Further Studies on the Synthesis and Biosynthesis of Isothebaine

By A. R. BATTERSBY,* T. J. BROCKSOM, and R. RAMAGE
(*The Robert Robinson Laboratories, University of Liverpool, Liverpool* L69 3BX)

PREVIOUS work[1,2] has shown the intermediacy of orientaline (1) and orientalinone (2 or 2a) for the biosynthesis of isothebaine (3) in *Papaver orientale*. It was suggested[3] that the final stages involve reduction of orientalinone to a dienol (see 4) followed by dienol–benzene rearrangement to generate isothebaine (3). Tests of this hypothesis *in vivo* and *in vitro* are now outlined.

The yield of orientalinone (2 or 2a) from ferricyanide oxidation of orientaline[4]† has been increased to 20% and iso-orientalinone (2a or 2) is also formed (1%); the latter was isolated as a 1 : 1 mixture with orientalinone. Further enrichment of iso-orientalinone has not been possible, but the n.m.r. spectra of the two dienones differ, so clear assignment can be made of that from the iso-form. Mild reduction of orientalinone with lithium aluminium hydride‡ gave crystalline orientalinol-I and orientalinol-II (see 4)

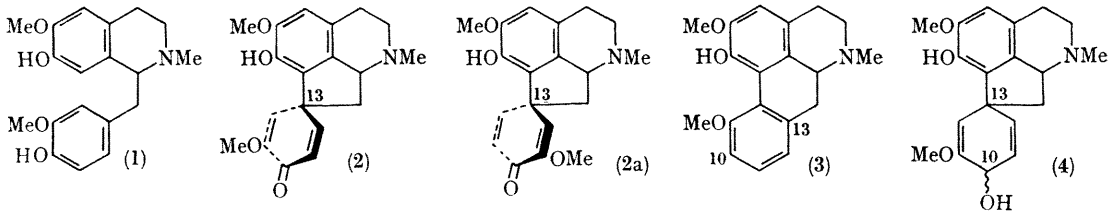
TABLE

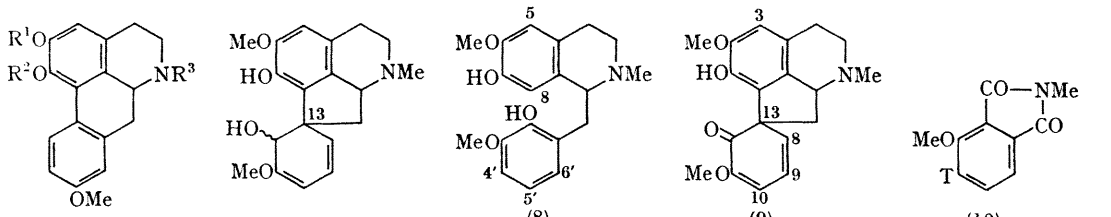
Expt. No.	Precursor	^3H:^{14}C Ratio (precursor)	Incorp. %	^3H:^{14}C Ratio (isothebaine)	^3H Retention at C-10(%)
1	[N-*methyl*-^{3}H,3-^{14}C]Orientaline (1)	1·54	0·59	1·54	
2	[N-*methyl*-^{3}H,10-^{3}H]Orientalinol-I (4)		2·1		76
3	[N-*methyl*-^{3}H,10-^{3}H]Orientalinol-II (4)		0·34		<1
4	[3,8,9,10-^{3}H]ortho-Orientalinols (7)		<0·001		

† All substances described are racemic, save natural isothebaine, and are fully characterised by spectroscopic and analytical data.
‡ Borohydride reduction[4] of orientalinone is now known to give largely the dihydro-derivative of (4).

which differ in configuration at C-10. Both are transformed almost instantaneously by mineral acid into (±)-isothebaine (3) together with a trace of the isomer (5); orientation of (5) was by n.m.r. and no other products were observed. In contrast, the set of dienols from similar reduction of the 1 : 1 mixture of orientalinone and isoorientalinone (2 and 2a) gave, on treatment with acid, equal quantities of (3) and (5). Thus the configuration at C-13 in the proaporphines (2 and 2a) apparently dictates the direction of aryl migration. Isolation of (5) constitutes a simple synthesis of the xylopine (6) system.

At present, the configurations at C-10 and C-13 of orientalinol-I (see 4) are unknown. If the rearrangement of (4) into (3) occurs by a concerted S_N2' process, the favoured steric arrangement of the hydroxy-function and migrating aryl group would be *cis*.[5] However, a similar step in morphine biosynthesis does *not* involve such a *cis*-relationship and prior allylic rearrangement was considered there as one of several explanations.[6] Allylic rearrangement of (4) would yield one of the four possible ortho-orientalinols (see 7) and this system (7) has been prepared for study as follows. Ferricyanide oxidation of the





(5) $R^1=R^3=Me$, $R^2=H$
(6) R^1, $R^2=CH_2$, $R^3=H$

The work *in vivo* established by experiment 1 (see Table) that a ^3H-label at the *N*-methyl group of orientaline is stable over the biological sequence to isothebaine. Rigorous use could then be made of [N-*methyl*-^{3}H,10-^{3}H] orientalinols-I and -II which were prepared as above with insertion of the C-10 label by lithium aluminium tritiide. Feeding experiments 2 and 3 prove that orientalinol-I is the precursor of isothebaine. The small incorporation of orientalinol-II must occur by redox conversion into the I-isomer, as indicated by the total loss of ^3H from C-10 in experiment 3. However, this cannot be an important process in *Papaver orientale*, a conclusion supported by the high retention (76%) of the C-10 label from orientalinol-I. These ^3H-retentions were determined by oxidation of isothebaine and isolation of the product as the phthalimide (10), tritiated as shown.

phenol (8) afforded ortho-orientalinone (9) in 22% yield [ν_{max} 1672, 1640, and 1612 cm.$^{-1}$; expected n.m.r. resonances for methyl groups together with τ 3·48 (1H, s, Ar-H), τ 3·7—4·0 (3H, m, olefinic H); M^+ 327·1476; required 327·1470]. Reduction with lithium aluminium hydride gave two separable dienols (see 7). Repetition of this sequence with [5,8,4',5',6'-^{3}H]diphenol (8) gave the [^{3}H]dienols (as 7) which were not incorporated into isothebaine (3) by *Papaver orientale* plants (experiment 4). It is not yet proved, however, that the configuration at C-13 of (9) corresponds to that of orientalinone and further work on the stereochemistry of the dienols (4) and (7) is in progress.

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