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STEREOSELECTIVE SYNTHESIS OF 2,4-BRIDGED PYRIDINOPHANES*[,1]

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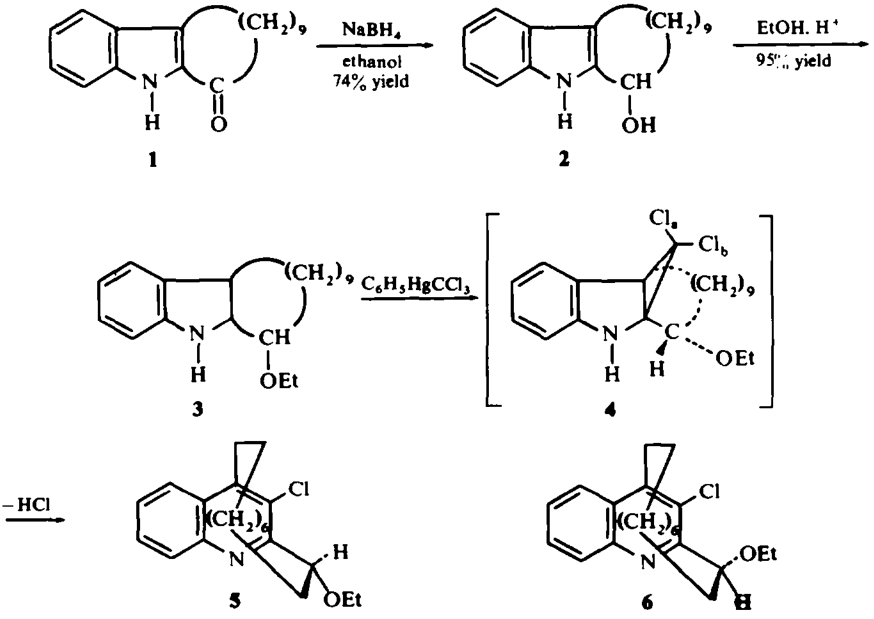
Abstract—Reaction of the indole ether **3** with phenyl (trichloromethyl) mercury gives the *syn*-metacyclophane **5**, exclusive of the *anti*-enantiomer **6**. These ethers are new and their structures were established by their independent synthesis from the corresponding alcohols **7** and **8**. These data are consistent with the conclusion that the intermediate cyclopropane **4** is formed by stereospecific addition of dichlorocarbene *trans* to the ethoxy group. Additional results are described providing evidence for the resistance of the benzylic carbon atoms in these highly constrained metacyclophanes to undergo change of hybridization from sp^3 to sp^2.

The reaction of phenyl (trichloromethyl) mercury with the indole **3**, prepared as shown in scheme 1 from the previously unknown ketone 1. gave the *syn*-ether **5** (60% yield. crude); thin layer chromatography confirmed that none of the *anti*-ether (**6**) was present in the reaction product.



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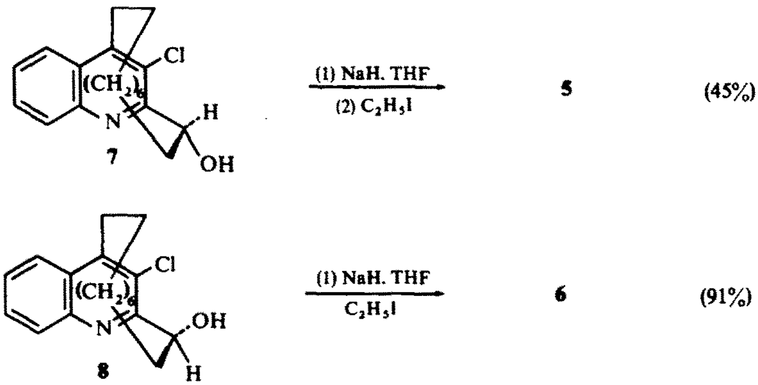
Both **5** and **6** were prepared independently from the known[1] *syn*- and *anti*-alcohols (**7** and **8**. respectively) as described in scheme 2. and mixtures of the two ethers were shown to be easily separated by TLC.*



Since the reactions leading to **5** were conducted in the relatively nonpolar solvent benzene. and in the presence of excess phenyl (trichloromethyl) mercury. it cannot be assumed that the elimination and ring opening reaction is concerted and that only the halogen marked "a" in **4** can serve as a leaving group in accordance with the steric consequence of the Woodward–Hoffmann rules.[2] On the other hand. steric considerations demand that the double bond formed in the product be *cis*. and that the ring opening reaction be a disrotatory process whether the overall reaction is concerted or non-concerted. The stereochemistry of the intermediate (**4**) is. therefore. fixed by the products obtained. and it is concluded that the addition of dichlorocarbene to **3** occurred stereospecifically *trans* to the OEt group. This conclusion is consistent with recent observations of Seyferth and Mai[3] who showed that the reaction of phenyl (trichloromethyl) mercury with 3-methoxycyclohexene and 3-methoxycyclononene gave only adducts in which the elements of dichlorocarbene added *trans* to the ether function.

