

Summary

1. Uracil-4-carboxylic acid (otrotic acid) known to occur in milk is most easily prepared in quantity by oxidation of 2-thiouracil-4-aldehyde or uracil-4-aldehyde with chromic acid.

2. The uracil-4-carboxylic acid thus obtained is identical with the natural otrotic acid from milk furnished to us for comparison by Dr. Bachstesz of Italy.

3. This is the only pyrimidine carboxylic acid thus far known to occur in nature.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

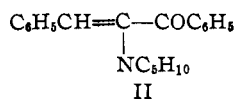
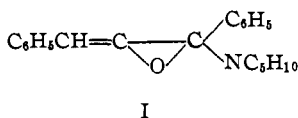
ALPHA PIPERIDINO BENZALACETOPHENONE

BY E. P. KOHLER AND W. F. BRUCE

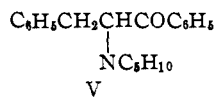
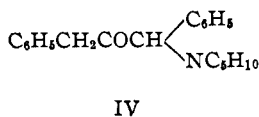
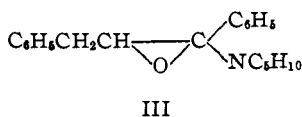
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In a recent paper Kohler and Addinall¹ expressed the opinion that a peculiar red piperidine derivative which was first described by Watson² and later studied with care by Dufraisse and Moureu³ is an unsaturated ethylene oxide (I). This view is erroneous; the substance is an unsaturated ketone and it has the structure assigned to it by Dufraisse and Moureu (II).



As a means of discrimination between the two formulas all methods of degradation by oxidation proved useless, but fairly convincing evidence was obtained from a series of transformations based on hydrogenation. In the presence of platinum the red compound combines with two atoms of hydrogen and forms a yellow addition product which reacts with a mole of methyl magnesium iodide without liberating gas. This compound might, therefore, be either a saturated oxide or one of two saturated ketones.



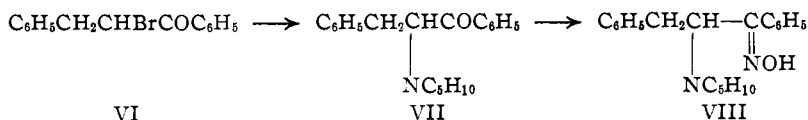
The yellow reduction product can be made by the action of piperidine on α -bromo benzylacetophenone and it reacts with hydroxylamine like

¹ Kohler and Addinall, *THIS JOURNAL*, **52**, 3728 (1930).

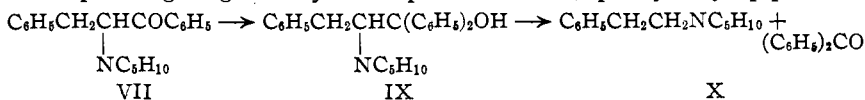
² Watson, *J. Chem. Soc.*, **85**, 1322 (1904).

³ Dufraisse and Moureu, *Bull. soc. chim.*, [4] **41**, 457 (1927).

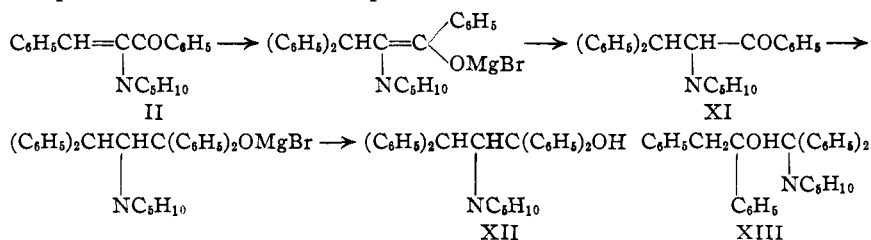
a ketone. Ordinarily this would be regarded as adequate evidence that the substance is the ketone V and the sequence of reactions would be represented as follows



But unfortunately in this case the evidence is inconclusive, because the reaction between piperidine and the bromo compound might lead to the formation of the oxide III,⁴ and it was not possible to regenerate the yellow compound from the product obtained in the reaction with hydroxylamine. Additional evidence as to the structure of the reduction product was obtained by treating it with phenyl magnesium bromide. It combined very readily with one equivalent of the reagent. The product of this reaction is colorless. It is stable to fairly high temperatures but above 280° it decomposes, giving mainly benzophenone and β -phenylethyl piperidine



These transformations are difficult to reconcile with any formula other than VII; but since the final step involved the use of high temperatures and we were reluctant to accept this formula without the best of evidence, we decided to study another series of transformations. To this end we treated the red compound itself with excess of phenyl magnesium bromide. It combined with but one mole; but the yellow compound that was obtained by decomposing the resulting magnesium derivative was capable of combining with a second equivalent of the reagent. This is the characteristic behavior of α,β -unsaturated ketones with which organic magnesium compounds form 1,4-addition products



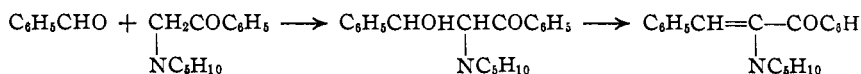
Since ethylene oxides are capable of combining with organic magnesium derivatives, it is possible to imagine a similar series of reactions beginning with an oxide like I and ending with the carbinol XIII. Between these two possible carbinols it was easy to decide, because when the final product of the reaction was oxidized with chromic acid, it yielded two molecules

⁴ Ref. 1, p. 3730.

of benzophenone. It is therefore the carbinol XII, and the red piperidine derivative must be the unsaturated ketone II.

