SYNTHESIS OF (±)-GLAZIOVINE, A PROAPORPHINE ALKALOID, THROUGH NITRENIUM INTERMEDIATE

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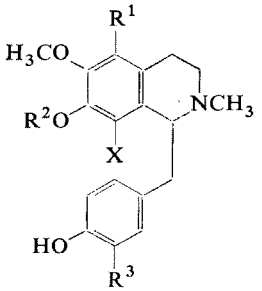
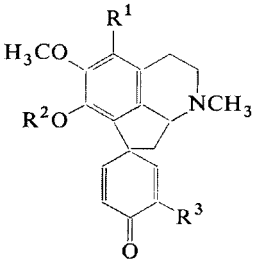
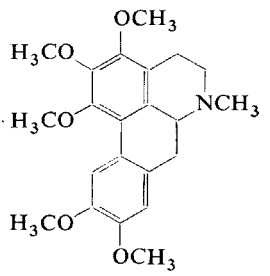
Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

(±)-Glaziovine (*IV*) was synthesized through nitrenium intermediate *XIV* from 1-(4-aminobenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (*IX*) by treatment with sodium hypochlorite and then potassium tert-butoxide.

Proaporphine alkaloids[1,2], such as glaziovine (*IV*), could be biosynthesized from the coclaurine type bases *I* and transformed into the aporphine alkaloids[3] in the Nature[4]. This biogenetic mechanism provides an useful route for the synthesis of the proaporphine alkaloids. We have accomplished the total synthesis of (±)-glaziovine[5] (*IV*) and (±)-thalicsimidine[6] (*VI*) from the appropriate diphenolic isoquinolines *I* and *II* by a phenolic oxidation[7], followed by a rearrangement of *V* along the biogenetic pattern. Moreover, the synthesis of the proaporphine alkaloids by intramolecular coupling between $C_{(8)}$ and $C_{(1')}$ in the 1-benzylisoquinolines could be achieved by the photochemical method[8]; thus, glaziovine (*IV*) was synthesized by photolysis of 8-bromo-2-methylcoclaurine[9] (*III*). In these syntheses, the intervention of a too







I, $R^1 = R^2 = R^3 = X = H$
II, $R^1 = OH$, $R^2 = CH_3$, $R^3 = OCH_3$, $X = H$
III, $R^1 = R^2 = R^3 = H$, $X = Br$

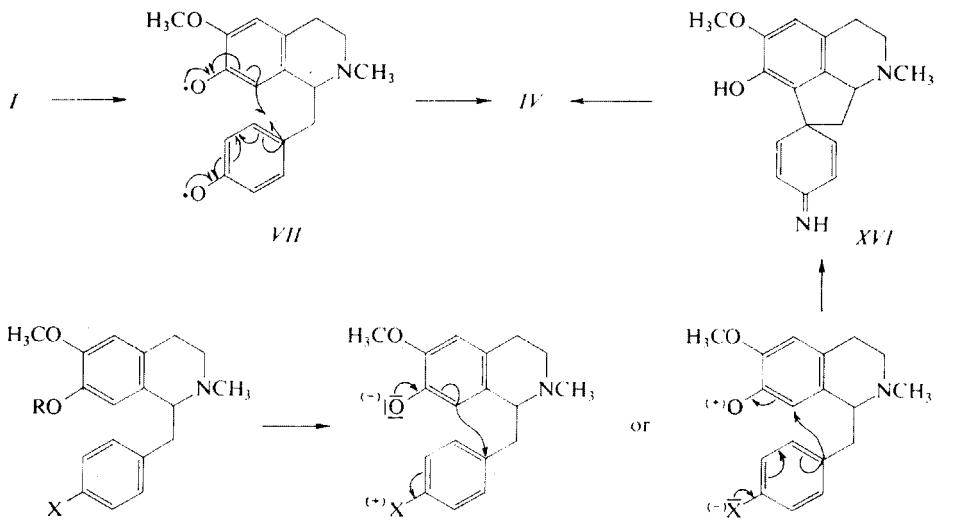
IV, $R^1 = R^2 = R^3 = H$
V, $R^1 = OH$, $R^2 = CH_3$, $R^3 = OCH_3$

VI

reactive radical intermediate *VII* made the reaction very complex and the formation of the dienone system very poor. An improvement of the yield could be expected when the radical intermediate *VII* could be substituted with an ionic intermediate *XIII* or *XV*, according to Scheme 1.

