Synthesis of *N*-nornarceine imide

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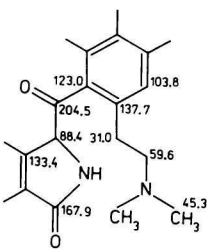
N-Nornarceine imide was prepared from (−)-α-narcotine *via* nornarceine, which on fusing with urea afforded the required substance. The attempt to demethylate narceine imide with nitrous acid resulted in formation of a nitrogen-like analogue of (±)-narlumidine.

N-Норнарцеинимид был получен из (−)-α-наркотина посредством его плавления с мочевиной. При попытке деметилирования нарцеинимида азотистой кислотой был выделен азотный аналог (±)-нарлумидина.

N-Nornarceine imide (*I*) is a suitable starting compound of alkaloidal nature for the synthesis of a series of new compounds. Nornarceine imide (*I*) can be in principle prepared by two ways: *a*) by demethylation of narceine imide (*II*), *b*) by conversion of (−)-α-narcotine (*III*).

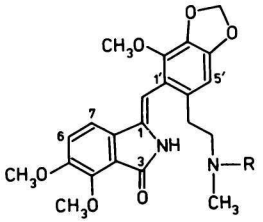
Tertiary amines can be demethylated by various methods, *e.g.* with nitrous acid they afford in a slightly acid medium *N*-nitrosodialkylamines; the latter gave with strong mineral acid dialkylammonium salts [1]. This procedure yielded 3,6-diacetyl-17-normorphine from 3,6-diacetylmorphine and 17-norcodeine from codeine [2]. Hydrogen peroxide or peracids react with tertiary amines to furnish *N*-oxides; these gave an aldehyde and dialkylamide with acylating agents [3]. These dialkylamides can be hydrolyzed to the corresponding dialkylamines. The most acylating agents used are acetic or trifluoroacetic anhydrides [4, 5]. Another possibility to demethylate tertiary amines offers the von *Braun* procedure [6] in which the reaction with bromocyane leads to alkyl bromide and dialkylcyanamide. Hydrolysis of the latter afforded the unstable dialkylcarbaminic acid, which decarboxylated to dialkylamine. This reaction was employed for the synthesis of *e.g.* 17-cyano-17-norcodeine, *N*-cyano-*N'*-methylnarceine imide, *etc.* [7]. Conversion of (−)-α-narcotine (*III*) to nornarceine imide (*I*) proceeds through nornarceine (*IV*) which could be alternatively prepared by cleavage of tetrahydroisoquinoline ring of compound *III* in dilute acetic acid [8], or by alkylation of *III* with benzyl bromide, decomposition of the quaternary salt with triethylamine and hydrogenolysis of the benzyl group [9].

In this paper narceine imide (*II*) was demethylated with nitrous acid in acetic acid. Two compounds were isolated from the mixture: the first, identical with 4,5-dimethoxyphthalimide originated by an oxidative decomposition of narceine imide (*II*), as has already been reported, *e.g.* with oxidation of *II* with potassium permanganate [10]. The second white crystalline product is still not the expected demethylation product of *II*, as evidenced by the estimated formula. The IR spectrum showed the band of the preserved amide group ($\tilde{\nu}$(N—H) = 3420 cm^{-1}), that of the carbonyl group ($\tilde{\nu}$(C=O) = 1715 cm^{-1}) is shifted towards higher wavenumber when compared with the starting compound. The UV spectrum indicated the discontinuance of conjugation of benzene rings linked through a vinyl bonding by appearance of the last absorption band at 308 nm (narceine imide *II* has λ_{max} = 348 nm). Another evidence for this assumption is the absence of the vinylic proton signal in the ^{1}H NMR spectrum of this compound. Position of the remaining proton signals is close to those of *II*. The mass spectrum provided an unambiguous proof only for the presence of a dimethylaminoethyl grouping in the side chain (m/z = 58, $CH_2=N^+(CH_3)_2$). The structure was definitely determined by the analysis of ^{13}C NMR spectrum. Molecule of the new compound consisted of a carbonyl group (δ = 204.5 ppm), linking the isoindoline and dimethylaminoethylbenzene moieties. ^{13}C NMR chemical shift values of other signals, significant for adduction of the structure are as follows

