Synthesis and Conformational Rigidity of [2,2]Metacyclo-2,6-pyridinophane

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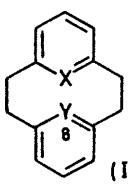
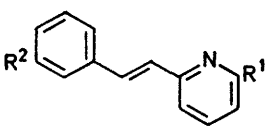
Summary The synthesis of the title compound is described, and the high barrier to ring inversion in conjunction with previous results show that non-bonded interactions increase in magnitude in the series N,N < CH,N < CH,CH.

THE conformational mobility of [2,2]metacyclophane and its heterocyclic analogues (I) provides a convenient method[1] for comparing the steric requirements of the groups X and Y [see (I)], and in a previous communication[2] we reported that the relatively low barrier to inversion of the chair-like conformation of [2,2]-2,6-pyridinophane (Ia) as compared to that of [2,2]metacyclophane (Ib) demonstrated the low steric requirements of the non-bonded electron pairs on the nitrogen atoms of (Ia). This investigation has now been extended to the cyclophane (Ic).

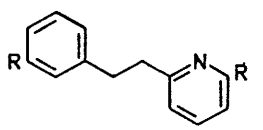


(I)

(a) X = Y = N
(b) X = Y = CH
(c) X = N, Y = CH



(II) R^1 = Me, R^2 = CO_2Et
(III) R^1 = CH_2OAc, R^2 = CO_2Et
(IV) R^1 = R^2 = CH_2OH



(V) R = CH_2OH
(VI) R = CH_2Br

Rearrangement[3] of the *N*-oxide of the stilbene analogue (II), prepared by the condensation of ethyl 3-formylbenzoate with 2,6-lutidine, afforded the diester (III) which was reduced by lithium aluminium hydride to the diol (IV). Catalytic reduction of the diol (IV) gave the dihydroderivative (V) which was converted by hydrobromic acid–acetic acid into the dibromide (VI). Ring closure of compound (VI) to give the cyclophane (Ic) was effected by reaction with n-butyl-lithium[4] (10% yield). The product (Ic) was clearly characterised† by its n.m.r. spectrum which showed the pyridine protons as an AX_2 system (τ_A 2·43, τ_X 2·95, J_{AX} 8 Hz) and the benzenoid protons as an AB_2 system together with a single high-field resonance (τ 5·60) characteristic[5] of a proton in position 8 [see (I)] of a [2,2]metacyclophane derivative. The methylene protons gave rise to an ABCD system which was unchanged at 200° demonstrating that the barrier to inversion of (Ic) is greater than 27 kcal./mole (based on a minimum observable line broadening of 0·5 Hz). This result demonstrates that the CH,N interaction in the transition state for inversion of (Ic) is of considerably greater magnitude than the analogous N,N interaction in the transition state for inversion of (Ia) ($\Delta G^{\ddagger}$ for inversion 14·8 kcal./mole).[2]

These results, to our knowledge, represent the first direct comparison of large non-bonded interactions between two nitrogen atoms, and a nitrogen atom and a CH group in comparable geometrical situations. Comparison with the results recently reported by Vogtle[6] shows clearly that the relative magnitudes of interactions of this type are: N,N < N, CH < CH, CH. This order applies, however, to

† All new compounds have been fully characterised by analysis and spectral properties.

188—190°, followed by a Claisen rearrangement in boiling *NN*-dimethylaniline gave the 2-allylxanthone (VIII), m.p. 179—180°. Methylation with dimethyl sulphate gave the trimethyl ether (IX), m.p. 151—152°, the double bond of which was cleaved with ozone, or better, with a catalytic quantity of osmium tetroxide in the presence of sodium chlorate followed by treatment with sodium metaperiodate,[4] to give the xanthonyl-2-acetaldehyde (X), m.p. 161° (decomp.).

Both the phosphonium salt (XI) and the unstable ylide (IV) can be prepared at atmospheric pressure in contrast to the vigorous conditions used previously:[5] the former, by reaction of triphenylphosphine with isopropyl iodide or bromide in benzene under reflux, and the latter, by treatment of the phosphonium salt suspended in dry ether with a slight deficiency of n-butyl-lithium at 0°. The aldehyde (X) and the ylide (IV) react rapidly at room temp. to form the 3,3-dimethylallylxanthone (V), m.p. 162—163°, identical with the trimethyl ether (V) of the natural product (II).†

The basis of the second method is the *in situ* formation and sigmatropic rearrangement of the otherwise inaccessible 1,1-dimethylallyl ether (XII). This was achieved by thermolysis of the acetate (XIII). 3,3-Dimethylallyl acetate (XIV)[6] was converted into the tertiary bromide (XV) by reaction with hydrogen bromide in cold glacial acetic acid. Using an excess of this reagent and potassium carbonate in acetone, the etherification of 1-hydroxy-3,5-dimethoxyxanthone (VI)[3] was followed by t.l.c. The ether (XIII), which was not isolated, eliminated acetic acid and rearranged at 190° in *NN*-dimethylaniline to form 2-(3,3-dimethylallyl)-1-hydroxy-3,5-dimethoxyxanthone (III), identical with the derivative (III) of the natural product.[1] However, the major product is 1-hydroxy-3,5-dimethoxyxanthone (VI) from ether (XIII) cleavage.

Demethylation and cyclisation of 2-(3,3-dimethylallyl)-1-hydroxy-3,5-dimethoxyxanthone (III) and the trimethyl ether (V) with boron tribromide[7] gave dihydro-6-deoxyjacareubin (I; 2H at C-4′ and C-5′) identical with the dihydro-derivative of the natural product.‡

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† These results were first presented at the Heterocyclic Group Meeting of the Chemical Society held at the University of Keele, September, 1968.

‡ The structures of all new compounds were supported by satisfactory analytical and spectral data.

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