

animals. Absence of syphilitic lesions in the transfer animals over a period of three months was taken as the criterion of cure. The results are given in Table II. In general, compounds which revert to 1 in solution had approximately equal activity, mercapto derivatives being about equally active. Substitution of hydroxyalkoxyl groups for hydroxyl may have decreased the activity slightly but substitution of amino hydrogen resulted in marked reduction of activity.

Summary

1. A number of new derivatives of 3-amino-4-hydroxybenzenearsonous acid have been pre-

pared for trypanocidal and treponemacidal studies. These consisted of variations in which easily and difficultly hydrolyzable groups were attached to the arsenic, nitrogen and phenolic oxygen atoms.

2. Animal studies indicated that none of the compounds was more active than the parent compound and that only those compounds having readily hydrolyzed groups retained any appreciable activity.

DETROIT, MICHIGAN

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Antimalarial Constituents of Chinese Drug, Ch'ang Shan, *Dichroa febrifuga* Lour

BY T. Q. CHOU, F. Y. FU AND Y. S. KAO

A brief account on the isolation of an antimalarial alkaloid named dichroine from the Chinese drug, Ch'ang Shan, identified as *Dichroa febrifuga* Lour., has been reported.¹ Mention should be made that the name dichroine has been used previously by Hartwich² to indicate a carbohydrate of an indefinite nature isolated from the same plant. The alkaloid dichroine has the composition $C_{16}H_{21}O_3N_3$ and easily undergoes isomeric change under the action of heat, acids, and alkalies, and even with different solvents used. Three isomerides, which are provisionally named, α -, β - and γ -dichroines, have been obtained, melting, respectively, at 136, 145 and 160°, and being convertible into each other under suitable conditions. Oxidized with potassium permanganate, dichroine yields 4-quinazolone and some other products not yet identified. Hydrolysis with sodium hydroxide gives easily the decomposition products, anthranilic acid, formic acid, and ammonia, together with a compound which behaves like a pyrrole derivative. Benzoylation with benzoyl chloride furnishes most probably a tribenzoyl derivative of dichroine according to its nitrogen content. No presence of carboxyl-, methoxyl- and methylenedioxy- groups could be detected in the molecule of dichroine. Dichroine forms both normal and acid salts and a nitroso compound. Besides dichroine, 4-quinazolone, a base with the composition $C_{13}H_{23}N_3O_3$, and umbelliferon have also been isolated from the roots of Ch'ang Shan; the first one may be originally present in the plant or resulted during chemical manipulation. Synthetic quinazoline derivatives used as antimalarials have recently been investigated extensively by Magidson and Yolovchinskaya³ and others. The isolation of 4-quinazolone from a natural plant affords a remarkable coincidence with the chemical re-

search along this line, although the quinazolone nucleus has already been found in certain alkaloids.⁴ Regarding the antimalarial activity of dichroines, the γ -isomeride shows the greatest, and α -isomeride the least; the curative dose for chicken malaria being found to be 4 mg. of γ -isomer per kg.⁵

Experimental

The finely powdered root of Ch'ang Shan is percolated with 90% alcohol at room temperature for two days and the extract evaporated in a vacuum. The residue is taken up with dilute hydrochloric acid, filtered, and extracted repeatedly with ether, which constitutes fraction A. The acid solution is rendered slightly alkaline with sodium bicarbonate and shaken well with ether containing about 20% of chloroform (fraction B). The aqueous solution is then made strongly alkaline with potassium carbonate and extracted several times with chloroform (fraction C).

Umbelliferon, $C_9H_6O_3$.—The residue obtained from fraction A, by distilling off ether, crystallizes from alcohol in colorless needles, m. p. 224–227°, sparingly soluble in water, but easily soluble in chloroform, alcohol, and alkaline solutions, the last possessing an intense blue fluorescence. Its properties and analysis correspond well to umbelliferon (7-hydroxycoumarin). *Anal.* Calcd. for $C_9H_6O_3$: C, 66.6; H, 3.7. Found: C, 66.6; H, 3.9.

4-Quinazolone.—Fraction B, on evaporation of ether-chloroform mixture, gives a product which crystallizes from alcohol in silky long needles, m. p. 212–213°. It is identical in all respects with a sample of 4-quinazolone prepared by heating 2 g. of anthranilic acid and 1 g. of formamide for two hours at 120–130° and crystallizing the resulting products from alcohol. Its analysis as well as those of its hydrochloride and platinum salt confirms its composition $C_8H_6ON_2$. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.8; H, 4.1; N, 19.1. Found: C, 65.6; H, 4.4; N, 19.1.

