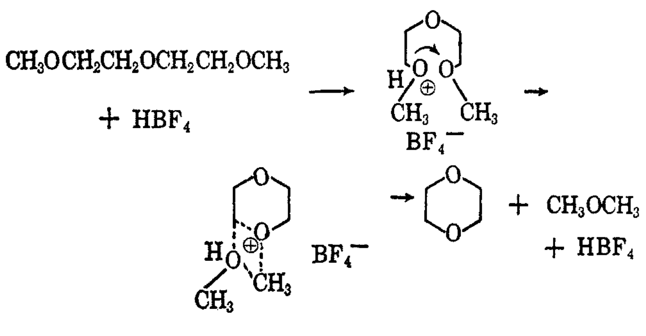
Table I

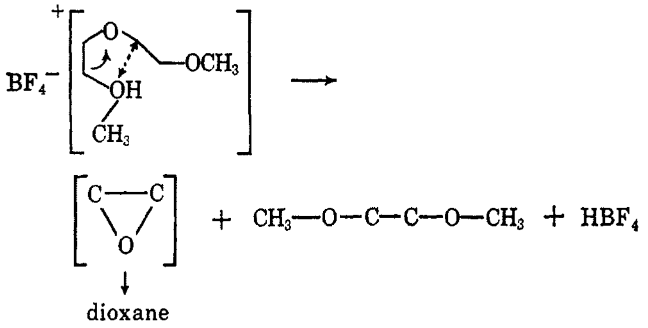
Formation of Dimethyl Ether from Bis(2-methoxyethyl) Ether

Diglyme, mole	BF_3, mole	HF, mole	Dimethyl ether formed, mole
0.40	0.08	None	0.005 in 5 days at 23°
0.40	0.20	None	0.037 in 3 days
0.40	0.20	0.20	0.25 in 21 hr
0.40	None	0.20	None in 5 days

Scheme I accommodates the above facts. Protonation of an ether oxygen occurs accompanied by partial charge separation in an adjacent C–O bond. Intramolecular attack of the resulting partially developed carbonium center on a nonprotonated ether oxygen forms an oxonium intermediate. This in turn breaks down into the observed products. If the incipient carbonium center resulting from protonation attacks the central oxygen (fifth atom in diglyme), Scheme I leads to 1,2-dimethoxyethane and ethylene oxide. In the presence of BF_3 ethylene oxide is known to form dioxane and a dark resinous product.[1] Should the central oxygen be protonated initially Scheme I leads to reformation of diglyme in which the positions of the specific carbon atoms are changed.

Scheme I





C–O–C–C–O–C–C–O–C ⟶ C–O–C–C–O–C–C–O–C
1 2 3 4 5 6 7 8 9   1 2 3 4 8 7 6 5 9

Experimental Section

Reaction of Bis(2-methoxyethyl) Ether with HF and BF_3.—Bis(2-methoxyethyl) ether (54 g, 0.40 mole) was placed in a weighed 200-ml round-bottom flask and cooled under nitrogen in an ice bath. Gaseous BF_3 was introduced (excluding atmospheric contact and moisture condensation as much as possible) until 13.6 g (0.20 mole) had been added. Then gaseous HF was cautiously introduced employing a plastic syringe barrel and flexible Teflon 17-gauge "needle" until 4.0 g (0.20 mole) had been added. Considerable heat is evolved during the step. The dark-colored reaction mixture flask was then connected directly to a volume-calibrated Dry Ice trap without delay. After 21 hr at room temperature (about 23°) the reaction mixture had lost 15 g in weight and about 17 ml of clear colorless liquid had been caught in the cold trap along with some colorless crystalline solids. The condensate was slowly bubbled through 25 ml of water and recondensed. The weight increase in the water (2.7 g) was assumed to be due principally to HF. One gram of liquid did not redistil at room temperature. The recondensed liquid (11.3 g) was shown to be dimethyl ether by comparison with known material on the three different gas chromatography columns and by proton nmr spectrum (single strong peak at τ 7.23).

The bulk of the reaction mixture was cautiously subjected to decreasing pressure until 1 mm at room temperature was achieved with no further bubbling. Volatiles removed during this process were caught in a Dry Ice cold trap. The liquid (at 23°) (14 g) trapped was placed in a soft glass vial and allowed to stand overnight. The dissolved HF reacted with the glass to form a white coating of solids. The remaining clear colorless liquid (11 g) was analyzed by gas chromatography on a 5-ft column of diatomaceous earth containing 10 wt % polypropylene glycol (mol wt 1000) at 90°. In this manner 0.10 mole of dioxane and 0.006 mole of 1,2-dimethyloxyethane were shown to be present. A trace of what was probably methanol could be seen when the polypropylene glycol column was employed but not when two other substrates were used.

