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STUDIES ON MORPHINE ALKALOIDS—VIII[1]

SOME REACTIONS OF 14β-BROMOCODEINE AND RELATED COMPOUNDS*

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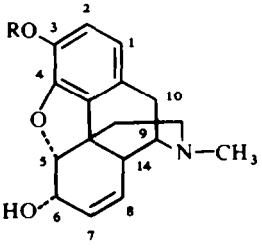
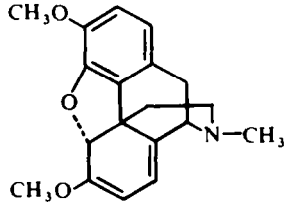
Abstract—Solvolysis of 14β-bromocodeine (V) was examined in detail and some considerations on the mechanism of this reaction are described.

OPIUM contains more than twenty basic components known as opium alkaloids with representative of morphine (I) alkaloids including codeine (II) and thebaine (III). Both morphine and codeine have useful pharmacological actions and are widely used but thebaine has a strong toxicity and has not been used in pharmaceutics.

CHART I



I R = H
II R = CH_3



III

Conversion of thebaine into useful alkaloids is now being studied and developed, and one such attempt is the introduction of various substituents into the morphine skeleton utilizing the reactivity of the diene system in the C-ring of thebaine. Many compounds have been synthesized using this method.

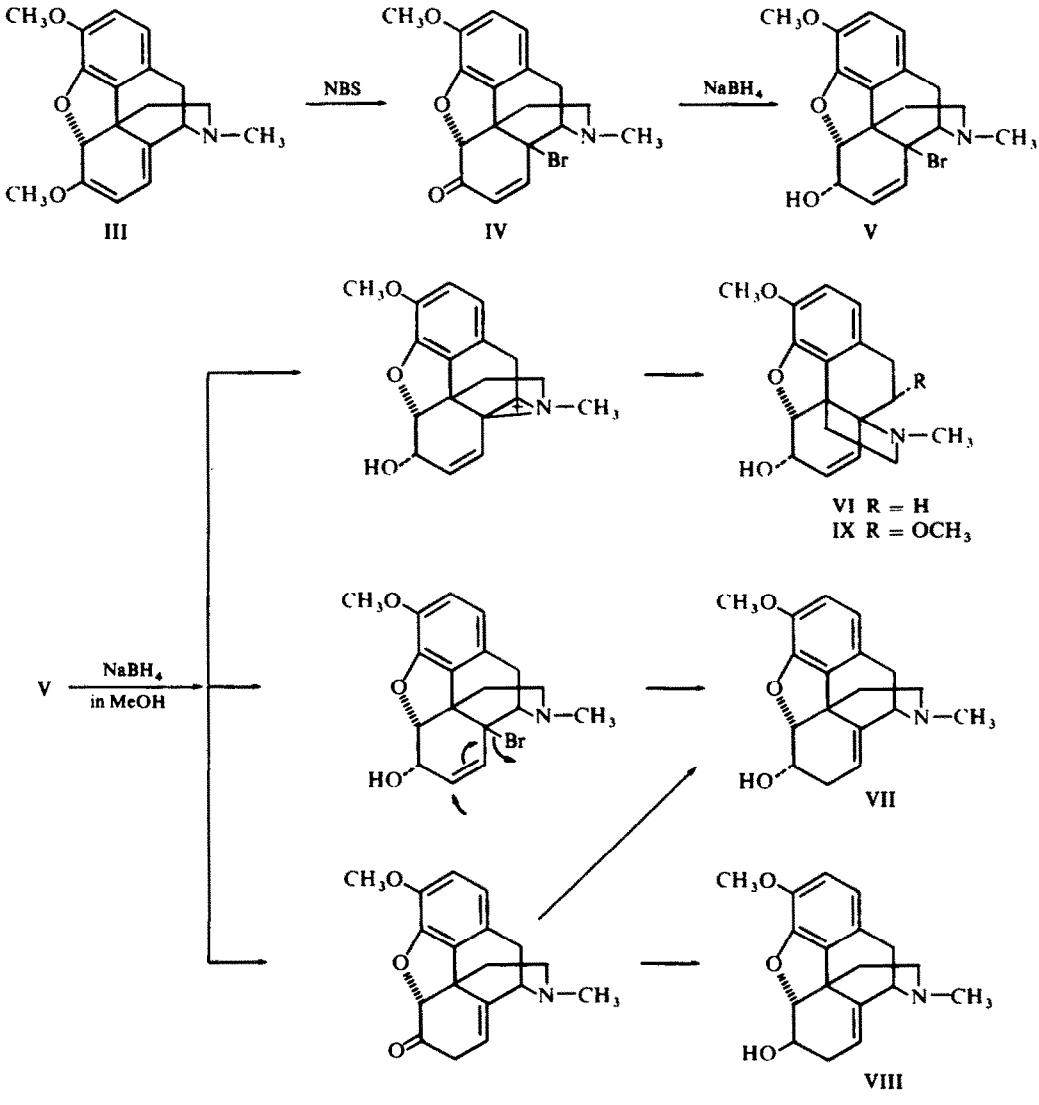
Application of N-bromosuccinimide to thebaine (III) gives a compound IV in which the C-14 position has been brominated.[2] Reduction of 14β-bromocodeinone (IV) with sodium borohydride gives 14β-bromocodeine (V) which possesses an allylic alcohol and an allylic bromide system in its molecule and is therefore highly reactive, revealing some interesting behaviour against various reagents.

Reaction of V with sodium borohydride in methanol[3] gives indolinocodeine (VI) formed by the rearrangement of the C—N bond, and neopine (VII) and isoneopine (VIII) formed by allylic rearrangement of the double bond. The formation mechanism

* Taken from the doctoral thesis of K. Abe, University of Tokyo (1970)

of these compounds was presumed to be as shown in Chart 2 from the analysis of this reaction using sodium borodeuteride.[4] Later, another compound, 9α-methoxyindolinocodeine (IX), was isolated as the fourth product of this reaction and its structure was determined.[5] IX may be considered to be formed at the time of the formation of VI by the attack of an OMe ion in the solvent in competition with the hydride ion on the C-9α position of V.

