in intramolecular tension, which in turn decreased the double bond-like property of the bridged bond ascribable to the tension.

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43. **Morizo Ishidate,* Minoru Sekiya,** Yoshiro Osaki,*** Ichiro Kurita,*** and Yukichi Harada**** : Studies on Xanthine and Related Compounds. II[1]. A New Synthesis of Xanthine from 4-Amino-5-phenylazouracil.

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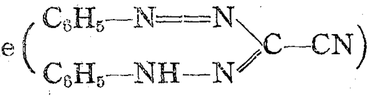
A new process for the synthesis of xanthine (I), using 4-amino-5-phenylazouracil as an intermediate material, was devised and is reported in the present paper. This process was found to be valuable for an industrial preparation of xanthine.

Although 5-phenylazobarbituric acid was first prepared in 1891,[2] 4-amino-5-phenylazouracil has not been found in literature. Todd *et al.*[3] synthesized purine nucleosides starting from 5-phenylazopyrimidine, but no report has been found on the preparation of xanthine from 4-amino-5-phenylazouracil.

The new compound, 4-amino-5-phenylazouracil (II), was prepared by the following two methods: (i) 4-Aminouracil (III) coupled with phenyldiazonium chloride, and (ii) cyanoacetylurea (IV) coupled with phenyldiazonium chloride yielding phenylazocyanoacetylurea (V), which was cyclized by alkali hydroxide solution.

Phenylazocyanoacetylurea thus obtained formed yellow plates decomposing at 206~209°. If this coupling reaction was carried out in strongly alkaline medium, formazyl cyanide  $\left(\begin{matrix} C_6H_5{-}N{=}N \\ C_6H_5{-}NH{-}N \end{matrix} \!>\! C{-}CN\right)$ was produced as a by-product.

By coupling 4-aminouracil with phenyldiazonium chloride 4-amino-5-phenylazouracil was obtained as orange yellow needles. This was reduced giving 4,5-diaminouracil (VI) in a good yield, either by zinc (or iron) powder with dilute sulfuric acid or by hydrogenolysis in acetic acid with palladium-carbon catalyst.

4-Amino-5-phenylazouracil was partially converted into xanthine by heating with formamide.[4] In this reaction, xanthine obtained was very impure and difficult to purify, so that its yield was very poor, but by carrying out the hydrogenolysis in the presence of formamide at high pressure and temperature with Raney nickel catalyst, the yield of xanthine could be increased to about 90%. In this catalytic procedure, instead of formamide, ammonium formate was also used. For the industrial preparation of xanthine derivative, such as caffeine, the process using 4-amino-5-phenylazouracil as an intermediate is regarded as the most valuable method in the present work on this series. As reported,[1] the catalytic procedure had already been tried on 4-

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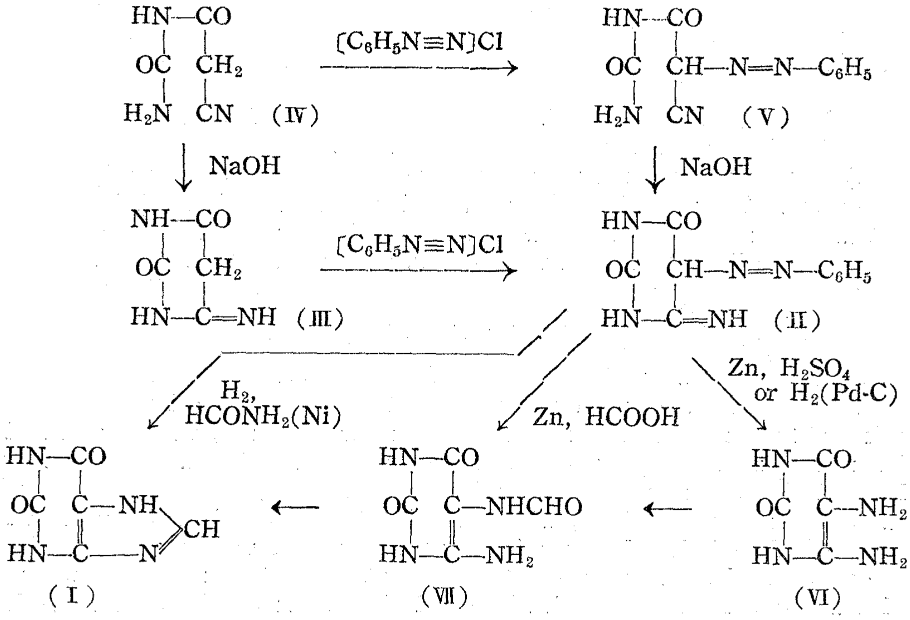
[1] Part I: J. Pharm. Soc. Japan, **74**, 420 (1954).

