Journal of Natural Products
Vol. 48, No. 4, pp. 654-657, Jul-Aug 1985

THE PHOTOLYSIS OF SALUTARIDINEMETHINE

MOHAMMED BASHIR, ALAN J. FREYER, MAURICE SHAMMA,

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

ATTA-UR-RAHMAN,

HEJ Research Institute of Chemistry, University of Karachi, Karachi 32, Pakistan

and GÜNAY SARIYAR

Faculty of Pharmacy, Istanbul University, Istanbul, Turkey

Although the isoquinoline alkaloids can be subdivided into more than forty structural subgroups, only the proaporphines (and homoproaporphines) and the morphinandienones possess a cross-conjugated cyclohexadienone system which may lend itself to photoisomerization. In this context, it is known that in vitro sunlight irradiation of proaporphines leads to C-9 oxygenated aporphines, a process that could conceivably be utilized by some plants, although formal proof for such a phototransformation in nature is lacking (1).

Rather surprisingly, no studies on the photolysis of morphinandienones and their derivatives have been reported. Our intent, therefore, was to study the products formed from the photolysis of morphinandienone analogs under conditions that would approximate natural conditions to determine if such transformations could possibly occur in vivo. Our investigation centered on the well-known morphinandienone (+)-salutaridine (**1**), a sample of which was available to us.

Sunlight irradiation of (+)-salutaridine (**1**) in 95% EtOH over a period of 4 h led to recovery of most of the starting material. No well-defined product could be isolated.

Because several isoquinoline alkaloids (e.g., the aporphines and the cularines) may undergo facile enzymatic *N*-methylation to *N*-metho quaternary salts followed by base induced Hofmann β-elimination, it was considered that the same sequence could also be followed by the morphinandienones. In vitro *N*-methylation of (+)-salutaridine in our hands, followed by treatment with NaOH, thus produced salutaridinemethine (**2**).

In contrast to salutaridine itself, sunlight irradiation of **2** in 95% EtOH for 4 h produced four amorphous products, **4-7**, albeit in low yields, which were duly separated by tlc.

The first photolysis product, (+)-**4**, analyzed for $C_{20}H_{23}NO_4$, and was thus isomeric with the starting salutaridinemethine (**2**). Its ir spectrum, ν max ($CHCl_3$) 1590, 1630, 1655 cm^{-1}, was diagnostic for the presence of a cross-conjugated dienone system (2). The uv spectrum, λ max (MeOH) 234, 263, 355 nm (log ε 4.19, 4.15, 3.61), resembled somewhat that of **2**, λ max (MeOH) 233, 266, 410 nm (log ε 4.06, 3.95, 3.62).

The nmr spectrum of this first photolysis product has been summarized in expression **4** and bears a certain similarity to that of **2**. The telling feature of a subsequent and detailed nmr nOeds study (3) was that the two methoxyl singlet absorptions at δ 3.74 and 3.92 could clearly be connected by an interlocking chain of signal enhancements, which has been indicated in expression **4**. Discounting the acidic phenolic proton, the only proton absorption which showed no nOe was the isolated vinylic singlet at δ 6.92.

It was evident, therefore, that isomerization had occurred during photolysis with migration of the dimethylaminoethyl side-chain. Furthermore, the side-chain had remained in-

tact following migration, since the base peak in the mass spectrum of **4** was *m/z* 58, denoting the dimethyliminium cation; while a very intense (98%) *m/z* 72 peak represented the originally triply allylic $CH_2CH_2N(CH_3)_2$ side-chain of species **4**.

The second and major compound generated by the photolysis proved to be the cyclopentenone derivative (−)-**5**. Elemental analysis by hrms again indicated the composition $C_{20}H_{23}NO_4$. The ir spectrum, ν max ($CHCl_3$) 1625, 1720 cm^{-1}, insinuated a conjugated cyclopentenone rather than a cross-conjugated cyclohexadienone system (4). On the other hand, the uv spectrum, λ max (MeOH) 244, 327 nm (log ε 4.24, 3.48), suggested a conjugated, possibly styrenoid system (5).

One compelling aspect of the nmr spectrum of **5** was the vinylic one-proton triplet at δ 5.78, and another was the vinylic one-proton singlet at δ 6.42. Again, a complete nmr nOe study supplied the balance of evidence required in support of expression **5**. In particular, a 7% enhancement of the δ 6.42 signal was observed upon irradiation at δ 5.78. This was complemented by a reciprocal nOe of 8% upon irradiation at δ 6.42. These data furnished an insight into the geometry of the dimethylaminoethylidene side-chain. Another significant observation was that the δ 6.42 vinylic singlet was interconnected with the δ 3.81 methoxyl singlet by reciprocal enhancements, so that these protons are proximate.

