

A NEW SYNTHESIS OF PYRIMIDO[5,4-e]-as-TRIAZINE DERIVATIVES

Keitaro Senga* and Sadao Nishigaki

Pharmaceutical Institute, School of Medicine, Keio University35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

The reaction of 5-arylaazo-6-arylidenehydrazino-1,3-dimethyluracils (II), prepared by the diazotization of 6-arylidenehydrazino-1,3-dimethyluracils (I), with dimethylformamide dimethylacetal afforded the corresponding 3-arylfervenulins (3-aryl-6,8-dimethylpyrimido[5,4-e]-as-triazine-5,7(6H, 8H)-diones) (V).

The discovery of the triad of antibiotics fervenulin, 2-methylfervenulone (MSD-92), and toxoflavin, has stimulated recent considerable interest in the chemistry of pyrimido[5,4-e]-as-triazines.¹ In connection with our studies on the pyrimido[5,4-e]-as-triazines as potential medicinal agents,² we now report a new synthetic approach to 3-arylfervenulins (3-aryl-6,8-dimethylpyrimido[5,4-e]-as-triazine-5,7(6H,8H)-diones) (Va-e) by the reaction of readily accessible 5-arylaazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h) with dimethylformamide dimethylacetal (DMFDMA).

Treatment of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils (Ia-e)³ with diazotized arylamines by the conventional method⁴ gave the desired starting materials (IIa-h) in 30-56% yields. Refluxing of the appropriate uracils (IIa-e) (0.0005 mol) with DMFDMA (2 ml) at 150°C for 5 h, followed by concentration of the reaction mixture in vacuo and addition of ethanol, caused the separation of the corresponding products (Va-e)⁵ in 20-60% yields. The yields of (Va-e) were depending upon the nature of arylidenehydrazino group of (IIa-e), i.e., the uracils with an electron-withdrawing arylidenehydrazino group gave better results than those with an electron-releasing group. Similar substituent effect was also observed on the arylazo group, i.e., treatment of the uracils (IIf-h), which possess a strong electron-withdrawing p-nitrophenylazo group, with DMFDMA caused pronounced improvement in the yield of (Va) (82-97%) (Table).⁶

It should be noted that the reaction of (IIa) with dimethylformamide in stead of DMFDMA under the same conditions resulted in the recovery of (IIa). Therefore, the reaction of (IIa-h) with DMFDMA leading to (Va-e) can be best explained by assuming the initial formation of the intermediate (III) through the enol form of (II), followed by 1,5-migration of the 1-methoxytrimethylamino group to give (IV), which possesses a triazahexatriene-type structure. This could undergo intramolecular cycloaddition and aromatization by loss of 1-arylamino-1-methoxytrimethylamine to give (V) as a final product. The C-O bond formation as exemplified by (III) has been speculated in the reaction of certain enols with DMFDMA⁷ and the intramolecular cycloaddition of aza analogs of hexatriene has ample precedents.⁸ To our knowledge, this is the first example in which 5-arylazopyrimidine was directly used as a nitrogen source for N-4 of the pyrimido[5,4-e]-as-triazine ring system (Scheme).

