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Ring-opening Reactions of Heterocyclic Organometallics. VIII.* On the Synthesis of Macrocyclic Alkylthiovinylacetylenes

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The reaction of 3-bromo-[11] (2,5)-thiophenophane (*7b*) with ethyllithium and ethyl iodide gives the macrocyclic alkylthiovinylacetylene, 1-ethylthio-1-cyclopentadecen-3-yne (*8*) in 45 % yield. The synthesis of *7b* is described.

We have recently shown that 2,5-dialkyl-3-thienyllithium derivatives ring-open to lithium enynethiolates, which react with alkylating agents to give alkylthiovinylacetylenes.[1,2] We were therefore interested to investigate the stability of the 3-thienyllithium derivatives with hydrocarbon chains connecting the 2- and 5-positions. Molecular models indicated that if the alkyl chain consisted of eight CH_2 groups or less, the strain energy of the cyclic enynethiolate would become too high and the thiophenophanelithium derivative should be stable. On the other hand, if the chain was made up of ten atoms or more, the ring-opening would offer the possibility for the synthesis of cyclic alkylthiovinylacetylenes, an unknown class of compounds difficultly available by other synthetic methods.

Starting from commercial cyclododecanone, *1* was prepared according to Helder.[3] The dione *1* has been cyclized by Nozaki *et al.*[4] to give *2a* in 51 % yield by the Paal-Knorr synthesis using phosphorus pentasulfide. Helder used hydrogen sulfide and hydrogen chloride in the cyclization step, and obtained an 80 % yield.[3] In our hands, despite several attempts, only a 20 % yield of *2a* was obtained together with a large amount of a nicely smelling yellow resin. However, no detectable amounts of *2b* were formed when *2a* was subjected to various bromination conditions (Br_2 in acetic acid, Br_2 in pyridine or *N*-bromosuccinimide in acetic acid). From the reaction with bromine in acetic acid a crude product was obtained, the NMR spectrum of which showed an AB quartet in the aromatic part, with a coupling constant of 3.4 Hz. This indicated the presence of an unsymmetrically 2,5-disubstituted thiophene. Helder [3] has reported rearrangements of *2a* in Friedel-Crafts *t*-butylation experiments. It was shown that *2a* gave 5-*t*-butyl-[8] (2,4)-thiophenophane together with other rearranged products upon treatment with *t*-butyl chloride and stannic chloride in carbon disulfide at room temperature. It seems therefore probable that due to the strain in the starting thiophenophane the electrophile attacks at the 2-position, giving the reactive carbonium ion *3*, which apparently can attack the 4-position in electrophilic substitution, or as is probable in our bromination be intercepted by a nucleophile such as acetate or bromide, or undergo other reactions (hydride shifts, elimination etc.).

Starting from commercial cyclodecapentanone (*4*), irradiation in petroleum ether gave crude *5*, which by oxidation with Jones' reagent [5] was converted to *6*. The crude product, which contained 75 % of *6*, was used for the next step. The reaction of *6* with hydrogen sulfide and hydrogen chloride gave only 4 % of analytically pure *7a*, while reaction with phosphorus pentasulfide gave 37 % of almost pure *7a* (20 % analytically pure). The bromination of *7a* with bromine in acetic acid was more successful than

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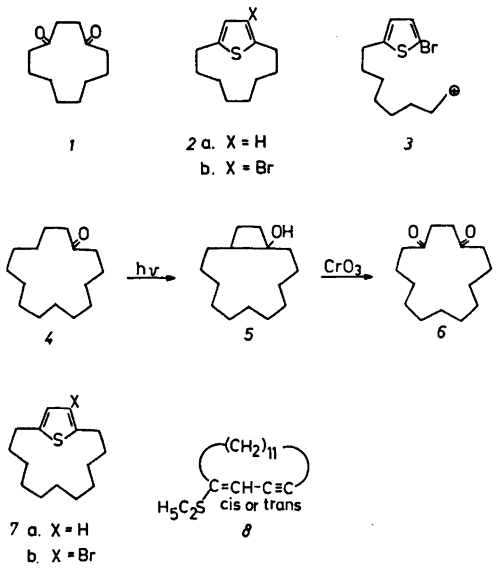

that of *2a*. GLC analysis of the crude product showed the presence of three components in the proportions 2:2:5 (increasing retention times). The main component was the desired *7b*, which was isolated in 25 % yield by vacuum distillation and recrystallization. No attempts were made to elucidate the structures of the other two components.

