CHEMISTRY OF PHENYL OSAZONES AND A STUDY OF CHELATION

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PHENYL HYDRAZINE was discovered by Emil Fischer in 1875. Though its reaction with a few carbonyl compounds like acetaldehyde, benzaldehyde and furfural were first noted, its general utility for giving sparingly soluble and beautifully crystalline derivatives of carbonyl compounds in general and the reducing sugars in particular came eight years later. Reaction with reducing sugars proceeded in an unexpected manner, since Fischer[1,2] found that 3 equivalents of the reagent were consumed. The crystalline products which he called *osazones* can be identified both from their temperature of decomposition and from their crystalline structures. Hence Fischer made an extensive application of these derivatives for the characterisation, isolation and study of the configuration of sugars which though crystalline singly show tendency to remain as syrup in mixtures. However, both the structure and the mechanism of the formation of osazones, explained to some extent by Fischer 80 years ago, have been clarified only recently.

Fischer[1,2] suggested the open chain structure (Chart I) for the phenyl osazone of glucose and it was accepted for a long time because it satisfactorily explained how D-glucose, D-mannose and D-fructose gave the same osazone. But a number of facts remained unexplained on the basis of this structure. For example, it was not clear why the reaction stops at the second carbon atom and does not continue further. Fieser and Fieser,[3] on purely theoretical grounds, first suggested two alternate chelate structures (II) and (IV) for sugar phenyl osazones, these being stabilised by resonance with the canonical forms (III) and (V) respectively. Since then, these structures have been supported by physical as well as chemical methods. Very recently, n.m.r. spectral studies have further distinguished among the various chelate structures and favoured the structures II and III.[4,5] Considering the behaviour of the sugar osazones and their u.v., i.r., and n.m.r. spectra, it seems probable that the structures (II) and (III) are the limiting forms of a quasiaromatic structure (VI). This is supported by the results of X-ray analysis,[6] which show that the 6-membered chelate ring is approximately planar and that its bond angles are about 120°. This formulation satisfactorily explains all the following characteristic properties of the phenyl osazones. (1) Reaction with phenyl hydrazine stops at the C_2 atom but that with N-methyl phenyl hydrazine continues further and all the carbon atoms in the sugar are affected giving
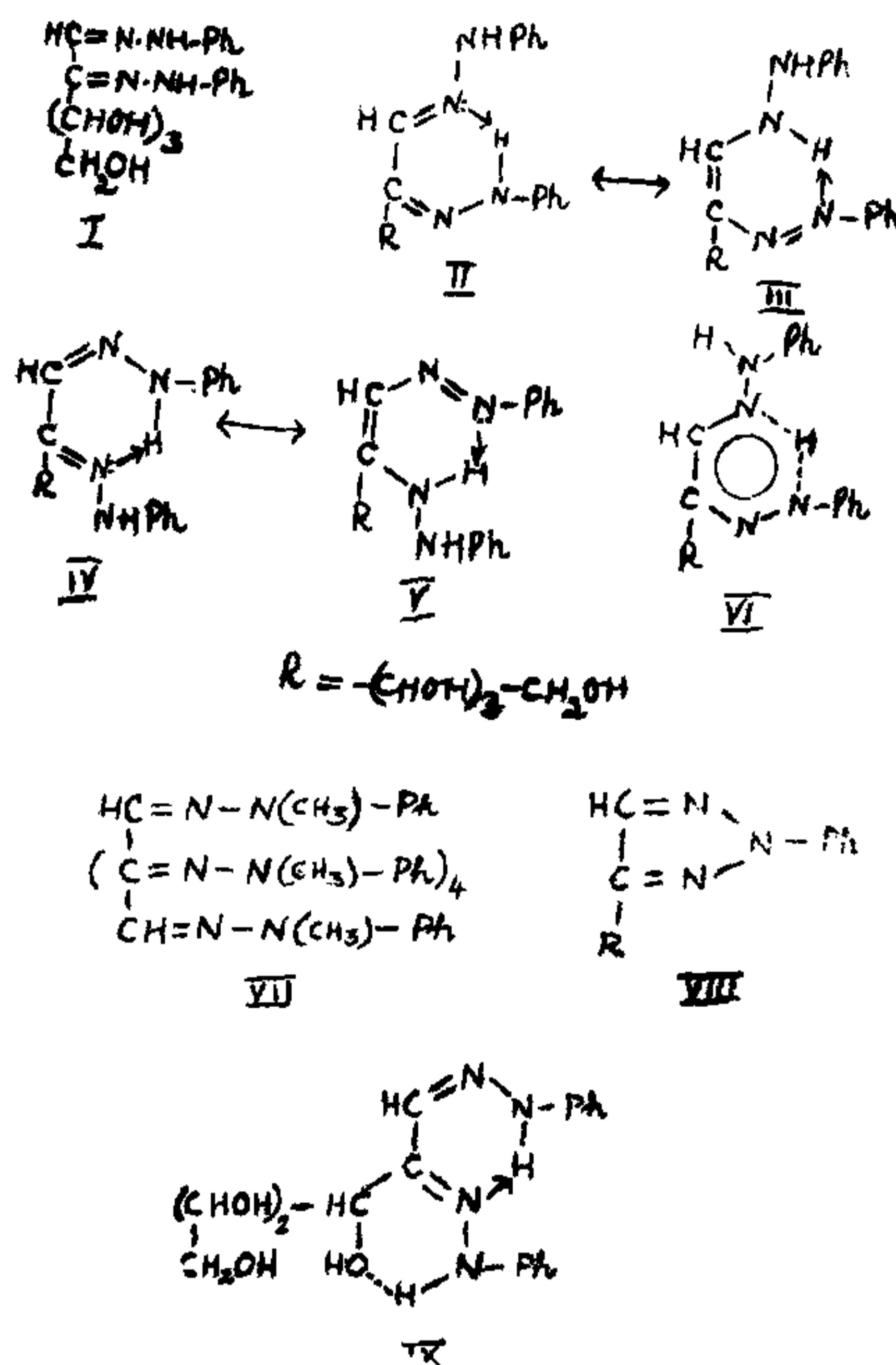

