REACTION OF PHERVENULIN-3-ONE WITH o-PHENYLENE DIAMINES

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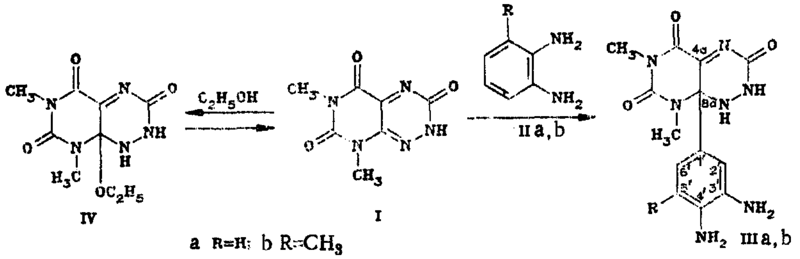
We have found that in the reaction of equimolar amounts of 2,3,5,6,7,8-hexahydro-6,8-dimethylpyrimido[5,4-e][1,2,4]triazine-3,5,7-trione (phervenulin-3-one) (I) and o-phenylenediamines IIa, b in boiling ethanol for 3 h in the presence of hydrochloric acid, 8a-derivatives of phervenulin-3-one hydrochloride IIIa, b form. Treatment of aqueous solutions of these hydrochlorides with sodium acetate can yield the free bases IIIa, b . The yield of 1,2,3,5,6,7,8,8a-octahydro-6,8-dimethyl-8a-(3,4-diaminophenyl)pyrimido[5,4-e][1,2,4]triazine-3,5,7-trione (IIIa) is 55-60%, mp 270-272°.



PMR spectrum (DMSO-D_6): 3.08 (s, N-CH_3); 3.28 (s, N-CH_3); 4.59 (br. s, 1- and 2-NH_2); 6.33 (d.d, 6'-H, $J_{6'5'}$ = 8.2 Hz, $J_{6'2'}$ = 2.2 Hz); 6.43 (d, 2'-H, $J_{2'6'}$ = 2.2 Hz); 6.51 (d, 5-H, $J_{5'6'}$ = 8.2 Hz); 7.80 (d, 1-NH, J_{12} = 1.90 Hz); 9.84 ppm (d, 2-NH, J_{21} = 1.90 Hz). ^{13}C NMR spectrum (DMSO-D_6): 28.4 (N-CH_3); 29.8 (N-CH_3); 59.7 $C_{(8a)}$); 110.2 ($C_{(2)}$); 113.8 ($C'_{(6)}$); 114.0 ($C'_{(5)}$); 125.5 ($C'_{(1)}$); 135.1 ($C_{(4a)}$); 136.0 ($C'_{(3)}$); 138.5 ($C'_{(4)}$); 149.7 ($C_{(7)}$); 151.4 ($C_{(3)}$); 165.9 ($C_{(5)}$). IR spectrum (in mineral oil): 1670, 1696, 1738 (CO); 3063, 3190, 3308, 3373, 3427 cm^{-1} (NH and NH_2). Yieled of 1,2,3,5,6,7,8,8a-octahydro-6,8-dimethyl-8a-(3,4-diamino-5-methylphenyl)pyrimido[5,4-e][1,2,4]triazine-3,5,7-trione (IIIb), 65-70%, mp 297-298°. PMR spectrum (DMSO-D_6): 1.96 (sm, CH_3); 3.00 (s, N-CH_3); 3.21 (s, N-CH_3); 4.31 (br. s, NH_2); 4.50 (br. s, NH_2); 6.24 (s, CH_{arom}); 7.83 (d, 1-NH, J_{12} = 1.80 Hz); 9.90 ppm (d, 2-NH, J_{21} = 1.80 Hz). IR spectrum (in mineral oil): 1685, 1696, 1742, (CO), 3056, 3158, 3193, 3395, 3428 cm^{-1} (NH and NH_2).

4-Chloro-, 4-methyl-, 4,5-dimethyl-, and 3,6-dimethoxy-o-phenylene diamines do not add to phervenulin-3-one because of steric hindrance. In these cases 1,2,3,5,6,7,8,8a-octahydro-6,8-dimethyl-8a-ethoxypyrimido[5,4-e][1,2,4]triazine-3,5,7-trione (IV) was isolated from the reaction mixture in 65-70% yield; heating it at 153° for 3-4 h gives phervenulin-3-one in quantitative yield. PMR spectrum of IV (DMSO-D_6): 1.06 (t, CH_3, J = 6.7 Hz); 3.11 (s, N-CH_3); 3.21 (s, N-CH_3); 3.37 (q, CH_2, J = 6.7 Hz); 8.78 (d, 1-NH, J = 1.90 Hz); 10.55 ppm (d, 2-NH, J= 1.90 Hz). The $C_{(8a)}$ signal in the ^{13}C NMR spectrum appears at 58.2 ppm. IR spectrum (in mineral oil): 1686, 1699, 1710, 1742 (CO), 3100, 3150, 3235, 3310 cm^{-1} (NH).

In the absence of acid, formation of III was not observed. Apparently because of salt formation, acid not only activates phervenulin-3-one with respect to nucleophiles, but also determines the orientation of the o-phenylenediamine molecule in the reaction.

This reaction, which is the first example of nucleophile addition at the nodal $C_{(8a)}$ atom in pyrimidotriazine antibiotics, opens up a new route to the modification of these compounds.

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