1-Methylhydantoin,[1] which had been synthesized from sarcosine (N-methylglycine) and potassium cyanate, was condensed with indole-3-aldehyde[2] to form 1-methyl-5-(3′-indolal)-hydantoin.[1] This hydantoin had been heated with ammonium sulfide in a sealed tube at 100° for 3 days, by Miller and Robson,[1] in order to reduce it to 1-methyl-5-(3′-indolylmethyl)-hydantoin. We found that this reduction could be carried out at 40–50° by the use of Raney nickel, and could be completed in 5–6 hours.

When the last-mentioned hydantoin was refluxed with barium hydroxide, according to the directions in the literature,[1] α-methylamino-β-(3-indolyl)-propionic acid was obtained. We converted this acid into the methyl ester hydrochloride, in quantitative yield, by the use of methanol and hydrogen chloride. The ester base was formed when the salt was treated with ammonia.

It was discovered that sarcosine could be prepared by a much simpler method than that which has been described,[3] namely, by interaction of chloroacetic acid and methylamine.

Experimental

Sarcosine.—Two liters of 30% aqueous methylamine was stirred and 47.5 g. of chloroacetic acid, dissolved in 30 cc. of water, was added slowly. After 24 hours, the solution was concentrated under reduced pressure to a thick sirup which was diluted with absolute ethanol until the volume was about 240 cc. The alcoholic solution was then kept at about −10° for 15 hours, the crystalline precipitate was removed by filtration and the filtrate was diluted with absolute ethanol until the volume was about 225 cc. When the solution was cooled to −10°, and maintained at that temperature, more crystalline material deposited. The combined precipitates were recrystallized twice from 95% ethanol; m.p. 212–215°,[4] yield 18.0 g. (40.5%).

1-Methyl-5-(3′-indolylmethyl)-hydantoin.—Five grams of activated Raney nickel[5] was added to a mixture of 5.0 g. of 1-methyl-5-(3′-indolal)-hydantoin[1] and 100 cc. of 1 *N* sodium hydroxide solution. The mixture was hydrogenated at 40–50° under an initial pressure of 40 pounds. After completed reduction (5–6 hours), the catalyst was removed by filtration and the filtrate was adjusted to a *p*H of 6.5 with 1:1 hydrochloric acid. The product, which separated from the cooled mixture, weighed 4.5 g. (90%); m.p. 212–213°.[6]

α-Methylamino-β-(3-indolyl)-propionic Acid.[7]—This substance was obtained by treatment of 1-methyl-5-(3′-indolylmethyl)-hydantoin with barium hydroxide solution by the procedure of Miller and Robson[1] in 80% yield; m.p. 272–275° dec.[8]

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 65.53; H, 6.46. Found: C, 65.19; H, 6.63.

The hydrochloride, prepared according to the directions in the literature,[1] melted at 220–222°.[9]

The picrate, prepared by a described method,[10] melted at 185–186° dec.[11]

Methyl α-Methylamino-β-(3-indolyl)-propionate and Hydrochloride.—A mixture of 5.0 g. of the propionic acid and 50 cc. of absolute methanol was cooled in an ice-bath and saturated with hydrogen chloride. The mixture was allowed to remain at room temperature whereupon the acid slowly dissolved. By slow evaporation of the solvent from the solution, under reduced pressure in a desiccator which contained calcium chloride, a crystalline residue was obtained. It was covered with methanol and the solvent was removed in the manner just described. If necessary, this process was repeated in order to remove the odor of hydrogen chloride. The hydrochloride, which was slightly contaminated by a light violet impurity, melted at 185–188°.

Anal. Calcd. for $C_{13}H_{17}O_2N_2Cl$: N, 10.42; Cl, 13.20. Found: N, 10.41; Cl, 13.56.

The finely powdered hydrochloride was suspended in absolute ether, the mixture was cooled and saturated with dry, gaseous ammonia. After 10 minutes, the mixture was filtered through a sintered glass funnel and the solvent was removed from the filtrate in the manner described above; the residue, the ester base, melted at 70–72°; yield 2.3 g. (45%).

Anal. Calcd. for $C_{13}H_{17}O_2N_2$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.34; H, 6.84; N, 12.28.

The picrate was obtained when the ester was treated with an alcoholic solution of picric acid; m.p. 180–182°.

The hydrobromide precipitated when an ethereal solution of the ester was treated with hydrogen bromide; m.p. 163–165° after recrystallization from absolute ethanol–ether.