CHART I

alkazones (VII)[7] in which no chelation is possible. (2) The two phenyl hydrazone residues differ in their behaviour towards methylation, reduction, *trans* osazonisation, formation of osone hydrazone and osotriazole (VIII). (3) Phenyl osazones are formed not only by reducing sugars but also by other α-hydroxy carbonyl compounds. For example benzoin and fisetol form phenyl osazones. (4) Phenyl osazones of sugars differ from those of non-sugars like benzoin and glyoxal. There is no convincing explanation so far for the difference. But there is no doubt that it is due to the presence of a 3-hydroxy group in sugar osazones. From the u.v. data on model

compounds. Henseke and Binte[8] inferred the presence of an additional C–O....H–N bond in sugar osazones and preferred formulæ (IV & V) which are capable of showing additional chelation as in (IX). But this does not agree with the conclusions of n.m.r. data. Obviously, there is a need for a closer study of this problem.

The mechanism of osazone formation from α-hydroxy carbonyl compounds has been difficult to understand. It apparently involves oxidation of an α-ketol system. Further it uses three moles of phenyl hydrazine and gives aniline and ammonia as the other products. The first stage is definitely the formation of phenyl hydrazone (Chart II, X) from one mole each of the phenyl hydrazone and the α-hydroxycarbonyl compound.