FISCHER INDOLIZATION OF THE PHENYLHYDRAZONES FROM 3-ETHYL- AND 3-(2-METHYLPROPYL)-SUBSTITUTED 1,3,4,6,7,11b-HEXAHYDRO-9,10-DIMETHOXY-2H-BENZO[a]QUINOLIZIN-2-ONE. IDENTIFICATION OF THE INDOLO[1',2':3,4]PYRIMIDO[6,1-a]ISOQUINOLINE SKELETON

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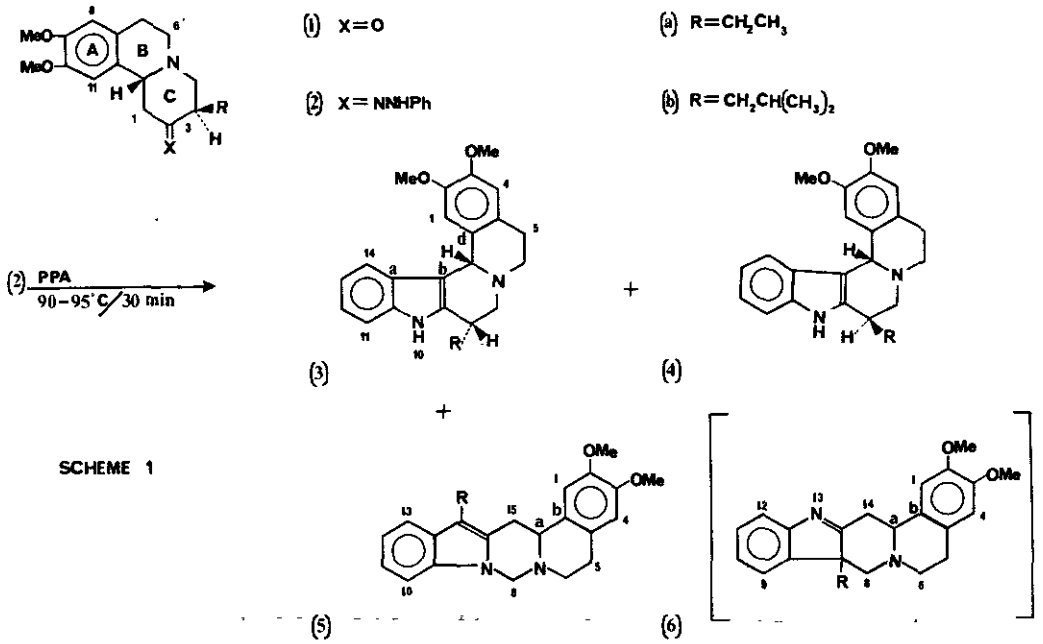
Abstract - A Fischer indolization of the phenylhydrazone (2a) derived from 3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizin-2-one (1a) gave the three products (3a), (4a) and (5a). The identity of (3a) and (4a) as diastereomeric benz[a]indolo[2,3-h]quinolizine derivatives was confirmed, but the third product, previously assigned the benz[a]indolo[3,2-g]quinolizine structure (6a), was identified as the indolo[1',2':3,4]pyrimido[6,1-a]isoquinoline derivative (5a), a representative of a new ring system. Similar results were obtained from the 3-(2-methylpropyl)- analogue (1b) ("Tetrabenazine") of the ketone (1a); indolization of its phenylhydrazone (2b) gave rise to (3b), (4b) and (5b).

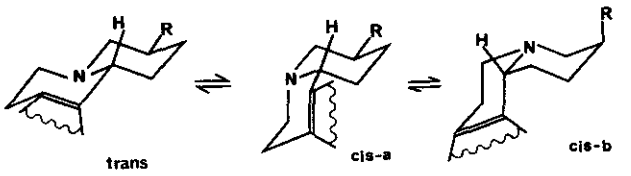
As part of a programme aimed at the synthesis of analogues and relatives of alkaloid and other azaheterocyclic systems, notably those with potential CNS activity, the synthesis of derivatives of some indolo[1,2] systems has been undertaken. Of particular interest was the extension of our studies on fused medium-ring heterocycles to the preparation of new systems containing the indolo[2] or isosteric [1]benzothieno[3] moieties, by cyanogen bromide-induced ring expansions of polycyclic precursor bases.

