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PHOTOTRANSFORMATIONS OF (+)-TAZETTINE

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SUMMARY

The sunlight irradiation of a methanolic solution of (+)-tazettine afforded a series of alkaloidal and nonalkaloidal photolysis products, the structures of five of which were elucidated by spectral analysis, including 2D NMR experiments. N-methylcrinasiadine and trisphaeridine, two already known Amaryllidaceae alkaloids, result from the photoconversion of the tazettine skeleton into the phenanthridine nucleus. 11-Oxo-N-formyl-3,4-dihydro-N-norgraciline and 11,12-dioxo-3,4-dihydro-N-norgraciline reveal that the tazettine nucleus undergoes a conversion to form the more recently established subgroup of Amaryllidaceae alkaloids, the gracilines. The fifth compound retains the tazettine nucleus, but C-6 is oxidized to form a five membered lactam. Thus, this compound is properly named as 6-oxotazettine.

ÖZET

(+)-Tazettin'in metanoldeki çözeltisinin güneş ışığına maruz bırakılmasıyla oluşan alkaloidal ve nonalkaloidal fotoliz ürünlerinden beş tanesinin yapıları, 2D NMR deneyleri de dahil olmak üzere spektral analizlerle aydınlatılmıştır. N-metilkrinasiadin ve trisferidin, bilinen iki Amaryllidaceae alkaloididirler ve tazettin iskeletinin bir fenantridin çekirdeğine dönüşümü sonucunda oluşmuşlardır. 11-Okso-N-formil-3,4-dihidro-N-norgrasilin ve 11,12-diokso-3,4-dihidro-N-norgrasilin, tazettin çekirdeğinin, Amaryllidaceae alkaloitlerinin yakın zamanda bulunmuş bir alt grubu olan grasilin çekirdeğine dönüştüğünü ortaya koymaktadır. Beşinci bileşikte tazettin çekirdeği muhafaza edilmiş, ancak C-6 konumunun oksidasyonuyla beş üyeli bir laktam halkası meydana gelmiştir. Dolayısıyla bu bileşik 6-oksotazettin olarak adlandırılmıştır.

Keywords: (+)-tazettine, Amaryllidaceae alkaloids, phototransformation, phenanthridine alkaloids, 3,4-dihydrograciline, 6-oxotazettine

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INTRODUCTION

Tritium labelled feeding studies have effectively documented that some subgroups of the Amaryllidaceae alkaloids are formed by biosynthetic interconversions. For example by feeding tritium-labelled alkaloids to Sprekelia formosissima, biosynthetic conversions of the 5,10b-ethanophenanthridine alkaloids (crinine and haemanthamine subgroups) to the 2-benzopyrano[3,4-c]indole skeleton (tazettine subgroup) were effectively demonstrated (1). Another simple Amaryllidaceae alkaloid, ismine, was also shown by tritium labelling studies to be a transformation product of the crinine-haemanthamine series (1-3).

Interconversions of the Amaryllidaceae alkaloids were also amply studied through synthetic chemical reactions, which resulted in the rearrangement of one subgroup into the other (4). For example, haemanthidine of the crinine subgroup could be converted in good yield to tazettine via the labile pretazettine, both of the tazettine subgroup (5). In turn, tazettine can be reduced chemically to tazettadiols, which are useful precursors to the haemanthamine ring system. (6).

Based on the above mentioned information on the chemical versatility of the Amaryllidaceae alkaloids and on the postulation that interesting interconversions may be encountered by exposing pure tazettine to sunlight, the structure identification of some of the photoreaction products were undertaken in this study. The result are hoped to provide insight to some of the biogenetic and chemical interconversion mechanisms of the Amaryllidaceaous alkaloids as well as to the light stability of (+)-tazettine.

RESULTS AND DISCUSSION

The most striking aspect of the ^{1}H NMR spectrum of compound **1**, as compared to that of the starting compound, (+)-tazettine, was the absence of signals in the aliphatic region with the exception of a sharp singlet at δ 3.80 integrating for three hydrogens. In the downfield region, there were signals for six aromatic hydrogens, two as singlets and four as members of a 1,2-disubstitutedbenzene ring. A two-proton singlet at δ 6.12 for a methylenedioxy group was also present. This information pointed out to the fact that only ring A of tazettine remained intact, but a completely different skeleton had been formed through cleavage of the other three rings followed by an oxidative aromatization.

