Synthesis of Benzodiaza[14]annulenes from 4,6-Dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine

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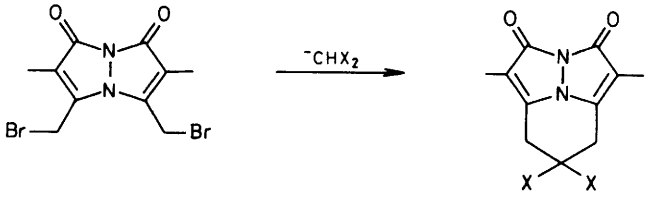
The reaction of 4,6-dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine with dimethyl malonate under basic conditions gives dimethyl 6,7-dihydro-2,10,4,8-propane-1,3-diylidene-5*H*-1,11-benzodiazacyclotridecine-6,6-dicarboxylate. Demethoxycarbonylation of this diester with lithium chloride in dimethylformamide–water affords epimeric monoesters. The reaction of dimethyl 5-bromo-6,7-dihydro-2,10,4,8-propane-1,3-diylidene-5*H*-1,11-benzodiazacyclotridecine-6,6-dicarboxylate with lithium chloride in dimethylformamide–water affords methyl 2,10,4,8-propane-1,3-diylidene-5*H*-benzodiazacyclotridecine-6-carboxylate. The reaction of 4,6-dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine with tetramethylethane-1,1,2,2-tetracarboxylate under basic conditions gives tetramethyl 5,6,7,8-tetrahydro-2,11,4,9-propane-1,3-diylidene-1,2-benzodiazacyclotetradecine-6,6,7,7-tetracarboxylate. Demethoxycarbonylation of this tetraester affords epimeric diesters. Elaboration of both the tetraester and these diesters afforded the [14]annulene, dimethyl 2,11,4,9-propane-1,3-diylidene-1,12-benzodiazacyclotetradecine-6,7-dicarboxylate.

In the preceding paper,[1] elaboration of the dibromide, 4,6-dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**1**), by reaction with amines and with hydrazines is reported. Cyclisation affords dihydro and tetrahydro precursors of benzotriaza- and benzotetra-aza-[14]annulenes respectively. In this paper we report further actions of compound (**1**): dimethyl malonate affords by successive nucleophilic displacements a product of cyclisation with incorporation of a C_1 unit and tetramethyl ethane-1,1,2,2-tetracarboxylate affords a product with incorporation of a C_2 unit. Subsequent elaboration affords a benzodiaza[14]annulene (**2**), a further example of a bridged heteroaromatic annulene.

In addition to the elaboration of bimanes (see Scheme 1) by reaction with amines the group of Kosower [2] describe products of cyclisation by reaction with malononitrile and with dialkyl malonates (Scheme 1). In an analogous manner, the dibromide (**1**) with dimethyl malonate in tetrahydrofuran in the presence of sodium hydride gives the crystalline ester (**3**) in 65% yield.

In compound (**3**), signals assigned to the resonance of the two methyl groups are observed at ≈τ 6.24 and 6.66. The relatively large difference in chemical shift between these resonances might be attributed to shielding effects induced by the conjugated aromatic system. Similar chemical shift differences are observed for the methylene resonances due to 5-H and 7-H. The respective assignments were clarified by a detailed spectroscopic analysis of the epimeric esters (**4**) and (**5**) after their isolation by demethoxycarbonylation of (**3**) by reaction [3] with lithium chloride in dimethylformamide–water at 110 °C.

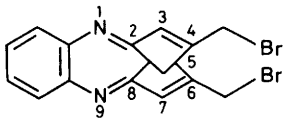


Scheme 1. X = CN, CO_2Me, or CO_2Et

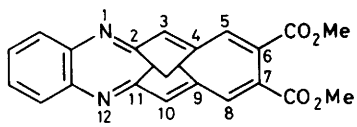
The analysis is based on n.O.e. results from the ^1H n.m.r. spectra of (**4**) and (**5**) recorded at 400 MHz, and on the coupling constants associated with 6-H.

The bridgehead proton 18-H must be situated on the same face (top or *exo*) as the one carbon bridge. Therefore, observation that the resonance at τ 6.59 (18-H) in Figure 1 is enhanced by perturbation of 6-H (resonating at τ 6.87) requires that the ester giving rise to Figure 1 is (**5**) with 6-H situated on the same face of the molecule as 18-H. Further n.O.e. results require a *cis* relationship between the protons resonating at τ 6.59 (18-H) and 7.24 (5-H_{exo} and 7-H_{exo}) and those resonating at τ 6.87 (6-H) and 7.24 (5-H_{exo} and 7-H_{exo}). On the bottom (*endo*) face, n.O.e. results define a *cis* relationship between the protons resonating at τ 7.00 (5-H_{endo} and 7-H_{endo}) and the ester group (characterised by the resonance at τ 6.76).

