A solution of 623 mg (2 mmol) of thebaine in 150 mL of methanol, freshly distilled from $Mg(OMe)_2$, was deoxygenated with a stream of dry nitrogen. This solution was irradiated with a Hanovia 450-W lamp through a Corex filter under a nitrogen purge for 2 h, at which time TLC analysis (silica gel, $CHCl_3$–MeOH, 85:15) showed that all the starting material had been consumed. The solution was rotary evaporated and the residue purified by column chromatography (silica gel, $CHCl_3$–MeOH, 94:6) to yield 538 mg (78%) of neopinone dimethyl ketal as a light golden oil. The crude product was Kugelrohr distilled to give 420 mg (61%) of the methanol adduct: bp 105–110 °C (0.02 mm Hg) [lit. bp 90 °C (0.01 mm Hg)]; NMR ($CHCl_3$) δ 1.80–2.90 (m, 11 H), 2.93 (s, 3 H), 3.50 (s, 3 H), 3.88 (s, 3 H), 4.65 (s, 1 H), 5.36 (d, d, 1 H, J = 6.3 Hz), 6.66 (m, 2 H).

Photochemical Formation of a Neopinone–Codeinone Mixture. A suspension of 643 mg (2.07 mmol) of thebaine in 165 mL of water was deoxygenated with a stream of dry nitrogen. To the solution there was added 250 mL of 1 N HCl (2.5 mmol) and the thebaine hydrochloride which formed slowly dissolved. The solution was irradiated with a Hanovia 450-W lamp through a Corex filter for 2.5 h, at which time TLC analysis ($CHCl_3$–MeOH, 85:15) showed that all the starting material had been consumed. To the aqueous solution there was added 1.0 g of anhydrous Na_2CO_3 and the resulting suspension was extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield 500 mg (81%) of a brown oil, which was shown by NMR analysis of the 5β proton[5] to be a 9:1 mixture of neopinone and codeinone.

Hydrolysis of Photochemically Formed Neopinone Dimethyl Ketal (6). A solution of 300 mg (0.875 mmol) of photochemically formed neopinone dimethyl ketal (**6**) in 20 mL of 3 N formic acid was stirred under nitrogen at room temperature for 4 days. A 100-mL portion of a saturated aqueous solution of K_2CO_3 was added and the solution was extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield a 2:1 mixture of starting material and enones **4** and **5**.

This same reaction procedure was repeated with the addition of 2 mg (0.006 mmol, 0.7 mol %) of $Hg(OAc)_2$ to yield 240 mg of a 1:5 mixture of starting material and enones; the corrected yield for enones **4** and **5** was 89%.

Hydrolysis of Thebaine (1). A solution of 234 mg (0.75 mmol) of thebaine and 31.9 mg (0.1 mmol, 13.3 mol %) of $Hg(OAc)_2$ in 20 mL of 3 N formic acid was stirred, under nitrogen, at room temperature for 4 days. The solution was diluted with 100 mL of a saturated aqueous solution of K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and rotary evaporated to give a straw-colored solid in 100% yield. The composition of this material was determined by NMR analysis of the 5β proton and by GC chromatography and it was shown to be a 3:1 mixture of codeinone (**4**) and neopinone (**5**).

Following the same procedure with varying amounts of $Hg(OAc)_2$ resulted in the formation of these two enones during the first 24 h, as analyzed by GC chromatography. When no $Hg(OAc)_2$ was added, no enones were produced in 5 days and the addition of only 0.8 mol % of $Hg(OAc)_2$ resulted in complete conversion of thebaine to the enone mixture in 18 days; however, in this latter case the yield of enones was low (~30%) and other byproducts were formed.

Conversion of Thebaine (1) to Codeine (2). A solution of 1.17 g (3.75 mmol) of thebaine (**1**) and 79.8 mg (0.25 mmol, 6.7 mol %) of $Hg(OAc)_2$ in 100 mL of 3 N formic acid was stirred, under nitrogen, for 6.5 h. The solution was diluted with 100 mL of saturated aqueous K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and rotary evaporated.

The residue was dissolved in 5.3 mL of $CHCl_3$ and allowed to react with 5.3 mL of a solution of 1.1 g of hydrogen chloride in 10 mL of ether. A precipitate formed immediately. The reaction was allowed to continue for 30 min and then diluted with 2.5 mL of CH_2Cl_2 and 2.5 mL of the above solution of hydrogen chloride in ether. The reaction was allowed to continue for an additional 15 min and then 250 mL of cold 0.2 N NaOH solution and 50 mL of $CHCl_3$ were added. The aqueous layer was reextracted with $CHCl_3$ and the organic extracts were washed with water, dried (Na_2SO_4), and rotary evaporated.

