[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Alkaloid Studies. XII.[1] Synthesis of Substituted 1-Isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinolines[2]

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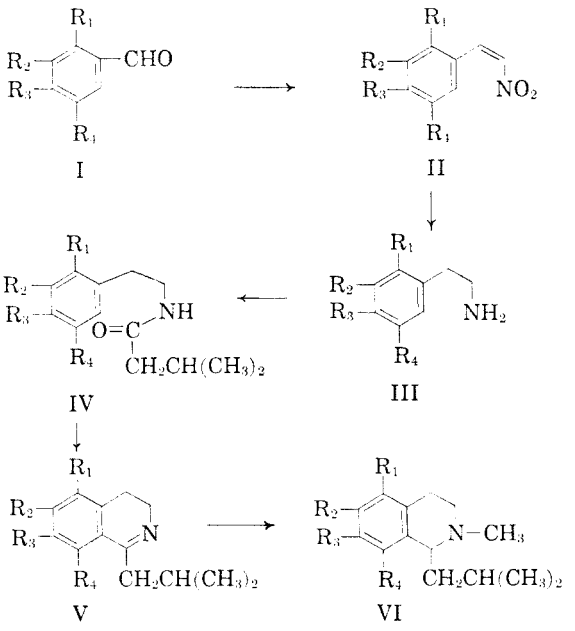
In connection with the characterization of certain cactus alkaloid degradation products, a series of 1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinolines was synthesized with varying substituents (methoxy or ethoxy) in positions 5, 6, 7, and 8.

The cactus alkaloid pilocereine[3] is of unusual interest since it represents a much larger and more complicated molecule than the previously isolated alkaloids of the *Cactaceae* plant family.[4] One of the key steps in the structure elucidation[5] of this alkaloid involved diaryl ether cleavage to smaller fragments of the 1-isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinoline series (VI) and the purpose of the present work was to synthesize several such compounds[6] for comparison purposes and also to make them available for pharmacological testing.

All but one (IX) of the required tetrahydroisoquinolines could be prepared from the appropriately substituted β-phenethylamine (III) by transformation to the corresponding isovaleryl amide (IV), cyclization by the Bischler-Napieralski procedure[7] to the 3,4-dihydroisoquinoline (V), conversion to the methiodide, and direct reduction[8] with sodium borohydride to the desired 1-isobutyl-2-methyltetrahydroisoquinoline (VI). Most of the starting amines (III) were obtained by known procedures from the substituted benzaldehydes (I) *via* the corresponding ω-nitrostyrenes (II) followed by reduction with lithium aluminum hydride[9] while 3,5-dimethoxy-β-phenethylamine (IIIe) was prepared by hydride reduction of the amide or nitrile of 3,5-dimethoxyphenylacetic acid.



a $R_1 = R_2 = CH_3O$; $R_3 = R_4 = H$
b $R_1 = R_4 = CH_3O$; $R_2 = R_3 = H$
c $R_2 = CH_3O$; $R_3 = C_2H_5O$; $R_1 = R_4 = H$
d $R_2 = C_2H_5O$; $R_3 = CH_3O$; $R_1 = R_4 = H$
e $R_2 = R_4 = CH_3O$; $R_1 = R_3 = H$
f $R_2 = CH_3O$; $R_1 = R_3 = R_4 = H$
g $R_2 = R_3 = R_4 = CH_3O$; $R_1 = H$

The only compound which could not be synthesized by the Bischler-Napieralski method was 1-isobutyl-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IX), since the directive influence of the *p*-methoxy substituent is so strong that a 6,7-dimethoxy isomer will be formed even if attempts are made to block this type of cyclization by bromination.[10] Consequently, the following alternate scheme was employed.

7,8-Dimethoxyisoquinoline[11] was prepared by a modified Pomeranz-Fritsch reaction[12] (using polyphosphoric acid in the cyclization step), and its derived methobromide (VII) was treated with isobutylmagnesium bromide[13] to yield 1-isobutyl-2-methyl-7,8-dimethoxy-3,4-dihydroisoquinoline

(1) Paper XI, Djerassi, Gorman, Pakrashi and Woodward, *J. Am. Chem. Soc.*, **78**, 1259 (1956).

