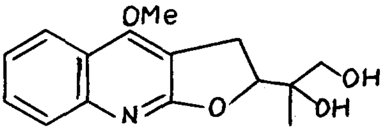
Tetrahedron Letters No. 49, pp 4727 - 4728, 1971. Pergamon Press. Printed in Great Britain

THE SYNTHESIS OF (±)-DUBINIDINE

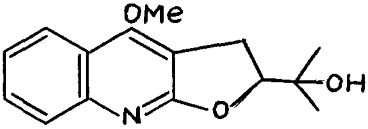
M. F. Grundon and K. J. James
School of Physical Sciences, The New University of Ulster,
Coleraine, Northern Ireland.

(Received in UK 25 October 1971; accepted for publication 3 November 1971)

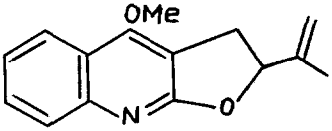
Dubinidine (1), a quinoline alkaloid first isolated from Haplophyllum dubium[1] (Rutaceae), has been used extensively in pharmacological studies which have shown that the principal activity of the compound is associated with depression of the central nervous system[2]. Several structures[3] have been proposed for this compound including (1) which represents a novel transformation of the isoprenoid unit in aromatic natural products.



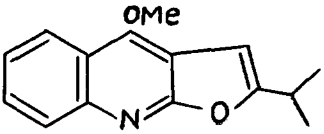
1



2



3



4

It was thought desirable, therefore, to synthesise this alkaloid for which the exo-olefin (3) is a key intermediate. Attempts to dehydrate (±)-platydesmine[4] (2) using conventional methods (e.g. PBr_3[5] in pyridine) resulted, inter alia, in the formation of the thermodynamically more stable endo-olefin[6](4). Our search for a mild dehydrating agent led us to use triphenyl phosphite dibromide[7] with potassium carbonate in refluxing isopropyl ether. Thus, (±)-platydesmine (2) was dehydrated to give a mixture of olefins, (3) (48%) and (4) (23%). We are investigating the scope of this reagent system for the preparation of olefins. The olefins (3) and (4) were separated on neutral alumina and the structure of (3) was deduced principally from the n.m.r. spectrum; the methyl signal of the isopropenyl group occurs as a singlet at 8.25, the olefinic protons appear as broad singlets at τ 4.85 and 5.06 and the dihydrofuran protons form an ABX system with signals centred at τ 4.82 (1H) and 6.50 (2H).

The exo-olefin (3) on reaction with osmium tetroxide in dioxan at room temperature gave (±)-dubinidine; the n.m.r. and mass spectra are in accord with the structure (1) and with the data recorded for the natural alkaloid.[3b,8] For example, the mass spectrum showed a parent peak at m/e 275.11574 (calc. 275.11574) and a base peak at m/e 200.07114 (calc. 200.07114) $(M^+-C_3H_7O_2)$.

REFERENCES

1. S. Yu. Yunusov and G. P. Sidyakin, *Zhur. Obshchei Khim.*, **25**, 2009, (1955). (Chem. Abs., **50**:9435i).
2. e.g. N. P. Polietsev, I. K. Kamilov and I. N. Zimon, *Farmakol.Alkaloidov*, No. 2,60,(1965). (Chem. Abs., **66**:64103). N. P. Polietsev and I. N. Zimon, *ibid*., No. 2,81,(1965). (Chem. Abs., **66**:64104).
3. (a) Other structures for dubinidine were given by:-

   N. P. Polietsev, *Izvest.Akad.Nauk Uz.S.S.R.,Ser.Med*., No. 6,66,(1959); (Chem. Abs., **54**:12479b); I. A. Bessonova, G. P. Sidyakin and S. Yu. Yunusov, *Dokl. Akad.Nauk Uz.S.S.R*., **19**,50,(1962). (Chem. Abs., 58:4609a).

   (b) Structure (1) was proposed by I. A. Bessonova and S. Yu. Yunusov, *Khim*. Prir. Soedin., **5**,29,(1969).
4. R. M. Bowman and M. F. Grundon, *J.Chem.Soc.(C)*. 1504, (1966).
5. e.g. M. Miyano and M. Matsui, *Ber*., **93**, 1194, (1960).
6. Compound (4) is the exclusive product from the acid catalysed dehydration of platydesmine; S. R. Hohns, J. A. Lamberton and A. A. Sioumis, *Aust. J. Chem*., **20**, 1975, (1967).
7. D. G. Coe, S. R. Landauer and H. N. Rydon, *J. Chem. Soc*., 2281, (1954).
8. I. A. Bessonova, Z.Sh. Faizutdinova, Ya. V. Rashkes and S. Yu. Yunusov, *Khim. Prir. Soedin*., 6, 446, (1970).