Iodination of Thebaine and Synthesis of 9-Substituted Indolinocodeinone Derivatives

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Iodination of thebaine in methanol, with or without silver salt catalysis, gives, in good yield, 7β-iodoneopinone dimethyl acetal, which reacts with a wide variety of nucleophiles to provide indolinocodeinone derivatives carrying the following 9α-substituents: OH, OMe, ONO, OAc, NC, N_3, NMe_2, CN, and SCN. 9,10-Didehydroindolinocodeinone dimethyl acetal and 9α-chloroindolinocodeinone have also been prepared. Treatment of the iodoacetal or 14-bromocodeinone dimethyl acetal with silver perchlorate in benzene gave an aziridinium salt believed to be an intermediate in the solvolytic rearrangement reactions of both halogeno-acetals.

BROMINATION or chlorination of thebaine (1) occurs with attack at C-14 to give,[1] in aqueous systems, the 14-halogenocodeinones (2; X = Br or Cl). Also, bromination in methanol gives [2,3] the acetal (3; X = Br). In contrast, we have found [4] that iodination in the presence of methanol, preferably with silver salt catalysis, affords 7β-iodoneopinone dimethyl acetal (4) in high yield. This derivative serves as a convenient starting material for the preparation of 9-substituted indolinocodeinone derivatives (5).

Treatment of thebaine (1), in chloroform–methanol, with iodine in the presence of silver nitrite [5] gave (75%) the iodo-compound (4). The same product was formed in the presence of silver acetate and, more slowly, in the absence of any silver salt. Thebaine reacted only slowly with *N*-iodosuccinimide in methanol to afford compound (4) in low yield. The n.m.r. spectrum of (4) showed signals (d, τ 4·27) for only one olefinic proton coupled to the neighbouring proton (d, τ 5·31) on C-7. The coupling constant (*J* 6·3 Hz) established [6] the β-configuration (steroid notation) for the iodo-substituent. One methoxy-group gave the high-field singlet (τ 7·06) expected [7] for a 6-acetal function; the proton at C-5 gave a singlet, τ 4·73. The iodo-compound (4) reacted with silver acetate in acetic acid to yield (33%) 9α-acetoxyindolinocodeinone dimethyl acetal (5; R = MeO, X = OAc). That substitution had occurred with rearrangement was shown most clearly by the appearance of an n.m.r. signal (t, *J* 2·7 Hz, τ 4·84) for a proton (9-H) attached to the carbon atom carrying the newly-introduced acetoxy-group. Furthermore, hydrolysis with cold dilute hydrochloric acid gave an enone (5; RR = O, X = OAc), $\nu_{max.}$ 1724 and 1702 cm^{-1}, 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). A minor product of the substitution reaction, arising perhaps from a silver-assisted, S_N2' process, was identified as the codeinone derivative (3; X = OAc) by hydrolysis with acid to yield the known [8] 14-acetoxycodeinone (2; X = OAc). The conversion of the iodo-compound (4) into the acetate (5; R = MeO, X = OAc) was effected in better yield (52%) with sodium acetate in aqueous dimethylformamide. Hydrolysis of the acetoxy-enone (5; RR = O, X = OAc) with alkali gave ill-defined products arising, perhaps, from vinylogous, retro-aldol cleavage

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[1] K. W. Bentley, 'The Chemistry of the Morphine Alkaloids,' Clarendon Press, Oxford, 1954, p. 188; H. Conroy, *J. Amer. Chem. Soc.*, 1955, **77**, 5960.

[2] W. Fleischhacker, F. Vieböck, and F. Zeidler, *Monatsh.*, 1970, **101**, 1215; *cf.* J.-P. Gavard, F. Krausz, and T. Rüll, *Bull. Soc. chim. France*, 1965, 486.

[3] K. Abe, Y. Nakamura, M. Onda, and S. Okuda, *Tetrahedron*, 1971, **27**, 4495.

[4] R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1970, 1346.