It is interesting to note that **5** reacts slowly with hot aqueous HBr (47%) to give **7**. and that **6** reacts similarly to give **8**. In neither case was any epimerization or conversion to benzyl bromides noted. These results are not those expected for ordinary benzylic ethers and provide further evidence[1,4] for the resistance of bridged carbon atoms in such highly constrained systems from under-going reactions which involve change of hybridization from sp^3 to sp^2.

EXPERIMENTAL SECTION

1.2-*Cyclododecadione phenylhydrazone*. The cold (0·5°) aqueous layer containing the sodium salt of 2-hydroxymethylenecyclododecanone. prepared from cyclododecanone (51·0 g. 0·28 mole) by a procedure

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* TLC of an authentic mixture of **5**, **6**, **7**, **8** and 1-bromo-12,13-benzo-16-chloro[10](2,4)pyridinophane on silica gel (petroleum ether B-diethyl ether, 40:60) established that accurate qualitative analysis was possible (Rf 0·59, 0·68, 0·59, 0·21 and 0·74, respectively). On alumina (petroleum ether B-diethyl ether, 50:50) Rf values of 0·50, 0·62, 0·27 and 0·04 were obtained for **5**, **6**, **7** and **8**, respectively.

essentially identical to that described for the preparation of 2-hydroxymethylenecyclohexanone from cyclohexanone,[5] was treated with a cold (0–5°) solution of benzenediazonium chloride [prepared from aniline (18·6 g, 0·2 mole), NaNO$_2$ (13·8 g, 0·2 mole), water (50 ml) and conc HCl (50 ml)][†] keeping the reaction temp at 0–5° during the addition, essentially as described by Coffey[6] for the related reaction with 2-hydroxymethylenecyclohexanone. There was obtained 64·3 g of crude product, recrystallized from EtOH-water to give 48·9 g (m.p. 178–180°, 61% yield) of pure 1,2-cyclododecadione phenylhydrazone: UV (max) (95% EtOH) 343, 296, 288 and 237 mμ (log ε 4·31, 3·76, 3·68 and 4·05, respectively); NMR (CDCl$_3$) δ 8·13–7·76 (m, 1, N–$\underline{H}$) and 3·13–2·50 (m, 4, C$\underline{H}_2$—C=O and C$\underline{H}_2$—C=N). (Calcd. for $C_{18}H_{26}N_2O$: C, 75·48; H, 9·15; N, 9·78. Found: C, 75·73; H, 8·99; N, 9·72%).

6-Oxo-6,7,8,9,10,11,12,13,14,15-decahydrocyclododec[b]*indole* (**1**). Ketone **1** was prepared from 1,2-cyclododecadione phenylhydrazone (45·0 g, 0·157 mole) according to the procedure described by Coffey[6] for related compounds (refluxing glacial AcOH, dry HCl, 2 hr). The crude ketone (**1**) was precipitated from the mixture with water and recrystallized from acetone-water to give 31·0 g (m.p. 176–178°, 73% yield) of pure **1**: UV max (95% EtOH) 315 and 238 mμ (log ε 4·10 and 3·99, respectively); IR (nujol) 3320 cm^{-1} (s) (N—H) and 1630 cm^{-1} (s) (C=O); NMR (DMSO-d$_6$) δ 8·94–8·74 (m, 1, N—H) and 3·23–2·73 (m, 4, benzylic C$\underline{H}_2$ and C$\underline{H}_2$—C=O). (Calcd. for $C_{18}H_{23}NO$: C, 80·26; H, 8·61; N, 5·20. Found: 80·46; H, 8·79; N, 5·13%).

