Synthesis of [6](2,4)Pyridinophanes

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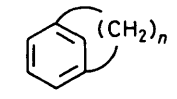
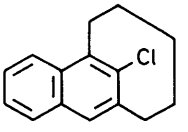
The [6](2,4)pyridinophane derivatives [(**11a**) and (**11b**)] have been prepared by treating 4,5,6,7,8,9-hexahydro-1*H*-cyclo-octa[*b*]pyrrole(**5b**) with dichloro- and dibromo-carbene, respectively. The respective yields of compounds (**11a**) and (**11b**) obtained were modest and poor.

The preparation of strained metacyclophanes[1] has, in recent years, received much attention. Following the synthesis of [6]metacyclophane (**1b**) by Hirano *et al.*[2] and of [5]metacyclophane (**1a**) by Bickelhaupt and his co-workers,[3] we reported[4] the synthesis of the condensed [5]metacyclophane derivative (**2**) by a procedure that now appears[5] to be the most effective for the generation of the [5]metacyclophane system. All of this synthetic work involves either the heat- or silver(I) ion-promoted ring-expansion of halogenocarbene adducts of condensed cycloalkene derivatives.



(**1**) a; *n* = 5
b; *n* = 6



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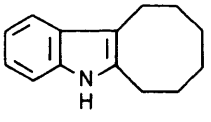
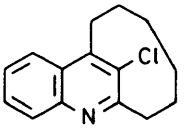
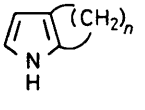


(**3**)



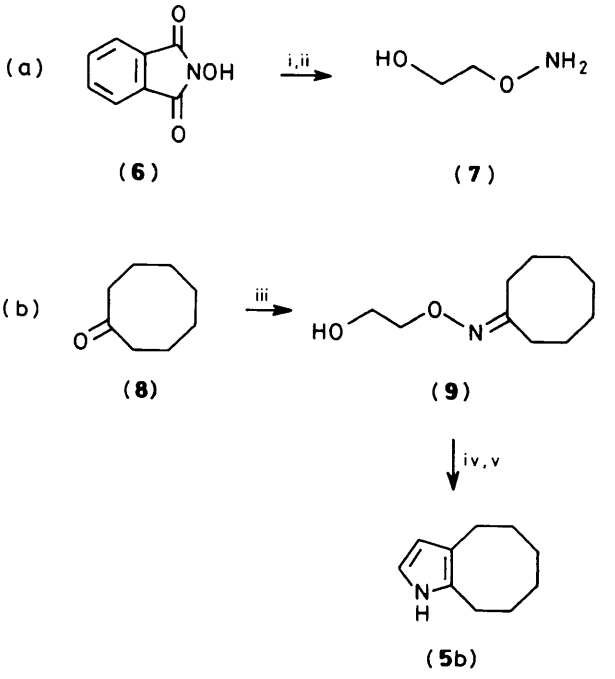
(**4**)



(**5**) a; *n* = 5
b; *n* = 6

Parham and his co-workers[6] pioneered this ring-expansion approach to metacyclophane synthesis, and showed[7] that it could also be used in the conversion of indole derivatives into (2,4)quinolinophanes. Thus, when 6,7,8,9,10,11-hexahydro-5*H*-cyclo-oct[*b*]indole (**3**) was heated with an excess of phenyl(trichloromethyl)mercury[8] in benzene solution, the [6](2,4)quinolinophane derivative (**4**) was obtained[7a] and was isolated from the products as a crystalline solid in 48.6% yield. The present study was undertaken in order to determine whether (2,4)pyridinophanes can be prepared by allowing the corresponding pyrrole derivatives (**5**) to react with dihalogenocarbenes.

It was decided in the first place to examine the reaction between dichlorocarbene and 4,5,6,7,8,9-hexahydro-1*H*-cyclo-octa[*b*]pyrrole[9] (**5b**). Although it is possible[10] to prepare compound (**5b**) from cyclo-octanone oxime, potassium hydroxide, and acetylene, this procedure[11] proved to be unsatisfactory in our hands. We have therefore developed a new pyrrole synthesis[9] especially for this study. When cyclo-octanone (**8**) was allowed to react with *O*-(2-hydroxyethyl)hydroxylamine[9,12] (**7**) in the presence of pyridine and acetic acid in ethanol solution, its *O*-(2-hydroxyethyl) oxime (**9**) was obtained in 87% yield [Scheme 1(b)]. The latter compound (**9**) was then treated with methyltriphenoxyphosphonium iodide[13] in acetonitrile solution and the product was heated, under