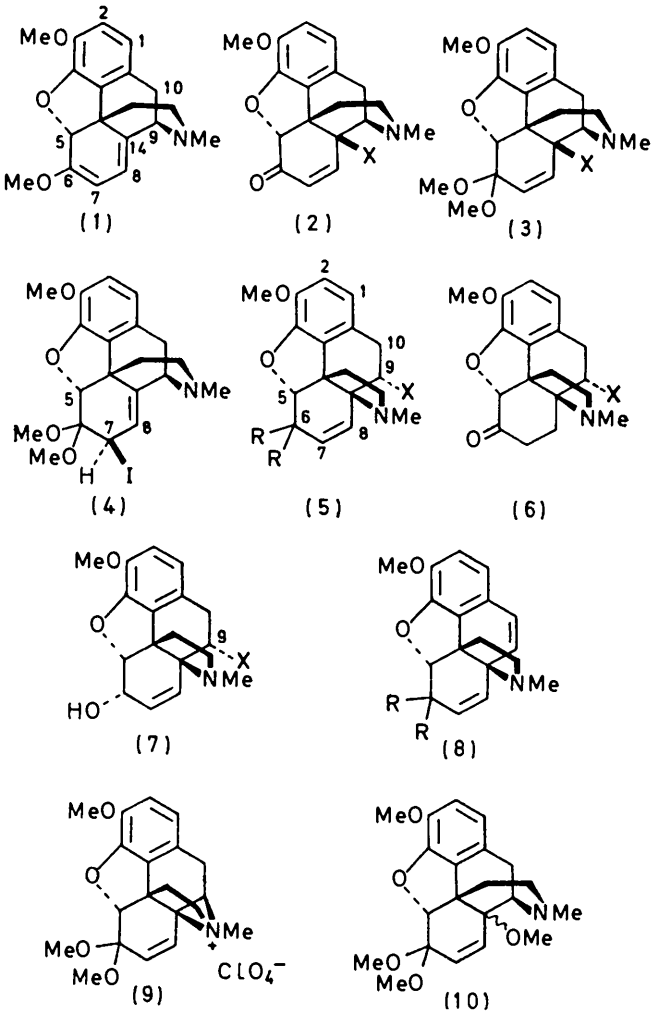
[5] *Cf.* A. Hassner, J. E. Kropp, and G. J. Kent, *J. Org. Chem.*, 1969 **34**, 2628.

[6] *Cf.* W. Fleischhacker, *Monatsh.*, 1971, **102**, 558.

[7] U. Eppenberger, M. E. Warren, and H. Rapoport, *Helv. Chim. Acta*, 1968, **51**, 381; K. W. Bentley, G. W. Kirby, A. P. Price, and Serjinder Singh, *J.C.S. Perkin I*, 1972, 302.

[8] Ref. 1, p. 259.

of the first-formed hydroxy-enone (5; RR = O, X = OH). However, the acetoxy-acetal (5; R = MeO, X = OAc) was hydrolysed quantitatively with alkali to



give the hydroxy-acetal (5; R = MeO, X = OH) which, with acid, gave the hydroxy-enone (5; RR = O, X = OH). Acetylation of this derivative then afforded the acetoxy-enone (5; RR = O, X = OAc), identical with material obtained directly (see before) from the corresponding acetal. Catalytic hydrogenation of the acetoxy-enone (5; RR = O, X = OAc) and the hydroxy-enone (5; RR = O, X = OH) gave the corresponding 7,8-dihydro-derivatives (6). The dihydro-derivative (6; X = OAc), unlike the parent enone (5; RR = O, X = OAc), was hydrolysed cleanly by alkali to give the alcohol (6; X = OH).

Indolinocodeine derivatives were first prepared by Okuda *et al.* during their studies on the formation and solvolysis of 14-bromocodeine. Reduction of 14-bromocodeinone (2; X = Br) with sodium borohydride gave,[9] *inter alia*, indolinocodeine (7; X = H); hydrolysis and acetolysis of 14-bromocodeine gave respectively the 9-hydroxy- (7; X = OH) and 9-acetoxy- (7; X = OAc) derivatives.[10] The structure of these rearranged products was established thoroughly by degradation. We related the structures of our products to those of the Japanese workers as follows. Reduction of the acetoxy-enone (5; RR = O, X = OAc) with sodium borohydride and hydrolysis of the product with alkali gave 9α-hydroxyindolinocodeine (7; X = OH) having physical properties agreeing well with those reported.[10] The same compound was obtained by reduction of the hydroxy-enone (5; RR = O, X = OH). The Japanese workers assigned the α-configuration to substituents at C-9 in structure (7) on the basis of i.r. and n.m.r. data. The n.m.r. arguments apply equally well to compounds (5) in our own series;* in particular, the 9α-configuration is characterised by two small (2—4 Hz) values for $J_{9.10}$ and, in the acetoxy-acetal (5; R = MeO, X = OAc), the axial acetate methyl group absorbs at high field (τ 8·24), presumably because of shielding by the aromatic ring.

Prolonged treatment of the iodo-compound (4) with sodium methoxide in methanol at room temperature gave the rearranged elimination product (8; R = MeO) as the major component (25%) of a mixture. Hydrolysis of this acetal with acid gave the corresponding enone (8; RR = O). The n.m.r. spectra of both styrenes revealed signals, with appropriate coupling constants, from four olefinic protons, thus showing that elimination had occurred with migration of nitrogen. The acetal (8; R = MeO) was also obtained (26%) from the iodo-compound (4) by treatment with sodamide in dimethylformamide. More recently, Reusser and Vieböck [11] have obtained the same styrenes (8) from the reaction of 14-bromocodeinone dimethyl acetal (3; X = Br) with methanolic potassium hydroxide.

