REACTION OF DIMETHYLAMINOETHYL DERIVATIVES OF 1-BENZYLIDENISOINDOLIN-3-ONE WITH EPOXIDES

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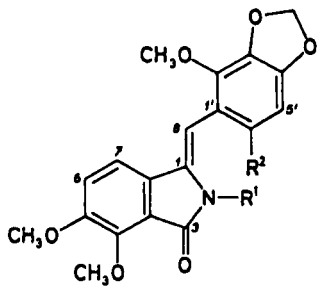
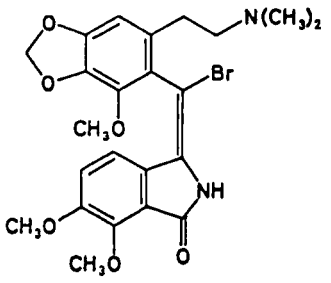
Derivatives of 1-(2-(2-dimethylaminoethyl)benzyliden)isoindolin-3-one underwent deamination on reaction with epoxides under mild conditions. Amide group of the substrate reacted slower with epoxide than the dimethylamino grouping whilst the alkanolamide was formed with a great excess of the epoxide only. Of epoxides used in this reaction 1,2-epoxy-3-phenoxypropane, 3-decyloxy-1,2-epoxypropane and 3-chloro-1,2-epoxypropane, the first was found to react most rapidly.

Primary and secondary amides react with epoxides to give alkanolamines, whilst the tertiary ones afforded compounds related to choline[1,2]. Carboxylic acid amides can react with epoxides through one or both amide hydrogens[3]. Cyclic amides react with epoxides far more rapidly, even at room temperature[4 - 6]. Narceine imide (*I*), a derivative of benzylidenisoindolin-3-one[7], which is an unnatural alkaloid, was our starting material for preparation of several biologically active substances[8,9]. This alkaloid contains nitrogen atoms in form of an amide and a tertiary amine in its molecule and therefore, it was treated with various epoxides aiming to obtain a choline derivative. Because this preliminary experiment failed we examined this reaction in more detail.

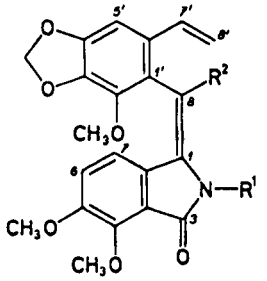
Narceine imide (*I*) furnished with a small excess of 1,2-epoxy-3-phenoxypropane in ethanol a compound identical, according to spectral measurements with narceone imide (*II*) prepared[10] originally by heating narceine imide methiodide in 30% aqueous KOH for several hours. Deamination of narceine imide (*I*) by means of epoxide is temperature dependent; thus a 2 h reflux in methanol converted 21.8% of *I* and in ethanol and butanol 84.6% and 97.7%, respectively. The deamination rate is also dependent on the constitution of the epoxide: a 2 h reflux of the amide *I* with 1,2-epoxy-3-phenoxypropane in ethanol afforded the amide *II* in a 86% yield, with 3-decyloxy-1,2-epoxypropane and 1,2-epoxy-3-(diethylamino)propane in 66.3 and 14.0% yield, respectively. An increasing amount of the epoxide accelerated the deamination but to the detriment of the product quality. The amide *II* being formed reacted with the excess of the epoxide to give the alkanolamide *III* (Fig. 1). Reaction of (*Z*)-*I* with epoxides has to be carried out in dark because both the starting compound and the product *II* are light-sensitive and underwent isomerization in light[11]. Dihydronarceine imide (*IV*) and



