Synthesis and Conformational Properties of [n.1.1]Paracyclo(2,5)thiophenoparacyclophanes

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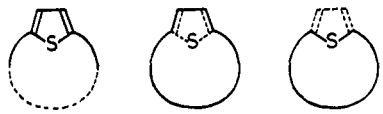
Cyclic diketo sulfides **4** (n = 3–8, 10) were condensed with glyoxal to give thiophenophanediones **6**. The NMR, IR, and UV spectral data of **6** are consistent with the following picture. The thiophene-2,5-dicarbonyl moiety in **6** (n = 10) is in the mean molecular plane and, unlike the corresponding open chain compounds, in an O,S,O trans,trans conformation. As n decreases, the benzene rings gradually become face-to-face as expected. The thiophene ring is, on the other hand, kept in the plane for n = 10 to 7 and becomes twisted out of the plane to an increasingly large extent when n is changed from 6 to 3. The Wolff–Kishner reduction of **6** afforded the title compounds **7**. The appearance of the UV spectrum of **7** (n = 3) is markedly different from those of the higher members of **7**, indicating the presence of significant transannular interactions between the thiophene and the adjacent benzene rings.

Methods for the synthesis of (2,5)thiophenophanes were, until our preliminary reports,[1,2] either (1) cyclization of a thiophene derivative (a)[3] or (2) construction of a thiophene ring on a macro ring by the Paal-Knorr synthesis (b).[4] We



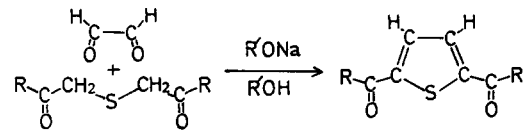
became interested in a new type of thiophenophane synthesis, i.e., incorporation of a sulfur atom in a thiacyclic compound into a thiophene ring (c), since cyclization by sulfide linkages is very efficient because of highly reactive thiolate ions and the resulting long C–S bonds.[5]

Diketo sulfide **1** with a variety of substituents R efficiently condenses with glyoxal to give 2,5-diacylthiophenes **2** (Scheme I).[6] For investigation of the applicability of this reaction to cyclic diketo sulfides, we selected the [n.1.1]paracyclo(2,5)thiophenoparacyclophane system because the condensation is much faster and cleaner for R = aryl (> 90% yields in a few minutes) than for R = alkyl.

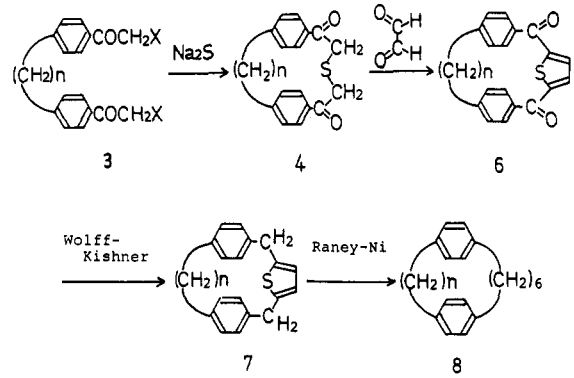
Results and Discussion

Synthesis. The synthetic route is outlined in Scheme II. Cyclizations of **3** (n = 2–8 and 10, X = Cl and n = 3, X = Br)[7,8] were carried out by adding their solutions and a solution of sodium sulfide to refluxing ethanol under

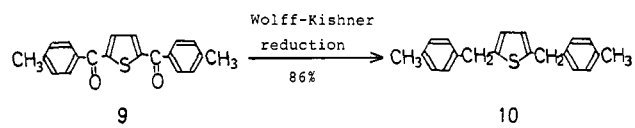
Scheme I



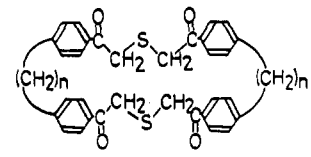
Scheme II



Scheme III



high-dilution conditions over 8–12 h. The desired monomeric diketo sulfides **4** (n = 3–8,10)[9] and the dimers **5**



(n = 2–8,10)[9] were obtained (Table I). Although shortening of the polymethylene chain reduced the yields of **4** with a concomitant increase in the yields of **5**, substitution

(1) Miyahara, Y.; Inazu, T.; Yoshino, T. *Chem. Lett.* **1978**, 563.

(2) Miyahara, Y.; Inazu, T.; Yoshino, T. *Chem. Lett.* **1980**, 397.

(3) For recent synthesis of thiophenophanes by intramolecular acylation, see: Catoni, G.; Galli, C.; Mandolini, L. *J. Org. Chem.* **1980**, *45*, 1906.

(4) (a) Nozaki, H.; Koyama, T.; Mori, T.; Noyori, R. *Tetrahedron Lett.* **1968**, 2181. (b) Nozaki, H.; Koyama, T.; Mori, T. *Tetrahedron* **1969**, *25*, 5357. (c) Helder, R.; Wynberg, H. *Tetrahedron* **1975**, *31*, 2551. (d) Gronowitz, S.; Frejd, T. *Acta Chem. Scand. Ser. B* **1976**, *B30*, 341.

(5) For examples in cyclophane chemistry, see: Bruhin, J.; Jenny, W. *Tetrahedron Lett.* **1973**, 1215. Otsubo, T.; Kitasawa, M.; Misumi, S. *Chem. Lett.* **1977**, 977. Vögtle, F. *Angew. Chem.* **1969**, *81*, 258. Haenel, M. W.; Flatow, A. W.; Taglieber, V.; Staab, H. A.; *Tetrahedron Lett.* **1977**, 1733.

(6) Miyahara, Y. *J. Heterocycl. Chem.* **1979**, *16*, 1147.