On this premise, we chose a phenolic 1-(4-chloroaminobenzyl)isoquinoline (*X*) as a key intermediate, which could generate a phenoxy-nitrenium intermediate *XIV*, electronically equivalent to *XIII*, on treating with a strong base, since the generation of a phenoxy–phenoxonium intermediate *XV* would be practically impossible. Here we wish to report a novel synthesis of glaziovine (*IV*) through nitrenium intermediate *XIV* along this mechanism.

The starting aminoisoquinoline *IX* was synthetised by a usual way[10] as follows: the amide *XXI*, obtained by a Schotten–Baumann reaction of 4-benzyloxy-3-methoxyphenylethylamine (*XVII*) with the chloride, derived from *XIX*, was cyclised with phosphoryl chloride in boiling chloroform to give the 3,4-dihydroisoquinoline *XXIV*, whose methiodide *XXVII* was converted into the starting *IX* by reduction with zinc and hot hydrochloric acid. Aminoisoquinoline *IX* was treated with 1% sodium hypochlorite at 0–5°C in dichloromethane and the resulting N-chloroaminoisoquinoline *X* was decomposed with potassium tert-butoxide at 10–15°C in tetrahydrofuran. Imino compound *XVI* was not obtained, but a hydrolysed compound, (±)-glaziovine[5]



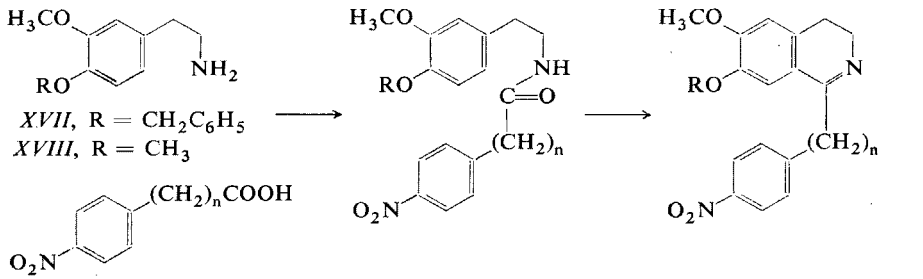
IX, R = H, X = NH_2
X, R = H, X = NHCl
XI, R = CH_3, X = NH_2
XII, R = CH_3, X = NHCl

XIII, X = O
XIV, X = NH

XV, X = O

SCHEME 1

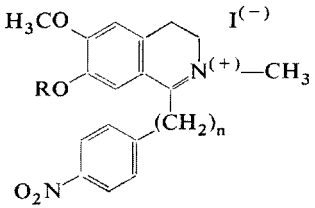
(*IV*), was formed in low yield, which was identical with the authentic sample according to spectral comparison and melting-point test. Moreover, the aminoisoquinoline *XI*, prepared from the phenylethylamine *XVIII* and *XIX* by the same method as shown in Scheme 2, was treated as the compound *IX*, but only azo compound *XXX* was obtained, *cf.*[11]. This compound showed typical absorption in UV spectrum and signals at δ 7·19, 7·77 (AA'BB' pattern) in the PMR spectrum. The same synthetic procedure was applied to 1-(4-aminophenylethyl)isoquinoline (*XXXI*), obtained from *XVII* and *XX* as shown in Scheme 2, but homoproaporphine *XXXII* was not



