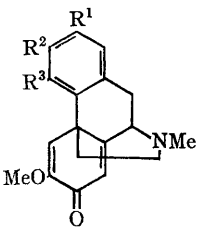
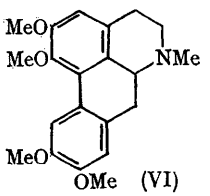
One-step Synthesis of Morphinandienone-type Compounds

By T. KAMETANI,* K. FUKUMOTO, F. SATOH, and H. YAGI

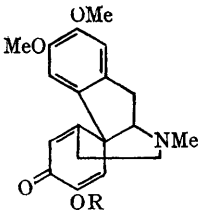
(*Pharmaceutical Institute, School of Medicine, Tohoku University, No. 85, Kitayobancho, Sendai, Japan*)

MANY morphinandienone-type alkaloids, *e.g.* salutaridine (I)[1] or flavinantine (II),[2] have recently been isolated. Salutaridine (I), which has been synthesised by phenolic oxidation of reticuline by Barton and his co-workers and converted chemically into thebaine, is a key precursor to thebaine, codeine and morphine. We report a general approach to the synthesis of morphinandienones and the conversion of 6′-aminolaudanosine (III) into *O*-methylflavinantine (IV).

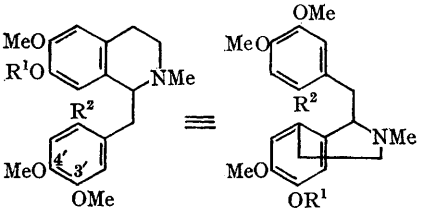




(VI)



(VII) R=Me
(IX) R=Et



(III) R^1=Me, R^2=NH_2
(V) R^1=Me, R^2=H
(VIII) R^1=Et, R^2=NH_2

	R^1	R^2	R^3
(I)	H	OMe	OH
(II)	OMe	OH	H
(IV)	OMe	OMe	H
(X)	—OCH_2O—		H

Aminolaudanosine (III), which was prepared by reduction of 6′-nitrolaudanosine [synthesised from papaverine], was diazotised with a slight excess of sodium nitrite in N-sulphuric acid at 0°, and the resulting diazonium salt was decomposed at 70° for 1 hr.[4] Careful silica gel chromatography with chloroform–methanol (98 : 2) as eluant afforded the cyclohexadienone in addition to the deamination product (V) and glaucine (VI), which was obtained by Gadamer[5] and Kametani and Noguchi,[6] independently, by catalytic decomposition of diazonium salt in the presence of copper or zinc. Further purification of the cyclohexadienone by alumina chromatography with benzene–chloroform (85 : 15) as eluant gave a pale yellow glass (1·4—2%), which was characterised as its methiodide, m.p. 222—223° (decomp.), ν_{max} (KBr) 1669, 1647, 1626, and 1518 cm.$^{-1}$, λ_{max} (in MeOH) 238sh and 284 mμ. The structure of this product was confirmed by the following evidence.

Mass spectrometry of the free base (M^+ : m/e 341) and microanalysis of the methiodide verified the molecular formula, $C_{20}H_{23}NO_4$, and it showed ν_{max} ($CHCl_3$) 1666, 1642, 1621, and 1508 cm.$^{-1}$ λ_{max} (MeOH) 238 and 282 mμ (log ϵ 4·13 and 3·81), which supports a cross-conjugated cyclohexadienone system. The n.m.r. spectrum ($CDCl_3$) showed the methyl resonances at τ 7·58 (s, NMe), 6·23 (s, olefinic OMe), and 6·17 and 6·15 (s, aromatic OMe), olefinic protons at 3·18 (s, 8-H) and 3·73 (s, 5-H), and the other aromatic protons at 3·53 and 3·40. These spectral data agree with either of two structures (IV and VII), but the structure (VII) was ruled out by the following evidence.

1-(2-Amino-4,5-dimethoxybenzyl)-7-ethoxy-1,2,-3,4-tetrahydro-6-methoxy-2-methylisoquinoline (VIII) was also diazotised to give the cyclohexadienone (IV) (1·4%), whose n.m.r. spectrum showed three methoxy-signals and no signal due to the ethyl group. If the structure of the cyclohexadienone from the first aminoisoquinoline (III) were (VII), diazotisation of the second aminoisoquinoline (VIII) would give a different product (IX). However, both products obtained by diazotisation of the two aminoisoquinolines (III and VIII) were proved to be identical by full i.r., u.v., and n.m.r. spectroscopic and chromatographic comparison.

These data showed the product to be a morphinandienone-type compound, namely *O*-methylflavinantine (IV), and a simple synthesis of morphinandienone skeleton has been accomplished.

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[5] J. Gadamer, *Arch. Pharm.*, 1911, **249**, 680.
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