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Reaction of Nitrous Acid on 5-Aminopyrimidines (I)

Sandmeyer Reaction of Diazotizated 5-Aminouracil. *

by

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5-Aminopyrimidine 유도체에 대한 아질산의 작용 [I]

Diazotizated 5-Aminouracil에 대한 Sandmeyer 반응

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요 약

Sandmeyer 반응으로 5-aminouracil 로부터 5-iodo-, 5-chloro- 및 5-bromouracil을 간편하게 합성하는 방법을 새로히 마련하였다.

이 방법에 따르면 5-halouracil이 75% 이상의 좋은 수율로 얻어지며, 부반응을 수반하지 않으므로 생성물의 정제가 쉽고 편리하게 5-halouracil을 얻을 수 있다는 이점이 있다.

Abstract

A new conventional method for the preparation of 5-iodo-, chloro- and bromouracil by Sandmeyer reaction was described.

According to this procedure, 5-halouracils have been prepared in high yields(up to 75%) without any difficulties to remove of impurities.

No appreciable competing reaction was observed.

In connection with a series of studies on the reaction of 5-aminopyrimidines with nitrous acid, this paper describes a novel and synthetically useful method for the preparation of 5-halouracils by Sandmeyer reactions. Despite of their numerous interesting physiological activities, particularly those of importance in potential anticancer activity, only limited number of synthetic methods for the preparation of 5-halouracils appeared in the literature as the complexity of reactions.

The reported yields of 5-halouracils were rather low (in most cases, they hardly exceeded over than 30 ~40%), and more frequently, several other competing reaction products were also formed from which complete removal of impurities are difficult.[1-8] The

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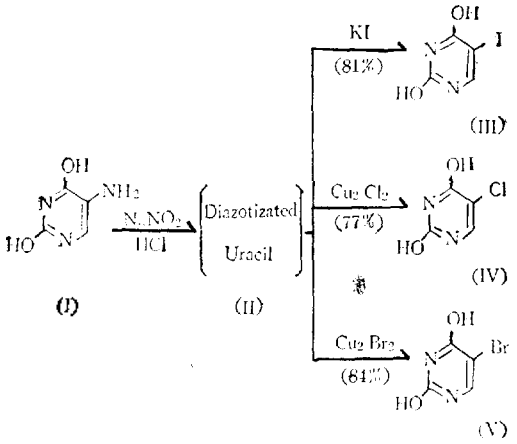
present work involved a conventional procedure in which the yield of 5-halouracils were 75% or more.

The Sandmeyer reaction was carried out according to the general procedure. In some instances, a slight modification of the general method increased the yield of 5-Iodouracil.

When solutions of 5-aminouracil diazotizated by Hodgson method[13] were poured into suspension of cuprous iodide in hydrochloric acid and hydrobromic acid, the yield of 5-Iodouracil were 85 per cent and 76 per cent, respectively. However, this procedure was rather complicated.

The reaction sequence as illustrated in following scheme was adopted.



In view of these results, those were observed in the processes of these Sandmeyer reaction, there were no difficulties to complete removal of impurities and neither competing reactions nor by-products were formed. The characteristic shape of these features were typical and advantage of this reaction. This evidence was proved in the case of the course to synthesize 5-chlorouracil.

The purity of the crude product, obtained by the above described method, was examined with the spectrum of Infrared and Ultraviolet without further purification, and it was found that the spectrum matched in any detail with the standard chart of spectrum published by Sadtler.[6]

Interestingly, there is no complexities to purify the products obtained from this method. With these methods not only the corresponding product of reaction formed in pure state but also the very satisfiable yields of the reaction product were obtained.

In addition to above stated advantage, this new method could be used for the large scale of preparation of 5-halouracil, as the starting materials are all easily accessible and the conventional procedure is utilized. As far as the results obtained by authors it is suggested this work has made possible the preparation of 5-halouracils with very satisfiable yield more consistently.

Regardless of whether the normal Sandmeyer reaction or the modified one was used, the result was almost identical.

Table 1 Physical and spectral data on 5-halouracils

Designation	M. P., U. V. (dec.)	max(mμ) [a] [b] (e×10⁻³)	Infrared [a] [b] [c] λ max(μ)	Beilstein test	Alkali fusion test
5-Iodo- (Ⅲ)	285~288°C	276 (2.86)	2.9, 3.2, 5.8, 6.0, 7.3, 8.1, 9.3, 9.9 11.5, 12.0, 13.1, 13.8 14.9	+	+
5-Chloro-(Ⅳ)	323~325	272 (2.46)	3.2, 5.9, 6.9, 7.5, 8.2, 9.2, 9.9, 10.6 11.5, 12.7, 13.2, 14.7	+	+
5-Bromo-(Ⅴ)	310~312	274 (7.0)	3.3, 5.9, 7.0, 7.5, 8.1, 8.7, 9.2, 9.5 10.0, 10.7, 11.6, 12.8, 13.3, 13.5, 14.8	+	+

