Synthesis of Tetraphenylporphyrin Molecules containing Heteroatoms other than Nitrogen. Part 4.† Symmetrically and Unsymmetrically Substituted Tetraphenyl-21,23-dithiaporphyrins

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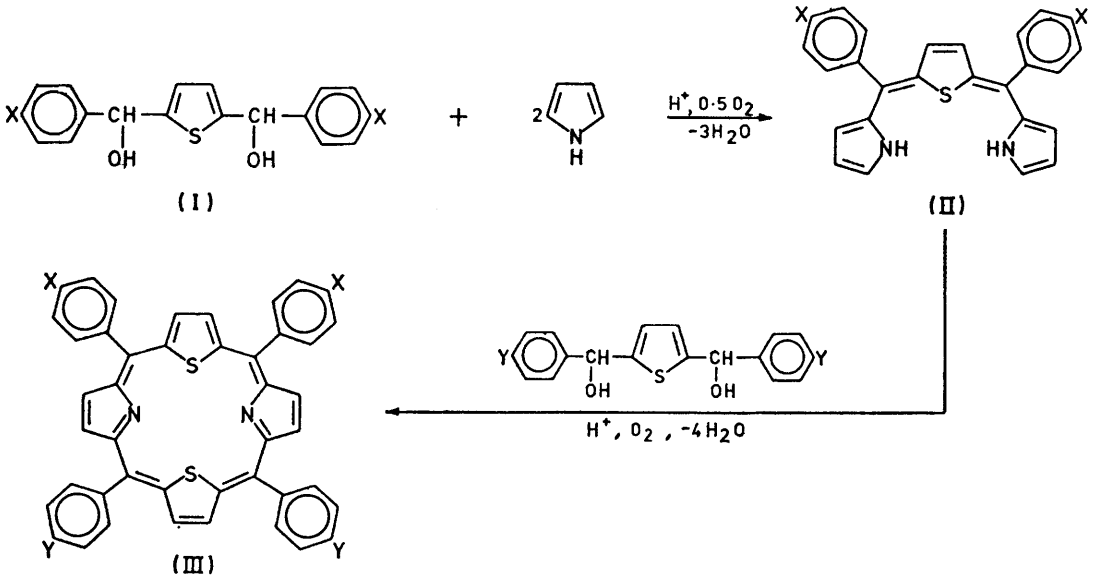
The synthesis of symmetrically as well as unsymmetrically substituted tetraphenyl-21,23-dithiaporphyrins (S_2TPP) is described. The reaction of 2,5-dilithiothiophen with substituted benzaldehydes is used for the preparation of substituted 2,5-bis(phenylhydroxymethyl)thiophens. Symmetrically substituted S_2TPP molecules result from reaction of these dialcohols with equimolar quantities of pyrrole. Unsymmetrically substituted S_2TPP molecules are obtained by first reacting one diol with an excess of pyrrole and subsequently reacting the intermediate obtained with another diol. The compounds prepared are the tetrakis-(*p*-methoxyphenyl)-, tetrakis-(*p*-chlorophenyl)-, tetrakis-(*p*-fluorophenyl), α,β-bis-(*p*-methoxyphenyl)-γ,δ-diphenyl-, α,β-bis-(*p*-fluorophenyl)-γ.δ,diphenyl-, α,β-bis-(*p*-chlorophenyl)-γ,δ-bis-(*p*-methoxyphenyl)-, and α,β-bis-(*p*-fluorophenyl)-γ,δ-bis-(*p*-methoxyphenyl)-porphyrins. The optical and ^{1}H n.m.r. (270 MHz) spectra of these porphyrins are presented.

THE synthesis of symmetrically substituted tetraphenylporphhrins (TPP) has been achieved by the almost classical procedure of Rothemund [1,2] and Adler and his co-workers.[3] Syntheses of unsymmetrically substituted TPP molecules were reported by Little *et al.*[4] In this work a mixture of aldehydes was reacted with pyrrole in propionic acid to give a mixture of three porphyrins which was then separated by chromatography. All the porphyrins prepared in this way contained three *p*-tolyl groups and one different substituted phenyl. This approach was not found suitable for the synthesis of various types of unsymmetrically substituted tetraphenylporphyrins.



