyl)porphyrin tetrasodium salt (mono-($NH_2CH_2CH_2NH$)-$TPPS_4$), **9**, was 50%. Similarly **9** was characterized as its palladium(II) complex, **10**. A 60 mg (0.056 mmole) sample of mono-($NH_2CH_2CH_2NH$)-$TPPS_4$ was mixed with 21.3 mg (0.056 mmole) of Na_2PtCl_4 and 3.5 ml of water. The reaction mixture was heated to 90° for 0.5 hour, the *p*H of the solution was adjusted to 7.0 with sodium carbonate solution and then heated for another 2 hours. The reaction mixture was allowed to stand at room temperature for 16 hours, 25 ml of acetone was added, and 52 mg of product was precipitated. The product was loaded on 2 g of silica gel which was put on the top of 5 g of silica gel in a small column. Methanol was used as eluant. The first 50 ml of eluant contained the desired product. The methaol eluant was concentrated and a small of ether was added. The precipitate was filtered and washed with ether, dried at 60° for 1 hour and 39.0 mg of purple colored product was obtained, yield 35%. This product was then heated under vacuum (2 mm Hg) at 150° until constant weight was achieved. The product contained 12 molecules of water per molecule of porphyrin. This product was purified by recrystallization from acetone-water several times; visible spectrum (in water): 412, 517, 555, 587 and 645 nm.

Anal. Calcd. for $C_{46}H_{32}Cl_2N_6Na_4O_{12}S_4Pt \cdot 12H_2O$: C, 35.32; H, 3.61; N, 5.37. Found: C, 34.97; H, 3.30; N, 4.88.

5-(3-*N*-[Dichloro-(2-aminoethylamino)palladium(II)]-4-sulfophenyl)-10,15,20-tris(4-sulfophenyl)porphyrinato-palladium(II) Tetrasodium Salt **10**.

The palladium(II) complex Na_2PdCl_4 (0.20 mmole, 58.8 mg) was mixed with 108 mg (0.10 mmole) of mono-($NH_2CH_2CH_2NH$)-$TPPS_4$ and 8 ml of water. Anhydrous sodium carbonate was added to adjust the *p*H of the solution to **7**, then heated at 100° for 24 hours. To the clear filtrate ten times the volume of acetone was added to precipitate the product, which was recrystallized from acetone-water, filtered and washed with acetone and ether, and dried at 80° for 1 hour. A 55.2 mg sample of product was obtained, yield 35%. This product was heated under vacuum (2 mm Hg) at 140° to constant weight. It has an empirical formula $C_{46}H_{30}N_6O_{12}S_4Cl_2Pd_2 \cdot 4H_2O$ with 4 water molecules; visible spectrum: 527 nm.

Anal. Calcd. for $C_{46}H_{30}N_6O_{12}S_4Cl_2Na_4Pd_2 \cdot 4H_2O$: N, 5.86; S, 8.94; Pd, 14.84. Found: N, 5.52; S, 9.09; Pd, 14.61. Atomic ratio of N:S:Pd = 6:4:2.

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