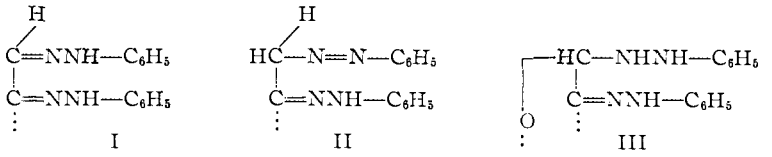
[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, TECHNICAL UNIVERSITY, BUDAPEST]

A New Interpretation of the Mutarotation of Sugar Osazones

BY LÁSZLÓ MESTER AND ADAM MAJOR

RECEIVED AUGUST 6, 1956

Mutarotation of a sugar osazone was first observed by Levene and Jacobs,[1] but they did not attempt to explain the phenomenon. Zerner and Waltuch[2] suggested that it should be ascribed to the tautomeric change of the bishydrazone form I into the azohydrazone form II. Haworth[3] favored the production of an equilibrium with the cyclic form III.



Discarding all earlier views, Engel,[4] in studying glucosazone, endeavored to show that mutarotation is due to hydrolysis, with phenylhydrazine splitting off.

Since evidence has lately been provided for the acyclic structure of sugar osazones[5,6,7] and since the previously postulated presence of a chelate ring (Fig. 1) has been confirmed,[5,6] it now appears necessary to revise current interpretations concerning their mutarotation.

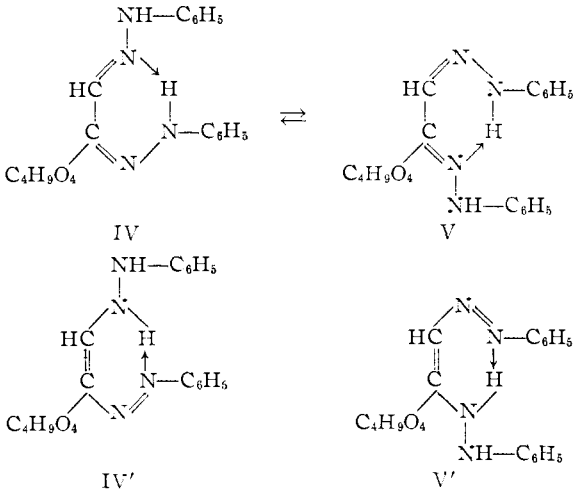


Fig. 1.

Experimental

Mutarotation of D-glucose phenylosazone[9] and D-glucose-1-methylphenyl-2-phenylosazone[10] was measured (c = 0.5) in a 1:1 mixture of pyridine and ethanol at 20 ± 2°; for D-glucose phenylosazone: $[\alpha]^{20}D$ −67.3° (10 min.), −45.5° (1 hr., 10 min.), −27.7° (5 hr., 10 min.), −23.8° (8 hr.), −23.8° (11 hr., 15 min.), −23.8° (24 hr.); for D-glucose-1-methylphenyl-2-phenylosazone: $[\alpha]^{20}D$ −52.2° (10 min.), −42.1° (1 hr., 15 min.), −36.1° (2 hr.), −26.1° (5 hr., 40 min.), −24.1° (7 hr., 10 min.), −20.1° (24 hr., 5 min.). The solutions were evaporated to dryness, and mutarotation was repeated with the substances recovered without purifying them; the same mutarotations were observed.

Ultraviolet spectra were determined with a Beckman DU-type spectrophotometer in samples taken from time to time from the above solutions and diluted with ethanol to 0.0001 mole (Fig. 2 for D-glucose phenylosazone).

