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A CONVERGENT SYNTHETIC ROUTE TO THE QUETTAMINES AND THE 7,8-DIOXYGENATED TETRAHYDROBENZYLISOQUINOLINE ALKALOIDS

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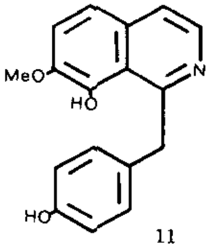
Abstract: (±)-Quettamine (1) chloride, (±)-norjuziphine (12), (±)-juziphine (13) and (±)-oblongine (14) iodide have been synthesized.

The quettamines are a small group of recently discovered isoquinoline alkaloids which incorporate either a benzofuran or a dihydrobenzofuran moiety within the molecular framework. They include (±)-quettamine (1) itself, which is the likely biogenetic precursor for the remaining two members of the group, namely secoquettamine (2) and (±)-dihydrosecoquettamine (3).[1] We now wish to report a synthesis of (±)-quettamine (1) in which the critical O-8 to C-α bond is formed in a manner which emulates, to some extent, the biogenetic pathway.

Treatment of the sodium salt of the known Reissert compound 4[2] with 4-benzyloxybenzaldehyde in benzene supplied benzoate ester 5 (70%) which was hydrolyzed to the corresponding alcohol 6 (70%). Various efforts to cyclize 5 or 6 by forming an O-8 to C-α bond were unsuccessful. It was therefore decided to work within the framework of the tetrahydrobenzylisoquinolines rather than the benzylisoquinolines.

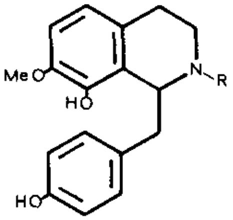
N-Methylation of 6 using methyl iodide in acetonitrile furnished quaternary iodide salt 7 which without purification was subjected to sodium borohydride reduction in a methanol-water mixture. The oily but stereochemically pure racemic tetrahydrobenzylisoquinoline alcohol 8 obtained as the major product was treated with trifluoroacetic acid (TFA) to produce in 35% yield the desired tetracyclic base 10. This cyclization proceeds through the likely intermediacy of benzylic cation 9 that is structurally close to the corresponding benzylic free radical or quinone methide which is the probable intermediate that undergoes cyclization in the natural process.[1]

It is interesting to note that tetracyclic base 10 was obtained as only one racemic diastereomer. The $CDCl_3$ NMR coupling constant between H-1 and H-α for this compound is 10.7 Hz, close to the corresponding coupling constant of 9.8 Hz reported for quettamine (1) chloride in TFA-d.[1] It appeared very likely at this stage, therefore, that TFA cyclization of 8 had proceeded to furnish the required diastereomer of 10 which incorporates a trans relationship between H-1 and H-α.



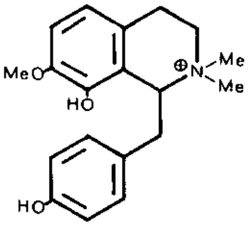
11

15 = MeI salt of 11

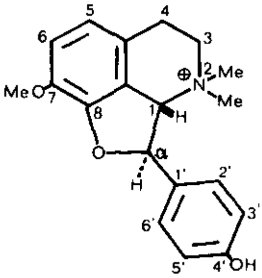


12, R = H

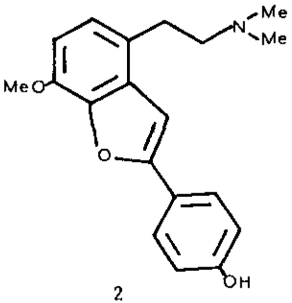
13, R = Me



14



1



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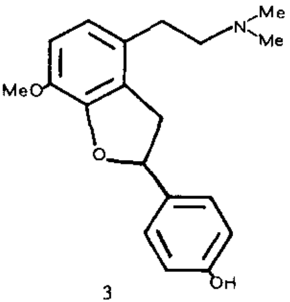

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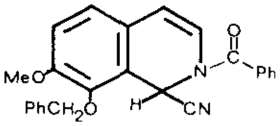

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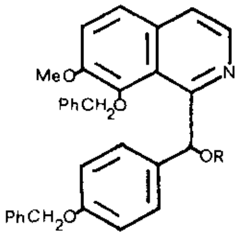
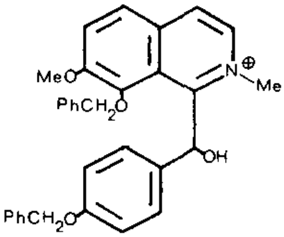


