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PHOTODIMERIZATION OF DEACETYLASPIDOSPERMINE*

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Abstract—Irradiation of deacetylaspidospermine gives a dimeric product, 15,15′-*bis*(deacetylaspidosperminyl). Some aspects of the photodimerization are discussed and compared with the results obtained by treatment of the alkaloid with potassium permanganate in acetone.

INTRODUCTION

Despite the growing interest in the photochemistry of alkaloids [1, 2] and in the photochemical routes for alkaloids syntheses [3–6], the effect of UV light on aspidospermine-type alkaloids has not been systematically studied. In this paper we report a study of the photoreaction of deacetylaspidospermine (**1**). It is interesting to mention that in this work a dimeric photoproduct has been obtained [15,15′-*bis*(deacetylaspidosperminyl), (**2**)] whose structure is similar to that of a dimeric alkaloid [15,15′-*bis*(*N*-acetyl-16,17-dihydroxyaspidospermidine) or 15,15′-*bis*(demethylaspidoscarpinyl)] isolated from *Aspidosperma melanocalyx* Muell. Arg. [7].

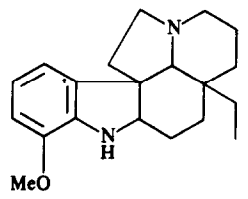
Since several *bis*isoquinoline [8, 9] and *bis*indole [10–13] alkaloids have been recently described a little is known about the enzymology of the formation of dimeric alkaloids. We think that the photochemical results could be of use in understanding the precise sequence of biosynthetic events and the reaction pathways at the enzymatic level of dimeric alkaloid formation.

RESULTS AND DISCUSSION

When a solution of (**1**) in CH_2Cl_2 was irradiated with a high-pressure Hg lamp in Pyrex or in a Vycor container, only a crystalline photoproduct was obtained (**2**) together with hydrochloric acid and chloroderivatives of ethane and ethene.

Control experiments show that (**1**) is stable under the reaction conditions (25–30° for 5 hr) in the absence of light or kept in the dark at 60–70° for 24 hr. Prolonged irradiation of (**1**) in EtOH, in hexane or in Me_2CO failed to produce any photoproducts.

The UV data of (**1**) in EtOH, CH_2Cl_2, Me_2CO and hexane are very similar (see Experimental). There is no doubt that this photoreaction may be due to the electronically excited alkaloid molecule (π, π^*)–CH_2Cl_2 molecule interaction. Thus, the excited charge transfer complex (exciplex) [14, 15] formed gives the alkaloidyl radical



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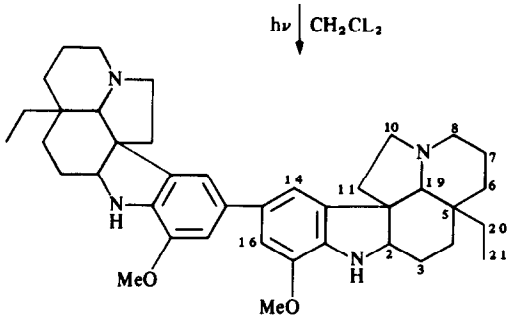

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Scheme 1. Photodimerization of deacetylaspidospermine.

cation: $Alk \xrightarrow{h\nu} Alk^* \xrightarrow{CH_2Cl_2} [Alk^{\delta+} \ldots CH_2Cl_2^{\delta-} \longleftrightarrow Alk^{+\cdot} \ldots Cl^- \ldots . CH_2Cl]^* \longrightarrow Alk^{+\cdot} + Cl^- + {}^{\cdot}CH_2Cl$. This stable radical cation, because of the marked stabilizing effect of the MeO group [16] does not react in the solvent cage. Then, the radical cation reacts with another molecule of (**1**), in the ground state, to give the dimer (**2**). The high quantum yield measured (0.92) for the formation of compound (**2**) agrees with the proposed dimerization. In the reaction media Cl^- ($AgNO_3/HNO_3$ test), CH_3Cl, $ClCH_2CH_2Cl$ and ClCHCHCl (GC/EIMS) were also detected.

Another result that allows us to discard a radical nature for this reaction is the result obtained with potassium permanganate; it is known [17] that oxidation

*To the memory of Prof. Dr. Venancio Deulofeu.

occurs through a radical mechanism. When alkaloid (**1**) was treated with this reagent we obtained only a dimeric product (**3**) whose UV, mass spectral and ^{1}H NMR data agree with the structure 15-(1′-deacetylaspidosperminyl)-1, 2-dehydrodeacetylaspidospermine (see Experimental).

