Synthesis of Biologically Active [2.2]Paracyclophanes

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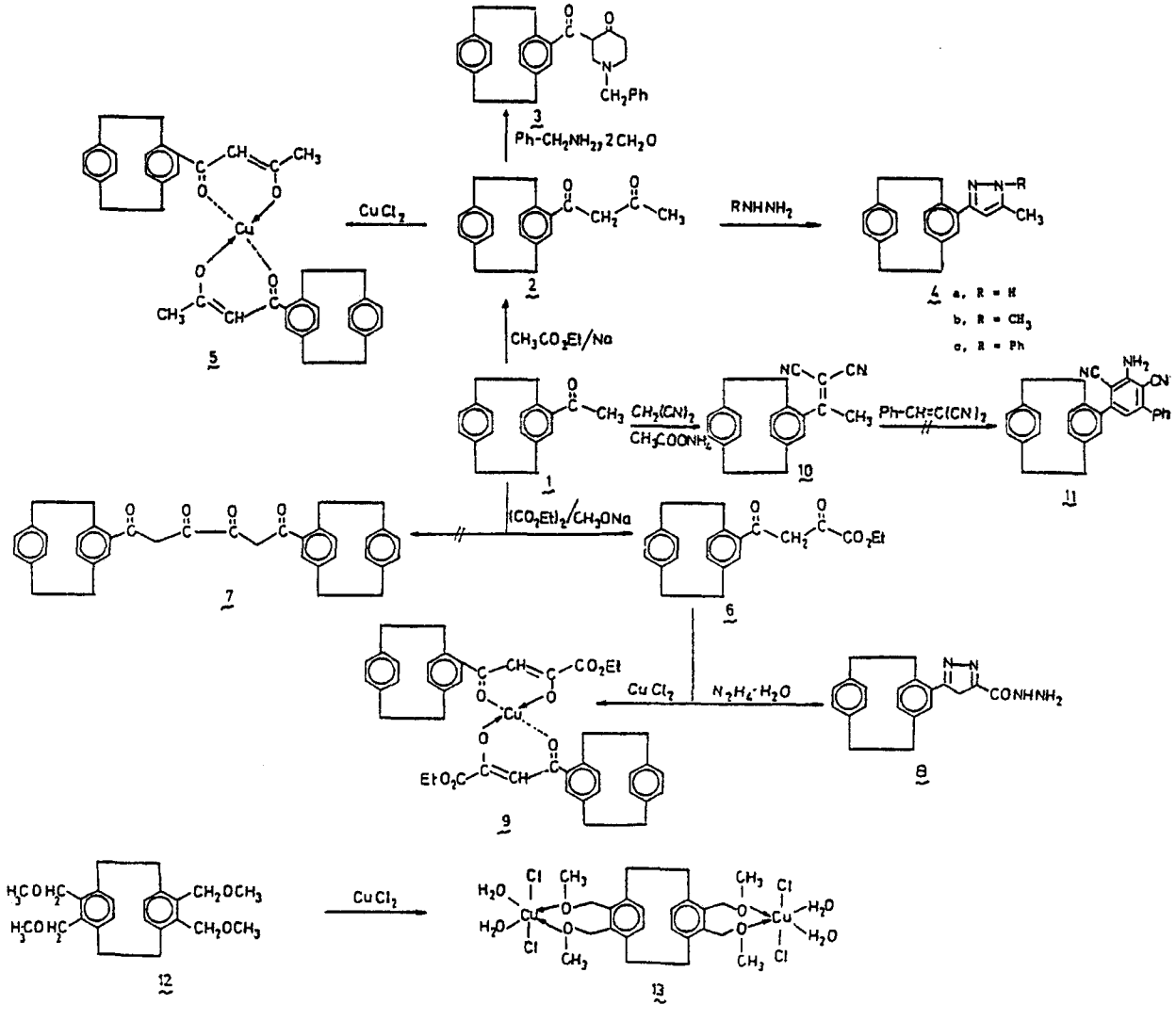
Claisen reaction of 4-acetyl[2.2]paracyclophane (**1**) with ethyl acetate and diethyl oxalate affords 4-acetoacetyl[2.2]paracyclophane (**2**) and ethyl(4-oxaloacetyl[2.2]paracyclophane) (**6**), respectively. Reaction of **2** and **6** with hydrazines and $CuCl_2$ gave the pyrazole derivatives **4** and **8** in addition to the metal complexes **5** and **9**. *Mannich* reaction of **2** with benzylamine and paraformaldehyde yielded the piperidinone derivative **3**. The biological activity of all new compounds was tested.