A blackish slurry of the reaction mixture then remained. It was not further examined except to show that it contained a substantial amount of dark flocculent (in water) solids. Reaction mixtures in other experiments not stripped of product dioxane readily pick up water from the atmosphere if allowed. Well-formed colorless crystals of a dioxane–boron trifluoride–water complex then developed from the flask walls.

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[1] F. G. A. Stone and H. J. Emeleus, *J. Chem. Soc.*, 2758 (1950).

Alkaloids of *Cassia* Species. II. The Side Chain of Cassine[1]

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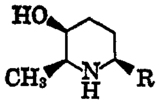
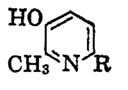
Characterization of the piperidine alkaloid cassine has led to the structure Ia.[1] Because condensation of the alkaloid with piperonal and benzaldehyde formed monopiperonylidine and monobenzylidine derivatives, respectively, it was inferred that the side chain was branched α to the ketone, and that structure Ib corresponded best to the degradative and spectral evidence available. The possibility of characterizing minute quantities of degradation products by mass spectrometry has now permitted further studies, which show



Ia, $R = C_{10}H_{20}COCH_3$
b, $R = (CH_2)_8CHCH_3COCH_3$
c, $R = (CH_2)_{10}COCH_3$
d, $R = (CH_2)_9CD_2COCD_3$



IIa, $R = (CH_2)_{10}COCH_3$
b, $R = (CH_2)_{11}CH_3$

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[1] Paper I: R. J. Highet, *J. Org. Chem.*, **29**, 471 (1964). Structure I corresponds to the mass spectral data noted in proof.

[2] After this work had been completed, we learned of synthetic studies which have subsequently confirmed these structures and established the absolute stereochemistry of cassine by the conversion of carpaine to the mirror image of N-methyl cassine. *Cf.* W. Y. Rice and J. L. Coke, *ibid.*, **31**, 1010 (1966). We are indebted to these authors for informing us of their results prior to publication.

that the aldehyde condensations are misleading, and that the alkaloid actually corresponds to Ic.[2]

Reduction of dehydrocassine (IIa) under Wolff–Kishner conditions produces a compound of the constitution $C_{18}H_{31}NO$. Spectral properties of this material show that the 3-hydroxy-2, 6-dialkylpyridine system is retained, as anticipated. The unbranched character of the 6-alkyl group was shown by oxidation by nitric acid to a small quantity of acidic material, which was converted to a mixture of methyl esters by treatment with diazomethane. Gas chromatography showed that the main component corresponds in retention time to methyl laurate. Isolation of this main component by gas chromatography provided material with a mass spectrum identical with that of known methyl laurate. As both gas chromatographic retention times[3] and mass spectral fragmentation patterns[4] of branched-chain esters are known to differ from the straight-chain isomers, these results require that the Wolff–Kishner product be 2-methyl-3-hydroxy-6-dodecylpyridine (IIb), and that cassine be regarded as Ic.

Characterization of cassine included base-catalyzed exchange in deuteriomethanol to a material characterized by combustion analysis as a tetradeuterio derivative.[1] However, the mass spectrum of this material reveals the presence of variously deuterated derivatives, with the heaviest ion corresponding to a pentadeuterated material (Id). These studies are therefore consistent with the correct structure for cassine (Ic).

Experimental Section[5]

2-Methyl-3-hydroxy-6-dodecylpyridine (IIb).—Dehydrocassine[1] (IIa, 61 mg) was heated on a steam bath in 3 ml of ethylene glycol with 172 mg of potassium hydroxide and 0.7 ml of hydrazine hydrate for 0.5 hr. The flask was equipped with a downward condenser and plunged into a wax bath heated to 210°. Distillation was continued until the distillate temperature reached 180°. After 3-hr reflux the solution was cooled, acidified with hydrochloric acid, then made weakly basic with ammonium hydroxide, and extracted twice with chloroform. The organic phase was concentrated to dryness to leave 68 mg of colorless low-melting solid. Crystallization from acetone provided 38 mg, mp 90–96°, shown by gas chromatography to retain 3% of starting material. Recrystallization provided material of mp 101–103.5°; nmr,[5] $\delta = 7.12$ (d, $J = 9$ cps, 1 H), 6.87 (d, $J = 9$ cps, 1 H), 2.70 (m, 2 H), 2.53 (s, 3 H), 1.25 (broad methylene absorption), and 0.97 ppm (m, 3 H); $\lambda_{\max}^{\mathrm{EtOH}}$ 224 mμ (ε 8240), 288 mμ (ε 5850); addition of potassium hydroxide shifted the ultraviolet maxima to 245 mμ (ε 11,500) and 310 mμ (ε 6200); addition of acid shifted the maxima to 231 mμ (ε 5750) and 301 mμ (ε 9500); infrared (KBr pellet), $\nu_{\max}$ 3500, 2700–2400, 1582, 1290, 830 cm^{-1}.