The iodo-compound (4) reacted with sodium cyanide in aqueous dimethylformamide to give (56%) the cyano-acetal (5; R = MeO, X = CN), $\nu_{max.}$ 2238 cm^{-1}, together with smaller amounts of the styrene (8; R = MeO). When the reaction was carried out in the presence of deuterium oxide no deuterium entered the product (5; R = MeO, X = CN). Thus the α-cyano-acetal was formed directly and not *via* base-catalysed epimerisation of a 9β-cyano-intermediate. Hydrolysis of the acetal in the usual way gave the enone (5; RR = O, X = CN). Treatment of compound (4) with silver cyanide in acetone yielded the isonitrile (5; R = MeO, X = NC), $\nu_{max.}$ 2140 cm^{-1}, as the major product (28%). This, with hydrochloric acid, gave the formamido-enone (5; RR = O, X = NH·CHO) together with a small quantity of the methoxy-compound (5; RR = O, X = OMe) (see later). Nucleophilic attack on the iodo-compound (4) by sodium azide in aqueous dimethylformamide gave (59%) the expected 9α-azido-acetal (5; R = MeO, X = N_3), $\nu_{max.}$

* N.m.r. data for compounds (2)—(9) are available as Supplementary Publication No. SUP 20614 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[9] S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1092.

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

[11] W. Reusser and F. Vieböck, *Monatsh.*, 1971, **102**, 1101.

2105 cm^{-1}, and, as a minor product (15%), 7β-azidoneopinone dimethyl acetal (4; N_3 in place of I). Substitution at C-7 with retention of configuration may involve S_N2' attack on an aziridinium intermediate (see later). The 9-azido-acetal was converted with acid into the enone (5; RR = O, X = N_3) and with lithium aluminium hydride into the amino-acetal (5; R = MeO, X = NH_2). Treatment of the latter with formic acid and acetic anhydride gave the formamido-enone (5; RR = O, X = NH·CHO) obtained earlier from the isonitrile (5; R = MeO, X = NC). Reduction of the azido-enone (5; RR = O, X = N_3) with sodium borohydride gave the azido-alcohol (7; X = N_3) which was, in turn, reduced with lithium aluminium hydride to the amino-alcohol (7; X = NH_2). Various acyl derivatives of the latter were prepared (see Experimental section).

Other substitution reactions of the iodo-compound (4) were briefly investigated. Prolonged heating in methanol gave a mixture from which the 9-methoxy-acetal (5; R = X = MeO) was isolated in low yield. Treatment with potassium thiocyanate in aqueous dimethylformamide gave the thiocyanate (5; R = MeO, X = SCN), $\nu_{max.}$ 2145 cm^{-1}, and silver nitrite in acetone afforded the nitrite (5; R = MeO, X = ONO) heavily contaminated with the corresponding alcohol (5; R = MeO, X = OH). Finally, treatment of (4) with dimethylamine in dimethylformamide gave the amine (5; R = MeO, X = NMe_2).