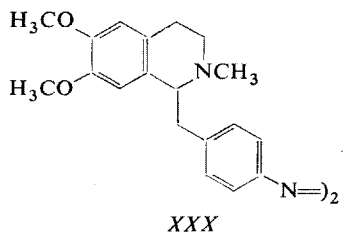
XVII, R = $CH_2C_6H_5$
XVIII, R = CH_3

XIX, n = 1
XX, n = 2

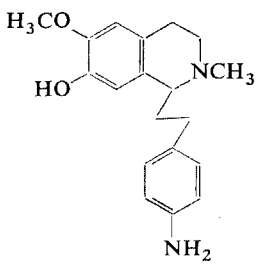
XXI, R = $CH_2C_6H_5$, n = 1 *XXIV*, R = $CH_2C_6H_5$, n = 1
XXII, R = CH_3, n = 1 *XXV*, R = CH_3, n = 1
XXIII, R = $CH_2C_6H_5$, n = 2 *XXVI*, R = $CH_2C_6H_5$, n = 2



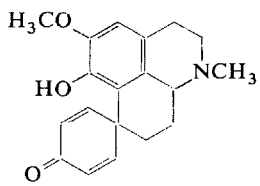
XXVII, R = $CH_2C_6H_5$, n = 1
XXVIII, R = CH_3, n = 1
XXIX, R = $CH_2C_6H_5$, n = 2



XXX



XXXI



XXXII

SCHEME 2

obtained. Finally, aminoisoquinoline *XI* was treated with lead tetraacetate in dichloromethane at −78°C to give only azo compound *XXX*, a nitrogen–nitrogen coupling product.

The synthesis of the proaporphine-type base by a carbon–carbon coupling through nitrenium intermediate could be applied to the synthesis of the morphinanedienone, aporphine, and phenanthridine alkaloids.

EXPERIMENTAL

Infrared (IR) and ultraviolet (UV) spectra were taken with type EPI-2 and EPS-3 Hitachi recording spectrophotometer. PMR spectra were taken with a Hitachi H-60 with tetramethylsilane as internal standard.

N-(4-*Benzyloxy*-3-*methoxyphenylethyl*)-4-*nitrophenylacetamide* (XXI). To a suspension of phosphorous pentachloride (19·3 g) in chloroform (100 ml) 4-nitrophenylacetic acid (*XIX*) (16·6 g) was added with stirring during 35 min. The mixture stirred for a further 1 h, and chloroform was evaporated. The residue was washed with n-hexane and dissolved in chloroform (200 ml). This solution was added dropwise to a solution of 4-benzyloxy-3-methoxyphenylethylamine *XVII* (23·5 g) in 5% sodium hydroxide solution (100 ml) and chloroform (200 ml) with stirring under cooling. The stirring was continued for 2 h, the organic layer was separated, washed with 10% hydrochloric acid, 5% sodium hydrogen carbonate, and water, dried over potassium carbonate and evaporated to leave the crystals. Recrystallization from methanol gave needles (28·0 g), m.p. 134·5–135·5°C. Infrared spectrum (chloroform): 1 350, 1 668, 3 450 cm^{-1}. For $C_{24}H_{24}N_2O_5$ (420·45) calculated: 68·56% C, 5·75% H, 6·66% N; found: 68·78% C, 5·89% H, 6·59% N.

7-*Benzyloxy*-3,4-*dihydro*-6-*methoxy*-1-(4-*nitrobenzyl*)*isoquinoline methiodide* (XXVII). A mixture of the amide *XXI* (5·0 g), phosphoryl chloride (3·7 g), and chloroform (50 ml) was refluxed for 2 h. After evaporation the residue was washed with n-hexane and extracted with chloroform. The extract was washed with water, 10% ammonia, and water, dried with sodium sulfate, and evaporated to give a syrup *XXIV* (4·5 g). A mixture of crude *XXIV* and methyl iodide (10 ml) was set aside at room temperature for 24 h; the methiodide *XXVII* was recrystallized from methanol–water to give prisms (4·2 g), m.p. 209–210°C. Infrared spectrum (potassium bromide): 1630 cm^{-1}. For $C_{25}H_{25}IN_2O_4$ (544·4) calculated: 55·15% C, 4·63% H, 5·15% N; found: 54·96% C, 4·68% H, 5·28% N.