The crystalline compound obtained [(**2**), 60% yield] showed in its EI mass spectrum a $[M]^+$ at *m/z* 622 (15%) corresponding to a dimer of (**1**) of molecular formula $C_{40}H_{54}N_4O_2$. The ^{1}H NMR spectrum showed only four aromatic protons and these appeared as two doublets at δ6.68 and 6.52 and two NH protons at δ10.13. Acetylation of (**2**) with acetic anhydride–pyridine gave a *bis-N*-acetyl derivative (**4**) whose EI mass spectrum showed a $[M]^+$ at *m/z* 706 (13%), molecular formula $C_{44}H_{58}N_4O_4$. Taking these facts into account, the mass spectral fragmentation is entirely in accord with structure (**2**), indicating two deacetylaspidospermine subunits linked [18, 19]. The indolic fragments found at *m/z* 160 in the EI mass spectrum of (**1**) are shifted to *m/z* 470 in (**2**) and to *m/z* 512 in (**4**); the difference in mass corresponds to substitution by a unit of structure (**1**) and [MeCO–(**1**)], respectively.

Comparison of the UV spectrum of the dimeric photoproduct (**2**) with that of the alkaloid (**1**) shows a substantial increase in intensity as well as a bathochromic shift, indicating considerable conjugation of the aromatic rings. Models show that the degree of coplanarity necessary for such conjugation could only be achieved if the linkage were 15–15′. The ^{1}H NMR signals at δ6.68 and 6.52 agree with this structure.

EXPERIMENTAL

Mps: uncorr. ^{1}H NMR spectra were determined in the FT mode (solvent $CDCl_3$; std TMS). EIMS were determined by direct inlet at 270° at 70 eV. Quantum yield of (**2**) formation was determined using the potassium-iron(III)-oxalate actinometer (Hatchard–Parker actinometer) [20–22]. GC analysis were performed as described elsewhere [15]. *Deacetylaspidospermine* (**1**) was obtained according to the method described in ref. [23]. Its authenticity was confirmed by comparison, mmp, UV, IR, ^{1}H NMR and EIMS and TLC analysis with an authentic sample. Colourless prisms (from hexane) mp 110–111° [19, 24, 25]; $[\alpha]_D^{20}$ +2.9° [EtOH, *c* 0.9]; (Found: C, 76.8; H, 8.7; N, 8.8; O, 5.6. $C_{20}H_{28}N_2O$ requires: C, 76.9; H, 8.9; N, 8.9; O, 5.2%). UV λ_{max}^{EtOH} nm (log ε): 291 (3.41), 247 (3.85); (cyclohexane) 290 (3.45), 245 (3.80); (CH_2Cl_2) 2.95 (3.45), 250 (3.84); (CCl_4) 2.94 (3.43), 249 (3.80). ^{1}H NMR: δ10.11 (1H, NH), 6.58 (3H, *m*, H-14, H-15 and H-16), 3.80 (3H, *s*, OMe), 3.49 (1H, *c*, *J* = 6 Hz and *J* = 10 Hz, H-2), 2.15 (1H, *s*, H-19), 2.02–0.75 (16H, *m*), 0.60 (3H, *t*, *J* = 6 Hz, CH_2Me). EIMS *m/z* (rel. int.): 313 (14), 312 ($[M]^+$, 63%), 311 (12), 284 (38), 174 (8), 160 (9), 156 (8), 152 (15), 125 (28), 124 (100).

Irradiation of deacetylaspidospermine (**1**). A N_2 purged soln of the alkaloid (**1**) (25 mg) in CH_2Cl_2 soln (50 ml) was irradiated in Pyrex Erlenmeyer flasks (125 ml) and in Vycor Erlenmeyer flasks (125 ml) with stirring. The light source was an ext high-pressure Hg lamp (Hanau-Quartz lampen GmbH, TQ 150) which was placed 10 cm from the flasks; the irradiation time was 5 hr. The progress of the reaction was followed by TLC (neutral alumina; C_6H_6–EtOH); spots were visualized with I_2 or UV light. Irradiation in EtOH, Me_2CO and in hexane were performed in a similar manner.

