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Photoinduced functionalization of diterpenes: transformation of the C-20 methyl of atractyligenin into a carbomethoxymethyl or carbamoylmethyl group

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Abstract

Irradiation of the nor-diterpene atractyligenin **1a** and of its methyl ester **1b** at $\lambda = 254$ nm in methanol or in methanol in the presence of nitrogen nucleophiles such as ammonia or methylamine gave, besides the decarboxylation product **2**, the ester **3a** or the amides **3b**, **3c**, respectively, providing the transformation of the C-20 angular methyl into a carbomethoxymethyl or carbamoylmethyl group. A photochemical pathway involves formation of C-19/C-20 bond in the excited state, followed by a collapse into a ketene intermediate which will capture the nucleophilic reagent.

Keywords: Natural compounds; Diterpenes; Photochemistry; Atractyligenin

1. Introduction

Extensive chemical work [1] was carried out on the structure of atractyligenin (**1**), the nor-diterpene aglycone of the glucoside atractyloside, occurring, together with its diterpene homologous carboxy-atractyloside, in the root of *Atractylis gummifera* L. (Compositae). The interest for these compounds was stimulated by the high toxicity [2] of both glucosides, responsible of many deadly poisoning in past time.

Our search of new reactions of atractyligenin led us to include it in our ongoing program on the photochemistry of diterpenoids. Moreover, efforts in pointing out photofunctionalization at the C-20 angular group appear noteworthy. In literature only a previous paper [3] had reported the irradiation of atractyligenin (**1**) in acetonitrile solution, yielding the decarboxylated derivative **2**, and in isopropyl alcohol–benzophenone solution in which a sensitized photoreaction took place involving the solvent and the allylic moiety of ring D.

At variance with these cited results, we recently reported in a preliminary communication [4] on the photoinduced functionalization of the C-20 methyl group of atractyligenin (**1a**), which was transformed in a carbomethoxymethyl-group. In fact, irradiation of compound **1a** in methanol, gave, besides the expected decarboxylation product **2** (30%), the methyl ester **3a** (20%). This unprecedented transformation, which assumes great significance in diterpenes photochemistry, differs from well-documented [5] oxidative photo-functionalizations of the C-20 methyl group of diterpenes involving the C-19 carboxylic moiety and producing lactones [6] and lactams [7]. It has been explained by assuming that the excited C-19 carboxylic group abstracts a hydrogen atom from the C-20 methyl group, in a key-step determined by the proximity of the two groups (due to their mutual stereochemistry) as well as by steric compression due to ring C. The resulting intermediate (**5**; R = H) will evolve through a C19/C 20 bond formation and then, in a thermal or photochemical reaction pattern, into the ketene **9** that, in its turn, will capture the nucleofilic methanol.

In order to prove this photochemical pathway and to extend this well promising photoinduced functionalization of the C-20 methyl group of a diterpenic structure we decided to investigate on the photochemical effects of the irradiation of atractyligenin (**1a**) and its methylester (**1b**) in methanol or in methanol in the presence of nitrogen nucleophiles such as ammonia and methylamine, well-cut reagent to react with the presumed ketene intermediate. In addition, use of nitrogen nucleophiles could allow the introduction of nitrogen functionality.

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2. Results and discussion

As expected, irradiation of atractyligenin (**1a**) in anhydrous methanol and in the presence of an excess of methanolic ammonia, besides the decarboxylation product **2** (23%), gave the amide **3b** (10%), whose structure was assigned on the basis of analytical and spectroscopic data (Scheme 1).

Compound **3b** had a molecular formula of $C_{19}H_{29}O_3N$ as indicated by MS (M^+ 319). The ^1H and ^{13}C NMR spectra of **3b** showed a number of similarities to those of compound **3a**, previously described [4]. In fact, there were clear evidences of the presence of an exocyclic double bond ($\delta_{H\text{-}17}$ 5.23 brs and 5.10 brs, $\delta_{C\text{-}16}$ 160.0 s and $\delta_{C\text{-}17}$ 108.5 t), of two hydroxyl groups ($\delta_{H\text{-}2}$ 3.83 dddd, $\delta_{C\text{-}2}$ 67.1 d; $\delta_{H\text{-}15}$ 3.85 brs, $\delta_{C\text{-}15}$ 83.1 d), of a methylene ($\delta_{H\text{-}20}$ 2.67 d and 2.32 d, $\delta_{C\text{-}20}$ 31.6 t) linked to a carbonyl group and of protons on nitrogen (δ_H 5.42 brs, 2-H) and, on the other hand, of the absence of the C-20 methyl group.

