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CONFORMATIONAL ANALYSIS—XIII[1]

SYN AND *ANTI* [3.2]-, [3.3]-, [4.2]-, AND [4.3]-METACYCLOPHANES

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Abstract—While in [3.3]metacyclophane (**19**) the aromatic rings preferentially adopt the *syn* arrangement, its lower and higher homologues, i.e. [2.2]-, [3.2]-, [4.2], and [4.3]-metacyclophane (**1, 6, 26** and **30**), adopt the *anti* conformation. Substituted [m.n]metacyclophanes do not necessarily behave similarly to the parent hydrocarbons. Substituted compounds exhibiting a different conformation are [3.2]metacyclophane-1,11-dione (**7**) (*syn*), [3.3]metacyclophane-2,11-dione (**24**) and the corresponding bis[propylene thioacetal] (**25**) (*anti*), [4.2]metacyclophane-2,12-dione (**27**) (*syn*), and [4.3]metacyclophane-2,13-dione (**31**) (*syn*). Thus, the solution conformation of an [m.n]metacyclophane is sensitive both to chain length [m.n] of the bridges and substitution. The ring inversion barriers determined by variable temperature ^{1}H NMR decrease with increasing length of the bridges and qualitatively correlate with the transanular strain present in the pertinent system.

Conformational changes of [2.2]metacyclophane (**1**) can be induced by introduction of substituents into the bridge which increase or decrease the bond angles.[1-3] In general the conformation of any derivative of **1** can be deduced from the respective geometrical behaviour of the cyclohexane chair. This is due to the same sequence of torsional angles in the ten membered ring of **1** and the cyclohexane chair responsible for the interdependence of bond- and torsional angles. This analogy holds true only for the step-like topology (*anti*-conformation) of **1**. Derivatives of **1**, e.g. **2–5**, always adopt the thermodynamically most stable *anti* conformation. Only in the case of certain intra-anularly substituted metacyclophanes where ring inversion is hindered even at elevated temperatures both *syn*- and *anti*-diastereoisomers have been isolated.[4,5] Hence, the conformational changes observed in derivatives of **1** involve a change in the interplanar angle, the *anti* arrangement of the aromatic rings being preserved. Insertion of methylene groups in the bridge of **1** leads to the homologues [3.2]- (**6**), [3.3]- (**19**), [4.2]- (**26**) and [4.3]-metacyclophane (**30**) representing isoconformers of the flexible ring systems cyclo-heptane, -octane, and -nonane.

The flexibility of the higher [m.n]metacyclophanes and the increased intraanular distance compared with the [2.2]-system should give rise to a lowering of the energy difference of *syn–anti* conformers. Hence, introduction of substituents into the bridges of higher [m.n]metacyclophanes may influence not only the interplanar angles but may also give rise to a change of the equilibrium position of *syn–anti* conformers (*cf* Fig. 1).

An extraordinary strong conformational dependence from substitution in 2-substituted [3.2]metacyclophanes has previously been ovserved by Griffin.[6] However no *anti* → *syn* transition was reported. For [3.3]metacyclophane (**19**) the *syn* conformation has been proposed on the basis of absorption/emission properties[7] (see also Ref. 8). Thus, the conformation of [m.n.]metacyclophanes seems also to be dependent from the length of the bridges.

In continuation of our previous efforts in the conformational analysis of [2.2]metacyclophanes[1-3,9-11] we now wish to report on a systematic conformational study of the higher members, i.e. [3.2]-, [3.3]-, [4.2]- and [4.3]-metacyclophanes. A synthesis for these phanes has been described recently.[12,13]

RESULTS AND DISCUSSION

For the assignment of the metacyclophanes **6–31** to the *syn*- and *anti*-conformation three methods were applied based on a comparison of (i) symmetry, (ii) torsional angles, and (iii) chemical shifts. While the last method is of general applicability, the first two are restricted to special compounds.

