The Cycloisomerization Reaction of [2.2]Metacyclophanes to 1,2,3,3a,4,5-Hexahydropyrenes. Substituent Effects and Directional Selectivity

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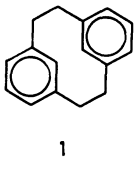
(Received July 13, 1981)

Substituent effects and directional selectivity in iodine-induced cycloisomerization reaction of [2.2]metacyclophane were tested using several derivatives of the latter. The reaction was found to be highly selective, and electron-donating groups gave a hexahydropyrene preserving a substituted aryl ring. On the other hand, an alkyl group *ortho* to the bridge gave a hexahydropyrene with a hydrogenated substituted ring.

Transannular reactions of mesocyclic compounds constitute an important synthetic strategy for constructing bridged systems.[1] We have found a highly efficient cycloisomerization reaction of [2.2]metacyclophane (**1**) to give 1,2,3,3a,4,5-hexahydropyrene (**2**) by treatment with a catalytic amount of iodine.[2] This remarkable transformation has been shown to be widely applicable for the synthesis, in high yields, of hitherto unaccessible alkyl-substituted hexahydropyrenes,[3] starting from alkyl derivatives of **1**.[2,4]

Instead of iodine, aluminium chloride,[2,5,6] bromine,[2] sulfuric acid[2,5] and silver salts[2] have also been used as the catalyst, but these were less selective and also less efficient than iodine. This paper will describe the substituent effects and directional control of the iodine-induced reaction using substituted [2.2]metacyclophanes, **3a**, **3b**, **6a**, **6b**, **9**, **13a**, **13c**, and **13d**, in which two benzene rings are differently substituted.



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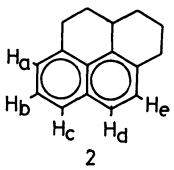

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Results. [2.2]Metacyclophanes prepared according to the method described before[7] were treated with 0.14 equiv. of iodine in benzene at 60 °C for 15—20 h. The reaction mixture was then analyzed by vapor-phase and column chromatography. The yields shown in Table 1 are for a diastereomeric mixture. The analytical data are shown in Table 2.

TABLE 1. IODINE-INDUCED CYCLOISOMERIZATION REACTION[a]

Compound	Hexahydro-pyrene(%)	Tetrahydro-pyrene(%)	Starting material recovery/%
3a	**4a**, 80		20
3b	**4b**, 100		
6a	**7a**, 88	**8a**, 6	6
6b	**7b**, 89	**8b**, 10	1
9	**10**, 98	**12**, 2	
13a	**15**, 100		
13c			100
13d			100

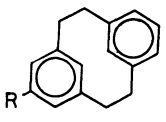
a) The relative yields were determined by gas chromatography after treating the substrate with 0.14 equiv. of iodine in benzene at 60 °C (for **9**, 45 °C) for 15—20 h.

TABLE 2. 1,2,3,3a,4,5-HEXAHYDROPYRENES

Compound	Mp θ_m/°C	Formula	Found (%) C	Found (%) H	Calcd (%) C	Calcd (%) H
4a	97—98	$C_{17}H_{18}$	91.97	8.17	91.84	8.16
4b	116—118	$C_{20}H_{24}$	90.60	9.18	90 85	9.15
7a	101[a]	$C_{19}H_{22}$	91.92	8.23	91.14	8 86
7b	108[a]	$C_{22}H_{28}$	90.45	9.41	90.35	9.65
10	Oil	$C_{20}H_{24}$	90.94	9.17	90.85	9.15
15	140—141	$C_{18}H_{20}$	85.65	8.05	85.67	7.99

a) Half crystalline.

5-Methyl derivative **3a** gave a 80% yield of **4a**, with 20% of the recovered material. That the product was not isomeric **5a** was proved by the appearance of a ^{1}H NMR resonance at δ 2.46 as a singlet. A methyl proton



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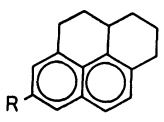

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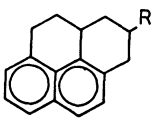

