UNPRECEDENTED CYANATION AND CYANOMETHYLATION FOLLOWING RING CLOSURE VERSUS DIMER FORMATION DURING ANODIC OXIDATION OF THE ASPIDOFRACTININE ALKALOID KOPSAMINE

Toh-Seok Kam,* Tuck-Meng Lim, and Guan-Huat Tan

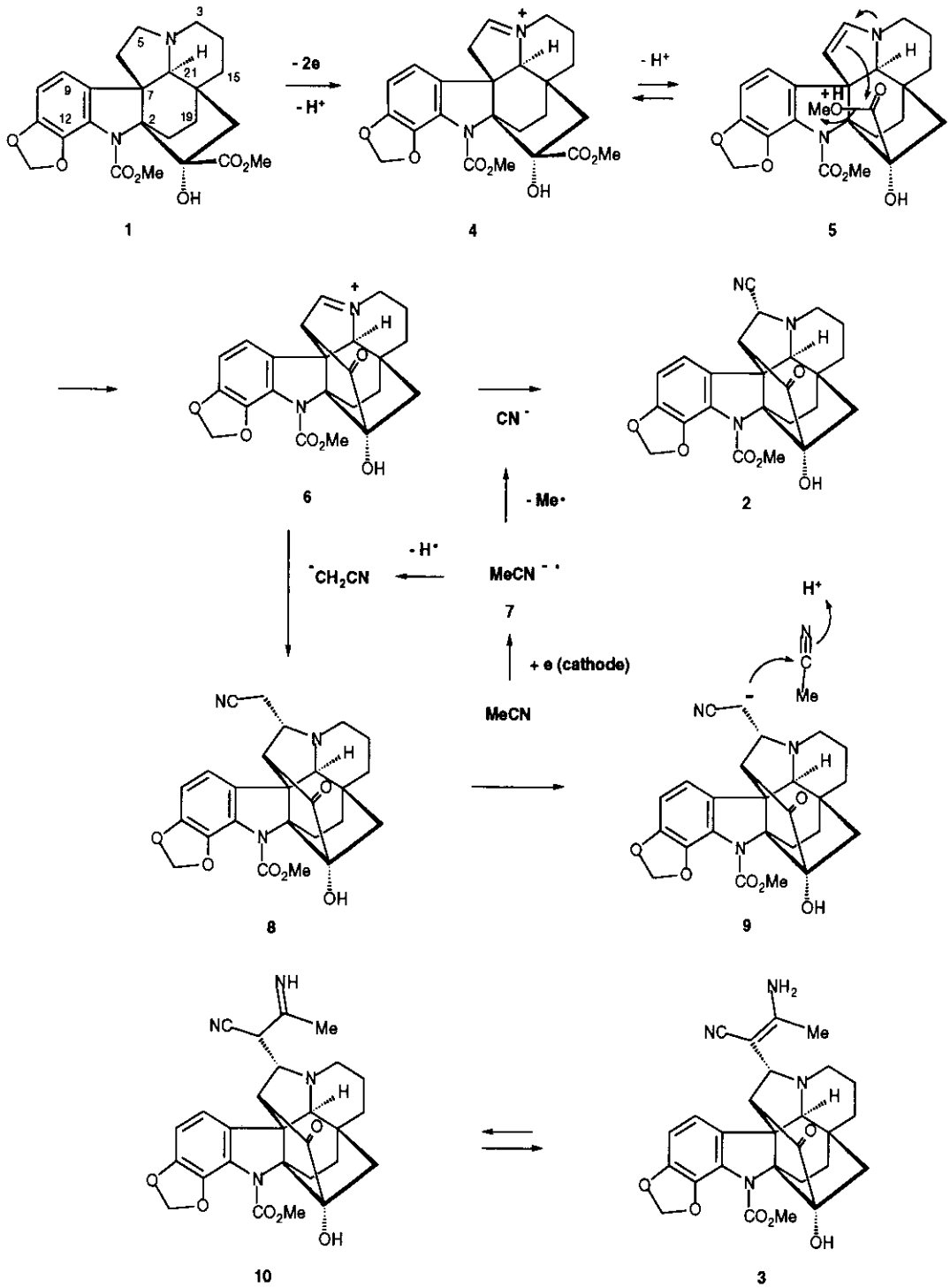
Department of Chemistry, University of Malaya