(7) Most of **3** have been reported. See: Gryszkiewicz-Trochimowski, E.; Gryszkiewicz-Trochimowski, O.; Levy, R. S. *Bull. Soc. Chim. Fr.* **1945**, 538.

(8) Gaudry, M.; Marquet, A. *Org. Synth.* **1976**, *55*, 24.

(9) According to the "Phane Nomenclature", the monomer **4** is either 3-thia[5.n]paracyclophane-1,5-dione (n = 3–5) or (n + 9)-thia[n.5]paracyclophane-(n + 7),(n + 11)-dione (n = 6–8,10) and the dimer **5** is either 3,(n + 20)-dithia[5.n.5.n]paracyclophane-1,5,(n + 18),(n + 22)-tetraone (n = 2–5) or (n + 9),(2n + 26)-ditha[n.5.n.5]paracyclophane-(n + 7),(n + 11), (2n + 24),(2n + 28)-tetraone (n = 6–8,10). See: Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847.

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Table I.[a] Cyclization of 4,4'-Polymethylenebis(ω-chloroacetophenones) (3)

	monomer 4				dimer 5			
n	yield, %	crystal form, solvent[b]	mp, °C	MS, M^+	yield, %	crystal form, solvent[b]	mp, °C	MS, M^+
2	0				5.6 (25.7)[c]	needles, DC	253-254 dec	592
3	29.3 (44.3)[d]	plates, B	169.5-170	310	14.9 (8.6)[d]	plates, B	281-218.5	620
4	24.2	prisms, B	183-184	324	9.9	needles, B-E	219-220	648
5	42.0	needles, CT	117-117.5	338	4.3	granules, B	151-152	
6	56.7	needles, B	131.5-132	352	6.9	needles, CH-E	213.5-214	
7	55.2	needles, B	126-126.5	366	4.7	plates, CH	163.5-164	
8	47.9	prisms, E	114-115	380	3.0	plates, B	175.5-176.5	
10	56.7	plates, E	85.5-86	408	5.2	needles, B	139.5-140	

[a] Satisfactory analytical data (±0.3% for C, H) were obtained for all compounds listed in this table. [b] Recrystallization solvent: B, benzene; CH, chloroform; CT, carbon tetrachloride; DC, 1,2-dichloroethane; E, ethanol. [c] $(Me_4N)_2S$ was used in place of Na_2S. [d] Bromide 3 (n = 3, X = Br) was used.

Table II.[a] [n.1.1]Paracyclo(2,5)thiophenoparacyclophane-(n + 7),(n + 13)-diones (6)

	yield, %		crystal form		IR (C=O) cm^{-1}	
n	in EtOH	in MeOH	(solvent)[b]	mp, °C	in KBr	in $CHCl_3$
3	9.0	7.4	prisms (E)	244-246	1674	1677
4	36.4		prisms (A)	224.5-225.5	1667	1673
5	34.2	42.2	needles (E)	246-247	1665	1667
6	43.9	60.6	needles (E)	241.5-242.5	1664	1664
7	67.3	64.3	prisms (A)	224-225	1653	1658
8	58.1	72.9	plates (A)	196.5-197.5	1648	1655
10	91.0	94.7	plates (A)	160.5-161.5	1642	1649

[a] Satisfactory analytical data (±0.3% for C, H) were obtained for all compounds listed in this table. [b] Recrystallization solvent: A, acetone; E, ethanol.

for the more reactive bromide favored the formation of 4.

Cyclization of 3 (n = 2) gave only the dimer 5 (n = 2) in low yield. Although the use of bis(tetramethylammonium) sulfide in place of sodium sulfide significantly improved the yield of 5 (n = 2), no monomer 4 (n = 2) could be detected.

When the cyclic diketo disulfides 4 were condensed with glyoxal in the presence of dilute sodium alkoxide solution, the desired 6 were obtained (Table II). Since even the apparently unstrained 4 (n = 10) reacted much slower than the open chain 1, the base solution had to be added very slowly to avoid self-condensations.

As expected, the yields of 6 gradually decreased when n was changed from 10 to 4. A sharp drop off to only 9% yield occurs at n = 3, demonstrating the high strain and rigidity of 4 and 6 (n = 3).

Reductions of 6 to the title compounds 7 (Table III), as well as those of 9 to 10 (Scheme III), were accomplished by the Wolff-Kishner reaction with extreme care to complete the conversions into the corresponding dihydrazones prior to addition of potassium hydroxide. Interestingly, the melting point of 7 shows its maximum at n = 5 and 6 in contrast to that of 6.

Reductive opening of the thiophene ring in 7 (n = 6) by Raney nickel provided 8 (n = 6)[10] in 90% yield.

Spectral Properties of 6. The open chain 2,5-diacylthiophenes 2 show their carbonyl bands at considerably lower frequencies[6] compared to the corresponding benzene derivatives [e.g., $\nu_{C=O}$ (KBr) cm^{-1}: 2 (R = Me) 1658; 2 (R = Ph) 1631; 1,4-diacetylbenzene 1674; 1,4-dibenzoylbenzene 1656]. Although the $\nu_{C=O}$ of 2 generally reflects the electronic character of the R groups, those of 2 having thiophene rings as R's are unusually low (1596–1598 cm^{-1}).[6]

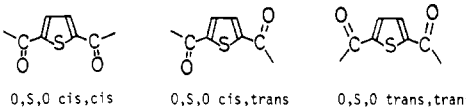
On the other hand, the thiophene protons in 2 appear in a rather narrow region (δ 7.66–7.75) in their NMR spectra, irrespective of widely different electronic and anisotropic properties, except, again, those having thiophene rings as R's (δ 7.87–7.91).[6]

Table III.[a] [n.1.1]Paracyclo(2,5)thiophenoparacyclophanes (7)

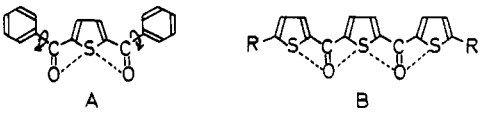
n	yield, %	crystal form (solvent)[b]	mp, °C
3	68.8	plates (E)	142.5-143.5
4	84.0	platelets (E-B)	189-189.5
5	81.1	needles (E)	230-230.5
6	91.0	needles (E-B)	229.5-230.5
7	94.9	needles (E-B)	193-193.5
8	82.9	needles (E)	168-168.5
10	68.7	plates (E)	143.5-144.5

[a] Satisfactory analytical data (±0.3% for C, H) were obtained all compounds listed. [b] Recrystallization solvent: B, benzene; E. ethanol.