Hexahydrobenz[a]indolo[3,2-h]quinolizines, analogues of recently reported benzo[1]benzothieno-quinolizines[3], have been prepared by several routes[4]; however, derivatives of the isomeric benz[a]indolo[2,3-h]quinolizine skeleton have only been reported once previously, by Gerszberg et al.[6] in 1972. These workers described the Fischer indolization of phenylhydrazones of type (2), derived from ketones of type (1), to give in each case three products, to which structures of types (3), (4) and (6) were assigned[6]. In 1982 Robinson[7] queried the claimed structures (6), suggesting that they might have rearranged, by a mechanism described by Ebnöther et al.[8] for the indolization of 1,3-disubstituted piperidin-4-one arylhydrazones, to compounds of type (5), derivatives of the as



SCHEME 1

Note: Stereochemistry shown is relative.



Conformational equilibria in benzo[a]quinolizidines

yet undescribed indolo[1',2':3,4]pyrimido[6,1-a]isoquinoline skeleton. Such a reformulation would, for example, explain[7] the absence of diastereomeric products for these compounds, as (5) has only one chiral centre, while (6) has two.

This paper describes the investigation and clarification of these structural problems raised by the Fischer indolization reactions performed by Gerszberg[6], starting with the ketones (1a) and (1b). This latter case is of particular interest as 'Tetrabenazine' (1b) is used as a tranquilizer, and neither its phenylhydrazone, nor derived indolization reactions, appear to have been reported.

The stereochemistry of benzoquinolizidines has been extensively studied[cf10,11]; B/C ring stereochemistry is interpreted in terms of three interconvertible forms: trans, cis a and cis b (see above).

Spectroscopic data for the ketones (1a) and (1b) indicated that they exist mainly in the

trans form, in agreement with Sugiura for (1, R=H)[11]. Particularly characteristic were the chemical shifts for the C6 and C7 carbon atoms, and for the H-11b proton, which were at δ 50.3, 29.2, and 3.52, d, J 10Hz (1a), and at δ 50.6, 29.8, and 3.50, d J 10Hz (1b), respectively. The 3-ethyl group and the 11b-hydrogen in (1a) have cis relative stereochemistry[9], and the same situation is thought to apply for (1b) on the basis of nmr spectroscopic similarities.

The preparation of the phenylhydrazones (2a) and (2b) proceeded readily, but both compounds were somewhat unstable in all solutions tested.

The Fischer indolization of the phenylhydrazone (2a) proceeded smoothly under conditions similar to those previously reported[6] (Scheme 1). Three main products were formed; those of lowest R_f were characterized as the diastereomeric benzo[a]indolo[2,3-h]quinolizidines (3a) (28%) and (4a) (11%). The high-field ^1H nmr and ^{13}C nmr spectra of both diastereomers generally supported the configurational and conformational conclusions reached by Gerszberg[6]. However, in (3a) the signal for the methylene protons of the ethyl group appeared as two one-proton multiplet arms at 1.4-1.5 ppm and 1.8-1.9 ppm.

Although Gerszberg[6] did not specify which type of cis conformation was preferred in compounds (3a) and (4a) his diagrams suggested a cis b (cis$_1$[5]) conformation. The cis b conformation was supported by the chemical shifts of the C5 and C6 carbons which were 23.0 and 51.6ppm for (3a) and 24.1 and 50.4ppm respectively for (4a).[10,11]

The Fischer indolization of the phenylhydrazone (2b) also gave three main products, of which the spectroscopic data for the two of lowest R_F corresponded closely to those observed for (3a) and (4a). These products were identified as (3b) (33%) and (4b) (14%). The chemical shifts of the C6 and C5 carbons again indicated a cis b conformation for both diastereomers, being at 51.6 and 23.1 ppm for (3b) and at 51.3 and 24.6 ppm for (4b), respectively.

