(4a*S*,7*S*,7a*R*)-Nepetalactam and (4a*S*,7*S*,7a*R*)-2-[(3*R*,4*R*,4a*R*,7*S*,7a*R*)-Octahydro-4,7-dimethyl-1-oxocyclopenta[*c*]pyran-3-yl]nepetalactam: Nitrogen Analogues of Nepetalactone and Nepetalic ψ-Anhydride

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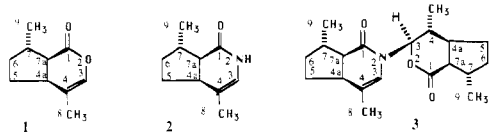
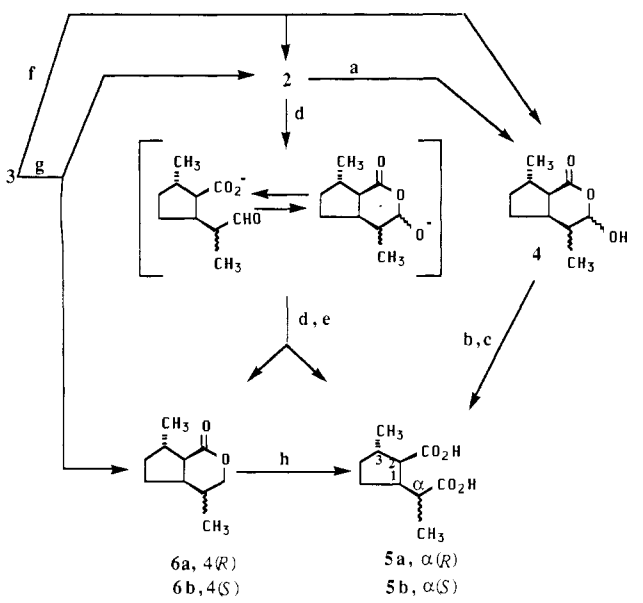
The structure and stereochemistry of (4a*S*,7*S*,7a*R*)-nepetalactam, isolated from a commercial sample of catnip oil, were established by spectroscopic studies and by conversion to δ-skytanthine and to known compounds derived from nepetalic acid and nepetalactone. Nepetalactam, shown to be the nitrogen analogue of (4a*S*,7*S*,7a*R*)-nepetalactone, also was prepared from nepetalic acid and nepetalactone. A mixed dimer of nepetalactam and nepetalic acid, (4a*S*,7*S*,7a*R*)-2-[(3*R*,4*R*,4a*R*,7*S*,7a*R*)-octahydro-4,7-dimethyl-1-oxocyclopenta[*c*]pyran-3-yl]nepetalactam, analogous to nepetalic ψ-anhydride, also was isolated from the above-mentioned catnip oil, characterized, and synthesized from nepetalic acid.

The catnip plant, *Nepeta cataria*, produces a steam-volatile oil consisting mainly of (4a*S*,7*S*,7a*R*)-nepetalactone (**1**).[2,3] Several groups[3,4] have previously utilized commercial oil of catnip as a source of **1**. We now report the isolation and structure proof of (4a*S*,7*S*,7a*R*)-nepetalactam (**2**), the nitrogen analogue of **1**, along with (4a*S*,7*S*,7a*R*)-2-[(3*R*,4*R*,4a*R*,7*S*,7a*R*)-octahydro-4,7-dimethyl-1-oxocyclopenta[*c*]pyran-3-yl]nepetalactam (**3**), a mixed "dimer" of **2** and nepetalic acid (**4**), from a commercial oil of catnip.[5] The preparation of **2** and **3** from **1** and **4** also is reported. These direct conversions provide evidence that **2** and **3** are artifacts of isolation or processing and result from contact of **1** and/or **4** with ammonia or ammonium salts. Nevertheless, their isolation and structure determination provide a significant extension of the chemistry of **1** and **4** and suggest an alternative method for isolating material, depending upon intended use, from the catnip plant. Nepetalactam (**2**) is an excellent crystalline derivative of **1**.



Lactams **2** and **3** were isolated by distillation and recrystallization or by high-pressure liquid chromatography (HPLC) from the above-mentioned oil. HPLC analysis of the unheated oil showed the presence of **2**, **3**, and (4*R*,4a*R*,7*S*,7a*R*)-dihydronepetalactone (**6a**)[4a-c,6] as 13, 25, and 4% respectively of the total oil.[5] Only traces of **1** (<1%) were observed.

Scheme I[a]



[a] (a) H_3O^+, Δ; (b) $KMnO_4$; (c) $Ba(OH)_2$, H_3O^+; (d) OH^-, Δ; (e) H_3O^+; (f) OH^-; H_3O^+; (g) $NaBH_4$, OH^-; H_3O^+; (h) RuO_2, $NaIO_4$, OH^-; H_3O^+.

