Octaethyl-21*H*,24*H*-bilin-1,19-dione (Octaethylbilatriene-*abc*)

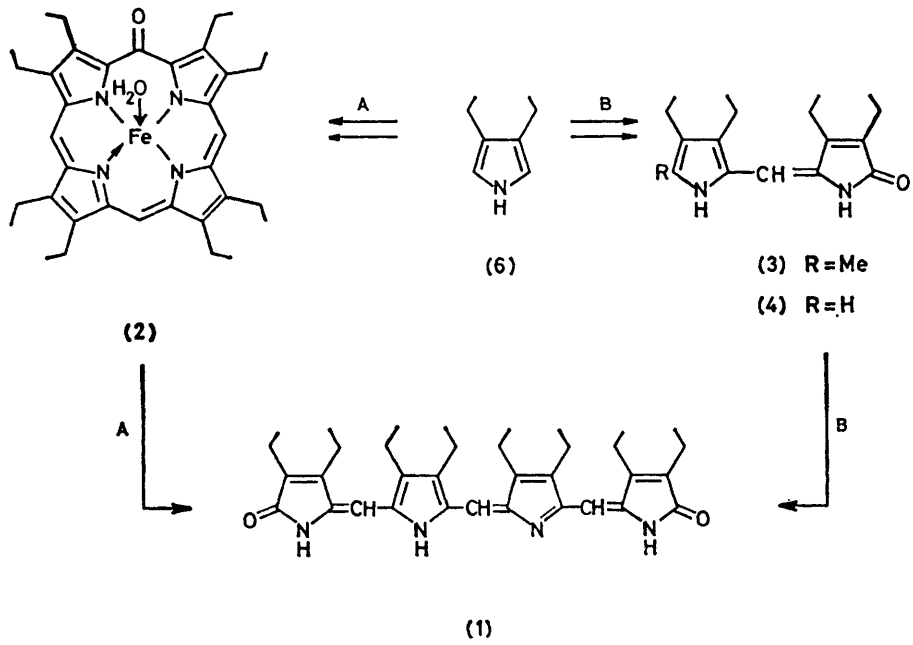
By **Raymond Bonnett,* Dennis G. Buckley,** and **Dariush Hamzetash,** Department of Chemistry, Queen Mary College, Mile End Road, London E1 4NS

A synthesis of the octaethylbilindione (1) from 3,4-diethylpyrrole is described which is suitable for the preparation of this valuable model compound in quantity.

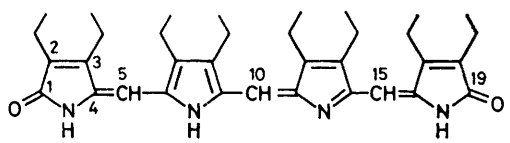
THE natural bilindiones (otherwise known as bilatrienes-*abc* and as verdins) have important biological roles. Thus biliverdin is an intermediate in haem catabolism, while biliproteins function as accessory photosynthetic pigments (*e.g.* phycocyanin, phycoerythrin) and as receptors involved in photomorphogenesis (phytochrome). Although the chemistry of the natural compounds has been explored to some degree, interpretation has often been complicated by the unsymmetrical nature of the β-substitution pattern.

We believe that the chemistry of this series would become clearer and more extensive if appropriate model compounds were available for study. Some years ago a similar approach to the porphyrin series led, for a variety of reasons, to the selection of octaethylporphyrin as the most satisfactory model.[1] This has, in turn, caused us to favour octaethylbilindione (1)† as the model of choice in the linear tetrapyrrole series.

Octaethylbilindione has been prepared by routes in which iron porphyrins are oxidatively cleaved. In practice iron(III) octaethyloxophlorin (2) or di(pyridine)-iron(II) octaethylporphyrin are the precursors.[4] While these biomimetic routes (Scheme 1, pathway A) are important as models for haem catabolism, they are difficult to control on a preparative scale, and yields tend to be low and variable. As a preparation this approach is inelegant and expensive. The same objection applies to the oxidative cleavage of octaethylchlorin or its zinc complex with thallium(III) trifluoroacetate, followed by dehydrogenation,[5] although here it must be recognised that the first-formed product, the 2,3-dihydrobilindione,



SCHEME 1 Alternative approaches to octaethylbilindione; A = biomimetic route;[4] B = pyrromethenone route



(1) Octaethylbilindione †

has value as a model for the bilin moiety of phytochrome.[6]