Reaction of *7b* with ethyllithium and ethyl iodide at room temperature for 4 h gave a 45 % yield of *8* and a 10 % yield of *7a* (isolated yields). The neutral ether phase from the reaction was shown to contain *7a* and *8* in the ratio of 20:80 (GLC). The structure of *8* followed from elemental analysis and spectral data. Its IR spectrum showed C≡C stretching at 2205 cm^{-1} (weak) and C=C stretching at 1575 cm^{-1}. In its ^1H NMR spectrum the resonance of the vinyl proton appeared at δ 5.48 as a broad unresolved triplet. The resonance of the thiophenic hydrogen of the isomeric 3-ethyl-[11] (2,5)-thiophenophane would occur at lower field. (*Cf.* δ 6.52 (β-H) in *7a*; the ethyl group could cause an upfield shift of 0.2 ppm.[6]) The quartet at δ 2.83 falls in the region characteristic for the $-S-CH_2$ grouping.[2] The resonances of the carbon chain protons and the methyl protons of the *S*-ethyl grouping appeared as two separate bands at δ 2.0 – 2.5 (4 H) and at 1.1 – 1.7 (21 H). A decoupled ^{13}C NMR spectrum of *8* showed the absorptions of the acetylenic carbons at δ 86.8 and 105.4, while those of the ethylenic carbons appeared at δ 114.9 and 155.7 (*cf.* Ref. 7). The low-field resonance of the ethylenic part might be assigned to the carbon attached to the sulfur atom, as in 2-methylthiophene the α-carbon resonance appears at lower field than the β-carbon resonance.[8] The resonance of C-2 in (*E*)-1-cyanopropene appears at δ 105.8 and of C-1 at δ 102.1, which also justifies the suggested assignment. The resonances of the saturated carbon atoms showed up as several lines between δ 22.2 and 43.7. It should perhaps be pointed out that the latter signal appears at an unusually low field to arise from an sp^3-hybridized carbon in an aliphatic chain.[7]

The relatively large amount (20 %) of *7a* formed in the synthesis of *8* might be due to slow ring-opening or a slow alkylation of the enynethiolate or both. The ring-opening might be slow due to some strain in the transition state leading to the lithium enynethiolate. The alkylation could be slow due to steric hindrance, as it appears from models that the sulfur atom is within a cavity of the molecule.

Our results, however, indicate that the ring-opening reaction may afford a synthetic route to macrocyclic thioenynes with more than 14 carbon atoms in the ring. Such compounds could be available starting from thiophene and then putting side-chains of suitable length and functionalities in the 2- and 5-positions. This approach to the syntheses of thiophenophanes has been extensively used by Gol'dfarb and coworkers.[9,10] We are continuing our investigation of the synthetic scope of this route to macrocyclic enynes.

EXPERIMENTAL

1,4-Cyclopentadecadione (6). A solution of 25.0 g (0.111 mol) of cyclopentadecanone (Fluka, m.p. 63 – 64 °C) in 900 ml of hexane was irradiated until the carbonyl absorption in the infrared had disappeared (48 h). This procedure was repeated 10 times, to give 250 g of a crude product which was believed to contain bicyclo[11.2.0]cyclopentadecan-1-ol (*5*). (When the solutions were more concentrated (> 5 %) with respect to cyclopentadecanone, the carbonyl absorption did not disappear even after irradiation for 100 h.) The crude product (250 g) was oxidized with Jones' reagent, which gave 216 g of a colourless oil which showed a

strong carbonyl absorption in the infrared (1720 cm^{-1}), but no hydroxylic band. Combined GLC-MS (column OV 1, 3 %, 150 – 300 °C, 10 °C/min) showed mainly two components in the proportions 1:3, with $m/e = 138$ and 238. The most abundant compound was evidently the title compound (calc. for $C_{15}H_{26}O_2 = 238$). The crude product was used without purification.

*[11] (2,5)-Thiophenophane (*7a*).* (a) A solution of 37.0 g (0.155 mol) of crude *6* in 1 l of ethanol (99.5 %) was cooled to 0 °C and hydrogen sulfide and hydrogen chloride were bubbled through the solution for 8 h (*cf.* Ref. 3). The temperature was kept below + 5 °C, and subsequently most of the solvent was evaporated. The residue was taken up in hexane, washed with water and dried. Evaporation of the solvent gave 30.4 g of a yellow oil which was dissolved in hexane and chromatographed on a silica gel column. Thus a fraction weighing 7.4 g was obtained, which gave 1.5 g (4.1 %) of the title compound in the cold (– 25 °C). Recrystallization from acetonitrile (– 25 °C) afforded pure *7a*, m.p. 51 – 53 °C. NMR (CCl_4): δ 6.52 (s, 2 H, β-H), 2.6 – 2.9 (m, 4 H, $-CH_2-$), 0.6 – 1.8 (18 H). [Found: C 76.17; H 10.25; S 13.56. Calc. for $C_{15}H_{24}S$ (236.42): C 76.21; H 10.23; S 13.56].

(b) A mixture of 150 g (0.629 mol) of *6* and 100 g (0.450 mol) of P_2S_5 was heated at 80 °C for 4 h under nitrogen (*cf.* Ref. 4). The reaction mixture was cooled and extracted with hexane, whereupon the combined organic extracts were washed with 2 N aq. NaOH, and water, and then dried. The solution was filtered through silica gel and the solvent was evaporated to give 55.2 g (37 %) of almost pure title compound. Crystallization from acetonitrile afforded 30.0 g (20 %) of *7a* with the same properties as mentioned above.