Combustion analysis and the mass spectrum (*m*/*z* 165, $M^{\bullet+}$) of **2** showed the formula to be $C_{10}H_{15}NO$. The ^{13}C NMR spectra (broad band decoupled and off resonance decoupled) of **2** established that it has a carbonyl group, a protonated and a nonprotonated olefinic carbon, three aliphatic methine carbons, two aliphatic methylene carbons, and two methyl carbons (Table I). The significant features of the ^1H NMR spectrum ($CDCl_3$) were a broad concentration-dependent NH proton resonance at δ 8.60, a vinyl proton resonance at δ 5.66–5.74 (multiplet), and methyl group resonances at δ 1.20 (d, *J* = 6 Hz) and δ 1.63 (narrow multiplet). The spectrum of a sample treated with D_2O verified that the NH is readily exchanged and, in addition, exhibited partial collapse of the vinyl proton multiplet, indicating that the vinyl proton is vicinal to NH. Irradiation at the methyl group resonance at δ 1.63 resulted in further coalescence of the vinyl proton resonance signal. The UV spectrum of **2**, λ_{max} at 260 nm (log ε = 3.77), and

(1) (a) Oklahoma State University. (b) Varian Instrument Group.
(2) We thank Dr. K. L. Loening and Joy Merritt, Chemical Abstracts Service, for advice on nomenclature used for **1–3** and **7**.
(3) (a) Meinwald, J. *J. Am. Chem.* Soc. **1954**, *76*, 4571. (b) McElvain, S. M.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1599. (c) Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1955**, *77*, 3383. (d) Eisenbraun, E. J.; Browne, C. E.; Irvin-Willis, R. L.; McGurk, D. J.; Eliel, E. L.; Harris, D. L. *J. Org. Chem.* **1980**, *45*, 3811. (e) Eisenbraun, E. J.; Browne, C. E.; Eliel, E. L.; Harris, D. L.; Rahman, A.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 3302. (f) Eisenbraun, E. J.; Bright, A.; Appel, H. H. *Chem. Ind. (London)* **1962**, 1242.
(4) (a) Sakan, T.; Isoe, S.; Hyeon, S. B.; Katsumura, R.; Maeda, T.; Wolinsky, J.; Dickerson, D.; Slabaugh, M.; Nelson, D. *Tetrahedron Lett.* **1965**, 4097. (b) Regnier, F. E.; Eisenbraun, E. J.; Waller G. R. *Phytochemistry* **1967**, *6*, 1281. (c) Bates, R. B.; Sigel, C. W. *Experientia* **1963**, *19*, 564.
(5) This oil was obtained as a gift from Fritzsche, Dodge and Olcott Inc., New York, NY. We thank Dr. Kurt Kulka for his help.
(6) Wolinsky, J.; Eustace, E. J. *J. Org. Chem.* **1972**, *37*, 3376.

0022-3263/88/1953-3968$01.50/0

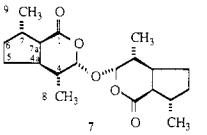
Table I. ^{13}C NMR Chemical Shifts and Assignments for 1-4 and 7[a]

carbon no.	1	2	3[b]	3[c]	4[d]	7
1	170.5	173.8	(171.4)	(173.7)	176.0	173.3
3	133.4	117.7	115.6	83.2	99.2	100.5
4	115.1	114.8	117.7	(41.7)	(40.2)	(39.2)
4a	(40.7)	(42.3)	(43.1)	(39.1)	(38.9)	(38.9)
5	(30.9)	(31.7)	(31.4)	(32.2)	(31.9)	(32.0)
6	(33.0)	(33.1)	(33.0)	(34.5)	(34.5)	(34.4)
7	(39.7)	(40.1)	(40.4)	(38.1)	(38.5)	(38.2)
7a	49.3	50.7	51.5	49.8	49.3	49.5
8	15.4	17.8	18.4	14.0	15.1	15.0
9	20.3	21.1	20.7	20.4	20.4	20.4

[a] Chemical shifts in parts per million downfield from Me_4Si (1.5–2 M solution of compound) in $CDCl_3$. Based on single frequency off resonance proton decoupled spectra and those of model compounds. Parentheses indicate uncertain assignment. [b] Nepetalactam moiety of 3. [c] Nepetalic acid moiety of 3. [d] Reference 3e.

IR (KBr) absorptions at 3200 (NH) and 1660 (C=O) cm^{-1} suggested a 3,4-dihydropyridinone structure.[7] Because of the source of **2** and the similarity of its ^1H and ^{13}C NMR spectra with those of **1** (Table I), structure **2** was tentatively assigned. The structure and stereochemistry of **2** were confirmed by degradation (Scheme I). Hydrolysis of **2** with dilute hydrochloric acid gave nepetalic acid (**4**) (epimeric at C-3 and C-4), which was oxidized with potassium permanganate to give a mixture of nepetalinic acids **5a** and **5b**. From this mixture was isolated **5a**, mp 82–84 °C, via its insoluble barium salt.[3b] This acid was shown to be identical by mixture mp, ^1H NMR spectra, and $[\alpha]_D$ with **5a** previously obtained from **1** and **4**.[3b,c] Hydrolysis of **2** with hot 10% sodium hydroxide resulted in a mixture of products from which **5a,b** and **6a,b** were isolated and then identified through comparison of their ^{13}C NMR spectra with those of known compounds.[3b,e,4a] It is assumed that they result from a Cannizzaro reaction on **4**. The lactones **6a** and **6b** were separated on the basis of faster basic hydrolysis of **6a** to the sodium salt of the corresponding acid.