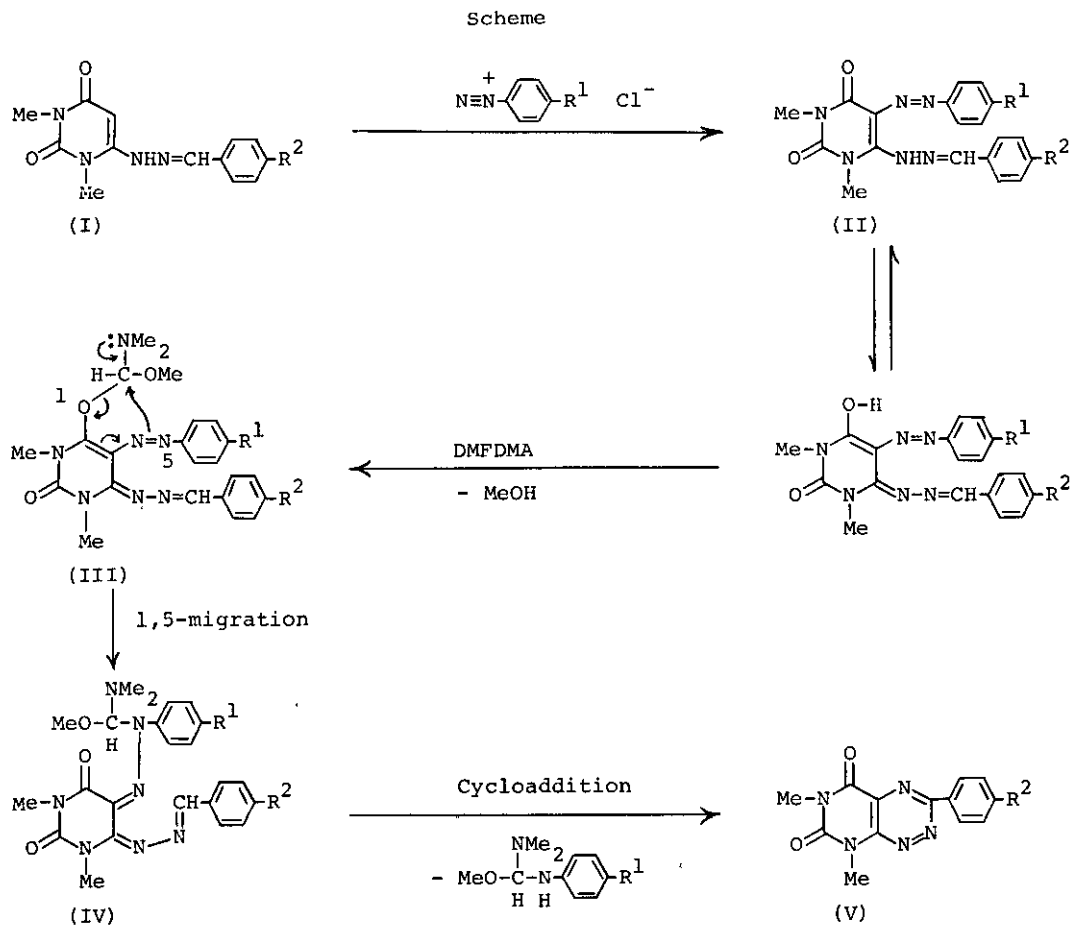


Table 5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils and 3-Arylfervenulins

| 5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils | | | | | 3-Arylfervenulins | | | |
|--|-----------------|------------------|---------|----------|----------------------|------------------|---------|----------|
| Compd. ^{a)} | R ¹ | R ² | Mp(°C) | Yield(%) | Compd. ^{b)} | R ² | Mp(°C) | Yield(%) |
| IIa | H | H | 187-188 | 56 | Va | H | 273-275 | 50 |
| IIb | H | Br | 213-215 | 47 | Vb | Br | >300 | 60 |
| IIc | H | Cl | 200-202 | 56 | Vc | Cl | 280-283 | 56 |
| IId | H | OMe | 144-145 | 31 | Vd | OMe | 263-264 | 26 |
| IIe | H | NMe ₂ | 176-178 | 30 | Ve | NMe ₂ | >300 | 20 |
| IIf | NO ₂ | H | 256-257 | 46 | Va | H | — | 88 |
| IIg | NO ₂ | Br | 235-236 | 42 | Va | H | — | 97 |
| IIh | NO ₂ | Cl | 223-225 | 34 | Va | H | — | 82 |

a) All compounds were recrystallized from DMF.

b) All compounds were recrystallized from EtOH.

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ACKNOWLEDGEMENT

The authors are grateful to Mr. K. Nagahara of Kitasato University for elemental analyses, and to Dr. K. Ishii and Mr. K. Chiba of this school for mass spectra.

Received, 17th December, 1980