(2) Fellowship support was provided by Eli Lilly and Co. and by the National Heart Institute of the National Institutes of Health (Grant No. H-2040).

(3) Djerassi, Frick, and Geller, *J. Am. Chem. Soc.*, **75**, 3632 (1953).

(4) *Cf.* Reti in Zechmeister's *Progress in the Chemistry of Organic Natural Products*, Springer, Vienna, 1950, Vol. VI, pp. 242–289.

(5) Djerassi, Figdor, Bobbitt, and Markley, *J. Am. Chem. Soc.*, **78**, 3861 (1956).

(6) One of these, 1-isobutyl-2-methyl-6,7-dimethoxytetrahydroisoquinoline, has already been synthesized (Djerassi, Beereboom, Marfey, and Figdor, *J. Am. Chem. Soc.*, **77**, 484 (1955).

(7) Whaley and Govindachari, *Org. Reactions*, **6**, 74 (1951).

(8) Witkop and Patrick, *J. Am. Chem. Soc.*, **75**, 4474 (1953); Torossian and Sannie, *Compt. rend.*, **236**, 824 (1953).

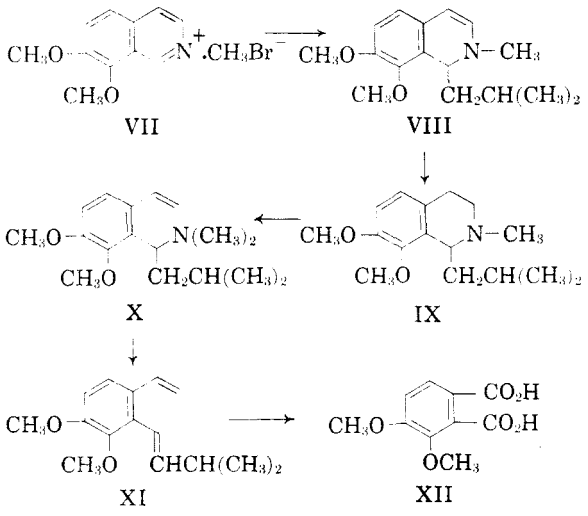
(9) *Cf.* Ramirez and Burger, *J. Am. Chem. Soc.*, **72**, 2781 (1950) and references cited therein.

(10) The expulsion of a bromine protecting group in order to permit *para* cyclization has already been noted by Haworth and Perkin [*J. Chem. Soc.*, 1448 (1925)] and was confirmed, using the appropriate isovaleryl amide, by Dr. S. P. Marfey in this laboratory.

(11) *Cf.* Perkin and Robinson, *J. Chem. Soc.*, 2376 (1914).

(12) Gensler, *Org. Reactions*, **6**, 191 (1951).

(13) *Cf.* Grewe, *Naturwiss.*, **33**, 333 (1946); Schnider and Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).



(VIII). This intermediate was not purified but was hydrogenated directly to the required tetrahydroisoquinoline (IX). The structure of the final product follows from the analytical data of the base and its derivatives as well as from the course of the Hofmann degradation. First stage Hofmann degradation afforded the substituted styrene X[14] while a repetition of this process led to a nitrogen-free compound (XI) which upon ozonization afforded hemipinic acid (XII), formaldehyde, and isobutyraldehyde.

EXPERIMENTAL[15]

ISOVALERYL AMIDES (IV)

The general procedure consisted of mixing 0.05 mole of amine (III) and 0.06 mole of isovaleric acid chloride in 500 cc. of benzene and either refluxing for 45 minutes or leaving at room temperature overnight. After washing thoroughly with dilute alkali and water, the benzene was removed and the product was distilled *in vacuo* to afford the amide in 65–80% yield. The source of the respective amines is given below under each example.

2,3-Dimethoxyphenethyl- (IVa). The amine (IIIa),[16] obtained in *ca.* 80% yield by lithium aluminum hydride reduction of the corresponding ω-nitrostyrene (IIa)[17] was characterized as the *picrate,* m.p. 181–183° (from ethanol).

