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Photoinduced functionalization of the C-20 methyl group of the nor-diterpene atractyligenin

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Abstract—Irradiation of the nor-diterpene atractyligenin at $\lambda = 254$ nm in methanol gave, on one hand, the decarboxylation product, and provided, on the other hand, the transformation of the C-20 angular methyl into a methylene-carbomethoxy group. A photochemical pathway involving formation of C-19/C-20 bond is suggested. © 2001 Elsevier Science Ltd. All rights reserved.

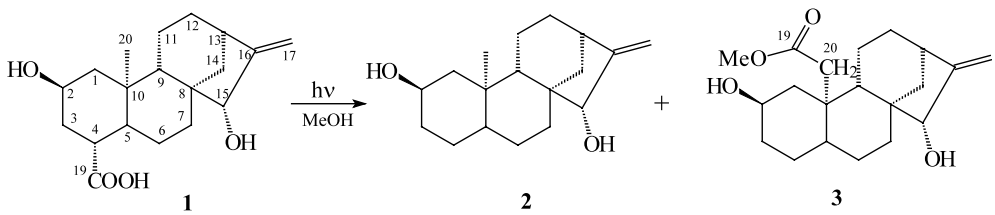
Atractyligenin **1**, the nor-diterpene aglycone of the toxic glucoside atractyloside, was the object of extensive chemical researches,[1] connected also with the study of the biological activity of its derivatives. With the view to a further investigation of its chemical reactivity and in the frame of our researches dealing with photoinduced functionalization of diterpenes, we now became interested in the study of the photochemical effect of irradiating atractyligenin **1** in MeOH solution.

Literature[2] reports irradiation of compound **1** in an aprotic solvent such as acetonitrile (from which only the decarboxylation product **2** was obtained) and in isopropyl alcohol–benzophenone in which a sensitized photoreaction took place involving the solvent and the allylic moiety of ring D.

At variance with these reports, we now succeeded in finding an interesting functionalization of the angular C-20 methyl group. In fact, besides the expected decarboxylation product **2**,[3] irradiation[4] of compound **1** in methanol gave the methyl ester **3**, whose structure was assigned on the basis of analytical and spectroscopic data[5] (Scheme 1).

Compound **3** had the molecular formula of $C_{20}H_{30}O_4$, as indicated by MS (M^+ 334). Its IR spectrum showed absorption for hydroxyl (3370 cm^{-1}), ester (1730 cm^{-1}) and olefinic (1655 cm^{-1}) groups and the ^1H and ^{13}C NMR spectra[5] revealed the existence, inter alia, of an exocyclic double bond ($\delta_{H\text{-}17}$ 5.22 brs and 5.09 brs, $\delta_{C\text{-}16}$ 159.9 s and $\delta_{C\text{-}17}$ 108.5 t), of two secondary hydroxyl groups ($\delta_{H\text{-}15}$ 3.83 brs, $\delta_{C\text{-}15}$ 83.1 d; $\delta_{H\text{-}2}$ 3.77 dddd, $\delta_{C\text{-}2}$ 66.9 d), of a carbomethoxy group ($\delta_{H\text{-}Me}$ 3.66 s, $\delta_{C\text{-}Me}$ 51.3 q, $\delta_{C\text{-}18}$ 173.2 s), of a methylene ($\delta_{H\text{-}20}$ 2.83 d and 2.39 d $J = 17.0$ Hz, $\delta_{C\text{-}20}$ 31.1 t) linked to a carbonyl group and, finally, the absence of the C-20 methyl group.

As for the photochemical pathway, it can be assumed that the excited C-19 carboxylic group will collapse into **2** by a C–C bond breaking on one hand; on the other hand, it will develop into compound **3** as shown in Scheme 2. In our opinion, considering the stereochem-



1 2 3

Scheme 1.

Keywords: atractyligenin; photochemistry; photofunctionalization of C-20 methyl.

