Medium-sized Cyclophanes. II. The Stereoselective Synthesis and Optical Resolution of 4, 14-Dimethyl[2.2]metacyclophane[1]

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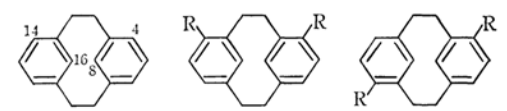
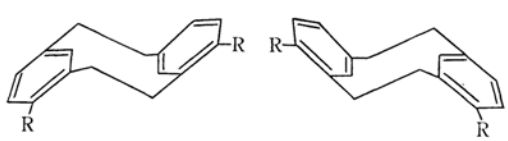
(Received January 25, 1966)

Among the medium-sized ring compounds, [2.2]metacyclophane (I) is unique in that it represents one of the few examples in which the conformations have been elucidated by X-ray measurements.[2] It has a step-like structure, containing two distorted benzene rings arranged in two parallel planes. The structural features of compound I have also been shown to be reflected in the NMR spectra.[3] In addition to an AB_2-type absorption of aryl protons at δ 7.18 and 6.97, a triplet appeared at δ 4.23; it is assignable to the intraannular aryl protons at C_8 and C_{16}, which are shifted to a higher magnetic field as they are extended over the ring current of the opposite benzene rings. An A_2B_2-type absorption centered at δ 2.55 indicates the presence of non-equivalent methylene protons. Since the ten-membered ring in compound I exists in a chair conformation, it is quite natural to assign these to axial and equatrial protons.

Our interest in the possible inversion of compound I prompted us to study the high-temperature NMR spectra. The spectra determined at 67 (in CCl_4), 126 and 190°C (both in hexachloro-1, 3-butadiene) were compared with those taken at room temperature and at a low temperature (ca. −80°C). It was not possible, however, to find any appreciable temperature dependence in the spectra. Especially, the A_2B_2 absorption was surprisingly held unchanged throughout the range of the temperature studied, indicating that the molecule is frozen in the chair conformation (e. g., IIa, b: R=H).



I II III



IIa IIb

These results were taken as an indication that there is a substantial conformational barrier between the inverted isomers. It is, then, to be expected that suitably-substituted cyclophanes, such as II, would become optically resolvable, IIa and IIb being the optical antipodes. The Wurtz reaction of 2, 4-bis(chloromethyl)toluene using disodium tetraphenylethane as a condensing agent in tetrahydrofuran afforded 4, 14-dimethyl-[2.2]metacyclophane, m. p. 68—69°C (Found: C, 91.34; H, 8.34%; mol. wt., 235 in a 21% yield. High-dilution conditions were realized by the combination of a slow addition (68 hr.) and a low reaction temperature (−60—70°C). The generation of the metacyclophane structure was confirmed by the NMR spectra, which consisted of four sets of absorption and which were consistent with the structure II (R=CH_3); an AB-type absorption of aryl protons at δ 6.90, a doublet for intraannular aryl protons at δ 4.18, A_2B_2 patterns centered around δ 2.43, and a singlet for the methyl group at δ 2.31.

The preferential formation of the II-type compound over the III-type compound, which should be the *meso* compound, due to the extremely mild reaction conditions used, was also encountered in the preparation of the methoxyl analog. By the coupling reaction described above, 2, 4-bis-(chloromethyl)anisole afforded compound II (R=OCH_3), m. p. 132—134°C (Found: C, 80.65; H, 7.45%; mol. wt., 260, as a major product, together with a small amount of a higher melting isomer, possibly II (R=OCH_3), m. p. 182°C (Mol. wt. Found: 278). The structure was determined by a comparison of the NMR spectra of methylene signals.

The optical resolution of compound II (R=CH_3) was achieved by using (−)-α-(2, 4, 5, 7-tetranitro-9-fluorenylideneaminooxy)-propionic acid[4] as a complex-forming reagent. A levorotatory isomer, $[\alpha]_{578}^{26}$ −3.4, and a dextrorotatory isomer, $[\alpha]_{578}^{26}$ +4.2 (ethanol), both with identical infrared spectra with a racemic compound, were obtained by the liberation of hydrocarbon by passing through an alumina column.

1) Part I: T. Sato, E. Yamada, Y. Okamura, T. Amada and K. Hata, This Bulletin, **38**, 1049 (1965).
2) C. J. Brown, *J. Chem. Soc.*, **1953**, 3278.
3) Cf. D. J. Wilson, V. Boekelheide and R. W. Griffin, Jr., *J. Am. Chem. Soc.*, **82**, 6302 (1960).
4) M. S. Newman and W. B. Lutz, ibid., **78**, 2469 (1956).