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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CDLXVII[1]

PHOTOLYTIC SYNTHESIS OF KREYSIGININE-TYPE COMPOUNDS

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Abstract—Photolysis of 1-(2-bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**10**) gave the kreysiginine-type enone **12** in addition to the thalifoline (**11**). Phenolic oxidation of **10** gave a *para-para* coupling product **13**.

IN THE LAST DECADE, many phenethylisoquinoline alkaloids were isolated from *Liliaceae* plants, and structures assigned by chemical and physical methods.[2] Among them, kreysiginine (**1**), isolated together with kreysigine and floramultine from *Kreysigia multiflora*,[3] is the most interesting structure[4–6] from a biogenetic viewpoint. Thus, the

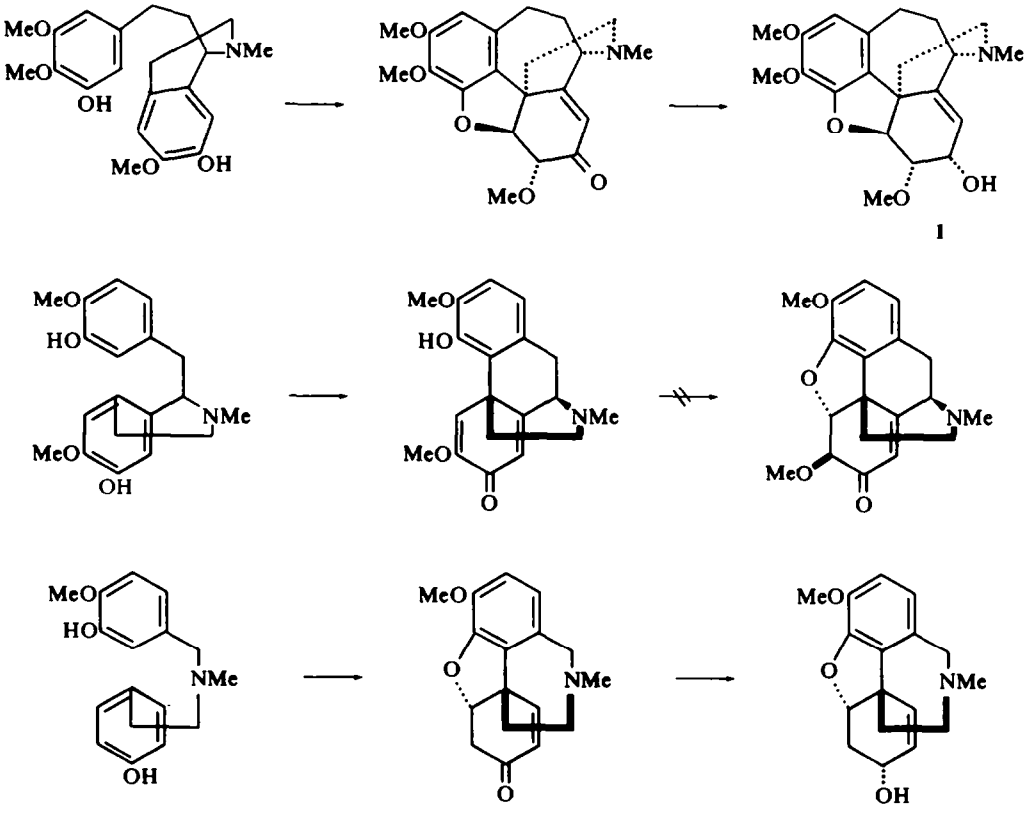

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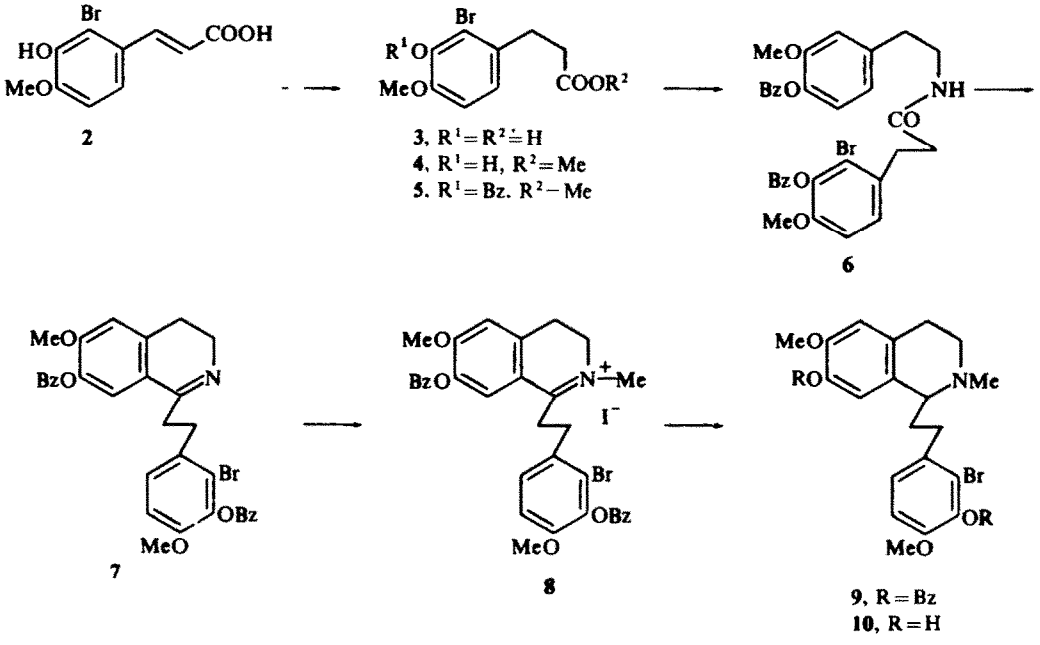
CHART 1

retention of an oxygenated function at the 7-position of a molecule having an oxygen bridge is in contrast to the situation which occurs in the biogenesis of morphine, but is closely similar to the biogenetic mechanism of galanthamine.[7]

In order to investigate whether oxygen bridge formation with retention of an oxygen function at the 7-position would occur or not, we examined the synthesis of a kreysiginine-type compound from 1-(2-bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**10**) by photolytic reaction and phenolic oxidation and we report these results.

