A Simple Route to a Pyridinyl[2.2]paracyclophane

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4-Acetyl[2.2]paracyclophane (**1**) is converted into the nitrone **2** by treatment with *N*-methylhydroxylamine·hydrochloride. When **2** is reacted with (*E*)-1,2-dibenzoylethene (**4**) the pyridinyl[2.2]paracyclophane **13** is formed in a novel condensation reaction. The structures of **2** and **13**, and the mechanism of formation of the latter are discussed.

Introduction

Chiral [2.2]paracyclophanes are growing in importance as ligands and auxiliaries in asymmetric synthesis,[1] and the number of mono- (any monosubstituted [2.2]paracyclophane is chiral) and polysubstituted derivatives of this class of layered compounds reported in the literature is increasing rapidly.[1−3]

Having been interested in [2.2]paracyclophanes that carry heterocyclic substituents for some time,[4] we now report on the preparation of a pyridyl-substituted [2.2]paracyclophane by a novel and efficient procedure. Considering the rich chemistry of the pyridine nucleus, we believe that this combination of carbo- and heterocyclic ring systems offers numerous perspectives in covalent and supramolecular chemistry.

Preparation of 2-(4′-[2.2]Paracyclophanyl)-6-phenylpyridine (13)

When a solution of 4-acetyl[2.2]paracyclophane (**1**)[5] and *N*-methylhydroxylamine·hydrochloride in ethanol is refluxed in the presence of potassium hydroxide, the nitrone **2** is obtained in 95% yield (Scheme 1). The structure of this derivative was established by the usual spectroscopic and analytical methods as described in the Exp. Sect. Of particular importance, indicating the *E*-configuration of **2** as shown in the Scheme, are the NMR spectroscopic data and the X-ray structure analysis of this derivative. The ^{1}H and ^{13}C NMR spectra of **2** were fully assigned (apart from the CH_2CH_2 bridges) by the use of two-dimensional H,H-COSY, C,H-HETCOR and C,H-COLOC techniques and by NOE difference spectra (see Exp. Sect.). The *E*-configuration of the nitrone group follows from the NOE at 5-H when the *N*-methyl signal is saturated.

As shown by the X-ray structure analysis, the molecular dimensions of **2** (Figure 1) may be regarded as normal; the C−N and N−O bond lengths are 1.306(2) and 1.308(2) Å, respectively. The nitrone group is essentially planar (mean deviation of 4 atoms 0.005 Å) and its orientation is defined by the torsion angles C3−C4−C17−N18 (60.6°) and C4−C17−N18−O (9.4°).

The packing involves two short contacts of the form $C-H_{methyl}\cdots O$: C19−H19A···O and C20−H20A···O, with H···O distances of 2.38 and 2.45 Å (for C−H normalized to 1.08 Å) and C−H···O angles of 162 and 169°. The net effect is to connect the molecules by the 2_1 screw axis to form chains parallel to the *y* axis (Figure 2).

Nitrones are a well-studied class of 1,3-dipoles that react with numerous unsaturated systems,[6] among them (*E*)- (**4**) and (*Z*)-1,2-dibenzoylethene,[7] to yield the corresponding isoxazolidine derivatives, usually under mild conditions and in good yield. To our surprise, the reaction between **2** and **4** required three days of reflux in toluene, and yielded a completely unexpected product: the pyridine derivative **13** (isolated yield 70%), together with a small sample of methylbenzoate (**12**, 5%). The structure elucidation of this unusual adduct, the formation of which required one equivalent each of **12** and water to be eliminated from its two starting materials, rests primarily on its ^{1}H and ^{13}C NMR spectra, which were fully assigned by the techniques men-