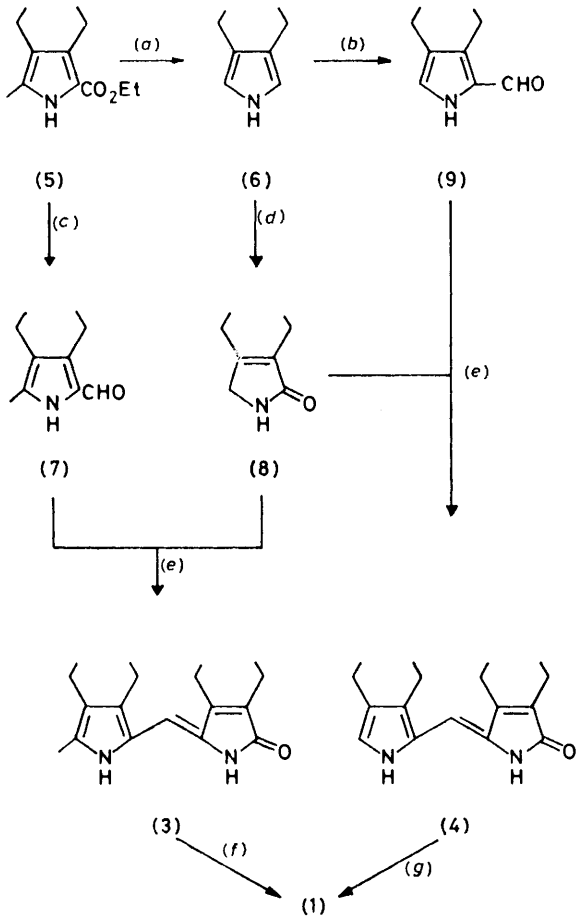
An attractive alternative strategy involves the pairing up of two pyrrole rings to give a pyrromethenone [(3),

† This short form of the name is used in this paper for the substance the preferred full name of which is 2,3,7,8,12,13,17,18-octaethyl-21*H*,24*H*-bilin-1,19-dione. Alternative names are listed in the Experimental section.[2] The configuration is believed to be 4*Z*, 10*Z*, 15*Z*: the boron complex made from (1) under mild conditions has this stereochemistry.[3]

(4)], which in turn is doubled up in some way to give the product (Scheme 1, pathway B). An early example of this approach to a polyalkylbilin derivative ('octamethylbilirubin') was recorded by Fischer and Aschenbrenner [7] and the recent literature has other examples.[8-10]

RESULTS AND DISCUSSION

The starting material for the present synthesis was 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole (5). Routes to this pyrrole, which can be stored for lengthy periods without decomposition, have recently been improved.[11,12] The pyrrole (5) was converted into 3,4-diethylpyrrole (6) (which may be stored under nitrogen



SCHEME 2 Syntheses of octaethylbilindione. (*a*) (*i*) SO_2Cl_2; (*ii*) aqueous NaOH; (*iii*) heat, catalyst (yield 74.5%, ref. 13; we observed similar yields): (*b*) $POCl_3$–DMF: (*c*) (*i*) aqueous NaOH; (*ii*) $POCl_3$–DMF (yield 44%, ref. 14; we observed similar yields): (*d*) H_2O_2–pyridine: (*e*) NaOH–EtOH (*f*) O_2–HOAc: (*g*) $HC(OMe)_3$–HCl

at −20 °C) by treatment with sulphuryl chloride, hydrolysis, and decarboxylation of the resulting 2,5-dicarboxylic acid.[13] 3,4-Diethylpyrrole is useful as an intermediate in syntheses both of octaethylporphyrin [13] and of octaethylbilindione.

Two alternative routes to the latter are shown in Scheme 2. The first route involved the base-catalysed condensation of 3,4-diethyl-2-formyl-5-methylpyrrole (7) with 3,4-diethyl-3-pyrrolin-2-one (8), the latter being obtained from the diethylpyrrole by treating it with hydrogen peroxide in pyridine.[15] The yield of the pyrromethenone (3) was low: this is attributed to steric factors, since the corresponding reactions with 2-formylpyrrole and with 4-ethyl-2,5-dimethyl-2-formylpyrrole proceeded in much better yield. The oxidative coupling of the methylpyrromethenone (3) using the procedure described by Lightner [8] gave the octaethylbilindione (1) but again the yield was disappointing. Attempts to improve this step using 2,3-dichloro-5,6-dicyanobenzoquinone as the oxidant [10] were not successful. The overall yield [(6) ⟶ (1)] by this route was 2.7%.