1-(4-*Aminobenzyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (IX). To a stirred solution of the methiodide *XXVII* (20 g) in concentrated hydrochloric acid (400 ml), glacial acetic acid (300 ml), and water (100 ml), zinc powder (120 g) was added during 80 min at room temperature, and the stirring was continued for 1·5 h at the same temperature and then for 30 min at 80°C. Inorganic material was filtered off, and the filtrate was basified over 28% ammonia under cooling with ice, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from chloroform–benzene to give prisms (7 g), m.p. 188–190°C (decomp.). Infrared spectrum (potassium bromide): 3 370, 3 450 cm^{-1}. PMR spectrum (deuteriochloroform): δ 2·40 (s, 3 H, NCH_3), 3·77 (s, 3 H, OCH_3), 6·30 (s, 1 H, $C_{(8)}$—H), 6·47 (s, 1 H, $C_{(5)}$—H), 6·52 (d, J = 8 Hz, 2 H, $C_{(3')}$—H and $C_{(5')}$—H) 6·87 (d, J = 8 Hz, 2 H, $C_{(2')}$—H and $C_{(6')}$—H). For $C_{18}H_{22}N_2O_2$ (298·4) calculated: 72·45 C, 7·43% H, 9·39% N; found: 72·71% C, 7·47% H, 9·45% N.

(±)-*Glaziovine* (IV). To a stirred solution of the aminoisoquinoline *IX* (2·0 g) in dichloromethane (200 ml) 1% sodium hypochlorite solution (40 ml) was added dropwise during 40 min at 0–5°C. The stirring was continued for 80 min at the same temperature, the organic layer was separated,

washed with water, dried over sodium sulfate, and evaporated to leave syrup *X*. A mixture of crude *X* and potassium tert-butoxide (0·50 g) in tetrahydrofuran was stirred for 16 h at 10—15°C. After evaporation, the residue was dissolved in water, basified with ammonium chloride (10 g), and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a syrup (1·3 g) which was chromatographed on silica gel (30 g) by monitoring with thin layer chromatography and infrared spectroscopy. Evaporation of the chloroform–1·5% methanol fractions gave a gum (39 mg) which was purified on thick layer chromatography using benzene–acetone–methanol (25 : 20 : 4). Extraction of appropriate zone (R_F 0·37) gave (±)-glaziovine (*IV*) (20 mg) as a solid, which was recrystallized from ether to give prisms, m.p. 227—228°C (decomp.) lit.[5], m.p. 227—228°C, identical (spectroscopical data) with an authentic specimen[5].

N-(3,4-*Dimethoxyphenylethyl*)-4-*nitrophenylacetamide* (XXII). To a suspension of phosphorous pentachloride (31·6 g) in chloroform (50 ml) 4-nitrophenylacetic acid (*XIX*) (25·0 g) was added under stirring during 30 min. The mixture was stirred for 1 h and evaporated. The residue was washed with n-hexane and the separated acid chloride was dissolved in chloroform (200 ml), whose solution was added dropwise to a solution of 3,4-dimethoxyphenylethylamine (*XVIII*) (25 g) in 5% sodium hydroxide solution (160 ml) and chloroform (200 ml) with stirring during 1 h under cooling. The stirring was continued for 2 h, the organic layer was separated, washed with 10% hydrochloric acid, 5% sodium hydrogen carbonate, and water, dried with potassium carbonate, and evaporated. Recrystallization from methanol gave needles (29·0 g), m.p. 122 to 123°C. Infrared spectrum (chloroform): 1350, 1670, 3450 cm^{-1}. For $C_{18}H_{20}N_2O_5$ (344·35) calculated: 62·78% C, 5·85% H, 8·14% N; found: 62·71% C, 5·97% H, 8·04% N.