Anal. Calcd for $C_{18}H_{31}NO$: mol wt, 277.236. Found: mol wt, 277.236.

Oxidation.—A 29-mg sample of the above pyridine was heated on a steam bath for 10 min with 0.03 ml of nitric acid. The solution was diluted with methanol and extracted three times by hexane; the upper phase was extracted with 1 *N* sodium hydroxide in 95% methanol; the basic extract was washed with hexane, acidified by hydrochloric acid, and extracted twice with hexane. The hexane solution was treated with ethereal diazomethane. Gas chromatography (4% SE-30 on Gas-Chrom P, 0.3 × 365 cm, 130°, 1400 g/cm^2) showed a mixture of which the major component had the retention time (16.0 min) of authentic methyl laurate.

The collected raffinates of the above sequence were made basic by sodium hydroxide and concentrated to dryness under reduced pressure. A single partition between methanolic hydrochloric acid and hexane provided a hexane extract which was treated with diazomethane. Gas chromatography showed this to be a mixture containing a similar amount of methyl laurate.

To provide a sample for mass spectrometric examination, the first hexane extract was chromatographed in the vapor phase over a column 1.6 cm in diameter, 273 cm long, 30% SE-30 on Gas-Chrom P, at 175°, 1400 g/cm^2. Fractions were collected by condensation in a trap chilled by liquid nitrogen, and the major component was obtained pure. This material was introduced into a mass spectrometer (Associated Electrical Industries, Ltd., MS-9) by direct inlet, and produced a spectrum identical in every respect with that from known methyl laurate.

Deuteriocassine,[1] introduced into the mass spectrometer as above, produced peaks corresponding to the following *m/e:* 302 (relative height 1.0), 301 (0.94), and 300 (0.56). The molecular ion of cassine, so introduced, corresponded to *m/e* 297.

The Furanoquinoline Alkaloids. III.[1] An Attempted Synthesis of *dl*-Lunacrine and Correction of the Structure of "Demethoxylunacrine"

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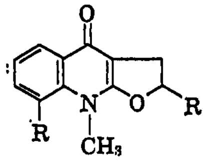
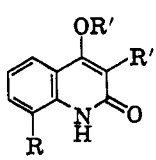
In an effort to explore the synthetic approach to furoquinoline alkaloids developed recently in these laboratories,[1] an attempt has been made to apply this synthesis to a total synthesis of *dl*-lunacrine (Ia).



Ia, R = OCH_3; R′ = $CH(CH_3)_2$
b, R = H; R′ = $CH(CH_3)_2$
c, R = OCH_3; R′ = $CH_2CH(CH_3)_2$
d, R = H; R′ = $CH_2CH(CH_3)_2$



IIa, R = OCH_3; R′ = H; R″ = $COCH_2CH(CH_3)_2$
b, R = OCH_3; R′ = CH_3; R″ = $COCH_2CH(CH_3)_2$
c, R = H; R′ = CH_3; R″ = $COCH_2CH(CH_3)_2$
d, R = OCH_3; R′ = CH_3; R″ = $CHOHCH_2CH(CH_3)_2$
e, R = OCH_3; R′ = CH_3; R″ = $CH_2COCH_2CH(CH_3)_2$

By analogy with the published synthesis of demethoxylunacrine (Ib),[1] the starting material of choice appeared to be 4-hydroxy-8-methoxy-2-quinolone,[2] which should be readily available from the cyclization of

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[3] A. Littlewood, "Gas Chromatography," Academic Press Inc., New York, N. Y., 1962, p 424; A. T. James and A. J. P. Martin, *Biochem. J.*, **63**, 144 (1956).

[4] R. Ryhage and E. Stenhagen in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, p 408.

[5] All melting points were observed on a Kofler microscope hot stage and are corrected. The authors are indebted to Mrs. K. S. Warren for spectrophotometric data. Ultraviolet spectra were recorded on a Cary Model 11 MS recording spectrophotometer. Infrared spectra were observed on a Perkin-Elmer Model 21 double-beam spectrophotometer. Molecular weights were determined on an Associated Electrical Industries MS-9 double-focusing mass spectrometer by comparison to an ion of slightly less weight from perfluorotributylamine. Mass spectra were obtained at 70-ev ionizing radiation. Nmr spectra were determined on a Varian Associates A-60 nmr spectrometer in deuteriochloroform solution, using tetramethylsilane as a reference (δ = 0.0 ppm). The following abbreviations are used: s, singlet; q, quartet; m, multiplet. The figures entered after the chemical shifts represent relative proton content determined by electronic integration.

[1] Part II: J. W. Huffman and L. E. Browder, *J. Org. Chem.*, **29**, 2598 (1964).

[2] B. Berinzaghi, A. Muruzabal, R. Labriola, and V. Deulofeu [*ibid.*, **10**, 181 (1945)] have prepared this compound in several steps from 2-nitro-3-methoxybenzoic acid.