CHART 2

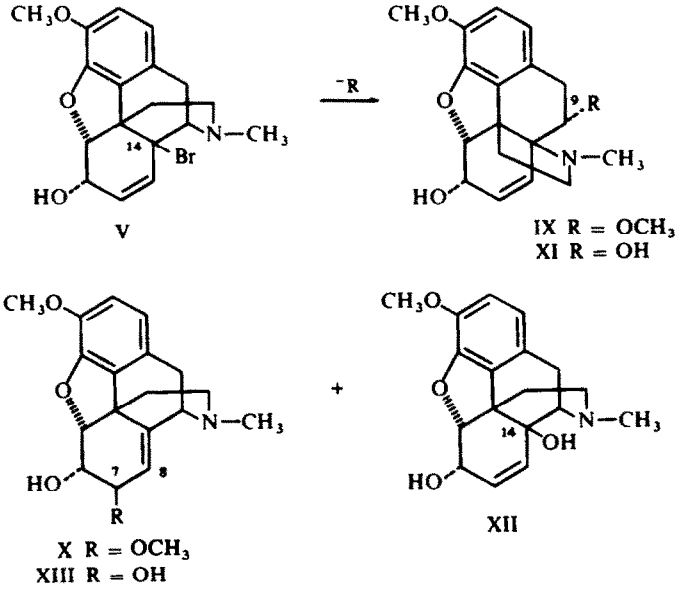


This assumption was confirmed by the formation of IX and X when V was converted directly with methanol. Thus, detailed examination of various reactions of 14β-bromocodeine (V) indicated that reactions due to the solvent used for the reaction

seem to occur besides changes by the reagent used, and solvolysis was found to progress at the same time. Examination of the stability of V in solvents showed that V is stable in aprotic, inactive solvents but is fairly labile in polar solvents like water and alcohol, and undergoes change even at room temperature. These changes in various solvents were reported in a previous paper.[6]

In the present work, hydrolysis of V was examined in detail and a third compound (XIII) was isolated besides the previously reported 9α-hydroxyindolinocodeine (XI) and 14β-hydroxycodeine (XII). The structure of XIII was determined and further considerations were made on the mechanism of this reaction and are described here.

CHART 3



7β-*Hydroxyneopine* (XIII). A solution of 14β-bromocodeine (V) dissolved in tetrahydrofuran and water (1:1) was stirred overnight at room temperature and the products were separated by column chromatography, by which three products (R_f 0·65, 0·45, 0·20)* were obtained in formation ratio of *ca* 2:1:5. Of these products, those with R_f 0·65* and 0·45* were respectively identified with XI and XII. The third compound (R_f 0·20)* was recrystallized from acetone as colorless needles, mp 167–168°. Its analytical values correspond to the molecular formula of $C_{18}H_{21}NO_4$ and indicate that XIII is an isomer of XI and XII. Its IR spectrum shows a strong absorption for an OH group. Acetylation of XIII with acetic anhydride in pyridine gives a diacetate. NMR spectrum of XIII is given in Fig. 1.

These data indicate that XIII is a neopine-type compound because the absorptions for protons at C-9α and C-10β, which appear characteristically around δ 3–4 in compounds having a morphine skeleton,[7] appear respectively at δ 3·55 and 3·25 and there is an absorption of one vinyl proton at δ 5·72. Comparison with the NMR

* TLC, R_f value; Silica gel plate, 0·25 mm, solvent system; $CHCl_3$:MeOH = 9:1

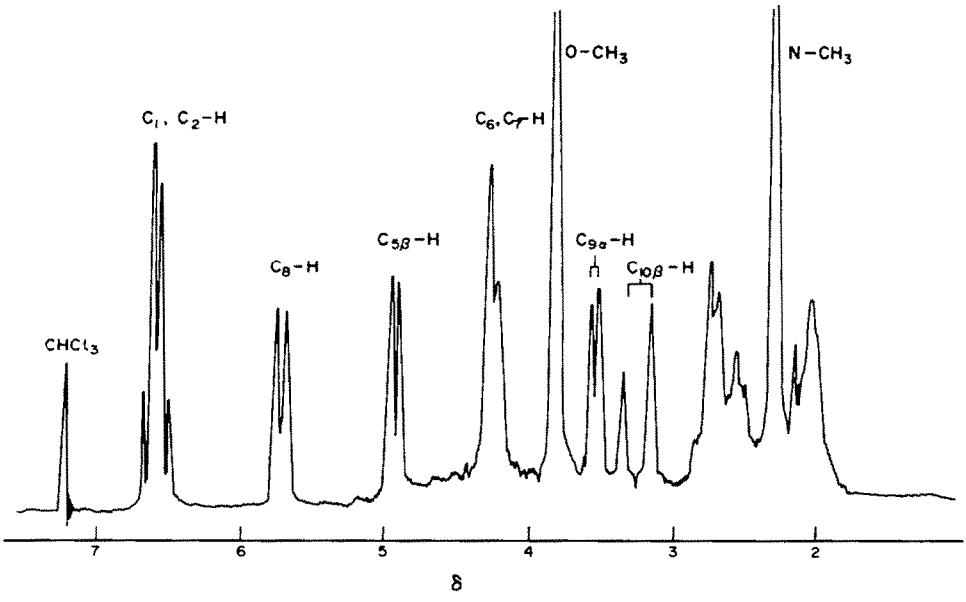


FIG. 1. NMR spectrum of XIII (100 Mc)

spectrum of neopine (VII) showed that, in XIII, the signal for C-8 proton has changed from a triplet to a doublet and that C-6β proton has undergone coupling with another proton besides that with C-5β proton. This evidence shows that there is only one proton at the C-7 position, that is, one substituent is present in C-7 position. This indicates that the position of newly introduced OH is at C-7.

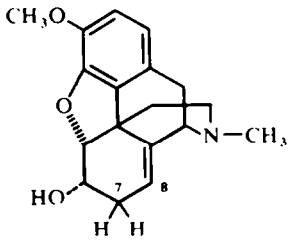
Configuration of the C-7 OH was determined in the following way. In the NMR spectrum of XIII, the C-8 proton appears as a doublet at δ 5·72 and its coupling constant is $J = 5{\cdot}6$. In the neopine series in general, the conformation of its C-ring takes a half-chair form.[8] The dihedral angle between C-7 and C-8 protons was measured from its molecular model and their coupling constants were calculated from it, giving values of $J_{7\alpha,8} = 5$–7, and $J_{7\beta,8} = 0{\cdot}5$–1·5. These values agree well with observed values of known neopine-type compounds (XIV and XV)[9] possessing a substituent in C-7 position. Therefore, the configuration of the C-7 OH in XIII is assumed to be β and this assumption was supported by its IR spectrum.

