of 50 ml. of ether. The extracts and original ether layer were combined, washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent yielded 246 mg. (75%) of white plates. After two recrystallizations from methanol a sample was obtained which melted at 141–142°.

Anal. Calcd. for $C_9H_{12}S_3$: C, 49.95; H, 5.59; S, 44.45. Found: C, 50.02; H, 5.65; S, 44.36.

The infrared spectrum of this compound contains bands at 3.33 μ (C—H of a strained ring), 7.05 μ (C—H of a strained ring), 9.58 μ and 9.76 μ (cyclopropane ring absorption region). An ultraviolet spectrum taken in dioxane showed λ_{max} 231 mμ, log ϵ 2.94.

The 60-Mc. n.m.r. spectrum of I shows only one signal from the twelve protons on the cyclopropane rings at −71 c.p.s. relative to tetramethylsilane as the internal standard.[5]

An Improved Synthesis of Noraporphines[1]

JERRY A. WEISBACH AND BRYCE DOUGLAS

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania

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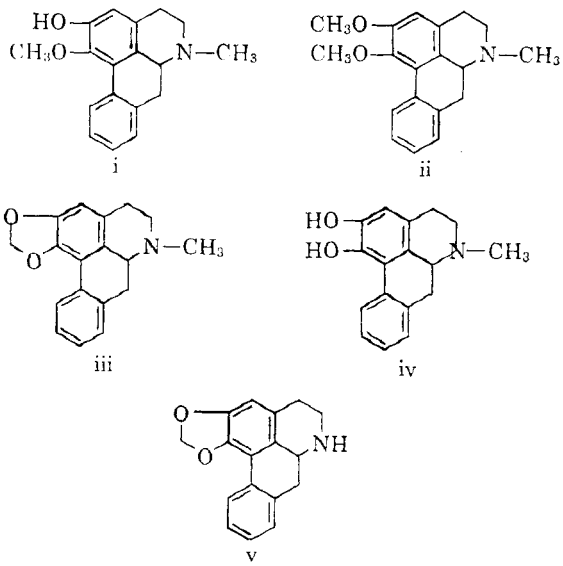
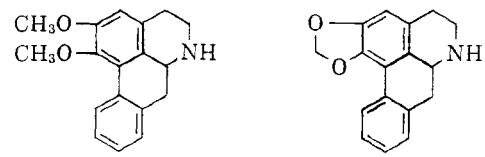
A great variety of aporphines and noraporphines have been isolated from natural sources.[3,4] The structures of a number of them were ascertained by degradation and verified by synthesis. However, the structures of subsequently isolated alkaloids have been determined more readily by using simple unambiguous conversions to one of the known compounds. In the noraporphine series this has been the usual procedure.[6–9] Thus there are only two of the natural noraporphines, anonaine[10,11] and laurotetanine,[12] which have been synthesized. A third, actinodaphne, was obtained as its O-methyl ether.[13]



During the course of a coordinated natural products isolation and pharmacological testing program, it became necessary to obtain a supply of nornuciferine I. As this molecule has not yet been found in nature,[13a] and since supplies of naturally occurring anonaine II were not available for transformation, a total synthesis was mandatory.



Application of the general procedure used by Barger and Weitnauer[10] in the preparation of anonaine II, modified at the reduction stage by the introduction of a current procedure, led to the preparation of a small amount of nornuciferine I, *via* III→IV→I. The unsatisfactory yield (3.3%) in the Pschorr cyclization is in contrast to the 22% of anonaine reported by the earlier workers. While the Pschorr reaction has never given good yields in the aporphine series,[14] it is not unreasonable to expect a yield of 10–20% in this series, if the final product is unsubstituted at position 4. Since this sequence did not seem promising as a source of the required amounts of nornuciferine, it was abandoned in favor of the following approach.

Reductive removal of masking O-benzyl groups is a well established procedure in aporphine chemistry since its introduction by Hey and Lobo.[13] However, a careful investigation of the aporphine literature revealed no precedent for the corresponding use and removal of N-benzyl groupings in this series. Since its application in this area gave promise of somewhat indirect, but more facile syntheses of all noraporphines as well as the needed supply of I, it was immediately applied. By utilizing the common intermediate III, and follow-

(1) A recent publication, M. Tomita, Y. Watanabe, and H. Furukawa [*J. Pharm. Soc. Japan*, **81**, 1644 (1961)] has designated *i* as nornuciferine. The use of the prefix *nor* to indicate an *O*-desmethyl relative of nuciferine[2] *ii* is contary to common usage in this family of compounds.[3,4] The only precedent for this nomenclature has been the naming[6] of the hydrolysis product of roemerine *iii* as norroemerine *iv*. This is a name which is more appropriately used to designate anonaine *v*. In this report we will use the prefix *nor* to indicate a des-N-methyl relationship and suggest that this policy be adhered to by future authors.

