Radical Mechanisms in Chromous Ion Reductions. An Improved Synthesis of 11β-Hydroxy Steroids[1]

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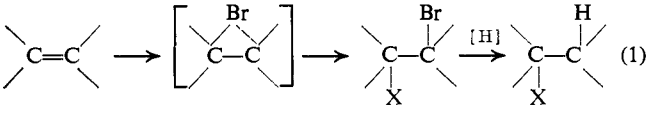
Abstract: The reduction of 9α-bromo-11β-hydroxy steroids by chromous ion, especially chromous acetate, has been studied systematically. Three types of product have been obtained: 11β-hydroxy-5,9-cyclopropanes, 11β-hydroxy steroids, and 9(11)-olefins, the normal reduction products. It has been demonstrated that the relative proportions of these products are dependent on the anion associated with the chromous ion, on the solvent, and, in particular, on the presence of compounds which are ready donors of hydrogen atoms. The intermediacy of a free radical giving rise to 11β-hydroxy steroids has been established. The other products are derived from two-electron reduction and probably involve a chromous–carbon intermediate. The variation of products on substitution of the 11β-hydroxyl group has been examined. The reduction of 9α-bromo-11β-hydroxy steroids in the presence of suitable hydrogen donors provides an efficient route to medicinally important 11β-hydroxy steroids. The reduction of other 1:2 bromohydrins has been studied and a rapid procedure for the synthesis of 6β-hydroxy steroids obtained. The reduction of 9α-bromo-11β-fluoro steroids has provided the hitherto unknown 11β-fluoro steroids, and a number of these compounds of potential biological interest have been prepared.

The ionic addition of bromine (or of other halogen) to an ethylenic linkage in the presence of a suitable nucleophile "X," followed by hydrogenolysis of the resulting bromo compound (eq 1) constitutes, in principle, an attractive procedure for the addition of the elements of "H–X" under mild conditions. In



(1)

most cases the location and orientation of the addenda would be controlled by well-explored steric and electronic factors.[2,3] The application of such a procedure could lead to compounds otherwise not easily accessible (for example, *vide infra*). However, to date, the reduction of this scheme to practice has frequently proved difficult. Catalytic hydrogenolysis,[4] or reduction with Raney nickel,[5] has served in several instances for the conversion of bromohydrin into alcohol. Although catalytic hydrogenation has also been of use in debrominating α-bromolactones the process is generally attended by elimination to give olefin.[6] Similarly, other common methods for the removal of halogen, such as reduction with zinc,[7] magnesium,[8] iodide ion,[9] or chromous ion,[10] when applied to halohydrins or related substances, usually afford olefinic products. The reaction of 9α-bromo-11β-hydroxy steroids with reagents for the reductive removal of bromine has been studied in some detail[11] because the products would be the medicinally important 11β-hydroxy compounds. In no case did the application of standard methods lead to synthetically useful results (the 9(11)-ene being formed in major yield instead).

In a recent communication[12] we have reported that bromohydrins, on reduction with chromous acetate in the presence of a hydrogen atom transfer agent, are converted in good yield into the corresponding alcohol. In the present paper we present a more detailed account of those results together with additional data pertinent to the mechanism and scope of the reaction.

It has been appreciated for some time that chromous salts are reducing agents of considerable interest and we cite especially studies on the reduction of halo compounds.[13] The reduction of simple alkyl or aralkyl halides usually effects the replacement of halogen by hydrogen. However, those halo compounds having a vicinal substituent eliminatable as an anion (*e.g.*, α-halo, −OH, −OR, −OCOR, etc.) usually give rise to olefins.[13] Normally chromous chloride is used in these reduction processes, but, by chance,[14] we had occasion to reduce a bromohydrin derivative with chromous acetate. The product contained, besides the expected olefin, a significant amount of debrominated material in the sense of eq 1 (see above). This result led us to a more extensive investigation of the use of chromous acetate and caused us to ponder on the mechanistic aspects of these reductions.

The model substrate chosen for our investigations was 9α-bromo-11β-hydroxyprogesterone.[11] Reduction of this with chromous acetate in aqueous acetone, tetrahydrofuran, dioxane, or N-methylpyrrolidone afforded a mixture of products containing 11β-hydroxy-

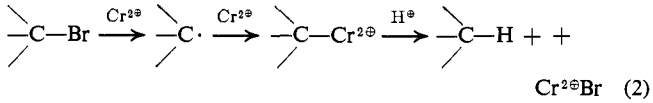
(1) This paper is communication no. 36 from the Research Institute for Medicine and Chemistry; for communication no. 35 see J. C. Sheehan, J. Preston, and P. A. Cruickshank, *J. Am. Chem. Soc.*, 87, 2492 (1965).
(2) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), 10, 44 (1956).
(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 520 ff.
(4) L. F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, 75, 1700 (1953); L. F. Fieser and X. A. Dominquez, *ibid.*, 75, 1704 (1953).
(5) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *ibid.*, 72, 5145 (1950); J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, 36, 1241 (1953).
(6) D. A. Denton, F. J. McQuillin, and P. L. Simpson, *J. Chem. Soc.*, 5535 (1964).
(7) F. J. Soday and C. E. Boord, *J. Am. Chem. Soc.*, 55, 3293 (1933); I. Schuman and C. E. Boord, *ibid.*, 55, 4930 (1933).
(8) E. D. Amstutz, *J. Org. Chem.*, 9, 310 (1944).
(9) W. G. Young, D. Pressman, and C. D. Coryell, *J. Am. Chem. Soc.*, 61, 1640 (1939); S. Winstein, D. Pressman, and W. G. Young, *ibid.*, 61, 1645 (1939).
(10) F. A. L. Anet and L. Marion, *Can. J. Chem.*, 33, 849 (1955).
(11) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, 79, 1130 (1957).
(12) D. H. R. Barton and N. K. Basu, *Tetrahedron Letters*, 3151 (1964).
(13) J. K. Kochi and P. E. Mocadlo, *J. Org. Chem.*, 30, 1134 (1965), and references cited therein.
(14) This experiment was carried out by Dr. A. G. Hortmann.

