

Nucleophilic Attack By Primary Amines and Thiophenols
on 2,4,7-Triamino-6-methylsulfonylpteridine (1)

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Sir:

We wish to report that the nucleophilic attack by primary amines on 2,4,7-triamino-6-methylsulfonylpteridine (I) (2) displaces the amino groups in *both* the pyrimidine and pyrazine moieties. Thiophenols, on the other hand, react with the same substrate giving nucleophilic displacement of only the methylsulfonyl group.

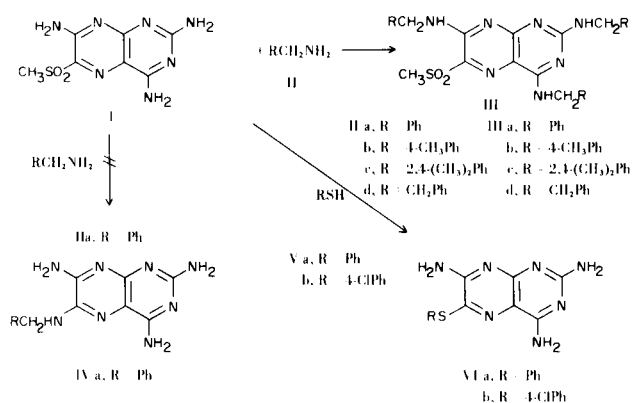
It was found that refluxing 2,4,7-triamino-6-methylsulfonylpteridine (I) in benzylamine (IIa) gave a new yellow solid, 2,4,7-tris(benzylamino)-6-methylsulfonylpteridine (IIIa, R = Ph) in 44% yield, instead of the expected 2,4,7-triamino-6-benzylaminopteridine (IVa) (3). The actual structure of (IIIa) was confirmed by physical and spectral data [m.p. 280-281°; uv (4.5% formic acid) λ max 278 nm ($\log \epsilon = 4.30$) and λ max 374 nm ($\log \epsilon = 4.22$); ir ν as (SO₂) 1348 (s), 1290 (w), ν s (SO₂) 1121 cm⁻¹ (s)]. Satisfactory C, H, N, S analyses were obtained. Additional verification of the structure was obtained by nmr data on 2,4,7-tris(4-methylbenzylamino)-6-methylsulfonylpteridine (IIIb, R = 4-CH₃Ph, 20% yield), [7.27 δ (12H), 4.77 δ (6H), 3.41 δ (3H), 2.38 δ (9H) in trifluoroacetic acid] and the 2,4,7-tris(2,4-dimethylbenzylamino) derivative (IIIc, R = 2,4-(CH₃)₂Ph, 21% yield) [7.17 δ (9H), 4.87 δ (6H), 3.41 δ (3H), 2.37 δ (18H) in trifluoroacetic acid]. No other solids than the designated products were isolated in any instance by refluxing compound I in the appropriate benzylamines (IIb and IIc).

Amine exchange on the pyrimidine moiety of pteridines has been reported by Taylor (4,5); also a general procedure for amine exchange on the 2- and 4- positions of the pyrimidine ring has been developed by Whitehead and Traverso (6). To our knowledge all heterocyclic amine exchanges reported in the literature have been on rings in which two or more nitrogen atoms are conjugated with each other, *i.e.* in a 1,3 relationship to one another. The mechanism which has been proposed for these amine exchanges, which involves ring opening-ring closing, requires two or more ring nitrogen atoms be in a 1,3 relationship. The amine exchange now observed in the 7-position of the pteridine system must proceed by a different mechanism since the nitrogen atoms in the pyrazine moiety are in a 1,4 relationship. The exchange in this position appears to proceed by direct nucleophilic displacement. Although the mechanism of exchange in the pyrimidine moiety might be different than the mechanism of exchange in the pyrazine moiety, the possibility of direct nucleophilic displacement in the pyrimidine amine exchanges must now be considered.

The product obtained by refluxing compound I with phenethylamine (IIc, R = CH₂Ph) is 2,4,7-tris(phenethylamino)-6-methylsulfonylpteridine (IIIc, R = CH₂Ph, 32% yield) indicating that primary amines other than benzylamines will undergo the observed amine exchange.

Contrary to the pattern observed for nucleophilic displacement on the 2-, 4- and 7-positions of compound I by primary amines, refluxing the starting pteridine (I) in thiophenol (Va) gave displacement of the 6-methylsulfonyl group to give in 85% yield 2,4,7-triamino-6-phenylthiopteridine (VIa). This product had identical paper chromatograph R_f values in three solvent systems, and identical ir spectra to the same compound prepared by Parish and Broadbent *via* a different route (7). Refluxing compound I with *p*-chlorothiophenol (Vb) in dimethylformamide gave 2,4,7-triamino-6-(4-chlorophenylthio)pteridine (VIb) in a 86% yield. This also had identical R_f values in three solvent systems and identical ir spectra to the same compound prepared *via* a different route (7).

The mechanism of the observed amine exchange, and



the reactivity of the 6-methylsulfonyl and 6-methylsulfonylpteridines to other nucleophiles is under current investigation.

REFERENCES

(1) This work was supported by a grant to Brigham Young University from Seagull Industries.

(2) This compound is available from Parish Chemical Company of Provo, Utah.

(3) The nucleophilic substitution by amines of the methylsulfonyl group on nitrogen heterocycles is well known. (a) G. B. Barlin and W. V. Brown, *J. Chem. Soc. (C)*, 2473 (1967). (b) D. J. Brown and P. W. Ford, *ibid.*, 2620 (1969). (c) D. J. Brown and P. W. Ford, *ibid.*, 2720 (1969). (d) D. J. Brown and B. T. England, *ibid.*, 425 (1971).

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