Anyhow, the surface of CB, a very hydrophobic adsorbent, is considered to be covered by a monolyaer of phenothiazine molecules as is expressed by Langmuir equation. The interfaces concerning the existing data shown in Table I also seem to be covered by a monolayer of phenothiazine molecules. On the other hand, SG is so hydrophilic that it may adsorb a large amount of water and offer a small area effective to the adsorption of phenothiazine molecules.

The values of cross-sectional area of phenothiazines calculated from Stokes' radius upon the permeation through cellulose membrane were a little larger than that evaluated from its steric structure. However, this result may be accepted on the consideration that a phenothiazine molecule takes a long and slender conformation upon the permeation through cellulose membrane.[13] In other words, it is unreasonable to assume a phenothiazine melecule to be cubic upon calculating the cross-sectional area.

According to Teller and Denber's molecular biological investigation,[14] a phenothiazine molecule may take a flexible conformation upon the permeation into biological membrane or upon the binding to protein, coming into a pore of about 7.5 Å in size in the protein layer of biological membrane, as is related to an onset of the tranquilizing effect. Since the size of a phenothiazine molecule evaluated from the adsorption on CB or from the permeation through cellulose membrane was considered to be common to that in biological membrane such as mentioned above, it was suggested in addition to the previous works[1,11] that various physico-chemical investigations regarding the behavior of phenothiazine molecules upon the adsorption from aqueous solution or upon the permeation through model membrane might give useful informations for understanding of biopharmaceutical phenomena.

Acknowledgement The authors gratefully acknowledge the award of Research Grants from Naito Foundation (to T.N.). Thanks are also given for the generous supports of the materials to Banyu Pharmaceutical Co., Ltd., Daiichi Pharmaceutical Co., Ltd., Dainippon Pharmaceutical Co., Ltd., Nippon Squibb Co., Ltd., Sumitomo Chemical Co., Ltd., and Yoshitomi Pharmaceutical Co., Ltd.

13) S. Yamabe, "Iyakuhin Bunshiron," Asakura-shoten, Tokyo, 1968.
14) D.N. Teller and H.C.B. Denber, "Diseases of the Nervous System," *GWAN, Suup.*, **29**, 93 (1968).

[Chem. Pharm. Bull. 19(5)1060—1062(1971)]

UDC 547.856.07 : 547.863.07

1,3,6,8-Tetramethyl-2,4,5,7(1H,3H,6H,8H)pyrimido[5,4-*g*]pteridinetetrone and 1,3,5,7-Tetramethyl-2,4,6,8(1H,3H,5H,7H)-pyrimido[4,5-*g*]pteridinetetrone

Fumio Yoneda and Sadao Nishigaki

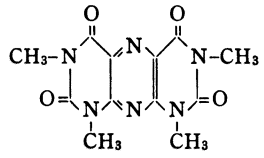
Pharmaceutical Institute, Keio Gijuku University[1]

(Received November 14, 1970)

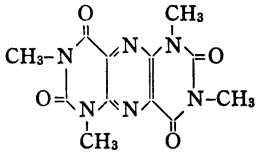
1,3,6,8-Tetramethyl-2,4,5,7(1H,3H,6H,8H)pyrimido[5,4-*g*]pteridinetetrone (I)[2] is the common product which has frequently been observed during the reactions using 6-amino-1,3-

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*
2) E.C. Taylor, C.K. Cain, and H.M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954).

dimethyl-5-nitrosouracil and 5,6-diamino-1,3-dimethyluracil. The identity of the products with I has been established in following reactions: (a) the condensation of the monohydrochloride of 5,6-diamino-1,3-dimethyluracil with 1,3-dimethylalloxan in aqueous solution,[3] (b) the action of 2N sulfuric acid[4] or hydrochloric acid[5] on 5,6-diamino-1,3-dimethyluracil or its monoacetyl derivative, (c) the reaction of 6-amino-1,3-dimethyl-5-nitrosouracil with 1,3-dimethylbarbituric acid,[6] and (d) the thermal and acid induced reaction of 6-amino-1,3-dimethyl-5-nitrosouracil.[7] Furthermore I has often been obtained as a byproduct in the purine and pteridine syntheses from 5,6-diamino-1,3-dimethyluracil and 6-amino-1,3-dimethyl-5-nitrosouracil.[8a-c]



