Keyphrases

Catalysts, model—penicillinase simulation
Benzylpenicillin hydrolysis—catalyst structure-activity relationship
Catechol morpholinomethyl derivative—penicillin hydrolysis
Pyrogallol morpholinomethyl derivative—penicillin hydrolysis
Potentiometric titration—pKa determination
UV spectrophotometry—pKa determination

Synthesis of (±)-Norargemonine

By KUO-HSIUNG LEE and T. O. SOINE*

(±)-Norargemonine was synthesized in good yield by a multiple-step process. The procedure involved Bischler-Napieralski ring closure of *N*-4-benzyloxy-3-methoxy-phenethyl-2-(3,4-dimethoxyphenyl)acetamide, reduction of the ensuing 3,4-dihydro base to the tetrahydro form, and dehydrogenation of the latter to yield the isoquinoline which, however, had been debenzylated during dehydrogenation. Rebenzylation of the phenol, conversion to the methiodide, reduction to the corresponding *N*-methyl-1,2-dihydro base, and acid catalyzed cyclization accompanied by simultaneous debenzylation afforded (±)-norargemonine to complete the synthesis.

NORARGEMONINE WAS FIRST isolated by Soine and Gisvold (1) in 1944 from *Argemone hispida* (Gray). It was shown to be the monophenolic precursor of argemonine (I) by methylation with diazomethane (2–4) and argemonine, itself, has been shown to be (−)-*N*-methylpavine (2, 4, 5).

In a recent communication, the structure of norargemonine has been shown by Stermitz *et al.* (6) to be II by the reduction of protopapaverine methochloride with tin in hydrochloric acid according to the method of Späth and Epstein (7). An alternate reduction, not utilized but simply mentioned, would have been the catalytic method of Schöpf and Thierfelder (8). The Späth and Epstein method yielded the tetrahydro derivative [*i.e.*, (±)-codamine] together with a small amount of the objective compound (II). Since II is essentially a by-product of the above procedure and is obtained in poor yield it appeared that a more feasible synthetic route would be needed for other studies with II contemplated in these laboratories.