50603 Kuala Lumpur, Malaysia

Abstract – Anodic oxidation of the aspidofractinine-type indole alkaloid kopsamine on platinum in Et_4NClO_4/MeCN results in an unprecedented cyanation-cynomethylation reaction following ring closure while oxidation on vitreous carbon in $LiClO_4$-MeOH yielded a dimerization product with a C_2 element of symmetry.

In continuation of our ongoing studies on the electroorganic chemistry of indole alkaloids,[1] we wish to report an unprecedented electrochemically-mediated transformation of the aspidofractinine alkaloid kopsamine (**1**). On electrochemical oxidation (Pt anode, MeCN, 0.1M Et_4NClO_4), kopsamine (**1**)[2] exhibits two irreversible waves at 0.86 and 1.66 V *versus* Ag/AgCl in the potential range studied as revealed by cyclic voltammetry. Controlled potential electrolysis (Pt gauze anode, Pt cathode) at the first potential peak (1.05 V) in the presence of lutidine as proton scavenger results in the consumption of 2.5 F mol^{-1}. Analysis of the electrolysed solution revealed the formation of two products in moderate yields (45 %) and chromatographic separation followed by extensive spectroscopic analysis (IR, MS, 2-D NMR) revealed the structures (**2**) (23 %) and (**3**) (22 %) for the two products.

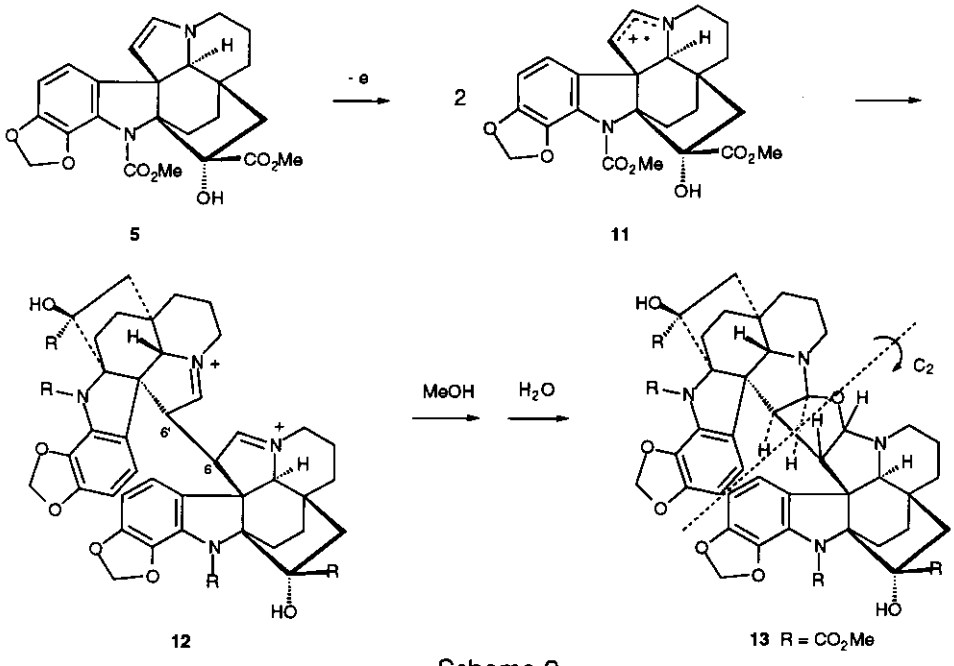
Compound (**2**) is a derivative of the known carbonyl-bridged heptacyclic alkaloid kopsine. The EIMS showed an M^+ at *m/z* 449 indicating the presence of a third nitrogen. The presence of a strong fragment peak due to loss of CN in the MS spectrum, an IR absorption band at 2230 cm^{-1} and a quaternary carbon resonance at δ 118.6 in ^{13}C NMR, indicated the presence of a cyano group. The structure is confirmed by 2-D NMR analysis which revealed a 5-cyanosubstituted kopsine derivative. Compound (**3**) analysed for $C_{27}H_{28}N_4O_6$, indicating incorporation of an additional mole of MeCN when compared with **2** ($C_{24}H_{23}N_3O_6$). The IR spectrum



