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N.M.R. STUDIES ON NITROGEN-CONTAINING SUGAR DERIVATIVES SUBSTITUTED BY ^{15}N.

PART I.: THE NATURE OF THE CHELATE RING IN SUGAR OSAZONES.

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The modern concept of the structure of sugar osazones was founded in 1944, when Fieser and Fieser (1) proposed on theoretical grounds two alternative chelate structures 1 and 3, these being stabilized by their resonance forms 2 and 4. In 1955 Mester (2) supplied the first chemical evidence in favor of the chelated acyclic structure 1 of sugar osazones and suggested that the six-membered chelate ring containing conjugated double bonds could be regarded as a quasi-aromatic system (2,3,4). Following a recent definition of "quasi-aromatic" character (5), molecules should be called quasi-aromatic if they contain an acyclic, conjugated π-electron system and show chemical properties typical of aromatic compounds. On the basis of energy arguments as well as N.M.R. considerations, Chapman (6) presented arguments in favour of the non-aromatic character of phenylosazones.

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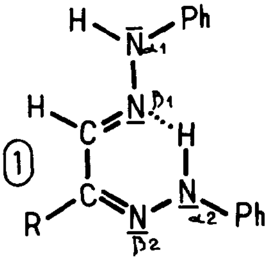

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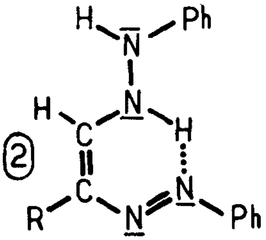

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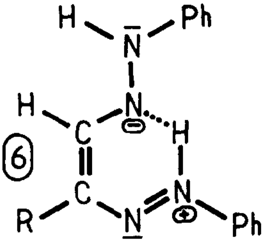

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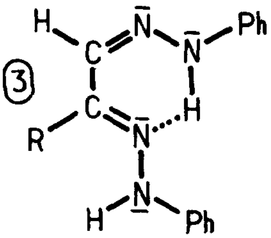

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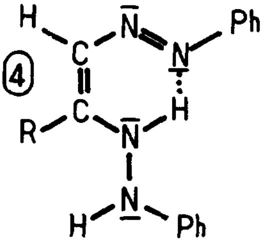

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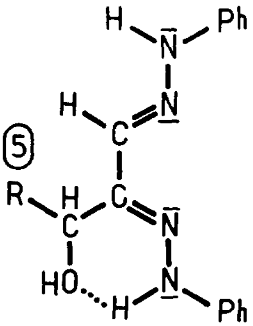

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We cannot agree that the energy difference between the chelated and non-chelated forms of the sugar osazones is very small (6). In all the cases reported for the equilibration of osazones which were examined by N.M.R. sceptroscopy, the final state is the chelated one: if the osazones have an open-chain structure, equilibration leads to the chelated forms e.g. pyruvaldehyde phenylosazone (7), propyl-glyoxal osazone (8), benzyl-glyoxal osazone (9), Where the osazones are present in chelated form, no isomerization has been observed, e.g. phenyl-glyoxal osazone (7,9), i-propyl-glyoxal osazone (8), except in the special case of sugar osazones, where the O-chelated form 5 (7,8) is equilibrated with the original N-chelated form. After equilibration, the amount of the O-chelated form is, however, only a few percent, owing to the greater stability of the N-chelated form and is absent completely if the formation of the O-chelate is hindered, e.g. by acetylation (9). The O-chelated form is only stabilized by solvatation, and after removal of the basic solvent, this form could in no case be isolated(10).

Chapman advanced N.M.R. evidence (6) which seemed to exclude in osazones the presence of an induced ring current as defined by Pople (11) for aromatic systems. He found namely a very small displacement(0.1 ppm) between the methyl resonance of pyruvaldehyde bis-phenylhydrazone in the open and in the N-chelated form. In contrast, we find the C-1 proton in sugar osazones to show after mutarotation an upfield shift of 0.25 ppm for D-xylosazone (9) and D-arabinosazone (7), and of 0.69 ppm for the osazones of D-glucose (8) and L-rhamnose (8). Following the reasoning of Chapman, these data rather favor an "aromatic" structure in sugar osazones.

There are at the present five ways of representing the chelate structure of osazones:

(i) as a classical bis-phenylhydrazone structure with hydrogen bond as proposed by Chapman, (ii) as a rapid tautomeric equilibrium between forms 1 and 2 with significant participation of both forms, as observed for N-substituted keto-amines (12) and also for sugar formazans (9), (iii) as a structure characterized by the resonance hybrids 1 and 2, as considered by Fieser and Fieser, (iv) as an acyclic, conjugated π-electron system with increased stability, defined as "quasi-aromatic", (v) as a "non-classical aromatic" system, stabilized by π-electron interaction through the hydrogen bond (13); such a π-electron interaction may exist in addition to the possible σ-resonance of the hydrogen bond (14).

To decide between these five possibilities, the N.M.R. spectra of sugar osazones substituted by ^{15}N, first in the α_1 and α_2 positions and then in the β_1 and β_2 positions, were prepared. The N.M.R. spectrum (dioxan, TMS, 60 MHz) of D-xylosazone substituted with two ^{15}N atoms at positions α_1 and α_2 (99 % enrichment) gives two doublets for the N-H signals (fig.I: 1,3): the chelated N-H (position α_2) 12.20 ppm, J = 94.5 Hz and the free N-H (position α_1), 9.21 ppm and J = 93 Hz.

