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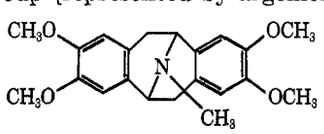
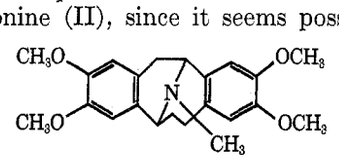
In the past 10 years a new class of poppy alkaloids, the pavine group [represented by argemonine (I)], has



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

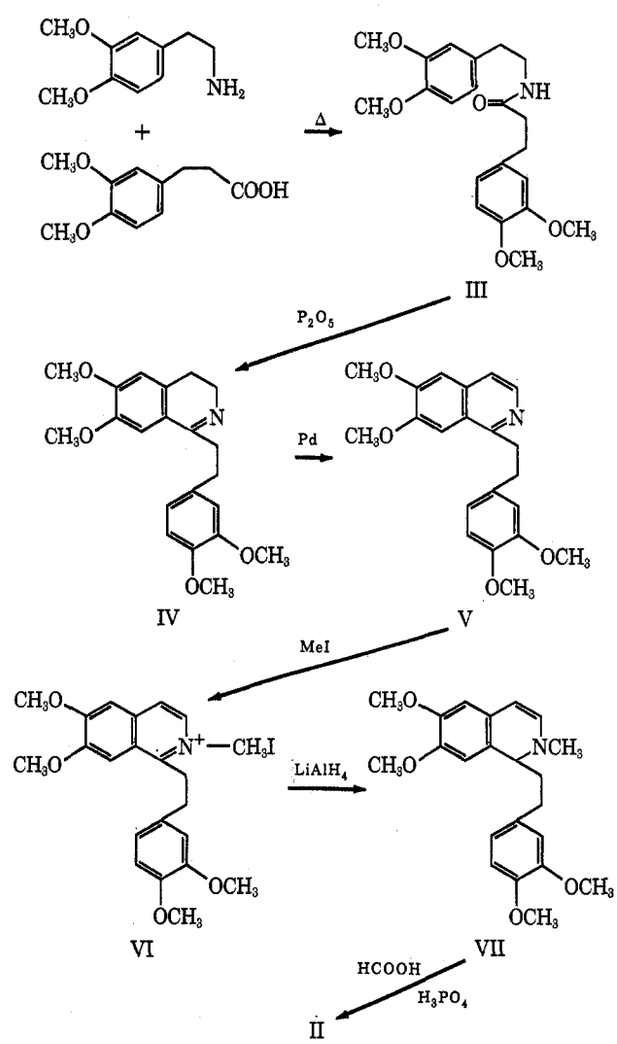


II

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).

was then extracted with three 75-ml portions of chloroform. The chloroform extracts were dried with K_2CO_3 and evaporated to leave the 3,4-dihydroisoquinoline IV as an oily residue. To this residue was added 100 ml of diphenyl ether and 2 g of palladium black. The mixture was heated with gentle stirring under nitrogen at 200° for 2 hr and was then diluted with benzene. The catalyst was removed by filtration and the filtrate was extracted with five 25-ml portions of 10 *M* HCl. The aqueous layer was made basic with cold NaOH solution and extracted with three 30-ml portions of chloroform. The chloroform extracts were dried with K_2CO_3 and evaporated to dryness and the resulting white solid was recrystallized from ethanol to yield 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxyisoquinoline (V), 19 g (80%), mp 147° (lit.[7] mp 147°).

(±)-Homoargemonine (6,11,12,13-Tetrahydro-2,3,8,9-tetramethoxy-14-methyl-5*H*-dibenzo[*a*,*e*]cyclononene-5,11-imine)(II).—V (14 g) was methylated with methyl iodide (60 ml) in 50 ml of methanol to yield 15 g of the *N*-methiodide VI. *N*-Methiodide VI was dried and was added to 2 g of $LiAlH_4$ in dry ether (250 ml). The mixture was stirred at room temperature for 3 hr and the excess $LiAlH_4$ was then decomposed by the addition of wet ether followed by a saturated solution of sodium potassium tartrate. The aqueous layer was further washed with ether (2 × 50 ml) and the ether portions were combined, dried with K_2CO_3, and evaporated to dryness to yield 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2-dihydro-2-methylisoquinoline, VII, as a yellow oil. This was then refluxed under N_2 with 100 ml of 7:5 $HCOOH$–H_3PO_4 for 8 hr. The reaction mixture was then diluted with water, washed with $CHCl_3$, made basic with NaOH solution, and extracted with three 50-ml portions of chloroform. The chloroform extract was dried with K_2CO_3 and evaporated to yield 9 g of brown oil. The oil was shown by tlc to be composed of two products. Column chromatography (Florisil 60–100 mesh) was used to separate the two products. The column yielded 2 g of a substance indicated by nmr and tlc to be 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 6 g of (±)-homoargemonine (II): mp 196° (ethanol); uv (CH_3OH) λ_{max} 277 nm (log ϵ 3.53); nmr ($CDCl_3$) δ 6.67–6.5 (m, 4 H, aromatic protons), 3.90 (s, 6 H, OCH_3), 3.85 (s, 6 H, OCH_3), 2.53 (s, 3 H, NCH_3), 4.23–2.37 (m, 8 H, ring CH and CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 369 (45), 204 (100), 218 (11), 368 (54).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.50; H, 7.65; N, 4.10.

