Pyrroles and Related Compounds. Part XXX.[1] Cyclisation of Porphyrin β-Keto-esters to Phaeoporphyrins [2]

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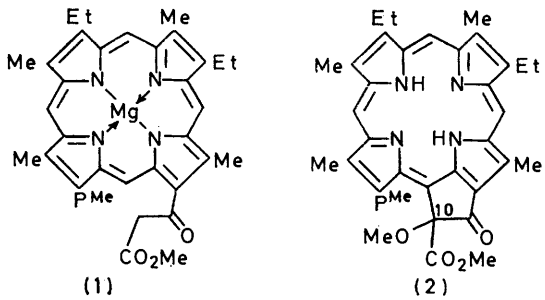
Porphyrin β-keto-esters are cyclised to the corresponding phaeoporphyrins in high yield by treatment of the former with 2 equiv. of thallium(III) trifluoroacetate, followed by photolysis and demetallation. In this way, the first formal total syntheses of phaeoporphyrin-a_5 dimethyl ester (6a) and 2-vinylphaeoporphyrin-a_5 dimethyl ester (6b) have been accomplished.

THE accompanying papers describe the results of a prolonged investigation into the synthesis and properties of pyrrole and porphyrin β-keto-esters. This paper describes what is in a way the chemical climax of this investigation,† incorporating the *in vitro* cyclisation of porphyrin β-keto-esters to give phaeoporphyrins.

In Part XXVIII [3] the cyclisation of a magnesium β-keto-ester (1) to give the phaeoporphyrin derivative (2), by use of sodium carbonate and iodine in methanol, was reported. We envisaged that the cyclisation proceeded by coupling between the magnesium porphyrin π-cation radical and the oxidised enolate side-chain; the additional 10-methoxy-group was an encumbrance which we sought to eliminate in our initial studies. To this end, we generated solutions of the enolate ion in dry benzene, by using the potassium hydroxide ' crown ' polyether complex [4] (3). Despite the use of a wide variety of oxidising agents, no phaeoporphyrin formation was observed spectrophotometrically; the magnesium β-keto-ester was either regenerated or else transformed into non-porphyrinic, highly polar, materials. In many cases, the oxidising agent was destroyed under the basic conditions of the reaction. A series of experiments was carried out with the specific one-electron oxidising agent tris-(*p*-bromophenyl)ammoniumyl hexachloroantimonate; [5] solutions of the magnesium keto-ester (1) and the correspondiug enolate ion were treated



P^{Me} = $CH_2 \cdot CH_2 \cdot CO_2Me$

with various proportions of this oxidant, but no cyclised products were detected.

A different approach led finally to the desired cyclisation; the high peripheral electron density in porphyrin chelates of electropositive metals led us to consider using electrophilic attack from a suitably modified β-keto-ester side-chain. We attempted to achieve this

† Biochemical feeding experiments, which are still in progress, will be reported elsewhere.

[1] Part XXIX, M. T. Cox, A. H. Jackson, G. W. Kenner, S. W. McCombie, and K. M. Smith, preceding paper.

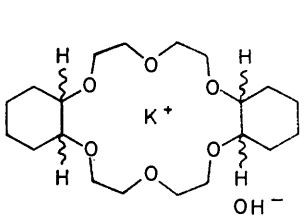
[2] Preliminary communication, G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Chem. Comm.*, 1972, 844.

[3] M. T. Cox, T. T. Howarth, A. H. Jackson, and G. W. Kenner, *J.C.S. Perkin I*, 1974, 512.

[4] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017.

[5] F. A. Bell, A. Ledwith, and D. C. Sherrington, *J. Chem. Soc.* (*C*), 1969, 2719.

by reaction of the latter with thallium(III) trifluoroacetate (TTFA), because McKillop and Taylor had



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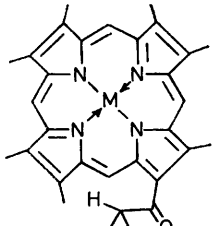
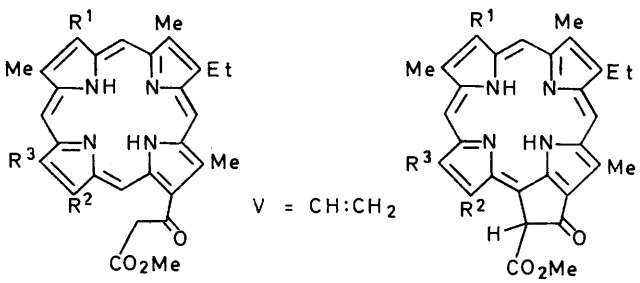


