Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1327-1330, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02468-5

Electrochemical Oxidation of Aspidofractinine-type Indole Alkaloids. A Facile, Electrochemically-mediated Conversion of Kopsingine to Kopsidines A, B, C and Kopsinganol

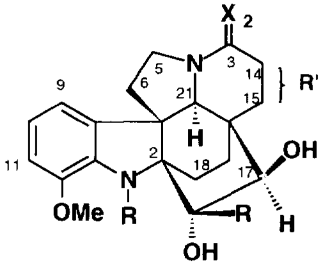
Guan-Huat Tan, Tuck-Meng Lim and Toh-Seok Kam*

Department of Chemistry, University of Malaya,
59100 Kuala Lumpur, Malaysia.

Abstract : *Kopsidine A, B, C and kopsinganol were synthesised from kopsingine in good yields via the stable imminium salt obtained from electrochemical oxidation of kopsingine. Electrooxidation of dihydrokopsingine on the other hand gave the 17-to-5 and 17-to-3 oxo-bridged alkaloids directly, while 3-oxokopsingine was inert to electrooxidation in the potential range employed.*

We wish to report novel electrochemically-mediated transformations of aspidofractinine-type alkaloids as exemplified by kopsingine **1** and its derivatives including an electrochemically-mediated, high yield, practically one pot synthesis of kopsidine A, B and C, **4-6** which are novel heptacyclic alkaloids that have been recently isolated from *Kopsia teoi* [1-3].

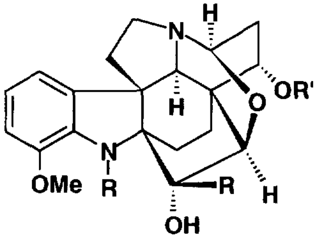
While carrying out preliminary electrochemical investigations on kopsingine **1**, we found that on electrochemical oxidation (Pt anode, 30 % CH_2Cl_2-MeCN, 0.1M Et_4NClO_4), kopsingine exhibits two irreversible waves (0.78 and 1.38 V *versus* Ag/AgCl) in the potential range studied as revealed by cyclic voltammetry. Controlled potential electrolysis (Pt gauze anode, Pt cathode) at the first potential peak (0.87 V) in the presence of lutidine as proton scavenger results in the consumption of 2.1 F mol^{-1}. TLC analysis of the anolyte after electrolysis showed complete consumption of kopsingine and revealed the presence of a polar product spot (presumably the imminium salt, *vide infra*) that is stained by Dragendorff reagent near the baseline just above that of the supporting electrolyte. Upon addition of methanol to precipitate out the bulk of the supporting electrolyte after evaporation of the solvent, it was found that a new product was formed which had R_f similar to that of kopsidine A. The formation of this product was monitored by TLC which showed that formation of kopsidine A was at the expense of the initial polar product which was progressively consumed as