(2) H. R. Arthur and H. T. Cheung, *J. Chem. Soc.*, 2306 (1959).

(3) R. H. F. Manske, "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, ed., Academic Press, New York, 1954, p. 119.

(4) H. G. Boit, "Ergebnisse der Alkaloid Chemie bis 1960," Akademie Verlag, Berlin, 1961, p. 261.

(5) S. Yunusov, R. A. Konovalova, and A. P. Orekhov, *J. Gen. Chem. USSR.* **9**, 1868 (1939); *Bull. soc. chim. France.* 70 (1940).

(6) F. Faltis, G. Wagner, and E. Adler, *Ber.*, **77**, 686 (1944).

(7) J. Schmutz, *Helv. Chim. Acta* **42**, 335 (1959).

(8) T. Nakasato and S. Nomura, *Yakugaku Zasshi*, **79**, 1267 (1959).

(9) A. Rüegger, *Helv. Chim. Acta*, **42**, 754 (1959).

(10) G. Barger and G. Weitnauer, *ibid.*, **22**, 1036 (1939).

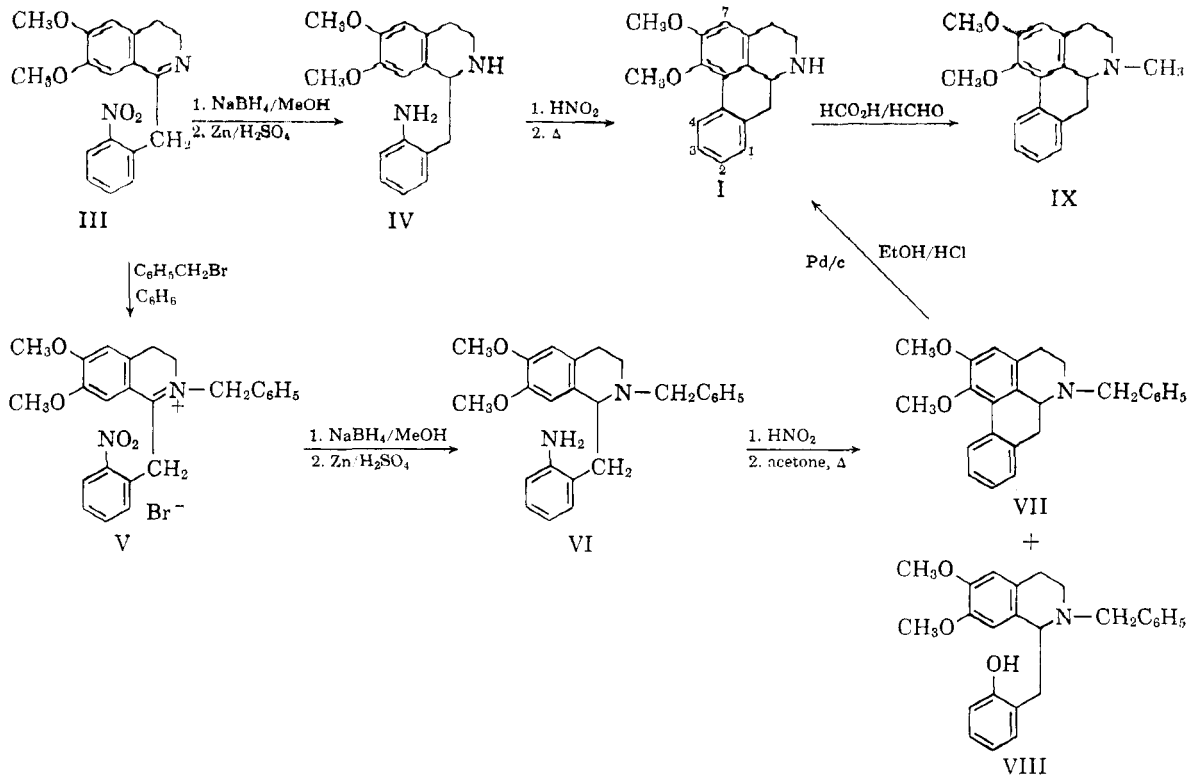
(11) L. Marion, L. Lemay, and R. Ayotte, *Can. J. Research*, **28B**, 21 (1950)

(12) I. Kikkawa. *J. Pharm. Soc. Japan*, **79**, 425 (1959).