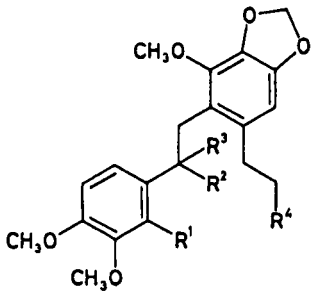
I, R^1= H ; R^2= $CH_2CH_2N(CH_3)_2$
II, R^1= H ; R^2= $CH{=}CH_2$
III, R^1= $CH_2CH(OH)CH_2OC_6H_5$; R^2= $CH{=}CH_2$
IV, R^1= H ; R^2= $CH_2CH_2N(CH_3)_2$, 1,8-dihydro
XIII, R^1= H ; R^2= $CH{=}CH_2$, 1,8-dihydro
XV, R^1= H ; R^2= $CH_2CH_2N^+(CH_3)_2CH_2CH(O^-)CH_2Cl$



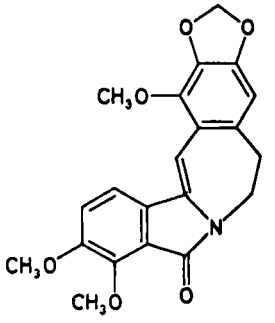
V



XI, R^1= $CH_2CH(OH)CH_3$; R^2= H
XII, R^1= CH_2COCH_3 ; R^2= H
XIV, R^1= H ; R^2= Br



VI, R^1= $CONH_2$; R^2, R^3= O ; R^4= $N(CH_3)_2$
VII, R^1= CH_2OH ; R^2= H ; R^3= OH ; R^4= $N(CH_3)_2$
VIII, R^1= $COOCH_2CH_3$; R^2, R^3= O ; R^4= $N(CH_3)_2$
IX, R^1= COO^- ; R^2, R^3= O ; R^4= $N^+(CH_3)_2CH_2CH(OH)CH_2OC_6H_5$



X

(*Z*)-α-bromonarceine imide (*V*) were also deaminated with 1,2-epoxy-3-phenoxypropane, the deamination rate of the latter being by three times slower. Narceine amide (*VI*) deaminated on reaction with 1,2-epoxy-3-phenoxypropane; nevertheless, a concurrent intramolecular condensation took place to produce the amide *II*. Narceine diol (*VII*) the molecule of which does not contain any amide grouping did not react with epoxides. Ethyl narceinate (*VIII*) yielded a choline derivative with 1,2-epoxypropane, but its ester group hydrolyzed to furnish an inner salt *IX*.

Narceine imide *I* afforded in addition to amide *II* also 3,4,13-trimethoxy-5-oxo-7,8-dihydro-5*H*,11*H*-[1,3]dioxolo[4″,5″ : 4′,5′]benzo[1′,2′ : 4,5]azepino[2,1-*a*]isoindole (*X*) when treated with 1,2-epoxy-3-chloropropane. This reaction course can rationalize the mechanism involving formation of a quaternary salt *XV* in the first step; it can be stabilized by elimination of a proton from β-carbon with respect to the nitrogen atom and a following decomposition of the amide *II* (Hofmann elimination), or by elimination of a proton from the amido group and an intramolecular cyclization leading to the compound *X*. Both eventualities involve an elimination of 1-chloro-3-dimethylaminopropanol.

The starting *I* and 1,2-epoxypropane furnished the alcohol *XI* in the ^{1}H NMR spectrum of which duplication of proton signals bound to carbons adjacent to the new chiral carbon was observed. Nonetheless, after oxidation of the hydroxyl group with pyridinium chlorochromate associated with disappearance of the chiral centre, the obtained compound *XII* showed in its ^{1}H NMR spectrum only one series of signals.

These experiments evidence that the 2-dimethylamino derivatives of 1-benzylidenisoindolin-3-one can be deaminated by the reaction with epoxides under milder conditions than by Hofmann degradation of the corresponding methiodides.

