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REDUCTION OF 14-ALKENYLCODEINONES BY SODIUM BOROHYDRIDE IN PYRIDINE

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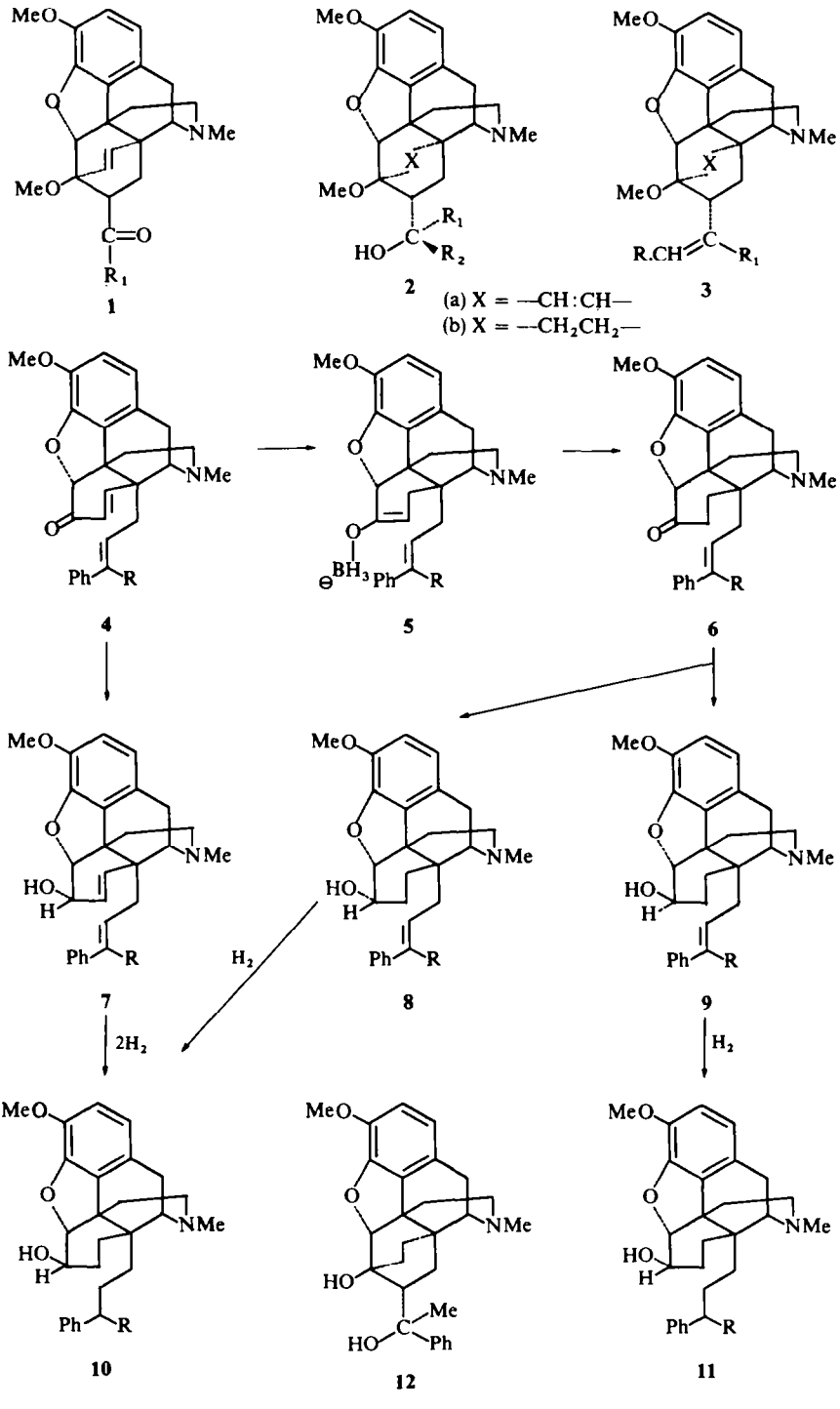
Abstract—Reduction with sodium borohydride in pyridine of 14-(3-phenylbut-2-enyl)codeinone and 14-(3,3-diphenylprop-2-enyl)codeinone gives the corresponding dihydrocodeinones, unobtainable by other methods. 7,8-Dihydro-14-(2-phenylbut-2-enyl)codeinone gives predominantly the dihydroisocodeine on reduction by sodium borohydride in pyridine whereas the dihydrocodeine is the principal product when the solvent is methanol.