A stepwise synthesis of unsymmetrical porphyrins is described by Harris *et al.* for mesoporphyrins, rhodoporphyrins, and γ-phyloporphyrins,[5] but no synthesis has yet been suggested for unsymmetrically substituted TPP molecules. This is rather important because of the thermal stability of TPP and because it is being widely used as a model for catalytic and biological systems.

The great advantage of using these molecules as catalysts and as biological models is that their structure can be modified in a controlled way and that correlations between various physical properties and structure can be obtained. This appeared to be very important in the case of tetraphenyl-21,23-dithiaporphyrin (S_2TPP) in connection with its redox potential ‡ as well as its n.m.r. spectrum.[6]

The TPP molecule is known to be a good model system for the study of substituent effects transmitted *via* the π-system [7] and it was found that systematic substitution of TPP and the investigation of its redox properties, n.m.r. spectra, *etc.*, gives important information which leads to a better understanding of its structure.

Here we report on the general procedure for preparing symmetrically as well as unsymmetrically substituted dithiaporphyrins.

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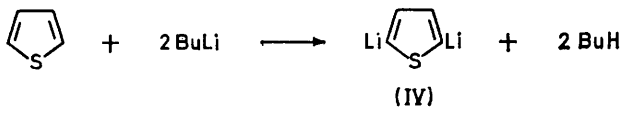
† Part 3, A. Ulmann, J. Manassen, F. Frolow, and D. Rabinovich, *Tetrahedron Letters*, 1978, 1885.

‡ $\Delta E_{\frac{1}{2}}$ in V *versus* saturated calomel electrode: first oxidation potential at +1.18, first reduction potential at −0.94 v.

The Synthesis.—It was clear from the beginning of this investigation that the stepwise synthesis used for unsymmetrically heterosubstitution, *i.e.* tetraphenyl-21-selena-23-thiaporphyrin [8] and tetraphenyl-21-tellura-23-thiaporphyrin [9] should, in principle, be the strategy for the synthesis of unsymmetrically substituted S_2TPP.

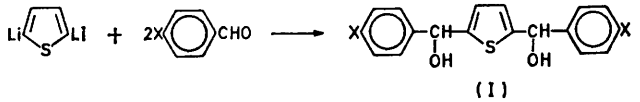
The problem was then reduced to the preparation of the dialcohol (I). Recently Chadwick and Willbe [10]



(IV)

Conditions: hexane–tetramethylethylenediamine; reflux for 0.5 h under argon

published the conditions for a high yield synthesis of 2,5-dilithiothiophen (IV). This dilithiothiophen was carboxylated and after esterification dimethyl thiophen-2,5-dicarboxylate was isolated. The advantage of the dilithiothiophen for our purpose is clear because it can give the various substituted 2,5-bis(phenylhydroxy-



(I)

Conditions: THF at 0—10 °C, then treatment with H^+

methyl)thiophens (I) with various substituted benzaldehydes.

The reaction of (I) with an equivalent amount of pyrrole gives the symmetrically substituted S_2TPP (III; X = Y). All the compounds were purified by chromatography on basic alumina columns. High resolution mass spectrometry was used to determine the molecular weights and formulae.

Optical Spectra.—The Table gives the optical spectra of the substituted S_2TPP molecules. For comparison the spectrum of S_2TPP itself is also included. We observe in the Table several effects due to the introduction of *para*-substituents in two or four phenyl rings in S_2TPP. (a) The absorption frequency of the Soret band shows small bathochromic shifts when strong electron donor substituents are present. (b) The absorption frequencies of the Q bands show roughly the same trend. (c) The extinction coefficients change much more than the absorption frequencies when *para*-substitution is concerned but only Q_I and Q_{III} show a gradual change with the donor–acceptor properties of the substituents. A detailed discussion of electron spectra of porphyrins in general and these effects in particular will be reported separately.