These properties are, in accord with the ESR results by Lunazzi et al.,[11] best rationalized in terms of an O,S,O cis,cis conformation in which strong C=O···S interactions



are possible.[12] Although the thiophene ring is thus held coplanar with the carbonyls, most of the R groups may be allowed to rotate freely, averaging the anisotropic effect of R upon the central thiophene protons (A). However,



(10) Abell, J.; Cram, D. J. J. Am. Chem. Soc. 1954, 76, 4406.

(11) Lunazzi, L.; Pedulli, G. F.; Tiecco, M.; Vincenzi, C.; Veracini, C. A. J. Chem. Soc., Perkin Trans. 2 1972, 751.

(12) An S–O electrostatic interaction has been assumed to be a dominant factor in determining the O,S cis conformation in thiophene-2-carbonyl derivatives. See: Nicole, D.; Delpuech, J-J.; Wierzbicki, M.; Cagniant, D. Tetrahedron 1980, 36, 3233.

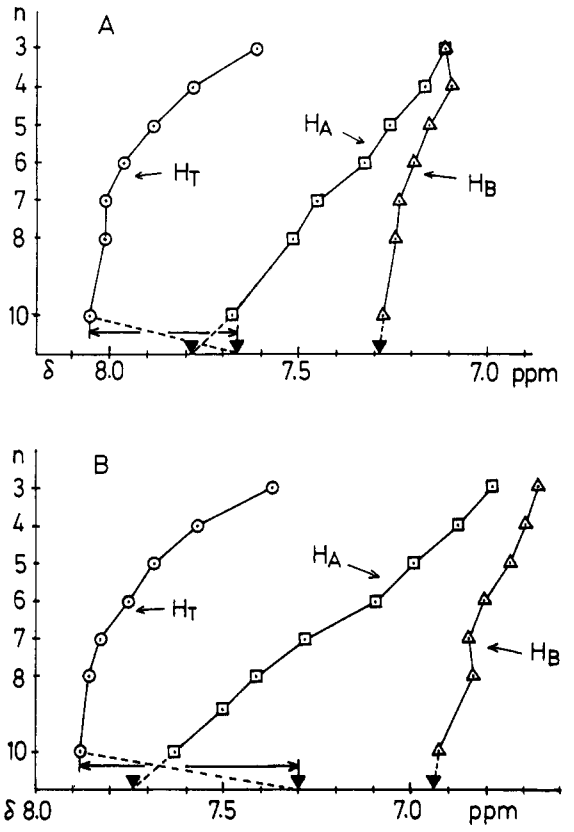
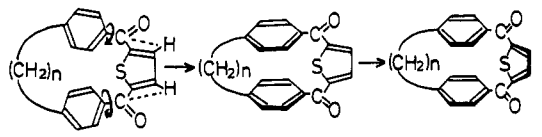


Figure 1. NMR spectral change of **6** as a function of n; (A) (above) in $CDCl_3$; (B) (below) in C_6D_6; (▼) corresponding signal positions of open chain **9**.

Scheme IV



when the R's are thiophene rings, they may now be held in a plane by the C=O···S interactions (B) and thus exert deshielding effects upon one another.

The effect of the polymethylene chain in **6** upon the conformation of the thiophene-2,5-dicarbonyl moiety seems to be most clearly manifested by alterations in their NMR spectra. Figure 1 shows plots of the chemical shifts of the thiophene (H_T, sharp singlet) and the benzene protons (H_A for the carbonyl side and H_B for the polymethylene side, approximately A_2B_2 quartet).

Molecular model inspection suggests that the decamethylene chain in **6** (n = 10) forces the conformation of the thiophene-2,5-dicarbonyl moiety from the usual O,S,O cis,cis into O,S,O trans,trans (I in Scheme IV). This appears to be supported by the considerable downfield shift of H_T compared to **9** [0.39 ppm in $CDCl_3$ (A) and 0.58 ppm in C_6D_6 (B)], in contrast to the upfield shift of H_A. Although the anisotropic effect of the benzene rings may not be cancelled out by rotation shown in I, the estimated amount (0.2 ppm, vide infra) is not sufficient to account for the observed deshielding. Therefore, the anisotropic effect of the carbonyl groups[13] in the O,S,O trans,trans conformation should also be present.

(13) For the deshielding effect in the plane of a carbonyl group, see: Knorr, R.; Schnegg, A.; Lattke, E.; Räpple, E. *Chem. Ber.* **1979**, *112*, 3490.

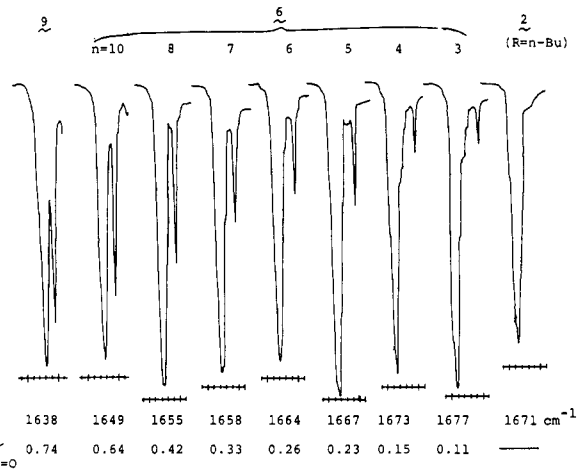


Figure 2. Double bond region of IR spectra of **6** and **9** in chloroform and their approximate intensity ratios.

