Total Synthesis of (±)-Amurine

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The diazotisation of 6,7-dimethoxy- and 7-ethoxy-6-methoxy-1-(2-amino-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (XII) and (XV), followed by thermal decomposition, gave amurine (Ib), as a result of which Döpke's structure for the alkaloid was proved to be correct.

AMURINE, isolated from Papaver amurense Hart (syn. P. nudicaule L. var. amurense), together with muramine (II), amurensine (III), amuronine (IV), and amuroline (V), was assigned tentatively the proaporphine structure (Ia) from spectroscopic data by Santavy. However, this structure was revised to the morphinandienone-type structure (Ib) through its chemical degradations and n.m.r. data by Döpke. The biogenesis of amurine (Ib) would involve para-para oxidative coupling of (-)-reticuline (VI), followed by subsequent cyclisation of the resulting o-methoxyphenol (VII). However, amurine could not be synthesised by phenol oxidation of the reticuline (VI) in the laboratory since the structure for amurine has a methylenedioxy-group at the para-position and a hydrogen at the ortho-position to the oxidative coupling site.

In previous papers, the general method for the synthesis of morphinandienone- and homomorphinandienone-type compounds (VIII) and (IX) from the corresponding aminoisoquinolines (X) and (XI) by a modified Pschorr reaction was reported and, therefore, we here wish to report a total synthesis of amurine by this method, which corroborates the structure (Ib) proposed by Döpke.
1-(2-Amino-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XII), which was prepared by the usual method, \(^8\) was diazotised with a slight excess of sodium nitrite and sulphuric acid at 0\(^\circ\)C, and the resulting diazonium salt was decomposed thermally at 70\(^\circ\)C to give the cyclohexadienone in 1.23% yield in addition to the deamination product \(^8\) (XIIa) and a trace of \((\pm\)-epidicentrine (XIII). \(^8\) The following evidence proved our synthetic cyclohexadienone to be \((\pm\)-amurine (Ib).

The high-resolution mass spectrometry of the free base \((M^+; m/e 325.133)\) and the microanalysis of its methiodide verified the molecular formula of \(C_{18}H_{19}NO_4\) Calc. mol. wt. 325.131, which showed the loss of one methyl group. I.r. \([\nu_{\text{max}}(\text{CHCl}_3) 1675, 1645,\) and 1620 cm\(^{-1}\)], u.v. \([\lambda_{\text{max}}(\text{MeOH}) 240\) and 290 nm \((\varepsilon 17,380\) and 8910)], and mass \([m/e 310-106 (M^+ - Me), 297-136 (M^+ - CO), 282-113 (M^+ - Me - CO), 266-117 (M^+ - CO - Me), 254-118 (M^+ - CO - Me - CO), and 240-079 (M^+ - C\(_3\)H\(_2\)N - CO)]\) spectra supported well cross-conjugated \(\alpha\)-methoxycyclohexadienone system. \(^6\),\(^7\),\(^9\) The n.m.r. spectrum \((\tau\) in CDCl\(_3\)) showed the presence of \(N\)-methyl and \(O\)-methyl groups at \(\tau 7.56\) and 6.21 as singlets respectively, methylene protons at \(\tau 4.09\) as a triplet with \(J\sim 1\) c./sec., two olefinic protons at \(\tau 3.72\) (8-H) and 3.68 (5-H) as singlets, and two aromatic protons at \(\tau 3.41\) (1-H) and 3.18 (4-H) as singlets. These data also indicated the presence of an \(\alpha\)-methoxy-cyclohexadienone system and the loss of one methyl group. \(^6\),\(^7\),\(^9\) Moreover, the ratio of the molecular extinction coefficient at 240 and 290 nm in the u.v. spectrum was 2:1 \((17,380:8910)\),\(^9\) and the \(\beta\)-olefinic proton next to the methoxy-group resonated at \(\tau 3.68\). These data also confirmed that the cyclohexadienone was a morphinandienone, namely amurine (Ib), and ruled out structure (XIV). Moreover, this fact was proved to be true by the synthesis of the amurine (Ib) from the second aminoisoquinoline (XV).

The amide (XVIII), prepared by condensation of the 4-ethoxy-3-methoxyphenethylamine (XVI)\(^{11}\) with methyl 3,4-methylenedioxyphenylacetate (XVII),\(^{12}\) was subjected to Bischler-Napieralski reaction with phosphoryl chloride in dry benzene, and the resulting 3,4-dihydroisoquinoline (XIX) was characterised as its hydrochloride. Dihydroisoquinoline (XIX) was converted into the methiodide (XX), followed by reduction with sodium borohydride, to give \(\alpha\)-methyltetrahydroisoquinoline (XXI). The nitration of this tetrahydroisoquinoline (XXI) with concentrated nitric acid in glacial acetic acid and chloroform afforded the 2'-nitroisoquinoline (XXII), which was reduced with zinc and concentrated hydrochloric acid to give the starting aminoisoquinoline (XV).