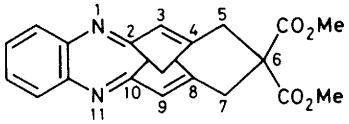
In contrast, for the ester (**4**) (shown in Figure 2) the lack of an enhanced signal requires that 18-H (resonating at τ 6.53) is on the opposite face of the molecule from 6-H (resonating at τ



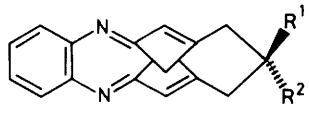
(**1**)



(**2**)



(**3**)



(**4**) $R^1 = CO_2Me$, $R^2 = H$
(**5**) $R^1 = H$, $R^2 = CO_2Me$

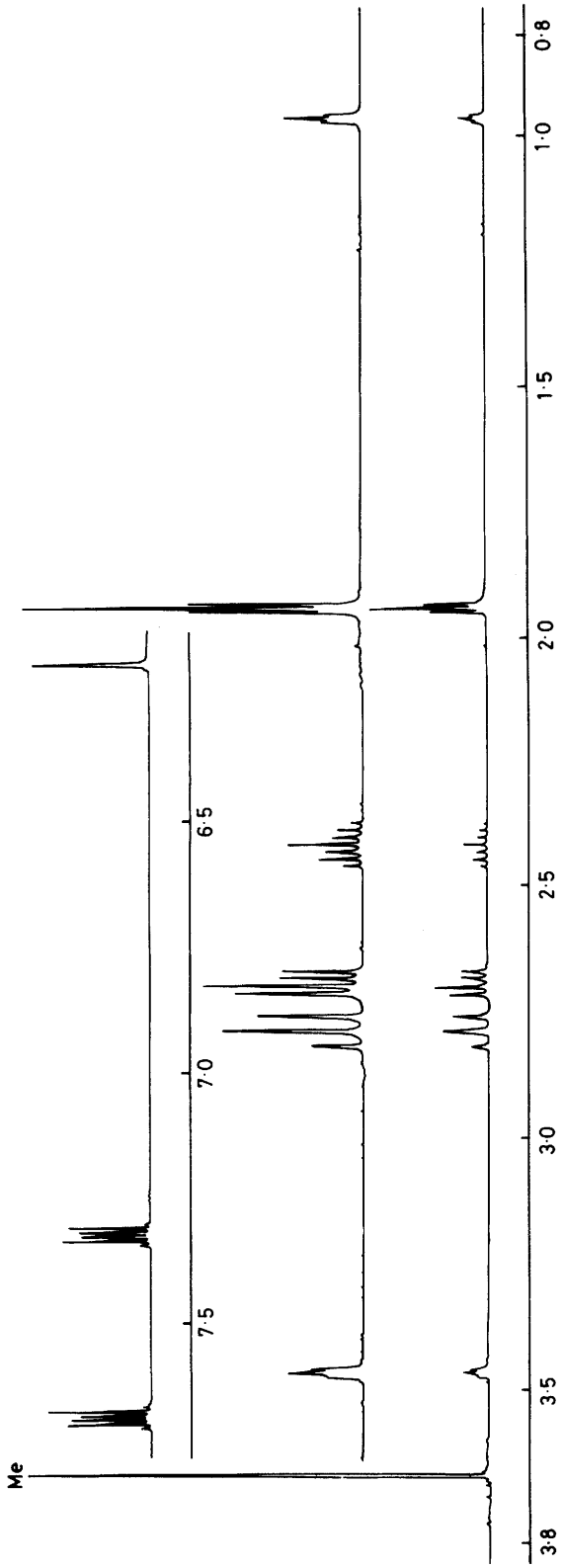


Figure 1. ^{1}H N.m.r. (400 MHz) spectrum of the methyl ester (**5**)

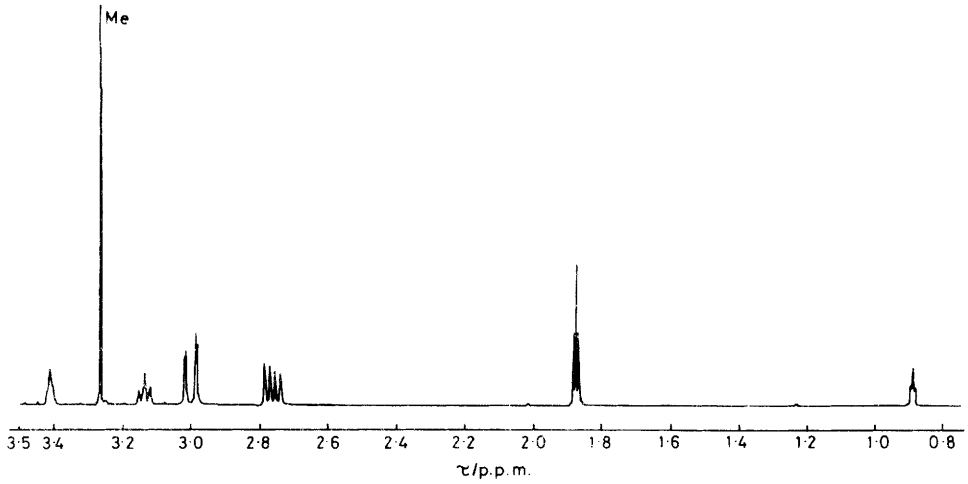


Figure 2. ^{1}H N.m.r. (400 MHz) spectrum of the isomeric methyl ester (**4**)

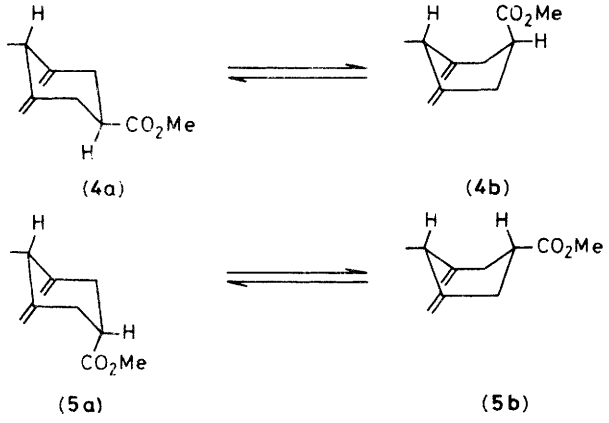


Figure 3.