The second crystalline product, **3**, was shown to have a molecular formula of $C_{20}H_{29}NO_3$ by combustion analysis and mass spectrometry, which showd ions at m/z 330 $(M - 1)^+$, 165, and 81. The presence of the latter ions suggested the structural similarity of **3** to **1** and **2**. The ^{13}C NMR spectrum of **3** showed 20 carbon resonances, 10 of which were very similar to those of **2** (Table I). The 10 other carbon resonances consisted of a carbonyl carbon, a methine carbon attached to two electronegative atoms (oxygen or nitrogen), four additional methine, two methylene, and two methyl carbons. Significant features of the ^1H NMR spectrum were a doublet at δ 6.28 (J = 10 Hz) attributed to a proton on a carbon substituted with two electronegative substituents (oxygen or nitrogen), a vinyl proton resonance at δ 5.82 (broad singlet), and four methyl group resonances at δ 1.70 (narrow multiplet), 1.22 (d, J = 6 Hz), 1.18 (d, J = 6 Hz), and 0.88 (d, J = 6 Hz). The IR spectrum (KBr) showed absorptions at 1725 (CO) and 1650 (dihydropyridinone) cm^{-1} while the UV spectrum (λ_{max} 255 nm, log ϵ = 3.53) was comparable to that of **2**. The absence of an NH proton resonance in the ^1H NMR spectrum and the absence of NH absorptions in the IR spectrum of **3** indicated that the nepetalactam moiety was joined to the remainder of the molecule through the nitrogen atom. The similarity of the ^{13}C NMR resonances (Table I) of **3** with those of **2** and (3*S*,4*R*,4a*R*,7*S*,7a*R*)-nepetalic ψ-anhydride (**7**)[8] and the presence of an aliphatic carbon bearing two electronegative atoms suggested structure **3**. In comparison, the ^{13}C NMR spectrum of **7** showed only the 10 lines expected of a symmetrical structure.



Treatment of **3** with base (Scheme I) followed by acidification gave **2** and **4** (epimeric at C-3 and C-4). Since **4** (Scheme I) was sensitive to epimerization, the configuration of C-4 in the pyranyl portion of **3** could not be inferred with certainty. To minimize epimerization, **3** was treated with sodium borohydride and base. The products were **2** and **6a**.[4] Epimer **6b** could not be detected by GC or HPLC, indicating that the reductive cleavage to **6a** is faster than epimerization at position 4 of the pyranyl ring. The relative and absolute configurations of **6a** were confirmed by its oxidation to **5a** using ruthenium dioxide and sodium periodate. Isolation of these products permitted stereochemical assignment to all chiral centers of **3** except the anomeric carbon, C-3. The proton attached to this carbon, H-3, was assigned an α orientation because of its large coupling (J = 10 Hz) to H-4. Comparison of **3** with β-D-glycosides[9] and the coupling constant expected for vicinal trans-diaxial protons (J = 8–10 Hz)[10] indicated that H-3 and H-4 are trans-diaxially attached; therefore, the C-8 methyl group is equatorially (α) oriented and the nepetalactam moiety also is equatorially (β) oriented so that C-3 has the *R* configuration. The IR stretching frequency of the lactone carbonyl group of **3**, 1725 cm^{-1}, also is consistent wtih a δ-lactone structure in a half-chair conformation.[11] Conversely, for **7**, H-3 shows an apparent singlet (δ 5.47) while the IR stretching frequency, at 1750 cm^{-1}, is to be expected for a δ-lactone in a boat conformation.[11] The small coupling between H-3 and H-4 of the lactone ring suggests that these protons are axially–equatorially arranged (average J_{ax-eq} = 2–3 Hz);[10] therefore, the C-8 methyl group of **7** is equatorially (α) oriented and the oxygen bridge is axially (α) oriented.[12]

Attempts to detect **2** or **3** in living *Nepeta cataria* plants were unsuccessful. Examination of solvent extracts of

(7) Ayer, W. A.; Berezowsky, J. A.; Iverach, G. G. *Tetrahedron* **1962**, *18*, 567.

(8) This paper describes the complete structure and stereochemistry of **7**. A partial structure had previously been reported: McElvain, S. M.; Walters, P. M.; Bright, R. D. *J. Am. Chem. Soc.* **1942**, *64*, 1828.

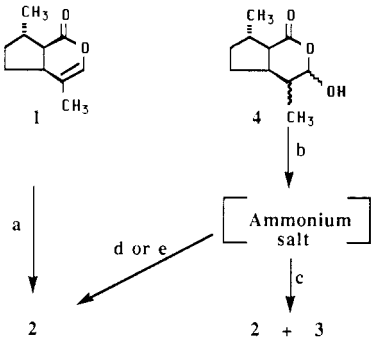
(9) Kupchan, S. M.; Merianos, J. J. *J. Org. Chem.* **1968**, *33*, 3735.

(10) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; p 209.

(11) Cheung, K. K.; Overton, K. H.; Sim, G. A. *Chem. Commun.* **1965**, 634.

(12) The axial orientation of the oxygen bridge in **7** (prepared from **4** under acidic conditions[8]) appears to be an additional example of the perference for an electronegative group to occupy an axial position when it is located adjacent to a heteroatom in a ring (anomeric effect); see: Eliel, E. L.; Giza, C. A. *J. Org. Chem.* **1968**, *33*, 3754 and references cited therein.