Synthesen von biologisch aktiven [2.2]Paracyclophan-Derivaten

Claisen-Reaktion von 4-Acetyl[2.2]paracyclophan (**1**) mit Essigsäureethylester und Diethyloxalat gab 4-Acetoacetyl[2.2]paracyclophan (**2**) und Ethyl-(4-oxaloacetyl[2.2]paracyclophan) (**6**). Reaktionen von **2** bzw. **6** mit Hydrazinen und $CuCl_2$ lieferten die Pyrazol-Derivate **4** und **8** und die Metall-Komplexe **5** und **9**. *Mannich*-Reaktion von **2** mit Benzylamin und Paraformaldehyd gab das Piperidinon-Derivat **3**. Die biologische Aktivität der neuen Verbindungen wurde untersucht.



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Although the synthetic methods now available in phane chemistry have grown in sophistication over the years, the introduction of the cyclophane nucleus and especially the [2.2]paracyclophane system into heterocyclic compounds has not been extensively studied sofar. Since [2.2]paracyclophanes differ considerably in their chemical behaviour from normal aromatic systems[1-5], it seemed worthwhile to start an investigation involving the preparation of biologically active substances the aromatic substitutent/s of which has/have been replaced by the [2.2]paracyclophane group.

In the present study we wanted to synthesize some polyketo compounds and pyrazoles containing the [2.2]paracyclophanyl group, and to study the effect of the paracyclophane nucleus on the biological properties.

Compounds having polyketo functionalities are biologically active[6,7]. We therefore used the well-known 4-acetyl[2.2] paracyclophane[8] as starting material for the synthesis of polyketo[2.2]paracyclophanes **2** and **6** (Scheme). The ketone **1** was subjected to *Claisen* condensation with ethyl acetate to afford **2** (60%). 4-Acetoacetyl[2.2]paracyclophane (**2**), a *Mannich* base, was treated with benzylamine and paraformaldehyde in a molar ratio of (1:1:2) in acetic acid to give 1-benzyl-4-([2.2]paracyclophanoyl)-piperidin-4-one (**3**). Interaction of **2** with hydrazines afforded the pyrazole derivatives **4**. Reaction of **2** with $CuCl_2$ provides the metal complex **5**.

The UV spectrum of **5** showed a band at 650 nm characteristic of a d-d transition of a copper ligand. The IR spectrum of **5** displayed a broad band at 1720 cm^{-1} (CO), clearly shifted from the one in compound **2** by about 26 cm^{-1} due to complexation.

Reaction of **1** with diethyl oxalate in the presence of $NaOCH_3$ and xylene led to the formation of ethyl (4-oxaloacetyl[2.2]paracyclophane) (**6**). Several attempts to synthesize the tetraketone **7** failed.

6 reacts with hydrazine hydrate and $CuCl_2$ to give **8** and **9**, respectively.

The UV spectrum of **9** showed a strong band at 650 nm, characteristic for Cu(II) complexes as discussed. The IR spectrum of **6** is dominated by a band at 1746 cm^{-1} (CO, ester), shifted from that in **9** by 26 cm^{-1}. Also, the carbonyl group of the β-diketo unit in **6** is shifted by about 120 cm^{-1}, as compared with **9**.

1 reacted with malononitrile to give 1,1-dicyano-2-methyl-2([2.2]paracyclophanyl)ethylene (**10**). An attempt to synthesize **11** by reaction of **10** with benzylidene malononitrile failed.

4,5,12,13-tetrakis-methoxymethyl[2.2]paracyclophane (**12**) reacted with $CuCl_2$ in a 1:2 ratio to form a bis-copper chloride dihydrate(4,5,12,13-tetrakis-methoxymethyl)-[2.2]paracyclophane) (**13**). The UV spectrum of **13** displayed a characteristic band at 710 nm, again due to d-d complexation. The IR spectrum gave ν OH at 3500 cm^{-1} and the methoxyl-linkage is shifted from that in **12** by approximately 35 cm^{-1}.

The antibacterial activity of seven compounds (Table 1) was studied against gram positive bacteria (*Bacillus cereus*, *Micrococcus roseus*) and gram negative bacteria (*Serratia*, *Pseudomonas*). As shown in Table 1, the maximum activity was found in **6** against *Bacillus cereus*, **4a**, **6** against *Micrococcus roseus*, and **4a** against *Serratia*. High activity was observed in **8** against *Bacillus cereus* and in **5** against *Serratia*. Sensitivity of the gram negative bacterium *Pseudomonas* against compounds studied was low in general. The data indicate also that the size of the R group in **4** has not only an effect on the reaction performed, but also on the biological activities of the compounds.

