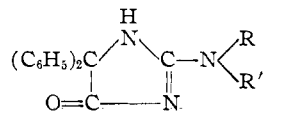
TABLE I

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).

cated but we have been unable to effect a satisfactory separation or purification in spite of considerable efforts. It is clear, however, that the names cereine, pachycereine and ochoterenine should be removed from the literature.

The earlier reported[6] isolation of pilocereine from the cactus *Lophocereus schottii* is of considerable significance since this alkaloid ($C_{30}H_{42}N_2O_4$) is clearly different from that of the common cactus alkaloids (thirteen carbon atoms or less).[7] We have now investigated the two remaining *Lophocereus* species, *L. australis*[8] and *L. gatesii*,[9] and in each instance we were able to isolate pilocereine. This raises to four the number of cactus species in which the presence of this new alkaloid has been demonstrated.

Our past experience with cacti of the genus *Lemaireocerus* (*L. thurberi*,[10a] *L. longispinus*,[10b] *L. dumortieri*[10c] and *L. stellatus*,[10d]) has demonstrated that it is rich in new triterpenoid saponins but devoid of alkaloids. It has now been possible to examine still another species, *L. weberi* (popular name "candelabro"), an impressive, tree-like cactus reaching up to 30 ft. in height which grows in the Mexican states of Oaxaca and Puebla. We have been unable to isolate any triterpenoid glycosides from this cactus but rather encountered an alkaloid which proved to be the known[7] anhalonidine (1-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline). It is pertinent to note that this alkaloid had previously been encountered only in *Anhalonium* (*Lophophora*) *lewinii* ("mescal button"), a cactus belonging to the sub-tribe *Echinocactanae*. *Lemaireocereus weberi* is thus one of the few giant cacti of the sub-tribe *Cereanae* which contains one of the "classical," small-molecular weight cactus alkaloids.[7] Whether our admittedly limited observation that triterpenoid glycosides and alkaloids are not found together in one and the same cactus is of significance remains to be proved.

Acknowledgment.—We are grateful to the American Heart Association, Inc., for financial support which enabled one of us (S.K.F.) to participate in this investigation and which defrayed the cost of the plant collections.

Experimental[11]

Isolation of Pilocereine from *Pachycereus Marginatus*.—Stalks of the plant (8 kg.)[12] were cut into small pieces, dried in an oven at 70–100°, pulverized and extracted by refluxing with 95% ethanol. Removal of the alcohol on a steam-bath under reduced pressure gave 283 g. of viscous residue. This was partitioned between ether and 10% hydrochloric acid after which the acid layer was made basic with concentrated ammonium hydroxide and extracted with ether. The ether was in turn extracted with 10% hydrochloric acid and the sequence repeated twice. The ether solution of crude alkaloids was then extracted with 7% potassium hydroxide solution to remove phenolic material, washed with water, dried over sodium sulfate and evaporated to dryness yielding 55.6 g. of the crude bases (A).

A portion of the crude base (10 g.) was chromatographed on 200 g. of neutral alumina (activity I to II[13]). Successive 100-cc. fractions of eluate were collected and combined according to their infrared spectra. The series 18–87 showed a sharp peak at *ca.* 2.95 μ corresponding to that at 2.97 μ in the pilocereine spectrum.[6] The later fractions (88–174), showing peaks at 2.80 and 2.95 μ, were examined by the countercurrent distribution method but no crystalline homogeneous fractions were isolated. The chromatogram fractions were obtained as follows.

Fraction	Eluant	Wt. combined fractions (g.)		
1–17	9:1 pet. ether–benzene	Fractions	1–17	Trace
18–60	7:3 pet. ether–benzene		18–33	2.00
			34–45	.40
			46–57	.23
61–77	1:1 pet. ether–benzene		58–74	.61
78–86	3:7 pet. ether–benzene		75–87	.43
87–109	Benzene		88–106	.72
110–116	9:1 benzene–ether		107–123	.79
117–123	7:3 benzene–ether			
124–137	1:1 benzene–ether		124–140	.91
138–142	Ether			
143–146	9:1 ether–acetone		141–153	.75
147–150	7:3 ether–acetone			
151–155	1:1 ether–acetone		154–160	.66
156–160	Acetone			
161–172	9:1 acetone–methanol		161–168	.79
173–174	7:3 acetone–methanol		169–174	.07

