THE SYNTHESIS OF (±)-THALPHENINE, THALIGLUCINE AND THALIGLUCINONE[1,2]

Maurice Shamma and Der-Yan Hwang

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

Photolysis of the phenolic tetrahydrobenzylisoquinoline 11 yielded de-N-methylthalphenine (14). Quaternization with methyl iodide then afforded thalphenine iodide (rac. 1) which upon Hoffman elimination supplied thaliglucine (2).

Although more than 85 aporphine alkaloids are presently known,[3] (+)-thalphenine (1) is the only aporphine to possess a methylenoxy bridge.[4] We herewith wish to report the total synthesis of this unusual alkaloid.

At the initiation of the synthetic work, it was reasoned that de-N-methylthalphenine (14), the free base corresponding to thalphenine, could be obtained in one step from the phenolic tetrahydrobenzylisoquinoline 11. Photolysis of 11 in basic solution would generate the aporphine 12 which would very readily eliminate the elements of methanol to form the unstable quinone methide 13. A simple electrocyclic process would then provide the needed de-N-methylthalphenine (14).

Treatment of methyl 2-bromo-4,5-methylenedioxyphenylacetate[5] (4) with chloromethyl methyl ether and zinc chloride in chloroform afforded the ester 5, $C_{11}H_{10}O_4BrCl$, mp 111-111.5° (ethyl acetate), in 68% yield. Refluxing of 5 with sodium hydroxide in methanol gave in 67% yield the acid 6, $C_{11}H_{11}O_5Br$, mp 161-162°

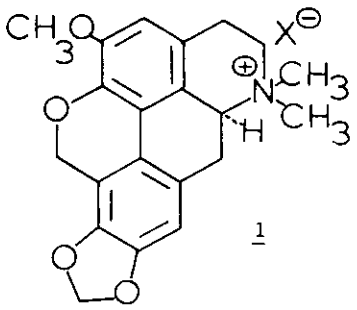
(ethyl acetate). The acid chloride of 6 was then utilized in the N-acylation of 3-methoxy-4-benzyloxy-β-phenylethylamine to provide the amide 7, $C_{27}H_{28}O_6NBr$, mp 163-164° (ethyl acetate), in 65% yield.

The colorless imine hydrochloride salt 8, $C_{27}H_{27}O_5NBrCl$, mp 219-221° (methanol), obtained in 81% yield through Bischler-Napieralski cyclization of 7 using PCl_5 in chloroform at room temperature, was converted to the free base and then treated with methyl iodide to supply (78%) the yellow immonium salt 9, $C_{28}H_{29}O_5NBrI$, mp 213-214° (methanol). Reduction of 9 with sodium borohydride in ethanol led in 75% yield to a colorless oil which was characterized as 1-(3',4'-methylenedioxy-5'-methoxymethyl-6'-bromobenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (10), $C_{28}H_{30}O_5NBr$; methiodide salt, $C_{29}H_{33}O_5NBrI$, mp 199-201° (methanol).

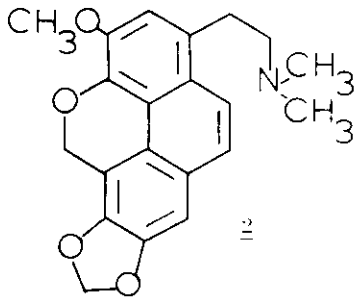
Selective hydrolysis of 10 using conc HCl in ethanol at room temperature generated the required phenol 11, 1-(3',4'-methylenedioxy-5'-methoxymethyl-6'-bromobenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline, $C_{21}H_{24}O_5NBr$, as an oil in 85% yield; nmr ($CDCl_3$) δ2.41 (3H, s, N-CH_3), δ2.6 3.4 (7H, complex, aliphatic H), δ3.41 (3H, s, CH_2OCH_3), δ3.84 (3H, s, $ArOCH_3$) δ4.60 (2H, s, CH_3OCH_2), δ5.96 (2H, s, OCH_2O), δ6.45 (1H, s, ArH), δ6.60 (1H, s, ArH), δ6.68 (1H, s, ArH).

Photolysis of a degassed solution of 11 in aq methanolic sodium hydroxide at 0° using a low pressure mercury lamp provided a 30% yield of colorless crystals of de-N-methylthalphenine (14), $C_{20}H_{19}O_4N$, mp 180-181° (methanol); nmr ($CDCl_3$) δ2.50 (3H, s, NCH_3), δ3.85 (3H, s, OCH_3), δ4.72-5.53 (2H, q, $ArOCH_2Ar$), δ5.91 (2H, d, OCH_2O), δ6.50 (1H, s, ArH), δ6.63 (1H, s, ArH); λ_{max}^{EtOH} 221, 233sh, 278sh, 286, 312 and 323sh nm (log ε 4.49, 4.34, 3.86, 3.98, 4.07 and 4.05).[6]

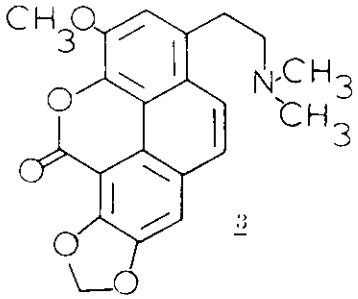
Quaternization of 14 with methyl iodide led to (±)-thalphenine iodide (rac. 1), mp 193-194° (methanol), identical in terms of tlc R_f values and uv and nmr spectra



