serpiline and elliptinine were not detected, although a colorless alkaloid (90 mg.) not found in *O. elliptica* was eluted after the yellow alkaloids. Suitable solvents for crystallization could not be found and the alkaloid was converted to its hydriodide in acetone. The salt (which was quite soluble in acetone) was recrystallized from water, m.p. 215° dec., $[\alpha]^{23}_{589}$ +27° and $[\alpha]^{23}_{460}$ +58° (*c* 0.45). The ultraviolet spectrum was examined: λ_{max} 238 and 290 mμ and λ_{min} 258 mμ; infrared spectrum: λ_{max} (mull) 3.01 and 6.24 μ.

BETHESDA 14, MD.

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

Alkaloids of *Lunasia amara* Blanco. Structure of Lunacrine

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Lunacrine has been assigned the structure I on the basis of the chemical reactions and interpretations of spectra described in this paper.

Lunacrine was first isolated in 1900 by Boorsma[1] from the bark of *Lunasia costulata* Miq. The alkaloid was characterized by its melting point (114°), solubility, precipitation reactions and color reactions. Wirth[2] carried out the first studies related to the structure of lunacrine in 1931, and reported the empirical formula to be $C_{16}H_{20}O_3N$. The presence of one methoxyl and one methylimino group, and the formation on zinc dust distillation of quinoline, skatole and ammonia were also reported.[2] A few years later, Dieterle and Beyl[3] corrected the obviously impossible formula and gave $C_{16}H_{19}O_3N$ which was later confirmed by Steldt and Chen.[4] The alkaloid described by the German workers,[3] although agreeing in melting point (116°) with that reported by others,[2,4] was said to be optically inactive whereas values had been given for $[\alpha]_D$ of −38°[2] and, later, −58°.[4] Lunacrine was stated to have a methylenedioxy group by virtue of the formation of the calculated amount of precipitate on heating with phloroglucinol–sulfuric acid.[3] Lunacrine methiodide on treatment with silver oxide followed by 40% alkali was reported to give a product, m.p. 85–86°, allegedly isomeric with lunacrine.[3] The alkaloid was found to be stable toward permanganate, chromic oxide and other oxidizing agents and was not affected by catalytic hydrogenation conditions.[3]

In the present study, lunacrine, m.p. 117–119°, $[\alpha]_{589}$ −50.4°, was isolated from the leaves of *Lunasia amara* Blanco of Philippine origin. The empirical formula and the presence of one methoxyl and one methylimino group were confirmed by analysis and, in addition, Kuhn–Roth determination indicated one terminal methyl group (or *gem*-dimethyl). The resistance of lunacrine toward catalytic hydrogenation was confirmed. No evidence was obtained for the presence of a methylenedioxy group; Labat and chromotropic acid color tests were negative. An examination of the infrared spectrum in the 3 μ region revealed no band at 3.60 μ, a diagnostic band for the methylenedioxy group; analysis of the 9.5–10.6 μ region was obscured by the presence of other bands.[5,6] The absence of a methylenedioxy group was shown conclusively by the absence of any signal in the appropriate region of the n. m. r. spectrum.[7,8]

The infrared spectrum[9] of lunacrine was devoid of absorption in the 5 μ region while the 6 μ region was very rich in bands; structural assignments were not possible. The ultraviolet spectrum[9] in alcohol was unaffected by the addition of alkali, but a marked change occurred on acidification (Fig. 1); the long wave length bands (313 and 326 mμ) exhibited a hypsochromic shift (300 mμ). Thus the nitrogen atom is a part of the chromophore and involved in a structure which would give this behavior in acid. This immediately eliminated from consideration the most prevalent nitrogen-containing nucleus in the Rutaceae alkaloids, *viz.*, quinoline whose long wave length ultraviolet absorption maxima exhibit pronounced bathochromic shifts in acid solution. This behavior of lunacrine was in fact reminiscent of 1-methyl-2-phenyl-4-quinolone, a derivative prepared from 4-methoxy-2-phenylquinoline, the first alkaloid isolated in the present study.[10] In the spectrum of this 4-quinolone the typical bifurcated maxima (325 and 337 mμ) were shifted to a single maximum at 304 mμ in acid. This is apparently a characteristic phenomenon of the 4-quinolone system as it has been found that the long wave length maxima (324 and 337 mμ) of 1-methyl-4-quinolone are shifted hypsochromically (plateau 303–313 mμ) in *N* hydrochloric acid.[11] After examination of the literature,[12] it would ap-

(1) W. G. Boorsma, *Bull. Inst. Bot. Buitenzorg*, **6**, 15 (1900).

(2) E. H. Wirth, *Pharm. Weekblad*, **68**, 1011 (1931); *C. A.*, **26**, 557 (1932).

(3) H. Dieterle and H. Beyl, *Arch. Pharm.*, **275**, 174, 276 (1937).