Scheme II[a]

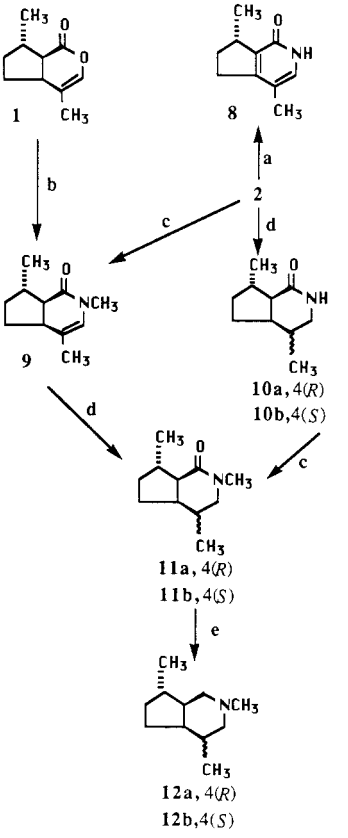


[a] (a) NH_3, Δ; (b) NH_3; (c) evacuate; 4, Δ; (d) Δ; (e) 1, Δ.

freshly harvested plants (no steam) by GC and by HPLC did not show any peaks corresponding in retention time to **2** or **3**. The origin of the commercial oil[5] from which **2** and **3** were obtained could not be determined, and the fact that previous investigators[3,4] did not report the presence of **2** or **3** in fresh plants or commercial oil suggested that these new products are artifacts.[13] This prompted an investigation of their possible origin from nepetalactone (**1**) and/or nepetalic acid (**4**) as shown in Scheme II. Treatment of **1** with ammonia at room temperature gave a mixture of products. Thin layer chromatography (TLC) studies showed **2** and **3** to be absent. However, when this product mixture was distilled, **2** formed as a crystalline product in 90+% yield. Various studies (mp, mp of a mixture wtih **2** from earlier studies, mass spectrometry, and IR as well as ^1H and ^{13}C NMR) showed this **2** to be identical with the material isolated from commercial oil of catnip.[5] Treatment of **4** with ammonia and heat under the same conditions also gave **2** in comparable yield. However, these experiments did not provide **3**. The successful preparation of **3** (Scheme II) was accomplished by treating **4** with ammonia at room temperature as a first stage. The excess ammonia was removed and an equivalent of **4** was added as a second stage. When this mixture was heated, **2** and **3** were formed. Both **2** and **3** from this experiment were indistinguishable, by the previously mentioned studies, from their counterparts isolated from catnip oil. Substituting **1** for **4** in the second stage did not provide **3**.

Additional exploratory studies, presented in Scheme III, showed that **2** could be dehydrogenated with Pd/C to (7*S*)-dehydronepetalactam (**8**) or converted to α- and δ-skytanthine (**12a** and **12b**).[3f] The conversion to **9**[14] was accomplished through methylation[15] of **2**. Catalytic hydrogenation of **9** to a mixture of *N*-methyl-3,4-dihydronepetalactams (**11a** and **11b**) followed by deoxygenation with borane-methyl sulfide complex (BMS)[16] gave a mixture of α- and δ-skytanthines (**12a** and **12b**) with the latter

Scheme III[a]



[a] (a) Pd/C, Δ; (b) CH_3NH_2, Δ; (c) CH_3I, KOH, Bu_4NBr, THF; (d) H_2, Pd/C; (e) BMS, THF; H_3O^+, Δ, OH^-.

predominating. The alternative route involved catalytic hydrogenation of **2** to a mixture of 3,4-dihydronepetalactams (**10a** and **10b**) with **10b** (4*S*,4a*R*,7*S*,7a*R*) being the major product. Approximately the same 5:1 ratio of products (**10b**/**10a**, **11b**/**11a**, **12b**/**12a**) was obtained from the two routes.

Experimental Section

^1H and ^{13}C NMR spectra (fully decoupled and single frequency off resonance proton decoupled) were recorded with a Varian XL-100 or XL-300 spectrometer. Some ^1H NMR spectra also were recorded with a Varian SC-360 (360 MHz) spectrometer. All chemical shifts are reported in parts per million downfield from Me_4Si. IR and UV spectra were recorded with a Beckman IR-5A and a Cary 14 instrument respectively. Mass spectra were recorded with a CEC 21-110B spectrometer at 70 eV. Melting points are uncorrected. Isohexane refers to commercial (Phillips Petroleum) isohexane, bp 55–60 °C. Gas chromatographic analyses were done on a Hewlett-Packard 5750 instrument with dual flame-ionization detectors using an 8 ft × 0.25 in. copper column packed with 5% UCW-98 coated on 80–100-mesh AW DMCS-treated Chromosorb G. Analytical and preparative high-pressure liquid chromatography (HPLC) were done by using a Waters Associates analytical or Prep-500 LC system equipped with UV (254 nm) and index of refraction detectors.

Isolation of 2 and 3 from Commercial Oil of Catnip. Fractionally distilled oil of catnip[5] boiling from 120 to 160 °C (0.2 mm) gave crystalline **2** after addition of isohexane and chilling. Fractions boiling from 160 to 200 °C (0.2 mm) partially solidified to give a mixture of crystalline **2** and **3**, and fractions boiling from 200 to 240 °C (0.2 mm) partially solidified to give crystalline **3**. The solid from each fraction was isolated by filtration. The mother liquors were combined and redistilled to give additional **2** and **3**.

Compounds **2** and **3** were best isolated by HPLC using a Waters C-18 μBondapak column with 60% CH_3CN/40% H_2O as the mobile phase. At a flow rate of 2 mL/min, retention volumes of **2** and **3** were 19.6 and 43.6 mL respectively.