The ^{13}C NMR and DEPT spectra revealed the presence of fifteen carbons as one methyl, one methylene, six methine and seven nonprotonated carbons. Among these, the most downfield signal at δ 161.0 suggested that there was a carbonyl moiety in the compound. This fact was confirmed by the IR spectrum, where a strong carbonyl stretching band at 1646 cm^{-1} suggested the probable presence of a six-membered lactam. Using the information gathered from the 2D NMR experiments ($^{1}H,^{1}H$ DQF COSY, TOCSY, HSQC and HMBC) (Table 1), two benzene rings, one with the methylenedioxy

substituent and two aromatic hydrogens resonating as singlets (Ring A), and the other with a 1,2-disubstitutedbenzene structure (Ring C) were readily characterized. In the HMBC spectrum, a $^{3}J_{CH}$ correlation of the singlet (δ 7.62) situated on Ring A to the carbon resonating at δ 119.2 established the biphenyl connection of the two rings, also verified by the ROESY interaction between δ 7.62 and 8.09 resonances. The three-bond interaction related the second singlet of Ring A (δ 7.91) to the carbonyl at δ 161.0. The $^{3}J_{CH}$ correlations of the three-proton singlet (δ 3.80) with the carbonyl carbon as well as with the nonprotonated carbon of Ring C (δ 137.5) established the presence of Ring B, thus describing a phenanthrene structure.

Table 1. ID and 2D NMR Data of N-Methylcrinasiadine

	^{1}H NMR	HSQC	^{1}H ^{1}H DQF COSY	HMBC	ROESY
H-1	8.09	122.91	7.30	128.88, 130.42, 137.45	7.30, 7.62
H-2	7.30	122.32	7.51, 8.09	115, 119.23, 122.91	7.51, 8.09
H-3	7.51	128.88	7.30, 7.40	115, 122.91, 137.45	7.30, 7.40
H-4	7.40	115.00	7.51	119.23, 122.32, 128.88	3.80, 7.51
H-7	7.91	107.02		100.41, 121.31, 130.42, 148.40, 152.18, 160.98	
H-10	7.62	100.41		107.02, 119.23, 121.31, 148.40, 152.18, 160.98	8.09
OCH_2O	6.12	101.93		148.40, 152.18	
NCH_3	3.80	30.00		115, 137.45, 160.98	7.40

The CI-MS and ESI-MS spectra both furnished 253 as the molecular weight, which was in accordance with the proposed molecular formula of $C_{15}H_{11}NO_3$. A literature survey showed that ***1*** is known as N-methylcrinasiadine, and has been isolated as a natural compound from a *Lapiedra* species (Amaryllidaceae) (7, 8). It may be postulated that tazettine has undergone an oxidative aromatization with the cleavage of bonds between C-6 and 12b, C-6a and O-7 and also N-5 and C-6 to afford ismine. The primary alcohol of ismine was then oxidized to a carboxylic acid which, in turn, formed a lactam by a condensation reaction.

The second compound (**2**) displayed a similar ^{1}H NMR spectral pattern as compared to that of **1**. However, the signal for an amidic N-methyl group was lacking. Moreover, there was a one-proton downfield singlet at δ 9.10. These two findings pointed at Ring B as the probable site of diversion from structure of **1**. In consonance with this suggestion, the lack of a carbonyl moiety was confirmed by the ^{13}C NMR and IR spectra. It was, therefore, postulated that **2** possessed a fully aromatic phenanthrene structure with a methylenedioxy substituent at C-8,9.

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Verification of the structure was done by 2D NMR experiments (^{1}H,^{1}H DQF COSY, HSQC, HMBC, ROESY) (Table 2), which also allowed the explicit assignments for the proton and carbon chemical shifts.

Table 2. ID and 2D NMR Data of Trisphacridine

	^{1}H NMR	HSQC	^{1}H ^{1}H DQF COSY	TOCSY	HMBC	ROESY
H-1	8.39	122.02	7.64	7.69, 7.64, 8.15	128.04, 130.04, 144.12	7.64, 7.93
H-2	7.64	126.72	7.69, 8.39	7.69, 8.39, 8.15	124.33, 130.04	8.39
H-3	7.69	128.04	7.64, 8.15, 8.39	7.64, 8.39, 8.15	122.02, 144.12	8.15
H-4	8.15	130.04	7.69	7.64, 8.15	124.33, 126.72	7.69
H-6	9.10	151.81			105.56, 123.12, 130.04 144.12	
H-7	7.35	105.56			130.04, 148.25, 151.81	
H-7	7.93	99.99	8.39, 9.10		123.12, 124.33, 148.25, 151.81	8.39
OCH_2O	6.17	101.94			148.25, 151.81	

The ESI-MS spectrum of **2** furnished m/z 223 as the molecular weight, which was in accord with the proposed a molecular formula, $C_{14}H_9NO_2$. Compound **2** is known as trisphaeridine, and its natural occurrence has been reported from a number of species in the Amaryllidaceae (7,9).