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

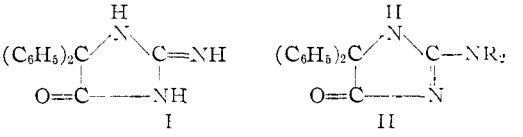
(1) E. J. Miller and W. Robson, *J. Chem. Soc.*, 1910 (1938).
(2) J. Elks, D. F. Elliot and B. A. Hems, *ibid.*, 629 (1944).
(3) W. Cocker, *ibid.*, 1693 (1937).
(4) Reference 3, m.p. 211–212°.
(5) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).
(6) Reference 1, m.p. 211–212°.
(7) The name N-methyltryptophan, which has been used for this compound, is an unsatisfactory one as has been pointed out by Miller and Robson.[1]
(8) Reference 1, m.p. 245°; W. G. Gordon and R. W. Jackson (*J. Biol. Chem.*, **110**, 154 (1935)), m.p. 297° dec.
(9) Reference 1, m.p. 192–193°; N. Ghatak (*Bull. Acad. Sci. United Provinces Agra Oudh, India*, **3**, 295 (1934); *C. A.*, **29**, 3344 (1935)), m.p. 221–222°.
(10) W. M. Cahill and R. W. Jackson, *J. Biol. Chem.*, **126**, 29 (1938).
(11) Reference 10, m.p. 185–186° dec.

The Preparation of 2-Disubstituted Amino-5,5-diphenyl-4(5H)-imidazolones[1]

BY C. K. CAIN AND SARA K. NAEGELE

RECEIVED DECEMBER 4, 1953

In spite of the large number of 5,5-disubstituted hydantoins which have been prepared and studied pharmacologically, the corresponding 2-imino compounds (glycocyamidines) have received little attention. Recently Hoffmann[2] reported the preparation of 5,5-diphenyl-2-iminohydantoin (5,5-diphenylglycocyamidine) (formula I) and Deliwala and Rajagopalan[3] described the synthesis of a few related compounds. No examples could be found in the literature of compounds containing a disubstituted amino group attached to the carbon atom between the two nitrogen atoms of the ring (formula II). Such a structure is of interest since the existence of the tautomeric form involving a double bond between carbon atom 2 and the exocyclic atom attached to it is not possible, at least in neutral or basic medium.

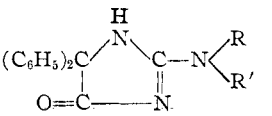


Several 2-disubstituted amino-5,5-diphenyl-4(5H)-imidazolones have been prepared in good yields by the reaction of 2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone with an excess of a secondary amine (Table I). Diisopropylamine failed to give any detectable reaction under the conditions tried.

(1) Presented before the Division of Medicinal Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., September, 1953.
(2) C. Hoffmann, *Bull. soc. chim. France*, 659 (1950).
(3) C. V. Deliwala and S. Rajagopalan, *Proc. Indian Acad. Sci.*, **31A**, 107 (1950).

TABLE I

2-DIALKYLAMINO-5,5-DIPHENYL-4(5H)-IMIDAZOLONES



R	R′	Solvent	Reaction conditions °C.	Hr.	Yield, %	M.p., °C.	Solvent[a]	Formula	Nitrogen, % Calcd.	Found
$-CH_3$	$-CH_3$	Isopropyl alc.	175 (bomb)	10	97	356–357	M	$C_{17}H_{17}N_3O$	15.1	15.3
$-C_2H_5$	$-C_2H_5$	Isopropyl alc.	175 (bomb)	12	50	277–278	M	$C_{19}H_{21}N_3O$[b]	13.7	13.7
$-C_2H_5$	$-C_2H_4OH$	Ethylene glycol	145	10	68	251–252	M	$C_{19}H_{21}N_3O_2$	13.0	13.0
$-C_6H_5$	$-C_6H_5$	Ethylene glycol	145	9	4	295–296	AW	$C_{27}H_{21}N_3O$	10.4	10.8
$-CH_3$	$-C_6H_5$	None	140	29	89	306–307	AW	$C_{22}H_{19}N_3O$	12.3	12.1
$-CH_2C_6H_5$	$-CH_2C_6H_5$	None	180	40	85	233–235	A	$C_{29}H_{25}N_3O$	9.7	9.9

[a] Solvent for crystallization: M, methanol; A, acetone; AW, aqueous acetone. [b] Calcd.: C, 74.3; H, 6.8. Found: 74.3; H, 6.5.

5,5-Diphenyl-2-thiohydantoin failed to react with diethylamine when the two substances were heated in isopropyl alcohol solution with or without the addition of lead oxide, although Hall and Arrigoni[4] reported good yields of products from the reaction of 2-thiobarbituric acids with primary amines in the presence of lead oxide.

Although 2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone reacted readily with diethylamine, 1-methyl-2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone failed to react with diethylamine under the same conditions.

The six compounds in Table I were tested for pharmacological activity in mice. Oral doses of as much as 1 g. of compound per kg. of body weight produced no obvious hypnosis or sedation; no animals died.

Experimental

5,5-Diphenyl-2-thiohydantoin was prepared by the method of Biltz.[5] After one recrystallization from methanol, the product melted at 238.5–240° (cor.).