For [3.2]- and [3.3]-metacyclophane (**6** and **19**) an unambiguous conformational assignment can be made on basis of the spectral type of their ^{1}H NMR spectra (method i) recorded at temperatures where interconversion is slow on the NMR time scale (**6**: 253 K, **19**: 213K). For the *syn* conformations of **6** (C_s) and **19** (C_{2v}) an AA'BB'CD-spectrum due to the protons of the C_3 bridge is to be expected. Inversely, the *anti* conformations of **6** (C_2) and **19** (C_{2h}) possess only three chemically different proton sorts (AA'BB'CC'), the protons at C-2 being equivalent. From the actual low temperature ^{1}H NMR spectra of the C_3 bridge of **6** (AA'BB'CC') and **19** (AA'BB'CD) the *anti*- and *syn*-conformation can be assigned unequivocally. The *syn* conformation for **19** is in accord with that given in Refs. 7 and 8. The method outlined would also be applicable for the conformational assignment of [4.3]metacyclophane (**30**). Unfortunately, interconversion is too rapid[13] on the NMR time scale and no appropriate spectrum could be obtained.

For compounds **1**, **6**, **19** and **26** the torsional angles of the C_2 and C_3 bridges could be evaluated by means of

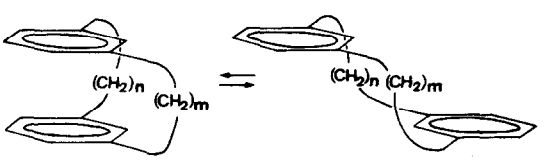
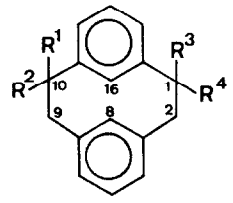
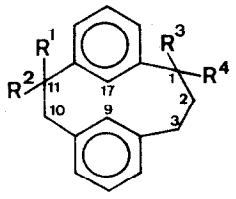


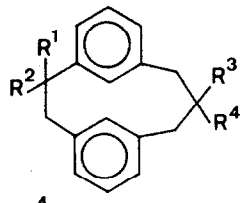
Fig. 1. Equilibrium between *syn*- and *anti*-conformers of an [m.n.]metacyclophane.

the R-value method[9,14] from the vicinal proton spin coupling constants (method ii). By this method a clear decision between *syn*- and *anti*-conformers is possible and, in addition, a more accurate evaluation of the geometry can be made. The torsional angle of the C_2 bridges of **1**, **6** and **26** should be 60° (*anti*) or 0° (*syn*). From the ^{1}H NMR spectra the torsional angles were calculated to be 57° (**1**),[9] 57°(**6**) and 63°(**26**) (*cf* Table 1). Interestingly, the vicinal proton spin coupling constants for the C_3 bridge of [3.2]metacyclophane (**6**) are all very similar among themselves. Therefrom we conclude that torsional motion of the C_3 bridge is rapid even at low temperatures, giving rise to the population of different *anti* conformers. Hence, the R-value-method yields a mean value of $\cos^2 \phi$ with $\phi = 46°$ (Table 1). For the *syn*- and *anti*-conformation of **19** ϕ should be 60° (*syn*) or 30° (*anti*). The value of 70° (Table 1) clearly reveals the perferred *syn* conformation. In contrast to **6**, the coupling constants of the C_3 bridges of **19** are different among themselves indicating a lower mobility of the C_3 bridges



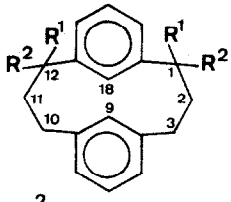
R^1	R^2	R^3	R^4	
H	H	H	H	**1**
	O		O	**2**
OH	OH	OH	OH	**3**
	O		$S(CH_2)_3S$	**4**
$S(CH_2)_3S$		$S(CH_2)_3S$		**5**

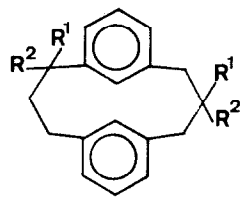


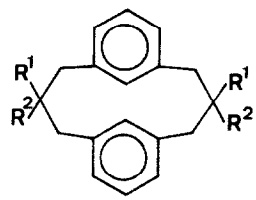


	R^1	R^2	R^3	R^4	
6	H	H	H	H	
7		O		O	**13**
8	OH	OH		O	**14**
9	OCH_3	OH		O	**15**
10	OH	OCH_3		O	**16**
11	$S(CH_2)_3S$			O	**17**
12	$S(CH_2)_3S$		$S(CH_2)_3S$		**18**

Scheme 1.