CARBINOLS of type **2a** prepared by the action of Grignard reagents on Diels–Alder adducts (**1**) derived from thebaine are transformed by acids into a complex series of rearrangement products.[1,2] Dehydration to olefins (**3a**) is brought about by brief boiling with 98–100% formic acid whereas more prolonged reaction results in fission of ring C to give 14-alkenylcodeinones (**4**). The 14-alkenyldihydrocodeinones (**6**) might be expected to be formed by formic acid treatment of the dihydrocarbinols (**2b**) but from such reactions only olefins (e.g. **3b**) and phenols resulting from more profound rearrangements were isolated.[2] Moreover, reduction of the codeinones by conventional chemical means could not be achieved without further attack on the molecule.

We have now found that 7,8-dihydro-14-(3-phenylbut-2-enyl)codeinone (**6a**) is formed by reduction of the codeinone (**4a**) with sodium borohydride in anhydrous pyridine. After 4 hr at room temperature practically all the codeinone had reacted. The dihydrocodeinone was obtained in 15% yield by chromatography on alumina. Quantitative TLC on a sample of the unpurified product showed that the latter contained 33% of the dihydrocodeinone. The loss in the chromatographic separation is probably due to the rearrangement on the column of the dihydrocodeinone to the very polar recyclised base (**12**). This rearrangement is easily achieved by treatment of the dihydrocodeinone at room temperature with 2N HCl[3] which prevented the use of acid in the isolation procedure. 7,8-Dihydro-14-(3,3-diphenylprop-2-enyl)codeinone (**6b**) was isolated after a similar reduction of the corresponding codeinone (**4b**).

Three alcohols were also isolated from the reduction of **4a** with sodium borohydride in pyridine. The codeine derivative **7** , identical with the product from the reduction of **4a** with sodium borohydride in 2-ethoxyethanol,[2] was obtained by continued elution of the column after removal of the dihydrocodeinone (**6a**). The other alcohols were obtained as a mixture from the chromatography column but could be isolated by preparative TLC of the analogous mixture obtained by sodium borohydride–pyridine reduction of **6a**. These alcohols were the dihydrocodeine derivative **8a** and the dihydroisocodeine (**9a**) since they were identical with the products of reduction of the dihydrocodeinone (**6a**) with sodium borohydride in


MeO
NMe
C=O
R1
1
X
R1
HO
R2
2
(a) X = —CH:CH—
(b) X = —CH2CH2—
R.CH
3
4
BH3
5
6
HO
H
Ph
R
7
8
9
H2
2H2
10
12
Me
Ph
11
(a) R = Me
(b) R = Ph

methanol. However, in the latter reaction the major product, which could be obtained pure by crystallization, corresponded to the minor product from the reduction in pyridine.

Reduction of codeinones with borohydrides gives exclusively the codeine (6α-OH group) whereas similar reduction of dihydrocodeinones gives mixtures of dihydrocodeines and dihydroisocodeines.[4,5] Hydrogenation of the alkenylcodeine (**7a**) should give the alkyldihydrocodeine (**10a**) which should also be formed by hydrogenation of one of the isomeric dihydrocodeines (**8a** and **9a**). The product obtained by hydrogenation of the dihydrocodeine obtained in the sodium borohydride–methanol reduction of **6a** corresponded (m.p., TLC, IR and NMR spectra) with the product obtained by similar hydrogenation of the alkenylcodeine (**7a**). The major product from the sodium borohydride–methanol reduction of **6a** must, therefore, be the 6α (axial) hydroxy compound (**9a**) and the major product from the reduction in pyridine the 6β (equatorial) isomer (**8a**).

The predominant formation of the dihydrocodeine in the reduction in methanol of **6a** was to be expected by analogy with the similar result obtained by Rüll[5] in the reduction of dihydrocodeinone. The reversal of stereochemistry in the pyridine reduction was unexpected since in cases where solvent effects in borohydride reductions have been studied in detail,[6,7] these have produced relatively small changes in the axial:equatorial ratio. Since it leads to the equatorial alcohol the reduction in pyridine may be regarded as "thermodynamically" controlled. This effect of the solvent is parallelled in the reduction of the codeinones (**4**) where 1,4-hydrogenation leading to an enolate system in which conjugation is preserved is the thermodynamically-controlled course.

