

The mercury could be removed by dialysis in the presence of 0.001 *M* cysteine.

Serum albumin repeatedly crystallized in this way contained one-half mole mercury per mole protein. Analytical evidence thus suggests that two albumin molecules are linked through one atom of mercury in the solid state. Further evidence for the existence of an albumin dimer was obtained from analyses of solutions of these crystals in the ultracentrifuge.³

Ultracentrifugal analyses of freshly prepared neutral solutions of crystals revealed two components: a small amount with sedimentation constant ($s_{20,w}$) 4.6S, typical of serum albumin, and a large amount with a sedimentation constant of approximately 6.5S. Upon standing, the amount of dimer decreased; and more rapidly the more acid the solution. At pH 4.0 no dimer could be detected.

Reversal of dissociation was demonstrated in a 20% neutral solution of albumin from which the mercury had been removed. The dimer gradually reappeared following addition of one-half mole mercury per mole albumin at 4°. At pH 7.5, 70% of the protein had a sedimentation constant of 6.5 after one week.

The 6.5S component completely disappeared in the presence of such reagents as cysteine, BAL, or one mole mercuric chloride per mole albumin. Observations of light scattering and of viscosity, following the addition of this amount of mercuric chloride, showed an immediate decrease to values characteristic of normal serum albumin in less than fifteen minutes at 0°. BAL appeared equally effective.

(3) All ultracentrifugal analyses have been carried out by C. Gordon and P. Baker under the direction of J. L. Oncley.

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AN ALKALOID WITH HIGH ANTIMALARIAL ACTIVITY FROM *DICHROA FEBRIFUGA*¹

Sir:

We wish to report the isolation of two new alkaloids, for which we propose the name febrifugine (I), (SN-15381)² and isofebrifugine (II), (SN-14821),³ the former from both the roots and leaves and the latter from the roots of botanically identified specimens of *Dichroa febrifuga* Lour. The plant has long been known to the Chinese to have antimalarial properties and in some localities the roots are referred to as "Ch'ang Shan."

(1) The work described was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

(2) The survey number, designated SN, identifies a drug in the Records of the Survey of Antimalarial Drugs, National Institute of Health, Bethesda, Maryland.

(3) "A Survey of Antimalarial Drugs, 1941-1945," F. V. Wiselogle, Editor, J. W. Edwards, Ann Arbor, Michigan, 1946.

Base I crystallizes from ethanol in colorless needles, m. p. 139-140° (cor.), $[\alpha]_D^{25} +6^\circ$ (*c* 0.5, chloroform) [calcd. for $C_{16}H_{19}O_3N_3$: C, 63.8; H, 6.4; N, 14.0; found: C, 63.5; H, 6.3; N, 13.9] and gives a colorless crystalline dihydrochloride (from 90% ethanol), m. p. 220-222° (dec., cor.) with previous darkening above 205°. Anal. Calcd. for $C_{16}H_{21}O_3N_3Cl_2$: N, 11.2; Cl, 18.9. Found: N, 10.9; Cl, 18.6. The base I is approximately one hundred fold as active as quinine when tested against *P. lophurae* in ducks.

Base II crystallizes from methanol in colorless, chunky prisms, m. p. 129-130° (cor.), $[\alpha]_D^{25} +131^\circ$ (*c* 0.35, chloroform) [calcd. for $C_{16}H_{19}O_3N_3$: C, 63.8; H, 6.4; N, 14.0; found: C, 63.5; H, 6.0; N, 14.0] and gives a hygroscopic hydrochloride, difficult to characterize. The base II has relatively slight activity against *P. lophurae* in ducks.

Both I and II in ethanol exhibit almost identical absorption in the ultraviolet, with principal maxima at 225, 266, 275 and 302 $m\mu$, and minima at 250, 271 and 288 $m\mu$. A tentative empirical formula for I and II is $C_{16}H_{19}O_3N_3$, and we have good evidence that two of the nitrogens are in a quinazoline ring. Furthermore, II is convertible to I by heat.

We estimate the total alkaloidal content to be about 0.1% of the dry weight of the roots. The antimalarial activity of root material is reasonably well accounted for by I on this basis. With respect to the leaf material, however, there is a great discrepancy between the antimalarial activity and alkaloidal content which suggests that another antimalarial principle may be present; this possibility is under investigation.

A detailed account of our investigation will be given in the near future and will include pertinent references to the literature as well as a botanical and pharmacological report. However, we wish to refer here to a communication by Jang, *et al.*,⁴ in which the isolation of two alkaloids (Dichroine A, m. p. 230° with decomposition and Dichroine B, m. p. 237-238° with decomposition) from Ch'ang Shan is reported. The great disparity in melting point behavior would appear to obviate the possibility that I or II is identical with either of the alkaloids reported by the Chinese authors.

We wish to thank Dr. K. K. Chen and Eli Lilly and Company, for the supply of Ch'ang Shan and technical assistance which made this investigation possible. The Abbott Laboratories generously made available botanically identified *D. febrifuga* for comparison.

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(4) C. S. Jang, F. Y. Fu, C. Y. Wang, K. C. Huang, G. Lu and T. C. Chou, *Science*, **103**, 49 (1946).