R^1	R^2		
H	H	**19**	
	O	**20**	**22** **24**
$S(CH_2)_3S$		**21**	**23** **25**

Scheme 2.

Table 1. ^{1}H NMR parameters (δ, ppm; J, Hz), R-values, and torsional angles (ϕ) of the C_2 and C_3 bridges of **1**, **6**, **19** and **26** at 250 MHz

C_2 bridge of	δ, J	R	ϕ
1[a]	($CDCl_3$, 318 K): AA'BB'm, H_A 3.05; H_B 2.06; J_{AB} -11.9; $J_{AA'}$ 3.4; $J_{BB'}$ 12.2; $J_{AB'}=J_{A'B}$ 3.8.	2.05	57.2°
6	(CD_2Cl_2, 253 K): AA'BB'm, H_A 3.05; H_B 2.16; J_{AB} -11.8; $J_{AA'}$ 3.1; $J_{BB'}$ 12.7; $J_{AB'}=J_{A'B}$ 3.9.	2.03	57.0°
26	($CDCl_3$, 233 K): AA'BB'm, H_A 3.14; H_B 2.34; J_{AB} -12.5; $J_{AA'}$ 4.9; $J_{BB'}$ 12.6; $J_{AB'}=J_{A'B}$ 2.9.	3.02	62.5°
C_3 bridge of			
6	(CD_2Cl_2, 253 K): AA'BB'CC'm, H_A 2.80; H_B 2.29; H_C 1.94; J_{AB} -13.8; J_{AC} 6.3; $J_{AC'}$ 6.3; J_{BC} 7.3; $J_{BC'}$ 6.4; $J_{CC'}$ ~ -13.	1.07	46.0°
19	(CD_2Cl_2, 213 K): AA'BB'CDm, H_A 2.98; H_B 2.50; H_C 2.17; H_D 1.69; J_{AB} -12.8; J_{CD} -12.5; J_{AC} 5.0; J_{AD} ~1.0; J_{BC} ~2.0; J_{BD} 13.0.	~6.0	~70°

[a] taken from Ref. 9.

in **19**. As can be seen from models the mobility of a C_3 bridge in **6** or **19** is always greater in the *anti* conformation. From the ϕ value of **19** (at 213 K) the angle comprising the two benzene planes was estimated to be 30°.

A further criterion in conformational analysis of cyclophanes is furnished by a consideration of their ring current.[3,5,6,11] This method, though less stringent than the two used in the foregoing can be applied to most compounds investigated in this study.

In Table 2 the chemical shifts of H_B and H_C and of the respective para-positioned extraanular protons H_A and H_D are compiled. H_A and H_B refer to protons of that benzene ring carrying no substituent in the benzylic position. Since the chemical shifts of these protons are less influenced by substituents in the bridge only the difference $\delta_{H_B} - \delta_{H_A}(\Delta\delta)$ was used as a conformational criterion. In the *anti* conformation H_B is shielded by the other benzene ring, while H_A is essentially unaffected. Hence, $\Delta\delta$ is negative. As the chain length of the [m.n]-metacyclophane becomes larger this influence decreases. Inversely, in the *syn* conformation, the intra- and extraanular aromatic protons experience a similar, but only weak shielding effect from the second benzene ring. Hence, for a *syn* conformation of [m.n]metacyclophanes a small absolute $\Delta\delta$-value is characteristic.

The utility of the method outlined has impressively been shown in [2.2]- and [3.3]-metacyclophanes where both *syn*- and *anti*-forms could be isolated as diastereoisomers.[4,5] The shift criterion is further corroborated by compounds **1–5** ($\Delta\delta = -1.4 - -3.2$ ppm), **6** ($\Delta\delta = -2.1$ ppm), **19** ($\Delta\delta = +0.1$ ppm), and **26** ($\Delta\delta = -1.5$ ppm the conformations of which have been assigned by methods (i) or (ii) or have been subject to an X-ray analysis.