Scheme 1. *Reagents:* i, $BrCH_2CH_2OH$, K_2CO_3–Me_2SO, 70 °C; ii, $N_2H_4 \cdot H_2O$–EtOH, reflux; iii, (**7**), AcOH–C_5H_5N–EtOH, reflux; iv, $(PhO)_3\overset{+}{P}MeI^-$–MeCN, room temperature; v, KOBu^t–Bu^{t}OH, reflux

reflux, with potassium t-butoxide in t-butyl alcohol solution to give the desired pyrrole derivative (**5b**) as a low melting crystalline solid in 60% overall yield. Cyclohexanone and cycloheptanone have also been converted[9] into the corresponding condensed pyrrole derivatives [(**5**; *n* = 4) and (**5a**), respectively] in satisfactory yields by this procedure. The feasibility of this pyrrole synthesis depends on the ready availability of *O*-(2-hydroxyethyl)hydroxylamine (**7**). We have developed[9] a two-step preparation of compound (**7**) [Scheme 1(a)] that is very much more convenient and efficient than that previously described[12] in the literature.

From earlier studies[7,10] on the reaction between dichlorocarbene and indole derivatives, it appears that higher yields of ring-expansion products are obtained when the latter substrates are protected on N-1. Furthermore, experiments carried out[10] with derivatives[14] of 6,7,8,9,10,11-hexahydro-5*H*-cyclo-oct[*b*]indole (**3**) suggested that the *N*-(t-butoxycarbonyl) derivative (**10**) of the pyrrole (**5b**) would be the most suitable starting material for the preparation of 12-chloro-8-aza[6]-metacyclophane (**11a**). Unfortunately, complex mixtures of products were obtained when compound (**10**) was treated with (i) chloroform and potassium t-butoxide,[15] (ii) chloroform, sodium hydroxide, and a phase-transfer catalyst,[16] or (iii) phenyl(bromodichloromethyl)mercury.[17] When, however, the

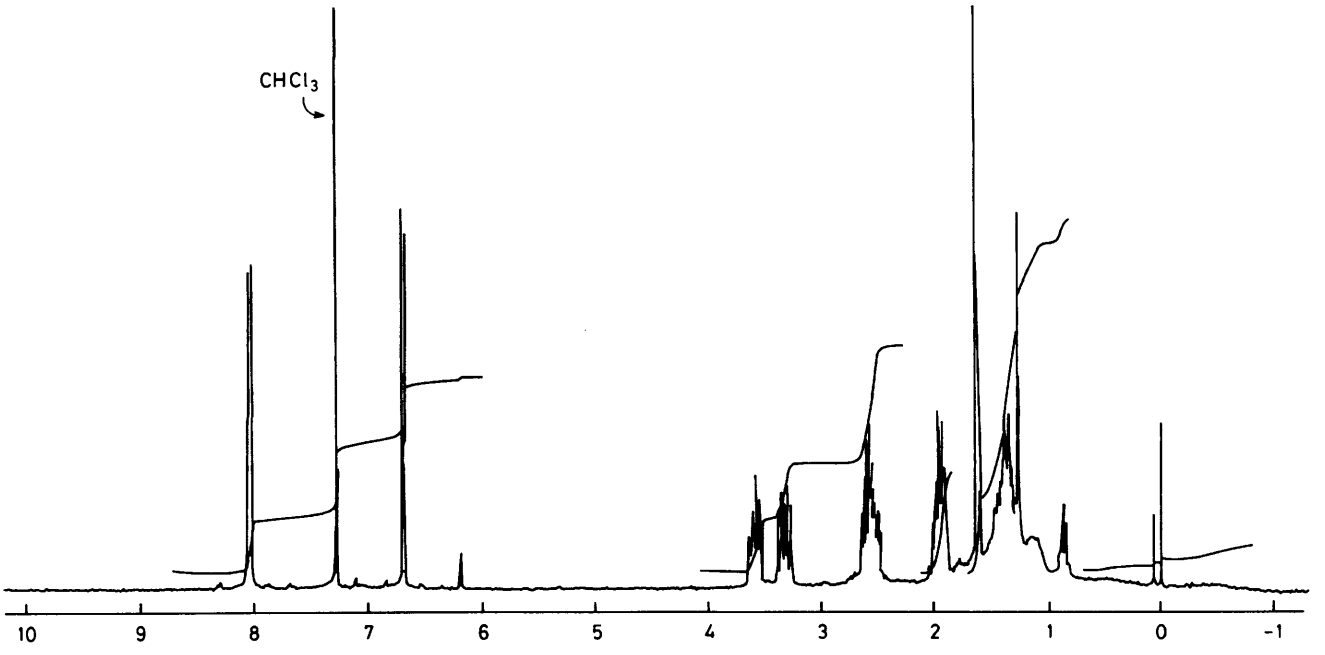
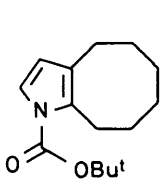
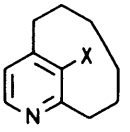


