Secophthalideisoquinolines

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The secophthalideisoquinolines can be subdivided into enol lactones, keto acids, diketo acids, and ene lactams. The diastereomeric β- and α-hydrastine methiodides (**8** and **9**) supply stereoselectively *Z* and *E* enol lactones **11** and **12**, respectively, in a syn β-elimination process. *N*-Methylhydrastine (**11**) reacts under mild conditions with methanol, water, or ammonia to produce keto ester **18**, keto acid **17**, or hydroxy lactam **36**, respectively. Treatment of hydroxy lactam **36** with acid results in rapid loss of water and formation of the *Z* ene lactam **33**. Photoequilibration of **33** gives rise to a mixture of *Z* and *E* ene lactams **33** and **34**. A biogenetic scheme is proposed for the secophthalideisoquinolines which includes the following sequence: classical phthalideisoquinoline → phthalideisoquinoline *N*-metho salt → secophthalide enol lactone → secophthalide keto acid → secophthalide diketo acid → fumariflorine-type alkaloid. Ene lactams **30–33**, as well as the hydroxy lactam fumschleicherine (**35**), are most probably artifacts of isolation.

The phthalideisoquinoline alkaloids can be divided into two broad classes, those possessing the classical tetracyclic nucleus incorporating a γ-lactone ring such as (−)-α-hydrastine (**1**), (−)-β-hydrastine (**2**), (+)-adlumidine (**4**) and its enantiomer (−)-capnoidine (**5**), (−)- and (+)-bicuculline (**6** and **7**), and (−)-α-narcotine (**3**) (Chart I). and those commonly referred to as secophthalideisoquinolines which are characterized by an open ring B.[3-5] This paper will be devoted to a discussion of the chemistry, spectroscopy, and biogenesis of the secophthalideisoquinolines, whose occurrence interestingly enough is limited to the plant families Fumariaceae and Papaveraceae.

Sixteen secophthalides have so far been reported in the literature. They can be conveniently subdivided into enol lactones, keto acids, diketo acids, and ene lactams.

(a) Secophthalideisoquinoline Enol Lactones. Three secophthalideisoquinoline enol lactones are known, namely, *N*-methylhydrastine (**11**), adlumidiceine enol lactone (**16**), and aobamidine (**15**) (see Chart II). The assignment of stereochemistry to these alkaloids ultimately revolves around the known conversion of (−)-bicuculline (**6**) of established stereochemistry to the *Z* enol lactone **10** whose structure was confirmed by an X-ray analysis.[5] Stilbene **10** shows characteristic high-intensity, long-wavelength peaks in its UV spectrum: λ_{max} (EtOH) 309 nm (log ϵ 4.10), 391 (4.34). It follows that the alkaloid aobamidine [**15**; λ_{max} (EtOH) 308 nm (log ϵ 4.10), 390 (4.28)] must possess the identical geometry.[7,8]

The alkaloid adlumidiceine enol lactone[9] has also been derived chemically from mild Hofmann elimination of adlumidine (**4**) methiodide. Its photoequilibration was found to yield a mixture of starting material plus aobamidine (**15**), so that adlumidiceine enol lactone was given the *E* stereochemistry as shown in expression **16**.[7,8,10]

Table I. 200-MHz FT ^{1}H NMR Chemical Shift Assignments for Enol Lactones and Ene Lactams

	chemical shift, δ			
	(*Z*)-**11**	(*E*)-**12**	(*Z*)-**33**	(*E*)-**34**
$N(CH_3)_2$	δ 2.38	δ 2.22	δ 2.29	δ 2.30
C-4′ OCH_3	3.96	3.89	3.95	3.87
C-5′ OCH_3	4.16	4.13	4.12	4.09
OCH_2O	5.97	5.98	5.98	6.00
H-1	6.47	6.65	6.42	6.35
H-5	6.70	6.83	6.77	6.85
H-8	7.71	6.85	6.85	6.89
H-2′[a]	7.49	6.90	7.48	6.80
H-3′[a]	7.28	7.06	7.18	6.91
NH			8.05	8.18

[a] Doublet, J = 8.0–8.2 Hz.

We were initially interested in studying the direction of the mild Hofmann elimination of classical-type phthalideisoquinoline *N*-metho salts. For this purpose, α-hydrastine methiodide (**9**) and the diastereomeric β-hydrastine methiodide (**8**) were subjected separately to β elimination at room temperature in a two-phase system consisting of methylene chloride and 5% aqueous sodium hydroxide at room temperature for 10 min. Under these conditions, the reaction is more than 90% stereoselective, with the erythro isomer **8** giving rise mainly to the *Z* enol lactone **11** and the threo isomer **9** to the *E* enol lactone **12**: λ_{max} (MeOH) 282 nm (log ϵ 3.99), 350 (4.05). Compound **11**, with λ_{max} (MeOH) 301 nm (log ϵ 4.09) and 380 (4.23),[11] corresponds in every respect to *N*-methylhydrastine, so that this alkaloid must incorporate the *Z* geometry.