1 R = CO_2Me, $X_2 = H_2$, R' = $\Delta^{14,15}$

2 R = CO_2Me, $X_2 = H_2$

3 R = CO_2Me, $X_2 = O$, R' = $\Delta^{14,15}$

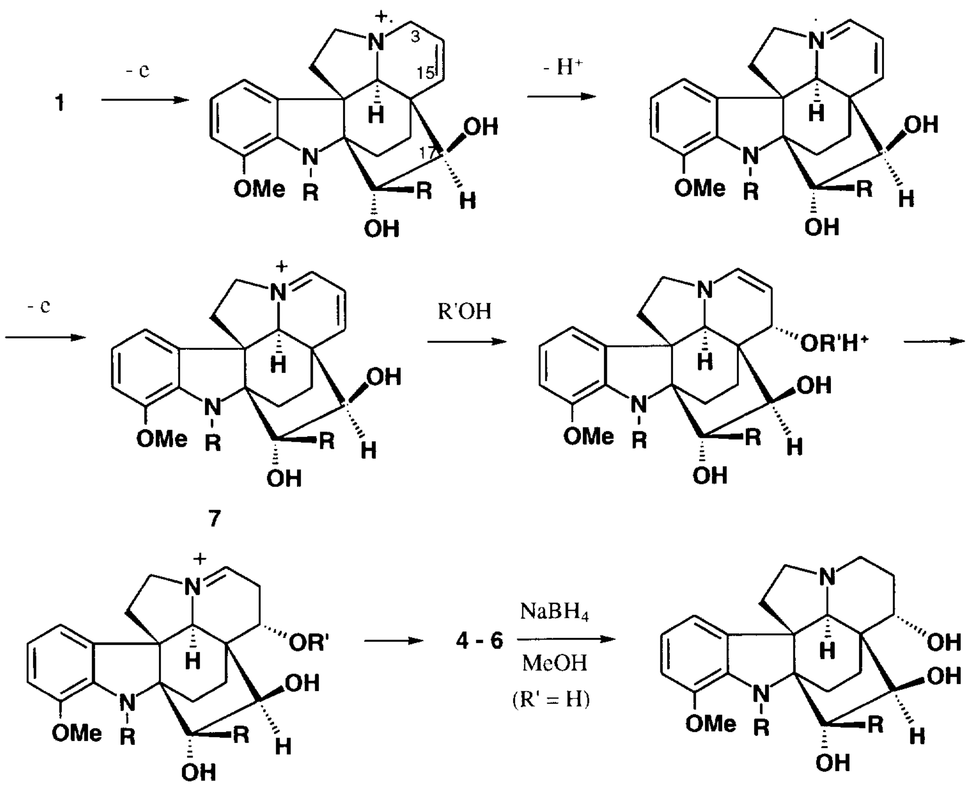


4 R = CO_2Me, R' = Me

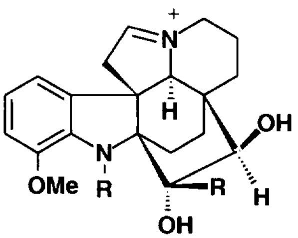
5 R = CO_2Me, R' = Et

6 R = CO_2Me, R' = H

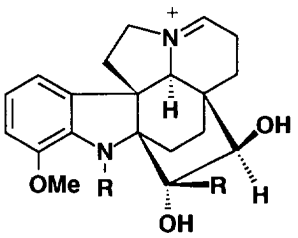
kopsidine A is formed. Chromatography of the product mixture (SiO_2, 1 % MeOH-$CHCl_3$) after 25 hours yielded kopsidine A **4** as the sole product in 72 % overall yield from kopsingine which had spectral data (MS, ^1H and ^{13}C NMR) and $[\alpha]_D$ identical with that of kopsidine A isolated from *Kopsia teoi*.[4]. Repetition of the same essential procedure but using ethanol in place of methanol (25 hours) gave kopsidine B **5**[5] in 70 % overall yield. Hydrolysis of the oxidation product in 1:1 MeCN-H_2O was slow in comparison with the alcohol reactions and resulted in only 15 % yield of kopsidine C **6**[6] after 4 days. Hydrolysis in a two phase medium with phase transfer catalysis (CH_2Cl_2 - H_2O) did not substantially improve matters (Yield of kopsidine C 20 %). Reduction of kopsidine C with sodium borohydride gave kopsinganol **9**[7], another novel aspidofractinine alkaloid from *Kopsia teoi* (90 % yield from kopsidine C). The reactions described can be rationalized as shown in Scheme 1. Electrooxidation results in stepwise loss of an electron, deprotonation, followed by loss of another electron to give the conjugated imminium salt **7** as the main product of the electrochemical process[8]. Addition of methanol triggers off a 1,4-addition of the nucleophile onto carbon-15 resulting eventually in another imminium ion intermediate **8** which then suffers intramolecular 1,2-addition of the 17-β-OH function yielding kopsidine A[9]. In the light of the above results it was of interest to investigate the behaviour of dihydrokopsingine **2**, to see what effect if any the 14,15-double bond of the piperidine ring has on the course of the electrooxidation. Compound **2** was readily obtained *via* catalytic hydrogenation (H_2, Pd/C) of kopsingine **1**. Preliminary cyclic voltammetry showed a similar pattern of oxidation as that observed for kopsingine **1** except that the oxidation peaks are observed at lower potentials compared to **1** (0.76 and 1.36 V). Controlled potential electrolysis at the first potential peak (0.81 V) under similar conditions as that used for **1** results also in the consumption of 2 F mol^{-1}. TLC analysis of the product mixture indicated two major products and subsequent chromatography gave the oxo-bridged compounds **12** and **13** in yields of 55 and 20% respectively. The structures of **12** and **13** were established based on extensive spectral analysis including 2-D NMR analysis. It is apparent that in the case of the dihydrocompound **2**, electrooxidation also results in formation of imminium ion intermediates such as **10** and **11** which unlike the more stabilized conjugated imminium ion **7**, do not persist but undergo facile intramolecular ring closure *via* 1,2-addition of the 17-β-



