

EXPERIMENTAL RESEARCHES OF 5-OXY-6-METHYLURACIL SYNTHESIS PROCESS BY 6-METHYLURACIL OXIDATION

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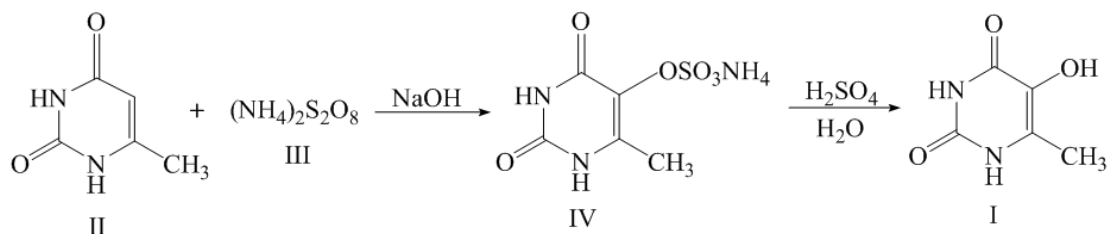
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The method of 5-oxy-6-methyluracil based on 6-methyluracil oxidation by ammonium persulfate in an alkaline medium and subsequent hydrolysis of isolated intermediate product - 6-methyluracil-5-ammonium sulfate by sulfuric acid was considered. The effective molar ratio of the raw materials and the reaction conditions for 5-oxy-6-methyluracil synthesis with high yield was found out.

Keywords: 5-oxy-6-methyluracil, method of production, persulfate oxidation, effective conditions of the synthesis, yield of the product

5-Oxy-6-methyluracil (I) is used for production of the high-performance medical product "Immureg", possessing an immunomodulating and a cardio stimulating activity [1].

Different oxidation variants of 6-methyluracil (II) – a condensation product of urea with acetoacetic ether to the target 5-oxy-6-methyluracil I have been described [2, 3]. By using ammonium persulfate (III) as an oxidizer in this reaction in an alkaline medium an intermediate product – 6-methyluracil-5-ammonium sulfate (IV) is obtained, that is quantitatively hydrolyzed by sulfuric acid till oxy derivative I [4].



Thereupon it was of interest to study the reaction of heterocycle II with an oxidizer III and determine the maximal yield conditions of the product IV.

EXPERIMENTAL PART

6-Methyluracil II, $(\text{NH}_4)_2\text{S}_2\text{O}_8$ III, H_2SO_4 , NaOH, decolorizing activated carbon, was used as raw materials. The reaction was made in distilled water. The purity of newly synthesized compounds IV and I was monitored by the method of thin-layer chromatography on Silufol UV 254 plates using chloroform-methanol, 4:1, solvent system. The spots of these substances were visualized with iodine vapor.

In half-liter round-bottom three-necked flask equipped with a mechanical stirrer, a backflow condenser and a thermometer 5 g (0.0397 mole) of reagent II was loaded, 20 ml of water was added and the mixture was stirred over 1 hour at 60 °C. After preliminarily prepared estimated quantity of sodium hydroxide solution was added to the obtained suspension. Some time after estimated quantity of dry ammonium persulfate was added to the reaction mixture by portions in 30 minutes. During adding the temperature of the reaction mixture was kept on definite level. After full adding of III the reaction mixture was stirred over definite time at this temperature, allowed to attain room temperature, acidified with concentrated sulfuric acid to pH = 6 - 7.

The reaction mixture was left for the night, crystals were filtered through the Buchner funnel, washed with acetone, dried on air and grayish-yellow salt IV with m.p. > 300 °C was got, that further was recrystallized from water with carbon. After recrystallization solution of salt IV in water was heated to 85 - 90 °C and concentrated sulfuric acid was instilled (2 mole of H_2SO_4 per 1 mole of IV). After full adding of H_2SO_4 the reaction mixture was allowed to attain room temperature, crystals were filtered, washed with cold water to a neutral medium, then washed with acetone, dried and the target product I in white powder with m.p. = 315 - 320 °C was got.

