Synthesis of 7,8-dihydro-5*H*-isoindolo[1,2-*b*][3]benzazepin--5-one from narceine imide *N*-oxide

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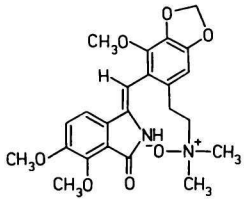
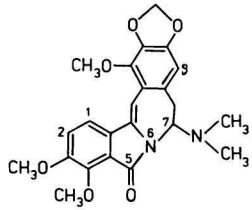
Narceine imide *N*-oxide (*I*) reacts with acetic anhydride to give not the anticipated demethylation product of compound *I*, but 7,8-dihydro-3,4,12--trimethoxy-7-dimethylamino-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]-benzazepin-5-one (*II*) *via* an intramolecular immonium salt. Hofmann degradation of *II* yielded 3,4,12-trimethoxy-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one (*III*).

В работе описывается реакция нарцеинимид-*N*-оксида (*I*) с ацетангидридом, при которой не образуется ожидаемый продукт деметилирования *I*, а внутримолекулярной нуклеофильной циклизацией промежуточной имониевой соли образуется 7,8-дигидро-3,4,12-триметокси-7-диметиламино-10,11-метилендиокси-5*H*-изоиндоло[1,2-*b*][3]бензазепин-5-он (*II*), из которого деградацией по Гофману был получен 3,4,12-триметокси--10,11-метилендиокси-5*H*-изоиндоло[1,2-*b*][3]бензазепин-5-он (*III*).

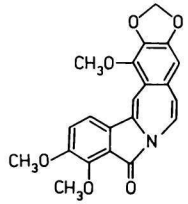
tert-Arylalkyl or *tert*-alkylamine *N*-oxides dealkylate with acetic anhydride [1, 2], trifluoroacetic anhydride [3] or organic acid chlorides [4, 5]; *Z* isomer of narceine imide *N*-oxide (*I*) furnished upon reaction with acetic anhydride at 40—70°C compound *II*, which was not the dealkylation product of *I*.



