

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.

University Biochemical
Laboratory, Madras,
August 9, 1944.

M. DAMODARAN.
P. K. VIJAYARAGHAVAN.

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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.

My best thanks are due to Dr. J. C. Bardhan for his kind interest in the work.

University College of Science
and Technology, Calcutta,
July 21, 1944

PIYUSKANTI CHAUDHURI.

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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

obtained in excellent yields by the interaction of molecular proportions of homopiperonylamine and the respective acid chlorides in the presence of dil. NaOH. The amides now prepared are α -naphthoyl homopiperonyl amide, m.p. 130-31°, β -naphthoyl homopiperonyl amide, m.p. 140-41° and α -naphthylacetyl homopiperonyl amide, m.p. 129-31°. These separated from alcohol in colourless needles. On being subjected to the dehydrating action of POCl₃ in toluene, α - and β -naphthoyl homopiperonyl amides underwent the classical Bischler-Napieralsky reaction¹ and furnished in satisfactory yields the corresponding 1-naphthyl dihydro isoquinolines: 1, α -naphthyl, 3:4-dihydro, 6:7-methylenedioxy isoquinoline separated from petroleum ether in colourless needles, m.p. 109-10° (Picrate, orange yellow needles from alcohol, m.p. 164-65°; Picrolonate, yellow needles from alcohol-acetic acid, m.p. 228-31° dec.); 1, β -naphthyl 3:4-dihydro, 6:7-methylenedioxy isoquinoline separated from alcohol in colourless, prismatic needles, m.p. 140-41° (Picrate, yellow needles from alcohol-acetic acid, m.p. 191-92°. Picrolonate, yellow needles from alcohol, m.p. 189-93° dec.). On the other hand, cyclodehydration of α -naphthylacetyl homopiperonyl amide through the agency of POCl₃ in boiling toluene was by no means smooth. The main product of the reaction was a neutral, chlorinated compound, m.p. 258-59° dec. At the same time a basic substance, presumably the desired 1, α -naphthyl methyl, 3:4-dihydro, 6:7-methylenedioxy isoquinoline, was also formed in poor yields. Furthermore, the aforementioned base and even its hydrochloride in solution were characteristically unstable, a property which may be ascribed to the presence of the reactive methylene group linking the isoquinoline and naphthalene nuclei. Nevertheless, it has been possible to characterise the 1, α -naphthylmethyl, 3:4-dihydro, 6:7-methylenedioxy isoquinoline as its picrate separating from alcohol-acetic acid in orange yellow crystals, m.p. 166-68° dec.

The customary procedure of heating with zinc and dil. sulphuric acid was inapplicable to the reduction of 1, α -naphthyl, 3:4-dihydro, 6:7-methylenedioxy isoquinoline to the corresponding tetrahydro derivative, since it led to the formation exclusively of a neutral, metal-free compound separating from alcohol in colourless needles, m.p. 252-54° dec. The attempt to reduce 1, β -naphthyl, 3:4-dihydro, 6:7-methylenedioxy isoquinoline by means of zinc and dil. sulphuric acid likewise did not meet with success but gave rise to a nonbasic, metal-free product separating from alcohol in colourless needles, m.p. 241-43° dec. An insight into the nature of the two neutral substances as also that of the chloro compound encountered in the cyclisation of α -naphthylacetyl homopiperonyl amide has not yet been gained.

It is hoped to investigate in detail the cyclisation if α -naphthylacetyl homopiperonyl amide and the reduction of the isomeric 1-naphthyl, 3:4-dihydro, 6:7-methylenedioxy isoquinolines to the respective tetrahydro-bases changing, necessarily, the experimental conditions. The

results of these studies under way will form the subject of a further communication.

Presidency College,
Madras,
July 26, 1944.

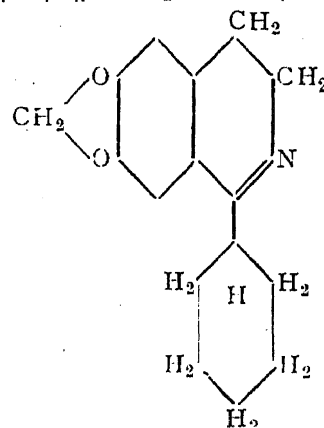
B. B. DEY.
S. RAJAGOPALAN.

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1-CYCLOHEXYL NORHYDRASTININE AND DERIVATIVES

IN a previous communication,¹ it was stated that the reduction of 1-benzyl, 1-cyclohexyl and 1-cyclohexyl methyl norhydrastinines with aluminium amalgam would be studied. Due to certain difficulties this has not been possible, but 1-cyclohexyl norhydrastinine and its derivatives prepared for purposes of this work have not been described in literature and are, therefore, reported here.

Cyclohexyl-3, 4-methylenedioxy phenyl ethyl amide was prepared by the action of cyclohexane carboxylic acid chloride on homopiperonyl amine (m.p. 135-36°; Found: N, 5.1; C₁₆H₂₁O₃N requires N, 5.8 per cent.)



(I)

The amide was converted by phosphorous oxychloride in boiling toluene to 1-cyclohexyl norhydrastinine (I). (Prisms from methanol or clusters of interlacing rhombic needles from ligroin, m.p. 82°. Found: N, 5.6; C₁₆H₁₉O₃N requires N, 5.5 per cent.; Picrate, crystallised from glacial acetic acid in rectangular blocks, m.p. 221°; Methiodide, m.p. 232-24°).

On reduction with zinc and sulphuric acid, the dihydro isoquinoline (I) gave in good yield 1-cyclohexyl norhydrohydrastine (Twig-shaped clusters of rhombic needles on slow crystallisation from petroleum ether, m.p. 47°; Picrate, crystallised from dilute alcohol, m.p. 206°; Hydrochloride sparingly soluble, hexagonal blocks, m.p. 244°; Hydrobromide, m.p. 237°; the nitroso derivative was formed at 0°, but decomposed instantaneously at room temperature).

Presidency College,
Madras,
August 3, 1944.

B. B. DEY.
T. R. GOVINDACHARI.

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