[9,10] The further conversion into phenyl osazone has been pictured in a number of ways. According to Fischer[2,9] the second molecule of phenyl hydrazine produced dehydrogenation to α-keto phenyl hydrazone (XI) itself decomposing into aniline and ammonia, and then the third molecule of the reagent condensed to give the osazone. Thus it visualised the intermolecular oxidation brought about by phenyl hydrazine which is ordinarily a reducing agent. In 1940, Weygand[11] proposed two other mechanisms (Scheme A and Scheme B) involving intramolecular oxidation and reduction and thus eliminated the above objectionable feature. According to Scheme A, the phenyl hydrazone (X) tautomerises to enamine (XII) which tends to undergo rupture of the N–N bond because of the stability of the resulting conjugated keto imine (XIII). The ketoimine subsequently takes up two molecules of phenyl hydrazine to give the phenyl osazone (I). In Scheme B, the phenyl hydrazone (X) suffers internal dehydrogenation and hydrogenation.
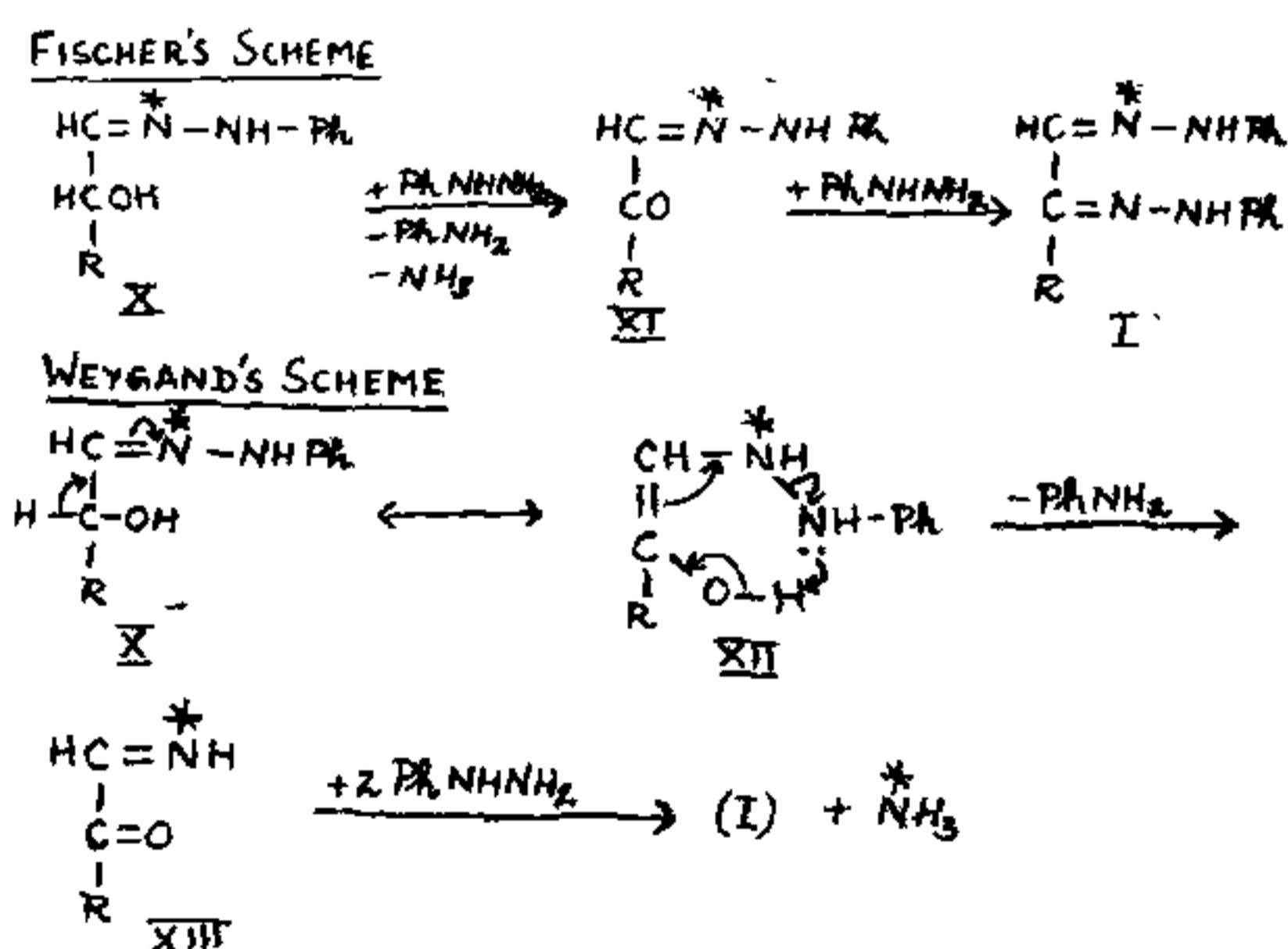
CHART II

