Synthesis of a Bridged Benzodiaza[14]annulene by Reaction of 4,6-Bis-bromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine with Dimethyl Acetonedicarboxylate

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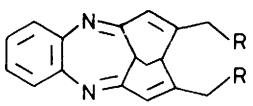
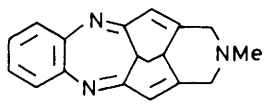
Reaction of 4,6-bisbromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**1**) under basic conditions with dimethyl acetone-1,3-dicarboxylate gives the ester (**10**) by 1,3-dialkylation. Oxidation of the ester (**10**) affords the bridged annulenone (**19**). The reaction of the dibromide (**1**) with the dimethyl ester of 2,2'-sulphinylbisacetic acid (**12**) or of 2,2'-sulphonylbis acetic acid (**11**) gives products not by 1,3-dialkylation but by *gem*-dialkylation.

Reaction of the dibromide (**1**) with amines and hydrazines[1] results in cyclisation giving bridged benzodiazepines with the creation of new six- and seven-membered rings respectively. Thus, methylamine affords the amine (**3**) and 1,2-dimethylhydrazine gives the hydrazine (**4**). Similarly, the dibromide (**1**) reacts with carbanions from dimethyl malonate and tetramethyl ethane-1,1,2,2-tetracarboxylate[2] to give further bridged benzodiazepines by the creation of a new six-membered ring in the case of the ester (**5**) and of a new seven-membered ring in the case of the ester (**8**). Subsequent elaboration of the ester (**8**) afforded the [14]annulene (**9**). We now report the reactions of the dibromide (**1**) with nucleophiles designed to give bridged benzodiazepines with the creation of a new eight-membered ring. We have found that the reaction of the dibromide (**1**) with dimethyl acetonedicarboxylate affords the ester (**10**) with the creation of an eight-membered ring, but in contrast the reaction with the ester (**11**) or (**12**) leads to the esters (**6**) and (**7**), or (**14**) respectively, with the preferential formation of a six-membered ring.

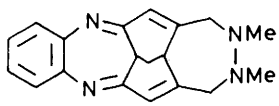
The reaction of the dibromide (**1**) with dimethyl acetone-1,3-dicarboxylate in tetrahydrofuran in the presence of sodium hydride afforded a single crystalline diester in 49% yield. Cyclisation might lead to the ester (**15**) or, by formation of an eight-membered ring, to a diester present either as an enol (**10**) or as a ketoester (**16**). In a related example, Kamada and Yamamoto[3] found that dimethyl acetonedicarboxylate reacted with the dibromide (**17**) to give the diester (**18**) with the formation of an eight-membered ring. The enol form (**18**) was stable with respect to equilibration to the tautomeric ketoesters, and Kamada and Yamamoto indicate that the initially isolated ketoesters are relatively stable and could be characterized spectroscopically. The enol form (**18**) showed a band ($\nu_{max.}$ 1 658 cm^{-1}) associated with the chelated ester and a band ($\nu_{max.}$ 1 621 cm^{-1}) associated with the alkene moiety. These bands were found to be absent in the keto tautomers. In the product isolated from the reaction of the dibromide (**1**) we observed bands at $\nu_{max.}$ 1 650 and 1 615 cm^{-1} and therefore concluded that the enol (**10**) had been formed. Further characterisation of this enol (**10**) is complicated by two factors. Although the absence of a band at $\nu_{max.}$ 1 720 cm^{-1} shows that a single tautomeric form of the ester (**10**) has been isolated, the ^1H n.m.r. spectrum is very complex. We have previously noted, for the hydrazine[1] (**4**) and the ester[2] (**8**), complex spectra associated with conformational equilibria resulting from the inversion of the seven-membered ring. We attributed the complex spectrum of the ester (**10**) to the existence of more than one conformer. The second complication which prevented a detailed variable temperature analysis of the ester (**10**) is the fact that it is extremely unstable.