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42. Found: C, 46.95; H, 4.37.

The *amide* (IVa) was obtained as a pale yellow oil, b.p. 140–146° at 2 mm.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74. Found: C, 67.93; H, 8.78.

2,5-Dimethoxyphenethyl- (IVb). The amine (IIIb)[18] was characterized as the *picrate,* m.p. 166.5–167.5°.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42. Found: C, 47.14; H, 4.23.

The amide (IVb) was recrystallized from hexane-benzene, m.p. 59–61°.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 67.51; H, 8.62; N, 5.49.

3-Methoxy-4-ethoxyphenethyl- (IVc). The amine (IIIc)[19] was isolated in 85% yield from the lithium aluminum hydride reduction of the nitrostyrene (IIc)[20] and converted to the yellow *picrate,*[19] m.p. 186–188°.

Anal. Calc'd for $C_{17}H_{20}N_4O_9$: C, 48.11; H, 4.75. Found: C, 48.13; H, 4.81.

The *amide* (IVc) was distilled, b.p. 174–179° at 0.09 mm. whereupon it crystallized, m.p. 65–67°.

Anal. Calc'd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02. Found: C, 68.49; H, 8.85.

3-Ethoxy-4-methoxyphenethyl- (IVd). The reduction of the nitrostyrene IId[20,21] proceeded in 76% yield and the amine (IIId)[19] was transformed directly into the picrate,[19] m.p. 185–187°.

Anal. Calc'd for $C_{17}H_{20}N_4O_9$: C, 48.11; H, 4.75. Found: C, 48.54; H, 4.61.

The distilled amide (b.p. 169–174° at 0.04 mm.) crystallized (m.p. 62–63°) on standing.

Anal. Calc'd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02. Found: C, 68.82; H, 9.03.

3,5-Dimethoxyphenethyl- (IVe). The amine (IIIe)[22] was synthesized by lithium aluminum hydride reduction of 3,5-dimethoxybenzyl cyanide[23] (85%) or of 3,5-dimethoxyphenylacetamide[24] (63%) and converted directly into its *picrate,* m.p. 217–218°.

Anal. Calc'd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42. Found: C, 47 34; H, 4.21.

The *amide* (IVe) was distilled at 0.005 mm. and a bath temperature of 160–170° and did not crystallize on cooling.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74. Found: C, 67.74; H, 8.38.

3-Methoxyphenethyl- (IVf). The amine (IIIf) was kindly furnished by Prof. R. B. Woodward[25] and the resulting amide (IVf) was distilled at 0.001 mm. and a bath temperature of 140°.

Anal. Calc'd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.56; H, 9.03.

3,4,5-Trimethoxyphenethyl- (IVg). This amide was pre-

(14) The structure of this methine was confirmed by ozonization to formaldehyde.

(15) Melting points (Kofler block) and boiling points are uncorrected. The microanalyses were performed by Spang Microanalytical Laboratory (Plymouth, Michigan) and by Dr. A. Bernhardt (Mülheim, Germany). The syntheses of VIe, f, and g were first attempted by R. Mirza in this Laboratory.

(16) Haworth, *J. Chem. Soc.,* 2281 (1927).

(17) Gairaud and Lappin, *J. Org. Chem.,* **18,** 1 (1953).

(18) Buck, *J. Am. Chem. Soc.,* **54,** 3661 (1932); Sugasawa and Shigehara, *Ber.,* **74,** 459 (1941). We are indebted to Mr. Roman Warszawski for the preparation of this amine.

(19) Spaeth and Dobrowsky, *Ber.,* **58,** 1274 (1925).

(20) Dornow and Petsch, *Arch. Pharm.,* **284,** 153 (1951).

(21) We are grateful to Dr. F. B. Zienty (Monsanto Chemical Company, St. Louis, Mo.) and to Prof. R. B. Woodward (Harvard University) for generous samples of isovanillin required for the preparation of the ethyl ether Id (Boeseken and Greup, *Rec. trav. chim.,* **58,** 531 (1939)).