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

(5) L. H. Briggs, L. D. Colebrook, H. M. Fales and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

(6) We are indebted to Dr. H. M. Fales for this information.

(7) S. Goodwin, J. N. Shoolery and L. F. Johnson, THIS JOURNAL, **81**, in press (1959).

(8) The first n.m.r. spectrum of lunacrine was obtained and interpreted by Dr. H. Conroy of Brandeis University, to whom we are indebted.

(9) Details of the infrared and ultraviolet spectra are given in the Experimental section.

(10) S. Goodwin, A. F. Smith and E. C. Horning, *ibid.*, **79**, 2239 (1957).

(11) G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946), found no shift in the spectrum of 4-quinolone in 0.01 *N* hydrochloric acid; however, in *N* hydrochloric acid, the strength generally used in this study, a hypsochromic shift to give a broad maximum at 300–307 mμ was observed.

(12) *Cf.* E. A. Steck, G. W. Ewing and F. C. Nachod, *ibid.*, **71**, 238 (1949), for the spectra of 6-, 7- and 8-methoxy-3-methyl-4-quinolones.

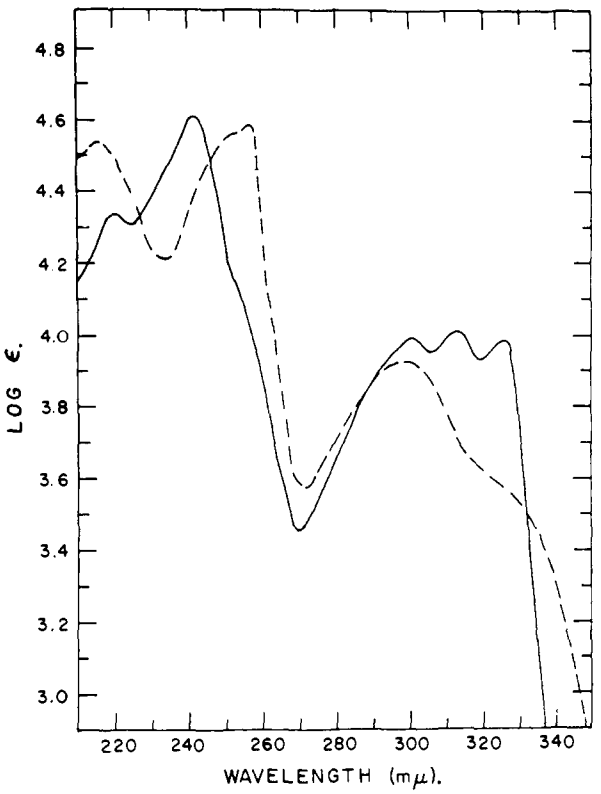


Fig. 1.—Ultraviolet spectra of lunacrine: —, in ethanol; ---, in 0.1 *N* hydrochloric acid in ethanol solution.

pear that although the trifurcation and shorter wave lengths of lunacrine cannot be explained completely on the basis of a bz-methoxy-1-methyl-4-quinolone structure, for example, compare 8-methoxy-1-methyl-4-quinolone,[13] λ_{max} 331 and 340 mμ (log ε 4.07 and 4.05, resp.) and indefinite inflection at 308 mμ (log ε 3.88), the shift in acid can best be explained by this system. The infrared spectrum of lunacrine in the 6 μ region is completely compatible with a 4-quinolone structure.

Lunacrine on refluxing with 15% aqueous alcoholic potassium hydroxide solution was converted in good yield to an alkali-soluble substance differing empirically from lunacrine by the addition of the elements of water. The product, $C_{19}H_{21}O_4N$, m.p. 160°, $[\alpha]_{589}$ −77.6°, had no bands in the 5 μ region of the infrared and still contained one methoxyl and one methylimino group. Treatment with ethereal diazomethane gave a non-crystallizable oil which was converted in moderate yield to a crystalline hydroperchlorate, $C_{17}H_{23}O_4N.HClO_4$, m.p. 148°, $[\alpha]_{589}$ +22.3°. The crystalline base, $C_{17}H_{23}O_4N$, m.p. 87°, $[\alpha]_{589}$ +28.1°, obtained almost quantitatively from the hydroperchlorate, was found to contain one methoxyl group more than lunacrine and its alkaline transformation product, and it also contained one active hydrogen atom. The sign of specific rotation changed in the methylation of the alkaline transformation product, a reaction in which inversion certainly did not occur.

The empirical formula and physical constants of the new base were nearly the same as those given for lunacridine, an alkaloid of unknown structure isolated previously from the bark of *Lunasia* species[1,4]; this alkaloid has not been found to date in the present study of the leaf alkaloids. A direct comparison by m.p., rotation and spectra of the diazomethane product and lunacridine[14] showed that they were identical in all respects.