For the *anti* conformations of the [3.2]metacyclophanes **7–18** a value close to that of the parent hydrocarbon **6** is to be expected. This holds true for all [3.2]metacyclophanes except for **7**. The value of **13** ($\Delta\delta = -1.0$ ppm) is rather low but most likely can be attributed to a small change in the interplanar angle preserving the global *anti* conformation in analogy to **2**.[1,3] Accordingly, from the [3.2]metacyclophanes investigated only compound **7** preferentially adopts the *syn* conformation.

The *syn* conformation of [3.3]metacyclophane (**19**) exhibits a $\Delta\delta$-value of +0.1 ppm. This conformation is likewise found in **20** and **21**, even if the interplanar angle might vary slightly. In the case of **22** and **23** no conformation can be assigned on the basis of the $\Delta\delta$-value. For these compounds a conformational equilibrium with appreciable population of *syn*- and *anti*-conformers in solution cannot be excluded. The low temperature spectra of **22** and **23** are not conclusive and the co-existence of two conformers could not be assessed. For **22** the lowest temperature of recording (183K) lies too close to the "coalescence temperature" (193K) of ring inversion. For **23** complications due to conformers of the

dithian moieties arise. In contrast to the parent hydrocarbon **19**, compounds **24** and **25** prefer the *anti* conformation.

The $\Delta\delta$-value of *anti*-[4.2]metacyclophane (**26**) is also found in the derivatives **28** ($\Delta\delta = -1.5$ ppm) and **29** ($\Delta\delta = -1.7$ ppm). Thus, the $\Delta\delta$-value of **27** (~ 0 ppm) indicates the *syn* conformation.

As for the [4.3]metacyclophanes investigated the hydrocarbon **30** preferentially adopts the *anti* conformation while for the ketone **31** the *syn* conformation is most likely.

It is remarkable that [3.3]metacyclophane (**19**) adopts the *syn* conformation, in contrast to the behaviour of its lower and higher homologues **1**, **6**, **26** and **30**. Hence, appreciable interactions due to the aromatic rings resembling that of [m.n]paracyclophanes are only possible in **19**. This is reflected in the electronic absorption spectra shown in Fig. 2. The gradual absorption from 300 nm up to 200 nm of **19** phenomenologically differs from that of the homologues **1**, **6**, **26** and **30** exhibiting well resolved and structured ^1L_b-bands. Unfortunately, the phenomenological differences in electronic absorp-

Table 2. Chemical shifts (δ, ppm) of intraanular (H_B, H_C) and para-positioned extraanular (H_A, H_D) aromatic protons, shift differences $\Delta\delta(\delta_{H_n}-\delta_{H_m})$ and proposed conformations of the metacyclophanes **1**–**31**. H_A and H_B refer to the protons of the benzene ring of the cyclophane under consideration carrying no substituent in the benzylic position