The residue was dissolved in 60 mL of methanol, 3.02 g (79 mmol) of $NaBH_4$ in 73 mL of methanol was added, under nitrogen, and the reduction was allowed to proceed for 15 h. The solution was concentrated to a volume of 60 mL, diluted with 60 mL of 10% NaOH solution, and heated to reflux. The reaction mixture was further diluted with 50 mL of water and extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and rotary evaporated to yield 890 mg (79%) of crude white codeine (**2**). GC analysis of this material indicated a 90% purity. The crude product was sublimed (100 °C, 0.03 mm Hg) to give codeine in 80% yield, mp 151–154 °C (lit.[4] mp 153–157 °C). The NMR spectrum was identical with a commercial sample of codeine.

Registry No.—**1**, 115-37-7; **2**, 76-57-3; **4**, 467-13-0; **5**, 509-66-0; **6**, 32398-20-2.

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(8) We wish to thank Ralph D. McLaughlin of the Lawrence Berkeley Laboratory for the determination of the amount of mercury by his atomic absorption procedure.

Ring Opening of Steroid Epoxides by Dichlorobis(benzonitrile)palladium(II)

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Epoxides are an important class of compounds by virtue of the versatility of their reactions. The opening of the oxirane ring by hydrogen halides leads to the formation of halohydrins, which can be converted into a number of other derivatives.[1]

We have found that a group of oxidocholestanes may be easily and quantitatively converted into the corresponding chlorohydrin derivatives using $Pd(PhCN)_2Cl_2$ in benzene. These reactions offer an example of the original reactivity of the coordination compound, which is acting through two concomitant effects, i.e., the activation of the reaction site by coordination and the participation of its ligands, which is proved by their presence in the reaction product.

The stereochemistry of the ring opening by dichlorobis(benzonitrile)palladium(II) appears to be the expected trans diaxial type and is similar to that observed for the same reactions in the presence of a large excess of hydrochloric or hydrobromic acids (Table I).[2-4]

The action pathway of the palladium complex probably involves the coordination of the oxirane oxygen through substitution of the labile benzonitrile ligands followed by nucleophilic attack of the chloride coordinated to another molecule of the complex.[5] This mechanism appears to be in agreement with the stereoelectronic features of the nucleophilic opening of the epoxide ring, where the attacking nucleophile approaches the ring carbons from a periplanar direction.[4,6]

The epoxide ring opening by $Pd(PhCN)_2Cl_2$ employs conditions milder than those in saturated solutions of hydrochloric or hydrobromic acids, and the chlorohydrin yields are essentially quantitative. Only the OH group at C-3 may give a competitive reaction with the epoxide opening since 3-cholestanols and coprostanols are transformed by the $Pd(PhCN)_2Cl_2$ into the 3-chloro derivatives in few hours, at 70 °C.[5]

As proved by compounds II–V, the carbonyl and ester groups are insensitive to $Pd(PhCN)_2Cl_2$ (at variance with the

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Table I. Oxidosteroid Ring Opening by Dichlorobis(benzonitrile)palladium(II) in Benzene

starting compd	registry no.	chlorohydrin	registry no.	mp, °C found	mp, °C lit.	yield, %
(I) 2α,3α-oxido-5α-cholestane	1753-61-3	2β-Cl, 3α-OH	14287-32-2	120	120[6]	95
(II) 3-acetoxy-5α,6-oxido-5α-cholestane	68974-60-7	6β-Cl, 5α-OH	68974-63-0	188	189[12]	90
(III) 3-acetoxy-5β,6-oxido-5β-cholestane	68974-61-8	5α-Cl, 6β-OH	68974-64-1	197	196[13]	95
(IV) 3-acetoxy-5α,6-oxido-5α-androstan-17-one	68974-62-9	6β-Cl, 5α-OH	68974-65-2	204	205[14]	90
(V) 17β-acetoxy-4α,5-oxido-5α-androstan-3-one	5178-01-8	4β-Cl, 5α-OH	68950-33-4	202	204[15]	85
(VI) 4β,5-oxido-5β-cholestan-3-one	1975-34-4	4α-Cl, 5β-OH	68950-34-5	137–139		90
(VII) 4ξ,5ξ-oxidopregnane-3,20-dione		4α-Cl, 5β-OH	68950-35-6	143–144		95
(VIII) 17β-hydroxy-4β,5-oxido-5β-androstan-3-one	2189-83-5	4α-Cl, 5β-OH	68950-36-7	181–182		90

behavior of Grignard reagents).[7,8] Other reagents such as CrO_2Cl_2 and $TiCl_2$ open the oxirane ring to give the corresponding alkene.[9]