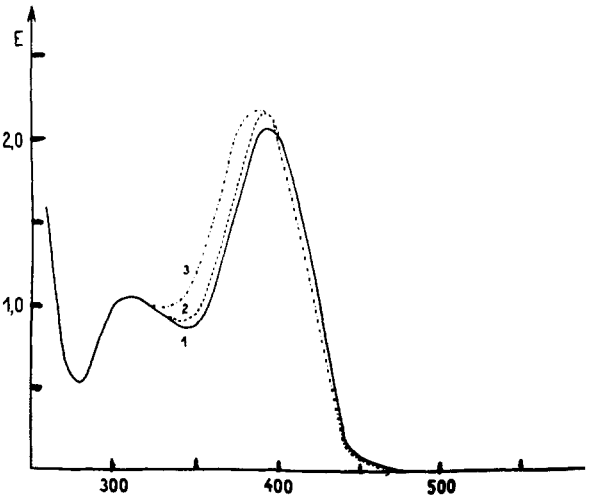


Fig. 2.—Ultraviolet spectrum of D-glucosazone: 1, immediately; 2, 1 hour; 3, 24 hours after solution.

Practically the same values and the same changes were observed for D-glucose-1-methylphenyl 2-phenylosazone.

The same results were obtained with recovered materials.

Formazan Reaction During Mutarotation.—From D-glucose phenylosazone a 0.1-mole stock solution was prepared in a 1:1 mixture of pyridine and ethanol. From this 50-ml. samples (1.8 g. of osazone) were taken at times and on adding 50 ml. of 2 N alcoholic potassium hydroxide were coupled to formazan with diazo solution prepared from 0.75 g. of aniline.[5] The crude formazans obtained were twice recrystallized from a mixture of four times the volume of pyridine and ten times the volume of ethanol; m.p. 198°.

Simultaneously, samples taken from the stock solution were diluted with a 1:1 mixture of pyridine and ethanol (c = 0.5), and the rotational changes observed. On completion of the mutarotation the stock solution was evaporated to dryness *in vacuo* and the above experiment repeated with the substances obtained without purifying them (Fig. 3).

Mutarotation of tetra-O-acetyl-D-galactose phenylosazone[11] was measured in dioxane (c = 0.5): $[\alpha]^{20}D$ +56° (10 min.), +60° (1 hr., 35 min.), +80° (38 hr., 40 min.). The solution on concentration to dryness, yielded the osazone unchanged; dissolving the recovered material in dioxane gave the same rotational values.

(1) P. A. Levene and W. A. Jacobs, *Ber.*, **42**, 3249 (1909).

(2) E. Zerner and R. Waltuch, *Monatsh.*, **35**, 1025 (1914).

(3) W. N. Haworth, "The Constitution of Sugars," Edward Arnold & Co., London, 1929, p. 7.

(4) L. L. Engel, THIS JOURNAL, **57**, 2419 (1935).

(5) L. Mester, *ibid.*, **77**, 4301 (1955).

(6) L. Mester and A. Major, *ibid.*, **77**, 4305 (1955).

(7) In the meantime V. C. Barry and co-workers[8] have proved that in dilute solution the osazones are present in the acyclic form only.

(8) V. C. Barry, J. E. McCormick and P. W. D. Mitchell, *J. Chem. Soc.*, 222 (1955).

(9) E. Fischer, *Ber.*, **17**, 579 (1884); **20**, 821 (1887).

(10) S. Akija and S. Tejima, *J. Pharm. Soc. Japan*, **72**, 1574 (1952); *C. A.*, **47**, 9275 (1953).

(11) M. L. Wolfrom, M. Königsberg and S. Soltzberg, THIS JOURNAL, **58**, 490 (1936).

The ultraviolet spectra were determined in samples taken from time to time from the mutarotational solution and diluted with dioxane to 0.0001 mole. They showed the same changes for both the original and the recovered material, and these changes were identical with those for D-glucose phenylosazone.

4-Desoxy-L-glycerotetrose phenylosazone dissolved in pyridine was subjected to mutarotation and evaporated to dryness; the osazone recovered was again dissolved in pyridine, and once more the mutarotation as described by Fried, *et al.*,[12] was observed.

Result and Discussion

Since mutarotation, spectral displacement and formazan formation after distillation of the solvent in the redissolved substance are reiterating processes, Engel's[4] view that mutarotation depends on the hydrolysis of osazones seems to be excluded.

