

The dioxime of this ketone, not recorded in the literature, prepared by the Bachmann-Boatner⁷ method, is a white crystalline solid, melting at 247°.

Anal. Calcd. for $C_{20}H_{20}O_2N_2$: N, 7.14. Found: N, 7.2.

4,4'-Diphenacetyl-diphenyl.—The ketone was obtained in 94% yield by the action of benzylmagnesium bromide on the 4,4'-dicyanide of diphenyl. The product, recrystallized from ethyl acetate, is a tan crystalline solid, melting at 208–210°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 86.1; H, 5.6. Found: C, 86.07; H, 6.7.

The dioxime, a white crystalline solid, melts at 202–205°.

Anal. Calcd. for $C_{23}H_{24}O_2N_2$: N, 6.62. Found: N, 6.65.

4,4'-Dipropionyl-diphenyl.—The ketone was prepared in 86% yield by the action of the 4,4'-dicyanide of diphenyl on ethylmagnesium bromide. Recrystallization from a solution of ethyl alcohol and pyridine gave tan crystals, melting at 163–165°.

(7) Bachmann and Boatner, *THIS JOURNAL*, **58**, 2097 (1936).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.76. Found: C, 81.16; H, 6.81.

The dioxime was obtained as a very pale yellow powder, melting at 226–229°.

Anal. Calcd. for $C_{18}H_{20}O_2N_2$: N, 9.46. Found: N, 9.32.

Summary

By means of the Sandmeyer reaction with the use of nickel cyanide as the catalyst 4,4'-dicyano-diphenyl has been prepared from benzidine.

By the use of the Grignard reaction for the preparation of ketones, three ketones, 4,4'-dibenzoyl-diphenyl, 4,4'-diphenacetyl-diphenyl, and 4,4'-dipropionyl-diphenyl, have been prepared from 4,4'-dicyano-diphenyl. The ketones have been characterized by the preparation of the dioximes.

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Study of Gelsemine. I. The Reduction of Gelsemine

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Gelsemine, the principal alkaloid of *Gelsemium sempervirens*, was first investigated in 1870 by Wormley¹ and subsequently by many others.² Moore³ was the first to obtain gelsemine in its pure state and assigned to it the formula $C_{20}H_{22}O_2N_2$, which was arrived at later by one of us.⁴ Gelsemine also has been isolated recently from the Chinese drug, Ta-Ch'a-Yeh, identified as *Gelsemium elegans* Benth.⁵ Knowledge of its chemistry however is still rudimentary. It is a monacidic and tertiary base, containing one hydroxyl group but no methoxyl or ethoxyl groups. When boiled with concentrated hydrochloric acid, it forms new bases by taking up one molecule of water or hydrogen chloride, while its alcoholic solution remains intact on boiling with sodium.⁶

The present communication describes a study of the reduction of gelsemine and some of its related reactions. First, it has been found that gelsemine is easily hydrogenated in the presence of Adams platinum catalyst, absorbing at most one mole of hydrogen with the quantitative forma-

tion of dihydrogelsemine. This crystallizes from acetone with one molecule of the solvent in prismatic needles or rhombic prisms, m. p. 224–225°, is optically active, having $[\alpha]_D^{17} +78.5^\circ$ in chloroform, and is easily soluble in most organic solvents except petroleum ether. It forms well crystallized salts and a methiodide. It gives sensitive color reactions with oxidizing agents, but is more stable than gelsemine, because after boiling with concentrated hydrochloric acid or even with fuming hydriodic acid, it remains unchanged.

Second, when gelsemine is treated with zinc and hydrochloric acid in the presence of a little platinum or palladium chloride, an anomalous change takes place, the chief product appearing to be an isomer of gelsemine, $C_{20}H_{22}O_2N_2$, but differing from gelsemine in its melting point and specific rotatory power. This has been designated isogelsemine. When catalytically hydrogenated, it is reduced to the same dihydrogelsemine mentioned above. In addition to this isomeride, a small amount of a crystalline substance, having the composition $C_{18}H_{22}O_4N$, has been isolated. It is levorotatory, melts at 265–267° with decomposition, and forms a well crystallized hydrobromide and methiodide. Its aqueous solution

(1) Wormley, *Am. J. Pharm.*, **41**, 1 (1870).