The ultraviolet spectrum of lunacridine (Fig. 2) was not changed by the addition of acid or alkali. Absorption maxima at 284 and 294 mμ, which

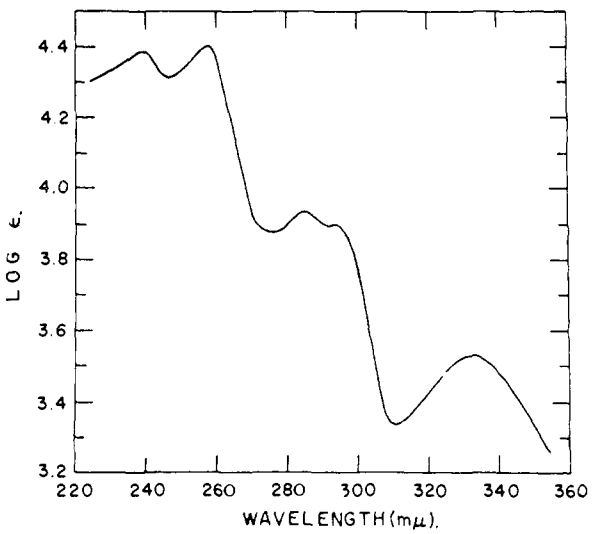


Fig. 2.—Ultraviolet spectrum of lunacridine in ethanol solution.

were not present in lunacrine, were observed. These features together with lower intensity absorption at 330 mμ suggested that a carbostyril system was present.[15,16] The fact that the maxima at 284 and 294 mμ are at considerably longer wave lengths than the corresponding maxima in the the spectrum of 4-methoxy-1-methylcarbostyril (268 and 278 mμ) can be attributed to further substitution. It is known that a 3-ethyl substituent causes a bathochromic shift of about 15 mμ in the 270 and 280 mμ maxima of 4-hydroxycarbostyril.

Since the transformation of lunacrine having a 4-quinolone system to lunacridine for which a 4-methoxy-3-alkylcarbostyril system has been postulated occurred without loss of carbon atoms, it is evident that lunacrine has either a furo- or a pyrano- system fused to the quinolone ring system. By analogy with the methoxyfuroquinoline alkaloids which abound in plants of this family, the oxygen-containing ring of lunacrine was assumed to be five-membered and a dihydrofuran rather than furan in accordance with the analytical data, the proved absence of an easily reducible double bond (furoquinoline alkaloids are converted to dihydro derivatives on hydrogenation over Pd–C in alcohol), and the ultraviolet spectrum.[17]

(13) R. D. Brown and F. N. Lahey, *Aust. Jour. Sci. Res.*, **A3**, 615 (1950).

(14) We are indebted to Dr. J. R. Price for this sample.

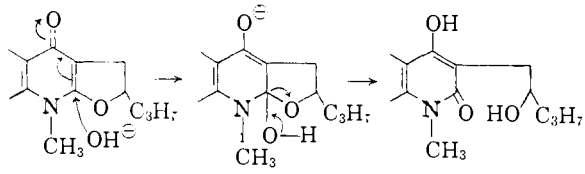
(15) M. F. Grundon, N. J. McCorkindale and M. N. Rodger, *J. Chem. Soc.*, 4284 (1955); M. F. Grundon and N. J. McCorkindale, *ibid.*, 2177 (1957).

(16) J. Berson, THIS JOURNAL, **75**, 3521 (1953).

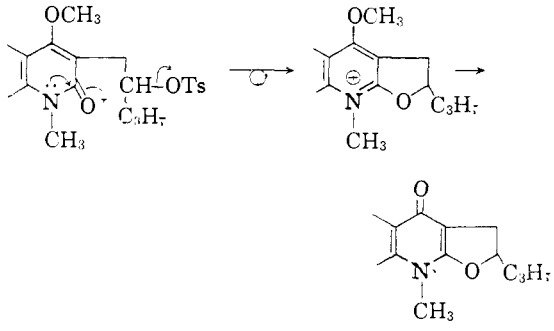
(17) Compare iso-γ-fagarine, λ_{max} 246, 304, 336 and 351 mμ, as given by V. Deulofeu and D. Basi, *Anales asoc. quim. Argentina*, **40**, 249 (1952).

In an investigation of the properties of (+)-lunacridine (derived from (−)-lunacrine), it was found that treatment of (+)-lunacridine with α-toluenesulfonyl chloride in pyridine gave, in low yield, a crystalline substance, m.p. 118–120°, which was identical with lunacrine in infrared and ultraviolet spectra, and in paper chromatographic behavior. However, on admixture with natural (−)-lunacrine the m.p. was elevated. A comparison of the more easily handled hydroperchlorates indicated that the reaction product was (+)-lunacrine; specific rotations of −35.9° and +35.1° were found for the hydroperchlorates of natural (−)-lunacrine and of the reaction product, respectively. The rise in m.p. after mixture of the two bases was evidently due to racemate formation.