(13) D. H. Hey and L. C. Lobo, *J. Chem. Soc.* 2246 (1954).

(13a) NOTE ADDED IN PROOF: The isolation of *l*-nornuciferine from the American Lotus, *Nelumbo lutea*, has recently been achieved. We wish to thank Professor M. Kupchan for informing us of this finding prior to publication.

(14) D. F. DeTar, *Org. Reactions*, 409 (1957).



ing the sequence III→V→VI prior to Pschorr cyclization, a mixture of N-benzylnornuciferine (VII) and the usual phenolic by-product VIII were obtained. These were conveniently separated by chromatography to give a 20.0% yield of the desired protected aporphine VII. Catalytic debenzylation of VII over 10% palladium on carbon in 30:1 ethanol–hydrochloric acid produced an 88% yield of crystalline nornuciferine hydrochloride. This compound was shown to be identical with the material obtained from the earlier direct synthesis by the identity of their melting points, the lack of depression of melting point upon mixing, and the superimposability of their infrared spectra. Methylation with formaldehyde–formic acid[15] produced *dl*-nuciferine (IX), identical in all respects with material prepared by the procedure of Gulland and Haworth.[16]

The use of the N-benzyl masking group in concert with the already common application of the O-benzyl grouping should greatly facilitate preparation of complex noraporphines and encourage total synthesis in this presently neglected area.

Experimental

Melting points were taken in unsealed capillaries and are uncorrected. Microanalyses were performed by Mrs. D. Rolston and her associates at Smith Kline & French Laboratories.

1-(2′-Aminobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (IV).—Sodium borohydride (42.0 g., 1.1 moles) was added portionwise to a stirred solution of 1-(2′-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (III)[16,17] (45 g., 0.13 mole) in methanol (450 ml.), and stirring was continued for 1 hr. Thereafter, zinc dust (90.0 g.) and sulfuric acid (10%, 1 l.) were added. After further stirring and heating for 10 min., the mixture was filtered. The filtrate was neutralized with aqueous ammonia and extracted with ether. After drying over sodium sulfate, the ethereal solution was concentrated *in vacuo* to give a gummy, brown residue. Treatment with methanol-ethereal hydrogen chloride yielded a tan, crystalline solid (37.2 g., 75.5%). Recrystallization from ethanol produced an analytical sample, m.p. 256–257° dec.

Anal. Calcd. for $C_{18}H_{24}Cl_2N_2O_2$: C, 58.22; H, 6.52; N, 7.54. Found: C, 58.28; H, 6.42; N, 7.52.

5,6-Dimethoxynoraporphine Hydrochloride (I).—To a stirred solution of 1-(2′-aminobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (IV) (50.0 g., 0.135 mole) in sulfuric acid (2 *N*, 1500 ml.) at 0° there was added dropwise a solution of sodium nitrite (10.2 g., 0.148 mole) in water (300 ml.). The stirred mixture was kept at 0° for 1 hr. Sulfamic acid (1.0 g., 0.01 mole) was added and the mixture stirred and vigorously heated on the steam bath for 30 min. Zinc dust (50.0 g.) and hydrochloric acid (60 ml.) were added and heating was continued for an additional 30 min. The hot mixture was filtered and the cooled filtrate made alkaline with aqueous ammonia and extracted with ether. The organic extract was dried over sodium sulfate and concentrated *in vacuo* to yield a viscous gummy material. Treatment with hydrochloric acid (6 *N*) yielded a white solid (1.4 g., 3.3%). Recrystallization from ethanol produced an analytical sample as white needles, m.p. 261–262° dec. λ_{max}^{EtOH} 231 mμ (log ε 4.35), 270 mμ (log ε 4.25), 310 mμ (log ε 3.36).

Anal. Calcd. for $C_{18}H_{20}ClNO_2$: C, 68.02; H, 6.34; N, 4.41. Found: C, 67.71; H, 6.60; N, 4.04.

1-(2′-Nitrobenzyl)-2-benzyl-6,7-dimethoxy-3,4-dihydro-

(15) R. N. Icke and B. B. Wisegarver, "Organic Syntheses," Vol. III, John Wiley & Sons, New York, p. 723.