7.58). Confirmation of this assignment comes from the n.O.e. result establishing the *cis* relationship of 18-H and the ester group (characterised by the resonance at τ 6.33). Further n.O.e. results require a *cis* relationship between the protons resonating at τ 6.53 (18-H and 7.21 (5-H_{exo} and 7-H_{exo}) and those resonating at τ 7.31 (5-H_{endo} and 7-H_{endo}) and 7.58 (6-H).

Hence both sets of Overhauser experiments unequivocally require assignment of the spectrum in Figure 2 to the epimer (**4**) and that in Figure 1 to the epimer (**5**). In both epimers (**4**) and (**5**) the ester group is attached to a six-membered ring capable of adopting either a chair or boat conformation [shown as the partial structures (**4a**) and (**4b**) and (**5a**) and (**5b**), Figure 3]. The proof of relative configuration by n.O.e. permits a definition of the dominant conformer for (**4**) and (**5**) by analysis of the magnitude of the coupling constants $J_{5exo6} = J_{67exo}$ and $J_{5endo6} = J_{67endo}$. The observation in (**4**) that $J_{5exo6} = J_{67exo} =$ 6.4 Hz and $J_{5endo6} = J_{67endo} = 1.2$ Hz implies dihedral angles of about 30 and 90°, respectively. The observation in (**5**) that $J_{5exo6} = J_{67exo} = 11.6$ Hz and $J_{5endo6} = J_{67endo} = 5.6$ Hz implies dihedral angles of about 180 and 60°, respectively. In the ester (**5**) where the *exo*-ester substituent can adopt an equatorial position there is no adverse steric interaction and hence a chair conformation is adopted, as shown by the *J* values. In contrast, in (**4**) an axial ester substituent can suffer adverse steric interactions with groups on the *endo* face. Relief from such interactions can be achieved by some movement away from a chair conformation towards a boat conformation, and the *J* values indicate that this takes place.

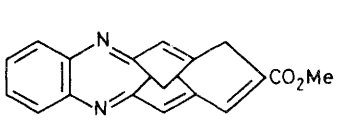
In the ester (**4**), proton 6-H (resonating at τ 7.58) is substantially shielded relative to proton 6-H (resonating at τ 6.87) in (**5**). Similarly, in (**5**) the protons of the methoxycarbonyl substituent (resonating at τ 6.76) are substantially shielded relative to those (resonating at τ 6.33) in (**4**). These chemical shift differences indicate that an *endo*-6-substituent is shielded relative to an *exo*-6-substituent. Hence the relative assignments in the diester (**3**) can be made. A strong shielding effect by the unsaturated rings in (**3**), (**4**), and (**5**) and related compounds is indicated.

The diester (**3**) is an attractive intermediate for a possible synthesis of the unsaturated ester (**6**) and hence of the fully conjugated bridged annulenes. The preparation of (**6**) has been attempted by three routes. The attempted bromination of (**3**) with *N*-bromosuccinimide failed, and only the starting diester (**3**) was recovered. This result is not very surprising as the steric bulk of the methoxycarbonyl groups probably prevents attack by the reagent. The alternative of monobromination of the monesters (**4**) and (**5**) was briefly examined, but was markedly inferior to the third route.

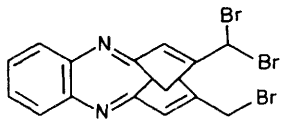
The reaction of the tribromide (**7**) with dimethyl malonate and sodium hydride in tetrahydrofuran gave the bromodiester (**8**) in 51% yield. Hydrolytic cleavage using lithium chloride in aqueous dimethylformamide afforded the ester (**6**) directly *via* a demethoxycarbonylation with elimination. The isolation of (**6**) in 48% yield suggests that this type of debromomethoxycarbonylation might be more widely applicable.

The reaction of the ester (**6**) with base might be expected to lead to a delocalised anion (**9**). Such an anion has the capacity to act as a nucleophile by reaction at several carbon sites or by reaction at nitrogen or oxygen. The ability to trap such intermediates in related bridged benzodiazepines has been shown using the benzodiazacycloundecine (**10**). When (**10**) was heated under reflux in toluene in the presence of benzoyl chloride and triethylamine, the bisdienamide (**11**) was isolated in 74% yield. However, (**6**) does not give the (**12**) under similar conditions; the attempted reaction with benzoyl chloride led only to the recovery of the starting ester (**6**) and there was no evidence of product formation. The behaviour of the ester (**6**) with stronger bases is more complex and is the subject of further studies.

In a manner similar to the formation of (**3**), the tetraester (**13**) was obtained in 80% yield by reaction of the dibromide (**1**) with



(6)



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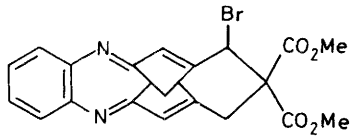

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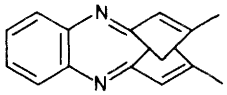
(9)



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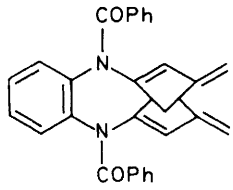

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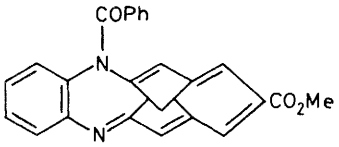

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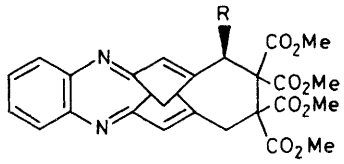
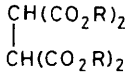


