A ONE STEP SYNTHESIS OF THE PHTHALIDEISOQUINOLINE ALKALOID CORDRASTINE

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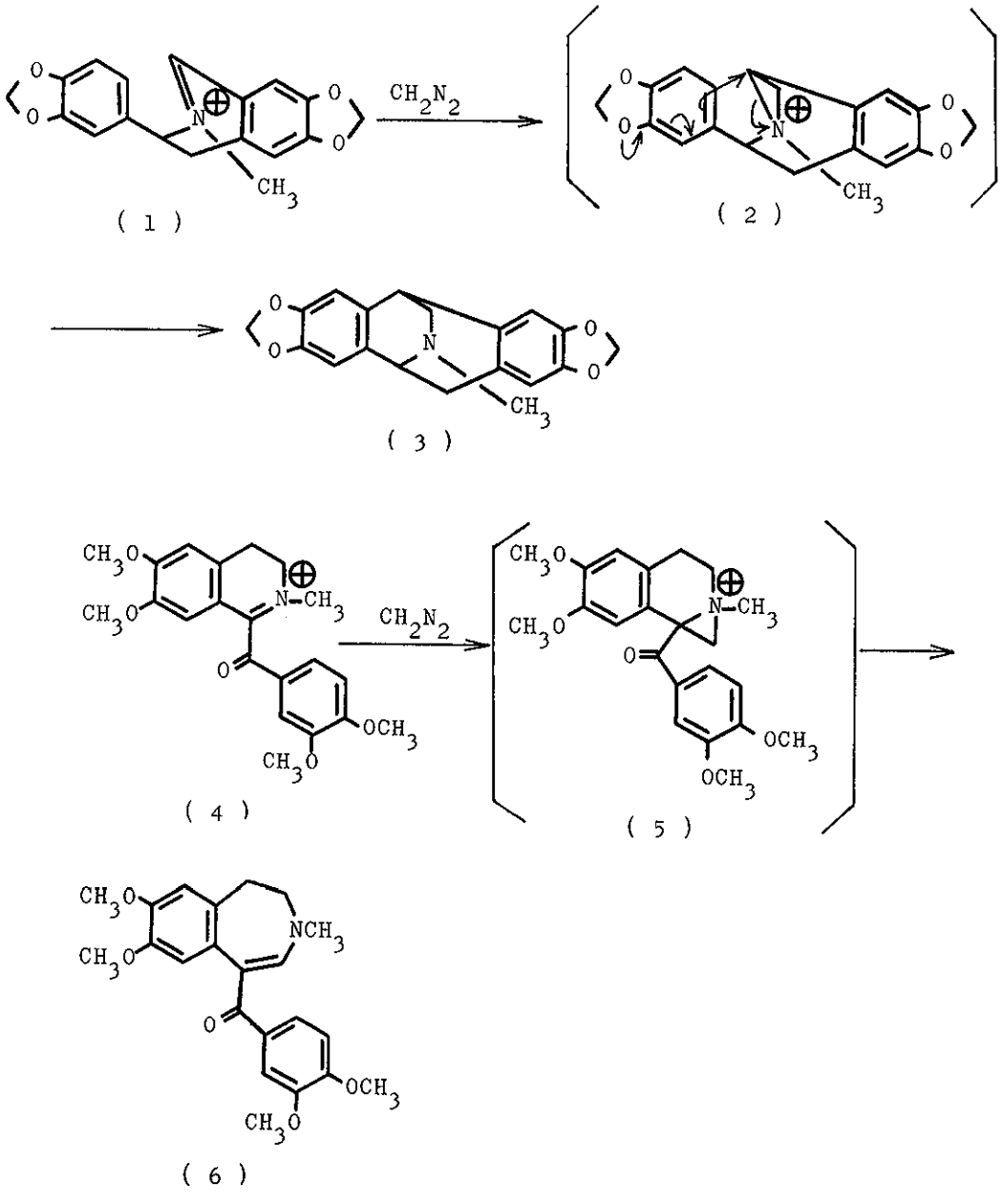
Cordrastine (11a) was synthesised by condensation of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium salt (7) with methyl 6-diazomethyl-2,3-dimethoxybenzoate (8a) derived from 6,7-dimethoxyphthalimidine (20a). Reaction of 7 with methyl 2-diazomethyl-4,5-dimethoxybenzoate (8b) gave the cordrastine isomer (11b).