(4)

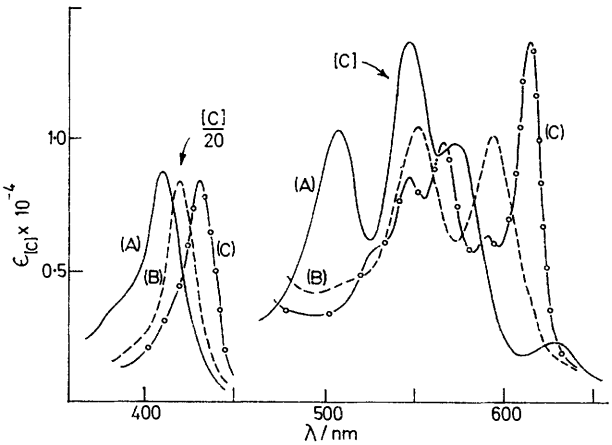
already suggested the occurrence of *C*-thallation of enolisable ketones in reactions involving thallium(III) nitrate (TTN).[6] A hypothetical intermediate for our system would be the species (4). In order to achieve the desired attack of the thallium(III) species on the side-chain, it was necessary to employ a metalloporphyrin with a relatively high oxidation potential because previous studies [7] had shown that magnesium and zinc porphyrins are rapidly attacked, by initial electron transfer, by TTFA. On the other hand, porphyrin chelates of ions such as Fe^{3+}, Ni^{2+}, Cu^{2+}, and Tl^{3+} were inert, because of the relatively high oxidation potentials of these compounds, towards attack by TTFA. The obvious choice * was the thallium(III) chelate, and treatment of the keto-ester (5a) in methylene chloride with 1 equiv. of TTFA in tetrahydrofuran gave material with a typical metalloporphyrin visible absorption spectrum, unchanged on exposure to light or heat. Addition of a further 1 equiv. of TTFA produced, in the dark, only broadening and small shifts in the visible spectrum; however, exposure of the solution to visible



(5) (6)

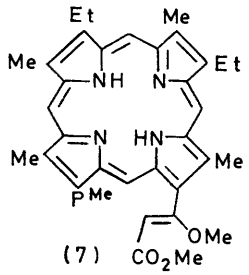
a; R^1 = Et, R^2 = P^{Me}, R^3 = Me
b; R^1 = V, R^2 = P^{Me}, R^3 = Me
c; R^1 = R^3 = Et, R^2 = Me
d; R^1 = $CH_2 \cdot CH(OMe)_2$, R^2 = P^{Me}, R^3 = Me

light (either sunlight or a quartz–iodine lamp) produced a dramatic spectral change (see Figure), with shift of the Soret band by *ca.* 12 nm to longer wavelength, and development of a complex four-banded spectrum having its major absorption at 613 nm. An essentially identical spectrum was obtained from authentic phaeoporphyrin-a_5 dimethyl ester (6a) after treatment with 1 equiv. of TTFA. Demetallation of the photoreaction product gave, after chromatography and crystallisation, a 69% yield of phaeoporphyrin-a_5 dimethyl ester (6a).† Similarly, treatment of the 2-vinyl-β-keto-ester (5b) with 2 equiv. of TTFA followed by irradiation and the usual work-up gave 2-vinylphaeoporphyrin-a_5 dimethyl ester (6b) † in 37% yield. The lower yield in the 2-vinyl series was presumably a consequence of attack by the



Visible absorption spectra of solutions in methylene chloride: (A) β-keto-ester (5a); (B) (5a) plus 2 equiv. of TTFA; (C) (5a) plus 2 equiv. of TTFA followed by irradiation [*i.e.* Tl^{III} chelate of (6a)]

reagent on the vinyl group (*cf.* ref. 8) as well as the tendency of vinylporphyrins to undergo photo-oxidative side-reactions.[9] The model β-keto-ester (5c) was also cyclised to the phaeoporphyrin (6c) in 57% yield.