(13) R = H
(19) R = Br



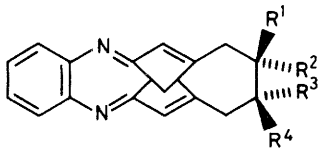
(14)

compound (**14**; R = Me) in tetrahydrofuran in the presence of sodium hydride. In contrast, the reaction in benzene only gave (**13**) in low yield. Precedent for such alkylations exists; the reaction[4] of diethyl diester (**14**; R = Et) with 1,3-dibromopropane in dimethyl sulphoxide in the presence of sodium methoxide gives a cyclic tetraester. Recently, Garratt *et al.*[5] developed annelation procedures using anions of dimethyl cyclopentane-1,2-dicarboxylate employing lithium di-isopropylamide. However, using similar conditions with dimethyl succinate or succinonitrile we have been unable to achieve cyclisations with the dibromide (**1**).

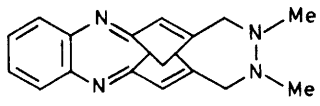
Hydrolysis of compound (**13**) using lithium chloride in aqueous dimethylformamide[3] gave two ester products *via* demethoxycarbonylation. Fractional crystallisation from ethyl acetate gave one isomer pure. The second isomer, even using preparative t.l.c., was always isolated slightly contaminated by the first isomer. The assignment of structures to the three possible diesters (**15**)—(**17**) is complicated by their conformational equilibria, leading to complex ^{1}H n.m.r. spectra. Ring inversion of the seven-membered ring can lead to interconversion of the conformers [*e.g.* (**17a**) ⇌ (**17b**), Figure 4]. In the related compound (**18**) the energy barrier to ring inversion is 17 kcal/mol.[1,*] In the case of the hydrolysis products from the tetraester (**13**), significant spectral changes were only observed above 50 °C indicating comparable activation energies. In spectra recorded at lower temperatures the isomer, which was isolated pure and tentatively assigned structure (**16**), was characterised by methyl resonances at τ 6.28 and 6.40. In the second isomer the methyl resonances were observed at τ 6.48. Both in the esters (**4**) and (**5**) where the methyl resonances are observed at τ 6.33 and 6.76, respectively, and in related compounds,[1] a considerable difference in chemical shift is observed for protons placed on the *exo* and *endo* faces: protons situated in an *endo* region are relatively shielded by the ring current of the aromatic moiety. Hence, the ester having resonances at τ 6.28 and 6.40 is tentatively assigned structure (**16**) and the ester having two methyl resonances at τ 6.48 is tentatively assigned structure (**17**).

From the pure esters (**13**) and (**17**) three successful routes to the aromatic diester (**2**) were developed. Allylic bromination of the tetraester (**13**) afforded the bromide (**19**). Even the use of an

* 1 kcal = 4.184 kJ.



(15) $R^1 = R^4 = CO_2Me$, $R^2 = R^3 = H$
(16) $R^1 = R^3 = CO_2Me$, $R^2 = R^4 = H$
(17) $R^1 = R^4 = H$, $R^2 = R^3 = CO_2Me$



(18)

(17a) (17b)

Figure 4.

excess of *N*-bromosuccinimide only gave a monobromide: the absence of a dibromide is attributed to extreme steric hindrance preventing the second hydrogen abstraction. However, the reaction of (**19**) with lithium chloride in dimethylformamide–water [3] gave two products, readily separated by preparative t.l.c. The products were readily identified as the esters (**16**) and (**2**). The reaction of the bromotetraester (**19**), therefore, involves both demethoxycarbonylation as observed from (**8**), and a concomitant disproportionation affording products (**16**) and (**2**).

A second route to the annulene (**2**) proceeded *via* oxidation of the ester (**16**), or a mixture of the isomers (**16**) and (**17**), with selenium dioxide. The reaction of (**16**) in aqueous dioxane gave (**2**) in 56% yield. A third route proceeding in lower yield consisted of bromination of the ester (**16**) with *N*-bromosuccinimide (2 equiv.) and direct dehydrobromination of the reaction mixture by triethylamine. This third route afforded the product (**2**) in 20% yield.

The diester (**2**) is a diaza analogue of the bridged carbocyclic[14]annulenes. The latter [6] are sufficiently planar to have a well developed aromatic character, as evidenced by strong shielding effects on the bridge and bridgehead protons and deshielding effects on the peripheral vinylic protons. In compound (**2**), such effects may be diminished by the benzo moiety and the ester substituents. However, the following relative chemical shifts of the protons in compounds (**10**) and (**2**) indicate the aromatic character of (**2**): (i) the signal of the bridge protons in (**10**) is observed at τ 7.98, but in (**2**) it occurs at τ 8.65, indicating considerable shielding.

(ii) The signal of the bridgehead proton in (**10**) is observed at τ 6.93, but in (**2**) the corresponding bridgehead proton 19-H is observed at τ 7.68, further indicating considerable shielding.

(iii) Deshielding effects on the peripheral protons in (**2**) are observed. Protons 3-H and 10-H in (**2**) resonate at τ 3.05, but in (**10**) the corresponding protons are observed at τ 3.77. Protons 5-H and 8-H in (**2**) are observed at τ 2.18.

This synthetic study shows that the readily prepared compound (**1**) [1] can be efficiently transformed to give aromatic annulenes by nucleophilic displacement of the leaving groups and subsequent elaboration of the products. Further methods for the elaboration of (**1**) to give different heteroaromatic annulenes are under investigation.

