[Chem. Pharm. Bull. 19(1) 206—207 (1971)]

UDC 547.856.07 : 547.866.07

A Variant Route to Alloxazines

Sadao Nishigaki, Shinobu Fukazawa, Kazuko Ogiwara and Fumio Yoneda

School of Medicine, Keio University[1]

(Received July 6, 1970)

A recent article has described the successful synthesis of 4-amino-2-phenylcyclopenta[*g*]-pteridine, consisting of treatment of 4,6-diamino-5-nitroso-2-phenylpyrimidine with 1-pyrrolidinocyclopentene.[2] We have extended this reaction to the preparation of cyclohexa[*g*]-pteridine, namely 6,7,8,9-tetrahydroalloxazines, which may be of use as the precursors for alloxazines (see Chart 1). Fusion of excess 1-morpholinocyclohexene with 6-amino-1,3-dimethyl-5-nitrosouracil, 6-amino-4-hydroxy-5-nitroso-2-phenylpyrimidine and 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine afforded, as was expected, 1,3-dimethyl-2,4 (1H,3H) cyclohexa[*g*]pteridinedione (I), 4-hydroxy-2-phenylcyclohexa[*g*]pteridine (II), and 4-hydroxy-2-methylcyclohexa[*g*]pteridine (III).

Dehydrogenation of I with sulfur gave under evolution of hydrogen sulfide 1,3-dimethylalloxazine (IV), which was identical in all respects with an authentic sample.[3] Similarly, dehydrogenation of II and III with sulfur gave 4-hydroxy-2-phenyl- (V) and 4-hydroxy-2-methylbenzo[*g*]pteridine (VI), respectively. The structure of V was identified by comparison with the authentic sample,[4] which was synthesized by the nitrosative cyclization of 6-anilino-4-hydroxy-2-phenylpyrimidine. The structure of VI was established by microanalysis, by a molecular weight determination by mass spectrometry, and by its several spectral data.

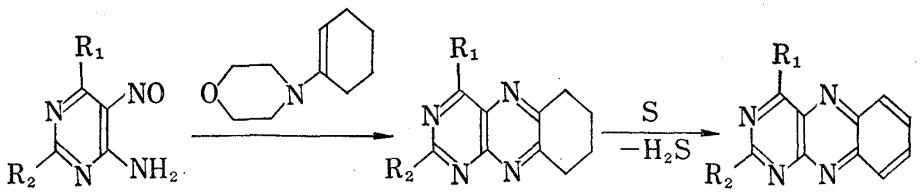

Chart 1

The value of this preparative procedure is exemplified by the limitation of the nitrosative cyclization[4] described above for the preparation of VI. The sensitive 2-methyl group of the pyrimidine moiety is altered by the latter method by oxidation or nitrosation[5] with nitrous acid yielding no desired product (VI).

Experimental[6]

Cyclohexa[*g*]pteridines General Procedure——A mixture of excess 1-morpholino-1-cyclohexene and a 6-amino-5-nitrosopyrimidine was gently refluxed for *ca.* 15 min. The initial intensely colored solution rapidly faded to yellow, at which time the reaction is judged complete. After cooling, the reaction mixture was diluted with $(C_2H_5)_2O$ and the precipitated product was filtered off, washed with $(C_2H_5)_2O$, dried and recrystallized from MeOH (Table I).

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*
2) J. Weinstock, R.Y. Dunoff, J.E. Carevic, J.G. Williams and A.J. Villani, *J. Med. Chem.*, **11**, 618 (1968).
3) H. Goldner, G. Dietz and E. Carstens, *Ann.*, **694**, 142 (1966).
4) E.C. Taylor and F. Yoneda, unpublished results.
5) D.T. Hurst, *Tetrahedron Letters*, **1970**, 979, and references cited therein.
6) All melting points were uncorrected.

