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STUDIES IN THE HETEROPHANES FIELD
[9]HETEROPHANES OF SIX-MEMBERED AROMATICS

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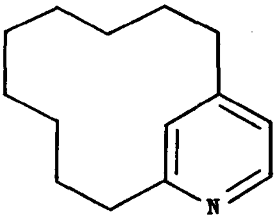
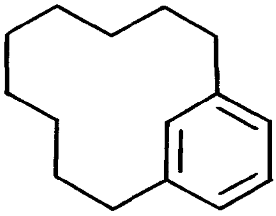
Certain methylene(s) in some 1,3-bridged five-membered heteroaromatics[1-3] have been found to be considerably shielded by the π electron cloud, but the effect is much weaker in a number of 1,3-bridged six-membered aromatics.[4-6] Observation of strong shielding effects in heterophanes appears to be dependent upon the site of chain junction, chain length, and geometry of the aromatic ring.

In this connection we now report preliminary results of PMR investigation of [9]2,4-pyridinophane (I) and [9]metacyclophane (II): new syntheses of (I) and (II) are also outlined.



(I)



(II)

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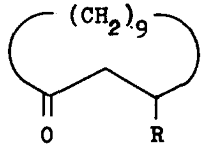
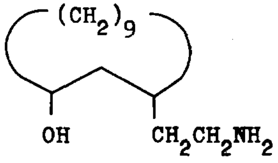
Michael addition of ethyl cyanoacetate to cyclododecen-2-one[7] gave quantitatively the cyanoketoester [(III) m.p. 71-72° from Et_2O-petrol ether; IR (nujol): ν_{CN} at 2240 cm^{-1}, ν_{CO} at 1700 and 1740 cm^{-1}; PMR: 6.27τ (1H,m,$C\underline{H}$-CN), 7.27-7.6τ (5H,m,$C\underline{H}_2$-CO-$C\underline{H}_2$-$C\underline{H}$)]. Alkaline hydrolysis of (III) (10% KOH in MeOH-H_2O, room temperature) gave the corresponding crude oily acid which was pyrolysed (180-200°, in the presence of copper powder) to the 3-cyanomethylenecyclododecanone [(IV), b.p.$_{0.1}$ 140-145°, m.p. 41-42°; IR (film): ν_{CN} at 2240 cm^{-1}, ν_{CO} at 1700 cm^{-1}]. The diastereomeric mixture of the amino alcohols [(V), m.p. 98° from $CHCl_3$-Et_2O] was prepared by reduction of (IV) with $LiAlH_4$ in Et_2O at room temperature. Spontaneous cyclisation to Δ^1-piperideine [(VI), b.p.$_{0.2}$ 105-107°, m.p. 41-42°; IR (film): $\nu_{C=N}$ at 1660 cm^{-1}; no olefinic protons in the PMR spectrum] occurred during Jones oxidation of (V) in acetone. Conversion of (VI) into the [9]2,4-pyridinophane [(I), b.p.$_{0.3}$ 115-120°; methoiodide m.p. 127-128° from $CHCl_3$-Et_2O] was realized by known methods[8] refluxing (VI) in xylene in the presence of nitrobenzene and of catalytic amounts of Pd-C 10%.

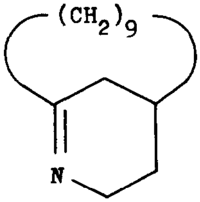
Michael addition of ethyl acetoacetate to cyclododecen-2-one gave the diketoester [(VII),mixture of stereoisomers, m.p. 68-83° from Et_2O-petrol ether; IR (nujol): ν_{CO} at 1700 cm^{-1}; PMR: 6.21 and 6.33τ (1H, two doublets, $C\underline{H}$-CO), 7.17-7.85τ (5H,m,$C\underline{H}_2$-CO-$C\underline{H}_2$-$C\underline{H}$), 7.77τ (3H,s,$COC\underline{H}_3$)] and of the hydroxycyclo-



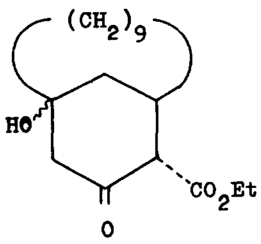
(III) R = $CH(CN)CO_2Et$
(IV) R = CH_2CN
(VII) R = $CH(CO_2Et)COCH_3$



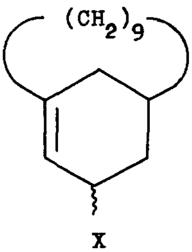
(V)



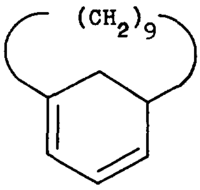
(VI)



(VIII)



