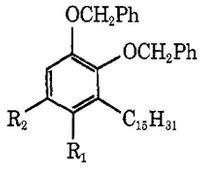
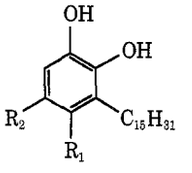
Loev and Dawson[5] and then chloromethylation of the dibenzyl ether **1a**. Earlier exploratory studies by Byck had indicated that chloromethylation leads to the formation of a monochloromethylated product.[6] In the present investigation we have thoroughly studied this reaction and have found that depending upon the proper conditions, either one or two chloromethyl groups can be introduced on the aromatic nucleus.

If the chloromethylation of **1a** is carried out with the passage of hydrogen chloride for 2 hr at 0° the product is 4-chloromethyl-3-pentadecylcatechol dibenzyl ether (**1b**). If, however, hydrogen chloride is allowed to pass through the reaction mixture for 6 hr at room temperature, then dichloromethylation is achieved, and the resulting product is 4,5-bis(chloromethyl)-3-pentadecylcatechol dibenzyl ether (**1c**). Infrared and nmr spectra have indicated that partial debenzylation occurs in the latter reaction. Since this does not interfere with the final step, no attempt was made to purify **1c**.

Both the mono- and dichloromethylated products can now be conveniently converted to 4-methyl-3-pentadecylcatechol (**2a**) and 4,5-dimethyl-3-pentadecylcatechol (**2b**), respectively, by hydrogenation with a 10% palladium on carbon catalyst. The structure of the hydrogenolysis products, as documented in the Experimental Section, verifies that the chloromethylation of **1a** can be made to give either **1b** or **1c**. This scheme thus provides a much simplified route of synthesis and an improved yield of several methylated analogs of 3-pentadecylcatechol.



1a, $R_1 = R_2 = H$
b, $R_1 = CH_2Cl$; $R_2 = H$
c, $R_1 = R_2 = CH_2Cl$



2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = CH_3$

Experimental Section[7]

4-Chloromethyl-3-pentadecylcatechol Dibenzyl Ether (1b).—A sample of 10.0 g (0.02 mol) of benzylated 3-pentadecylcatechol (**1a**), mp 51.0–52.0° (lit.[5] mp 52.4–53.0°), 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were cooled in an ice bath, and dry hydrogen chloride was passed through the mixture with continuous stirring. After 45 min the solution became clear, and the hydrogen chloride passage was continued for an additional 2 hr. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized twice from hexane to give 8.2 g (75%) of a white solid (**1b**): mp 50.0–51.0°; nmr (CCl_4) τ 2.7 (s, 10 H, C_6H_5–), 3.1 (q, 2 H, aromatic), 4.9 (s, 4 H, OCH_2–), 5.5 (s, 2 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at 8.6–9.2 integrated for 29 H; mass spectrum m/e 549 (M^+).

4,5-Bis(chloromethyl)-3-pentadecylcatechol Dibenzyl Ether (1c).—Samples of 10.0 g of **1a**, 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were mixed in an ice bath and hydrogen chloride was passed through the mixture for 0.5 hr. The ice bath was removed and passage of hydrogen chloride was continued for 6 hr at room temperature. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized from hexane to yield 8.36 g (70%) of a white solid (**1c**): mp 79.0–81.0°; ir (CCl_4) 2.86 μ (w, OH, indicating partial debenzylation had occurred); nmr (CCl_4) τ 2.6 (s, 8 H, C_6H_5–), 3.2 (s, 1 H, aromatic), 4.3 (broad s, minor, OH, resulting from partial debenzylation), 4.9 (s, 3 H, OCH_2–), 5.2–5.3 (d, 4 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at τ 8.6–9.2 integrated for 29 H.