Similarly, irradiation of **1a** in the presence of an excess of methylamine, allowed us to isolate the methylamide **3c** (14%). Compound **3c**, had a molecular formula of $C_{20}H_{31}O_3N$ (M^+ 333), and showed IR, ^1H and ^{13}C NMR spectra very similar to compound **3b**, the only difference being the presence, in the ^1H and ^{13}C NMR spectra, of an additional methyl group (δ_H 2.79 d, δ_C 26.3 q) linked to the amidic nitrogen.

We then explored the photoreactivity of atractyligenin methyl ester **1b** [1a, 8] prepared from **1a** and CH_2N_2. Again, irradiation of **1b** in methanol gave both the decarboxylation product **2** (13%) and the carbomethoxy compound **3a** (13%). Moreover, similarly to what observed for atractyligenin **1a**, irradiation of methylester **1b**, in the presence of ammonia and methylamine, besides compound **2**, also gave the amides **3b** and **3c**, respectively.

As for irradiation in methanol, formation of **2** from the methylester **1b** clearly will arise from a typical n,π^* transition to give intermediate **4**, and then an alpha C–C bond breaking of the excited ester group involving removal of a stabilized fragment [9]. In turn, formation of compound **3a** may proceed through an unusual δ–H-abstraction by oxygen radical (**4**) to give alkoxy radical intermediate (**5**), which collapse to new cycle **6**. This cyclization is favoured when there are system where steric factors promote the reaction. In our case, the particular stereochemistry of methyl group C-20 and carboxylic group C-19 promote the δ–H-abstraction and the cyclization reaction.

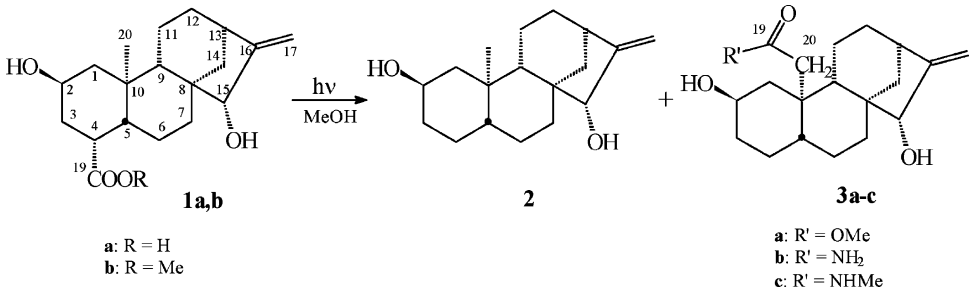
In general the most favourable intramolecular hydrogen abstraction involves a six-membered cyclic transition state in the abstraction step, but in some systems there are factors which make abstraction from other position [10]. An example of δ-abstraction and formation of cyclopentanol is reported for the photochemistry of some phenyl alkyl ketones [11]. Whereas an efficient method of functionalization of C-19 methyl group (followed by oxidative ring opening and subsequent cyclization) is reported for photochemical reaction of some 11-ketosteroids [12].

A direct conversion of **1b** into **3a** could have been hypothesized but not for the reaction of **1a** or for the irradiations in the presence of ammonia or methylamine. In fact, involvement of an amide **11** collapsing into **12** as a precursor of final product **3b** must be excluded: neither **1a** nor **1b** react with ammonia in giving the amide **11**, and a separate irradiation of the previously prepared **11** did not give **3b** (see Scheme 3).