Diazotisation of the second aminoisoquinoline (XV), followed by thermal decomposition, gave the cyclohexadienone, whose n.m.r. spectrum showed no ethoxy-group but a methoxy-group. If the structure of the cyclohexadienone from the first aminoisoquinoline (XII)
were (XIV), the product from the second aminoisouquinoline (XV) should be (XXIII), which had an ethoxy group and should be different from the product from the first one (XII). However, both products from the two aminoisouquinolines (XII) and (XV) were identical by spectroscopic (i.r. and n.m.r.) and chromatographic comparison and mixed m.p. of their methiodides. These data indicated the product to be (+)-amurine (Ib), and, in fact, the synthetic and the natural amurine were proved to be identical by spectroscopic (i.r. in chloroform and n.m.r. in deuterochloroform) and chromatographic \( R_f \) values (Wakogel, 0.2 mm.; CHCl₃ : MeOH = 5 : 1) comparison. Thus, we have accomplished the total synthesis of amurine, which corroborated the suggested structure by Döpke.

**Experimental**

The i.r. spectra were taken in chloroform with a Hitachi EPI-S, spectrophotometer, and u.v. spectra were taken in methanol on a Hitachi EPS-3 recording spectrophotometer. High-resolution mass spectra were measured on a Hitachi RMU-7 mass spectrometer with peak matching method using perfluorokerosene as a reference. N.m.r. spectra were measured on a Hitachi H-60 in deuteriochloroform using tetramethylsilane as internal standard.

N-(4-Ethoxy-3-methoxyphenethyl)-3,4-methylenedioxyphenylacetamide (XVIII).—A mixture of 4-ethoxy-3-methoxyphenyl ethanamine (XVI)\(^1\) (18 g.) and methyl 3,4-methylenedioxyphenylacetate (XVII)\(^2\) (18 g.) was heated at 180—190° in an oil bath for 2 hr. in 1.5% of concentrated nitric acid (d 1.38; 37.7 ml.) in glacial acetic acid (55 ml.) was added dropwise to a solution of tetrahydroisoquinoline (XXI) (19 g.) in chloroform (200 ml.) with stirring at 5—10° within 0.5 hr. and the stirring was continued for 20 min. at the same temperature as above. The reaction mixture was poured into an excess of ice-water and the organic layer was washed with water, 10% aqueous sodium carbonate, and water. After drying with K₂CO₃, the chloroform layer was evaporated to leave the nitroisouquinoline (XXII) (14 g.) as a brown viscous syrup \( [\rho_{\max} \text{ (CHCl₃)} 1330 \text{ cm}^{-1} \text{ (NO₂)}] \), which was characterised as its picrate. Recrystallisation from methanol gave yellow needles, m.p. 173—175° (Found: C, 51.6; H, 4.6; N, 10.9; C₂₀H₂₂N₂O₂ requires C, 51.5; H, 4.3; N, 11.15%).

1-(2-Amino-4,5-methylenedioxybenzyl)-7-ethoxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XV).—Zinc powder (32 g.) was added in small portions to a stirred mixture of nitroisoquinoline (XXII) (13 g.), concentrated hydrochloric acid (280 ml.), and water (75 ml.) within 0.5 hr. The reaction mixture was then stirred for 0.5 hr. at room temperature and then heated at 90° for 0.5 hr. After the excess of zinc had been filtered off, the colourless filtrate was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K₂CO₃), and evaporated to leave 3,4-dihydroisoquinoline (XIX) (25 g.) as a pale brown viscous syrup, which was characterised as its hydrochloride. Recrystallisation from methanol gave colourless needles, which was characterised as its hydrochloride. Recrystallisation from methanol—ether gave colourless prisms, m.p. 236—239° (decomp.) (Found: C, 63.95; H, 5.9; N, 7.5; C₂₀H₁₇ClN₂O₄ requires C, 63.5; H, 6.3; N, 3.8%), \( \nu_{\max} \text{ (CHCl₃)} 2300—2750 \text{ (=NH)} \), 1645 cm⁻¹ \( \text{ (C=NH)} \).

7-Ethoxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-(3,4-methylenedioxybenzyl)isoquinoline (XXI).—A mixture of the above 3,4-dihydroisoquinoline (25 g.), methyl iodide (22 ml.), and acetone (50 ml.) was allowed to stand for 2 hr. at room temperature, and the excess of methyl iodide and acetone was distilled to leave the methiodide (XX) as a brown viscous syrup. To a solution of this syrup in methanol (800 ml.) was added in small portions with stirring sodium borohydride (10 g.) at 0° and the stirring was continued for 25 min. at 0° and then for 25 min. at room temperature. After refluxing for 0.5 hr., methanol was distilled off, and the residue was decomposed with water. The separated oil was extracted with chloroform, and the extract was washed with water, dried (K₂CO₃), and evaporated to give the tetrahydroisoquinoline (XXI) (19 g.), whose recrystallisation from methanol gave colourless needles, m.p. 84—85° (Found: C, 66.9; H, 6.65; N, 4.3%), \( \nu_{\max} \text{ (CHCl₃)} 2775 \text{ cm}^{-1} \text{ (NCH₃)} \).

