SYNTHESIS OF THE 6-AZA ANALOG OF TRIMETHOPRIM

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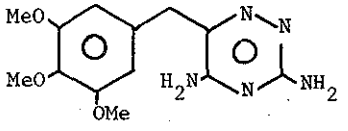
The synthesis of the 6-aza analog of Trimethoprim, 3,5-diamino-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine, a potential antibacterial and antimalarial agent, is described.

Trimethoprim, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine is a therapeutically useful drug in the treatment of various bacterial infections. A mixture of Trimethoprim and Sulfalene has shown dramatic effects in clinical trials against Pyrimethamine-resistant Plasmodium falciparum malaria.[1] Trimethoprim has also been effective in cases of blood induced Vivax malaria.[1] The biological activity of this compound suggested that its 6-aza analog, 3,5-diamino-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazine (1), might exhibit similar properties.



1

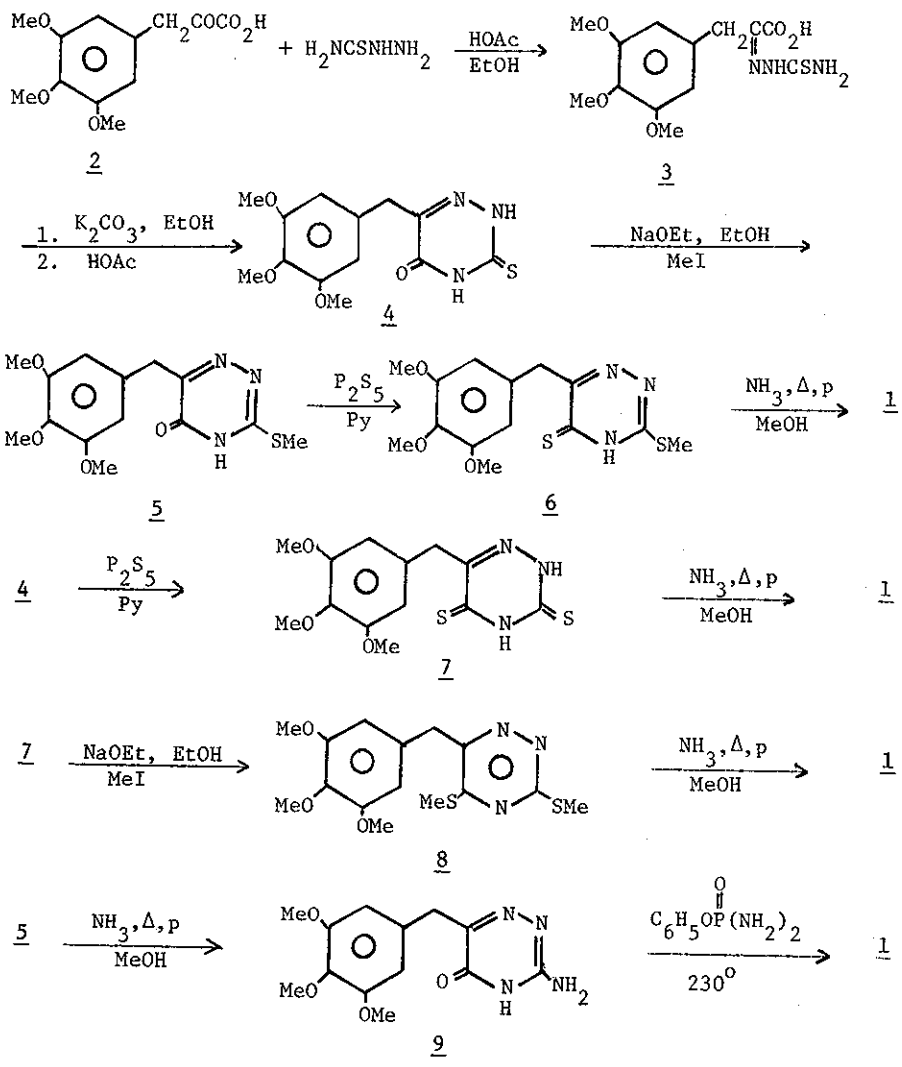
There is only one instance of a 3,5-diamino-6-benzyl-1,2,4-triazine cited in the literature but no procedure is given for its synthesis.[2] An unsuccessful attempt to prepare 1 has been previously reported.[3] This