(13) For that matter, nepetalic acid (**4**) and the α- and δ-nepetalinic acids, **5a** and **5b**, all of which are found in commercial catnip oil,[3b] are likely artifacts formed by hydrolysis and oxidation of nepetalactone (**1**).

(14) *N*-Methylnepetalactam (**9**) also may be prepared by treatment of **1** with methylamine followed by distillation. See also: Casinovi, C. G.; Delle Monache, F.; Marini-Bettolo, G. B.; Bianchi, E.; Garbarino, J. A. *Gazz. Chim. Ital.* **1962**, *92*, 479. In this paper, the structures are drawn in the opposite absolute configuration of the correct formulation. Also, it is unclear whether both methyl nepetalate and **4** were converted to **9** since the discussion section and a scheme indicate only **4** reacting with methylamine to give **9**, whereas the experimental section mentions only methyl nepetalate as being used to prepare **9**.

(15) Takahata, H.; Hashizume, T.; Yamazaki, T. *Heterocycles* **1979**, *12*, 1449.

(16) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

Several recrystallizations from isohexane gave **2**: mp 95–96 °C; $[\alpha]^{25}_D$ −46.5° (*c* 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, *J* = 6 Hz), 1.63 (narrow m, 3 H), 1.00–2.86 (m, 7 H), 5.66–5.74 (m, 1 H, br s after D_2O treatment), 8.60 (br s, 1 H, D_2O-exchangeable); ^{13}C NMR data are presented in Table I; IR (KBr) 3200 (NH), 1660 cm^{-1}; MS (70 eV), *m/z* (relative intensity) $M^{\bullet+}$ 165 (100), 150 (33), 136 (27), 110 (24), 109 (27); UV (95% EtOH) λ_{max} 260 nm (log ε = 3.77). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.80; H, 9.03; N, 8.52.

Several recrystallizations from isohexane gave **3**: mp 116–117 °C; $[\alpha]^{25}_D$ 3.8° (*c* 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (d, 3 H, *J* = 6 Hz), 1.18 (d, 3 H, *J* = 6 Hz), 1.22 (d, 3 H, *J* = 6 Hz), 1.70 (narrow m, 3 H), 1.00–2.80 (m, 15 H), 5.82 (br s, 1 H), 6.28 (d, 1 H, *J* = 10 Hz); ^{13}C NMR data are presented in Table I; IR (KBr) 1725, 1650 cm^{-1}; MS (70 eV), *m/z* (relative intensity) $(M-1)^{\bullet+}$ 330 (25), 205 (26), 166 (31), 165 (100), 81 (90); UV (95% EtOH) λ_{max} 255 nm (log ε = 3.53). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.24. Found: C, 72.61; H, 8.90; N, 4.19.

Degradation of 2 to 5a and 6a. A. Acid Hydrolysis and Permanganate Oxidation of 2 to 5a. A slurry of **2** (600 mg, 3.6 mmol) in 10% HCl (50 mL) was heated at reflux for 8 h. The cooled solution was triply extracted with ether, and the combined ether extracts were extracted with 5% $NaHCO_3$. The aqueous layer was separated, and to it was added $KMnO_4$ (500 mg). After the mixture was stirred for 10 min, $Na_2S_2O_5$ and 10% HCl were added. The solution was triply extracted with ether, and the combined ether extracts were evaporated. To the stirred residue was added saturated barium hydroxide solution until the solution was strongly alkaline.[3b] The precipitated barium salt of **5a** was collected by filtration, rinsed with water and then with ether, and treated with 10% HCl, and the solution was extracted with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated, and the residue was recrystallized from isohexane/THF to give 220 mg (30%) of **5a**: mp 82–84 °C; mixture mp 84–86 °C; $[\alpha]^{23}_D$ +32.8° (*c* 2.44, $CHCl_3$) (lit.[3b] +30.2°); ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, *J* = 7 Hz), 1.12–1.28 (m, 1 H), 1.21 (d, 3 H, *J* = 7 Hz), 1.35–1.50 (m, 1 H), 1.81–2.00 (m, 2 H), 2.09–2.25 (m, 1 H), 2.43–2.60 (m, 2 H), 2.65–2.78 (m, 1 H), 11.40 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.1 (q), 18.8 (q), 30.5 (t), 34.0 (t), 39.5 (d), 41.8 (d), 44.1 (d), 54.6 (d), 182.5 (s), 183.5 (s).

B. Alkaline Hydrolysis and Isomerization of 2 to 5a,b and 6a,b. A sample of **2** (1.65 g, 10.0 mmol) was hydrolyzed in refluxing 10% NaOH. After GC analysis indicated all of **2** was consumed, the product mixture was acidified, extracted with ether, and separated into a lactone fraction and the sodium salts of **5a** and **5b** by using saturated sodium bicarbonate and ether. The salts were treated with saturated barium hydroxide solution, which selectively precipitated **5a** as the tetrahydrate.[3b] This salt was treated with dilute hydrochloric acid and extracted with ether to give **5a** identical with **5a** from the acidic hydrolysis of **2**. The filtrate yielded **5b**: mp 115–117 °C; ^1H NMR ($CDCl_3$) δ 1.21 (d, 3 H, *J* = 7 Hz), 1.28–1.46 (m, 1 H), 1.39 (d, 3 H, *J* = 7 Hz), 1.71–1.90 (m, 1 H), 1.92–2.05 (m, 1 H), 2.14–2.28 (m, 1 H), 2.37–2.60 (m, 2 H), 2.64–2.70 (m, 1 H), 2.72–2.84 (m, 1 H), 11.68 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.0 (q), 21.9 (q), 30.3 (t), 33.4 (t), 38.5 (d), 41.4 (d), 45.8 (d), 53.0 (d), 181.9 (s), 182.8 (s).

