

ENAMIDE PHOTOCHEMISTRY. THE ELIMINATION OF ORTHO-SUBSTITUENTS
IN THE PHOTOCYCLIZATION OF
2-AROYL-6,7-DIMETHOXY-1-METHYLENE-1,2,3,4-TETRAHYDROISOQUINOLINES

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The photochemical reactions of enamides have proven to be very useful synthetically. Simple enamides undergo a facile 1,3-acyl shift to give vinylogous amides.¹ Enamide photochemistry has been used in the isoquinoline series to synthesize a variety of natural products: dehydroaporphines², aporphines³, protoberbine alkaloids⁴, and berlambine alkaloids (oxyprotoberberines)⁵. The purpose of this communication is to demonstrate a new photochemical elimination reaction in enamide photochemistry and the use of this photoreaction for the synthesis of benzylisoquinoline alkaloids of the oxyprotoberberine, oxoberbine, lambertine, and tetrahydroprotoberberine types.

The 2-Aroyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinolines 1 were synthesized in good yield by reacting 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline, in pyridine, with the appropriate benzoic anhydride (prepared in situ using N,N-diethyl-1-aminopropyne⁶) in refluxing benzene⁷. The enamides are stable in the absence of acid, but hydrolyze quickly in the presence of even weak acids.

Compound 1 (X = OAc, Y = H), 1.0 g, was dissolved in t-butanol, degassed by successive freeze-thaw cycles, and irradiated in a Rayonet photoreactor with 3000 Å lamps. After 1.5 hr, 1 had been converted into a single product which was isolated in 80% yield by evaporation of solvent and crystallization from methanol. Compound 3 (mp 181-2°) showed the loss of acetoxy group in the nmr spectrum and the appearance of the characteristic uv spectrum of the oxyprotoberberine ring system. 368 nm (ε 11,000), 350 nm (18,000), 333 nm (22,500),

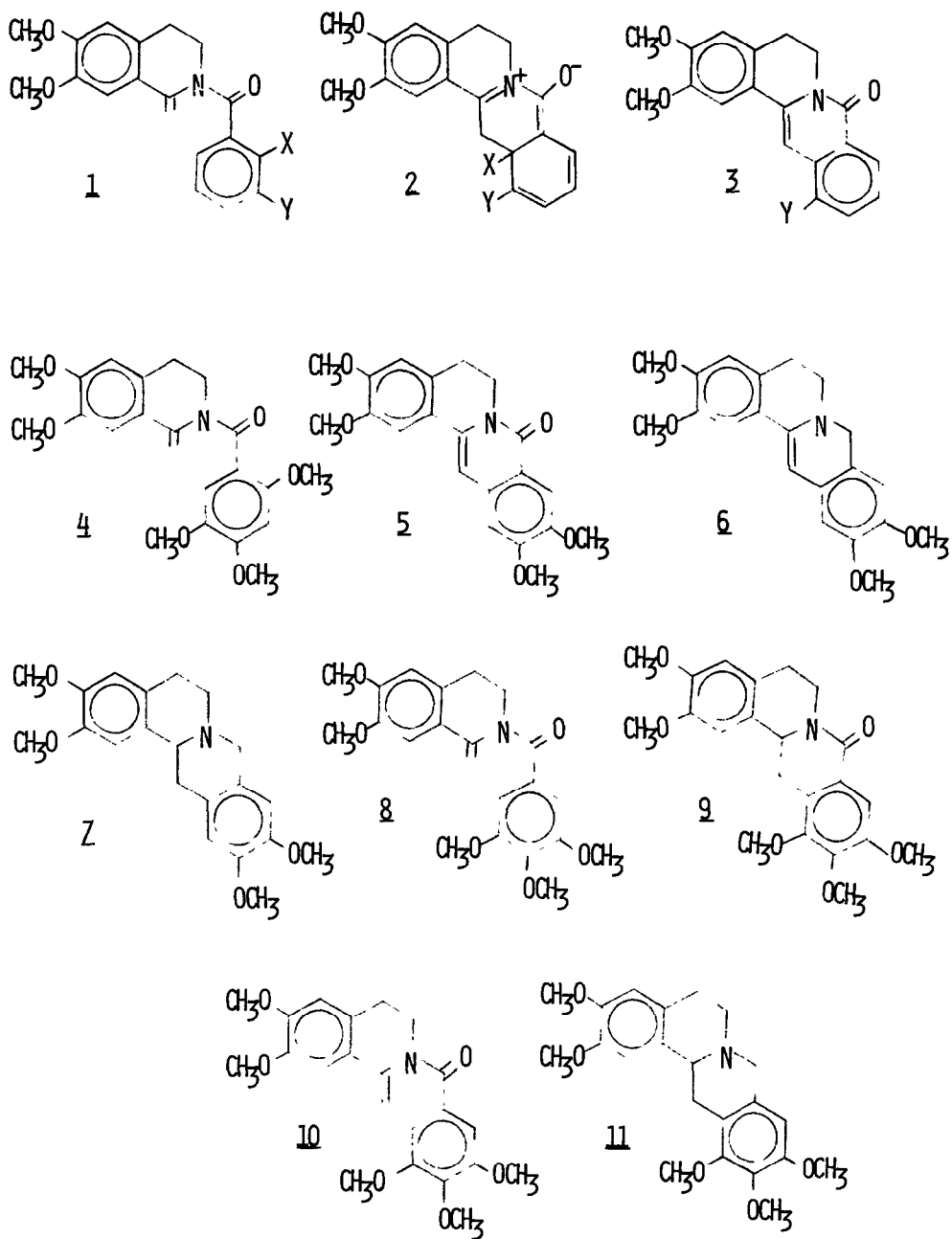
280 nm (min, 4000), 257 nm (11,000), 244 nm (sh, 15,000), 227 nm (28,000).⁷ Mass spectra confirmed the molecular weight as 307.1213 (calc. 307.1208). Comparison with an authentic sample prepared from 1-benzylidene-2-carbethoxy-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, mp 122-4°, by the photoacylation reaction⁵, confirmed the structure of 3. The reaction is viewed as a hexatriene-cyclohexadiene ring closure to generate the intermediate 2, which then loses the elements of HX to form the aromatic oxyprotoberbine system 3. The initial electrocyclic ring closure to give the intermediate 2 is well documented in the enamide system.^{4,5,8} Several other ortho-substituted derivatives of 1 have been studied and found capable of photoeliminating to form 3 and these are collected in the table. In general, if X is capable of acting as a leaving group, photoelimination will occur.