(22) Bailey, Bates, Ing, and Warne, *J. Chem. Soc.,* 4534 (1952) prepared but did not characterize this amine.

(23) Adams, MacKenzie, and Loewe, *J. Am. Chem. Soc.,* **70,** 664 (1948).

(24) 3,5-Dihydroxyphenylacetic acid was prepared by Dr. S. P. Marfey from dimethyl acetonedicarboxylate by the procedure of Theilacker and Schmid (*Ann.,* **570,** 15 (1950)) and converted *via* methyl 3,5-dimethoxyphenylacetate to the amide, m.p. 127–128°.

Anal. Calc'd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71. Found: C, 61.37; H, 6.62.

(25) *Cf.* V. Georgian, Ph.D. Thesis, Harvard University, 1950, p. 173.

pared from commercially available mescaline (IIIg) and exhibited m.p. 92–93°.

Anal. Calc'd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.19; H, 8.37; N, 4.69.

1-ISOBUTYL-3,4-DIHYDROISOQUINOLINES (V)

To a solution of 0.04 mole of the amide IV in 250 cc. of boiling toluene was added 35 g. of phosphorus pentoxide in portions over a period of 30 minutes. After refluxing for one additional hour, the excess reagent was decomposed by the careful addition of water, the layers were separated, and the toluene was washed with dilute hydrochloric acid. The combined aqueous solutions were made strongly basic with solid potassium hydroxide, and the product was extracted with ether or chloroform, washed, dried, evaporated and distilled *in vacuo*. In those cases where no analysis is given for the base, it was immediately transformed into the crystalline picrate and stored as such. When required, the base was recovered by passing a methanol solution of the picrate through a column of methanol-washed Amberlite IRA-400 anion exchange resin. The yields in the Bischler-Napieralski cyclization step ranged from 60–85% and the purity of product was established in each case by infrared examination.

5,6-Dimethoxy- (Va). The *picrate* was recrystallized from methanol, m.p. 159–160°.

Anal. Calc'd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08. Found: C, 52.93; H, 4.99.

5,8-Dimethoxy- (Vb). The free base was purified by distillation, b.p. 150–153° at 0.003 mm., n_D^{25} 1.5453.

Anal. Calc'd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.64; N, 5.59.

The *methiodide* was prepared in benzene solution (room temperature, overnight) and recrystallized from hexane-acetone, m.p. 158–159°.

Anal. Calc'd for $C_{16}H_{24}INO_2$: C, 49.36; H, 6.21; N, 3.60. Found: C, 49.43; H, 6.21; N, 3.69.

6-Methoxy-7-ethoxy- (Vc). The *picrate* was recrystallized twice from ethanol whereupon it showed m.p. 198–200°.

Anal. Calc'd for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 53.89; H, 5.43.

6-Ethoxy-7-methoxy- (Vd). The *base* was distilled (b.p. 125–130° at 0.07 mm.) but was not analyzed and converted immediately to the *picrate*, m.p. 185–186°.

Anal. Calc'd for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34. Found: C, 53.86; H, 5.39.

6,8-Dimethoxy- (Ve). The base (n_D^{25} 1.5488) was distilled at 0.005 mm. and a bath temperature of 110° and converted directly to the *picrate*, m.p. 155–156°.

Anal. Calc'd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.14; H, 4.92; N, 11.77.

6-Methoxy- (Vf). The *picrate* crystallized from ethanol, m.p. 167–168°.

Anal. Calc'd for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97. Found: C, 53.85; H, 4.88.

The *methiodide* was formed in benzene solution and was recrystallized from methyl ethyl ketone, m.p. 169–170°.

Anal. Calc'd for $C_{15}H_{22}INO$: C, 50.15; H, 6.18. Found: C, 50.22; H, 6.05.

6,7,8-Trimethoxy- (Vg). The *picrate* exhibited m.p. 149–150° after recrystallization from ethanol.

Anal. Calc'd for $C_{22}H_{26}N_4O_{10}$: C, 52.17; H, 5.18; N, 11.06. Found: C, 52.27; H, 5.05; N, 11.12.