Compound	Solvent	δ				$\Delta\delta$	Conformation
		H_A	H_B	H_C	H_D		proposed
1	a	7.2	4.2			-3.0	anti
2	a	7.3	5.9	4.2	7.3	-1.4	anti
3	b	7.2	4.3	5.3	7.2	-2.9	anti
4	a	7.2	4.9	5.6	7.6	-2.3	anti
5	a	7.1	3.9	6.7	7.5	-3.2	anti
6	a	7.2	5.1			-2.1	anti
7	a	6.9	7.3	7.5	7.3	+0.4	syn
8	c	7.2	5.1	6.0	7.2	-2.1	anti
9	d	7.3	5.2	5.9	7.5	-2.1	anti
10	d	7.3	5.0	6.1	7.5	-2.3	anti
11	a	7.3	5.1	6.8	7.6	-2.2	anti
12	a	7.1	4.5	7.3	7.5	-2.6	anti
13	a	7.2	6.2	5.3	7.2	-1.0	anti
14	b	7.2	5.2	5.7	7.3	-2.0	anti
15	d	7.2	5.1	5.8	7.2	-2.1	anti
16	d	7.2	5.2	5.5	7.2	-2.0	anti
17	a	7.3	5.0	6.3	7.5	-2.3	anti
18	a	7.2	4.7	6.0	7.4	-2.5	anti
19	a	6.8	6.9			+0.1	syn
20	a	6.5	7.5	7.8	7.2	+1.0	syn
21	a	6.7	6.9	8.4	6.9	+0.2	syn
22	a	7.1	6.5	6.8	7.3	-0.6	---
23	a	6.8	6.6	7.5	7.0	-0.2	---
24	a	7.3	5.8			-1.5	anti
25	a	7.1	5.8			-1.3	anti
26	a	7.2	5.7			-1.5	anti
27	a	7.0	7.0	7.1	7.3	0.	syn
28	d	7.0	5.5	5.8	7.0	-1.5	anti
29	a	7.1	5.4	6.5	7.5	-1.7	anti
30	a	7.2	6.1			-1.1	anti
31	a	6.8	6.9	7.1	7.2	+0.1	syn

Solvents: a, $CDCl_3$; b, THF-d_8; c, dioxane-d_8 – D_2O (20% v/v);
d. $CDCl_3$ – CD_3OD (50% v/v).

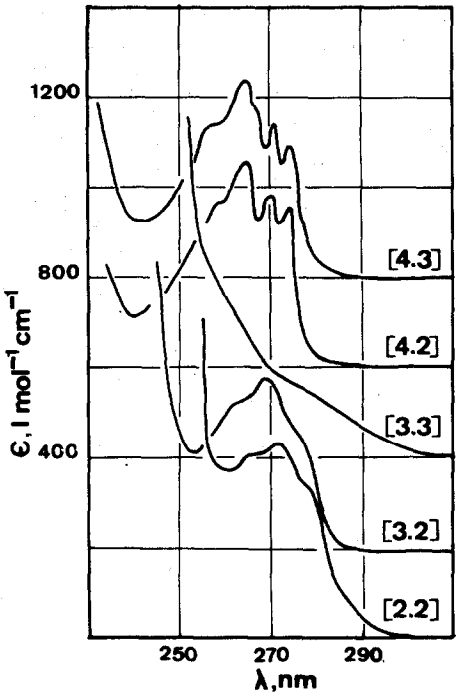
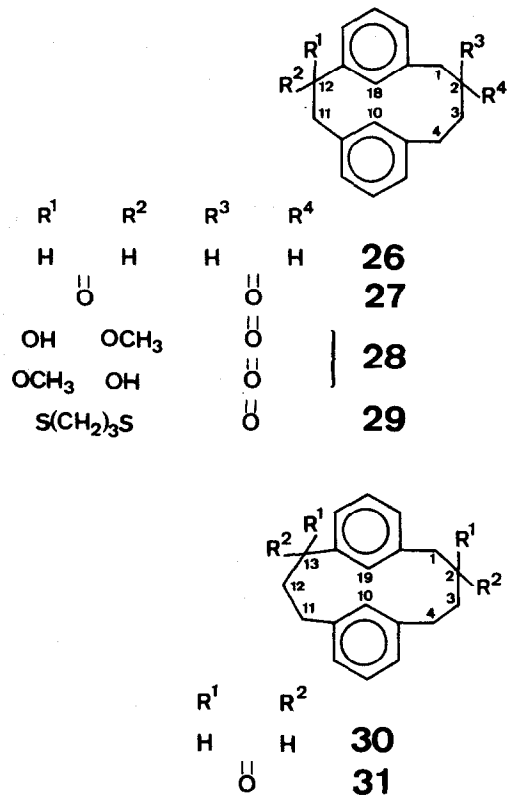


Fig. 2. Electronic absorption spectra of [2.2]- (1), [3.2]- (6), [3.3]- (19), [4.2]- (26) and [4.3]- (30) metacyclophane at room temperature in cyclohexane (1.2×10^{-3} M). At $\lambda = 310$ nm all compounds reveal $\epsilon = 0$. With the exception of 1 the ordinate scale for the hydrocarbons is moved by a multiple of 200 l.mol^{-1}.cm^{-1}.



