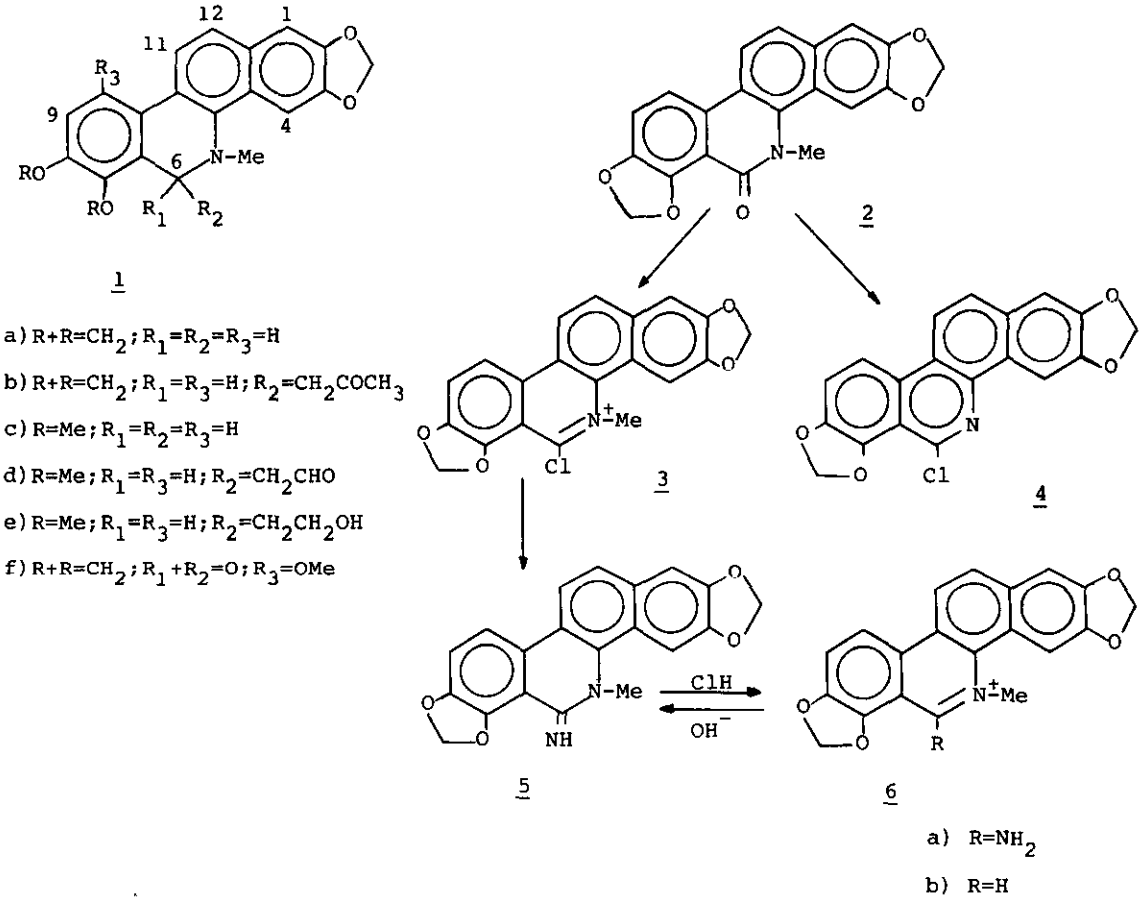
STRUCTURE AND SYNTHESIS OF 6-IMINOSANGUINARINE, A NEW BENZOPHENANTHRIDINE ARTEFACT[1]

Luis Castedo*, Domingo Domínguez, Manuel Pereira, José Saá and Rafael Suau
Departamento de Química Orgánica de la Facultad de Química e Instituto de Productos Naturales Orgánicos (Sección Alcaloides) del C.S.I.C.
Santiago de Compostela (Spain)

Abstract- 6-iminosanguinarine (5), a novel benzophenanthridine artefact was isolated from the roots of Glaucium flavum Cr. var. vestitum. The structure was determined by spectral data and synthesis.