Experimental Part

On the assumption that the red piperidine derivative has the structure assigned to it by Dufraise and Moureu, the simplest and best proof of its structure would be its synthesis by the condensation of benzaldehyde and ω -piperidino acetophenone



Since the red compound is readily hydrolyzed by acids, it was necessary to undertake the condensation in the presence of bases; all attempts to effect condensation under these conditions were unsuccessful.

Another relatively simple method of differentiating between the two possible formulas of the red compound might be ozonization. This also was tried; a solution of the substance in carbon tetrachloride absorbed ozone with avidity. After removing the solvent and manipulating the residue in the usual manner, the products were benzaldehyde, benzoic acid and an oil which could not be purified but which gave piperidine and phenyl glyoxylic acid when it was digested with alkali. Inasmuch as these products might be formed both from the ketone and from the oxide the results are inconclusive.

Hydrogenation.—The red compound was hydrogenated in methyl alcohol with Adams' platinum oxide as the catalyst. It absorbed hydrogen rapidly at first, but the rate gradually fell off and there was no sharp break in the rate curve at the point representing the addition of two hydrogen atoms. After some preliminary experiments it was found advantageous to interrupt the operation when one mole of hydrogen had been absorbed, even though not all of the substance had been hydrogenated. Thus, a solution of 10 g. of the red compound in about 300 cc. of methyl alcohol was shaken with 0.2 g. of platinum oxide and hydrogen until 840 cc. of the latter had been absorbed. Most of the catalyst was then removed by filtration, the remainder with active charcoal. The clarified solution, on concentration, deposited a mixture which was partially separated by crystallization. It yielded 7.1 g. of pure saturated ketone and 1.5 g. of a mixture of the original substance and its reduction product that was difficult to separate.

α -Piperidino Benzylacetophenone, VII.—The hydrogenation product is readily soluble in ether, moderately soluble in methyl alcohol. It crystallizes in pale yellow needles and melts at 81°. It dissolves readily both in dilute and in concentrated hydrochloric acid. The solution in 6 *N* acid deposited a colorless solid in large hexagonal prisms—doubtless the hydrochloride—from which alkalies regenerated the yellow base.

Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{ON}$: C, 81.8; H, 7.9. Found: C, 81.9; H, 7.9.

Preparation from α -Bromobenzylacetophenone.—One gram of the bromo compound was added to 3 cc. of piperidine; it dissolved with cooling but the temperature soon rose rapidly and the solution became yellow. After half an hour it was diluted with water, whereupon it deposited an oil that soon solidified. After recrystallization from methyl alcohol the product melted at 80–81° and a mixed melting point determination proved its identity with the substance obtained by hydrogenation.

Reaction with Hydroxylamine.—A solution of 0.5 g. of the substance, 0.8 g. of hydroxylamine hydrochloride and 2 g. of potassium hydroxide in 25 cc. of methyl alcohol was boiled for half an hour, then poured into water. The product was recrystallized from methyl alcohol, from which it separated in colorless needles melting at 141–142°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{ON}_2$: C, 77.9; H, 7.9; N, 9.1. Found: C, 77.9; H, 8.0; N, 9.1.

The substance is, doubtless, the oxime VIII, which might be expected to resist hydrolysis. It is slightly soluble in 30% potassium hydroxide, and soluble in both dilute and concentrated acids—as would be expected in view of its piperidine group. In an attempt at hydrolysis it was heated overnight at 100° with 6 *N* hydrochloric acid. The result was a white solid melting at 240° which was not attacked by sodium bicarbonate but from which potassium hydroxide regenerated the oxime. With concentrated hydrochloric acid the result was the same.

Attempts to effect a Beckmann rearrangement were equally unsuccessful. Phosphorus pentachloride in cold ether immediately produced a white precipitate—doubtless the chloride—and when the solution was heated the result was a mixture of decomposition products among which benzonitrile was recognized by the odor. Hot formic acid merely transformed the substance into a salt—the formate—from which bases regenerated the oxime. After recrystallization from 5% aqueous formic acid the salt melted at 177–178°.

Anal. Calcd. for $C_{21}H_{26}O_3N_2$: C, 71.2; H, 7.4. Found: C, 71.1; H, 7.4.