(2) A survey of literature can be found in (3) and (4).

(3) Moore, *J. Chem. Soc.*, **97** 2223 (1910).

(4) Chou, *Chinese J. Physiol.*, **131** (1931).

(5) Chou, *ibid.*, **79**, (1936).

(6) Moore, *J. Chem. Soc.*, **99**, 1231 (1911).

gives, however, a weak acidic reaction toward litmus paper.

Experimental

I. Dihydrogelsemine.—Two grams of gelsemine (acetone free) is dissolved in 70 cc. of methanol and reduced by shaking with hydrogen in the presence of 0.1 g. of platinum oxide. In twelve minutes, the theoretical amount of 1 mole of hydrogen is almost all taken up (150 cc., at 22°, 767 mm.). At the end of forty minutes, the reaction is complete. After filtering off the catalyst, the methanol is thoroughly removed by distillation, and the residue taken up with a little acetone, from which dihydrogelsemine crystallizes out with one molecule of the solvent of crystallization. The pure substance thus obtained is in colorless prismatic needles or rhombic prisms, sintering at 222° and melting at 224–225°. It is dextrorotatory in chloroform, $[\alpha]^{17}_D +78.5^\circ$. The yield is almost quantitative. The results of combustion analyses conform to the formula $C_{20}H_{24}O_2N_2 \cdot CH_3COCH_3$, as shown in Table I.

The presence of acetone in the molecule also has been confirmed qualitatively by distilling a little of the substance with water and submitting the distillate to the iodoform test, which is positive. Dihydrogelsemine is found to be easily soluble in methanol, ethanol, benzene, ether and chloroform, less so in acetone, slightly soluble in water, and insoluble in petroleum ether. Its aqueous solution gives a strong basic reaction toward litmus paper. Unlike gelsemine, it remains intact when boiled with concentrated hydrochloric acid.⁶ It is also unaffected by refluxing with fuming hydriodic acid (sp. gr. 1.96) and red phosphorus in glacial acetic acid for four to five hours. Acetylation and benzylation by usual methods are unsuccessful, starting material being recovered in both cases. Dihydrogelsemine, dissolved in concentrated sulfuric acid to a colorless solution, becomes blood-red, then brownish-red, and finally dark yellow upon the addition of a crystal of potassium dichromate. With concentrated nitric acid (sp. gr. 1.42), it produces at first a colorless solution and then, according to the length of time, develops a series of colorations, ranging from bright green to dark blue.

Hydrochloride.—A solution of 150 mg. of the base in 3 cc. of methanol is neutralized with concentrated hydrochloric acid previously diluted with methanol. On adding a sufficient quantity of ether, the hydrochloride of dihydrogelsemine crystallizes out in colorless prismatic

needles, m. p. 318–320° with decomposition, and is easily soluble in water. The analytical data are indicated in Table I.

Hydrobromide.—This is prepared by neutralizing the base with hydrobromic acid in methanol. Recrystallized from methanol, it forms colorless prismatic needles, m. p. 328–330° with decomposition, and is easily soluble in water. It becomes purple in color on long exposure to the air. Figures from analyses also agree with those for the monobasic salt (Table I).

Hydriodide.—This salt is obtained by treating a saturated aqueous solution of the hydrochloride with a concentrated solution of potassium iodide. The hydriodide separates out as a colorless, fine precipitate which becomes gummy on standing. It is filtered, washed quickly with a little water and recrystallized from alcohol. It forms prismatic needles and is fairly soluble in water. Other data are shown in Table I.