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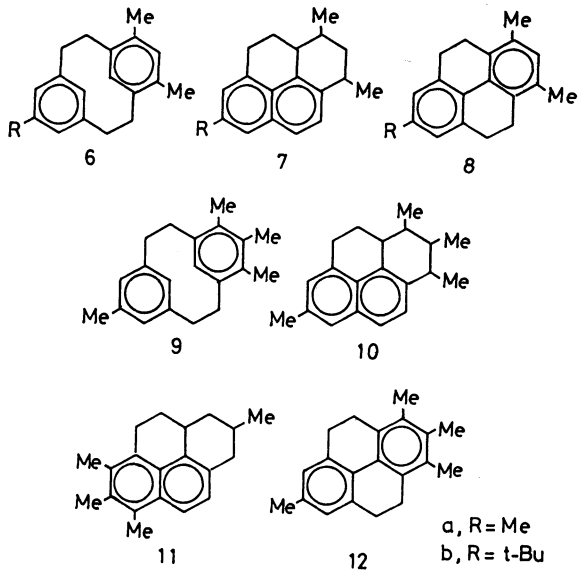
a, R=Me
b, R=t-Bu

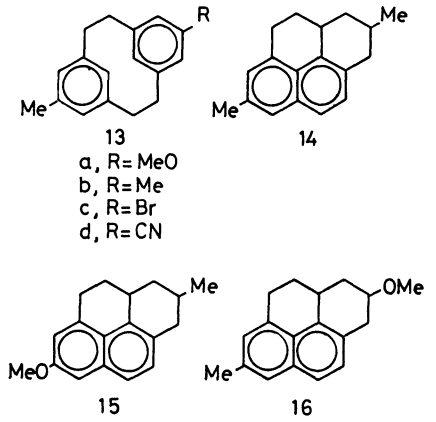
resonance in **5a** would require a doublet at around δ 1.10, as is observed in the 2,7-dimethyl derivative **14** prepared from **13b**.[2] The substitution pattern in a naphthalene ring was consistent with **4a**, as was proved by the UV and NMR spectra (see below). Similarly, the *t*-butyl derivative **3b** gave a quantitative yield of **4b**.

The directional selectivity was then studied using trialkyl and tetraalkyl derivatives, **6** and **9**. Compound **6a** gave 88% of **7a**. Similarly, **6b** and **9** gave 89 and 98% respectively of **7b** and **10**. In addition, these gave dehydrogenation products, 4,5,9,10-tetrahydropyrenes, **8a** (6%), **8b** (14%), and **12** (2%) as by-products. In any case, no isomeric hexahydropyrene in which a multi-substituted aryl ring was preserved as in **11** was isolated, as was evidenced by a careful examination of the reaction mixture by means of UV and NMR.

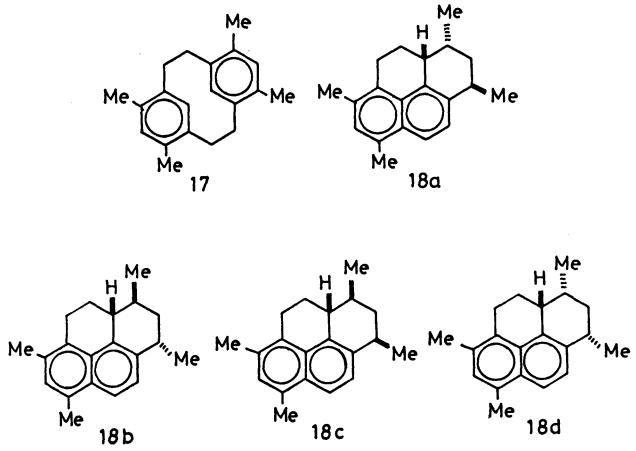
Competition between a methyl group and several functional groups were then studied using compounds **13a**, **13c**, and **13d**. Dimethyl derivative **13b** has been shown to give **14** in a quantitative yield.[2] 5-Methoxy-13-methyl derivative **13a** gave **15** exclusively. A methoxy methyl proton resonance at δ 3.90 suggests



the formation of an aromatic ether **15** but not the isomeric **16**. On the other hand, two bromo and cyano derivatives, **13c** and **13d**, gave no isomerization reaction product and were recovered unchanged under the present reaction conditions.



Structural Evidence. When an alkyl-substituted aryl ring becomes hydrogenated, the reaction mixture has been shown to be a diastereomeric mixture.[2] These isomers were separated partially by passing through alumina containing silver nitrate. The mixture could be completely analyzed by means of NMR spectroscopy with the aid of the ASIS and NOE methods and also shift reagents.[2] For example, the tetramethyl derivative **17** has been shown to give three isomeric tetramethylhexahydropyrenes, **18a**, **18b**, and **18c**, each as in a *dl* pair. The possible fourth isomer involving 1,3-diaxial methyl interaction, **18d**, could not be detected.[2]



In view of the lack of stereospecificity in this transformation, no attempt was made in the present studies to separate and characterize diastereomers. Structural evidence for the suggested structure is illustrated by the case of **10**, formed from **9**. The assignment of the five aromatic protons in **2**, H_a—H_e, has already been reported.[2] The aryl proton resonances in **10** are in agreement with the suggested substitution pattern. The compound showed a three-proton singlet corresponding to an aromatic methyl resonance at δ 2.38. The methyl groups on saturated carbon showed complex resonances at δ 0.5—1.5, suggesting a diastereomeric mixture.

