was a methosulfate, prepared according to Horwitz, and not the methiodide.) This phenol betaine shows the characteristic and very striking color variations with solvent[7]: in acid, yellow; in alcoholic alkali blue; in aqueous alkali, red to purple.

EXPERIMENTAL

Preparation of compounds. The general procedure for synthesis of the 2-styryl-8-hydroxyquinolines is as follows. 8-Hydroxyquinaldine (3.2 g.) is mixed with an equivalent amount of the aromatic aldehyde and 5 ml. acetic anhydride added. The mixture is refluxed 4–6 hr., then poured into water and neutralized with 10% sodium hydroxide solution. The precipitate is filtered, washed with 5% sodium bicarbonate and water, and then heated 1 hr. with 50 ml. 10% sodium hydroxide to hydrolyze the acetate. After neutralization with hydrochloric acid the product is filtered, washed with sodium bicarbonate and water, and recrystallized from ethanol. Since there are usually appreciable impurities at this point, the compound is dissolved in hot ethanol and 3–5 ml. concentrated hydrochloric acid added. A bulky precipitate of the hydrochloride forms quickly and this is recrystallized once or twice from ethanol containing hydrochloric acid.

Compounds 4 and 8 in Table I were similarly prepared from 8-hydroxylepidine, and compound 6 from 8-methoxyquinaldine. An attempt to condense chloral with 8-hydroxyquinaldine produced only extensive decomposition.

All melting points were taken on a Kofler hot stage, and are within a two-degree range of the values in Table I except as noted there. All the hydrochlorides melted with decomposition, and several were observed to sublime from the top of the slide to the cover glass well below the melting point. Melting points for free bases corresponding to some of the hydrochlorides of Table I are as follows: compound 3, 86°; 4, 150°; 5, 215°; 8, 153°; 9, 131°; and 13, 132°. These free bases were obtained by neutralizing the hydrochloride followed by recrystallization from ethanol. No differences in properties of the free bases before and after hydrochloride formation were observed other than minor melting point variations.

The styrylquinolines and methosulfates from quinaldine or 6-ethoxyquinaldine and piperonal were prepared according to the literature.[4] Melting points of the free bases agreed with published values within two degrees. Condensation of quinaldine with vanillin[5] also gave the same free base previously reported; quaternization was performed by Horwitz's method with dimethyl sulfate.

Spectra. All ultraviolet and visible spectra were recorded with a Beckman DK Spectrophotometer in ethanol 0.1*M* in hydrochloric acid, except the methosulfates which were run in ethanol alone. Concentrations ranged from 1 to 4 × $10^{-5}M$.

Infrared spectra were determined by the potassium bromide pellet technique on a Baird AB-2 Spectrophotometer in the range 2–16 μ.

Acknowledgment. This work was supported by a grant (NSF G5447) from the National Science Foundation. The DK Spectrophotometer was also supplied by an NSF grant (G4074).

LOUISVILLE, KY.

(7) S. Hünig and O. Rosenthal, *Ann.*, **592**, 161 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF CONNECTICUT]

Synthesis of Isoquinoline Alkaloids. I. Lophocerine[1]

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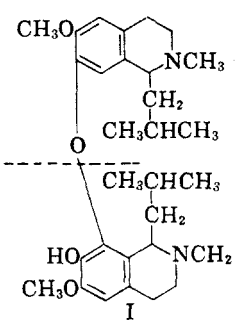
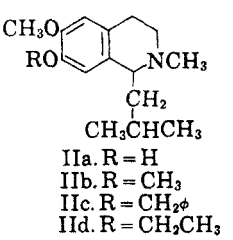
The cactus alkaloid lophocerine (1-isobutyl-2-methyl-6-methoxy-7-hydroxy-12,3,4-tetrahydroisoquinoline) which can be isolated from *Lophocereus Schottii* as its methyl ether has been synthesized.

Three alkaloids have been isolated from the giant cactus *Lophocereus Schottii* by Djerassi and his coworkers. Two of these alkaloids, pilocereine[3–5] and piloceredine[6] (diastereoisomers of I) could be considered *dimeric* since they contain two isoquinoline residues. When the phenolic alkaloidal fraction



I



from *L. Schottii* was distilled and methylated, a third compound was isolated and shown to be 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIb).[6] It was suggested that this methyl ether represented a *monomeric* alkaloid to be called lophocerine. The free phenol group was assigned to the 7-position (structure IIa) by anal-

(1) This investigation was supported in part by Research Grant CY-3905 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Abstracted from the M.S. thesis of Tsu-teh Chou, The University of Connecticut, 1959. Present address: Institute of Materia Medica, Academia Sinica, Shanghai, China.

