5% aqueous sodium hydroxide was boiled under reflux for one hour. The clear solution was cooled and then acidified with 2 *N* sulfuric acid. The white substance which precipitated was collected by filtration and washed with water. The material was recrystallized from ethanol, m.p. 211–212° dec. The yield was 1.5 g. (52.1%).

Anal. Calcd. for $C_8H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.67; H, 3.74; N, 7.54.

The filtrate, after removal of 3-carboxy-7-methyl-2-isoxazolono[2,3-a]pyridine, was exhaustively extracted with chloroform. The chloroform extracts were dried over magnesium sulfate and the chloroform removed under reduced pressure. The crystalline residue was recrystallized from ethanol. The yield was 1.1 g. (44.2%) of 6-methyl-2-pyridylacetic acid 1-oxide (XVII), m.p. 146–147° dec.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43. Found: C, 57.86; H, 5.37.

Hydrolysis of 3-Carbethoxy-2-isoxazolono[2,3-a]pyridine (IV): 3-Carboxy-2-isoxazolono[2,3-a]pyridine (VII) and 2-Pyridylacetic Acid 1-Oxide (XVI).—A mixture of 3.0 g. of 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) and 30 ml. of 5% aqueous sodium hydroxide was treated as described for its 7-methyl derivative. A yield of 0.8 g. (30.9%) of 3-carboxy-2-isoxazolono[2,3-a]pyridine (VII), m.p. 204–205° dec., resulted from acidification of the alkaline solution.

Anal. Calcd. for $C_8H_5NO_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.67; H, 2.78; N, 7.73.

From the filtrate 0.4 g. (18.0%) of 2-pyridylacetic acid 1-oxide (XVI), m.p. 140° dec., was obtained.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.14. Found: C, 54.60; H, 4.54; N, 8.82.

Hydrogenation of 3-Carbethoxy-2-isoxazolono[2,3-a]pyridine (IV): 3-Carbethoxy-2-isoxazolono[2,3-a]piperidine (XX).—A suspension of 0.4 g. of 3-carbethoxy-2-isoxazolono[2,3-a]pyridine (IV) in 100 ml. of ethanol was hydrogenated in the presence of platinum oxide catalyst. An uptake of 92 ml. of hydrogen at 24° and 745 mm. was observed (theoretical for 2 moles at 24° and 745 mm. is 96.0 ml.) The catalyst was removed by filtration and the filtrate was concentrated until the substance started to crystallize. Ether was added and after cooling the compound was collected by filtration. It was recrystallized from ethanol–ether, m.p. 157–158°.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.64. Found: C, 56.71; H, 6.23; N, 6.37.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Alkaloids of *Lunasia amara* Blanco. 4-Methoxy-2-phenylquinoline

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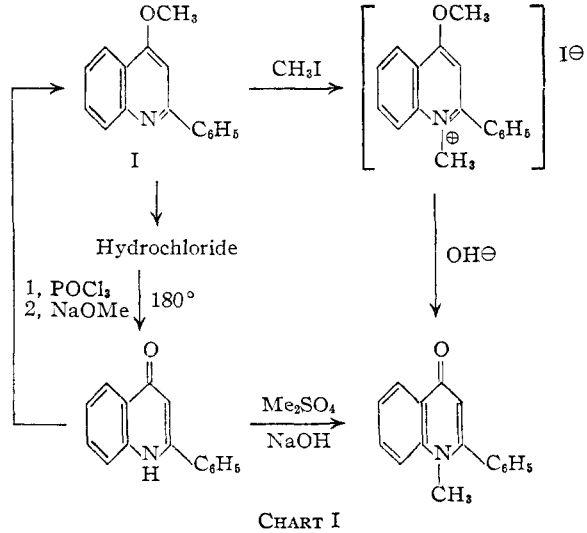
From the leaves of *Lunasia amara* Blanco there was isolated an alkaloid which did not correspond to any of the previously reported *Lunasia* alkaloids. It was identified as 4-methoxy-2-phenylquinoline. This substance has not hitherto been reported to occur in nature.

Alkaloids of the genus *Lunasia* (fam. *Rutaceae*) have been investigated on several occasions since their discovery by Lewin[1] and by Boorsma.[1] Several alkaloids of unknown structure were described by Steldt and Chen,[2] who found that, contrary to previous reports, the alkaloids did not possess a digitalis-like action. Pertinent early references are given by Steldt and Chen.

In the present work, a number of alkaloids were isolated from leaves of *Lunasia amara* Blanco obtained from the Philippine Islands.[3] Of the total of seven compounds isolated by chromatography on alumina, only the one eluted first will be discussed in this paper. This material, with an empirical formula $C_{16}H_{13}ON$, crystallized from pentane in colorless, optically inactive needles melting at 66–67°. It was identified through its reactions and by synthesis as 4-methoxy-2-phenylquinoline (I). This substance has not heretofore been reported as a naturally occurring compound, and it was not observed in earlier *Lunasia* work.