Assignment of the structures of the third, and highest R_F products from the indolization of (2a) and (2b) as the fused indolopyrimidines (5a) and (5b) respectively, and not the previously assigned[6] indoloquinolizidine structure as in (6a) and (6b), is based on the following evidence:

In the ^1H nmr spectrum of (5a) the signal attributed to the 8-CH_2 protons consisted of two doublets at δ 4.78 and 5.17 (J 10Hz), respectively. It would be unlikely for the 8-CH_2 proton signal from (6a) to be so far downfield, as there is only one adjacent N atom. In (5a) the position of this downfield signal is explicable, as the 8-CH_2 group is flanked by two N atoms, one of which is part of an indolic ring system. Comparison with proton shifts observed in similar environments[8] supported this assignment. In the ^{13}C nmr spectrum of this product the C8 signal was at 66.1 ppm, again considered to be too far downfield if this C atom was adjacent to only one N atom[12]; CH connectivity correlations from 2D- nmr confirmed the structure as (5a) and not (6a). The chemical

shift of the multiplet at 2.7-2.8ppm assigned to the methylene protons of the ethyl group is more consistent with (5a) than (6a), as in (5a) these protons would be attached to a carbon which was adjacent to an unsaturated carbon of an indole ring. The uv spectrum was similar to those of the two lower R_F diastereomeric indole products (3a) and (4a), suggestive of an indole derivative rather than an indolenine. There was also no C=N absorption in the ir, and no obvious imine quaternary carbon signal, expected near 170ppm[12], in the ^{13}C nmr spectrum.

Treatment of (5a) with 5M HCl was reported to give[13] a substantial amount of 6,7-dimethoxy-3,4-dihydroisoquinoline. Gerszberg[13] used this fact to support structure (6a), based on observations of Brossi et al.[14] that the formation of hexahydro-2H-benzo[a]quinolizin-2-ones from 3,4-dihydroisoquinolines and methyl vinyl ketones was reversible. However this mechanism cannot be applied to (6a) as one of the necessary tautomeric equilibria is blocked by the ethyl substituent. A satisfactory mechanism for the above fragmentation of (5a) can be proposed, however, involving initial hydrolytic cleavage of the N-CH_2-N grouping.

The chemical shifts of the C5, C6 and H15a signals in the relevant nmr spectra of (5a) were 29.0, 46.0 and 4.00 ppm respectively, suggesting a preferred cis a conformation[11].

The above arguments applied similarly to spectroscopic data on the third, high R_F, product of the indolization reaction of the phenylhydrazone (2b) of the 3-(2-methylpropyl) ketone, which was therefore identified as the indolopyrimidoisoquinoline derivative (5b), not the benzindoloquinolizidine structure (6b). This assignment was also confirmed by CH correlations from 2D- nmr analysis. The corresponding C5, C6 and H15a signals were observed at 28.9, 46.0 and 3.97 ppm, respectively, again indicating a preferentially cis a conformation.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were measured at 300MHz, and ^{13}C NMR spectra at 75 MHz on a Bruker AM300 spectrometer, in $CDCl_3$ as solvent and tetramethylsilane as internal standard; assignments with the same superscript letters may be interchanged. MS were determined on a V.G. MM 7070F mass spectrometer. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. UV spectra were recorded on a Varian DMS100 UV-Visible spectrophotometer. R_F values refer to TLC on silica gel and chromatographic solvent mixtures were made up by volume. Assigned stereochemistry is relative.

(3R*,11bR*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizin-2-one (1a). This compound was prepared essentially by the method of Whittaker[15]. ^{13}C NMR δ: 210.1, C2; ^{A}148.1, C10; ^{A}147.7, C9; 128.9, C11a; 126.4, C7a; 111.3, C8; 107.7, C11; 62.2, C11b; 60.6, C4; ^{B}55.8, 10-OCH_3; ^{B}55.7, 9-OCH_3; 50.9, C3; 50.3, C6; 47.4, C1; 29.2, C7; 19.1, CH_2CH_3; 11.5, CH_2CH_3.

(3R*,11bR*)-1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one (1b). This compound was obtained from Roche Products Pty. Ltd., Sydney. mp 125-126°C (lit.[16] 125-126°). ^{13}C NMR δ: 210.3, C2; A148.0, C10; A147.8, C9; 128.8, C11a; 126.3, C7a; 111.7, C8; 108.0, C11; 62.7, C11b; 61.7, C4; 56.2, 2xOCH_3; 50.6, C6; 47.6, C1; 47.5, C3; 35.4, $CH_2CH(CH_3)_2$; 29.8, C7; 25.9, $CH_2CH(CH_3)_2$; 23.3, $CH_2CH(CH_3)CH_3$; 20.6, $CH_2CH(CH_3)CH_3$.