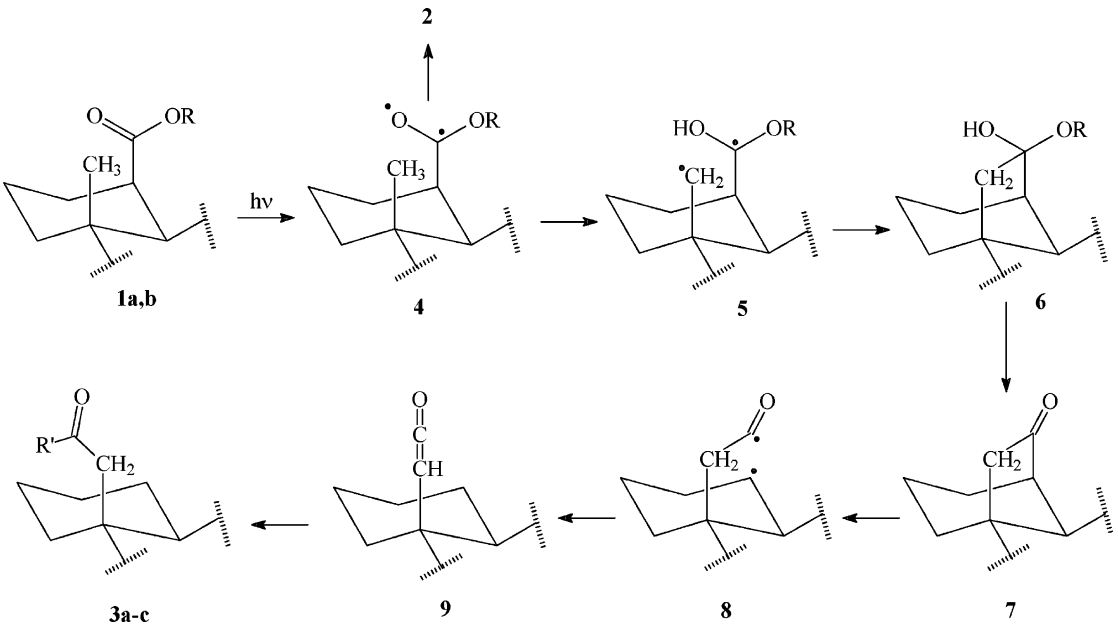
On the other hand, a direct collapse of the presumed (**6**; R = Me) into **3a** appears unlike since it would involve an unfavored heterolytic C–C bond breaking. Therefore, we suggest that the hemiacetalic intermediate **6** gives ketone **7** and, then, *alpha*-cleavlage of bicylic pentanone affords ketene **9**, although, we were not able to isolate this intermediate from the reaction mixture (see Scheme 2).

As for irradiations **1a** and **1b** in the presence of nitrogen nucleophiles, the same photochemical pathway may be suggested: that is, the nitrogen reagent will react with the presumed ketene intermediate in giving compounds **3b**, **3c** (Scheme 3).

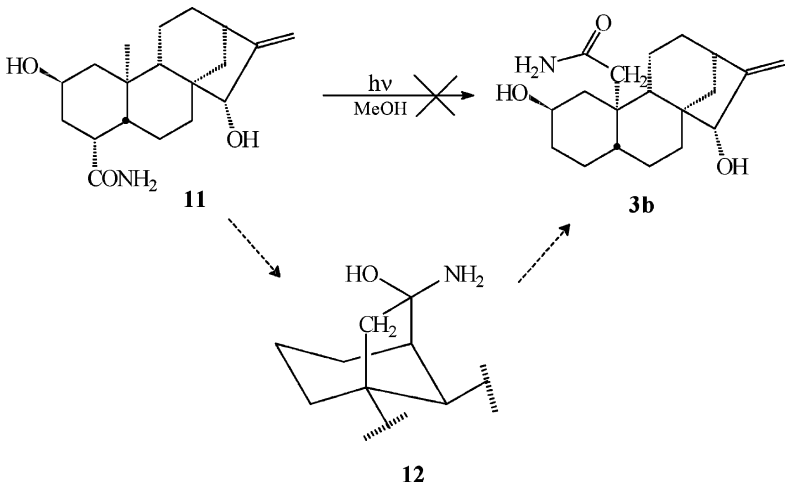
As a conclusive comment, it is worthy to note that the observed photoreactivity open new strategies in functionalization of diterpenes. In this respect, further investigations both from mechanistic and synthetic point of view are in progress, also to explain the influence of mutual stereochemistry of C-19/C-20 groups, by using model structures. Furthermore, we could put forward the hypothesis that the occurrence of functionalization at carbon C-20, observed in several natural



Scheme 1.



Scheme 2.



Scheme 3.

diterpenoids, could originate from a photochemical effect and outline a new biogenetic pathway.

3. Experimental

3.1. General

Melting points were determined on a Reichart-Thermovar hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin Elmer 257 instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ solution using a Bruker AC 250E instrument at 250 MHz, and chemical shifts are reported with respect to residual $CHCl_3$ ($\delta = 7.27$) solvent signal. ^{13}C NMR spectra were recorded in $CDCl_3$, solution on the same apparatus at 62.7 MHz, and chemical shifts are reported with respect to solvent signals, ($CDCl_3$: $\delta_C = 77.00$). MS were recorded on a Finnigan TSQ70 instrument (70 eV, direct inlet). Elemental analysis was carried out with a Perkin-Elmer 240 apparatus. Flash chromatography was performed by using silica gel (Merck, 0.040–0.063 mesh) and mixtures of EtOAc and light petroleum (fraction boiling in the range 40–60 °C) in varying ratios. Anhydrous methanol (from Romil Pure Chemicals) and methylamine (33% in absolute ethanol, from Fluka.) were used as received. Freshly prepared saturated methanolic ammonia was used.