Earlier workers suggested [3,10] that solvolysis of the 14-bromocodeine proceeds, at least in part, *via* an aziridinium ion intermediate. This suggestion rested solely on the isolation of products resulting, formally, from a 1,2-migration of nitrogen. We sought [12] more direct evidence for an intermediate of this type. Treatment [13] of the iodo-compound (4) in benzene with silver perchlorate (1 equiv.) at room temperature caused an immediate precipitation of silver iodide. Filtration and evaporation of the filtrate gave the amorphous aziridinium perchlorate (9). The n.m.r. spectrum showed bands for 8-H [τ 3·58 (d, *J* 10·5 Hz)] and the *N*-methyl group [τ 6·60(s)] at unusually low field, indicating [13,14] the presence of positively charged nitrogen. Moreover the same salt (n.m.r. comparison) was obtained by the same method from 14-bromocodeinone dimethyl acetal (3; X = Br). This aziridinium salt, in dimethylformamide, reacted, separately, with sodium acetate and sodium cyanide to yield the products (5; R = MeO, X = OAc) and (5; R = MeO, X = CN) obtainable directly from the iodo-compound (4) with the same reagents. If the aziridinium ion (9) is an obligatory intermediate, then solvolysis of the halides (3; X = Br) and (4) under well-defined conditions should give rearrangement products in the same yield. Heinisch *et al.* reported [15] that the bromo-compound (3; X = Br) was converted, in methanol containing sodium carbonate, into a methoxy-derivative [formulated as (10)] (23% yield). We have confirmed this result and obtained the same derivative (27%) from the iodo-compound (4) under these conditions. However the product was quickly recognised * as the rearranged ether (5; R = X = MeO) obtained (see before) from methanolysis of the iodo-compound (4) in the absence of base. Substitution at C-9 in indolinocodeinone derivatives may also involve an aziridinium ion. Treatment of the hydroxy-enone (5; RR = O, X = OH) with methanesulphonyl chloride in pyridine gave the chloro-compound (5; RR = O, X = Cl). The α-configuration for chlorine was established from the n.m.r. spectrum, which displayed the expected double doublet, τ 5·68 (*J* 2·7 and 3·3 Hz), for 9β-H. Substitution with overall retention of configuration is understandable if an intermediate methanesulphonate [16] (5: RR = O, X = O·O_2SMe) collapses to an aziridinium ion which is attacked by chloride ion, with inversion, at C-9. Similarly, involvement of the ion (9) may explain the unexpected formation of the enone (5; RR = O, X = OMe) as a by-product from the conversion of (5; R = MeO, X = NC) into (5; RR = O, X = NH·CHO). Protonation of the isonitrile group on carbon, a necessary prelude to hydration, could allow expulsion of hydrogen cyanide and production of (9) which might be attacked, no doubt inefficiently, by methanol liberated from concomitant hydrolysis of the acetal function.

EXPERIMENTAL

M.p.s were measured with a Kofler hot-stage apparatus. Chloroform and deuteriochloroform were used as solvents for i.r. and n.m.r. (60 MHz) spectra, respectively. Grade III neutral alumina was used throughout for column chromatography, and Merck GF_{254} and PF_{254} alumina for t.l.c.

Hydrolysis of 6-Acetal Groups.—Hydrolysis of acetals of the type (5; R = MeO) and (3), to give the corresponding ketones was carried out as follows. The acetal was suspended in water and treated dropwise with 2N-hydrochloric acid, sometimes with brief warming, until a clear solution was obtained. After 1 h at room temperature the mixture was basified with sodium hydrogen carbonate and the ketone (yield generally >90%) extracted with chloroform.

7β-*Iodoneopinone Dimethyl Acetal* (4).—Silver nitrite (1·49 g) and iodine (4·91 g) were stirred vigorously in chloroform (60 ml) and methanol (6 ml) for 0·5 h under dry nitrogen. Thebaine (1·50 g) in chloroform (6 ml) was added and stirring continued for 5 h at room temperature. The mixture was filtered and the filtrate washed successively with aqueous sodium hydrogen sulphite and sodium chloride. The solution was dried ($MgSO_4$), evaporated to small volume, and percolated through alumina to remove

* Professor F. Viebōck has informed us that he and his colleagues have independently adopted the revised constitution (5; R = X = MeO) for this product.

[12] R. M. Allen and G. W. Kirby, *Chem. Comm.*, 1971, 1121.
[13] *Cf.* N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, 1965, **30**, 821.
[14] G. A. Olah and P. J. Szilagyi, *J. Amer. Chem. Soc.*, 1969, **91**, 2949.
[15] G. Heinisch, V. Klintz, and F. Viebōck, *Monatsh.*, 1971, **102**, 530.
[16] *Cf.* K. Abe, Y. Nakamura, M. Onda, and S. Okuda, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 1917; R. S. Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 121.

coloured impurities. Evaporation gave an oil (1·80 g) which eventually crystallised. Later batches crystallised readily when seeded. Recrystallisation from methanol gave the light-sensitive 7β-*iodoneopinone dimethyl acetal*, m.p. 144—147° (Found: C, 51·2; H, 5·7; N, 3·3. $C_{20}H_{24}INO_4$ requires C, 51·2; H, 5·15; N, 3·0%).

9α-*Acetoxyindolinocodeinone Dimethyl Acetal* (5; R = MeO, X = OAc).—7β-Iodoneopinone dimethyl acetal (1·80 g) was stirred in the dark in acetic acid (25 ml) containing silver acetate (0·73 g) for 12 h at room temperature. The mixture was filtered and the filtrate neutralised with aqueous sodium hydrogen carbonate. Extraction with chloroform gave a mixture (1·66 g) which was chromatographed on alumina (100 g). Elution with benzene–chloroform (1 : 1) gave 9α-*acetoxyindolinocodeinone dimethyl acetal* (0·51 g), m.p. 123—124·5° (methanol), $\nu_{max.}$ 1723 cm^{-1} (Found: C, 65·8; H, 6·8; N, 3·5. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·8; N, 3·5%). Further elution yielded a mixture (66 mg) separated on alumina plates developed with benzene–chloroform (1 : 1). The major component (31 mg) was 14β-*acetoxycodeinone dimethyl acetal*, m.p. 184—186° (methanol), $\nu_{max.}$ 1722 cm^{-1} (Found: C, 66·1; H, 6·5; N, 3·5. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·8; N, 3·5%).

