NEW DERIVATIVES OF 1-BENZYLIDENISOINDOLIN-3-ONE FROM NARCEINE IMIDE

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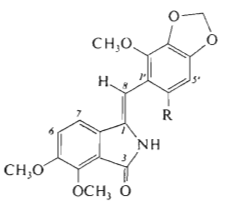
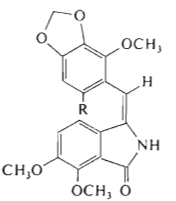
Isolation and identification of the (*E*)-isomer of narceine imide and the synthesis of new derivatives of 1-benzylidenisoindolin-3-one from (*Z*) and (*E*)-isomers of the minor opium alkaloid narceine imide are described.

The aim of this paper was to utilize the minor opium alkaloid narceine imide for preparation of new, potentially biologically active substances. Narceine imide, prepared also synthetically[1], and its degradation product narceone imide[1,2] are suitable starting substances for the synthesis of new derivatives of 1-benzylideneisoindolin-3-one. Both substances exist, due to the asymmetrically substituted $C_{(1)}$—$C_{(8)}$ double bond in two isomeric forms as (*Z*) and (*E*)-narceine imides (*I* and *II*), or (*Z*) and (*E*)-narceone imides (*III* and *IV*).





I, R = $CH_2CH_2N(CH_3)_2$
III, R = $CH{=}CH_2$
V, R = $CH_2CH_2\overset{+}{N}(CH_3)_2\ O^{(-)}$
VI, R = $CH_2CH_2N(CH_3)COCH_3$
VII, $C_{(1)}$—$C_{(8)}$ dihydro; R = $CH{=}CH_2$
VIII, $C_{(1)}$—$C_{(8)}$ dihydro; R = CH_2CH_3
IX, R = CH_2CH_3

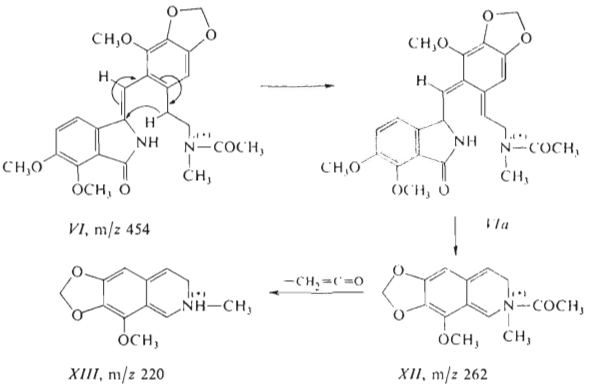
II, R = $CH_2CH_2N(CH_3)_2$
IV, R = $CH{=}CH_2$
X, R = $CH(OH)CH_3$
XI, R = $CH(CH_3)OCOCH_3$

Whereas isolation of the (*Z*)-isomer of *I* was already described[3], the presence of the (*E*)-isomer *II* was anticipated and only indirectly proved[2]; this paper also deals with the isolation and characterization of *II*. Both geometric isomers differ from each other in the hypso and hypochromic shifts of the last UV absorption band: 350 nm (log ε 4·24) *I* and 345 nm (log ε 4·04) *II*. The structure of isomers of 3-benzylidenephthalide was adduced analogously on the basis of UV spectra: hence, the λ_{max} 340 nm (log 4·32) was assigned the (*Z*)-isomer, whilst λ_{max} 324 (log ε 4·11) the (*E*)-isomer[4,5]. The IR spectra of *I* and *II* differ in the skeletal vibration range (1000–1150 cm^{-1}); the region characteristic of the double bond vibration at 1650 cm^{-1} (ref.[6,7]) was overlapped by the strong band of the lactam carbonyl group at 1690 cm^{-1}. Both substances have identical mass spectra. Oxidation of *I* with hydrogen peroxide in acetone afforded the (*Z*)-isomer of narceine imide N-oxide (*V*). Its mass spectrum did not contain, in contrast to other N-oxides, peaks of ions M−16 and M−17 (ref.[8,9]), nor those at *m/z* 234 and especially at *m/z* 58, typical of narceine imide. On the other hand, species at *m/z* 381 formed from $M^{+\cdot}$ (*m** 328·4) and an untypical one at *m/z* 60 were observed; their appearance provided an argument that instead of oxygen dimethylamino oxide group was released from the molecular radical ion of *V*. Acetic anhydride reacted with *V* at 0°C to give *VI*, the UV spectrum of which traced that of (*Z*)-1-benzylidenisoindolin-3-ones and its IR spectrum showed vibration bands of the 5-membered lactam ring (ν(C=O) 1696 and ν(N—H) 3140 cm^{-1} were maintained), of a methylene group (ν_{as}(C—H) 2940, ν_s(C—H) 2840, δ(C—H) 1460 cm^{-1}) and a benzene ring (1620, 1494, 1480 cm^{-1}). The most important evidence for the structure assignment of *VI* was the mass spectrum displaying a series of ion peaks at *m/z* 454 (M^+), 411, 381, 366, 262, 220, 192, 86, 44, 43 and 28. The presence of ions at *m/z* 411 ($M-\overset{(+)}{C}H_3C^{\cdot}O$), 381 ($M-CH_3.\overset{(+)}{C}ONHCH_3$), 86 ($CH_2=\overset{(+)}{N}(CH_3)COCH_3$) and 44 ($CH_2=\overset{(+)}{N}HCH_3$) indicated the 2′-(N-acetyl-N-methylamino)ethyl group in the side chain of the narceine imide backbone, which itself showed intense peaks of ions at *m/z* 381 and 192. The structure of fragments at *m/z* 262 (originating from the molecular radical ion, *m** 158·3) and 220 can be represented by formulas *XII* and *XIII* as illustrated in Scheme 1.