[2] Kühlung: Ber., **24**, 4141 (1891); *ibid.*, **31**, 1973 (1898).

[3] Lythgoe, Todd, Topham: J. Chem. Soc., **1944**, 315; Baddiley, Lythgoe, Todd: *Ibid.*, **1944**, 318; Kenner, Lythgoe, Todd: *Ibid.*, **1944**, 652.

[4] A similar reaction to 4-iminovioluric acid has already been reported (cf. Footnote 1).

iminovioluric acid with poor results owing to a complex formation between the acid and the nickel catalyst.



Analyses were performed by Mr. E. Kimura of the Medical Faculty, University of Tokyo, to whom the authors' thanks are due.

Experimental

Phenylazocyanoacetylurea—Aniline (5.4 g.) was dissolved in 10% HCl (60 cc.) and the solution cooled to 0° was diazotized with $NaNO_2$ solution (4 g. in 30 cc. of water). The diazotized solution was added to a solution of cyanoacetylurea (7.3 g) in NaOH solution (2.5 g. in 1000 cc. of water). To the resulting solution was added $NaHCO_3$ in small portions to adjust the reaction mixture to about pH 6 and simultaneous precipitation of the azo compound was observed. After standing overnight, the precipitate was collected, washed with watar, and dried (yield, 12.5 g.). The compound, recrystallized from glacial AcOH, formed yellow prisms, m.p. 206~209°(decomp.). *Anal.* Calcd for $C_{12}H_9O_2N_5$: C, 51.91; H, 3.83; N, 30.29. Found: C, 52.11; H, 3.92; N, 30.01.

Formazyl Cyanide—In the experiment described above for phenylazocyanoacetylurea, when the coupling was carried out in strongly alkaline medium, a brownish solid was obtained. This was extracted with benzene and the extract was evaporated to leave a residue which was purified from glacial AcOH forming brown red plates, m.p. 158~159°. It gave violet blue coloration with conc. H_2SO_4 and no depression of m.p. was observed on admixture with an authentic sample of formazyl cyanide. *Anal.* Calcd for $C_{14}H_{11}N_5$: C, 67.46; H, 4.45. Found: C, 67.76; H, 4.50.

4-Amino-5-phenylazouracil—a) Aniline (10 g.) dissolved in 10% HCl (110 cc.) was diazotized with $NaNO_2$ solution (7.5 g. in 50 cc. of water). The diazotized solution was added to a solution of 4-aminouracil (13.5 g.) in aq. NaOH (8.6 g. in 300 cc. of water) with external cooling. The azo compound preciptated at once and after standing overnight, the precipitate was collected, washed with water containing AcOH, and dried (yield, 22 g.). The compound, recrystallized from glacial AcOH, formed yellow needles. *Anal.* Calcd. for $C_{10}H_9O_2N_5$: C, 51.91; H, 3.83; N, 30.29. Found: C, 51.75; H, 4.16; N, 29.86.

b) With constant agitation cyanoacetylurea (12.7 g.) was added in small portions to 40% NaOH solution (12.5 g. in 19 cc. of water) and the agitation was continued for about 40 mins., the temperture being maintained below 40° during the reaction. The reaction mixture was dissolved in water (250 cc.) and to this was added the diazotized solution prepared from aniline (9.5 g.). The resulting precipitate was collected, washed with water containing AcOH, and dried (yield, 20 g.).

c) Phenylazocyanoacetylurea (25 g.) was added to 25% NaOH solution (150 cc.). The mixture was heated in an oil bath at 100~110° for 0.5 hr. with occasional agitation. The mixture partially changed into a solution and soon precipitate began to separate. During the reaction some NH_3 evolved. After cooling to the room temperature, the reaction mixture was filtered and washed with water. The product was suspended in water, acidified with AcOH, and the resulting precipitate was collected and washed with hot water (yield, 18 g.).