Fractions 18–87 yielded a total of 1.11 g. of pilocereine with m.p. 173.5–174.5°. Identity was established by mixture melting point and comparison of the ultraviolet and infrared spectra with those of an authentic specimen.[6] The residue remaining after the separation of pilocereine was acetylated by stirring for 18 hours with 69 cc. of acetic anhydride and 1.1 g. of *p*-toluenesulfonic acid. Attempted crystallization from hexane yielded 0.1 g. of an amorphous acetate, the infrared spectrum of which differed from that of pilocereine acetate and indicated the presence of phenolic (5.68 μ) and alcoholic (5.82 μ) acetates together with a broad band at 6.1 μ indicative of an amide. This substance, therefore, appears to be a triacetate, in which case the parent compound would correspond to $C_{24}H_{36}N_2O_3$ with a free NH group as well as alcoholic and phenolic functions.

Anal. Calcd. for $C_{30}H_{42}N_2O_6$: C, 68.41; H, 8.04; N, 5.32; eq. wt., 527. Found: C, 68.73; H, 8.17; N, 5.27; eq. wt., 500.

A ten-stage countercurrent distribution was performed on 2 g. of the crude base (A) above. Chloroform and sodium phosphate–citric acid buffer of *p*H 4.2, 50 cc. per layer, was used whereupon the following distribution was obtained.

Funnel no.	Wt. g.	Funnel no.	Wt. g.
1	0.23	6	0.33
2	.23	7	.35
3	.17	8	.28
4	.19	9	.10
5	.26	10	.13

Fractions 5, 6 and 7 yielded pilocereine but no other crystalline fraction could be obtained.

Pilocereine from *Lophocereus australis* and *L. gatesii*: *L. australis*.[14]—The isolation procedure was essentially the same as that described above for *P. marginatus*. After the spines and the central woody core had been removed 4.9 kg. of cactus gave 399 g. of dry material. On Soxhlet extraction with 95% ethanol 52.5 g. of residue was obtained from which 9 g. of base yielded 5 g. of non-phenolic crude alka-

(7) L. Reti in L. Zechmeister, "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Vienna, 1950, pp. 242–289.

(8) Some authors (ref. 3, 4) question the assignment of a new species to this cactus and consider it only a local variation of *L. schottii*.

(9) M. E. Jones, *Cactus and Succulent J.*, **5**, 546 (1934).

(10) (a) C. Djerassi, L. E. Geller and A. J. Lemin, THIS JOURNAL, **75**, 2254 (1953); (b) C. Djerassi, R. N. McDonald and A. J. Lemin, *ibid.*, **75**, 5940 (1953); (c) C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, *ibid.*, **76**, 2969 (1954); (d) L. H. Liu, unpublished observation.

(11) Melting points are uncorrected.

(12) Collected by Dr. Alberto Sandoval of the Universidad Nacional Autonoma de Mexico near the "Barranca de los Venados" in the State of Hidalgo.

(13) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

(14) Obtained through the courtesy of Mr. Howard E. Gates, Corona, California.

loids. This was chromatographed on 150 g. of neutral alumina (activity II–III)[13] and from the 7:3 benzene–ether eluates was isolated 2.0 g. of pilocereine. Crystallization from ethyl acetate furnished 1.1 g. of pure pilocereine, the identity of which was confirmed by mixture melting point and infrared comparison.

L. gatesii.[14]—Fresh cactus (3.3 kg.) yielded 300 g. of dry powdered material which on extraction gave 39.6 g. of residue. This was partitioned and separated as previously described into 3 g. of phenolic and 5.4 g. of non-phenolic base. The non-phenolic base was chromatographed on 150 g. of alumina to yield 1.5 g. of pilocereine identified as before.

