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Yasuo Makisumi: Studies on the Azaindolizine Compounds. XIII.[*2] Alkylation of 5-Methyl-*s*-triazolo[1,5-*a*]pyrimidin-7-ol.

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Since 1936, various *s*-triazolopyrimidines have been suggested as additions to photographic emulsions to inhibit the development of fog.[1] Especially, 5-methyl-*s*-triazolo-[1,5-*a*]pyrimidin-7-ol (I) is useful as the stabilizing agent of photographic emulsions.

Recently, the structure and reactivity of I were investigated in order to interpret its photographic behavior by Chambers,[2] and it was reported that the ethylation of the silver salt of I with ethyl iodide afforded the two N-ethylated derivatives which were not identical with the known O-ethyl VI and C-ethyl (VIIa and VIIIa) derivatives. One IIa of these products was assigned to be 4-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one from the result that IIa was identical with the condensate of ethyl acetoacetate and 5-ethylamino-*s*-triazole (Va) which was obtained by the ethylation of 5-amino-*s*-triazole (IV). Moreover, Chambers supposed that the other product IIIa would be 3-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one, but the structure of IIIa was not proved. In the case of the ethylation of I with diethyl sulfate in alkaline solution, only IIa was obtained by Chambers.

On the other hand, Allen and his co-workers[3] reported that the methylation of I with dimethyl sulfate in alkaline solution afforded the two products which showed the

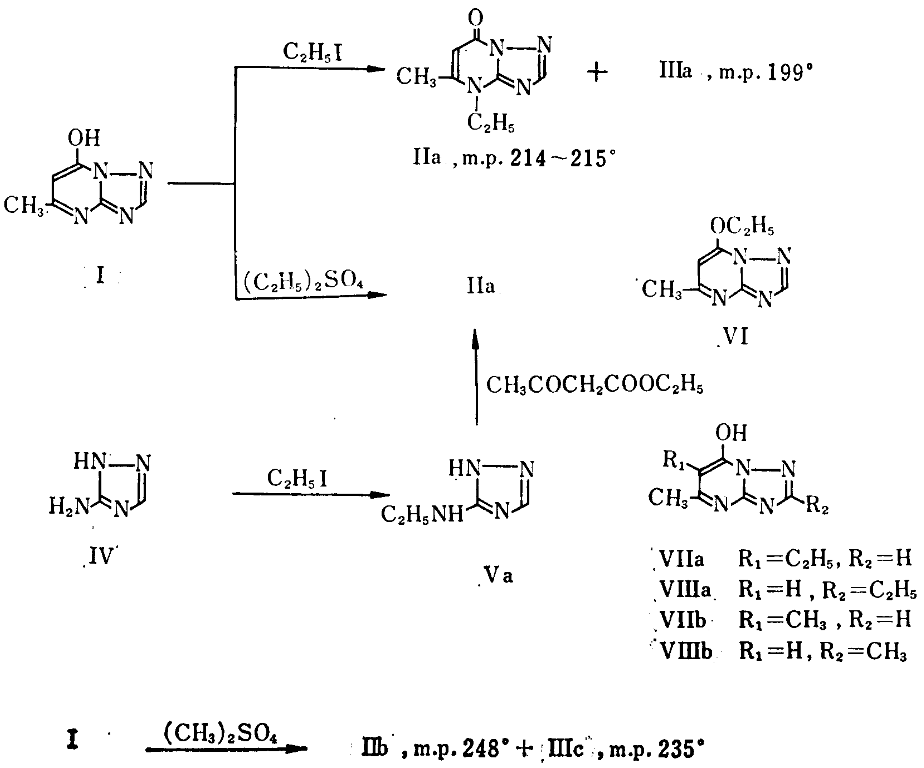

Chart. 1

[*1] Fukushima-ku, Osaka (牧角徳夫).

[*2] Part XII. Y. Makisumi, H. Kanō: This Bulletin, **11**, 69 (1963).

1) E. J. Birr: Z. wiss. Photo. **47**, 2 (1952); N. Heimbach, W. Kelly: U. S. Pat., 2,444,605 (1948).

2) V. C. Chambers: J. Am. Chem. Soc., **82**, 605 (1960).

3) C. F. H. Allen, G. A. Reynolds, J. F. Tinker, L. A. Williams: J. Org. Chem., **25**, 361 (1960).

melting points at 248° IIb and 235° IIIc, and those were assigned to be the N-methylated derivatives from the results that those were not identical with the known C-methyl derivatives (VIIb and VIIIb) and that those indicated lack of O-methylation by the Zeisel determinations. But, structure of these products (IIb and IIIc) was not made clear.