In recent years, Weygand et al.[12-15] have studied this reaction with the aid of deuterium

and tritium labels and concluded that both the mechanisms proceed simultaneously. But his experiments were not free from exchange reactions. More recently, Shemyakin et al.,[16] have convincingly proved by using ^{15}N labels and avoiding exchange reactions that only mechanism A operates. Thus when p-nitrophenyl hydrazones of benzoin, cyclohexanolone and D-fructose having ^{15}N bound to C_1 were converted into osazones with ordinary phenyl hydrazine, most of the ^{15}N appeared in ammonia. This is possible only in Scheme A; in Fischer's scheme, ammonia should not be radioactive at all whereas according to Weygand's Scheme B, it should be only 50%. Further, the intermediate ketimine, expected for Scheme A, has been isolated in the case of cyclohexanolone p-nitrophenyl hydrazone (XIV) in the form of the N-acyl derivative (XV) and it gives the osazone in a high yield with excess of p-nitrophenyl hydrazine in dilute acidic solution.
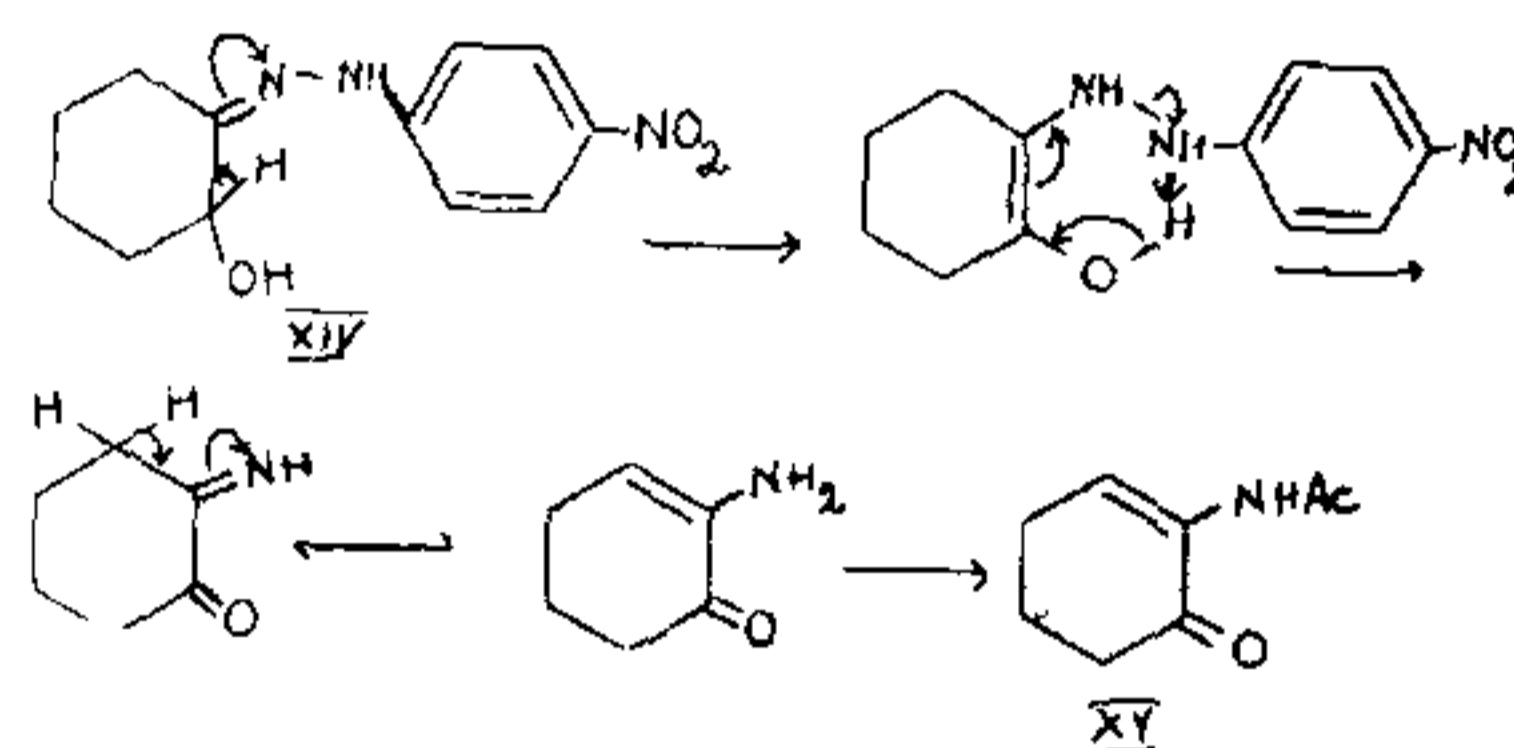
CHART III