6-Hydroxy-6,7,8,9,10,11,12,13,14,15-decahydrocyclododec[b]*indole* (**2**). NaBH$_4$ (7·5 g, 0·2 mole) was added to a solution of ketone **1** (26·0 g, 0·097 mole) in boiling EtOH. The mixture was heated at reflux for 3 hr, EtOH removed, and the residue diluted with ether (1 l) and extracted with NaOH aq (1 l, 5%). The dried (MgSO$_4$) ether layer was concentrated and the residue crystallized from 95% EtOH to give 19·8 g (m.p. 135–138°) of a white solid. This was recrystallized from 95% EtOH to give 19·3 g (m.p. 147–148·5°, 74%) of **2**. The m.p. of **2** was dependent on the rate of crystallization: the higher melting form was obtained on slower crystallization. Both crystalline forms showed identical NMR and IR spectra and could be interconverted with no material loss: UV max (95% EtOH) 293, 284, 277 and 226 mμ (log ε 3·88, 3·94, 3·91 and 4·66, respectively); IR (nujol) 3370 cm^{-1} (s) (N—H) and 3300 cm^{-1} (broad shoulder) (O—H); NMR (CDCl$_3$) δ 8·43–8·03 (m, 1, N—$\underline{H}$) and 5·03 (t, 1, $J = 6$ Hz, C$\underline{H}$—O). (Calcd. for $C_{18}H_{25}NO$: C, 79·66; H, 9·29; N, 5·16. Found: C, 79·39; H, 9·41; N, 4·91%).

6-Ethoxy-6,7,8,9,10,11,12,13,14,15-decahydrocyclododec[b]*indole* (**3**). Conc HCl (1 ml) was slowly added to a cool (ice bath) solution of **2** (3·3 g, 0·122 mole) in abs EtOH (50 ml). The solution was allowed to warm to room temp (15 min) and KOH aq (50 ml, 4%) was added which caused precipitation of a light yellow solid. The solid was removed by filtration and air dried to give 3·5 g (m.p. 158–164°, 95%) of **3**. The ether (**3**) was recrystallized from abs EtOH to give 3·4 g (m.p. 170–171·5, 92% of **3**: UV max (95% EtOH 292, 285, 275 and 225 mμ (log ε 3·82, 3·91, 3·85 and 4·58, respectively); IR (nujol) 3270 cm^{-1} (s) (N—H) and 1140 cm^{-1} (s) (C—O—C); NMR (CDCl$_3$) δ 8·98 (m, 1, N—$\underline{H}$), 4·76 (t, 1, $J = 6$ Hz, C$\underline{H}$—O), 3·40 (q, 2, $J = 8$ Hz, CH$_3$C$\underline{H}_2$—O), 3·0–2·6 (m, 2, benzylic C$\underline{H}_2$) and 1·20 (t, 3, $J = 8$ Hz, C$\underline{H}_3$CH$_2$—O). (Calcd. for $C_{20}H_{29}NO$: C, 80·22; H, 9·76; N, 4·68. Found: C, 80·24; H, 9·76; N, 4·49%).

syn-1-Ethoxy-12,13-benzo-16-chloro[10](2,4)*pyridinophane* (**5**). A mixture of **3** (3·1 g, 10·3 mmole), phenyl (trichloromethyl) mercury (11·0 g, 28·0 mmole) and benzene (200 ml, dried over CaH$_2$) was heated at reflux (pot temp 110°) for 48 hr under N$_2$ atmosphere. The mixture was cooled and analysis of the filtrate (TLC on alumina, petroleum ether B (b.p. 60–70°) -diethyl ether 75:25; and by NMR[*]) obtained subsequent to the removal of phenylmercuric chloride (7·5 g, 86%) showed the presence of *syn*-ether (**5**) and some starting material; the *anti*-ether (**6**) was not detected. The mixture was chromatographed [280 g of neutral alumina, petroleum ether B-diethyl ether, 75:25 as eluent] to give **5** (2·1 g, 59%) as an oil; NMR (CDCl$_3$) δ 8·84–7·4 (m, 4, aromatic $\underline{H}$), 5·38 (doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 14$ Hz), 1, —C$\underline{H}$—O), 3·51 (q, 2, $J = 7$ Hz, O—C$\underline{H}_2$CH$_3$) and 1·2 (t, 3, $J = 7$ Hz, O—CH$_2$C$\underline{H}_3$). Attempts to crystallize **5** failed. Ether **5** gave a very hygroscopic product with dry HCl in ether; regeneration of the free base gave an oil which was essentially identical by NMR analysis to the oil described above: UV max (95% EtOH) 323, 312, 235 and 215 mμ (log ε 3·58, 3·61, 4·67 and 4·52, respectively); IR (neat) 1100 cm^{-1} (s) (C—O—C). The

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[*] Only *endo* CH–O absorption at δ 5·38 was observed; none of the *exo*-ether **6** (C$\underline{H}$–O absorption at δ 4·76) could be detected.