The reaction of the glucosazone with the diazo solution in samples taken from the mutarotating solution yields less and less osazone formazan (Fig. 2). This is due obviously to the same structural change which is optically perceivable during mutarotation. Since Haworth's cyclic formula III is unable to yield formazan, the transformation of the two anomers into each other cannot possibly be regarded as the cause of mutarotation. It now remains to be ascertained whether the open-chain compound I changes into Haworth's cyclic form III during mutarotation. Were it so, owing to the disappearance of one chromophoric group, the maximum of the ultraviolet spectrum would have to show a substantial alteration of the characteristics.[8]

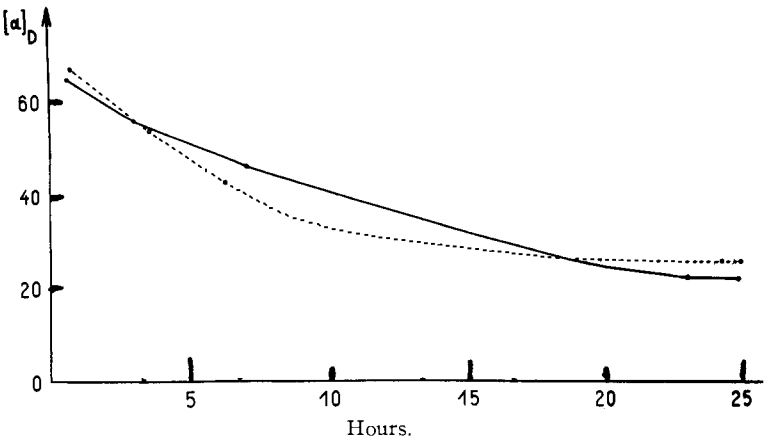


Fig. 3.—Repeated mutarotation of D-glucosazone in a mixture of pyridine and alcohol.

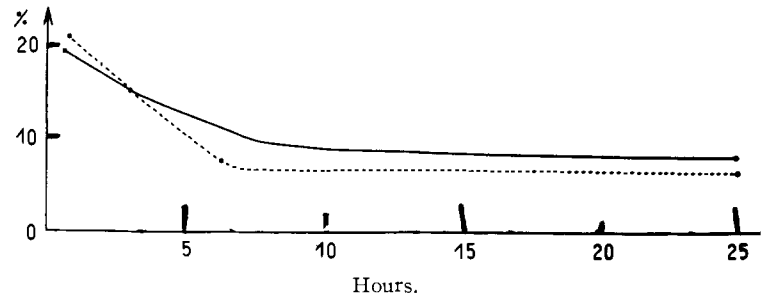


Fig. 4.—Yields of D-glucosazone formazan (twice recrystd).

The observations of Weygand, *et al.*,[13] on the mutarotation of 5,6-di-O-methyl-D-glucose *p*-bromophenylosazone, and those of Gorin, *et al.*,[14] on the mutarotation of L-*glycero*tetrulose phenylosazone and its derivatives, leave no room for a concept which holds that mutarotation might be caused by cyclization departing from the second carbon.

Finally, the mutarotation in tetra-O-acetyl-D-glucose phenylosazone,[11] in tetra-O-acetyl-D-galactose phenylosazone and in 4-desoxy-L-glycero-D-tetrose phenylosazone,[12] can in no way be explained by cyclization, since in these cases there is definitely no possibility for ring formation to take place.[15]

It also seems impossible that a stable conjugated system I of double bonds should change into an unstable compound II of isolated double bonds, as has been suggested by Zerner and Waltuch.[2] Nevertheless, on the evidence of our findings above it would appear that the real cause of the mutarotation is to be sought in the electron displacement which takes place in the chelate structure of the osazones upon the action of the solvent,[17-19] and which amongst others reveals itself in a displacement of the ultraviolet spectra and in a decrease of the coupling capacity.

The two latter observations suggest the conclusion that in the course of mutarotation there is a structural shift from somewhere near the IV state toward the IV′ state, since while the former is suitable, the latter is definitely unsuited for coupling and for the change in the ultraviolet spectra, the above structural shift seem to be responsible.[24,26]

(12) J. Fried, S. E. Walz and O. Wintersteiner, THIS JOURNAL, **68**, 2746 (1946).

