Pteridines Bearing Acetylene-Containing Sidechains at C-2: Preparation and Attempted Cycloaddition Reactions

Norbert Haider [1] and Henk C. van der Plas*

Department of Organic Chemistry, Agricultural University of Wageningen, Dreyenplein 8, NL-6703 HB Wageningen, The Netherlands

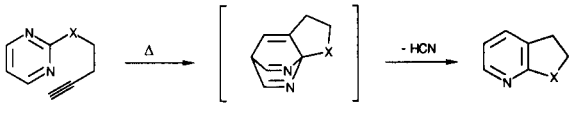
Received November 27, 1989

The preparation of a series of pteridine derivatives **1a-d** bearing S-, O-, or C-linked ω-alkynyl side chains at C-2 is described. Furthermore, an improved synthesis of 2-chloropteridine is proposed. Compounds **1a-d** were found not to undergo intramolecular cycloaddition reactions under thermolytic conditions.

J. Heterocyclic Chem., **27**, 1095 (1990).

In the course of ongoing studies of the behavior of π-electron-deficient heteroaromatics in intramolecular inverse-electron-demand Diels-Alder reactions, carried out in this laboratory [2], we became interested in the preparation of 2-substituted pteridines featuring ω-alkynyl substructures. Such bicyclic compounds can be regarded as structurally related to 2-substituted pyrimidines (carrying acetylene-containing sidechains) which are known to undergo thermally induced intramolecular cycloaddition reactions to afford condensed pyridines [2a, 2b, 2d, 2e] (Figure 1). In the case of the pteridine congeners **1**, potential formation of an intramolecular cycloadduct would involve sp^3 hybridization of the ring carbon atoms C-2 and C-4a. Thus it appeared to be of interest, whether or not such a reaction would take place, as both condensed heterocycles would have to abandon aromaticity in the intermediate cycloadduct (eventually followed by elimination of hydrogen cyanide and rearomatization).

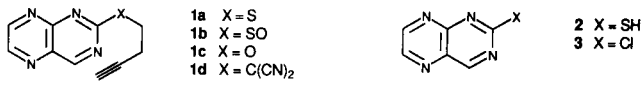
Figure 1



In order to prepare the butynylthio-substituted pteridine **1a**, we started from 2-mercaptopteridine **2** [3]. In contrast to the high-yield *S*-methylation of **2** with methyl iodide described in ref. [4], analoguous treatment of **2** with 4-iodo-1-butyne [5] in dilute aqueous potassium hydroxide gave only poor results. However, the yields of **1a** could be raised significantly (74%) simply on addition of a cosolvent (tetrahydrofuran) to the reaction mixture. Oxidation of **1a** with sodium periodate in water afforded the sulfoxide **1b**, which was of interest as a potential cycloaddition educt, too.

For the synthesis of the butynyloxy derivative **1c** and the dicyanopentynyl compound **1d**, 2-chloropteridine **3** [6,7] was required as starting material. The first reported synthesis of **3** consists of condensation of 2-chloro-4,5-diaminopyrimidine with glyoxal in boiling methanol [6]. Whereas the low yields (20%) of this method, owing to partial methanolysis of the target product **3**, were reported to be enhanced to 65-70% by optimization of the reaction conditions [7], also this latter procedure (which requires column chromatography for work-up) proved to be troublesome, in our hands. It was found, however, that **3** can be prepared in almost quantitative yield by reacting 2-chloro-4,5-diaminopyrimidine [6,7] and glyoxal in a two-phase solvent system (toluene/water), thus protecting the reactive chloro compound **3** by immediate extraction into the (aprotic) organic layer from solvolysis.

Figure 2



On treatment of **3** with sodium 3-butyn-1-olate or with the sodium salt derived from 5,5-dicyano-1-pentyne [8], respectively, nucleophilic displacement of the chloro substituent took place smoothly, affording the ether **1c** or the dinitrile **1d**, respectively.

Attempts to induce intramolecular cycloaddition reactions by heating solutions of compounds **1a-d** in nitrobenzene to 210° (in analogy to ref [2d]) failed: ^{1}H-nmr monitoring did not indicate the formation of a defined reaction product, only slow decomposition was observed. Also refluxing of **1a-d** in trifluoroacetic acid (conditions which were reported recently [2h] to accelerate intramolecular inverse-electron-demand Diels-Alder reactions as compared to heating in neutral solvents) resulted only in resinification. Furthermore, the butynylthiopteridine **1a** was subjected to flash vacuum pyrolysis; whereas at lower temperatures (600°; 10^{-5} mbar) the starting material was recovered unchanged, application of higher temperatures (800°, 10^{-5} mbar) resulted in thermal cleavage of the side chain, leading to the formation of the thiol **2** (identified by ^{1}H-nmr); similar observations have been described for the thermolysis of 1,2,4-triazine derivatives bearing *N*-, *O*-, or *S*-linked cyanoethyl side chains [9].