It has been well known that aziridines and their quaternary salts[1] are easily attacked by nucleophiles[2] or electrophiles[3] with formation of ring opened amines, and this type of reaction has been applied to a total synthesis of ibogamine and related alkaloids.[3] Moreover, an aziridine system is assumed as an intermediate in the formation of a variety of heterocyclic compounds.[4]

We have reported the synthesis of isopavine (3)[5] and benzazepine (6) systems[6] by a ring expansion reaction of the 3,4-dihydro-2-methylisoquinolinium salts 1 and 4 with diazomethane through the aziridinium salts 2 and 5. As an extension of this work, we have investigated a reaction of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium salt

Chart 1

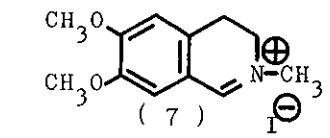


(7) with the α-diazotoluene-2-carboxylates 8 in order to get the rheadans 10 or phthalideisoquinolines 11. We here wish to report a one step synthesis of cordrastine (11a) by this reaction.

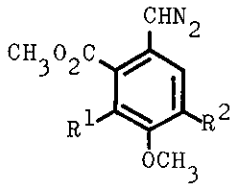
The synthetic route is summarised in Chart 2. Thus, it is possible that the intramolecular nucleophilic attack of the carboxylate group on the aziridinium system (9) could take place by route A or route B, leading to the formation of oxyalpinigenine (10a), which had been already converted into alpinine (12) by Manske,[7] or cordrastine (11a). We have consequently investigated the synthesis of the α-diazotoluenes 8 and their reaction with the 3,4-dihydroisoquinolinium salt 7.

Ethyl 6-bromoveratrate (18b) was treated with cuprous cyanide in refluxing dimethylformamide for 4 hr to give the corresponding nitrile (19b) [m.p. 118 - 119°; νmax ($CHCl_3$) 2220 and 1720 cm^{-1}; δ ($CDCl_3$) 7.06 and 7.42 (each 1H, s, ArH)], which was reduced on Raney nickel in ethanol at 80° under 80 atm of hydrogen to afford 5,6-dimethoxyphthalimidine (20b) [m.p. 229 - 231°; νmax ($CHCl_3$) 3450 and 1680 cm^{-1}; δ ($CDCl_3$) 3.88 (2H, s, CH_2), 3.90 (6H, s, 2 x OCH_3), 6.91 (1H, s, ArH) and 7.53 (1H, s, ArH)]. Treatment of this product with sodium nitrite in concentrated hydrochloric acid at room temperature gave the N-nitrosophtalimidine 21b [m.p. 128 - 129°; δ ($CDCl_3$) 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), and 3.96 (2H, s, OCH_3)], which was treated with 5 N sodium methoxide in methanol by Oppé's method[8] to form the unstable α-diazotoluene 8b [νmax ($CHCl_3$) 2060 and 1705 cm^{-1}]. The α-diazotoluene 8b in ethereal solution was added to the 3,4-dihydro-2-methylisoquinolinium iodide (7) in methanol-chloroform solution (v/v 1 : 1) and the mixture was allowed to stand at room temperature for 2 days

Chart 2

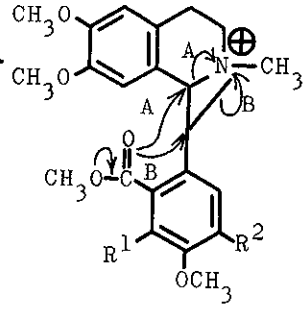


(7)