The ^{1}H NMR spectrum of **3** taken in $CDCl_3$, accounting for eighteen hydrogens, displayed relevant signals for an aliphatic methoxyl and a methylenedioxy substituents, two aromatic protons appearing as singlets, two pairs of isolated aliphatic methylenes and three further aliphatic hydrogens as one methine and one methylene. Of particular interest were the resonances for two olefinic hydrogens and a downfield signal at δ 8.78, the latter of which was identified by an HSQC experiment to be the hydrogen of a formyl group.

The ^{13}C NMR and DEPT spectra revealed the presence of eighteen carbons as four methylenes, six methines and eight nonprotonated carbons. Two most downfield resonances were at δ 160.8 and 204.3, pointing to the presence of two carbonyl groups. The presence of the latter were verified by two prominent bands at 1764 and 1675 cm^{-1} in the IR spectrum of **3**. The δ 160.8 and 1764 cm^{-1} values were in consonance with the presence of the aforementioned formyl moiety. Other noteworthy ^{13}C chemical shifts at δ 89.8 and 57.0 for two aliphatic quaternary carbons suggested that the compound may have a 10b,4a-ethanoiminodibenzo[b,d]pyrane nucleus, found in the recently established graciline subgroup of the Amaryllidaceae alkaloids (10). Detailed 2D NMR experiments (^{1}H,^{1}H DQF COSY, TOCSY, HSQC, HMBC and ROESY) (Table 3) were undertaken to elucidate the chemical structure and to substantiate the conversion of the tazettine skeleton into the 10b,4a-ethanoiminodibenzo[b,d]pyrane nucleus.

The key experiment was the HMBC, which, aside from providing a complete map of carbon chemical shifts, displayed unambiguous $^2J_{CH}$ and $^3J_{CH}$ correlations to establish the proposed structure of **3**. For example, the formyl hydrogen (δ 8.78) was connected to the isolated methylene carbon at δ 49.5 (C-12). In turn, H-12 (δ 4.05 and 3.98) were correlated to the quaternary carbons at δ 204.3 and 89.8. The ketone carbonyl (δ 204.3) was, therefore, placed at C-11, which is a previously established site of oxidation for this skeleton, as is described for 11-acetoxygraciline from Galanthus gracilis (Amaryllidaceae) (10). Thus, the structure of **3** was determined to be 11-oxo-N-formyl-3,4-dihydro-N-norgraciline.

The similarity between the CD spectra of **3** and of 3-hydroxy-3,4-dihydrograciline (10) suggested that **3** may share the same ∝-oriented ethanoimino bridge stereochemistry as the other known gracilines.

The route or the mechanism of the transformation from the tazettine skeleton into the 10b,4a-ethanoiminodibenzo[b,d]pyrane nucleus can not be safely postulated unless the photochemical reaction is conducted in a multistepwise manner, during which all alkaloidal and nonalkaloidal intermediate products shall be exhaustively investigated. This certainly calls for a further detailed study on this issue.

In the ^{1}H NMR spectrum of compound **4**, taken in $CDCl_3$, the signals in the 4-7 ppm region displayed a strikingly similar pattern with those of the parent compound, (+)-tazettine.

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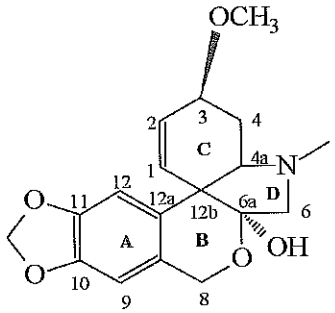
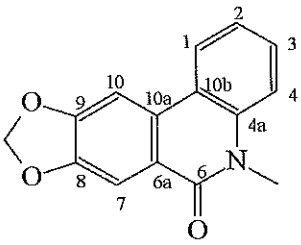


(+)-tazettine



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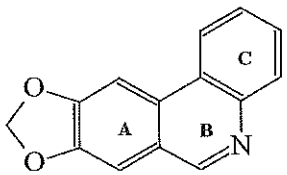