progesterone (**4**) the 9(11)-olefin **7**, and the 5,9-cyclosteroid **8**. The constitution of the latter is based on sound analogy,[15] on its physical properties, and on the fact that oxidation with chromium trioxide in pyridine[16] followed by chromatography over alumina (**10**, see arrows) gave 11-ketoprogesterone (**9**).

Although in the above reductions the best yields of 11β-hydroxyprogesterone (**4**) were obtained in aqueous tetrahydrofuran, the yields were in fact variable. Variation of the reaction conditions did not effect the product composition in a reproducible fashion. Reduction of the bromohydrin **1** with chromous acetate in dimethyl sulfoxide or dimethylformamide gave mainly the cyclosteroid **8** together with traces of the olefin **7**. Reduction with chromous chloride in aqueous ethanol afforded mainly the olefin **7** together with the acid-catalyzed decomposition products (*vide infra*) of the cyclosteroid **8**.

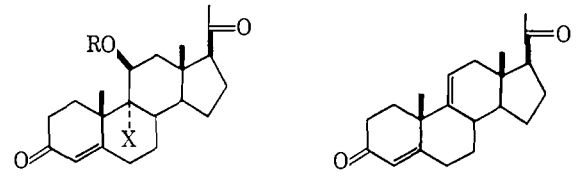
Reflection on the possible mechanism of the reduction suggested that the radical **11** might be the first intermediate rather than the chromous derivative **13**. If the radical were involved, then the addition of hydrogen radical transfer agents such as mercaptans should improve the yield of 11β-hydroxyprogesterone (**4**). In the event, reduction of **1** with chromous acetate in dimethyl sulfoxide in the presence of an excess of butane-1-thiol gave 11β-hydroxyprogesterone (**4**) in 80% yield. As will be discussed in the sequel, the generality of this progress has been confirmed by application to a number of bromohydrins and α-bromo fluorides.

The currently accepted view[17-19] on the reduction of organic halides by chromous salts is that two discreet one-electron transfers are involved (eq 2). The first transfer is considered to produce an intermediate radical which, in a rapid second step, is captured by a second chromous ion to furnish an organometallic intermediate. Protonolysis of the latter than completes the replacement of halogen by hydrogen. Kochi and his collaborators have lent convincing support to these views with their recent isolation of the "benzyl chromium"

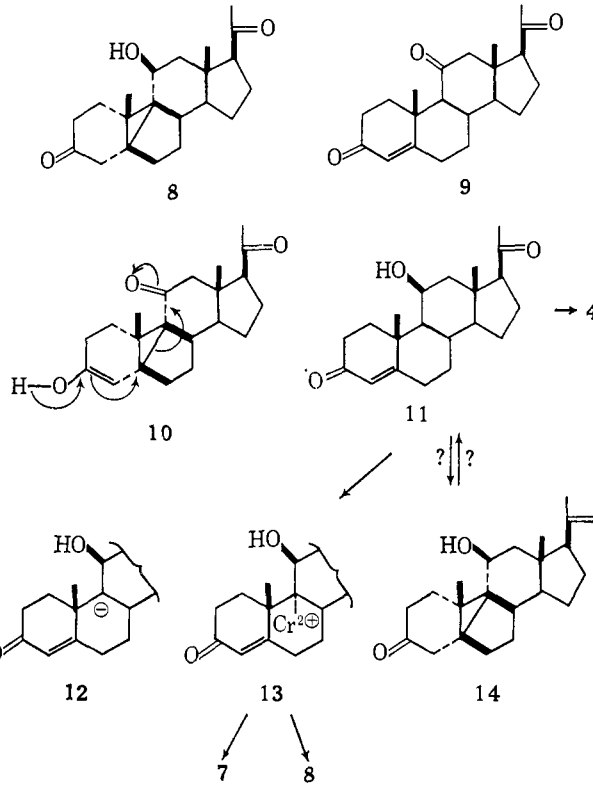


$Cr^{2\oplus}Br$ (2)

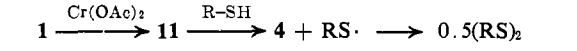
ion and subsequent detailed studies of its formation[20] and decomposition.[21] No direct evidence has, however, been forthcoming in support of free radicals as intermediates. Although the formation of dimeric products during the reduction of aralkyl halides with chromous ion has been attributed to the involvement of free radicals,[22] it has recently been shown that this coupling results from the reaction of unconsumed halide with an organochromium intermediate.[21] Reported attempts to capture radicals formed during the reduction of aralkyl halides by the addition of mercaptan[19] or dienes[20] have also been unsuccessful. We have, therefore, taken considerable pains to demonstrate the existence of a free-radical intermediate in the conversion of progesterone bromohydrin **1** to 11β-hydroxyprogesterone (**4**).