In the reduction of the alkenylcodeinone (**4a**) the saturated ketone (**6a**) is the product of 1,4-hydrogenation via the enol borohydride (**5a**). Previously reported reductions of αβ-unsaturated ketones with sodium borohydride in pyridine resulted in exclusive formation of saturated alcohols.[8,9] The latter are believed to be formed by *in situ* hydrolysis of the enol borohydride to the ketone followed by further reduction[8] despite the fact that precautions to exclude moisture were taken. If this explanation is applied to the present reaction, isolation of the ketone may be due to lack of sufficient water or other source of protons to complete the hydrolysis of the enol borohydride. This was shown not to be the case by carrying out the reduction with three moles of added water when the proportions of the products showed no detectable change compared with the reaction under "anhydrous" conditions.

It is more likely that isolation of saturated ketone is due to the slowness of the hydrolysis of the enolate derivative. Since mineral acids cause rearrangement of the alkenyldihydrocodeinones, the products were isolated by pouring the reaction mixture into a large volume of water. The initial aqueous mixture was an emulsion from which a solid separated after 10–15 minutes. When in one experiment no solid separated for several hours the proportion of saturated ketone in the product was appreciably reduced. It is possible, therefore, that the saturated alcohol formed in the "anhydrous" reaction may result from reduction of the saturated ketone liberated during the isolation procedure by undecomposed sodium borohydride.

EXPERIMENTAL

M.ps are uncorrected. TLC was carried out using alumina (Merck GF 254) developed with di-isopropyl

ether or di-isopropyl ether (7%) in methylene chloride. Quantitative TLC was performed with the Chromoscan (Joyce–Loebl Co.). NMR spectra were recorded on a Perkin–Elmer 40 m/c instrument.

14-(3-Phenylbut-2-enyl)codeinone (**4a**), m.p. 160–162°, was prepared in 62% yield by the action of 98–100% formic acid on 6,14-endoetheno-7α(1-hydroxy-1-methylbenzyl)-6,7,8,14-tetrahydrothebaine (**2a**, R_1 = Me, R = Ph).[2]

14-(3,3-*Diphenylprop*-2-*enyl*(*codeinone* (**4b**)

6,14-endoEtheno-7α(1-hydroxy-1-phenylbenzyl)-6,7,8,14-tetrahydrothebaine (4·0 g) was heated under reflux with 98–100% formic acid (15 ml) for 3 hr. The mixture was diluted with water and basified (ammonia). The recovered solid (3·5 g) was recrystallized from EtOH to give 14-(3,3-*diphenylprop*-2-*enyl*)-*codeinone*, m.p. 189–191°. (Found: C, 80·7; H, 6·3; N, 2·9. $C_{33}H_{31}NO_3$ requires: C, 81·0; H, 6·4; N, 2·9%.)

Reaction of 14-(3-*phenylbut*-2-*enyl*)*codeinone with sodium borohydride in pyridine*

(a) 14-(3-Phenylbut-2-enyl)codeinone (8·0 g) was added to a soln of $NaBH_4$ (3·5 g) in anhyd pyridine (125 ml). The mixture was set aside at room temp for 4 hr and was then poured into water (1200 ml). The turbid soln was stirred vigorously until a solid separated (10–15 min). The dried solid (7 g) was dissolved in benzene and chromatographed on a column of alumina (Grade 1, neutral). Elution with EtOAc (2%) in benzene gave 7,8-*dihydro*-14-(3-*phenylbut*-2-*enyl*)*codeinone* (1·2 g, 15%), which recrystallized from MeOH had m.p. 159–162°, ν_{max} 1730 cm^{-1}. (Found: C, 78·4; H, 7·1; N, 3·3. $C_{28}H_{31}NO_3$ requires: C, 78·2; H, 7·3; N, 3·3%.) Further elution with EtOAc (50%) in benzene gave 14-(3-phenylbut-2-enyl)codeine (1·0 g, 12%), identical (m.p. and mixed m.p., IR spectrum and R_f value) with the product obtained by reduction of the codeinone with $NaBH_4$ in 2-ethoxyethanol[2] and finally a mixture of the above codeine, 7,8-dihydro-14-(3-phenylbut-2-enyl)codeine, and 7,8-dihydro-14-(3-phenylbut-2-enyl)isocodeine.

(b) The experiment was repeated on a small scale and the dried, unpurified solid was subjected to quantitative TLC using authentic samples of the dihydrocodeinone and codeine obtained above. The mixture was shown to contain: 7,8-dihydro-14-(3-phenylbut-2-enyl)codeinone (33%); 14-(3-phenylbut-2-enyl)codeine (42%); 7,8-dihydro-14-(3-phenylbut-2-enyl)codeine (total) (24%).

(c) Experiment (b) was repeated with the initial addition of water (3 moles). The proportions of the above products were 30:46:24, respectively.