Registry No.—II, 39013-26-8; III, 20944-13-2; IV, 20944-14-3; V, 39013-29-1; VI, 39013-30-4; VII, 39013-31-5; 3-(3,4-dimethoxyphenyl)propionic acid, 2107-70-2; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7.

(7) G. Scheuing and B. Walach, German Patent 576,532 (1933); *Chem. Abstr.*, **27**, 5896 (1933).

Organocopper Chemistry. Reactions of Lithium Dialkylcopper Reagents with Activated Vinylcyclopropanes. An Instance of 1,7 Addition

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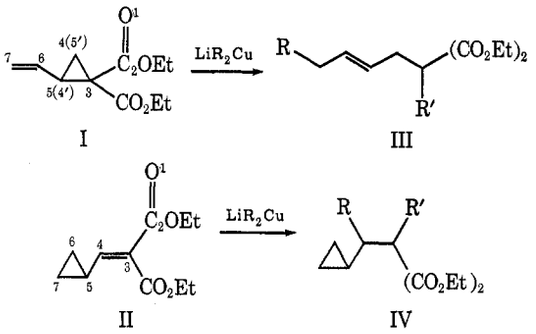
Alkylation of a wide variety of organic substrates using alkylcopper(I) "ate" complexes continues to be a subject of active interest.[1] The recently reported capabilities of organocopper species to perform 1,5 and 1,6 additions[2] (ω alkylation) prompts us to report our results concerning the reaction of I and II with lithium



dimethylcopper ($LiMe_2Cu$) and lithium di-*n*-butylcopper ($LiBu_2Cu$). In addition we report further observations which allow for simultaneous ω (1,7 or 1,4)[3a] and α-alkylation *via* addition of an alkylcopper "ate" complex to either I or II followed by alkylation[3b] of the resultant malonate anion.

In principle, compounds I and II possess multiple electrophilic sites. In addition to the trivial possibility of 1,2 addition, compound II might be attacked by nucleophiles in a 1,4 or 1,7 sense. Likewise, compound I might suffer nucleophilic attack in a 1,5, 1,5′, or 1,7 sense.[4] Our studies demonstrate, in each case, remarkable specificity toward olefin attack.

Treatment of I[5] with $LiMe_2Cu$ (1.25 equiv) in ether at 0° for 1 hr afforded an 87% yield of IIIa (R = CH_3; R′ = H). Its structure is assigned on the basis of the following data: ir max ($CHCl_3$) 5.80, 10.30 μ; nmr (CCl_4) δ 5.45 (m, 2 H, olefinic protons), 3.24 [t, 1 H, C**H**$(CO_2Et)_2$], 0.98 (t, 3 H, CH_2CH_3); *m/e* 228. This reaction constitutes a preferential and unambiguous 1,7 addition.[6-9] Similarly, $LiBu_2Cu$ underwent almost exclusive 1,7 addition in high yield (Table I).

In sharp contrast, treatment of II[10] with $LiMe_2Cu$ under similar conditions gave IVa (R = CH_3; R′ = H) in 92% isolated yield. The structure is assigned on the basis of the following data: ir max ($CHCl_3$) 5.80 μ; nmr (CCl_4) δ 3.25 [d, 1 H, C**H**$(CO_2Et)_2$], 1.08 (d, 3 H, $CHCH_3$), 0.80–0.05 (m, 5 H, cyclopropyl moiety);

(1) G. M. Whitesides, W. F. Fischer, Jr., J. SanFilippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1968); E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967), and **90**, 5615 (1968), and references cited therein.

(2) (a) E. J. Corey and P. L. Fuchs, *J. Amer. Chem. Soc.*, **94**, 4014 (1972); E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *ibid.*, **94**, 4395 (1972); G. Daviaud and P. Miginiac, *Tetrahedron Lett.*, 997 (1972). (b) For previous precedent in Sn2′-type displacements using $LiMe_2Cu$, see R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970); E. E. van Tamlen and J. P. McCormick, *ibid.*, **92**, 737 (1970); R. J. Anderson, *ibid.*, **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970).

(3) (a) For a recent review of organocopper 1,4-addition reactions, see G. H. Posner, *Org. React.*, **19**, 1 (1972). (b) For alkylation of an enolate anion generated by addition of an organometallic reagent to an α,β-unsaturated ketone, see G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968).

(4) We suggest the terms 1,5 and 1,5′ (which arises from alternative numbering) to signify alternate modes of homoconjugate addition and 1,7 to signify vinylogous homoconjugate addition. The terms 1,4 and 1,6 are thus reserved for classical Michael reactions.

(5) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952).

(6) The normal mode of addition of nucleophiles to I is in the 1,5 sense.[7,8] The two serious exceptions to this rule are 1,7-mercaptan addition[7] and 1,7-enamine addition.[8] The former case is most probably the result of a free radical pathway.[9] The latter case may well be the result of 1,5-alkylation at nitrogen followed by Claisen rearrangement.

(7) J. M. Stewart and G. K. Pagenkopf, *J. Org. Chem.*, **34**, 7 (1969).

(8) S. Danishefsky, G. Rovnyak, and R. Cavanaugh, *Chem. Commun.*, 636 (1969).

(9) S. Danishefsky and R. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820 (1972).

(10) Prepared from the Knoevenagel condensation of diethyl malonate with cyclopropanecarboxaldehyde (see G. Rovnyak, Ph.D. Thesis, University of Pittsburgh, 1970).