[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

THE SYNTHESIS OF 5,6-DIHYDROPYRINDINE

BY WILLARD C. THOMPSON

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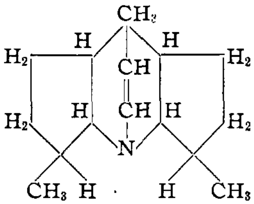
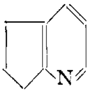
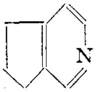
Introduction



(A)

In connection with American Petroleum Institute Project 20 there appeared recently a paper describing a hydroaromatic base of the formula $C_{16}H_{25}N$[1] to which was assigned provisionally the structure shown (A). This substance, the first hydroaromatic base to be obtained from petroleum in pure form, is now being investigated in the Texas Laboratory in order to clear up certain doubtful features in connection with the above formula.

5,6-Dihydropyrindine  was discovered in shale oil by Takashi Eguchi[2] in 1927 but, because of the failure of *Chemical Abstracts* to abstract that part of the Eguchi paper[3] dealing with the base in question, this work was overlooked until after the Thompson and Bailey paper had been submitted for publication. Therefore, the assignment of the pyrindacine structure to the $C_{16}H_{25}N$ compound was in no way influenced by the discovery of the Japanese chemist.

At the suggestion of Professor Bailey the author has synthesized 5,6-dihydropyrindine, following a method suggested by von Braun's synthesis[4] of 5,6,7,8-tetrahydroquinoline, and thus confirmed the structure originally assigned to the C_8H_9N shale oil base.[5] The fact that Eguchi obtained quinolinic acid on oxidation of his product excluded the isopyridine structure,  and leaves no doubt as to the discovery of the first base of this type to be found in nature.

In recent preliminary experiments in the Texas Laboratory in connection with the bases occurring in California crude kerosene distillates, the procedure for the isolation of a number of these in pure form has been developed. Their refractivity indicates both aromatic and hydroaromatic types, and, along with the difficulty of resolution of the distillation

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[1] Thompson and Bailey, THIS JOURNAL, **53**, 1002 (1931).

[2] Eguchi, *Bull. Chem. Soc. Japan*, **3**, 239 (1928); *Chem. Zentr.*, **100**, 331 (1929).

[3] Eguchi, *Chem. Abstracts*, **23**, 391 (1929).

[4] Von Braun and Lemke, *Ann.*, **478**, 191 (1930).

[5] For other syntheses in the pyrindine series, see T. Zincke, *Ann.*, **290**, 321 (1896); Curt Striegler, *J. prakt. Chem.*, [2] **86**, 241 (1913).

fractions into individual components, the wide range of 180 to 335° in their boiling points suggests an exceptionally complex mixture. In line with the cyclopentane structure, so typical of many petroleum hydrocarbons and naphthenic acids, it may be expected that, even if the Eguchi base does not occur among the kerosene bases, numerous hydrides of pyrindine or methylated pyrindines, or it may be isopyrindines, will be encountered.[6]

Since the method employed in the synthesis of 5,6-dihydropyrindine is analogous to that followed by von Braun for 5,5,7,8-tetrahydroquinoline, an outline of von Braun's procedure is subjoined. (1) 2-Hydroxymethylenecyclohexanone (A) results in the Claisen condensation of cyclohexanone with amyl formate.[7] (2) Product (A) with cyanacetamide yields 2-hydroxy-3-cyano-5,6,7,8-tetrahydroquinoline (B) and 2-keto-3-cyano-8a-hydroxy-1,2,3,5,6,7,8,8a-octahydroquinoline (C).[8] (3) Products (B) and (C) yield on heating with concentrated hydrochloric acid 2-hydroxy-5,6,7,8-tetrahydroquinoline, (D).[9] (4) With phosphorus pentachloride product (D) is converted to 2-chloro-5,6,7,8-tetrahydroquinoline, (E).[4] (5) Finally product (E) is reduced to 5,6,7,8-tetrahydroquinoline, (F).[4]