3.2. Synthesis of compound **1b**

Compound **1b** was prepared from **1a** and CH_2N_2 as previously reported [8].

3.3. Synthesis of compound **11**

Compound **1a** (800 mg, 2.5 mmol) was dissolved in a mixture of dry dichloromethane (10 ml) and pyridine (0.5 ml) and then *N*,*N*′-dicyclohexylcarbodiimide (515 mg, 2.5 mmol) and 4-dimethylaminopyridine (305 mg, 2.5 mmol) were added. The mixture was stirred for 1 h at room temperature and then added of *N*-hydroxy-benzotriazole (337 mg, 2.5 mmol) and stirred for an additional hour. Ammonia was bubbled until saturation of the solution, that was evaporated at reduced pressure and chromatographed by CC (silica gel, ethyl acetate–methanol 7:3) to give **11** (660 mg, 82%) as white solid. Mp 211–213 °C. IR (nujol) ν_{max} = 3310, 1655, 1620, 1600, 1305, 1145, 1030, 900 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 5.87 (brs, 1H, N–H), 5.71 (brs, 1H, N–H), 5.12 (brs, 1H, H-17a), 4.79 (brs, 1H, H-17b), 4.39 (dddd, 1H, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\beta,2\alpha}$ = $J_{2\alpha,3\beta}$ = 11.9, $J_{2\alpha,3\alpha}$ = 4.0, H-2_α), 3.76 (brs, 1H, H-15), 2.63 (m, 1H, H-13), 2.48 (m, 1H, H-14), 2.32 (m, 1H, H-3_α), 2.17 (ddd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\alpha,3\alpha}$ = 1.9, H-1_α), 0.67 (dd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\beta,2\alpha}$ = 11.9, H-1_β). ^{13}C NMR (62.7 MHz, $CDCl_3$): δ 176.8 (C-19), 159.8 (C-16), 108.0 (C-17), 82.3 (C-15), 63.5 (C-2), 52.8 (C-9), 49.3 (C-1), 48.6 (C-5), 47.4 (C-8), 44.8 (C-4), 42.1 (C-13), 40.4 (C-10), 37.9 (C-14), 36.0 (C-3), 34.9 (C-7), 32.2 (C-12), 25.9 (C-6), 17.9 (C-11), 16.3 (C-20). EIMS *m/z* (%): 319 $[M]^+$ (16), 301 (25), 224 (36), 143 (27), 99 (31), 56 (100). $C_{19}H_{29}NO_3$ (319.45): calculated C, 71.44, H, 9.15, N, 4.38; found C, 71.30, H, 9.10, N, 4.30.

3.4. General procedure for photochemical reactions

A solution of compounds **1a** or **1b** (0.6 mmol) in anhydrous methanol (150 ml) was partitioned into six quartz tubes, purged by nitrogen bubbling (10 min). In the case of irradiation in the presence of nucleophiles, a large excess of methanolic ammonia (6 mmol) or methylamine (6 mmol) was added. The solution was then irradiated by using a Rayonet RPR-100 photoreactor equipped with 16 Hg lamps at λ = 254 nm (RPR-2573 Å) and a merry-go-round apparatus. The photoreaction was followed by TLC and irradiation was stopped after 6–8 h to avoid a deep degradation. The solvent was evaporated to dryness under reduced pressure at low temperature (25°) yielding a residue which was subjected to column chromatography eluting with light petroleum/ethyl acetate at various correctness. Yields referred to reacted product.

3.4.1. Irradiation of **1a** in methanol

Compound **1a** gave, in order of increasing polarity, **2** (30 mg, 25%), compound **3a** [4] (20 mg, 14%) and starting material (60 mg).

3.4.2. Irradiation of **1b** in methanol

Compound **1b** gave, in order of increasing polarity, **2** (10 mg, 13%), compound **3a** (12 mg, 13%) and starting material (90 mg).

3.5. Irradiation of **1a** in methanol in the presence of ammonia

Compound **1a** gave, in order of increasing polarity, **2** (20 mg, 23%), starting material (100 mg) and compound **3b** (10 mg, 10%).