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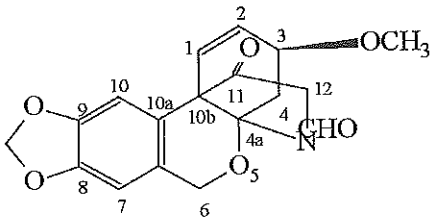

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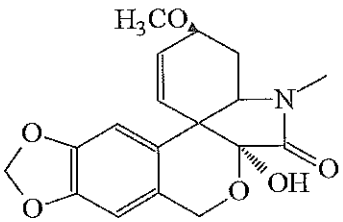

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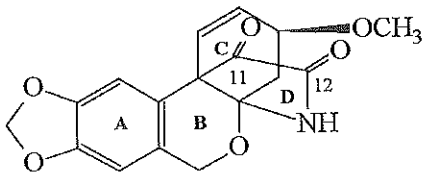

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Table 3. 1D and 2D NMR Data of 11-oxo-N-formyl-3,4 dihydro N-Norgraciline

	^{1}H NMR	HSQC	^{1}H ^{1}H DQF COSY	TOCSY	HMBC	ROESY
H-1	5.90	126.40	3.99(4.02), 5.90, 6.12	2.24, 2.61, 3.99(4.02), 3.98, 4.05, 6.12	49.51, 56.74(57.03), 73.37, 89.8, 204.31,123.39	2.61, 6.99
H-2	6.12	130.90	3.99(4.02), 5.90	2.24, 2.61, 3.99(4.02), 3.98, 4.05, 5.90	32.87, 56.74(57.03)	2.61, 3.98, 3.99'4.02),4.05
H-3	3.99(4.02)	73.37	2.24, 2.61	2.24, 2.61, 6.12, 5.9, 8.78	89.8, 204.31	
H-4α	2.61	32.87	2.24, 3.98, 3.99(4.02), 4.05	2.24, 3.98, 3.99(4.02), 4.05	56.74(57.03), 73.37, 89.8, 130.9	3.98, 3.99(4.02), 4.05, 6.12
H-4ß	2.24	32.87	2.61, 3.98, 3.99(4.02), 4.05	2.61, 3.98, 3.99(4.02), 4.05, 5.9	56.74(57.03), 73.37, 89.8, 130.9	3.98, 3.99(4.02), 4.05, 6.12
H-6	4.76	63.83	4.61	4.61, 6.51	89.8, 104.49, 123.39, 125.23	2.24, 6.51
H-6	4.61	63.83	4.76	4.74, 6.51	89.8, 104.49, 123.39, 125.23	6.51
H-7	6.51	104.49		4.61, 4.76, 6.99	63.83, 108.08, 123.39, 147.63	4.61, 4.76
H-10	6.99	108.08		6.51	56.74(57.03), 104.49, 123.39, 125.23, 147.43	5.90
H-12	4.05	49.51	2.24, 2.61	2.24, 2.61, 6.12, 5.9, 8.78	89.8, 204.31	2.24, 2.61, 3.41, 6.12
H-12	3.98	49.51	2.24, 2.61	2.24, 2.61, 5.9, 6.12, 8.78	89.8, 204.31	
CHO	8.78	160.83		3.98, 3.99(4.02), 4.05	49.51	2.61, 3.98, 3.99(4.02), 4.05
OCH_3	3.41	56.74			73.37	2.61, 3.98, 3.99(4.02), 4.05, 6.12
OCH_2O	5.97	101.43			147.43, 147.63	
OCH_2O	5.96	101.43			147.43, 147.63	

However, some immediately noticeable differences in the spectrum of **4** were the lack of the two doublets for the isolated hydrogens at C-6 and the downfield shifts of H-4a as well as of the N-methyl signal, all pointing to Ring D as the site of diversion from (+)-tazettine structure. In the IR spectrum, a strong carbonyl stretching absorption at 1701 cm^{-1} was in conformity with the presence of a five-membered lactam in Ring D, thus pointing to an oxidation of the methylene in ∝-position to the nitrogen (C-6). The δ 170.3 signal in the ^{13}C NMR spectrum also verified the presence of the suggested structure. Further support for the formation of a lactam was again provided by the ^{1}H

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NMR data, where the chemical shifts of H-4a (δ 3.72) and of the N-methyl signal (δ 2.93) were shifted downfield as compared to the corresponding chemical shifts (δ 2.86 and 2.36 signals, respectively) in the ^{1}H NMR spectrum of (+)-tazettine, also recorded in $CDCl_3$ for comparison.