In the present work, the alkylation of I was investigated in connection with the alkyl rearrangement of 5-methyl-7-alkoxy-*s*-triazolo[1,5-*a*]pyrimidines in the preceding work.*[2]

When ethylation of the silver salt of I with ethyl iodide was carried out by the Chambers's method, two ethylated products were obtained which showed the melting points at 248~249° and 260~261° respectively. The former was identical with the authentic sample*[2] of 4-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one which was obtained by the condensation of ethyl acetoacetate with 5-ethylamino-*s*-triazole (Va). The latter was also identical with 3-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one*[2] which was obtained by the condensation of ethyl acetoacetate with 4-ethyl-5-amino-*s*-triazole (IXa). Therefore, it was confirmed that the compound IIIa reported by Chambers is 3-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one.

Ethylation of I with diethyl sulfate in aqueous sodium hydroxide gave two products and IIIa in addition to IIa reported by Chambers were isolated.

On the other hand, methylation of the silver salt of I with methyl iodide was carried out by the similar procedure to the Chambers's method and the two methylated products were obtained which showed the melting points at 248~249° IIb and 260~261° IIIb. The former was identical with 4,5-dimethyl-*s*-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one which was obtained by the authors*[2] from 5-methylamino-*s*-triazole (Vb). The latter was also identified with 3,5-dimethyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one*[2] which was obtained from 4-methyl-5-amino-*s*-triazole (IXb). Methylation of I with dimethyl sulfate in aqueous sodium hydroxide afforded two methylated products. One product corresponding to the compound, m.p. 248° which was obtained by Allen, was identified with IIb as shown above. The other product with differed in the melting point from the compound IIIc reported by Allen, was identical with IIIb as also shown above. In this work, the product corresponding to IIIc was not isolated.

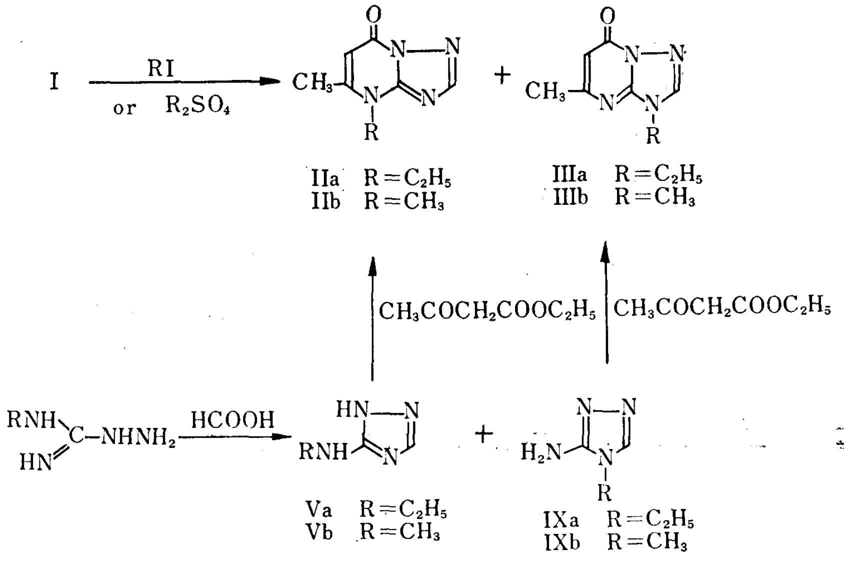

Chart 2.

From these results, the structure of the alkylated products of I was established and it was made clear that the alkylation of I occurs at the 3- and 4-positions of the *s*-triazolo[1,5-*a*]pyrimidine ring.

Experimental[*3]

Reaction of the Silver Salt of (I) with Ethyl Iodide——This reaction was carried out by the method of Chambers2) and colorless scales IIa, m.p. 214~215° and colorless needles IIIa, m.p. 199~200° were obtained in a ratio of about 2 : 1. IIa and IIIa were identified respectively with the authentic samples[*2] of 4-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one and 3-ethyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one by mixed melting point and by IR spectral comparison.