(3R*,11bR*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizin-2-one Phenylhydrazone (2a). To a refluxing solution of the ketone (1a) (10.1 g, 0.035 mol) and glacial acetic acid (2.1g, 0.035 mol) in EtOH (100 ml) was added phenylhydrazine (5.3 g, 0.049 mol). The solution was refluxed for 3 h under N_2, cooled to room temperature and concentrated to 30 ml. The solid that formed at 4°C overnight was filtered off and washed with EtOH (100 ml) to give the phenylhydrazone (2a) as a colourless microcrystalline powder (9.3 g, 70%), mp 169-170°C. R_F 0.6 ($CHCl_3$/5% MeOH). This compound was prepared by Gerszberg[6], but was not purified nor characterised. MS: m/z 379 (M, 55%, accurate mass 379.2258. $C_{23}H_{29}N_3O_2$ calc. $M^{+\cdot}$, 379.2260), 287(15), 246(20), 206(20), 205(100), 192(96), 191(25), 190(44), 188(44), 159(26), 93(35). IR (nujol): 3340 (NH), 1604 (C=N) cm^{-1}. ^1H NMR δ: 7.15-7.3, m, 2ArH, NH; 7.0-7.15, m, 2ArH; 6.75-6.85, m, ArH; 6.72, s, ArH; 6.60, s, ArH; 3.82, s, OCH_3; 3.78, s, OCH_3; 2.9-3.2, m, $2CH_2$, CH; 2.4-2.7, m, $2CH_2$; 2.0-2.1, m, CH; 1.7-1.8, m, 3-CH_2CH_3; 0.90, t, J 7.4 Hz, 3-CH_2CH_3.

(3R*,11bR*)-1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one Phenylhydrazone (2b). The 3-(2-methylpropyl)ketone (1b) (11.1 g, 0.035 mol) was reacted by the same procedure used above; the phenylhydrazone (2b) was obtained as a microcrystalline colourless powder (11.4 g, 80%), mp 168-170°C. R_F 0.65 ($CHCl_3$/5% MeOH). MS: m/z 407 (M, 34%, accurate mass 407.2561. $C_{25}H_{33}N_3O_2$ requires $M^{+\cdot}$, 407.2572), 315(10), 216(15), 206(17), 205(93), 192(100), 190(30), 159(22), 93(23). IR (nujol): 3340 (NH), 1604 (C=N) cm^{-1}. ^1H NMR δ: 7.5-7.6, m, NH; 7.2-7.3, m, 2ArH; 7.1-7.15, m, 2ArH; 6.85-6.90, m, ArH; 6.74, s, ArH; 6.62, s, ArH; 3.82-3.92, m, 2xOCH_3; 2.4-3.4, m, 8H; 1.1-2.3, m, 5H; 0.80-1.0, m, $3CH_2CH(CH_3)_2$. Anal. Found: C, 73.51; H, 8.05; N, 10.31. $C_{25}H_{33}N_3O_2$ requires C, 73.67; H, 8.16; N, 10.31%.

General Procedure for the Fischer Indolization of the Phenylhydrazones (2a) and (2b). A mixture of the phenylhydrazone (8 g) and polyphosphoric acid (100 ml) was stirred vigorously at 90-95°C for 30 min. After pouring into crushed ice, the mixture was kept at 0°C for 2 h with occasional stirring. The resulting suspension was basified with 12M NaOH and extracted with 5% MeOH/$CHCl_3$ (3x150 ml). The extracts were dried (Na_2SO_4) and evaporated to give the crude mixture of products.