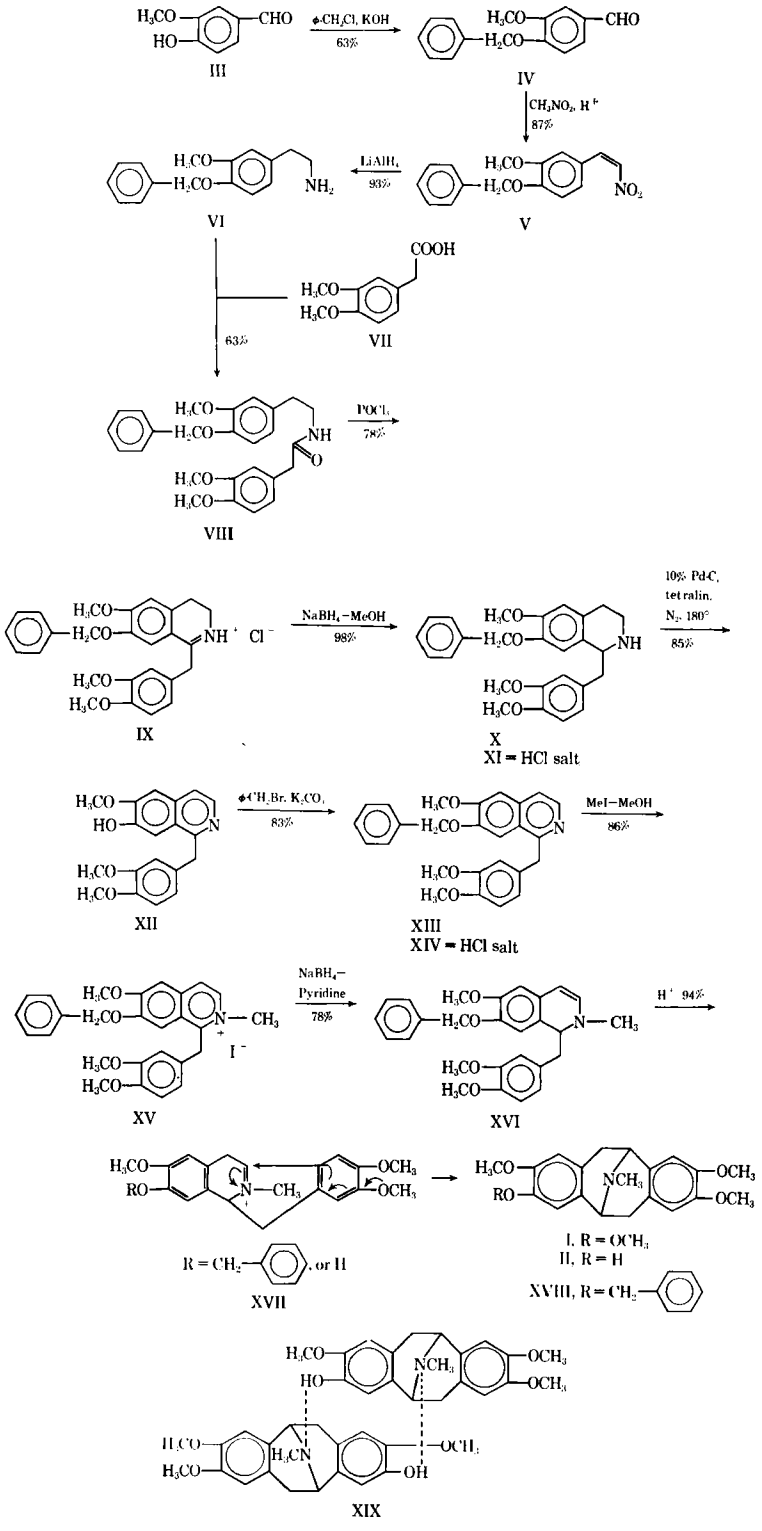
DISCUSSION

Benzyl vanillin (IV), prepared by benzylation of vanillin (III) according to Tomita *et al.* (9) was condensed with nitromethane, as described by Gairaud *et al.* (10) to furnish a good yield of 4-benzyloxy-3-methoxy-β-nitrostyrene (V). The latter was then subjected to lithium aluminum hydride reduction to give 4-benzyloxy-3-methoxyphenethylamine (VI), characterized as its formate salt. Condensation of VI and 3,4-dimethoxyphenylacetic acid (VII) was effected by application of the method reported by Shepard *et al.* (11) to yield the corresponding acid amide (VIII), *viz.*, *N*-(4-benzyloxy-3-methoxyphenethyl) - 2 - (3,4 - dimethoxyphenyl)acetamide (Scheme I).

Cyclization of VIII by the Bischler-Napieralski procedure (12) led to the expected 3,4-dihydroisoquinoline which was isolated as its hydrochloride (IX). Sodium borohydride reduction of IX furnished a quantitative yield of the corresponding 1,2,3,4-tetrahydroisoquinoline (X) which showed 3,300 cm.$^{-1}$ (ν NH) in the IR spectrum in mineral oil and was very unstable, decomposing within 24 hr. at room temperature. Characterization of this compound was carried out by preparing its stable hydrochloride salt (XI) which exhibited a group of relatively sharp bands over 2,440–2,700 cm.$^{-1}$ (ν $\overset{+}{N}H_2$) in the IR spectrum. It also showed a typical benzyltetrahydroisoquinoline UV absorption and no bathochromic shift was observed upon the addition of sodium hydroxide. The NMR (τ, in $CDCl_3$) of this compound showed signals at 6.26 (3H, s, C_3'-$OC_3\underline{H}$),[1] 6.18 (6H, s., C_4'-$OC\underline{H}_3$ and C_6-$OC\underline{H}_3$),[1] 5.20 (2H, s, C_7-$OC\underline{H}_2C_6H_5$), 3.83 (1H, s, C_8-$\underline{H}$),[1] 2.75 (5H, s, C_7-$OCH_2C_6\underline{H}_5$), and the remaining aromatic protons appeared at 3.34–3.45 (4H).

