The Preparation of Ethyl 7-Azapteroate and Related Compounds (1)

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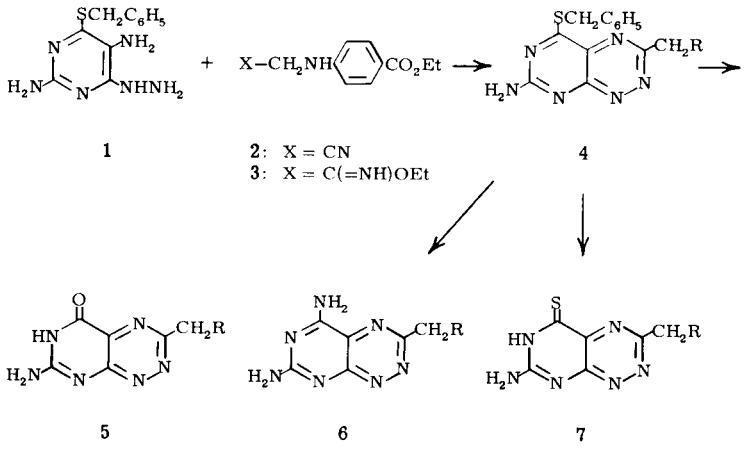
Sir:

The importance of the action of dihydrofolic reductase on the pyrazine ring of folic acid, especially the 7,8-double bond, and the structural relationship of the pteridine ring of folic acid to the 7-azapteridine (pyrimido[5,4-*e*]-*as*-triazine) ring of toxoflavin (2) and related antibiotics (2,3) prompted us to investigate the preparation and ascertain the biological properties of 7-azafolic acid and its analogs. In this report the preparation of ethyl 7-azapteroate and its 4-amino and 4(3*H*)-thione analogs is described.

Alkylation of ethyl *p*-aminobenzoate with cyanomethyl *p*-toluenesulfonate (4) in ethyl acetate for 48 hours gave ethyl *p*-[(cyanomethyl)amino]benzoate (**2**) in 78% yield (5). The base catalyzed (6) addition of ethanol to the cyano group of **2** gave the imino ether **3** which was not isolated but condensed at room temperature with the 5-amino-4-hydrazinopyrimidine **1** (7) to give directly the 7-azapteridine **4** (8) in 41.5% yield. Apparently a dihydro derivative of **4** is first formed, which undergoes air oxidation to give the heteroaromatic 7-azapteridine. Previously we demonstrated that the benzylthio group of this type of compound is readily displaced with nucleophiles (7). Treatment of an aqueous DMSO solution of **4** with potassium bicarbonate at 90° for 18 hours gave a 21% yield of ethyl 7-azapteroate (**5**) (8). Similarly, the reaction of **4** with a mixture of DMAc and 10% ethanolic ammonia at 60° for 5 hours gave the corresponding diamino-7-azapteridine **6** (8) in 61% yield. The corresponding thione **7** (8) was obtained in 74% yield by reaction of **4** with hydrated sodium hydrosulfide in DMF at 80° for 2 hours. Several methods are being investigated for the incorporation of the remaining portion of the folic acid side chain.



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(8) Satisfactory elemental analyses and spectral data were obtained for this compound.