(IX) X = =O
(Xa) X = OH
(Xb) X = OH



(XI)
double bonds in the four
possible endocyclic positions

hexanones [(VIII),mixture of stereoisomers, m.p. 107° from Et_2O; IR (nujol):ν_{OH} at 3450 cm^{-1}, ν_{CO} at 1700 and 1725 cm^{-1}; PMR: 6.92τ (1H,d,J_{ax-ax}= 12Hz,$C\underline{H}$-CO), 7.4τ (2H,s,$C\underline{H}_2$-CO)]. Separation of (VII) from (VIII) was achieved by column chromatography (SiO_2, Et_2O-pentane, 1:1). Both (VII) and (VIII) were converted into the cyclohexenone [(IX), m.p. 116° from Et_2O-pentane; IR (nujol): ν_{CO} at 1670 cm^{-1}, $\nu_{C=C}$ at 1630 cm^{-1}; PMR: 4.14τ (1H,bs,=$C\underline{H}$-CO)] by heating under reflux in $AcOH-H_2O-H_2SO_4$. Carbonyl reduction with $LiAlH_4$ in ether afforded the stereomeric mixture of the alcohols (Xa) and (Xb) in the ratio ca. 1:4, separated by column chromatography (SiO_2, Et_2O-pentane, 1:1) [(Xa), b.p.$_{0.3}$ 116-118°, m.p. 67-68°; IR (nujol): ν_{OH} at 3240-3300 cm^{-1}, $\nu_{C=C}$ at 1665 cm^{-1}; PMR: 4.47τ (1H,bs,=$C\underline{H}$), 5.85τ (1H,m,$C\underline{H}OH$), 8.26τ (1H,s,$O\underline{H}$)] and [(Xb), m.p. 88-89° from Et_2O-pentane; IR (nujol): ν_{OH} at 3150-3300 cm^{-1}, $\nu_{C=C}$ at 1665 cm^{-1}; PMR: 4.6τ (1H,bs,=$C\underline{H}$), 5.85τ (1H,bm,$C\underline{H}OH$), 8.35τ (1H,s,$O\underline{H}$)]. The proton α to the hydroxy group in (Xb) gives rise to a multiplet broader than in (Xa): this suggests a cis configuration for the former with axial-axial and axial-equatorial couplings. A mixture of four isomeric cyclohexadienes (XI) (v.p.c. analysis) were obtained by dehydration of the alcohols (X) with PBr_3 and pyridine in ether. Catalytic hydrogenation (Pd-C 10% in AcOMe) of this mixture gave only the bicyclo[9.3.1]pentadecane (b.p.$_{0.1}$ 100-105°), while oxidation with DDQ in benzene gave the [9]metacyclophane [(II), b.p.$_{0.5}$ 100-105°).

The main feature of the PMR spectra of pyridinophane (I) and cyclophane (II) is the absence of a strong shielding effect of the π electron cloud on the polymethylene chain: the central methylenes give rise to a broad signal at 9-9.5τ. This result is different from that found in the [9]1,3-bridged five-membered heteroaromatics: the length of the chain being equal, it must be the geometry of the six-membered rings that affects the conformation of the chain; such a situation is possibly present also in [9]3,5-pyridinophane[4], [10]metacyclophane[5], and [10]1,3-naphthalenophane[6]. The chemical shifts of the central methylenes appears to be temperature independent (from room temperature to -105° in CS_2 and CF_2Cl_2). Comparison with the behaviour of [7]2,6-dithiametacyclophane[9] leads to the conclusion that length and heterosubstitution in the chain are important factors for shielding effects to be detectable at low temperatures. At -100° however, methylenes α and β to the ring begin to collapse: while the chemical shift of the former do not change appreciably [(I): 7.18 and 7.35τ; (II): 7.35τ] the latter is split into two multiplets [(I): from 8.3τ at 40° to 8.1 and 8.45τ at -100°; (II): from 8.3τ at 40° to 8.25 and 8.6τ at -100°]. In the quasi frozen conformation the axial and equatorial β methylene protons are expected to be magnetically non equivalent : moreover, in this situation they could be differently deshielded by the π electron cloud.

The extension of the syntheses here outlined to several other six-membered 1,3-bridged heterocycles is under investigation.

All new products gave satisfactory analyses.

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REFERENCES

1 - W.E.Parham and J.F.Dooley, J.Org.Chem., 33, 1476 (1968).

2 - H.Nozaki,T.Koyama, and T.Mori, Tetrahedron, 25, 5357 (1969).

3 - S.Bradamante,R.Fusco,A.Marchesini, and G.Pagani, Tetrahedron Letters, 11 (1970).

4 - A.T.Balaban, Tetrahedron Letters, 4643 (1968).

5 - A.T.Blomquist,R.E.Stahl,Y.C.Meinwald, and B.H.Smith, J.Org.Chem., 26, 1687 (1961).

6 - W.E.Parham,D.R.Johnson,C.T.Hyghes,M.K.Meilhan, and J.K.Rinehart, J.Org.Chem., 35, 1048 (1970); W.E.Parham, R.W.Davenport, and J.K.Rinehart, J.Org.Chem., 35,2662 (1970).

7 - H.Minato and T.Nagasaki, J.Chem.Soc.,(C),377 (1966).

8 - R.F.Parcell and F.P.Hauck jun., J.Org.Chem., 28, 3468 (1963).

9 - R.H.Mitchell and V.Boekelheide, J.Heterocyclic Chem., 6, 981 (1969).