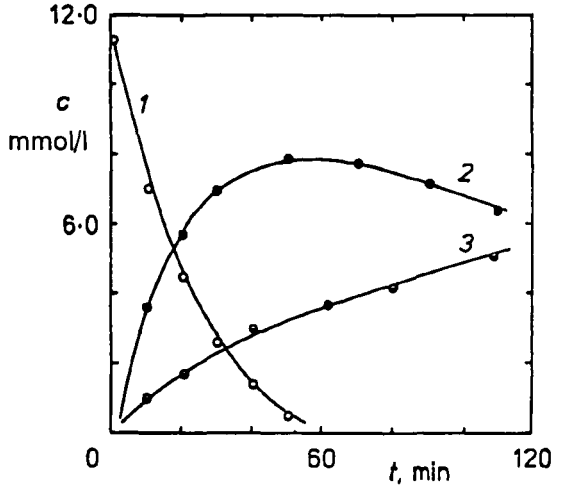


FIG. 1
Time dependence illustrating the composition of the mixture on reaction of (*Z*)-narceine imide (*I*) with 1,2-epoxy-3-phenoxypropane in ethanol; *1* (*Z*)-narceine imide (*I*), *2* narceone imide (*II*), *3* compound *III*

EXPERIMENTAL

Melting points were measured on a Kofler micro hot-stage, the electron-impact mass spectra were run with a Jeol JMS 100D apparatus at 70 eV and 300 μA and the ^{1}H NMR spectra were recorded with a Bruker AM 300 spectrometer, chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. A column 150 × 3 mm packed with Separon SGX C18 7 μm, mobile phase methanol–water (75 : 25, flow rate 0.4 ml min^{-1}) and detector 254 nm were applied for high-performance liquid chromatography; Alufol and Silufol sheets were the carriers for thin-layer chromatography in solvent systems chloroform–methanol (10 : 1, S_1), benzene–methanol (9 : 1, S_2), detection by UV_{254} light.

3-Phenoxy, 3-decyloxy and 3-(diethylamino)-1,2-epoxypropane were prepared from 3-chloro-1,2-epoxypropane and the respective alcohol or diethylamine[12,13].

Reaction of (*Z*)-Narceine Imide with 1,2-Epoxy-3-phenoxypropane

(*Z*)-Narceine imide (*I*, 1 065 mg, 2.5 mmol) and 1,2-epoxy-3-phenoxypropane (450 mg, 3 mmol) were refluxed in ethanol (50 ml) for 2 h. After all the starting material was consumed (monitored on Alufol sheets in S_1, or by HPLC at 1 : 10 dilution) the mixture was concentrated and the residue dissolved in $CHCl_3$–CH_3OH (20 : 1) was filtered through a column of alumina, the eluate was concentrated and the product was crystallized from methanol to give 743 mg (78%, m.p. 210 – 211 °C) of a compound identical with narceone imide (*II*).

Dihydronarceone imide[10] (*XII*, m.p. 177 – 179 °C) was obtained in analogous way from dihydronarceine imide (*IV*) in 83% yield; (*Z*)-α-bromonarceine imide[14] (*XIV*, m.p. 191 – 192 °C, 85%) and narceone imide (*II*, m.p. 211 – 212 °C, 81%) were prepared similarly from (*Z*)-α-bromonarceine imide (*V*) and narceine amide[15] (*VI*), respectively. The products were identified by spectral (IR, mass and NMR) means.

Reaction of Ethyl Narceinate with 1,2-Epoxy-3-phenoxypropane

Ethyl narceinate (*VIII*, 200 mg, 0.42 mmol) and 1,2-epoxy-3-phenoxypropane (70 mg, 0.53 mmol) were refluxed in ethanol (20 ml) for 2 h. The mixture was concentrated, the residue was dissolved in chloroform and chromatographed on an alumina-packed column with chloroform–methanol in a gradient mode. Fractions of R_F 0.10 (Silufol, S_1) afforded compound *IX* (m.p. 189 – 190 °C, 140 mg) after a work-up and crystallization from ether–acetone. For $C_{32}H_{37}NO_{10}$ (595.6) calculated: 64.53% C, 6.26% H, 2.35% N; found: 64.46% C, 6.21% H, 2.34% N. Mass spectrum, *m/z* (% rel.): 382 (100), 367 (11), 196 (62), 151 (15), 107 (14), 94 (21). ^{1}H NMR spectrum (CD_3OD): 7.27 d, 1 H (H-5, *J*(4,5) = 8.1), 7.24 d, 1 H (H-4); 7.00 – 6.65 m, 5 H (arom. H); 6.50 s, 1 H (H-5'); 5.88 s, 2 H (OCH_2O); 4.42 m, 1 H (CHO); 3.92, 3.86, 3.80 s, 9 H (OCH_3); 3.08 s, 6 H (N^+Me_2).