Whereas the H_A regularly shifts upfield from n = 10 to 3, the chemical shift of H_A is almost unchanged for n = 10–7, indicating that the planar O,S,O trans,trans conformation is maintained. The gradual shifts of H_A clearly show the diminishing conjugational and anisotropical effects of the C=O groups upon the benzene rings and hence the increasing twisting of the benzene rings out of the mean molecular plane of **6**.

For $n < 6$, as indicated by the increasingly large upfield shift of H_T, the thiophene ring may no longer stay in the mean molecular plane but increasingly tilt as in III.

The double bond regions of the IR spectra of **6**, **9**, and **2** (R = n-Bu) are shown in Figure 2 along with the ratios of the molecular extinction coefficients of the aromatic C=C bands at 1608 cm^{-1} to those of the C=O bands. Since these ratios can be correlated with the extent of the conjugation between the benzene ring and the carbonyl groups,[14] the gradual decrease by the chain shortening may also support the increasing twisting of the benzene rings.

The C=O absorption of the strain-free **6** (n = 10) occurs at a higher frequency than that of **9** by 11 cm^{-1}, probably due to the loss of C=O···S interactions in **6** (n = 10) in an O,S,O trans,trans conformation. The strain of **6** of small n as well as the reduction in carbonyl–benzene conjugation may account for the shifts of $\nu_{C=O}$ to the higher frequencies.

The electronic spectra of **6** (Figure 3) also support the above conformational change. Thus, the π–π^* band[15] of **9** reveals a blue shift (8 nm) upon bridging by a decamethylene chain [**9**: λ_{max} 305 nm (ϵ 26 500); **6** (n = 10): λ_{max} 297 nm (ϵ 22 800)], probably as a result of change from O,S,O cis,cis in **9** to O,S,O trans,trans. As n decreases, the intensity of this band as well as that of an n–π^* absorption (350–380 nm) decreases accordingly [**6** (n = 3): λ_{max} 301 nm (ϵ 12 500)], indicating gradual loss of the thiophene–carbonyl conjugation.

Spectral Properties of 7. Figure 4 shows the plots of the NMR chemical shifts of the thiophene (H_T) and the benzene protons [H_B, singlet for n = 4–8,10 and AA'BB' multiplet for n = 3] along with the intervening methylene protons (H_M) against n. Unlike the plots of **6**, all three curves were quite similar to each other. The increasingly large upfield shifts by the change of n from 10 to 3 are

(14) Avram, M.; Mateescu, Gh. D. "Infrared Spectroscopy"; Wiley-Interscience: New York, 1972; p 214. Alpert, N. L.; Keiser, W. E.; Szymanski, H. A. "IR: Theory and Practice of Infrared Spectroscopy", Rosetta ed.; Plenum: New York; p 263.

(15) For UV spectra of thienyl ketones, see: Magini, A.; Tundo, A. *Z. Electrochem.* **1960**, *64*, 694.

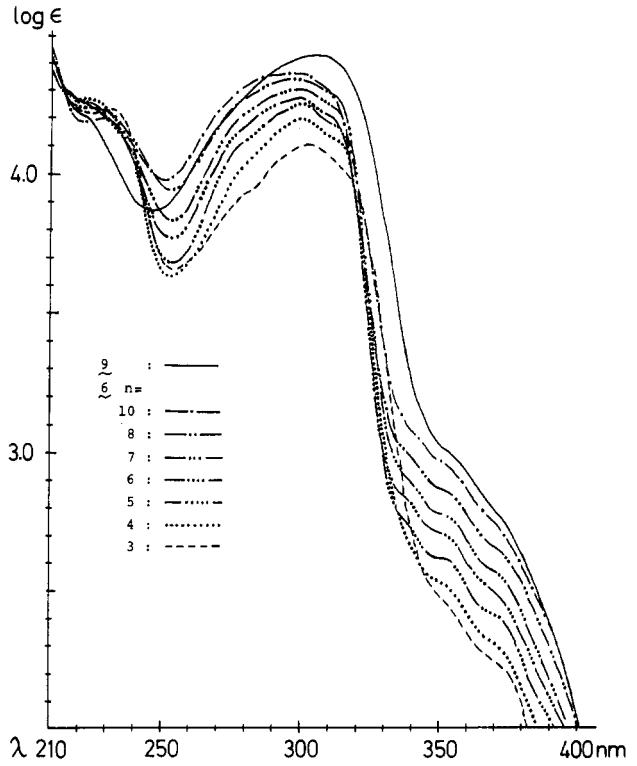


Figure 3. Electronic spectra of **6** and **9** in cyclohexane.