These results indicated that (−)-lunacrine was converted to (+)-lunacridine by a sequence involving an alkali-induced ring opening reaction, and that (+)-lunacridine was in turn convertible to (+)-lunacrine in a cyclization reaction. The resultant formation of the enantiomorph of lunacrine required, in view of the reactions involved, that lunacrine have only a single asymmetric center which must be the α-carbon atom of the dihydrofuran ring; thus the three unassigned carbon atoms of lunacrine must be placed at this position. The suggested mechanism for the alkaline hydrolysis of lunacrine may be represented by

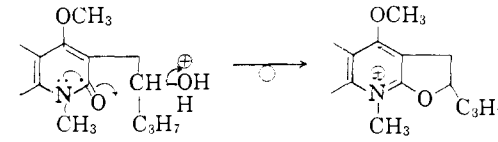


and the cyclization may be represented as



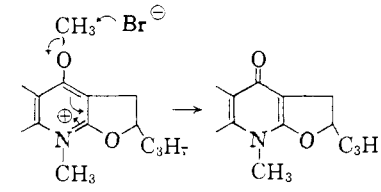
The hydrolysis is viewed as proceeding without inversion and the cyclization with inversion. The participation of an amide group in the displacement of tosylate and the stereochemical course of the reaction have been demonstrated by Winstein and Boschan.[18] The conversion of the postulated quinolinium ion intermediate to (+)-lunacrine could conceivably occur either by SN2 displacement by chloride ion on the methyl carbon of the 4-methoxyl group or hydrolytically during the work-up of the reaction mixture. That the first possibility was probably correct was shown in the following manner.

It had been observed that lunacridine hydroperchlorate (m.p. 148°) melted at a much higher temperature (about 194°) on reheating. When the fusion was carried out on a larger scale, a nicely crystalline product, $C_{17}H_{22}O_3N^{(+)}ClO_4^{(-)}$, m.p. 196°, $[\alpha]_{589}$ +33.9°, containing two methoxyl groups, was obtained. The ultraviolet spectrum of this substance was almost identical with that of lunacrine in acid solution. The structure of the product was evidently that of the (+)-quinolinium perchlorate resulting from the acid-catalyzed cyclization with inversion of configuration of (+)-lunacridine hydroperchlorate as represented by



Again it is interesting to note that the direction of rotation does not change during the postulated inversion. The quinolinium perchlorate was recovered unchanged after treatment with 30% perchloric acid at 100° for 3 hours, indicating that acidic hydrolytic conditions[19] were not responsible for the formation of lunacrine in the α-toluenesulfonyl chloride–pyridine reaction.

When the (+)-quinolinium perchlorate was heated in acetonitrile in the presence of a large excess of lithium bromide, the product formed was (+)-lunacrine. The mechanism of this reaction may be shown as



The stability of the quinolinium ion to perchlorate ion but not to halide ion may be explained by the poor nucleophilic character of the perchlorate ion.[20] The lability of the quinolinium ion to attack by halide ion was further demonstrated by the fact that lunacrine methiodide reverted to lunacrine on being boiled vigorously in aqueous solution, as well as on sublimation *in vacuo* at its m.p. and on refluxing in acetonitrile with lithium bromide.

The quinolinium perchlorate may be assigned the name (+)-lunasine perchlorate in accord with the demonstration by J. R. Price[19] that the alkaloid lunasine is the methyllunacrinium ion. The infrared and ultraviolet spectra of (−)-lunacrine methiodide ((−)-lunasine iodide) and the (+)-quinolinium perchlorate were essentially identical.

The remaining problems of structure for lunacrine concerned the position of the methoxyl group and the nature of the side chain. An assignment of the position of the methoxyl group in the alkaloid and its transformation products by the comparison

(18) S. Winstein and R. Boschan, THIS JOURNAL, 72, 4669 (1950).

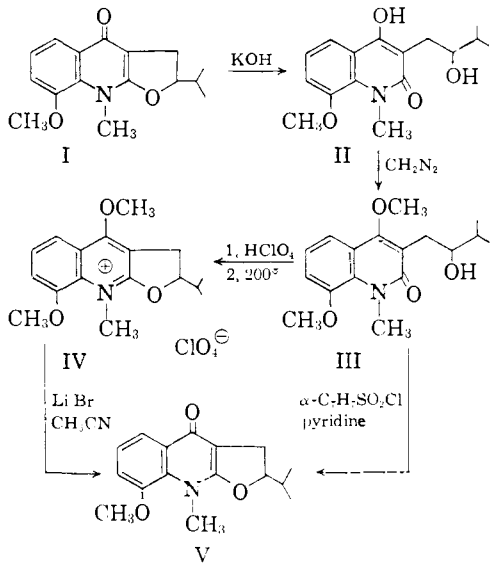
(19) Alkaline hydrolysis of quinolinium ions of this type takes a different course affording carbostyril derivatives according to J. R. Price (private communication; see also "Current Trends in Heterocyclic Chemistry," Academic Press, Inc., New York, N. Y., 1958, p. 92).