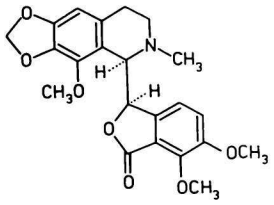


All data presented allowed to ascribe structure of 1-(2′-methoxy-6′-(2″-dimethylamino)ethyl)-3′,4′-(methylenedioxy)benzoyl-4,5-dimethoxyisoindolin-3-one to compound *V*. Compound *V* could be considered an analogue of secophthalidisoquinoline alkaloid (±)-narlumidine (*VI*), isolated from *Fumaria indica* PUGSLEY [11]. Upon heating in methanolic potassium hydroxide *V* gave the hemiketal *VII* as evidenced by elemental analysis fitting the formula $C_{24}H_{30}N_2O_8$, by IR spectrum (vibration of the free hydroxyl group $\tilde{\nu}$(O—H) = 3580 cm^{-1}, amide group $\tilde{\nu}$(N—H) = 3420 cm^{-1} and carbonyl group $\tilde{\nu}$(C=O) = 1705 cm^{-1}), ^{1}H NMR spectrum (aliphatic methoxyl group at δ = 3.55 ppm), and mass spectrum with peaks at m/z: 456 ($M-H_2O$), 425 ($M-H_2O-CH_3$), 411 ($M-H_2O-CH_3NHCH_3$), 398, 394, 380, 183, 176, 58. Hofmann degradation of the methiodide of *V* yielded a white crystalline compound of molecular formula

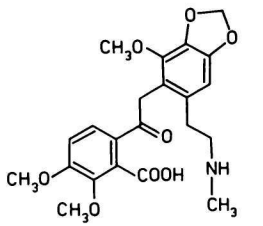
$C_{21}H_{19}NO_7$. Its IR spectrum displayed bands at $\tilde{\nu} = 3420\ cm^{-1}$ (ν(N—H)) and $1705\ cm^{-1}$ (ν(C=O)) and the ^1H NMR signals at $\delta = 1.68$ ppm (3H, d) and $\delta = 5.69$ ppm (1H, q, $J = 6.1$ Hz) are attributable to the CH_3—CH< grouping, which might be formed by an intramolecular cyclization of the not isolated



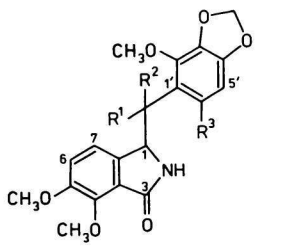
I R = H
II R = CH_3
XI R = $COCH_3$



III



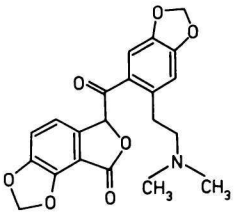
IV



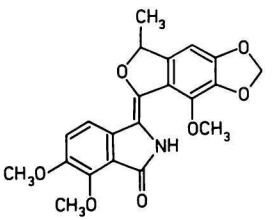
	R^1, R^2	R^3
V	O	$CH_2CH_2N(CH_3)_2$
VII	OCH_3, OH	$CH_2CH_2N(CH_3)_2$
VIII	O	$CH{=}CH_2$

Scheme 1

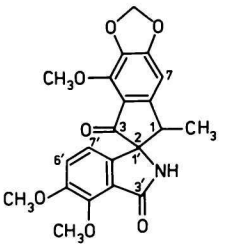
intermediate *VIII* (Scheme 1). Since the amide grouping could not take part in the cyclization (appearance of the signal $\delta = 8.33$ ppm in the ^1H NMR spectrum and the band at $\tilde{\nu} = 3420\ cm^{-1}$ in the IR spectrum) this reaction could lead to compound *IX* or *X* (Scheme 2). Provided the product of cyclization is compound *IX*, the UV spectrum would contain a band at 340—350 nm due to conjugation of benzene rings, as is the case *e.g.* with compound *II*. Since bands at $\lambda = 236$ nm and 304 nm (sh) were observed in the UV spectrum, the more probable structure is *X*. A compound of an analogous structure was obtained by cyclization of narceone imide [12].



VI



IX



X

Scheme 2

Another access to nornarceine imide (*I*) was the demethylation of narceine imide (*II*) *via* narceine imide *N*-oxide by treatment with acetic anhydride; the resulting *N*-acetylnornarceine imide (*XI*) was isolated besides of other compounds [13]. This compound resisted all deacetylation attempts, so that compound *I* could not be obtained in this way.

Nornarceine imide (*I*) was finally synthesized from (−)-α-narcotine (*III*) by a long-lasting heating with acetic acid leading to nornarceine (*IV*) [8], which, when fused with urea and purified by chromatography afforded *I*. Due to asymmetrically substituted benzylidene double bond, compound *I* can exist in two isomeric forms. The obtained product was ascribed (*Z*)- arrangement, since the position of H-6 and H-7 protons in the ^{1}H NMR spectrum (7.70 d and 7.27 d, $J_{6,7} = 8$ Hz) coincided with those of (*Z*)-nornarceine imide [14]. Compounds *I* and *II* could not be sufficiently separated by thin-layer chromatography; far better results were obtained by liquid chromatography using columns packed with a reverse-phase sorbent: the peak resolution R_s was 4.46 and retention time for *I* and *II* t_R was 2.26 min and 5.67 min, respectively.