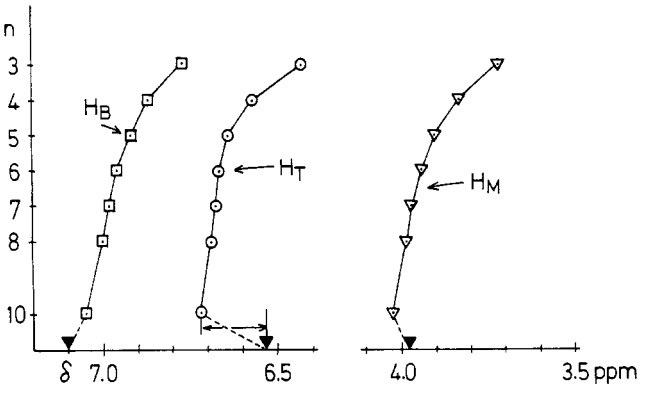
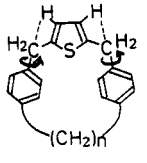


Figure 4. NMR spectral change of **7** as a function of n in $CDCl_3$; (▼) corresponding signal positions of open chain **10**.

evidently associated with the shielding by the benzene and the thiophene rings. Therefore, as n becomes smaller, both the benzene and the thiophene rings become increasingly more twisted out of the mean molecular plane. It is worth noting that the H_T in **7** (n = 10) is, unlike the H_B and H_M, appreciably deshielded (ca. 0.2 ppm) compared to the open chain **10**. This deshielding may be ascribed to the anisotropic effects of the benzene rings, which does not seem to be cancelled out by rotation of the benzene rings around the axes depicted. The value is in agreement with that



estimated from the Johnson–Bovey ring current model.[16]

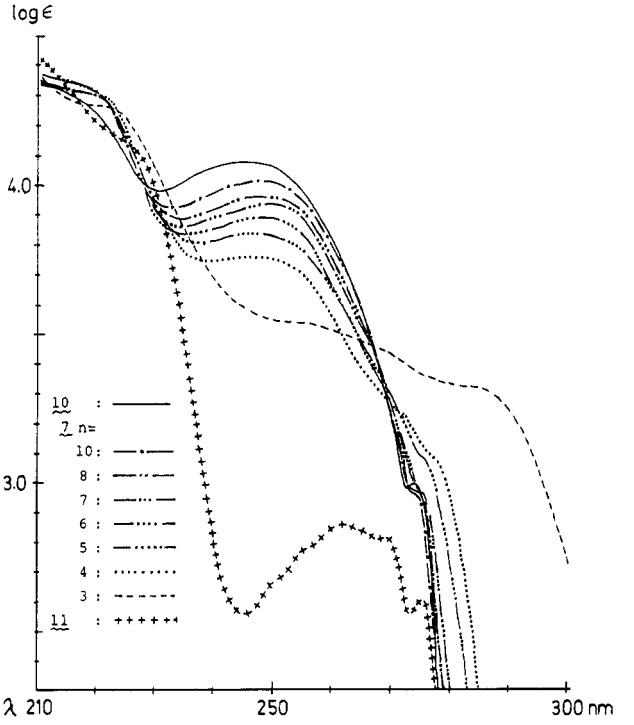


Figure 5. Electronic spectra of **7**, **10**, and **11** in cyclohexane.

The electronic spectra of **7** together with those of **10** and 1,4-dibenzylbenzene (**11**) are depicted in Figure 5. The open chain reference **10** has a strong absorption arising from the thiophene ring at 245 nm (ε 11 900). The corresponding band of **7** shows a gradual red shift and its intensity is progressively diminished as n decreases from 10 to 4. A drastic change occurs at n = 3, where this band reduces markedly in its intensity and the longest wavelength maximum [^1L_b band, **7** (n = 10): λ_{max} 274 nm (ε 952)] shows a large red shift with much enhanced intensity [**7** (n = 3): λ_{max} 285 nm (ε 2090)], indicating strong transannular interactions between the thiophene and the benzene rings.

Experimental Section

All the melting points were determined in capillary tubes and are uncorrected. The NMR spectra were recorded in deuteriochloroform with tetramethylsilane as an internal standard on a Hitachi R-20B spectrometer operating at 60 MHz. The IR spectra were obtained on a Hitachi 215 Infrared Spectrophotometer and calibrated with a polystyrene film.

4,4′-Polymethylenebis(ω-chloroacetophenones) (3, X = Cl). For the bis(chloroacetylation) of 1,ω-diphenylalkanes the following procedure, exemplified for n = 7, appears to be superior to those reported in the literature.[6]

4,4′-Heptamethylenebis(ω-chloroacetophenone) (3, X = Cl, n = 7). Chloroacetyl chloride (freshly distilled, 120 g, 1.06 mol) was added to a vigrously stirred suspension of aluminum chloride (anhydrous, 140 g, 1.05 mol) in carbon disulfide (150 mL) at 5 °C. After stirring for 1 h, a solution of 1,7-diphenylheptane (88.2 g, 0.349 mol) in carbon disulfide (50 mL) was added to the complex at 0–5 °C over a period of 30 min, and the mixture was stirred at room temperature for 5 h and at 30–40 °C for 30 min. Removal of the carbon disulfide layer by decantation and treatment of the complex with ice and hydrochloric acid gave a pale yellow precipitate, which was extracted with a mixture of chloroform and benzene (1:4, 1.5 L). The solution was washed with water, dried over magnesium sulfate, and passed through a column of silica gel (benzene). After solvent evaporation, the residue was crystallized from benzene–ethanol to yield pale yellow needles, 125.3 g (88.5%). Recrystallization from ethanol gave colorless needles, mp 71–72 °C.

The other bis(chloroacetyl) compounds were prepared in a similar manner and the results are summarized in Table IV.

(16) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: London, 1969; p 94.
(17) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691.