Furthermore, molecular models indicate that the direction of the β elimination is syn rather than the more usual anti. The reason for this somewhat unexpected stereochemistry of elimination can be understood in terms of preferred conformational isomers **8** and **9** for β- and for α-hydrastine methiodides, respectively. In each of these salts, the presence of two relatively bulky methyl groups on the nitrogen atom induces the small hydrogen atom attached to C-9 to position itself on the same plane and syn (eclipsed) with the nitrogen. Syn elimination also prevails in the instances referred to earlier, that is in the conversion of (−)-bicuculline (**6**) into enol lactone **10**[5] and

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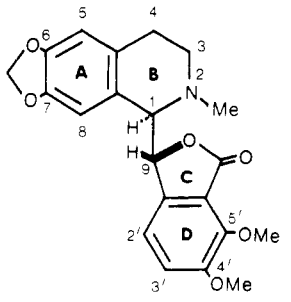
(2) Faculty of Pharmacy, University of Ankara, Ankara, Turkey.
(3) F. Santavý in "The Alkaloids", Vol. XVII, R. H. F. Manske and R. Rodrigo, Eds., Academic Press, New York, 1979, p 467.
(4) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp 359–379; M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972–1977", Plenum Press, New York, 1978, pp 307–323.
(5) For a complete listing of phthalideisoquinolines and their spectral data, see G. Blaskó, D. J. Gula, and M. Shamma, *J. Nat. Prod.*, in press.
(6) W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **55**, 2228 (1972).
(7) T. Kametani, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 723 (1976).
(8) T. Kametani, M. Takemura, M. Ihara, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 390 (1977).
(9) V. Preininger, V. Simanek, O. Gašič, F. Santavý and L. Dolejš, *Phytochemistry*, *12*, 2513 (1973).
(10) V. Preininger, J. Novák, V. Simanek and F. Santavý, *Planta Med.*, **33**, 398 (1978).
(11) Because of the rapid reaction of **11** and **12** with methanol, the ultraviolet spectra of these compounds were also recorded in chloroform (see Experimental Section).

0022-3263/82/1947-0880$01.25/0

Chart I



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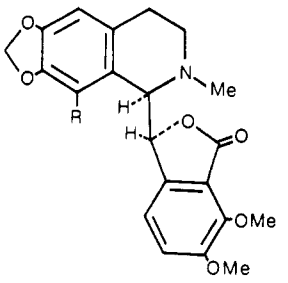

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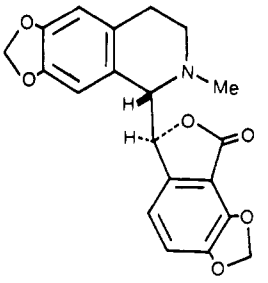
3, R = OCH_3



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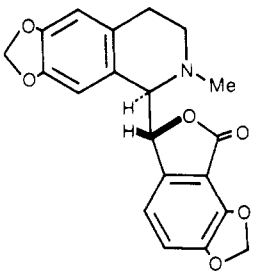

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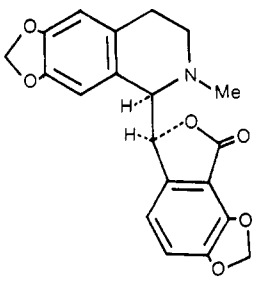

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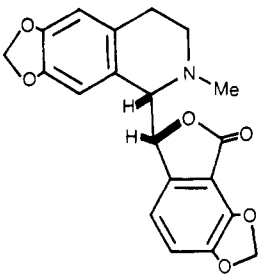

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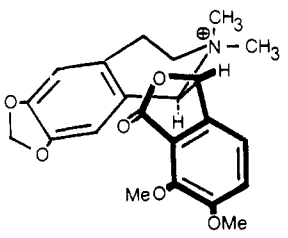

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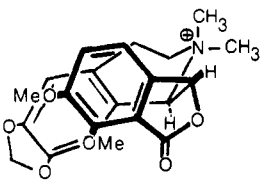

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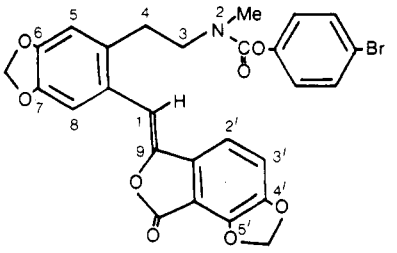


10

of adlumidine (4) methiodide into adlumidiceine enol lactone (16),[7,8] as well as in the known transformation of capnoidine (5) methiodide into enol lactone 16.[9]

In our hands, photoequilibration of chloroform solutions of pure enol lactones 11 and 12, obtained from the hydrastines, resulted in an ~3:2 mixture in favor of the thermodynamically more stable *Z* isomer.

The NMR spectral assignments so far reported in the literature for the enol lactones are somewhat ambiguous since the three one-proton singlets due to H-1, H-5, and H-8[12] had not generally been specifically indicated.[7,8] In one instance, though, they had been assigned but without the proper substantiation.[13] A series of nuclear Overhauser enhancement (NOE) studies were, therefore, undertaken first on the *Z* isomer *N*-methylhydrastine (11) and then on its corresponding *E* isomer 12.

The NMR spectrum of *N*-methylhydrastine (11) shows one-proton singlets at δ 6.47, 6.70, and 7.71 (Table I). Irradiation of the C-4 methylene protons at δ 2.92 resulted in 5.6% and 3.5% enhancements of the δ 6.70 and 6.47 singlets, respectively. The δ 7.71 signal can thus be assigned to H-8 which is distant from C-4 and unaffected by the irradiation. The H-8 signal (δ 7.71), however, suffered a 14.6% increment when the singlet at δ 6.47 was irradiated, indicating the latter signal to belong to H-1. The molecule must be able to assume a conformation in which H-1 and H-8 are proximate to each other through rotation around the central carbon to carbon single bond axis as indicated in expression 11. Another change observed upon irradiation of the δ 6.47 singlet is a 4.6%

