

Synthesis of New Macrocycles. Part III.¹ Cyclic Tetraesters from Dipotassium Δ^2 -1,4-Dicarboxylates and Mono- and Di-acetylenic Dibromides

By Siegfried E. Drewes^{*} and Brian G. Riphagen, Department of Chemistry, University of Natal, Pietermaritzburg, South Africa

Condensation of the dipotassium salts of maleic, citraconic, and phthalic acids with 1,4-dibromobut-2-yne and with 1,6-dibromohexa-2,4-diyne has afforded six new acetylenic cyclic tetraesters. Those esters with four acetylenic groups are light-sensitive.

In our previous investigations¹ into the scope of the dihalide-dipotassium dicarboxylate reaction, $\alpha\alpha'$ -dibromo-*o*-xylene, which possesses a requisite 'rigid group,'² was condensed with a homologous series of dicarboxylic acids, starting with oxalic acid. Apart

from oxalic acid, the acids were all 'non-rigid' and became increasingly flexible as the length of the hydro-

¹ S. E. Drewes and B. G. Riphagen, *J.C.S. Perkin I*, 1974, 323.

² W. Baker, J. F. W. McOmie, and W. D. Ollis, *J. Chem. Soc.*, 1951, 200.

carbon chain increased. In the present work *both* reaction partners possess minimal flexibility. Thus, maleic, citraconic, and phthalic acid (each with four coplanar atoms) were each condensed with a molecule essentially linear over four (dibromobutyne) or six (dibromohexadiyne) carbon atoms.

All the products gave satisfactory analytical figures and were further characterized by their mass and n.m.r. spectra (see Table). The citraconic acid derivatives

Chemical shifts (τ values) for protons of compounds (1)—(6) in trifluoroacetic acid

Cyclic ester	Ring CH ₂	Vinylic H (Aromatic H)	Vinylic Me
(1)	4.97 (s)	3.49 (s)	
(2)	4.97 (s)	3.87 (d)	7.80 (d)
(3)	4.80 (s)	(2.00—2.38)	
(4)	4.97 (s)	3.53 (s)	
(5)	4.95 (d)	3.87 (d)	7.80 (d)
(6)	4.87 (s)	(2.00—2.44)	

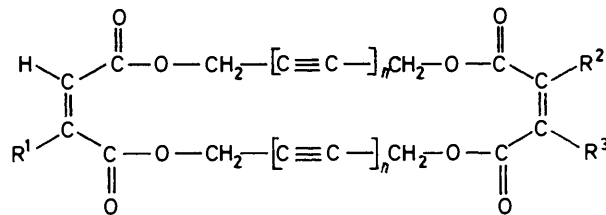
(2) and (5) showed the anticipated allylic coupling³ between the vinylic methyl group and the vinylic proton. In (2) this splitting is barely discernible but in (5) it is pronounced. For compounds (1), (3), (4), and (6) the ring methylene protons gave rise to singlets, (2) showed a broad singlet, and (5) exhibited a clear doublet (J 4.0 Hz). This J value is too large for mutual long-range splitting of the methylene protons over six carbon atoms.⁴ However, if the molecule had a 'twisted' conformation, the methylene protons might be non-equivalent.

The dimeric nature of all six cyclic esters was shown by mass spectrometry. Instead of a molecular ion peak all spectra showed a small ($M + 1$)⁺ peak. In common with other macrocyclic esters,^{5,6} compounds (1)—(3) gave a prominent ($M/2 + 1$)⁺ peak as well as a strong peak corresponding to the ion characteristic of the parent acid,¹ at m/e 99, 113, or 149. All the spectra contained the ion corresponding to (7). The fragmentation of the tetraynes (4)—(6) revealed certain differences. The ($M + 1$)⁺, ($M/2 + 1$)⁺, and parent acid peaks were clearly discernible but were not prominent. Major fragments corresponded to the ions (8) and (9) shown for the maleic acid ester.

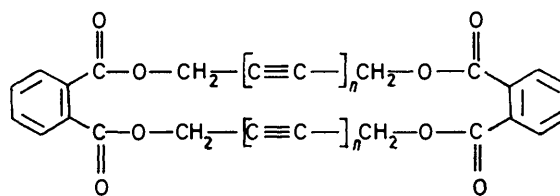
Yields were low (2—5%) for compounds (1)—(5) but an 11% yield was obtained for (6). The rigidity of the reactants does not appear to have promoted cyclization. For the related unstrained diyne (10), Nakagawa and Toda⁷ report a 40% yield from use of the oxidative coupling technique.