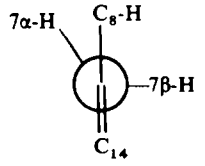
The IR spectrum of XIII in dilute carbon tetrachloride solution shows an absorption of a free OH at 3635 cm^{-1} and a weak absorption of an intramolecular H-bonded OH at 3598 cm^{-1}. This spectral pattern is almost the same as that of neopine (VII) and indicates that the C-7 OH in XIII is in a position that cannot undergo strong H-bonding with the C-6 OH group, and reveals that the C-7 OH takes a β-configuration, taking 1,2-*trans* diaxial position with respect to C-6 OH. From this evidence, the structure of XIII was determined as 7β-hydroxyneopine.

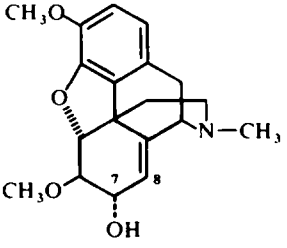
Periodical changes of 14β-*bromocodeine* (V). In order to examine the reaction course of solvolysis of V, the reaction products were checked by TLC and its result is shown in Fig 3.

With the disappearance of the starting material (V), spots for the three products (XI, XII, XIII) begin to appear but there is another large spot (XVI) at around R_f

CHART 4

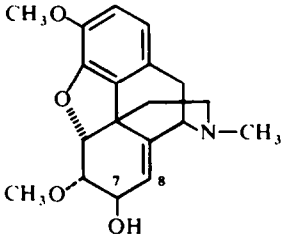






XIV

$J_{7\beta,8} = 1{\cdot}5$



XV

$J_{7\alpha,8} = 5$

	7α-, 8-H	7β-, 8-H
θ	20–25°	85–90°
J	6–7 cps	0–1 cps

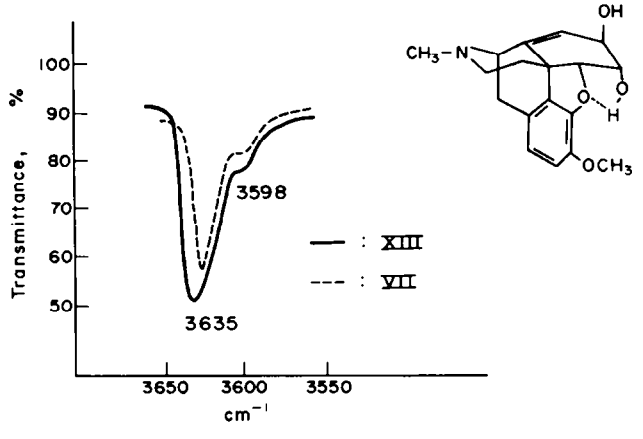


FIG. 2. IR spectra of XIII and VII (0·002 mole/l in CCl_4)

0·6. This spot always appears on the chromatogram during reaction of a few hours to overnight and seems to be fairly stable under this condition. When the reaction is continued for a long period, this product changes gradually into other products. The reaction was stopped after complete disappearance of the spot of the starting material and the mixture was made alkaline with ammonia and extracted with chloroform. The oily product obtained was purified by column chromatography in an

attempt to isolate XVI, but the compound seemed to be considerably labile in this state and disappeared during the long hours of chromatographic procedure, only the above-mentioned three products being obtained. Therefore, preparative TLC was carried out with a silica gel plate (0·5 mm), XVI was extracted and isolated, and its structural determination was carried out.

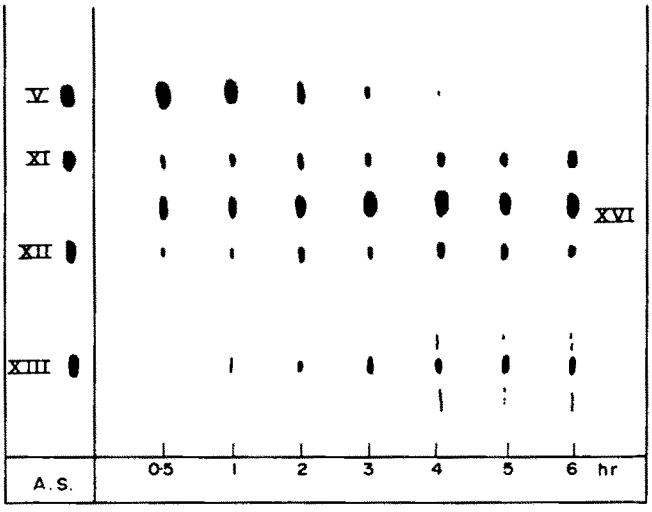


FIG. 3. Periodical changes of 14β-bromocodeine(V)
Thin-layer chromatography (silica gel plate, solvent; $CHCl_3$:MeOH = 9:1)

XVI was obtained as a colorless oil which did not crystallize. Its mass, IR, and NMR spectra were determined by using a sample which seemed to be pure from its thin-layer chromatogram. Its mass spectrum showed M^+; *m/e* 297·1324, corresponding to $C_{18}H_{19}NO_3$. There was no absorption for OH group in its IR spectrum and in its stead a characteristic absorption for an epoxide ring was present at 1250, 927, and 845 cm^{-1}. Its NMR spectrum exhibited absorptions due to C-9α and C-10β protons at δ 3–4 and that for one vinyl proton at δ 5·80, indicating that XVI is a neopine-type compound. The signals for C-5β and C-8 protons at δ 4·93 and 5·80 as doublets indicate the presence of one proton at C-6 and C-7 position. Absorptions for two protons at around δ 3–4, besides those for C-9α and C-10β protons, are probably due to C-6 and C-7 protons. Analysis of these signals by the decoupling method revealed the presence of a partial structure in XVI shown in Fig. 4.

From these results, it was assumed that XVI possesses a 6,7-epoxide structure which should be a *cis* type epoxide from the value of the coupling constant of C-6 and C-7 protons (J = 3·5 c/s). Catalytic reduction of XVI gives neopine (VII) which is also obtained by the reduction of XVI with sodium borohydride. This result suggests that reductive cleavage of the epoxide ring at the allylic position occurred to produce VII and, since the configuration of C-6 OH group in VII is α, the original epoxide is known to be in α-configuration.