1, R = H; X = Br
2, R = CHO; X = Br
3, R = H; X = Br, 1,2-dehydro
4, R = X = H
5, R = CHO; X = H
6, R = X = H, 1,2-dehydro



Our view of the formation of **4** (eq 3) requires that a mercaptyl radical be produced for each mole of the alcohol **4**. Using *n*-butyl mercaptan under conditions where the oxidation of thiol to disulfide by dimethyl sulfoxide[23] is negligible, the reduction, in accord with



(3)

eq 3, produces the disulfide in theoretical yield. This is good evidence for the existence of radical **11**. It might, however, be argued that mercaptans are capable of protonolyzing an organochromium intermediate. This would not be due to the acidity of the mercaptan since acetic acid, phenol, and hydrochoric acid do not promote the formation of the alcohol **4**. It might, however, be due to the phenomenon of nucleophilic

(15) O. Gnoj, E. P. Oliveto, C. H. Robinson, and D. H. R. Barton, *Proc. Chem. Soc.*, 207 (1961).
(16) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953).
(17) F. A. L. Anet and E. LeBlanc, *ibid.*, 79, 2649 (1957); F. A. L. Anet, *Can. J. Chem.*, 37, 58 (1959); R. P. A. Sneeden and H. P. Throndsen, *Chem. Commun.*, 509 (1965).
(18) C. E. Castro and W. C. Kray, *J. Am. Chem. Soc.*, **85**, 2768 (1963).
(19) L. H. Slaugh and J. H. Raley, *Tetrahedron*, 20, 1005 (1964).
(20) J. K. Kochi and D. D. Davis, *J. Am. Chem. Soc.*, **86**, 5264 (1964).
(21) J. K. Kochi and D. Buchanan, *ibid.*, **87**, 853 (1965).
(22) C. E. Castro, *ibid.*, **83**, 3262 (1961).
(23) *Cf.* T. J. Wallace, *ibid.*, **86**, 2018 (1964).

assistance.[24] The effect of additional hydrogen transfer reagents, which could not be regarded as capable of protonolysis of a carbon–chromium bond, was therefore investigated. 1-Benzyl-1,4-dihydronicotinamide, 1,4-dihydrobenzene, and cyclopentadiene all served as suitable hydrogen donors affording, under standard conditions, 11β-hydroxyprogesterone (**4**) in yields of 67, 67, and 46%, respectively. Triphenyltin hydride,[25] triphenylsilane, and hypophosphorous acid (yields: 65, 40, and 87%, respectively) were also effective. We regard these results as definitive evidence for the free-radical intermediate **11**.

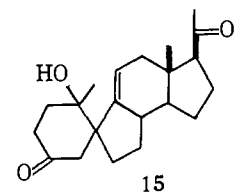
At this point it may be well to consider the difference between the complex, chromous acetate, and the uncomplexed chromous ion. Although chromous acetate is a diamagnetic binuclear complex,[26] the uncoordinated chromous ion is strongly paramagnetic (four unpaired electrons[27]). This difference made it possible that the formation of a capturable intermediate radical in the reduction of **1** by chromous acetate might be the result of a process quite different from that involved in reduction by the uncomplexed chromous ion. It was found, however, that addition of 1,4-dihydrobenzene to the bromohydrin **1** in the presence of chromous chloride in aqueous ethanol promoted the formation in good yield of 11β-hydroxyprogesterone (**4**). In the absence of 1,4-dihydrobenzene the major product was the olefin **7**. These results suggest that chromous ion reacts with the bromohydrin **1**, as does chromous acetate, to produce a capturable radical intermediate **11**. In keeping with expectation, we found that relatively large concentrations of 1,4-dihydrobenzene were needed to ensure capture of the radical **11** in the presence of the paramagnetic chromous ion. Table I summarizes the effect on this reduction of the variation of chromous ion concentration in the presence of a fixed concentration of the hydrogen donor 1,4-dihydrobenzene. These data show clearly that reduction of the radical intermediate **11** is competitive with the consumption of a second equivalent of chromous ion to furnish the olefin **7**.

Table I[a]

Vol of $CrCl_2$ soln added, ml	Products, % Olefin **7** + cyclosteroid **8**	Alcohol **4**
1	79	21
0.5	60	40
0.2	29	71

[a] Each experiment was based on bromohydrin **1** (50 mg) 1,4-dihydrobenzene (1 ml), absolute ethanol (12.5 ml), and sufficient water to make a total of 17.5 ml. The chromous chloride solution contained chromous chloride (1.9 g; Fisher) in water (10 ml).