5, R = Benzoyl

6, R = H



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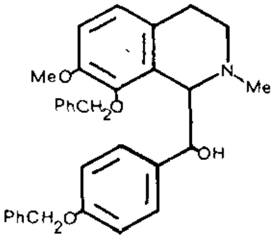

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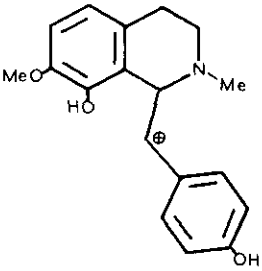

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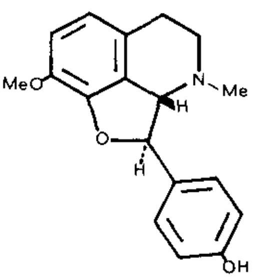

10

Methylation of 10 with methyl iodide gave quaternary iodide *salt* 1 which was passed through a chloride anion exchange column to furnish racemic quettamine (1) chloride, identical with the natural product. Since natural (±)-quettamine (1) is known to possess the relative trans stereochemistry between H-1 and H-α, the synthetic precursor 10 must partake of the identical steric relationship.

It had previously been established[1] that Hofmann elimination of natural quettamine (1) leads to secoquettamine (2), while Emde reduction of 1 yields dihydrosecoquettamine (3), the present sequence thus represents also a synthesis of 2 and 3.

In the course of the above work, it was observed that reaction of alcohol 6 with TFA produced benzylisoquinoline 11 in 30% yield. The yield of 11 could be increased to 60% by using zinc dust and hydrobromic acid in place of TFA. At this stage, benzylisoquinoline 11 seemed to be an appropriate intermediate for the synthesis of the racemic tetrahydrobenzylisoquinoline alkaloids norjuziphine (12),[3] juziphine (13),[4] and oblongine (14),[5] which are oxygenated at C-7 and C-8, and are thus biogenetically related to the quettamines.

Indeed, catalytic reduction of the perchlorate salt of 11 over Adams catalyst led to (±)-norjuziphine (12). On the other hand, quaternization of 11 with methyl iodide gave rise to methiodide salt 15 whose sodium borohydride reduction produced (±)-juziphine (13). Further N-methylation of (±)-juziphine led to (±)-oblongine (14) iodide.

The present effort represents the first syntheses of quettamine (1), secoquettamine (2), and dihydrosecoquettamine (3), as well as of the tetrahydrobenzylisoquinolines norjuziphine (12), juziphine (13), and oblongine (14).

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EXPERIMENTAL

Melting points are uncorrected. IR spectra are in chloroform and UV spectra in methanol solutions. NMR spectra were recorded on a Bruker 200 or 360 MHz Supercon (FT) spectrometer in $CDCl_3$ with TMS as internal standard. TLC was on Merck F-254 silica gel glass plates.

Reissert Compound 4. Prepared as per ref. 2; mp 132-133° C (MeOH), (lit.[2] mp 135° C).

Benzoate Ester 5. A 60% dispersion of NaH in oil (100 mg, 2.5 mmol) was washed free of oil with petroleum ether, and dry benzene (5 mL) was added under a N_2 atmosphere. Reissert compound 4 (500 mg, 1.26 mmol) in dry benzene (10 mL) was added, and the mixture was refluxed for 10 min after which 4-benzyloxybenzaldehyde (268 mg, 1.26 mmol) in dry benzene (5 mL) was added. Heating was continued until TLC showed the disappearance of 4. The product was cooled and 0.5 mL of ethanol added. The mixture was filtered, washed with water, dil hydrochloric acid, and water, and then dried. Filtration and solvent evaporation left crude crystals which were recrystallized from methanol, *510 mg (70%)*, $C_{38}H_{31}NO_5$, *mp 160-161° C (MeOH)*, IR *ν max 1715* cm^{-1}; R_f *0.62* ether-benzene (10:90 v/v).

Alcohol 6. *Hydrolysis of 5 in ethanol was with aq potassium* hydroxide and refluxing under N_2 overnight. The yield of 6, $C_{31}H_{27}NO_4$, was 70%, mp 93-94° C (ether-MeOH); IR νmax 3320 cm^{-1} (broad); R_f 0.14 ether-benzene (10:90).

