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PHTHALIDEISOQUINOLINE ENOL LACTONES

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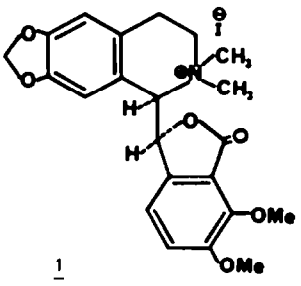
Abstract: (Z)-Narceine enol lactone (10) is thermodynamically less stable than its geometric isomer 11, and solvolyses faster in methanol to provide keto ester 9. In the less hindered hydrastine series, however, the order is reversed, and it is the E isomer 4 which is less stable than the Z analog 3, and which solvolyses faster to keto ester 6.

It has been established that the diastereomeric β- and α-hydrastine methiodides (1 and 2) can supply stereoselectively the Z and E enol lactones 3 and 4, respectively, in a Hofmann syn β-elimination process.[1] Compound 3, named N-methylhydrastine, also occurs as a natural product in various members of the Fumariaceae.[2,3]



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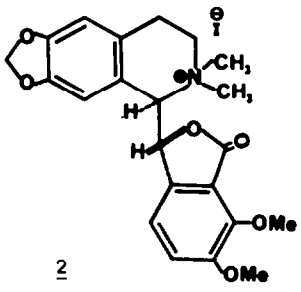

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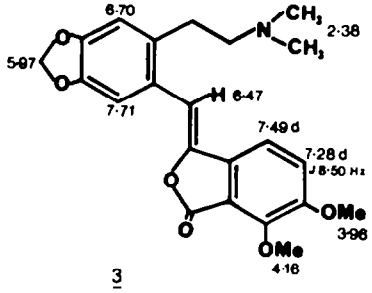

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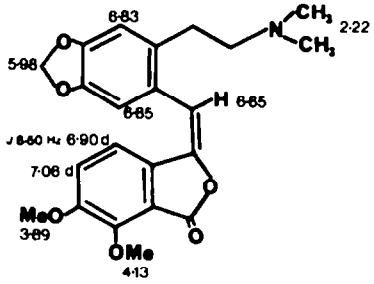

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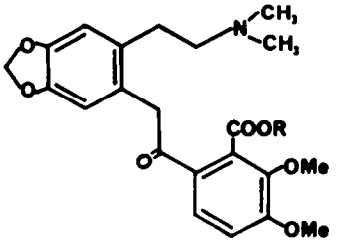
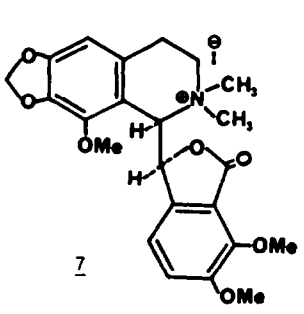


5: R = H
6: R = CH_3

It is also known that photoequilibration of 3 and 4 results in an approximately 3:2 mixture in favor of the thermodynamically more stable Z isomer 3. Additionally, when 3 and 4 were allowed to stand in aqueous acetone at room temperature, the product in each case proved to be the naturally occurring keto acid N-methylhydrasteine (5).[1]

The above reaction sequences do not find an exact analogy in the sterically more hindered narcotine series. Hofmann elimination of α-narcotine methiodide (7) supplied the keto acid narceine (8) directly. Furthermore, while acetic anhydride treatment of N-methylhydrasteine (5) provided (Z)-N-methylhydrastine (3), no parallel transformation could be observed from similar treatment of narceine (8) followed by work-up.[1] The Z and E narceine enol lactones 10 and 11 were, therefore, unknown at the initiation of the present study.