4-Methyl-3-pentadecylcatechol (2a).—A sample of 5.5 g (0.01 mol) of **1b** was dissolved in 100 ml of ethyl acetate containing 2 drops of sulfuric acid, and the solution was hydrogenated in a Parr pressure reaction apparatus for 6 hr over 0.3 g of 10% palladium on carbon catalyst at an initial hydrogen pressure of 60.0 psi and at room temperature. The catalyst was then removed by filtration, and the solution was diluted with ether and washed with 10% sodium bicarbonate followed by water. The residual oil obtained after drying the solution and removal of solvent was recrystallized several times from ligroin to give 3.18 g (95%) of **2a**. This compound was identical in melting point (55.0–56.0°) and spectra (ir and nmr) with an authentic sample of 4-methyl-3-pentadecylcatechol.[3]

4,5-Dimethyl-3-pentadecylcatechol (2b).—An identical hydrogenolysis procedure was performed on 6.0 g (0.01 mol) of **1c**. The residual oil obtained after the work-up was recrystallized from hexane to yield 3.17 g (91%) of **2b**. This compound was identical in melting point and spectra (ir and nmr) with an authentic sample of 4,5-dimethyl-3-pentadecylcatechol.[2]

Registry No.—**1a**, 2792-00-9; **1b**, 39533-51-2; **1c**, 39533-52-3; **2a**, 16273-11-3; **2b**, 7771-22-4.

Acknowledgment.—This investigation was supported in part by Contract PH-43-64-76 with the Division of of Biologics Standards of the National Institutes of Health.

(5) B. Loev, and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).
(6) J. S. Byck, laboratory notes, Columbia University, 1967.
(7) Melting points were measured on a Thomas-Hoover apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. The nmr spectra were run on a Varian T-60 instrument and employing 20–50% solutions in CCl_4 with a drop of TMS as internal standard. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU-6d instrument.

The Reaction of Trimethylsilyl Enol Ethers with Simmons–Smith Reagent. A Facile Synthesis of Trimethylsilyl Cyclopropyl Ethers and Cyclopropanols

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The reaction of trimethylsilyl enol ethers,[1] (**1**) with Simmons–Smith reagent[2] followed by cold, rapid work-up (method A) affords a mixture of trimethylsilyl cyclopropyl ethers (**2**) and cyclopropanols (**3**) enriched in **2**. Work-up at ambient conditions with no emphasis placed on rapid manipulation (method B) leads to a mixture of **2** and **3** enriched in **3**. The ether **2** upon treatment with aqueous acid gives **3** in good yield. These findings are outlined below in Scheme I, and representative yields are given in Table I.

Structural proof for the ethers **2** rests mainly on the spectral data of the compounds. Each ether **2** shows a characteristic nmr peak at *ca.* δ 0.05 representing the $Si(CH_3)_3$ moiety. The ir of **2** indicates that no OH grouping is present, and absorptions at 1250 and

(1) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(2) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); (b) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

SCHEME I

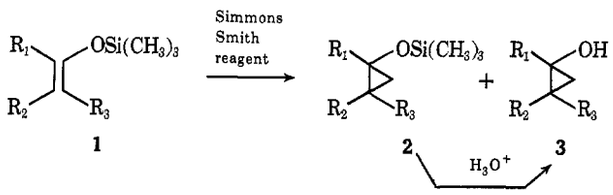
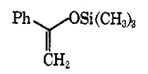
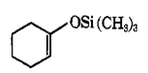
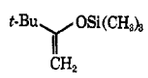
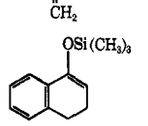


TABLE I

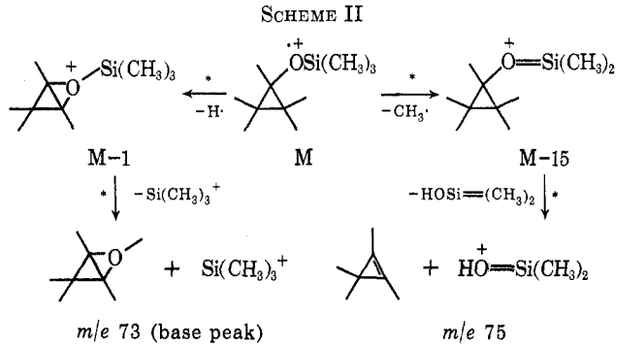
REACTION OF TRIMETHYLSILYL ENOL ETHERS WITH SIMMONS–SMITH REAGENT[a-c]

Trimethylsilyl enol ether 1	Method	2, %	Method	3, %
	A	67	A	10
	B	4 (2a)	B	73 (3a)
	A	18 (2b)	A	37 (3b)
	B	Trace	B	78
	A	57 (2c)	A	10 (3c)
	A	58 (2d)	A	20 (3d)

[a] Fast, cold work-up (method A). [b] Slow, ambient work-up (method B). [c] All compounds give ir, nmr, and mass spectral data in accord with the proposed structures.

