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A NEW PTERIDINE SYNTHESIS

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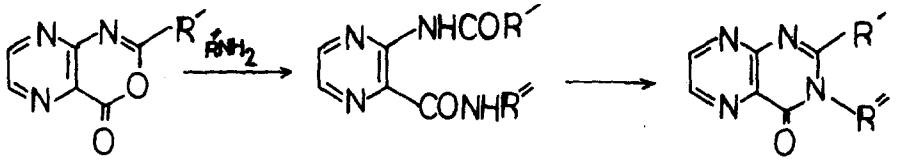
Pteridine derivatives are found widely in nature and are concerned with growth processes and the metabolism of one carbon units. Additionally many synthetic pteridines have been found useful in medicine as anticancer, antiviral, and diuretic drugs.[1] Such compounds have mainly been prepared from pyrimidine intermediates although synthesis from pyrazines are known.[2] In view of the recent preparation of several pteridin-4(3H)-ones[3] we wish to report a new synthesis of pteridines from pyrazines which enables 2,3-disubstituted pteridinones to be prepared.[4]



1 2 3

Treatment of 2-aminopyrazine-3-carboxylic acid with propionic anhydride under reflux for 30 min. yielded 2-ethylpyrazine[2,3-d] - [1,3]oxazin-4-one (1;R'=C_2H_5) m.p. 142° in 68% yield. Acetic anhydride similarly yielded the 2-methyl derivative (1;R'=CH_3) m.p. 150° (96%). The oxazinones were identified by the characteristic νC=O absorption at 1780-1790cm^{-1} and by n.m.r. and mass spectrometry. The oxazinones proved to be reactive towards nucleophiles and hydrolysis by moisture occurred rapidly to regenerate the amino acid. Trituration of the 2-ethyloxazinone

with ammonia (0.88d) yielded 2-propionamidopyrazine-3-carboxamide (2;R'=C_2H_5,R"=H) which was converted into 2-ethylpteridin-4(3H)-one (3;R'=C_2H_5, R"=H) m.p. 300° (decomp.) in 70% yield by further treatment with ammonia for 24h. This pteridinone was also prepared by the action of ammonia on methyl 2-propionamidapyrazine-3-carboxylate. The 2-methyloxazinone yielded 2-methylpteridin-4(3H)-one (3;R'=CH_3, R"=H) m.p. 334° (decomp.) (80%) under similar conditions. Cyclisation to the pteridinone (2→3) was indicated by an increase in νC=O (1680 1705 cm^{-1}) and a decrease in N-H (3400 3200 cm^{-1}) infrared absorptions. The mass spectra of the pteridinones indicated a main fragmentation initiated by loss of CO and then R'-CN from the molecular ion. The 2-ethyl compound additionally showed an intense M-H fragment.

Pteridinones were also obtained when the oxazinones were treated with aromatic amines such as aniline (3;R'=CH_3, R"=C_6H_5, m.p. 237°) and with hydroxylamine (3;R'=CH_3, R"=OH, m.p. 257°). This latter amine yielded cyclic hydroxamic acids which gave a deep wine-red colour with ferric chloride. Aliphatic amines such as benzylamine or methylamine yielded amides (2) which could not be cyclised on treatment with base or heat, but dissolution in phosphoryl chloride yielded the pteridinone. In this way 2-acetamidopyrazine-3-benzylamide gave 3-benzyl-2-methyl-pteridin-4(3H)-one (3;R'=CH_3, R"=C_6H_5-CH_2).

REFERENCES

1. A. Burger, 'Medicinal Chemistry', Third Edition 1970, Wiley-Interscience, New York.
T.S. Osdene, P.B. Russel, and L.J. Rane, J.Med.Chem., 1967, 10, 431.
C.P. Hegarty, R. Fagan and T.S. Osdene, Ann. N.Y. Acad.Sci. (1965), 130, 469.
M.E. Rosenthale and C.G. Van Arman, J.Pharm.Exptl.Ther. 1963, 142, 111.
2. W. Pfleiderer, Angew,Chem. (Intern.Ed) 1964, 3, 114.
L. Capuano, W.Ebner, and J. Schrepper, Chem.Ber. 1970, 103, 82.
A. Albert and K. Ohta, J.Chem.Soc. (C) 1971, 2357.
J.B. Bicking, J.W. Mason, O.W. Woltersdorf, J.H. Jones, S.F. Kwong, C.H. Robb and J.E. Cragoe, J.Med.Chem. 1965, 8, 638.
3. E. Felder, D. Pitrie, and S. Boveri, J.Medicin.Chem.,1972, 15, 210.
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