I

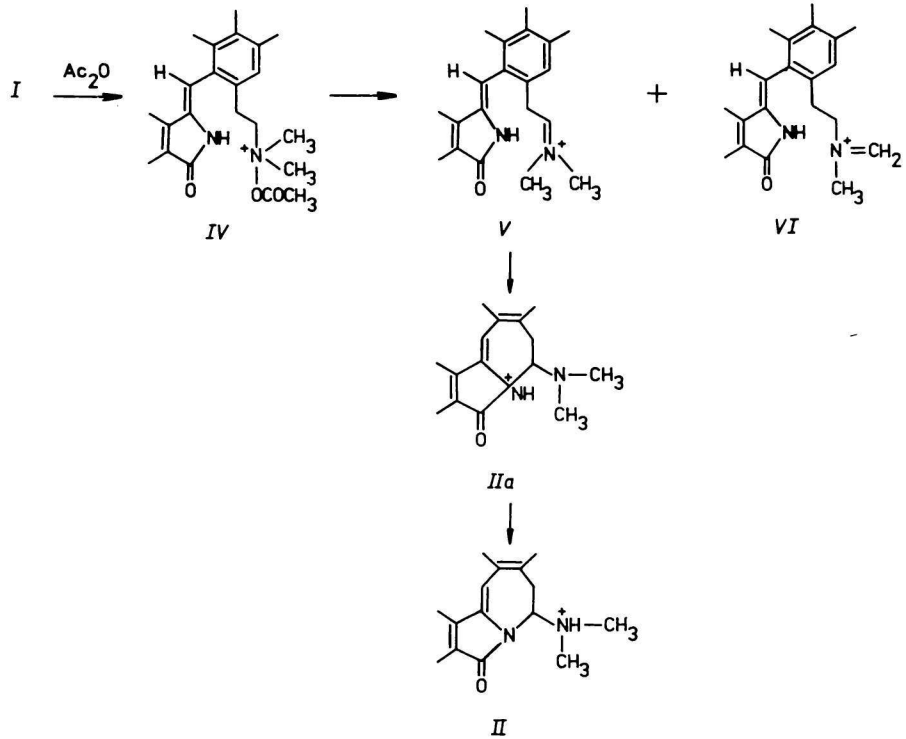


II



III

Compound *II* obtained in an optically inactive form does not absorb the u.v. radiation in the range typical of 1-benzylideneisoindolin-3-ones, but displays a u.v. spectrum characteristic of 7,8-dihydro-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-ones [6—8]. The i.r. spectrum of *II* revealed the presence of a 5-membered lactam ring (ν(C=O) 1693 cm^{-1}) without amide hydrogen and a double bond conjugated with aromatic rings (ν(C=C) 1645 and γ(CCH) 955 cm^{-1}). Of diagnostic value are also bands of a methyl group ($\nu_{as}(CH_3)$ 2950, $\nu_s(CH_3)$ 2860, and $\delta(CH_3)$ 1460 cm^{-1}), aromatic ring (1608, 1496, 1480 cm^{-1}) and those of a penta- (γ(CCH) 857 cm^{-1}) and a tetrasubstituted (γ(CCH) 811 cm^{-1}) benzene rings. The ^{1}H-n.m.r. spectrum is also in favour of the proposed structure and differs from that of the starting material: AA'BB' multiplet of the $ArCH_2CH_2N\lessdot$ grouping changed into an ABX multiplet of $ArCH_2\underset{|}{C}H$—N group, whilst signal of the NH group disappeared. The mass spectrum of *II* displayed noticeable peaks at *m/z* 424 (M^+), 409 ($M-15$), 392 ($M-32$), 380, 379, 364, 236, 235, 220, and 45; the presence of a dimethylamino group bound to the benzazepine skeleton was indicated by peaks at *m/z* 380 ($M-\overset{+}{C}H_2NH=CH_2$) *m** 340.5 (424→380), 379 ($M-CH_3NHCH_3$) *m** 338.6 (424→379), 45, and 44. The species at *m/z* 364 originated from the



Scheme 1

radical ion at *m/z* 379 by the loss of a methyl radical (*m** 349.6, 379→364). The molecular radical ion gave rise to an ion at *m/z* 235 (*m** 130.2), which, upon cleavage of a methyl radical, afforded an ion at *m/z* 220 (*m** 205.9). Hofmann degradation of *II* furnished *III* having the u.v. spectrum close to that of *II*. The i.r. spectrum of *III* showed significant bands characterizing a 5-membered lactam ring (ν(C=O) 1690 cm^{-1}), a double bond conjugated with benzene rings (ν(C=C) 1640 cm^{-1}), and an aromatic skeleton (1605, 1495, 1482 cm^{-1}). Mass spectrum of *III* substantially differed from that of *II*; the most intense peaks were found at *m/z* 379 (M^+), 364 ($M-15$), 281, 207, 194, and 178.

The presented arguments allow to ascribe structural formulas 7,8-dihydro--3,4,12-trimethoxy-7-dimethylamino-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*]-[3]benzazepin-5-one and 3,4,12-trimethoxy-10,11-methylenedioxy-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one to compounds *II* and *III*, respectively.

We suggest that *N*-acyloxyammonium salt *IV* is the intermediate when reacting *I* with acetic anhydride; similarly as with other amine *N*-oxides [9, 10] *IV* forms a transition immonium compound existing in two isomeric forms *V* an *VI* (Scheme 1).

Stereo-nonspecific intramolecular nucleophilic cyclization of the substituted isoindolin-3-one *V* leads to the benzazepine derivative *II*. The probability of cyclization of *VI* to a 9-membered ring is, due to sterical hindrance, low, nonetheless this compound can be the source of polymers accompanying *II* under the given reaction temperature.

Experimental

Melting points were determined on a Kofler hot-stage, mass spectra were measured with a JMS-100 D apparatus at an ionization energy 70 eV, u.v. spectra with Specord UV VIS (Zeiss, Jena), i.r. spectra with Perkin—Elmer, model 457, and ^{1}H-n.m.r. spectra (δ scale, p.p.m.) with Tesla BS 487 B spectrometers. Samples for ^{1}H-n.m.r. measurement were $CDCl_3$ solutions containing tetramethylsilane as an internal reference. For analytical thin-layer chromatography on Silufol UV-254 plates and for preparative thin-layer chromatography on Kieselgel GF 254 (Merck) following solvent systems were employed: S_1 (chloroform—methanol 9:1), S_2 (benzene—methanol 9:1), S_3 (benzene—acetone 2:1), S_4 (ethyl acetate—n-hexane 2:1); visualization at 254 nm.