We now turn to a more detailed discussion of how further reduction of radical **11** affords the olefin **7** and the cyclosteroid **8**. A thorough study of the factors influencing the partition of the intermediate radical by further reduction into **7** and **8** was rendered difficult by the sensitivity of cyclosteroid **8**. This compound decomposes slowly in aqueous dimethyl sulfoxide in the presence of chromic salts or in aqueous ethanol containing chromic chloride. The decomposition, which is acid catalyzed, affords the olefin **7** in small amount together with the alcohol **15** and the di-olefin **16**. The constitutions assigned to these latter two compounds are based upon analogy[28] and upon



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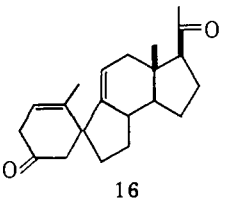

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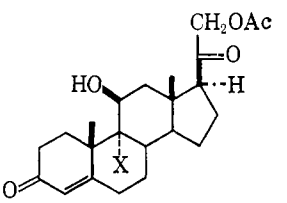
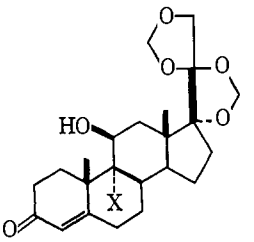
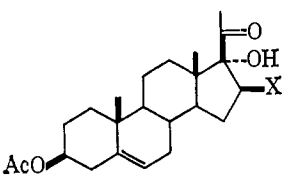


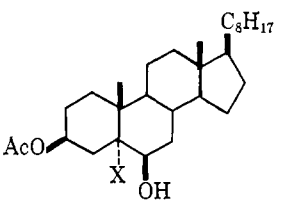
17, X=Br
18, X=H
19, X=Br, 1,2-dehydro
20, X=H, 1,2-dehydro



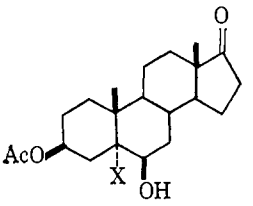
21, X=Br
22, X=H



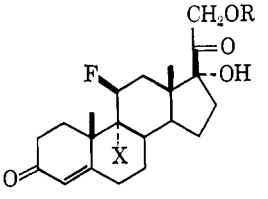
23, X=Br
24, X=H



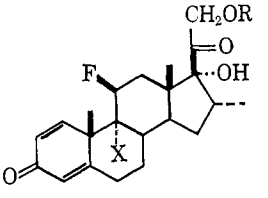
25, X=Br
26, X=H



27, X=Br
28, X=H



29, X=Br; R=Ac
30, X=H; R=Ac
31, X=Br; R=Ac, 1,2-dehydro
32, X=H; R=Ac, 1,2-dehydro



33, X=Br; R=CO_2Et
34, X=H; R=CO_2Et

(24) R. E. Dessy and F. E. Paulik, *J. Am. Chem. Soc.*, **85**, 1812 (1963); R. E. Dessy, T. Hieber, and F. Paulik, *ibid.*, **86**, 28 (1964).

(25) During the course of our work the thermal debromination of organic halides by triphenyltin hydride was reported: H. G. Kuivila, L. W. Menapace, and C. R. Warner, *ibid.*, **84**, 3584 (1962). We subsequently observed that this reagent will convert **1** to **4** at *elevated* temperature in the absence of chromous acetate.

(26) W. R. King, Jr., and C. S. Garner, *J. Chem. Phys.*, **18**, 689 (1950); J. N. van Niekerk, F. R. L. Schoening, and J. F. de Wet, *Acta Cryst.*, **6**, 501 (1953).

(27) E. Cartmelland and G. W. A. Fowles, "Valency and Molecular Structure," 2nd ed, Academic Press Inc., New York, N. Y., 1961, p 231.

the following considerations. The alcohol **15** was stable to sublimation, to treatment with base, and to chromic acid oxidation. Its nmr spectrum showed absorption at τ 4.78 (C_{11} olefinic proton), at 9.44 (C_{18} methyl group), and at 8.75 (Me attached to carbon bearing hydroxyl but no hydrogen). Dehydration of the alcohol **15** with thionyl chloride–pyridine gave the diolefin **16**. This showed nmr absorption at τ 4.62 (two olefinic protons), 9.35 (C_{18} methyl group), and 8.38 (methyl attached to C=C).

The second stage of reduction must afford the anion **12** or a structural equivalent. Although in our preliminary communication[12] we assigned a role to anion **12**, consideration of recent work[20] makes us favor an organochromium intermediate **13**. This intermediate must be short lived since the presence of acid does not cause protonolysis and formation of alcohol **8**. If the anion **12** were an intermediate it should certainly suffer the same fate. Conversion of **13** to chromic ion gives the equivalent of an anion at C_9, which could stabilize itself by addition to C_5 (cyclopropane formation) or by β elimination to give the olefin **7**. The addition of benzylchromium to acrylonitrile might provide a precedent for the former process.[20]

We have compared the reduction of the bromohydrin **1** and its formate and trifluoroacetate under the same conditions and in the absence of hydrogen donors. The relative amounts of olefin **7** formed in the three experiments were as 0.23:0.83:1.0. Clearly, attachment of an electronegative group at C_{11} directs the partition of **13** toward the olefin **7**. Such a result is in keeping with the above discussion and would appear to eliminate the possible equilibrium **11** $\rightleftharpoons$ **14** with subsequent fast reduction as well as an activated transfer of **11** to **14** followed by reduction. The polarity of the substituent at C_{11} should not alter markedly the relationships between two radicals such as **11** and **14**.

From the standpoint of synthetic utility, the most significant aspect of the above discussion is the susceptibility of the intermediate radical to reduction by hydrogen transfer reagents (see eq 1). Chromous acetate appears to be the reductant of choice, as it is readily prepared in pure form and relatively stable. Although a variety of solvents is acceptable, dimethyl sulfoxide and dimethylformamide are particularly suitable, since chromous acetate as well as many organic substrates are adequately dissolved by either. Similarly any of a number of hydrogen donors may be used with success, as has already been illustrated.

