Synthesis of Oxometacyclophanes with the Dieckmann Condensation

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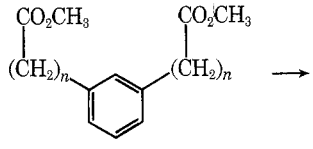
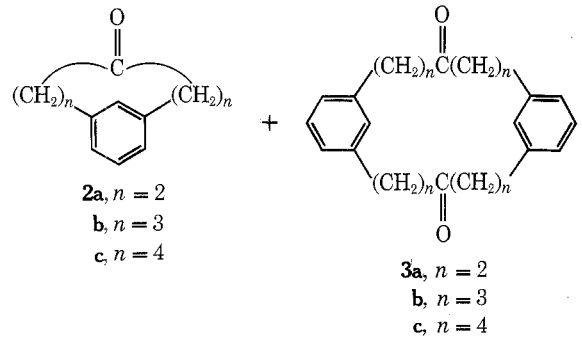
Received November 29, 1974

The Dieckmann condensation under conditions of high dilution has been used with methyl esters of *m*-benzenedialkanoic acids. The products, metacyclophanes with carbonyl groups at the centers of the meta bridges, are described. The particular meta-bridged compounds are **3** (n = 2, 3, 4) and a derivative of **2** (n = 4).

We have studied the preparation of oxometacyclophanes[1] with the Dieckmann condensation.[2] We originally wished to prepare phenalene[3] from 4-oxo[7]metacyclophane (**2b**); however, the ketone could not be prepared from ester **1b**. Therefore, we continued to investigate the



1a, $n = 2$
b, $n = 3$
c, $n = 4$



2a, $n = 2$
b, $n = 3$
c, $n = 4$

3a, $n = 2$
b, $n = 3$
c, $n = 4$

condensation to determine the limitations of the reaction and to study the properties of the ketone products.

Results and Discussion

The cyclization was conducted in the high-dilution manner used earlier[4,5] except for the following two changes. (1) Hydrolysis–decarboxylation of the intermediate keto esters in alcohol solution was changed to saponification followed by acidification and decarboxylation. Ketone product and recovered ester starting material boiled too close for facile separation. Starting material was isolated by extraction with bicarbonate, followed by acidification. (2) The ketones were isolated by vacuum distillation and sublimation of the neutral portion of the reaction mixture, instead of by recrystallization.

The Dieckmann cyclization did not lead to **2b**, the metacyclophane with a strategically placed functional group for phenalene synthesis. The isolable cyclic product was **3b**, 4,17-dioxo[7.7]metacyclophane. Homologous diesters were cyclized to **3a** as the only isolable cyclic product and to **3c** as major isolable cyclic product. A minor product from cyclization of **1c**, 5-oxo[9]metacyclophane (**2c**), was recognized but not isolated and purified.

Infrared spectra of the diketones were unusual. Each spectrum of the solid (mulled in mineral oil) contained one carbonyl stretching frequency band, while each carbon tetrachloride solution spectrum had two bands. In each solution spectrum, the higher frequency band was slightly less intense than the lower frequency band.

Nuclear magnetic resonance spectra of the diketones indicated two different environments for the aromatic hydrogens between the bridges in the smaller rings, **3a** and **3b**, but identical environments for the corresponding aromatic hydrogens in the largest ring **3c**.

Unsubstituted monoketones and diketones with structural formulas like **2** and **3** have been prepared earlier. 7-Oxo[13]metacyclophane [**2** (n = 6)] was prepared by pyrolysis of the cerium salt of *m*-benzenediheptanoic acid.[6] **3a** was prepared by the Thorpe–Ziegler cyclization of *m*-benzenedipropanenitrile, followed by hydrolysis.[7] Without high dilution the Dieckmann condensation of dimethyl *m*-benzenediacetate gave the intermediate salt of the keto ester, which was treated with methyl iodide to give the dimethyldicarbomethoxy derivative of **3** (n = 1), undoubtedly a mixture of isomers.[8]