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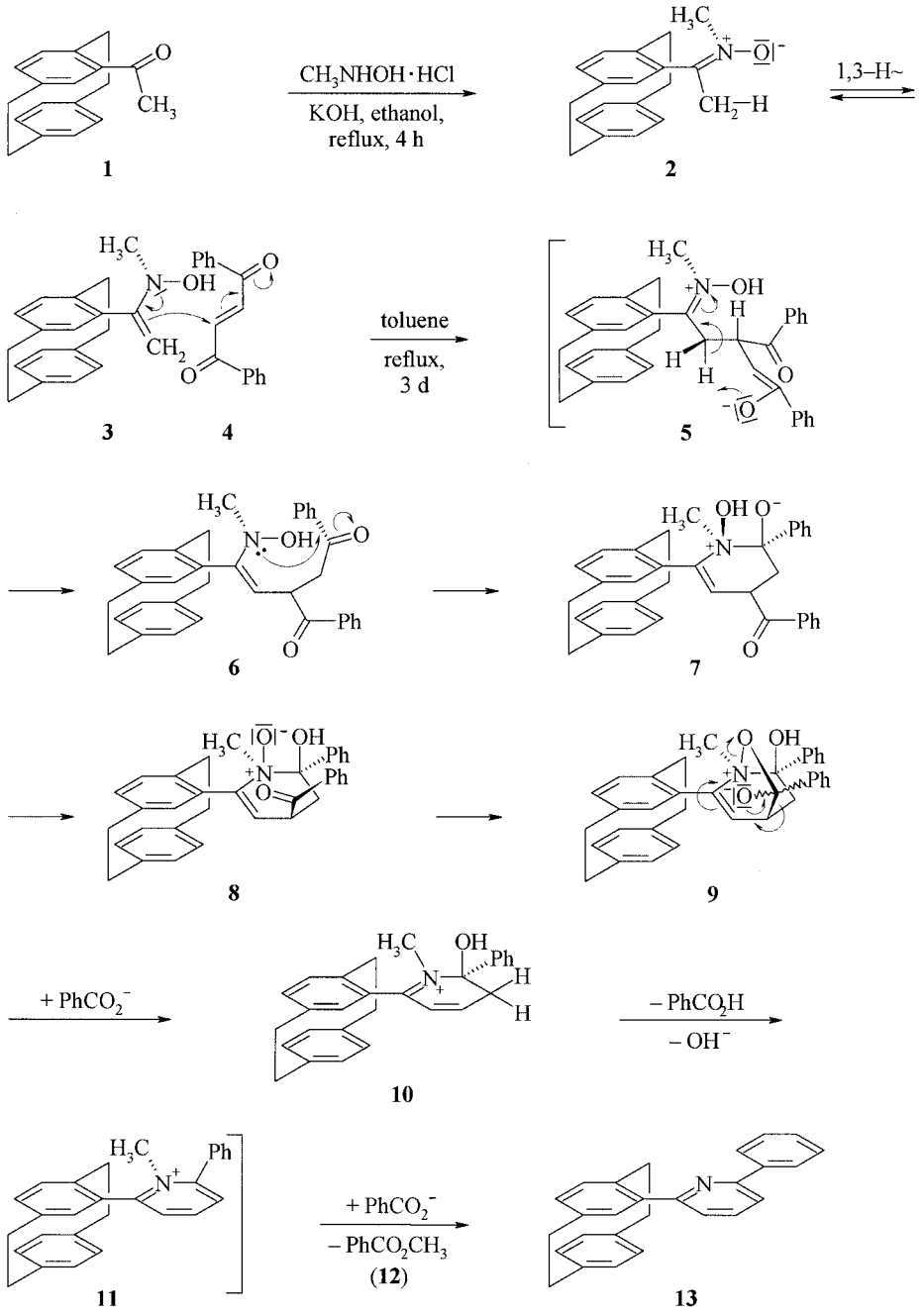

Scheme 1. From the [2.2]paracyclophane nitrone **2** to the pyridyl derivative **13**

tioned above. The proton signals of the paracyclophanyl moiety were analyzed by iterative fitting of the full band-shape. The points of attachment of the paracyclophanyl, phenyl and pyridinediyl groups follow from the cross-peaks in the C,H-COLOC spectrum and from the spin-coupling patterns in the proton signals of the disubstituted pyridine ring.

Mechanism of Formation of the Pyridinylcyclophane 13

To rationalize the formation of **13**, we propose the rather long, but consistent route summarized in Scheme 1. As a decisive initial step we postulate the isomerization of **2** to the hydroxylamine **3** by a hydrogen transfer process. Since **3** is also an enamine, it can attack the activated double bond of the dipolarophile **4** in a Michael-fashion to furnish the intermediate enolate **5**. As shown in Scheme 1, the charged oxygen atom could then remove a hydrogen atom of the methylene group in **5** via a six-membered transition state to provide the next reaction intermediate: the hydroxylamine derivative **6**, itself a derivative of its starting material **3**. In the next step of the sequence, intramolecular cyclization takes place — again involving a six-membered transition state — to provide **7**, from which the structure of the finally isolated product slowly begins to emerge. To remove benzoate, intermediate **7** — after reprotonation to