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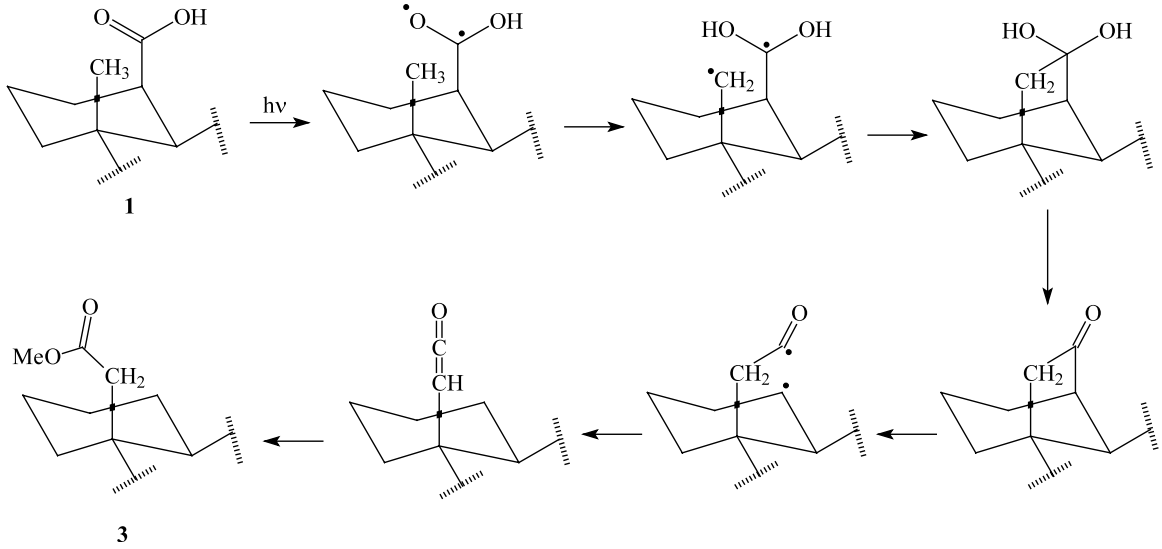

Scheme 2.

istry of our substrate, the proximity of carboxylic and C-20 methyl groups as well as the steric compression also due to ring C could appear the most probable cause determining hydrogen abstraction from the C-20 methyl and subsequent C-19/C-20 bond formation. Although we have no clear evidence, the collapse of this first formed species could then evolve in a thermal/photochemical reaction pattern involving the ketene intermediate that will capture methanol. Probably, the protic solvent could play a role in this last reaction and also in the stabilization of key intermediates to some extent.

On the whole, this observed C-20 functionalization differs from well-documented[6] oxidative photo-functionalizations of the C-20 methyl group of diterpenes involving the C-19 carboxylic moiety and producing lactones[7] and lactams.[8] On the other hand, this photoreaction opens new strategies in photoinduced functionalization of diterpene structures.