[†] Low yields of 2-hydroxymethylenecyclododecanone were obtained if an equivalent amount of diazonium salt was employed, possibly due to formazan formation. See R. R. Philips in "Organic Reactions", Vol. X, Chap. 2, p. 158 R. Adams, Ed., John Wiley and Sons, New York, N.Y., (1959).

ether 5 was characterized as its picrate (m.p. 189–191·5° from 95% EtOH). Calcd. for $C_{27}H_{31}ClN_4O_8$: C. 56·40: H. 5·43: N. 9·74: Cl. 6·17. Found: C. 56·25; H. 5·30; N. 9·49: Cl. 6·24%).

Preparation of 5 *and* 6. NaH (0·28 g. 6·6 mmole) was suspended in 50 ml of dry THF (distilled from CaH_2) and *anti*-1-hydroxy-12.13-benzo-16-chloro[10](2.4)pyridinophane[1] (8) (1·0 g. 3·2 mmole) was added. The mixture was protected from atmospheric moisture and heated at reflux for 5 hr. EtI (1·1 g. 7·0 mmole) was added. and the solution was heated for 2 hr. The solvent was evaporated (rotary evaporator) and the solid residue suspended in water and filtered. The residue was recrystallized from EtOH to give 1·0 g (91%) of 6: m.p. 107·5–110°. UV max (95% EtOH) 325. 311. 234 and 215 mμ (log ε 3·48. 3·42. 4·62 and 4·41. respectively); IR (nujol) 1100 cm^{-1} (s) (C—O—C); NMR ($CDCl_3$) δ 4·76 (doublet of doublets (X portion of ABX. $J_{AX} + J_{BX} = 16$ Hz). 1. C$\underline{H}$—O). 8·2–7·5 (m. 4. aromatic $\underline{H}$). 1·23 (t. 3. $J = 7$ Hz. O—$CH_2C\underline{H}_3$). and 3·80–3·26 (m. 4. benzylic $C\underline{H}_2$ and O—$C\underline{H}_2CH_3$). (Calcd for $C_{21}H_{28}ClNO$: C. 72·90; H. 8·16; N. 4·05. Found: C. 73·16; H. 8·44; N. 3·83%).

When the same conditions were employed starting with *syn*-alcohol[1] 7 (0·9 g. 2·9 mmole) the product (0·45 g. 45%). obtained subsequent to chromatography (neutral alumina. petroleum ether B^{10}-diethyl ether. 85:15 to 67:33). was an oil identical by NMR analysis to the product (5) obtained from the reaction of 3 with phenyl(trichloromethyl)mercury' The oil was characterized as its picrate: m.p. 189–191° from EtOH. m.m.p. 189–191°. (Calcd for $C_{27}H_{31}ClN_4O_8$: C. 56·40; H. 5·43; N. 9·74; Cl. 6·17. Found: C. 56·47; H. 5·32; N. 9·57; Cl. 6·20%).

Reaction of 5 *with Hydrogen Bromide.* A solution of *syn*-ether 5 (0·7 g. 2·1 mmole) in 47% HBr (30 ml) was heated at reflux for 20 hr. The cooled mixture was poured into water (150 ml); some solid precipitated. The combined solid and acid solution was neutralized (NaOH aq) and extracted with $CHCl_3$ (3 × 100 ml). Analysis of the crude product by TLC$_3$ (silica gel. petroleum ether B (b.p. 60–70°)-diethyl ether. 40:60) showed that only *syn*-alcohol[1] 7 and unchanged 5 were present; *anti*-alcohol[1] 8. *anti*-ether 6 or 1-bromo-12.13-benzo-16-chloro[10](2.4)pyridinophane[1] could not be detected. The crude product was recrystallized from petroleum ether B to give *syn*-alcohol 7 (270 mg. 36%. m.p. 157–159°. m.m.p. 156–160°). Treatment of the residue from the mother liquor with ethanolic picric acid gave the picrate of 5 (280 mg. m.p. 188–191° from 95% EtOH. m.m.p. 188–191°) in 23% yield.

Reaction of 6 *with Nydrogen Bromide.* The conditions were identical to those described above for the *syn*-ether 5. Analysis of the crude product by TLC (alumina, petroleum ether B (b.p. 60–70°) -diethyl ether, 75:25) showed the presence of *anti*-alcohol[1] 8 and unchanged 6 only; none of the *syn*-alcohol[1] 7 was observed. Recrystallization of the crude product from $CHCl_3$-petroleum ether B (1:6) gave 210 mg (57%) of pure *anti*-alcohol 8 (m.p. 203–205°. m.m.p. 204–207°). Recovered 6 (95 mg. m.p. 105–107·5°. m.m.p. 106–109·5°. 24%) was obtained from the mother liquor by recrystallization from 95% EtOH.

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