(16) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

(17) We thank Dr. H. Reiff of our laboratories for a generous supply of this compound.

isoquinolinium Bromide (V).—A mixture of 1-(2′-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline, III, (110 g., 0.337 mole), benzyl bromide (216 g., 1.25 moles), and benzene (400 ml.) was boiled at reflux for 4 hr. and kept at 25° for 12 hr. The precipitated solid was filtered and triturated with warm benzene to yield a yellow, crystalline solid (138 g., 82.5%). Recrystallization from ethanol produced an analytical sample as fine, yellow needles, m.p. 209–209.5° dec.

Anal. Calcd. for $C_{25}H_{25}BrN_2O_4$: C, 60.37; H, 5.07; N, 5.63. Found: C, 60.63; H, 5.12; N, 6.00.

1-(2′-Aminobenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI).—Sodium borohydride (31.5 g., 0.83 mole) was added in portions to a stirred solution of 1-(2′-nitrobenzyl)-2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide (V) (125 g., 0.25 mole) in methanol (1250 ml.). The mixture was stirred for 30 min., zinc dust (500 g.) was added, and sulfuric acid (2 *M*, 1750 ml.) added carefully. The mixture was stirred for an additional 30 min. The warm solution was filtered, made alkaline with aqueous ammonia, and extracted with ether. The extract was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* produced a yellow, gummy material, which on trituration with absolute alcohol yielded a white solid, m.p. 113–115° (74.3 g., 77%). Recrystallization from ethanol yielded an analytical sample, m.p. 117–119°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.08; H, 7.38; N, 7.34.

N-Benzyl-5,6-dimethoxy-noraporphine (N-Benzylnornuciferine), (VII).—To a cold (*ca.* 10°), stirred solution of 1-(2′-aminobenzyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI) (55.5 g., 0.143 mole) in acetic acid (575 ml.) and sulfuric acid (40 ml.) there was added dropwise a solution of sodium nitrite (11.60 g., 0.168 mole) in water (107 ml.). Upon completion of addition, the mixture was stirred at 10° for 20 min. Sulfamic acid (1.0 g., 0.013 mole), cuprous chloride, (0.5 g., 0.005 mole), and acetone (1200 ml.) were added and the mixture was heated at reflux for 30 min. The solution was concentrated *in vacuo* to remove the acetone and the aqueous concentrate made alkaline with dilute ammonia and extracted exhaustively with ether. The combined ethereal extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* produced a viscous oil which was chromatographed over an alumina column (Woelm No. 1 neutral, 12 in. by 4.75 in. diameter) prepared in ether. The total ether eluate yielded a white solid (10.6 g., 20%). Recrystallization from methanol produced an analytical sample, m.p. 98–99.5°. λ_{max}^{EtOH}: 230 mμ (log ε 4.31), 270 mμ (log ε 4.20), 312 mμ (log ε 3.19).

Anal. Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.72; H, 6.95; N, 3.70.

Elution of the column with ethanol and concentration of the eluate yielded a white solid, m.p. 126–128°, (22.6 g., 40.5%). Recrystalliztion from ethanol produced an analytical sample as white plates, m.p. 127–128°. λ_{max}^{EtOH}: 282 mμ (log ε 3.82).

Anal. Calcd. for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 77.20; H, 7.02; N, 3.58.

5,6-Dimethoxynoraporphine Hydrochloride (I).—A mixture of *N*-benzyl-5,6-dimethoxynoraporphine (0.503 g., 0.0018 mole), 95% ethanol (300 ml.), hydrochloric acid (10 ml.), and 10% palladium on carbon (3.0 g.) was shaken with hydrogen at *ca.* 3 atm. for 16 hr. The mixture was filtered and concentrated *in vacuo* (*ca.* 50 ml.). White, felty needles separated and were filtered with suction. Dilution of the filtrate with ether yielded additional amounts of the same product, (total, 3.62 g., 88.4%). Recrystallization from methanol gave thin, white needles, m.p. 262° dec. This compound was shown to be identical with a sample of 5,6-dimethoxynoraporphine hydrochloride prepared by a procedure analogous to that of Barger and Weitnauer[10] by their melting points, the lack of depression of melting point on mixing, and the superimposability of their infrared spectra.

Methylation with formaldehyde–formic acid[15] yielded 5,6-dimethoxyaporphine, identical in all respects with a sample prepared by the procedure of Gulland and Haworth.[16]

Acknowledgment.—The authors express their thanks to Drs. I. J. Pachter and R. F. Raffauf for helpful discussions, Mr. C. Kormendy for literature work, and to Mr. F. Farina for technical assistance.