RESULTS AND DISCUSSION

By changing molar ratio alkali (NaOH):reagent II we have found, that the yield of the product IV is maximal at fourfold excess of NaOH (figure 1).

Earlier it is noted [5] that excess of alkali brings to displacement of equilibrium in uracil II to more active enol form. Apparently at more than fourfold excess of NaOH fast consumption of oxidizer in side reactions is occurred, that has been observed earlier in paper [6].

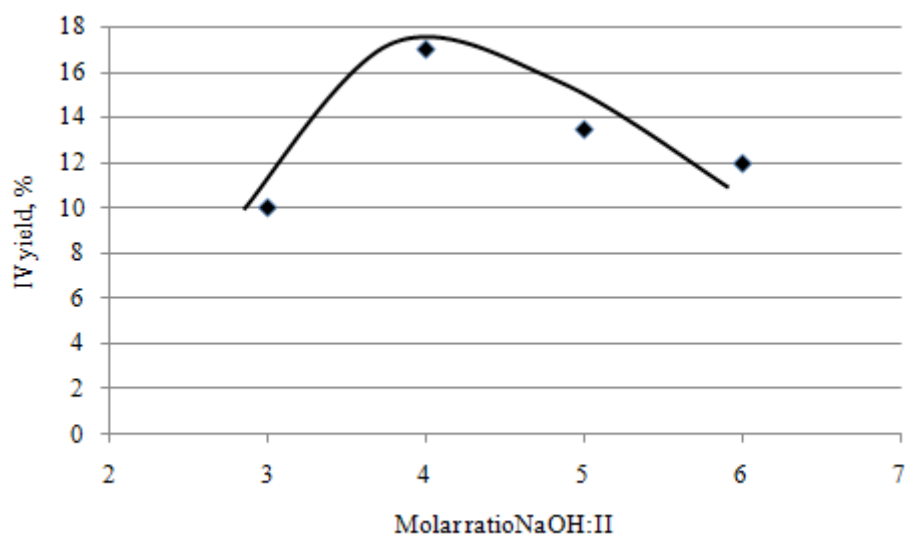


Figure 1. Dependence of salt IV yield on molar ratio NaOH:II
 Reaction conditions: T = 60 °C; NaOH concentration 24 %;
 molar ratio [III]:[II]=1.3:1; oxidation time 4 hours

We have determined the influence of alkali solution concentration on run of oxidation (figure 2).

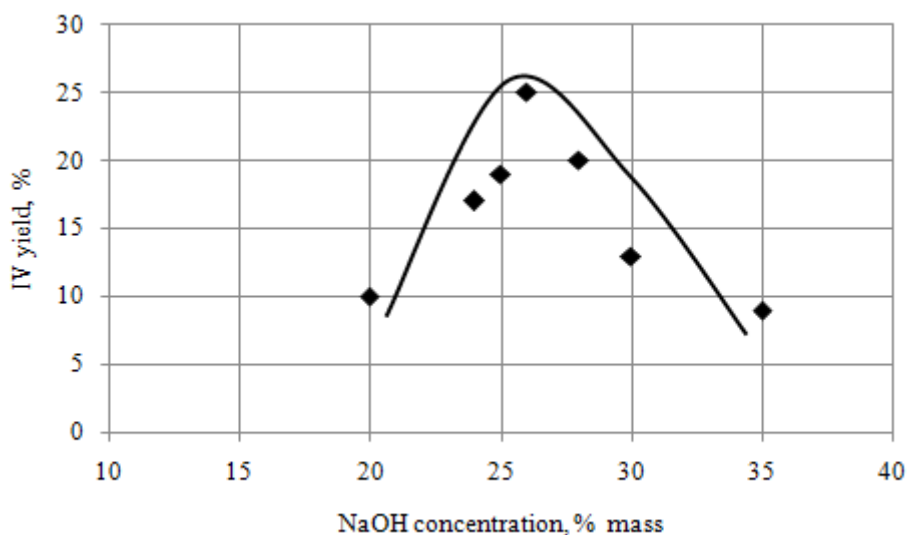


Figure 2. Dependence of salt IV yield on NaOH mass concentration
 Reaction conditions: T =60 °C; molar ratio [II]:[NaOH]:[III]=1:4:1.3;
 oxidation time 4 hours

The yield of the product IV increases with increasing of NaOH concentration from 20 to 26 %. Further increasing of concentration from 26 to 35 % leads to sharp loss of oxidation selectivity. Possibly in concentrated alkali mediums share of secondary conversions of compound IV is increased.