^1H *N.m.r. Spectra.*—The n.m.r. spectra of the new substituted S_2TPP molecules were measured in $CDCl_3$ and clearly indicate the structure of the compounds. Thus in the case of symmetrically substituted S_2TPP

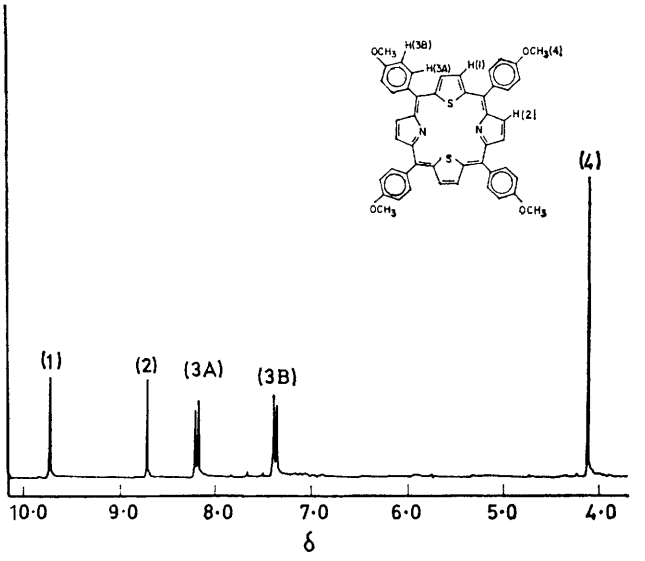


FIGURE 1 270 MHz ^1H N.m.r. spectrum of tetrakis-(*p*-methoxyphenyl)-21,23-dithiaporphyrin ($CHCl_3$ excluded)

(Figure 1) a single sharp peak is obtained for four β-pyrrole protons and another single sharp peak for the four β-thiophen protons. The four phenyl protons appear, as expected, as an AB system. In the unsymmetrically substituted S_2TPP there are two cases, the first is disubstituted S_2TPP (Figure 2) in which two sharp singlets are obtained for four β-thiophen protons and an AB system for the four β-pyrrole protons. The two kinds of phenyl rings are sharply distinguished; thus while for the substituted phenyl the usual AB system is obtained, for the unsubstituted one the four *ortho*-protons appear as one multiplet and the *meta*- and *para*-protons appear as another. The second case is that of unsymmetrically substituted S_2TPP (Figure 3) in which the four thiophen protons appear as two sharp singlets and the four β-pyrrole protons as an AB system as before, but in this case in both phenyls the protons

Optical spectra of different substituted S_2TPP molecules

	$\lambda_{max.}$/nm (ε)				
		Q bands			
	Soret band	IV	III	II	I
S_2TPP [6]	435 (297500)	515 (29625)	548 (7250)	635 (2200)	699 (3900)
$(CH_3O)_2S_2TPP$	438 (264390)	516 (23430)	552 (8900)	635 (1715)	700 (4930)
$(CH_3O_4S_2TPP$	441 (268870)	519 (21950)	555 (11790)	638 (1595)	704 (5800)
$(CH_3O)_2F_2S_2TPP$	438 (290520)	517 (24600)	552 (10300)	635 (1950)	700 (5740)
$(CH_3O)_2Cl_2S_2TPP$	439 (279540)	517 (23645)	552 (10000)	634 (1840)	700 (5180)
F_2S_2TPP	435 (304070)	513 (30980)	547 (7290)	632 (2110)	696 (4750)
F_4S_2TPP	435 (285560)	513 (29240)	546 (7090)	632 (2100)	696 (4635)
Cl_4S_2TPP	436 (243320)	514 (23950)	548 (6760)	633 (1840)	696 (3550)

exhibit the AB system. In this specific case the two *ortho*-parts overlap and the two *meta*-parts appear separately.