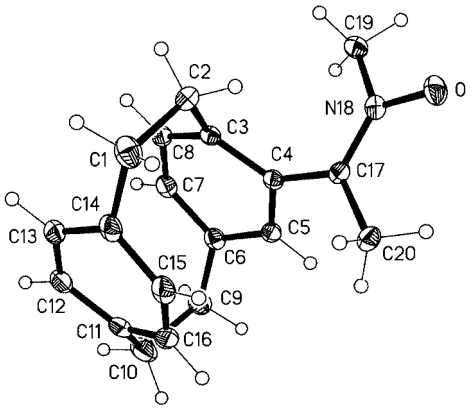

Figure 1. The molecule of compound **2** in the crystal; ellipsoids represent 30% probability levels; H atom radii are arbitrary

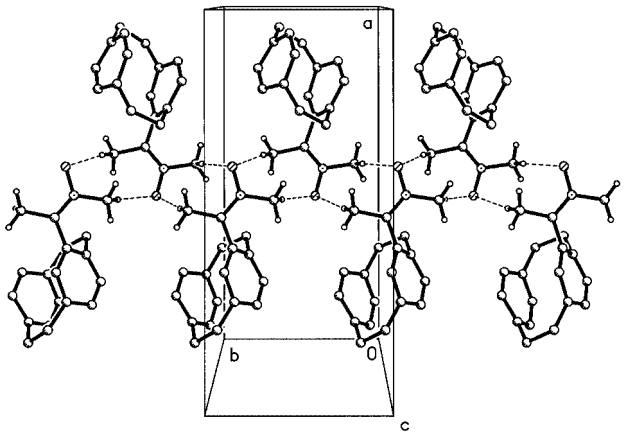

Figure 2. Packing of compound **2**, showing hydrogen bonds as dashed lines

8 — undergoes transannular attack of the benzoyl substituent, and the resulting bicyclic intermediate **9** fragments as indicated by the arrows in Scheme 1. The resulting compound **10** loses water (the benzoate functions as the elimination reagent), and the resulting pyridinium salt **11** transfers its methyl group thus generating the two isolated products, **12** and **13**.

Clearly, to produce other substituent patterns in **13**, and therefore determine the scope of this serendipitous observation, the nature of the dipolarophile must be varied.

Experimental Section

General: Melting points: Büchi melting point apparatus, uncorrected. TLC: Macherey−Nagel Polygram SilG/UV254 and Polygram Alox N/UV 254. Column chromatography: Merck Kieselgel 60 (70−230 mesh). IR: Perkin−Elmer 1420 and Nicolet 320 FT-IR. NMR: Bruker AM-400, 400 MHz (^{1}H) and 101 MHz (^{13}C), solvent $CDCl_3$, internal standards: TMS for ^{1}H (δ = 0.00 ppm) and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C. Abbreviations: *pc* = [2.2]paracyclophanyl, *ph* = phenyl, *py* = pyridinediyl; the subscripts *a* and *s* indicate bridge protons *anti* and *syn*, respectively, relative to the 4-substituent at the *pc* system. Positions in the second *pc*-ring are numbered such that C-12 is pseudo-*geminal* to C-7 etc. Results of NOE difference experiments are given as *irradiated signal* → *enhanced signal*. The spin systems of the aromatic protons of **2** and **13** were analyzed iteratively with Bruker's WIN-DAISY program. UV/Vis: Beckman UV 5230.