I



II

Chart 1

The isomeric 1,3,5,7-tetramethyl-2,4,6,8(1H,3H,5H,7H)pyrimido[4,5-*g*]pteridinetetrone (II) is a product of rare. The only published formation is the methylation of 2,4,6,8-tetrahydroxypyrimido[4,5-*g*]pteridine, which was obtained by deamination of 2,4,6,8-tetraminopyrimido[4,5-*g*]pteridine, an oxidative self-condensation product of 2,4,5,6-tetraminopyrimidine.[9]

We now record a simple preparative method of II and its spectral data comparing with those of I. Heating 5,6-diamino-1,3-dimethyluracil and trichloroacetic acid in dimethylformamide under reflux for a few hour results in the formation of II along with a small amount of I. The formation of II appears to depend upon the solvent effect of dimethylformamide, because the reaction without the solvent led to the formation of I as the main product.

The compound II was also obtained from the fusion of 5,6-diamino-1,3-dimethyluracil and anthranilic acid. It is interesting to note that in the presence of polyphoshoric acid these two compounds formed a hexacyclic purine derivative.[10]

Experimental

1,3,5,7-Tetramethyl-2,4,6,8(1H,3H,5H,7H)pyrimido[4,5-*g*]pteridinetetrone (II)——(A) A solution of 1.7 g (0.01 mole) of 5,6-diamino-1,3-dimethyluracil and 2.4 g (0.015 mole) of trichloroacetic acid in 20 ml of DMF was heated under reflux for 3 hr. After cooling, the yellow solid which separated was collected by filtration to give 0.6 g of crude 1,3,5,7-tetramethyl-2,4,6,8(1H,3H,5H,7H)pyrimido[4,5-*g*]pteridinetetrone (II). The filtrate was evaporated to dryness, the residue washed with MeOH and the remained crystals were collected by filtration to yield 0.2 g of a mixture of II and 1,3,6,8-tetramethyl-2,4,5,7(1H,3H,6H,8H)pyrimido[5,4-*g*]pteridinetetrone. Combined products were recrystallized from DMF to give 0.65 g

3) H. Bredereck, I. Henning, W. Pfleiderer, and O. Deschler, *Chem. Ber.*, **86**, 845 (1953).
4) H. Bredereck and W. Pfleiderer, *Chem. Ber.*, **87**, 1268 (1954).
5) F.F. Blicke and H.C. Godt, *J. Am. Chem. Soc.*, **76**, 2798 (1954).
6) G.M. Timmis, U.S. Pat. 2581, 889 [*Chem. Abstr.*, **46**, 7594 (1952)].
7) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4721 (1964).
8) *a*) R.D. Youssefyeh and A. Kalmus, *Chem. Commun.*, **1969**, 1426; *b*) In the 8-methyltheophylline synthesis from 5,6-diamino-1,3-dimethyluracil and acetic acid I was obtained as a byproduct; K. Senga, unpublished result; *c*) F. Yoneda, K. Ogiwara, M. Kanahori, S. Nishigaki, and E.C. Taylor, "Chemistry and Biology of Pteridines," ed. by Y. Iwanami, *et al.* International Academic Printing Co., Ltd., Tokyo, 1970, p. 145.
9) E.C. Taylor, H.M. Loux, E.A. Falco, and G.H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2243 (1955).
10) E.C. Taylor and F. Yoneda, *Angew. Chem.*, **79**, 901 (1967).