(3) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901).

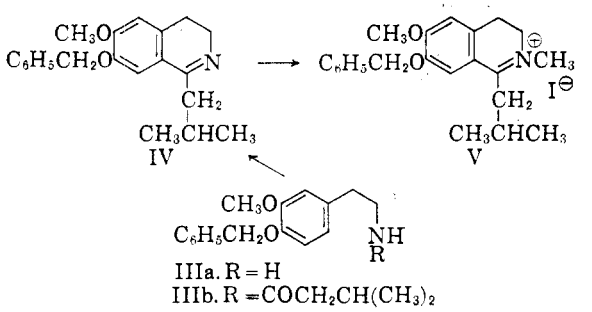
(4) C. Djerassi, N. Frick, and L. E. Geller, *J. Am. Chem. Soc.*, **75**, 3632 (1953).

(5) C. Djerassi, S. K. Figdor, J. M. Bobbitt, and F. X. Markley, *J. Am. Chem. Soc.*, **78**, 3861 (1956); **79**, 2203 (1957).

(6) C. Djerassi, T. Nakano, and J. M. Bobbitt, *Tetrahedron*, **2**, 58 (1958).

ogy with other cactus alkaloids[7] and biogenetic reasoning.[8] It was also noted[6] that the dimeric alkaloids might be formed in the plant by the oxidative coupling[8] of two molecules of lophocerine (dotted line in I). Lophocerine, IIa, has now been synthesized.

Vanillin was benzylated[9] and the resulting 3-methoxy-4-benzyloxybenzaldehyde (85%) was condensed with nitromethane[10] to yield 3-methoxy-4-benzyloxy-ω-nitrostyrene[11] (81%). The nitrostyrene was reduced with lithium aluminum hydride to yield 2-(3-methoxy-4-benzyloxyphenyl)ethylamine, IIIa (80.2%, isolated as hydrohcloride[11]). A good yield of amine was obtained only when the reaction mixture was hydrolyzed by the elegant method of



IIIa. R = H
IIIb. R = $COCH_2CH(CH_3)_2$

Amundsen and Nelson.[12] In general, the amine was converted, without isolation, to *N*-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, (81.5% from nitrostyrene) by reaction with isovaleryl chloride in the presence of an anhydrous anion exchange resin (Amberlite IRA-400). The resin was found to be more convenient than the conventional bases, sodium hydroxide, and calcium hydroxide. The amine hydrochloride could also be converted directly to the amide by a resin technique.

N-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, was converted to 1-isobutyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline, IV (57%, isolated and characterized as a picrate) with phosphorus pentachloride.[13] The dihydroisoquinoline, IV, was regenerated from its picrate with the modified anion exchange resin Amberlite IRA-400-HCO_3[14] and converted, without isolation, to the methiodide, V (97% from picrate). The methiodide was hydrogenated with Adams catalyst and passed over Amberlite IRA-400-HCO_3[14] (to remove hydriodic acid) to yield benzyllophocerine, IIc (1 - isobutyl - 2 - methyl - 6 - methoxy - 7-benzyloxy-1,2,3,4-tetrahydroisoquinoline, 91.3%). Benzyllophocerine was not crystalline but was characterized by a picrate and a styphnate. The methiodide, V, was hydrogenated with Adams catalyst, passed over Amberlite IRA-400-HCO_3 and again hydrogenated with palladium on charcoal to yield lophocerine, IIa (90%). No conditions were found for carrying out both reductions simultaneously. Lophocerine was also not crystalline but was characterized by a picrate and a styphnate.

The structure of synthetic lophocerine was further established by methylation (diazomethane) and ethylation (diazoethane) to the methyl, IIb, and ethyl, IId, ethers. The respective picrates and styphnates of these ethers were identical with authentic specimens.[15]

EXPERIMENTAL

The melting points were determined on a Kofler Hot Stage melting point apparatus and are corrected. The vanillin used was contributed by the Dow Chemical Company of Midland, Mich. Unless noted, all other chemicals were commercial materials used without purification. The microanalyses were performed by Geller Laboratories, Bardonia, N. Y.