(*E*)-*N*,α-Dimethyl-α-(4′-[2.2]paracyclophanyl)nitrone (2): A solution of *N*-methylhydroxylamine·hydrochloride (5.00 g, 60 mmol) in water (20 mL) was added to a gently heated stirred solution of 4-acetyl-[2.2]paracyclophane (**1**)[6] (2.50 g, 10 mmol) in ethanol (400 mL). Subsequently, a solution of potassium hydroxide (3.40 g, 60 mmol) dissolved in a mixture of water (25 mL) and ethanol (25 mL) was added. The mixture was refluxed whilst stirring for 4 h, while the progress of the reaction was monitored by TLC. After cooling, the reaction mixture was thoroughly extracted with diethyl ether (600 mL), and the combined organic phases were washed several times with water. After removal of the solvents in vacuo, the residue was dissolved in dichloromethane and purified by silica gel column chromatography with dichloromethane (150 mL) as eluent to provide 0.08 g (3%) of **1**. Further elution with absolute ethanol (400 mL) gave **2**, which on recrystallization from toluene gave (2.65 g, 95%) as colorless needles (R_f = 0.4, CH_2Cl_2/diethyl ether, 1:1). M.p. 182 °C. IR (KBr): $\tilde{\nu}$ = 3007 cm^{-1} (s), 2925 (w), 2890 (m), 2852 (m), 1903 (vs), 1670 (vs), 1664 (vs), 1590 (s), 1566 (m), 1500 (m), 1451 (m), 1435 (m), 1396 (s), 1373 (m), 1269 (s), 1016 (m), 943 (s), 902 (m), 885 (m), 837 (m), 821 (m), 791 (s), 738 (m), 721 (m). UV (CH_3CN): $\lambda_{max.}$ (log ε) = 294 nm (3.10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (q, 3 H, CMe), 2.87−3.16 (m, 8 H, 2 CH_2CH_2; shifts from C,H-HETCOR: 2.92, 2.97, 3.01, 3.07, 3.08, 3.10, 3.11, 3.12), 3.47 (q, 3 H, NMe), 6.38 (dd, 1 H, 16-H), 6.44 (dd, 1 H, 15-H), 6.44 (d, 1 H, 5-H), 6.48 (d, 1 H, 8-H), 6.49 (dd, 1 H, 7-H), 6.63 (dd, 1 H, 13-H), 6.65 ppm (dd, 1 H, 12-H); $J_{5,7}$ = 1.8, $J_{7,8}$ = 7.8, $J_{12,13}$ = 7.8, $J_{12,16}$ = 2.0, $J_{13,15}$ = 2.0, $J_{15,16}$ = 8.0, $J_{Me,Me}$ = 1.3 Hz. NOEs: NMe → 5-H; CMe → 5-H,15-H, 16-H. The spin systems of the bridge protons could not be analyzed. Hence, chemical shifts for the bridge ^{1}H and ^{13}C nuclei are unassigned. ^{13}C NMR: δ = 20.1 (q, CMe), 33.6, 35.0, 35.2, 35.3 (4 t, CH_2), 47.9 (q, NMe), 130.4 (d, C-5), 131.2 (d, C-15), 132.1 (d, C-16), 132.2 (d, C-12), 133.0 (d, C-13), 134.4 (s, C-4), 135.0 (d, C-7), 135.2 (d, C-8), 138.4 (s, C-3), 139.1 (s, C-14), 139.4 (s, C-11), 140.0 (s, C-6), 147.3 ppm (s, C=N). MS (EI): *m*/*z* = 279 [M$^+$] (40), 262 (8), 175 (30), 162 (100), 158 (44), 144 (14), 117 (28), 104 (24), 103 (20), 77 (6), 56 (10). $C_{19}H_{21}NO$ (279.38): calcd. C 81.68, H 7.58, N 5.01; found C 81.55, H 7.60, N 5.05.

2-(4′-[2.2]Paracyclophanyl)-6-phenylpyridine (13): A mixture of **2** (0.279 g, 1 mmol) and (*E*)-1,2-dibenzoylethene (**4**, 0.236 g, 1 mmol) was refluxed in dry toluene (100 mL) under N_2 for 3 days. The solvent was evaporated in vacuo, and the residue was purified by plate chromatography on silica gel with toluene. The two separated zones were extracted with acetone. The more slowly migrating zone contained methyl benzoate (**12**, 0.007 g, 5%, R_f 0.3, CH_2Cl_2), which was identified by comparison with an authentic sample (NMR spectra). The faster migrating zone contained **13** (R_f 0.5, CH_2Cl_2), which was recrystallized from ethanol to give (0.25 g, 70%) as colorless plates. M.p. 75 °C. IR (KBr): $\tilde{\nu}$ = 3066 cm^{-1} (vs), 3023 (vs), 2962 (vs), 2946 (s), 2926 (m), 2891 (s), 2850 (s), 1586 (m), 1567 (w), 1500 (s), 1457 (m), 1442 (w), 1411 (s), 1377 (s), 1158 (s), 901 (s), 860 (s), 816 (m), 798 (m), 763 (w), 746 (m), 720 (m). UV (CH_3CN): λ_{max} (log ε) = 335 nm (3.20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70 (m_c, 1 H, 1-H_s), 2.87−3.18 [m, 6 H; shifts from C,H-HETCOR: 2.89 (1-H_a), 2.90 (2-H_a), 2.99 (9-H_s), 3.01 (10-H_a), 3.09 (9-H_a), 3.13 (10-H_s)], 3.80 (m_c, 1 H, 2-H_s), 6.51 (dd, 1 H, *pc*-7-H), 6.52 (dd, 1 H, *pc*-13-H), 6.548 (d, 1 H, *pc*-8-H), 6.551 (dd, 1 H, *pc*-