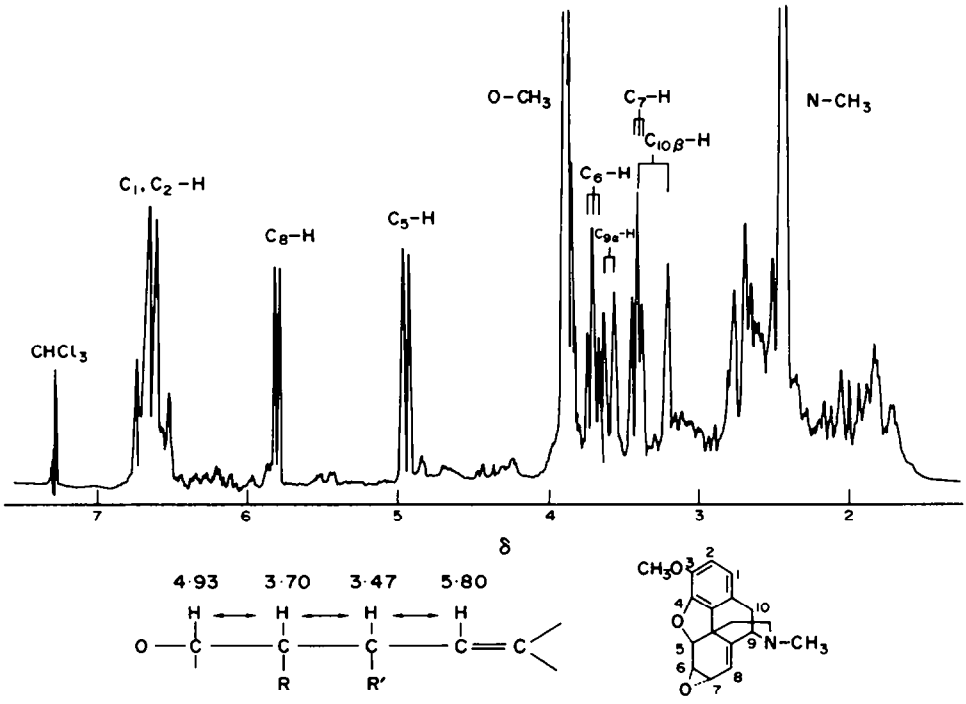


FIG. 4. NMR spectrum of XVI

Further reaction of XVI under the same conditions as the hydrolysis of V affords XIII which is also obtained when XVI is passed through an alumina column. This evidence suggests that XIII is formed via XVI by the hydrolysis of V.

Examination of reaction conditions. Examination was first made on the difference in reaction products formed according to pH of the reaction mixture. The solutions were adjusted to pH 4–9 using a phosphate buffer, and in addition, aqueous solutions of 10% HCl and 10% NaOH were used as the strongly acidic and basic solutions. The reaction was carried out at various pH's at room temperature and reaction products were checked by TLC. Changes found in various reaction mixtures after 24 hr are shown in Fig 5.

Compound V is fairly labile in an aqueous alkaline solution, the starting material disappears 30 minutes after start of the reaction, and the solution begins to color. This colored substance is transmitted to the aqueous layer by the extraction procedure after the reaction, and the yield of the products obtained from the organic solvent layer becomes very low. Thus, most of V is considered to undergo decomposition in an alkaline solution and changes into a water-soluble substance. In the buffer solutions of pH 9–4, as is clear from the thin-layer chromatogram, there is no great difference according to difference in pH except that there is only a gradual diminishing of the spot of XI with lowering of pH value. In contrast, the spot of XVI diminishes with increasing alkalinity and the spot of XIII becomes larger concurrently. Since the formation of XVI cannot be seen by reaction in strongly alkaline solution. XVI is probably labile in alkaline and changes immediately into XIII.

In an acidic solution, the reaction progress is much slower than that in alkaline solution but there is no coloring of the reaction mixture and V changes almost quantitatively into the products shown in Fig 5. In a highly acidic solution, there is no formation of XI, XII, or XIII, and the main product is a compound giving a spot at around R_f 0·5. Details of this compound will be given later.

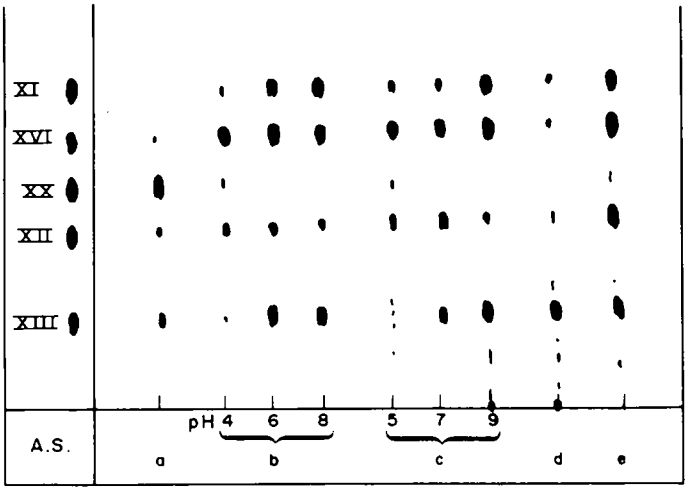


FIG. 5. Results of TLC of the solvolysis in different pH's solution
A.S. authentic samples
(a) 10% HCl solution
(b) Macllavine buffer sol. (pH 4, 6, 8)
(c) Kolthoff buffer sol. (pH 5, 7, 9)
(d) 10% NaOH sol
(e) pure H_2O sol.

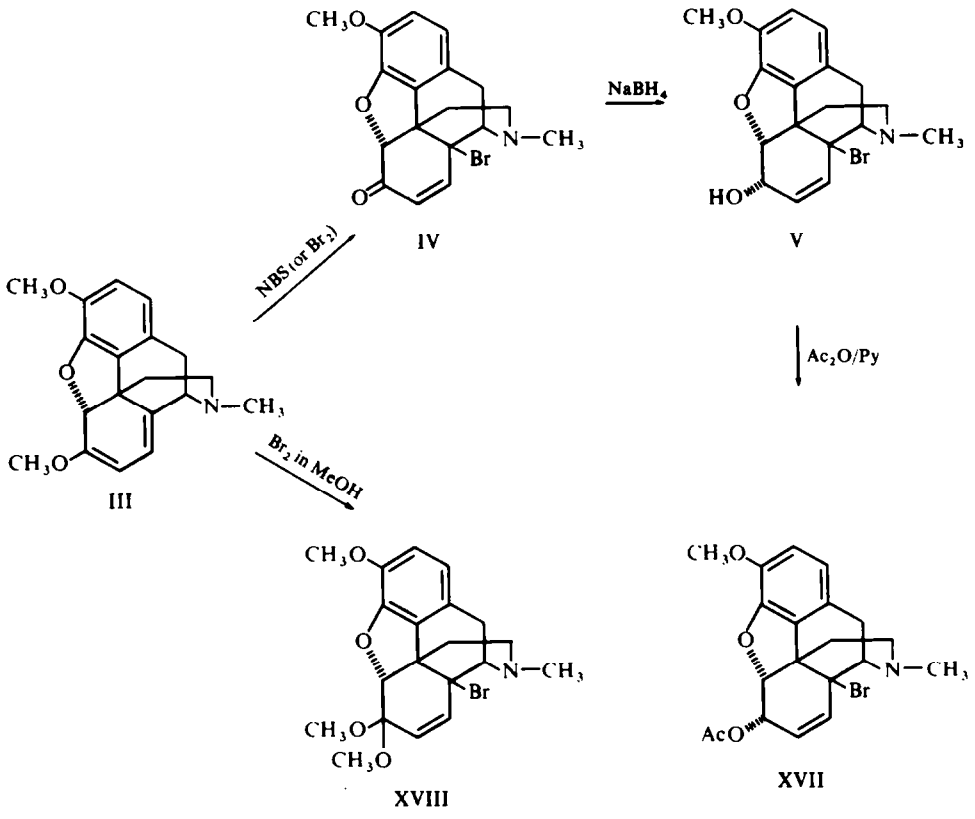
Next, in order to examine the reactivity of 14β-bromocodeine (V), hydrolysis was carried out on several compounds obtained by converting the functional group at C-6 position of V. Attempts were made to synthesize isomers of V with respect to the OH at C-6 but reduction of 14β-bromocodeinone (IV) with sodium borohydride or LAH afforded only the compound V with an OH group of α-configuration, and C-6 isomers were not obtained. Acetylation of V by the conventional method gives C_6-acetate (XVII) of V in a good yield. Bromination of thebaine (III) with bromine in methanol affords 14β-bromocodeinone dimethylketal (XVIII).