Alternatively, the iodo-compound (1·80 g) was treated in dimethylformamide (30 ml) with sodium acetate (1·00 g) in water (5 ml) for 12 h at room temperature. The mixture was diluted with water (150 ml) and the product extracted with ether (2 × 100 ml). The extract was washed with aqueous sodium chloride and dried ($MgSO_4$). Chromatography of the product, as before, gave the 9α-acetoxy-acetal (0·80 g) and no detectable amounts of 14-substituted by-products.

9α-*Acetoxyindolinocodeinone* (5; RR = O, X = OAc).—Prepared from the corresponding acetal, 9α-*acetoxyindolinocodeinone* had m.p. 137—138° (aqueous methanol), $\nu_{max.}$ 1724 and 1702 cm^{-1} (Found: C, 67·5; H, 6·2; N, 3·8. $C_{20}H_{21}NO_5$ requires C, 67·6; H, 6·0; N, 3·9%).

9α-*Hydroxyindolinocodeinone Dimethyl Acetal* (5; R = MeO, X = OH).—The acetoxy-acetal (5; R = MeO, X = OAc) (3·20 g) was hydrolysed in ethanol–water (8 : 1; 45 ml) containing 2N-sodium hydroxide (5 ml) for 12 h at room temperature. 9α-*Hydroxyindolinocodeinone dimethyl acetal* (2·84 g) crystallised from aqueous methanol, m.p. 118·5—119·5°, $\nu_{max.}$ 3490 cm^{-1} (Found: C, 66·55; H, 7·15; N, 3·9. $C_{20}H_{25}NO_5$ requires C, 66·8; H, 7·0; N, 3·9%).

9α-*Hydroxyindolinocodeinone* (5; RR = O, X = OH).—This *hydroxy-enone* formed needles from methanol, m.p. 209—211°, $\nu_{max.}$ 3570 and 1695 cm^{-1} (Found: C, 68·8; H, 6·15; N, 4·6. $C_{18}H_{19}NO_4$ requires C, 69·0; H, 6·1; N, 4·5%).

7,8-*Dihydro*-9α-*hydroxyindolinocodeinone* (6; X = OH).—The hydroxy-enone (5; RR = O, X = OH) (0·30 g) was hydrogenated catalytically (10% Pd–C in methanol) to give the 7,8-dihydro-derivative (0·28 g), m.p. 168—169° (methanol), $\nu_{max.}$ 3360 and 1730 cm^{-1}, *m/e* 315·1475 (M^+; $C_{18}H_{21}NO_4$ requires *M*, 315·1470).

9α-*Acetoxy*-7,8-*dihydroindolinocodeinone* (6; X = OAc).—The acetoxy-enone (5; RR = O, X = OAc) (0·184 g) was hydrogenated (as before) to give the 7,8-dihydro-derivative (0·133 g) as an oil, $\nu_{max.}$ 1735 cm^{-1}, forming a crystalline *picrate* from methanol (Found: C, 53·0; H, 4·75; N, 9·5. $C_{20}H_{23}NO_5,C_6H_3N_3O_7$ requires C, 53·2; H, 4·5; N, 9·55%).

9α-*Hydroxyindolinocodeine* (7; X = OH).—9α-Acetoxyindolinocodeinone (0·10 g) in methanol (6 ml) was treated with sodium borohydride (0·25 g) at 0 °C for 2 h then at room temperature for 2 h. The solvent was evaporated and the residue shaken with 2N-sodium hydroxide (5 ml) for 3 h. The product was extracted with chloroform: evaporation of the solvent gave 9α-hydroxyindolinocodeine (0·073 g), m.p. 185—187° (aqueous acetone) (lit.,[10] 193—195°), $[\alpha]_D$ +158° (*c* 0·332 in EtOH) (lit.,[10] +159°), $\nu_{max.}$ 3575 and 3380 cm^{-1}. The same compound was obtained by reduction of 9α-hydroxyindolinocodeinone with sodium borohydride.