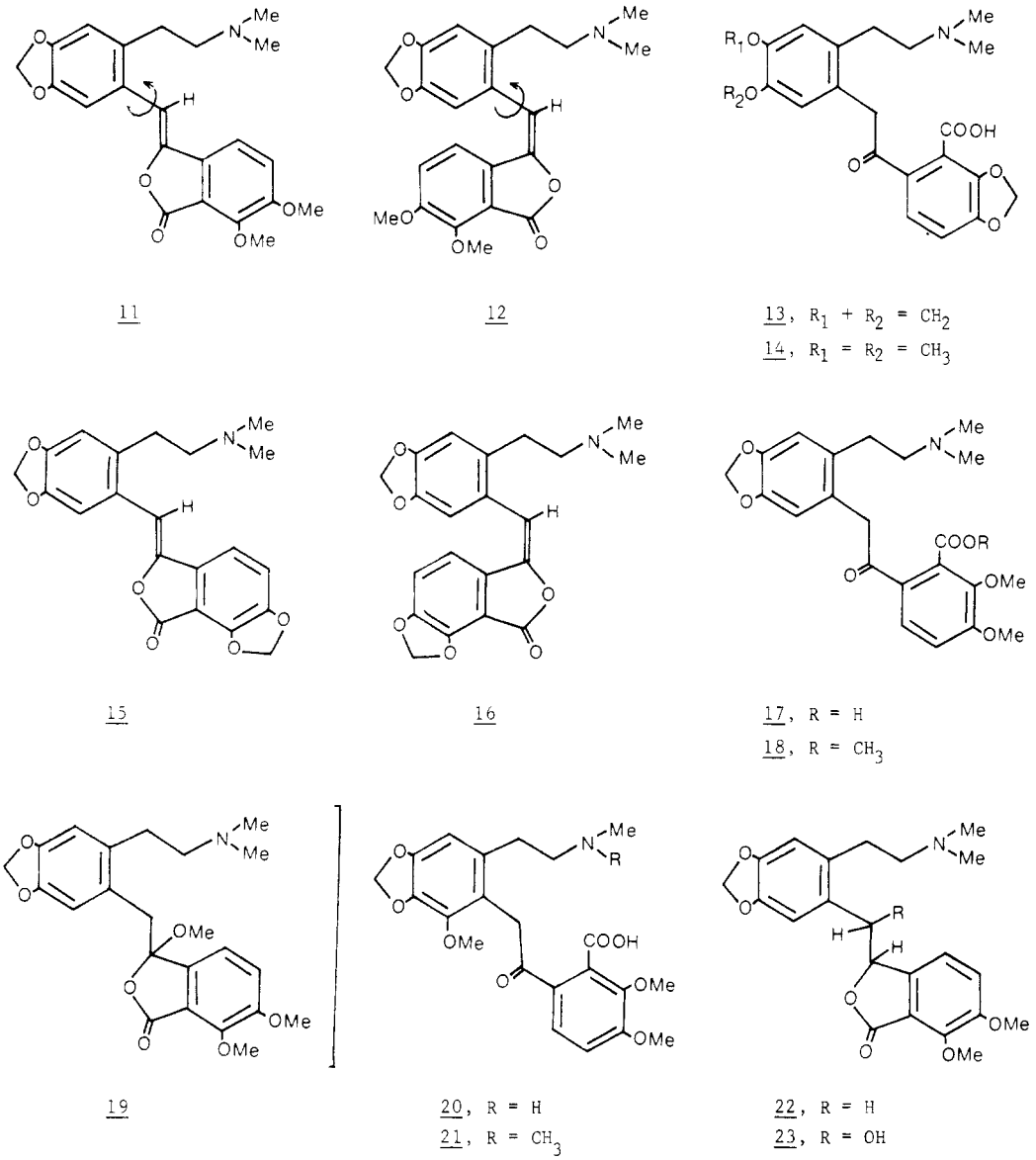
Table II. NOE Study of Enol Lactones

compd	proton irradiated at δ value	proton obsd at δ value	% area increase
(*Z*)-11	H-5 (6.70)	H-4 (2.92)	1.0
	H-1 (6.47)	H-8 (7.71)	14.6
		H-2′ (7.49)	4.6
		H-3′ (7.28)	−1.0
	H-4 (2.92)	H-5 (6.70)	5.6
		H-1 (6.47)	3.5
	H-3′ (7.28)	C-4′ OCH_3 (3.96)	1.8
(*E*)-12	H-8 (6.85)	H-1 (6.65)	2.5
		H-2′ (6.90)	2.5
	H-5 (6.83)	H-4 (2.72)	1.5
	H-1 (6.65)	H-8 (6.85)	11.2
		H-4 (2.72)	1.0
	H-2′ (6.90)	H-8 (6.85)	3.5
		H-3′ (7.06)	1.2
	H-4 (2.72)	H-1 (6.65)	4.5
		H-5 (6.83)	4.0

(12) For convenience, the numbering system adopted here for the secophthalideisoquinolines corresponds to that for the phthalideisoquinolines.

(13) P. Forgacs, J. Provost, R. Tibergien, J. Desconclois, G. Buffard, and M. Pesson, *C. R. Hebd. Seances Acad. Sci., Ser. D*, **276**, 105 (1973).

Chart II



increase of the δ 7.49 doublet assigned to H-2′. Finally, irradiation of the H-3′ doublet at δ 7.28 led to a 1.8% enhancement of the δ 3.96 C-4′ methoxyl signal (Table II).