· 3,4-*Dihydro*-6,7-*dimethoxy*-1-(4-*nitrobenzyl*)*isoquinoline methiodide* (XXVIII). A mixture of the amide *XXII* (25 g), phosphoryl chloride (22 g), and chloroform (300 ml) was refluxed for 5 h. After evaporation, the residue was washed with n-hexane and extracted with chloroform. The extract was washed with water, 10% ammonia, and water, dried over sodium sulfate, and evaporated to leave a syrup *XXV*. A mixture of crude *XXV*, methyl iodide (30 g), and methanol (150 ml) was refluxed for 1 h, and kept overnight. The precipitated methiodide was recrystallized from methanol–ether to give yellow needles (24 g), m.p. 162—163°C. Infrared spectrum (potassium bromide): 1624 cm^{-1}. For $C_{19}H_{21}IN_2O_4.1/2\,H_2O$ (477·3) calculated: 47·81% C, 4·65% H; found: 47·75% C, 4·56% H.

1-(4-*Aminobenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (XI). To a stirred solution of the methiodide *XXVIII* (23 g) in concentrated hydrochloric acid (400 ml), glacial acetic acid (300 ml), and water (100 ml), zinc powder (120 g) was added during 80 min under cooling with ice-water, and the stirring was continued for 2 h at room temperature. The solid was filtered off, and the filtrate was basified with 28% ammonia under cooling with ice, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated (9·5 g). The hydrochloride of this base afforded needles, m.p. 218—221°C (methanol–ether). PMR spectrum (deuteriochloroform): δ 2·49 (s, 3 H, NCH_3), 3·54 (s, 3 H, OCH_3), 3·78 (s, 3 H, OCH_3), 6·01 (s, 1 H, $C_{(8)}$—H), 6·48 (s, 1 H, $C_{(5)}$—H), 6·50 (d, J = 8 Hz, 2 H, $C_{(3')}$—H and $C_{(5')}$—H), 6·83 (d, J = 8 Hz, 2 H, $C_{(2')}$—H and $C_{(6')}$—H). For $C_{19}H_{24}N_2O_2.2\,HCl$ (385·3) calculated: 59·22% C, 6·80% H, 7·27% N; found: 59·34% C, 6·99% H, 7·32% N.

Synthesis of azo compound (XXX). To a stirred solution of aminoisoquinoline *XI* (0·5 g) in dichloromethane (100 ml) was added calcium hypochlorite (0·60 g) at 0—5°C and the stirring was continued for 5 h at the same temperature. The reaction mixture was washed with water, dried over sodium sulfate, and evaporated to leave a syrup *XII*. A mixture of crude *XII* and potassium tert-butoxide (0·3 g) in tetrahydrofuran was stirred for 4 h at 0—5°C. After evaporation

the residue was dissolved in water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a syrup which was chromatographed on silica gel (13 g). Evaporation of chloroform–1% methanol fractions gave the azo compound *XXX* (10 mg) which was recrystallized from methanol–chloroform–ether to give an orange powder, m.p. 212–215°C, identical with the authentic sample described later.