Inspection of Dreiding models and Fisher–Taylor–Hirschfelder models reveals that refusal to form the eight-membered ring in **2a** and the ten-membered ring in **2b** and reluctance to form the 12-membered ring in **2c** should be expected. Interaction between nonbonded atoms severely reduces the frequency of collisions between carbanion moiety and ester moiety in the ring closure step to make monoketone. Interaction between these hydrogen atoms does not appreciably reduce the rates of reactions to make larger rings and linear polymers. Considering the coplanarity requirement of five ring atoms, three aromatic and two benzyl carbon atoms, the synthetic pattern is consistent with earlier investigations of the Dieckmann condensation. In the aliphatic series cyclononanone and cyclodecanone could not be prepared while cyclohendecanone and cyclododecanone were formed in extremely low yields.[5] In the paracyclophane series where six ring atoms, four aromatic and two benzyl carbon atoms, must remain coplanar, the smallest ring was the 17-membered ring in 7-oxo[13]paracyclophane.[4]

Experimental Section

***m*-Benzenedipropanoic Acid.**[9] One gram of 5% palladium on carbon was added to a solution of 150 ml of water, 65 ml of 20% aqueous NaOH, and 43.6 g (0.2 mol) of *m*-benzenediacrylic acid, which had been prepared from isophthalaldehyde and malonic acid in a Döbner synthesis:[7] mp 277–286° dec (lit.[10] mp 280° dec). The mixture was hydrogenated at room temperature in the Parr low-pressure apparatus. After catalyst had been removed by filtration, the filtrate was acidified with concentrated HCl. Then 50 ml of acetic acid was added and the suspension was digested at 80°. The mixture was cooled and filtered. After being dried, the product weighed 33.8 g (76%) and melted at 148–150.5° (lit.[11] mp 146–147°).

Dimethyl *m*-Benzenedipropanoate (1a). *m*-Benzenedipropanoic acid (1.6 mol) and 4.8 mol of thionyl chloride were refluxed until the mixture was homogeneous (1 hr). Excess thionyl chloride was removed by distillation at water aspirator vacuum. The molten acyl chloride was added slowly to 32 mol of methanol which was being stirred and chilled in an ice bath. The precipitate was removed by filtration, washed with cold methanol and with water, and dried in the vacuum desiccator. **1a** weighed 354 g (88%) and melted at 53.5–55° (lit.[12] mp 50–52°).

***m*-Benzenedipropanol.** In the customary manner,[4] 0.5 mol of **1a** was treated with lithium aluminum hydride to give 85.4 g (88%) of the glycol, bp 158° (0.5 mm) [lit.[6] bp 165–168° (0.2 mm)].

***m*-Bis(3-bromopropyl)benzene.** A mixture of 83.5 g (0.43 mol) of *m*-benzenedipropanol, 180 g of sodium bromide, and 155 ml of water was refluxed for 2 hr, while 128 ml of concentrated H_2SO_4 was added dropwise. After refluxing for 2 more hr, the mixture was cooled and extracted with ether. The ether solution was washed with aqueous $NaHCO_3$, water, aqueous $Na_2S_2O_3$, and water. The solution was dried and distilled, giving 115 g (83%) of the dibromide, bp 130–133° (0.3 mm) [lit.[6] bp 165–168° (0.2 mm)].

Higher boiling material, bp 190–250° (0.3 mm), and the undistillable residue showed strong absorption near 1110 cm^{-1} but only absorption due to C-H in the 3-μ region. This indicated some hydrolysis of the dibromide and ether formation during extraction.

***m*-Benzenedibutanoic Acid.** In the customary manner,[4] 32 g (0.1 mol) of *m*-bis(3-bromopropyl)benzene was treated with potassium cyanide to give *m*-benzenedibutanenitrile, bp 160–164° (0.2 mm). This nitrile was hydrolyzed to give 23.6 g (94%) of the acid, mp 131–135°. The analytical sample, recrystallized once from acetic acid and once from ethanol, melted at 135–136.2°[13]: NMR (CD_3SOCD_3) δ 11.8 (s, broad, 2, $-CO_2H$), 6.9–7.2 (m, 4, ArH), 2.56 (t, 4, J = 7 Hz, $ArCH_2-$) (contribution of CD_3SOCD_2H was subtracted out), 2.15 (m, 4, $-CH_2CO_2H$), 1.75 (m, 4, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.24; H, 7.24.

Dimethyl *m*-Benzenedibutanoate (1b). In the customary manner,[4] 23 g (0.092 mol) of *m*-benzenedibutanoic acid was esterified to give 21.4 g (77%) of **1b**: bp 143–146° (0.2 mm); NMR ($CDCl_3$) δ 7.03 (m, 3, ArH), 7.00 (s, 1, ArH), 3.65 (s, 6, $-CO_2CH_3$), 2.62 (t, 4, J = 6 Hz, $ArCH_2-$), 2.22 (t, 4, J = 6 Hz, $-CH_2CO_2-$), 2.00 (m, 4, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.15; H, 7.88.