Received June 3, 1968, from the Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455
Accepted for publication July 24, 1968.
* To whom all correspondence should be addressed.

[1] These assignments are based mainly on the suggestions of Tomita *et al.* (13) together with direct comparison with the series of closely related compounds prepared during the present studies.



Scheme I

Catalytic dehydrogenation of X to the isoquinoline (XII) was readily achieved by the use of palladium-charcoal catalyst. The dehydrogenated product thus formed gave a negative ferric chloride test for phenol and failed to show hydroxy group absorption in the IR spectrum. However, the phenolic

character of this compound was indicated by its UV spectrum; *i.e.*, it gave a characteristic isoquinoline absorption which showed a bathochromic shift upon the addition of sodium hydroxide. The isoquinoline character together with the absence of the 7-benzyloxy group of XII was further indicated by its NMR (τ, in $CDCl_3$) spectrum which shows signals at 6.35 (3H, s, C_3'-OCH_3), 6.29 (3H, s, C_4'-OCH_3), 6.05 (3H, s, C_6-OCH_3), 5.62 (2H, s, C_1-CH_2), 2.64 (1H, d, C_4-H, $J_{3,4}$ = 6 c.p.s.), and 1.78 (1H, d, C_3-H, $J_{3,4}$ = 6 c.p.s.). From the above evidence, XII was considered to be identical with the compound prepared by Billek (14) by an alternate but less productive procedure. Debenzylation combined with dehydrogenation of X to yield XII in place of the expected 7-benzyloxyisoquinoline (XIII) appears to be a phenomenon thus far not reported, although the debenzylation can be readily rationalized in terms of hydrogenolysis by hydrogen transfer.

O-Benzylation of XII afforded the corresponding free base of the 7-benzyloxyisoquinoline (XIII) after liberation from its hydrochloride salt (XIV). The UV spectrum of XIII showed no bathochromic shift upon addition of sodium hydroxide and its NMR (τ, in $CDCl_3$) spectrum further indicated the presence of the methylene protons of the 7-benzyloxy group as a singlet at 4.88 τ. Conversion of XIII to the methiodide (XV) was readily achieved in good yield by conventional procedures. The NMR spectrum of XV showed a singlet at 5.02 τ (3H) ($\overset{+}{N}$—CH_3) in addition to other expected peaks. Reduction of XV to the 1,2-dihydroisoquinoline (XVI) was carried out smoothly and in excellent yield by using sodium borohydride in pyridine according to Barton *et al.* (15). XVI showed a characteristic 1,2-dihydroisoquinoline UV absorption almost identical with that of 1,2-dihydro-*N*-methyl papaverine and the singlet for protons of the *N*-methyl group in the NMR spectrum was shifted upfield from 5.02 τ in XV to 7.15 τ in XVI. Acid-catalyzed ring closure of XVI proceeds by way of the C-protonated intermediate (XVII) to the pavine (*i.e.*, argemonine) type skeleton according to Battersby *et al.* (16, 17) and was effected in almost quantitative yield. The cyclized product, m.p. 218–220°, gave every evidence of being the desired (±)-norargemonine based on its melting point and characteristic UV spectrum. The lack of a bathochromic shift on addition of sodium hydroxide and its failure to show significant hydroxyl absorption in the IR are similarly in keeping with the behavior of norargemonine from natural sources. However, because the starting material for cyclization was an *O*-benzyl derivative it seemed desirable to exclude the possibility that the product might be an *O*-benzyl norargemonine (XVIII). Thus, the compound obtained was further subjected to debenzylating conditions by refluxing it with concentrated hydrochloric acid in ethanol. No change in properties was observed under this treatment and, thus, it was concluded that debenzylation had occurred during the acidic cyclization process. This was not unexpected and is in keeping with the known lability of benzyloxy groups under these acidic hydrolytic conditions. The product, when compared with natural norargemonine, showed identical silica gel TLC behavior, UV and IR spectra and its NMR spectrum and melting point were in complete agreement with those of Stermitz *et al.* (6).