A. Indolization of 3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizin-2-one phenylhydrazone (2a) gave a crude product which showed three main compounds by TLC, R_F 0.80, 0.33 and 0.16 ($CHCl_3$/5% MeOH). Column chromatography on silica gave the following:

(i) 14-Ethyl-5,6,15,15a-tetrahydro-2,3-dimethoxyindolo[1',2':3,4]pyrimido[6,1-a]isoquinoline (5a) was firstly eluted. Recrystallization from CH_2Cl_2/hexane gave the indolopyrimidine (5a) as pale yellow prisms (2.90 g, 39%), mp 166-167°C (lit.[6] 167-168°C). MS: m/z 362 (M, 17%, accurate mass 362.1993. $C_{23}H_{26}N_2O_2$ calc. $M^{+\cdot}$, 362.1994), 172(18), 171(100), 156(30), 115(10). UV ($CHCl_3$/50% MeOH): λ_{max} (log ε) 285 (4.78), 289 sh. nm (4.75). ^{1}H NMR δ : 7.55-7.65, m, H13; 7.1-7.3, m, 3ArH; 6.73, s, 6.68, s, H1 and H4; 5.17, d, 4.78 d, J 10Hz, $8CH_2$; 4.00, dd, J_1 11.6Hz, J_2 4.2Hz, H15a; 3.93, s, OCH_3; 3.89, s, OCH_3; 3.25-3.4, m, CH of $6CH_2$, CH of $15CH_2$; 2.8-3.05, m, 4H; 2.7-2.8, m, CH_2CH_3; 1.25, t, J 7.5Hz, CH_2CH_3. ^{13}C NMR δ : ^{A}147.9, C3; ^{A}147.5, C2; 134.7, C9a; ^{B}129.9, C14a; ^{B}129.6, C13a; ^{B}128.0, C15b; 125.7, C4a; 120.4, C11; 119.1, C12; 118.3, C13; 112.7, C14; 111.6, C4; ^{C}108.8, C1; ^{C}108.4, C10; 66.1, C8; 56.4, C15a; 56.1, OCH_3; 55.9, OCH_3; 46.0, C6; 29.0, C5; 28.1, C15; 17.0, CH_2CH_3; 15.3, CH_2CH_3.

(ii) (9R*,14cS*)-9-Ethyl-5,6,8,9,10,14c-hexahydro-2,3-dimethoxybenz[a]indolo[2,3-h]quinolizine (4a) was secondly eluted from the column. Recrystallization from CH_2Cl_2/hexane gave the indoloquinolizine (4a) as colourless needles (0.81 g, 11%), mp 102-104°. MS: m/z 362 (M, 56%, accurate mass 362.1979. $C_{23}H_{26}N_2O_2$ calc. $M^{+\cdot}$, 362.1994), 361(100), 358(15), 357(10), 333(11), 331(13), 306(11), 305(10). ^{13}C NMR δ : 147.5, C2 and C3; ^{A}136.4, C9a; ^{A}136.0, C10a; 129.7, C14d; 127.4, C14a; 125.4, C4a; 121.1, C12; 119.5, C13; 119.0, C14; 114.9, C14b; 111.4, C4 and C1; 110.8, C11; 56.0, C14c; 55.8, $2xOCH_3$; 50.4, C6; 48.9, C8; 35.2, C9; 26.9, CH_2CH_3; 24.1, C5; 12.3, CH_2CH_3.

(iii) (9R*,14cR*)-9-Ethyl-5,6,8,9,10,14c-hexahydro-2,3-dimethoxybenz[a]indolo[2,3-h]quinolizine (3a) was thirdly eluted from the column. Recrystallization from CH_2Cl_2/hexane gave the indoloquinolizine (3a) as colourless needles (2.13 g, 28%), mp 160-162° (lit.[6] 117-119°C). MS: m/z 362 (M, 50%, accurate mass 362.1977. $C_{23}H_{26}N_2O_2$ calc. $M^{+\cdot}$, 362.1994), 361(100), 358(11), 357(7), 333(7), 331(12), 306(7), 305(7). ^{13}C NMR δ : 147.4, C2 and C3; ^{A}136.7, C9a; ^{A}136.1, C10a; 130.1, C14d; 127.8, C14a; 124.7, C4a; 121.2, C12; 119.7, C13; 118.5, C14; 112.3, C14b; ^{B}111.5, C1; ^{B}111.3, C4; 110.8, C11; 55.8, $2xOCH_3$; 55.5, C14c; 51.6, C6; 49.0, C8; 36.1, C9; 25.2, CH_2CH_3; 23.0, C5; 11.1, CH_2CH_3.