Alcohol 8. A mixture of 6 in acetonitrile and methyl iodide was refluxed overnight with periodic additions of methyl iodide. Work-up gave the methiodide salt. This was dissolved in methanol-water, and sodium borohydride was added. The mixture was refluxed for 3 h. Work-up gave as the major product oily 8, $C_{32}H_{33}NO_4$, in 50% yield, NMR δ 2.20 (3H, s, NCH_3), 3.91 (1H, m, H-1), 3.93 (3H, s, OCH_3), 4.97 (2H, s, OCH_2Ph), 5.02 (2H, d, J_{gem} 11.0 Hz, CH_2Ph), 5.25 (1H, d, J_{vic} 11.0 Hz, H-α), 6.71 (2H, d, J_{vic} 8.5 Hz, ArH), 6.72 (1H, d, J_{vic} 8.3 Hz, ArH), 6.88 (2H, d, J_{vic} 8.5 Hz, ArH), 7.31 (1H, d, J_{vic} 8.3 Hz, ArH), 7.26-7.43 (10H, m, ArH); MS m/e 496 $(M + 1)^+$ (0.1), 91 (100); R_f 0.65 MeOH-$CHCl_3$ (3:97).

Tetracyclic Base 10. Alcohol 8 (100 mg, 0.2 mmol) was stirred in TFA for 18 h. The solvent was removed without excessive heating, and the residue partitioned between aq sodium bicarbonate and ethyl acetate. The organic layer was dried, filtered, and the solvent evaporated. TLC of the residue afforded 21 mg (35%) of colorless crystals, $C_{18}H_{19}NO_3$, mp 187-189° C decomp (MeOH); λmax 208, 231, 275 nm (log ε 4.49, 4.26, 4.04); NMR δ 2.13 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.22 (1H, q, H-1), 5.37 (1H, d, J 10.7 Hz, H-α), 6.68 (1H, d, J 8.3 Hz, ArH), 6.78 (1H, d, J 8.3 Hz, ArH), 6.84 (2H, d, J 8.6 Hz, ArH), 7.46 (2H, d, J 8.6 Hz, ArH); MS m/e 297 (M^+, 76), 174 (100); R_f 0.57 MeOH-$CHCl_3$ (3:97).

(±)-Quettamine (1). Base 10 *was dissolved in acetonitrile and methyl iodide, and the mixture* refluxed for 1 h. Work-up gave 1 iodide, which was dissolved in MeOH-acetone (3:1) and passed through an Amberlite IRA-400 chloride column. Evaporation of the solvent afforded amorphous 1 chloride in 91% yield, identical with the natural product.

Diphenol 11. Alcohol 6 (100 mg, 0.21 mmol) was dissolved in 2 mL of TFA, and the mixture stirred overnight. Excess TFA was removed without excessive heating, and the residue partitioned between aq sodium bicarbonate and chloroform. The organic layer was dried, filtered, and the solvent evaporated. TLC of the residue afforded 11 (18 mg, 30%), $C_{17}H_{15}NO_3$, mp 219-221° C decomp (ethyl acetate-MeOH); NMR δ 4.00 (s, 3H, OCH_3), 4.85 (s, 2H, H-α), 6.64 (2H, d, J 8.5 Hz, ArH), 7.10 (2H, d, J 8.5 Hz, ArH), 7.35 (1H, d, J 8.8 Hz, ArH), 7.39 (1H, d, J 5.5 Hz, ArH), 7.41 (1H, d, J 8.8 Hz, ArH), 8.30 (1H, d, J 5.5 Hz, ArH); MS m/e 281 (M^+, 12), 57 (100); R_f 0.79 MeOH-$CHCl_3$ (8:92).

Alternatively, 6 (200 mg, 0.42 mmol) in acetic acid (6 mL) was cooled to 10° C, and HBr gas passed for 10 min. The mixture was allowed to stand for 12 h at 10° C. Zinc dust (275 mg, 4.2 mmol) was added over 15 min, and the solution heated at 60° C for 30 min. Work-up afforded 11 (71 mg, 60%).

(±)-Norjuziphine (12). A solution of 11 (100 mg, 0.36 mmol) in 30 mL of ethanol containing 70% perchloric acid was hydrogenated over Adams catalyst at 35 psi for 2 h. Work-up, including neutralization with ammonium hydroxide, and TLC, afforded amorphous 12, 45 mg (45%), identical with the natural product,[3] NMR δ 3.88 (3H, s, OCH_3), 4.41 (1H, close dd, H-1), 6.62 (1H, d, J 8.3 Hz, ArH), 6.69 (2H, d, J 8.0 Hz, ArH), 6.74 (1H, d, 8.3 Hz, ArH), 7.11 (2H, d, J 8.0 Hz, ArH).