The NMR spectrum of the *E* isomer **12** shows one-proton singlets at δ 6.65, 6.83, and 6.85 (Table I). Irradiation of the C-4 methylene protons at δ 2.72 resulted in 4% and 4.5% enhancements of the δ 6.83 and 6.65 singlet signals, respectively. It follows that the singlet at δ 6.85, which is unaffected, can be assigned to H-8. The δ 6.85 singlet, however, experienced an 11.2% area increase upon irradiation of the δ 6.65 signal; hence the latter must represent H-1. It can be concluded that the δ 6.83 singlet is due to H-5 (Table II).[14]

Ring A in stilbene **12** may, therefore, rotate around the axis of the central carbon to carbon single bond as shown in expression **12**. It will be noticed that the H-2′ doublet appears relatively upfield at δ 6.90 since H-2′ falls, at least part of the time, within the shielding zone of ring A due to the lack of planarity of the molecule.

(b) Secophthalideisoquinoline Keto Acids. Five secophthalideisoquinoline keto acids are known: *N*-methylhydrasteine (**17**), adlumidiceine (**13**), adlumiceine (**14**), narceine (**21**), and nornarceine (**20**).[5] Of these five, nornarceine is suspect as a true alkaloid since it is the only supposedly naturally occurring secophthalide which does not possess the complete (dimethylamino)ethyl side chain. It was isolated only once, and that time from opium, under the name "oxynarcotine", and it may very well have arisen from the N-demethylation of narcotine (**3**) in acid solution.[15] It is known that when narcotine is heated in acid, such a change does occur.[16]

Presently, we have found that a new and biogenetically relevant transformation of enol lactones **11** and **12** takes place when they are allowed to stand in aqueous acetone at room temperature for 2 days. In each case, the product, obtained in 50% yield (70% conversion), is the naturally occurring keto acid *N*-methylhydrasteine (**17**).[17] This reaction, therefore, offers an explanation for the formation

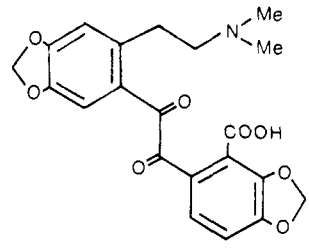
(14) In the reported NMR spectral values for **15** and **16**, the H-1, H-5, and H-8 absorptions were not originally specified.[7,8] The literature assignments for these protons in the case of **11**[13] should now be modified in the light of the present NOE study.

(15) J. Stanek and R. H. F. Manske in "The Alkaloids", Vol. IV, R. H. F. Manske and H. L. Holmes, Eds., Academic Press, New York, 1954, p 179.

(16) P. Rabe and A. Mc. Millian, *Justus Liebigs Ann. Chem.*, **377**, 223 (1910).

(17) Our natural *N*-methylhydrasteine (**17**) was isolated from *Corydalis solida* (L.) Swart. (syn. *Corydalis densiflora*) (Fumariaceae), collected in outer Anatolia near Mt. Isik, Turkey.

Chart III



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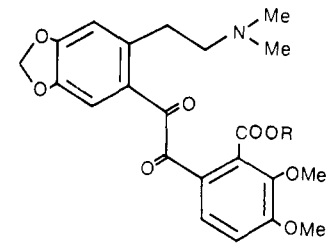
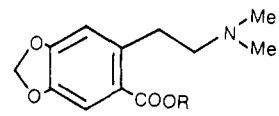
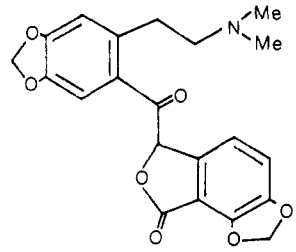


25, R = H
26, R = CH_3



27, R = H
28, R = C_2H_5



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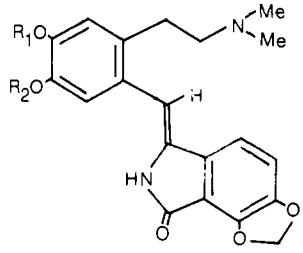
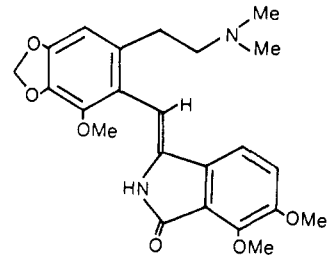


30, $R_1 + R_2 = CH_2$
31, $R_1 = R_2 = CH_3$



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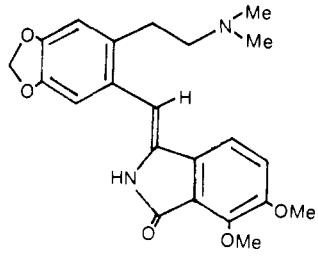

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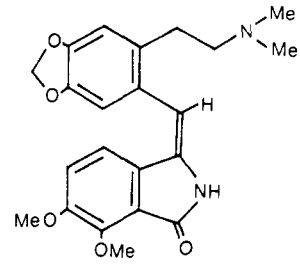

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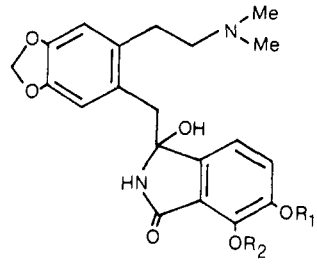

35, $R_1 + R_2 = CH_2$
36, $R_1 = R_2 = CH_3$

of the secophthalide keto acids obtained from natural sources. They must be derived from hydration of the corresponding enol lactones.

When the Hofmann elimination of (−)-α-narcotine (**3**) methiodide was attempted, we observed that the keto acid narceine (**21**) is formed directly and that the corresponding secophthalideisoquinoline enol lactone cannot be isolated. Hydration of the intermediate enol lactone must occur with great ease. This is the reason why narceine enol lactone has never been isolated. Additionally, while we found that acetic anhydride treatment of *N*-methylhydrasteine (**17**) produced selectively (*Z*)-*N*-methylhydrastine (**11**), no change was observed following the workup upon similar treatment of narceine (**21**).