Based upon the presented evidence, the dealkylation product *VI* of (*Z*)-narceine imide is (*Z*)-1-(6′-(2″-N-acetyl-N-methylamino)ethyl-2′-methoxy-3′,4′-methylenedioxy)benzylidene-4,5-dimethoxyisoindolin-3-one.

Further compounds synthesized from narceone imide, prepared from narceine imide iodomethylate[1], were separated by crystallization from ethanol into isomers *III* and *IV* (ref.[2]). Although the preparation of dihydro (*VII*) and tetrahydro (*VIII*) derivatives of narceone imide by catalytic hydrogenation was already described[2], the dihydro derivative *IX*, having the $C_{(1)}$—$C_{(8)}$ double bond preserved has not been reported yet. Compound *IX* was obtained from reaction with hydrazine in the presence of atmospheric oxygen. Since hydrazine itself is not suitable for reduction

of organic substances, an oxidation of this reagent to diimide, which is the true reduction agent, has therefore to precede[10]. Of various kinds of double bonds the terminal one is known[10,11] to undergo the most rapid reduction. This fact was utilized



when reducing *III* to the single product *IX*. Its ^{1}H-NMR spectrum (ppm, δ scale) differed from that of the starting material in the appearance of signals of a $\mathbf{CH_3CH_2}$ group at 1·22 (t) and a $\mathrm{CH_3}\mathbf{CH_2}$ group at 2·69 (q, J = 7·0 Hz) and disappearance of the ABX multiplet of vinyl group. As seen in the UV spectra of *VII*–*IX* and *III*, *IV*, the disruption of conjugation by saturation of the $C_{(1)}$—$C_{(8)}$ double bond resulted in the shift of the last absorption bands.

Compound *III* cyclized in acid medium to yield 6,7-dihydro-3,4,11-trimethoxy--7-methyl-9,10-methylenedioxy-5*H*-isoindolo[1,2-*b*]isoquinol-5-one[2], whereas *IV* furnished *X*. The ^{1}H-NMR spectrum of the latter, when contrasted with the starting material *IV*, lacked the ABX multiplet of a vinyl group and revealed a doublet at 0·95 (3 H, J = 6 Hz, $\mathbf{CH_3}$(OH)CH—) and a multiplet between 4·67 and 4·84 ($\mathrm{CH_3}$. .(OH)$\mathbf{CH}$—). Ions M − 18 and M − 17 in the mass spectrum indicated the presence of a hydroxyl group in the aliphatic chain. The O-acetyl derivative *XI* obtained from *X* showed in its mass spectrum a base peak at m/z 381 (M − $\mathrm{CH_3COOH}$) and its IR spectrum a vibration band at 1738 cm^{-1} (ν(C=O) of an ester group) instead of that at 3360 cm^{-1} (hydroxyl group) in *X*. The last band in the UV spectra of both compounds at 350 nm disappeared and a new one appeared at 298 nm. This phenomenon can result from the discontinuance of coplanarity in the double bond system and benzene ring caused by 1″-hydroxyethyl or 1″-acetoxyethyl group at $C_{(6')}$.