7-Ethoxy-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-(4,5-methylenedioxy-2-nitrobenzyl)isoquinoline (XXII).—Concentrated nitric acid (d 1.38; 37.7 ml.) in glacial acetic acid (55 ml.) was added dropwise to a solution of tetrahydroisoquinoline (XXI) (19 g.) in chloroform (200 ml.) with stirring at 5—10° within 0.5 hr. and the stirring was continued for 20 min. at the same temperature as above. The reaction mixture was poured into an excess of ice-water and the organic layer was washed with water, 10% aqueous sodium carbonate, and water. After drying with K₂CO₃, the chloroform layer was evaporated to leave the nitroisouquinoline (XXII) (14 g.) as a brown viscous syrup \( [\rho_{\max} \text{ (CHCl₃)} 1330 \text{ cm}^{-1} \text{ (NO₂)}] \), which was characterised as its picrate. Recrystallisation from methanol gave yellow needles, m.p. 173—175° (Found: C, 51.6; H, 4.6; N, 10.9; C₂₀H₂₂N₂O₂ requires C, 51.5; H, 4.3; N, 11.15%).

1-(2-Amino-4,5-methylenedioxybenzyl)-7-ethoxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XV).—Zinc powder (32 g.) was added in small portions to a stirred mixture of nitroisoquinoline (XXII) (13 g.), concentrated hydrochloric acid (280 ml.), and water (75 ml.) within 0.5 hr. The reaction mixture was then stirred for 0.5 hr. at room temperature and then heated at 90° for 0.5 hr. After the excess of zinc had been filtered off, the colourless filtrate was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K₂CO₃), and evaporated to leave the amino-isouquinoline (XV) (7 g.) as a pale brown viscous syrup, which was unstable in the air and therefore used in the following reaction without purification.

(±)-Amurine.—(a) From 1-(2-amino-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XII).—To a solution of amino-isouquinoline (XII)* (21 g.) in 5% sulphuric acid (70 ml.) was added dropwise 10% sodium nitrite solution (7 ml.) with stirring at 6° during 20 min. and the stirring was continued at 5° for 1 hr. and then at 70° for 1 hr. The cooled mixture was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (K₂CO₃), and evaporated to
leave a dark brown gum (1.2 g.), which was subjected to chromatography on silica gel (50 g.). Evaporation of the first chloroform eluant gave the deamination product (XIIa), whose hydrochloride showed m.p. 222—224°C after recrystallisation from methanol, and then a trace of (+)-epidicentrine (XIII) [α]D (MeOH) 282, 310°mp. Removal of the second methanol-chloroform (2:98) eluant afforded the crude (+)-amurine (Ib) (81.8 mg.) as an orange syrup, which was purified by alumina (10 g.) chromatography using benzene as solvent. Removal of the benzene eluant gave (+)-amurine (Ib) (23.4 mg.) as a pale yellow viscous syrup, vwm (CHCl₃) 1675, 1645, 1620, and 1482 cm.⁻¹, λmax (MeOH) 240 and 280 mp (log ε 4.24 and 3.95), m/e 325-133 (M⁺ - C₂H₃NO₂), 310-106 (M⁺ - Me), 297-136 (M⁺ - CO), 282-113 (M⁺ - CO - Me), 269-074 (M⁺ - C₃H₇N), 266-117 (M⁺ - C₃H₂O₂), 254-118 (M⁺ - CO - CH₃CO), 240-079 (M⁺ - C₃H₂N - CO), τ (CDCl₃) 7.56 (NCH₃, 3H, s), 6.21 (OCH₃, 3H, s), 4-09 (OCH₃O, 2H, J ~ 1 c/sec.), 3.72 (8-H, 1H, s), 3.68 (5-H, 1H, s), 3.41 (1-H, 1H, s), and 3.18 (4-H, 1H, s), Rf 0.60 ± 0.053 (Wakogel, 0.2 mm., CHCl₃; MeOH = 5:1). The i.r. (CHCl₃) and n.m.r. (CDCl₃) spectra of synthetic sample were superimposable on those of natural amurine.

The synthetic amurine was characterised as its methiodide, which was recrystallised from methanol to give pale yellow needles, m.p. 222—224°C (Found: C, 60.65; H, 4.95; N, 2.6. C₁₉H₂₁NO₄·H₂O requires C, 60.45; H, 4.85; N, 2.95%).

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