When we attempted to measure the UV spectra in methanol of the *Z* and *E* enol lactones **11** and **12**, it was determined that within 10 min the original spectra had changed dramatically. In both instances, the same spectrum was eventually obtained: λ_{max} (MeOH) 226 nm (log ε 4.33), 273 (4.11), 293 (4.13), 377 (3.78).

In order to explain the above behavior, we treated *N*-methylhydrastine (**11**), with methanol at room temperature for 10 h, either in the dark or in sunlight, to obtain secophthalide keto ester **18**. This species is probably formed through nucleophilic attack by methanol on the carbonyl carbon of the intermediate lactoketal **19**. It shows infrared carbonyl peaks at 1685 and 1730 cm^{-1}, while the spectrum for the keto acid **17** possesses a broad peak at 1695 cm^{-1}, and that for *N*-methylhydrastine (**11**) incorporates a peak at 1775 cm^{-1}. Alternatively, **18** could have been formed from **11** by direct methanolysis. The UV spectrum given in the previous paragraph corresponds exactly to that of **18**.

Sodium borohydride reduction of either enol lactone **11** or keto acid **17** readily supplied the saturated γ-lactone **22** whose infrared carbonyl peak appears as expected at 1760 cm^{-1}.

The NMR spectrum of lactone **22** includes two distinct doublets of doublets centered at δ 2.70 and 3.09 and reflecting the nonequivalent methylene protons at C-1. In the case of the keto acid **17**, the same methylene protons appear as a singlet at δ 4.27 since the two hydrogens in question are now equivalent. The generalization can thus be drawn that the secophthalide keto acids exist in the keto acid rather than the hydroxy lactone (γ-lactol) form. Upon reduction, however, the resulting hydroxy acids immediately lactonize. One reason for the prevalence of the open keto acid form over the corresponding closed hydroxy lactone (γ-lactol) form must be due to the lesser degree of steric crowding, as well as freer rotation, of the former species around the central C-1 to C-9 axis.

(c) Secophthalideisoquinoline Diketo Acids. Only two secophthalideisoquinoline diketo acids have been recognized, *N*-methyloxohydrasteine (**25**) and bicucullinine

(24) (see Chart III), and neither of them had been synthesized prior to the present study.[5]

It seemed that a possible biomimetic route to this group of alkaloids would be through simple air oxidation of secophthalideisoquinoline keto acids. Indeed, air oxidation of *N*-methylhydrasteine (17) in methanolic potassium hydroxide furnished *N*-methyloxohydrasteine (25) identical with the natural product.[13,18]

Diazomethane methylation of the diketo acid 25 led to diketo ester 26. Alternatively, sodium borohydride reduction of 25 gave rise to the saturated γ-lactone 23.

An alkaloid related to the secophthalideisoquinoline diketo acids, and yet standing separate from them, is the racemic base narlumidine (29) which possesses a γ-lactone ring as well as a ketonic function. We shall refrain from discussing the biogenesis of this unique secophthalideisoquinoline since it could be formed a priori by a variety of different pathways, all originating from a classical-type phthalideisoquinoline alkaloid.

It is appropriate at this stage, however, to mention the important alkaloid fumariflorine (27), found in *Fumaria parviflora* Lam. (Fumariaceae) and characterized as its ethyl ester 28.[19] In all probability, this simple alkaloid is a final metabolite of secophthalideisoquinoline alkaloids.

(d) Secophthalideisoquinoline Ene Lactams. Four secophthalideisoquinoline ene lactams are known. These are fumaramine (30), fumaramidine (31), fumaridine (33), and narceine imide (32).[5] Very recently, a fifth base, fumschleicherine (35), has been described[20] which differs from the first four in that it is hydrated and does not incorporate a central stilbenoid double bond.

Refluxing β-hydrastine methiodide (8) in concentrated ammonium hydroxide is known to generate hydrastinimide which is identical with fumaridine (33).[21] We conjectured that this reaction, carried out at relatively high temperature, probably gave the *Z* isomer. To ascertain this point, we treated α-hydrastine methiodide (9), diastereomeric with β-hydrastine methiodide (8), in the same manner. Again, fumaridine (33) was found to be the major product, indicating that the reaction is not stereoselective but yields instead the thermodynamically more stable product.

To obtain the other geometric isomer, hitherto never described in the literature, we photoisomerized the *Z* ene lactam 33 in chloroform solution to a separable mixture of *Z* and *E* isomers (33 and 34, respectively) in an ~3:2 ratio. As in the case of the enol lactones, UV spectroscopy was of assistance in establishing the stereochemistry. The *Z* isomer 33 shows intense long-wavelength maxima at 295 nm (log ε 4.16) and 361 (4.41), while the *E* analogue 34 has maxima at 265 nm (log ε 3.98) and 345 (4.02).

Likewise, the NMR spectra for the *Z* and *E* isomers bear a distinct similarity to those for the *Z* and *E* enol lactones 11 and 12. In the spectrum of the *E* ene lactam 34, the aromatic doublet of doublets representing H-2′ and H-3′ is again at higher field than that in the spectrum of the corresponding *Z* isomer 33 (Table I).

On the basis of the NMR and UV data available for the four known stilbenoidal secophthalideisoquinoline lactams 30–33, it can now be stated that they all partake of the *Z* geometry.

In our hands, when *N*-methylhydrastine (11) was treated with dilute ammonium hydroxide at room temperature for only 3 h, a crystalline compound was obtained which proved to be hydroxy lactam 36, which is an analogue of fumschleicherine (35).[20] A meaningful feature of the NMR spectrum of hydroxy lactam 36 is the two distinct doublets at δ 3.15 and 3.54 (J_{gem} = −14.0 Hz) due to the C-1 methylene protons. This phenomenon finds an analogy in the NMR spectrum of the saturated γ-lactone 22 where again the corresponding methylene group is split into a doublet of doublets.