4,5-Diaminouracil Sulfate—a) 4-Amino-5-phenylazouracil (20 g.) was suspended in 20% H_2SO_4 (270 cc.). With vigorous stirring, Zn powder (14 g.) was added to the mixture in small portions, at 30~35°. When the suspending yellow material was almost decolorized, the mixture was filtered with suction, the crude product obtained was dissolved in dil. NaOH solution, and was reprecipitated with dil. H_2SO_4. The precipitate was filtered, washed with water, and dried (yield, 15.5 g.). By heating with formamide, this compound produced xanthine in a good yield and it was identified as caffeine by methylation.

b) Use of iron instead of zinc as in a) gave 4,5-diaminouracil as well.

c) 4-Amino-5-phenylazouracil (7 g.) suspended in glacial AcOH (100 cc.) was catalytically reduced with 5% Pd-C (2 g.) at ordinary temperature and pressure. H_2 was absorbed rapidly and the absorption stopped in about 5 mins. The reduction mixture was filtered with suction and the product contaminated with the catalyst was extracted with hot water. To this extract was added dil. H_2SO_4 and the resulting precipitate was collected, washed with water, and dried. From the filtrate majority of AcOH was removed under a diminished pressure and to the residue was added dil. H_2SO_4 to give a small amount of 4,5-diaminouracil sulfate (total yield, 5.1 g.).

4-Amino-5-formylaminouracil—4-Amino-5-phenylazouracil (10 g.) suspended in 88% HCOOH (100 cc.) was mixed with Zn powder (6 g.). The mixture was heated on a water bath and agitated from time to time. The phenylazouracil went into solution and the color faded to precipitate both formylaminouracil and Zn formate. The reaction mixture was filtered, the separated solid was washed with dil. HCl in order to remove Zn formate and the excess Zn, and it was purified by dissolving it in an aq. alkaline solution and reprecipitation with an acid (yieid, 5 g.). By treating it with alkali, this compound was converted to xanthine, which was identified as caffeine after methylation.

Xanthine—a) 4-Amino-5-phenylazouracil (25 g.) was mixed with formamide (100 cc.) and the mixture was heated in an oil bath at 170~180° for about 9 hrs. The reaction mixture was filtered, the separated solid was dissolved in hot dil. NaOH solution, and reprecipitated with dil. AcOH to yield a very impure xanthine (6 g.). Caffeine (about 1 g.) was obtained by its methylation.

b) In an autoclave 4-amino-5-phenylazouracil (32 g.) suspended in formamide (150 cc.) was mixed with Raney Ni (4 g. as 50% alloy) catalyst. Under a high H_2 pressure (90 kg/cm^2), the mixture was heated at 140° with constant shaking. The calculated amount of H_2 was absorbed mostly in about 15 mins. The temperature was slowly raised to 170~180° and maintained there for 30 mins. Next day, the reaction mixture was filtered with suction, the separated solid containing xanthine and Ni was extracted with dil. NaOH solution, and then reprecipitated with dil. AcOH. Pure xanthine was thus obtained (yield, 17 g.). After distilling off formamide *in vacuo* from the filtrate, the residue was treated with EtOH to give a small portion of impure xanthine (1.5 g) and the residue, after evaporating EtOH, was distilled in a high vacuum to yield formanilide. Xanthine obtained was identified as caffeine by its methylation.

c) In an autoclave 4-amino-5-phenylazouracil (32 g.), mixed with $HCOONH_4$ (170 g.) and Raney Ni (6 g. as 50% alloy), was reduced in the same manner as for (b). After the usual work-up, xanthine was obtained (yield, 19 g.).

Summary

Xanthine was synthesized through a new process using 4-amino-5-phenylazouracil as the intermediate. The new compound, 4-amino-5-phenylazouracil, was prepared by two methods: (i) Coupling 4-aminouracil with phenyldiazonium chloride, and (ii) phenylazocyanoacetylurea, obtained by coupling cyanoacetylurea with phenyldiazonium chloride, cyclized by alkali hydroxide solution.

Reduction of 4-amino-5-phenylazouracil to give 4,5-diaminouracil was carried out by either zinc with a mineral acid or a catalytic hydrogenation. Its reduction with zinc and 90% formic acid resulted in the formation of 4-amino-5-formylaminouracil.

Xanthine was obtained when it was heated with formamide or hydrogenated in the presence of formamide using Raney nickel catalyst under pressure. The latter method gave a higher yield of xanthine.

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