Reaction of (I) with Diethyl Sulfate——To a stirred solution of 7.5 g. of I in 50 cc. of 5% NaOH, 8 g. of Et_2SO_4 was added in small portions over a period of 2 hr. and the mixture was stirred at 45~50° for 5 hr. An additional 12.5 cc. of 20% NaOH was added and then 8 g. of Et_2SO_4 was further added in small portions at 45~50°. The mixture was stirred continuously at the same temperature for 8 hr. and the reaction mixture was extracted thrice with $CHCl_3$. The extract was dried over $CaCl_2$ and evaporated to leave crude products (4.75 g.). The aqueous layer was concentrated to dryness in a reduced pressure and the residue was extracted with hot $CHCl_3$ giving 0.2 g. of the crude products. The both crude products were combined, dissolved in $CHCl_3$, and passed through a column (30×1.5 cm.) of alumina. The column was eluted with $CHCl_3$ and the first product (2.21 g.) was recrystallized from EtOH to give 1.85 g. of colorless scales, m.p. 214~215°. *Anal.* Calcd. for $C_8H_{10}ON_4$: C, 53.92; H, 5.66; N, 31.45. Found : C, 53.85; H, 5.73; N, 31.24. This was identified with IIa by mixed melting point. The second product (1.9 g.) was recrystallized from EtOH to yield 1.58 g. of colorless needles, m.p. 199~200°. *Anal.* Calcd. for $C_8H_{10}ON_4$: C, 53.92; H, 5.66; N, 31.45. Found : C, 54.07; H, 5.79; N, 31.35. This showed no depression of melting point on admixture with IIIa obtained as above.

Reaction of the Silver Salt of (I) with Methyl Iodide——In a 300 cc. flask fitted with reflux condenser were placed 12.9 g. of Ag salt and 100 cc. of dry benzene. The apparatus was dried by azeotropic distillation of benzene and H_2O. To the resulting mixture, 7.8 g. of MeI and 0.7 cc. of pyridine were added and the mixture was refluxed for 10 hr. The solids were separated by filtration and triturated with hot $CHCl_3$. The $CHCl_3$ and benzene filtrates were combined and evaporated to dryness (2.85 g.). This was dissolved in $CHCl_3$, passed through a column (30×1.5 cm.) of alumina, and the column was eluted with $CHCl_3$. The first product (1.66 g.), m.p. 243~246° was recrystallized from EtOH to give 1.38 g. of IIb as colorless scales, m.p. 248~249°. *Anal.* Calcd. for $C_7H_8ON_4$: C, 51.21; H, 4.91; N, 34.13. Found : C, 51.34; H, 5.08; N, 34.12. This was identified by meixed melting point and the IR spectrum with 4,5-dimethyl-*s*-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one.[*2] The second product (0.64 g.), m.p. 255~257° was recrystallized from EtOH to 0.52 g. of IIIb as white needles, m.p. 260~261°. *Anal.* Calcd. for $C_7H_8ON_4$: C, 51.21; H, 4.91; N, 34.13. Found : C, 51.27; H, 4.88; N, 34.18. This was identical with respect to IR spectrum and mixed melting point with 3,5-dimethyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-one.

Reaction of (I) with Dimethyl Sulfate——To a stirred solution of 7.5 g. of I in 50 cc. of 5% NaOH, 6.8 g. of Me_2SO_4 was added in small portions over a period of 2 hr. and the mixture was stirred at 45~50°. An additional 12.5 cc. of 20% NaOH was added after 2 hr. and then 6.2 g. of Me_2SO_4 was further added in small portions into this solution. The mixture was stirred continuously at the same temperature for 7 hr. The reaction mixture was extracted thrice with $CHCl_3$, the extract was dried over Na_2SO_4, and evaporated to dryness giving 3.65 g. of the crude products. The aqueous layer was concentrated to dryness in a reduced pressure and the residue was extracted with hot $CHCl_3$ giving 2.05 g. of the crude products. The both crude products were combined, dissolved in $CHCl_3$, and passed through a column of alumina. The column was eluted with $CHCl_3$ and the first product (2.88 g.) was recrystallized from EtOH to yield 2.13 g. of colorless scales, m.p. 248~249°, which was identified with IIb by mixed melting point and the IR spectrum. The second product (1.87 g.) was recrystallized from EtOH to afford 1.68 g. of white needles, m.p. 260~261°, which was identified with IIIb by mixed melting point and the IR spectrum.

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Summary

The alkylation of 5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7-ol (I) with alkyl iodide and dialkyl sulfate always afforded the two N-alkylated products (IIa-b and IIIa-b). The structure of these products was established to be 4-alkayl-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidin-7(4*H*)-ones and 3-alkyl-5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7(3*H*)-ones respectively.

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[*3] All melting points are uncorrected.