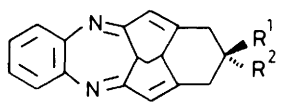
(**1**) R = Br
(**2**) R = H



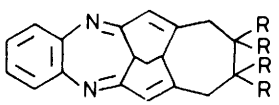
(**3**)



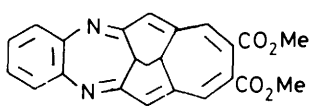
(**4**)



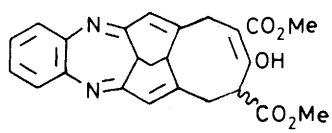
(**5**) $R^1 = R^2 = CO_2Me$
(**6**) $R^1 = SO_2CH_2CO_2Me$, $R^2 = CO_2Me$
(**7**) $R^1 = CO_2Me$, $R^2 = SO_2CH_2CO_2Me$



(**8**) R = CO_2Me



(**9**)

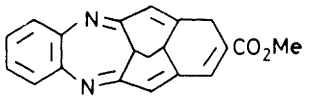


(**10**)

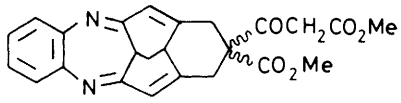
Exposure of the pale coloured solution of the ester (**10**) to air resulted in rapid colouration. When a solution of the ester (**10**) in chloroform was exposed to air for a week and then chromatographed, a new ester was isolated in 17% yield. This ester, isolated as bright orange needles, was found to be the annulenone (**19**). This assignment is based on the microanalysis, mass spectrum [parent ion at 414 (100%)] and supporting ^1H and ^{13}C n.m.r. and i.r. data.

$MeO_2CCH_2XCH_2CO_2Me$

(11) X = SO_2
(12) X = SO
(13) X = S



(14)



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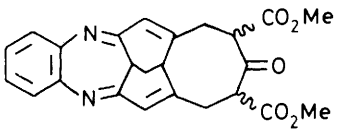
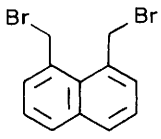


(16)



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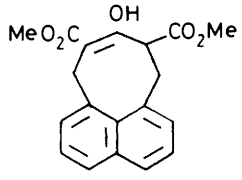
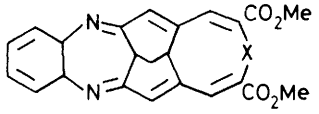


(18)

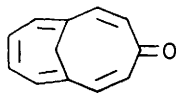


(19) X = CO
(20) X = S
(21) X = SO
(22) X = SO_2

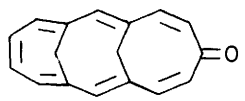
The ester (**19**) can be considered[4–6] to be a 14π electron analogue of other previously reported annulenones. Annulenones such as (**23**)[4] and (**24**)[5] are characterized by their ^1H n.m.r. spectra in which the downfield shift of the vinylic protons and the upfield shift of the bridge protons indicate a diamagnetic ring current associated with aromatic character. Such shifts in the spectrum of the ester (**19**) are relatively small. For the bridge and bridgehead protons in compound (**19**) small shielding effects are observed. The bridge protons resonate at δ 1.78 in (**19**) but at δ 2.02 in the benzodiazepine (**2**) which has no closed π electron system. Similarly the bridge proton 18-H is shielded in compound (**19**) (δ 0.8) relative to that in (**2**) (δ 1.37). The peripheral vinyl protons 3-H and 11-H at δ 6.90 in the ester (**19**) are deshielded relative to those of the benzodiazepine (**2**). Hence these spectral observations suggest that although some of the characteristics of aromaticity are found with compound (**19**) such effects are much less important than with the simpler annulenones (**23**) and (**24**).

Having completed the synthesis of the annulenone (**19**) we turned our attention to the possible synthesis of the thiaannulene analogues (**20**)—(**22**). Such a synthesis requires the construction of an eight-membered ring from the dibromide (**1**) by reaction with anions derived from the ester (**11**), (**12**), or (**13**), and a subsequent oxidation. An example of dialkylation of the diethyl ester (**25**) has been reported[7] to give 1,3-dialkylated products without concomitant *gem*-dialkylation.