In the preferred route all four rings are derived from 3,4-diethylpyrrole. The condensation of the 3-pyrrolin-2-one (8) with 3,4-diethyl-2-formylpyrrole (9) gave the α-free pyrromethenone (4). Two of these units were then linked through a *meso*-carbon provided by reaction with trimethyl orthoformate–hydrogen chloride [9] to generate the octaethylbilindione (1) in 90% yield. The overall yield from (6) is 35%, and the synthesis can be carried out on a gram scale without difficulty.

Octaethylbilindione is an excellent ligand. Complexes of manganese, cobalt, nickel, copper, and zinc possessing a 1 : 1 stoicheiometry have been prepared, and await further study.

EXPERIMENTAL

3,4-Diethyl-2-formylpyrrole (9).—To stirred dry ice-cooled dimethylformamide (15 ml) was added dropwise phosphorus oxychloride (6.2 ml) followed by 3,4-diethylpyrrole [13] (5 g) in dimethylformamide (8 ml). The mixture was stirred with ice cooling for 15 min, then at 40—50 °C overnight. The solution was poured onto an excess of crushed ice, and solid sodium hydrogencarbonate was added to pH 8—9. The mixture was warmed (water-bath, *ca.* 90 °C, 10—15 min) when the crude aldehyde floated to the surface as a clear dark oil. The cooled mixture was extracted with ether, the extract was dried (Na_2SO_4), and the solvent was removed. The residual oil was sublimed (110 °C, 1 mmHg) to give *3,4-diethyl-2-formylpyrrole* (5.4 g, 88%) as pale lemon granules, m.p. 45 °C. Re-sublimation gave a white solid, m.p. 45.5 °C (Found: C, 71.65; H, 8.75; N, 9.35. $C_9H_{13}NO$ requires C, 71.5; H, 8.65; N, 9.25%); $\lambda_{max.}$ (CH_3OH) 300 nm (ε 18 300); $\nu_{max.}$ (Nujol) 3 275, 1 642, 950, and 815 cm^{-1}; δ ($CDCl_3$) 9.82 (br, NH), 9.52 (d, *J* 1 Hz, CHO), 6.84 (d, *J* 2.5 Hz, 5-H), 2.71, 2.44 (q, q, *J* 7.5 Hz, 2 × CH_2), and 1.19 (m, 2 × Me), *m/e* (25 °C) 151 (*M*, 65%), 136 (*M* − Me, 100), and 122 (*M* − CHO, 14).

3,4-Diethyl-3-pyrrolin-2-one (8). (*with M. J. Dimsdale* [15]). —*Safety screen.* 3,4-Diethylpyrrole (6.8 g) in dry pyridine (10 ml) was heated (water-bath, *ca.* 80—85 °C) with aqueous hydrogen peroxide (28%, 8 ml) for 5 min. After the initial reaction had subsided more aqueous hydrogen peroxide (2 ml) was added, and the mixture was heated (water-bath) for a further 10 min. The aqueous pyridine was removed under reduced pressure, and the residue was dissolved in ether, washed with 2M-NaOH, and dried ($MgSO_4$). The ether was evaporated, and the light-brown oily residue was distilled under vacuum to give the crude product (4.9 g, 64%), b.p. 124—126 °C/1 mmHg as a pale yellow oil which

crystallised as it cooled. The product was re-distilled (102 °C/0.1 mmHg) and then crystallised from petroleum (b.p. 40—60 °C) to give 3,4-*diethyl*-3-*pyrrolin*-2-*one* (3.1 g, 42%) as hygroscopic colourless *prisms*, m.p. 43—47 °C. The analytical sample had m.p. 47.5—49 °C (Found: C, 69.2; H, 9.25; N, 10.15. $C_8H_{13}NO$ requires C, 69.05; H, 9.4; N, 10.05%); $\lambda_{max.}$ (EtOH) 214 nm (ε 14 100); $\nu_{max.}$ (Nujol) 3 200 and 1 690 cm^{-1}; δ ($CDCl_3$) 7.50 (br, NH), 3.85 (s, 5-CH_2), 2.43 (q, *J* 7 Hz, 3′-CH_2), 2.30 (q, *J* 7 Hz, 4′-CH_2), and 1.10 (m, 2 × Me).

In subsequent experiments, a small quantity of manganese dioxide has been added to the cooled reaction before removing the aqueous pyridine (yield 41%).