Reaction of (*Z*)-Narceine Imide with 1,2-Epoxy-3-chloropropane

Compound *I* (500 mg, 1.17 mmol) and 1,2-epoxy-3-chloropropane (540 mg, 5.8 mmol) were refluxed in ethanol (25 ml) for 12 h. The mixture was concentrated, the residue was dissolved in chloroform, the unreacted starting *I* was removed by extraction with 2% acetic acid (25 ml), the chloroform solution was concentrated and the products *II* (36 mg) and *X* (39 mg) obtained by preparative thin-layer chromatography on silica gel in S_2 were identified by contrasting the spectral data obtained with those of the specimens[10].

Reaction of (*Z*)-Narceine Imide with 1,2-Epoxypropane

Compound *I* (500 mg, 1.17 mmol) and 1,2-epoxypropane (680 mg, 11.7 mmol) were refluxed in ethanol (20 ml) for 48 h. The residue after removal of the solvent was crystallized from ether to furnish compound *XI*, m.p. 160 – 162 °C (420 mg). For $C_{24}H_{25}NO_7$ (439.5) calculated: 65.59% C, 5.73% H, 3.19% N; found:

65.50% C, 5.78% H, 3.16% N. Mass spectrum, *m/z* (% rel.): 439 (100), 424 (2), 421 (2), 394 (7), 381 (12), 366 (29). ^{1}H NMR spectrum ($CDCl_3$): 7.57 d, 1 H (H-7, *J*(6,7) = 8.2); 7.16 d, 1 H (H-6); 6.84, 6.81 s, 1 H (H-8); 6.71, 6.70 dd, 1 H (H-7, *J*(7',8a') = 11.5, *J*(7',8b') = 17.4); 6.29, 6.27 s, 1 H (H-5'); 5.99 s, 2 H (OCH_2O); 5.58 dd, 1 H (H-8b', *J*(8a',8b') = 1.0) ; 5.16 dd, 1 H (H-8a'); 4.11, 3.96, 3.93 s, 9 H (OCH_3); 0.8 d, 3 H (CH_3C, *J* = 5.6).

(*E*)-2-(2-Oxopropyl)-4,5-dimethoxy-1-(6-ethenyl-3,4-methylenedioxy-2-methoxy)benzylidenisoindolin-3-one (*XII*)

The alcohol *XI* (200 mg, 0.46 mmol) and pyridinium chlorochromate (200 mg, 0.93 mmol) were stirred in dichloromethane (10 ml) for 5 h, the mixture was concentrated and the residue was purified by a preparative thin-layer chromatography on silica gel in S_1 and crystallized from methanol to afford substance *XII*, m.p. 213 – 215 °C, $C_{24}H_{23}NO_7$ (437.5). Mass spectrum, *m/z* (% rel.): 437 (80), 422 (8), 395 (20), 381 (35), 366 (58), 285 (36), 246 (100). ^{1}H NMR spectrum ($CDCl_3$): 6.88 d, 1 H (H-7, *J*(6,7) = 8.1); 6.87 s, 1 H (H-5'); 6.69 dd, 1 H (H-7', *J*(7',8a') = 17.4, *J*(7',8b') = 11.5); 6.60 d, 1 H (H-6); 5.99 s, 2 H (OCH_2O); 5.77 s, 1 H (H-8); 5.53 dd, 1 H (H-8a', *J*(8a',8b') = 1.0); 5.05 dd, 1 H (H-8b'); 4.63 s, 2 H (NCH_2CO); 4.07, 3.86, 3.85 s, 9 H (OCH_3); 2.23 s, 3 H ($COCH_3$).

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