(20) This reaction is analogous to the easy formation of 2-phenyl-4-quinolone from 4-methoxyl-2-phenylquinoline hydrochloride on heating at its melting point; the corresponding hydroperchlorate melted without demethylation.

of their ultraviolet spectra with less substituted model compounds could not be made with certainty. The 7-position was definitely eliminated by comparison of the ultraviolet spectra of the 4-hydroxycarbostyril derived from lunacrine and 3-ethyl - 4 - hydroxy - 7 - methoxy - 1 - methylcarbostyril,[21] a derivative of evolitrine[22]; major differences in both alcohol and alkaline solution were found. Analysis of the nuclear magnetic resonance spectrum of lunacrine revealed conclusively that the methoxyl group was in the 8-position.[7]

The n.m.r. spectrum also indicated that the side chain hydrogen atoms were present in an isopropyl group. This is in accord with biogenetic considerations since it affords an isoprene unit attached to the 3-position of a 4-hydroxycarbostyril derivative, a situation known to occur in the alkaloid flindersine.[23]

All features of the structure I assigned to lunacrine are in complete agreement with the n.m.r. spectrum.[7] The structure III has been derived for lunacridine and the significant transformations are summarized below.



Acknowledgment.—We are very grateful to Dr. J. R. Price, C.S.I.R.O., Melbourne, for a stimulating exchange of information and for compounds pertaining to the *Lunasia* alkaloids. The relationship between lunasine and lunacridine has been established in Melbourne. We are also indebted to Miss A. F. Smith for assistance in the isolation of the lunacrine used in this study.

Experimental

Melting points were taken on a Kofler block. Rotations and ultraviolet spectra were determined in absolute ethanol, and infrared spectra were taken in chloroform, unless otherwise specified. Only a selected number of infrared absorption bands, principally in the 6 μ region, are given as characterization features of the substances (s = strong, m = medium and w = weak). Instrumental measurements were made by Mr. H. F. Byers, Misses P. A. Wagner and C. Monaghan, and Mrs. K. Warren. Analyses were made by Mr. W. Manser, Zürich, and Mr. J. F. Alicino, Metuchen, N. J. The paper chromatographic systems[18] used were the following: A, isoamyl alcohol saturated with water and paper impregnated with *p*H 2.4 MacIlvaine buffer (citrate–phosphate); and B, benzene–hexane (1:1) and paper impregnated with a 1:1 mixture of ethylene glycol and *p*H 2.2 MacIlvaine buffer.

(−)-**Lunacrine.**—The alkaloids of *Lunasia amara* leaves were separated by chromatography on acid-washed alumina (Merck); lunacrine was eluted with chloroform and crystallized from ethyl acetate–hexane. Wet ether was also found to be a good crystallization medium; the hydrate crystallized in good recovery as fine colorless needles of indefinite melting point. The analytical sample was crystallized from ethyl acetate, m.p. 117–119°, $[\alpha]^{25}_{589}$ −50.4°, $[\alpha]^{25}_{436}$ −113° (*c* 0.806) (reported[4] m.p. 115°, $[\alpha]^{28}_{D}$ −58° (95% alcohol)); infrared spectra: λ_{max} 6.18(s), 6.29(s), 6.45(s), 6.64(s), 6.84(m), 6.96(w), 9.37(s), 9.88(v.w), 10.61(s) (compare, 1-methyl-4-quinolone: λ_{max} 6.15(s), 6.30(s), 6.44(m), 6.70(s); 3-μ region (Beckman IR-3) $\lambda^{CCl_4}_{max}$: 3.24(v.w.), sh3.31(m), 3.36(s), 3.46(m), 3.51(m); ultraviolet spectra: λ_{max} 220, 242, 300, 313 and 326 mμ (log ϵ 4.34, 4.61, 4.00, 4.01 and 3.99, resp.); λ_{min} 225, 269, 306 and 319 mμ (log ϵ 4.32, 3.45, 3.95 and 3.93, resp.); in 0.1 *N* HCl, λ_{max} 216, 253sh, 257, 300 and 320sh (log ϵ 4.54, 4.57, 4.59, 3.89 and 3.58, resp.); λ_{min} 234 and 271 mμ (log ϵ 4.21 and 3.62, resp.).

Anal. Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13; OCH_3, 11.35; $(N)CH_3$, 5.50; $(C)CH_3$ 5.50. Found: C, 69.91; H, 7.12; N, 5.08; OCH_3, 10.23; $(N)CH_3$, 6.13; $(C)CH_3$, 3.44.