effort involved the condensation of 3,4,5-trimethoxyphenylpyruvonitrile with aminoguanidine bicarbonate; the starting pyruvonitrile and the corresponding phenylacetic acid were the sole compounds recovered. To date, this condensation has only been accomplished with pyruvonitriles disubstituted on the methylene carbon. Results obtained in our laboratory[4] confirmed this report and prompted us to explore alternate synthetic pathways for the preparation of 1. Scheme I represents the first successful synthesis of 1 as well as a general route to substituted 3,5-diamino-6-benzyl-1,2,4-triazines.

Our initial approach involved the preparation of (3,4,5-trimethoxyphenyl) pyruvic acid 2-thiosemicarbazone, (3), mp 203-204°, via the reaction of the corresponding pyruvic acid (2) with thiosemicarbazide (92% yield). Compound 3 was cyclized with potassium carbonate in ethanol. Acidification of the reaction mixture with glacial acetic acid afforded 3,4-dihydro-3-thioxo-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazin-5(2H)-one, (4), mp 219-220° in 72% yield. Compound 4 was treated with phosphorus pentasulfide in boiling pyridine to give the corresponding 3,5-dithioxo derivative, (7), in 40% yield, mp 231-233°.

Triazine 4 was converted to 3-(methylthio)-6-(3,4,5-trimethoxybenzyl)-1,2,4-triazin-5(2H)-one, (5), mp 244-247°, via methyl iodide in ethanolic sodium ethoxide (73% yield). Compound 7 was similarly treated to give the corresponding 3,5-bis(methylthio) derivative, (8), mp 144-146°, in 67%

Scheme I


MeO
CH2COCO2H
MeO
OMe
+ H2NCSNHNH2
HOAc
EtOH
CH2CCO2H
NNHCSNH2
2
3
1. K2CO3, EtOH
2. HOAc
NH
O
N
H
S
4
NaOEt, EtOH
MeI
SMe
5
P2S5
Py
6
NH3, Δ, p
MeOH
1
7
8
MeS
9
C6H5OP(NH2)2
230°

The reaction of 5 with phosphorus pentasulfide in pyridine gave the 5-thioxotriazine 6, mp 186-189° (49% yield). Treatment of 6, 7, and 8 with methanolic ammonia in an autoclave at 150-160° afforded 1 in 23%, 10%, and 10% yields, respectively; M^+ 291 (49%); ν_{max}^{KBr} 3520, 3485, 3345, 1620, 1585, and 1120 cm^{-1}; δ (DMSO-d_6) 3.61 (s, 6H, meta-ArOMe), 3.71 (s, 3H, para-ArOMe), 3.87 (s, 2H, $-CH_2Ar$), 6.03 (s, 2H, NH_2), 6.60 (s, 2H, (Ar-H), and 6.75 ppm (s, 2H, NH_2).

Compound 1 was also prepared by converting 5 to the corresponding 3-amino derivative, (9), mp 272-274°, with methanolic ammonia in an autoclave (47% yield). When 9 was heated with phenylphosphorodiamidate,[5] at 230°, 1 was obtained in 11% yield.

All compounds gave satisfactory microanalyses and had the correct M^+ peak in their mass spectra.

ACKNOWLEDGEMENT. The authors wish to thank Ms. Vinka Parmakovich and Ms. Frances Hoffman of Columbia University, New York, N.Y. for providing the mass spectra of the compounds reported in the present communication.

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Received, 14th May, 1976