Table IV.[a] 4,4′-Polymethylenebis(ω-chloroacetophenones) (3)

n	yield, %	crystal form, solvent[b]	mp, °C (Lit.[c])	NMR ($CDCl_3$, δ) -C_6H_4-	(AA′BB′)	$COCH_2Cl$	$(CH_2)_n$
2	81.7	prisms, DC	142-143.5 (141-142)	7.87	7.27	4.66	3.02 (s)
3	90.2	prisms, E	86.5-87.5 (83-84)	7.90	7.31	4.66	2.5-2.9, 1.6-2.3
4	86.0	prisms, D	161-163 (160-161)	7.89	7.29	4.66	2.5-3.0, 1.5-1.9
5	58.9	needles, E	69-70.5 (63-64)	7.82	7.33	4.71	2.5-2.9, 1.3-2.0
6	70.9	prisms, D	134.5-135.5	7.84	7.25	4.67	2.5-2.8, 1.1-1.9
7	88.5	needles, E	71-72	7.85	7.27	4.63	2.4-2.9, 1.1-1.9
8	84.1	granules, E	103-104	7.86	7.29	4.67	2.5-2.9, 1.1-2.0
10	72.5	plates, B	87.5-88.5	7.86	7.28	4.64	2.4-2.9, 1.1-2.0

[a] Satisfactory analytical data (±0.3% for C, H) were obtained for all of the new compounds and for **3** (n = 10) which has been reported as a viscous mass. [b] Recrystallization solvent: B, benzene; E, ethanol; D, dioxane; DC, 1,2-dichloroethane. [c] Reference 7.

4,4′-Trimethylenebis(ω-bromoacetophenone) (3, X = Br, n = 3). When 4,4′-trimethylenebis(acetophenone) (**3**, X = H, n = 3)[18] was brominated under the usual conditions (ether, 0 °C), impure **3** (X = Br, n = 3) was obtained only in a moderate yield. However, the selective monobromination procedure developed by Gaudry and Marquet[8] readily provided pure **3** (X = Br, n = 3) in a high yield.

To a stirred solution of **3** (X = H, n = 3, 28.0 g, 0.1 mol) in methanol (200 mL) and dioxane (150 mL) was added bromine (32.0, 0.2 mol) over 5 min at 8–10 °C. The red solution was stirred at 8–10 °C until the color disappeared completely (1 h). Then, water (50 mL) was added and, after stirring for 3 h at room temperature, the reaction mixture was left standing overnight. Colorless crystals which had separated were collected on a filter, washed with water, and dried. Recrystallization from benzene afforded colorless plates, which contained 1 mol of benzene as determined by NMR spectroscopy and changed gradually into a white powder with loss of the included benzene. The yield was 38.8 g (88.7%) as a well-dried powder, mp 105.5-106.5 °C. Anal. Found: C, 51.98; H, 4.07. Calcd for $C_{23}H_{26}O_2Br_2$: C, 52.08; H, 4.14.

Cyclization of 4,4′-Polymethylenebis(ω-haloacetophenone) (3, X = Cl or Br). Typical procedure for the cyclization of **3** with sodium sulfide is illustrated below for **3** (X = Cl, n = 6).

(a) Synthesis of 15-Thia[6.5]paracyclophene-13,17-dione (4, n = 6) and 15,38-Dithia[6.5.6.5]paracyclophane-13,17,36,40-tetraone (5, n = 6). To refluxing ethanol (1.0 L) were added a solution of **3** (X = Cl, n = 6, 15.6 g, 40 mmol) in tetrahydrofuran (250 mL) and a solution of sodium sulfide (9.6 g as nonahydrate, 40 mmol) in 70% aqueous ethanol (250 mL) separately over a period of 8 h under high-dilution conditions in an inert atmosphere. Extreme care was taken to avoid the addition of excess of sodium sulfide throughout the reaction. After refluxing for 30 min, the hot reaction mixture was filtered and the solvents were evaporated. Benzene (100 mL) was added to the residue and evaporated to eliminate the residual water. The residue was then dissolved in chloroform and the solution was chromatographed on silica gel (chloroform–benzene 1:1). The monomer **4** (n = 6) eluted first, followed by the less soluble dimer **5** (n = 6). Crystallization of **4** (n = 6) from benzene afforded colorless plates as a benzene solvate, which on heating collapsed to a benzene-free white powder: mp 131.5–132.0 °C; yield, 7.94 g (56.7%). The less soluble **5** (n = 6) was recrystallized from chloroform–ethanol, yielding pale yellow granules: mp 213.5–214 °C; 974 mg (6.9%).

The other **4** were prepared similarly except that the solvent for **3** was changed from THF to benzene (n = 5,7) or to a benzene–dioxane mixture (n = 8,10) according to solubility. The results are summarized in Table I.

For the cyclization of **3** (X = Cl, n = 2), the following modification was used in the hope that the solubility of the intermediates might be improved.

(b) Synthesis of 3,22-Dithia[5.2.5.2]paracyclophane-1,5,20,24-tetraone (5, n = 2) Using Bis(tetramethylammonium) Sulfide. Sodium sulfide nonahydrate (9.6 g, 40 mmol) and tetramethylammonium chloride (9.0 g, 82 mmol) were dissolved in 30 mL of water. The solution was diluted with 200 mL of anhydrous ethanol in order to precipitate sodium chloride. After filtration and washing with ethanol (50 mL), the sulfide solution, diluted to 300 mL with ethanol, was added through a pressure-equalizing dropping funnel to refluxing ethanol (1 L), while at the same time a solution of **3** (X = Cl, n = 2, 13.4 g, 40 mmol) in THF (300 mL) was added from the other dropping funnel. The addition was conducted under high-dilution conditions in an atmosphere of nitrogen over 11 h. The reaction mixture was refluxed for an additional 1 h and filtered hot. After cooling, white crystals of the dimer **5** (n = 2) were collected by filtration. The filtrate was evaporated and the residue was, after addition of water, extracted twice with chloroform. The extracts were dried over magnesium sulfate and chromatographed on silica gel (chloroform) with heating the outside of the column by a heating tape. Colorless platelets of **5** (n = 2) were obtained making the total yield 3.04 g (25.7%) of colorless needles from 1,2-dichloroethane, mp 253–254 °C dec.

The method was superior to that using sodium sulfide (5.6%). However, the corresponding monomeric product **4** (n = 2) could not be detected in the crude reaction mixture as determined by NMR spectroscopy.