Amino oxidation of aminoisoquinoline (XI). To a stirred solution of aminoisoquinoline *XI* (0·70 g) in dichloromethane (100 ml) lead tetraacetate (0·99 g) was added in portions during 10 min at −78°C (dry ice–acetone). The mixture was stirred for 1·5 h at −78°C. After the precipitate had been filtered off the filtrate was washed with 5% ammonia and water, dried over sodium sulfate, and evaporated to leave a syrup which was purified on thick layer chromatography using chloroform–methanol (7 : 1). Extraction of the appropriate zone gave the azo compound *XXX* (72 mg) which was recrystallized from methanol–chloroform–ether, orange powder, m.p. 212–215°C. Ultraviolet spectrum (ethanol): 230, 280, 342 nm. PMR spectrum (deuteriochloroform): δ 2·51 (s, 3 H, NCH_3), 3·54 (s, 3 H, OCH_3), 3·80 (s, 3 H, OCH_3), 6·09 (s, 1 H, $C_{(8)}$—H), 6·51 (s, 1 H, $C_{(5)}$—H), 7·19 (d, J = 8 Hz, 2 H, $C_{(3')}$—H and $C_{(5')}$—H), 7·77 (d, J = 8 Hz, 2 H, $C_{(2')}$—H and $C_{(6')}$—H). For $C_{38}H_{44}N_4O_4.1/2\,H_2O$ (629·8) calculated: 72·47% C, 7·20% H, 8·90% N; found: 72·11% C, 7·10% H, 9·01% N.

N-(4-*Benzyloxy*-3-*methoxyphenylethyl*)-4-*nitrophenylpropionamide* (XXIII). A mixture of 4-benzyloxy-3-methoxyphenylethylamine *XVII* (14·5 g) and *p*-nitrophenylpropionic acid *XX* (9·2 g) was heated at 170–180°C for 2 h, allowed to stand at room temperature until it solidified, and recrystallized from methanol to give yellow needles (14·8 g), m.p. 123–125°C. Infrared spectrum potassium bromide): 1 350, 1 515, 1 640, 3 316 cm^{-1}. For $C_{25}H_{26}N_2O_5$ (434·5) calculated: 69·18% C, 6·04% H, 6·46% N; found: 69·38% C, 6·10% H, 6·27% N.

7-*Benzyloxy*-3,4-*dihydro*-6-*methoxy*-1-(4-*nitrophenylethyl*)*isoquinoline methiodide* (XXIX)). A mixture of the amide *XXIII* (14·8 g), phosphoryl chloride (10·34 g) and chloroform (200 ml) was refluxed for 2 h. After evaporation, the residue was treated with water, basified with ammonia and extracted with chloroform. The extract was washed with water, dried with sodium sulfate, and evaporated to give yellow needles of *XXVI* (14 g). A mixture of crude *XXVI* and methyl iodide (15 g) in methanol (100 ml) was refluxed for 30 min. Evaporation and recrystallization of the residue from methanol afforded yellow needles (12·1 g), m.p. 158–159°C. Infrared spectrum (potassium bromide): 1 340, 1 508, 1 623 cm^{-1}. For $C_{26}H_{27}IN_2O_4$ (558·4) calculated: 5·02% N; found: 4·54% N.

1-(4-*Aminophenylethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (XXXI). To a stirred solution of the methiodide *XXIX* (12·1 g) in concentrated hydrochloric acid (300 ml), glacial acetic acid (225 ml) and water (75 ml) zinc powder (90 g) was added during 80 min at room temperature. The stirring was continued at room temperature for 80 min and at 80°C for 30 min. The solid was filtered off and the filtrate was basified with 28% ammonia under cooling with ice and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue after recrystallization from benzene afforded yellow prisms (3·8 g), m.p. 132–133°C. Infrared spectrum (chloroform): 3 380, 3 560 cm^{-1}. PMR spectrum (deuteriochloroform): δ 2·44 (s, 3 H, NCH_3), 3·82 (s, 3 H, OCH_3), 6·50 (s, 1 H, $C_{(8)}$—H), 6·62 (s, 1 H, $C_{(5)}$—H), 6·55 (d, J = 8 Hz, 2 H, $C_{(5')}$—H and $C_{(3')}$—H), 6·97 (d, J = 8 Hz, 2 H, $C_{(2')}$—H and $C_{(6')}$—H). For $C_{19}H_{24}N_2O_2$ (312·4) calculated: 72·86% C, 7·75% H, 8·98% N; found: 72·86% C, 7·72% H, 8·50% N.

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