Nitrate.—This is obtained either by double decomposition or by neutralizing the base suspended in water with dilute nitric acid (1:3). Recrystallized from aqueous alcohol, the nitrate is obtained as colorless six-sided prisms, m. p. 285° with decomposition. It is fairly soluble in water, and is a monobasic salt (Table I).

Methiodide.—A solution of 200 mg. of the base, 5 cc. of methanol, and 1.5 cc. of methyl iodide is refluxed on a water-bath for fifteen minutes and then allowed to stand overnight in a cold dark place. The methiodide crystallizes out as almost colorless prismatic needles, m. p. 301–302° with decomposition, and is soluble in water. The results of analyses are given in Table I.

II. Isogelsemine.—Twenty grams of granular zinc is covered with water and treated with 1 cc. of a 5% solution of platinum chloride or palladium chloride. The zinc becomes black in color. A solution of 0.5 g. of gelsemine hydrochloride in water is then added and followed slowly with shaking by 10 cc. of concentrated hydrochloric acid. After standing overnight, the whole is warmed over a water-bath to dissolve any precipitate that might separate out, then filtered, made alkaline with potassium carbonate, and the precipitate extracted with ether. The ethereal solution is dried and distilled, and the residue is crystallized out easily from acetone in colorless prismatic needles, containing one molecule of the solvent of crystallization. When crystallized pure from acetone and air-dried, isogelsemine does not possess a definite melting point, froth-

TABLE I
PHYSICAL CHARACTERISTICS AND CHEMICAL COMPOSITION OF THE COMPOUNDS DESCRIBED IN THIS REPORT

Name	Formula	M. p., °C.	Solvent for crystn.	Specific rotation, D-line	Calcd.	Percentage composition				
						Carbon Found	Calcd.	Hydrogen Found	Calcd.	
Dihydrogelsemine ^a	$C_{20}H_{24}O_2N_2$	224–225	Acetone	$[\alpha]^{17} +78.5$	74.07	74.06	73.85	7.40	7.30	7.46
Hydrochloride	$C_{20}H_{24}O_2N_2 \cdot HCl$	318–320	Methanol	66.57	66.64	66.46	6.93	7.10	6.94
Hydrobromide	$C_{20}H_{24}O_2N_2 \cdot HBr$	328–330	Methanol	59.26	59.20	59.35	5.89	6.18	5.98
Hydriodide	$C_{20}H_{24}O_2N_2 \cdot HI$	294–295	Ethanol	53.10	52.95	5.53	5.53	5.68	
Nitrate	$C_{20}H_{24}O_2N_2 \cdot HNO_3$	285	Ethanol	62.01	62.12	6.46	6.46	6.56	
Methiodide	$C_{20}H_{24}O_2N_2 \cdot CH_3I$	301–302	Methanol	54.08	53.87	5.79	5.79	6.01	
Isogelsemine	$C_{20}H_{22}O_2N_2$	200–202	Acetone	$[\alpha]^{10} +38.8$	74.53	74.47	74.50	6.83	7.03	7.05
Methiodide	$C_{20}H_{22}O_2N_2 \cdot CH_3I$	279–280	Methanol	54.31	54.15	5.39	5.39	5.52	
Unnamed base ^b	$C_{18}H_{22}O_4N$	265–267	Methanol	$[\alpha]^{18} -14.9$	68.35	68.03	68.44	6.96	6.83	6.74
Hydrobromide	$C_{18}H_{22}O_4N \cdot HBr$	305–308	Methanol	54.40	54.24	54.30	5.79	6.01	6.11

^a Analysis for N: calcd. 8.64; found 8.49, 8.61. ^b Analysis for N: calcd. 4.43; found 4.23, 4.39.

ing at 105°, then solidifying, and finally melting at 198–202°. When dried previously on a water-bath or in an oven at 110°, it melts at 200–202°, while gelsemine dried under the same condition melts at 175–177°. It is dextrorotatory (Table I) and has the formula $C_{20}H_{22}O_2N_2 \cdot CH_3COCH_3$ when air-dried. Isogelsemine is found to be easily soluble in most common organic solvents. When dissolved in concentrated sulfuric acid it is colorless, but on the addition of a little potassium bichromate, it becomes cherry-red, then dark brownish-yellow. Its solution in concentrated nitric acid is colorless at first, and then becomes greenish-yellow and finally light yellow. It bleaches permanganate solution immediately.