3b: Amorphous solid—IR (KBr) ν_{max}: 3400, 2930, 2870, 1650, 1640, 1465, 1365, 1045 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 5.42 (brs, 2H, N–H_2), 5.23 (brs, 1H, H-17a), 5.10 (brs, 1H, H-17b), 3.85 (brs, 1H, H-15), 3.83 (dddd, 1H, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\beta,2\alpha}$ = $J_{2\alpha,3\beta}$ = 11.9, $J_{2\alpha,3\alpha}$ = 4.0, H-2_α), 3.23 (ddd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\alpha,3\alpha}$ = 1.9, H-1_α), 2.78 (m, 1H, H-13), 2.67 (d, 1H, $J_{20\alpha,20\beta}$ = 16.6, H-20a), 2.32 (d, 1H, $J_{20\alpha,20\beta}$ = 16.6, H-20b), 0.67 (dd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\beta,2\alpha}$ = 11.9, H-1_β). ^{13}C NMR (62.7 MHz, $CDCl_3$): δ 174.1 (C-19), 160.0 (C-16), 108.5 (C-17), 83.1 (C-15), 67.1 (C-2), 52.1 (C-9), 48.9 (C-5), 47.4 (C-8), 45.6 (C-1), 42.1 (C-13), 41.6 (C-10), 37.2 (C-3), 35.2 (C-14), 33.9 (C-12), 33.9 (C-7), 31.6 (C-20), 27.7 (C-4), 25.2 (C-6), 18.0 (C-11). EIMS *m/z* (%) = 319 $[M]^+$ (66), 302 $[M - OH]^+$ (14), 301 $[M - H_2O]^+$ (24), 284 $[M - H_2O–OH]^+$ (7), 260 (100), 243 $[M - H_2O–CH_2CONH_2]^+$ (32), 242 (76), 184 (51), 159 (48), 91 (70), 79 (50). $C_{19}H_{29}NO_3$ (319.45): calculated C, 71.44; H, 9.15; N, 4.38; found: C, 71.40; H, 9.20; N, 4.30.

3.6. Irradiation of **1a** in methanol in the presence of methylamine

Compound **1a** gave, in order of increasing polarity, gave **2** (20 mg, 23 %), starting material (100 mg) and compound **3c** (15 mg, 14%).

3c: Amorphous solid—IR (KBr) ν_{max}: 3410, 2935, 2865, 1660, 1640, 1460, 1365, 1045 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 5.47 (broad, 1H, N–H), 5.22 (brs, 1H, H-17a), 5.09 (brs, 1H, H-17b), 3.85 (brs, 1H, H-15), 3.81 (dddd, 1H, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\beta,2\alpha}$ = $J_{2\alpha,3\beta}$ = 11.9, $J_{2\alpha,3\alpha}$ = 4.0, H-2_α), 3.23 (ddd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\alpha,2\alpha}$ = 3.9, $J_{1\alpha,3\alpha}$ = 1.9, H-1_α), 2.79 (d, 3H, J = 3.3, N–CH_3), 2.76 (m, 1H, H-13), 2.55 (d, 1H, $J_{20\alpha,20\beta}$ = 16.2, H-20a), 2.29 (d, 1H, $J_{20\alpha,20\beta}$ = 16.2, H-20b), 0.66 (dd, 1H, $J_{1\alpha,1\beta}$ = 12.2, $J_{1\beta,2\alpha}$ = 11.9, H-1_β). ^{13}C NMR (62.7 MHz, $CDCl_3$): δ 172.6 (C-19), 159.9 (C-16), 108.5 (C-17), 83.1 (C-15), 67.0 (C-2), 52.2 (C-9), 48.7 (C-5), 47.3 (C-8), 45.9 (C-1), 42.2 (C-13), 41.8 (C-10), 37.1 (C-3), 35.0 (C-14), 34.8 (C-12), 33.9 (C-7), 31.4 (C-20), 27.7 (C-4), 26.3 (NHCH_3), 25.2 (C-6), 17.9 (C-11). EIMS *m/z* (%.): 333 $[M]^+$ (100), 316 $[M - OH]^+$ (15), 315 $[M - H_2O]^+$ (59), 298 $[M - H_2O–OH]^+$ (7), 260 (46), 243 $[M - H_2O–CH_2CONHCH_3]^+$ (22), 242 (41), 184 (33), 159 (38), 91 (57), 73 (85). $C_{20}H_{31}NO_3$ (333.47): calculated C, 72.04; H, 9.37; N, 4.20; found: C, 71.90; H, 9.20; N, 4.10.

*3.7. Irradiation of **1b** in methanol in the presence of ammonia*

Compound **1b** gave, in order of increasing polarity, **2** (20 mg, 21%), starting material (80 mg) and compound **3b** (15 mg, 12%).

*3.8. Irradiation of **1b** in methanol in the presence of methylamine*

Compound **1b** gave, in order of increasing polarity, **2** (20 mg, 23%), starting material (90 mg) and compound **3c** (15 mg, 14%).

Acknowledgements

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