1-ISOBUTYL-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINES (VI)

Equal weights of the dihydroisoquinoline V and methyl iodide were mixed in benzene solution and after standing overnight, the methiodide (if crystalline) was filtered (in which case the constants are indicated above under V) or the solvent was decanted and the insoluble, oily methiodide was washed with ether. The salt was refluxed for 2 hours in methanol solution with an equal weight of sodium borohydride, concentrated, acidified with dilute hydrochloric acid and extracted with ether (discarded). The aqueous phase was made strongly alkaline, the base was extracted with ether and after suitable washing was distilled *in vacuo;* yield, 75–85%.

5,6-Dimethoxy- (VIa). The *base* possessed b.p. 110–114° at 0.05 mm.

Anal. Calc'd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57. Found: C, 72.88; H, 9.56.

The *picrate* was recrystallized from ethanol, m.p. 147–148°.

Anal. Calc'd for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73. Found: C, 53.74; H, 5.51.

5,8-Dimethoxy- (VIb). The *base* exhibited b.p. 142–145° at 1.5 mm., n_D^{25} 1.5253.

Anal. Calc'd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.17; H, 9.37; N, 5.11.

The *methiodide* was prepared in benzene solution and was recrystallized from acetone–benzene, m.p. 138–140°.

Anal. Calc'd for $C_{17}H_{28}INO_2$: C, 50.37; H, 6.96. Found: C, 50.21; H, 7.01.

The *picrate* was recrystallized from ethanol, m.p. 118–120°.

Anal. Calc'd for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73. Found: C, 53.94; H, 5.87.

6-Methoxy-7-ethoxy- (VIc). The *base* was distilled at 0.05 mm. and a bath temperature of 120–130°; it was not analyzed but was converted into two derivatives. The *picrate* was recrystallized from ethanol, m.p. 151.5–152.5°.

Anal. Calc'd for $C_{23}H_{30}N_4O_9$: C, 54.54; H, 5.97. Found C, 54.66; H, 6.21.

The *styphnate* showed m.p. 183–184° after recrystallization from ethanol.

Anal. Calc'd for $C_{23}H_{30}N_4O_{10}$: C, 52.87; H, 5.79. Found: C, 53.05; H, 6.08.

6-Ethoxy-7-methoxy- (VId). The once-distilled base (0.07 mm. and bath temperature of 110°) was characterized as the *picrate*, m.p. 160–161.5°.

Anal. Calc'd for $C_{23}H_{30}N_4O_9$: C, 54.54; H, 5.97. Found: C, 54.74; H, 6.00.

6,8-Dimethoxy- (VIe). The *base* exhibited b.p. 162–166° at 3.5 mm., n_D^{25} 1.5262, λ_{max}^{EtOH} 279 mμ, log ε 3.33, λ_{max}^{EtOH} 252 mμ, log ε 2.96.

Anal. Calc'd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32; —OCH_3, 23.57; C—CH_3, 5.71; N—CH_3, 5.71. Found: C, 72.49; H, 9.45; N, 5.55, —OCH_3, 22.54; C—CH_3, 5.01; N—CH_3, 6.15.

The *methiodide* was formed in benzene solution and recrystallized from acetone, m.p. 194–195°.

Anal. Calc'd for $C_{17}H_{28}INO_2$: C, 50.37; H, 6.96; N, 3.46; I, 31.31. Found: C, 50.20; H, 7.17; N, 3.47; I, 31.45.

The *picrate* was recrystallized from alcohol solution, m.p. 149–151°.

Anal. Calc'd for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38. Found: C, 53.92; H, 5.63; N, 11.52.

6-Methoxy- (VIf). The *base* (b.p. 99–105° at 0.01 mm.) was not analyzed but was characterized by two derivatives. The *picrate* showed m.p. 151.5–153°.

Anal. Calc'd for $C_{21}H_{26}N_4O_8$: C, 54.54; H, 5.67. Found: C, 54.62; H, 5.68.

The *styphnate* was recrystallized from ethanol, m.p. 152.5–154°.

Anal. Calc'd for $C_{21}H_{26}N_4O_9$: C, 52.71; H, 5.48. Found: C, 53.16; H, 5.76.