Hydroperchlorate.—Lunacrine hydroperchlorate was prepared in ethanol–ether. The analytical sample was crystallized from the same solvent pair; m.p. 178–180°, $[\alpha]^{24}_{589}$ −35.9°, $[\alpha]^{24}_{436}$ −78.5° (*c* 0.720); λ^{KBr}_{max} 6.08(m), 6.21(m), 6.51(s) and 6.70(s) μ.

Anal. Calcd. for $C_{16}H_{19}O_3N\cdot HClO_4$: C, 51.41; H, 5.39; N, 3.75. Found: C, 51.62; H, 5.50; N, 3.72.

Picrate.—The picrate crystallized from acetone as bright yellow crystals, m.p. 213–214° (reported[3] 208°).

Anal. Calcd. for $C_{22}H_{22}O_{10}N_4$: C, 52.59; H, 4.41; N, 11.15. Found: C, 52.51; H, 4.42; N, 11.16.

Color Tests.—Lunacrine which had been rigorously purified formed a colorless solution in concd. sulfuric acid which on the addition of gallic acid (Labat test), accompanied by heating on the steam-bath, became rose in color. In the chromotropic acid test no color developed.

Hydrogenation Conditions.—A solution of 0.3 g. of lunacrine in 10 ml. of ethanol was added to a mixture of prereduced platinum from 80 mg. of platinum oxide in 10 ml. of ethanol. There was no hydrogen absorption after stirring for 3 hours. The catalyst was tested by the addition of 1 ml. of cyclohexene and found to be quite active. Lunacrine was recovered unchanged.

Alkaline Hydrolysis of Lunacrine.—A solution of 3.36 g. of lunacrine, 40 ml. of ethanol and 40 ml. of 30% potassium hydroxide solution was refluxed for 10 hours. The pale yellow reaction mixture was diluted with water and washed with methylene chloride which removed a trace (0.06 g.) of material. The aqueous solution was adjusted to *p*H 5 with sulfuric acid and extracted with methylene chloride. Evaporation of the solvent afforded a crystalline residue (3.35 g.) which on crystallization from a small volume of ethyl acetate gave 3.15 g. of colorless rods melting at 159–160°. The product was soluble in aqueous sodium hydroxide solution and gave a negative ferric chloride test. The analytical sample, m.p. unchanged, was crystallized from ethyl acetate and dried at 80° (0.1 mm.), $[\alpha]^{25}_{589}$ −77.6°, $[\alpha]^{25}_{436}$ −187° (*c* 0.99°); $[\alpha]^{24}_{589}$ −78.2°, $[\alpha]^{24}_{436}$ −196° (*c* 0.825, chloroform); infrared specta: λ_{max} 6.10(s), 6.18(s), 6.30(s) μ; ultraviolet spectra: λ_{max} 237, sh 245, sh 253, 284, 294 and 325 mμ (log ϵ 4.48, 4.43, 4.39, 3.93, 3.95 and 3.52, resp.); λ_{min} 278, 288 and 310 (log ϵ 3.81, 3.91 and 3.48, resp.); λ_{max} (0.1 *N* KOH) 307 (log ϵ 4.03) (compare, 3-ethyl-4-hydroxy-7-methoxy-1-methylcarbostyril: λ_{max} is 226, sh 242, 252, sh 277, 286, 317 and 328 mμ (log 4.73 4.11, 4.06, 3.76, 3.83, 4.15 and 4.14, resp.)); λ_{min} 248, 262, 295 and 324 mμ (log ϵ 3.80, 3.61, 3.73 and 4.06, resp.); in 0.1 *N* potassium hydroxide: λ_{max} 316 mμ (log ϵ 4.28).

Anal. Calcd. for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81; OCH_3, 10.65; $(N)CH_3$, 5.16; $(C)CH_3$, 5.16. Found:

(21) We are grateful to Dr. R. G. Cooke, Melbourne, for this sample.

(22) R. G. Cooke, *Austral. J. Chem.*, **7**, 273 (1954).

(23) R. F. C. Brown, J. J. Hobbs, G. K. Hughes and E. Ritchie, *ibid.*, **7**, 348 (1954).

C, 66.08; H, 7.32; N, 4.82; OCH_3, 10.48; $(N)CH_3$, 5.22; $(C)CH_3$, 3.42.

(+)-Lunacridine. (A) From the Alkaline Hydrolysis Product.—A solution of 2.11 g. of the hydrolysis product in 10 ml. of methanol was treated with a large excess of diazomethane in ether (prepared from 18 g. of N-methyl-N-nitrosotoluene-*p*-sulfonamide). There was an immediate decolorization of the diazomethane solution accompanied by gas evolution. The yellow solution was allowed to stand in an ice-bath for several hours and then overnight at room temperature. Evaporation of the solvents afforded a pale yellow oil which could not be crystallized from a variety of solvents and it was therefore converted to a salt by treatment of an ethereal solution of the oil with a solution of 2 ml. of perchloric acid and 2 ml. of methanol. The hydroperchlorate crystallized as shiny, colorless flakes, 1.49 g. (51%). The analytical sample was crystallized from methanol–ether and dried at 80° (0.1 mm.) for 6 hours, m.p. 146–148° (clear, colorless melt), re-melt 193–195°, $[\alpha]^{25}_{589}$ +22.3°, $[\alpha]^{25}_{436}$ +60.7° (*c* 0.750); λ_{max} (Nujol); 6.25 and 6.51 μ.