Upon treatment with dilute hydrochloric acid in methanol at room temperature, hydroxy lactam 36 underwent facile dehydration within a matter of a few minutes to produce the *Z* ene lactam 33.

One is now faced at this stage with the problem of deciding which of the above secophthalideisoquinolines are true alkaloids and which are artifacts.

The most logical chemical sequence for the production of the different varieties of secophthalideisoquinolines as discussed above is as follows: classical phthalideisoquinoline → phthalideisoquinoline *N*-metho salt → secophthalide enol lactone → secophthalide keto acid → secophthalide diketo acid → fumariflorine type alkaloid. The fact that no phthalideisoquinoline *N*-metho salt has so far been isolated from nature is simply due to the ease of β-elimination of such species.

Although the secophthalideisoquinoline enol lactones are probably true alkaloids, the same cannot be claimed for the secophthalideisoquinoline hydroxy lactam 35 and ene lactams 30–33. They are most probably formed as delineated above by treatment of the secophthalideisoquinoline enol lactones with ammonia to produce hydroxy lactams which are then dehydrated to the ene lactams. It can thus be stated that unless and until the presence of secophthalideisoquinoline hydroxy lactams and ene lactams is conclusively demonstrated in the crude plant extracts *prior* to treatment with ammonia, members of this group of secophthalides can be considered to be artifacts of isolation.

Experimental Section

General Procedures. Melting points are uncorrected. NMR data were collected on a Bruker 200-MHz Supercon (FT) spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard. Mass spectra were taken with an AEI MS-902 instrument. Ultraviolet spectra are of methanol solutions unless stated otherwise, and infrared spectra are of chloroform solutions. The TLC R_f values given were obtained on silica gel HLF-Uniplates (Analtech) in a chloroform–methanol (100:15 v/v) system. Preparative TLC was on silica gel F-254 Merck plates with either the above system or else benzene–methanol (100:20 v/v). Molecular compositions were obtained by high-resolution mass spectroscopy. The NOE experiments were carried out by FT NOE difference spectroscopy which allows signal enhancements as low as 0.5% to be observed. A 20-s equilibration time was used, which corresponds to at least 10 T_1.

(*Z*)-*N*-Methylhydrastine (11) and (*E*)-*N*-Methylhydrastine (12). β-Hydrastine methiodide (8; 120 mg, 0.23 mmol) was dissolved in dichloromethane (40 mL) and the solution treated with 5% aqueous sodium hydroxide (12 mL) for 10 min at room temperature. The organic layer was washed and dried, and the solvent was evaporated. The crude product was separated by TLC with benzene–methanol (100:20 v/v) to furnish 11 (70.2 mg, 77%) and 12 (5.4 mg, 6%). Further purification was achieved by TLC with chloroform–methanol (100:10).

11: mp 155–156 °C ($CHCl_3$) (lit.[13] mp 153 °C);[13] $C_{22}H_{23}O_6N$; UV ($CHCl_3$) λ_{max} 243 nm (log ε 4.22), 262 (sh, 3.88), 310 (4.06), 385 (4.26); UV λ_{max} 228 nm (log ε 4.33), 240 (sh, 4.22), 301 (4.09), 380 (4.23); IR ν_{max} 1775 cm^{-1}; mass spectrum, *m/e* (relative intensity) 397 (M^+, 27.6), 352 (2.4), 311 (1.0), 294 (1.5), 280 (1.2),

(18) Our natural *N*-methyloxohydrasteine 25 was obtained from *Fumaria microcarpa* Boiss. (Fumariaceae), growing in the vicinity of the village of Gevaş, near Lake Van, Turkey.

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265 (1.3), 236 (6.9), 204 (19), 149 (2.4), 58 (100); R_f 0.57.

12: amorphous; $C_{22}H_{23}O_6N$; UV ($CHCl_3$) λ_{max} 242 nm (log ϵ 4.24), 284 (3.98), 353 (4.05); UV λ_{max} 224 nm (log ϵ 4.32), 232 (4.34), 282 (3.99), 350 (4.05); IR ν_{max} 1775 cm^{-1}; mass spectrum, identical with that of **11**; R_f 0.58.

α-Hydrastine methiodide (**9**; 42 mg, 0.08 mmol) was dissolved in dichloromethane (15 mL) and treated with 5% aqueous sodium hydroxide (4 mL) for 10 min at room temperature. After the workup, **12** (22.4 mg, 71%) and **11**, (2.2 mg, 7%) were obtained.

Photoequilibration of 11 and 12. Compound **11** (52 mg, 0.13 mmol) was allowed to stand in a Pyrex bottle in chloroform solution in sunlight for 6 h. After removal of the solvent in vacuo, the mixture was separated by TLC to supply **11** (24.8 mg, 47.7%) and **12** (16.5 mg, 31.7%). The same isomer ratio was obtained by starting with **12**.