Bioassay tests of some compounds against 4th instar larvae of *Culex pipiens* were undertaken. On treatment of larvae with **4c** and **3** (0.2 ppm), a high mortality after 24 h was observed, 100% and 90%, respectively. Compound **4** did not give any effect at the same concentration.

When **4c** and **13** were tested against larvae of cotton leafworm *Spodoptera litteralis*, the tested concentration showed

Table 1: Sensitivity of gram positive and gram negative bacteria.

Bacteria / Compounds	Bacillus cereus gram + ve	Micrococcus roseus gram + ve	Serratia gram -ve	Pseudomenas gram - ve
2	+	-	+	+
4a	-	++++	++++	-
4b	-	+	-	+
4c	+	+	-	-
5	+	+	+++	-
6	++++	++++	-	-
8	+++	+	-	+

a highly accumulative mortality after 13 days feeding on treated leaves (96 and 93%, respectively). Compounds **4a** and **6** showed moderate effects (66 and 56%, respectively). In all bioassay tests against *Culex pipiens* and *Spodoptera litteralis* blank experiments were undertaken.

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Experimental Part

Melting points: uncorrected.- IR spectra: Nicolet 320 FT-IR, KBr.- ^{1}H-NMR and ^{13}C-NMR spectra: $CDCl_3$, TMS as internal stand., Bruker WM 400 (400.1 MHz) spectrometer.- Mass spectra: Finigan 8430, all compounds show correct $M^{+\cdot}$.- UV spectra: Perkin-Elmer Lambda 2.

4-Acetoacetyl[2.2]paracyclophane (**2**)

A solution of **1** (0.5 g, 0.002 mol) in 50 ml ethyl acetate was slowly added to sodium sand (1 g, 0.0425 g-atom). The reaction mixture was refluxed for 5 h and the excess ethyl acetate was evaporated. Ice-cold water and diluted HCl were then added to the mixture, which was extracted with chloroform, washed with water and dried ($CaCl_2$). The solvent was evaporated and the residue was purified by prep. chromatoplates, toluene:petroleum ether (1:2) as eluent. A solid colorless product was obtained which recrystallized from petroleum ether to give **2**, yield 0.35 g (60%), m.p. 80°C.- $C_{20}H_{20}O_2$ (292.4) Calc. C 82.2 H 6.89 Found C 82.3 H 6.94.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.2 (s, 3H, $COCH_3$); 3.1-3.4 (m, 10 H, CH_2); 6.5-6.8 (m, 7H, PC*-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 25.43 (CH_3); 34.60; 34.70; 35.40; 35.70 (CH_2); 100.00 (C=C-OH); 131.79; 133.00; 133.10; 133.21; 135.71; 136.43; 136.79; 139.28; 140.00; 141.40 (PC-C=C); 187.85; 192.14 ($COCH_2CO$).- IR (KBr): 2931-2854 (aliph.-CH); 1694 cm^{-1} (CO).- UV (CH_2Cl_2) λ max (log ε) = 325 nm (3.64).

1-Benzyl-3([2.2]paracyclophanoyl)piperdin-4-one (**3**)

A mixture of **2** (0.292 g, 0.001 mol), benzylamine (0.114 g, 0.001 mol), and paraformaldehyde (0.060 g, 0.002 mol) in acetic acid (30 ml) was heated to boiling, then left overnight at room temp. The mixture was treated with NaOH (20%), extracted with chloroform, washed several times with water and dried. Chloroform was evaporated and the residue was chromatographed on tlc plates using toluene:ethyl acetate (10:1) to give red crystals of **3**, 0.25 g (59%), m.p. 80°C (EtOH).- $C_{29}H_{29}NO_2$ (423.5) Calc. C 82.2 H 6.90 N 3.31 Found C 82.2 H 7.00 N 3.3.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (s, CH_2Ph); 1.9 t, J = 6.8 Hz, 1H, piperidone-CH); 2.8-3.5 (m, 14H, CH_2); 6.2-7.4 (m, 12 H, PC-H and Ph-H).- IR (KBr): 3434-3422 (OH, enolic); 3062-3009 (Ar-CH); 2927 (aliph.-CH); 1721 (CO, piperidone); 1652 cm^{-1} (CO, β-diketone).