Experimental

General methods are reported elsewhere.[1] ^{1}H N.m.r. spectra (400 MHz) were recorded on a Bruker 400 MHz spectrometer at Warwick University. Ether refers to diethyl ether.

Dimethyl 6,7-Dihydro-2,10,4,8-propane-1,3-diylidene-5H-1,11-benzodiazacyclotridecine-6,6-dicarboxylate (**3**).—To a stirred solution of 4,6-dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine [1] (**1**) (2.0 g, 4.9 mmol) at 0 °C in dry tetrahydrofuran (100 ml) containing sodium hydride (390 mg, 16.3 mmol) was added dropwise a solution of dimethyl malonate (715 mg, 5.4 mmol) in dry tetrahydrofuran (5 ml). The resulting suspension was stirred for 10 min at 0 °C under nitrogen. Excess of sodium hydride was removed by filtering the solution under suction and the solvent was removed under reduced pressure to give an oil. This was dissolved in chloroform (100 ml), washed with water (3 × 50 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure gave an orange oil (2.2 g) which crystallised on addition of ethyl acetate to give the *diester* (**3**) (1.2 g, 65%) as yellow crystals, m.p. 135—136 °C (dec.) (Found: C, 69.85; H, 5.3; N, 7.4. $C_{22}H_{20}N_2O_4$ requires C, 70.20; H, 5.36; N, 7.44%); $\nu_{max.}$($CHCl_3$) 1 743, 1 613, and 1 563; *m/z* 376 (M^+; 27%); τ 2.28 (2 H, m, 12- and 15-H), 2.64 (2 H, m, 13- and 14-H), 3.76 (2 H, s, 3-and 9-H), 6.24 (3 H, s, CO_2Me), 6.47 (1 H, m, 18-H), 6.66 (3 H, s, CO_2Me), 6.68 (2 H, d, *J* 13 Hz, 5- and 7-H), 6.94 (2 H, d, *J* 13 Hz, 5- and 7-H), 8.06 (2 H, t, *J* 3 Hz, 17-H), and 9.05 (1 H, m, 16-H); ^{13}C n.m.r. (p.p.m.) 22.26 (C-17), 37.81 (CO_2Me), 40.89 (C-5 and -7), 43.67 (CO_2Me), 52.83 (C-16), 53.26 (C-18), 66.44 (C-6), 121.01 (C-3 and -9), 124.85 (C-13 and -14), 128.02 (C-12 and -15), 139.36 (C-11a and -15a), 143.24 (C-4 and -8), 144.06 (C-2 and -10), and 168.49, 169.63 (2 × CO_2Me).

Demethoxycarbonylation of the Diester (**3**).—The diester (**3**) (800 mg, 2.1 mmol) was dissolved in dimethylformamide (50 ml) and lithium chloride (385 mg, 6.3 mmol) and water (80 mg, 4.4 mmol) were added. The mixture was stirred at 110 °C for 10 h under nitrogen. Removal of the solvent under high vacuum gave a brown residue which was extracted with chloroform (50 ml), washed with water (3 × 100 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a brown oil (760 mg). Preparative t.l.c. (50% ether–50% ethyl acetate) afforded the more polar isomer (**5**) (250 mg, 37%) and the less polar one (**4**) (160 mg, 23.7%). Recrystallisation of the more polar fraction from ethyl acetate afforded *methyl 6,7-dihydro-2,10,4,8-propane-1,3-diylidene-5H-1,11-benzodiazacyclotridecine-6-carboxylate* (**5**) (180 mg, 26.6%) as pale yellow crystals, m.p. 178—180 °C (dec.) (Found: C, 75.1; H, 5.7; N, 8.8. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80%); *m/z* 318 (M^+, 100%); τ (100 MHz) 2.34 (2 H, m, 12- and 15-H), 2.70 (2 H, m, 13- and 14-H), 3.84 (2 H, s, 3- and 9-H), 6.59 (1 H, m, 18-H), 6.73 (3 H, s, CO_2Me), 6.8—7.40 (5 H, complex, 5-, 7- and 6-H), 8.13 (2 H, t, *J* 3 Hz, 17-H), and 9.12 (1 H, m, 16-H) (see also Figure and text).

The less polar fraction crystallised on the addition of ether to afford the isomer (**4**) (111 mg, 16.4%) as pale yellow crystals, m.p. 180—181 °C (dec.) (Found: C, 75.25; H, 5.7; N, 8.8. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80%); *m/z* 318 (M^+; 100%); τ (100 MHz) 2.27 (2 H, m, 12- and 15-H), 2.68 (2 H, m, 13- and 14-H), 3.78 (2 H, s, 3- and 9-H), 6.29 (3 H, s, CO_2Me), 6.49 (1 H, m, 18-H), 7.0—7.80 (5 H, complex, 5-, 7- and 6-H), 8.02 (2 H, t, *J* 3 Hz, 17-H), and 9.00 (1 H, m, 16-H) (see also Figure and text).

