NOVEL METHOD FOR THE SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINE-2,4-DIONES FROM 5,7-DIMETHYLPYRIMIDO[4,5-e]-1,2,4-TRIAZINE-6,8-DIONE

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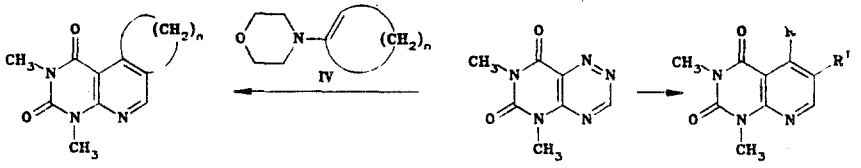
We have found that 5,7-dimethylpyrimido[4,5-e]-1,2,4-triazine-6,8-dione (I) (isofervenulin) undergoes ($4\pi + 2\pi$) cycloaddition reactions with reverse electronic requirements and is converted in the process to pyrido[2,3-d]pyrimidinediones. Treatment of compound I with acetone in the presence of diethylamine, triethylamine, or boron trifluoride etherate leads to the formation of 1,3,5-trimethylpyrido[2,3-d]pyrimidine-2,4-dione [IIa, mp 158-159°C, 25-94% yield, PMR spectrum ($CDCl_3$): 2.84 (3H, d, $J_{CH_3,6}$ = 0.6 Hz, 5-CH_3), 3.46 (3H, s, 3-CH_3), 3.71 (3H, s, 1-CH_3), 6.97 (1H, dd, J_{67} = 5.1, J_{6,CH_3} = 0.6 Hz, 6-H), 8.43 ppm (1H, d, J_{76} = 5.1 Hz, 7-H)].



IIIa,b I IIa-g

III a n=3, b n=4; II a, c, f, g R=CH_3, b R=H, d R=C_2H_5, e R=C_6H_5; a, b, d, e R^1=H, c R^1=CH_3, f R^1=$COCH_3$, e R^1=$COOC_2H_5$

When a large excess of diethylamine was used in the reaction, compound IIb was isolated as a side product in the reaction [mp 163-164,C, 17% yield, PMR spectrum ($CDCl_3$): 3.49 (3H, s, 3-CH_3), 3.73 (3H, s, 1-CH_3), 7.21 (1H, dd, J_{65} = 7.7, J_{67} = 4.8 Hz, 6-H), 8.47 (1H, dd, J_{56} = 7.7, J_{57} = 1.9 Hz, 5-H), 8.66 ppm (1H, dd, J_{76} = 4.8, J_{75}= 1.9 Hz, 7-H)]. Treatment of isofervenulin I with methyl ethyl ketone, acetophenone, acetylacetone, and acetoacetate ester resulted in the formation of pyridopyrimidinediones IIc-g (IIc, mp 150-152°K, 80% yield; IIe, mp 186-187°C, 56% yield; IIf, mp 186-187°C, 95% yield; IIg, mp 117-118°C, 72% yield).

Isofervenulin I reacts with enamines IV in the absence of a catalyst to give cycloalkano[c]pyrido[2,3-d]pyrimidinediones IIIa, b as well as cyclic ketones in the presence of diethylamine. Compound IIIa: mp 164-165°C, 58-76% yield; PMR spectrum ($CDCl_3$): 2.19 (2H, m, CH_2), 2.96 (2H, m, CH_2), 3.46 (3H, s, 3-CH_3), 3.47 (2H, m, CH_2), 3.71 (3H, s, 1-CH_3), 8.42 ppm (1H, s, 7-H). Compound IIIb: mp 127-129°C, 82-94% yield.

In contrast to the behavior of compound I, its naturally occurring analog fervenulin (6,8-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7-dione) reacts with acetone in the presence of diethylamine to generate the addition product about the N(4)-C(4a) bond, namely, 4a-acetonylfervenulin [mp 138-140°C; 12% yield; PMR spectrum ($CDCl_3$): 2.06 (3H, s, $COCH_3$), 3.00 (2H, m, CH_2), 3.31 (3H, s, N-CH_3), 3.34 (3H, s, N-CH_3), 7.51 ppm (1H, br.s, 3-H)].

Since isofervenulin [1] is an accessible compound, the reactions discussed above open up new possibilities in the synthesis of pyrido[2,3-d]pyrimidinediones.

LITERATURE CITED

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