The substitution pattern in the naphthalene nucleus can conveniently be learned from a UV spectral comparison. Alkyl substitution at an α position causes both bathochromic and hyperchromic shifts of the ^1L_a bands, whereas β substitution results in a red shift and intensity increase in the ^1L_b bands.[8] Figure 1 shows the UV spectra for **10**, **14**, and **18**. The examination of both the ^1L_a and ^1L_b bands suggests that the substitution pattern in the naphthalene ring for **10** is similar to that of **14**.[2] An alternative structure, **11**, would require a further shift of these bands beyond **18**.

Mass-spectral measurements also served as structural

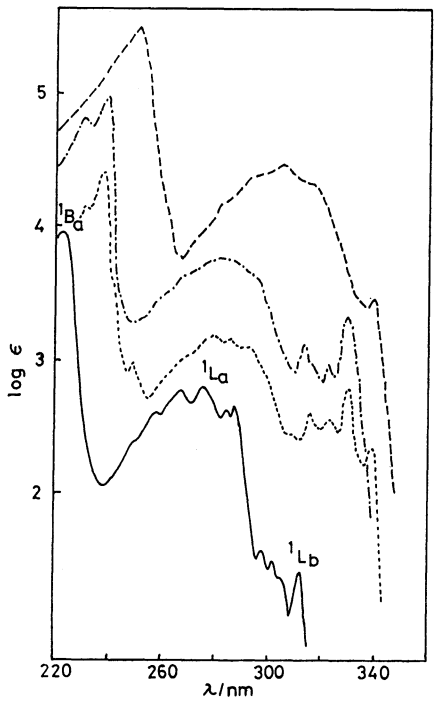


Fig. 1. The UV spectra for —— naphthalene, -·-·- 1,2,3,7-tetramethyl- (**10**), ····· 2,7-dimethyl- (**14**), and ---- 1,3,6,8-tetramethyl-1,2,3,3a,4,5-hexahydropyrenes (**18a**, **18b**, and **18c**) determined in cyclohexane. Absorption, log ε, is for compound **10**.

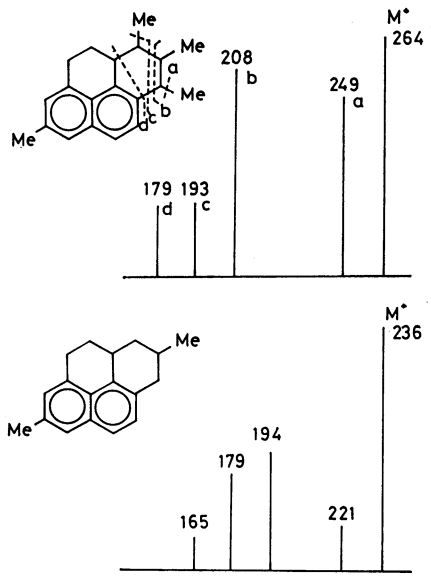


Fig. 2. The mass-spectral fragmentation for 2,7-dimethyl (**14**) and 1,2,3,7-tetramethyl-1,2,3,3a,4,5-hexahydropyrenes (**10**) determined at 70 eV.

proof. Figure 2 shows a comparison of the fragmentation pattern for **10** and **14**. The appearance of assigned peaks for **10** excludes the alternative structure, **11**, which possesses a hydroaromatic partial structure similar to that of **14**.

Compound **7a** gave poor analytical data, probably because of difficulty in purification. Its formation was supported by GC-MS carried out on an OV-1 column, which separated the diastereomeric mixture into two fractions. Both fractions gave essentially the same fragmentation pattern, with *m/e* at 208 ($-C_3H_6$: *cf.* Fig. 2, fragmentation b), 235 ($-CH_3$), and 250 (parent peak). In going into **7a** from **6a**, the NMR signals at δ 2.26, 4.08, and 4.20 in **6a** disapeared and methyl signals appeared at δ 2.40 ($ArCH_3$) and at around 1.3 (aliphatic CH_3).