EXPERIMENTAL

Melting points were determined on a Kofler block, mass spectra were measured with a JMS-100 D apparatus at an ionization energy 70 eV, UV spectra with Specord UV-VIS (Zeiss, Jena) in methanol, IR spectra with Perkin–Elmer, model 457 and ^{1}H-NMR spectra with Tesla 487 B (with tetramethylsilane as an internal reference substance) instruments. Silufol UV-254 (Kavalier, Votice) plates were used for thin-layer chromatography and Kieselgel GF-254 (Merck) for preparative chromatography in the following solvent systems: dichloromethane–methanol–ammonia 85 : 16 : 2 (S_1), chloroform–methanol 9 : 1 (S_2), benzene–methanol 9 : 1 (S_3), ethyl acetate (S_4), methanol–ammonia 99 : 1 (S_5), chloroform–cyclohexane–2-butylamine 4 : 4 : 1 (S_6), acetone–xylene–methanol–ammonia 50 : 40 : 5 : 4 (S_7), chloroform–diethylamine 9 : 1 (S_8).

(*E*)-Narceine Imide (*II*)

Oxalate of narceine imides *I* and *II* (10 g) was dissolved in water (200 ml) and hot precipitated with 10% K_2CO_3; the suspension was cooled and the solid after filtration crystallized from ethanol–water 2 : 1. Compound *II* was accumulated in mother liquors, as evidenced by thin-layer chromatography in S_1 (R_F 0·81 *I*, 0·62 *II*). Crystals from the mother liquor were filtered off, solvent from the filtrate distilled off and the residue was separated using thin-layer chromatography in S_1. Elution with acetone afforded a material, which was purified as above and crystallized from acetone–cyclohexane 1 : 2. Yield 120 mg R_F 0·62 (S_1), 0·39 (S_6), 0·47 (S_7), 0·75 (S_8); m.p. 142–144°C. For $C_{23}H_{26}N_2O_6$ (426·2) calculated: 64·77% C, 6·14% H, 6·56% N; found: 64·64% C, 6·01% H, 6·55% N. UV spectrum λ (log ε): max 345 (4·04), 261 (4·25); min 298 (3·10), 246 (4·20). IR spectrum ($CHCl_3$): 3150, 2900, 1690, 1600, 1480, 1460, 1250, 1080, 1040 cm^{-1}. Mass spectrum *m/z*: 426·1787 (M^+ calculated: 426·1791, 17%), 381 (38), 366 (16), 350 (8), 338 (8), 234 (100), 220 (5), 192 (55), 190 (9), 178 (7), 176 (17).

(*Z*)-Narceine Imide N-Oxide (*V*)

(*Z*)-Narceine imide (5 g) dissolved in acetone (25 ml) was poured into 30% hydrogen peroxide (4·5 ml) and the mixture was refluxed for 1 h. After 5 h further acetone (100 ml) was added, the separated compound filtered off, washed with acetone and crystallized from acetone–water 5 : 1. Yield 3·4 g, m.p. 158–159°C. For $C_{23}H_{26}N_2O_7$ (442·4) calculated: 62·43% C, 5·92% H, 6·33% N; found: 62·28% C, 5·80% H, 6·30% N. UV spectrum λ (log ε): max 350 (4·13), 264 (4·06), 214 (4·40); min 316 (3·86), 250 (4·01). IR spectrum (KBr): 2940, 1694, 1610, 1500, 1475, 1360, 1275, 1120, 1080, 1070, 1050 cm^{-1}. Mass spectrum *m/z*: 381 (50), 355 (15), 355 (15), 281 (40), 208 (24, 207 (100), 206 (83), 194 (44), 192 (66), 165 (67), 60 (98).

(*Z*)-1-(6′-(2″-N-Acetyl-N-methylamino)ethyl-2′-methoxy-3′,4′-methylenedioxy)benzylidene--4,5-dimethoxyisoindolin-3-one (*VI*)

Acetic anhydride (5 ml) cooled to 0°C was mixed with *V* (1·0 g) and left to stand at room temperature. The separated crystals were filtered off and crystallized from pyridine. Yield 0·42 g, R_F 0·67 (S_2), 0·52 (S_5), 0·56 (S_6); m.p. 242–244°C. For $C_{24}H_{26}N_2O_7$ (454·2) calculated: 63·48% C, 5·77% H, 6·16% N; found: 63·36% C, 5·69% H, 6·14% N. UV spectrum λ (log ε): max 350 (4·27), 269 (4·17), 210 (4·66); min 313 (3·98), 252 (4·14). IR spectrum (KBr): 3140, 2940, 1696, 1620, 1494, 1475, 1270, 1112, 1086, 1047. Mass spectrum *m/z*: 454·1735 (M^+ calculated 454·1734, 33%), 411 (8), 396 (5), 381 (100), 366 (38), 352 (12), 338 (13), 322 (10), 262 (16), 220 (35), 206 (8), 192 (88), 190 (9), 178 (11), 176 (18), 86 (12), 44 (90), 43 (35), 28 (11).