Hydrochloride.—It is obtained by treating an alcoholic solution of 4-quinazolone with hydrochloric acid gas dissolved in alcohol and adding a sufficient quantity of ether; needles, m. p. 247°. Its aqueous solution is acid to litmus paper. *Anal.* Calcd. for $C_8H_6ON_2 \cdot HCl$: N, 15.3; Cl, 19.4. Found: N, 15.0; Cl, 19.2.

Platinum Salt.—It is obtained by treating an alcoholic solution of 4-quinazolone with an aqueous solution of platinum chloride in the presence of hydrochloric acid and

(1) Chou, Jang, Fu, Kao and Huang, *Science (Chinese)*, **29**, No. 2, 49 (1947).

(2) Hartwich, *Neue Arzneidrog.*, 127 (1897).

(3) Magidson and Yolovchinskaya, *J. Gen. Chem. (U. S. S. R.)*, **8**, 1797 (1938).

(4) Asahina, Manske and Robinson, *J. Chem. Soc.*, 1708 (1927).

(5) Jang and co-workers, private communication.

TABLE I
ANALYTICAL RESULTS OF THREE DICHROINES, THEIR SALTS, AND DERIVATIVES DESCRIBED IN THIS PAPER

	Formula	M. p., °C.	Carbon, %		Hydrogen, %			Nitrogen, %		Chlorine, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
α -Dichroine	$C_{16}H_{21}O_3N_3$	136	63.3	63.5 63.4	7.0	7.3 6.7	13.9	14.1			
α -Dichroine mono-hydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	210	56.6	56.3	6.5	6.4	12.4	12.2	10.4	10.4	
α -Dichroine sulfate	$(C_{16}H_{21}O_3N_3)_2 \cdot H_2SO_4$	220	54.5	54.8 54.3	6.3	5.9 6.1	11.9	11.5		..	
Nitroso- α -dichroine	$C_{16}H_{20}O_4N_4$	182	16.9	17.2		..	
β -Dichroine	$C_{16}H_{21}O_3N_3$	145	63.3	63.3 63.1	7.0	6.9 6.5	13.9	14.0 13.8		..	
β -Dichroine mono-hydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	220	56.5	56.4 56.8	6.5	6.2 6.5	12.4	12.2 12.3	10.4	10.4	
β -Dichroine dihydrochloride	$C_{16}H_{21}O_3N_3 \cdot 2HCl$	236	51.5	51.1	6.2	6.2	11.2	11.3	18.9	19.1	
β -Dichroine sulfate	$(C_{16}H_{21}O_3N_3)_2 \cdot H_2SO_4$	224	54.5	54.61	6.3	6.5		
Tribenzoyl- β -dichroine	$C_{16}H_{18}O_3N_3(C_6H_5CO)_3$			6.8	7.2		..	
Nitroso- β -dichroine	$C_{16}H_{20}O_4N_4$	170		16.9	17.0		..	
γ -Dichroine	$C_{16}H_{21}O_3N_3$	160	63.3	63.4	7.0	6.7	13.9	13.9		..	
γ -Dichroine mono-hydrochloride	$C_{16}H_{21}O_3N_3 \cdot HCl$	220		10.4	10.4	
Nitroso- γ -dichroine	$C_{16}H_{20}O_4N_4$	170		16.9	16.9		..	

recrystallizing the resulting precipitate from aqueous alcohol; yellowish prisms, m. p. above 250°. *Anal.* Calcd. for $(C_8H_6ON_2 \cdot HCl)_2 \cdot PtCl_4$: Pt, 27.8. Found: Pt, 28.0.

Alkaloid, $C_{16}H_{23}O_3N_3$.—It is isolated from the mother liquor of 4-quinazolone by fractional crystallization with alcohol. When crystallized pure from acetone, it forms small prisms, m. p. 212–213°. *Anal.* Calcd. for $C_{16}H_{23}O_3N_3$: C, 65.6; H, 7.0; N, 12.7. Found: C, 65.6; H, 6.7; N, 12.6.

Dichroines.—Three isomerides, which are named α -, β - and γ -dichroines, are isolated as follows: the chloroform extract (fraction C) is evaporated and the residue taken up with about five times its volume of absolute alcohol. On neutralizing with hydrochloric acid gas in alcohol, a mixture of hydrochlorides, chiefly of β - and γ -dichroines, crystallizes rapidly. The alcoholic mother liquor is evaporated in a vacuum, and the residue taken up with water and filtered. On alkalization with sodium carbonate, the liberated base is extracted with chloroform, distilled, and neutralized with sulfuric acid in alcohol, at which time α -dichroine sulfate crystallizes out in almost a pure state, being soluble in alcohol or cold water with difficulty.