(7)

TTN also served to cyclise the keto-ester (5a), the photoreaction being carried out in methylene chloride–methanol. When the 2-vinyl-keto-ester (5b) was irradiated with 3 equiv. of TTN in the same solvent mixture, the expected phaeoporphyrin acetal (6d) was obtained.

* The major consideration here was the ease with which the thallium atom could be removed, as compared with the alternative metal chelates mentioned.[7]

† By virtue of our earlier syntheses of the starting β-keto-esters,[1,3] this constitutes the first total syntheses of these important chlorophyll degradation products.

[6] *E.g.* A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1973, **95**, 3340.

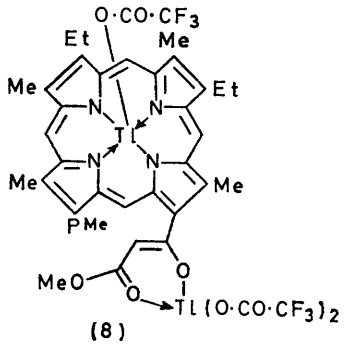
[7] K. M. Smith, *Chem. Comm.*, 1971, 540; S. W. McCombie and K. M. Smith, *Tetrahedron Letters*, 1972, 2463; G. H. Barnett, M. F. Hudson, S. W. McCombie, and K. M. Smith, *J.C.S. Perkin I*, 1973, 691.

[8] G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Chem. Comm.*, 1972, 1347; *Annalen*, 1973, 1329.

[9] *Cf.* H. H. Inhoffen, K. M. Bliesener, and H. Brockmann, jun., *Tetrahedron Letters*, 1966, 3779; *Annalen*, 1969, **730**, 173.

The side-chain modification was anticipated on the basis of our earlier work.[8]

Working with the diethyl β-keto-ester (5a), we studied this unusual photocyclisation in more detail. The observations of efficient cyclisation with filtered light (λ 546 nm) and a relatively small concentration dependence of the rate, demonstrated that rapid reaction of the thallium(III) keto-ester chelate with TTFA yields an intermediate which photocyclises by a process involving its absorption in the visible region. The *C*-thallation concept (*cf.* ref. 6) was disproved by use of the enol ether (7), obtained from (5a) by reaction with diazomethane at 0° during several days. Treatment of this porphyrin with 2 equiv. of TTFA gave a photostable metalloporphyrin, from which (7) could be regenerated by



(8)

cautious demetallation. From these observations we conclude that the photoreactive species is the cyclic chelate (8). No thermal cyclisation was observed up to the decomposition point (*ca.* 120°) of the complex dissolved in 1,2-dibromoethane, and hence we surmise that the increased electron density at the *meso*-carbon atom in the excited state is essential for carbon–carbon bond formation, with the favourable $Tl^{III} \longrightarrow Tl^{I}$ change providing the remainder of the driving force. Analogous behaviour was not apparent with lead tetra-acetate when it was caused to react with the thallium keto-ester; no phaeoporphyrin formation was observed either on heating or on irradiation. Lead tetra-acetate had previously been employed as a possible cyclisation agent for magnesium keto-esters, but in this case had given rise to extensive destruction of the macrocycle.

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. Neutral alumina (Merck) was used for all chromatographic separations, and reactions were followed by t.l.c. and spectrophotometry as described in earlier parts of this series. Electronic absorption spectra were determined (solutions in methylene chloride) with a Unicam SP 800 spectrophotometer, ^1H n.m.r. spectra (in deuteriochloroform with tetramethylsilane as internal standard) with a Varian HA-100 instrument, and mass spectra with either an A.E.I. MS 902 or an A.E.I. MS 12 spectrometer (at 50 μA and 70 eV; direct inlet with source temperature 200—220°).

[10] H. Fischer and A. Stern, 'Die Chemie des Pyrrols,' Akademische Verlag, Leipzig, vol. IIii, 1940, p. 171.