Isolation of Anhalonidine from *Lemaireocereus weberi*.[14]—By the usual procedure 9.27 kg. of cactus gave 48 g. of alcoholic residue which was extracted with ether until no more color was removed. The ether extract, weighing less than 2 g., did not contain alkaloids (Mayer's reagent) and only traces of oily material were obtained when this fraction was processed in the usual manner for triterpenes. The dark brown, ether-insoluble fraction (46 g.) was refluxed for 3 hr. with 1 l. of methanol and 200 cc. of concentrated hydrochloric acid. After cooling and dilution with water this was extracted with ether but evaporation left only traces of oily material. The aqueous acidic solution was neutralized with ammonium hydroxide and extracted with ether; evaporation yielded 1.73 g. of crude alkaloids which were chromatographed on 100 g. of activated alumina. Elution with chloroform–methanol (99:1) furnished a solid (0.65 g.) crystallizing as needles, m.p. 156–158° from acetone–hexane. The analytical sample after recrystallization from acetone showed m.p. 161–161.5°; reported[15] for anhalonidine, m.p. 160–161°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27; $(OCH_3)_2$, 27.6; neut. equiv., 223. Found: C, 64.43; H, 7.80; N, 6.50; OCH_3, 26.9; neut. equiv., 215.

The picrate, prepared by adding a saturated solution of picric acid to a solution of the base gave needles, m.p. 200.5–201.5°, after recrystallization from ethanol; reported[15] m.p. 201–208°.

Anal. Calcd. for $C_{18}H_{20}N_4O_{10}$: C, 47.79; H, 4.46. Found: C, 48.03; H, 4.54.

(15) E. Spaeth, *Monatsh.*, **43**, 477 (1922).

DEPARTMENT OF CHEMISTRY
WAYNE UNIVERSITY
DETROIT, MICHIGAN, AND
INSTITUTO DE QUIMICA
UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO
CIUDAD UNIVERSITARIA
MEXICO, D. F.

Some New 1-(Nitroxyalkyl)-3-nitroguanidines and their Cyclic Products[1]

BY LAWRENCE FISHBEIN AND JOHN A. GALLAGHAN

RECEIVED JANUARY 18, 1954

The cyclization of the N-(β-substituted ethyl)- and N-(β-nitroxypropyl)-N′-nitroguanidines to salts of 1-nitro-2-amino-Δ^2-1,3-diazacyclopentene and 1-nitro-2-amino-5-methyl-Δ^2-1,3-diazacyclopentene nitrate, respectively, was first reported by McKay.[2] A six-membered ring compound has also been formed by cyclizing N-(γ-nitroxybutyl)-N′-nitroguanidine to 1-nitro-2-amino-6-methyl-Δ^2-1,3-diazacyclohexene nitrate.[3]

It was of interest to this Laboratory to determine whether larger ring systems could be synthesized through cyclization of higher homologs of 1-(nitroxyalkyl)-3-nitroguanidines, the free bases of which are isomeric to those reported by McKay and Wright.[4] The cyclization of 1-(ω-nitroxypropyl)- and 1-(β-nitroxy-*t*-butyl)-3-nitroguanidine proceeded rapidly in boiling *n*-butanol to 1-nitro-amino-Δ^2-1,3-diazacyclohexene nitrate and 1-nitro-2-amino-4-dimethyl-Δ^2-1,3-diazacyclopentene nitrate, respectively. However, 1-(ω-nitroxybutyl)- and 1-(ω-nitroxyamyl)-3-nitroguanidine failed to cyclize to the respective seven- and eight-membered rings: *viz.*, 1-nitro-2-amino-Δ^2-1,3-diazacycloheptene and 1-nitro-2-amino-Δ^2-1,3-diazacycloöctene nitrate salts. Failure of the higher homologs to cyclize can be attributed to the greater strain in the seven- and eight-membered rings. In addition, attempts to prepare 1-nitro-2-amino-4-ethyl-Δ^2-1,3-diazocyclopentene nitrate by cyclizing 1-(α-nitroxy-β-butyl)-3-nitroguanidine were unsuccessful.

