

LETTERS TO THE EDITOR

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THE P.A. FACTOR AND PHENYLHYDRAZINE ANÆMIA

EXPERIMENTAL animals made anæmic with phenylhydrazine have been used for some time in this laboratory for the study of the hæmopoietic action of amino-acids and proteins with very satisfactory results (Yeshoda, 1942¹; Damodaran & Vijayaraghavan, 1943²; Yeshoda, 1943³). It occurred to us to investigate if the method could not be used for the biological assay of the factor present in liver extracts active in pernicious anæmia (hereafter referred to as the P.A. factor) for which no satisfactory method at present exists. Similarity of the blood pictures in pernicious anæmia and experimental phenylhydrazine anæmia has been frequently noted (cf. Paton and Goodall, 1903⁴; Price Jones, 1911⁵). Erdos (1935)⁶ has shown that in rabbits made anæmic by means of phenylhydrazine the onset of anæmia is delayed by the administration of liver extract and has suggested the utilization of this effect for comparing the potency of such extracts. On the contrary Wright and Arthur (1930),⁷ who also experimented upon rabbits, came to the

conclusion that "the regeneration from anæmia resulting from the injection of phenylhydrazine or from hæmorrhage is not affected by the administration of the substance effective in pernicious anæmia".

In the present experiments it has been found that liver extract exerts a markedly beneficial effect on the recovery of rats from phenylhydrazine anæmia. All the animals received a basal diet containing 3 per cent. casein which has been shown in previous experiments to be the minimum amount of protein to bring about normal blood-regeneration (Damodaran and Vijayaraghavan, *loc. cit.*). The P.A. factor was given orally in the form of Cohn's Fraction G (Cohn, Minot and Murphy, 1927⁸). Starting from the fourth day after injection of phenylhydrazine, when the anæmia reaches its peak, 1 ml. of the extract was fed to each animal daily. Aqueous solutions containing 5 per cent., 2.5 per cent., and 1.25 per cent. of Fraction G were tried on three different groups of animals. The control group received no liver extract.

Table I which gives the average values of

TABLE I

Group	Number of animals	Average RBC millions/c.mm.				Average Hb gm./100 ml.			
		4th Day	12th Day	% Inc.	Excess over control	4th Day	12th Day	% Inc.	Excess over control
A 5% Liver Extract	6	3.89	7.56	94.4	42.3	8.86	13.62	53.7	-1.4
B 2.5% Liver Extract	6	3.46	6.03	74.3	22.2	8.40	13.31	58.4	3.3
C 1.25% Liver Extract	6	3.96	6.25	58.1	6.0	9.13	13.96	52.9	-2.2
Control	5	4.01	6.10	52.1	-	8.98	13.93	55.1	-

R.B.C. and hæmoglobin for the four groups of animals shows clearly that liver extract in suitable concentrations exercises a marked effect on the rate of red blood cell regeneration in phenylhydrazine anæmia. The results also indicate that in one important respect the hæmopoietic action of the liver extract differs from that of amino-acids and proteins previously reported. The action of liver extract lies solely in the increase of erythrocytes without a corresponding increase in the percentage of hæmoglobin. This is in conformity with the view that amino-acids and proteins provide the structural material for the formation of hæmoglobin while the action of the P.A. factor is on the hæmopoietic apparatus, i.e., on the reticulo-endothelial system.

Although Cohn's Fraction G is not known to contain any hæmopoietically active substance other than the P.A. factor it would be rash to conclude from these experiments that the effects noted are due in fact to this factor. Wright and Arthur (*loc. cit.*) came to their negative conclusion quoted above in spite of finding that the anæmia induced by phenylhydrazine is much less acute in liver-fed rabbits than in control animals receiving no liver treatment. These authors were inclined to the view that the mitigating influence of liver extracts was not due to the P.A. factor but to the presence in it of some other substance which neutralised the destructive effect of phenylhydrazine on blood corpuscles. Although their experimental data hardly bear out this view there is no doubt that much further experimentation, accompanied by clinical trials, will be necessary before the regeneration of erythrocytes in phenylhydrazine anæmia can be accepted as a suitable method for the assay of the P.A. factor.

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DERIVATIVES OF 3-(p-METHOXY-PHENYL)-CYCLOHEXANONE

THE following is a brief account of experiments of an exploratory nature which were made with the object of preparing 3-(p-methoxyphenyl)-cyclohexanone required in connection with another research.

5-p-Methoxyphenyldihydroresorcinol¹ when treated with phosphorus trichloride² readily yields 5-chloro-3-(p-methoxyphenyl)- Δ^5 -cyclohexenone, m.p. 70° which on reduction with sodium and moist ethereal solution, gives 3-(p-methoxyphenyl)-cyclohexanol, m.p. 83-84°. The latter on cautious oxidation with

Beckmann's chromic acid mixture furnishes, 3-(p-methoxyphenyl)-cyclohexanone, b.p. 155°/4 mm. (semicarbazone, m.p. 194°). The same ketone can also be made directly by the reduction of 5-chloro-3-(p-methoxyphenyl)- Δ^5 -cyclohexenone by means of hydrogen in presence of colloidal palladium.³

The unstable δ -lactonic ester⁴ derived from ethyl γ -anisoylbutyrate, zinc and ethyl bromoacetate on hydrolysis with 10 per cent. alcoholic potash furnishes an unsaturated dicarboxylic acid, C₁₁H₁₄O₅, m.p. 153-154°. The corresponding diethyl ester, b.p. 189-192°/4 mm. readily absorbs one equivalent of hydrogen in presence of Adams platinum catalyst giving ethyl β -(p-methoxyphenyl)-pimelate, b.p. 190°/5 mm. This on hydrolysis affords β -(p-methoxyphenyl)-pimelic acid, m.p. 92-93°. The latter on ketonisation with acetic anhydride smoothly furnishes 3-(p-methoxyphenyl)-cyclohexanone, described above, identified by its b.p. 148-150°/5 mm., and semicarbazone, m.p. 194°. The unsaturated acid, m.p. 153-154°, under precisely similar conditions affords 3-(p-methoxyphenyl)- Δ^2 -cyclohexenone, m.p. 84°, semicarbazone, m.p. 217-219°, evidently identical with the ketone represented by Banerjee⁵ as 3-(p-methoxyphenyl)-cyclohexanone.

Finally, the unsaturated ketone, m.p. 84°, described above, was synthesised by the action of ω -chloro-p-methoxypropiophenone⁶ on ethyl sodio-acetoacetate followed by alkaline hydrolysis of the resulting product, which leaves no further room for doubt regarding the structure assigned to this compound.

It follows, therefore, that Banerjee's ketone, m.p. 83°, must be correctly represented as 3-(p-methoxyphenyl)- Δ^2 -cyclohexenone, although the analytical results actually found for the ketone by Banerjee are in excellent accord with those calculated for 3-(p-methoxyphenyl)-cyclohexanone.

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SYNTHESES OF 1-NAPHTHALENE-SUBSTITUTED ISOQUINOLINES

IN connection with a scheme for study of isoquinoline bases containing the naphthalene ring which may prove physiologically active it became necessary to investigate the synthesis of substances containing naphthyl residues in the 1-position of the isoquinoline molecule. The latter had in common homopiperonylamine as the starting material. The necessary intermediate N-acyl homopiperonylamides were