Could a similar series of reactions be carried out, with cyclopentanone replacing cyclohexanone in the first step, it is obvious that in step (5) 5,6-dihydropyrindine would result. Here the only part of the synthesis previously effected involves the condensation of cyclopentanone with amyl formate to yield hydroxymethylenecyclopentanone.[10] Steps corresponding to (1), (2) and (4) when applied to the synthesis of 5,6-dihydropyrindine, under the conditions employed by the author, result in poor yields; the other reactions proceed smoothly. The dihydropyrindine, although not prepared in an amount sufficient for purification through fractional distillation, was analyzed in the form of picrate. In accordance with the method of Skraup the synthetic product was oxidized to quinolinic acid and this proved to be identical with quinolinic acid made from quinoline. Furthermore, its physical properties are entirely in agreement with those determined by Eguchi on the shale oil base.

The various reactions involved in the synthesis as outlined can be elucidated through the following structural formulas

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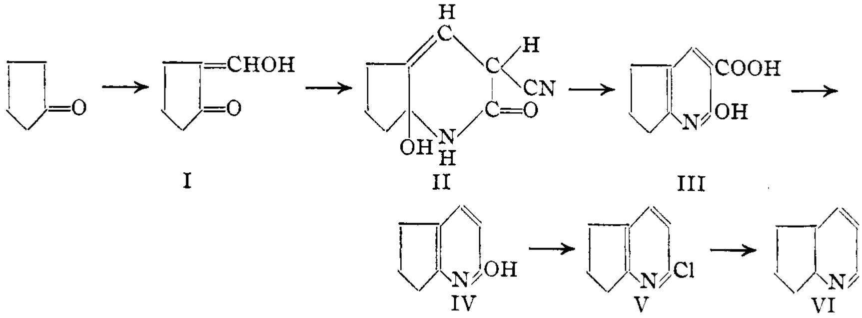
[6] The Texas Laboratory has obtained recently three barrels of kerosene bases, extracted from 9000 barrels of crude kerosene distillate, from the Union Oil Company of California, and a search will be instituted in fractions in the 200° zone for the C_8H_9N shale-oil base as soon as this large supply has been submitted to exhaustive fractional distillation.

[7] Wallach, *Ann.*, **329**, 117 (1903).

[8] Sen-Gupta, *J. Chem. Soc.*, **107**, 1354 (1915).

[9] Ref. 8, p. 1357.

[10] Adolf Steindorff, "Dissertation," Göttingen, **1903**, p. 32; Wallach, *Ann.*, **329**, 114 (1903).



Experimental Part

2-Hydroxymethylenecyclopentanone, I.—In this preparation the procedure of Steindorff[10] was followed with minor modifications. To a cooled solution of 20 g. of cyclopentanone and 17.6 g. of ethyl formate in 100 cc. of anhydrous ether was added 5.5 g. of sodium in small pieces. Most of the sodium reacted within an hour and, after standing in the ice box overnight, the mixture was treated with 100 cc. of ice water. The aqueous layer was extracted with ether, the reaction product precipitated as an oil with the required amount of acetic acid, and the oil taken up in ether. On evaporation of the ether solution, previously dried over calcium chloride, the hydroxymethylenecyclopentanone was obtained as a viscous liquid which, after sublimation at 100° in a vacuum, melted at 73°. A 15 to 20% yield was obtained. The use of isoamyl formate instead of ethyl formate did not give an increase in yield.

2-Keto-3-cyano-7a-hydroxy-1,2,3,5,6,7a-hexahydropyrindine, II.—Enough alcohol to effect solution was added to a mixture of 8.4 g. of cyanacetamide, 11.2 g. of hydroxymethylenecyclopentanone, 2 cc. of piperidine and 35 cc. of water. After standing for several days at 40°, 4 g. of a crude crystalline condensation product separated. This was decolorized by boiling its acetic acid solution with animal charcoal and after several recrystallizations from hot glacial acetic acid it was obtained as microscopic, rhombic prisms which did not melt even at 310°. The substance is only slightly soluble in water, alcohol and ether.

