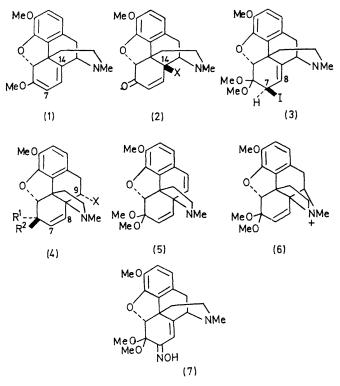# Iodination of Thebaine: a New Route to 9-Substituted Indolinocodeinone Derivatives

By R. M. ALLEN and G. W. KIRBY*

(Chemistry Department, University of Technology, Loughborough, Leicestershire LE11 3TU)

Summary Iodination, unlike chlorination or bromination, of thebaine (1) occurs predominantly at C-7 rather than C-14 to give, in the presence of methanol, 7-iodoneopinone dimethyl acetal (3), a convenient starting material for the synthesis of 9-substituted indolinocodeinone derivatives.

CHLORINATION and bromination of thebaine (1) occurs[1] at C-14 to give the corresponding 14-halogenocodeinones (2). Recently, Bach et al.[2] reported that bromination of thebaine metho-salts gives 7-bromo-derivatives; presumably, an additional substituent on nitrogen hinders approach of the reagent to C-14. We now report that iodination, like nitrosation,[3] of thebaine occurs, apparently exclusively, at C-7. Thebaine reacted at room temperature with an excess of iodine in chloroform–methanol (9:1) to give (75% yield) the light-sensitive iodo-compound (3), m.p. 144—147°. The protons at C-7 and C-8 gave an AB quartet (τ 5·31, 4·27) with a splitting (J 6·3 Hz) suggesting a β-configuration (steroid convention) for the iodine. One methoxy-group gave the high field (τ 7·06) singlet expected[3,4] of a 6-acetal function. Formation of (3) was accelerated by addition of silver nitrite or nitrate. Treatment of (3) with silver

acetate in acetic acid caused rearrangement with displacement of iodide to yield (33%) the indolinocodeine derivative (4; $R^1=R^2=MeO$, X=OAc), m.p. 124—125°. The structure (4; $R^1=R^2=MeO$, X=OAc) was shown by the appearance of triplet (τ 4·84, J 2·7 Hz) for 9-H and the quantitative formation of an enone (4; $R^1=R^2=O$, X=OAc), τ 3·30 (d, J 11 Hz, 8-H), 3·82 (d, J 11 Hz, 7-H), and 4·78 (dd, J 2·2 and 3·5 Hz, 9-H), on hydrolysis with cold, dilute hydrochloric acid. Reduction of this ketone with sodium borohydride followed by hydrolysis with alkali gave the known[5] diol (4; $R^1=OH$, $R^2=H$, X=OH). Similarly, (3) reacted in anhydrous acetone with silver cyanide to form the isonitrile (4; $R^1=R^2=MeO$, X=NC) [ν_{max} (CCl_3) 2140 cm^{-1}]. Hydrolysis with dilute hydrochloric acid gave the formamido-derivative (4; $R^1R^2=O$, X=NHCHO). Sodium azide in aqueous dimethylformamide converted (3) into a mixture of azido-derivatives one of which (4; $R^1=R^2=MeO$, X=N$_3$) (59% yield), after successive reduction with lithium aluminium hydride and treatment with formic acid and acetic anhydride, gave the same formamido-derivative (4; $R^1R^2=O$, X=NHCHO). In contrast, sodium methoxide in methanol converted (3) into the styrene (5) which was hydrolysed by acid to the corresponding enone.

Indolinocodeinone derivatives, having oxygen substituents at C-9, had previously been prepared[5] by the solvolysis of 14-bromocodeine, and indolinocodeine itself by solvolysis in the presence of sodium borohydride. Probably, the silver-catalysed rearrangement of (3) involves an aziridinium intermediate (6), analogous to that postulated by the Japanese workers, which is attacked, with inversion at C-9, by the appropriate anion. The α-configuration for the 9-substituent is supported by the n.m.r data.

Examples are now available of electrophilic attack on thebaine predominantly either at C-14 or C-7, there being no obvious correlation between the nature of the electrophile and the site of the attack. Thus, thebaine reacts[3] with nitrosyl chloride in methanol to give the 7-oximino-derivative (7) but with methanolic tetranitromethane the dimethyl acetal of 14-nitrocodeinone, hydrolysable to the parent ketone (2; X=NO$_2$), m.p. 172·5—173°, is formed. However, oxidation of 14-hydroxyaminocodeinone (2; X=NHOH) with periodic acid yields[6] the oximino-ketone corresponding to (7) rather than 14-nitrosocodeinone (2; X=NO). Possibly, nitrosation of thebaine can occur at C-14 but the product is unstable relative to the 7-oximino-derivative. Similarly, iodination of thebaine may occur at C-14, the product then undergoing an S_N2' reaction involving attack by iodide at C-7 to form the observed product (3).

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[5] S. Okuda, K. Abe, and M. Onda, Chem. and Pharm. Bull. (Japan), 1968, 16, 1124, and references cited.
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