Whereas intramolecular inverse-electron-demand Diels-Alder reactions have been reported for appropriately substituted azalumazines (7-substituted-6-azalumazines [10] and 6-substituted 7-azalumazines [11]) and azapterins [10], it appears that as soon as a bridgehead carbon atom

of a fully aromatic condensed system is to be involved in bond formation, the energy required for cycloaddition becomes too high despite the entropic assistance provided by linkage of the dienophilic alkyne moiety to the azadiene system.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian EM 390 (90 MHz) spectrometer; chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ units. Mass spectral data were obtained on an AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed on Merck silica gel 60 (230-400 mesh ASTM).

2-Chloropteridine (**3**) [6,7].

To a solution (obtained by short refluxing) of 433 mg (3 mmoles) of 2-chloro-4,5-diaminopyrimidine [6] (prepared according to reference [7]) in 30 ml of water at 80° was added 60 ml of toluene and a suspension of 738 mg (3 mmoles) of glyoxal trimer dihydrate in 10 ml of water. The mixture was stirred vigorously at 80° for 15 minutes, then the phases were separated (while still warm), and the aqueous layer was repeatedly extracted with ethyl acetate. The combined organic phases were dried with magnesium sulfate and evaporated *in vacuo* to give 490 mg (98%) of essentially pure (tlc, nmr) 2-chloropteridine, mp 105-107° (dec, from light petroleum) (reference [6], mp 106-107°, dec).

2-(3-Butynylthio)pteridine (**1a**).

To a solution of 364 mg (2 mmoles) of 2-mercaptopteridine monohydrate (**2**) [3] in 5 ml of 0.5*N* aqueous potassium hydroxide was added a solution of 450 mg (2.5 mmoles) of 4-iodo-1-butyne [5] in 4 ml of tetrahydrofuran. The mixture was vigorously stirred at room temperature for 16 hours under an atmosphere of nitrogen, then it was diluted with 30 ml of water and extracted with diethyl ether. The extract was dried with magnesium sulfate and evaporated *in vacuo* to afford 320 mg (74%) of almost colorless crystals, mp 96-98° (from light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.45 (s, H-4, 1H), 9.10, 8.85 (each d, J = 2.0 Hz, H-6, H-7, 2H), 3.50 (t, J = 7.0 Hz, S-CH_2-C, 2H), 2.75 (dt, J = 3.0, 7.0 Hz, - CH_2-CH_2-C≡CH, 2H), 2.05 (t, J = 3.0 Hz, C≡CH, 1H).

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.53; H, 3.73; N, 25.91. Found: C, 55.33; H, 3.62; N, 25.87.

2-(3-Butylnylsulfinyl)pteridine (**1b**).

To a suspension of 216 mg (1 mmole) of **1a** in 20 ml of water was added 257 mg (1.2 mmoles) of sodium periodate, and the mixture was stirred for 4 days at room temperature. It was then extracted exhaustively with dichloromethane. The combined extracts were dried with magnesium sulfate and evaporated *in vacuo* to afford 110 mg (44%) of colorless crystals, mp 173-175° (from ethanol-diethyl ether); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 9.35 (s, H-4, 1H), 8.55, 8.25 (each s, H-6, H-7, 2H), 3.20 (t, J = 7.0 Hz, S(O)-CH_2-C, 2H), 2.85 (t, J = 3.0 Hz, -C≡CH, 1H), 2.60 (dt, J = 3.0, 7.0 Hz, -CH_2-CH_2-C≡CH, 2H).

Anal. Calcd. for $C_{10}H_8N_4OS{\cdot}H_2O$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.02; H, 3.92; N, 22.70.

2-(3-Butynyloxy)pteridine (**1c**).

To 1 ml of dry 3-butyn-1-ol was added 23 mg (1 mmole) of sodium, and the solution was stirred at room temperature under an atmosphere of nitrogen for 0.5 hours. It was then cooled to 0°, and 167 mg (1 mmole) of **3** was added in small portions. The mixture was stirred at room temperature for 3 hours. Dichloromethane (30 ml) was added, and the solution was repeatedly washed with water. The organic layer was dried with magnesium sulfate and evaporated *in vacuo* to give 130 mg (65%) of blue-grey crystals, mp 140-142° (from ethyl acetate-light petroleum); ^{1}H-nmr (deuteriochloroform): δ 9.55 (s, H-4, 1H), 9.10, 8.85 (each d, J = 1.5 Hz, H-6, H-7, 2H), 4.75 (t, J = 7.5 Hz, O-CH_2-C, 2H), 2.85 (dt, J = 3.0, 7.5 Hz, -CH_2-CH_2-C≡CH, 2H), 2.05 (t, J = 3.0 Hz, C≡CH, 1H).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.93; H, 4.18; N, 28.14.