Phaeoporphyrin-a_5 *Dimethyl Ester* (6a).—(a) *From the* β*-keto-ester* (5a) *with TTFA.* 2,4-Diethyl-6-methoxycarbonylacetyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin [3] (61 mg, 0·1 mmol) in dry methylene chloride (20 ml) and dry tetrahydrofuran (20 ml) was treated with a solution of TTFA (110 mg, 0·2 mmol) in dry tetrahydrofuran (10 ml). After 2 min, the solution was left in sunlight until a sample examined spectrophotometrically showed the expected shift of the Soret absorption band (*ca.* 10 min). The solution was then treated briefly with sulphur dioxide gas and stirred during 1 min with conc. hydrochloric acid (0·5 ml) before being diluted with methylene chloride (50 ml) and washed with water (3 × 100 ml). The solution was evaporated and the residue was chromatographed on grade V alumina, the product being eluted as a grey-green band, leaving brownish by-products on the column. The *product* (41·5 mg, 69%) was obtained as fine purple needles (from methylene chloride–methanol), m.p. 271—273° (lit.,[10] 273°). A mixed m.p. determination with authentic material prepared by the modified method described in (c) (m.p. 269—272°) gave a value of 270—273° (Found: C, 71·1; H, 6·4; N, 9·1. Calc. for $C_{36}H_{38}N_4O_5$: C, 71·3; H, 6·3; N, 9·1%).

(b) *From the* β*-keto-ester* (5a) *with TTN.* The diethyl β-keto-ester (5a) (61 mg) in methylene chloride (40 ml) and methanol (5 ml) was treated with a solution of TTN trihydrate (97 mg, 2·2 equiv.) in methanol (10 ml). After 5 min, the solution was exposed to sunlight, after dilution with methylene chloride (50 ml). When the reaction was shown to be complete by spectrophotometry, the product was worked up as in (a), to give the phaeoporphyrin (33 mg, 55%), m.p. 270—272° (from methylene chloride–methanol), identical with the material from (a).

(c) *From methyl phaeophorbide-*a. Methyl phaephorbide-*a* [11] (600 mg) in dry tetrahydrofuran (300 ml) containing triethylamine (1 drop) and 10% palladised charcoal (300 mg) was hydrogenated until the blue-black colour had disappeared. The solution was filtered on Celite, which was washed with a little hot tetrahydrofuran, and the combined filtrates were treated with 2,3-dichloro-5,6-dicyanobenzoquinone (700 mg) in benzene (100 ml). After 5 min, the reddish purple solution was evaporated *in vacuo* and the residue was chromatographed on grade III alumina. Elution with methylene chloride gave the porphyrin (295 mg, 49%) as purple plates, m.p. 269—271° (lit.,[10] 273°) (from methylene chloride–methanol).

2-*Vinylphaeoporphyrin-*a_5 *Dimethyl Ester* (6b).—(a) *From the* β*-keto-ester* (5b) *with TTFA.* 4-Ethyl-6-methoxycarbonylacetyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-2-vinylporphin [1] (121 mg) in dry methylene chloride (50 ml) and dry tetrahydrofuran (30 ml) was treated with a solution of TTFA (222 mg, 2·05 equiv.) in dry tetrahydrofuran (10 ml). The solution was purged with nitrogen in diffuse light during 10 min and then irradiated under nitrogen with a tungsten lamp. After 10 min (when the reaction was shown to be complete by spectrophotometry) the product was worked-up with sulphur dioxide and concentrated hydrochloric acid as before, and chromatographed on grade V alumina. Elution with methylene chloride and crystallisation from methylene chloride–n-hexane gave tiny purple needles (44 mg, 37%), m.p. 288—290° (lit.,[12] 288—292°), mixed m.p. with authentic material (m.p. 287—289°),

[11] G. W. Kenner, S. W. McCombie, and K. M. Smith, *J.C.S. Perkin I*, 1973, 2517.

[12] Ref. 10, p. 230.

286—289° (Found: C, 71·2; H, 6·0; N, 9·0. Calc. for $C_{36}H_{36}N_4O_5$: C, 71·5; H, 6·0; N, 9·3%).

(b) *From methyl phaeophorbide*-a. Methyl phaeophorbide-*a* [11] (500 mg) was heated under reflux (nitrogen atmosphere) in dry acetone (50 ml) during the dropwise addition of 2,3-dichloro-4,5-dicyanobenzoquinone (500 mg) in dry benzene (50 ml) over 30 min. The mixture was refluxed during a further 30 min, then evaporated to dryness, and the residue was chromatographed on grade V alumina (100 g in a short wide column) with methylene chloride as eluant; polar by-products were thus removed. The eluates were evaporated and the residue was stirred during 30 min with hexane (20 ml) and ether (100 ml). The porphyrin was filtered off and recrystallised from methylene chloride–methanol, giving purple needles (140 mg, 28%), m.p. 287—289° (lit.,[12] 288—292°).