It is of interest to point out the absence or, at best, extremely weak absorption of the phenolic hydroxy group in the IR spectra of both synthetic and natural norargemonine in mineral oil. It is possible that this may be due to the existence of II in dimeric form through an intermolecular hydrogen bonding between the hydroxy and *N*-methyl group of two molecules as shown in XIX. Models certainly indicate the feasibility of such bonding. The behavior on addition of trace amounts of concentrated hydrochloric acid to the chloroform solutions of both synthetic and natural norargemonine supports this suggestion. Thus, identical IR spectra as well as a new free hydroxy absorption band were obtained and generated at $\nu_{max.}$ 3,640 cm.$^{-1}$ in both compounds, suggesting elimination of hydrogen bonding.

EXPERIMENTAL

Melting points were determined in capillary tubes in a Thomas-Hoover melting point apparatus checked for accuracy against a set of standard samples and are uncorrected. Microanalyses were determined by the Microanalytical Laboratory, School of Chemistry, University of Minnesota. UV spectra were determined on a Cary recording spectrophotometer, model 14. IR spectra were determined on a Perkin-Elmer 237 B grating infrared spectrophotometer. NMR spectra were determined on a Varian Associates A-60 instrument using tetramethylsilane (TMS) as the internal standard and s refers to singlet, d to doublet.

4-Benzyloxy-3-methoxybenzaldehyde [O-Benzy vanillin (IV)]—Prepared in 63% yield according to the method of Tomita *et al.* (9), m.p. 60.5–61.5°. Lit. (9) reported m.p. 64°.

4-Benzyloxy-3-methoxy-β-nitrostyrene (V)—This was prepared in 87% yield from IV by the method of Gairaud *et al.* (10), m.p. 118–119°. Lit. (18) reported m.p. 120–121°. IR $\nu_{max.}$ mineral oil cm.$^{-1}$: 1,510 and 1,330 (strong) (NO_2).

4-Benzyloxy-3-methoxyphenethylamine (VI)—A solution of V (30 g., 0.11 mole) in anhydrous tetrahydrofuran (240 ml.) was added dropwise to a cooled and stirred suspension of lithium aluminum hydride (15 g., 0.4 mole) in anhydrous ether (600 ml.) protected from moisture by means of a calcium chloride tube. After the addition (approximately 1 hr.), the mixture was further refluxed for 1.5 hr. The complex after cooling was decomposed by cautious successive addition of wet ether (20 ml.), water (50 ml.), 10% sodium hydroxide (10 ml.), and water (5 ml.). The resultant mixture was filtered and washed well with ether. The combined filtrates were dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 25 g. of orange-yellow oily amine (93%). Confirmation of the identity of this amine was made by preparing its formate salt which showed fine colorless scales, m.p. 142–144° [lit. (9) m.p. 146–149°], obtained by dissolving the above amine (2 drops) in a small amount of ethanol followed by adding 90% formic acid (1 drop) and then a large quantity of anhydrous ether. The free amine showed ν_{NH_2} at 3,330 cm.$^{-1}$ in its IR spectrum in liquid film.

