An Improved Phenanthrene Synthesis: a Simple Route to (±)-Tylophorine

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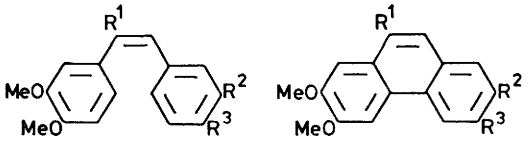
Summary Vanadium trifluoride oxide was found to convert a variety of 1,2-diarylethylene derivatives into phenanthrenes in high yield and provided the means for an efficient synthesis of (±)-tylophorine.

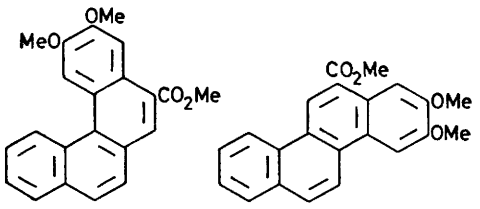
IN spite of recent improvements[1,2] the limitations imposed by classical syntheses of the phenanthrene nucleus often hinder the preparation of natural products containing such nuclei. It has been observed that vanadium trifluoride oxide (VOF_3) can induce intramolecular coupling between non-phenolic aromatic nuclei[3] and it seemed appropriate to investigate its effect upon stilbenes with a view to a new phenanthrene synthesis.

It was found that VOF_3 (2·2 equiv.) in trifluoroacetic acid (TFA)–methylene chloride at 0 °C readily converted the stilbene derivatives (**1**)—(**3**) into the corresponding phenanthrenes (**4**)—(**6**), in high yield† (Scheme 1) [(**4**), m.p. 201—203 °C, 75% yield; (**5**), m.p. 212—214 °C, 85%; (**6**), m.p. 265—267 °C, 91%]. This oxidative cyclisation procedure was equally applicable to the preparation of the benzophenanthrenes (**7**) (m.p. 145—147 °C, 68%) and (**8**) (m.p. 183—185 °C, 88%) as well as methyl

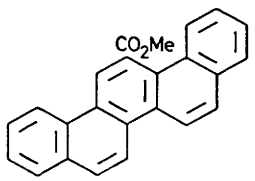


(1) R^1=CO_2Me, R^2=R^3=OMe (4)
(2) R^1=CO_2Me, R^2,R^3=$-OCH_2O-$ (5)
(3) R^1=CN, R^2R^3=$-OCH_2O-$ (6)

SCHEME 1



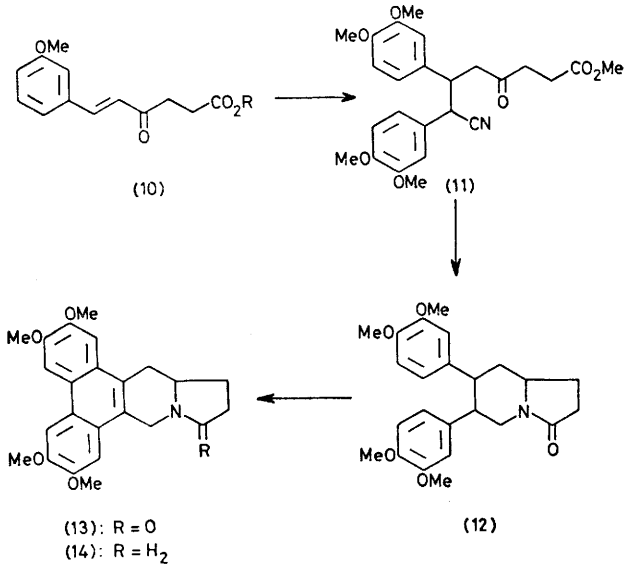
(7) (8)



(9)

† A 69% yield of the phenanthrene (**4**) was obtained from (**1**) with $Tl(OAc)_3$ under similar conditions. Compound (**4**) has been obtained previously in 31% yield by photocyclization of (**1**); R. B. Herbert and C. J. Moody, *Chem. Comm.*, 1970, 121.

picene-14-carboxylate (**9**) (m.p. 230—233 °C, 47%), from the corresponding 1,2-diarylethylene precursors.



SCHEME 2

This convenient cyclisation made possible the design of a simple total synthesis of (±)-tylophorine (**14**) (Scheme 2), a member of the phenanthroindolizidine group of alkaloids. These alkaloids exhibit a wide range of biological activities[4] and a convenient general synthesis could facilitate the exploitation of these properties.

Veratraldehyde was condensed with potassium laevulinate in aq. MeOH to give the carboxylic acid (**10**, R=H) (m.p. 143—145 °C, 64%), after extraction of unchanged aldehyde and subsequent acidification. Esterification with refluxing MeOH containing $BF_3{\cdot}OEt_2$ gave the ester (**10**, R=Me) (m.p. 80—81 °C) which underwent a Michael addition when fused with an excess of 3,4-dimethoxybenzyl cyanide (1·2 equiv.) at 140 °C in the presence of catalytic amounts of anhydrous K_2CO_3 to form (**11**) (61% after chromatography on silica).

The subsequent hydrogenation of (**11**) over 10% Pt–C in 10% HOAc–EtOAc at 20 °C during 4 days resulted in a double ring closure and gave the lactam (**12**) [ν_{max} (Nujol) 1685 cm^{-1}] in one step in 86% yield. The phenanthrene ring was found to be formed readily when (**12**) was treated with VOF_3 (4·4 equiv.) in TFA–CH_2Cl_2 at 0 °C. These conditions resulted in ring closure with simultaneous dehydrogenation to (**13**), (m.p. 273 °C, decomp., 59%). Although reduction of (**13**) with an excess of diborane in tetrahydrofuran gave only a borane adduct of the alkaloid [m.p. 290 °C, decomp., ν_{max} (Nujol) 2400 cm^{-1}, 91%], this was readily cleaved when heated at 130 °C for 1 h in dimethylformamide (N_2 atmosphere) to afford an 85% yield of (±)-tylophorine (**14**), identical with the natural alkaloid (t.l.c., i.r., u.v., and mass spectrum) except in optical activity.

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[4] B. Chauncy and E. Gellert, *Austral. J. Chem.*, 1970, **23**, 2503.