2-Methylmercapto-5,5-diphenyl-4(5H)-imidazolone was prepared by the method of Cattelain and Chabrier.[6]

1-Methyl-2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone was made by a modification of the procedure of Cattelain and Chabrier.[6] A mixture of 10.0 g. (0.04 mole) of 5,5-diphenyl-2-thiohydantoin, 125 ml. of methanol, 3.2 g. (0.08 mole) of sodium hydroxide dissolved in 25 ml. of water and 22.7 g. (0.16 mole) of methyl iodide was heated on the steam-bath for 1.5 hours. The tan solid which started separating when the mixture was heated and which increased on cooling overnight was collected by filtration and washed with methanol, yield 8.5 g. (72%), m.p. 174–175°. Crystallization from a mixture of acetone and methanol did not change the melting point.

2-Dialkylamino-5,5-diphenyl-4(5H)-imidazolones were prepared by heating the methylmercapto compound and a large excess (approximately 5-fold) of the proper amine as summarized in Table I. When a low-boiling amine was used, it was dissolved in isopropyl alcohol, the methylmercapto compound added and the reaction mixture sealed in a glass bomb before heating. After the bomb had cooled, the crystalline aminoimidazolone was collected by filtration, washed with acetone and recrystallized. When a high-boiling amine was used, either ethylene glycol or excess amine served as the solvent. Cooling the reaction mixture after the heating period caused the product to separate as a solid which was washed with ether or ligroin and purified by crystallization.

Starting materials were recovered unchanged when: (1) a solution of 5,5-diphenyl-2-thiohydantoin in isopropyl alcohol was (a) heated with excess diethylamine in a bomb at 180° for 10 hours or (b) refluxed for 40 hours with excess diethylamine in the presence of lead oxide; (2) 2-methylmercapto-5,5-diphenylhydantoin was (a) heated with excess diisopropylamine in isopropyl alcohol at 170° for 10 hours in a sealed tube or (b) treated with excess diisopropylamine, methanol and pyridine and the mixture refluxed for 38 hours; and (3) 1-methyl-2-methylmercapto-5,5-diphenyl-4(5H)-imidazolone was (a) heated with excess diethylamine and isopropyl alcohol at 170° for 10 hours in a sealed tube or (b) treated with excess diethylamine, methanol and pyridine and the mixture refluxed for 30 hours.

McNEIL LABORATORIES, INC.
PHILADELPHIA 32, PENNSYLVANIA

(4) N. A. Hall and L. Arrigoni, *J. Am. Pharm. Assoc.*, **39**, 240 (1950).

(5) H. Biltz, *Ber.*, **42**, 1792 (1909).

(6) E. Cattelain and P. Chabrier, *Bull. soc. chim. France*, 639 (1947).

Alkaloid Studies. III.[1] Isolation of Pilocereine and Anhalonidine from Four Cactus Species

BY CARL DJERASSI, C. R. SMITH,[2a] S. P. MARFEY,[2b] R. N. MCDONALD, A. J. LEMIN, S. K. FIGDOR AND H. ESTRADA

RECEIVED FEBRUARY 16, 1954

In connection with our work on cactus alkaloids and triterpenes, we have investigated four giant cacti of the subtribe *Cereanae*[3] and we should like to report briefly our results.

Pachycereus marginatus, popularly known as "organo," is one of the most common cacti of central Mexico[4] where it is widely used for fences. We were particularly interested in this cactus since it had been reported[5] that it contained three alkaloids, named cereine, pachycereine and ochoterenine. Inspection of the original literature[5] indicates that while the presence of alkaloids had been demonstrated by color and precipitation reactions, it was unjustified to introduce three new names into the alkaloid literature on the basis of the isolation of three amorphous fractions, obtained by partial precipitation and not characterized by physical constants or analyses. The present reinvestigation of this cactus using chromatographic and countercurrent distribution techniques resulted in the isolation of pilocereine, a novel cactus alkaloid obtained recently in this Laboratory from *Lophocereus schottii*.[6] The presence of other alkaloids is indi-

(1) Paper II, C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso, THIS JOURNAL, **75**, 5446 (1953).

(2) (a) Eli Lilly Predoctorate Research Fellow, 1952–1954; (b) Warner Institute Predoctorate Research Fellow, 1952–1953.

(3) N. L. Britton and J. N. Rose, "The Cactaceae," Vol. II, Carnegie Institution of Washington, Washington, D. C., 1920.

(4) H. Bravo, "Las Cactaceas de Mexico," Mexico, D. F. 1937, p. 235.

(5) J. Roca, *Anal. Inst. Biol. Mex.*, **1**, 204 (1930); *ibid.*, **2**, 133 (1931); **3**, 19 (1932).

(6) C. Djerassi, N. Frick and L. E. Geller, THIS JOURNAL, **75**, 3632 (1953).