Tetrahedron Letters No. 1, pp. 11-14, 1970, Pergamon Press. Printed in Great Britain.

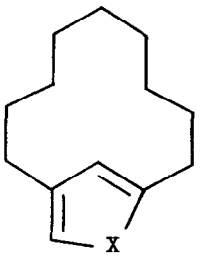
STUDIES IN THE HETEROPHANES FIELD.
[9]HETEROPHANES.

S. Bradamante, R. Fusco*, A. Marchesini, and G. Pagani
Istituto di Chimica Industriale dell'Universita' di Milano

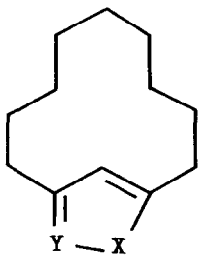
(Received in UK 18 November 1969; accepted for publication 7 December 1969)

Bridged aromatic compounds have received in the last few years a considerable amount of interest.[1] Both length and conformation of the chain are thought to influence deeply the planarity of the ring, affecting its reactivity and its spectroscopic properties; conversely, shielding effects experienced by protons of certain methylene of the chain were expected[2] owing to the ring current of the aromatic cycle.

We report the synthesis of a number of [9]heterophanes, as well as some preliminary results of PMR investigation of their properties.



(Ia) X = O
(Ib) X = S



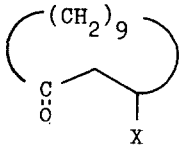
(IIa) X = O Y = N
(IIb) X = NH Y = N
(IIc) = (IIb)HCl

Reaction of acetone cyanohydrin with cyclo-dodecen-2-one [3] in aqueous alcohol and in the presence of sodium carbonate afforded 3-cyano-cyclo-dodecanone [(III)

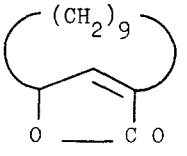
*) To whom enquiries should be addressed

m.p. 73-74°, from pentane; IR (nujol): ν_{CN} at 2210 cm^{-1}, ν_{CO} at 1705 cm^{-1}; PMR: 7τ(3H,broad multiplet, CN-C<u>H</u>-C<u>H</u>$_2$-CO-), 7.56τ(2H,m,-CO-C<u>H</u>$_2$-)]; conversion of the nitrile into the corresponding methyl ester [(IV) b.p.$_{0.05}$ 115-120°, m.p. 60° from Et_2O-pentane] has been accomplished by treatment with hydrogen chloride in methanol; subsequent alkaline hydrolysis in aqueous methanol of (IV) gave the corresponding acid [(V) m.p. 111° from Et_2O-pentane]. The action of acetic anhydride in the presence of a small amount of sodium acetate on the keto-acid (V) gave rise to a neutral reaction product (b.p.$_{0.05}$ 120-125°), which appeared from VPC analysis to be a complex mixture of at least four components: the nature of this mixture is still under investigation, nonetheless sufficient evidence of the presence of the α,β-unsaturated-δ-lactone (VI) was gained to attempt the reduction of the crude material with di-isobutylaluminium hydride, a reagent known [4] to convert α,β-unsaturated-δ-lactones into furans. In fact from this reaction a low-boiling fraction was obtained in <u>ca.</u> 15% yield, which was shown to be the [9]2,4-furanophane [(Ia) b.p.$_{0.05}$ 65-70°; PMR: see Table].

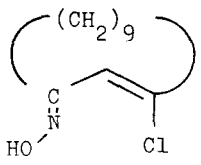
Gentle heating of an intimate mixture of the sodium salt of the keto-acid (V) and P_2S_5 afforded in <u>ca.</u> 10% yield the [9]2,4-thiophenophane [(Ib) b.p.$_{0.03}$ 80-85°; PMR: see Table].



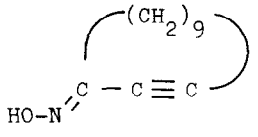
(III) X = CN
(IV) X = $COOCH_3$
(V) X = COOH



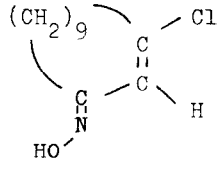
(VI)



(VII)



(VIII)



(IX)

3-Chloro-cyclo-dodecen-2-one[5] underwent cyclisation to the [9]3,5-pyrazolophane [(IIb) b.p.$_{0.05}$ 130-135°, m.p. 107°; IR: ν_{NH} at 3200-3100 cm^{-1}; PMR: see

Table] upon treatment with hydrazine.