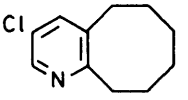
Figure. ^{1}H N.m.r. spectrum (250 MHz, in $CDCl_3$ solution) of 12-chloro-8-aza[6]metacyclophane (**11a**)



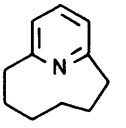
(**10**)



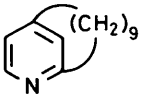
(**11**) a ; X = Cl
b ; X = Br



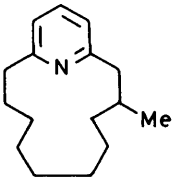
(**12**)



(**13**)



(**14**)



(**15**)

unprotected pyrrole (**5b**) was heated, under reflux, in an atmosphere of nitrogen with an excess of sodium trichloroacetate[18] in 1,2-dimethoxyethane solution, the desired [6](2,4)pyridinophane (**11a**) was obtained as a colourless oil in 28% isolated yield; the latter compound (**11a**) was similarly obtained in 20% isolated yield by heating the pyrrole (**5b**) with phenyl(bromodichloromethyl)mercury,[17] under reflux, in benzene solution. 12-Chloro-8-aza[6]metacyclophane (**11a**) was characterised on the basis of its ^{1}H n.m.r. spectrum (Figure, and see below) and the elemental analysis of its crystalline picrate. In the reaction between the pyrrole (**5b**) and sodium trichloroacetate, a minute quantity of a by-product, probably with structure (**12**), was obtained. If dichlorocarbene added to the less substituted double bond of the pyrrole derivative (**5a**), the initial product would be expected to undergo ring-expansion to give compound (**12**).

When the bicyclic pyrrole derivative (**5b**) was heated, under reflux, with phenyl(tribromomethyl)mercury[8] in benzene solution, 12-bromo-8-aza[6]metacyclophane (**11b**) was obtained but only in 6% isolated yield. The ^{1}H n.m.r. spectrum of the [6]metacyclophane (**11b**) is virtually identical with that of the [6](2,4)pyridinophane (**11a**) (Figure). It can be seen from the Figure that there are separate resonance signals at δ 3.32 and 3.57 p.p.m., assignable to a pair of methylene protons (presumably attached to C-6) in the ^{1}H n.m.r. spectrum of compound (**11a**). The magnetic non-equivalence of 'benzylic' protons is a characteristic feature of strained metacyclophanes, such as [6]metacyclophane (**1b**) itself.[2] It is noteworthy that the methylene protons in compounds (**11a**) and (**11b**) are less shielded than the corresponding protons in 12-bromo[6]-metacyclophane;[2] indeed no significant absorption can be observed above *ca.* δ 0.8 in the ^{1}H n.m.r. spectrum of either compound. The methylene protons of [6](2,6)pyridinophane (**13**) (see below) have similarly been found[19] not to be strongly shielded.

Prior to this work, [9](2,4)pyridinophane (**14**) was, to the best of our knowledge, the (2,4)pyridinophane with the smallest methylene bridge described[20] in the literature. Due, most probably, to muscopyridine[21] (**15**) being a constituent of natural musk, much more work has been carried out on the synthesis of the (2,6)pyridinophane system. Thus [6](2,6)pyridinophane (**13**) has been prepared[19] in 11% yield by the action of the bis-Grignard reagent derived from a 1,6-dihalogenohexane on 2,6-dichloropyridine, and [7](2,6)pyridinophane has been prepared[22] in 44% yield by the action of hydroxylamine hydrochloride on cyclododecane-1,5-dione. We have, so far, had no success in converting the pyrrole derivative (**5a**)[9] into a halogenated [5](2,4)pyridinophane.