(8) a R^1=OCH_3, R^2=H

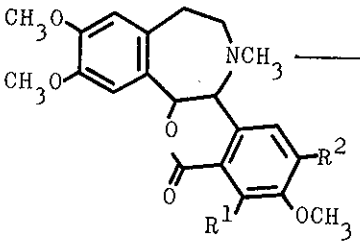
b R^1=H, R^2=OCH_3



(9)

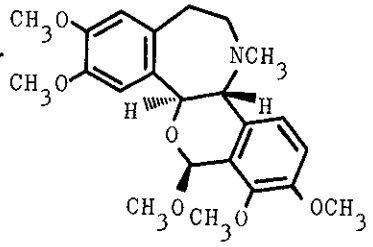
A

B

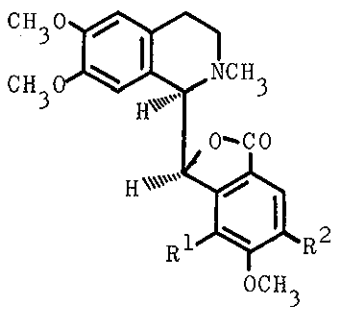


(10) a R^1=OCH_3, R^2=H

b R^1=H, R^2=OCH_3



(12)

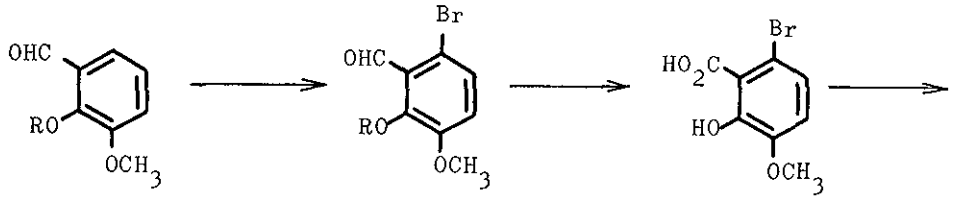


(11) a R^1=OCH_3, R^2=H

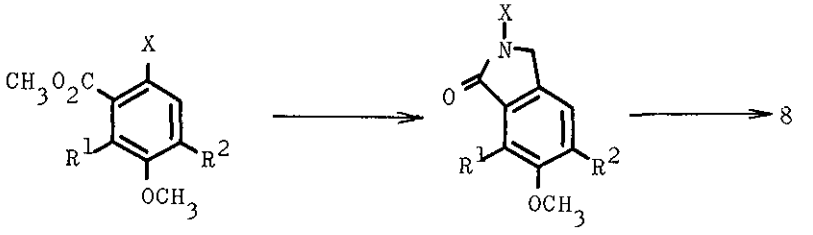
b R^1=H, R^2=OCH_3

to give the phthalideisoquinoline (11b)[9] in 10 % yield after purification on silica gel column chromatography. No rheadan type com-

Chart 3



(13) R=H
(14) R=CO_2CH_3
(15) R=CO_2CH_3
(16) R=H
(17)



(18) a R^1=OCH_3, R^2=H, X=Br
b R^1=H, R^2=OCH_3, X=Br
(19) a R^1=OCH_3, R^2=H, X=CN
b R^1=H, R^2=OCH_3, X=CN
(20) a R^1=OCH_3, R^2=X=H
b R^1=X=H, R^2=OCH_3
(21) a R^1=OCH_3, R^2=H, X=NO
b R^1=H, R^2=OCH_3, X=NO

pound (10b) could be detected. The structure of 11b was determined by i.r. [ν max ($CHCl_3$) 1755 - 1750 cm^{-1}] and n.m.r. [δ ($CDCl_3$) 2.58 (3H, s, NCH_3), 3.73, 3.78, 3.86, and 3.92 (each 3H, s, 4 x OCH_3), 4.07 (1H, d, $\underline{J}$ 4 Hz, C_1-H), 5.56 (1H, d, $\underline{J}$ 4 Hz, C_9-H), 6.18, 6.48,

6.62, and 7.25 (each 1H, s, 4 x ArH) spectra, which were superimposable upon those of an authentic sample.[10]