In some recent publications[2] it has been pointed out that some benzophenanthridine derivatives isolated from natural sources are artefacts formed during extraction. All of them are dihydrobenzophenanthridines substituted at C_6 position by oxygen or carbon nucleophiles produced most probably, in the isolation by an attack of the solvents used to that position of benzophenanthridine quaternary salts.
We like now to report our own results concerning the isolation of benzophenanthridines from the roots of Glaucium flavum Cr. var. vestitum. 6-iminosanguinarine (5) was now obtained and shown to be an artefact. It represents the first benzophenanthridine having a nitrogen substituent at its C_6 position.
Air dried and powdered roots, moistened with ammonia for 24 hours, were extracted with CH_2Cl_2 followed by the usual acid-base treatment providing a basic extract which was chromatographed on silica gel. In addition to previously reported isoquinoline alkaloids in the plant[3], small amounts of dihydrosanguinarine (1a), dihydrochelerythrine (1c), 6-acetonylsanguinarine (1b), oxychelirubine (1f) and a new base, 6-iminosanguinarine (5), have now been obtained.
6-iminosanguinarine was isolated as the hydrochloride (6a)[4] which easily was reverted to compound (5) under basic treatment (Scheme 1). 6-iminosanguinarine (5) thus obtained crystallized from EtOH/$CHCl_3$ (4/1) as colorless needles having mp 241-2ø C which analyzed for $C_{20}H_{14}O_4N_2$ containing one mole of water. Mass spectrometry confirmed the above molecular formula by showing the molecular ion at m/e (%) 346 (78, M^+). Noteworthy is the observation that the UV spectrum of 6-iminosanguinarine (5) in aprotic solvents such as CCl_4 or DMF was very similar to that of oxysanguinarine (2) and superimposable on that of hydrochloride (6a) in basic solution[4]. However, in protic solvents (EtOH) or on addition of acid it was identical to that of quaternary salt (6a)[4]. The IR of compound (5) gave absorptions (KBr) at 3360, 1610 and 1575 cm^{-1} and its pmr (80MHz, $CDCl_3$) revealed δ 3.84(3H, s, NMe), 6.02, 6.17(2H each, s, $-OCH_2O-$), 7.04(1H, s, H_1), 7.49(1H, s, H_4) and two AB quartets {J=8.5 Hz, δ_A=7.33 and δ_B=7.77 (H_{11} and H_{12}); J=8.5 Hz, δ_A=7.05 and δ_B=7.61 (H_9 and H_{10})}. As expected the pmr of compound (5) in $CDCl_3$/TFA-d_1 was superimposable on that of quaternary salt (6a)[4]. Further evidence



SCHEME 1

for the basic skeleton and substitution pattern of 6-iminosanguinarine (5) was obtained from its reduction with sodium borohydride in methanol which afforded a quantitative yield of dihydrosanguinarine (1a).

The structure (5) of 6-iminosanguinarine was confirmed by its synthesis from oxysanguinarine (2) as shown on scheme 1. Heating of oxysanguinarine (2) with phosphorus oxychloride under reflux for 10 hours afforded 6-chloronorsanguinarine (4) *in 80% yield, as white needles,* {mp 292° C(d)($CHCl_3$); λ_{max}(EtOH),244, 282, 298 (sh) and 330 nm; pmr($CDCl_3$/TFA-d_1) δ 6.13 and 6.36(2H each, s, $-OCH_2O-$), 7.16(1H, s, H_1), 8.18(1H, s, H_4), and two AB quartets (J=9Hz, δ_A=7.63 and δ_B=8.14 (H_9 and H_{10}); J=9Hz, δ_A=7.83 and δ_B=8.14 (H_{11} and H_{12})); m/e (%) 351, 353 (100, 33, M^+)}. However, when the reaction was carried out under milder conditions (at 80° C for 5 hours) 6-chlorosanguinarine chloride (3) resulted in an almost quantitative yield {pmr ($CDCl_3$/TFA-d_1) δ 4.76 (3H, s, NMe), 6.21 and 6.47 (2H each, s, $-OCH_2O-$), 7.37 (1H, s, H_1), 7.58 (1H, s, H_4), and two AB quartets (J=9Hz, δ_A=8.07 and δ_B=8.34 (H_{11} and H_{12}); J=9Hz, δ_A=7.82 and δ_B=8.29 (H_9 and H_{10}))}. This without

further purification was treated with a suspension of sodium amide in ether under nitrogen for 72 hours resulting a 69% yield of iminosanguinarine (5) identical in all respects with the sample isolated from the plant (mp, tlc, UV, IR, PMR and MS). As 6-iminosanguinarine (5) appeared to be most probably an artefact of isolation produced by the action of ammonia on a benzophenanthridine alkaloid, the extraction was repeated under different conditions. Thus, root material was extracted with hot methanol followed by identical work up as above. In addition to dihydrosanguinarine (1a), dihydrochelerythrine (1c) (both found now in higher amounts than above[5]), oxychelirubine (1f) and acetonylsanguinarine (1b), dihydrochelerythrine-6-acetaldehyde (1d) and 6-hydroxymethyldihydrochelerythrine (bocconoline) (1e) have now been isolated.