(±)-Juziphine (13). A mixture of 11 (100 mg, 0.35 mmol) in methanol and methyl iodide was refluxed for 8 h. The salt 15 was then reduced with sodium borohydride to give oily 13, 64 mg (60%), identical with the natural product;[4] NMR δ 2.40 (3H, s, NCH_3), 3.89 (3H, s, OCH_3), 4.19 (1H, close q, H-1), 6.45 (2H, d, J = 8.5 Hz, ArH), 6.63 (1H, d, J 8.2 Hz, ArH), 6.75 (1H, d, J 8.2 Hz, ArH), 7.07 (2H, d, J 8.5 Hz, ArH).

(±)-Oblongine (14) Iodide. Free base 13 *(50 mg, 0.167 mmol) in methanol was refluxed with methyl* iodide (0.5 mL) for 1 h. Additional methyl iodide was added at intervals. Work-up afforded 66 mg

(90%) of amorphous material, identical with natural oblongine iodide;[5] NMR (TFA-*d*) δ 3.17 and 3.28 (2 x 3H, s, $N(CH_3)_2$), 4.01 (3H, s, OCH_3), 5.01 (1H, m, H-1), 6.91 (1H, d, J 8.0 Hz, ArH), 6.95 (2H, d, J 7.8 Hz, ArH), 7.08 (2H, d, J 7.8 Hz, ArH), 7.11 (1H, d, J 8.0 Hz, ArH).

References and Footnotes

1. M.H. Abu Zarga, G.A. Miana and M. Shamma, Tetrahedron Lett., 22, 541 (1981).
2. B.C. Uff, J.R. Kershaw and S.R. Chhabra, J. Chem. Soc., Perkin I, 479 (1972); and A.H. Jackson and G.W. Stewart, Chem. Commun., 149 (1971). See also L.R. Walters, N.T. Iyer and W.E. McEwen, J. Am. Chem. Soc., 80, 1177 (1957); and H.W. Gibson and F.D. Popp, J. Chem. Soc. (C), 1860 (1966).
3. Norjuziphine (12) has been found in Fumaria vaillantii Loisel. (Fumariaceae), where it is reported to have $[\alpha]_D$ -18° (MeOH): M. Alimova, I.A. Israilov, M.S. Yunusov and S. Yu. Yunusov, Khim. Prirodn. Soedin., 874 (1979); Chem. Natural Compounds, 783 (1980). Racemic norjuziphine (12) is present in Polyalthia acuminata Thwait (syn. Enicosanthum acuminatum Thwait) (Annonaceae): M. Shamma and M.H. Abu Zarga, unpublished results.
4. Juziphine (13) has been found in Ziziphus jujuba Mill. (Rhamnaceae), where it is reported to have $[\alpha]_D$ +18° ($CHCl_3$): R. Ziyaev, T. Irgashev, I.A. Israilov, N.D. Abdullaev, M.S. Yunusov and S. Yu. Yunusov, Khim. Prirodn. Soedin., 239 (1977); Chem. Natural Compounds, 204 (1977). Racemic 13 is present in Polyalthia acuminata as in Ref. 3.
5. Oblongine (14), as the iodide salt, has been found in Berberis oblonga where it apparently has $[\alpha]_D$ +8.5° (MeOH): A. Karimov, N.D. Abdullaev, M.V. Telezhenetskaya, K. Lutfullin and S. Yu. Yunusov, Khim. Prirodn. Soedin., 117 (1976); Chem. Natural Compounds, 111 (1976). Racemic oblongine is present in Tiliacora funifera Engl., ex Diels (Menispermaceae): A.N. Tackie, J.B. Reighard, M.M. El-Azizi, D.J. Slatkin, P.L. Schiff, Jr., and J.E. Knapp, Phytochem., 19, 1882 (1980); as well as in Berberis zabeliana Schneider and B. baluchistanica Ahrendt (Berberidaceae): M. Shamma, M.H. Abu Zarga and J.E. Leet, unpublished results. Our synthetic 12, 13, and 14 corresponded with natural racemic 12, 13, and 14, respectively.

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