α -Dichroine can be prepared easily by dissolving its sulfate as described above in warm water, making alkaline with sodium carbonate, and extracting the liberated base with chloroform. It crystallizes from alcohol in colorless hard prisms, m. p. 136°, being soluble in chloroform, alcohol, or acetone and much less so in cold water. When heated to its melting point and maintained at that temperature for a few minutes, or its aqueous solution is warmed on the water-bath for an hour or so, it is converted into β -dichroine, m. p. 145°. It forms a hydrochloride, prismatic needles from alcohol, m. p. 210°; a sulfate, silky needles from alcohol, m. p. 220°; and a nitroso compound, needles from alcohol or acetone, m. p. 182°. Its dihydrochloride and acid sulfate can also be prepared when excess of respective acids is used (all analyses are given in Table I).

β -Dichroine.—When the crude dichroine bases are crystallized from an organic solvent such as chloroform, it is always the β -dichroine which crystallizes out slowly on standing; needles, m. p. 145°. It is much more soluble in cold water than α -dichroine. It forms a hydrochloride, prisms, m. p. 220°, easily soluble in methyl alcohol or water; a dihydrochloride, needles, m. p. 236°; a neutral sulfate, needles, m. p. 224°; and a nitroso derivative, rhombic prisms, m. p. 170°; alcohol being

used for crystallization of either the salts or nitroso compound (see Table I for analyses).

γ -Dichroine is prepared by heating α - or β -dichroine to a temperature of about 145° for ten to twenty minutes and crystallizing the resulting product rapidly from a small amount of acetone. It forms silky needles, m. p. 160°. When crystallized slowly from alcohol or chloroform, it converts back to β -dichroine, m. p. 145°. Its hydrochloride, dihydrochloride, sulfate, and nitroso compound are found to be the same as those of β -dichroine, possessing the same physical and chemical properties (Table I).

Benzoylation.—A solution of 0.5 g. of β -dichroine in 3 cc. of 10% sodium hydroxide is treated with 1.5 cc. of benzoyl chloride with vigorous shaking. The resulting semi-solid mass is taken up with ether and the ethereal solution washed with dilute sodium carbonate solution, dried with anhydrous sodium sulfate, and distilled. The residue refuses to crystallize from any of the usual organic solvents tried. Its nitrogen content corresponds to that of the tribenzoyl derivative when analyzed (Table I). Similar results are obtained with either α - or γ -dichroine.

Oxidation with Potassium Permanganate.—To a solution of 0.2 g. of α -dichroine in 20 cc. of water is added 10 cc. of a 5% potassium permanganate solution. After being allowed to stand at room temperature for two hours, the aqueous solution is filtered, decolorized with a few drops of sodium thiosulfate solution, mixed with some sodium bicarbonate, and extracted with ether. The ethereal solution is dried and distilled, and the residue taken up with a little alcohol, whereupon 4-quinazolone crystallizes in needles, m. p. 212–213°. When mixed with a pure specimen of 4-quinazolone isolated from the plant or prepared synthetically, as above described, its melting point remains unchanged.

Hydrolysis with Sodium Hydroxide.—A solution of 2 g. of α -dichroine in 40 cc. of water with addition of 20 cc. of 15% sodium hydroxide solution is refluxed on the water-bath for an hour and then steam distilled. The distillate smells of ammonia. When neutralized with hydrochloric acid and evaporated to dryness, the residue crystallizes from dilute alcohol in needles, subliming when heated, and being identical to ammonium chloride. The alkaline solution, after steam distillation, is acidified with acetic acid and extracted with ether. The ethereal solution is distilled and the residue crystallized from hot water, small prisms, m. p. 145°; when mixed with pure anthranilic acid, its melting point remains unchanged. *Anal.* Calcd. for anthranilic acid, $C_7H_7O_2N$: C, 61.3;

H, 5.2; N, 10.2. Found: C, 61.3; H, 5.4; N, 10.5. After removal of anthranilic acid, as above, the acid solution is made alkaline with sodium bicarbonate and extracted with ether. The ethereal solution, when evaporated, leaves behind an oily basic residue which behaves like a pyrrole derivative, imparting a red color to a pine shaving moistened with hydrochloric acid. The alkaline solution is again acidified with sulfuric acid and steam distilled. The steam distillate is acid to congo paper, and after neutralization with sodium hydroxide and evaporation, leaves behind a salt identical to sodium formate. *Anal.* Calcd. for HCOONa: Na, 33.3. Found: Na, 31.8.