An interesting property of this compound, which provided one of the first keys to its structure, was observed through the melting point behavior of the hydrochloride. The salt melted with effervescence to a colorless liquid which resolidified and thereafter melted above 240°. These effects suggested a thermal demethylation to yield a 2- or 4-quinolone. Salts of cusparine (a 4-methoxyquinoline) were reported to yield a 4-quinolone on heating to decomposition temperature,[4] and a preparative pyrolysis of the *Lunasia* alkaloid hydrochloride



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was therefore carried out. The high-melting (256–258°) product, later recognized as 2-phenyl-

(1) L. Lewin, "Lehrbuch der Toxikologie," 2nd Ed., Urban and Schwarzenberg, Vienna and Leipzig, 1897, p. 271; W. G. Boorsma, *Bull. Inst. Bot. Buitenzorg*, **6**, 15 (1900).

(2) F. A. Steldt and K. K. Chen, *J. Am. Pharm. Assoc., Sci. Ed.*, **32**, 107 (1943).

(3) S. H. Kooders and T. Valeton (*Meededeel. uit's Lands Plant.*, **17**, 226 (1896)) suggest that the species found in the Malayan and Philippine archipelagoes and described by Miquel are actually varieties of *L. amara*. Steldt and Chen used *L. amara* bark from the Philippines.

(4) J. Troger and W. Beck, *Arch. Pharm.*, **251**, 246 (113); J. Troger and W. Muller, *ibid.*, **252**, 459 (1914).

4-quinolone, was obtained in good yield in this way.

The methiodide of the alkaloid was prepared in nearly quantitative yield by heating the base with methyl iodide at 100°. Under these circumstances, some methoxyquinolines are converted into N-methylquinolones; this is true, for example, for dictamnine. Since the immediate reaction product in this instance was the methiodide, it was treated in aqueous solution with dilute sodium hydroxide, and an *iso*alkaloid separated in excellent yield. These results pointed to a 4-methoxyquinoline structure.

The chief problem in selecting the most likely structure for synthesis involved a few points of non-correspondence with the literature. 4-Methoxy-2-phenylquinoline was described about fifty years ago by Knorr[5] with a melting point (69–70°) very close to that found for the *Lunasia* alkaloid, but treatment with methyl iodide at 90° was reported to give 1-methyl-2-phenyl-4-quinolone directly. This behavior was not duplicated in our experience. In addition, the N-methylquinolone was reported as melting at both 85°[5] and 136°,[6] while the reaction product obtained in this work melted at 143.5–144.5°. The first structural comparison selected for investigation was that for 2-phenyl-4-quinolone (the pyrolysis product); the materials derived from synthesis and from the alkaloid were found to be identical. 4-Methoxy-2-phenylquinoline was then prepared, and identity was established for the synthetic and natural substances.

The synthetic route followed Fuson and Burness[7] in the preparation of 2-phenyl-4-quinolone from ethyl anthranilate and acetophenone diethyl ketal. Treatment of the quinolone with phosphorus oxychloride gave the 4-chloro compound, and this was converted to the 4-methoxy compound by sodium methoxide in methanol at 100°. Relationships between the synthetic and natural series are indicated in the reaction chart. Comparisons were made by mixed m.p., infrared and ultraviolet spectra for 4-methoxy-2-phenylquinoline, 2-phenyl-4-quinolone and 1-methyl-2-phenyl-4-quinolone.

The infrared and ultraviolet absorption spectra for 4-methoxy-2-phenylquinoline showed no novel effects. The ultraviolet maxima were at 254 and 294 mμ, and the second maximum was shifted to 316 mμ in the hydrochloride. This is characteristic of quinolines and isoquinolines.[8]

The presence of 4-methoxy-2-phenylquinoline in a plant of the *Rutaceae* recalls the occurrence of cusparine, galipine and simpler quinolines in angostura (*Cusparia febrifuga* Humb.) bark and suggests that a quinoline or quinolone structure may be involved in other alkaloids of the *Lunasia* group. Isolation and structural studies on other *Lunasia* bases are in progress.

Acknowledgment.—We are indebted to the Section of Plant Introduction, Agricultural Research Service, U. S. Department of Agriculture, for obtaining and identifying the plant material and to Dr. Felipe R. Amos, Director, Bureau of Forestry, Department of Agriculture, Republic of the Philippines, for making available the collections. Extractions were carried out by Mr. D. L. Rogerson and Mr. J. Link. The instrumental work was carried out by Mr. H. F. Byers and Miss Catherine Monaghan. Analyses were performed in the laboratories of Mr. W. Manser, Zurich, Switzerland, and Dr. W. C. Alford, National Institute of Arthritis and Metabolic Diseases.