The starting bromophenolic compound (**10**) was synthesized as follows. 2-Bromo-3-hydroxy-4-methoxycinnamic acid (**2**) obtained from 2-bromoisovanillin,[8] was hydrogenated over platinum oxide to give 2-bromo-3-hydroxy-4-methoxyphenyl propionic acid (**3**), which, after esterification and benzylation, condensed with 4-benzyloxy-3-methoxyphenethylamine to afford amide **6**. Bischler-Napieralski reaction of **6** gave the corresponding dihydroisoquinoline (**7**), which was converted into its methiodide (**8**). Reduction of **8** with $NaBH_4$ gave the 1,2,3,4-tetrahydro-2-methylisoquinoline derivative (**9**) which on debenzylation with alcoholic HCl yielded 1-(2-bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (**10**).

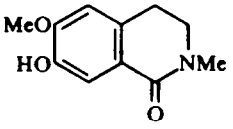
CHART 2



The bromophenolic isoquinoline **10** was irradiated for 7 hr in the presence of NaOH and NaI (Riko 400 W mercury lamp using a Pyrex filter) yielding two compounds, in addition to a major amount of starting material. The first was thalifoline (**11**), the structure of which was assigned by spectral comparisons with an authentic sample.[9] The second had molecular formula $C_{20}H_{23}O_4N$ (mass spectrum and methiodide microanalysis), and the IR spectrum in $CHCl_3$ revealed absorption bands at 1685 and 1630

cm^{-1}; no hydroxy group absorption was observed. The enone system was also indicated by a UV band at 229 nm. Moreover, the NMR spectrum showed two coupled methine protons (revealed by decoupling experiments) at τ 5·37 and 6·11 in addition to an olefinic proton at 4·11, two aromatic protons at 3·30, two O-Me's at τ 6·14 and 6·38, and one N-Me resonance at 7·41. The coupling constant (J 9·5 Hz) indicated that both protons should be located in *vicinal* and *trans* configuration. These facts reveal that the second product is the kreysiginine-type structure **12**, and ring-closure to the enone has also taken place.