Conclusion. The results obtained so far can be summarized as follows: 1) The iodine-induced cycloisomerization of substituted [2.2]metacyclophanes proceeds with a high directional selectivity. 2) An electron-donating group at the 5- (or 13-) position directs the transformation toward hexahydropyrene formation, preserving the substituted aryl ring (*cf.* compounds **3a**, **3b**, and **13a**). 3) An electron-withdrawing substituent gives no cycloisomerization reaction products under the present reaction conditions.[9] 4) When an alkyl group is present at the *ortho* position of the bridge (4,6,12,14-positions), the hydrogenation occurs on the alkyl-bearing aromatic ring. 5) An alkyl group ortho to the bridge not only enhance the rate of cycloisomerization, but gives a dehydrogenation product (*cf.* **6**→**8**, **9**→**12**).

With regard to 4) and 5), we have observed[4] that the cycloisomerization reaction of the tetramethyl derivative, **17**, and a hexamethyl derivative[4] are quite rapid compared with that of **1** and also with those of less highly substituted derivatives. The enhanced reactivity for these has been attributed to an additional strain imposed on the bridging methylene group by the vicinal methyl group. The driving force of the cycloisomerization reaction is assumed to be the internal strain of a ten-membered ring, the proximity of two reacting aryl positions, and the π-basicity of the benzene ring(s) for complexation with iodine.[2,4] With **6** and **9**, the additional strain term outweighs the normal substituent effects operating in **3** and directs the reaction toward the formation of **7** and **10**, but not **11** or the isomeric **7**, with a different naphthalene ring disposition.

Experimental

[2.2]Metacyclophane Derivatives. Compounds **3a**,[10] **3b**,[11] **6a**,[10] **6b**,[10] **13a**,[7] **13b**,[2] **13c**,[7] and **13d**[7] were prepared as has been described in the literature.

2,11-Dithia-5,6,7,15-tetramethyl[3.3]metacyclophane. 4,5,6-Trimethyl-α,α'-dichloro-*m*-xylene was treated with thiourea in ethanol and then with a potassium hydroxide solution to give 4,5,6-trimethyl-*m*-xylene-α,α'-dithiol. Benzene solutions (200 cm^3) of the dithiol (5.1 g, 24 mmol) and α,α'-dibromomesitylene (6.7 g, 24 mmol) were dropped, slowly and simultaneously, into a solution of 1.9 g (48 mmol) of sodium hydroxide in benzene (200 cm^3)–ethanol (1000 cm^3) during 24 h under reflux. The solvent was then evaporated, and washed dichloromethane extracts were passed through a silica-gel column. The bis(sulfide) was thus obtained in a 55% yield: mp 123—124 °C: NMR ($CDCl_3$) δ 2,12 (3H, s, Me), 2.16 (9H, s, Me), 3.62 (4H, s, CH_2), 3.68 (4H, s, CH_2), and 6.92 (4H, m, ArH).

Found: C, 72.86; H, 7.27%. Calcd for $C_{20}H_{24}S_2$: C, 73.11; H, 7.36%.

4,5,6,13-Tetramethyl[2.2]metacyclophane (9). The above bis(sulfide) was converted to bis(sulfone), 2,11-dithia-5,6,7,15-tetramethyl[3.3]metacyclophane 2,2,11,11-tetraoxide by oxidation with 30% hydrogen peroxide in benzene–acetic acid at room temperature. The pyrolysis of bis(sulfone) at 550 °C gave **9** (mp 113.5—114.5 °C) after chromatography on silica gel: NMR ($CDCl_3$) δ 2.29 (9H, s, Me), 2.36 (3H, s, Me), 1.9 and 3.2 (8H, m, CH_2), 4.13 (1H, t, C-16H), 4.30 (1H, s, C-8H), and 6.89 (2H, ArH).

Found: C, 90.71; H, 1.13%. Calcd for $C_{20}H_{24}$: C, 90.85; H, 9.15%.

Cycloisomerization of 9 to Give 10. A solution of (820 mg, 3.1 mmol) and iodine (110 mg, 0.43 mmol) in 9.6 cm^3 of benzene was warmed at 45 °C for 14 h. Column chromatography on alumina eluted with hexane gave **10** as an oily diastereomeric mixture in a 98% yield. Further elution gave a 2% yield of tetrahydropyrene **12**:[10] mp 117—121 °C. The cycloisomerization was nearly complete within 20 min at 51 °C, as has been observed in a preliminary experiment carried out in a NMR tube in C_6D_6: NMR ($CDCl_3$) δ 0.5—1.5 (9H, m, Me), 2.38 (3H, m, MeAr), 7.01 (1H, s, a-ArH), 7.33 (1H, s, c-ArH), 7.42 (2H, dd, d,e-ArH) (for the designation of naphthalene proton, see Formula **2**).

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