When irradiation was stopped the soln was washed with $NaHCO_3$–H_2O (2%) soln; TLC analysis of the CH_2Cl_2 phase showed the non-converted starting alkaloid and one spot of lower R_f value. The residue obtained by evapn of the solvent (CH_2Cl_2) was chromatographed on a neutral aluminium oxide column. C_6H_6 and mixts of C_6H_6–EtOH were used as eluents. From the first eluted fraction the non-converted alkaloid was isolated (conversion 60%, identified from its R_f, mp and EIMS). The second eluted fraction, which was fluorescent (λ_{366}), yielded 15,15′-bis(deacetylaspidosperminyl) [compound (**2**), 14.9 mg]; $[\alpha]_D^{20}$ +1.3°[EtOH; *c* 1.1]; mp 294–296° (Found: C, 76.9; H, 8.6; N, 9.2; O, 5.2. $C_{40}H_{54}N_4O_2$ requires: C, 77.1; H, 8.7; N, 9.0; O, 5.1%). UV λ_{max}^{EtOH} nm (log ε): 312 (3.22), 294 (3.67), 254 (3.96). ^{1}H NMR: δ10.13 (2H, NH), 6.68 (2H, *d*, *J* = 2 Hz, H-14 and H-14′), 6.52 (2H, *d*, *J* = 2 Hz, H-16 and H-16′), 3.80 (6H, *s*, OMe and OMe′), 3.49 (2H, *m*, H-2 and H-2′), 2.18 (2H, *s*, H-19 and H-19′), 2.00–0.80 (32H, *m*), 0.64 (6H, *t*, *J* = 6 Hz, CH_2Me and CH_2Me′). EIMS *m/z* (rel. int.): 622 ($[M]^+$, 15%), 470 (7), 312 (23), 311 (67), 284 (15), 174 (21), 160 (17), 152 (8), 138 (15), 124 (100).

Irradiation of (**1**) in EtOH, Me_2CO or hexane through Quartz, Vycor or Pyrex for 24 hr, with TLC and ^{1}H NMR monitoring, revealed only the presence of unchanged (**1**) in the photolysed material.

Acetylatoin of (**2**) *to give* 15,15′-*bis*(*aspidosperminyl*) (**4**). The diacetyl derivative (**4**) was obtained from (**2**) as an amorphous solid (from hexane) mp 303–305° (Found: C, 74.6; H, 8.0; N, 8.0; O, 9.4. $C_{44}H_{58}N_4O_4$ requires: C, 74.8; H, 8.2; N, 7.9; O, 9.1%). IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O), 1590 (Ar), 1180 (C–O). UV λ_{max}^{EtOH} nm (log ε): 318 (4.63), 296 (3.70), 260 (3.10), 220 (4.40). ^{1}H NMR: δ6.75 (2H, *d*, *J* = 2 Hz, H-14 and H-14′), 6.68 (2H, *d*, *J* = 2 Hz, H-16 and H-16′), 4.60 (2H, *m*), 3.90 (6H, *s*, OMe and OMe′), 3.26–3.00 (8H, *m*), 2.20 (6H, *s*, NAc and NAc′), 2.21 (2H, *s*), 2.00–0.76 (24H, *m*), 0.60 (6H, *t*, *J* = 6 Hz, CH_2Me and CH_2Me′). EIMS *m/z* (rel. int.): 706 ($[M]^+$, 6%), 512 (11), 354 (11), 353 (13), 352 (11), 339 (10), 338 (7), 325 (13), 312 (10), 174 (15), 172 (13), 160 (18), 152 (22), 130 (15), 124 (100).

Oxidation of (**1**) *with* $KMnO_4$. Alkaloid (**1**) (20 mg) dissolved in a min vol of Me_2CO, was heated at 70°. To this soln a satd $KMnO_4$ soln (in Me_2CO) was added dropwise [16, 26]. The reaction was monitored by TLC and the formation of a fluorescent product of lower R_f was observed. The MnO_2 was removed by filtration and the reaction mixt sepd by prep. TLC (silica gel; C_6H_6–EtOH). The non-converted alkaloid (**1**) (conversion 85%) was isolated and characterized by its R_f, mp and EIMS. From the fluorescent fraction a residue was obtained which after crystallisation gave the dimeric compound (**3**) as colourless prisms (from hexane) mp 278° (Found: C, 77.2; H, 8.5; N, 9.1; O, 5.1. $C_{40}H_{52}N_4O_2$ requires: C, 77.4; H, 8.4; N, 9.0; O, 5.1%). UV λ_{max}^{EtOH} nm (log ε): 345 (4.20), 310 (3.93), 260 (3.94). ^{1}H NMR: δ7.15–6.80 (3H, *m*, H-14′, H-15′ and H-16′), 6.43 and 6.38 (2H, *dd*, *J* = 2 Hz, H-14 and H-16), 3.88 and 3.75 (6H, *ds*, OMe and OMe′), 4.30–0.45 (41H, *m*). EIMS *m/z* (rel. int.): 620 ($[M]^+$, 9%), 368 (15), 351 (11), 326 (14), 312 (22), 310 (18), 309 (26), 284 (15), 281 (19), 174 (5), 160 (5), 152 (4), 138 (9), 125 (25), 124 (100).

When the dimer (**3**) was treated with Ac_2O–pyridine, according to the general method [27], no evidence of any reaction was found.

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