2-(3-Methoxy-4-benzyloxyphenyl)ethylamine, IIIa (*hydrochloride*). 3-Methoxy-4-benzyloxy-ω-nitrostyrene[10,11] (28.5 g., 0.1 mole) was placed in the thimble of a Soxhlet extractor and washed gradually (30 hr.) into 500 ml. of stirred, refluxing, anhydrous ether containing 19.0 g. (0.5 mole) of lithium aluminum hydride. The mixture was cooled in an ice bath and stirred vigorously during the successive addition of 10 ml. of water, 8 ml. of 20% aqueous sodium hydroxide and 37 ml. more of water. The mixture was stirred for 15 min., the ether layer was decanted and the residue was washed three times with ether. The combined decantate and washings were dried over potassium hydroxide, again decanted, and saturated with anhydrous hydrogen chloride. The white crystalline hydrochloride was recrystallized from ethanol to yield 23.5 g. (80.2%) of product, m.p. 176–178° (rec. 173–175°[11]).

N-[2-(3-Methoxy-4-benzyloxyphenyl)ethyl]isovaleryl amide, IIIb. The dried ether solution containing the amine, IIIa, described above was diluted to 1500 ml. with ether, combined with 80 g. (about 0.2 equiv.) of dry Amberlite IRA-400[16] and vigorously stirred during the dropwise addition of 18.3 ml. (18 g., 0.15 mole) of isovaleryl chloride. The mixture was stirred under reflux until the white precipitate, which formed immediately, was dissolved (24 hr.). The resin was separated by filtration and the filtrate was washed with 2*N* sodium hydroxide, 2*N* hydrochloric acid and dried over sodium sulfate. On evaporation, 27.8 g. (81.5% from the nitrostyrene) of amide, m.p. 111–114° was obtained. The m.p.

(7) L. Reti in R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Vol. IV, Academic Press, New York, 1954, pp. 7–28.

(8) R. Robinson, *The Structural Relations of Natural Products*, Oxford University Press, London, 1955, p. 85; R. H. F. Manske, ref. 7, p. 1.

(9) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(10) K. H. Slotta and G. Szyszka, *J. prakt. Chem.*, **137**, 339 (1933); *Chem. Abstr.*, **57**, 4221 (1933).

(11) S. Kobayashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **6**, 149 (1927); *Chem. Abstr.*, **22**, 1345 (1928).

(12) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(13) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 280 (1933).

(14) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).

(15) (a) C. Djerassi, F. X. Markley, and R. Ehrlich, *J. Org. Chem.*, **21**, 975 (1956); (b) C. Djerassi, J. J. Beereboom, S. P. Marfey, and S. K. Figdor, *J. Am. Chem. Soc.*, **77**, 484 (1955). We are indebted to Professor Djerassi for authentic samples of these compounds.

(16) This resin was donated by the Rohm and Haas Company, Philadelphia, Pa. It was regenerated to its basic form with 4% sodium hydroxide, washed with water followed by methanol and dried over calcium chloride under vacuum for 12–14 hr.

was 114–115° after one recrystallization from hexane-benzene.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.9; H, 8.0; N, 4.1. Found: C, 73.9; H, 8.0; N, 4.2.

1-Isobutyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline, IV (*picrate*). A solution of 6.84 g. (0.02 mole) of *N*-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, in 100 ml. of dry chloroform was added slowly to a stirred and cooled (ice bath) suspension of 30 g. (0.145 mole) of phosphorus pentachloride in 160 ml. of the same solvent. The mixture was stirred at 0° for 1 hr. and allowed to stand at 5° overnight and at 25° for 3 days. Crushed ice (600 g.) was added with stirring and 5 ml. of methanol was added to break the emulsion. The separated chloroform layer was evaporated to a dark oil and treated with 5.6 g. (0.024 mole) of picric acid in 100 ml. of ethanol. The mixture was warmed and then cooled to deposit 7.12 g. of crude picrate which was recrystallized from benzene to give 6.28 g. (57%) of dihydroisoquinoline picrate, m.p. 170–171°. Three recrystallizations from benzene yielded the analytical sample, m.p. 171–172°.

Anal. Calcd. for $C_{27}H_{28}N_4O_9$: C, 58.7; H, 5.1; N, 10.1. Found: C, 58.7; H, 5.2; N, 10.2.

1-Isobutyl-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline methiodide, V. 1-Isobutyl-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline picrate (0.55 g., 0.001 mole) was dissolved in 50 ml. of 6% aqueous acetone and poured slowly over a column of Amberlite IRA-400-HCO_3[14] (25 ml.) previously washed with the same solvent. The column was washed with an additional 50 ml. of solvent, and the eluents were concentrated in vacuum to about 20 ml. and extracted with 50 ml. of benzene. Excess methyl iodide (1.2 ml., 2.7 g.) was added and, after 2 days, the solution deposited 0.45 g. (97%) of methiodide, V, m.p. 208–211°. Three recrystallizations from ethanol yielded the analytical sample, m.p. 209–211°.