Dimethyl *m*-Benzenedipentanoate (1c). Using the malonic ester synthesis, 80 g (0.25 mol) of *m*-bis(3-bromopropyl)benzene was starting material for preparation of *m*-benzenedipentanoic acid. After decarboxylation of the tetracarboxylic acid, the crude diacid was used to prepare **1c** by the method outlined above for **1b**. The product, **1c**, 48.8 g (64% after two steps from the dibromide), boiled at 164–165° (0.3 mm): NMR ($CDCl_3$) δ 7.03 (m, 3, ArH), 7.00 (s, 1, ArH), 3.65 (s, 6, $-CO_2CH_3$), 2.60 (t, 4, J = 6 Hz, $ArCH_2-$), 2.33 (t, 4, J = 6 Hz, $-CH_2CO_2-$), 1.65 (m, 8, $-CH_2CH_2-CH_2-$).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.42; H, 8.59.

A small quantity of **1c** was saponified. The mixture was acidified. The solid was recrystallized from benzene to give *m*-benzenedipentanoic acid: mp 85.9–87.2°; NMR ($CDCl_3$) δ 11.5 (s, 2, COOH), 7.12–6.88 (m, 3, ArH), 7.02 (s, 1, ArH), 2.60 (t, 4, J = 6 Hz, $ArCH_2-$), 2.37 (t, 4, J = 6 Hz, $-CH_2CO-$), 1.65 (m, 8, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.32; H, 7.71.

4,14-Dioxotricyclo[15.3.1.1^{7,11}]docosa-1(21),7,9,11(22),17,19-hexaene (3a) (3,14-Dioxo[5.5]metacyclophane). In the manner reported earlier[4] and with the two exceptions noted in the Results and Discussion section, 12.5 g (0.05 mol) of **1a** was treated with potassium *tert*-butoxide in xylene to give, after sublimation [180–200° (0.5 mm)] of the neutral residue and recrystallization of the sublimate from absolute ethanol, 0.90 g (11.3%) of **3a**: mp 117–118° (lit.[7] mp 116–117.5°); ir (5% in CCl_4) 1716 and 1708 cm^{-1} (carbonyl) and (mineral oil mull) 1701 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.22–6.86 (m, 6, ArH), 7.00 (s, 1, ArH), 6.78 (s, 1, ArH), 3.0–2.4 (m, 16, $ArCH_2CH_2CO-$).

Starting acid could not be recovered from the acidic fraction of the isolated products. Infrared spectra of these materials indicated presence of ketone and carboxylic acid groups, leading to the conclusion that the acidic fraction was composed of noncyclic condensation products.

5,17-Dioxotricyclo[19.3.1.1^{9,13}]hexacosa-1(25),9,11,13(26),-21,23-hexaene (3b) (4,17-Dioxo[7.7]metacyclophane). In the manner outlined above, 13.9 g (0.05 mol) of **1b** was treated with potassium *tert*-butoxide in xylene. Isolated were 5.00 g of *m*-benzenedibutanoic acid (40% of starting material recovered as acid) and 1.98 g of crude **3b**. This product was sublimed at 230° (0.3 mm) and the sublimate was triturated with 20 ml of boiling ethanol to give 1.38 g (14.6%) of **3b**, colorless plates: mp 164–166.3°; ir (1% in CCl_4) 1717 and 1710 cm^{-1} (carbonyl) and (mineral oil mull) 1706 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.07 (m, 6, ArH), 7.00 (s, 1, ArH), 6.83 (s, 1, ArH), 2.60 (t, 8, J = 6 Hz, $ArCH_2-$), 2.08 (t, 8, J = 6 Hz, $-CH_2CO-$), 1.93 (m, 8, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57; mol wt, 376.52. Found: C, 82.87; H, 8.47; mol wt (Rast), 350.

6-Oxobicyclo[9.3.1]pentadeca-1(15),11,13-triene (2c) Semicarbazone (5-Oxo[9]metacyclophane Semicarbazone) and 6,20-Dioxotricyclo[23.3.1.1^{11,15}]triaconta-1(19),11,13,15(30),-25,27-hexaene (3c) (5,20-Dioxo[9.9]metacyclophane). In the manner outlined above, 15.3 g (0.05 mol) of **1c** was treated with potassium *tert*-butoxide in xylene to give 5.5 g of *m*-benzenedipentanoic acid (40% of starting material recovered as acid), a very small amount of **2c**, and 0.51 g of **3c**.