This method was applied to a total synthesis of cordrastine (11a) as follows. Methoxycarbonylation of orthovanillin (13) with methyl chlorocarbonate and triethylamine in benzene gave the nonphenolic aldehyde (14) [b.p. 150°/5 mm; ν max ($CHCl_3$) 1760 and 1690 cm^{-1}], which was converted into O-methoxycarbonyl-6-bromoorthovanillin (15) [m.p. 120 - 122°; ν max ($CHCl_3$) 1760 and 1690 cm^{-1}; δ ($CDCl_3$) 7.07 and 7.47 (each 1H, d, J 8 Hz)] with bromine in the presence of iron and sodium acetate in acetic acid at room temperature. Hydrolysis with sodium hydroxide in boiling aqueous methanol afforded 6-bromo-orthovanillin (16) [m.p. 93 - 95°; ν max ($CHCl_3$) 1635 cm^{-1}; δ ($CDCl_3$) 6.88 and 7.08 (each 1H, d, J 9 Hz)], whose oxidation with silver oxide and sodium hydroxide, followed by methylation with diazomethane, gave methyl 6-bromo-2,3-dimethoxybenzoate (18a) as a viscous oil [ν max ($CHCl_3$) 1725 cm^{-1}; δ ($CDCl_3$) 3.82 (6H, s, 2 x OCH_3) 3.91 (3H, s, OCH_3), 6.79 and 7.15 (each 1H, d, J 9 Hz)]. Cyanation of this bromide with cuprous cyanide, followed by the catalytic reduction of the resulting nitrile (19a) [m.p. 137 - 140°; ν max ($CHCl_3$) 2230 and 1715 cm^{-1}; δ ($CDCl_3$), 3.88, 3.94 and 3.97 (each 3H, s, OCH_3), 6.97 and 7.39 (each 1H, d, J 9 Hz, ArH)] with hydrogen and Raney nickel as above, afforded 6,7-dimethoxyphthalimidine (20a) [m.p. 140 - 141°]. N-Nitrosation of 20a with sodium nitrite and concentrated hydrochloric acid as expected provided 21a [m.p. 145 - 147°], which was treated with sodium methoxide by Oppé's method[8] to yield the α-diazotoluene (8a) [ν max ($CHCl_3$) 2055 and 1715 cm^{-1}]. The condensation of this diazo compound with 3,4-dihydro-2-methylisoquinolinium iodide (7) gave in 5 - 10% yield cordras-

tine (11a), which was characterised as the picrate, m.p. 198 - 199° [lit.,[11] m.p. 202°]. The i.r. [ν max ($CHCl_3$) 1750 cm^{-1}] and n.m.r. spectra [δ ($CDCl_3$) 2.57 (3H, s, NCH_3)], 3.36, 3.85, 3.87, and 4.03 (each 3H, s, OCH_3), 5.57 (1H, d, J 4 Hz, ArCH-O-; the higher field of this doublet was obscured by other resonances), 6.29 and 6.58 (each 1H, s, ArH), 6.52 and 7.06 (each 1H, d, J 8 Hz, ArH)] of the free base were identical with those of an authentic sample. No oxyalpinigenine (10a) could be detected.

The mechanism for the formation of this type of phthalideisoquinoline would proceed *via* the aziridinium salt (9) from the 3,4-dihydro-2-methylisoquinolinium salt and α-diazotoluene by route B as shown in Chart 2, since the isolation of azirino[2,3-a]isoquinoline methiodide and a formation of benzazepines from hydrastinine and diazoalkanes have been reported.[12,13]

A one step synthesis of cordrastine (11a) from readily available simple isoquinolines has therefore been achieved, thus providing the fourth synthetic route[10] to the phthalideisoquinolines.

ACKNOWLEDGEMENT We thank Dr. S. Teitel, Hoffmann-La Roche Inc., Nutley, New Jersey, for a gift of natural cordrastine hydrochloride.

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Received, 1st October, 1975