The transformations summarized in Table II illustrate the utility of our method of reduction especially in the synthesis of 11β-hydroxy steroids. The yields given are minimal since 11β-hydroxyprogesterone, subjected to the same experimental conditions, could only be recovered in about 80% yield on the scale on which our studies were undertaken.

A further application of our reduction procedure was in the synthesis of 11β-fluoro steroids,[29] a group of compounds not hitherto characterized, or studied from the point of view of physiological activity. The conversion of a 9α-bromo-11β-fluoro steroid[30] into an 11β-fluoro compound amounts to the addition of HF to the ethylenic linkage under neutral conditions in the sense of eq 1. Depending on stereochemical factors (direction of opening of the bromonium ion) this procedure can place the fluorine atom on the less substituted carbon, which is the opposite to the direction of addition of hydrofluoric acid.

Table II

Compd reduced	Product	Yield, %
1	**4**	80
3	**6**	80
17[a]	**18**	78
19[b]	**20**	74
21[c]	**22**	80
23[d]	**24**	35
25[e]	**26**	67
27[f]	**28**	65
29[g]	**30**	80
31[h]	**32**	32
33	**34**	46

[a] J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer, and P. Numerof, *J. Am. Chem. Soc.*, **76**, 1068 (1955). [b] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *ibid.*, **77**, 4181 (1955). [c] M. Akhtar, D. H. R. Barton, J. M. Beaton, and A. G. Hortmann, *ibid.*, **85**, 1512 (1963). [d] P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *ibid.*, **72**, 5145 (1950). [e] D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 4224 (1954). [f] V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *ibid.*, 4105 (1957); M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964). [g] A. Bowers, L. C. Ibáñez, E. Denot, and R. Becerra, *ibid.*, **82**, 4001 (1960). [h] C. H. Robinson, L. Finckenov, E. P. Oliveto, and D. Gould, *ibid.*, **81**, 2194 (1959).

The 11β-fluoro steroids prepared by this method are also listed in Table II. Reduction of the typical 9α-bromo 11β-fluoride (**29**) in the absence of a hydrogen donor gave only the elimination product (9(11)-olefin). Mild hydrolysis of compounds **32** and **34** afforded the corresponding alcohols.

Experimental Section

Microanalyses were performed by Dr. A. Bernhardt of the Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were run on a Perkin-Elmer 137 Infracord. Melting points were taken on a Kofler-type hot stage and are reported uncorrected. Optical rotations were measured with a Rudolph photoelectric polarimeter and refer to 0.5–1.0% w/v in $CHCl_3$ unless otherwise noted. Nuclear magnetic resonance spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer. All reactions with chromous salts were carried out under carbon dioxide.

Preparation of Chromous Acetate. Chromium metal powder (9 g, Fisher, 99+% purity) was allowed to react completely with excess hydrochloric acid (100 ml, 6 *M*) with stirring and water-bath (room temperature) cooling. A deoxygenated solution of sodium acetate (50 g in deoxygenated water (100 ml)) was added and stirring was continued at ice-bath temperature. The precipitated chromous acetate was collected and washed with deoxygenated water, ethanol, and ether (12 g, 80–85% purity as titrated for reducing power). This material could be transferred in air without undue decomposition and could be stored for several months in stoppered vials under carbon dioxide.

Formation of 11β-Hydroxy-5,9-cyclopregnane-3,20-dione (8). 9α-Bromo-11β-hydroxyprogesterone (500 mg) in dimethyl sulfoxide (40 ml) was treated at room temperature with chromous acetate (5 moles), stirred for 5 hr at room temperature, and then left over-

(28) C. H. Robinson, O. Gnoj, E. P. Oliveto, and D. H. R. Barton, *J. Org. Chem.*, in press.

(29) A mixture of 11β-fluoro- and 9α-fluoroprogesterone, obtained from 11α-hydroxyprogesterone in poor yield, has been mentioned by D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(30) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *J. Am. Chem. Soc.*, **81**, 2191 (1959); A. Bowers, *ibid.*, **81**, 4107 (1959).

night. Dilution with water, extraction into methylene dichloride, and chromatography over acid-washed alumina (20 g) gave, on elution with methylene dichloride, 9(11)-dehydroprogesterone (24 mg). Further elution with 0.5% methanolic methylene dichloride, and crystallization from ethyl acetate–hexane, afforded 11β-hydroxy-5,9-cyclopregnane-3,20-dione (235 mg), mp 132–143°. After further recrystallization the analytical sample had mp 139–147°, $[\alpha]D$ −25°, ν_{max}^{KBr} 3550 (s), 1723 (s), and 1690 (s) cm^{-1}, and showed no high intensity ultraviolet absorption down to 210 mμ.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.53; H, 9.12; O, 14.47. This hydroxy diketone (100 mg) in pyridine (5 ml) was added to chromium trioxide (250 mg) in pyridine (5 ml) and kept at room temperature for 20 min. Addition of water and extraction from pyridine gave a product (40 mg) which was chromatographed over acid-washed alumina. Elution with 0.4% methanolic methylene dichloride and crystallization from ethyl acetate gave 11-ketoprogesterone (30 mg).