The diynes (1)—(3) are completely photostable, but the tetraynes (4)—(6) became pink on exposure to light. The material producing the discolouration, which was confined to the surface of the crystals, was virtually insoluble in all organic solvents. A very dilute solution in dimethylformamide showed λ_{max} 470 nm. Similar

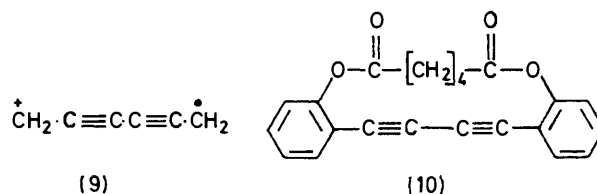
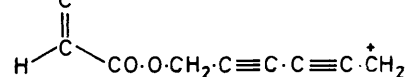
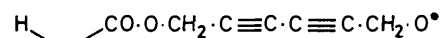
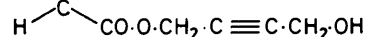
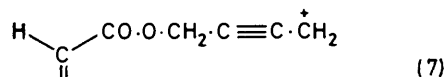
discolouration phenomena have been observed⁸ for the cyclic diyne (11). Why the tetraynes (4)—(6) should be less stable than the diynes (1)—(3), is not clear, since



- (1) $n = 1$, $R^1 = R^2 = R^3 = \text{H}$
 (2) $n = 1$, $R^1 = \text{Me}$, $R^2 = \text{Me}$ or H , $R^3 = \text{H}$ or Me
 (4) $n = 2$, $R^1 = R^2 = R^3 = \text{H}$
 (5) $n = 2$, $R = \text{Me}$, $R^2 = \text{Me}$ or H , $R^3 = \text{H}$ or Me



- (3) $n = 1$
 (6) $n = 2$



angular and transannular strain should be the same in the two groups.

The various strains imposed on cyclic systems containing one or more alkyne groups have been summarized recently⁹ by Meier, who points out that incorporation of unsaturated bonds or aromatic systems into rings of 10—12 atoms leads to considerable instability, as in

³ L. M. Jackman and S. Sternhell, 'Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 322.

⁴ J. D. Roberts, *J. Amer. Chem. Soc.*, 1962, **84**, 1582.

⁵ S. E. Drewes and P. C. Coleman, *J.C.S. Perkin I*, 1972, 2148.

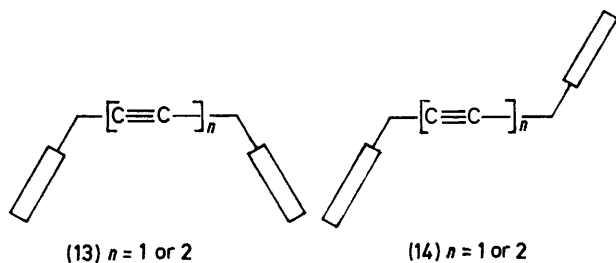
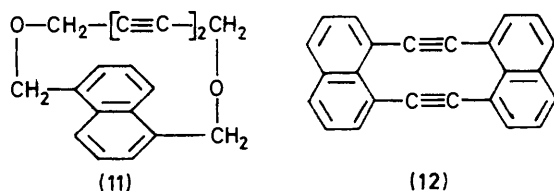
⁶ P. Margaretha, F. P. Schmoock, H. Budzikiewicz, and O. E. Polansky, *Monatsh.*, 1968, **99**, 2539.

⁷ M. Nakagawa and F. Toda, *Chem. and Ind.*, 1959, 458.

⁸ T. Ando and M. Nakagawa, *Bull. Chem. Soc. Japan*, 1967, **40**, 363.

⁹ H. Meier, *Synthesis*, 1972, 235.

compound (12) for example. In the present series the ester bond in the macrocycle ensures considerable



flexibility, thus minimizing transannular interaction. Inspection of accurate molecular models of the cyclic esters, coupled with the n.m.r. evidence, leads to the conclusion that the esters exist in either conformation (13) or (14). In the citraconic acid esters (2) and (5) it is possible that the double bonds at the 'ends' of the molecule are twisted relative to one another, as has been shown by an X-ray study¹⁰ for the cyclic dimeric ethylene ester of phthalic acid. This would account for the non-equivalence of the protons of each methylene group.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian T60 instrument and mass spectra with a Varian CH7 spectrometer at 70 eV.

The cyclization procedure was the same throughout and followed the method described before.¹

1,6,11,16-Tetraoxacycloicosin-3,13-diene-8,18-diyne-2,5,12,15-tetrone (1).—Dipotassium maleate (8.14 g, 42.0 mmol) and 1,4-dibromobut-2-yne¹¹ (8.90 g, 42.0 mmol) in dimethylformamide (100 ml) were heated at 70° for 28 h. The crude product, isolated as before,¹ was separated on an alumina column with chloroform as eluant and gave a main fraction which crystallized as *needles* (100 mg) from ethyl acetate; m.p. 184° (Found: C, 57.6; H, 3.9. C₁₈H₁₂O₈ requires C, 57.8; H, 3.65%), ν_{\max} (KBr) 2900, 1761, 1235, 1163, 823, and 806 cm⁻¹, λ_{\max} 243 nm (ϵ 1300).