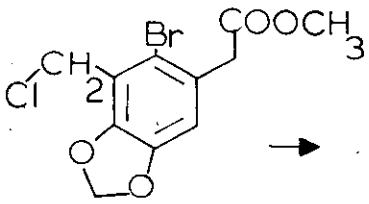
1



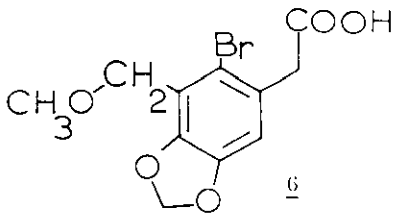
2



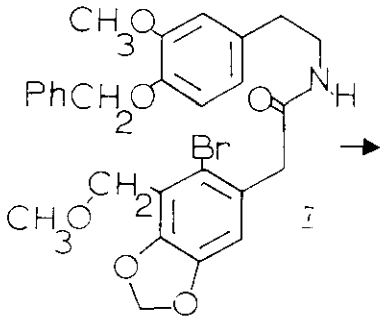
3



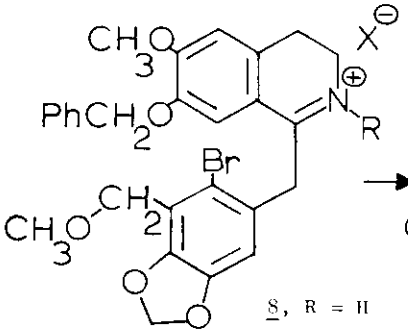
5



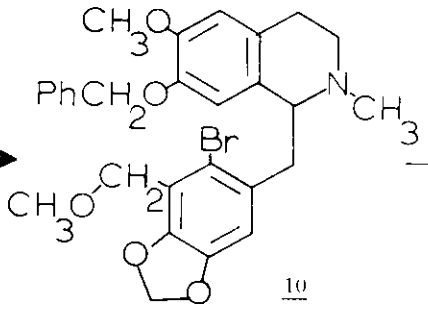
6



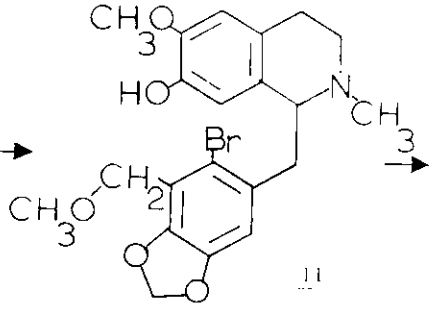
7



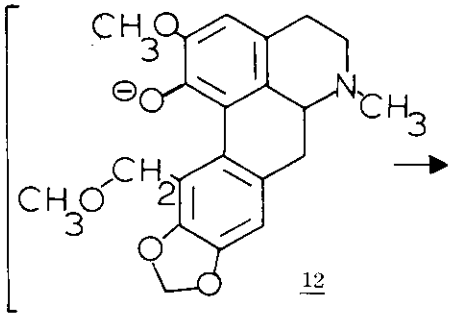
8, R = H
9, R = CH_3



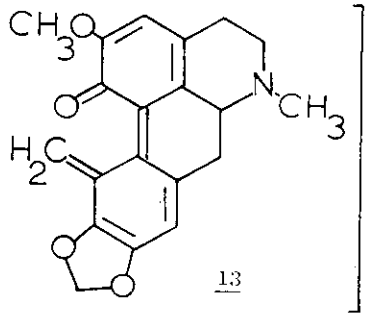
10



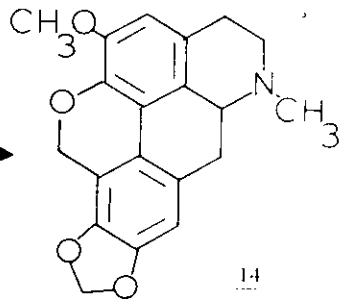
11



12



13



14

with a sample of the natural product. Base catalyzed Hoffman elimination then afforded thaliglucine (2) identical in all respects with the natural product. Since dichromate oxidation of thaliglucine is known to give the alkaloid thaliglucinone (3),[7] the present sequence represents also a synthesis of the latter base.

REFERENCES

1 This investigation was supported by Public Health Service Research Grant No. CA-11450 from the National Cancer Institute.

2 Acceptable elemental analyses and high resolution mass spectra were obtained for the new compounds.

3 For a recent review on the aporphine alkaloids see M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, and Verlag Chemie, Weinheim, 1972, p. 194.

4 M. Shamma, J.L. Moniot, S.Y. Yao and J.A. Stanko, Chem. Commun., 1972, 408.

5 T. Kametani, O. Umezawa, Y. Satoh, K. Ogasawara, S. Shibuya, M. Ishiguro and D. Mizuno, J. Pharm. Soc. Japan, 1963, 83, 838.

6 De-N-methylthalphenine (14) was most probably formed via the intermediacy of the quinone methide 13. However the possibility of an intramolecular S_N2 attack by the phenoxide anion in species 12, with methoxide anion as the leaving group, cannot be excluded.

7 N.M. Mollov, L.N. Thuan and P.P. Panov, C.R. Acad. Bulg. Sci., 1971, 24, 1047.

Received, 19th June, 1973