N - (4 - Benzyloxy - 3 - methoxyphenethyl) - 2-(3,4-dimethoxyphenyl)acetamide (VIII)—A mixture of 54 g. (0.27 mole) of 3,4-dimethoxyphenylacetic acid (VII) and 70 g. (0.27 mole) of the foregoing 4-benzyloxy-3-methoxyphenethylamine (VI) was

condensed according to the method of Shepard *et al.* (11). The partially cooled mixture was poured into 300 ml. of absolute methanol. The suspension of crystals was held at 10° for 1 hr., filtered and redissolved in a mixture of absolute ethanol (800 ml.) and absolute methanol (200 ml.), decolorized with charcoal and allowed to cool. The crystals were filtered, washed with anhydrous ether to give colorless needles (74.7 g., 63%), m.p. 121–123°. A second recrystallization of this compound showed m.p. 124°. Lit. (18) reported m.p. 124°. IR $\nu_{max.}$ mineral oil cm.$^{-1}$: 3,290 (NH) and 1,630 (C=O).

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-benzyloxy - 3,4 - dihydroisoquinoline Hydrochloride (IX)—A mixture of VIII (2 g., 0.0046 mole), phosphorus oxychloride (2 ml., Mallinckrodt AR), and dry toluene (10 ml.) was heated for 2 hr. in a system protected by a calcium chloride tube with an oil bath temperature of 115°. The reaction mixture was evaporated *in vacuo* to dryness. The residue, after being washed three times with anhydrous skellysolve B, was then dissolved in absolute ethanol (10 ml.) and treated with 10% hydrochloric acid (10 ml.). Upon cooling in an ice bath, it crystallized easily to yield the imine hydrochloride salt which was filtered off, washed well with anhydrous ether, a mixture of absolute ethanol–anhydrous ether (1:50), and finally anhydrous ether again. This furnished, after drying, 1.55 g. (78%) of yellow needles, m.p. 219–220°. Lit. (18) reported m.p. 219–220°. IR $\nu_{max.}$ mineral oil cm.$^{-1}$: 2,540 (broad and strong), 1,850–1,925 (immonium band), and 1,640 (C=$\overset{+}{\text{N}}$H). The free base of this compound showed $\nu_{C=N}$ 1,653 cm.$^{-1}$ in liquid film.

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-benzyloxy - 1,2,3,4 - tetrahydroisoquinoline (X)—To a solution of IX (1 g.) in methanol (100 ml.) and water (5 ml.) was added, portionwise, sodium borohydride (1 g.) at room temperature. The mixture was allowed to stand for 10 min. and further refluxed on a steam bath for 1 hr. Removal of the solvent gave a residue which was admixed with water and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and distilled to give a pale yellow glassy residue (900 mg., 98%) after drying in a desiccator overnight. Characterization of this base was effected by preparing its hydrochloride salt derivative using dry ethereal hydrogen chloride. The hydrochloride (XI) formed as colorless needles and had m.p. 220.5–222°, after two recrystallizations from methanol–ether.

Anal.—Calcd. for $C_{26}H_{30}ClNO_4$: C, 68.48; H, 6.63; N, 3.07. Found: C, 68.40; H, 6.82; N, 3.01. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 235 (4.23, shoulder), 282 (3.80); $\lambda_{min.}^{EtOH}$ mμ (log ε): 254(2.97).