Synthesis of [n.1.1]Paracyclo(2,5)thiophenoparacyclophane-(n + 7),(n + 13)-diones (6). A solution of glyoxal hydrate was prepared by dissolving glyoxal trimer dihydrate (Merck-Schhardt, 5.07 g) in anhydrous methanol (300 mL) with stirring and refluxing for 2 h. To a solution of **4** (4.0 mmol) in 30 mL of dioxane, after addition of the glyoxal solution (40 mL) and dilution with methanol (160 mL), was added with magnetic stirring a methanolic solution of sodium methoxide (0.11 g of sodium dissolved in 20 mL of methanol) over a period of 12 h by means of a motor-driven syringe (Furue "Microfeeder") at room temperature. The mixture was stirred for an additional 12 h at room temperature and then heated on a hot plate for 30 min. After evaporation of the solvents, the residue was treated with dilute hydrochloric acid and extracted twice with chloroform. The extracts were washed with water, dried over magnesium sulfate, and passed through a short column of silica gel (chloroform). The crystals obtained on evaporation of solvent were recrystallized from acetone to give pale yellow crystals. The results are summarized in Table II.

Synthesis of [n.1.1]Paracyclo(2,5)thiophenoparacyclophanes (7). The usual Huang-Minlon procedure for the Wolff–Kishner reduction of **6** gave tars and had to be modified as illustrated below for n = 6. To a refluxing mixture of ethylene glycol (distilled from potassium hydroxide, 30 mL) and hydrazine hydrate (100%, 30 mL) was added a warm solution of **6** (n = 6, 500 mg) in dioxane (10 mL) over 10 min. Refluxing was continued for 30 min, during which time light yellow crystals precipitated. After cooling and addition of potassium hydroxide (3.0 g), the mixture was refluxed for 30 min and then most of the hydrazine was distilled off and heated for 1 h in an oil bath at 220 °C. Water was added to the cooled reaction mixture and extracted twice with benzene. The extracts were washed with water, dilute hydrochloric acid, and water and, after addition of magnesium sulfate, filtered through a short column of silica gel (benzene). Crystallization from ethanol gave pale yellow needles, 421 mg (91.0%). Further recrystallization from benzene–ethanol gave colorless needles, mp 229.5–230.5 °C.

The other thiophenophanediones **6** were reduced to **7** by the same procedure and the results are given in Table III.

Synthesis of [6.6]Paracyclophane (8, n = 6). A mixture of

7 (n = 6, 3.02 g), Raney nickel W-2[18] (prepared from 55 g of Raney alloy), and dioxane (100 mL) was refluxed for 1 h. After filtration and solvent evaporation, the residue was chromatographed on a short column of silica gel (benzene). The yield, after crystallization from methanol, was 2.52 g (90.2%): colorless plates; mp 100–100.5 °C (lit.[9] mp 99.6–100.6 °C).

Registry No. **3** (X = H; n = 2), 68114-93-2; **3** (X = H; n = 3), 6337-58-2; **3** (X = Br; n = 3), 68114-87-4; **3** (X = Cl; n = 3), 67442-67-5; **3** (X = Cl; n = 4), 67442-69-7; **3** (X = Cl; n = 5), 67442-71-1; **3** (X = Cl; n = 6), 67442-73-3; **3** (X = Cl; n = 7), 67442-75-5; **3** (X = Cl; n = 8), 67442-77-7; **3** (X = Cl; n = 10), 67442-79-9; **4** (n = 3), 67449-47-2; **4** (n = 4), 67449-48-3; **4** (n = 5), 67449-49-4; **4** (n = 6), 67449-50-7; **4** (n = 7), 67449-51-8; **4** (n = 8), 67449-52-9; **4** (n = 10), 67629-81-6; **5** (n = 2), 88686-37-7; **5** (n = 3), 88686-38-8; **5** (n = 4), 88686-39-9; **5** (n = 5), 88686-40-2; **5** (n = 6), 88686-41-3; **5** (n = 7), 88686-42-4; **5** (n = 8), 88686-43-5; **5** (n = 10), 88686-44-6; **6** (n = 3), 67449-60-9; **6** (n = 4), 67449-61-0; **6** (n = 5), 67449-62-1; **6** (n = 6), 67449-63-2; **6** (n = 7), 67449-64-3; **6** (n = 8), 67449-65-4; **6** (n = 10, 67449-66-5; **7** (n = 3), 67449-53-0; **7** (n = 4), 67449-54-1; **7** (n = 5), 67449-55-2; **7** (n = 6), 67449-56-3; **7** (n = 7), 67449-57-4; **7** (n = 8), 67449-58-5; **7** (n = 10), 67449-59-6; **8** (n = 6), 4384-23-0; glyoxal, 107-22-2; chloroacetyl chloride, 79-04-9; 1,7-diphenylheptane, 22906-09-8; sodium sulfide, 1313-82-2.

(18) Mozingo, R. "Organic Synthesis"; Wiley: New York, 1955; Collect Vol III, p 181.

Synthesis and Chemistry of 2,8-Disubstituted Noradamantanes

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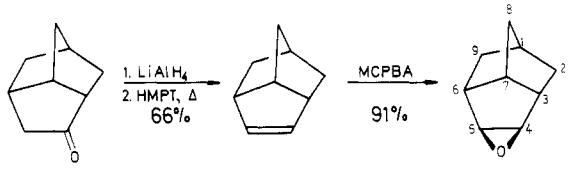
4,5-*exo*-Epoxybrendane (**3**) rearranged readily with sulfuric acid in acetone, and with boron trifluoride etherate in acetic acid, yielding, upon a hydrolytic workup, 86% of 2-*exo*-8-*exo*-noradamantanediol and 93% of 8-*exo*-acetoxy-2-*exo*-noradamantanol, respectively. Starting epoxide **3** was prepared in 60% overall yield from readily available 4-brendanone. Consequently, the acid solvolysis of **3** provides a convenient, general entry to the noradamantane system functionalized at carbons 2 and 8.