B. Indolization of 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one phenylhydrazone (2b) gave three main products. R_F 0.71, 0.36 and 0.26 ($CHCl_3$/5% MeOH). Column chromatography on silica gave the following:

(i) 5,6,15,15a-Tetrahydro-2,3-dimethoxy-14-(2-methylpropyl)indolo[1',2':3,4]pyrimido[6,1-a]-isoquinoline (5b) was firstly eluted from the column. Recrystallization from CH_2Cl_2/hexane gave the indolopyrimidine (5b) as yellow prisms (1.88 g, 25%), mp 129-130°C. MS: m/z 390 (M, 19%), 389 (M-H,

1%, accurate mass 389.2222. $C_{25}H_{29}N_2O_2$ requires M-H, 389.2227), 317(10), 316(19), 274(31), 260(24), 232(11), 205(12), 199(47), 191(61), 187(21), 156(39), 144(100). UV (MeOH): λ_{max} (log ε) 234 (4.62), 286 (4.20), 291 nm (4.11). ^{1}H NMR δ : 7.5-7.6, m, H13; 7.2-7.3, m, H10; 7.05-7.2, m, 2ArH; 6.67, s, 6.63, s, H1 and H4; 5.17, d, 4.77, d, J 10Hz, 8-CH_2; 3.97, dd, J_1 11.4Hz, J_2 4.4Hz, H15a; 3.91, s, OCH_3; 3.87, s, OCH_3; 3.2-3.3, m, CH of 6-CH_2, CH of 15-CH_2; 2.8-3.0, m, CH of 5-CH_2, CH of 6-CH_2, CH of 15-CH_2; 2.35-2.7, m, CH of 5-CH_2, $CH_2CH(CH_3)_2$; 1.95-2.05, m, $CH_2CH(CH_3)_2$; 0.96, d, J 6.6Hz, $CH_2(CH_3)CH_3$; 0.88, d, J 6.6Hz, $CH_2CH(CH_3)CH_3$. ^{13}C NMR δ : ^{A}147.8, C3; ^{A}147.4, C2; 134.6, C9a; 131.0, C14a; ^{B}129.5, C13a; ^{B}128.7, C15b; 125.7, C4a; 120.2, C11; 119.0, C12; 118.5, C13; 111.6, C4; 110.4, C14; ^{C}108.9, C1; ^{C}108.3, C10; 66.1, C8; ^{D}56.5, 3-OCH_3; ^{D}56.1, 2-OCH_3; 55.8, C15a; 46.0, C6; 33.1, $CH_2CH(CH_3)_2$; 29.7, $CH_2CH(CH_3)_2$; 28.9, C5; 28.4, C15; 22.8, $CH_2CH(CH_3)CH_3$; 22.6, $CH_2CH(CH_3)CH_3$. Anal. Found: C, 76.55; H, 7.75. $C_{25}H_{30}N_2O_2$ requires C, 76.89; H, 7.74%.