Reaction of these compounds (IV, XVII, and XVIII) under the conditions as for the solvolysis of V resulted in total absence of the reaction. More drastic conditions as regards reaction temperature and time showed that XVII and XVIII undergo the same reaction as V but not IV. These facts indicate the important contribution of the OH group at C-6 in the whole reaction of the solvolysis of V.

Substitution reaction under solvolytic conditions. As stated, V undergoes change in various solvent systems and the reaction progresses in several directions. The changes

in these directions according to the nature of the reaction mixture (kind of solvent used, pH, etc) have already been stated and it was assumed that the direction might also change according to the nucleophilic nature of other reagents. In order to test this assumption, the substitution reaction was carried out under the conditions used in the foregoing reaction and examinations were made on the manner of this reaction and its products.

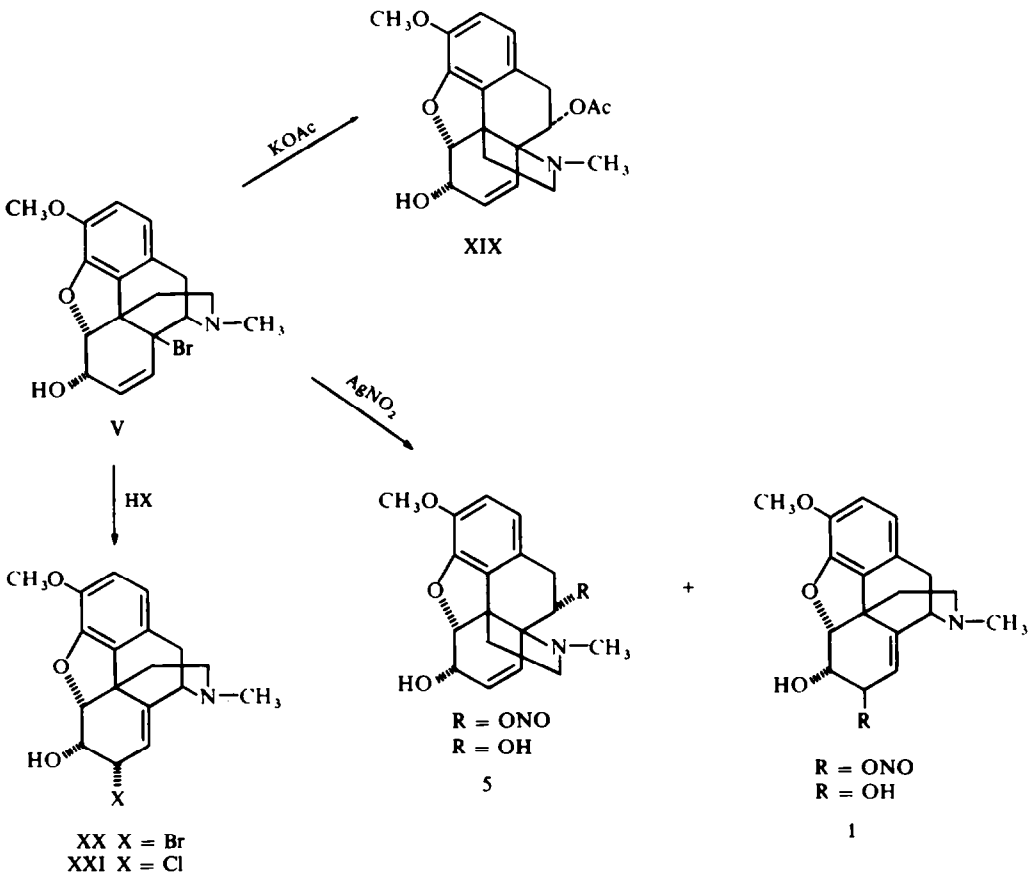
CHART 5



As reported,[6] application of potassium acetate to V in methanol gives 9α-acetoxyindolinocodeine (XIX) in a good yield while reaction with silver nitrite in acetone gives 9α-hydroxyindolinocodeine (XI). In these reactions, indolinocodeine-type compounds are obtained as the main product and the yield of corresponding codeine-type and neopine-type compounds is small. This is assumed to be due to the fact that bromine liberated by this reaction is trapped by the reagent and prevents the mixture from becoming acidic, so the lone-pair electrons of the ring nitrogen are not inhibited, and the reaction progresses towards the formation of an indolinocodeine-type compound. In contrast, when the reaction is carried out in an acid solution, a compound XX with R_f 0·50 is obtained as the main product, as stated, and indolinocodeine compounds are not obtained. As described, the indolinocodeine-type compounds

are obtained as a rearrangement product by the participation of the lone-pair electrons of ring-nitrogen and such a participation is likely to be completely inhibited in an acidic solution by the presence of protons in the solution and the rearrangement is therefore difficult.