Decomposition Products of 11β-Hydroxy-5,9-cyclopregnane-3,20-dione. The cyclosteroid **8** (370 mg) was taken up in ethanol (40 ml) and water (25 ml) containing chromous chloride (1 g) and left at room temperature for 24 hr. After concentration *in vacuo* and dilution with water the gummy product (370 mg) was recrystallized from ether–hexane to furnish the spiro alcohol **15** (165 mg), mp 148–152°, $[\alpha]D$ +42°, ν_{max}^{KBr} 3700 (m) cm^{-1} and 1705 (vs) cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.62; H, 8.82; O, 14.73.

This alcohol was recovered unchanged after sublimation *in vacuo* under 0.45 mm at 255–270° and after treatment for 6 hr with 0.4% methanolic sodium hydroxide under reflux.

The spiro alcohol **15** (50 mg) in pyridine (1 ml) was treated at 0° with thionyl chloride (0.02 ml). After 30 min (control by thin layer chromatography) the solution was diluted with water and filtered. Crystallization of the product from aqueous methanol gave the olefin **16**, mp 122–135°, $[\alpha]D$ +65°, ν_{max}^{KBr} 1720 (vs) cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03; O, 10.24. Found: C, 80.60; H, 8.85; O, 10.33.

Formation of 11β-Hydroxyprogesterone (4). Chromous acetate (5 moles) was added with stirring at room temperature to 9α-bromo-11β-hydroxyprogesterone (500 mg) in dimethyl sulfoxide (40 ml, Matheson Coleman and Bell, not further purified) containing *n*-butanethiol (1 ml, *ca.* 7.5 moles) and the stirring was continued for 15 hr. After pouring into ice water and extraction into methylene dichloride, removal of the solvent *in vacuo* gave, on digestion with ethyl acetate, 11β-hydroxyprogesterone (300 mg), mp 182–185°. Chromatography of the ethyl acetate mother liquors over acid-washed alumina furnished, on elution with 0.4% methanolic methylene dichloride, further 11β-hydroxyprogesterone (24 mg).

When pure 11β-hydroxyprogesterone (500 mg) was taken through the whole of the above procedure the percentage recovery was 80%.

The following thiols, added in the same molar proportions, gave the same yield of 11β-hydroxyprogesterone: methanethiol, ethanethiol, and thiophenol.

Additional hydrogen donors were investigated under the same conditions of reaction and work-up. The relative proportions of reactant used and the yields obtained are listed in Table III.

Table III

Bromohydrin **1**, mg	$Cr(OAc)_2$, mg	Dimethyl sulfoxide, ml	Hydrogen donor (quantity)	11β-Hydroxyprogesterone **4**, mg
250	750	10	N-Benzyldihydronicotinamide (340 mg)	135
500	1400	30	1,4-Cyclohexadiene (0.25 and 2.0 ml)	268
140	300	15	Cyclopentadiene (0.5 ml)	80
500	1400	35	Ph_3SnH (3.2 g)	261
500	1400	35	Ph_3SiH (1.5 g)	163
285	800	10	H_3PO_2 (0.5 ml of 50% aqueous)	200

In a related experiment the bromohydrin **1** (250 mg) in dimethyl sulfoxide (11 ml) containing triphenyltin hydride (1.07 g) was heated on the steam bath for 4 hr. Working-up as above, including chromatography over acid-washed alumina, gave 11β-hydroxyprogesterone (**4**, 122 mg, 61%).

The following experiments were carried out using the bromohydrin **1** (1 mmole) and chromous acetate (5 mmoles) in solvent (25 ml) to test the effects of various additives. The reaction period was 18 hr. See Table IV for results.

Table IV

Additive (quantity)	Products
In Dimethyl Sulfoxide	
None	Cyclosteroid **8** + olefin **7** (*ca.* 10%)
CH_3CO_2H (2 ml)	Cyclosteroid **8** + olefin **7** (*ca.* 10%)
Cyclohexadiene (2 ml)	11β-Hydroxyprogesterone (**4**)
CH_3CO_2H (2 ml) + cyclohexadiene (2 ml)	11-β-Hydroxyprogesterone (**4**)
Et_2NH	Cyclosteroid **8** + olefin **7** (*ca.* 25%)
In 80% Aqueous Dimethyl Sulfoxide	
None	Cyclosteroid **8** + olefin **7** (*ca.* 35%)
CH_3CO_2H (1 ml)	Cyclosteroid **8** + olefin **7** (*ca.* 35%)
Cyclohexadiene (2 ml)	11β-Hydroxyprogesterone (**4**)

Reduction of 9α-Bromopregna-1,4-dien-11β-ol-3,20-dione (3). Pregna-1,4,9(11)-triene-3,20-dione (24.5 g) in purified dioxane (1.6 l.) containing 1 *N* aqueous perchloric acid (164 ml) and water (328 ml) was treated with N-bromoacetamide (16.4 g) at room temperature with stirring for 3 hr. Excess of dilute, aqueous sodium sulfite was added and the solution was thoroughly extracted with methylene dichloride. The extract was washed with dilute aqueous sodium hydrogen carbonate and with water and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Trituration of the residue with ethyl acetate afforded 9α-bromopregna-1,4-dien-11β-ol-3,20-dione (**3**, 25 g) as prisms, mp 164–167° dec. Thin layer chromatography showed only a trace (<5%) content of starting material. Further crystallized from methanol, the analytical specimen had mp 177–178° dec; ν_{max}^{KBr} 3500 (m, br), 1710 (s) 1665 (vs), 1625 (s), and 1615 (s) cm^{-1}.