Reduction of *N*-Methylhydrastine (17). Compound **17** (17 mg, 0.04 mmol) was dissolved in methanol (3 mL) and chloroform (3 mL). Sodium borohydride was added slowly to the stirred mixture at reflux. The reaction was monitored by TLC. The mixture was cooled, acidified with acetic acid, and evaporated. The residue was partitioned between chloroform and water at pH 8–9. The organic layer was separated. The workup including TLC provided amorphous **22**: 10 mg (61%); $C_{22}H_{25}O_6N$; UV λ_{max} 220 nm (log ϵ 4.39), 232 (sh, 4.22), 294 (3.90), 308 (sh, 3.76); IR ν_{max} 1760 cm^{-1}; NMR δ 2.32 (s, 6 H, $N(CH_3)_2$), 2.70 (q, J_1 = 6.8 Hz, J_2 = 12.0 Hz, 1 H, H_a-1), 3.09 (q, J_1 = 6.8 Hz, J_2 = 12.0 Hz, 1 H, H_b-1), 3.91 (s, 3 H, 4′-OCH_3), 4.10 (s, 3 H, 5′-OCH_3), 5.49 (t, J = 6.8 Hz, 1 H, H-9), 5.93 (s, 2 H, OCH_2O), 6.71 (s, 2 H, H-5 and H-8), 6.82 (d, J = 8.2 Hz, 1 H, H-2′), 7.17 (d, J = 8.2 Hz, 1 H, H-3′); mass spectrum, m/e (relative intensity) 399 (M^+, 1.0), 354 (0.3), 204 (2.3), 193 (2.3), 149 (1.1), 58 (100); R_f 0.43.

Reduction of (*Z*)-*N*-Methylhydrastine (11). Sodium borohydride was added slowly to a solution of **11** (24 mg, 0.06 mmol) in methanol (5 mL) and chloroform (5 mL) at reflux. The product (21 mg) was purified by TLC to give **22**, 18.3 mg (76%).

***N*-Methylhydrasteine Methyl Ester (18).** Compound **11** (24 mg, 0.06 mmol) was allowed to stand in methanol (20 mL) overnight at room temperature. A workup including TLC led to amorphous **18**, 20.2 mg (78%). The compound reverts slowly to **11** upon being allowed to stand: $C_{23}H_{27}O_7N$; UV λ_{max} 208 nm (log ϵ 4.45), 226 (4.33), 273 (4.11), 293 (4.13), 377 (3.78); IR ν_{max} 1730, 1685 cm^{-1}; NMR δ 2.32 (s, 6 H, $N(CH_3)_2$), 3.86 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.20 (s, 2 H, CH_2), 5.91 (s, 2 H, OCH_2O), 6.61 (s, 1 H, H-5), 6.73 (s, 1 H, H-8), 6.97 (d, J = 8.5 Hz, 1 H, H-2′), 7.76 (d, J = 8.5 Hz, 1 H, H-3′); R_f 0.30.

***N*-Methylhydrasteine (17).** *N*-Methylhydrastine (**11**; 60 mg, 0.15 mmol) in acetone (2 mL) was treated with water (5 mL) for 2 days at room temperature. The acetone was removed in vacuo and the residue extracted with chloroform. A workup including chromatography gave **11** (22 mg) and amorphous **17** (28 mg, 49%), which crystallized from chloroform–methanol. The conversion was 70.5%, accounting for recovered **11**: mp 146–147 °C ($CHCl_3$–MeOH) (lit.[13] mp 150 °C); $C_{22}H_{25}O_7N$; UV λ_{max} 208 nm (log ϵ 4.39), 208 (4.15), 226 (sh, 3.95); IR ν_{max} 3200–3500, 1695 cm^{-1}; NMR δ 2.82 (s, 6 H, $N(CH_3)_2$), 3.90 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.27 (s, 2 H, CH_2), 5.95 (s, 2 H, OCH_2O), 6.61 (s, 1 H, H-5), 6.68 (s, 1 H, H-8), 6.84 (d, J = 8.5 Hz, 1 H, H-2′), 7.24 (d, J = 8.5 Hz, 1 H, H-3′); mass spectrum, m/e (relative intensity) 397 (M - H_2O, 13.6), 352 (1.1), 311 (0.6), 294 (0.7), 280 (0.7), 236 (1.8), 204 (14), 149 (5.4), 58 (100); R_f 0.15.

Conversion of Narcotine (3) into Narceine (21). The methiodide of **3** (100 mg, 0.18 mmol) was dissolved in dichloromethane (50 mL), and aqueous 5% sodium hydroxide was added with stirring. After 15 min the organic layer was separated. A workup including TLC supplied **21**: 61.2 mg (76%); mp 142–143 °C (MeOH–ether) (lit.[22] mp 145 °C); $C_{23}H_{27}O_8N$; UV λ_{max} 220 nm (log ϵ 4.38), 271 (4.15), 288 (sh, 3.99); NMR δ 2.25 (s, 6 H, $N(CH_3)_2$), 3.86 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.22 (s, 2 H, CH_2), 5.90 (s, 2 H, OCH_2O), 6.46 (s, 1 H, H-5), 6.99 (d, J = 8.5 Hz, 1 H, H-2′), 7.84 (d, J = 8.5 Hz, 1 H, H-3′); R_f 0.28.

Dehydration of 17. Compound **17** (13 mg, 0.03 mmol) dissolved in pyridine (0.5 mL) was treated with acetic anhydride (0.5 mL) at room temperature overnight. The solution turned bright yellow. Following evaporation of the solvent, the residue was purified by TLC to supply **11** (9.6 mg, 72%). The identical procedure on narceine gave only starting material.