3,13(or 14)-Dimethyl-1,6,11,16-tetraoxacycloicosin-3,13-diene-8,18-diyne-2,5,12,15-tetrone (2).—Similarly, dipotassium citraconate (10.01 g, 48.1 mmol) and 1,4-dibromobut-2-yne (10.2 g, 48.1 mmol) gave white *needles* (200 mg), m.p. 254° (from ethyl acetate) (total reflux time only 4 h) (Found: C, 60.3; H, 4.85. Calc. for C₁₈H₁₆O₈: C, 60.0;

¹⁰ M. J. Laing, P. C. Coleman, and S. E. Drewes, *J. S. African Chem. Inst.*, in the press.

¹¹ A. W. Johnson, *J. Chem. Soc.*, 1946, 1009.

H, 4.5%), ν_{\max} (KBr) 2874, 1724, 1256, 1163, and 769 cm⁻¹, λ_{\max} 242 nm (ϵ 1500).

8,9,20,21-Tetrahydro-7,10,19,22-tetrahydridibenzo[c,m]-[1,6,11,16]tetraoxacycloicosin-5,12,17,24-tetrone (3).—Dipotassium phthalate (6.90 g, 28.3 mmol) and 1,4-dibromobut-2-yne (6.0 g, 28.3 mmol) in dimethylformamide (100 ml) were stirred for 16 h at 20° and for 1 h at 60°. White *needles* (200 mg), m.p. 280° (from dioxan), were obtained directly (Found: C, 66.4; H, 4.00. C₂₄H₁₆O₈ requires C, 66.7; H, 3.73%), ν_{\max} (KBr) 1725, 1270, 1125, and 747 cm⁻¹, λ_{\max} 275 (ϵ 2400) and 245 nm (3300).

1,6,13,18-Tetraoxacyclotetracosin-3,15-diene-8,10,20,22-tetrayne-2,5,14,17-tetrone (4).—Prop-2-yn-1-ol was dimerized to hexa-2,4-diyne-1,6-diol,^{12,13} which was converted into the corresponding dibromo-compound.¹⁴ Dipotassium maleate (7.23 g, 37.2 mmol) and 1,6-dibromohexa-2,4-diyne (8.8 g, 37.2 mmol) in dimethylformamide (100 ml) were stirred for 16 h at 20° and then for 9 h at 65°. Fine white *needles* (200 mg), m.p. 160° (decomp.) (from ethyl acetate), were isolated by the usual method and turned pink on exposure to light (Found: C, 63.4; H, 3.6. C₂₀H₁₂O₈ requires C, 63.2; H, 3.2%), ν_{\max} 2924, 1730, 1220, 1153, and 806 cm⁻¹, λ_{\max} 260 (ϵ 1600) and 246 nm (2100).

3,15(or 16)-Dimethyl-1,6,13,18-tetraoxacyclotetracosin-3,15-diene-8,10,20,22-tetrayne-2,5,14,17-tetrone (5).—Dipotassium citraconate (10.22 g, 49.1 mmol) and 1,6-dibromohexa-2,4-diyne (11.6 g, 49.1 mmol) in dimethylformamide gave, after 16 h at 20° and 2.5 h at 60°, white *needles* (250 mg), m.p. 160° onwards (decomp.). The crystals formed slowly from an oil after 3 days at 0° and were recrystallized from ethyl acetate. They turned dark pink on exposure to light. The coloured material was insoluble in ethyl acetate and could be removed by recrystallization (Found: C, 64.2; H, 3.9. Calc. for C₂₂H₁₆O₈: C, 64.7; H, 3.95%), ν_{\max} 2985, 1736, 1263, 1126, and 781 cm⁻¹, λ_{\max} 260 (ϵ 1600) and 246 nm (2500).

8,9,10,11,22,23,24,25-Octahydro-7,12,21,26-tetrahydridibenzo[c,o]-[1,6,13,18]tetraoxacyclotetracosin-5,14,19,28-tetrayne (6).—Dipotassium phthalate (7.33 g, 30.0 mmol) and 1,6-dibromohexa-2,4-diyne (7.1 g, 30.0 mmol) in dimethylformamide afforded white *needles* (800 mg), m.p. 160° (decomp.) (from dioxan), after stirring for 16 h at 20° and for 1 h at 60°. The crystals separated slowly (0°) from a brown oil and were extremely susceptible to light (Found: C, 72.5; H, 3.75. C₂₈H₁₆O₈ requires C, 72.4; H, 3.45%), ν_{\max} 2890, 1730, 1271, 1073, 790, and 746 cm⁻¹, λ_{\max} 277 (ϵ 1900), 260 (1900), and 247 nm (3100). A solution of (6) in dioxan did not become discoloured but the dry crystalline material rapidly turned deep pink to give a pigment of λ_{\max} 470 nm (in dimethylformamide).

We thank I. Antonowitz and V. B. Seethal for elemental analyses and the South African Council for Scientific and Industrial Research for financial assistance and a Bursary (to B. G. R.).

[4/657 Received, 1st April, 1974]

¹² H. A. Stansbury and W. R. Proops, *J. Org. Chem.*, 1962, **27**, 320.

¹³ M. D. Cameron and G. E. Bennett, *J. Org. Chem.*, 1957, **22**, 557.

¹⁴ J. B. Armitage and M. C. Whiting, *J. Chem. Soc.*, 1952, 2005.