Experimental

Melting points were determined on a Kofler micro hot-stage, the mass spectra were recorded with a JMS-100D apparatus at an ionization energy 70 eV, the UV spectra were

measured with a Specord UV VIS (Zeiss, Jena) spectrophotometer, the IR spectra were run with a Specord IR 71 spectrometer, and the ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM-300 FT NMR spectrometer; samples were dissolved in deuteriochloroform containing tetramethylsilane as an internal reference substance. Silufol UV 254 sheets were used for thin-layer chromatography and chloroform—methanol (volume ratio = 9 : 1) (S_1) and ethanol (S_2) were the solvent systems. Columns 250 mm × 4 mm packed with Li-Chrosorb RP-8, 10 μm, mobile phase methanol—1 % aqueous ammonium hydroxide (volume ratio = 6 : 4) were used for liquid chromatography at a flow rate 2 cm^3 min^{-1} and 263 nm detector wavelength.

Nornarceine imide (I)

Nornarceine (*IV*) was prepared from (−)-α-narcotine (*III*) according to [8]; its mixed melting point with the authentic specimen showed no depression and its UV, IR, and ^{1}H NMR spectra were in agreement with those reported. Nornarceine (*IV*) (0.8 g) was fused at 135—140 °C with urea (3 g). The cooled product was dissolved in water and extracted with chloroform (3 × 20 cm^3), the combined extracts were dried, the solvent was removed and the residue was crystallized from benzene. The crystalline mixture was chromatographed on alumina, chloroform—methanol (volume ratio = 4 : 1) being the eluent. Course of the chromatography was monitored by thin-layer chromatography in S_1. Evaporation of the solvent from the combined fractions *8—10* and crystallization of the residue from benzene afforded *I* as yellow crystals; yield = 0.16 g, m. p. = 196—198 °C. For $C_{22}H_{24}N_2O_6$ (M_r = 412) w_i(calc.): 64.25 % C, 5.86 % H, 6.79 % N; w_i(found): 64.12 % C, 5.92 % H, 6.66 % N. UV spectrum (methanol), λ_{max}/nm (log {ε}): 214 (4.57), 263 (4.21), 352 (4.26). IR spectrum (chloroform), $\tilde{\nu}$/cm^{-1}: 3460 (ν(N—H)), 2900, 2800, 2790 (ν(C—H)), 1700 (ν(C=O)), 1660 (ν(C=C)), 1600, 1480, 1465, vibrations associated with the aromatic ring. Mass spectrum *m/z* (I_r/%): 412 (2.1), 397 (1), 381 (4.5), 368 (2.8), 365 (4), 350 (0.9), 220 (2.1), 219 (3.0), 206 (4.7), 205 (4.3), 193 (3.0), 192 (10.0), 178 (8.3), 176 (4.5), 164 (15), 55 (8), 44 (14.9), 43 (100). ^{1}H NMR spectrum, δ_r/ppm: 7.95 (1H, s, NH), 7.70 (1H, d, H-6), 7.27 (1H, d, $J_{6,7}$ = 8 Hz, H-7), 6.55 (1H, s, =CH—), 6.37 (1H, s, H-5), 5.95 (2H, s, OCH_2O), 3.98 (3H, s, OCH_3), 3.90 (6H, s, 2 × OCH_3), 3.20—2.80 (4H, m, CH_2CH_2N), 2.73 (3H, s, $NHCH_3$).

1-(2′-Methoxy-6′-(2″-dimethylamino)ethyl)-3′,4′-methylenedioxy)-benzoyl-4,5-dimethoxyisoindolin-3-one (V)

To narceine imide (*II*, 13.5 g) dissolved in 35 % acetic acid (300 cm^3) and heated to 70 °C potassium nitrite (40 g) in water (100 cm^3) was added with stirring during 3 h. The mixture was left to stand overnight and the product was taken into chloroform (3 × 50 cm^3), the extract was successively washed with 2 % NH_4OH (25 cm^3), water (50 cm^3), and 2 % hydrochloric acid (2 × 50 cm^3). The acidic extracts were combined, the pH was adjusted to 8.0, the separated precipitate was filtered off and crystallized from ethanol. Yield = 8.4 g,