NII-Electronic Library Service

Table I

Product	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	78	185	$C_{12}H_{14}O_2N_4$	58.52	5.73	22.75	58.41	5.69	22.83
II	95	316	$C_{16}H_{14}ON_4$	69.05	5.07	20.13	69.01	5.08	20.35
III	70	322	$C_{11}H_{12}ON_4$	61.09	5.59	25.91	60.99	5.48	26.02

1,3-Dimethylalloxazine (IV)——A mixture of I (0.5 g, 0.002 mole) and sulfur (0.26 g, 0.008 g atom) was heated at 240—250° for 40 min under occasional stirring. Treatment of the tarry brown product with EtOH turned into powder, which was extracted with $(C_2H_5)_2O$ several times. The extracts gave upon evaporation a yellow powder (IV) (0.28 g, 58%), mp 241°, which was identified by infrared (IR) spectra.

4-Hydroxy-2-phenylbenzo[*g*]pteridine (V)——A mixture of II (0.10 g, 0.00036 mole) and sulfur (0.05 g, 0.0016 g atom) was heated at 240—250° for 20 min under occasional stirring. The crude product was recrystallized from EtOAc to afford a yellow powder (V) (0.08 g, 80%), mp >300°, which was identified with the authentic sample[4] in all respects.

4-Hydroxy-2-methylbenzo[*g*]pteridine (VI)——A mixture of III (0.12 g, 0.00056 mole) and sulfur (0.04 g, 0.0013 g atom) was heated at 250—260° for 40 min. The tarry product was washed with $(CH_3)_2CO$ to give the crude product as a brown powder. Recrystallization from EtOH gave VI as dark yellow powder (0.05 g, 42.4%), mp >300°. *Anal.* Calcd. for $C_{11}H_8ON_4$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.34; H, 3.91; N, 25.99.

[Chem. Pharm. Bull. 19(1) 207—208 (1971)]

UDC 547.567.3.02 : 547.918.02 : 581.192

Constituents of Three Thai Medicinal Plants: *Ardisia polycephala* (Myrsinaceae), *Rhabdia lycioides* (Boraginaceae), and *Balanophora polyandra* (Balanophoraceae)[1]

Verapong Podimuang,[2] Stang Mongkolsuk,[3a] Kunitoshi Yoshihira, and Shinsaku Natori[3b]

Faculty of Medical Sciences, University of Medical Sciences, Bangkok[3a] and National Institute of Hygienic Sciences[3b]

(Received July 25, 1970)

The root of *Ardisia polycephala* Wight (Myrsinaceae) (in Thai, Phi-Lang-Ka-Sa) is one of the shrubs used by Thai old style doctors as antivenom. An orange pigment was isolated from the hexane extract of the root in a high yield (1.4%) and identified with rapanone (I), one of the 2,5-dihydroxy-3-alkylbenzoquinone derivatives widely distributed among Myrsinaceae plants.[4,5]

The wood of *Rhabdia lycioides* Mart. (Boraginaceae) (in Thai, Takrai-Hangnak) is used as diuretic. The ether extract of the wood afforded a mixture of triterpenoids, from which

1) This paper constitutes Part V of "Studies on Thai Medicinal Plants" by S. Natori and K. Nishimoto. Part IV: K. Yoshihira, S. Natori, and P. Kanchanapee, *Tetrahedron Letters*, **1967**, 4857.
2) A part of this work was carried out at National Institute of Hygienic Sciences, where one of us (V. P.) stayed in 1969—1970 as a Columbo Plan Fellow.
3) Location: *a*) *Rama VI Road, Bangkok, Thailand*; *b*) *Kamiyoga-1-chome, Setagaya-ku, Tokyo.*
4) H. Ogawa and S. Natori, *Phytochem.*, **7**, 773 (1968).
5) R. Hegnauer, "Chemotaxonomie der Pflanzen," Band 5, Birkhäuser Verlag, Basel, 1969, p. 154.

NII-Electronic Library Service