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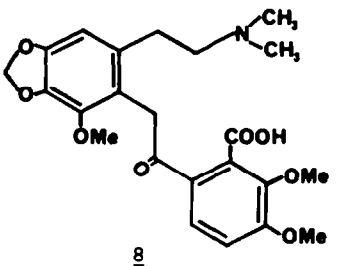

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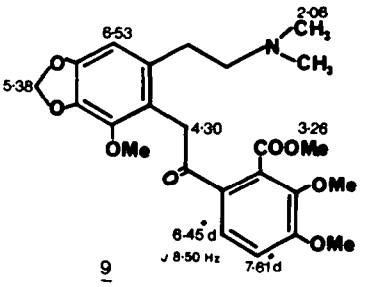

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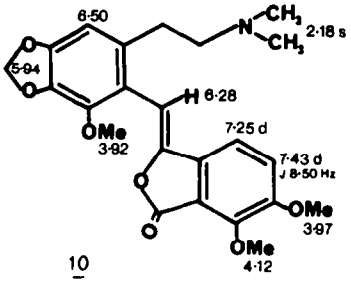

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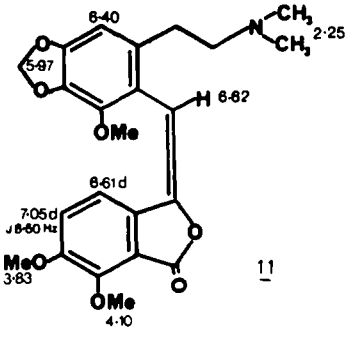

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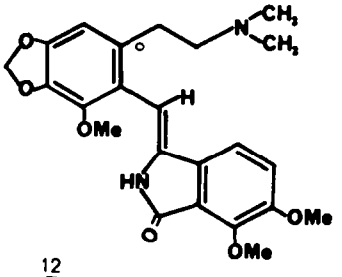

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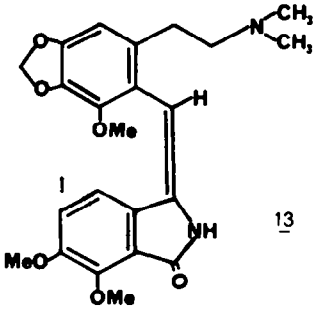
It was realized, however, that compounds 10 and 11 could be prepared, since the corresponding ene lactams 12 and 13 are known.[2,4] We conjectured also that enol lactones 10 and 11, if prepared, would readily hydrolyse to keto acid 8. The challenge in preparing enol lactones 10 and 11 thus reduced itself to finding a non-solvolytic medium for running the Hofmann elimination of α-narcotine methiodide (7) and its diastereomer β-narcotine methiodide (14).



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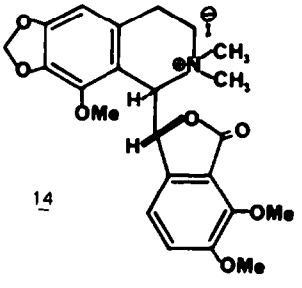

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In a trial run, β-hydrastine methiodide (1) was dissolved in dichloromethane and Fétizon's reagent,[5] silver carbonate on celite, was added. After a half hour of stirring, the reagent was filtered off, and the solvent evaporated. The residue was recrystallized from chloroform to provide once again the product of a syn β-elimination, namely (Z)-N-methylhydrastine (3) in 74% yield.[3] Similar treatment of α-hydrastine methiodide (2) furnished, following preparative TLC, (E)-N-methylhydrastine (4) in 64% yield and (Z)-N-methylhydrastine (3) in 6% yield.

Our attention then turned to α-narcotine methiodide (7) and β-narcotine methiodide (14). The latter salt was obtained by epimerization of α-narcotine in base,[6] followed by quaternization with methyl iodide. Reaction of α-narcotine methiodide (7) with the Fétizon reagent supplied, after recrystallization from dichloromethane, the desired Z enol lactone 10 in 72% yield.[3]

Purification of the Hofmann product from β-narcotine methiodide (14) proved to be more difficult, and could not be realized by recrystallization. The TLC system dichloromethane-methanol (10:1) could effect an efficient separation. (E)-Narceine enol lactone (11) was thus isolated in 69% yield. The minor product was narceine methyl ester (9). At this stage, we suspected that 9 had been formed by rapid methanolysis of the Z enol lactone 10 , while the E isomer 11 would be much slower in its rate of methanolysis.