Summary

From the Chinese drug, Ch'ang Shan, identified as *Dichroa febrifuga* Lour., there have been isolated umbelliferon, 4-quinazolone, a base with the composition $C_{18}H_{23}O_3N_3$, and a water soluble alkaloid named dichroine. The last compound has the

composition $C_{18}H_{21}O_3N_3$ and undergoes easily isomeric change with the formation of three isomerides, which are provisionally named α -, β - and γ -dichroines, being convertible into each other under suitable conditions. Regarding their antimalarial activity, the γ -isomeride shows the greatest, and the α -isomeride the least. Based on the results of oxidation and alkaline hydrolysis, dichroine appears to be composed of 4-quinazolone and a pyrrole derivative which requires further investigation. Dichroine forms both normal and acid salts and a nitroso compound. The isolation of 4-quinazolone from a natural plant, Ch'ang Shan, affords a remarkable coincidence with the chemical research for antimalarials along this line.

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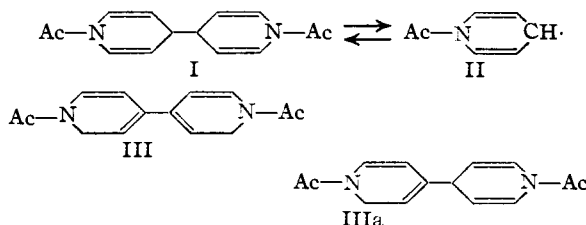
Pyridines. II. The Dissociation of N,N'-Diacetyltetrahydro-4,4'-dipyridyl¹

BY ROBERT L. FRANK, FLOYD PELLETIER AND FRED W. STARKS

The reductive acetylation of pyridine by means of zinc and acetic anhydride was first reported by Dimroth and Heene² to yield the bimolecular product N,N'-diacetyltetrahydro-4,4'-dipyridyl (I). They observed that the compound exists in two interconvertible modifications, one white, the other yellow. Dimroth and Frister³ later suggested that the yellow color might be due to an impurity, N,N'-diacetyldihydro-4,4'-dipyridyl.

It has occurred to us that either of two phenomena might be responsible for the existence of the two forms of this compound. The easy cleavage of the 4,4' valence bond between the rings in compounds of this type²⁻⁶ suggests that the yellow color is connected with dissociation of the colorless form (I) into radicals (II).⁷ On the other hand the work of Mumm and co-workers⁵ on N-alkylated tetrahydrodipyridyls and the fact that α -dihydropyridines are yellow while the γ -isomers are colorless⁸ presents the alternative proposition that the white and yellow forms may be represented by Structures I and III (or IIIa), respectively, owing to isomerism of double bonds.

The evidence presented herein favors the dissociation theory and renders unlikely the rearrangement of double bonds.



The interconversion of the two modifications depends on the solvent and on the temperature. If the white form is dissolved in methanol, ethanol, acetone or dioxane, it stays white until heated, then turns yellow. On cooling it again becomes colorless. In acetic acid or chloroform the white form turns yellow on standing at room temperature, or more quickly on heating.

Both forms have been reported to have the same m. p.² The reason for this is that the white crystals can be observed to turn yellow before melting. This change is first evident at about 105° and the material is bright yellow just before melting at 130-131°. This thermal conversion from white to yellow conforms with the idea that the yellow form contains radicals, since dissociation should be more likely at elevated temperatures.

Further, the yellow color in solutions is dispelled by small amounts of air. This is to be expected of radicals,⁹ and may signify the formation of a peroxide from the dissociated form. No peroxide has been found, however, and complete air oxidation either of solutions or of the crystalline forms, yields 4,4'-dipyridyl.²

Measurements of the magnetic susceptibility of the two crystalline forms further indicate the presence of radicals in the yellow modification. The

(1) For the previous communication on pyridine chemistry, see Frank, Blegen, Dearborn, Myers and Woodward, *THIS JOURNAL*, **68**, 1368 (1946).

(2) Dimroth and Heene, *Ber.*, **54**, 2934 (1921).

(3) Dimroth and Frister, *ibid.*, **55**, 1223 (1922).

(4) Emmert, *ibid.*, **53**, 370 (1920).

(5) Mumm, Roder and Ludwig, *ibid.*, **57**, 865 (1924); Mumm and Ludwig, *ibid.*, **59**, 1605 (1926).

(6) Wibaut and Arens, *Rec. trav. chim.*, **60**, 119 (1941).

(7) Structure II represents only one of the several possible resonance forms for such a radical.

(8) Karrer, Schwarzenbach, Benz and Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(9) Gomberg and Cone, *Ber.*, **37**, 3538 (1904).