As expected, the ^{13}C NMR and DEPT spectra revealed that there were only two aliphatic methylenes in **4** as opposed to the presence of three methylenes in (+)-tazettine. Relatively upfield chemical shifts were in evidence for the carbons of the lactam ring (Ring D), whereas the remaining carbon chemical shifts displayed values similar to those observed for (+)-tazettine.

Among the 2D NMR experiments (^{1}H,^{1}H DQF COSY, TOCSY, HSQC, HMBC and ROESY) (Table 4) performed on **4**, HSQC and HMBC experiments allowed the complete assignment of the carbon chemical shifts. The two $^3J_{CH}$ correlations of the N-methyl hydrogens to the signals at δ 60.7 (C-4a) and 170.3 (C-6) firmly established the position of the carbonyl as C-6.

The molecular weight, calculated as 345 for the molecular formula of $C_{18}H_{19}NO_6$, was verified by the ESI-MS spectrum. Thus compound **4** is (+)-6-oxotazettine, formed from (+)-tazettine by the photooxidation of position C-6.

The key information for the structure of compound **5** was furnished by the ^{13}C NMR spectrum, which displayed the characteristic quaternary carbon chemical shifts at δ 53.2 and 85.5, pointing once again to the presence of a 10b,4a-ethanoiminodibenzo[b,d]pyrane nucleus. ^{13}C NMR and DEPT spectra accounted for seventeen hydrogens, as one methyl, three methylene, five methine and eight nonprotonated carbons, two of the latter at δ 160.9 and 194.0 indicating the presence of two different carbonyl groups, possibly of amide and ketone nature, respectively. In the IR spectrum, the carbonyl stretching absorptions were superimposed around 1740 cm^{-1} to form a triplet-like signal. This intense absorption may possibly have resulted from the interaction between two proximal carbonyl groups (11). The magnitude of the absorption suggested that there may be a five-membered lactam. The presence of a strong signal at 3223 cm^{-1} was in accord with the NH stretching vibration of a five-membered lactam (11).

In the ^{1}H NMR spectrum of **5**, relevant signals for two aromatic and two olefinic protons, a methylenedioxy group, a deshielded isolated methylene and an aliphatic three-spin system were observed. However, no signals defining an ethylene bridge in Ring D of the 10b,4a-ethanoiminodibenzo[b,d]pyrane structure were in evidence, suggesting that a probable photooxidation converted positions 11 and 12 into carbonyl functions. Moreover, no signal was present for a N-methyl group. Therefore, Ring D seemed to possess a five-membered lactam with an additional ∝-carbonyl function. Further proof to the suggested structure was obtained from the 2D experiments (^{1}H,^{1}H DQF COSY, HSQC, HMBC and ROESY) (Table 5), which allowed the complete assignments of hydrogen and carbon chemical shifts and also the verification of the structure as a 10b,4a-ethanoiminodibenzo[b,d]pyrane ring system with a double bond between C-1 and C-2.

Table 4. 1D and 2D MR Data of 6-Oxolazettine

	^{1}H NMR	HSQC	^{1}H ^{1}H DQF COSY	TOCSY	HMBC	ROESY
H-1	5.57	127.88	3.72(3.74),6.12	1.98, 2.43 3.72(3.74) 6.12	45.21, 60.72, 70.86	
H-2	6.12	129.36	3.72(3.74), 5.57	1.98, 2.43, 3.72(3.74), 5.57	25.76, 45.21	3.47
H-3	3.74	70.86	1.98, 2.43	1.98, 2.43, 5.57, 6.12	56.24, 70.86, 127.88, 129.36	2.93, 3.47
H-4α	2.43	25.76	1.98, 3.72(3.74)	1.98, 3.72(3.74)	45.21, 60.72, 70.86, 129.36	2.93
H-4ß	1.98	25.76	2.43, 3.72(3.74)	2.43, 3.72(3.74)	60.72, 70.86	3.72
H-4a	3.72	60.72	1.98, 2.43	1.98, 2.43, 5.57, 6.12	56.24, 70.86, 127.88, 129.36	2.93, 3.47
H-6a	4.05	95.68				
H-8α	5.03	61.65	4.61	4.61	95.68, 104.10, 109.83, 125.77, 147.00	
H-8ß	4.61	61.65	5.03	5.03	95.68, 104.10, 125.77	6.52
H-9	6.52	104.10			45.21, 61.65, 109.83, 125.77, 146.89(147)	4.61, 5.03
H-12	6.85	109.19			45.21, 104.10, 125.71, 146.89(147)	1.98, 3.72(3.74), 5.57, 6.12
NCH_3	2.93	27.85			60.72, 170.27	3.72(3.74)
OCH_3	3.47	56.24			70.86	1.98, 2.43,2.93, 3.72(3.74), 6.12
NCH_3O						