The reaction of the dibromide (**1**) with the ester (**11**) in tetrahydrofuran in the presence of sodium hydride afforded a major product (51%) which could be separated from a minor isomeric product (9%) by flash chromatography. The structure (**6**) could be assigned to the major product on the basis of the microanalytical and spectroscopic evidence. A distinction from



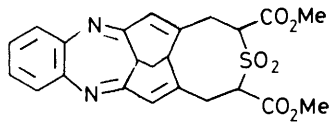
(23)



(24)

$EtO_2CCH_2SO_2CH_2CO_2Et$

(25)



(26)

an eight-membered ring sulphone (**26**) could be made by the observation in the ^{13}C n.m.r. spectrum of a resonance associated with a quaternary carbon at 82.32 p.p.m., and the resonance associated with a methylene carbon at 54.78 p.p.m. (SO_2CH_2), and by other features in the ^1H n.m.r. spectrum.

The reaction of the dibromide (**1**) with the ester (**12**) under similar conditions afforded after chromatography a single product (24%) identical (t.l.c., m.p., and spectra) with the ester (**14**) prepared[2] by bromination and debromomethoxycarboxylation of the ester (**5**). A third route to give the eight-membered ring based on the alkylation of the ester (**13**) was briefly examined. However, following the attempted reaction with the dibromide (**1**) the ester (**13**) could be recovered unchanged but the dibromide (**1**) had undergone complete decomposition. It is possible that anions derived from compound (**13**), which will be stronger bases than the corresponding bases derived from (**11**) or (**12**), preferentially react by proton abstraction from the dibromide (**1**).

The formation of the ester (**10**) from dimethyl acetone-1,3-dicarboxylate occurs with preferential 1,3-dialkylation to give an eight- rather than a six-membered ring. In contrast, the formation of the epimers (**6**) and (**7**) and the ester (**14**) from the esters (**11**) and (**12**) respectively, implies that preferential *gem*-alkylation to give the smaller ring has occurred. In the formation of the ester (**14**) an intermediate sulphoxide undergoes elimination under the basic reaction conditions to give the conjugated ester (**14**).

We consider that this difference in the formation of the larger ring from dimethyl acetone-1,3-dicarboxylate and the smaller ring from the esters (**11**) and (**12**) originates from a kinetic difference in the relative rates of the cyclisation in the second alkylation step. In the case of the sulphoxide and sulphone intermediates, the larger C–S bond lengths relative to the C–C bond lengths in the intermediate derived from dimethyl acetone-1,3-dicarboxylate make cyclisation to the larger ring more difficult. We are unaware of an example which illustrates so clearly the different alkylation behaviour of the esters (**11**) and (**12**) from that of dimethyl acetone-1,3-dicarboxylate.

Experimental

M.p.s. were determined in a capillary tube and are uncorrected. I.r. spectra were obtained using a Perkin-Elmer 157G grating spectrometer. ^1H and ^{13}C N.m.r. spectra were obtained using a Varian Associates XL-100 spectrometer. Tetramethylsilane was used as an internal standard and deuteriochloroform was used as solvent. U.v. spectra were obtained for solutions in ethanol using a Pye-Unicam SP 800 spectrophotometer. Mass spectra were obtained at 70 eV using a Kratos MS-30 spectrometer equipped with a DS 505 Data System. Flash chromatography was carried out on Macherey Nagel silica gel 60. Organic extracts were dried over anhydrous magnesium sulphate and solvent evaporation was carried out at reduced pressure using a rotatory evaporator. Elemental analyses were performed by C.H.N. Analysis Limited, Alpha House, South Wigston.