840 cm^{-1} are diagnostic for $Si(CH_3)_3$.[3] Perhaps the clearest information concerning the structure of the ethers **2** comes from the mass spectra. The generalized fragmentation pattern is shown in Scheme II.

SCHEME II

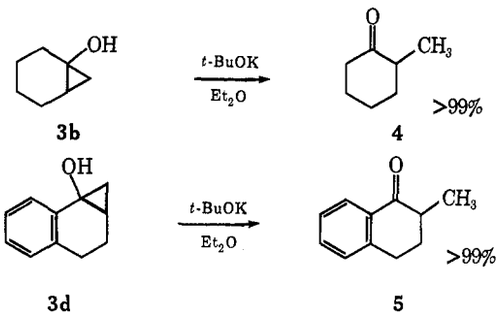


* = metastable transition

All the ethers **2** have a base peak at *m/e* 73 [$^+Si(CH_3)_3$] with intense peaks at *m/e* 75 [$HO{=}Si(CH_3)_2^+$], M − 15 ($-CH_3\cdot$), and M − 1 ($-H\cdot$). The proposed mode of fragmentation is verified by the appearance of metastable transitions between the fragments indicated. Spectral evidence for the structures of the cyclopropanols **3** is also consistant with the proposed formulations.

Chemical evidence for the structure of cyclopropanols **3b** and **3d** was obtained by a study of their reaction with potassium *tert*-butoxide. The results of this study are in agreement with those obtained by DePuy,[4] as we observed only the formation of α-methyl ketones **4** and **5**. These observations, outlined below in Scheme III, not only verify the structures

SCHEME III



3b and **3d** but are illustrative of an efficient method for the introduction of a methyl group α to a keto function. Since the conversion of **2** into **3** has been shown to be feasible, the production of the α-methyl ketones serves as structural proof for the ethers **2**.

We are attempting to extend the scope of the addition reaction to include trimethylsilyl ketene ketals and trimethylsilyl phenols.[5]

Experimental Section

General Procedure for the Reaction of Simmons–Smith Reagent with Trimethylsilyl Enol Ethers.[2b]—To a stirred, refluxing slurry of 0.02 mol of zinc–copper couple, under nitrogen, in 20 ml of dry ether containing a trace of diiodomethane, was added a solution of 0.01 mol of trimethylsilyl enol ether and 0.014 mol of diiodomethane in 10 ml of dry ether. After the addition was complete (*ca* 0.5 hr), the resulting mixture was refluxed for 20–24 hr. After cooling, the reaction mixture was worked up in the following manner.

Method A. Isolation of Trimethylsilyl Cyclopropyl Ethers.—The cooled reaction mixture was filtered through a plug of glass wool and immediately diluted with 25 ml of cold 10% hydrochloric acid. The layers were separated and the aqueous portion was rapidly extracted with 2 × 20 ml of cold ether. The combined ethereal extracts were then washed successively and rapidly with 20 ml of cold 10% hydrochloric acid and 2 × 20 ml of cold water. After drying over anhydrous magnesium sulfate, the ethereal solution was filtered and solvent was removed *in vacuo* to afford a mixture of **2** and **3** which was enriched in trimethylsilyl cyclopropyl ethers **2**. Column chromatography on 0.5–0.2 mesh silica gel utilizing hexane–ether mixtures as eluting solvent gave pure **2** and **3** as judged by spectral and tlc (silica gel 7G, hexane–ether mixtures) data.

Method B. Isolation of Cyclopropanols.—The same procedure outlined in method A was followed, except that all manipulations were carried out with reagents and solvents at ambient temperature, and no emphasis was placed on rapid extractions.