Reaction of the Tribromide (**7**) *with Dimethyl Malonate.*—To a stirred solution of 6-bromomethyl-4-dibromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**7**) (1.0 g, 2.1 mmol) in dry tetrahydrofuran (75 ml) containing sodium hydride (240 mg, 10 mmol) was added dropwise a solution of dimethyl malonate (326 mg, 2.5 mmol) in dry tetrahydrofuran (5 ml). The resulting suspension was stirred for 1 h at room temperature under nitrogen. The excess of sodium hydride was removed by filtering the solution under suction and the solvent was removed under reduced pressure to give a brown oil. This was dissolved in chloroform (50 ml), washed with water (3 × 50 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a tan oil (730 mg) which crystallised on addition of ethyl acetate to give *dimethyl 5-bromo-6,7-dihydro-2,10,4,8-propane-1,3-diylidene-5H-1,11-benzodiazacyclotridecine-6,6-dicarboxylate* (**8**) (480 mg, 51%) as yellow crystals, m.p. 196—198 °C (dec.) (Found: C, 57.9; H, 4.2; Br, 16.9; N, 6.11. $C_{22}H_{19}BrN_2O_4$ requires C, 58.03; H, 4.21; Br, 17.55; N, 6.15%); *m/z* 454 and 456 (M^+); τ 2.28 (2 H, m, 12- and 15-H), 2.64 (2 H, m, 13- and 14-H), 3.28 (1 H, s, 3-H), 3.78 (1 H, s, 9-H), 4.55 (1 H, s, 5-H), 6.16 (3 H, s, CO_2Me), 6.44 (1 H, m, 18-H), 6.76 (3 H, s, CO_2Me), 6.78 (2 H, m, 7-H), 8.00 (2 H, t, *J* 3 Hz, 17-H), and 8.95 (1 H, m, 16-H).

Attempted bromination of the diester (**3**) using *N*-bromosuccinimide to give compound (**8**) was not successful and the starting diester (**3**) was recovered unchanged.

Methyl 2,10,4,8-Propane-1,3-diylidene-5H-1,11-benzodiazacyclotridecine-6-carboxylate (**6**).—Dimethyl 5-bromo-6,7-dihydro-2,10,4,8-propane-1,3-diylidene-5*H*-1,11-benzodiazacyclotridecine-6,6-dicarboxylate (**8**) (500 mg, 1.1 mmol) was dissolved in dimethylformamide (50 ml) and lithium chloride (200 mg, 4.7 mmol) and water (72 mg, 4 mmol) were added. The mixture was stirred at 110 °C for 3½ h under nitrogen. Removal of the solvent under high vacuum gave a brown residue which was extracted with chloroform (100 ml), washed with water (3 × 50 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a brown oil (361 mg). Preparative t.l.c. (90% ether–10% ethyl acetate) afforded a less polar fraction (**6**) (237 mg, 68%) and a more polar fraction (52 mg) which was found to be polymeric. Recrystallisation of the less polar fraction from ethyl acetate afforded the product (**6**) (160 mg, 48%) as bright yellow crystals, m.p. 220—222 °C (dec.); $\nu_{max.}$($CHCl_3$) 1 715, 1 605, and 1 570 cm^{-1}; *m/z* 316 (M^+; 100%); τ 2.21 (2 H, m, 12- and 15-H), 2.62 (2 H, m, 13- and 14-H), 2.50 (1 H, br s, 7-H), 3.58, 3.63 (2 H, 2 s, 3- and 9-H), 6.21 (3 H, s, CO_2Me), 6.34 (1 H, d, *J* 18 Hz, 5-H), 6.97 (1 H, d, *J* 18 Hz, 5-H), 6.44 (1 H, m, 18-H), 8.06 (2 H, m, 17-H), and 9.14 (1 H, m, 16-H); ^{13}C N.m.r. (p.p.m.) 21.39 (C-17), 37.32 (C-5), 37.98 (C-16), 39.33 (C-18), 52.21 (CO_2Me), 120.44 (C-3), 122.13 (C-9), 125.07, 125.30, 128.29, and 128.29 (C-12, -13, -14, and -15), 138.67 (C-7), 139.03, 139.23, 139.48 (C-6, -11a, and -15a), 139.77 (C-4 and -8), 142.87, 143.21 (C-2 and -10), and 166.22 (CO_2Me).

1,9-Dibenzoyl-4,6-dimethylene-5,2,8-ethanylylidene-1,9-benzodiazacycloundecine (**11**).—4,6-Dimethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**10**) (1.0 g, 4.0 mmol) was dissolved in toluene (100 ml) and benzoyl chloride (3.0 g, 21.4 mmol) and triethylamine (2.2 g, 21.8 mmol) were added. The mixture was heated under reflux for 15 h under nitrogen. The precipitate of triethylamine hydrochloride was filtered off and the filtrate was stirred with a saturated solution of sodium hydrogen carbonate for 8 h. The organic solution was washed with water (2 × 100 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure gave a yellow solid (1.6 g). Recrystallisation from ether–ethyl acetate (1:1) afforded the *product* (**11**) (1.4 g, 74%) as pale yellow crystals, m.p. 208—210 °C (dec.) (Found: C, 80.4; H, 5.3; N, 6.0. $C_{31}H_{24}N_2O_2$ requires C, 80.53; H, 5.59; N, 6.48%); $\nu_{max.}$($CHCl_3$) 1 655, 1 605, and 1 580 cm^{-1}; $\lambda_{max.}$ 238 nm (ε 28 700); *m/z* 456 (M^+; 9%) τ 2.3—3.20 (14 H, m, 10-, 11-, 12-, 13-H and remaining aromatic protons), 3.82 (2 H, s, 3- and 7-H), 4.96, 5.12 (4 H, 2 s, $=CH_2$), 6.53 (1 H, t, *J* 3 Hz, 5-H), 7.24 (1 H, t, *J* 3 Hz, 14-H), and 8.06 (2 H, br m, 15-H); ^{13}C n.m.r.* (p.p.m.) 28.71 (C-15), 41.32 (C-14), 42.86 (C-5), 110.66, 115.67, 128.04, 128.98, 129.52, and 131.23 ($=CH_2$, C-10, -11, -12, -13, -b, -c, -d, -e, and -f, 139.86 (C-a), 145.93 (C-9a and -13a), 147.94 (C-4 and -6), 148.09 (C-2 and -8), and 170.00 (CO).

