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TRIS-N, N',N''- (3',4',5'-TRIMETHOXYPHENETHYL)-1,3,5-HEXAHYDROTRIAZINE, A METHYLENEMESCALINE TRIMER: CHARACTERIZATION AND SELECTIVE CYCLIZATION TO ANHALININE UNDER NON-AQUEOUS CONDITIONS

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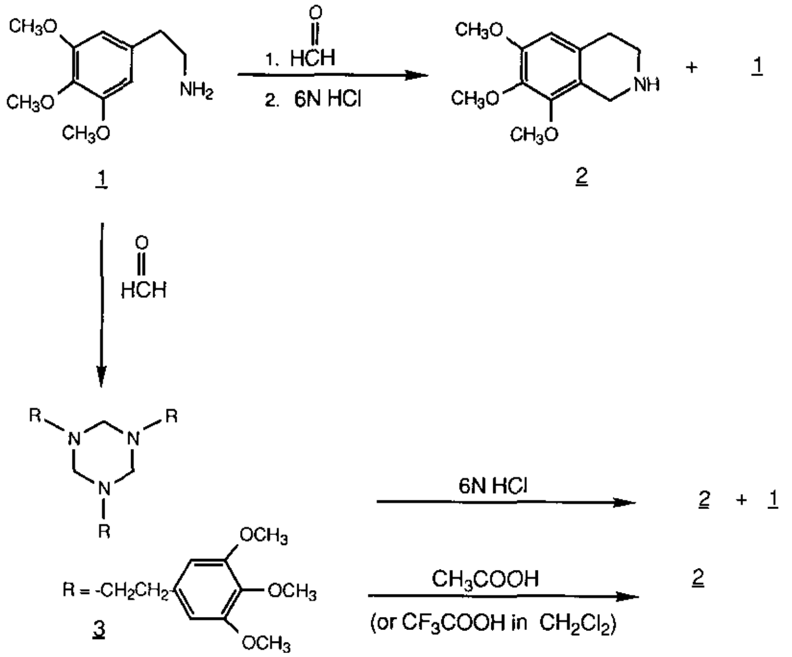
Abstract - The product obtained from the reaction of mescaline with aqueous formaldehyde was assigned the hexahydrotriazine structure 3, on the basis of ms and ^{1}H-nmr spectral data, and microanalysis. Reaction of 3 with hydrochloric acid in aqueous milieu afforded a mixture of anhalinine (2) and mescaline (1), however, exclusively 2 was obtained when the reaction was performed under non-aqueous conditions in glacial acetic acid or in dichloromethane with trifluoroacetic acid.

Condensation of mescaline base with formaldehyde under highly concentrated conditions was performed by Späth, who assumed that the oily material which separated was the Schiff base (4)[1]. Addition of 6N HCl to this oil afforded anhalinine hydrochloride (2.HCl)[1] in 60% yield (no other product was identified). Since it seemed unlikely that a Schiff base of structure 4 was formed under these reaction conditions we decided to repeat this experiment and to determine the structure of this oil using spectral data. These provided evidence that the product, which was obtained crystalline, is in fact the hexahydrotriazine 3. Such triazines have been obtained by reaction of benzylamines and aromatic amines with formaldehyde[2,3], but were never reported for the physiologically more interesting phenethylamines as represented by mescaline (1).

The oily material obtained by Späth's procedure could be crystallized from EtOH-H_2O or EtOAc-Et_2O (Et_2O was saturated with H_2O), after the CH_2Cl_2 solution of the oil was washed exhaustively with H_2O to remove excess mescaline. The colorless needles of mp 48-49°C were insoluble in H_2O or Et_2O. The ir spectrum obtained from the product did not exhibit peaks characteristic for an imine[4], and resembled that of mescaline, except for the absence of primary amine signals at 3310 and 3380 cm^{-1} clearly visible in 1. The uv spectrum exhibited a maximum and peak shape identical to that obtained with mescaline 1. ^{1}H-Nmr spectra obtained for the crystalline product 3, mescaline hydrochloride (1.HCl) and anhalinine.HCl (2.HCl) showed for 1.HCl and 2.HCl two pairs of adjacent methylene protons with different chemical shifts and vicinal couplings of J = 6.5 Hz (see Table 1.). For 3 the 4 ArCH$_2$CH$_2$-protons were chemical shift equivalent showing a slightly broadened singlet peak. For 2.HCl, the C(1)-methylene protons (Ha,a') were visible as a sharp singlet, whereas 3 exhibited a very broad Ha, Ha' signal which sharpened considerably when the temperature was increased from the usual 20°C to 50°C. This suggested that 3 possesses different conformations which are in rapid equilibrium, showing conformational changes as seen with N, N'-dimethyl-