Conversion of Trimethylsilyl Cyclopropyl Ether 2d into Cyclopropanol 3d.—A solution of 1.16 g (5.0 mmol) of **2d** in 25 ml of ether was stirred for 0.5 hr at room temperature with 25 ml of 10% hydrochloric acid (under nitrogen). The acid was then removed and the ethereal solution was washed with 25 ml of water and dried over anhydrous magnesium sulfate. Filtration and removal of solvent *in vacuo* gave a solid residue, which was crystallized from pentane to afford 0.48 g (60%) of cyclopropanol **3d**, mp 100–104°. The nmr and ir of synthetic **3d** were identical with those of authentic **3d**, and the tlc behavior of synthetic **3d** was identical with that of authentic **3d** (silica gel 7G, hexane–ether, 4:1).

Conversion of 3b into 2-Methylcyclohexanone by Treatment with Base.—A slurry of 0.08 g (0.7 mmol) of cyclopropanol **3b** and 0.11 g (1.0 mmol) of potassium *tert*-butoxide in 10 ml of dry ether was refluxed overnight with stirring under a nitrogen atmosphere. After cooling, the mixture was diluted with 1 ml of water and the layers were separated. The aqueous layer was extracted with 1 ml of ether and the combined ethereal solution

(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958.

(4) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(5) For a recent example of the addition of Simmons–Smith reagent to a bis(trimethylsiloxy)diene, see J. M. Denis and J. M. Conia, *Tetrahedron Lett.*, 4593 (1972).

was washed with 1 ml of water. After drying over anhydrous magnesium sulfate, the ethereal solution was filtered and solvent was removed *in vacuo* to afford 0.08 g (100%) of 2-methylcyclohexanone (4). The synthetic material was identical with an authentic sample (Columbia) as judged by identical ir, nmr, and glpc behavior (12 ft, 20% DEGS at 148°).

Registry No.—**1a**, 13735-81-4; **1b**, 6651-36-1; **1c**, 17510-46-2; **1d**, 38858-72-9; **2a**, 38858-73-0; **2b**, 38858-74-1; **2c**, 38858-75-2; **2d**, 38858-76-3; **3a**, 29526-96-3; **3b**, 34737-45-6; **3c**, 38858-79-6; **3d**, 38858-80-9.

The Synthesis of *N*-Methylhomopavine [(±)-Homoargemonine][1]

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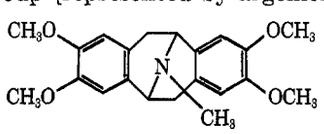
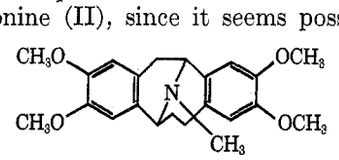
In the past 10 years a new class of poppy alkaloids, the pavine group [represented by argemonine (I)], has



I

been discovered and a number of alkaloids having varying substituent placements on the basic pavinane[2] ring structure have been described.[3] A number of the natural alkaloids as well as some simple synthetic analogs have shown[4] weak analgetic activity or toxicity in mice. Because substituent modifications on the pavinane ring structure did not lead to increased analgetic activity, we decided to modify the basic structure itself. A particularly attractive modification appeared to be one with expansion of the central ring as in (±)-homoargemonine (II), since it seems possible that II