2,4,8-*Triethyl*-6,γ-(2-*methoxycarbonyl*-1-*oxoethano*)-1,3,5,7-*tetramethylporphin* (6c).—2,4,8-Triethyl-6-methoxycarbonylacetyl-1,3,5,8-tetramethylporphin [1] (46 mg) in dry methylene chloride (60 ml) was treated with TTFA (94 mg, 2·05 equiv.) in dry tetrahydrofuran (15 ml). The solution was irradiated with a quartz–iodine lamp until spectrophotometry showed cyclisation to be complete (10—15 min). The demetallation and work-up procedures were as used in the foregoing phaeoporphyrin cyclisations, and the crude product was chromatographed on grade III alumina (elution with methylene chloride containing 2% acetone). A single deep green band was obtained, giving a purple-green eluate which was evaporated; the residue was crystallised from methylene chloride–methanol to give the *phaeoporphyrin* (26 mg, 57%) as purple needles, m.p. >300° (Found: C, 74·0; H, 6·5; N, 9·95. $C_{34}H_{36}N_4O_3$ requires C, 74·4; H, 6·6; N, 10·2%), τ ($CF_3{\cdot}CO_2H$) −1·16, −0·98, and −0·92 (3 *meso*-H), 2·46 (C*H*·CO_2Me), 5·96 and 5·98 (5-Me and OMe), 6·22, 6·25, and 6·33 (1-, 3-, and 7-Me), and 8·11 (t), 8·15 (t), 8·18 (t), and 5·65 (m) (3Et), $\lambda_{max.}$ 419 (ε 180,000), 524 (7300), 567·5 (16,300), 586·5 (12,700), and 635 nm (1900), $\lambda_{max.}$ (CH_2Cl_2–trace $CF_3{\cdot}CO_2H$) 418 (ε 210,000), 559 (11,400), and 592 nm (10,400), $\lambda_{max.}$ [CH_2Cl_2–CF_3CO_2H (1 : 1)] 416 (320,000), 525sh (2800), 549sh (7200), 567 (10,500), 601 (5200), and 618 nm (6600).

2-*De-ethyl*-2-(2,2-*dimethoxyethyl*)*phaeoporphyrin*-a_5 *Dimethyl Ester* (6d).—4-Ethyl-6-methoxycarbonylacetyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethyl-2-vinylporphin [1] (61 mg) in methylene chloride (90 ml) and dry methanol (10 ml) was treated with a solution of TTN (140 mg, 3·1 equiv.) in dry methanol (10 ml). After 5 min in the dark, the solution was irradiated under nitrogen with a quartz–iodine lamp during 15 min (followed spectrophotometrically). The solution was treated briefly with sulphur dioxide gas, and then very briefly with hydrogen chloride gas before being washed with water (3 × 100 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on grade V alumina (elution with methylene chloride); this gave a single green band. The *acetalphaeoporphyrin* was obtained as fine purple plates (36 mg, 53%), m.p. 256—257° (from methylene chloride–methanol) (Found: C, 68·4; H, 6·2; N, 8·65. $C_{38}H_{42}N_4O_7$ requires C, 68·45; H, 6·35; N, 8·4%), τ (0·05M), 0·13, 0·25, and 0·40 (3 *meso*-H), 3·25 (C*H*·CO_2Me), 5·97 (d), 5·03 (t), and 6·60 (s) [$CH_2{\cdot}CH(OMe)_2$], *ca.* 6·1 (m), 7·14 (t), and 6·29 (s) ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), *ca.* 6·1 (m) and 8·22 (t) (Et), 6·24 and 6·26 (CO_2Me and 5-Me), and 6·56 and 6·67 (6H) (1-, 3-, and 8-Me), $\lambda_{max.}$ 420 nm (ε 189,000), 524 (8000), 567 (15,700), 587 (14,200), and 635·5 (1800), $\lambda_{max.}$ (CH_2Cl_2–trace $CF_3{\cdot}CO_2H$), 418 (203,000), 552 (12,700), and 593 nm (11,800), $\lambda_{max.}$ (CH_2Cl_2–5% $CF_3{\cdot}CO_2H$) 420 (245,000), 560infl (9800), 518·5 (12,700), 603 (5800), and 619 nm (6200).