A rather complex mechanism was suggested by Micheel and Dijong[17,18] who claimed to have proved with the aid of ^{14}C phenyl hydrazine that oxido-reduction is not an intramolecular reaction. According to them the reaction is initiated by the decomposition of a little amount of phenyl hydrazine into aniline, ammonia, benzene and nitrogen; but convincing data are lacking. Further, Shemyakin et al.[16] noted no decomposition in their carefully planned experiments. Hence the most acceptable mechanism is provided by Weygand's Scheme A.

ω-Hydroxyacetophenones possessing an α-ketol system also form phenyl osazones just like reducing sugars and benzoin. The first case studied was ω, 4-trihydroxyacetophenone by Leon et al.[19] and a later one was ω-2, 4-trihydroxyacetophenone by Charlesworth et al.[20] More recently this property has been used by us[21] in distinguishing between flavones and flavonols (see Chart IV). The ketone resulting from the fission of the fully methylated flavone (a) or flavonol (d) is demethylated with hydrobromic acid. In the case of flavonol, ω-hydroxyacetophenone (e) would result which yields phenyl osazone (f)

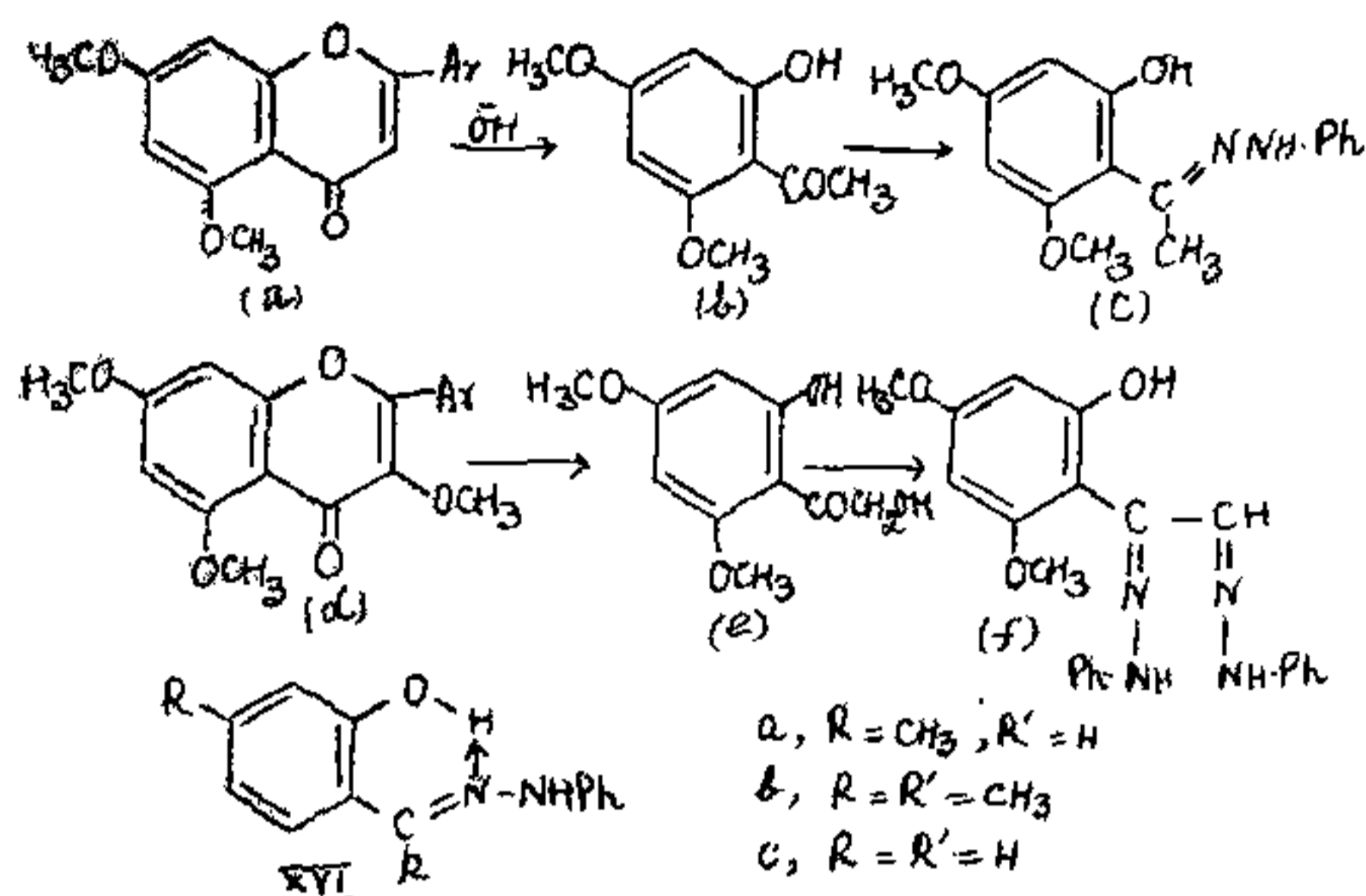but flavone (a) yields acetophenone (b) which forms phenyl hydrazone (c) only.
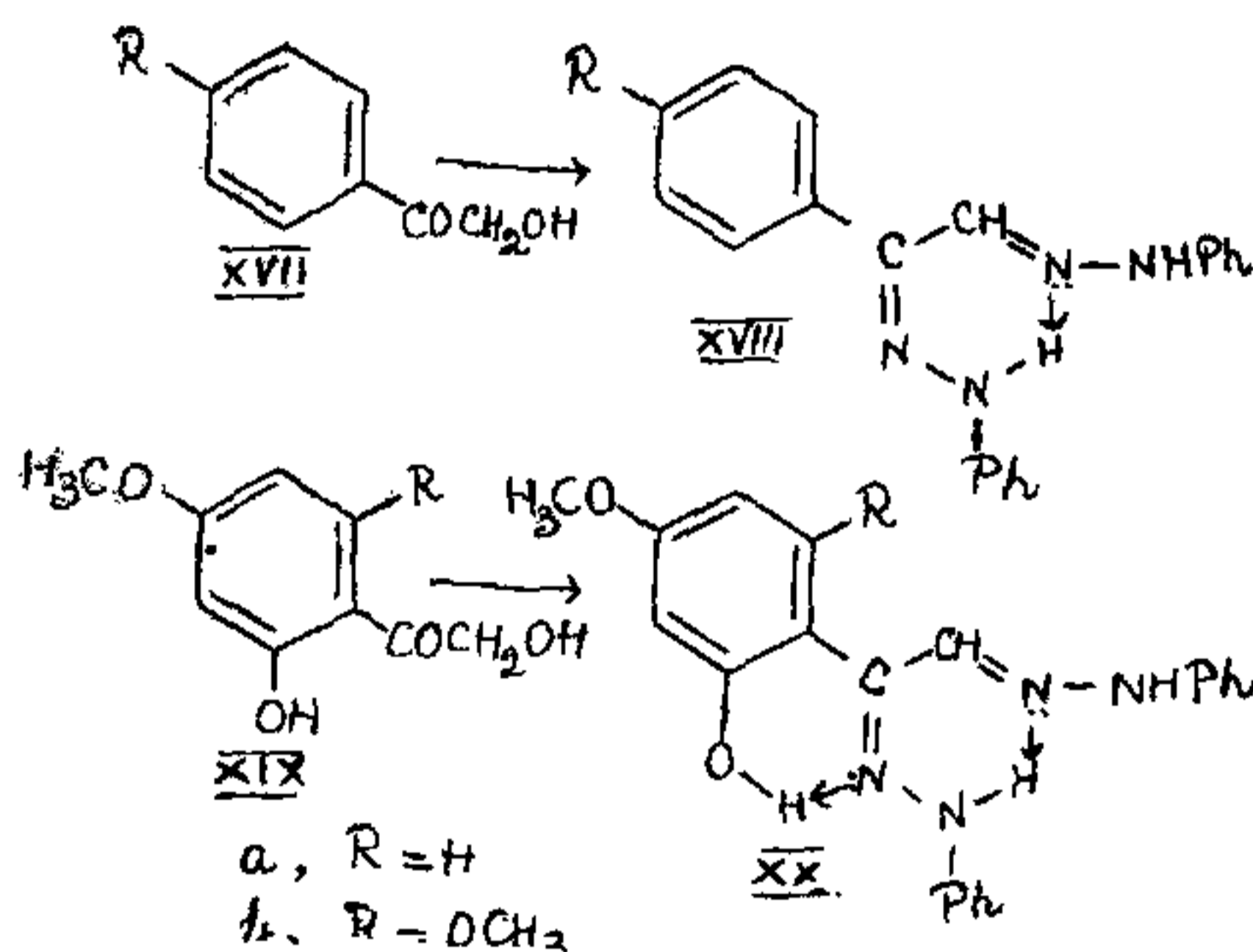