Anal. Calcd for $C_{21}H_{27}BrO_3$: C, 61.92; H, 6.68; Br, 19.62; O, 11.78. Found: C, 61.71; H, 6.94; Br, 19.82; O, 11.90.

The above bromohydrin **3** (8.83 g) in dimethyl sulfoxide (340 ml, redistilled) containing butane-1-thiol (7.9 moles) was treated with chromous acetate (12 g) with stirring for 17 hr. The solution was diluted with water and extracted with methylene dichloride. Concentration of the solvent *in vacuo* gave 11β-hydroxypregna-1,4-diene-3,20-dione (3.82 g), mp 228–233°; ν_{max}^{KBr} 3650, 3500 (s, doublet), 1700 (s), 1665 (vs), 1620 (s), and 1610 (w, shoulder) cm^{-1}. The filtrate was evaporated and the residue was chromatographed in methylene dichloride containing increasing amounts of methanol, to give (i) dibutyl disulfide (2.4 g), bp 130–135° (22 mm), 2.05 g, identified by infrared spectrum, thin layer chromatography, and refractive index; and (ii) 11β-hydroxypregna-1,4-diene-3,20-dione (1.87 g), mp 230–233° (total yield 80%). The analytical specimen, crystallized from methanol, had mp 242–243°.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14.62. Found: C, 76.72; H, 8.57; O, 14.83.

In a similar experiment the bromohydrin (8.37 g), reduced with chromous acetate (11 g) in dimethyl sulfoxide (340 ml, redistilled) containing butane-1-thiol (22.2 ml) for 17 hr, gave dibutyl disulfide (1.83 g, purified by distillation) and 11β-hydroxypregna-1,4-diene-3,20-dione (75%). An identical experiment, but without the steroid added, gave, after 18.5 hr, dibutyl disulfide (460 mg).

Application of Standard Debromination Conditions. All reactions were carried out at room temperature the solutions being stirred overnight. Table V summarizes the results obtained.

Preparation of 11β-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione 21-Acetate (30). The bromo fluoride **29** (600 mg) in dimethyl sulfoxide (50 ml) containing *n*-butanethiol (2 ml) was treated with chromous acetate (1.5 g) and stirred overnight at room temperature. Chromatography of the product over acid-washed alumina afforded 11β-fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate (**30**, 474 mg). Crystallized, from ethyl acetate, this compound had mp 206–208°, $[\alpha]D$ +162°, λ_{max}^{MeOH} 239 mμ (ε 15,400); ν_{max}^{KBr} 3300 (m), 1740 (s), 1720 (s), and 1660 (vs) cm^{-1}.

Anal. Calcd for $C_{23}H_{31}FO_5$: C, 67.96; H, 7.69; F, 4.67. Found: C, 67.85; H, 7.77; F, 4.82.

Table V

Compd reduced, mg	Dimethyl sulfoxide, ml	Chromous acetate, mg	*n*-Butanethiol, ml	Product, %
17, 602	34	1400	1.0	**18**, 78
19, 600	35	1400	1.0	**20**, 74
21, 571	60	1260	1.05	**22**, 80
23, 555	34	1400	1.0	**24**, 35
25, 275	25	780	1.0	**26**, 67
27, 522	35	1400	1.5	**28**, 65[a]

[a] M. Akhtar, D. H. R. Barton, and P. G. Sammes, *J. Am. Chem. Soc.*, **87**, 4601 (1965).

In a control experiment the bromo fluoride **29** (100 mg) in dimethyl sulfoxide (9 ml) was treated with chromous acetate (300 mg) as in the above experiment. The homogeneous product (thin layer chromatography), crystallized from methylene dichloride–methanol, gave only 9(11)-anhydrocortisol acetate.

Mild alkaline hydrolysis as for the 16α-methyl steroid described below gave 11β-fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione. Recrystallized from methylene dichloride–methanol, this compound had mp 235–240°, $[\alpha]_D$ +170° (*c* 0.33, 11 methanol–methylene dichloride); λ_{max}^{MeOH} 239 mμ (ε 16,000); ν_{max}^{KBr} 3400 (s), 1710 (s), 1660 (vs), and 1610 (m) cm^{-1}.

Anal. Calcd for $C_{21}H_{29}FO_4$: C, 69.21; H, 8.02; F, 5.21. Found: C, 69.03; H, 8.05; F, 5.28.

Preparation of 11β-Fluoro-17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-Acetate (32). The bromofluoride **31** (200 mg) in dimethyl sulfoxide (10 ml) containing *n*-butanethiol (0.5 ml) was treated with chromous acetate (750 mg) overnight at room temperature. Chromatography of the product over acid-washed alumina afforded 11β-fluoro-17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate (**32**, 52 mg). Crystallized from acetone–cyclohexane, this compound had mp 206–209°, $[\alpha]_D$ +103°, λ_{max}^{MeOH} 241 mμ (ε 14,500); ν_{max}^{KBr} 3500 (m), 1740 (s), 1710 (s), 1660 (vs), 1630 (m), and 1610 cm^{-1}.