Action of Phenyl Magnesium Bromide, α, α, γ -Triphenyl- β -piperidinopropanol, IX.—An ethereal solution of 2.9 g. of the reduction product was added to a solution of the reagent that had been prepared from 0.96 g. of magnesium. Reaction occurred readily at 10° but the mixture was boiled for half an hour after all of the ketone had been added. The magnesium derivative was decomposed with ammonium chloride in the usual manner. The ethereal layer on evaporation left a solid and a small quantity of yellow oil. By recrystallization from methyl alcohol the solid carbinol was obtained in colorless plates melting at 148–149°.

Anal. Calcd. for $C_{26}H_{29}ON$: C, 84.1; H, 7.9. Found: C, 84.2; H, 7.8.

Pyrolysis of the Carbinol.—A tube containing 1.6 g. of the carbinol was exhausted to 11 mm., then sealed and heated at 260–280° for seven hours in a Carius furnace. It was thus converted into a slightly discolored oil which was almost completely volatile with steam. In order to separate basic and non-basic constituents, the ethereal extract of the distillate was shaken with dilute hydrochloric acid. The non-basic residue (0.82 g.) was identified as benzophenone by a mixed melting point. The acid solution, on treatment with alkali, yielded 0.50 g. of an oily base. The base formed a hydrochloride which crystallized in pearly plates, melting at 223° when crude and at 228° after recrystallization from methyl alcohol and ether. In the literature the melting point of β -phenylethyl piperidine hydrochloride is reported as 223°.⁵

Anal. Calcd. for $C_{13}H_{20}NCl$: C, 69.2; H, 8.9. Found: C, 69.1; H, 8.7.

Action of Phenyl Magnesium Bromide on the Unsaturated Ketone.— α -Piperidino- β, β -diphenylpropiofenone, XI.—A solution of 11 g. of the red ketone in 85 cc. of ether was added slowly to a solution of the reagent which had been made from 2.5 g. of magnesium. A deep blood-red coloration appeared where the solution met the reagent. At 0° this color persisted, but at the boiling point of the mixture it disappeared almost immediately. The mixture was boiled for an hour, then decomposed with ice and ammonium chloride. The ethereal layer was washed, dried and evaporated. It left a yellow solid and an oil. The oil was removed with methyl alcohol, and the solid was recrystallized from benzene and methyl alcohol. The ketone crystallized in yellow needles melting at 163°; yield, 61%.

Anal. Calcd. for $C_{26}H_{27}ON$: C, 84.5; H, 7.4. Found: C, 84.6; H, 7.3.

Action of Phenyl Magnesium Bromide, α, α -Diphenyl- β -piperidino- γ, γ -diphenylpropanol, XII.—No perceptible reaction occurred when a benzene solution of one gram

⁵ Kindler, *Arch. Pharm.*, 265, 405 (1927).

of the yellow ketone was added to a solution of the reagent containing 0.2 g. of magnesium, but when the solution was boiled the yellow color gradually disappeared. After an hour's boiling, the solution was treated with ammonium chloride in the usual manner. The ethereal layer, on evaporation, left an oil which could not be induced to crystallize.

In the hope of securing a solid, an ethereal solution of the oil was treated with hydrogen chloride gas. The acid converted it into a product which likewise had a tendency to separate from solutions as an oil but which was finally obtained as a solid by the addition of petroleum ether to its solution in chloroform. An analysis of this solid, which melted at 162–164°, indicated that it was not a simple hydrochloride of the piperidine compound but that the strong acid had also replaced the hydroxyl group of the carbinol with chlorine.

Anal. Calcd. for $C_{22}H_{33}NCl_2$: C, 76.5; H, 6.6. Found: C, 75.5; H, 6.8.

From the chloro compound the carbinol was regenerated by shaking a suspension of the substance in ether with 10% sodium hydroxide. The ethereal layer, on evaporation, left an oil, but this was finally converted into a solid by dissolving it in benzene, concentrating and adding petroleum ether to the solution. The solid separated gradually in large and well-defined crystals melting at 136–137°.

Anal. Calcd. for $C_{22}H_{33}ON$: C, 85.9; H, 7.4. Found: C, 85.6; H, 7.8.

Oxidation of the Carbinol.—To a solution of 0.45 g. of the carbinol was added 1.1 g. of powdered sodium bichromate; the solution was kept at 44–45° for an hour, then diluted with 100 cc. of water, made alkaline with sodium hydroxide and distilled with steam. The distillate was thoroughly extracted with ether, and the dried extract evaporated. The oily residue was kept over potassium hydroxide in a vacuum desiccator until entirely dry. It solidified completely when touched with benzophenone and a mixed melting point showed that it was pure. The yield was 0.35 g. instead of 0.36 g. calculated on the assumption that one molecule of carbinol yields two molecules of benzophenone.

Summary

The brilliant red compound which is formed by the action of piperidine and bases on α -bromobenzalacetophenone is α -piperidino benzalacetophenone. It has the structure assigned to it by Dufraisse and Moureu.

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