Anal. Calcd. for $C_9H_{10}O_2N_2$: C, 60.68; H, 5.62; N, 15.73. Found: C, 60.23; H, 5.72; N, 15.62.

2-Hydroxy-5,6-dihydropyrindine-3-carboxylic Acid, III.—Product II was heated with concentrated hydrochloric acid in a sealed tube at 120–130° for two hours. The solution was diluted with an equal volume of water and boiled with animal charcoal. After filtering and cooling the acid separated in a 50% yield as a white solid and was recrystallized from boiling water, from which it separated as fine slender needles, melting at 272° with decomposition. It is slightly soluble in cold but readily soluble in hot water and alcohol. Its aqueous solution gives a red coloration with ferric chloride and a yellow coloration with ferrous sulfate. A silver salt, insoluble in cold water and soluble in hot water, is formed with silver nitrate.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.32; H, 5.06; N, 7.82. Found: C, 59.87; H, 5.20; N, 7.95. *Equivalent weight.* Calcd. for $C_9H_9O_3N$: 179. Found: 170.

2-Hydroxy-5,6-dihydropyrindine, IV.—Five grams of product II and 15 cc. of concentrated hydrochloric acid were heated for two hours at 120–130° and then at 150–160° for three hours. From the acid solution, diluted with an equal volume of water and boiled with animal charcoal, there separated on cooling 3.5 g. of the hydroxy base as fine slender rods. After several recrystallizations from hot water the base was obtained as a white product, melting at 187–188°. It is slightly soluble in cold water and cold alcohol but dissolves readily in ether, hot water and hot alcohol. The hydroxy compound gives a red coloration with ferric chloride and yields a picrate that can be recrystallized from alcohol in the form of small, flat, right prisms, melting at 164°.

Anal. Calcd. for C_8H_9ON: C, 71.08; H, 6.71; N, 10.36. Found: C, 70.79; H, 6.85; N, 10.46.

2-Chloro-5,6-dihydropyrindine, V.—Four grams of 2-hydroxy-5,6-dihydropyrindine, 4 g. of phosphorus oxychloride, and 15 g. of phosphorus pentachloride were heated at 120–130° under pressure for four hours. The chlorodihydropyrindine, admixed with a considerable amount of tarry material, was treated with ice water, made alkaline and steam distilled. About 0.5 g. of a white solid, insoluble in water, was obtained. After several recrystallizations from 50% alcohol the product separated in the form of colorless rhombic prisms melting at 70–71°.

Anal. Calcd. for C_8H_9NCl: N, 9.12. Found: N, 8.87.

5,6-Dihydropyrindine, VI.—Three grams of 2-chloro-5,6-dihydropyrindine was heated with 15 g. of zinc dust and 60 cc. of concentrated hydrochloric acid for six hours. The solution was then diluted with an equal volume of water, filtered, made alkaline and steam distilled. The distillate was extracted with ether, which, on evaporation, yielded 2–3 cc. of a base having a pyridine-like odor. The product was distilled under reduced pressure, a middle fraction of about 0.3 cc. being reserved for refractive index and boiling point determinations. The freshly distilled base is colorless but soon darkens on standing. The following physical constants were determined: b. p. at 750 mm. 199°; n_D^{25} 1.5407. The corresponding constants of the Eguchi base are: b. p. at 761 mm. 199.8°; n_D^{25} 1.541.

The first runnings and residue in the distilling flask were dissolved in alcohol and the base precipitated as picrate. After several recrystallizations from alcohol the yellow picrate was obtained in the form of flat rhombic prisms melting at 181–182°. The picrate of the shale-oil base as described by Eguchi crystallizes in "flat needles," soluble in hot alcohol and melting at 181°.

Anal. Calcd. for $C_8H_9N \cdot C_6H_2OH(NO_2)_3$: C, 48.28; H, 3.45; N, 16.09. Found: C, 48.36; H, 3.63; N, 16.05.