Anal. Calcd. for $C_{17}H_{23}O_4N\cdot HClO_4$: C, 50.31; H, 5.96; N, 3.45; OCH_3, 15.29; $(N)CH_3$, 3.71. Found: C, 50.39; H, 5.98; N, 3.54; OCH_3, 15.22; $(N)CH_3$, 3.92.

The free base was prepared by treatment of a solution of 1.13 g. of the hydroperchlorate in 5 ml. of methanol with 1 ml. of concd. ammonia; water was added until cloudy (2.5 ml. required). (+)-Lunacridine (0.80 g., 94%) crystallized on scratching. The product was recrystallized from methanol–water for analysis, m.p. 86–87°, $[\alpha]^{25}_{589}$ +28.1, $[\alpha]^{25}_{436}$ +76.5° (*c* 0.935). The sample was dried at 56° (0.1 mm.). Lunacridine is not visibly soluble in 0.1 *N* or 2 *N* hydrochloric acid at room temperature or with warming and the aqueous portions of these mixtures remained clear on the addition of Mayer reagent; infrared spectra: λ_{max} 3.0 (broad), 6.11(s), 6.19(m), 6.30(s) μ; ultraviolet spectra: λ_{max} 239, 257, 285, 294 and 333 mμ (log ϵ 4.38, 4.41, 3.94, 3.91 and 3.55, resp.); λ_{min} 224, 246, 275, 291 and 310 mμ (log ϵ 4.31, 4.31, 3.89, 3.90 and 3.36, resp.). The spectrum in *N* hydrochloric acid in alcohol is identical with the spectrum in alcohol. Lunacridine does not form a picrate.

Anal. Calcd. for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.59; N, 4.59; OCH_3, 20.33; $(N)CH_3$, 4.92. Found: C, 66.86; H, 7.52; N, 4.54; OCH_3, 20.04; $(N)CH_3$, 5.00.

This material was identical with (+)-lunacridine isolated from *Lunasia* bark by the C.S.I.R.O. group. The Australian sample, m.p. 85°, $[\alpha]^{25}_{589}$ +30.1°, $[\alpha]^{25}_{436}$ +80.4° (*c* 0.900), showed no depression of m.p. on admixture and the infrared spectra were identical.

B. From Lunacrine Methiodide.—A solution of 0.35 g. of lunacrine in 10 ml. of methyl iodide was allowed to stand for three days; after 24 hours a colorless crystalline precipitate began to form. Ethyl acetate (20 ml.) was added to remove unchanged lunacrine and the product was collected by filtration, 0.38 g. (72%), m.p. 130° dec., $[\alpha]^{24}_{589}$ −26.3°, $[\alpha]^{24}_{436}$ −60.3° (*c* 0.873); λ_{max} 254, 302 and *ca.* 330(sh) mμ (log ϵ 4.51, 3.81 and 3.45, resp.); 6.12(m), 6.23(m), 6.54(s) and 6.71(s) μ. The methiodide reverted readily to lunacrine on (a) sublimation at 130–140° (*ca.* 0.001 mm.), (b) boiling in water and (c) refluxing in acetonitrile with lithium bromide. These reactions were studied by means of the ultraviolet spectra of the reaction mixtures and paper chromatography using system B which readily distinguishes between lunacrine, R_f about 0.5; lunacridine, at the solvent front; and lunacrine methiodide, at the origin.

Conversion of the methiodide to lunacridine was effected according to Price[19] by warming a solution of 30 mg. of the methiodide in 3 ml. of methanol with 1 ml. of 1 *N* sodium hydroxide solution. Crystallization of the product yielded 17 mg. (78%) of (+)-lunacridine, m.p. 85–87°, $[\alpha]^{24}_{589}$ +30.1°, $[\alpha]^{24}_{436}$ +81.8° (*c* 1.007). The infrared spectrum in chloroform was identical with that of lunacridine prepared by the diazomethane method.

