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

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Abstract—Photolysis of the phenolic tetrahydrobenzylisoquinoline **11** in basic solution yielded (±)-de-N-methylthalphenine (**14**). Quaternization with methyl iodide then afforded thalphenine iodide (*rac.* **1**) which upon Hofmann elimination supplied thaliglucine (**2**). Thaliglucinone (**3**) is obtained by oxidation of thaliglucine (**2**).

Of the more than one hundred aporphine alkaloids presently known, (+)-thalphenine (**1**), found in *Thalictrum polygamum* Muhl. (Ranunculaceae), is the only one to possess a methylenoxy bridge.[2] Since several syntheses of the aporphine skeleton are available, the main problem in the laboratory preparation of thalphenine revolved around the construction of the unusual methylenoxy bridge.[3]

Spangler and Boop had shown that an efficient route to the aporphines consisted of the intramolecular photocyclization of a 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline in basic solution.[4] It was, therefore, reasoned that the 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline **11** could be the required precursor for a synthesis of thalphenine (**1**). Irradiation of **11** in the presence of sodium hydroxide would then lead to the aporphine anion **12** which possessed the extra carbon at C-11 necessary for the eventual formation of the methylenoxy bridge.

An important observation from the literature was that the 2-chloromethylphenol **15** upon treatment with base was immediately converted to the unstable quinone methide **16** which could be trapped by styrene to yield the chroman **17**.[5] It was consequently a plausible assumption that the aporphine anion **12**, upon being formed, could be readily converted to the homologous quinone methide **13** which in turn would undergo rapid bond isomerization to de-N-methylthalphenine (**14**).

In order to test the above hypothesis, it was necessary first to prepare the required 7-hydroxy-2'-bromotetrahydrobenzylisoquinoline **11**. Friedel–Crafts alkylation of the known methyl 2-bromo-4,5-methylenedioxyphenylacetate[6] with chloromethyl methyl ether using zinc chloride in chloroform[7] led to a crystalline product which was assigned the chloromethyl ester structure **5**. The alternate structure **4** for the product could be discarded since refluxing **5** in sodium hydroxide followed by acidification did not lead to a lactonic product, while a structure such as **4** would indeed have been expected to generate a δ-lactone under such conditions.

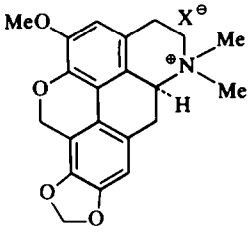
The compound obtained from the treatment of the chloromethyl ester **5** with methanolic sodium hydroxide was the methoxymethyl ether **6**. The acid chloride of **6** was then utilized in the N-acylation of 3 - methoxy - 4 - benzyloxy - β - phenethylamine[8] to produce the crystalline amide **7**.

The next three steps in the synthesis followed essentially classical lines. The colorless imine hydrochloride salt **8** was obtained through Bischler–Napieralski cylization of **7** using PCl_5 in chloroform at room temperature. Liberation of the free base and reaction with methyl iodide then supplied the imine methiodide salt **9** which was reduced with sodium borohydride to the tetrahydrobenzylisoquinoline **10**.

The selective hydrolysis of the benzyloxy protective group in **10** while keeping the methoxymethyl ether linkage intact was brought about at room temperature using equal volumes of ethanol and conc HCl, so that the 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline **11** was obtained as an oil in 73% yield from **10**.

Photolysis of **11** to the aporphine system was achieved in 34% yield when the following experimental conditions were satisfied: (a) the precursor **11** had to be purified prior to irradiation; this was usually accomplished by column chromatography over neutral alumina, (b) the photolysis was sensitive to oxidation and was carried out in a closed, degased, system at 0°, and (c) a low, rather than high, pressure mercury lamp was utilized.