2-(1,1-Dicyano-4-pentyn-1-yl)pteridine (**1d**).

To a stirred suspension of 60 mg (2 mmoles) of sodium hydride (80% oil dispersion) in 10 ml of dry tetrahydrofuran was added 236 mg (2 mmoles) of 5,5-dicyano-1-pentyne [8] at room temperature. After the initial effervescence had ceased, a solution of 333 mg (2 mmoles) of **3** in 5 ml of dry tetrahydrofuran was added. The mixture was stirred under an atmosphere of nitrogen at room temperature for 6 hours. The residue obtained on evaporation *in vacuo* was partitioned between water and dichloromethane. The organic layer was dried with magnesium sulfate and evaporated *in vacuo* to afford a dark oil which was subjected to column chromatography (diethyl ether). The pure product (tlc, nmr) was obtained as a light-green oil (350 mg, 70%) which rapidly became dark; ^{1}H-nmr (deuteriochloroform): δ 9.85 (s, H-4, 1H), 9.35, 9.20 (each d, J = 1.5 Hz, H-6, H-7, 2H), 3.0-2.5 (m, CH_2CH_2, 4H), 1.85 (t, J = 3.0 Hz, C≡CH, 1H); ms: m/e Calcd. for $C_{13}H_8N_6$: 248.0810; Found: 248.0809.

Acknowledgements.

The authors wish to express their gratitude to Dr. T. Klunder and coworkers, University of Nijmegen, for assistance with the flash vacuum pyrolysis experiment. In addition, we are indebted to Mr. H. Jongejan and Mr. C. Teunis for carrying out the microanalyses and the accurate mass measurement. We also wish to thank Dr. D. de Bie and Mr. G. Geurtsen for advice and discussion. N. H. gratefully acknowledges grants from the Dutch *Stichting IAC* and from the Austrian *Bundesministerium für Wissenschaft und Forschung.*

REFERENCES AND NOTES

[1] Postdoctoral fellow, University of Vienna, Austria.

[2a] A. E. Frissen, A. T. M. Marcelis and H. C. van der Plas, *Tetrahedron Letters*, 1589 (1987); [b] A. E. Frissen, A. T. M. Marcelis, G. Geurtsen, D. A. de Bie and H. C. van der Plas, *Rec. Trav. Chim.*, **106**, 547 (1987); [c] D. A. de Bie, A. Ostrowicz, G. Geurtsen and H. C. van der Plas, *Tetrahedron*, **44**, 2977 (1988); [d] A. E. Frissen, A. T. M. Marcelis and H. C. van der Plas, *ibid.*, **45**, 803 (1989); [e] A. E. Frissen, A. T. M. Marcelis, G. Geurten, D. A. de Bie and H. C. van der Plas, *ibid.*, **45**, 5151 (1989); [f] A. E. Frissen, A. T. M. Marcelis, D. G. Buurman, C. A. M. Pollmann and H. C. van der Plas, *ibid.*, **45**, 5611 (1989); [g] M. Biedrzycki, D. A. de Bie and H. C. van der Plas, *ibid.*, **45**, 6211 (1989); [h] B. Geurtsen, D. A. de Bie and H. C. van der Plas, *ibid.*, **45**, 6519 (1989); [j] V. N. Charushin, B. van Veldhuizen, H. C. van der Plas and H. C. Stam, *ibid.*, **45**, 6499 (1989); [j] W. A. W. Stolle, A. T. M. Marcelis, A. Koetsier and H. C. van

der Plas, *ibid.*, **45**, 6511 (1989); [k] M. Biedrzycki, D. A. de Bie and H. C. van der Plas, *ibid.*, in the press; [l] A. E. Frissen, G. Geurtsen, A. T. M. Marcelis and H. C. van der Plas, *ibid.*, in the press; [m] A. E. Frissen, A. T. M. Marcelis, W. C. Melger and H. C. van der Plas, *ibid.*, in the press.

[3] G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **69**, 2553 (1947).

[4] A. Albert, D. J. Brown and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

[5] G. Eglinton and M. C. Whiting, *ibid.*, 3650 (1950).

[6] A. Albert, D. J. Brown and G. Cheeseman, *ibid.*, 474 (1951).

[7] A. Nagel, H. C. van der Plas and A. van Veldhuizen, *Rec. Trav. Chim.*, **94**, 45 (1975).

[8a] E. C. Taylor and J. E. Macor, *Tetrahedron Letters*, 2107 (1986); [b] J. E. Macor, Ph.D. Thesis, Princeton University, 1986.

[9] E. C. Taylor, J. L. Pont and J. C. Warner, *Tetrahedron*, **43**, 5159 (1987).

[10] E. C. Taylor, J. C. Warner and J. L. Pont, *J. Org. Chem.*, **53**, 800 (1988).

[11] E. C. Taylor, J. L. Pont and J. C. Warner, *ibid.*, **53**, 3568 (1988).