These results imply that 6-iminosanguinarine (5) is an artefact. Acetonylsanguinarine (1b), dihydrochelerythrine-6-acetaldehyde (1d) and 6-hydroxymethyldihydrochelerythrine (bocconoline) (1e) have already been suggested to be artefacts[2d,2e,2f].

Since quaternary benzophenanthridines in basic solution are known to give the corresponding oxybenzophenanthridines by disproportionation[6], we reasoned that 6-iminosanguinarine (5) could have been resulted by the action of ammonia on sanguinarine (6b) present in the plant by a similar mechanism. However, all attempts to obtain 6-iminosanguinarine (5) from sanguinarine (6b) by treatment with ammonia under different conditions were failed.

The above results give a further support to the most likely possibility that all the 6-substituted dihydrobenzophenanthridines found in nature are artefacts of isolation.

ACKNOWLEDGMENT

To the Comisión Asesora de Investigación Científica y Técnica (Spain) for its financial support.

REFERENCES

1. Isoquinoline alkaloids XVIII. Part XVII: L. Castedo, T. Iglesias, A. Puga, J. M. Saá and R. Suau, Heterocycles, in press.

2. a) F. G. Torto, P. Sefcovic, and B. A. Dadson, Tetrahedron Letters, 1966, 181; b) P. D. Desai, T. R. Govindachari, K. Nagarajan, and N. Viswahathan, Indian J. Chem., 1967, 5, 41; c) D. B. MacLean, D. E. F. Gracey, J. K. Saunders, R. Rodrigo, and R. H. F. Manske, Can. J. Chem., 1969, 47, 1951; d) T. Furuya, A. Ikuta, and K. Syōno, Phytochem., 1972, 3041; e) N. Decaudain, N. Kunesch, and J. Poisson, Phytochem., 1974, 13, 505; H. Ishi, T. Ishikawa, K. Hosoya, and N. Takao, Chem. Pharm. Bull., 1978, 26, 166; E. M. Assen, I.A.Benages, and S. M. Albonico, Phytochem., 1979, 18, 511.

3. L. Castedo, D. Domínguez, J. M. Saá, and R. Suau, Tetrahedron Letters, 1978,

2923; L. Castedo, D. Domínguez, J. M. Saá, and R. Suau, Tetrahedron Letters, 1979, 4589.

4. The quaternary salt (6a) crystallized from EtOH as yellow plates {mp 186-7º C (d); λ_{max} (EtOH) (log ε) 246 (4.57), 277 (sh, 4.46), 286 (4.56), 320 (4.10), 353 (sh, 3.86) and 405 (3.84) nm; λ_{max} (EtOH+NaOH) (log ε) 242 (4.53) 286 (sh, 4.55), 296 (4.63), 350 (4.02), 370 (sh, 3.94) and 390 (sh, 3.85) nm; ν_{max}(KBr) 3400 (b), 1655 (b), 1600 cm^{-1}; pmr (DMSO-d_6) 4.03 (3H, s, NMe), 6.21 (2H, s, $-OCH_2O-$), 6.44 (2H, s, $-OCH_2O-$), 7.48 (1H, s, H_1), 7.64 (1H, s, H_4), two AB quartets (J=8.5Hz, δ_A=7.67 and δ_B=8.19 (H_9 and H_{10}); J=8.5Hz, δ_A=7.81 and δ_B=8.29 (H_{11} and H_{12}), and 9.31 (2H, b, NH_2)); m/e (%) 345 (75, M^+),345(100)}.

5. F. Y. Chou, K. Hostettman, I. Kubo, K. Nakanishi, and M. Taniguchi, Heterocycles, 1977, 7, 969.

6. H. R. Arthur, W. H. Hui, and Y. L. Ng, J. Chem. Soc., 1959, 1840.

Received, 4th December, 1980