6,7,8-Trimethoxy- (VIg). The *base* was distilled at 0.001 mm. and a bath temperature of 100°.

Anal. Calc'd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.67; H, 9.12; N, 4.87.

The *picrate* was recrystallized from ethanol whereupon it showed m.p. 134–135°.

Anal. Calc'd for $C_{23}H_{30}N_4O_{10}$: C, 52.87; H, 5.79. Found: C, 53.17; H, 5.78.

7,8-Dimethoxyisoquinoline methobromide (VII). The Schiff base[11] (39 g.), prepared from 2,3-dimethoxybenzaldehyde and aminoacetal, was heated on the steam-bath for 14 hours with 400 g. of polyphosphoric acid. The mixture was cooled, poured into 2.5 l. of ice-water, warmed for 30 minutes at 50°, and then filtered through Celite. The dark filtrate was made alkaline with solid potassium hydroxide, and the product was extracted with ether and purified by extracting again with acid and working up in the usual manner. The crude product was dissolved in benzene and allowed to stand overnight with an excess of methyl bromide. The bright yellow crystals (12–17%) were collected and washed with benzene. After recrystallization from ethyl acetate–methanol, the salt decomposed at 166–170° (Kofler) when heated slowly but when inserted into a preheated bath at 170°, it did not decompose until 193°.

Anal. Calc'd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.91. Found: C, 50.38; H, 5.23; N, 4.81.

No product at all was isolated when the cyclization was carried out with 72% sulfuric acid.[11,12]

1-Isobutyl-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IX). The solid methobromide VII (12.5 g.) was added to an ethereal solution of isobutylmagnesium bromide, prepared from 16.5 g. of isobutyl bromide and 3.0 g. of magnesium, and refluxed with stirring overnight. The Grignard solution was hydrolyzed with ammonium chloride, made alkaline with ammonium hydroxide, and extracted with ether. The ether layer was extracted with three 100-cc. portions of 10% hydrochloric acid and the acid solution of the 3,4-dihydroquinoline VIII was hydrogenated directly with 2.0 g. of platinum oxide catalyst at room temperature and atmospheric pressure in 1 hour. The catalyst was filtered, and the filtrate was made basic, extracted with ether, and the crude base[26] was fractionally distilled; yield, 7.0 g., b.p. 117–120° at 0.7 mm. The distillate was crystallized from dilute acetone whereupon it melted at 50–52°, λ_{max}^{EtOH} 279 mμ, log ε 3.23, λ_{min}^{EtOH} 252 mμ, log ε 2.63.

Anal. Calc'd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32; —OCH_3, 23.57; N—CH_3, 5.71; C—CH_3, 5.71. Found: C, 72.71; H, 9.59; N, 5.12; —OCH_3, 23.26; N—CH_3, 5.08; C—CH_3, 4.31.

The *methiodide* was formed in benzene solution (2 days at room temperature) and was recrystallized from hexane–acetone; m.p. 165–166°.

Anal. Calc'd for $C_{17}H_{28}INO_2$: C, 50.37; H, 6.96; N, 3.46. Found: C, 50.62; H, 7.14; N, 3.51.

The *picrate* was recrystallized from absolute ethanol, m.p. 133–135°.

Anal. Calc'd for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38. Found: C, 53.94; H, 5.82; N, 11.56.

Hofmann degradation of 1-isobutyl-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IX). A 1.3-g. sample of the methiodide of IX was added to 80 cc. of boiling 40% potassium hydroxide solution and refluxing was continued for 2.5 hours. The solution was diluted with water, extracted with ether, and the latter solution was extracted three times with 10% hydrochloric acid solution. The acid extracts were made alkaline and the product was taken up in ether, dried, and evaporated to yield 0.66 g. of the substituted styrene X.[27] This product was converted by means of methyl iodide in benzene solution to the crystalline methiodide (0.70 g.) which was subjected directly to the Hofmann reaction as described above. The liberated trimethylamine was swept into an alcoholic solution of picric acid and the picrate (0.17 g.) after recrystallization exhibited m.p. 206–210°, undepressed upon admixture with authentic trimethylamine picrate.