5-Methyl-3-[2.2]paracyclophanyl)pyrazole (**4**)

A mixture of **2** (0.292 g, 0.001 mol) and hydrazine hydrate (0.5 mol) or its derivatives in ethanol solution (10 ml) was refluxed for 2 h. The mixture was treated with water and extracted with chloroform, then washed with water and finally dried ($CaCl_2$).

4a: colorless crystals, 0.25 g (87%) EtOH, m.p. 202-203°C.- $C_{20}H_{20}N_2$ (288.4) Calc. C 83.3 H 6.99 N 9.7 Found C 83.4 H 6.90 N 9.7.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.20 (s, 3H, CH_3); 2.8-3.2 (m, 10 H, CH_2); 6.4-6.6 (m, 7H, PC-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 12.57 (CH_3); 34.65; 34.75; 35.27; 35.46 (CH_2); 104.45 (C=C-NH); 130.28; 132.03; 132.14; 132.48; 132.74; 133.06; 135.85; 137.51; 139.41 (PC-C=C); 139.61; 140.05 (N=C-C=C-NH).- IR (KBr): 3192-3007 (Ar-CH); 2986 cm^{-1} (aliph.-CH).

4b: colorless crystals, yield 0.25 g (83%) (EtOH/petroleum ether), m.p. 205°C.- $C_{21}H_{22}N_2$ (302.4) Calc. C 83.4 H 7.33 N 9.26 Found C 83.5 H 7.28 N 9.2.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.6 (s, 3H, CH_3); 2.8-3.2 (m, 8H, CH_2); 3.8 (s, 3H, NCH_3); 6.4-6.7 (m, 8H, CH= and PC-H).- IR (KBr): 3102-3009 (Ar-CH); 2926-2853 cm^{-1} (aliph.-CH).

4c: yellow crystals, 0.30 g (82%) (petroleum ether), m.p. 195°C.- $C_{26}H_{24}N_2$ (364.5) Calc. C 85.7 H 6.64 N 7.7 Found C 85.9 H 6.60 N 7.7.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.5 (s, 3H, CH_3); 2.8-3.2 (m, 8H, CH_2); 6.2-6.7 (m, 8H, CH= and PC-H); 7.0-7.2 (m, 5H, Ph-H).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 13.83 (CH_3); 33.53; 34.85; 35.14; 35.41 (CH_2); 107.80 (C=C-N-Ph); 124.43; 126.43; 128.32 (Ph-C=C); 129.66; 130.29; 132.19; 132.28; 132.89; 133.25; 134.10; 135.13; 138.78; 139.30; 139.72; 139.83 (PC-C=C); 140.17; 144.58 (N=C-C=C-N-Ph); 149.53; (C of Ph attached directly to N).- IR (KBr): 2952-2887 (aliph.-CH); 1623 cm^{-1} (C=C).

Bis-(4-acetoacetyl[2.2]paracyclophane)copper(II) (**5**)

A mixture of **2** (0.05 g, 0.17 m. mol) and $CuCl_2$ (0.001 g, 0.007 m. mol) in EtOH (10 ml) was refluxed for 0.5 h. The mixture was concentrated and left in a refrigerator overnight. Green crystals of **5** were isolated, washed with water, petroleum ether and dried, yield 0.08 g (72%), m.p. 215°C (dec.).- $C_{40}H_{38}CuO_4$ (646.3) Calc. C 74.3 H 5.93 Found C 74.5 H 5.90.

Ethyl(4-oxaloacetyl[2.2]paracyclophane) (**6**)

To a stirred solution of **1** (0.5 g, 0.002 mol) and diethyl oxalate (2 g, 0.01 mol) in 30 ml of xylene, a solution of $NaOCH_3$ (1 g, 0.0185 mol) in 10 ml of xylene was added dropwisely. The mixture was heated for 5 h, at 110°C, cooled and acidified with dil. HCl. The mixture was extracted with chloroform, neutralized with $NaHCO_3$, washed with water and dried ($CaCl_2$). The solution was concentrated and chromatographed on prep. tlc plates using toluene as an eluent. **6** was then recrystallized from petroleum ether: colorless crystals, 0.4 g (57%), m.p. 90°C.- $C_{22}H_{22}O_4$ (350.4) Calc. C 75.4 H 6.33 Found C 75.4 H 6.25.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.40 (t, J = 7 Hz, 3H, CH_3); 2.8-3.2 (m, 8H, CH_2); 4.20 (q, J = 7 Hz, 2H, CH_2); 6.3-6.7 (m, 8H, CH= and PC-H).- IR (KBr): 2927-2853 (aliph.-CH); 1746 (CO, ester); 1728 (α-keto ester); 1702 cm^{-1} (CO, β-diketone).- UV (CH_2Cl_2) λ max (log ε) = 325 nm (3.25).