Scheme 1

showed the presence of cyano (2186 cm^{-1}) and NH_2 (3262, 3246 cm^{-1}) functions in addition to hydroxyl, carbonyl and carbamate absorptions. Detailed analysis of the NMR spectrum revealed a kopsine-

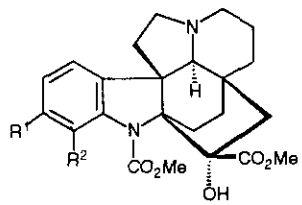
like derivative substituted at position-5 by the four-carbon side chain as shown in **3**. We rationalize the formation of these unusual products as shown in Scheme 1. Electrooxidation of **1** results in stepwise loss of an electron, deprotonation, followed by loss of another electron to give the iminium ion intermediate (**4**).[1] A further deprotonation of **4** gives the enamine (**5**) which undergoes cyclization to the iminium ion (**6**) which on subsequent reaction with CN^- gives compound (**2**). The source of the CN^- anion is probably from decomposition of the acetonitrile anion radical (**7**) (formed by a side reaction in the counter electrode chamber) which can undergo the alternative decomposition to the cyanomethyl anion.[3,4] Attack of this anion on the iminium intermediate (**6**) gives the 5-cyanomethylated derivative (**8**) which on subsequent reaction with a second mole of MeCN as shown, eventually results in compound (**3**).



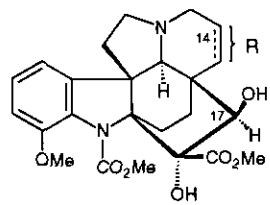
Scheme 2

Since electrolysis under the above conditions gave rise to these unusual products, caused in part by decomposition of the acetonitrile solvent, we were prompted to test electrolysis under a different set of conditions. In the event, electrolysis of **1** at a vitreous carbon anode in 0.1M $LiClO_4$/MeOH (0.95 V *versus* Ag/AgCl, Pt cathode) resulted in the formation of a single product (**13**) in moderate yield (30%). That this product was dimeric was indicated by API-LCMS, FABMS (MH^+ *m/z* 925) as well as HREIMS which

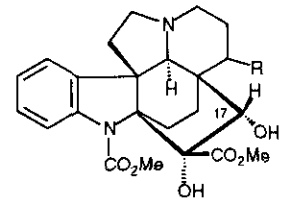
yielded the molecular formula $C_{48}H_{52}N_4O_{15}$.[5] The ^1H and ^{13}C NMR spectra however showed homotropic behavior, displaying resonances for only one half of the dimeric molecule, suggesting the presence of an element of symmetry.[6] The NMR data showed position-5 and -6 to be methines and furthermore position-5 was shown to be oxygenated (δ_H 4.97; δ_C 96.2; α to both N and O). The H-5 and H-6 resonances were doublets with J 5 Hz which is consistent with their being *cis* with respect to each other in a five-membered ring. The presence of an element of symmetry is satisfied in structure (**13**) for the dimeric product which has a C_2 axis passing through the oxygen of the central 5-membered tetrahydrofuran ring.[6] The formation of this dimeric product is rationalized in Scheme 2. A further one electron oxidation of the enamine (**5**) gives the cation radical intermediate (**11**) which on head-to-head coupling in the manner shown results in the formation of the C6-C6' linkage.[7] The resulting diiminium ion (**12**) is immediately quenched by methanol to give a biscarbinol amine ether, which then undergoes a presumably facile hydrolysis/condensation to the cyclic ether (**13**).