The lactone fraction, in 50 mL of ether, was vigorously stirred with 50 mL of 5% NaOH for 20 min. The layers were separated, and the ether layer was found to contain only **6b**. The acidified alkaline layer gave a mixture of **6a** and **6b** with **6a** predominating. This process was repeated several times to separate **6a** and **6b** completely. Gas chromatography showed base-line separation of **6a** and **6b** with **6a** emerging first from a Carbowax 20M column. The separated lactones were distilled [Kugelrohr at 80 °C (0.5 mm)] to give **6a** and **6b**. (4*R*,4a*R*,7*S*,7a*R*)-Dihydronepetalactone (**6a**):[4a] mp 24–26 °C; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, *J* = 7 Hz), 1.12–1.34 (m, 2 H), 1.20 (d, 3 H, *J* = 7 Hz), 1.55–1.69 (m, 1 H), 1.80–1.92 (m, 1 H), 2.00–2.19 (m, 2 H), 2.21–2.31 (m, 1 H), 2.38 (dd, 1 H, *J* = 11, 9 Hz), 3.92 (dd, 1 H, *J* = 11, 10 Hz), 4.15 (dd, 1 H, *J* = 11, 4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.5 (q), 20.0 (q), 31.7 (t), 34.2 (t), 35.1 (d), 38.6 (d), 44.4 (d), 48.8 (d), 72.6 (t), 174.8 (s); no observable $[\alpha]_D$ (*c* 11, $CHCl_3$).

(4*S*,4a*R*,7*S*,7a*R*)-Dihydronepetalactone (**6b**):[4a] ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, *J* = 7 Hz), 1.07–1.28 (m, 1 H), 1.10 (d, 3 H, *J* = 7 Hz), 1.30–1.52 (m, 1 H), 1.67–1.79 (m, 1 H), 1.83–2.08 (m, 2 H), 2.14–2.32 (m, 1 H), 2.41 (dd, 1 H, *J* = 11, 9 Hz), 2.47–2.61 (m, 1 H), 3.96–4.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.1 (q), 19.4 (q) 26.4 (t), 31.0 (d), 35.1 (t), 40.5 (d), 41.4 (d), 50.5 (d), 69.9 (t), 174.0 (s).

Degradation of 3. A. Reduction of 3 with $NaBH_4$ to 2 and 6a. To a solution of $NaBH_4$ (1.0 g) and NaOH (1.0 g) in methanol (40 mL) and H_2O (10 mL) was added **3** (3.0 g, 9.1 mmol). The solution was stirred for 3 h until HPLC analysis of an acidified aliquot indicated only **2** and **6a** to be present. The solution was extracted with ether (3×), and the combined ether extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was recrystallized from isohexane to give 1.2 g (80%) of **2**, mp 94–96 °C, identical by mixture mp and ^1H NMR with material previously isolated from the oil. The aqueous solution was acidified and extracted with ether (3×), and the ether extracts were combined, dried (Na_2SO_4), and distilled at 50–70 °C (0.1 mm) to give 1.1 g (73%) of **6a** described above.

B. Oxidation of 6a to α-Nepetalinic Acid (5a). To a solution of NaOH (150 mg, 3.7 mmol) in H_2O (5 mL) was added **6a** (504 mg, 3.0 mmol). The mixture was stirred and heated until homogeneous. After cooling, the pH was carefully adjusted to 8 (AcOH) and RuO_2 (20 mg) was added. A solution of $NaIO_4$ (1.71 g, 8.0 mmol) in H_2O (15 mL) was added dropwise. After an additional 15 min of stirring, EtOH (2 mL) was added and the RuO_2 was collected by filtration. The filtrate was acidified with HCl, extracted with ether (3×), treated with saturated barium hydroxide,[3b] and filtered to give the barium salt of **5a** (300 mg, 50%).

Conversion of 1 to 2. Nepetalactone (**1**) (100 mg) was treated with anhydrous ammonia for 1 h at room temperature to give a complex mixture of products (^{13}C NMR analysis). Distillation [Kugelrohr at 80 °C (0.5 mm)] gave 90 mg (91%) of **2**. Melting point, mass spectrum, ^1H and ^{13}C NMR, and IR data were identical with those of **2** isolated from the Fritzsche, Dodge and Olcott oil of catnip.[5] Alternatively, ammonia was bubbled for 15 min through 100 mg of **1** dissolved in 10 mL of dichloromethane. The remainder of this procedure was identical with the earlier description and gave the same result.