5-Hydrazinoyl-3-(4-[2.2]paracyclophanyl)pyrazole (**8**)

By the procedure as described for **4**, **8** was prepared from **6** (0.2 g, 0.57 m. mol). Colorless crystals, 0.15 g (79%), m.p. 210°C.- $C_{20}H_{20}N_4O$ (332.4) Calc. C 72.3 H 6.06 Found C 72.5 H 6.00.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.8-3.2 (m, 10 H, CH_2); 6.4-7.1 (m, 9H, PC-H and NH_2); 8.6 (s, NH).- IR (KBr): 3100-3400 (NH, NH_2); 2280-2290 (aliph.-CH); 1720 cm^{-1} (CO).

Bis-(ethyl-4-oxaloacetyl[2.2]paracyclophane)copper(II) (**9**)

9 was prepared as described for **5**: green crystals, 0.085 g (78%), m.p. 215°C dec.- $C_{44}H_{42}CuO_8$ (762.3) Calc. C 69.3 H 5.55 Found C 69.2 H 5.50.

1,1-Dicyano-2-methyl-2([2.2]paracyclophanyl)ethylene (**10**)

A mixture of **1** (0.5 g, 0.002 mol); malononitrile (0.132 g, 0.002 mol) and ammonium acetate (1 g, 0.016 mol) was heated to 120°C in an oil path for 6 h. The resulting fused product was washed with hot water, filtered, and then recrystallized from EtOH-petroleum ether to give **10** as colorless crystals, 0.35 g (61%), m.p. 150°C.- $C_{21}H_{18}N_2$ (298.4) Calc. C 84.5 H 6.08 N 9.4 Found C 84.4 H 6.10 N 9.4.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.5 (s, 3H, CH_3); 2.9-3.2 (m, 8H, CH_2); 6.3-6.7 (m, 7H, PC-H).- IR (KBr): 2929-2853 (aliph.-CH); 2231 (CN); 1571 cm^{-1} (=CH).

* PC stands for paracyclophanyl.

4,5,12,13-Tetrakis-methoxymethly[2.2]paracyclophane (**12**)

A suspension of 4,5,12,13-tetrahydroxymethyl[2.2]paracyclophane[9] (0.328 g, 0.001 mol) and anhydrous K_2CO_3 (0.3 g, 0.002 mol) in 10 ml (0.085 mol) of trimethylphosphate was heated under reflux for 4 h. After cooling to room temp. the solution was poured into 100 ml of cold water. Extraction with chloroform, washing with water, drying ($CaCl_2$) and evaporation of the solvent afforded white **12**. Recrystallization from EtOH: colorless crystals, 0.3 g (78%), m.p. 138°C.- $C_{24}H_{32}O_4$ (384.5) Calc. C 75.0 H 8.39 Found C 74.8 H 8.30.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.1-3.2 (m, 16 H, CH_2); 4.1-4.2 (s, 12 H, OCH_3); 6.4-6.6 (m, 4H, PC-H).- IR (KBr): 2800-3000 (aliph.-CH); 1080 cm^{-1} (CH_2OMe).

Bis-copper chloride dihydrate(4,5,12.13-tetrakis-methoxymethyl [2.2]paracyclophane) (**13**)

12 (0.038 g, 0.0001 mol) was dissolved in EtOH and added to $CuCl_2$ (0.035 g, 0.002 mol) in 5 ml water. The mixture was refluxed for 5 h, concentrated *in vacuo*, and left in a refrigerator overnight. Crystals of the green metal complex **12** were obtained, which were washed with water and chloroform: green crystals, 0.035 g (49%), m.p. > 300°C dec.- $C_{24}H_{40}Cl_4Cu_2O_8$ (725.5) Calc. C 39.7 H 5.56 Found C 39.9 H 5.50.

Determination of biological activity

Four species were used for these determinations: (a) Serratia (gram - ve), (b) Pseudomenas (gram - ve), (c) Bacillus cereus (gram - ve), and (d) Micrococcus roseus (gram + ve). The biological assay was performed according to the filter paper disc method, in which the diameter of the zone of inhibition means: - = < 1 cm; + = 1 to 1.5 cm; ++ = 1.5 to 2 cm; +++ = 2 cm; ++++ = > 2 cm; the solvent used was DMF. Assay plates were incubated at 25°C 1 day for the bacteria used[10].

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