More specifically, methanolysis of the Z enol lactone 10 had to have taken place not during the preparative TLC in dichloromethane-methanol, but in the desorption of the products from the TLC plate which could best be achieved with a 7:3 mixture of dichloromethane-methanol. This conclusion follows from the observation that compound 10 is yellow, and its TLC band could be readily followed especially under UV light. Yet, by the time the isolation of the TLC bands had been achieved, compound 10 had completely disappeared, to be replaced by colorless keto ester 9. In any case, desorption of the products from the TLC plate could not be realized without the use of a solvent system containing a relatively high percentage of methanol.

As a test of the above hypothesis, the pure Z enol lactone 10 was placed on a TLC plate, and eluted with dichloromethane and methanol. After the usual methanolic work-up, only keto ester 9 could be isolated. The E enol lactone 11, on the other hand, was recovered essentially unchanged from the TLC plate under the same conditions. In line with these results, it was found that the Z enol lactone 10 solvolyses in methanol at room temperature in less than one hour to supply keto ester 9, while the E isomer 11 took six hours to be converted to 9.

Since enol lactones 3 and 4 derived from the hydrastines are known to photoisomerize, the Z enol lactone 10 was dissolved in chloroform and subjected to sunlight for a total of 18 hours. TLC using dichloromethane-methanol (10:1) followed by methanolic work-up provided E enol lactone 11 in 48% yield and narceine methyl ester 9 in 32% yield; the latter product being formed mostly from Z enol lactone 10 during work-up. Significantly, photolysis of the corresponding E enol lactone 11 led to the same 3:2 mixture of 11 and 9.

The high resolution NMR chemical shifts for enol lactones 3,[2] 4,[2] 10 and 11, are given around their respective structural formulas. It should be noted that the vinylic hydrogen directly attached to the carbon bridge connecting the two aromatic rings is further downfield in the E series (compounds 4 and 11; δ 6.65 and 6.62) since this hydrogen lies syn to the oxygen atom which forms an integral part of the γ-lactone ring. In the Z series, the vinylic hydrogen is anti to the oxygen in question, and appears relatively upfield (compounds 3 and 10; δ 6.47 and 6.28).

The NMR spectrum of the keto ester 9 (in C_6D_6) at room temperature indicated that this molecule exists in solution as two conformers with restricted rotation. A double pattern of peaks was obtained, with almost every peak possessing a companion 0.01 to 0.02 ppm away. This duality disappeared above 60° C, producing the clean spectrum which has been summarized around expression 9.

Since (Z)-narceine enol lactone (10) is thermodynamically less stable than its geometric isomer 11, and also solvolyses faster in methanol to provide keto ester 9, it was decided to carry out a comparative rate study for the methanolysis of enol lactones 3 and 4 derived from the hydrastines. It was known that in methanol both eventually led to N-methylhydrasteine methyl ester (6). Presently, however, the thermodynamically more stable Z enol lactone 3 took between ten and eleven hours to be consumed in methanol at room temperature, whereas the less stable E isomer 4 reacted completely within five hours. With both the hydrastine and narceine enol lactones, therefore, we find that the thermodynamically less stable isomer is the one that solvolyses faster to the keto ester.

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Experimental

The NMR spectra were obtained in $CDCl_3$ solution at 100 MHz. Molecular compositions for the new compounds were confirmed by high resolution mass spectroscopy. TLC R_f values are on Silica Gel 60 F-254 glass plates in dichloromethane-methanol (10:1 v/v).

(Z)-N-Methylhydrastine (3) and (E)-N-Methylhydrastine (4): β-Hydrastine methiodide (120 mg, 0.23 mmol) was dissolved in dichloromethane (50 mL) and the Fétizon reagent[5] (150 mg) was added to the stirred solution at room temperature. The reagent was filtered off half and hour later, and the solvent evaporated in vacuo. Recrystallization from chloroform furnished 3 (67.5 mg, 74%); mp 154-155° C (lit.[2] m.p. 156° C); λ max $CHCl_3$ 262 sh, 310, 385 nm (log ε 3.88, 4.06, 4.26).