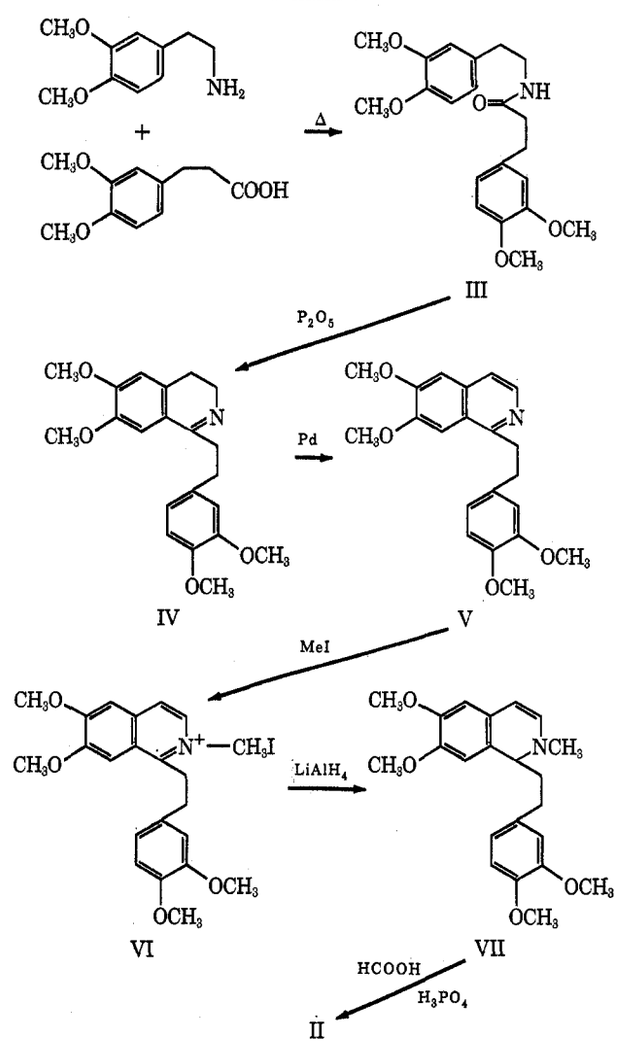


II

could also represent a member of a new, as yet undiscovered, but highly probable alkaloid class. The requisite biogenetic precursor of II would be a 1-phenethyl-1,2,3,4-tetrahydroisoquinoline. Such 1-phenethyl derivatives have now been found in nature and have also been shown to be precursors of some natural homomorphinandienones, colchicines, and similar alkaloids.[5] The structural requirements involved in the cyclization which yields I-type compounds have not been explored and the lack of II-type compounds in nature could have been ascribed to a failure in the seemingly simple extension of I biosynthesis pathways to the case of II. This note reports the ready synthesis of the new ring system exemplified by II.

The synthesis of II was accomplished by means of the reactions in Scheme I as described in the Experimental Section. Data on pharmacological activity will be published elsewhere when it is available.

SCHEME I



Experimental Section

***N*-2-(3,4-Dimethoxyphenyl)ethyl-3-(3,4-dimethoxyphenyl)propionamide (III).**—A mixture of 22.0 g of 3-(3,4-dimethoxyphenyl)propionic acid (prepared from reduction of 3,4-dimethoxycinnamic acid purchased from Aldrich) and 25 g of 2-(3,4-dimethoxyphenyl)ethylamine (Aldrich) was heated under N_2 at 190° for 2 hr. The mixture was then cooled, dissolved in ethyl acetate, and washed with dilute HCl, dilute NaOH, and water in that order. The solvent was then removed and the product was recrystallized from ethanol to give 30 g (77%) of amide as a white solid, mp 99° (lit.[6] mp 99–100°).

1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (V).—The amide (25 g) was dissolved in 250 ml of dry toluene, 125 g of P_2O_5 was added, and the mixture was refluxed for 1 hr under N_2. After the mixture cooled, the excess P_2O_5 was decomposed by the addition of ice and the toluene was extracted with three 50-ml portions of warm water. The aqueous extracts were cooled and taken to pH 10 with cold NaOH solution. The basic mixture

(1) Part XVIII in the series "Alkaloids of the Papaveraceae." For part XVII see L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, in press. This work was supported in part by Grant GM-19234 from the National Institute of General Medical Sciences, U. S. Public Health Service, and in part by Vipont Chemical Co.

(2) C. H. Chen and T. O. Soine, *J. Pharm. Sci.*, **61**, 55 (1972).

(3) F. Santavy in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, p 370.

(4) Unpublished results from our laboratories with A. E. Jacobson, L. B. Kier, and T. O. Soine, *J. Amer. Pharm. Assoc.*, **49**, 187 (1960).

(5) I. D. Spencer in "Chemistry of the Alkaloids," S. W. Pelletier, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, Chapter 21.

(6) S. Sagawa and H. Yoshikawa, *J. Chem. Soc.*, 1583 (1933).