Experimental[5]

1-(ω-Hydroxypropyl)-3-guanidinium Nitrate.—Seventy-five grams (1.0 mole) of 3-amino-1-propanol (obtained from American Cyanamid; b.p. 85° (10 mm.)) was added, slowly with stirring, to 139.2 g. (0.5 mole) of 2-methyl-2-thiopseudouronium sulfate in a 1-liter beaker. Thirty cc. of water was then added to the mixture. Considerable foaming and evolution of methyl mercaptan occurred immediately. The reaction mixture was allowed to stand overnight at room temperature. The product, a clear, viscous oil, was treated with an equivalent weight of hot aqueous barium nitrate solution. The barium sulfate precipitate was removed by filtration, and the filtrate evaporated yielding 108 g. (60.0% yield) of crude product which melted at 85–88°. One crystallization from 95% ethanol raised the m.p. to 91–92°.

Anal. Calcd. for $C_4H_{12}N_4O_4$: C, 26.6; H, 6.7; N, 31.1. Found: C, 26.7; H, 6.9; N, 31.0.

The picrate salt, crystallized from ethanol, melted at 127–128°.

Anal. Calcd. for $C_{10}H_{14}N_6O_8$: C, 34.9; H, 4.1; N, 24.4. Found: C, 34.8; H, 4.3; N, 24.3.

1-(ω-Hydroxypropyl)-3-nitroguanidine.—1-(ω-Hydroxypropyl)-3-nitroguanidine was prepared in 90% yield by the procedure of Fishbein and Gallaghan[6] utilizing 2-methyl-1(or 3)nitro-2-thiopseudourea and 3-amino-1-propanol. The crude m.p. of 123–126° was raised to 128–129° by one crystallization from 95% ethanol.

Anal. Calcd. for $C_4H_{10}N_4O_3$: C, 29.6; H, 6.2; N, 34.6. Found: C, 29.4; H, 6.1; N, 34.3.

1-(ω-Nitroxypropyl)-3-nitroguanidine. 1. From 1-(ω-Hydroxypropyl)-3-guanidinium Nitrate.—Forty-three grams (0.23 mole) of 1-(ω-hydroxypropyl)-3-guanidinium nitrate was added portionwise to a nitrating mixture composed of 88.0 g. of 95% sulfuric acid and 30 g. of 98% nitric acid. The nitration was performed at 0–5°. After stirring for five minutes the mass was poured into 500 g. of ice; the contents were stirred for an additional five minutes and filtered. Forty-four grams (93.1% yield) of white crystals was obtained, which on crystallization from 95% ethanol (350 cc.) gave 33 g. of crystals melting at 121–122°.

Anal. Calcd. for $C_4H_9N_5O_5$: C, 23.2; H, 4.3; N, 33.8. Found: C, 23.0; H, 4.5; N, 33.8.

2. From 1-(ω-Hydroxypropyl)-3-nitroguanidine.—1-(ω-Hydroxypropyl)-3-nitroguanidine was nitrated according to the procedure of McKay and Milks.[2a] An 85% yield of product was obtained melting at 121–122°. A mixed m.p. with an authentic sample was not depressed.

1-Nitro-2-amino-Δ^2-1,3-diazacyclohexene Nitrate.—Ten grams (0.05 mole) of 1-(ω-nitroxypropyl)-3-nitroguanidine was dissolved in 25 cc. of boiling *n*-butanol. After five minutes of refluxing, a crystalline precipitate formed. The

(1) Publication approved by the Bureau of Ordnance, Navy Department.

(2) (a) A. F. McKay and J. E. Milks, THIS JOURNAL, **72**, 1616 (1950); (b) A. F. McKay, *Chem. Revs.*, **51**, 340 (1952); (c) R. H. Hall, A. F. McKay and G. F Wright, THIS JOURNAL, **73**, 2205 (1951); (d) A. F. McKay, *J. Org. Chem.*, **16**, 1395 (1951); (e) A. F. McKay and R. O. Brawn, *ibid.*, **16**, 1829 (1951).

(3) A. F. McKay and H. P. Thomas, *Can. J. Chem.*, **29**, 391 (1951).

(4) A. F. McKay and G. F Wright, THIS JOURNAL, **70**, 430 (1948)

(5) All melting points are uncorrected.

(6) L. Fishbein and J. A. Gallaghan, THIS JOURNAL, **76**, 1877 (1954).