7,8-Dihydro-3,4,12-trimethoxy-7-dimethylamino-10,11-methylenedioxy--5H-isoindolo[1,2-b][3]benzazepin-5-one (II)

Z narceine imide *N*-oxide (0.6 g) dissolved in acetic anhydride (5 ml) was heated to 50°C and left to cool. A 5% KOH was added after 2 h into the mixture to pH 7 and 5% NH_4OH

to pH 9. The separated substance was filtered off, the aqueous solution extracted with chloroform (3 × 25 ml), the solvent distilled off and the residue combined with the first crop [11]. The crude *II* (0.32 g) was purified by a preparative thin-layer chromatography in S_3; m.p. 220—222°C (acetone), R_f 0.86 (S_1), 0.27 (S_2), 0.46 (S_3), 0.26 (S_4); M = 424.1698 (for $C_{23}H_{24}N_2O_6$ calculated 424.1701); UV spectrum λ_{max}^{MeOH}, nm (log ε): 387 (4.34), 316 (3.92), 273 (4.08), 212 (4.40), λ_{min}^{MeOH}, nm (log ε): 338 (3.82), 295 (3.75), 255 (3.88); IR spectrum (KBr): 2980, 2950, 2780, 1693, 1645, 1608, 1495, 1480, 1438, 1420, 1400, 1378, 1345, 1309, 1280, 1270, 1217, 1135, 1086, 1060, 1045, 1000, 980, 955, 930, 911, 857, 811 cm^{-1}. Mass spectrum *m/z:* 424 (60%), 409 (6%), 392 (5%), 381 (34%), 380 (100%), 379 (60%), 364 (18%), 350 (12%), 264 (5%), 236 (12%), 235 (75%), 220 (15%), 207 (20%), 205 (12%), 190 (21%), 185 (11%), 45 (95%), 44 (17%). ^{1}H-N.m.r. spectrum ($CDCl_3$): 7.52 (d), 7.15 (d), ABq, H_1H_2, $J_{1,2}$ 8 Hz; 6.95 (s, 1H) H_{13}; 6.47 (s, 1H) H_6; 5.93 (s, 2H) OCH_2O; 4.13 (s, 6H) 2 × OCH_3; 3.92 (s, 3H) OCH_3; 2.33 (s, 6H) $N(CH_3)_2$; 5.06 (X portion), 3.21—2.98 (AB portion ABX, m) $ArCH_2CH$—N.

3,4,12-Trimethoxy-10,11-methylenedioxy-5H-isoindolo[1,2-b][3]-benzazepin-5-one (III)

Methyl iodide (50 mg) was added to *II* (25 mg) dissolved in chloroform; the mixture was refluxed for 2 h, the solvent evaporated and 30% KOH (5 ml) added to the distillation residue. This suspension was heated on a steam bath for 3 h, the solid filtered off, washed with water and crystallized from acetone. Yield 18 mg of red crystals, m.p. 254—255°C, M = 379.1054 (for $C_{21}H_{17}NO_6$ calculated 379.1056); UV spectrum λ_{max}^{MeOH}, nm (log ε): 386 (4.17), 303 (4.28), 280 (4.18), 213 (4.43), λ_{min}^{MeOH}, nm (log ε): 346 (3.93), 256 (4.11). IR spectrum (KBr): 2980, 2950, 2830, 1690, 1640, 1605, 1482, 1450, 1440, 1420, 1400, 1378, 1370, 1340, 1309, 1290, 1272, 1243, 1200, 1088, 1070, 1050, 980, 970, 930, 911, 845, 815 cm^{-1}. Mass spectrum *m/z:* 379 (100%), 364 (21%), 336 (10%), 321 (10%), 281 (13%), 207 (75%), 206 (11%), 194 (11%), 190 (17%), 178 (44%), 160 (29%).

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