Reaction of 4,6-*Bisbromomethyl*-5,2,8-*ethanylylidene*-5H-1,9-*benzodiazacycloundecine* (**1**) *with Dimethyl* 2,2′-*Sulphonylbisacetate* (**1**).—To a stirred solution of 4,6-bisbromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine[1] (**1**) (1.0 g, 2.45 mmol) in dry tetrahydrofuran (50 ml) containing sodium hydride (243 mg 10.1 mmol) a solution of dimethyl 2,2′-sulphonylbisacetate[8] (**11**) (570 mg, 2.7 mmol) in dry warm tetrahydrofuran (30 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 3 h. The excess of sodium hydride was filtered off, the filtrate was poured into saturated ammonium chloride solution and extracted with dichloromethane (2 × 100 ml). The organic layer was washed with brine (2 × 50 ml), water (50 ml), dried and filtered. Evaporation of the solvent gave a yellow oil (1.20 g). Flash chromatography afforded a less polar fraction (570 mg) [eluant ethyl acetate–diethyl ether (1:3)] and a minor, more polar fraction (100 mg) [eluant ethyl acetate–diethyl ether (1:1)]. Recrystallisation of the less polar fraction from ethyl acetate afforded one *stereoisomer* (**6**) of *methyl* 6-*methoxycarbonylmethylsulphonyl*-6,7-*dihydro*-2,10:4,8-*propane*-1,3-*diylidene*-5H-1,11-*benzodiazacyclotridecine*-6-*carboxylate* (**6**) (51%), m.p. 135—138 °C (Found: C, 60.8; H, 4.95; N, 6.1; S, 6.9. $C_{23}H_{22}N_2O_6S$ requires C, 60.8; H, 4.9; N, 6.2; S, 7.05%); $\nu_{max.}$(KBr) 1 750, 1 560, 1 440, and 1 140 cm^{-1}; *m/z* 454 (M^+, 16%), 318 (100), and 316 (68); δ 0.9—1.0 (1 H, m, 16-H), 1.98 (2 H, t, *J* 3 Hz, 17-H), 3.3—3.65 (8 H, complex, 7-H, 18-H, and OMe), 3.85 (3 H, s, OMe), 4.22 (2 H, s, CH_2), 6.25 (2 H, br s, 3-H and 9-H), and 7.3–7.8 (4 H, complex, aromatic); δ_C 21.98 (C-17), 37.14 (C-5 and C-7), 37.69 (C-16), 42.81 (C-18), 53.54 (OMe), 54.05 (OMe), 54.78 (SO_2CH_2), 82.32 (C-6), 122.03 (C-3 and C-9), 125.16 (C-13 and C-14), 127.95 (C-12 and C-15), 139.18 and 140.52 (C-4 and C-8), 143.65 (C-2 and C-10), and 161.92 and 166.27 (CO_2Me).

Recrystallisation of the more polar fraction from ethyl acetate afforded the *stereoisomer* (**7**) (9%), m.p. 190—192 °C (decomp.). $\nu_{max.}$($CHCl_3$) 1 740, 1 520, and 1 140 cm^{-1}; *m/z* 318 (100%) and 316 (50); δ 0.84—0.98 (1 H, m, 16-H), 1.86—2.00 (2 H, m, 17-H), 3.2—3.6 (13 H, complex, 5-H, 7-H, 18-H, OMe and SO_2CH_2), 6.22 (2 H, s, 3-H and 9-H), and 7.3—7.8 (4 H, complex, aromatic); δ_C 21.97 (C-17), 37.65 (C-16), 39.07 (C-5 and C-7), 42.84 (C-18), 53.75 (OMe), 84.24 (C-6), 122.43 (C-3 and C-9), 125.18 (C-13 and C-14), 128.03 (C-12 and C-15), 139.16 and 139.76 (C-4 and C-8), 143.54 (C-2 and C-10), and 165.01 (CO_2Me).

Methyl 2,10,4,8-*Propane*-1,3-*diylidene*-5H-1,11-*benzodiazacyclotridecine*-6-*carboxylate* (**14**).—To a stirred solution of 4,6-bisbromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**1**) (300 mg, 0.738 mmol) in dry tetrahydrofuran (30 ml) containing sodium hydride (63 mg, 2.65 mmol) at 0 °C, a solution of dimethyl 2,2′-sulphinylbisacetate[9] (**12**) (172 mg, 0.886 mmol) in dry tetrahydrofuran (20 ml) was added dropwise. The reaction mixture was gently warmed to 10 °C and stirred under nitrogen at 10 °C for 15 min. The excess of sodium hydride was filtered off, and the filtrate was poured into saturated ammonium chloride solution (100 ml) and extracted with ethyl acetate (2 × 100 ml). The combined organic layers were washed with brine (2 × 50 ml), dried, and filtered. Evaporation of the solvent gave a dark brown oil (100 mg). Purification by flash chromatography [eluant diethyl ether–ethyl acetate (1:4)] gave an orange oil (55 mg, 24%) and crystallisation (ethyl acetate) afforded as yellow crystals methyl 2,10,4,8-propane-1,3-diylidene-5*H*-1,11-benzodiazacyclotridecine-6-carboxylate (**14**), identical (m.p., i.r., ^1H n.m.r., and t.l.c.) with a sample prepared[2] by bromination and debromomethoxycarbonylation of the ester (**5**).