(13) F. Weygand, H. Grisebach, K. Kirchner and M. Haselhorst, *Ber.*, **88**, 487 (1955).

(14) P. A. J. Gorin, L. Hough and J. K. N. Jones, *J. Chem. Soc.*, 2699 (1955).

(15) Some objections expressed by E. E. Percival and E. G. V. Percival[16] to the acyclic structure of the osazone acetates proposed by M. L. Wolfrom, *et al.*,[11] are contradictory to our findings concerning the structure of tetra-O-acetyl-D-glucose phenylosazone formazan.[5]

(16) E. E. Percival and E. G. V. Percival, *J. Chem. Soc.*, 1320 (1937).

(17) Reference is made to Burawoy, *et al.*,[18] concerning 1-phenylazo-2-naphthol and 1,2-naphthoquinon-2-phenylhydrazone, the chelate structure of which can be influenced by the solvent.

(18) A. Burawoy, A. G. Salem and A. R. Thompson, *J. Chem. Soc.*, 4793 (1952).

(19) There are several references in the literature pointing out that an α,β-unsaturated azo-structure forms in the *p*-nitrophenylhydrazones of unsaturated ketones[20-22] and that the rearrangement of hydrazone of the compound of azo-structure takes place upon the action of a solvent, finally that this is a somewhat slow process causing changes in the optical rotation.[23]

(20) F. Ramirez and A. F. Kirby, THIS JOURNAL, **75**, 6026 (1953).

(21) J. van Alphen, *Rec. trav. chim.*, **64**, 305 (1945).

(22) R. J. W. Le Fèvre, M. F. O'Dwyer and R. L. Werner, *Chemistry & Industry*, 378 (1953).

(23) W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5812 (1952).

(24) As regards D-glucose 1-methylphenyl-2-phenylosazone, of the chelate structures proposed by Fieser and Fieser[25] the V and V′ structures must be discarded because of the presence of the methyl group, and only the IV and IV′ structures can be taken into consideration. In our view, the extraordinary resemblance of the mutarotation, the ultraviolet spectrum and the polarographic behavior of glucosazone

Experiments to disclose the mechanism of this structural displacement are in progress.

to those of glucose-1-methylphenyl-2-phenylosazone justifies discarding the V and V′ formulas of glucosazone as well. All the more so, as the methylation of glucosazone, as has already been pointed out,[5] invariably leads to D-glucose-1-methylphenyl 2-phenylosazone derivable from the IV and IV′ forms, and so, so far, it has proved impossible to prepare methylated D-glucosazone from the chelate structures V and V′ neither by direct methylation nor in some roundabout way. The so-called mixed osazone B, which could be supposed to possess this structure, has been proved to be D-glucosazone contaminated with mixed osazone A.[5]

Acknowledgment.—We wish to express our indebtedness to Professor G. Zemplén for valuable advice given and to thank Dr. W. Cieleszky for the determination of the ultraviolet spectra, finally, Miss Ilona Batta for the microanalyses.

(25) L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1944, p. 351.

(26) F. Ramirez and R. J. Bellet, THIS JOURNAL, **76**, 491 (1954).

BUDAPEST, HUNGARY

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

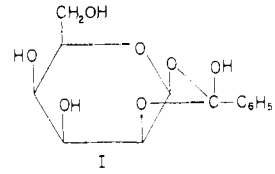
1-*O*-Benzoyl-α-D-talopyranose

BY HARRY B. WOOD, JR., AND HEWITT G. FLETCHER, JR.