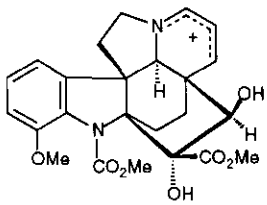
14 $R^1 = R^2 = H$; **15** $R^1 = R^2 = OMe$



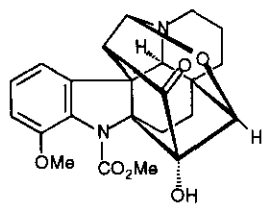
16 $R = \Delta^{14,15}$; **17** R = nil



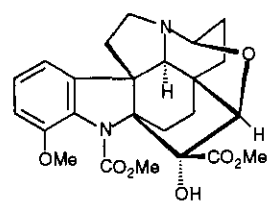
18 R = α-OH



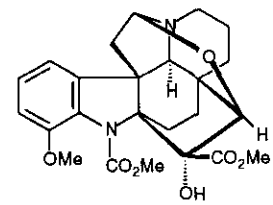
19



20



21



22

To explore the generality and scope of this reaction, electrooxidation of the following substrates (**14–18**) was next investigated. The behavior noted above for kopsamine (**1**) is reproduced in both kopsiflorine (**14**) and 11-methoxykopsilongine (**15**), suggesting that modifications in the aromatic ring do not substantially

alter the reaction course. In the case of compound (**16**), electrooxidation in MeCN-CH_2Cl_2 resulted in the formation of a stable conjugated iminium salt (**19**). If the piperidine double bond is removed, as in compound (**17**), electrooxidation in methanol yields **20**, **21** and **22**. The oxo-bridged products (**21**) and (**22**) are the result of direct intramolecular capture of the intermediate iminium ions by the appositely oriented 17β-OH, while formation of the caged product (**20**) is a result of a sequence involving iminium ion formation, deprotonation to an enamine, followed by two successive intramolecular cyclizations. If the C(17)-OH is inappropriately oriented for intramolecular closure as in compound (**18**) (17-α-OH), electrooxidation in methanol results in the formation of a C_2 symmetric dimer similar to that observed for compounds (**1**, **14**, and **15**). These novel transformations provide valuable clues concerning the possible origin of the kopsine as well as the more recently uncovered kopsinitarine group of alkaloids[8] and full details will be reported in due course.

ACKNOWLEDGEMENTS

We thank the University of Malaya and IRPA for financial support of this work.

REFERENCES

1. G. H. Tan, T. M. Lim, and T. S. Kam, *Tetrahedron Lett.*, 1995, **36**, 1327.
2. T. S. Kam, G. Subramaniam, and W. Chen, *Phytochemistry*, 1998, in press.
3. The electrolysis is accompanied by changes in the counter electrode compartment as indicated by the development of a brownish coloration as the reaction progresses. This however appears to be a reproducible feature of the reaction.
4. H. Ohmori, C. Ueda, K. Yamagata, and M. Masui, *J. Chem. Soc., Perkin Trans. II*, 1987, 1065.
5. HREIMS found, *m/z* 924.3397 (calcd for $C_{48}H_{52}N_4O_{15}$, 924.3429).
6. T. S. Kam, K. Yoganathan, and H. Y. Li, *Tetrahedron Lett.*, 1996, **37**, 8811.
7. D. Koch and H. Schafer, *Angew. Chem., Int. Ed. Engl.*, 1973, **42**, 245.
8. T. S. Kam, K. Yoganathan, and C. H. Chuah, *Tetrahedron Lett.*, 1994, **35**, 4457.

Received, 15th October, 1998