7,8-*Dihydro*-14-(3,3-*diphenylprop*-2-*enyl*)*codeinone* (**6b**)

14-(3,3-Diphenylprop-2-enyl)codeinone (2·0 g) was reduced with $NaBH_4$ (2·0 g) in pyridine in the manner described above. Chromatographic separation on alumina using EtOAc (2%) in benzene afforded 7,8-*dihydro*-14-(3,3-*diphenylprop*-2-*enyl*)*codeinone* (0·2 g), m.p. 167–170°, ν_{max} 1730 cm^{-1}. (Found: C, 80·4; H, 6·7; N, 2·8. $C_{33}H_{33}NO_3$ requires: C, 80·6; H, 6·8; N, 2·9%.)

Reaction of 7,8-*dihydro*-14-(3-*phenylbut*-2-*enyl*)*codeinone with sodium borohydride*

(a) *In pyridine.* 7,8-Dihydro-14-(3-phenylbut-2-enyl)codeinone (0·4 g) was dissolved in pyridine (2 ml) and added to a soln of $NaBH_4$ (0·15 g) in pyridine (5 ml). The mixture was allowed to stand at room temp for 4 hr and was then poured into water (50 ml). The turbid soln was saturated with NaCl and extracted with $CHCl_3$. The extract was washed (with water) and dried (Na_2SO_4) and the $CHCl_3$ removed. The resulting gum was subjected to preparative TLC to give 7,8-*dihydro*-14-(3-*phenylbut*-2-*enyl*)*isocodeine* (0·15 g), recrystallized from EtOH, m.p. 150–152°. (Found: C, 77·5; H, 7·7; N, 3·5. $C_{28}H_{33}NO_3$ requires: C, 77·9; H, 7·7; N, 3·3%) and 7,8-dihydro-14-(3-phenylbut-2-enyl)codeine (0·02 g), m.p. 129–131°, showing no depression when mixed with the product of the reduction in MeOH (see below). The NMR spectrum showed absorptions at 4·2 τ (triplet, 1 proton, vinyl) and 5·69 τ ($J_{6\alpha}$ 6·2 c/s) (doublet, 1 proton, $C_{5\beta}$).*

(b) *In methanol.* 7,8-Dihydro-14-(3-phenylbut-2-enyl)codeinone (0·25 g) and $NaBH_4$ (0·15 g) in MeOH (20 ml) were heated under reflux for1 hr. The soln was cooled and diluted with water. Recrystallization of the crude product from MeOH afforded 7,8-dihydro-14-(3-phenylbut-2-enyl)codeine, m.p. 130°. (Found: C, 77·9; H, 7·7; N, 3·1. $C_{28}H_{33}NO_3$ requires: C, 77·9; H, 7·7; N, 3·3%.) The NMR spectrum showed absorptions at 4·3 τ (multiplet, 1 vinyl proton) and 5·32 τ ($J_{6\beta}$ 6·9 c/s).

7,8-*Dihydro*-14-(3-*phenylbutyl*)*codeine*

(a) 14-(3-Phenylbut-2-enyl)codeine (2·0 g) in glacial AcOH (25 ml) was hydrogenated at atm temp and

* cf. Dihydroisocodeine, $C_{5\beta}$ doublet centred at 5·66 τ (J_6 6·0 c/s); dihydrocodeine, $C_{5\beta}$ doublet centred at 5·42 τ (J_6 7·3 c/s).[10]

press in the presence of 10% Pd–C (0·2 g) until H_2 absorption ceased; 140 ml (2 mole ≡ 171 ml) was absorbed in 7 hr. The catalyst was replaced and hydrogenation continued for a further 5 hr at 2 atmospheres. Removal of the catalyst and most of the solvent followed by basification (NH_4OH) gave 7,8-dihydro-14-(3-phenylbutyl)codeine, a low-melting solid (1·7 g) (hydrochloride, m.p. 155–157°) which was removed by filtration. (Found: C, 77·4; H, 8·2; N, 3·1. $C_{28}H_{35}NO_3$ requires: C, 77·6; H, 8·1; N, 3·2%.) The NMR spectrum showed a doublet centred at 5·45 τ ($C_{5\beta}$).[10]

(b) 7,8-Dihydro-14-(3-phenylbut-2-enyl)codeine (1·0 g) was hydrogenated at atm press in glacial AcOH in the presence of a 10% Pd–C catalyst. Isolation of the product as above gave 7,8-dihydro-14-(3-phenylbutyl)codeine, having identical R_f value (TLC), IR and NMR spectra. The hydrochloride had m.p. 158° undepressed in a mixture with the product from the hydrogenation of the codeine.

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