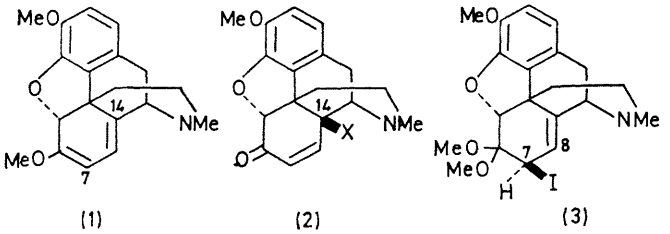
Iodination of Thebaine: a New Route to 9-Substituted Indolinocodeinone Derivatives

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

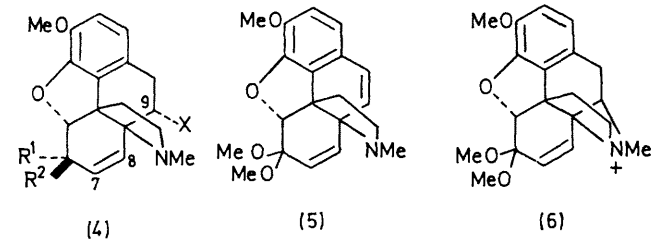
(*Chemistry Department, University of Technology, Loughborough, Leicestershire* LE11 3TU)

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.

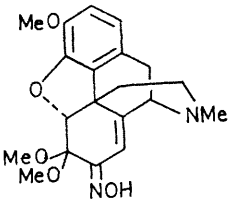
CHLORINATION and bromination of thebaine (**1**) occurs[1] at C-14 to give the corresponding 14-halogenocodeinones (**2**). Recently, Bach *et al.*[2] reported that bromination of thebaine metho-salts gives 7-bromo-derivatives; presumably, an additional substituent on nitrogen hinders approach of the 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.



(1) (2) (3)



(4) (5) (6)



(7)

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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