Solubility test									
Cold H_2O	Hot H_2O	Cold EtOH	Hot EtOH	Et_2O	CCl_4	Dioxane	Petroleum ether	5%NaOH soln.	5% HCl soln.
I.S [e]	S [d]	I.S	S	I.S	I.S	I.S	I.S	S(d) [f]	S(Color change was observed, when heated.)
I.S	S	I.S	S	I.S	I.S	I.S	I.S	S(d)	S(Color change was observed)
I.S	S	I.S	S	I.S	I.S	I.S	I.S	S(d)	S(Color change was observed, when heated.)

a) The measurement was done with Beckman Model DK-2A and Perkin Elmer Infracord Model 137.
b) The Infrared spectrum and UV absorption maxima of chlorouracil was identical with that of Standard Spectrum by Sadtler. [6]
c) In 5-halouracils, the absorption peaks at shorter frequency was almost identical.
d) S; stands for soluble.
e) I.S; stands for insoluble.
f) d; stands for decomposition.

Table 1 shows the physical and spectral data of 5-halouracils obtained by this method.

The 5-halouracils have been shown in Table 1, the physical data are identical with that of published previously.[1-12]

Experimental

5-Iodouracil(Ⅲ) : A mixture of 130 mg. of 5-aminouracil(Ⅰ) and 7 ml. of 3 *N*-hydrochloric acid was heated on a water bath to dissolve, and then set in ice bath to cool. Into the cooled reaction mixture at 0°C, a solution of 100 mg. of sodium nitrite in 2 ml. of water was added drop by drop for 20 minutes with stirring. To this diazotizated mixture, with continuous stirring, a solution of 80 mg. of KI in 1 ml. of water was added for 5 minutes and stirred for another 15 minutes.

The dark brown colored reaction mixture was heated on a water bath for 40 minutes under stirring to complet the reaction. At this point the color of reaction mixture turned to yellow. During this treatment, vigorous reaction took place and large amount of gas was evolved. The reaction mixture was set in an ice box overnight and 5-iodouracil was separated out as yellowish crystals. The product was recrystallized from hot ethanol and dried over concentrated sulfuric acid in a vacuum desiccator. The yield 193 mg. (81% calculated from 5-aminouracil), yellowish prism, m. p., 285~288°C(dec.) [lit., m.p., 286°C(dec.)].[1,9,10]

5-Chlorouracil(Ⅳ) : To the stirred diazotizated mixture prepared as above, a solution of 120 mg. of cuprous chloride dissolved in 15 ml. of concentrated hydrochloric acid was added over the period of 7 minutes at 0°C, then the reaction mixture was heated on a water bath for 30 minutes to complete the reaction under stirring.

At this point, the reaction took place vigorously and gas was evolved. The dark-yellow reaction mixture turned to colorless. The resulting solution was set in an ice box overnight. The faintly yellow colored crystals were separated out and recrystalized from hot ethanol. The product was dried over concentrated sulfuric acid in a vacuum desiccator. Yield 103 mg. (77% calculated from 5-aminouracil), faint yellowish prism, m.p., 323~325°C(dec.)[lit., m.p. 324~325° (dec.),[8] m.p. 318~318.5°C(dec.)[11]].

5-Bromouracil(Ⅴ) : Diazotization was carried out as above. A solution of 110 mg. of cuprous bromide in 15 ml. of concentrated hydrobromic acid was added drop by drop to a stirred diazotizated mixture over the period of 10 minutes. The reaction mixture was stirred for additional 10 minutes. In this case, gas was bubbled mildly. Then reaction mixture was heated on a water bath for 30 minutes to complete the reaction under continuous stirring. The color of reaction mixture was changed first from green to dark brown and turned to colorless, and then finally, turned to dark brown again.

On standing overnight in an ice box, yellowish solid crystallized out from dark brown solution. The crystals were collected and the filtrate was concentrated under diminished pressure. From this concentrated filtrate, some additional crystals were afforded. The combined product was recrystallized from hot ethanol to give 160 mg. of 5-bromouracil(84% calculated from 5-aminouracil) as yellowish prism. m.p., 310~312°C (dec.) [lit., m.p. 311~312°(dec.)[12]].

Conclusion

Preparation of 5-iodo-, chloro- and bromouracils from 5-aminouracil by Sandmeyer reaction was described. According to this conventional procedure, 5-halouracils have been prepared in high yields. This method may account for a novel and synthetically useful way for the preparation of 5-halouracils.

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