(5) L. Knorr and E. Fertig, *Ber.*, **30**, 937 (1897).

(6) B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3855 (1952).

(7) R. C. Fuson and D. M. Burness, *ibid.*, **68**, 1270 (1946).

(8) G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946).

Experimental[9]

Natural Series. Isolation of 4-Methoxy-2-phenylquinoline from *Lunasia amara* Leaves.—A 20-kg. quantity of dried, ground leaves was extracted with 30 gal. of 95% ethanol at 50–60° for 1 hr. The treatment was repeated, and the combined extracts were concentrated under reduced pressure to a volume of 8 l. The concentrate was processed in two parts. To 4 l. of concentrate there was added 3 l. of water and 1 l. of 2 *N* sulfuric acid, and the mixture was filtered (Supercel). The combined filtrate and filtrate washings (500 ml. of 2 *N* sulfuric acid and 500 ml. of water) were extracted with trichloroethylene (the wash contained no alkaloids and was discarded). The solution was made alkaline with sodium carbonate, and an organic base fraction was separated by extraction with trichloroethylene (fifteen 200-ml. portions) and by continuous extraction with chloroform. From the combined organic solvent phases from the entire run there was obtained 300 g. (1.5%) of black viscous residue.

An 80-g. portion of this residue was dissolved in 200 ml. of ethanol, and this was added with rapid stirring to 2 l. of 1% hydrochloric acid at 50°. After filtration (Supercel), the combined filtrate and washings (500 ml. of water at 70°) were cooled and washed with ether to yield 6.8 g. of discolored, viscous oil which gave weak positive tests with Mayer and silicotungstic acid reagents. The aqueous solution was made alkaline (potassium carbonate) and the organic bases were extracted with chloroform to yield 42 g. of crude, mixed alkaloids.

This residue was treated with 400 ml. of warm benzene (about 1 g. of insoluble material remained); the benzene solution was filtered and used for chromatography with 1400 g. of alumina (Merck, acid-washed). Sixty fractions were collected. Fractions 1–6 (benzene, 1.5 l. total) gave 0.19 g. of non-basic oil; fractions 7–14 (benzene, 3.5 l. total) gave 2.02 g. of colorless oil which soon solidified.[10] Recrystallization from pentane gave colorless needles, m.p. 66–67°.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.42; H, 5.47; N, 5.90.

Alkaloid Derivatives.—The hydrochloride was prepared from 200 mg. of the base with hydrogen chloride in methanol. Recrystallization from methanol–ether gave an analytical sample whose melting point exhibited an unusual behavior. The crystalline material sintered at 110–120° and melted at 148–151° with gas evolution; the colorless melt solidified on cooling and thereafter melted at 240–243°. The latter m.p. is close to that of 2-phenyl-4-quinolinol (2-phenyl-4-quinolone), indicating that demethylation occurred during the heating period.

Anal. Calcd. for $C_{16}H_{13}ON\cdot HCl\cdot H_2O$: C, 66.31; H, 5.62; N, 4.84; OMe, 10.71. Found: C, 66.28; H, 5.54; N, 4.87; OCH_3, 10.62; NCH_3, none.

The perchlorate was prepared from 160 mg. of base in ethanol with perchloric acid. Recrystallization from ethanol gave an analytical sample; colorless rods, m.p. 215–218°.

Anal. Calcd. for $C_{16}H_{13}ON\cdot HClO_4$: C, 57.23; H, 4.20; N, 4.17. Found: C, 57.30; H, 4.32; N, 4.17.

The methiodide was prepared from 500 mg. of the base by heating in methyl iodide (2 ml.) at 100° for 18 hr. The product (780 mg.) was recrystallized from methanol to yield bright yellow needles, m.p. 148–151°.

Anal. Calcd. for $C_{17}H_{16}ONI$: C, 54.12; H, 4.28; N, 3.71. Found: C, 54.12; H, 4.39; N, 3.73.

(9) All melting points were taken with a Kofler stage.

(10) Continuing elution of the column with the usual solvent mixtures gave a series of fractions from which six additional compounds, in varying states of purity, were obtained. These will be described in connection with structural studies.

2-Phenyl-4-quinolinol (2-Phenyl-4-quinolone).—A small sample (50 mg.) of the base hydrochloride was heated (oil-bath) at 180° for 5 minutes (the material melted and resolidified). The product was dissolved in 1 *N* sodium hydroxide solution (2 ml.), precipitated by acidification with acetic acid, and recrystallized from aqueous ethanol to give 32 mg. of colorless needles, m.p. 256–258° with crystal transformations at 215° and at 247–251° (partial melting and resolidification occurred at the latter temperature).

A mixed m.p. with synthetic material showed the same effects, and the infrared spectra (potassium bromide disks) of the synthetic material and that obtained *via* the plant alkaloid were identical.