CHART 3



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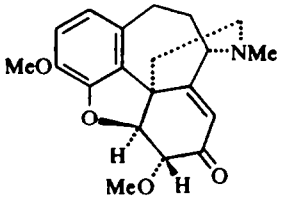
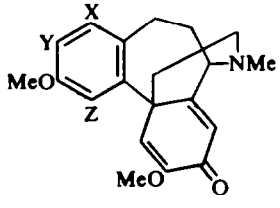


12

Secondly, phenolic oxidation of **10** was examined with the expectation that *ortho-para* coupling might occur to give the dienone **14**, which would be transformed immediately to enone **12**, because oxidation of a phenolic compound with a bromine atom *para* to a phenolic function gives the coupled product (after removal of a bromine atom).[10, 11] Oxidation of **10** with potassium ferricyanide gave the *para-para* coupling product (**13**) with retention of a bromine atom. The above structure was confirmed by the following data. Microanalysis of the free base verified the molecular formula as $C_{20}H_{22}O_4NBr$, it had an α-alkoxylated cyclohexadienone system as revealed by its IR absorption at 1655, 1635 and 1615 $cm.^{-1}$ The NMR spectrum showed the presence of one N-Me, two OMe groups, and two olefinic and one aromatic protons; the chemical shift of an olefinic proton indicated the product to be coupled in a *para-para* mode.[12]

CHART 4



13, X=Br, Y=OH, Z=H
14, X=Y=H, Z=OH

Thus, kreysiginine could be biosynthesized by a similar route with the biogenetic mechanism of galanthamine.

EXPERIMENTAL

IR spectra were measured with a Hitachi EPI-3 spectrophotometer, UV spectra with a Hitachi EPS-3 spectrophotometer, and NMR spectra with a Hitachi R-20 spectrometer and a Varian HA-100 spectro-

meter with TMS as internal standard. Mass spectra were taken with a Hitachi RMU-7 spectrometer. M.p.s are not corrected.

2-Bromo-3-hydroxy-4-methoxycinnamic acid (2). A mixture of 40 g 2-bromoisovanillin,[8] 20 g molanic acid, 2 ml piperidine and 68 g pyridine was heated at 100° for 1·5 hr, and refluxed for 0·5 hr. The reaction was cooled to room temp. and poured into ice and conc. HCl. A precipitate separated was collected and crystallized from MeOH to afford 3 g of the cinnamic acid (**2**) as pale yellow needles, m.p. 248–250°. (Calc. for $C_{10}H_9O_4Br$: C, 43·95; H, 3·29. Found: C, 43·81; H, 3·13%).

2-Bromo-3-hydroxy-4-methoxyphenylpropionic acid (3). A solution of 6 g **2** in 400 ml MeOH was hydrogenated over 140 mg PtO_2. After absorption of the calc. amount of H_2, catalyst was filtered and the solution distilled to leave 4·7 g of **3** as colorless leaflets, m.p. 67–69° (from hexane); ν_{max} ($CHCl_3$) 1725 cm^{-1} (C=O). (Calc. for $C_{10}H_{11}O_4Br$: C, 43·66; H, 4·00. Found: C, 44·08; H, 4·22%).

Methyl 2-bromo-3-hydroxy-4-methyoxyphenylpropionate (4). A mixture of 14 g of the above propionic acid **3**, 1·5 ml conc. H_2SO_4 and 180 ml dry MeOH was refluxed for 5 hr and the solvent distilled off. The residue was poured into water and $CHCl_3$ extracted. The extract was washed with $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to leave 11 g of crude methyl ester (**4**), which recrystallized from hexane as colorless prisms, m.p. 72–74°. (Calc. for $C_{11}H_{13}O_4Br$: C, 45·67; H, 4·45. Found: C, 45·82; H, 4·66%).