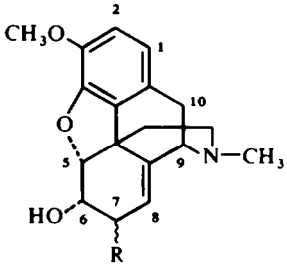
CHART 6



Examination on the structure of the product XX will be described. 14β-bromocodeine (V) was dissolved in 48% hydrogen bromide under ice cooling and the solution was maintained overnight at 0–5°. The mixture was diluted with water, rendered alkaline with ammonia, and extracted with chloroform. Usual after-treatment and evaporation of the solvent under a reduced pressure left colorless needles which were recrystallized from acetone–ether to colorless needles, mp 195–197°, yield, 65%, $C_{18}H_{20}NO_3Br$, (M^+; *m/e* 378), IR $\nu_{max}^{CHCl_3}$ 3550 cm^{-1} (–OH). NMR data of XX is given in Table 1.

By comparison of this spectrum with that of other analogous compounds, it became clear that XX is a compound with bromine in C-7 position of neopine and that it is in α-configuration from the coupling constant of C_8-H. From this experimental evidence, the structure of XX was determined as 7α-bromoneopine.

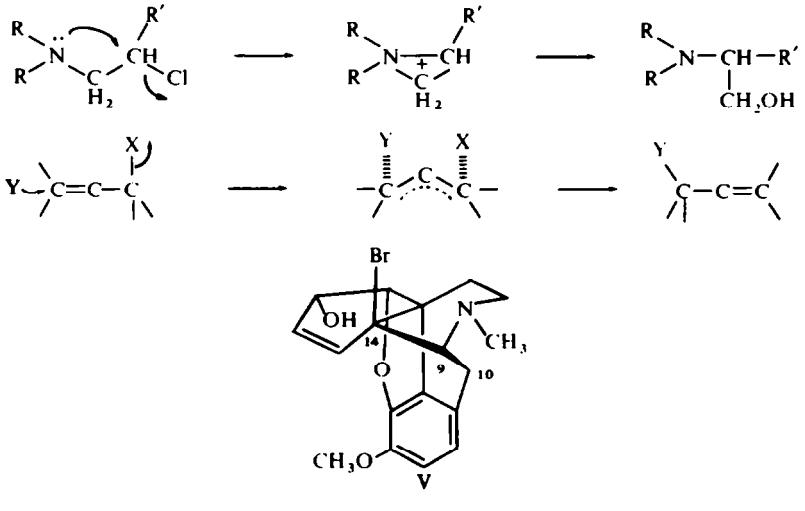
TABLE 1. COMPARISON OF NMR SPECTRAL DATA OF XX WITH THAT OF VII, XIII



Compd.	C_1, C_2	O-CH_3	C-5β	C-6β	C-7	C-8	C-9α	C-10β	N-CH_3
XX	6·68	3·87	4·72	4·28	4·82	5·62	3·68	3·25	2·40
	(q)	(s)	(d)	(b)	(q)	(s)	(d)	(d)	(s)
R = αBr			$J_{5,6}$ = 5·0		$J_{7,8}$ = 0·5		$J_{9\alpha,10\alpha}$ = 6·0		
							$J_{10\alpha,10\beta}$ = 18·0		
VII	6·60	3·86	4·64	4·22	—	5·48	3·57	3·27	2·45
	(q)	(s)	(d)	(b)		(t)	(d)	(d)	(s)
R = H			$J_{5,6}$ = 4·6		$J_{7,8}$ = 3·8		$J_{9\alpha,10\alpha}$ = 6·0		
							$J_{10\alpha,10\beta}$ = 18·0		
XIII	6·60	3·83	4·93	4·25	4·25	5·72	3·55	3·25	2·30
	(q)	(s)	(d)	(b)	(b)	(d)	(d)	(d)	(s)
R = βOH			$J_{5,6}$ = 4·8		$J_{7,8}$ = 5·6		$J_{9\alpha,10\alpha}$ = 6·0		
							$J_{10\alpha,10\beta}$ = 18·0		

Similar reactions in conc hydrochloric acid or 10% hydrochloric acid soln resulted in the introduction of chlorine into C-7α position and the product, 7α-chloroneopine (XXI) was obtained in a good yield. 7α-bromoneopine (XX) was obtained in 20–25% yield when potassium acetate was applied to 14β-Bromocodeine (V) in glacial acetic acid but the anticipated 7-acetoxy compound was not obtained in this case.

CHART 7



Considerations on the reaction mechanism. In the reactions described, all the products were formed stereospecifically and isomers with respect to the substituted positions were not obtained. This indicates that this reaction as a whole is controlled stereospecifically in some form. In general, neighbouring group participation of the lone-pair electrons of a N atom is said[10] to occur most readily when the leaving group and the C—N bond are in 1,2-*trans* diaxial position. It is also known[11] that, in the SN_2' type reaction, the leaving group and newly incoming group possess the same configuration.

In the present reaction the liberating bromide has a β-configuration and the liberation of this β-bromine is accompanied by the rearrangement of C-9β-N bond or formation of 7α-substituted compound. This makes it difficult to adopt the above mechanism *per se* to the present reaction. As already stated, this reaction as a whole is greatly affected by the OH group in C-6 position and the following may be considered as the mechanism of this reaction.

In the liberation of bromine as an ion, with reference to the participation of the C-6 OH group, an intermediate (XXII) with the protection of C-14 position from the α side can be presumed[12] and the whole reaction can be explained by assuming that the reaction progresses through this intermediate. In the formation of indolinocodeine type compounds, C-14α and C-9β-N bonds are in 1,2-*trans* diaxial relation and, when the participation of OH to C-14α is severed, the lone-pair electrons attack the C-14 position from the β side, resulting in the formation of an aziridinium ion. Its following rearrangement is accompanied by the attack of the reagent on C-9α position and various derivatives are formed. In codeine type compounds, SN_2 type substitution reaction occurs with this intermediate at C-14 position, while in the formation of neopine series compounds, the allylic rearrangement is accompanied by that towards the same direction as at C-14α, i.e., attack of the reagent on C-7α. Formation of 7β-substituted compound in solvolysis, as was already stated, can be considered to pass through a 7α-epoxide which by further attack of the reagent at C-7 changes into a 7β-substituent.

These solvolyses, various types of substitution reactions, and reduction with sodium borohydride all belong to different categories but all these reactions, including the steric state of the products, can be explained by the same mechanism if it is considered that the OH group in C-6α position participated in a solvolytic change of 14β-bromocodeine (V).