9,10-*Didehydroindolinocodeinone Dimethyl Acetal* (8; R = MeO).—7β-Iodoneopinone dimethyl acetal (1·064 g) was treated with sodium methoxide in methanol at room temperature for 96 h. The chloroform-soluble products were separated on alumina plates developed with benzene–chloroform (1 : 1). 9,10-Didehydroindolinocodeinone dimethyl acetal was obtained as an oil (0·191 g), *m/e* 341·1628 (M^+; $C_{20}H_{23}NO_4$ requires *M*, 341·1627). The same product was obtained in similar yield from the reaction of the iodo-compound (0·94 g) with sodamide (1·00 g) in dimethylformamide (40 ml) at room temperature for 12 h.

9,10-*Didehydroindolinocodeinone* (8; RR = O).—This enone was obtained from the acetal as an oil, $\nu_{max.}$ 1685 and 1573 cm^{-1}, *m/e* 295·1215 (M^+; $C_{18}H_{17}NO_3$ requires *M*, 295·1208).

9α-*Cyanoindolinocodeinone Dimethyl Acetal* (5; R = MeO, X = CN).—The iodo-compound (4) (1·00 g) was treated with sodium cyanide (0·60 g) in aqueous dimethylformamide [see preparation of (5; R = MeO, X = OAc)]. Chromatography of the product (0·56 g) on alumina (40 g) and elution with benzene–chloroform (1 : 1) gave 9α-*cyanoindolinocodeinone dimethyl acetal* (0·44 g), m.p. 157·5—158·5° (methanol), $\nu_{max.}$ 2238 cm^{-1} (Found: C, 69·0; H, 7·0; N, 7·5. $C_{21}H_{24}N_2O_4$ requires C, 68·5; H, 6·6; N, 7·6%). Further elution gave 9,10-didehydroindolinocodeinone dimethyl acetal (0·021 g).

9α-*Cyanoindolinocodeinone* (5; RR = O, X = CN).—Prepared from the acetal, this *cyano-enone* had m.p. 218—220° (methanol), $\nu_{max.}$ 2238 and 1705 cm^{-1} (Found: C, 70·4; H, 5·8; N, 8·7. $C_{19}H_{18}N_2O_3$ requires C, 70·8; H, 5·6; N, 8·7%).

9α-*Isocyanoindolinocodeinone Dimethyl Acetal* (5; R = MeO, X = NC).—7β-Iodoneopinone dimethyl acetal (1·67 g) was stirred with silver cyanide (0·50 g) in dry acetone (40 ml) in the dark for 12 h at room temperature. The mixture was filtered and the filtrate evaporated. The residue was extracted with methanol to give a mixture of products (1·25 g). Chromatography on alumina (85 g) and elution with benzene–chloroform (1 : 1) gave 9α-*isocyanoindolinocodeinone dimethyl acetal* (0·37 g), m.p. 152—153° (methanol), $\nu_{max.}$ 2140 cm^{-1} (Found: C, 68·4; H, 6·5; N, 7·6. $C_{21}H_{24}N_2O_4$ requires C, 68·5; H, 6·6; N, 7·6%).

9α-*Formylaminoindolinocodeinone* (5; RR = O, X = NH·CHO).—The foregoing isocyano-acetal (0·31 g) was hydrolysed with 2N-hydrochloric acid in the usual way to give a mixture (0·31 g). Elution with benzene–chloroform (1 : 1) from alumina (30 g) gave first, 9α-methoxyindolinocodeinone (0·02 g) (see later) and then, 9α-*formylaminoindolinocodeinone* (0·25 g), m.p. 227·5—228° (methanol), $\nu_{max.}$ 3420 and 1705—1680 cm^{-1} (Found: C, 66·9; H, 6·3; N, 8·1. $C_{19}H_{20}N_2O_4$ requires C, 67·0; H, 5·9; N, 8·2%).

9α-*Azidoindolinocodeinone Dimethyl Acetal* (5; R = MeO, X = N_3) *and* 7β-*Azidoneopinone Dimethyl Acetal* (4; N_3 in place of I).—7β-Iodoneopinone dimethyl acetal (1·70 g) was treated, in the usual way, with sodium azide (1·50 g) in

aqueous dimethylformamide to give a crystalline mixture (1·25 g). Chromatography on alumina (100 g) and elution with benzene–chloroform (1 : 1) gave *9α-azidoindolinocodeinone dimethyl acetal* (59%), m.p. 115—116° (methanol), $\nu_{max.}$ 2105 cm^{-1} (Found: C, 62·4; H, 6·3; N, 14·6. $C_{20}H_{24}N_4O_4$ requires C, 62·5; H, 6·3; N, 14·6%). Further elution gave the oily 7β-azidoneopinone dimethyl acetal (15%), $\nu_{max.}$ 2105 cm^{-1}, which formed a crystalline *picrate* from methanol, m.p. 169—170° (Found: C, 51·2; H, 4·8; N, 16·2. $C_{20}H_{24}N_4O_4,C_6H_3N_3O_7$ requires C, 50·9; H, 4·4; N, 16·0%).