Dimethyl 7-*Oxo*-2,12,4,10-*propane*-1,3-*diylidene*-1,13-*benzodiazacyclopentadecine*-6,8-*dicarboxylate* (**19**).—To a stirred solution of 4,6-bisbromomethyl-5,2,8-ethanylylidene-5*H*-1,9-benzodiazacycloundecine (**1**) (2.0 g, 4.9 mmol) in dry tetrahydrofuran (50 ml) containing sodium hydride (407 mg, 16.95 mmol, 60% suspension) a solution of dimethyl acetone-1,3-dicarboxylate (0.96 g, 5.65 mmol) in dry tetrahydrofuran (30 ml) was added. The reaction mixture was heated at 50 °C for 3 h under nitrogen. The excess of sodium hydride was filtered off and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate (200 ml) and the resulting solution was washed with brine (2 × 50 ml) and water (50 ml), dried and filtered. Evaporation of the solvent gave a red oil (2.05 g) which crystallized from ethyl acetate to afford dimethyl 7-hydroxy-8,9-dihydro-2,12:4,10-propane-1,3-diylidene-5*H*-1,13-benzodiazacyclopentadecine-6,8-dicarboxylate (**10**) (0.95 g, 49%) as a white, unstable solid, m.p. 154—155 °C; *m/z* 418 (M^+, 100%); $\nu_{max.}$(KBr) 1 750, 1 650, and 1 615 cm^{-1}; δ 1.4—1.6 (1 H, m, 18-H), 1.9—2.2 (2 H, m, 19-H), 2.9—4.35 (6 H, complex, 5-H, 8-H, 9-H, and 20-H), 3.70 (3 H, s, OMe), 3.78 (3 H, s, OMe), 6.2—6.4 (2 H, complex, 3-H and 11-H), and 7.2—7.75 (4 H, complex, aromatic).

A solution of the ester (**10**) in chloroform (30 ml) became highly coloured on exposure to air at room temperature for 7 days. Evaporation of the solvent afforded a red residue which, on purification by flash chromatography [eluant diethyl ether—dichloromethane (1:4)], gave as bright orange crystals *dimethyl* 7-*oxo*-2,12,4,10-*propane*-1,3-*diylidene*-1,13-*benzodiazacyclopentadecine*-6,8-*dicarboxylate* (**19**) (17%), m.p. 252—254 °C (Found: C, 69.2; H, 4.5; N, 6.75. $C_{24}H_{18}N_2O_5$ requires C, 69.5; H, 4.4; N, 6.8%); *m/z* 414 (M^+, 100%) and 386 (31); $\nu_{max.}$(KBr) 1 710, 1 690, and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 303 nm (ε 34 000); δ 0.8—0.9 (1 H, m, 18-H), 1.78 (2 H, t, *J* 3 Hz, 19-H), 3.3—3.5 (1 H, m, 20-H), 3.86 (6 H, s, OMe), 6.90 (2 H, s, 3-H and 11-H) 7.66 (2 H, s, 5-H and 9-H), and 7.3—8.0 (4 H, complex, 14-H, 15-H, 16-H, and 17-H); δ_C 24.60 (C-19), 31.80 (C-18), 37.14 (C-20), 53.02 (OMe), 126.58 (C-3 and C-11), 128.80 (C-15 and C-16), 131.49 (C-14 and C-17), 134.05 (C-4 and C-10), 139.18 (C-6 and C-8), 140 (C-5 and C-9), 141.15 (C-2 and C-12), 163.84 (CO_2Me), and 195.49 (C-7).

Acknowledgements

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