CHART IV

CHART V

Phenyl osazones of ω-hydroxyacetophenones are interesting from another point of view. When o-hydroxy group is present, it could further stabilise the quasiaromatic osazone ring by additional chelation (see Chart V, XX). Before studying this, the possible chelation in phenylhydrazones of o-hydroxycarbonyl compounds was investigated.

The u.v. spectra of the phenylhydrazones of several o-hydroxy and o-methoxy carbonyl compounds have been studied and they are given in Table I. The u.v. spectrum of the phenyl

TABLE I

U.V. absorption data on phenyl hydrazones

Carbonyl compound	$\lambda_{max.1}$ mμ (log ϵ)	$\lambda_{max.2}$ mμ (log ϵ)
o-Methoxyacetophenone*	285 (3·90)	..
Salicylaldehyde (XVI)*	298 (4·28)	340 (3·98)
o-Hydroxyacetophenone (XVI a)*	296 (4·30)	335 (4·14)
Peonol (XVI b)†	305 (4·19)	335 (4·42)

* Spectra taken in $CHCl_3$ solution;

† Spectrum taken in CCl_4 solution.

hydrazone of o-methoxyacetophenone[22] in which chelation is not possible shows only one band but those of o-hydroxy compounds, *viz.*, o-hydroxy acetophenone,[23] salicylaldehyde[24] and peonol[25] show an additional band at higher wavelength. This suggests the possible chelation in the phenyl hydrazones of o-hydroxy carbonyl compounds (see formula XIX) and it is further supported by the greater stability of the hydroxy compounds in comparison with the methyl ethers. Thus the phenyl hydrazone of o-methoxy acetophenone decomposed completely in 2 days,[26] and that of 2, 4-dimethoxyacetophenone is difficult to isolate.[25] A recent application of the presence of chelation in the phenyl hydrazone of o-hydroxy acetophenone is in the estimation of palladium.[27]

Next the phenyl osazones of four ω-hydroxyacetophenones, *viz.*, simple one (XVII a), 4-methoxy-(XVII b), 2-hydroxy-4-methoxy-(XIX a), and 2-hydroxy-4, 6-dimethoxy-(XIX b) have been studied. They are crystalline solids and are useful for characterisation of ketones. They are all stable; even osazones (XVIII a) and (XVIII b) which lack o-hydroxyl are stable as compared with the phenyl hydrazones because of the quasiaromatic osazone ring.