3,4-*Diethyl*-5-(*pyrrolyl*-2-*methylidene*)-3-*pyrrolin*-2-*one*.—2-Formylpyrrole (95 mg), 3,4-diethyl-3-pyrrolin-2-one (139 mg), aqueous sodium hydroxide (4M, 40 ml), and ethanol (40 ml) were refluxed for 2 h. The mixture was poured into an excess of crushed ice, and the yellowish precipitate was removed by filtration and washed with water until neutral. The product (166 mg, 77%) was crystallised from aqueous ethanol to give pale yellow micro-needles (143 mg, 66%) of 3,4-*diethyl*-5-(*pyrrolyl*-2-*methylidene*)-3-*pyrrolin*-2-*one*, m.p. 185 °C (Found: C, 71.85; H, 7.65; N, 12.7%; M^+, 216.126. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.45; N, 12.95%; *M*, 216.126). $\lambda_{max.}$ (CH_3OH) 381 nm (ε 32 000); $\nu_{max.}$ (Nujol) 3 340, 3 165, 3 100, 1 670, 1 637, 1 032, and 725 cm^{-1}; δ ($CDCl_3$) 11.12 and 10.80 (br, 2 × NH), 7.09 (m, pyrrole α-H), 6.45 and 6.29 (m, 2 × pyrrole β-H), 6.17 (s, *meso*-H), *ca.* 2.50 (m, 2 × CH_2), and 1.20 (m, 2 × Me); *m/e* (138 °C) 216 (*M*, 100%), 201 (*M* − Me, 33), 187 (7), 185 (8), 173 (4), 172 (6), 159 (5), and 108 (6).

3,4-*Diethyl*-5-(4-*ethyl*-3,5-*dimethylpyrrol*-2-*ylmethylidene*)-3-*pyrrolin*-2-*one*.—An analogous reaction with 4-ethyl-2-formyl-3,5-dimethylpyrrole and 3,4-diethyl-3-pyrrolin-2-one gave the title compound (58%, recrystallised from aqueous pyridine) as shiny yellow needles, m.p. 233—235 °C (lit.,[8] m.p. 233 °C).

3,4-*Diethyl*-5-(3,4-*diethyl*-5-*methylpyrrol*-2-*ylmethylidene*)-3-*pyrrolin*-2-*one* (3).—3,4-Diethyl-2-formyl-5-methylpyrrole [14] (475 mg), 3,4-diethyl-3-pyrrolin-2-one (400 mg), aqueous sodium hydroxide (4M, 75 ml), and ethanol (70 ml) were refluxed for 22 h, the reaction being followed by the appearance of an absorption maximum at 418 nm. The solution was poured into an excess of crushed ice, and the precipitate was collected and washed with water until neutral. The product (255 mg, 31%) was recrystallised from aqueous ethanol to give fine yellow micro-prisms (213 mg, 26%) of 3,4-*diethyl*-5-(3,4-*diethyl*-5-*methylpyrrol*-2-*ylmethylidene*)-3-*pyrrolin*-2-*one*, m.p. 233—235 °C (decomp.) (Found: C, 75.4; H, 9.0; N, 10.1. $C_{18}H_{26}N_2O$ requires C, 75.5; H, 9.15; N, 9.8%); $\lambda_{max.}$ (CH_3OH) 418 nm (ε 34 000); $\nu_{max.}$ (KBr) 3 350, 3 150, 1 662, 1 625, 1 600, 1 268, 1 165, 1 007, 866, and 670 cm^{-1}; δ ($CDCl_3$) 6.11 (s, *meso*-H), *ca.* 2.50 (m, 4 × CH_2), 2.40 (s, α-Me), and 1.15 (m, 4 × Me); *m/e* (114 °C) 286 (*M*, 100%), 271 (*M* − Me, 22), 257 (9), 241 (10), 227 (9), 198 (6), 149 (15), and 136 (10).