Interestingly enough, the product of the photolysis was (±)-de-N-methylthalphenine (**14**), so that species **12** and **13** were never isolated. Quaternization of **14** with methyl iodide led to (±)-thalphenine iodide (*rac.* **1**), identical in terms of TLC R_f values, and UV and NMR spectra with a sample of the natural product.[2] (±)-De-N-methylthalphenine (**14**) was most probably formed in this study via the intermediacy of the quinone methide **13**. As mentioned earlier, such a



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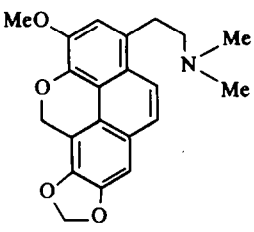

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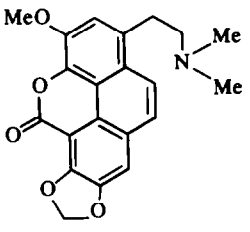

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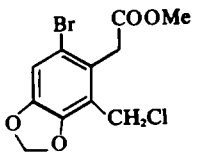

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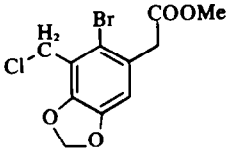

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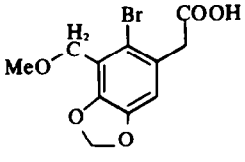

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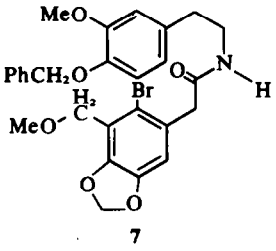

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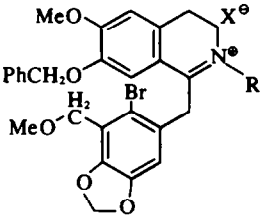
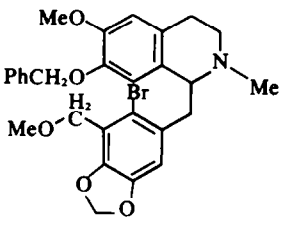


8: R = H
9: R = Me



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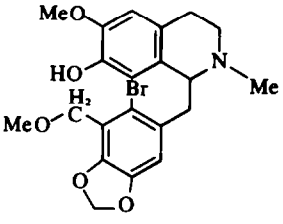

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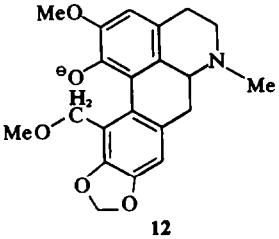

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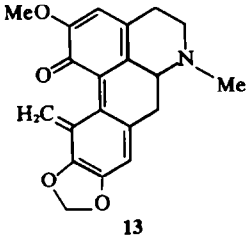

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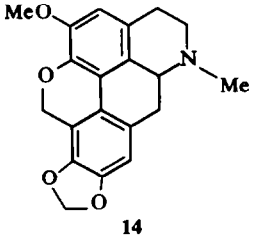

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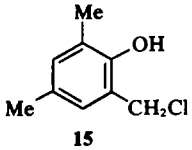

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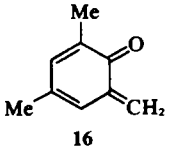

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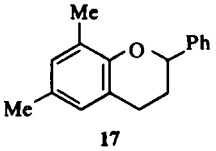

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transformation bears strong similarity to the production of the chroman **17** from the ortho-quinone methide **16** and styrene. However, the possibility of an intramolecular S_N2 attack by the phenoxide anion in species **12**, with methoxide anion as the leaving group, cannot be totally excluded.

Two optically inactive alkaloids related to thalphene (**1**) are thaliglucine (**2**) and thaliglucinone (**3**), also found in *Thalictrum* species.[2,9] In the present study, base catalyzed Hofmann elimination of (±)-thalphenine (*rac.* **1**) gave rise to thaliglucine (**2**), identical in all respects with the natural product. Since dichromate oxidation of thaliglucine (**2**) is known to lead to thaliglucinone (**3**),[9] the sequence under consideration also represents a synthesis of the latter base.