The ir spectrum, ν max ($CHCl_3$) 1625, 1720 cm^{-1}, as well as the uv spectrum, λ max (MeOH) 246, 338 nm (log ε 4.25, 3.41) of the third photolysis product, (−)-**6**, $C_{17}H_{16}NO_4$, were almost superimposable on those for compound (−)-**5**, pointing to a similarity of structural features. The nmr spectrum, summarized around expression **6**, immediately indicated the absence of the dimethylaminoethyl moiety and the presence of an exocyclic methylene as represented by one-proton vinylic singlets at δ 5.50 and 6.13. Otherwise, the spectrum was a near replica of that for the accompanying compound **5**.

The nmr spectrum of the fourth and last photochemical product, (−)-**7**, $C_{18}H_{16}O_4$, also resembled that of **5** except for the appearance of a two-proton doublet at δ 4.90 and the absence of the dimethylamino signal. The δ 4.90 doublet is due to the methylene protons of a pyran system. The pyran ring must be formed by intramolecular attack of the phenolate oxygen of **5** at the methylene carbon of the dimethylaminoethylidene side-chain and resulting loss of dimethylamine from **5**. In further support of structural expression **7**, the ir spectrum of this fourth product exhibited ν max ($CHCl_3$) 1620 and 1715 cm^{-1}, pointing to a conjugated cyclopentenone system. The uv spectrum, λ max (MeOH) 258, 311 nm (log ε 4.04, 3.42), denoted an appreciably conjugated system. Significantly, the mass spectral molecular ion peak for compound **7**, *m/z* 296, was also the base peak.

At this stage, it is possible to postulate an overall mechanism which can not only rationalize the formation of products **4-6**, but also indicates the stereochemistry of the compounds in question.

The photoisomerization of cross-conjugated cyclohexadienones takes place via an $n\mapsto\pi^*$ excited triplet state. If one wishes to adopt the Woodward-Hoffmann designation, we are here dealing with a $\sigma^2a+\pi^2a$ transformation (6). The initial product is the unisolated lumiketone **3**, which may decompose by any of three related pathways.

Migration of the side-chain of **3** from C-4b to C-8a with concomitant dienone formation would lead to base **4**. The genesis of the second photolysis product **5** would then involve stereospecific loss of one of the two C-11 hydrogens of lumiketone **3** with formation of a C-4b to C-11 double bond. This process

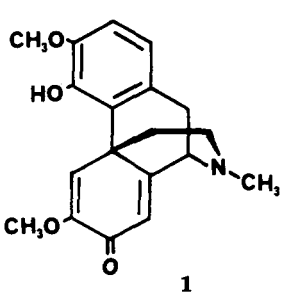
would be accompanied by cleavage of the C-4b to C-5 linkage. Evidently, this is the preferred route, since compound **5** is the main product of the reaction.

Formation of base **6**, the third and most minor of the photolysis products, can be explained through a mechanism closely related to the one just discussed, but where the C-4b to C-11 double bond is formed through loss of the dimethylaminomethyl moiety rather than a hydrogen.

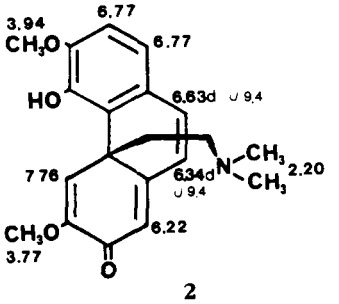
The genesis of **7**, which is also a minor product, is through loss of dimethylamine from species **5**, as previously discussed.

When the photolysis was run for a shorter time, the same four products could still be detected in ratios nearly identical to those obtained after 4 h, although the overall yields were lower. This finding indicated that the products were not derived from each other.

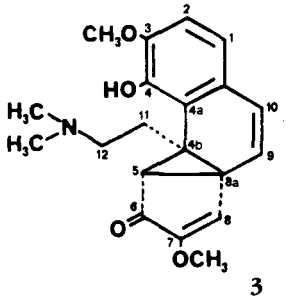
Irradiation for more than 4 h did not increase the yields and eventually led to decomposition. Because our aim was to try to duplicate any related in vivo photolytic process, no attempt was made