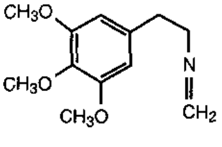


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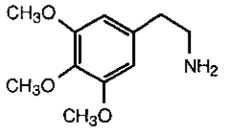
Table 1. ^{1}H-Nmr: δ and J values for compounds 1, 2, and 3.



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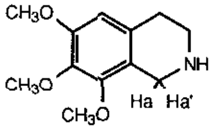

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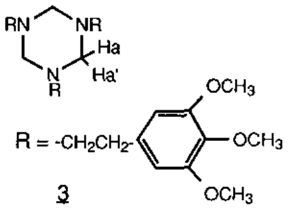

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Compound	Solvent	δ,ppm^a (multiplicity) ArCH$_2$CH$_2$N- protons	J, Hz	Ha,Ha'
1.	$CDCl_3$	2.70 (t) 2.95 (t)	6.7	---
2.	CD_3OD	3.03 (t) 3.42 (t)	6.2	4.19 (s)
3.	$CDCl_3$	2.72 (br s)^b	--	3.46 (s)

^{a}Ppm measured from internal standard. Spectra acquired on a Varian XL-300 nmr spectrometer at 300 MHz at 20°C. ^{b}At 50°C, the peak observed for these protons is sharpened considerably.

piperazine[5]. Final proof of the hexahydrotriazine structure 3 rested on the determination of the mass of the compound. In our case, use of CI (NH_3) or EI mass spectometry gave only a fragment peak of mass 223 identical to the mass of anhalinine (2) and the putative Schiff base 4. The fragmentation pattern seen with 3 [m/z 223, 211, 181 (base peak), 148, 136] was similar to that obtained with 1.HCl [m/z 211, 182 (base peak), 167], but differed markedly from that obtained with 2.HCl [m/z 223, 222 (base peak), 206, 194, 179, 151. Using Californium^{252} plasma mass spectrometry the molecular weight of 3 was determined to be 669. This is three times the apparent mass peak of 223 given by the GC/EI-mass spectrum, and supports our assignment as the trimer 3 of the molecular composition $C_{36}H_{51}N_3O_9$.
Additional evidence was provided by chemical reactions. Treatment of 3 with excess $NaBH_4$ in refluxing MeOH for >24 h resulted in three products plus a substantial amount of starting material. When crystalline hexahydrotriazine 3 was stirred with 6N aqueous HCl under the conditions used by Späth[1], 2.HCl precipitated from the solution and was obtained in 65% yield. From the mother liquors of that reaction, after alkalinisation with 10% KOH and

extraction of basic material with CH_2Cl_2, we obtained mescaline (1) in 20% yield. Identity of both anhalinine (2) and mescaline (1) was secured by comparision with authentic samples of their hydrochlorides (tlc, mp, and ir). When 3 was treated with acid under non-aqueous conditions, such as glacial acetic acid, anhalinine (2) was the only product, obtained in 82% yield. Similarly, if 3 was treated in CH_2Cl_2 solution with trifluoroacetic acid, only 2 was obtained.

The Pictet-Spengler synthesis is considered to be a crucial reaction in the biosynthesis of the isoquinoline alkaloids, however, in vitro this reaction is often conducted under non-physiological conditions and may therefore result in a variety of products such as trimer 3 obtained here from mescaline (1) and formaldehyde. Formation of 3 was observed to occur in dilute aqueous solution at neutral pH, and may for this reason be of biological significance. Non-aqueous acid catalysis of trimer 3, affording the isoquinoline 2 as a single product and in much improved yield, may in addition be of synthetic importance.