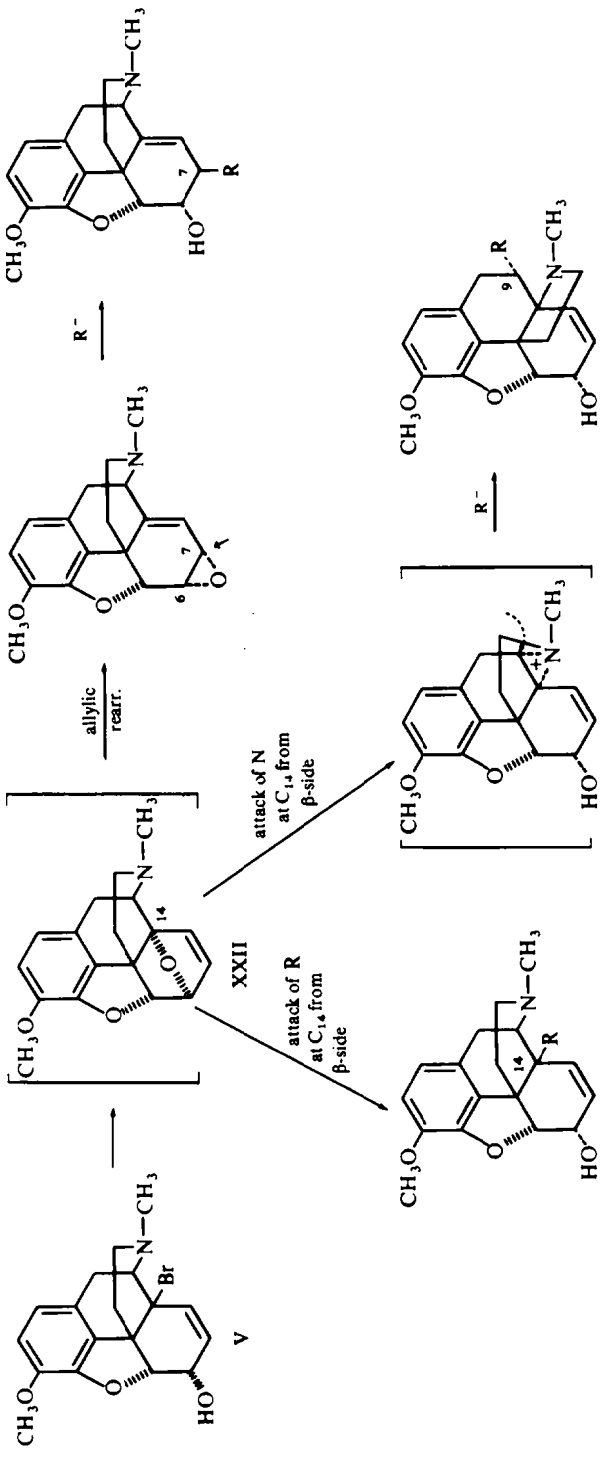
These mechanisms are summarized in Chart 8.

EXPERIMENTAL

Mps were uncorrected. IR spectra were recorded on Shimazu IR-27G spectrophotometer in $CHCl_3$ soln. NMR spectra were measured with a JEOL's 4H-100 spectrometer. Chemical shifts were given in δ values, using TMS as internal reference and coupling constants (J) in c/s. Following abbreviations are used for the representation of NMR data: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Mass spectra were determined on a JEOL's JMN-OIS Mass spectrometer with the direct sample inlet system, with ionizing potential at 70 eV.

14β-Bromocodeine (V). To a stirred soln of IV (5 g) in benzene (200 ml) was added dropwise a soln of $NaBH_4$ (250 mg) in MeOH (5 ml) over a period of 10 min, while the temp was maintained at 0–5°. After the soln was stirred at 5–10° for 1 hr, H_2O was added and the organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* at low temp to give colorless prisms (4·7 g, 94%), mp. 173–176°,

CHART 8


V
XXII
allylic rearr.
attack of N at C_{14} from β-side
attack of R at C_{14} from β-side
R^-
R^-

IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 3600 (OH), and no absorption of ketone (1680 cm^{-1}). This compound was identified with the authentic sample of V by comparison of IR and NMR spectra.

Hydrolysis of 14β-*bromocodeine* (V). To a soln of V (1 g) dissolved in THF* (10 ml) H_2O (10 ml) was added and the mixed soln was stirred overnight at room temp. After evaporation of organic solvent *in vacuo*, the mixture was made alkaline with NH_4OH and extracted with $CHCl_3$, washed with H_2O, dried over $NaSO_4$. After evaporation of solvent, the oily residue obtained (640 mg) was dissolved in benzene and benzene-soluble substance (560 mg, 67%) was chromatographed on neutral alumina (Woelm, activity grade III) column (50 g). The first fractions eluted with benzene were recrystallized from n-hexane to give colorless needles of XI (110 mg), mp 194–195°. The next fractions eluted with benzene–AcOEt (1:1) were recrystallized from ether–light petroleum to give XII (60 mg), mp 159–160°. These compounds were identical respectively with the authentic samples by the comparison of IR and NMR spectra and mixed mp. The eluates with AcOEt and with AcOEt–MeOH (9:1) were recrystallized from acetone to afford colorless needles of XIII (310 mg), mp 167–168°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3635, 3598 (OH). (Found: C, 67·52; H, 7·02; N, 4·19. Calc for $C_{18}H_{21}NO_4 1/4 H_2O$: C, 67·62; H, 6·82; N, 4·38. MS, *m/e* 315·1436 (M^+), calc for $C_{18}H_{21}NO_4$, 315·1471).

6α, 7α-*Epoxy-6-desoxyneopine* (XVI). Hydrolysis of V was carried out as described above and after 4 hr, when the spot of starting material disappeared completely on TLC, the reaction was stopped. After usual work up, the oily residue (525 mg) was passed through an alumina column (10 g) during a period of 10–20 min, using benzene as developing solvent to be separated in non-polar and polar substances. The non-polar fraction was subjected to preparative TLC (silica gel plate, 0·5 mm, solvent; $CHCl_3$:MeOH = 9:1) to afford XVI (28 mg) which was homogeneous by TLC (R_f 0·6), IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 1250, 927, 845. MS; *m/e* 297·1324 (M^+), calc for $C_{18}H_{19}NO_3$; 297·1365.

Catalytic reduction of XVI. A soln of V (100 mg) in THF-H_2O (1:1) (10 ml) was stirred at room temp for 4 hr. Then the mixture was shaken with 10% Pd-C (20 mg) under a stream of H_2 at room temp. After uptake of H_2 ceased (40 min), the catalyst was filtered off and the solvent was removed under reduced pressure, made alkaline with NH_4OH and extracted with $CHCl_3$. After working up, the products were chromatographed on neutral alumina column. Fractions eluted with benzene–AcOEt were recrystallized to afford colorless needles of VII (24 mg), mp 127–128°, which was identified with the authentic sample by mixed mp.