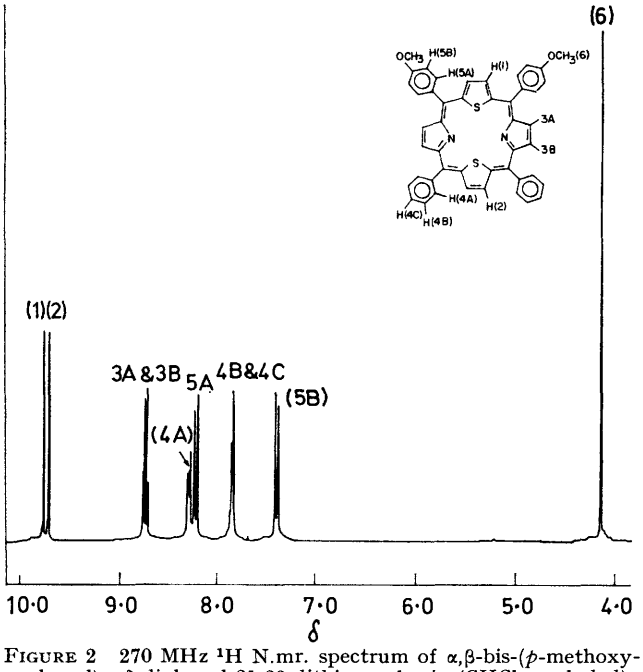


FIGURE 2 270 MHz ^{1}H N.mr. spectrum of α,β-bis-(*p*-methoxyphenyl)-γ,δ-diphenyl-21,23-dithiaporphyrin ($CHCl_3$ excluded)

EXPERIMENTAL

N.m.r. spectra were determined with a Bruker 270 MHz spectrometer using tetramethylsilane as internal reference. Optical spectra were determined with a Cary 14 spectrophotometer. Mass spectra were obtained by direct insertion into the ion source of a high resolution Varian MAT 731 mass spectrometer.

2,5-*Dilithiothiophen* (IV).—The apparatus was dried and flushed with dry argon before the introduction of reagents. During the reaction argon was bubbled through slowly to maintain a positive pressure. Dry and distilled hexane (400 ml) was added to a three-necked, round-bottomed flask equipped with a gas inlet tube, a reflux condenser, and a rubber septum. Tetramethylethylenediamine (29 g) and n-butyl-lithium (125 ml of *ca.* 2M solution in hexane) were injected into the stirred solution (magnetic stirring was used). Thiophen (8.5 g, 0.1 mol) was injected and the solution was refluxed gently for 1 h. After cooling to room temperature the condenser was replaced by a simple siphon apparatus.

General Procedure for the Preparation of Substituted 2,5-*Bis*(*phenylhydroxymethyl*)*thiophen* (I).—A substituted benzaldehyde (0.25 mol) was dissolved in THF (500 ml) which had been passed over a basic alumina (0.5 kg) column. The solution was cooled in an ice-bath and argon was bubbled through for 15 min. The 2,5-dilithiothiophen suspension was slowly transferred *via* a siphon (15 min; the argon pressure was used to control the rate of the addition). After the addition was completed the mixture was allowed to warm to room temperature. Ice-cold NH_4Cl solution (500 ml, *ca.* 1M) was added with stirring. The phases were separated and the water layer was extracted with ether (3 × 250 ml). The organic layers were combined, washed with water (3 × 500 ml) and saturated brine (500 ml), and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residual oil was crystallized.

2,5-*Bis*-(p-*methoxyphenylhydroxymethyl*)*thiophen*. Crystallization from toluene gave 16.7 g (47%), m.p. 154 °C, δ 7.09 (8 H, AB, J_{AB}, 8.5, Δν 41.89 Hz), 6.68 (2 H s), 5.90 (2 H, s), 3.79 (6 H, s), and 2.30 (2 H, s) (Found: C, 67.25; H, 5.6. $C_{20}H_{20}O_4S$ requires C, 67.4; H, 5.6%).

2,5-*Bis*-(p-*chlorophenylhydroxymethyl*)*thiophen*. Crystallization from CCl_4 gave 18.7 g (51%), 127—128 °C, δ 7.32 (4 H, s), 7.24 (4 H, s), 6.70 (2 H, s), 5.93 (2 H, s), 2.39 (1 H, s), 2.40 (1 H, s), 1.58 (1 H, s), and 1.57 (1 H, s) (Found: C, 59.1; H, 3.8. $C_{18}H_{14}Cl_2O_2S$ requires, C, 59.2; H, 3.85%).

2,5-*Bis*-(p-*fluorophenylhydroxymethyl*)*thiophen*. Crystallization from toluene–heptane gave 21.8 g (66%), m.p. 103—104 °C, δ 7.35 (4 H, m), 7.00 (4 H, t, $J_{HH} = J_{FH}$ = 8.50 Hz), 6.69 (2 H, s), and 5.94 (2 H, s) (Found: C, 64.95; H, 4.2. $C_{18}H_{14}F_2O_2S$ requires C, 65.05; H, 4.2%).