An ESI-MS spectrum provided the molecular ion at m/z 329, which is in accordance with the molecular formula of $C_{17}H_{15}NO_6$, corresponding to the suggested structure. Thus compound **5** is 11,12-dioxo-3,4-dihydro-N-norgraciline. For the probable formation of **5**, it may be postulated that, following the photoconversion of the tazettine nucleus into a graciline skeleton, the resulting compound was further oxidized at positions C-11 and C-12. N-Demethylation was probably via the the oxidation of the N-methyl to a formyl and then to a carboxyl, followed by a decarboxylation.

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Table 5. ID and 2D NMR Data 11,12-dioxo-3,4-dihydro-N-norgraciline

	^{1}H NMR	HSQC	^{1}H ^{1}H DQF COSY	HMBC	HMBC	ROESY
H-1	5.88	124.39	4.00, 6.20	2.00, 4.00	53.24, 73.14, 85.47	
H-2	6.20	133.28	4.00, 5.88	4.00, 5.88	53.24	
H-3	4.00	73.14	2.00, 2.44, 6.20	2.00, 2.44, 5.88		
H-4	2.44	35.05	2.00, 4.00	2.00, 4.00	53.24, 73.14, 85.47, 133.28	
H-4	2.00	35.05	2.44, 4.00	2.44, 4.00	53.24, 73.14, 85.47, 133.28	
H-6 H-6	4.59 4.47	63.11 63.11	4.47 4.59	4.47 4.59	85.47, 105.28, 124.26, 127.13	
H-7	6.58	105.28	4.47, 4.59	4.59, 4.47	63.11, 124.26, 147.3, 147.87	
H-10	7.08	107.99			53.24, 127.13, 147.3, 147.87	
NH	7.88	56.63				2.44, 3.41
OCH_3	3.41	101.49			73.14	
OCH_2O	599	101.49			147.87, 147.3	
OCH_2O	5.98					

EXPERIMENTAL

Instruments: Optical rotations: Perkin-Elmer 241 Polarimeter; UV: Perkin-Elmer 555 Spectrophotometer; CD: Jasco J-715 Spectropolarimeter; IR: Perkin-Elmer 297 Infrared Spectrometer; 1D and 2D NMR spectra: Bruker AMX-600 Spectrometer at 300 K; EI-MS: Finnigan MAT SSQ 700; ESI-MS: Finnigan MAT TSQ 700.

Material: The pure sample of natural (+)-tazettine utilized in this experiment was isolated from *Galanthus plicatus* Bieb. subsp. *Byzantinus* (Baker) D. A. Webb and G. *gracilis* Celak (Amaryllidaceae) in the course of phytochemical studies carried out in the Department of Pharmacognosy, Faculty of Pharmacy, Ege University, Izmir, Turkey, and its structure was authenticated by spectral analyses (12,13).

Photochemical Reaction: 7.2 mg Pure (+)-tazettine was dissolved in 5 ml methanol and subjected to sunlight irradiation. The reaction was monitored by TLC at 24 hr intervals. No reaction was detected within the first 24 hr period. At the end of 48 hrs,

new alkaloidal spots were observed along with unreacted (+)-tazettine. TLC controls at the end of the third day revealed the presence of a number of Dragendorff positive spots, while no more (+)-tazettine could be detected. In order to obtain the reaction mixture in amounts sufficient for the isolation of individual photoreaction products, the experiment was repeated with 459.8 mg of (+)-tazettine in 300 ml methanol. The solution was exposed to direct sunlight until TLC controls showed that no (+)-tazettine remained in the reaction medium (5 days).