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-hydroxyisoquinoline (XII)—The tetrahydro base (X) (320 mg.) obtained from the above procedure, without delay, was dissolved in tetralin (5 ml., Mallinckrodt OR) and combined with 10% palladium on charcoal (50 mg.). The air remaining in the reaction flask was first displaced by a current of dry nitrogen gas for 5 min., and the mixture was heated under dry nitrogen gas at 180° (oil bath temperature) for 50 min. Examination of the mixture by TLC (alumina with chloroform and visualized with iodine vapor) indicated that the slower moving tetrahydroisoquinoline spot had disappeared completely in favor of a much faster moving isoquinoline spot. The cooled mixture was diluted with absolute methanol and filtered to remove the catalyst and the filtrate, after removal of the methanol *in vacuo*, was treated with anhydrous ether (*ca.* 20 ml.). The resulting white crystals were filtered and washed well with anhydrous ether to yield 190 mg. (77%) of the aromatized isoquinoline, m.p. 164.5–166.5°. Lit. (14) reported m.p. 165–167°. The mother liquor was further digested with 10% hydrochloric acid and washed with ether several times. The acidic solution was rendered alkaline with 10% ammonium hydroxide and extracted with chloroform until the chloroform layer gave a negative test to Mayer's reagent. The extracts were then washed with water, dried over anhydrous potassium carbonate, and evaporated under reduced pressure to furnish a brown viscous oil which crystallized on rubbing with a small amount of absolute ethanol. Recrystallization from absolute ethanol afforded colorless prisms (20 mg.), m.p. 164–165°. Total yield: 85%. IR: absence of the secondary amine absorption in mineral oil. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 240 (4.43), 273 (3.46, shoulder), 281 (3.46), 321 (3.29, shoulder) and 332 (3.35), and upon the addition of sodium hydroxide, $\lambda_{max.}^{EtOH}$ mμ (log ε): 229 (4.02, shoulder), 259 (4.28), 282 (3.59), and 288 (3.59, shoulder).

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-benzyloxyisoquinoline (XIII)[2]—A stirred mixture of XII (100 mg., 0.3 mmole), anhydrous potassium carbonate (110 mg., 0.78 mmole, Baker AR granular), benzyl bromide (164 mg., 0.9 mmole), and dry methanol (4 ml.) was refluxed for 5.5 hr. The solvent was evaporated and the residue dissolved in water and extracted with ether. The extracts, after washing with 1% sodium hydroxide and water, were then extracted with 10% hydrochloric acid several times. The acidic solution was made alkaline with 20% ammonium hydroxide in the cold, and extracted with ether. The extract, after being washed with water, dried over anhydrous potassium carbonate, and evaporated *in vacuo*, gave a greenish oily substance (105 mg., 83%). This was dissolved in a small amount of absolute ethanol and treated with dry ethereal hydrogen chloride. The pale yellow precipitate was collected by filtration and recrystallized from chloroform–ethanol to yield the hydrochloride salt (XIV) as a white solid, m.p. 232–233.5°.

Anal.—Calcd. for $C_{26}H_{26}ClNO_4$: C, 69.09; H, 5.79; N, 3.09. Found: C, 68.58; H, 5.88; N, 2.96. IR $\nu_{max.}$ mineral oil cm.$^{-1}$: 2,440 (broad and strong), 1,925–1,975 (immonium band), and 1,635 (C=$\overset{+}{\text{N}}$H).

A suspension of 180 mg. of XIV in water was rendered alkaline with 10% ammonium hydroxide and extracted with ether until the ethereal extract gave a negative test to Mayer's reagent. The extract was washed with water, dried over anhydrous potassium carbonate, and evaporated to yield the free base as yellow prisms, m.p. 129–131°. Recrystallization from absolute ethanol–anhydrous ether gave white prisms with m.p. 131–132° (XIII).

Anal.—Calcd. for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 74.99; H, 6.26; N, 3.15. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 240 (4.65), 270 (3.69, shoulder), 279 (3.69), 314 (3.39), and 328 (3.49). NMR (τ, in $CDCl_3$): 6.28 (3H, s, $C_{3'}$-OC$\underline{H}_3$), 6.22

[2] An alternate synthesis for this compound has recently been published by Brochmann-Hanssen, E., and Hirai, K., *J. Pharm. Sci.*, **57**, 940(1968).

(3H, s, C_4'-OC$\underline{H}_3$), 6.05 (3H, s, C_6-OC$\underline{H}_3$), 5.62 (2H, s, C_1-C$\underline{H}_2$), and 4.88 (2H, s, C_7-OC$\underline{H}_2C_6H_5$).