Scheme 3.

tion spectra of *syn*- and *anti*-[m.n] metacyclophanes are blurred by additional bands in the substituted compounds. Inversely, the electronic absorption spectrum of **19** has been used to establish its *syn* conformation[7] though proper compounds for spectral comparison were lacking. In this connection it should be mentioned that the conformation of the dithia-[15] and hexathia-[16] analogues of **19** has likewise been reported to be *syn*.

The conformations of the cyclophanes **6–31** clearly show that their global geometry not only depends on bridge lengths but also on substituents. The sensitivity towards substitution in the higher [m.n]metacyclophanes remarkably contrasts the behaviour of the [2.2]metacyclophane-system where any substitution in the bridge never affects the predominance of *anti* conformers. Clearly, as transanular steric compression decreases with increasing m and n, additional conformation determining factors operative in substituted compounds should gain more importance. These influences may either stabilize the conformation of the parent hydrocarbon or, if counteracting, give rise to a conformational change. Since the energy differences between *syn*- and *anti*-conformers in the flexible [3.2]-, [3.3]-, [4.2]- and [4.3]-metacyclophanes are apparently low, it is difficult to weigh the individual conformation governing influences caused by substitution. The solution of these problems awaits a comparative force-field calculation.

The ring inversion barriers of the homologous [m.n]-metacyclophanes compiled in Table 3 expectedly decrease with increasing lengths of the bridges. Moreover, the spectra obtained below coalescence temperatures reveal conformational homogeneity. The values for **6**, **7** and **13** are in fair agreement with those given for 2-substituted [3.2]metacyclophanes.[6,17] The order of barriers found ([2.2] > [3.2] > [4.2] > [3.3] > [4.3]) qualitatively correlates with the sequence of the transanular strain present in the ground state of the pertinent system.[12,18] Hence, the transition state exhibits a larger dependence from m and n than the ground state.

However, the increase of barriers with increasing ring strain in the ground state found experimentally for **1**, **6**, **19**, **26** and **30** is not self-evident and could not be predicted. A cyclophane experiencing a larger enhancement of free energy in its ground state than in its transition state would exhibit a lower barrier. This situation is found in [2.2](2, 6)pyridinophane which-though less strained than [2.2](2, 6)pyridinophan-1-ene-possesses a higher ring inversion barrier.[19,20] Further examples are reported in the [2.2]metaparacyclophane-series.[21] Likewise, the larger barrier reported for [4.1]metacyclophane (82 kJ mol^{-1})[22] compared with that for the more strained [3.1]metacyclophane (69 kJ mol^{-1})[23] might reflect this situation and might not necessarily be due to a "questionable NMR analysis" as has been stated in Ref. 23.

A closer inspection of Table 3 furthermore reveals a negligible difference of barriers for *anti*- (**6** and **13**) and *syn*-(**7**) [3.2]metacyclophanes. This might be accidental but suggests, in general, that the ground state energy difference of *syn*- and *anti*-conformers of any higher [m.n]metacyclophane is much lower than that of the [2.2]-system. The conclusions drawn are compatible with the observed conformational sensitivity towards substitution. It is further corroborated by recent findings on the conformational behaviour of dithia- [3.3]metacyclophanes.[15,24]

Table 3. Ring inversion barriers $\Delta G^{\ddagger}_{T}$ (kJ mol^{-1}) at the temperature T(K) of [m.n]metacyclophanes in decahydronapthalene (1)[a], perchlorobutadiene (6[b], 7[b] and 13[b]), CD_2Cl_2 (19[b], 20[b,c] and 30[b,d]), and $CDCl_3$ (26[b,d])

	[2.2]	[3.2]			[3.3]		[4.2]	[4.3]
	1	6	7	13	19	20	26	30
$\Delta G^{\ddagger}_{T}$	133	73	74	76	50[e]	56	60	< 38
(T)	(442)	(363)	(353)	(373)	(253)	(293)	(308)	(<193)

[a] by racemisation of optically active derivatives, taken from Ref. 2.