Conversion of 4 to a Mixture of 2 and 3. Ammonia was bubbled for 30 min through a solution of nepetalic acid (**4**) (100 mg) in CH_2Cl_2 (5 mL). At the beginning of this treatment, a solid precipitated. TLC analysis indicated the absence of **2** and **3**. However, GC analysis showed a peak corresponding to **2**. Distillation at this point gave **2** as sole product. Excess ammonia and CH_2Cl_2 were removed by rotary evaporation, and a solution of **4** (100 mg) in CH_2Cl_2 (5 mL) was added. The swirled mixture did not become completely homogeneous. The reaction product was concentrated, Kugelrohr distilled, and chromatographed by using 80:20 hexane/ether on silica gel to give 95 mg of **2** and 90 mg of **3**. Both products were shown by ^{13}C NMR to be identical with the materials isolated from commercial catnip oil. If **4** was replaced by **1** in either step above, **2** but not **3** was produced.

(3*S*,4*R*,4a*R*,7*S*,7a*R*)-Nepetalic ψ-anhydride (7) was prepared as previously described:[8] mp 138–140 °C (lit.[8] mp 139–140 °C); ^1H NMR ($CDCl_3$) δ 1.04 (d, 6 H, *J* = 6 Hz), 1.10–2.40 (m, 16 H), 1.26 (d, 6 H, *J* = 6 Hz), 5.47 (s, 2 H); IR (KBr) 1750 (CO) cm^{-1}; ^{13}C NMR data are presented in Table I.

Dehydrogenation of 2 to (7*S*)-Dehydronepetalactam (8). A sample of **2** (1.00 g) was heated at 270 °C in the presence of 10% Pd/C (0.10 g) for 4 h. Workup gave a white solid (0.80 g), which was purified by sublimation at 125 °C (0.4 mm) to give **8**: mp 182–183 °C; ^1H NMR ($CDCl_3$) δ 1.31 (d, 3 H, *J* = 7 Hz), 1.63–1.78 (m, 1 H), 2.04 (s, 3 H), 2.22–2.38 (m, 1 H), 2.65–2.79 (m, 1 H), 2.81–2.95 (m, 1 H), 3.40 (br s, 1 H), 7.13 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.1 (q), 19.2 (q), 31.0 (t), 31.8 (t), 37.9 (d), 114.0 (s), 130.8 (d), 134.9 (s), 156.8 (s), 162.7 (s). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.59. Found: C, 73.65; H, 7.95; N, 8.45.

Preparation of (4a*S*,7*S*,7a*R*)-*N*-Methylnepetalactam (9). A. The Treatment of 1 with Anhydrous Methylamine. A 100-mg sample of **1** was treated with anhydrous methylamine. Within 2 min, crystals formed, but some oil remained after 15-min treatment. TLC analysis showed that all of **1** was consumed but that **9** had not formed. ^{13}C NMR suggested that a 3-hydroxy-3,4-dihydronepetalactam had formed. GC analysis also showed that **1** had been consumed and a GC peak corresponding to **9** had appeared. Kugelrohr distillation gave **9** identical with material

from N-methylation of **2** as obtained below.

B. N-Methylation of 2 to 9. To a solution of **2** (1.65 g, 10 mmol) in THF (50 mL) was added iodomethane (3.55 g, 25 mmol), powdered KOH (1.40 g), and tetrabutylammonium bromide (0.64 g, 2 mmol).[15] The mixture was stirred overnight at room temperature, concentrated, and distilled [Kugelrohr at 60 °C (0.3 mm)] to give 1.69 g (94%) of pale yellow **9**: ^{1}H NMR ($CDCl_3$) δ 1.06–1.28 (m, 1 H), 1.19 (d, 3 H, J = 6 Hz), 1.38–1.57 (m, 1 H), 1.65 (s, 3 H), 1.73–1.86 (m, 1 H), 1.92–2.06 (m, 1 H), 2.21–2.35 (m, 2 H), 2.72 (q, 1 H, J = 9 Hz), 3.01 (s, 3 H), 5.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 21.0 (q), 31.4 (t), 33.0 (t), 33.9 (q), 40.0 (d), 42.4 (d), 51.1 (d), 115.5 (s), 123.2 (d), 170.6 (s).

Catalytic Hydrogenation of 2 to Dihydronepetalactam (10a,b). A sample of **2** (1.00 g) was hydrogenated in the presence of 10% Pd/C (0.10 g) in acetic acid. The product was distilled [Kugelrohr at 120 °C (0.2 mm)] to give 1.00 g of a 1:5 mixture of **10a** and **10b** as shown by GC analysis. The hydrogenation was repeated by using PtO_2 in ethanol and $Pd/BaSO_4$ in ethanol to give the same results. The major isomer **10b** showed the following: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz), 1.08–1.24 (m, 1 H), 1.19 (d, 3 H, J = 7 Hz), 1.28–1.44 (m, 1 H), 1.61–1.74 (m, 1 H), 1.79–1.92 (m, 1 H), 2.00–2.18 (m, 2 H), 2.25 (dd, 1 H, J = 10, 7 Hz), 2.30–2.43 (m, 1 H), 3.07 (dd, 2 H, J = 8, 3 Hz), 7.79 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.0 (q), 21.1 (q), 25.3 (t), 30.4 (d), 34.2 (t), 40.9 (d), 41.9 (d), 43.9 (t), 51.3 (d), 176.7 (s). Signals due to **10a** were as follows: ^{13}C NMR ($CDCl_3$) δ 17.2 (q), 33.1 (d), 39.0 (d), 44.6 (d), 47.4 (t), 50.2 (d).