(43%) of yellow prisms of II, mp 348—350°(lit.[9] 358—360°). *Anal.* Calcd. for $C_{12}H_{12}O_4N_6$: C, 47.33; H, 3.98; N, 27.62. Found: C, 47.59; H. 3.78; N. 27.90.

(B) A mixture of 1.7 g (0.01 mole) of 5,6-diamino-1,3-dimethyluracil and 1.4 g (0.01 mole) of anthranilic acid was fused at 200° for 1 hr. After cooling the reaction mixture was recrystallized from DMF to give 0.5 g of II, which was identical with the product obtained above.

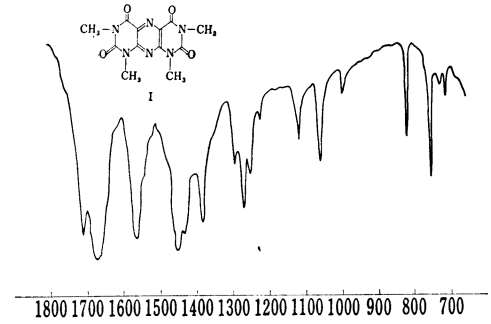


Fig. 1a. IR Spectrum of I (in Nujol)

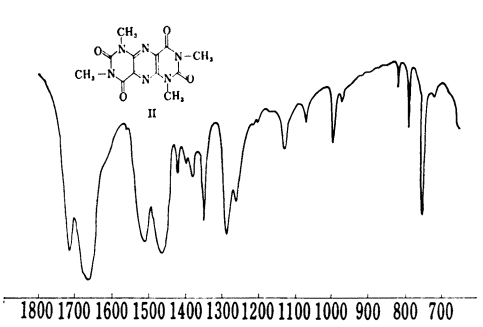


Fig. 1b. IR Spectrum of II (in Nujol)

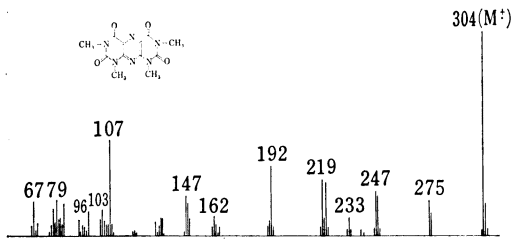


Fig. 2a. Mass Spectrum of I (75 eV)

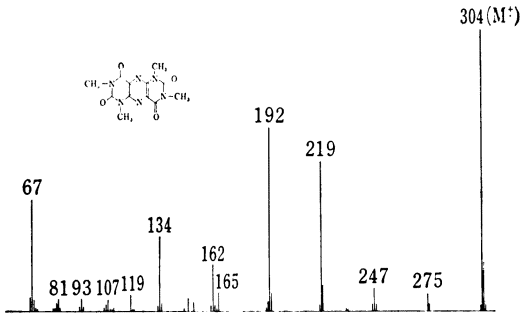


Fig. 2b. Mass Spectrum of II (75 eV)

[Chem. Pharm. Bull. 19(5)1062—1065(1971)]

UDC 547.466.8.09 : 615.31.076.9

Effect of Penicillamine on the Glycosaminoglycan Composition of Rat Aorta

Yo Mori, Kazushige Tanuma, Shinkichi Niinobe,[1a] and Riza Bashey[1b]

Tokyo College of Pharmacy[1a] and Department of Pathology, Albert Einstein College of Medicine[1b]

(Received November 25, 1970)

Administration of penicillamine (β,β-dimethylcysteine) results in a great loss of strength of skin with increase in solubility of collagen as in lathyrism.[2] However, the chemical nature of penicillamine and the difference in its effect on crosslinking formation of elastin and col-

1) Location: *a) 20, Kitashinjuku 3-chome, Shinjuku-ku, Tokyo; b) 1300 Morris Park Avenue, Bronx, New York, 10461, U.S.A.*

2) M.E. Nimni, *J. Biol. Chem.*, **243**, 1457 (1968).