2,4-*Diethyl*-6-(1-*methoxy*-2-*methoxycarbonylvinyl*)-7-(2-*methoxycarbonylethyl*)-1,3,5,8-*tetramethylporphin* (7).—2,4-Diethyl-6-methoxycarbonylacetyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin [3] (54 mg) in methylene chloride (40 ml) was treated with a solution of diazomethane [prepared from 'diazald' (4 g)] in ether (20 ml) at 0° during 3 days. The solution was evaporated and the residue was chromatographed on grade III alumina (elution with methylene chloride). A single major band was eluted (leaving a polar minor band on the column); evaporation and crystallisation of the residue from methylene chloride–methanol gave the *enol ether* (45 mg, 80%) as fluffy red needles, m.p. 206—208° (Found: C, 71·1; H, 6·7; N, 9·0. $C_{37}H_{42}N_4O_5$ requires C, 71·4; H, 6·8; N, 9·0%), τ (0·03M) −0·13, −0·05, and 0·00 (2H) (4 *meso*-H), 4·19 (:C*H*·), 5·60 (t), 6·76 (t) and 6·36 (s) ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), 5·87 (q), 5·95 (q), 8·16 (t), and 8·18 (t) (2Et), 6·09 and 6·12 (CO_2Me and OMe), and 6·31, 6·36, 6·37, and 6·51 (1-, 3-, 5-, and 8-Me), $\lambda_{max.}$ 403 (ε 184,000), 502 (10,700), 538 (12,100), 568 (5900), and 624 nm (1500), $\lambda_{max.}$ (CH_2Cl_2–$CF_3{\cdot}CO_2H$) 409 (257,000), 550·5 (14,300), and 598 nm (5600), *m/e* 622 (M^+).

6-(1-*Acetoxy*-2-*methoxycarbonylvinyl*)-2,4-*diethyl*-7-(2-*methoxycarbonylethyl*-1,3,5,8-*tetramethylporphin* [*Enol Acetate of* (5a)].—2,4-Diethyl-6-methoxycarbonylacetyl-7-(2-methoxycarbonylethyl)-1,3,5,8-tetramethylporphin [3] (58 mg) in dry pyridine (2·5 ml) and acetic anhydride (1·0 ml) was heated at 100° during 30 min. The solution was cooled, diluted with methylene chloride and methanol, and set aside during 30 min. It was then washed with water (2 × 100 ml), dried (Na_2SO_4), and evaporated, and the residue was chromatographed on grade V alumina (elution with methylene chloride). The eluates were evaporated and the residue was crystallised from methylene chloride–n-hexane to give the *enol acetates* (54 mg, 82%) as red prisms. On the hot-stage apparatus, needles formed at 170—175° and complete melting was observed between 220 and 228°. The isomers (*ca.* 7 : 1 ratio by n.m.r.) could be separated on a small scale by t.l.c. but not by column chromatography. The n.m.r. spectrum (major isomer) showed τ −0·27, −0·09, and 0·03 (2H) (4 *meso*-H), 6·07, 3·44 (1H), and 7·54 ($MeO_2C{\cdot}CH{:}C{\cdot}O{\cdot}COMe$), 5·62 (t), 6·74 (t), and 6·38 (s) ($CH_2{\cdot}CH_2{\cdot}CO_2Me$), 6·1 (m), 8·19 (t), and 8·21 (t) (2Et) and 6·27, 6·42, 6·44, and 6·55 (1-, 3-, 5-, and 8-Me). The signals of the minor component were lost in background noise, except for τ 4·78 (C*H*·CO_2Me) and 7·83 (O·CO*Me*) (Found: C, 69·9; H, 6·6; N, 8·4. $C_{38}H_{42}N_4O_6$ requires C, 70·1; H, 6·5; N, 8·6%), $\lambda_{max.}$ 402 (ε 197,000), 503 (9600), 542 (16,400), 571 (7800), and 629 nm (1300), $\lambda_{max.}$ (CH_2Cl_2–$CF_3{\cdot}CO_2H$) 410 (278,000), 552 (15,400), and 601 nm (8500), *m/e* 650 (100%), 577 (58), 504 (20), and 325 (5).

[3/1972 *Received*, 25*th September*, 1973]