9α-Azidoindolinocodeinone (5; RR = O, X = N_3).—This *azido-enone* had m.p. 124—125° (methanol), $\nu_{max.}$ 2100 and 1702 cm^{-1} (Found: C, 63·6; H, 5·5; H, 16·5. $C_{18}H_{18}N_4O_3$ requires C, 63·9; H, 5·4; N, 16·6%).

9α-Aminoindolinocodeinone Dimethyl Acetal (5; R = MeO, X = NH_2).—The foregoing 9α-azido-acetal (0·642 g) in dry ether (20 ml) was added to a suspension of lithium aluminium hydride (0·672 g) in ether (40 ml). The mixture was heated under reflux for 3 h. Work-up in the usual way gave *9α-aminoindolinocodeinone dimethyl acetal* (0·438 g), m.p. 123—124° (ether), $\nu_{max.}$ 3370 and 3300 cm^{-1} (Found: C, 67·1; H, 7·3; N, 7·95. $C_{20}H_{26}N_2O_4$ requires C, 67·0; H, 7·3; N, 7·8%). Treatment [17] of this amine (0·184 g) in formic acid (98%; 10 ml) dropwise with acetic anhydride (4 ml) at 50—55 °C under nitrogen gave 9α-formylaminoindolinocodeinone (5; RR = O, X = NH·CHO) (0·143 g).

9α-Azidoindolinocodeine (7; X = N_3).—The azido-enone (5; RR = O, X = N_3) (0·65 g) was reduced with an excess of sodium borohydride in methanol in the usual way to give *9α-azidoindolinocodeine* (0·55 g), m.p. 171—172° (methanol), $\nu_{max.}$ 3455 and 2100 cm^{-1} (Found: C, 63·6; H, 6·2; N, 16·5. $C_{18}H_{20}N_4O_3$ requires C, 63·5; N, 5·9; N, 16·5%).

9α-Aminoindolinocodeine (7; X = NH_2).—The foregoing azido-compound (1·90 g) was reduced with lithium aluminium hydride (2·10 g) in ether (600 ml) (as before). The oily product (0·823 g) was chromatographed on alumina (80 g). Elution with benzene–chloroform (1 : 3) gave *9α-aminoindolinocodeine* (0·538 g), m.p. 232—234° (methanol) (Found: C, 68·8; H, 7·2; N, 8·9. $C_{18}H_{22}N_2O_3$ requires C, 68·8; H, 7·05; N, 8·9%).

Acyl Derivatives of 9α-Aminoindolinocodeine (7; X = NH_2).—The amine was acetylated with acetic anhydride in pyridine at room temperature overnight and the crude product hydrolysed with 2N-sodium hydroxide in aqueous ethanol at room temperature to give *9α-acetylaminoindolinocodeine*, m.p. 241—242° (methanol), $\nu_{max.}$ 3340, 1660, and 1540 cm^{-1} (Found: C, 67·2; H, 7·0; N, 7·8. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8; N, 7·9%). Acetylation in pyridine under reflux for 3 h without subsequent hydrolysis gave 9α-acetylaminoindolinocodeine acetate as an oil, $\nu_{max.}$ 3420, 1748, 1668, and 1535 cm^{-1}, *m/e* 398·1841 (M^+; $C_{22}H_{26}N_2O_5$ requires *M*, 398·1842). Treatment of the amine with an excess of methyl chloroformate in methanol at room temperature afforded the oily 9α-methoxycarbonylaminoindolinocodeine, $\nu_{max.}$ 3340, 1708, and 1530 cm^{-1}, which formed a crystalline *picrate* from methanol, m.p. 207—210° (Found: C, 51·7; H, 4·8; N, 11·9. $C_{20}H_{24}N_2O_5,C_6H_3N_3O_7$ requires C, 51·9; H, 4·5; N, 11·6%).

9α-Methoxyindolinocodeinone Dimethyl Acetal (5; R = X = MeO).—7β-Iodoneopinone dimethyl acetal (0·925 g) was heated under reflux in methanol (40 ml) for 8 h. The product mixture (0·835 g) was chromatographed on alumina (100 g). Elution with benzene–chloroform (1 : 1) gave *9α-methoxyindolinocodeinone dimethyl acetal* (0·032 g), m.p. 104—104·5° (methanol) (Found: C, 67·45; H, 7·0; N, 4·1. $C_{21}H_{27}NO_5$ requires C, 67·5; H, 7·3; N, 3·75%).