EXPERIMENTAL

Melting points were obtained on a Fisher-Johns hot-stage apparatus and are uncorrected. Ir spectra were run as films, on a Beckman IR 4230 instrument, ν values in cm^{-1}. ^1H-Nmr spectra were obtained on a Varian-XL-300 spectrometer at 300 MHz, and the chemical shifts are reported in ppm from an internal solvent standard. The chemical ionization mass spectra were acquired on a Finnegan-1015D spectrometer with a model 6000 data collection system. Electron impact mass spectra were obtained at 70 ev using a VG 7070F mass spectrometer. Californium^{252} plasma desorption mass spectra were obtained using a home built instrument. Uv spectra (λ_{max}, nm) were recorded in ethanol using a Hewlett-Packard-8450-A uv/vis spectrophotometer. Analytical tlc was performed on silica plates obtained from Analtech, Inc. (Newark, DE). Elemental analysis was performed by Atlantic Microlab Inc. (Atlanta, GA).

Tris-N, N', N''-(3',4',5'-trimethoxyphenethyl)-1,3,5-hexahydrotriazine (3).

1 (5.3 g, 25 mmol) was dissolved in 5 ml of warm H_2O, then 2.6 ml of 37% formaldehyde was added. A viscous yellow oil separated from the reaction mixture, which was stirred while heating (H_2O bath) for 1 h. The upper white layer was decanted from the oil, which was then washed with H_2O (5 x 25 ml). The oil was dissolved in 10 ml of CH_2Cl_2 and the solution was washed thoroughly with H_2O (3 x 10 ml). The organic layer is dried ($MgSO_4$) and concentrated under high vacuum (<1 mmHg) to give 5.4 g of viscous yellow oil (96% yield), which was crystallized from EtOAc/Et_2O (Et_2O was saturated with H_2O) to yield 3.3 g (63%) of colorless needles, mp 48-49°C. Uv (EtOH):λ_{max} 269 nm; ir (film): 2925, 2820, 1590, 1510, 1460, 1420,

1330 (br), 1249 (br), 1160-1100 (br), 1010, 820; ^{1}H-nmr ($CDCl_3$): δ 6.42 (s, 2H, Ar-H), 3.83-3.81 (m, 9H, 3 x $-OCH_3$), 3.46 (br s, 2H, $-N-CH_2-N-$), 2.72 (s, 4H, $Ar-CH_2-CH_2-N$); cims (NH_3): m/z 223 (base peak); eims: m/z 223, 211, 181 (base peak), 148, 136; Cf^{252} ms: m/z 669, 654, 446 (base peak), 431; $C_{36}H_{51}N_3O_9$, calcd for C, 64.55%; H, 7.64%; N, 7.68%; found: C, 64.45%; H, 7.64%; N, 6.23%.

Anhalinine.HCl (2.HCl)

A. Compound 3 (254 mg, 0.38 mmol) was dissolved in 0.5 ml of EtOH, followed by the addition of 2.0 ml of 6N HCl. The solution was stirred under N_2 for 1 h at 60°C, during which time 2.HCl precipitated. The hydrochloride of 2 was removed by filtration, and washed with 6N HCl to yield 186 mg (63%) of material of mp 258-260°C (lit.[1] mp 248-250°C). The hydrochloride was identical by tlc, ir and nmr with an authentic sample of 2.HCl. The mother liquor was made basic by the addition of 20% KOH (pH 13), then the basic material extracted with CH_2Cl_2. After drying ($MgSO_4$) and removal of solvent, 47 mg of mescaline was recovered (19% yield). The base was converted to the HCl salt, mp 180-181°C (lit.[6] mp 181°C) and was found identical by tlc, ir, and nmr with an authentic sample of mescaline hydrochloride (1.HCl).

B. Compound 3 (182 mg, 0.27 mmol) was dissolved in 2 ml of glacial acetic acid and the solution was stirred under N_2 for 3 h. The acetic acid was removed under reduced pressure at 50°C, and the residue obtained was dissolved by gentle heating in 2 ml of 6N HCl. The colorless crystals of 2.HCl (173 mg, 82%) collected upon cooling had mp 253-256°C (lit.[1] mp 248-250°C) and were identical by tlc, ir and nmr with an authentic sample of 2.HCl.

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