Tetramethyl 5,6,7,8-Tetrahydro-2,11,4,9-propane-1,3-diylidene-1,2-benzodiazacyclotetradecine-6,6,7,7-tetracarboxylate (**13**).—To a stirred solution of 4,6-dibromomethyl-5,2,8-ethylylidene-5*H*-1,9-benzodiazacycloundecine (**1**) (6.0 g, 14.8 mmol) in dry tetrahydrofuran (200 ml) containing sodium hydride (1.17 g, 48.8 mmol) was added dropwise a solution of tetramethyl ethane-1,1,2,2-tetracarboxylate (**14**) (4.26 g, 16.3 mmol) in dry tetrahydrofuran (25 ml). The resulting suspension was heated under reflux for 1 h under nitrogen. The excess of sodium hydride was removed by filtering the solution under suction and the solvent was removed under reduced pressure to give a tan oil. This was dissolved in chloroform (150 ml), washed with water (3 × 100 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a tan solid (7.2 g). Recrystallisation from ether–ethyl acetate (1:1) afforded the *product* (**13**) (6.0 g, 80%) as yellow crystals, m.p. 194—196 °C (dec.) (Found: C, 64.1; H, 5.1; N, 5.5. $C_{27}H_{26}N_2O_8$ requires C, 64.02; H, 5.17; N, 5.53%); $\nu_{max.}$($CHCl_3$) 1 730, 1 610, and 1 570 cm^{-1}; *m/z* 506 (M^+; 100%); τ 2.31 (2 H, m, 13- and 16-H), 2.67 (2 H, m, 14- and 15-H), 3.82 (2 H, m, 3- and 10-H), 6.0—7.10 (5 H, m, 5-, 18-, and 19-H), 6.08, 6.10, 6.20, 6.88 (12 H, 4 s, CO_2Me), 8.05 (2 H, m, 18-H), and 8.85 (1 H, m, 17-H).

Dimethyl 5,6,7,8-Tetrahydro-2,11,4,9-propane-1,3-diylidene-1,12-benzodiazacyclotetradecine-6,7-dicarboxylates (**16**) *and* (**17**).—The tetraester (**13**) (6.0 g, 15.4 mmol) was dissolved in dimethylformamide (120 ml) and lithium chloride (6.4 g, 104.7 mmol) and water (2.3 g, 127.8 mmol) were added. The mixture was stirred at 110 °C for 24 h under nitrogen. Removal of the solvent under high vacuum gave a brown residue. This was extracted with chloroform (200 ml), washed with water (3 × 100 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a brown oil (5.9 g). Filtration flash column chromatography (90% ether–10% ethyl acetate) gave the isomers (**16**) and (**17**) (3.84 g, 83%) as a yellow solid. Fractional recrystallisation from ethyl acetate afforded one pure *isomer* (**16**) (2.2 g, 47.6%), as yellow crystals, m.p. 186—188 °C (dec.) (Found: C, 69.9; H, 5.6; N, 7.0. $C_{23}H_{22}N_2O_4$ requires C, 70.25; H, 5.68; N, 7.18%); $\nu_{max.}$($CHCl_3$) 1 730, 1 610, and 1 570 cm^{-1}; *m/z* 390 (M^+; 100%); τ 2.31 (2 H, m, 13- and 16-H), 2.66 (2 H, m, 14- and 15-H), 3.76 (2 H, s, 3- and 10-H), 6.28 (3 H, s, CO_2Me), 6.40 (3 H, s, CO_2Me), 6.4—7.60 (7 H, complex, 5-, 6-, 7-, 8-, and 19-H), 8.01 (2 H, t, *J* 3 Hz, 18-H), and 8.80 (1 H, m, 17-H); ^{13}C n.m.r. (p.p.m.) 24.85 (C-18), 37.27

† In the n.m.r. assignments the carbon atoms of the phenyl substituent are labelled Ca–j (positions 1–6, respectively).

and 37.65 (C-6 and -7), 38.45 and 39.99 (C-5 and -8), 44.46 (C-17), 45.76 (C-19), 52.23 (CO_2Me), 52.35 (CO_2Me), 121.95 and 122.49 (C-3 and -10), 125.02 (C-14 and -15), 127.95 (C-13 and -16), 139.06 and 139.14 (C-12a and -16a), 141.88 and 142.73 (C-4 and -9), 144.80 and 145.06 (C-2) and -11), 173.89 (CO_2Me), and 174.83 (CO_2Me). Further crystallisation (ethyl acetate) afforded a mixture of isomers (1.1 g, 24%), m.p. 171—174 °C (dec.), *m/z* 390 (M^+; 100%). ^1H N.m.r. spectroscopy indicated that the mixture was mainly isomer (**17**), characterised by resonances at τ 2.30, 2.65, 3.75, 6.27, 6.40, 6.48, 6.5—7.5 (complex), 8.00, and 8.80.