EXPERIMENTAL

Standard experimental procedures. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis. M.ps are uncorrected. The NMR data were recorded at 60 MHz in $CDCl_3$ unless indicated otherwise; TMS was the internal reference. Mass spectra were obtained on an AEI MS-902 spectrometer. All TLC was on Merck Silica Gel-254 plates.

Methyl 2 - bromo - 3 - chloromethyl - 4,5 - methylenedioxyphenylacetate (**5**). A soln of methyl 2 - bromo - 4,5 - methylenedioxyphenylacetate (6·77 g; 247 mmol), and $ZnCl_2$ (6·77 g) and chloromethyl methyl ether (6·77 g, 85 mmol) in 226 ml $CHCl_3$ was stirred at room temp for 65 h. The $CHCl_3$ soln was filtered, and the solvent evaporated. The solid residue was recrystallized from MeOH, 5·29 g (67% yield), colorless needles, m.p. 111–111·5°. (Found: C, 41·21; H, 3·26. Calcd. for $C_{11}H_{10}O_4BrCl$: C, 41·08; H, 3·13%).

2 - Bromo - 3 - methoxymethyl - 4,5 - methylenedioxyphenylacetic acid (**6**). A mixture of **5** (5 g; 0·0155 mol) in 175 ml of 1N NaOH and 175 ml MeOH was stirred and refluxed for 50 min. The soln was washed with ether and acidified with 2N HCl. Heating on a steam bath for 30 min and then standing at room temp for 2 h gave a ppt which was extracted with ether. The soln was dried ($MgSO_4$) and evaporated to give 3·02 g colorless crystals (EtOAc), 64% yield, m.p. 161–162°; NMR (DMSO-d_6) δ 3·3 (3H, s, OCH_3), 3·69 (2H, s, CH_2COOH), 4·45 (2H, s, CH_3OCH_2), 6·10 (2H, s, OCH_2O), 7·00 (1H, s, ArH). (Found: C, 43·54; H, 3·77. Calcd. for $C_{11}H_{11}O_5Br$: C, 43·58; H, 3·65%).

N - β - (3 - Methoxy - 4 - benzyloxyphenylethyl) - 2' - bromo - 3' - methoxymethyl - 4',5' - methylenedioxyphenylacetamide (**7**). Powdered PCl_5 (6·5 g) was added in portions to **6** (6·5 g; 21·4 mmol) in 130 ml $CHCl_3$. The soln was stirred at room temp for 3 h and then dropped directly with stirring into a two layer mixture made from 3-methoxy-4-benzyloxy-β-phenethylamine hydrochloride (6·27 g; 21·4 mmol) and Na_2CO_3 (19·5 g) in 150 ml $CHCl_3$ and 150 ml water. The mixture was stirred for an additional 90 min. The $CHCl_3$ layer was washed with dil HCl, water, and then dried. Evaporation of the solvent left a residue which was recrystallized from EtOH, 7·5 g, 65% yield, m.p. 163–164°. (Found: C, 59·40; H, 5·07. Calcd. for $C_{27}H_{28}NO_6Br$: C, 59·78; H, 5·20%).

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxybenzyl) - 6 - methoxy - 7 - benzyloxy - 3,4 - dihydroisoquinoline hydrochloride (**8**). The above amide **7** (3·0 g; 5·55 mmol) and 3·0 g PCl_5 in 30 ml $CHCl_3$, were stirred at room temp overnight. Evaporation to half volume and addition of ether gave a ppt which was collected and recrystallized from MeOH to give 2·43 g colorless crystals in 78% yield, m.p. 219–221°. (Found: C, 56·39; H, 5·03. Calcd. for $C_{27}H_{27}NO_5BrCl$. 1 MeOH: C, 56·72; H, 5·27%).