The u.v. spectra of the phenyl osazones in carbon tetrachloride solution are mentioned in Table II. Compounds (XVIII a and b) which

TABLE II

U.V. spectra of phenyl osazones of ω-hydroxyacetophenones in CCl_4 solution

Compound	$\lambda_{max.1}$ mμ (log ϵ)	$\lambda_{max.2}$ mμ (log ϵ)	$\lambda_{max.3}$ mμ (log ϵ)
XVIII a	285–302 (4·41)	..	407–412 (4·38)
XVIII b	283 (4·16)	..	412–417 (4·03)
XX a	284 (4·04)	340 (3·95)	417–427 (3·90)
XX b	273 (4·34)	346 (4·25)	410–427 (4·40)

have no *ortho* hydroxy group show two bands of which the lower one could be attributed to the aromatic rings and the higher to the osazone chelate ring. Both these bands are retained in the other phenyl osazones (XX a and b) which possess the *ortho* hydroxyl group. But, in addition, there is a third band near 340 mμ which could be considered due to the additional chelate ring arising from o-hydroxyl of the benzene nucleus as shown in formula XX. That this additional chelation stabilises the osazone ring is supported by the bathochromic shift of the longest wavelength band in the spectra of (XX a and b) as compared to those of (XVIII a and b).

It may be emphasised here that osazones of o-hydroxy compounds have resemblance to sugar osazones which also exhibit three absorption bands though at comparatively lower wavelengths.[8] This would support the presence of the extra chelation involving the hydroxyl in both cases.

PREPARATION OF PHENYL HYDRAZONES

Phenyl hydrazones were prepared by adding phenyl hydrazine hydrochloride (0·5 g.) and sodium acetate (0·8 g.) in water (5 ml.) to a solution of the carbonyl compound (0·4 g.) in a little alcohol and warming the resulting solution at 80–85° for 10 minutes. The solids were collected and crystallised from ethanol.

Phenyl hydrazones of o-methoxyacetophenone,[22] o-hydroxyacetophenone,[23] salicylaldehyde[24] and peonol[25] agreed with the earlier recordings in literature.

PREPARATION OF PHENYL OSAZONES

(i) *From* ω-*hydroxy-4-methoxyacetophenone* (*XVII* b).—The ketone[28] (XXI, 500 mg.) was dissolved in warm 70% acetic acid (2·5 ml.) and added to a solution of freshly distilled phenyl hydrazine (1·30 g.) in 70% acetic acid (0·3 ml.). The mixture was heated at 80–85° for 30 minutes when a yellow crystalline mass separated. It was cooled, filtered and the solid washed first with a few drops of 70% acetic acid followed by a few drops of methanol. The osazone (450 mg.) crystallised from ethyl acetate as orange yellow needles, m.p. 196° d (Found: N, 16·3. $C_{21}H_{20}N_4O$ requires N, 16·4%).

(ii) *From* ω-*hydroxyacetophenone* (*XVII* a).— The osazone was obtained as yellow needles, m.p. 152° (lit.,[29] 152°).

(iii) *From* ω-*2-dihydroxy-4-methoxy acetophenone* (*XIX* a).—The ketone[30] (100 mg.) was reacted with phenyl hydrazine (0·260 g.) in the same way as above. The osazone crystallised from ethyl acetate as yellow needles, m.p. 220° (Found: C, 69·5; H, 5·6%; $C_{21}H_{20}N_4O_2$ requires C, 70·0; H, 5·6%).

(iv) *From* ω-*2-dihydroxy-4, 6-dimethoxy acetophenone* (*XIX* b).—The ketone[30] (300 mg.) was dissolved in acetic acid (3 ml.) and diluted

with water (0·5 ml.). This solution was mixed with phenyl hydrazine (0·9 g.) in 70% acetic acid solution (1·5 ml.) and the mixture heated for 1 hour at 90–95°. After cooling, the product was filtered, dried and crystallised from ethyl acetate when the osazone separated as yellow needles, m.p., 222–23° (Found: C, 67·2, H, 5·5; $C_{22}H_{22}N_4O_3$ requires C. 67·7; H, 5·6%).

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