Column Chromatographic Fractionation of Photoreaction Products: At the termination of photochemical reaction, metanol was distilled in vacuo to furnish the crude reaction product as an amorphous white solid, which was fractionated on a column of silica gel 60H (Merck) (20 g). The elution was initiated by collecting 5 ml fractions, using Bz-$CHCl_3$-EtOAc (18:1:2) as the solvent system. Alkaloidal spots were detected on TLC plates (Kieselgel $60F_{254}$) by viewing under 254 nm UV light and spraying with Dragendorff reagent. Similar fractions were combined. The combined frs 10-12 (9.1 mg) eluted with Bz-$CHCl_3$-EtOAc (18:1:2) afforded **1** (7.7 mg) as a white amorphous powder upon evaporation of the elution solvent. Further elution with the same solvent system afforded the combined frs 56-99 (83.2 mg), which contained a number of Dragendorff-positive spots, and were, therefore, subjected to preparative TLC on silica gel plates. For the double development, solvents systems Bz-$CHCl_3$-EtOAc (1:2:2, saturated with NH_3 vapors), and Bz-$CHCl_3$-EtOAc (2:2:1, saturated with NH_3 vapors) were used consecutively. Of the four Dragendorff-positive bands eluted from the silica gel with $CHCl_3$-MeOH (4:1), one afforded pure **2** (6.4 mg). The other three bands afforded compounds **3** (4.4 mg), **4** (11.5 mg) and **5** (9.3 mg). The latter three compounds had to be further purified by preparative TLC on silica gel plates, using double development in solvent systems Bz-$CHCl_3$-EtOAc (5:1:4) and Bz-$CHCl_3$-EtOAc (1:2:2) consecutively, furnishing pure **3** (1.9 mg), **4** (6.7 mg) and **5** (5.8 mg).

N-Methylcrinasiadine (1): Amorphous solid; IR bands ($CHCl_3$): 2919, 2850, 1646, 1624, 1603, 1485, 1464, 1395, 1345, 1314, 1242, 1090, 1034, 931 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.09 (1H, dd, J 8.1, 1.1 Hz, H-1), 7.91 (1H, s, H-7), 7.62 (1H, s, H-10), 7.51 (1H, ddd, J 8.3, 7.2, 1.4 Hz, H-3), 7.40 (1H, d, J 8.1 Hz, H-4), 7.30 (1H, td, J 7.6, 1.0 Hz, H-2), 6.12 (2H, s, OCH_2O), 3.80 (3H, s, NCH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.0 (NCH_3), 100.4 (C-10), 101.9 (OCH_2O), 107.0 (C-7), 115.0 (C-4), 119.2 (C-10b), 121.3 (C-6a), 122.3 (C-2), 122.9 (C-1), 128.9 (C-3), 130.4 (C-10a), 137.5 (C-4a), 148.4 (C-8), 152.2 (C-9), 161.0 (C-6) ppm; CI MS: m/z 254 [$M+H^+$]; ESI MS: m/z 254 [$M+H^+$].

Trisphaeridine (2): Amorphous solid; UV λmax (MeOH): 203.51 (log ε, 3.90), nm; ^1H NMR (600 MHz, $CDCl_3$): δ 9.10 (1H, s, H-6), 8.39 (1H, d, J 8.2 Hz, H-1), 8.15 (1H, d, J 8.2 Hz, H-4), 7.93 (1H, s, H-10), 7.69 (1H, td, J 8,1 Hz, H-3), 7.64 (1H, td,

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J 8, 1 Hz, H-2), 7.35 (1H, s, H-7), 6.17 (2H, s, OCH_2O) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 99.99 (C-10), 101.94 (OCH_2O), 105.56 (C-7), 122.02 (C-1), 123.12 (C-6a), 124.33 (C-10b), 126.72 (C-2), 128.04 (C-3), 130.04 (C-4), 130.31 (C-10a), 144.12 (C-4a), 148.25 (C-8), 151.53 (C-9), 151.81 (C-6) ppm.