m.p. = 184—185 °C. For $C_{23}H_{26}N_2O_7$ (M_r = 442) w_i(calc.): 62.44 % C, 5.88 % H, 6.34 % N; w_i(found): 61.92 % C, 5.80 % H, 6.22 % N. UV spectrum (methanol), λ_{max}/nm (log {ε}): 216 (4.62), 308 (3.60). IR spectrum (chloroform), $\tilde{\nu}$/cm^{-1}: 3420 (ν(N—H)), 2980, 2940, 2830 (ν(C—H)), 1715 (ν(C=O)), 1610, 1490, 1480 (aromatic rings). ^{1}H NMR spectrum, δ_r/ppm: 8.33 (1H, s, NH), 7.31 (1H, d, H-6), 7.12 (1H, d, $J_{6,7}$ = 8.2 Hz, H-7), 6.33 (1H, s, H-5′), 5.90 (2H, dd, OCH_2O), 4.03 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.50—2.12 (4H, m, CH_2CH_2N), 2.09 (6H, s, $N(CH_3)_2$). The chloroform extract after separation of *V* was evaporated and the residue was crystallized from ethyl acetate. Yield = 0.70 g of compound identical with 3,4-dimethoxyphthalimide according to melting point, UV and IR spectra.

2′-Methoxy-6′-(2″-dimethylamino)ethyl-3′,4′-methylenedioxyphenyl-4,5--dimethoxyisoindolin-3-on-1-yl-methoxymethanol (VII)

Compound *V* (0.9 g) was refluxed in a 1 % methanolic potassium hydroxide (40 cm^3) for 2 h. The solvent was removed under diminished pressure, the residue was treated with water, pH was adjusted with acetic acid to 7, the suspension was extracted with chloroform (3 × 10 cm^3), the organic layer was evaporated and the residue was crystallized from benzene—ethanol (volume ratio = 1 : 1). Yield = 0.5 g, m.p. = 140 °C (decomp.). For $C_{24}H_{30}N_2O_8$ (M_r = 474) w_i(calc.): 60.78 % C, 6.36 % H, 5.90 % N; w_i(found): 60.62 % C, 6.29 % H, 5.83 % N. UV spectrum (methanol), λ_{max}/nm (log {ε}): 215 (4.62), 306 (3.42). IR spectrum, $\tilde{\nu}$/cm^{-1}: 3580 (ν(O—H)), 3415 (ν(N—H)), 1700 (ν(C=O)), 1600, 1480, 1493 (aromatic ring). ^{1}H NMR spectrum, δ_r/ppm: 7.90 (1H, s, NH), 7.08 (1H, d, H-6), 6.95 (1H, d, H-7), 6.41 (1H, s, H-5′), 5.92 (2H, dd, OCH_2O), 4.07 (3H, s, arom-OCH_3), 3.94 (3H, s, arom-OCH_3), 3.84 (3H, s, arom-OCH_3), 3.55 (3H, s, aliph-OCH_3), 3.14 (1H, s, H-1), 2.6—2.2 (4H, m, CH_2CH_2), 2.23 (6H, s, $N(CH_3)_2$). Mass spectrum *m/z* (I_r/%): 456 ($M - H_2O$, 8.3), 425 (6.3), 411 (76.8), 398 (12), 396 (6), 394 (11), 380 (15), 338 (64), 183 (13), 176 (92), 58 (100).

4,4′,5′-Trimethoxy-1-methyl-5,6-methylenedioxyspiro-(indan-2,1′-isoindolin-3,3′-dione) (X)

Compound *V* (1.0 g) dissolved in chloroform (50 cm^3) was mixed with methyl iodide (3 cm^3) and the solution was allowed to stand overnight, the solvent was distilled off, the residue was dissolved in methanolic solution of sodium methoxide (3 g of sodium in 50 cm^3 of methanol). That solution was refluxed for 4 h, methanol was removed and the residue was treated with water, pH was adjusted with acetic acid to 7 and the solution was extracted with chloroform (3 × 10 cm^3). Crystallization of the evaporated residue from benzene—n-heptane (volume ratio = 2 : 1) gave 0.4 g of *X*, m.p. 194—196 °C. For $C_{21}H_{19}NO_7$ (M_r = 397) w_i(calc.): 63.51 % C, 4.82 % H, 3.53 % N; w_i(found): 63.39 % C, 4.73 % H, 3.47 % N. UV spectrum (methanol), λ_{max}/nm (log {ε}): 236 (4.50), 261 sh (4.23), 304 (3.85). ^{1}H NMR spectrum, δ_r/ppm: 8.33 (1H, s, NH), 7.07 (1H, d, H-6′), 6.97 (1H, d, $J_{6',7'}$ = 7 Hz,

H-7'), 6.36 (1H, s, H-7), 5.90 (2H, dd, OCH_2O), 3.95 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 5.69 (1H, q, H-1), 1.68 (3H, d, $J = 6.1$ Hz, C-1—CH_3).

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