(ii) (9R*,14cS*)-5,6,8,9,10,14c-Hexahydro-2,3-dimethoxy-9-(2-methylpropyl)benz[a]indolo[2,3-h]-quinolizine (4b) was secondly eluted from the column. Recrystallization from CH_2Cl_2/hexane gave the indoloquinolizine (4b) as colourless needles (1.04 g, 14%), mp 177-179°C. A trace of CH_2Cl_2 was observable in the ^{1}H nmr spectrum of the analytical sample. MS: m/z 390 (M, 56%), 389 (M-H, 100%), accurate mass 389.2225. $C_{25}H_{29}N_2O_2$ requires M-H, 389.2227), 347(15), 344(20), 334(15), 333(18), 331(16), 306(15), 305(14). IR (nujol): 3360 (NH) cm^{-1}. UV (MeOH): λ_{max} (log ε) 228 (4.50, 282 (3.70), 289 nm (3.66). ^{1}H NMR δ : 8.15, bs, NH; 7.6-7.7, m, ArH; 7.2-7.3, m, ArH; 7.0-7.2, m, 3ArH; 6.61, s, H4; 5.27, s, H14c; 3.81, s, 3-OCH_3; 3.58, s, 2-OCH_3; 3.4-3.6, m, CH of 6-CH_2; 3.2-3.4, m, CH of 6-CH_2, CH of 8-CH_2; 2.9-3.1, m, 9-CH, CH of 5-CH_2; 2.6-2.9, CH of 5-CH_2, CH of 8-CH_2; 1.7-1.85, m, $CH_2CH(CH_3)_2$; 1.5-1.6, m, $CH_2CH(CH_3)_2$; 0.9-1.0, m, $CH_2HC(CH_3)_2$. ^{13}C NMR δ : ^{A}148.0, C3; ^{A}147.6, C2; ^{B}137.5, C9a; ^{B}136.6, C10a; 130.4, C14d; 128.0, C14a; 126.0, C4a; 121.6, C12; 120.1, C13; 119.4, C14; 115.5, C14b; ^{C}112.1, C4 and C11; ^{C}111.4, C1; 56.5,56.4, 2xOCH_3; 55.6, C14c; 51.3, C6; 49.8, C8; 43.8, $CH_2CH(CH_3)_2$; 32.0, C9; 26.5, $CH_2CH(CH_3)_2$; 24.6, C5; 24.1, $CH_2CH(CH_3)CH_3$; 22.6, $CH_2CH(CH_3)CH_3$. Anal. Found: C, 74.34; H, 7.56; N, 6.92. $C_{25}H_{30}N_2O_2(0.2CH_2Cl_2)$ requires C, 74.28; H, 7.52; N, 6.90%.

(iii) (9R*,14cR*)-5,6,8,9,10,14c-Hexahydro-2,3-dimethoxy-9-(2-methylpropyl)benz[a]indolo[2,3-h] quinolizine (3b) was thirdly eluted from the column. Recrystallization from CH_2Cl_2/hexane gave the indoloquinolizine (3b) as colourless needles (2.52 g, 33%), mp 160-162°C. A trace of CH_2Cl_2 was observable in the ^{1}H NMR spectrum of the analytical sample. MS: m/z 390 (M, 40%, accurate mass 390.2311. $C_{25}H_{30}N_2O_2$ requires $M^{+\cdot}$, 390.2305), 389(80), 386(27), 385(18), 345(27), 344(100), 331(25), 329(11), 206(35), 182(16), 172(12). IR (nujol): 3150 (NH) cm^{-1}. UV (MeOH): λ_{max} (log ε) 234 (4.34), 282 (4.06), 289 nm (4.01). ^{1}H NMR δ : 8.1, bs, NH; 7.65-7.70, m, ArH; 7.25-7.35, m,

ArH; 7.0-7.2, m, 3ArH; 6.61, s, H4; 5.30, s, H14c; 3.85, s, 3-OCH_3; 3.56, s, 2-OCH_3; 3.55-3.65, m, CH of CH_2; 3.0-3.45, m, 4H; 2.6-2.8, m, 2H; 1.35-1.8, m, $CH_2CH(CH_3)_2$; 0.97, d, J 6.5Hz, $CH_2CH(CH_3)CH_3$; 0.90, d, J 6.5Hz, $CH_2CH(CH_3)CH_3$. ^{13}C NMR δ : 147.3, 147.2, C2 and C3; ^{A}137.0, C9a; ^{A}136.0, C10a; 130.1, C14d; 127.7, C14a; 124.7, C4a; 120.9, C12; 119.5, C13; 118.3, C14; 112.0, C14b; ^{B}111.3, 111.1, C1 and C4; ^{B}110.7, C11; 55.8, 2xOCH_3; 55.6, C14c; 51.6, C6; 49.8. C8; 41.7, $CH_2CH(CH_3)CH_3$; 32.8, C9; 25.2, $CH_2CH(CH_3)_2$; 23.9, $CH_2CH(CH_3)CH_3$; 23.1, C5; 21.5, $CH_2CH(CH_3)CH_3$. Anal. Found: C, 76.06; H, 7.75; N, 6.93. $C_{25}H_{30}N_2O_2.0.1CH_2Cl_2$ requires C, 75.74; H, 7.65, N, 7.04%.

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