Sodium borohydride reduction of XVI. Hydrolysis of V (250 mg) was carried out as described and the products (pale yellow oily substance, 160 mg) dissolved in abs MeOH (10 ml) was added $NaBH_4$ (100 mg) and the mixture was stirred at 40° for 1 hr. After working up and chromatography on alumina, VII was obtained (48 mg) which was identical with an authentic sample of VII by mixed mp.

Hydrolysis of XVI. Compound XVI (10 mg), isolated from the hydrolysis products of V by preparative TLC, was dissolved in THF-H_2O (1:1) (5 ml) and the soln was stirred overnight at room temp. The product obtained was checked with TLC and GLC, the main spot of which was identified as XIII (82% by area intensity of gas–liquid chromatogram).

Hydrolysis of V *in different pH's solution.* The buffer solns used were as follows: Macllavine buffer soln consisting of 0·1 M citric acid and 0·2 M Na_2HPO_4, adjusted to pH 4, 6, and 8; Kolthoff buffer soln, consisting of 0·1 M KH_2PO_4 and 0·5 M $Na_2B_4O_7$, adjusted to pH 5, 7, and 9. Compound V (100 mg) in THF was added to each pH's soln and the mixture was stirred at room temp with periodic analysis of the reaction products utilizing TLC and GLC. Changes found in various mixtures after 24 hr are shown in Fig 5.

14β-*Bromocodeine-6-acetate.* To an ice cooled soln of V (500 mg) dissolved in abs Ac_2O (5 ml) was added dry pyridine (0·5 ml) and the mixture was kept overnight at room temp. The soln was poured on ice, made alkaline with NH_4OH, and the resulting ppts were dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with H_2O, dried, evaporated *in vacuo* to afford a crystalline residue (466·3 mg). Recrystallization from ether–light petroleum gave colorless prisms (371 mg) of XVII, mp 153–154°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 ($OCOCH_3$), NMR (δ) 5·92 (q, J = 2·5, 10, C_7-H), 5·69 (d, J = 10, C_8-H), 5·45 (q, J = 2·5, 8, C_6-H), 5·06 (d, J = 8, C_5-H), 2·15 (3H, s, O—$COCH_3$). (Found: C, 57·44; H, 5·28; N, 3·30; Br, 19·31. Calc for $C_{20}H_{22}NO_4Br$, C, 57·15; H, 5·26; N, 3·35, Br, 19·04%).

14β-*Bromocodeinone dimethylketal* (XVIII). To a stirred suspension of III (3·11 g, 10·0 mmol) in abs MeOH (10 ml) was added dropwise Br_2 (1·68 g, 10·5 mmol) while the temp was maintained at 0°. After stirring at −5~0° for 30 min, the mixture was poured gradually into a soln of Na (100 mg) in abs MeOH

* THF was added for increasing the solubility of V in the solution.

(10 ml) with stirring and the stirring was continued for 10 min at below 0°. The resulting ppt was washed well with H_2O and dried to afford XVIII (2·14 g). Recrystallization from ether afforded colorless needles. mp 167–169°, Beilstein test positive, NMR (δ), 6·00, 5·60 (2H, AB-q, J = 10, C_7-, C_8-olefinic H), 4·64 (1H, s, C_5-H), 3·85 (C_3-OCH_3), 3·40, 3·13 (C_6-OCH_3). (Found: C, 57·00; H, 5·64; N, 3·40; Br, 18·98. Calc for $C_{20}H_{24}NO_4Br$; C, 56·87; H, 5·68; N, 3·31; Br, 18·95%).

Hydrolysis of IV, XVII, *and* XVIII. Hydrolysis of these compounds was carried out by the procedure employed for V. Changes during these reactions were checked periodically and the products were identified utilizing TLC and GLC.

Reaction of 14β-*bromocodeine* (V) *with* $AgNO_2$. Compound V (1g) was added to a stirred suspension of $AgNO_2$ (1 g) in abs acetone (10 ml) and the mixture was stirred at room temp for 1 hr. The black ppt was washed well with acetone, and the filtrate was evaporated *in vacuo*. H_2O was added and the residue was made alkaline with NH_4OH and extracted with $CHCl_3$. The resulting oily products (691 mg, 76%) were chromatographed on neutral alumina column (50 g). Fractions eluted with $CHCl_3$ were recrystallized from n-hexane–acetone to afford XI (320 mg), mp 194–195°. The next fraction eluted with AcOEt was recrystallized from acetone to give XIII (58 mg), mp 168°. These compounds were identical with the authentic samples by mixed mp, IR and NMR spectra.

7α-*Bromoneopine* (XX). 14β-*Bromocodeine* V was dissolved in 48% HBr (3 ml) and kept overnight at 0–5°. The mixture was poured into ice-water, made alkaline with NH_4OH and extracted with $CHCl_3$. After usual work up, a crystalline residue (800 mg) was obtained. Recrystallization from acetone–ether gave colorless needles (560 mg) of XX, mp 195–197°C (rapid heating). Beilstein test, positive, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), MS, *m/e* 377·0591 (M^+). Calc for $C_{18}H_{20}NO_3Br$; 377·0627, *m/e* 298·1467 ([M-Br],$^+$ base peak), calc for $C_{18}H_{20}NO_3$: 298·1443.

7α-*Chloroneopine* (XXI). Compound V (1 g) was dissolved in conc HCl (5 ml) under ice cooling and kept at 5–10° overnight. After treatment as described above, a colorless crystalline (800 mg, 90%) was obtained. Recrystallization from ether–light petroleum gave colorless needles of XXI (367 mg), mp 146–148°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), NMR (δ) 5·48 (d, J = 0·5, 1H, C_8-H), 4·70 (2H, C_5-H, C_7-H), 4·25 (m, 1H, C_6-H,), MS *m/e* 333·1149 (M^+). Calc for $C_{18}H_{20}NO_3Cl$: 333·1137, *m/e* 298·1420 ([M-Cl],$^+$ base peak). Calc for $C_{18}H_{20}NO_3$: 298·1443.

Reaction of 14β-*bromocodeine* (V) with acetic acid. Compound V (100 mg) was dissolved in AcOH (3 ml) and the soln was kept overnight at room temp. After usual work up, the colorless needles, (23·4 mg) were identical with an authentic sample of XX by mixed mp. Reaction of V with AcOK in acetic acid at 80° for 1 hr also gave XX (19%).

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