Experimental

^{1}H and ^{13}C N.m.r. spectra were measured at 250 and 62.9 MHz, respectively, with a Bruker WM 250 spectrometer; tetramethylsilane was used as an internal standard. Merck silica gel H was used for short column chromatography. Acetonitrile, t-butyl alcohol, and 1,2-dimethoxyethane were dried by heating over calcium hydride, under reflux, and were then distilled. Dimethyl sulphoxide was dried by stirring with calcium hydride at room temperature, and was then distilled under reduced pressure.

N-(2-*Hydroxyethoxy*)*phthalimide*.—*N*-Hydroxyphthalimide (2.0 g, 12.3 mmol), 2-bromoethanol (4.6 g, 36.8 mmol),

anhydrous potassium carbonate (5.1 g, 37 mmol), and dimethyl sulphoxide (20 ml) were stirred together at 80 °C. After 30 min, the cooled products were poured into water (30 ml). The resulting mixture was extracted with dichloromethane (3 × 15 ml) and the combined organic extracts were washed with water (3 × 20 ml), then dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil, which solidified with time, was crystallized from aqueous ethanol to give the *title compound* (Found: C, 57.6; H, 4.4; N, 6.7. $C_{10}H_9NO_4$ requires C, 58.0; H, 4.4; N, 6.8%) as colourless crystals, m.p. 73 °C (2.02 g, 79%); $\delta_H(CDCl_3)$ 3.51 (1 H, br s), 3.81 (2 H, m), 4.31 (2 H, m), 7.79 (2 H, m), and 7.88 (2 H, m); $\delta_C(CDCl_3)$ 59.56, 79.94, 123.84, 128.80, 134.85, and 164.44.

O-(2-*Hydroxyethyl*)*hydroxylamine* (**7**).—Hydrazine hydrate (5.7 g, 0.114 mol) was added to a solution of *N*-(2-hydroxyethoxy)phthalimide (17.0 g, 82 mmol) in absolute ethanol (170 ml) at room temperature, and the reactants were then heated under reflux. After 2 h, the cooled products were filtered, and the filtrate was evaporated under reduced pressure. Distillation of the residue gave the *title compound* as a colourless liquid, b.p. 55 °C/0.07 mmHg (5.44 g, 86%), identical with material prepared by the previously reported procedure.[12]

4,5,6,7,8,9-*Hexahydro*-1H-*cyclo-octa*[b]*pyrrole* (**5b**).—A solution of *O*-(2-hydroxyethyl)hydroxylamine (1.34 g, 17.4 mmol) in ethanol (5 ml) was added to a stirred solution of cyclooctanone (1.10 g, 8.7 mmol), pyridine (1.4 ml, 17.3 mmol), and acetic acid (1.0 ml, 17.5 mmol) in ethanol (10 ml) at room temperature. The reactants were then heated, under reflux. After 1 h, the products were cooled, concentrated under reduced pressure, and partitioned between dichloromethane (20 ml) and water (10 ml). The dried ($MgSO_4$) organic layer was evaporated and the residue was distilled under reduced pressure (0.2 mmHg) in a Kugelrohr apparatus (oven temperature, 100 °C) to give the putative *O*-(2-hydroxyethyl) oxime of cyclooctanone (1.40 g, 87%) as a colourless liquid.

A solution of the latter material (1.1 g, 5.9 mmol) in acetonitrile (10 ml) was added to a stirred solution of methyltriphenoxyphosphonium iodide[23] (3.90 g, 8.6 mmol) in acetonitrile (10 ml) at room temperature. After 20 min, water (30 ml) was added and the products were extracted with dichloromethane (2 × 30 ml). The combined organic layers were washed with aqueous sodium thiosulphate (2 × 15 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), and then dried ($MgSO_4$). The residue obtained following the evaporation of the solvent was dissolved in t-butyl alcohol (6 ml), and the solution was added to a solution of potassium t-butoxide (4.01 g, 35.7 mmol) in t-butyl alcohol (20 ml). The resulting mixture was then heated, under reflux. After 5 h, the products were cooled, treated with water (15 ml), and extracted with dichloromethane (2 × 30 ml). The combined organic layers were washed with aqueous sodium hydroxide (20% w/w; 25 ml) and then with water (30 ml); the resulting solution was dried ($MgSO_4$) and concentrated. The residue obtained was distilled under reduced pressure (0.2 mmHg) in a Kugelrohr apparatus (oven temperature, 60 °C) to give the *title compound* (Found: C, 80.3; H, 10.0; N, 9.1. $C_{10}H_{15}N$ requires C, 80.5; H, 10.1; N, 9.4%) as a colourless solid, m.p. 35—36 °C (0.617 g, 60% for the three steps starting from cyclo-octanone); $\delta_H(CDCl_3)$ 1.6—1.9 (8 H, m), 2.57 (2 H, m), 2.64 (2 H, m), 5.97 (1 H, m), 6.45 (1 H, m), and 7.69 (1 H, br s); $\delta_C(CDCl_3)$ 24.86, 25.42, 25.51, 25.84, 29.58, 30.63, 109.05, 114.18, 118.92, and 128.38.