The use of $Pd(PhCN)_2Cl_2$ is particularly valuable in the opening of 4,5-oxido-3-ketosteroids. 17β-Acetoxy-4α,5-oxido-5α-androstan-3-one (V), 4β,5-oxido-5β-cholestan-3-one (VI), 4ξ,5ξ-oxidopregnane-3,20-dione (VII), and 17β-hydroxy-4β,5-oxido-5β-androstan-3-one (VIII) are reported to react with hydrochloric acid in acetone to give the corresponding 4-halo-4-ene-3-keto derivatives through the rapid (especially for VII and VIII) elimination of water from the initially formed halohydrins.[10,11] Camerino et al. found that isolation of the halohydrins from oxides VII and VIII by the use of HCl was unsuccessful also under controlled conditions.[16]

In the reactions promoted by dichlorobis(benzonitrile)-palladium(II), only the expected 4-chloro-5-hydroxy-3-keto compounds were isolated in excellent yields (Table I). In the opening of 4,5-oxidopregnane-3,20-dione, two halohydrins were isolated, the 4α-chloro-5β-hydroxypregnane-3,20-dione as major product (80%) together with 4β-chloro-5α-hydroxypregnan-3,20-dione (20%). This result is in agreement with the view that the epoxide from progesterone is a mixture of isomers with the β form predominating.[11] The NMR spectrum of this mixture suggests that the two oxides are in a ratio of 4:1.

In conclusion, it appears that owing to the mild reaction conditions, the quantitative yields, and the general interest toward the halogenated steroidic hormones, dichlorobis-(benzonitrile)palladium(II) may be usefully employed in the opening of oxidosteroids containing acid-sensitive functions.

Experimental Section

The steroid epoxides were prepared by the literature methods and characterized by infrared and NMR spectra and melting points. Dichlorobis(benzonitrile)palladium(II) was prepared by the method of Kharasch.[17]

The standard procedure for the preparation of the steroid halohydrins was as follows. The epoxide and coordination compound (2-mmol amounts) were allowed to react in 6 mL of benzene for 8–10 h. The mixture was then hydrolyzed with water and extracted with ether. The aqueous phase was evaporated to dryness to recover the palladium salt. The evaporated ether extracts were chromatographed on a SiO_2 column by eluting with 1:4 hexane–ether. For compound III, the experimental conditions (1 day, 25 °C) were found to be important for a quantitative yield owing to the decomposition of the reaction product.

The reaction products were characterized by IR and NMR spectra, which were found to be in agreement with the reported configurations. Halohydrins VI–VIII gave satisfactory elemental analyses (±0.2% for C and H).

Registry No.—4β,5β-Oxidopregnane-3,20-dione, 17597-24-9; 4α,5α-oxidopregnane-3,20-dione, 17503-05-8; dichlorobis(benzonitrile)palladium(II), 14220-64-5.

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Alkylation of Styrylacetic Acid Systems Using Lithium Diisopropylamide–Hexamethylphosphoramide. Effect of Temperature Variation

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In connection with a program directed toward the study of hypocholesteremic agents containing a styrylacetic acid system, we became interested in the potential utility of the lithium diisopropylamide–hexamethylphosphoramide (LDA–HMPA) complex for the preparation of certain α-methylated derivatives. We had previously attempted to prepare (*E*)-2,3-dimethyl-4-phenyl-3-butenoic acid (1) by dehydration and saponification of the corresponding β-hydroxy ester (Reformatsky product). This procedure, however, led to a complex mixture of isomeric olefins, **2** (apparently containing all five of the possible isomers), from which we were unable to isolate **1** in pure form although it was the major isomer present. We therefore became interested in possible methods for isomerizing the double bond exclusively into the β,γ position.

It had been previously reported that in the anions derived from α,β- or β,γ-unsaturated aliphatic esters[1] and the dianions of the corresponding acids[2] the charge is predominantly localized at the α position, and electrophilic reagents (e.g., H^+

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