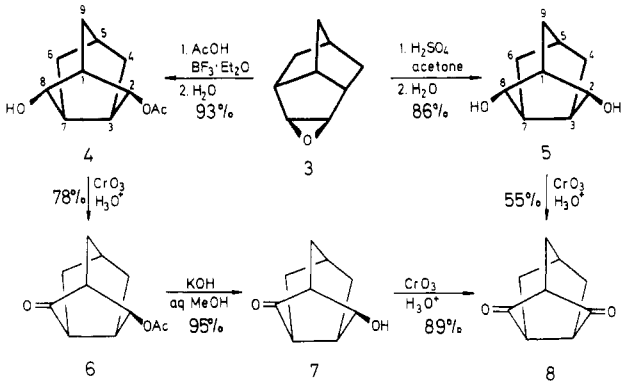
Noradamantane has attracted considerable attention since its first syntheses[1] due to its unique position as the next lower homologue of adamantane and the tricyclononane stabilomer.[2] Noradamantane derivatives have been used as starting materials for preparations of [2]diadamantane,[3a] dinoradamantanes,[3b] 5-substituted protoadamantanes,[3c] 9-substituted 9-homonoradamantanes,[3d] triaxanes,[3e] and ethanonoradamantanes,[3f] as well as substrates in numerous solvolytic,[3g] spectroscopic,[3h] carbene,[3i] and nitrene studies.[3j] The latter two led to unambiguous syntheses of adamantene and 2-azaadamantene.

Because of the lower symmetry of noradamantane compared to adamantane, five monosubstituted noradamantane isomers (1-, 2-*exo*-, 2-*endo*-, 3-, and 9-noradamantanes) are possible. All five noradamantanols and

Scheme I



Scheme II



their numerous derivatives are known.[4] However, only a few synthetic routes to disubstituted noradamantanes

(1) (a) Vogt, B. R.; Hoover, J. R. E. *Tetrahedron Lett.* **1967**, 2841. (b) Schleyer, P. v. R.; Wiskott, E. *Ibid.* **1967**, 2845. (c) Nickon, A.; Pandit, G. D.; Williams, R. O. *Ibid.* **1967**, 2851.

(2) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005. Godleski, S. A.; Schleyer, P. v. R.; Osawa, E.; Wipke, W. T. *Prog. Phys. Org. Chem.* **1981**, *13*, 63.

(3) (a) Graham, W. D.; Schleyer, P. v. R.; Hagaman, E. W.; Wenkert, E. *J. Am. Chem. Soc.* **1973**, *95*, 5785. (b) Vogt, B. R.; Suter, S. R.; Hoover, J. R. E. *Tetrahedron Lett.* **1968**, 1609. (c) Farcasiu, M.; Farcasiu, D.; Slutsky, J.; Schleyer, P. v. R. *Ibid.* **1974**, 4059. Nakazaki, M.; Naemura, K.; Hashimoto, M. *J. Org. Chem.* **1983**, *48*, 2289. (d) Majerski, Z.; Djigaš, S.; Vinković, V. *Ibid.* **1979**, *44*, 4064. (e) Nickon, A.; Simons, J. R.; Ho, B. *Ibid.* **1977**, *42*, 800. Nickon, A.; Pandit, G. D. *Tetrahedron Lett.* **1968**, 3663. (f) Godleski, S. A.; Schleyer, P. v. R.; Osawa, E.; Inamoto, Y.; Fujikura, Y. *J. Org. Chem.* **1976**, *41*, 2596. Godleski, S. A.; Schleyer, P. v. R.; Osawa, E. *J. Chem. Soc., Chem. Commun.* **1976**, 38. (g) Bingham, R. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 3189. Bingham, R. C.; Sliwinski, W. F.; Schleyer, P. v. R. *Ibid.* **1970**, *92*, 3471. Su, T. M.; Sliwinski, W. F.; Schleyer, P. v. R. *Ibid.* **1969**, *91*, 5386. Smith, M. R.; Harris, J. M. *J. Org. Chem.* **1978**, *43*, 3588. Bingham, R. C.; Schleyer, P. v. R. *Tetrahedron Lett.* **1971**, 23. (h) Gorrie, T. M.; Engler, E. M.; Bingham, R. C.; Schleyer, P. v. R. *Ibid.* **1972**, 3039. Kovač, B.; Klasinc, L. *Croat. Chem. Acta* **1978**, *51*, 55. (i) Martella, D. J.; Jones, M., Jr.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1978**, *100*, 2896. (j) Sasaki, T.; Eguchi, S.; Takashi, O. *Tetrahedron Lett.* **1982**, *23*, 4969.

(4) **Noradamantane, 1-substituted:** Wishnok, J. S.; Schleyer, P. v. R.; Funke, E.; Pandit, G. D.; Williams, R. O.; Nickon, A. *J. Org. Chem.* **1973**, *38*, 539. **2-Substituted:** references 2c, 3e, 3f, 6, and 18. Murray, R. K., Jr.; Goff, D. L.; Ford, T. M. *J. Org. Chem.* **1977**, *42*, 3870. **3-Substituted:** references 2a and 8. Black, R. M.; Gill, G. B. *J. Chem. Soc., Chem. Commun.* **1970**, 972. Graham, W. D.; Schleyer, P. v. R. *Tetrahedron Lett.* **1972**, 1179. Janjatović, J.; Majerski, Z. *J. Org. Chem.* **1980**, *45*, 4892. Shchegoleva, T. A.; Shashkova, E. M.; Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 2169. **9-Substituted:** references 3d and 6. Vegar, M. R.; Wells, R. J. *Tetrahedron Lett.* **1969**, 2565.

0022-3263/84/1949-1182$01.50/0