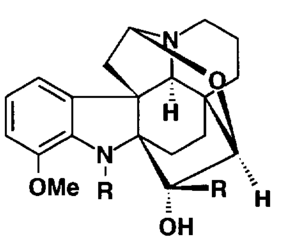
Scheme 1



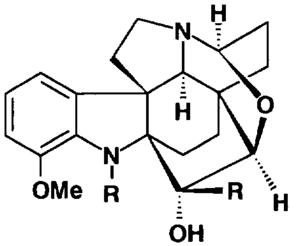
10



11



12



13

OH. The behaviour of the 3-oxo-kopsingine derivative **3** was also investigated but it was found to be inert to electrooxidation in the potential range investigated (up to 1.8 V). It appears that the course of electrooxidation in the aspidofractinine type alkaloids is sensitive to modifications of the piperidine ring (ring E) in these alkaloids. In any case the above procedure has shed valuable light on the electrochemical behaviour of the aspidofractinine alkaloids and in the case of kopsingine has provided a convenient and facile entry into the group of novel heptacyclic indole alkaloids which include the kopsidines and the singapurensines[10]. Further work is in progress to isolate and characterise the initial imminium salt **7** and to investigate further reactions of the imminium ion as well as the electrochemical behaviour of other aspidofractinine alkaloids.

A typical experimental procedure is as follows : Kopsingine **1** (100 mg, 0.2 mmol) in 40 ml of a mixed solvent (30 % CH_2Cl_2-MeCN) containing Et_4NClO_4 (0.1 M) and 2,6-lutidine (0.4 mmol) was placed in a divided cell under nitrogen. The anodic potential (Pt gauze, 2 x 9 cm) was maintained at 0.87 V *vs* Ag/AgCl and the electrolysis continued until 2.1 F mol^{-1} had been transferred. The progress of electrolysis was also monitored by TLC as well as by cyclic voltammetry. The solution was then evaporated to dryness and methanol (12 ml) was added. The precipitated electrolyte was then filtered off and the residue washed with methanol. The methanol solution was then stirred for 25 h and the solvent was removed under reduced pressure. The resulting product was then chromatographed over silca gel (1 % MeOH-$CHCl_3$) to afford pure kopsidine A **4** (72 % from kopsingine **1**).

Acknowledgements : We would like to thank the University of Malaya and IRPA (04-07-04-139) for financial support and Mr. K. Yoganathan for his interest in this work.

References and Notes

1. Kam, T. S., Yoganathan, K. and Chuah, C. H., *Tetrahedron Lett.*, **1993**, *34*, 1819.
2. Kam, T. S., Yoganathan, K., Chuah, C. H. and Chen Wei, *Phytochemistry*, **1993**, *32*, 1343.
3. Kam, T. S. and Yoganathan, K., unpublished results.
4. Kopsidine A **4**, $[\alpha]_D$ +17° ($CHCl_3$, *c* = 0.76); **4** from *K. teoi*, $[\alpha]_D$ =+16° ($CHCl_3$, *c* = 0.21).
5. Kopsidine B **5**, $[\alpha]_D$ +15° ($CHCl_3$, *c* = 0.27); **5** from *K teoi*, $[\alpha]_D$ =+11° ($CHCl_3$, *c* = 0.073).
6. Kopsidine C **6**, $[\alpha]_D$ +48° ($CHCl_3$, *c* = 0.20); **6** isolated from *K.teoi* was insufficient for an accurate determination. Spectral data of kopsidine C will be published separately elsewhere.
7. Kopsinganol **9**, $[\alpha]_D$ +46° ($CHCl_3$, *c* = 0.12); **9** from *K teoi*, $[\alpha]_D$ = +39° ($CHCl_3$, *c* = 1.80).
8. Gunic, E., Tabakovic, I., Gasi, K. M., Miljkovic, D. and Juranic, I., *J. Org. Chem.*, **1994**, *59*, 1264.
9. While this work was in progress a semisynthesis of kopsidine A and B from kopsingine *via* the Polonovski-Potier reaction has also been reported : Kan-Fan, C, Quirion, J.- C. and Husson H.- P., *Natural Product Lett..*, **1993**, *3*, 291.
10. Awang, K., Thoison, O., Hamid, H. A., Pais, M. and Sevenet, T., *Natural Product Lett.*, **1993**, *3*, 283.

(*Received in UK* 26 *October* 1994; *revised* 1 *December* 1994; *accepted* 21 *December* 1994)