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxybenzyl) - 6 - methoxy - 7 - benzyloxy - 3,4 - dihydro - 2 - methylisoquinolinium iodide (**9**). The aforementioned hydrochloride salt **8** (3·0 g; 5·35 mmol) together with Na_2CO_3 (8 g) in 40 ml water and 100 ml $CHCl_3$, was shaken for 10 min in a separatory funnel. The $CHCl_3$ layer was separated, washed with water, and dried. Evaporation of the solvent gave the imine which was taken into 60 ml MeOH and 24 ml MeI. After two days in a closed flask the solvent was evaporated. The methiodide salt was recrystallized from MeOH–ether, 2·76 g yellow crystals, 77% yield, m.p. 213–214°. This material was pure enough to use in the next step.

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxy) - 2 - methyl - 6 - methoxy - 7 - benzyloxy - 1,2,3,4 - tetrahydrobenzylisoquinoline (**10**). To the immonium iodide salt **9** (3·18 g; 4·8 mmol) in 150 ml EtOH cooled with ice water, was added in portions 1·5 g $NaBH_4$. The mixture was then stirred for 20 min at 0°. The solvent was removed and the residue taken up in $CHCl_3$ and water. The $CHCl_3$ layer was separated, washed with water, and dried. Evaporation left a residue which was chromatographed over neutral alumina. Elution with $CHCl_3$–EtOAc (4:1) supplied 1·92 g colorless oil, 74% yield; NMR δ 2·44 (3H, s, N–CH_3), 3·42 (3H, s, CH_2OCH_3), 3·85 (3H, s, $ArOCH_3$), 4·61 (2H, s, CH_3OCH_2), 4·90 (2H, s, $PhCH_2$), 5·87 and 5·91, J_{gem} = 1·2 Hz (2H, q, O–CH_2O), 6·35 (1H, s, ArH), 6·60–6·62 (2H, 2s, ArH), and 7·35 (5H, s, C_6H_5).

Methiodide salt, m.p. 199–201° (MeOH): (Found: C, 50·94; H, 5·06; I, 18·35; and N, 2·04. Calcd. for $C_{29}H_{33}NO_5IBr$: C, 51·04; H, 4·87; I, 18·59; N, 2·05%).

1 - (2' - Bromo - 2' - methoxymethyl - 4',5' - methylenedioxy - 2 - methyl - 6 - methoxy - 7 - hydroxy - 1,2,3,4 - tetrahydrobenzylisoquinoline (**11**). The amine **10** (0·49 g; 0·91 mmol) in 45 ml EtOH, was mixed with 45 ml conc HCl, and allowed to stand at room temp under N_2 in a closed flask for one week. The soln was cooled in an ice-bath, made slightly basic with conc NH_4OH, and extracted with $CHCl_3$. The organic layer was dried and evaporated to give 0·39 g of an oil. Chromatography over neutral alumina and elution with $CHCl_3$, ether and MeOH (2:2:1) furnished 0·30 g of an oil (73%) pure enough to be used in the next transformation; NMR δ 2·41 (3H, s, N–CH_3), 3·41 (3H, s, CH_3–O–CH_2), 3·84 (3H, s, $ArOCH_3$), 4·60 (2H, s, CH_3–O–CH_2), 5·96 (2H, s, OCH_2O), 6·45 (1H, s, ArH), 6·60 (1H, s, ArH), 6·68 (1H, s, ArH).

Low resolution mass measurement, *m/e* 448 and 450 (0·24) $(M–H)^+$, 418 and 420 (0·24) $(M–MeO)^+$, 355 (0·95) $(M–Br–Me)^+$, 192 (100).

High resolution mass measurement for base peak: Found: *m/e* 192·1019. Calcd. for $C_{11}H_{14}NO_2$: *m/e* 192·1024.