(*Z*)-1-(6′-Ethyl-2′-methoxy-3′,4′-methylenedioxy)benzylidene-4,5-dimethoxyisoindolin-3-one (*IX*)

A mixture of *III* (0·5 g) and $NH_2NH_2.H_2O$ (1·0 g) in ethanol (50 ml) was refluxed for 10 h, concentrated to 10 ml and allowed to crystallize. The yellow crystals had R_F 0·85 (S_2), 0·47 (S_3), 0·74 (S_4): m.p. 175–176°C. For $C_{21}H_{21}NO_6$ (383·4) calculated: 65·78% C, 5·52% H, 3·65% N; found: 65·58% C, 5·59% H, 3·63% N. UV spectrum λ (log ε): max 351 (4·25), 269 (4·17), 220 (4·48); min 319 (3·99), 253 (4·13). IR spectrum ($CHCl_3$): 3425, 3005, 1695, 1610, 1495, 1476, 1369, 1270, 1111, 1090, 1055 cm^{-1}. Mass spectrum *m/z*: 226 (10), 224 (31), 194 (25), 192 (100), 177 (10), 160 (65), 149 (40), 128 (49), 96 (57). ^{1}H-NMR spectrum ($CDCl_3$): 7·93 (1 H, s) NH, 7·50 (1 H, d), 7·21 (1 H, d) AB q H_1H_2 ($J_{1,2}$ = 8 Hz), 6·58 (1 H, s) $H_{5'}$, 6·30 (1 H, s) H_8, 6·00 (2 H, s) OCH_2O, 4·18 (3 H, s), 4·00 (6 H, s) 3 × OCH_3, 2·69 (2 H, q) $ArCH_2CH_3$ (J = 7 Hz), 1·22 (3 H, t) $ArCH_2CH_3$ (J = 7 Hz).

(*E*)-1-(6′-(1″-Hydroxyethyl)-2′-methoxy-3′,4′-methylenenedioxy)benzylidene-4,5-dimethoxyisoindolin-3-one (*X*)

A 36% HCl (2·0 ml) was added to a hot-dissolved *IV* (1·5 g) in acetic acid (50 ml). After 15 min standing the mixture was poured into water (200 ml), the separated substance filtered off, dried and crystallized from benzene. Yield 1·1 g, R_F 0·41 (S_2), 0·35 (S_3), 0·71 (S_5); m.p. 245°C. For $C_{21}H_{21}NO_7$ (399·1) calculated: 63·6% C, 5·70% H, 3·50% N; found: 63·02% C, 5·18% H, 3·43% N. UV spectrum λ (log ε): max 296 (3·90), 218 (4·83); min 273 (3·52). IR spectrum (KBr): 3360, 3220, 2930, 1688, 1619, 1490, 1455, 1305, 1265, 1118, 1070, 1044, 1032, 1024 cm^{-1}. Mass spectrum *m/z*: 399·1316 (M^+ calculated 399·1318, 13%), 381 (9), 366 (9), 350 (4), 207 (27), 192 (100), 178 (6), 149 (8), 137 (4). ^{1}H-NMR spectrum (pentadeuteriopyridine): 9·82 (1 H, s) NH, 6·58 (1 H, s) $H_{5'}$, 6·86 (1 H, d), 6·27 (1 H, d) AB q H_1H_2 ($J_{1,2}$ = 8 Hz), 6·00 (1 H, s) H_8, 5·91 (2 H, s) OCH_2O 4·21, 4·05, 3·72 (9 H, ss) OCH_3, 4·76–4·84 (1 H, m) $C\underline{H}(OH)CH_3$, 0·95 (3 H, d) $CH(OH)C\underline{H}_3$ (J = 6 Hz).

(*E*)-1-(6′-(1″-Acetoxyethyl)-2′-methoxy-3′,4′-methylenedioxy)benzylidene-4,5-dimethoxyisoindolin-3-one (*XI*)

Compound *X* (0·1 g) in pyridine (3 ml) and acetic anhydride (2 ml) was heated for 15 min, poured into water and the separated product was filtered off and crystallized from ethyl acetate. Yield 85 mg, R_F 0·77 (S_2), 0·55 (S_3), 0·82 (S_5); m.p. 276°C (decomp.). For $C_{23}H_{23}NO_8$ (441·4) calculated: 62·57% C, 5·25% H, 3·17% N; found: 62·45% C, 5·17% H, 3·16% N. UV spectrum λ (log ε): max 296 (3·88), 218 (4·81); min 272 (3·52). IR spectrum ($CHCl_3$): 3420, 2960, 2940, 2880, 1738, 1694, 1620, 1490, 1460, 1423 cm^{-1}. Mass spectrum *m/z*: 441 (10), 381 (100), 366 (60), 352 (30), 336 (26), 322 (16), 308 (16), 192 (36), 60 (80), 45 (92).

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