Methodide.—A solution of 100 mg. of the base, 5 cc. of methanol, and 0.5 cc. of methyl iodide is refluxed on a water-bath for about fifteen minutes when the methodide crystallizes out in colorless six-sided prisms, m. p. 279–280° with decomposition. Analyses confirm the expected composition (Table I).

Catalytic Reduction of Isogelsemine.—Three hundred milligrams of isogelsemine freed from acetone by drying is dissolved in 30 cc. of methanol and reduced by shaking with hydrogen in the presence of 50 mg. of platinum catalyst. Within twelve minutes, 24 cc. of hydrogen (15°, 773 mm.), corresponding to 2 H, is taken up. At the end of forty-five minutes, no more hydrogen is absorbed and the reduction is stopped. After filtering off the catalyst, the solvent is distilled, and the residue is taken up with a little acetone, from which the reduced product crystallizes out in colorless prismatic needles. When mixed with dihydrogelsemine, no depression in melting point is observed. The experiment can be repeated with the same amount of gelsemine (acetone-free) under similar conditions and the resulting compound is the same.

The Substance $C_{18}H_{22}O_4N$.—From the acetone mother liquid of isogelsemine as described above, there is isolated a small amount of a crystalline substance which becomes insoluble in acetone even on warming. It crystallizes from methanol in colorless and shining plates, sintering at 261°, and decomposing at 265–267°. It is levorotatory in methanol, and its composition and that of its salts are shown in Table I. This crystalline substance is sparingly soluble in most organic solvents except pyridine. It is slightly soluble in water, dilute hydrochloric acid, or dilute soda solution, but easily soluble in 5% sodium hydroxide

solution or concentrated hydrochloric acid. Its aqueous solution is not basic but slightly acidic toward litmus paper, bleaches permanganate solution immediately with the precipitation of manganese dioxide, and gives no coloration with a 2% solution of ferric chloride. When dissolved in concentrated nitric acid, it forms a yellow solution which remains unchanged for a long time. With concentrated sulfuric acid, it forms a colorless solution which, on the addition of potassium bichromate, becomes brownish-red and then brownish-yellow.

Hydrobromide.—Concentrated hydrobromic acid is dropped carefully into a suspension of 100 mg. of the substance in 2 cc. of methanol until the substance just goes into solution. The hydrobromide gradually separates out as colorless fine plates, m. p. 305–308° with decomposition. Its aqueous solution is slightly acidic toward litmus paper.

Methodide.—A mixture of 125 mg. of the substance, 10 cc. of methanol, and 1.2 cc. of methyl iodide is refluxed on a water-bath for twenty minutes. The clear solution is cooled down to room temperature and treated with ether until a slight turbidity persists. After standing overnight in a dark place, the methodide is obtained as rosetts of slightly yellow leaflets, decomposing at 262–265°. It is soluble in water, and its aqueous solution gives a weak acidic reaction toward litmus paper.

Summary

Catalytic hydrogenation of gelsemine gives rise to dihydrogelsemine, $C_{20}H_{24}O_2N_2$. The latter has been characterized, and its salts and methodide have been prepared.

By the reaction of zinc and hydrochloric acid upon gelsemine in the presence of a platinum or palladium salt, isogelsemine, $C_{20}H_{22}O_2N_2$, is obtained as the chief product. In addition, a small amount of a crystalline substance $C_{18}H_{22}O_4N$ also can be isolated. Isogelsemine is reduced easily by catalytic hydrogenation to dihydrogelsemine which is identical with that obtained from gelsemine directly.

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