TABLE

<u>1</u>	mp <u>1</u>	% <u>3</u>	Remarks
X,Y = OAc,H	108-110°	80	
OCH ₃ ,OCH ₃	120-2°	60	mp 219-20°
Cl,H	143-4°	50	
Br,H	146-7°	50	
NO ₂ ,H	189-90°	11	20% <u>1</u> recovered

Polysubstitution on the benzoyl group seems to have little effect on the photocyclization as the pentamethoxy 4, mp 222-5°, is smoothly converted in 82% yield into the known oxyprotoberbine 5.^{7,9} Compound 5 was converted with LAH to the known 6, which possesses the basic lambertine alkaloid skeleton.⁹ Compound 6 may be further reduced with NaBH₄ to the tetrahydroprotoberbine alkaloid, xylopinine.¹⁰

If the ortho positions of the enamide are unsubstituted, photocyclization also occurs to give an intermediate analogous to 2, which then undergoes a 1,5-hydride shift to give 8-oxoberbines. For example, 8, mp 107-9°, is smoothly cyclized to 9, mp 127-130°, in 90% yield.¹ Compound 9 shows the loss of exocyclic methylene protons in the nmr and a uv spectrum characteristic of 8-oxoberbines: 306 nm (ϵ 2,500), 291 nm (sh, 5,500), 264 nm (9,000), 245 nm



(min, 7,000), 220 nm (end, 35,000).⁷ Compound 9 can be dehydrogenated in 80% yield by DDQ to the oxyprotoberbine 10, mp 170-172°.⁷ Compound 10 can also be formed directly from 8 by irradiation in the presence of either oxygen or iodine, but the yield is much lower and the two step sequence is preferred. Compound 9 can be converted to the tetrahydroprotoberbine, HCl salt, mp 189-194°,⁷ with LAH.

The irradiation of enamides 1 with suitable substitution patterns can lead to facile synthesis of oxyprotoberbine, lambertine, tetrahydroprotoberbine and 8-oxoberbine alkaloids, in high yields.

REFERENCES

1. N. C. Yang and G. R. Lenz, *Tetrahedron Letters*, 4897 (1967); I. Ninomiya, T. Naito and T. Mori, *Tetrahedron Letters*, 2259 (1969).
2. M. P. Cava, S. C. Havlicek, A. Lindert and R. J. Spangler, *Tetrahedron Letters*, 2937 (1966); N. C. Yang, G. R. Lenz and A. Shani, *Tetrahedron Letters*, 2941 (1966).
3. M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert and R. J. Spangler, *J. Org. Chem.*, 35 175 (1970).
4. G. R. Lenz and N. C. Yang, *Chem. Comm.*, 136 (1967).
5. N. C. Yang, A. Shani and G. R. Lenz, *J. Amer. Chem. Soc.* 88, 5369 (1966).
6. H. G. Viehe, R. Fuks and M. Reinstein, *Angew. Chem.*, 76, 571 (1964).
7. All new compounds gave satisfactory analysis and spectra in accord with the assigned structures. Spectral details will be described in the full paper.
8. I. Ninomiya, T. Naito, S. Higuchi, *Chem. Comm.*, 1662 (1970); I. Ninomiya, T. Naito and T. Kiguchi, *Tetrahedron Letters*, 4451 (1970); I. Ninomiya, T. Naito and T. Mori, *Tetrahedron Letters*, 3643 (1969).
9. A. Pictet and T. Q. Chou, *Ber.*, 49 373 (1916).
10. J. Schmutz, *Hew. Chim. Acta*, 42, 335 (1959).
11. After the syntheses outlined in this communication were finished, I. Ninomiya and T. Naito [*Chem. Comm.*, 137 (1973)] published on the photoconversion of an enamide to an 8-oxoberbine which was subsequently converted to xylopinine.