Allylic Bromination of the Tetraester (**13**).—The tetraester (**13**) (270 mg, 0.53 mmol) was dissolved in carbon tetrachloride (40 ml) and *N*-bromosuccinimide (200 mg, 1.12 mmol) was added. The solution was heated under reflux for 1 h under nitrogen. White light was used as the free radical initiator. Succinimide formed during the reaction was filtered off, and the solvent was removed under reduced pressure to give a yellow solid (334 mg). Recrystallisation from ether afforded the unstable tetramethyl 5-bromo-5,6,7,8-tetrahydro-2,11,4,9-propane-1,3-diylidene-1,12-benzodiazacyclotetradecine-6,6,7,7-tetracarboxylate (**19**) (180 mg, 57.6%) as bright yellow crystals, m.p. 180—183 °C (dec.); *m/z* 584 and 586 (M^+); τ 2.30 (2 H, m, 13- and 16-H), 2.66 (2 H, m, 14- and 15-H), 3.77 (2 H, m, 3- and 10-H), 4.22 (1 H, s, 5-H), 5.33 (1 H, m, 19-H), 5.87 (2 H, d, *J* 14 Hz, 8-H), 6.80 (3 H, s, CO_2Me), 6.12 (3 H, s, CO_2Me), 6.24 (3 H, s, CO_2Me), 6.94 (3 H, s, CO_2Me), 7.09 (2 H, d, *J* 14 Hz, 8-H), 7.98 (2 H, m, 18-H), and 8.80 (1 H, m, 17-H).

Dimethyl 2,11,4,9-Propane-1,3-diylidene-1,12-benzodiazacyclotetradecine-6,7-dicarboxylate (**2**).—(*a*) The monobromotetraester (**19**) (1.5 g, 2.6 mmol) was dissolved in dimethylformamide (100 ml) and lithium chloride (445 mg, 10.5 mmol) and water (216 mg, 12 mmol) were added. The mixture was stirred at 100 °C for 18 h under nitrogen. Removal of the solvent under high vacuum gave an oil which was dissolved in chloroform (200 ml), washed with water (3 × 100 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a dark brown oil (1.04 g). Preparative t.l.c. (80% chloroform–20% ethyl acetate) afforded the more polar isomer (**16**) (96 mg, 10%), identical (by ^1H n.m.r. and mass spectrum and t.l.c.) with the diester obtained by the hydrolysis of the tetraester (**13**) using lithium chloride in dimethylformamide–water, and the less polar compound (**19**) (270 mg, 27%). Recrystallisation of the less polar fraction from ethyl acetate afforded *dimethyl 2,11,4,9-propane-1,3-diylidene-1,12-benzodiazacyclotetradecine-6,7-dicarboxylate* (**2**) (202 mg, 20%) as dark red crystals, m.p. 185—187 °C (dec.) (Found: C, 71.4; H, 4.8; N, 7.2. $C_{23}H_{18}N_2O_4$ requires C, 71.49; H, 4.70; N, 7.25%); $\nu_{max.}$(CHCl$_3$) 1 728, 1 558, and 1 493 cm^{-1}; $\lambda_{max.}$ 297 (ε 81 000) and 450sh nm (11 300); *m/z* 386 (M^+, 100%); τ 1.94 (2 H, m, 13- and 16-H), 2.18 (2 H, s, 5- and 8-H), 2.40 (2 H, m, 14- and 15-H), 3.05 (2 H, m, 3- and 10-H), 6.15 (2 H, s, CO_2Me), 7.68 (1 H, m, 19-H), 8.65 (2 H, t, *J* 3 Hz, 18-H), and 8.74 (1 H, m, 17-H); ^{13}C n.m.r. (p.p.m.) 21.64 (C-18), 32.62 (C-17), 36.39 (C-19), 52.82 (CO_2Me), 124.82 (C-3 and -10), 126.26 (C-14 and -15), 129.39 (C-13 and -16), 130.39 (C-12a and -16a), 131.34 (C-4 and -9), 135.80 (C-6 and -7), 138.48 (C-5 and -8), 139.53 (C-2 and -11), and 169.06 (CO_2Me).

(*b*) *Reaction of the diester* (**16**) *with selenium dioxide*. The diester (**16**) (200 mg, 0.51 mmol) was dissolved in aqueous dioxane (90% dioxane–10% water) and selenium dioxide (124 mg, 1.1 mmol) was added. The mixture was heated under reflux for 10 min under nitrogen. Analytical t.l.c. showed that the total consumption of the starting material had occurred. Removal of the solvent afforded a reddish brown oil. Flash column chromatography (ether) afforded the annulene diester (**2**) (110 mg, 56%) as a dark red oil which was identical (t.l.c., ^1H n.m.r. and mass spectrum) with the product obtained by the hydrolysis of the monobromotetraester (**18**) using lithium chloride in dimethylformamide–water.

(*c*) *Allylic bromination of the diester* (**16**). The diester (**16**) (200 mg, 0.51 mmol) was dissolved in carbon tetrachloride (50 ml), and *N*-bromosuccinimide (192 mg, 1.1 mmol) was added. The resulting solution was heated under reflux for 2 h under nitrogen. White light was used as the free radical initiator. Analytical t.l.c. showed the formation of four products. Succinimide formed during the reaction was filtered off and the solvent was removed under reduced pressure to obtain a tan oil (220 mg). This was dissolved in methylene dichloride (25 ml) and triethylamine (1 ml) was added. The resulting solution was stirred at room temperature for 15 h, washed with water (3 × 50 ml), dried ($MgSO_4$), and filtered. Removal of the solvent under reduced pressure afforded a crude oil. Preparative t.l.c. (10% ether–90% ethyl acetate) afforded the annulene diester (**2**) (40 mg, 20%) as a red solid which was identical (t.l.c., ^1H n.m.r.) with the product obtained by the hydrolysis of the monobromotetraester (**19**) using lithium chloride in dimethylformamide–water.

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