RECEIVED JANUARY 26, 1957

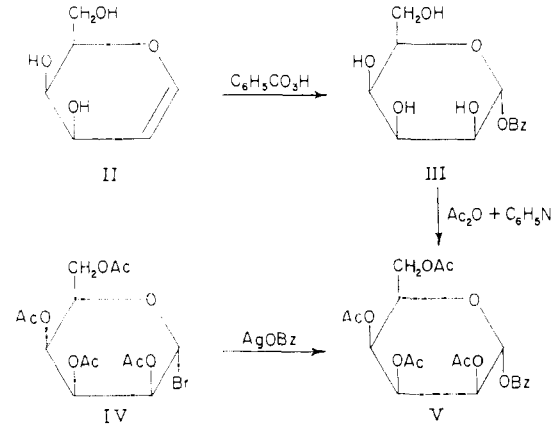
Oxidation of D-galactal with perbenzoic acid has given a new D-talose monobenzoate. Acetylation of this ester afforded an amorphous ester which is identical with 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose synthesized from 2,3,4,6-tetra-*O*-acetyl-α-D-talopyranosyl bromide. The new substance is, therefore, 1-*O*-benzoyl-α-D-talopyranose. The possible structure of another D-talose monobenzoate, described earlier in the literature, is discussed.

In 1937, Pigman and Isbell[1] described a mono-*O*-benzoyl-D-talose which they had obtained as a by-product in the preparation of D-talose *via* the oxidation of D-galactal (II) with perbenzoic acid. Owing to the fact that the substance was stable in dilute acid solution but mutarotated in water, methanol, dilute alkali and pyridine, a cyclic orthoacid structure (I) was assigned to it.



I

The lability of this substance compared with the stability of the well-characterized 1-*O*-benzoyl-β-D-glucopyranose prepared somewhat earlier by Zervas[2] and the widespread currency of the cyclic orthoacid concept which had first been suggested by Emil Fischer,[3] combined to make such a tentative assignment of structure a reasonable one at that period.[4] However, subsequent advances in the chemistry of the sugar esters have shown (a) that acyl groups are very prone to migrate from C_1 to C_2 of an aldose when the hydroxyl at C_2 is free and spatially accessible to C_1[5,6] and (b) that cyclic orthoacid structures such as I are not likely to be sufficiently stable for isolation.[6] Furthermore, Isbell and his co-workers[7] have shown recently that the sample of D-talose monobenzoate prepared in 1937 had undergone no change in physical properties during the intervening years and was indeed a normal ester as shown by its characteristic ester carbonyl absorption in the infrared.



In all known additions to the double bond of glycals[8] the anionic portion of the adding molecule has been found attached to C_1 of the sugar and it seems reasonably certain, therefore, that the substance reported by Pigman and Isbell is a 1-*O*-benzoyl-D-talopyranose. Its failure to mutarotate in acid solution[1] and to give a phenylhydrazone[7] appear to support this assumption. The mutarotations in water, methanol, dilute alkali and pyridine reported by Pigman and Isbell[1,7] may then represent acyl migration from C_1 to C_2 or some other position. Indeed these mutarotations, which start in a *levo* direction and then turn in the *dextro* direction, suggest that an initial acyl migration frees a β-hydroxyl at C_1 and that normal equilibration of the anomeric forms then ensues. If the instability of the ester is due to a $C_1 \rightarrow C_2$ migration we must expect it to be the β- rather than the α-1-*O*-benzoyl-D-talopyranose, for such a *cis* isomer would resemble the easily rearranged 1-*O*-mesitoyl-α-D-glucose[5] and 1,3,5-tri-*O*-benzoyl-α-D-ribose[6] while the

(1) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 189 (1937).

(2) L. Zervas, *Ber.*, **64**, 2289 (1931).

(3) E. Fischer, *ibid.*, **53**, 1624 (1920).

(4) *Cf.* E. Pacsu, *Advances in Carbohydrate Chem.*, **1**, 78 (1945).

(5) H. B. Wood, Jr., and H. G. Fletcher, Jr., THIS JOURNAL, **78**, 2849 (1956).

(6) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **78**, 4710 (1956).

(7) H. S. Isbell, J. E. Stewart, H. L. Frush, J. D. Moyer and F. A. Smith, *J. Research Natl. Bur. Standards*, **57**, 179 (1956).

(8) See, for instance, B. Helferich, *Advances in Carbohydrate Chem.*, **7**, 210 (1952).