3,4-*Diethyl*-5-(3,4-*diethylpyrrol*-2-*ylmethylidene*)-3-*pyrrolin*-2-*one* (4).—3,4-Diethyl-2-formylpyrrole (1.5 g), 3,4-diethyl-3-pyrrolin-2-one (1.38 g), aqueous sodium hydroxide (4M, 150 ml), and ethanol (175 ml) were refluxed for 20 h (new absorption at 402 nm). The mixture was treated as before to give 1.89 g (70%) of precipitated product, which on re-precipitation from aqueous ethanol gave 3,4-*diethyl*-5-(3,4-*diethylpyrrol*-2-*ylmethylidene*)-3-*pyrrolin*-2-*one*, m.p. 172.5—173 °C, as a yellow amorphous solid (1.65 g, 61%). (Found: C, 75.2; H, 9.4; N, 10.25. $C_{17}H_{24}N_2O$ requires C, 74.95; H, 8.9; N, 10.3%); $\lambda_{max.}$ (CH_3OH) 402 nm (ε 31 900); $\nu_{max.}$ (KBr) 3 345, 3 140, 1 625, 945, 768, 708, and 673 cm^{-1}; δ ($CDCl_3$) 11.18 (br, 2 × NH), 6.78 (d, *J* 3 Hz, pyrrole α-H), 6.14 (s, *meso*-H), 2.50 (m, 4 × CH_2), and 1.20 (m, 4 × Me), *m/e* (107 °C) 272 (*M*, 65%), 257 (*M* − Me, 17), 243 (10), 223 (12), 149 (100), and 136 (9).

2,3,7,8,12,13,17,18-*Octaethyl*-21H,24H-*bilin*-1,19-*dione* (1); (2,3,7,8,12,13,17,18-*Octaethyl*-21,24-*dihydrobilin*-1,19-*dione*; 2,3,7,8,12,13,17,18-*Octaethyl*-1,19,21,24-*tetrahydro*-1,19-*dioxobilin*; *Octaethylbilatriene*-abc).—(*a*) The tetraethylpyrromethenone (4) (2.00 g, 0.01 mol) in a saturated solution of anhydrous hydrogen chloride in ether (600 ml) was vigorously stirred at room temperature while trimethyl orthoformate (30 ml, large excess) was added over a period of 2—3 min. After 25 h the violet-blue precipitate was removed by filtration and washed with water.

A solution of the solid in chloroform was washed with 0.2M-sodium hydrogencarbonate then water, and dried ($MgSO_4$) before the solvent was removed. The residue was crystallised from chloroform–light petroleum (b.p. 60—80 °C) to give 2,3,7,8,12,13,17,18-octaethyl-21*H*,24*H*-bilin-1,19-dione (1.65 g, 81%) as minute dark blue crystals, m.p. 253—257 °C (decomp.) [lit.,[4] m.p. 251—257 °C (decomp.)]. A further 0.19 g was obtained following column chromatography [basic grade IV Al_2O_3; toluene–ether (9 : 1)] of the filtrate to give a total yield of 90% (Found: C, 76.05; H, 8.45; N, 10.05. Calc. for $C_{35}H_{46}N_4O_2$: C, 75.8; H, 8.35; N, 10.1%); $\lambda_{max.}$ (CH_3OH) 298infl. (ε 23 600), 367 (54 500), and 647.5 nm (16 100); $\lambda_{max.}$ (CH_3OH + CF_3CO_2-H) 297 (ε 19 500), 360 (58 000), 638infl. (22 500), and 691 nm (31 600); $\nu_{max.}$ (KBr) 3 430, 3 244, 1 684, 1 615, 1 585, 1 204, 1 005, 943, 736, 704, and 617 cm^{-1}; δ ($CDCl_3$) 7.90 (br, 3 × NH), 6.62 (s, H-10), 5.88 (s, H-5 and H-15), *ca.* 2.50 (m, 6 × CH_2), 2.30 (q, *J* 7.5 Hz, 2 × *exo*-CH_2), and 1.20 (m, 8 × Me); *m/e* (179 °C) 554 (*M*, 100%), 539 (*M* − Me, 8), 525 (5), 277 (M^{2+}, 9), 223 (10), 205 (8), 149 (92), and 122 (16).

(*b*) Oxygen was bubbled through a stirred solution of the tetraethylmethylpyrromethenone (3) (143 mg) in acetic acid (15 ml) at 80—90 °C for 22 h. The solvent was removed under reduced pressure and the residue was chromatographed twice [t.l.c., 2 plates, 400 × 400 × 2 mm, Merck Kieselgel HF; $CHCl_3$–CH_3OH (19 : 1); R_F *ca.* 0.7] to give the octaethylbilindione. Crystallisation as before gave fine dark blue crystals (34.8 mg, 25%) of octaethylbilindione identical (i.r., mixed t.l.c., mixed m.p.) with the sample prepared above.