The treatment of 3-chloro-cyclo-dodecen-2-one with hydroxylamine hydrochloride in aqueous methanol solution in the presence of sodium acetate did not afford the corresponding isoxazole: instead, a complex mixture of at least three isomeric chloroximes was obtained (b.p.$_{0.05}$ 140-145°). On long standing a pentane solution of the reaction mixture gave a pure isomer of 3-chloro-cyclo-dodecen-2-one oxime [(VII) m.p. 136°, from Et_2O-pentane; IR (nujol): ν_{OH} at 3080-3500 cm^{-1}; PMR: 4τ (1H,s, =CH-), 7.5τ(4H,m)] to which a trans anti configuration was assigned. With sodium ethoxide the compound readily eliminated hydrogen chloride to give the cyclo-dodecyn-2-one oxime [(VIII) m.p. 110°, from Et_2O-pentane; IR (nujol): ν_{OH} at 3140-3500 cm^{-1}, $\nu_{C\equiv C}$ at 2250 cm^{-1}; PMR: 7.55τ(4H,m), 8.52τ(14H,m)]. By treatment of the crude mixture of chlorovinyl oximes (b.p.$_{0.05}$ 140-145°) with sodium ethoxide in ethanol three products were obtained in comparable yields: the [9]3,5-isoxazolophane [(IIa) b.p.$_{0.2}$ 100-105°; PMR: see Table], the 3-chloro-cyclo-dodecen-2-one oxime [(IX) m.p. 122°, from Et_2O-pentane; IR (nujol):ν_{OH} at 3050-3400 cm^{-1}; PMR: 4τ(1H, bs, =CH-), 7.5τ(4H,m)] to which the cis anti configuration was assigned and also the cyclo-dodecyn-2-one oxime (VIII). This latter compound, stable in alkaline media, underwent a quantitative cyclisation to the isoxazolophane (IIa) on treatment with H_2SO_4 in THF. The configuration of chlorovinyl oximes (VII) and (IX) was based on the assumption that ring closure to isoxazole derivatives would require a syn configuration, and on the fact that alkaline media do not alter oxime configuration. Consequently, chlorovinyl oximes (VII) and (IX) must be geo-

T A B L E

PMR data of [9]heterophanes[a)]

Compd.	Aromatic	Methylenes α to the ring	Methylenes β to the ring	Undeshielded methylenes	Shielded methylenes
(Ia)	2.81(5,1H,m) 3.96(3,1H,m)	7.42(2,2H,m) 7.71(4,2H,m)	8.30 (12H,m)	9.08	9.64(2H,m)
(Ib)	3.13(5,1H,m) 3.34(3,1H,m)	7.32(4H,m)	8.43(4H,m)	8.76(6H,m)	9.05(4H,m)
(IIa)	3.97(1H,s)	7.29(4H,m)	8.37(4H,m)	8.78(8H,m)	9.49(2H,m)
(IIb)	3.92(1H,s)	7.28(4H,m)	8.38(4H,m)	8.80(6H,m)	9.22(4H,m)
(IIc)	3.68(1H,s)	7.12(4H,m)	8.27(4H,m)	8.78(6H,m)	9.15(4H,m)

a) τ Values relative to TMS in $CDCl_3$ solution; Temp.=39.8°; values of the multiplets are given as the center of the pattern; underlined figures in brackets refer to the position of the heterocycle to which the peak has been assigned.

metrical isomers at the double bond: the cis configuration was then assigned to the isomer (IX) which is stable in basic conditions.

The definite proof of the structure of the isoxazolophane (IIa) was obtained by catalytic hydrogenation followed by acidic hydrolysis of the intermediate ring opened β-imino-ketone to give the cyclo-dodecan-1,3-dione.[5]

At room temperature several methylene protons of the saturated chain appear to be appreciably shielded (see Table). This diamagnetic effect can be due both to the ring current of the heteroaromatic cycle and to the anisotropy of the heteroatom(s): however no discrimination can be made between the two contributions at the present time. In fact, the constancy of the shielding effect experienced by the shielded methylene protons of [9]pyrazolophane (IIb) and of its hydrochloride (IIc) suggests that such shift is largely independent of the anisotropy of nitrogen atoms and that the diamagnetic shift can be accounted for by ring current effects. Conversely the fact that the largest upfield shift of the shielded methylene protons is observed in the case of oxygen containing heterocycles, which are not the most aromatic substrates in the series here considered, suggests that the anisotropy of the oxygen atom might be important. In any case, at room temperature, certain methylene protons of the chain are found in the shielding zone of the heteroaromatic ring. As their position in the space depends on the conformational equilibrium of the saturated chain, their chemical shift values are found to be temperature dependent. A detailed account on this subject will be reported in due course.

All new compounds gave satisfactory analyses.

ACKNOWLEDGMENTS.- This work was supported by the Consiglio Nazionale delle Ricerche, Rome.

REFERENCES

1 - B.H.Smith, "Bridged Aromatic Compounds", Editor A.T.Blomquist, Academic Press, New York, 1964.

2 - J.A.Pople, W.G.Schneider, and H.J.Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, 1959, p.180.

3 - H.Nozaki, T.Mori, and R.Noyori, Tetrahedron, 22, 1207 (1966).

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

5 - K.Schank and B.Eistert, Chem.Ber., 99, 1414, (1966).