(±)-De-N-methylthalphenine (**14**). A soln of **11** (0·075 g; 0·164 mmol) and NaOH (0·19 g) in 9 ml MeOH and 1 ml water was degassed by evacuating the liquid N_2 cooled soln several times, and photolyzed with a low pressure UV-Products mercury lamp at 0° for about 3½ h. The product was submitted to TLC separation on alumina plates, Alphate-FT-22, using $CHCl_3$–EtOAc (8:1). De-N-methylthalphenine, 19 mg, 34% yield, was thus obtained and crystallized from MeOH, m.p. 179–180°; NMR δ 2·50

(3H, s, NCH_3), 3·85 (3H, s, OCH_3), 4·90 and 5·45, J_{gem} = 14 Hz (2H, q, Ar–O–CH_2Ar), 5·94 and 5·98, J_{gem} = 1 Hz(2H, q, OCH_2O). 6·50 (1H, s, ArH), 6·63 (1H, s, ArH); λ_{max}^{EtOH} 221, 233sh, 278sh, 286, 312 and 323sh (log ϵ 4·49, 4·34, 3·86, 3·98, 4·07 and 4·05). (Found: C, 70·80; H, 5·88, Calcd. for $C_{20}H_{19}NO_4$: C, 71·20; H, 5·67%).

(±)-*Thalphenine iodide* (rac. **1**). The racemate **14** (45 mg) was dissolved in 25 ml ether, 4 ml MeOH and 2 ml MeI. The flask was stoppered under N_2 at, and the mixture allowed to stand for one day. Evaporation and recrystalization from MeOH provided 55 mg, 86% yield, of colorless crystals m.p. 193–194°. (Found: C, 51·87; H, 5·13. Calcd. for $C_{21}H_{22}NIO_4$·MeOH: C, 51·67; H, 5·12%). TLC R_f 0·41 in $CHCl_3$–MeOH (4:1), identical with (+)-thalphenine iodide. The NMR spectrum in DMSO-d_6 corresponded to that for the natural product.[2]

Thaliglucine (**2**). Racemic thalphenine iodide (38·8 mg) in 15 ml MeOH and 15 ml 3N KOH was heated at 45–55° for 6 h. The soln was evaporated to half volume and extracted with $CHCl_3$. The organic layer was dried and evaporated. Recrystallization from MeOH gave 24·1 mg (85%) of methine crystals, m.p. 121–122°, identical with the natural product.[2,9] Comparisons were in terms of TLC R_f values, UV, NMR and mass spectra.

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REFERENCES

[1]This paper has been presented in communication form: M. Shamma and Der-Yan Hwang, *Heterocycles* **1**, 31 (1973)

[2]M. Shamma, J. L. Moniot, S. Y. Yao and J. A. Stanko, *Chem. Commun.* 408 (1972)

[3]For recent reviews on the aporphines see M. Shamma, *The Isoquinoline Alkaloids*, p. 194. Academic Press, New York, and Verlag Chemie, Weinheim (1972); and M. Shamma and S. S. Salgar, *Specialist Periodical Reports, The Alkaloids*, Vol. 4, p. 000. The Chemical Society, London (1974)

[4]R. J. Spangler and D. C. Boop, *Tetrahedron Letters* 4851 (1971)

[5]M. Wakselman and M. Vilkas, *C.R. Acad. Sci., Paris*, **258**, 1526 (1964). For related references see also: [a] A. B. Turner, *Quart. Rev.* **18**, 347 (1964); [b] P. D. Gardner, H. S. Rafsanjani and L. Rand, *J. Am. Chem. Soc.* **81**, 3364 (1959); [c] S. B. Cavitt, H. Sarrafizadeh and P. D. Gardner, *J. Org. Chem.* **27**, 1211 (1962); and [d] A. Merijan, B. A. Shoulders and P. D. Gardner, *Ibid.*, **28**, 2148 (1963)

[6]T. Kametani, O. Umezawa, Y. Satoh, K. Ogasawara, S. Shibuya, M. Ishiguro and D. Mizuno, *J. Pharm. Soc. Japan* **83**, 838 (1963)

[7]*Roussel-UCLAF Neth. Appl.* **6**, 501, 747 (1965); *Chem. Abstr.* **64**, 2135 (1966)

[8]D. H. Hey and A. L. Palluel, *J. Chem. Soc.* 2926 (1957)

[9]N. M. Mollov, L. N. Thuan and P. P. Panov, *C.R. Acad. Bulg. Sci.* **24**, 1047 (1971)