11-Oxo-N-formyl-3,4-dihydro-N-norgraciline (3): Amorphous solid; $[\alpha]_D$ -132.5 (c 0.40, $CHCl_3$); UV λmax (MeOH): 210.53 (log ε, 4.16), nm; IR bands ($CHCl_3$): 2924, 2854, 1764, 1676, 1504, 1486, 1373, 1243, 1120, 1089, 1036, 935 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 8.78 (1H, s, CHO), 6.89 (1H, s, H-10), 6.12 (1H, dd, J 10.0, 2.2 Hz, H-2), 6.51 (1H, s, H-7), 5.97 (1H, d, J 1.3 Hz, OCH_2O), 5.96 (1H, d, J 1.3 Hz, OCH_2O), 5.90 (1H, dd, J 10.1, 1.5 Hz, H-1), 4.76 (1H, d, J 15.0 Hz, H-6), 4.61 (1H, d, J 15.0 Hz, H-6), 4.05 (1H, d, J 9.7 Hz, H-12), 3.99 (4.02) (1H, m, H-3), 3.98 (1H, d, J 9.8 Hz, H-12), 3.41 (3H, s, OCH_3), 2.61 (1H, dd, J 13.9, 5.5 Hz, H-4∝), 2.24 (1H, dd, J 13.9, 8.7 Hz, H-4β) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.87 (C-4), 49.51 (C-12), 56.74 (OCH_3), 57.03 (C-10b), 63.83 (C-6), 73.37 (C-3), 89.80 (C-4a), 101.43 (OCH_2O), 104.49 (C-7), 108.08 (C-10), 123.23 (C-10a), 125.23 (C-6a), 126.40 (C-1), 130.90 (C-2), 147.43 (C-8), 147.63 (C-9), 160.83 (CHO), 204.31 (C-11) ppm; ESI MS: m/z 398 $[M+H^+]$.

6-Oxotazettine (4): Amorphous solid; $[\alpha]_D$ + 128.5 (c 0.35, $CHCl_3$); UV λmax (MeOH): 209.93 (log ε, 4.11), nm; IR bands ($CHCl_3$): 3281, 2923, 2853, 1701, 1504, 1486, 1384, 1352, 1245, 1186, 1081, 1038, 933 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.85 (1H, s, H-12), 6.52 (1H, s, H-9), 6.12 (1H, dt, J 10.5, 1.5 Hz, H-2), 5.93 (2H, s, OCH_2O), 5.57 (1H, dt, J 10.5, 1.4 Hz, H-1), 5.03 (1H, d, J 14.6 Hz, H-8∝), 4.61 (1H, d, J 14.6 Hz, H-8β), 3.74 (1H, m, H-3), 3.72 (1H, m, H-4a), 3.47 (3H, s, OCH_3), 2.93 (3H, s, NCH_3), 2.43 (1H, dddd, J 10.1 Hz, H-4∝), 1.98 (1H, ddd, J 2.8, 4.3, 10.1 Hz, H-4β) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.76 (C-4), 45.21 (C-12b), 56.24 (OCH_3), 57.03 (C-10b), 60.72 (C-4a), 61.65 (C-8), 70.86 (C-3), 95.68 (C-6a), 101.11 (OCH_2O), 104.10 (C-9), 125.71 (C-8a), 125.77 (C-12a), 127.88 (C-2), 129.36 (C-1), 146.89 (C-11), 147.00 (C-10), 160.83 (OCH_3), 170.27 (C-6) ppm.

11,12-dioxo-3,4-dihydro-N-norgraciline (5): Amorphous solid; $[\alpha]_D$ - 307.0 (c 0.29, $CHCl_3$); UV λmax (MeOH): 203.18 (log ε, 4.171), nm; IR bands ($CHCl_3$): 2925, 2853, 1740, 1505, 1486, 1242, 1093, 1037, 934 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.88 (1H, bs, NH), 7.08 (1H, s, H-10), 6.58 (1H, s, H-7), 6.20 (1H, d, J 10.1 Hz, H-2), 5.99 (1H, d, J 1.0 Hz, OCH_2O), 5.98 (1H, d, J 1.0 Hz, OCH_2O), 5.88 (1H, dd, J 10.1, 1.6 Hz, H-1), 4.59 (1H, d, J 14.8 Hz, H-6), 4.47 (1H, d, J 14.8 Hz, H-6), 4.00 (1H, m, H-3), 3.41 (3H, s, OCH_3), 2.44 (1H, dd, J 5.5, 13.5 Hz, H-4), 2.00 (1H, dd, J 9.9, 13.5, H-4) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 35.05 (C-4), 53.24 (C-10b), 56.63 (C-OCH_3), 63.11 (C-6), 73.14 (C-3), 85.47 (C-4a), 101.49 (OCH_2O), 105.28 (C-7), 107.99 (C-10), 124.26 (C-10a), 124.39 (C-1), 127.13 (C-6a), 133.28 (C-2), 147.3 (C-8), 147.87 (C-9), 160.92 (C-12), 193.97 (C-11) ppm; ESI MS: m/z 352 $[M+H^+]$.

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