The influence of molar ratio oxidizer III:reagent II on the yield of the product IV has been studied (figure 3).

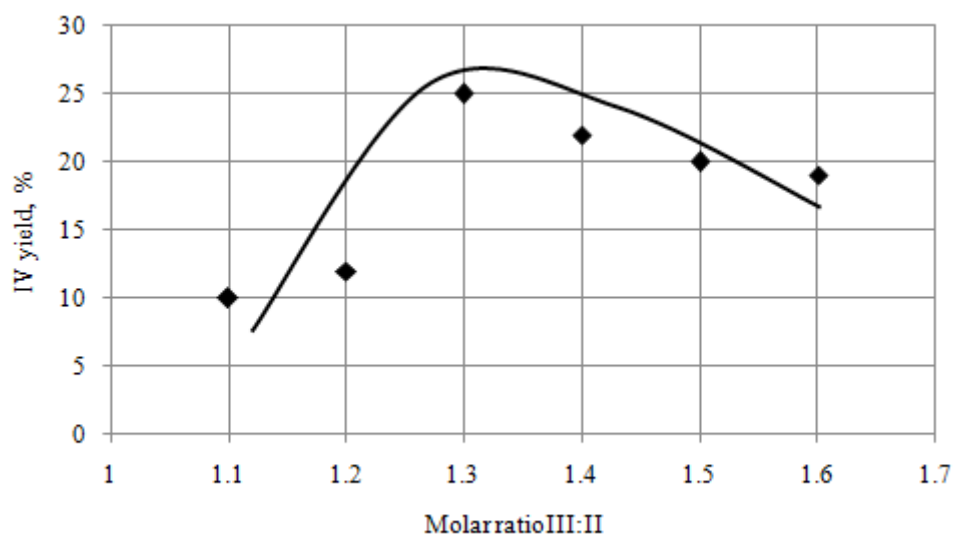


Figure 3. Dependence of salt IV yield on molar ratio III:II
Reaction conditions: T = 60 °C; NaOH concentration 26 %;
molar ratio NaOH:II=4:1; oxidation time 4 hours

Small excess of oxidizer III in the range from 1:1 to 1.3:1 increases the yield of the product IV. But further rising of this ratio leads to loss of selectivity that is obviously connected with salt IV oxidative conversion and impurities formation (its decomposition products).

The dependence of the product IV yield on oxidation time has been determined (figure 4).

The largest yield of the product IV is achieved at the oxidation time 4 hours. Further increasing of oxidation time leads to resinification of the reaction mixture and drop of selectivity.