***N*-Methyloxohydrasteine Methyl Ester 26.** Compound **25** (6 mg, 0.014 mmol) was dissolved in methanol and treated with diazomethane in ether–dichloromethane solution. After the mixture was allowed to stand overnight at room temperature, a workup including TLC gave **26**: 4.7 mg (74%); amorphous; $C_{23}H_{25}O_8N$; UV λ_{max} 227 nm (log ϵ 4.35), 240 (sh, 4.11), 284 (3.90), 322 (3.97); NMR δ 2.79 (s, 6 H, $N(CH_3)_2$), 3.77 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.08 and 6.10 (q, J_{gem} = 1.0 Hz, 2 H, OCH_2O), 6.89 (s, 1 H, H-5), 7.33 (s, 1 H, H-8), 6.97 (d, J = 8.0 Hz, 1 H, H-2′), 7.20 (d, J = 8.0 Hz, 1 H, H-3′); mass spectrum, m/e (relative intensity) 443 (M^+, 0.2), 442 (1.7), 409 (3.9), 384 (1.5), 350 (5.5), 221 (13.7), 207 (10.9), 206 (11.0), 190 (57.1), 150 (23.2), 134 (19.2), 120 (21.2), 58 (100); R_f 0.28.

γ-Lactone 23. Compound **25** (6 mg, 0.014 mmol) was dissolved in methanol–chloroform (1:1), and sodium borohydride was added at reflux. The workup and TLC generated amorphous **23**: 2.1 mg (36%); $C_{22}H_{25}O_7N$; UV λ_{max} 223 nm (log ϵ 4.24), 233 (sh, 4.16), 294 (3.83), 308 (sh, 3.65); NMR δ 2.44 (s, 6 H, $N(CH_3)_2$), 3.78 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.85 (d, J = 7.6 Hz, 1 H, H-1), 5.68 (d, J = 7.6 Hz, 1 H, H-9), 6.18 (s, 2 H, OCH_2O), 6.67 (s, 1 H, H-5), 6.97 (s, 1 H, H-8), 7.09 (d, J = 8.1 Hz, 1 H, H-2′), 7.20 (d, J = 8.1 Hz, 1 H, H-3′); mass spectrum, m/e (relative intensity) 397 [(M - 18)$^+$, 1.7], 204 (5.8), 193 (6.7), 58 (100); R_f 0.22.

Conversion of 17 to *N*-Methyloxohydrasteine 25. Compound **17** (4 mg, 0.01 mmol) was vigorously stirred in methanol (5 mL) containing potassium hydroxide (50 mg) in an open vessel for 8 h. The workup and purification by TLC led to **25**: 0.8 mg (19%); mp 234–235 °C ($CHCl_3$–MeOH) [lit.[13] mp 203 °C (H_2O)]; $C_{22}H_{23}O_8N$; UV λ_{max} 204 nm (log ϵ 4.28), 215 (4.15), 260 (sh, 3.88), 288 (sh, 3.68), 332 (3.65); IR ν_{max} 1675 cm^{-1}; NMR δ 2.44 (s, 6 H, $N(CH_3)_2$), 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.16 (s, 2 H, OCH_2O), 6.83 (s, 1 H, H-5), 7.85 (s, 1 H, H-8), 6.94 (d, J = 8.0 Hz, 1 H, H-2′), 7.28 (d, J = 8.0 Hz, 1 H, H-3′); mass spectrum, m/e (relative intensity 411 [(M - 18)$^+$, 6.0)], 369 (69.6), 354 (53.1), 341 (13.4), 336 (19.0), 326 (34.2), 310 (17.1), 284 (32.2), 267 (11.1), 192 (59.8), 179 (28.0), 151 (30.7), 58 (100); R_f 0.12.

Photoequilibration of 33. Compound **33** (35 mg, 0.09 mmol) was allowed to stand in a Pyrex bottle in chloroform (20 mL) solution under sunlight for 6 h. Following removal of the solvent in vacuo, the material was separated by TLC to supply **33** (15.7 mg, 44.8%) and **34** (11.4 mg, 32.6%).

33: mp 191–192 °C ($CHCl_3$) [lit.[21] mp 189–190 °C ($CHCl_3$–MeOH)]; $C_{22}H_{24}O_5N_2$; UV λ_{max} 209 nm (log ϵ 4.55), 226 (4.52), 273 (4.16), 295 (4.16), 361 (4.41); IR ν_{max} 3400, 1710 cm^{-1}; R_f 0.45.

34: mp 193–194 °C ($CHCl_3$); $C_{22}H_{24}O_5N_2$; UV λ_{max} 209 nm (log ϵ 4.37), 228 (sh, 4.30), 265 (3.98), 345 (4.02); IR ν_{max} 3400, 1710 cm^{-1}; R_f 0.16.

Hydroxy Lactam 36. Aqueous ammonium hydroxide (1 mL, 28%) was added to **11** (20 mg, 0.05 mmol) dissolved in a little acetone. After 4 h, the mixture was extracted with chloroform. The workup gave a crude product which was purified by TLC to give **36**: 14.5 mg (69%); mp 112–114 °C ($CHCl_3$); $C_{22}H_{26}O_6N_2$; UV λ_{max} 212 nm (log ϵ 4.45), 296 (3.73), 313 (sh, 3.46); IR ν_{max} 3380, 1710 cm^{-1}; NMR δ 2.00 (s, 6 H, $N(CH_3)_2$), 3.15, 3.54 (q, J_{gem} = 14 Hz, 2 H, CH_2), 3.92 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.80 and 5.83 (q, J_{gem} = 1.2 Hz, 2 H, OCH_2O), 6.19 (s, 1 H, H-5 or H-8), 6.53 (s, 1 H, H-8 or H-5), 7.16 (d, J = 8.1 Hz, 1 H, H-2′), 7.37 (d, J = 8.1 Hz, 1 H, H-3′), 7.89 (s, 1 H, NH); R_f 0.09.

Dehydration of 36. Compound **36** (4 mg, 0.01 mmol) in methanol (10 mL) was treated with methanolic hydrogen chloride (1 mL). After 10 min the solvent was removed in vacuo. The product was **33**.

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