Anal. Calcd for $C_{23}H_{29}FO_5$: C, 68.30; H, 7.23; F, 4.70. Found: C, 68.40; H, 7.42; F, 4.07.

Preparation of 11β-Fluoro-16α-methylpregna-1,4-diene-17α,21-diol-3,20-dione. The bromofluoride **33** (1.91 g) in dimethyl sulfoxide (35 ml) containing *n*-butanethiol (5.0 ml) was treated with chromous acetate (4.6 g) overnight at room temperature. Chromatography of the product over acid-washed alumina (50 g) gave the fluoro steroid **34** (750 mg). Crystallized from methanol, this compound had mp 176–178°, $[\alpha]_D$ +80°, λ_{max}^{MeOH} 242 mμ (ε 14,700); ν_{max}^{KBr} 3500 (s), 175 (s), 1730 (s), 1660 (vs), 1620 (m), and 1600 (m) cm^{-1}.

Anal. Calcd for $C_{25}H_{33}FO_6$: C, 66.95; H, 7.42; F, 4.24. Found: C, 66.76; H, 7.32; F, 3.97.

This ester **34** in methylene dichloride and methanol (20 ml) was treated with aqueous sodium hydroxide (2.75 ml of 1.0 *N*) for 1 hr at room temperature. Chromatography of the product over acid-washed alumina giave 11β-fluoro-16α-methylpregna-1,4-diene-17α,21-diol-3,20-dione (410 mg). Crystallized from acetone–cyclohexane, this compound had mp 175–189°, $[\alpha]_D$ +64°, λ_{max}^{MeOH} 241 mμ (ε 15,000); λ_{max}^{KBr} 3600 (s), 1700 (s), 1660 (vs), and 1620 (m) cm^{-1}.

Anal. Calcd for $C_{22}H_{29}FO_4$: C, 70.19; H, 7.76; F, 5.05. Found: C, 70.04; H, 7.80; F, 5.20.

Comparative Reduction of 9α-Bromo-11β-acyloxy Compounds. For this study 9α-bromo-11β-formyloxyprogesterone was prepared by standard methods.[31] Recrystallized from methylene dichloride–ether, this compound had mp 160–173° dec, $[\alpha]_D$ +208°, ν_{max}^{KBr} 3000, 1735, 1710, 1660, and 1150 cm^{-1}.

Anal. Calcd for $C_{22}H_{29}BrO_4$: C, 60.42; H, 6.68; O, 14.63; Br, 18.27. Found: C, 60.32; H, 6.90; O, 14.55; Br, 18.02.

The following compounds (a) 9α-bromo-11β-hydroxyprogesterone (163 mg), (b) 9α-bromo-11β-formyloxyprogesterone (172 mg), and (c) 9α-bromo-11β-trifluoroacetoxyprogesterone (200 mg) were each separately reduced with chromous acetate (240 mg) in dimethyl sulfoxide (10 ml) for 45 min. The reaction mixtures were diluted with ether (70 ml) and washed with water (25 ml). Standardized aliquots of each organic extract were scanned for ultraviolet absorption at 240 mμ. The balance was dried and the solvent was removed *in vacuo*. The residue was assayed by thin layer chromatography and the major product crystallized. Compound a gave mainly cyclosteroid; b and c gave largely 9(11)-dehydroprogesterone. The relative amounts of the latter for a, b, and c were 0.23, 0.83, and 1.0 as determined by ultraviolet measurements and checked by thin layer chromatography.

(31) C. H. Robinson and L. E. Finckenor, U. S. Patent 2,986,564 (1965).

Photochemical Reactions of Metal-Complexed Olefins. II. Dimerization of Norbornene and Derivatives[1]

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Abstract: The cuprous halide catalyzed photodimerization of norbornene has been studied in detail. In all instances the reaction was highly stereoselective to the cyclobutane-fused *exo,trans,exo* dimer. Quantum-yield measurements suggest that the mechanism involves attack of a photoexcited norbornene–cuprous halide complex on two uncomplexed ground-state norbornenes, with the dimerization proceeding *via* a transient 3:1 olefin–CuX tetrahedral intermediate. Spectral data have been gathered in an effort to elucidate the nature of the metal–olefin complex.

Until quite recently, examples of photochemical reactions involving metal–olefin complexes were few.[2] In 1959, Pettit reported[3] the light-catalyzed dimerization of norbornadiene in the presence of pentacarbonyliron(0). However, subsequent work showed that the reaction also proceeded in the dark.[4] More recently, Srinivasan reported[5] a variety of intramolecular rearrangements of dienes, both acyclic and cyclic. These photoinduced reactions required the presence of

(1) For part I, see D. J. Trecker, J. P. Henry, and J. E. McKeon, *J. Am. Chem. Soc.*, **87**, 3261 (1965).

(2) For a review, see W. Strohmeier, *Angew. Chem. Intern. Ed. Engl.*, **3**, 730 (1964).

(3) R. Pettit, *J. Am. Chem. Soc.*, **81**, 1266 (1959).

(4) C. W. Bird, D. L. Colinese, R. C. Cookson, J. Hudec, and R. O. Williams, *Tetrahedron Letters*, 373 (1961).

(5) (a) R. Srinivasan, *J. Am. Chem. Soc.*, **85**, 3048 (1963); (b) R. Srinivasan, *ibid.*, **86**, 3318 (1964).