Alternatively,[15] the iodo-compound (1·45 g) was heated under reflux for 12 h in methanol (50 ml) containing sodium carbonate (previously heated at 150 °C for 2 h; 164 mg). The products were separated after treatment [15] with methyl iodide. The 9α-methoxy-acetal was obtained in 27% yield. Similarly, 14-bromocodeinone dimethyl acetal gave the same product (21%).

9α-Methoxyindolinocodeinone (5; RR = O, X = OMe).—This *methoxy-enone* had m.p. 158·5—159·5° (methanol), $\nu_{max.}$ 1695 cm^{-1} (Found: C, 70·0; H, 6·4; N, 4·1. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%).

9α-Thiocyanatoindolinocodeinone Dimethyl Acetal (5; R = MeO, X = SCN).—7β-Iodoneopinone dimethyl acetal (1·69 g) was treated with potassium thiocyanate (2·0 g) in aqueous dimethylformamide in the usual way. The product mixture (0·90 g) was chromatographed on alumina (100 g). Elution with benzene–chloroform (2 : 3) gave *9α-thiocyanatoindolinocodeinone dimethyl acetal* (0·15 g), m.p. 171—172° (methanol), $\nu_{max.}$ 2145 cm^{-1} (Found: C, 63·15; H, 6·2; N, 6·9. $C_{21}H_{24}N_2O_4S$ requires C, 63·0; H, 6·0; N, 7·0%).

9α-Nitroso-oxyindolinocodeinone Dimethyl Acetal (5; R = MeO, X = ONO).—7β-Iodoneopinone dimethyl acetal (1·73 g) was stirred with silver nitrite (2·0 g) in dry acetone (50 ml) at room temperature for 12 h. The products were chromatographed on alumina (100 g). Elution with benzene–chloroform (1 : 1) gave the nitroso-oxy-acetal (5; R = MeO, X = ONO) (0·205 g) contaminated with the more polar component of the mixture, the hydroxy-acetal (5; R = MeO, X = OH). Purification of the nitrite was frustrated by further decomposition to the alcohol. However the n.m.r. spectrum and mass spectrum (*m/e* 388, 373, 358, 342, and 327) supported the assigned structure.

9α-Dimethylaminoindolinocodeinone Dimethyl Acetal (5; R = MeO, X = NMe_2).—Dimethylamine (5 ml) was added to a cold solution of 7β-iodoneopinone dimethyl acetal (0·765 g) in dry dimethylformamide. The mixture was kept at 0 °C for 12 h and then allowed to warm to room temperature. The products were chromatographed on alumina in the usual way. The oily 9α-dimethylaminoindolinocodeinone dimethyl acetal (0·165 g) was converted in methanol into its crystalline *picrate* (Found: C, 54·9; H, 5·4; N, 11·3. $C_{22}H_{30}N_2O_4,C_6H_3N_3O_7$ requires C, 54·6; H, 5·4; N, 11·4%).

The Aziridinium Perchlorate (9).—Silver perchlorate (0·70 g) in benzene (30 ml) was added to a vigorously stirred solution of 7β-iodoneopinone dimethyl acetal (1·58 g) in benzene (20 ml). After 2 min the mixture was filtered through Celite. Evaporation of the filtrate gave the aziridinium perchlorate (0·48 g) as a white foam. The same product was likewise obtained from 14-bromocodeinone dimethyl acetal [2,3] in similar yield.

Treatment of this perchlorate (0·48 g) with sodium acetate (0·50 g) in aqueous dimethylformamide (see before) gave 9α-acetoxyindolinocodeinone dimethyl acetal (0·18 g). Similarly, the salt (0·71 g) with sodium cyanide (0·60 g) yielded 9α-cyanoindolinocodeinone dimethyl acetal (0·20 g).

9α-Chloroindolinocodeinone (5; RR = O, X = Cl).—9α-Hydroxyindolinocodeinone (0·377 g) was treated with methanesulphonyl chloride (0·2 ml) in pyridine (2 ml) at 0 °C for 1 h then at room temperature overnight. The

[17] J. C. Sheehan and D.-D. H. Yang, *J. Amer. Chem. Soc.*, 1958, **80**, 1154.

mixture was poured into iced water (40 ml) and basified cautiously with aqueous ammonia. The solution was extracted with ethyl acetate (2 × 40 ml) and the combined extracts washed with water, dried ($MgSO_4$), and evaporated. The residue (0·279 g) was percolated through alumina in chloroform. 9α-Chloroindolinocodeinone (0·132 g) had m.p. 116—120° (methanol), $\nu_{max.}$ 1702 cm^{-1}, *m/e* 296·1291 [$(M - Cl)^+$; $C_{18}H_{18}NO_3$ requires *M*, 296·1287].

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