1 - (3',4' - Dimethoxybenzyl) - 2 - methyl - 6-methoxy-7-benzyloxy-isoquinoline Iodide (XV)—To a solution of XIII (105 mg.) in absolute methanol (3 ml.) was added methyl iodide (1 ml.) and the mixture, after heating under reflux on a steam bath for 4 hr., was further treated with methyl iodide (1 ml.) and refluxed for an additional 4.5 hr. The mixture was allowed to stand in the refrigerator overnight, following which the solvent was removed by distillation to leave a yellowish brown glassy substance (148 mg.) which crystallized on rubbing with absolute ethanol and was collected by filtration. The residue was washed well with absolute ethanol to give 120 mg. (86%) of pale yellow solid, m.p. 202–204° (dec.) which upon recrystallization from absolute ethanol showed m.p. 203–205°.

Anal.—Calcd. for $C_{27}H_{28}INO_4$: C, 58.11; H, 5.02; N, 2.51. Found: C, 57.97; H, 5.26; N, 2.43. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 222 (4.67), 2.59 (4.83), 286 (3.92, shoulder), and 3.18 (4.06). NMR[3] (τ, in $CDCl_3$): 6.22 (6H, s), 5.89 (3H, s) (3 OC$\underline{H}_3$), 5.54 (2H, s, C_1-C$\underline{H}_2$), 4.72 (2H, s, 7-OC$\underline{H}_2C_6H_5$), and 5.02 (3H, s, $\overset{+}{N}$-C$\underline{H}_3$).

1 - (3',4' - Dimethoxybenzyl) - 2 - methyl - 6-methoxy-7-benzyloxy-1,2-dihydroisoquinoline (XVI)—The foregoing methiodide (XV) (500 mg.) was reduced with sodium borohydride-pyridine in exactly the same manner as described by Barton (15) for 1,2-dihydro-*N*-methyl papaverine from papaverine methiodide. A yellowish semicrystalline substance separated on addition of a small amount of anhydrous ether, m.p. *ca.* 120° (300 mg., 78%). Two recrystallizations from chloroform–absolute ethanol afforded fine colorless tufts, m.p. 120–122°.

Anal.[4]—Calcd. for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Calcd. for $C_{27}H_{29}NO_4 \cdot 1/4\ H_2O$: C, 74.37; H, 6.70; N, 3.21. Found: C, 74.39; H, 7.05; N, 3.22. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 256 (3.81, shoulder), 283 (3.33), and 335 (3.67). NMR (τ, in $CDCl_3$): 6.29 (3H, s, C_3'-OC$\underline{H}_3$), 6.18 (6H, s, C_4'-OC$\underline{H}_3$ and C_6-OC$\underline{H}_3$), and 7.15 (3H, s, N-C$\underline{H}_3$).

Acid-Catalyzed Ring Closure of (XVI) to (±)-Norargemonine (II)—A solution of XVI (320 mg.) in a mixture of 85.6% phosphoric acid (1 ml.) and 90.8% formic acid (5 ml.) was heated at 100–105° for 2 hr. until the UV spectrum showed no further changes. The mixture was then left overnight at room temperature, diluted with water (10 ml.), and extracted three times with ether. The aqueous solution was made alkaline with cold 10% sodium hydroxide and extracted with chloroform until the chloroform extracts gave a negative test with Mayer's reagent. The combined chloroformic extracts were washed with water, filtered, and dried over anhydrous potassium carbonate. The dried extract was evaporated under reduced pressure to give a greenish brown residue (285 mg.) which crystallized on rubbing with anhydrous ether, m.p. 218–219° (sintered at 214°) (240 mg., 94%). Recrystallization from absolute ethanol provided fine white crystals, m.p. 218–219.5°. UV $\lambda_{max.}^{EtOH}$ mμ (log ε): 226 (4.18, shoulder), and a well-defined triplet at 283 (3.94, shoulder), 287 (3.98) and 293 (3.94, shoulder); $\lambda_{min.}^{EtOH}$ mμ (log ε): 254 (3.31), and upon addition of sodium hydroxide, $\lambda_{max.}^{EtOH}$ mμ: 283 (shoulder), 287, 293 (shoulder), and 310 (shoulder); $\lambda_{min.}^{EtOH}$ 262 mμ. Attempted debenzylation of this compound was carried out as follows: A solution of the foregoing product (141 mg.) in ethanol (5 ml.) and concentrated hydrochloric acid (8 ml.) was heated under reflux on a steam bath for 2 hr., and the solvent was evaporated *in vacuo* to leave a residue which was dissolved in water and extracted with ether to remove benzyl chloride. The aqueous solution was basified with 10% aqueous sodium hydroxide and extracted with ether. To the above ether-extracted alkaline solution was added an excess of crystalline ammonium chloride, and the ammoniacal solution was extracted three times with chloroform. The chloroformic extract was washed with water, dried over anhydrous potassium carbonate, and evaporated *in vacuo* to give a greenish brown syrup (96 mg.) which crystallized when rubbed with a small amount of absolute ethanol, m.p. 218–220° (sintered at 210°). One recrystallization from absolute ethanol yielded fine colorless needles, m.p. 218–220°. The UV and IR spectra, together with the TLC behavior of this compound, were superimposable on those of the above starting material (m.p. 218–219.5°) and natural norargemonine (II).