Oxidation of Dihydropyrindine.—To 0.2 g. of the base, in 25 cc. of water and heated under reflux in a boiling water-bath, 1.5 g. of potassium permanganate was added in small portions over a period of eight hours. Finally the solution was heated to boiling, filtered and evaporated to dryness. The residue was dissolved in water and the quinolinic acid precipitated as silver salt, from which it was recovered in the usual way. The acid was recrystallized from alcohol and on heating in a capillary tube a vigorous evolution of gas took place at 180–190°. As the heating was continued, the product solidified at about 200° and melted at 231°. A mixture of this product with a sample of quinolinic acid, prepared according to the directions of Skraup,[11] showed the same behavior on heating. With copper sulfate solution the acid gave a blue precipitate, insoluble in boiling water and boiling acetic acid, and with ferrous sulfate an orange coloration, characteristic properties of quinolinic acid.

Conclusion

The discovery in the Texas Laboratory of a petroleum base of the formula $C_{16}H_{25}N$, which is probably a hydro-pyrindacine, has directed

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[11] Skraup, *Monatsh.*, **2**, 147 (1881); Hoogewerff and Van Dorp, *Rec. trav. chim.*, **1**, 107 (1882).

attention to the possibility of cyclic nitrogen bases occurring in petroleum distillates of the pyrindine type. The structural relationship of pyrindine to pyrindacine is similar to that between quinoline and acridine.

The occurrence of 5,6-dihydropyrindine in shale oil distillates and the $C_{16}H_{25}N$ base in crude kerosene distillates contributes to the importance of the five-membered carbon ring and will direct the attention of the chemist toward a further search for natural products of these types. Furthermore, it is to be expected that further research in the Texas Laboratory on the kerosene bases will develop a relationship between petroleum bases and naphthenic acids, more especially as concerns cyclopentane structure.

A synthesis of 5,6-dihydropyrindine seemed desirable in confirmation of Eguchi's interpretation of his C_8H_9N base, although the proof of structure furnished by the Japanese chemist was apparently conclusive. It is realized that the method of preparing this substance, as described in the present paper, must be improved in several steps before 5,6-dihydropyrindine becomes available in quantity for further research.

AUSTIN, TEXAS

[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO]

THE C_4-SACCHARINIC ACIDS. V. THE PREPARATION OF 2,3-DIHYDROXYBUTYRIC ACID LACTONE. 3-HYDROXYISOCROTONIC ACID LACTONE. AN ATTEMPT TO PREPARE 2,2'-DIHYDROXYISOBUTYRIC ACID[1]

BY J. W. E. GLATTFELD, GLADYS LEAVELL, GEORGE E. SPIETH AND DONALD HUTTON

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The resolution of 2,3-dihydroxybutyric acid (hereafter called "2,3-acid") has already been reported in a paper from this Laboratory.[2] The acid used for the resolution experiments was prepared in accordance with the procedures of the two previous workers, Hanriot, and Nef.[3] As neither of these authors was interested specifically in this acid, they did not make a very extended study of its preparation. No mention is made by them, for instance, of the simultaneous formation of an unsaturated acid, 3-hydroxyisocrotonic acid, although the formation of this acid is mentioned by Carré.[4] This unsaturated acid was formed to some extent in every one of our runs, in some cases even to the exclusion of the desired 2,3-acid. It was isolated in the form of its lactone in large quantities during

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[1] This article is constructed largely from dissertations presented by Gladys Leavell, George E. Spieth and Donald Hutton in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

[2] Glattfeld and Miller, THIS JOURNAL, **42**, 2314 (1920).

[3] Hanriot, *Ann. chim. phys.*, [5] **17**, 104 (1879); Nef, *Ann.*, **376**, 35 (1910).

[4] Carré, *Bull. soc. chim.*, [4] **3**, 834 (1908); *Compt. rend.*, **146**, 1282 (1908).