α-Hydrastine methiodide (100 mg, 0.19 mmol) was treated under identical conditions. Following work-up including TLC using benzene-methanol (9:1), 4 was obtained (48.2 mg, 64%); λ max $CHCl_3$ 242, 284, 353 nm (log ε 4.24, 3.98, 4.05); together with 3 (48 mg, 6%).

(Z)-Narceine Enol Lactone (10): α-Narcotine methiodide (7) (600 mg, 1.08 mmol) was dissolved in dry dichloromethane (300 mL) and Fétizon's reagent (600 mg) added. The mixture was worked up after one hour stirring. The crude product was recrystallized from dichloromethane to give 10 (332.4 mg, 72%); m.p. 105-107° C; ν max $CHCl_3$ 1778 cm^{-1}; λ max $CHCl_3$ 286, 305 sh, 357 nm (log ε 4.05, 3.97, 4.10); ms m/z 427 (M^+, $C_{23}H_{25}NO_7$, 10), 382 (0.5), 369 (0.1), 234 (6), 220 (4), 193 (0.6), 165 (0.3), 58 (100); R_f 0.45.

(E)-Narceine Enol Lactone (11): β-Narcotine methiodide (100 mg, 0.18 mmol) in dichloromethane (50 mL) was treated with Fétizon's reagent (100 mg) for one hour. Work-up including preparative TLC using dichloromethane-methanol (10:1) and desorption with dichloromethane-methanol (7:3) led to 11 (53.0 mg, 69%) and ester 9 (6.1 mg, 7%).

Compound 11; amorphous; ν max $CHCl_3$ 1775 cm^{-1}; λ max $CHCl_3$ 272, 348 nm (log ε 4.11, 4.05); ms m/z 427 (M^+, $C_{23}H_{25}NO_7$, 12), 382 (0.2), 369 (0.1), 249 (0.3), 234 (8), 220 (5), 193 (0.6), 165 (0.3), 58 (100); R_f 0.56.

Compound 9; m.p. 118-120° C (chloroform-ether); ν max $CHCl_3$ 1690 and 1730 cm^{-1}; λ max MeOH 216, 231 sh, 274, 298 sh nm (log ε 4.40, 4.17, 4.08, 3.97); ms m/z 459 (M^+, $C_{24}H_{29}NO_8$, 17), 427 (20), 413 (0.2), 382 (0.5), 285 (2), 234 (13), 223 (6), 195 (2), 178 (3), 58 (100); R_f 0.47

Photoequilibration of 10 and 11: Compound 10 (50 mg, 0.12 mmol) was allowed to stand in a Pyrex bottle in chloroform under sunlight for 3 x 6 h. After removal of the solvent in vacuo, the mixture was analyzed by TLC. The ratio of the Z (10) to E (11) isomers was estimated to be approximately 2:3. Preparative TLC and methanolic work-up furnished ester 9 (17.2 mg, 32%) and enol lactone 11 (23.9 mg, 48%). Identical results were obtained starting with compound 11.

Methanolysis of 10 and 11: Enol lactone 10 (25 mg, 0.06 mmol) was dissolved in methanol (3 mL) and the solution kept at room temperature. The reaction was monitored by TLC. Within less than one hour, the starting material had completely disappeared to supply quantitatively ester 9. Similar treatment of enol lactone 11 took 6 hours to provide ester 9 with no trace of 11.

References and Footnotes

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3. Any assignment of stereochemistry to the phthalideisoquinoline enol lactones ultimately revolves around the conversion of (-)-bicuculline of established stereochemistry to its Z enol lactone whose structure was confirmed by an x-ray study. See Klötzer, W.; Teitel, S.; Brossi, A. Helv. Chim. Acta 1972, 55, 2228.
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