REFERENCES

(1) Soine, T. O., and Gisvold, O., *J. Am. Pharm. Assoc., Sci. Ed.*, **33**, 185(1944).
(2) Martell, M. J., Jr., Soine, T. O., and Kier, L. B., *J. Am. Chem. Soc.*, **85**, 1022(1963).
(3) Schermerhorn, J. W., and Soine, T. O., *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 19(1951).
(4) Martell, M. J., Jr., Soine, T. O., and Kier, L. B., *J. Pharm. Sci.*, **56**, 973(1967).
(5) Stermitz, F. R., Lwo, S.-Y., and Kallos, G., *J. Am. Chem. Soc.*, **85**, 1551(1963).
(6) Stermitz, F. R., and Seiber, J. N., *Tetrahedron Letters*, **11**, 1177(1966).
(7) Späth, E., and Epstein, H., *Chem. Ber.*, **61**, 334(1928), and references contained therein.
(8) Schöpf, C., and Thierfelder, K., *Ann.*, **537**, 143 (1939).
(9) Tomita, M., and Watanabe, H., *J. Pharm. Soc. Japan*, **58**, 783(1938).
(10) Gairaud, C. B., and Lappin, G. R., *J. Org. Chem.*, **18**, 1(1953), and references cited therein.
(11) Shepard, E. R., and Noth, J. F., *J. Am. Chem. Soc.*, **72**, 4364(1950).
(12) Whaley, W. M., and Govindachari, T. R., in "Organic Reactions," Vol. 6, Wiley, New York, N. Y., 1951, p. 74.
(13) Tomita, M., Shingu, T., Fujitani, K., and Furugawa, H., *Chem. Pharm. Bull.*, **13**, 921(1965).
(14) Billek, G., *Monatsch. Chem.*, **87**, 106(1956).
(15) Barton, D. H. R., Hesse, R. H., and Kirby, G. W., *J. Chem. Soc.*, **1965**, 6379.
(16) Battersby, A. R., and Binks, R., *ibid.*, **1955**, 2888.
(17) Barker, A. C., and Battersby, A. R., *ibid.*, **1967**, 1317.
(18) Shamma, M., and Slusarchyk, W. A., *Tetrahedron*, **23**, 2563(1967).

Keyphrases

(±)-Norargemonine—synthesis
TLC—identity
IR spectrophotometry—structure
NMR spectroscopy—structure
UV spectrophotometry—structure

[3] The spectrum was taken without delay after XV was dissolved in $CDCl_3$ because of slow decomposition at room temperature.

[4] This analysis was the best obtainable in spite of several attempts. Its NMR, UV, and IR characteristics, however, are in accord with the suggested structure.