Tetrahedron Letters No. 9, pp 675 - 678, 1975. Pergamon Press. Printed in Great Britain.

ON THE STEREOSELECTIVE SYNTHESIS OF 4,14-DIMETHYL[2.2]METACYCLOPHANE

C.Glotzmann, E.Langer, H.Lehner and K.Schlogl*

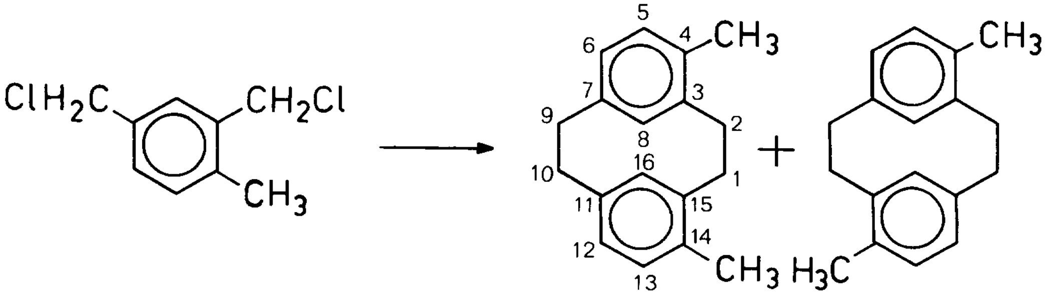
Lehrkanzel fur Organische Chemie der Universitat, A-1090 Wien

(Received in UK 19 December 1974; accepted for publication 22 January 1975)

For our studies on optical and chiroptical properties of aromatic chromophores conformationally homogenous compounds belonging to point group C_2 were of particular interest; in this context 4,14-dimethyl[2.2]metacyclophane (1) seemed to be especially suitable.

1 was claimed to be the sole reaction product of a "stereoselective" synthesis employing a Wurtz coupling of 2,4-bis(chloromethyl)toluene with sodium-tetraphenylethylene at -70 to -60°C in tetrahydrofuran (1). (Cf. also Ref.2).

We are now reporting results which are in contrast to this claim (1) and prove unambiguously that the product from this reaction (mp 64-66°) is a mixture of the isomers 1 and 2 (4,12-dimethyl[2.2]metacyclophane), although it seems to be uniform according to GC and 60 MHz ^{1}H-NMR analysis (3). ^{1}H-NMR speotroscopy at 100 MHz, however, turned out to be a more accurate tool for the detailed investigation of the absorption pattern in the region of the bridge protons (3.5 to 1.6 ppm). Here, in addition to the AA'BB' spin system

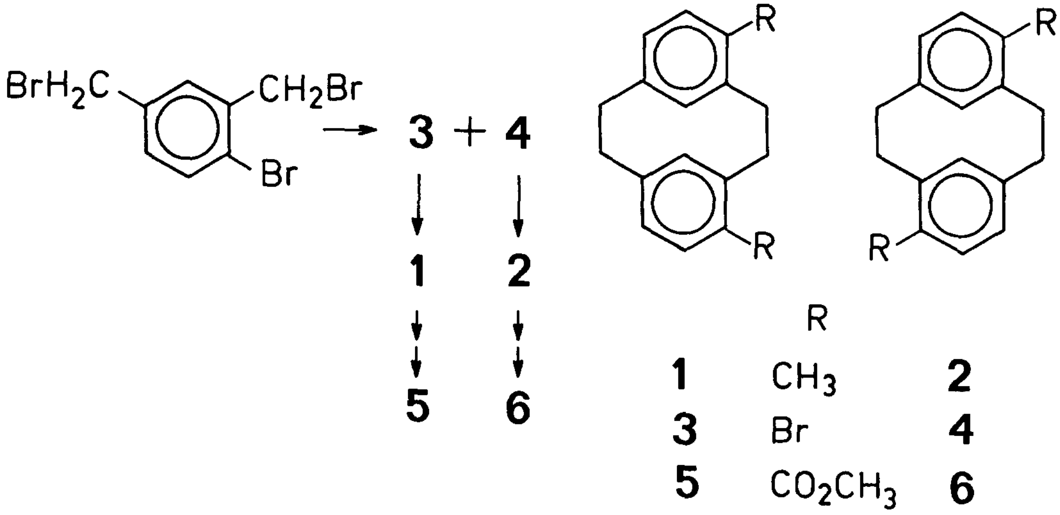


1 2

expected for 1, pronounced lines were observed in the same range which could not be detected in the 60 MHz spectrum due to the overlapping of bands. These additional bands were assigned to an ABCD spin system as could be expected for the bridge protons of the stereoisomeric (meso) dimethylmetacyclophane 2. Accordingly, an appreciable amount of 2 (appr. 30% according to the 100 MHz spectrum) should be present in the product of mp 64-66°. This assumption could then be proven by the following independent synthesis of the isomers 1 and 2:

Coupling of 1-bromo-2,4-bis(bromomethyl)benzene with phenyllithium in ether benzene afforded the isomeric bromides 3 (mp 130-133°) (4) and 4 (mp 171°) in equal amounts (5) (overall yield 20%), which could be separated by column chromatography on alumina. From these products the methylderivatives 1 (mp 63-65°) and 2 (mp 110-112°) (6) were obtained *via* lithiation with n-butyllithium and subsequent treatment with dimethylsulphate.

Line intensity analyses of 1 and 2 were performed applying the program LAOCOON III; the isomeric distribution (70% 1 and 30% 2, vide supra) found for the product mixture obtained according to Ref. (1) was then confirmed by recording a 100 MHz spectrum of a synthetic mixture of 1 and 2.



	R	
1	CH_3	2
3	Br	4
5	CO_2CH_3	6

Additional support for the reliability of this isomeric ratio was gained by transforming the mixture of the dimethylderivatives **1** and **2** (obtained according to Ref. 1) into the stereoisomeric methylesters **5** and **6** by the synthetic sequence: R = $CH_3 \rightarrow CH_2Br \rightarrow CHO \rightarrow COOH \rightarrow COOCH_3$ (7). For the mixture of **5** and **6** (mp's 138-140° and 156-158°, resp. for the pure products), LC analysis (8) revealed the ratio of 70:30, i.e. in full accord with the abovementioned NMR results.

According to Ref. (1) the stereoselectivity claimed for the Wurtz coupling reaction should in part be due to the low reaction temperature. Consequently, the isomeric distribution ought to be temperature dependent.

This is not the case, however, as was demonstrated by performing the coupling reaction at different temperatures: In all cases (at −70°, −60°, −40° and −20°) the mixtures contained practically the same amount of **2** (28±2%).

ACKNOWLEDGMENTS

The authors are grateful to the "Österreichischer Fonds zur Forderung der wissenschaftlichen Forschung" for financial support (projects No.1010 and 1635) and indebted to Drs. U.Herzig and W.Silhan for recording the NMR spectra.

REFERENCES AND FOOTNOTES

1. S. Akabori, T. Sato and K. Hata, J.Org.Chem. **33**, 3277 (1968).
2. T. Sato, S. Akabori, M. Kainosho and K. Hata, Bull.Chem.Soc.Japan **39**, 856 (1966); **41**, 218 (1968).

   T. Sato, S. Akabori, S. Muto and K. Hata, Tetrahedron **24**, 5557 (1968).

   F. Vogtle and P. Neumann, Angew.Chem. **84**, 75 (1972); Intern.Edit. **11**, 73 (1972).

   F. Vogtle and P. Neumann, Synthesis **1973**, 85.
3. Conditions: 100 ft SCOT columns SE 30, XE 60 and Carbowax 20 M at various temperatures.
4. Full details of this synthesis will be published in the near future. Satisfying elemental analyses were obtained for all new compounds.

5. The composition of the mixture (50:50) was determined by GC analysis on a 50 ft SCOT column XE 60 at 200°.

6. **1** (needles) and **2** (rhombic plates) form solid solutions but are not isomorph. A partial incorporation of **2** into the lattice of **1** seems to take place without pronounced change of crystal type and mp: Both **1** and the 70:30 mixture of **1** and **2** form needles.

7. A separation of the stereoisomeric 4,12- and 4,14-disubstituted [2.2]metacyclophanes cannot be accomplished on an earlier stage of the reaction sequence (prior to the methylesters **5** and **6**); hence, this preparative route turns out to be rather laborious.

   On the other hand, coupling of 1-bromo-2,4-bis(bromomethyl)benzene with phenyllithium offers a very suitable method, since
   1. a separation of isomers can be achieved already at the first step (with **3** and **4**) and
   2. access to **5** and **6** is possible by a series of only two straightforward reaction steps.

8. Conditions: 6 ft by 1/4 in SIL X II column; n-hexane containing 2.5% chloroform as solvent; flow: 0.5 ml/min.