1-Methyl-2-phenyl-4-quinolone.—To a solution of 160 mg. of the alkaloid methiodide in 10 ml. of warm water there was added 2 ml. of 1 *N* sodium hydroxide solution. After warming (steam) for 10 minutes, the product was collected, dried (crude yield, 91%) and recrystallized from ethyl acetate–pentane to give 62 mg. of colorless needles, m.p. 142.5–144.5°. Further crystallization from ethyl acetate gave a sample with m.p. 143.5–144.5°.

Synthetic Series. 2-Phenyl-4-quinolinol (2-Phenyl-4-quinolone).—This compound was prepared according to Fuson and Burness[7] from acetophenone diethyl ketal and ethyl anthranilate. The crude product (74%, m.p. 249–251°) was recrystallized from aqueous ethanol to give colorless needles, m.p. 257–258°, with crystal transformations at 243° and 250° (reported[7] m.p. 259–260°).

2-Phenyl-4-chloroquinoline.—2-Phenyl-4-quinolone was converted to the 4-chloro compound by heating with phosphorus oxychloride according to Knorr.[5] The product (crude yield 97%) was recrystallized from ethanol; colorless needles, m.p. 60–61.5° (reported[5] m.p. 63–64°).

4-Methoxy-2-phenylquinoline (I).—To a solution of 2.7 g. of sodium in 65 ml. of anhydrous methanol there was added 5.0 g. of the 4-chloro compound. After 48 hr. at 90–100° the product was isolated by the usual manipulations. A 4.5-g. (92%) yield of colorless needles, m.p. 66–67° (from pentane) was obtained. This material was unchanged in melting point on further recrystallization from pentane (reported[5] m.p. 69–70°). A mixed melting point with the natural alkaloid was not depressed. The ultraviolet and infrared absorption spectra of this material were found to be identical with those of the natural alkaloid.

1-Methyl-2-phenyl-4-quinolone.—One gram of 2-phenyl-4-quinolone was methylated with dimethyl sulfate, using a total of 80 ml. of 20% sodium hydroxide solution and 25 ml. of dimethyl sulfate. The crude product (1.0 g., 92%) was recrystallized several times from ethyl acetate to yield colorless rods, m.p. 143.5–144.5°, which proved to be identical (mixed m.p., ultraviolet and infrared spectra) with the corresponding material obtained as described in the previous section.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.39; H, 5.71; N, 6.03.

This melting point is not in complete agreement with literature values.[5,6] It was found that crystallization from aqueous ethanol formed a labile material, m.p. 70–79°, followed by resolidification and remelting at 142–145°. The infrared spectrum of this material in chloroform was essentially the same as that of the usual product, but in a Nujol mull two new medium intensity bands at 2.91 and 5.97 μ were noted. After drying *in vacuo* only the higher m.p. was observed, and the Nujol mull spectrum was identical with that of the product obtained from ethyl acetate. In one experiment a sample melting at 136° was obtained.

Ultraviolet absorption spectra were taken with a Cary model 11 spectrophotometer. Values for significant compounds are in Table I.

TABLE I

ULTRAVIOLET SPECTRA DATA

λ_{max}, mμ	log max.	λ_{min}, mμ	log min.
4-Methoxy-2-phenylquinoline (95% ethanol)			
254	4.64	230	4.32
294	4.01	276	3.97
4-Methoxy-2-phenylquinoline hydrochloride (95% ethanol)			
231	4.37	239	4.31
254	4.51	283	3.90
316	4.16		
1-Methyl-2-phenyl-4-quinolone (95% ethanol)			
251	4.52	227	4.24
326	4.12	285	3.40
338	4.18	330	4.11
1-Methyl-2-phenyl-4-quinolone (0.9 *N* hydrochloric acid)			
234	4.65	282	3.64
314	4.17		
2-Phenyl-4-quinolone (95% ethanol)			
257	4.55	227	4.13
310 sh	3.90	285	3.64
325 sh	4.06		
334	4.08		
2-Phenyl-4-quinolone (1 *N* hydrogen chloride in ethanol)			
231	4.36	216	4.30
250 sh	4.36	240	4.24
268	4.49	283	3.79
318	4.28		
2-Phenyl-4-quinolone (1 *N* potassium hydroxide in 90% ethanol)			
262	4.27	234	3.94
325	3.59	290	3.30

Infrared absorption spectra were taken with a Perkin–Elmer model 21 instrument. Reference spectra[11] were obtained for 4-methoxy-2-phenylquinoline (chf.), 4-methoxy-2-phenylquinoline hydrochloride (Nujol) and 1-methyl-2-phenyl-4-quinolone (chf.).

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(11) These spectra have been deposited as Document Number 5075 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, by check or money order payable to Chief, Photoduplication Service, Library of Congress