Metal Complexes of Octaethylbilindione.—Octaethylbilindione (33.2 mg, 0.06 mmol) in ethanol (20 ml) was treated with a warm solution of metal(II) diacetate (0.48 mmol) in ethanol (10 ml) and the mixture was warmed to *ca.* 60 °C for 2—3 min. The mixture was stirred at room temperature for 20 min, the solvent was largely removed under reduced pressure, and the moist residue was taken up in chloroform (30 ml). The chloroform solution was washed with water (2 × 50 ml) and dried (Na_2SO_4). The solution was concentrated, and the complex was crystallised from chloroform–hexane. For the zinc complex, after the 20 min period of stirring, the crystalline precipitate was removed at the centrifuge and washed with ethanol.

Manganese complex, olive-green prisms, (93%), m.p. >350 °C (Found: C, 69.25; H, 7.5; N, 9.15; Mn, 9.05. $C_{35}H_{43}N_4O_2Mn$ requires C, 69.3; H, 7.15; N, 9.25; Mn, 9.05%). In this, and the following analyses, the observed

analytical figures do not distinguish between the H_{43} and the H_{44} formulae.

Cobalt complex, green needles, (75%), m.p. >330 °C, with loss of crystallinity at 249—251 °C (Found: C, 68.65; H, 7.15; N, 9.35; Co, 9.65. $C_{35}H_{43}N_4O_2Co$ requires C, 68.85; H, 7.1; N, 9.2; Co, 9.65%).

Nickel complex, brownish green needles, (94%), m.p. >330 °C, with loss of crystallinity at 230—234 °C (Found: C, 69.15; H, 6.95; N, 9.0; Ni, 9.8. $C_{35}H_{43}N_4NiO_2$ requires C, 68.85; H, 7.1; N, 9.2; Ni, 9.6%).[16]

Copper complex, olive green needles, (99%), m.p. >350 °C (Found: C, 68.35; H, 7.25; N, 9.33; Cu, 10.3. $C_{35}H_{44}CuN_4O_2$ requires C, 68.2; H, 7.2; N, 9.1; Cu, 10.3%).

Zinc complex, green elongated prisms, (90%), m.p. >340 °C (Found: C, 67.8; H, 7.1; N, 9.1; Zn, 10.6. $C_{35}H_{44}N_4O_2Zn$ requires C, 68.0; H, 7.15; N, 9.05; Zn, 10.6%).

[0/468 *Received*, 27*th March*, 1980]

REFERENCES

[1] R. Bonnett and G. F. Stephenson, *J. Org. Chem.*, 1965, **30**, 2791, and subsequent papers in that series.
[2] IUPAC-IUB, ' Nomenclature of Tetrapyrroles, Provisional Recommendations 1978,' *Pure Appl. Chem.*, 1979, **51**, 2251.
[3] D. Hamzetash and J. Trotter, unpublished results.
[4] R. Bonnett and M. J. Dimsdale, *J.C.S. Perkin I*, 1972, 2540.
[5] J. A. S. Cavaleiro and K. M. Smith, *J.C.S. Perkin I*, 1973, 2149.
[6] H. Scheer, *Z. Naturforsch*, 1976, **31C**, 413.
[7] H. Fischer and J. Aschenbrenner, *Z. physiol. Chem.*, 1937, **245**, 107.
[8] D. A. Lightner, G. B. Quistad, and C. S. Pak, *Synthesis*, 1976, 335.
[9] H. von Dobeneck, E. Brunner, and U. Sommer, *Annalen*, 1977, 1435.
[10] H. Falk and K. Grubmayr, *Synthesis*, 1977, 614.
[11] J. B. Paine III, W. B. Kirschner, D. W. Moskowitz, and D. Dolphin, *J. Org. Chem.*, 1976, **41**, 3857.
[12] C. B. Wang and C. K. Chang, *Synthesis*, 1979, 548.
[13] U. Eisner, A. Lichtarowicz, and R. P. Linstead, *J. Chem. Soc.*, 1957, 733; H. W. Whitlock and R. Hanauer, *J. Org. Chem.*, 1968, **33**, 2169.
[14] D. Dolphin, R. L. N. Harris, J. L. Huppatz, A. W. Johnson, and I. T. Kay, *J. Chem. Soc. (C)*, 1966, 30.
[15] M. J. Dimsdale, Ph.D. Thesis, London, 1968.
[16] J. V. Bonfiglio, R. Bonnett, M. B. Hursthouse, and K. M. A. Malik, *J.C.S. Chem. Comm.*, 1977, 83.