Synthesis of *N*-Methyl-3,4-dihydronepetalactam (11a,b). A. Hydrogenation of 9 to 11a,b. A sample of **9** (1.00 g), prepared by methylation of **2**, was dissolved in ethanol and treated with H_2 in the presence of 10% Pd/C (0.10 g) catalyst. The product, 0.90 g of colorless oil, gave the following NMR data, which closely matched that of **11a,b** prepared through methylation of **10a,b**. Major isomer **11b**: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz), 1.05–1.24 (m, 1 H), 1.17 (d, 3 H, J = 7 Hz), 1.26–1.41 (m, 1 H), 1.58–1.72 (m, 1 H), 1.75–1.88 (m, 1 H), 1.98–2.09 (m, 1 H), 2.11–2.40 (m, 3 H), 2.92 (s, 3 H), 2.99 (dd, 1 H, J = 12, 5 Hz), 3.20 (t, 1 H, J = 12 Hz); ^{13}C NMR ($CDCl_3$) δ 15.5 (q), 20.7 (q), 24.5 (t), 29.4 (d), 33.4 (t), 34.4 (q), 40.3 (d), 41.6 (d), 51.1 (d), 51.2 (t), 172.3 (s). Minor isomer **11a**: ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 20.4, 29.2, 32.2 (d), 34.0, 38.4 (d), 44.4 (d), 50.3 (d), 55.0 (t), 172.0 (s).

B. N-Methylation of 10a,b to 11a,b. To a solution of **10a,b** (1.67 g, 10 mmol) in THF (50 mL) were added iodomethane (3.55 g, 25 mmol), powdered KOH (1.40 g), and tetrabutylammonium bromide (0.60 g, 2 mmol). The mixture was stirred at room temperature for 12 h, concentrated, and distilled [Kugelrohr at 60 °C (0.3 mm)] to give 1.67 g of **11a,b**. This mixture showed essentially the same NMR spectra as obtained in the previous section.

Deoxygenation of 11a,b to 12a,b. A sample of **11a,b** (1.00 g) dissolved in dry THF (1.0 mL) was brought to reflux, and borane–methyl sulfide complex in THF (6.0 mL of 2.0 M) was added dropwise. After addition was complete, the solvent was removed in vacuo, HCl (10 mL of 6 N) was added, and the mixture was heated at reflux for 1 h. The cooled reaction mixture was neutralized and extracted with ether, and the extract was dried ($MgSO_4$), filtered, concentrated, and distilled [Kugelrohr at 35 °C (3 mm)] to give 0.60 g (62%) of a mixture of **12a** and **12b**. The ^{13}C NMR spectrum showed signals of a major isomer identical with that of an authentic sample of δ-skytanthine (**12b**) available from earlier work:[3b] ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 3 H, J = 7 Hz), 0.97 (d, 3 H, J = 7 Hz), 1.05–1.19 (m, 1 H), 1.38–1.73 (m, 5 H), 1.75–1.85 (m, 1 H), 1.88–2.01 (m, 1 H), 2.02–2.14 (m, 2 H), 2.23 (s, 3 H), 2.46–2.59 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.5 (q), 22.2 (t), 22.7 (q), 30.9 (d), 31.4 (t), 36.5 (d), 40.3 (d), 46.2 (q), 46.6 (d), 57.3 (t), 58.0 (t).

Substituted *o*-Iodoso- and *o*-Iodoxybenzoic Acids: Synthesis and Catalytic Activity in the Hydrolysis of Active Phosphorus Esters and Related Systems

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2-Iodoso- and 2-iodoxybenzoic acids containing alkyl, alkyloxy, nitro, carboxyl, and water-solubilizing substituents have been synthesized, and their influence on the rates of hydrolysis of *p*-nitrophenyl diphenyl phosphate (PNPDPP), *p*-nitrophenyl isopropylphenylphosphinate (NPIPP), and *p*-nitrophenyl hexanoate (PNPH) has been determined in the presence of added cetyltrimethylammonium chloride (CTAC). All the compounds are true catalysts, with rates increasing with increasing catalyst concentration. 2-Iodoxybenzoic acids possess 60–110% of the activity of their 2-iodosobenzoic acid analogues in 0.001 M CTAC. The effects of substituents of variable electronic and aqua/lipophilic character upon catalytic activity have been determined. Lipophilic substituents significantly enhanced the rates while simple ring substitutions with electron-releasing and -withdrawing and water-soluble groups had only moderate effects. Extraordinary rate enhancements were obtained with 5-(2-hydroxyethoxy)-2-iodoxybenzoic acid and 5-(alkyloxy)-2-iodosobenzoic acid and -2-iodoxybenzoic acid derivatives, giving second-order rate constants of 400–5000 M^{-1} s^{-1}. The efficient catalysis of the hydrolysis of active phosphorus derivatives renders these aromatic 2-iodoso- and 2-iodoxybenzoic acids potentially useful decontaminants.

Introduction

Fluorophosphate, fluorophosphonate, phosphate, phosphonate, and phosphinate esters are persistent acetylcholinesterase inhibitors[1] and neurotoxic agents. Many are, or have been, used as potent pesticides.[2] Their decomposition rates under various conditions are clearly of considerable importance, and effective methods for their detoxification have attracted the attention of numerous research groups over the past several years.[3]

Potentially significant applications of such detoxification methods are the cleanup of chemical spills and, in military

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