Anal. Calcd. for $C_{22}H_{28}INO_2$: C, 56.8; H, 6.1; I, 27.3; N, 3.0. Found: C, 56.7; H, 6.2; I, 27.0; N, 3.0.

Benzyllophocerine (*1-isobutyl-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline*) IIc. One gram (0.022 mole) of methiodide, V, dissolved in 35 ml. of methanol was hydrogenated (48 p.s.i., 25°) in the presence of 0.1 g. of Adams catalyst. After 3 hr. the catalyst was removed by filtration; the solution was passed over 20 ml. of IRA-400-HCO_3[14] (previously washed with methanol) and the solvent was evaporated under vacuum to yield 0.68 g. (91.3%) of a faint yellow oil. The analytical sample was sublimed (152°, 0.5 mm.).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.8; H, 8.6; N, 4.1. Found: C, 77.4; H, 8.7; N, 4.3.

A *picrate* was prepared in absolute ethanol and recrystallized twice from the same solvent to give the analytical sample, m.p. 151–152°.

Anal. Calcd. for $C_{28}H_{32}N_4O_9$: C, 59.1; H, 5.7; N, 9.9. Found: C, 59.4; H, 5.9; N, 9.8.

A *styphnate* was prepared in absolute ethanol, m.p. 138–141°,[17] and recrystallized twice from the same solvent to give an analytical sample, m.p. 151.5–153°.

Anal. Calcd. for $C_{28}H_{32}N_4O_{10}$: C, 57.5; H, 5.5; N, 9.6. Found: C, 57.8; H, 5.8; N, 9.6.

Lophocerine (*1-isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline*, IIa. Benzyllophocerine, IIc, in methanol (100 ml.) was prepared as described above from 3.0 g. (0.0065 mole) of methiodide, V, and again hydrogenated (45 p.s.i., 25°) over 0.2 g. of 5% palladium-on-charcoal. After 3 hr., the catalyst was removed by filtration and the filtrate was evaporated under vacuum to yield 1.46 g. (90%) of heavy orange oil which gave a purple coloration with ferric chloride. The analytical sample was sublimed (96–104°, 0.5 mm.).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.2; H, 9.3; N, 5.6. Found: C, 72.2; H, 9.4; N, 5.7.

A *picrate* was prepared in benzene, m.p. 172–175°,[17] and recrystallized twice from the same solvent to give the analytical sample, m.p. 191.5–193°.

Anal. Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.7; H, 5.5; N, 11.7. Found: C, 52.7; H, 5.4; N, 12.0.

A *styphnate* was prepared in absolute alcohol and recrystallized six times from the same solvent to give the analytical sample, m.p. 171–172°.

Anal. Calcd. for $C_{21}H_{26}N_4O_{10}$: C, 51.0; H, 5.3; N, 11.3. Found: C, 51.3; H, 5.3; N, 11.4.

Lophocerine methyl ether, IIb, *and lophocerine ethyl ether*, IId. Lophocerine was methylated in 50% methanolic ether at 5° with excess diazomethane prepared from the di(*N*-nitroso-*N*-methylamide) of terephthalic acid[18] by distillation.[19] After 40 hr., the excess diazomethane was evaporated, additional ether was added, and the resulting ether-methanol was washed with 2*N* sodium hydroxide, dried over sodium sulfate, and evaporated. One portion was treated with picric acid in ethanol to give a picrate, m.p. 180–182° (rec.[15b] 183–185°) and the other portion was treated with styphnic acid in ethanolic to give a styphnate, m.p. 210–212° (rec.[15b] 212–214°). Mixture melting points with authentic samples were undepressed.

Lophocerine was ethylated at 25° with excess diazoethane prepared by distillation[19] from *N*-ethyl-*N*-nitrosourea.[20] After seven days the reaction mixture was treated as described above to yield a picrate, m.p. 150–153° (rec.[15a] 153–153.5°) and a styphnate, m.p. 182–183° (rec.[15a] 183–184°). Mixture melting points with authentic specimens were undepressed.

STORRS, CONN.

(17) Because of its sharpness, this might represent a crystalline modification. The high melting form could not be converted to the low melting form.

(18) This compound was donated by the Explosives Division of E. I. du Pont de Nemours Co. of Wilmington who sell it as EXR-101.

(19) F. Arndt, *Org. Syntheses*, **Coll. Vol. II**, 165 (1943).

(20) Prepared by the procedure given in A. I. Vogel, *Practical Organic Chemistry*, 3rd ed., Longmans Green, London, 1956, p. 969, for *N*-nitroso-*N*-methylurea.