[b] by variable temperature NMR.

[c] taken from Ref. 12.

[d] taken from Ref. 13.

[e] A preliminary value of 46 kJ mol^{-1} has been mentioned in Ref. 8.

EXPERIMENTAL

Compounds **6–31** have been prepared as described in Refs. 12 and 13. ^{1}H NMR measurements were taken with a Bruker WM 250 instrument (FT mode) using spectrograde dioxane-d_8, methanol-d_4, tetrahydrofuran-d_8, perchlorobutadiene-benzene-d_6, CD_2Cl_2, $CDCl_3$ and D_2O. The concentrations ranged from 5 to 15 mg/ml. Electronic absorption spectra were run with a Cary 15 instrument in spectrograde cyclohexane (1 cm quartz cuvettes, room temp). For the evaluation of coupling constants of the proton spin systems of the bridges of **1**, **6**, **19** and **26** (listed in Table 1) approximate parameters were taken from the actual spectra and fitted with a LAOCOON III computer program.

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REFERENCES

[1] Part XII: D. Krois, E. Langer and H. Lehner, *Tetrahedron* **36**, 1345 (1980).
[2] H. Keller and H. Lehner, *Ann. Chem.* 595 (1978).
[3] H. Lehner, *Monatsh. Chem.* **105**, 895 (1974).
[4] D. Kamp and V. Boekelheide, *J. Org. Chem.* **43**, 3470 (1978).
[5] H. A. Staab, C. P. Herz and A. Döhling, *Chem. Ber.* **113**, 233 (1980).
[6] R. W. Griffin, Jr. and R. A. Coburn, *J. Am. Chem. Soc.* **89**, 4638 (1967).
[7] T. Otsubo, M. Kitasawa and S. Misumi, *Bull. Chem. Soc. Japan* **52**, 1515 (1979).
[8] T. Shinmyozu, T. Inazu and T. Yoshino, unpublished results cited in T. Shinmyozu, T. Inazu and T. Yoshino, *Chemistry Lett.* 1319 (1978).
[9] Ch. Krieger, E. Langer and H. Lehner, *Monatsh. Chem.* **107**, 19 (1976).
[10] H. Lehner, *Ibid.* **107**, 565 (1976).
[11] H. Keller, E. Langer and H. Lehner, *Ibid.* **108**, 1371 (1977).
[12] D. Krois and H. Lehner, *J. Chem. Soc. Perkin I* 477 (1982).
[13] D. Krois and H. Lehner, *Ibid.* in press.
[14] H. R. Buys, *Rec. Trav. Chim. Pays-Bas* **89**, 1244, 1253 (1970); J. B. Lambert, *Acc. Chem. Res.* **4**, 87 (1971).
[15] W. Anker, G. W. Bushnell and R. H. Mitchell, *Can. J. Chem.* **57**, 3080 (1979).
[16] F. Bottino, S. Foti, S. Pappalardo and N. Bresciani-Pahor, *Tetrahedron Lett.* 1171 (1979).
[17] R. W. Griffin, Jr. and R. A. Coburn, *Ibid.* 2571 (1964).
[18] D. Krois and H. Lehner, *Monatsh. Chem.* **113**, 1019 (1982).
[19] I. Gault, B. J. Price and I. O. Sutherland, *J. Chem. Soc. Chem. Commun.* 540 (1967).
[20] M. P. Cooke, Jr., *J. Org. Chem.* **46**, 1747 (1981).
[21] D. T. Hefelfinger and D. J. Cram, *J. Am. Chem. Soc.* **93**, 4767 (1971); C. B. Shana, S. M. Rosenfeld and P. M. Keehn, *Tetrahedron* **33**, 1081 (1977).
[22] M. Atzmüller and F. Vögtle, *Chem. Ber.* **111**, 2547 (1978).
[23] Ch.-I. Lin, P. Singh, M. Maddox and E. F. Ullmann, *J. Am. Chem. Soc.* **102**, 3261 (1980).
[24] K. Böckmann and F. Vögtle, *Chem. Ber.* **114**, 1065 (1981).