The observed equal values for the chelated and the non-chelated N-H coupling indicates that the two N-H bonds are of the same nature and the participation of a significant σ-resonance (15) between the two forms 1 and 2, as proposed by Fieser and Fieser (possibility iii), seems excluded. A rapid internal equilibrium between 1 and 2 with significant participation of both forms (possibility ii), can be excluded by the observation that $J_{^{15}N-H}$ has a value of 94 Hz. A rapid tautomerism would imply an average of the coupling constants (12,15, 9), according to the relation $J_{obs} = J_1p_1 + J_2p_2$ (J_1 and J_2 are the ^{15}N-H and ^{14}N-H couplings respectively, and p_1 and p_2 are the percentages of forms 1 and 2) : the coupling constant would be less than 93 Hz, which is not the case. The value of a ^{15}N-H coupling constant can be related to the hybridization of the nitrogen atom; a range of values between 89 and 93 Hz appears characteristic of compounds where the lone pair of nitrogen is conjugated with a π-electron system (15). The values found in the case of sugar osazones fall in the range of the sp^2 hybridization for the nitrogen atom, which supports possibility (iv).[*]

No change was observed for the non-chelated N-H proton signal of D-xylosazone substituted by ^{15}N in position β_1 and β_2 (enrichment 95%) in dioxan or pyridine (TMS; 60 MHz) (fig. I: 4). In contrast, the chelated N-H peak appeared as quadruplet, $J \sim 5.0$ and $J \sim 2.0$ Hz, resulting from the coupling with both of the ^{15}N atoms. This observation is incompatible with a classical hydrogen-bonded bis-phenylhydrazone structure (possibility i). The coupling between the ^{15}N atom in position β_1 and the chelated hydrogen could represent an interaction between both nuclei through the hydrogen bond, as involved in the "non-classical aromatic" system (possibility v). The small coupling could also reflect the presence of a strongly conjugated structure with participation of resonance forms such as 1 and 6 (possibility iv).

Similar results were obtained with D-galactosazone substituted by ^{15}N at the same positions.

Even if the reported N.M.R. evidence supports possibilities (iv) or (v) to the same extent, and at the present stage it is difficult to give a more accurate picture of the chelated ring, the use of the concept of "quasi-aromaticity" in respect of sugar osazones is justified, and is necessary for a correct interpretation of their structure.

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[*] Our ^{15}N experiment furnished additional support for the O-chelated structure 5 of sugar osazones in mutarotation (8), showing that in a 24 hours old dioxan solution of D-xylosazone (fig. I: 2,3) the two new N-H signals are still linked to the ^{15}N atoms.

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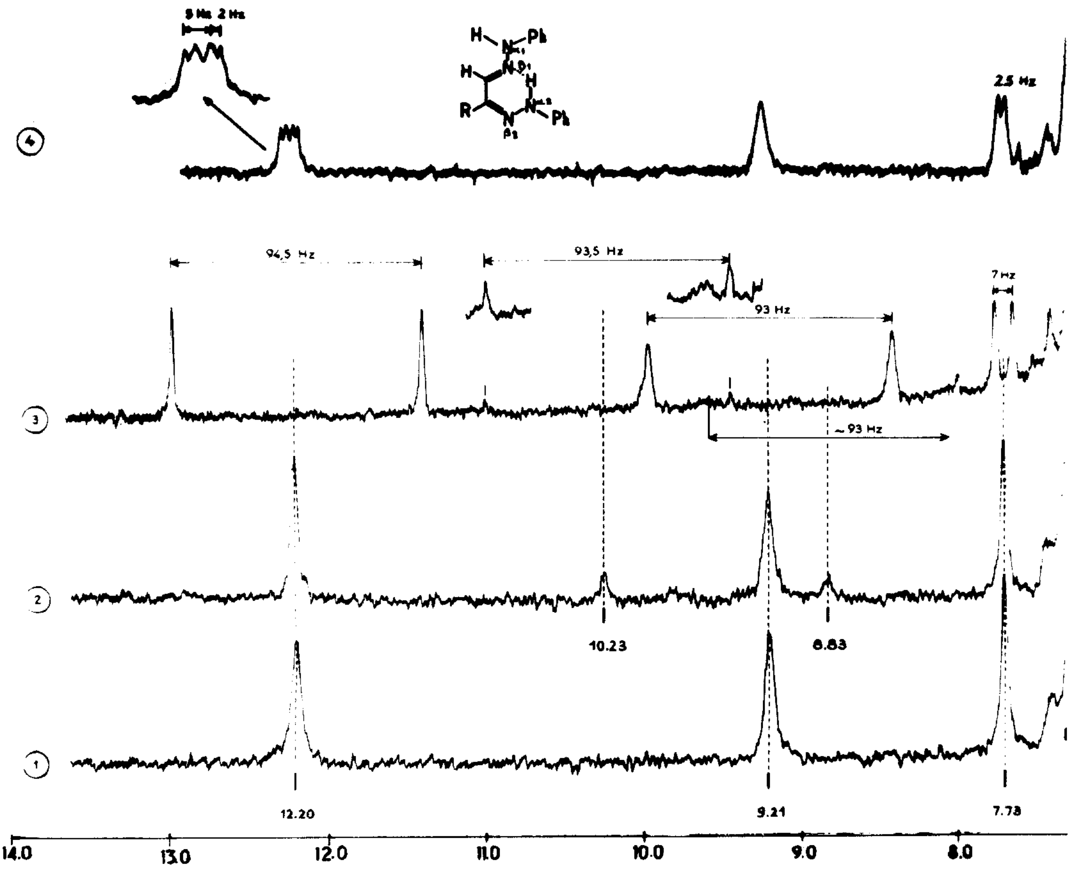

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