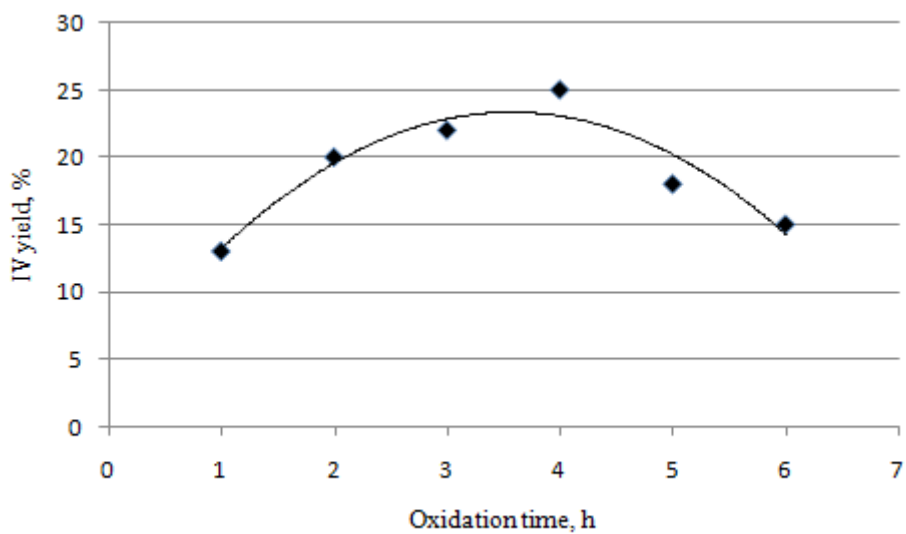


Figure 4. Dependence of salt IV yield on oxidation time
Reaction conditions: molar ratio [II]:[NaOH]:[III]=1:4:1.3;
T = 60 °C; NaOH concentration 26 %

The influence of temperature on the yield of the product IV has been determined in the range 30 - 80 °C (figure 5).

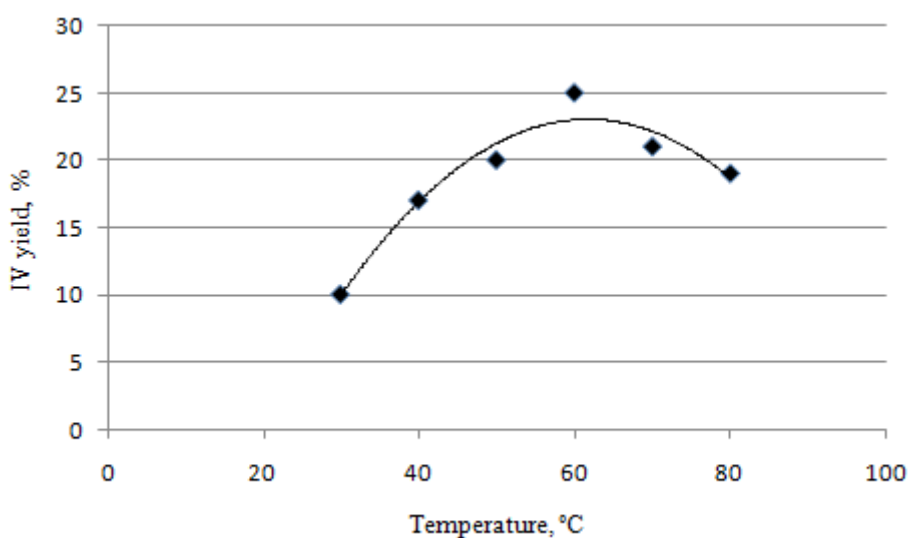


Figure 5 – Dependence of salt IV yield on temperature
Reaction conditions: molar ratio [II]:[NaOH]:[III]=1:4:1.3;
NaOH concentration 26 %; oxidation time 4 hours

It is determined, that the largest yield of the product IV is observed at the temperature 60°C.

Thereby, the following effective conditions of salt IV production can be suggested at the present stage of research on the basis of received results: temperature 60°C, NaOH concentration 26%, molar ratio of the raw materials [II]:[NaOH]:[III]=1:4:1.3, the oxidation time 4 hours.

References

1. Лазарева Д.Н. Стимуляторы иммунитета. М.: Медицина, 1985. 256 с.
2. Behrond R., Grunewald R. Oxydation des metyluracils // Justus Liebigs Annalen der chemie. 1962. P. 186-204.
3. Hurst D. T. Application of the Elbs Persulfate Oxidation to the preparation of 5-hydroхуриминес // Aust. J. Chem. 1983. No. 36. P. 1285-1289.
4. 6-Метилурацил-5-аммонийсульфат в качестве исходного соединения для синтеза оксипроизводных 6-метилурацила: пат. 2000298 Рос. Федерация; опубл. 07.09.1993, Бюл. № 33.
5. Иванов С.П., Старикова З.А., Муринов Ю.И. Кето-енольное равновесие и самосборка 5-гидрокси-6-метилурацила в водных растворах: тез. докл. 1 Международной молодежной конференции. – Казань, 2002.
6. Кривоногов В.П., Толстиков Г.А., Ахунов И.Р. и др. Кинетические закономерности окисления метилурацила в реакции Эльбса // Химия гетероциклических соединений. 1997. № 12. С. 36-39.