*Attempted synthesis of 3-bromo-[8] (2,5)-thiophenophane (*2b*).* Samples of 1.2 g (6.2 mmol) of *2a* [4] were treated as follows:

(a) With bromine (1.0 g, 6.3 mmol) in 25 ml of acetic acid at room temperature for 30 min. After the usual work-up (hexane extraction), 1.4 g of a crude product was obtained. NMR (CCl_4) showed an AB quartet: δ 6.83 (d) and 6.62 (d); ($J = 3.4$ Hz), and several absorptions in the aliphatic region.

(b) With *N*-bromosuccinimide (1.1 g, 6.2 mmol) in 25 ml of acetic acid. A yellow crude product containing several components according to GLC (column OV 1, 3 %, 100 – 300 °C, 15 °C/ min) was obtained.

(c) With bromine (1.0 g, 6.3 mmol) in 10 ml of pyridine. A yellow resin that did not give a reproducible gas chromatogram was obtained.

*3-Bromo-[11] (2,5)-thiophenophane (*7b*).* To a solution of 15.0 g (0.0634 mol) of *7a* in 500 ml of acetic acid, 10.4 g (0.065 mol) of bromine in 50 ml of acetic acid was added dropwise at room temperature. The mixture was stirred for 2 h, neutralized with $NaHCO_3$ and extracted with ether. Drying and evaporation yielded 17.5 g of a crude product containing three components (2:2:5) according to GLC (column OV 1, 3 %, 200 – 300 °C, 10 °C/min). Distillation of 15.0 g of the crude product gave 5.2 g (30 %) of the title compound, b.p. (5×10^{-3} mmHg) 140 – 144 °C, which crystallized. Recrystallization from *N*,*N*-dimethylformamide in the cold (– 25 °C) gave 4.3 g of pure *7b*, m.p. 45 – 46 °C. NMR ($CDCl_3$): δ 6.57 (s, 1 H, 4-H), 2.60 – 2.95 (m, 4 H, $-CH_2-$), 0.60 – 1.85 (m, 18 H). [Found: C 56.6; H 7.39; S 10.3. Calc. for $C_{15}H_{23}BrS$ (315.32): C 57.14; H 7.35; S 10.17].

*1-Ethylthio-1-cyclopentadecen-3-yne (*8*).* Nitrogen gas was supplied for 30 min to the pre-dried, hot (110 °C) apparatus, consisting of a three-necked round-bottomed flask fitted with a condenser (drying tube, $CaCl_2$), stirrer, dropping funnel and a neck for the gas inlet. The dropping funnel was also supplied with nitrogen gas. To 2.00 g (6.34 mmol) of *7b* in 25 ml of anhydrous ether, 8.0 ml (6.4 mmol) of 0.80 M ethereal ethyllithium was added at room temperature. After 10 min, 5.0 g (32 mmol) of ethyl iodide was added and the mixture stirred for 4 h. The reaction mixture was hydrolyzed with water and the aqueous phase was extracted three times with ether. The combined ether phases were washed with water and dried over magnesium sulfate. Evaporation of the ether gave 1.55 g of crude product, which combined GLC-MS analysis (column OV 1, 3 %, 150 – 250 °C, 15 °C/min) showed to consist of *7a* ($m/e = 236$; calc. for $C_{15}H_{24}S = 236$) and of *8* ($m/e = 264$; calc. for $C_{17}H_{28}S = 264$) in the proportions of 1:4. The two components were separated and isolated by preparative TLC (silica gel, 1 mm, hexane), which gave 0.15 g (10 %) of *7a* (R_F 0.48 – 0.55) and 0.75 g (45 %) of the title compound (R_F 0.10 – 0.39). IR: C≡C 2205 cm^{-1} (weak), C=C 1575 cm^{-1}. ^1H NMR (CCl_4): δ 5.48 (bt, 1 H, 2-H), 2.83 (q, 2 H, $S-CH_2-$), 2.0 – 2.5 (4 H, alkyl), 1.1 – 1.7 (21 H). $J_{SCH_2-CH_3} = 7$ Hz. ^{13}C NMR (acetone, decoupled spectrum): δ 155.7 (1-C), 114.9 (2-C), 86.8 and 105.4 (3-C and 4-C), 22.2 – 43.7 (5-C – 15-C), 43.7 ($S-CH_2-$), 22.2 ($-CH_3$). [Found: C 76.4; H 10.5; S 11.9. Calc. for $C_{17}H_{28}S$ (264.48): C 77.20; H 10.67; S 12.12].

GLC analyses were performed with a Perkin-Elmer 900 gas chromatograph. Mass spectra were recorded on an LKB-9000 mass spectrometer with an ionization energy of 70 eV. ^1H NMR spectra were recorded on a Varian A-60 NMR spectrometer and ^{13}C NMR spectra on a Jeol FX-60 NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 257 grating infrared spectrometer.

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