12-*Chloro*-8-*aza*[6]*metacyclophane* (**11a**).—(a) 4,5,6,7,8,9-Hexahydro-1*H*-cyclo-octa[*b*]pyrrole (5.0 g, 33.5 mmol) was added to a stirred suspension of sodium trichloroacetate (27.0 g, 0.146 mol) in anhydrous 1,2-dimethoxyethane (300 ml). The reactants were then heated, under reflux, in an atmosphere of nitrogen for 4 h. The products were then filtered through a pad of Celite and the residue was washed with dichloromethane (50 ml). The combined filtrate and washings were concentrated under reduced pressure to give a deep brown residual oil. The latter material was dissolved in dichloromethane (50 ml) and the solution was extracted with 6M-phosphoric acid (2 × 25 ml). The combined aqueous extracts were cooled, carefully neutralized (to pH 7) by the addition of 6M-aqueous sodium hydroxide, and were then extracted with dichloromethane (2 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by chromatography on silica gel: the column was eluted with light petroleum (b.p. 40—60 °C)–ethyl acetate (95:5 v/v) and the appropriate fractions were combined and evaporated under reduced pressure to give (i) a very small quantity (*ca.* 0.006 g) of a compound {$\delta_H(CDCl_3$, 60 MHz) 1.2—2.0 (>8 H, m), 2.6—3.05 (4 H, m), 7.36 (1 H, m), and 8.33 (1 H, d, J ~2 Hz) with R_F 0.3 [light petroleum (b.p. 40—60 °C)–ethyl acetate (9:1 v/v)]} and (ii) the *title compound* (**11a**) (1.84 g, 28%) as an oil with R_F 0.15. The latter compound was characterised on the basis of its ^1H n.m.r. spectrum [$\delta_H(CDCl_3)$ 0.9–1.65 (6 H, m), 1.95 (2 H, m), 2.54 (2 H, m), 3.32 (1 H, m), 3.57 (1 H, m), 6.69 (1 H, d, J 4.5 Hz), and 8.03 (1 H, d, J 4.5 Hz)] and on the combustion analysis of its crystalline (from ethanol) *picrate* (Found: C, 48.0; H, 4.35; N, 13.2. $C_{17}H_{17}ClNO_7$ requires C, 48.1; H, 4.0; N, 13.2%), m.p. 226—227 °C.

(b) Phenyl(bromodichloromethyl)mercury[17] (0.595 g, 1.23 mmol) was added to a solution of 4,5,6,7,8,9-hexahydro-1*H*-cyclo-octa[*b*]pyrrole (0.105 g, 0.70 mmol) in dry benzene (5 ml), and the mixture was heated in an atmosphere of nitrogen, under reflux, for 6 h. The products were then worked up and purified as above to give the *title compound* (**11a**) (0.027 g, 20%), identical (t.l.c., ^1H n.m.r.) with the material described in (a) above.

12-*Bromo*-8-*aza*[6]*metacyclophane* (**11b**).—Phenyl(tribromomethyl)mercury[8] (0.688 g, 1.3 mmol) was added to a solution of 4,5,6,7,8,9-hexahydro-1*H*-cyclo-octa[*b*]pyrrole (0.106 g, 0.71 mmol) in dry benzene (7 ml), and the mixture was heated in an atmosphere of nitrogen, under reflux, for 24 h. The products were worked up and purified as described above in the preparation of the corresponding 12-chloro compound to give the *title compound* (**11b**) (0.01 g, 6%) as an oil; $\delta_H(CDCl_3)$ 0.8—1.8 (6 H, m), 1.95 (2 H, m), 2.63 (2 H, m), 3.30 (1 H, m), 3.60 (1 H, m), 6.63 (1 H, d, J 4.4 Hz), and 8.02 (1 H, d, J 4.4 Hz). The latter n.m.r. spectrum corresponds closely to that of 12-chloro-8-aza[6]metacyclophane (**11a**) (see above).

Acknowledgements

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