Preparation of Symmetrically Substituted S_2TPP.—Substituted 2,5-bis(phenylhydroxymethyl) thiophen (5×10^{-3} mol) and pure pyrrole (350 mg, 5.2×10^{-3} mol) were dissolved in propionic acid (500 ml) containing acetic anhydride (2% v/v). The mixture was refluxed for 1 h. After cooling, the solution was poured into a beaker (5 l) containing ice (*ca.* 1.5 l) and ammonia (600 ml of 25% solution). The product was then extracted with chloroform (2 × 250 ml), the chloroform layers were combined, washed with ammonia (2 × 250 ml of 5% solution) and water (250 ml), and dried ($MgSO_4$). The solvent was evaporated to *ca.* 25 ml, benzene (25 ml) was added, and the crude product was chromatographed on basic alumina, with chloroform–benzene 1 : 1) as eluant for F_4S_2TPP and Cl_4S_2TPP and chloroform–benzene (3 : 1) for $(CH_3O)_4S_2$TPP. Crystallization was performed in a desiccator containing pentane, from a concentrated chloroform solution.

(a) Tetrakis-(*p*-methoxyphenyl)-21,23-dithiaporphyrin. (157 mg, 8.2%) was obtained, δ 9.69 (4 H, s), 8.69 (4 H, s), 8.17 (8 H, J_{AB} 8.85 Hz), 7.36 (8 H, d, J_{AB} 8.85 Hz), and 4.11 (12 H, s), *m/e* 768 (M^+).

(b) Tetrakis-(*p*-chlorophenyl)-21,23-dithiaporphyrin (154 mg, 7.9%) was obtained, δ 9.67 (4 H, s), 8.67 (4 H, s),

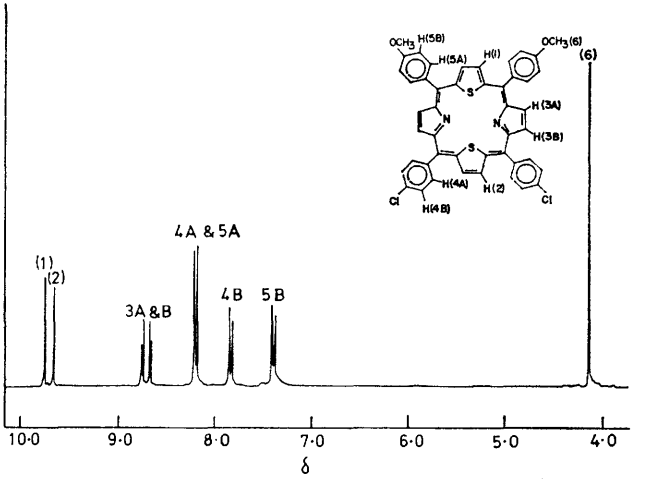


FIGURE 3 270 MHz ^{1}H N.m.r. spectrum of α,β-bis-(*p*-chlorophenyl)-γ,δ-bis-(*p*-methoxyphenyl)-21,23-dithiaporphyrin

8.17 (8 H, d, J_{AB} 8.4 Hz), and 7.82 (8 H, d, J_{AB} 8.4 Hz), *m/e* 784 (M^+ for ^{35}Cl).

(c) Tetrakis-(*p*-fluorophenyl)-21,23-dithiaporphyrin (144

mg, 8%) was obtained, δ 9.64 (4 H, s), 8.65 (4 H, s), 8.18 (8 H, q, ABX, J_{AB} 8.79, J_{AX} 5.27 Hz), and 7.51 (8 H, line coincident in the ABX system, $J_{AB} = J_{BX} = 8.79$ Hz), *m/e* 720 (M^+).

Preparation of Disubstituted S_2TPP.—2,5-*Bis*-(α-*phenylpyrrylmethylene*)*thiophen* (II, X = H). 2,5-Bis(phenylhydroxymethyl)thiophen [6] (1.48 g, 5×10^{-3} mol) and pyrrole (1 g) were refluxed (1 h) in dry benzene (500 ml) with added chloroacetic acid (2% w/w). Chromatography on a dry, acid-washed alumina column (750 g) with benzene as eluant gave a pale yellow solution. Evaporation gave the product 1.76 g, 90%, *m/e* 392 (M^+).