12-H), 6.58 (dd, 1 H, *pc*-16-H), 6.65 (dd, 1 H, *pc*-15-H), 6.89 (d, 1 H, *pc*-5-H), 7.32 (dd, 1 H, *py*-3-H), 7.40 (*para*-type m, 1 H, *ph*-4-H), 7.49 (*meta*-type m, 2 H, *ph*-3,5-H), 7.62 (dd, 1 H, *py*-5-H), 7.69 (t, 1 H, *py*-4-H), 8.18 ppm (*ortho*-type m, 2 H, *ph*-2,6-H); coupling constants: a) *py*: $J_{3,4}$ = 7.8, $J_{3,5}$ = 0.9, $J_{4,5}$ = 7.8 Hz, b) *pc*: $J_{5,7}$ = 2.0, $J_{7,8}$ = 7.8, $J_{12,13}$ = 7.9, $J_{12,16}$ = 2.2, $J_{13,15}$ = 2.0, $J_{15,16}$ = 7.8 Hz. NOEs: *ph*-2,6-H → *py*-5-H, *ph*-3,5-H, *pc*-15-H, *pc*-16-H; *pc*-5-H → *py*-3-H, *pc*-16-H, *pc*-9-H_s. ^{13}C NMR: δ = 34.6 (t, *pc*-C-2), 35.0 (t, *pc*-C-1), 35.2 (t, *pc*-C-9), 35.4 (t, *pc*-C-10), 117.7 (d, *py*-C-5), 122.6 (d, *py*-C-3), 126.8 (d, 2 C, *ph*-C-2,6), 128.7 (d, 2 C, *ph*-C-3,5), 128.8 (d, *ph*-C-4), 130.8 (d, *pc*-C-15), 132.4 (d, 2 C, *pc*-C-12,16), 132.8 (d, *pc*-C-13), 133.0 (d, *pc*-C-7), 133.1 (d, *pc*-C-5), 135.9 (d, *pc*-C-8), 136.8 (d, *py*-C-4), 138.2 (s, *pc*-C-3), 139.2 (s, *pc*-C-11), 139.5 (s, *pc*-C-6), 139.7 (s, 2 C, *ph*-C-1, *pc*-C-14), 140.6 (s, *pc*-C-4), 156.5 (s, *py*-C-6), 158.7 ppm (s, *py*-C-2). MS (EI): *m*/*z* = 361 [M^+] (28), 258 (20), 257 (100), 241 (12), 92 (18), 91 (22), 77(8). $C_{27}H_{23}N$ (361.49): calcd. C 89.71, H 6.41, N 3.87; found C 89.55, H 6.40, N 3.80.

X-ray Structure Determination of Compound 2. Crystal Data for $C_{19}H_{21}NO$: Monoclinic, space group $P2_1/c$, a = 15.736(3), b = 7.3166(14), c = 12.540(4) Å, β = 97.82(2)°, U = 1430.3 Å^3, Z = 4, μ(Mo-K_α) = 0.08 mm^{-1}, T = −130 °C. Data collection: A colorless tablet, approximately 0.7 × 0.6 × 0.16 mm, was used to record 3222 intensities on a Stoe STADI-4 diffractometer to $2\theta_{max.}$ 50°. Structure refinement: The structure was refined anisotropically on F^2 (program SHELXL-97, G. M. Sheldrick, University of Göttingen) to *wR*2 0.130, *R*1 0.048 for 193 parameters and all 2529 unique reflections; S = 1.07, max. $\Delta\rho$ = 0.21 e·Å^{-3}. Hydrogen atoms, identifiable as well-resolved maxima in difference syntheses, were included using a riding model or as rigid methyl groups.

CCDC-238142 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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