2c was in a fraction (0.15 g) that distilled at 160° (0.7 mm). The carbonyl absorption frequency (1710 cm^{-1}, neat) distinguished **2c** from the precursor ester with absorption at 1735 cm^{-1}. The distillation fraction slowly turned pink while standing for several days in a vial. It had a musky odor characteristic of macrocyclic ketones. Attempts to purify **2c** were unsuccessful, although a small portion was used to prepare a semicarbazone: mp 198–199.5°; NMR ($CDCl_3$) δ 7.93 (s, 1, =NNHCO–), 7.3–6.9 (m, 4, ArH), 5.52 (s, broad, 2, $CONH_2$), 2.75 (m, 4, $ArCH_2-$), 2.0–1.2 (m, 12).

Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.47; mol wt, 273.38. Found: C, 70.50; H, 8.52; mol wt (Rast), 304.

3c was isolated by subliming at 180–220° (0.3 mm) the residue after distilling **2c**, above. The sublimate was recrystallized from ethanol to give 0.51 g (4.7%) of **3c**, colorless plates: mp 71–73.6°; ir (5% in CCl_4) 1719 and 1707 cm^{-1} (carbonyl) and (mineral oil mull) 1703 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.01 (m, 6, ArH), 6.97 (s, 2, ArH), 2.57 (t, 8, J = 6 Hz, $ArCH_2-$), 2.30 (t, 8, J = 6 Hz, $-CH_2CO-$), 1.53 (m, 16, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32; mol wt, 432.62. Found: C, 83.20; H, 9.30; mol wt (Rast), 455.

Registry No.—**1a**, 6221-61-0; **1b**, 54698-69-0; **1c**, 54698-70-3; **2c**, 54698-71-4; **2c** semicarbazone, 54698-72-5; **3a**, 54698-73-6; **3b**, 54698-74-7; **3c**, 54738-98-6; *m*-benzenedipropanoic acid, 6082-86-6; *m*-benzenediacrylic acid, 37710-81-9; *m*-benzenedipropanol, 41009-85-2; *m*-bis(3-bromopropyl)benzene, 41009-86-3; *m*-benzenedibutanoic acid, 54698-75-8; *m*-benzenedibutanenitrite, 54698-76-9; *m*-benzenedipentanoic acid, 54698-77-0.

References and Notes

(1) The metacyclophane nomenclature is that proposed by R. W. Griffin, Jr., *Chem. Rev.*, **63**, 45 (1963), and B. H. Smith, "Bridged Aromatic Compounds", Academic Press, New York, N.Y., 1964. Systematic names are also given in the Experimental Section.

(2) For a review of the Dieckmann condensation, see J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 1 (1967).

(3) For a review of phenalene, see D. H. Reid, *Q. Rev., Chem. Soc.*, **19**, 274 (1965).

(4) C. W. Schimelpfenig, Y.-T. Lin, and J. F. Waller, Jr., *J. Org. Chem.*, **28**, 805 (1963).

(5) N. J. Leonard and C. W. Schimelpfenig, *J. Org. Chem.*, **23**, 1708 (1958).

(6) L. Ruzicka, J. B. Buijs, and M. Stoll, *Helv. Chim. Acta*, **15**, 1220 (1932).

(7) K. Ziegler and A. Lüttringhaus, *Justus Liebigs Ann. Chem.*, **511**, 1 (1934).

(8) A. F. Titley, *J. Chem. Soc.*, 2571 (1928). The catalyst for this condensation was a combination of sodium, originally present, and sodium methoxide, formed during the reaction. Acyloins are possible coproducts in this reaction.

(9) It is a pleasure to acknowledge the help of Dr. Kurt L. Loening, Chemical Abstracts Service, in naming many of the compounds in the systematic manner.

(10) P. Ruggli and A. Staub, *Helv. Chim. Acta*, **17**, 1523 (1934).

(11) F. S. Kipping, *J. Chem. Soc.*, **53**, 21 (1888).

(12) P. Ruggli and A. Staub, *Helv. Chim. Acta*, **19**, 439 (1936).

(13) W. Reppe, *Justus Liebigs Ann. Chem.*, **596**, 158 (1955). Reppe suspected this acid to be a component in a mixture, but he never isolated and characterized the compound.