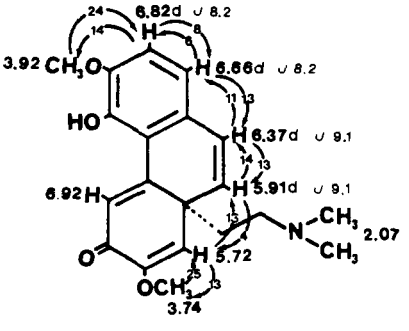
1



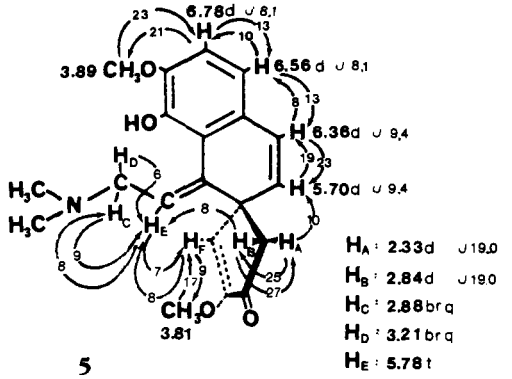
2



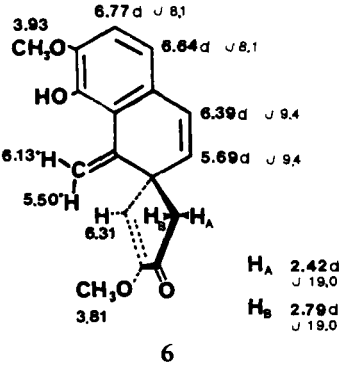
3



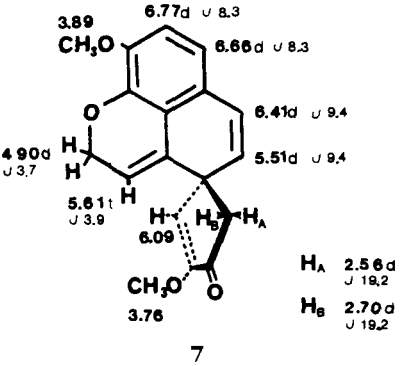
4



5



6



7

J values are in Hz units. Chemical shifts with identical superscripts are interchangeable.

to use a low-pressure mercury lamp instead of sunlight or to substitute 1,4-dioxane or other inert solvent for EtOH.

It should be pointed out in conclusion that no alkaloids related to compounds **4-7** have yet been found, so that photolysis of salutaridinemethine (**2**) does not appear to be a natural process.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mass spectra are at 70 eV, and nmr spectra are at 360 MHz.

SALUTARIDINEMETHINE.—(+)-Salutaridine (**1**) (130 mg) was dissolved in MeOH (15 ml) and MeI (7 ml) was added. The solution was allowed to stand, and on the next day was concentrated to a gum. This material was dissolved in 1 N NaOH (25 ml), and the solution was not extracted with $CHCl_3$ until the next day. Work-up provided amorphous **2** (120 mg).

PHOTOLYSIS.—Methine **2** (120 mg) was dissolved in 95% EtOH (30 ml), and the solution photolysed for 4 h in sunlight. The crude product was subjected to silica gel column chromatography. Elution was with 10% MeOH in $CHCl_3$ containing a trace of NH_4OH. The products were obtained in the following order: **7** (1.2 mg), **6** (1.8 mg), **5** (10 mg), and **4** (3 mg). Elemental compositions were confirmed by hrms.

SALUTARIDINEMETHINE (**2**).—$[\alpha]^{25}D$ +447° (c 0.12, $CHCl_3$); ms *m/z* 341 (M^+, 5), 270 (60), 255 (33), 72 (87), 58 (100).

DIENONE **4**.—$[\alpha]^{25}D$ +150° (c 0.17, MeOH); ms *m/z* 341 (M^+, 2), 270 (71), 255 (51), 72 (98), 58 (100).

CYCLOPENTENONE **5**.—$[\alpha]^{25}D$ −87° (c 0.10, MeOH); ms *m/z* 341 (M^+, 15), 296 (22), 270 (15), 255 (12), 58 (100).

CYCLOPENTENONE **6**.—$[\alpha]^{25}D$ −88° (c 0.03, MeOH); ms *m/z* 284 (M^+, 100), 269 (25), 255 (11), 241 (40), 209 (18), 181 (19), 152 (14), 128 (10).

CYCLOPENTENONE **7**.—$[\alpha]^{25}D$ −19° (c 0.04, MeOH), ms *m/z* 296 (100), 295 (25), 281 (13), 265 (9), 253 (15), 237 (18), 225 (10), 211 (10), 165 (9), 152 (7), 84 (13).

ACKNOWLEDGMENTS

This research was supported by grant INT-8217601 from the National Science Foundation.

LITERATURE CITED

1. S.F. Hussain, M.T. Siddiqui, G. Manikumar, and M. Shamma, *Tetrahedron Lett.*, **21**, 723 (1980).
2. K.L. Stuart and M.P. Cava, *Chem. Rev.*, **68**, 321 (1968); *ibid.*, **71**, 47 (1971).
3. L.D. Hall and J.K.M. Sanders, *J. Am. Chem. Soc.*, **102**, 5703 (1980).
4. K. Nakanishi and P.H. Solomon, *Infrared Absorption Spectroscopy*, 2nd ed. New York, Holden-Day, Inc., 1977, p. 38.
5. A.I. Scott, *UV Spectra of Natural Products*, New York, Macmillan Co., 1964, p. 99.
6. R.B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, New York, Academic Press, 1970, pp. 89-100. See also, J.R. Williams, R.H. Moore, R. Li, and C.M. Weeks, *J. Org. Chem.*, **45**, 2324 (1980).

Received 15 March 1985