Methyl 3-benzyloxy-2-bromo-4-methoxyphenylpropionate (5). A mixture of 10 g of the above ester **4**, 8·7 g K_2CO_3, 8 g benzyl chloride and 100 ml dry MeOH was heated under reflux for 6 hr. After filtration of the inorganic material, the filtrate was concentrated to give a reddish viscous syrup, which was taken up in $CHCl_3$. The extract was washed with dilute alkali and water, dried (Na_2SO_4) and evaporated to give 10 g of benzyl derivative (**5**) as viscous oil.

N-β-(4-Benzyloxy-5-methoxyphenetyl)-3-benzyloxy-2-bromo-4-methoxyphenethylamide (6). 4-Benzyloxy-3-methoxyphenthylamine (20 g) was fused with 15 g ester **5** at 180° for 3 hr *in vacuo*, and the mixture cooled and $CHCl_3$ extracted. The extracts were washed with dil. HCl, dil. NaOH, water, and dried (Na_2SO_4). The residue obtained after evaporation was chromatographed over silica gel using $CHCl_3$ as eluant, 22 g of the amide (**6**) being obtained as colorless needles (from benzene-hexane), m.p. 108–110°; ν_{max} ($CHCl_3$) 3400 (NH) and 1660 cm^{-1} (C=O). (Calc. for $C_{33}H_{34}O_5NBr$: C, 65·57; H, 5·63; N, 2·31. Found: C, 65·96; H, 5·96; N, 2·52%).

7-Benzyloxy-1-(3-benzyloxy-2-bromo-4-methoxyphenethyl)-3,4-dihydro-6-methoxyisoquinoline (7). A mixture of 15 g of amide **6**, 20 ml $POCl_3$ and 500 ml dry benzene was refluxed for 2 hr and poured into excess hexane. The yellow precipitate was collected, washed and crystallized from MeOH–Et_2O to give 9 g 3,4-dihydroisoquinoline (**7**) hydrochloride as pale yellow, hygroscopic needles, m.p. 196–198°; ν_{max} ($CHCl_3$) 1645 cm^{-1} (>C=$\overset{+}{N}$—). (Calc. for $C_{33}H_{32}O_4NBr.HCl$: C, 63·62; H, 5·30; N, 2·25. Found: C, 63·43; H, 5·63; N, 2·14%). The hydrochloride was taken up in $CHCl_3$, the extract of which was made basic with NH_4OH, washed with water, and dried (Na_2SO_4). Evaporation of solvent gave 8 g of free base (**7**) as brown syrup, which was then treated with MeI to give the methiodide (**8**) as pale yellow needles, m.p. 107–109° (from $CHCl_3$–hexane). (Calc. for $C_{34}H_{35}O_4NBrI$: C, 56·06; H, 4·81; N, 1·92. Found: C, 55·88; H, 5·15; N, 2·04%).

7-Benzyloxy-1-(3-benzyloxy-2-bromo-4-methoxyphenethyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (9). To cooled solution of 12g of the above methiodide **8** in 500 ml MeOH was added in small portions 10g $NaBH_4$. The mixture was stirred for 0·5 hr at room temp and then refluxed for 2 hr. After the evaporation of solvent, the residue was diluted with H_2O and $CHCl_3$ extracted. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave 10·5 g of 1,2,3,4-tetrahydroisoquinoline (**9**) as pale yellow viscous syrup; NMR ($CDCl_3$) τ 7·59 (s, 3, NMe), 6·21 (s, 3, OMe), 6·25 (s, 3, OMe), 5·10 (s, 2, $OC\underline{H}_2Ph$), 5·00 (s, 2, $OC\underline{H}_2Ph$), 2·75 (m, 10, $2 \times OCH_2C_6\underline{H}_5$).