(+)-Lunacrine. (A) Tosylate Method.—A solution of 0.455 g. of (+)-lunacridine in 5.5 ml. of pyridine was treated with 1.08 g. of *α*-toluenesulfonyl chloride. The reaction mixture became red and warm. After standing for several days, most of the pyridine was evaporated *in vacuo*. The residue was treated with 80 ml. of 0.5 *N* sodium hydroxide solution and the mixture was extracted with ether. The combined ethereal extracts were extracted with 2 *N* sulfuric acid. The acid extract was made alkaline with potassium hydroxide and extracted with ether. A discolored crystalline solid was obtained on treating the ether residue with about 5 ml. of ethyl acetate and 2 ml. of pentane. Four recrystallizations from the same solvent pair afforded 60 mg. of shiny, prismatic crystals, m.p. 119–120°, $[\alpha]^{25}_{589}$ +66°, $[\alpha]^{25}_{436}$ +100° (*c* 0.58). The infrared spectrum in chloroform, the ultraviolet spectrum in alcohol and the R_f in system B were identical with (−)-lunacrine. The analytical sample was dried for 20 hours at 80° (0.1 mm.).

Anal. Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13; OCH_3, 11.35; $(N)CH_3$, 5.50. Found: C, 69.85, 69.92; H, 6.69, 6.88; N, 5.08; OCH_3, 10.21, 10.26; $(N)CH_3$, 6.6. The marginal analytical results are ascribed to the difficulty in purifying a small sample of lunacrine, due to its great solubility and to its propensity to hydrate; the hydroperchlorate may be handled with greater ease.

Hydroperchlorate.—The hydroperchlorate was prepared in methanol–ether. The analytical sample, crystallized from the same solvent pair, m.p. 176°, was dried at 80° (0.1 mm.) for analysis; $[\alpha]^{25}_{589}$ +35.1°, $[\alpha]^{25}_{436}$ +78.0° (*c* 0.295).

Anal. Calcd. for $C_{16}H_{19}O_3N\cdot HClO_4$: C, 51.41; H, 5.39. Found: C, 51.32; H, 5.45.

(*dl*)-Lunacrine.—A mixture of 20 mg. of natural (−)-lunacrine and 20 mg. of (+)-lunacrine on crystallization from ethyl acetate–pentane afforded prismatic crystals, m.p. 146–148°, $[\alpha]^{25}_{589}$ +2.3°, $[\alpha]^{25}_{436}$ +4.2° (*c* 0.864). The crystallization residue was converted to the hydroperchlorate, $[\alpha]^{25}_{589}$ +1.7°, $[\alpha]^{25}_{436}$ 0° (*c* 0.208).

(B) *Via* **(+)-Lunasine Perchlorate.**—(+)-Lunacridine hydroperchlorate (0.314 g.) was heated in an oil-bath for two minutes at a bath temperature of 200°. Crystallization of the residue from methanol afforded 0.202 g. of tan crystals, m.p. 180–190°. The analytical sample was recrystallized from methanol and dried at 80° (0.2 mm.) for 20 hours, m.p. 195–196°, $[\alpha]^{24}_{589}$ +33.9°, $[\alpha]^{42}_{436}$ +70.7° (*c* 0.193); infrared spectra: λ_{max} 6.14(m), 6.24(m), 6.54(s), 6.72(s) μ; ultraviolet spectra: λ_{max} 254, 303 and shoulder *ca.* 330 mμ (log ϵ 4.56, 3.80 and 3.46, resp.); λ_{min} 232 and 273 mμ (log ϵ 3.93 and 3.43, resp.).

Anal. Calcd. for $C_{17}H_{22}O_4N^{(+)}ClO_4^{(-)}$: C, 52.65; H, 5.72; N, 3.61; OCH_3, 16.01. Found: C, 52.57; H, 5.89; N, 3.75; OCH_3, 16.30.

On paper chromatography in system A, (+)-lunasine perchlorate, R_f 0.61, appeared with bright blue fluorescence and gave an orange Dragendorff color; lunacrine and lunacridine travel with the solvent front in this system.

(+)-Lunasine perchlorate (10 mg.) was recovered unchanged on heating at 100° for 3 hours in 2 ml. of 35% perchloric acid.

A solution containing 77 mg. of (+)-lunasine perchlorate and 0.8 g. of lithium bromide in 8 ml. of acetonitrile was refluxed for 12 hours. After removing most of the solvent *in vacuo*, water was added and the product was extracted with methylene chloride. The residue was converted to the hydroperchlorate in methanol–ether and recrystallization from the same solvents afforded colorless crystals, m.p. 178–180°, $[\alpha]^{23}_{589}$ +35.4°, $[\alpha]^{24}_{436}$ +79.7° (*c* 0.280), having identical infrared spectra and paper chromatographic behavior with (−)-lunacrine hydroperchlorate.

Anal. Calcd. for $C_{16}H_{19}O_3N\cdot HClO_4$: N, 3.75. Found: 3.88.

Instrumental Measurements.—Infrared spectra were obtained with a Perkin–Elmer spectrophotometer model 21, ultraviolet spectra with a Cary recording spectrophotometer model 11, and rotations were measured in 2-dm. cells using a Rudolph photoelectric polarimeter model 80.

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