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3. Compound **2**: mp 196–202°C (from ethyl acetate/light petroleum) (lit.[2] reports mp 121–122°C; however, in our hands photodecarboxylation of **1** in acetonitrile solvent gave **2** having mp 196–202°C); IR (film) ν_{max} cm^{-1}: 3330; ^{1}H NMR (250 MHz, CD_3OD): 5.19 (1H, brs, H-17a), 5.08 (1H, brs, H-17b), 3.79 (1H, dddd, $J_{1\alpha,2\alpha}=3.9$, $J_{1\beta,2\alpha}=J_{1\alpha,3\beta}=11.9$, $J_{2\alpha,3\alpha}=4.0$, H-2α), 3.77 (1H, brs, H-15), 2.72 (1H, m, H-13), 2.14 (1H, ddd, $J_{1\alpha,1\beta}=12.2$, $J_{1\alpha,2\alpha}=3.9$, $J_{1\alpha,3\alpha}=1.9$, H-1α), 099 (3H, s, CH_3-20), 0.62 (1H, dd, $J_{1\alpha,1\beta}=12.2$, $J_{1\beta,2\alpha}=11.9$, H-1β) ppm; ^{13}C NMR (62.7 MHz, CD_3OD): 160.4 (C-16), 109.1 (C-17), 83.8 (C-15), 67.9 (C-2), 53.4 (C-9), 49.7, (C-1), 49.7 (C-8), 48.6 (C-5), 43.6 (C-13), 40.8 (C-10), 37.7 (C-3), 37.0 (C-14), 35.6 (C-7), 33.6 (C-12), 28.5 (C-4), 27.0 (C-6), 19.2 (C-11), 16.2 (C-20) ppm; EI-MS m/z (rel. int.): 276 $[M]^+$ (11), 259 $[M-OH]^+$ (15), 258 $[M-H_2O]^+$ (100), 243 $[M-H_2O-CH_3]^+$ (86), 225 (26), 200 (49), 175 (30), 107 (38), 91 (37), 79 (63), 57 (72).
4. A solution of compound **1** (200 mg) in anhydrous methanol (150 ml) was partitioned into six quartz tubes, purged by nitrogen bubbling (10 min), and then irradiated by using a Rayonet RPR-100 photoreactor equipped with 16 Hg lamps irradiating at $\lambda=254$ nm (RPR-2537Å) and a merry-go-round apparatus. The reaction was followed by TLC and irradiation was stopped after 6 h to avoid a deep degradation. The solvent was evaporated to dryness under reduced pressure at low temperature (25°C) yielding a residue which was subjected to column chromatography eluting with cyclohexane/EtOAc 1:1 to give, in order of increasing polarity compound **2** (30 mg), compound **3** (20 mg) (yields: 25 and 14%, respectively, referred to reacted product) and unreacted atractyligenin **1** (60 mg).
5. Compound **3**: amorphous solid; IR (film) ν_{max} cm^{-1}: 3370, 2910, 2850, 1730, 1655, 1450, 1430, 1350, 1195, 1170, 1135, 1045, 1015, 990, 900, 735; ^{1}H NMR (250 MHz, $CDCl_3$): 5.22 (1H, brs, H-17a), 5.09 (1H, brs, H-17b), 3.83 (1H, brs, H-15), 3.77 (1H, dddd, $J_{1\alpha,2\alpha}=3.9$, $J_{1\beta,2\alpha}=J_{2\alpha,3\beta}=11.9$, $J_{2\alpha,3\alpha}=4.0$, H-2α), 3.66 (3H, s, OCH_3), 3.09 (1H, ddd, $J_{1\alpha,1\beta}=12.2$, $J_{1\alpha,2\alpha}=3.9$, $J_{1\alpha,3\alpha}=1.9$, H-1α), 2.83 (1H, d, $J_{20a,20b}=17.0$, H-20a), 2.76 (1H, m, H-13), 2.39 (1H, d, $J_{20a,20b}=17.0$, H-20b), 0.67 (1H, dd, $J_{1\alpha,1\beta}=12.2$, $J_{1\beta,2\alpha}=11.9$, H-1β) ppm; ^{1}H NMR (250 MHz, CD_3OD): 5.18 (1H, brs, H-17a), 5.08 (1H, brs, H-17b), 3.77 (1H, brs, H-15),

3.70 (1H, dddd, $J_{1\alpha,2\alpha}=3.9$, $J_{1\beta,2\alpha}=J_{2\alpha,3\beta}=11.9$, $J_{2\alpha,3\alpha}=4.0$, H-2α), 3.67 (3H, s, OCH_3), 3.10 (1H, ddd, $J_{1\alpha,1\beta}=12.2$, $J_{1\alpha,2\alpha}=3.9$, $J_{1\alpha,3\alpha}=1.9$, H-1α), 2.85 (1H, d, $J_{20a,20b}=17.0$, H-20a), 2.71 (1H, m, H-13), 2.46 (1H, d, $J_{20a,20b}=17.0$, H-20b), 0.62 (1H, dd, $J_{1\alpha,1\beta}=12.2$, $J_{1\beta,2\alpha}=11.9$, H-1β) ppm; ^{13}C NMR (62.7 MHz, $CDCl_3$):173.2 (C-19), 159.9 (C-16), 108.5 (C-17), 83.1 (C-15), 66.9 (C-2), 52.0 (C-9), 51.3 (OCH_3), 48.7 (C-5), 47.2 (C-8), 45.5 (C-1), 42.1 (C-13), 41.2 (C-10), 37.0 (C-3), 35.3 (C-14), 33.9 (C-7), 32.8 (C-12), 31.1 (C-20), 27.5 (C-4), 25.1 (C-6), 17.8 (C-11) ppm; ^{13}C NMR (62.7 MHz, CD_3OD):174.8 (C-19), 160.3 (C-16), 109.0 (C-17), 84.1 (C-15), 67.5 (C-2), 53.9 (C-9), 51.7 (OCH_3), 50.2, (C-5), 48.6 (C-8), 46.2 (C-1), 43.6 (C-13), 42.4 (C-10), 37.9 (C-3), 36.6 (C-14), 35.6 (C-7), 33.8 (C-12), 32.3 (C-20), 28.6 (C-4), 26.3 (C-6), 18.9 (C-11) ppm; EI-MS m/z (rel. int.): 334 $[M]^+$ (38), 317 $[M-OH]^+$ (42), 316 $[M-H_2O]^+$ (63), 284 (17), 260 (22), 243 $[M-H_2O-CH_2COCH_3]^+$ (100), 183 (33), 159 (45).

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