1-(2-Bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (10). A mixture of 10 g of **9**, 500 ml EtOH, and 350 ml conc. HCl was refluxed for 6 hr and EtOH distilled off. The resulting acidic solution was made basic with NH_4OH and $CHCl_3$ extracted. The extract was washed with water, dried (Na_2SO_4) and evaporated to give 6 g of **10** as a colorless solid, the hydrochloride of which recrystallized from hexane as colorless needles, m.p. 83–84°; ν_{max} ($CHCl_3$) 3500 cm^{-1} (OH). (Calc. for $C_{20}H_{24}O_4NBr.HCl$: C, 52·34; H, 5·45; N, 3·05. Found: C, 52·18; H, 5·24; N, 3·03%).

Photolysis of **10**. A solution of 3 g of the diphenolic isoquinoline (**10**) in 11 (liter) 1% aq. EtOH containing 3 g of NaOH and 3 g of NaI was irradiated with a Riko 400 W mercury lamp using a Pyrex filter for 7 hr at room temp with stirring. The mixture was treated with excess NH_4Cl, saturated with NaCl, and extracted with $CHCl_3$. The extract was washed with sat NaCl aq, dried (Na_2SO_4), and evaporated. The resulting brown oil (1·6 g) was chromatographed on silica gel (20 g) with $CHCl_3$–MeOH (v/v 99·5:0·5) to give 8

mg of thalifoline (**11**), m.p. 211–212° (from MeOH), identical with an authentic sample,[9] and with $CHCl_3$–MeOH (v/v 99 : 1) as eluant to give 100 mg of enone fraction. Rechromatography of the enone fraction on neutral Al_2O_3 (benzene as eluant) afforded 30 mg of **12** as colorless needles, m.p. 145–147°; ν_{max} ($CHCl_3$) 1685, 1630 cm^{-1} (cyclohexenone system); λ_{max} (EtOH) 229 nm (log ε 4·215), 277 nm (log ε 3·529); NMR ($CDCl_3$) τ 7·41 (s, 3, NMe), 6·38 (s, 3, OMe), 6·14 (s, 3, OMe), 6·11 (d, 1, J = 9·5 Hz, C-6), 5·37 (d, 1, J = 9·5 Hz, C-5), 4·11 (s, 1, C-8), 3·30 (s, 2, aromatic protons). (Calc. for $C_{21}H_{26}NO_4I$ [methiodide of **12**, m.p. 198–200° (decomp) (from MeOH–Et_2O)]: C, 52·18; H, 5·42. Found: C, 52·36; H, 5·53%).

Oxidation of **10**. To a mixture of 1 g of **10** in 100 ml $CHCl_3$ was added a solution of 4 g $NaHCO_3$ in 75 ml H_2O, to which was added dropwise a solution of 2·3 g $K_3Fe(CN)_6$ in 75 ml H_2O with stirring. Conc. NH_4OH (2 ml) was added dropwise to the above mixture and the stirring continued for 45 min. After separation of the $CHCl_3$ layer the aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4) and distilled to leave a dark gum, which was chromatographed on 50 g of silica gel. Elution with $CHCl_3$–MeOH (v/v 98 : 2) gave 100 mg of a crude dienone **13**. On rechromatography on 8 g of neutral Al_2O_3, the $CHCl_3$ eluant gave 20 mg of **13** as a colorless powder (from hexane), m.p. 147–149°; ν_{max} ($CHCl_3$); 3500 (OH), 1655, 1635 and 1615 cm^{-1} (cyclohexadienone system); NMR ($CDCl_3$) τ 7·64 (s, 3, NMe), 6·63 (s, 3, OMe), 6·19 (s, 3, OMe), 3·99, 3·70 and 3·09 (each 1, two olefinic and one aromatic protons). (Calc. for $C_{20}H_{22}O_4NBr$: C, 57·15; H, 5·23. Found: C, 56·80; H, 5·83%).

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