Ether extraction of the alkaline reaction mixture followed by washing with dilute acid, water, and evaporation led to 0.3 g. (40% over-all yield based on methiodide of IX) of the crude olefin XI. It was ozonized in 8 cc. of ethyl acetate (alcohol, aldehyde, and water-free) at −70° until a pale blue color persisted (20 minutes), water was added and the mixture was steam-distilled into 50 cc. of an ethanolic solution of 2,4-dinitrophenylhydrazine. The hydrazone mixture was extracted with benzene and freed from excess reagent by passage through a column of acid-washed alumina, the reagent remaining on the column. The mixture of hydrazones recovered from the benzene eluates then was chromatographed on a column[28] consisting of 16 g. of Bentonite (U.S.P., Fisher Scientific Co.) and 4 g. of Kieselguhr (E. H. Sargent and Co.) and the 2,4-dinitrophenylhydrazone of isobutyraldehyde (117 mg., m.p. 183–186°) was eluted with 200 cc. of benzene. Further elution with ethanol-benzene (1:9) afforded 40 mg. of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 163–166°. Identity was established in each instance by mixture melting point determination and infrared spectral comparison.

In order to isolate hemipinic acid (XII), the ozonization of XI was carried out by the inverse technique[29] by adding a standardized solution of ozone in ethyl acetate at −70° to the diene XI until a blue color persisted. Most of the solvent was evaporated, water was added, and the volatile aldehydes (see above) were removed by steam-distillation. The residual solution was made alkaline with potassium hydroxide and oxidized on the steam-bath with a 2% aqueous potassium permanganate solution until the purple color remained (*ca.* 75 cc.). The solution was treated with sodium sulfite, the manganese dioxide was filtered, and the filtrate was acidified with sulfuric acid and extracted with ether. Evaporation of the ether and sublimation of the residue at 180–190° and 0.05 mm. gave 150 mg. of crude hemipinic acid (XII) anhydride, m.p. 161–166°. For adequate characterization, it was refluxed in benzene solution with 172 mg. of *p*-bromoaniline, and the amide was collected and recrystallized from acetone-benzene to yield 160 mg. of the mono-*p*-bromoanilide of hemipinic acid, m.p. 178–180°, undepressed upon admixture with an authentic specimen.[30] The infrared spectrum (potassium bromide) exhibited the typical broad acid absorption in the 3.4 μ region as well as bands at 5.90 (carboxyl), 6.00 (amide carbonyl), and 6.50 μ (NH deformation of secondary amide).

Anal. Calc'd for $C_{16}H_{14}BrNO_5$: C, 50.55; H, 3.71. Found: C, 50.75; H, 4.02.

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(26) 1-Isobutyl-2-methyl-1,2,3,4-tetrahydroisoquinoline was prepared by the same procedure; b.p. 81–84° at 0.5 mm.

Anal. Calc'd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.76; H, 10.55; N, 7.02.

The *methiodide* crystallized from hexane–acetone as colorless needles, m.p. 165–167°.

Anal. Calc'd for $C_{15}H_{24}IN$: C, 52.20; H, 5.66; N, 4.06. Found: C, 51.83; H, 5.49; N, 3.96.

The *picrate* was recrystallized from ethanol, m.p. 120–122°.

Anal. Calc'd for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.84; H, 5.57; N, 13.20.

(27) The structure of the styrene follows from the ozonization which yielded approximately 20% of formaldehyde (isolated as the dimedone derivative). Hydrogenation of the methine X followed by Hofmann degradation and ozonization furnished *ca.* 25% of isobutyraldehyde (as the 2,4-dinitrophenylhydrazone).

(28) *Cf.* Elvidge and Whalley, *Chemistry & Industry*, 589 (1955).

(29) Bladon, Henbest, Jones, Wood, and Woods, *J. Chem. Soc.*, 4890 (1952).

(30) Prepared by oxidation of opianic acid which was kindly furnished by Dr. Max Tishler (Merck and Co., Rahway, N.J.).