α,β-*Bis*-(p-*methoxyphenyl*)-γ,δ-*diphenyl*-21,23-*dithiaporphyrin* (III; X = OCH_3, Y = H). 2,5-Bis-(α-phenylpyrrylmethylene)thiophen (1.76 g, 4.5×10^{-3} mol) and 2,5-bis-(*p*-methoxyphenylhydroxymethyl)thiophen (1.6 g, 4.5×10^{-3} mol) were refluxed (1 h) in propionic acid (500 ml) containing acetic anhydride (2% v/v). The mixture was worked up as described above. Chromatography on basic alumina with chloroform–benzene (3 : 1) as eluant, gave product (302 mg, 9.5%) after evaporation and crystallization, δ 9.71 (2 H, s), 9.65 (2 H, s), 8.68 (4 H, AB, J_{AB} 4.4, Δν 10.6 Hz), 8.24 (4 H, m), 8.17 (4 H, d, AB, J_{AB} 8.85 Hz), 7.80 (6 H, m), 7.35 (4 H, d, AB, J_{AB} 8.85 Hz), and 4.09 (6 H, s), *m/e* 708 (M^+).

α,β-*Bis*-(p-*fluorophenyl*)-γ,δ-*diphenyl*-21,23-*dithiaporphyrin* (III; X = F, Y = H). 2,5-Bis-(α-phenylpyrrylmethylene)thiophen (1.38 g, 3.5×10^{-3} mol) and 2,5-bis-(*p*-fluorophenylhydroxymethyl)thiophen (1.17 g, 3.5×10^{-3} mol) gave the porphyrin (230 mg, 9.7%) under the same conditions, δ 9.69 (2 H, s), 9.65 (2 H, s), 8.67 (4 H, AB, J_{AB} 4.78, Δν 12.50 Hz), 8.23 (8 H, m), 7.81 (6 H, m), and 7.52 (4 H, t, $J_{HH} = J_{FH} = 8.46$ Hz), *m/e* 684 (M^+).

Preparation of Unsymmetrically Substituted S_2TPP.—2,5-*Bis*-[α-(p-*methoxyphenyl*)*pyrrylmethylene*]*thiophen* (II; X = OCH_3). 2,5-Bis-(*p*-methoxyphenylhydroxymethyl)thiophen (1.78 g, 5×10^{-3} mol) was reacted with pyrrole by the previously described procedure giving the product (2.1 g, 92%) after chromatography, *m/e* 452 (M^+).

α,β-*Bis*-(p-*chlorophenyl*)-γ,δ-*bis*-(p-*methoxyphenyl*)-21,23-*dithiaporphyrin* (II; X = Cl, Y = OCH_3). 2,5-Bis-[α-(*p*-methoxyphenyl)pyrrylmethylene]thiophen (2.1 g, 4.65×10^{-3} mol) and 2,5-bis-(*p*-chlorophenylhydroxymethyl)-thiophen (1.7 g, 4.65×10^{-3} mol) gave the porphyrin (350 mg, 9.7%) under the above conditions, δ 9.73 (2 H, s), 9.63 (2 H, s), 8.68 (4 H, AB, J_{AB} 4.4, Δν 22.56 Hz), 8.17 (8 H, AB, J_{AB} 8.4 Hz), 7.80 (4 H, AB, J_{AB} 8.4 Hz), 7.36 (4 H, d, AB, J_{AB} 8.4 Hz), and 4.10 (6 H, s), *m/e* 776 (M^+ for ^{35}Cl).

α,β-*Bis*-(p-*fluorophenyl*)-γ,δ-*bis*-(p-*methoxyphenyl*)-21,23-*dithiaporphyrin* (III; X = F, Y = OCH_3). 2,5-Bis-[α-(*p*-methoxyphenyl)pyrrylmethylene]thiophen (1.94 g, 4.25×10^{-3} mol) and 2,5-bis-(*p*-fluorophenylhydroxymethyl)thiophen (1.41 g, 4.25×10^{-3} mol^{-1}) gave the porphyrin (300 mg, 2.5%), δ 9.72 (2 H, s), 9.62 (2 H, s), 8.67 (4 H, AB J_{AB} 4.78, Δν 20.1 Hz), 8.18 (8 H, m), 7.52 (4 H, t, $J_{HH} = J_{FH} = 8.82$ Hz), 7.36 (4 H, d, J 8.82 Hz), and 4.10 (6 H, s), *m/e* 744 (M^+).

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