Mercuration of α,β-Unsaturated Steroidal Ketones and Other Unsaturated Systems[1]

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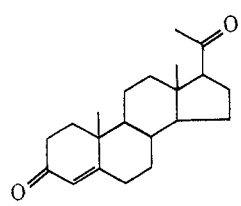
Received June 7, 1972

For the preparation of androgen and progesterone receptor inhibitors, the oxymercuration of α,β-unsaturated ketones was studied. In contrast to a number of model compounds, steroidal α,β-unsaturated ketones were unreactive when treated with mercuric acetate in methanol at room temperature. For those 3-keto steroids with a readily abstractable allylic proton, heating of the steroid with mercuric acetate in methanol and in acetic acid resulted in the formation of mercurous acetate, presumably due to oxidation of the steroid. For those 3-keto steroids without this structural feature and with a C-1 double bond, addition of acetoxymercuri ion occurs in acetic acid at the α side of the C-1 double bond. The proton at C-2 is abstracted, and the 2-acetoxymercuri-1-en-3-one is formed. The acetate ion was replaced with chloride ion, and 2-chloromercuri-5α-androst-1-ene-3,17-dione, 2-chloromercuri-1,4-androstadiene-3,17-dione, 2-chloromercuri-1,4,6-androstatriene-3,17-dione, 2-chloromercuri-1,4,6-androstatrien-17β-ol-3-one, 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one, and 2-chloromercuri-1,4,6-pregnatriene-3,20-dione were isolated.

The isolation from the chick oviduct of a protein which binds progesterone (**1**) with great affinity ($k_d \simeq 8.3 \times 10^{-10}$ mol/l. in 0.3 *M* KCl at 1–4°) has been described by Sherman, Corvol, and O'Malley.[3] This protein may function as a progesterone target tissue receptor. The addition of sodium *p*-chloromercuribenzoate to the oviduct receptor eliminates the binding of progesterone, indicating the presence of sulfhydryl groups at or near the binding site. It is feasible that if a functionalized steroid could be synthesized which would bind irreversibly to a sulfhydryl group, progesterone binding to the oviduct receptor would be blocked.

Chin and Warren[4] have described the synthesis of 4-acetoxymercuriestradiol (**2**) and its use for the affinity



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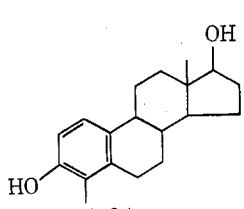


2

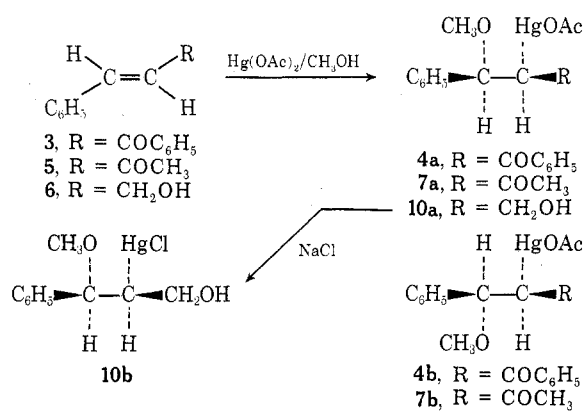
labeling of sulfhydryl groups. Muldoon and Warren[5] demonstrated that this mercurated steroid mimics estradiol in the production of certain biological responses and in the mode of its binding to uterine estradiol receptors. Further experiments[6] now indicate that 4-acetoxymercuriestradiol binds irreversibly to an estradiol receptor.

This work encouraged us to attempt the synthesis of mercurated steroids which would bind irreversibly to progesterone or androgen receptors. Our aim was to introduce mercury into the steroidal skeleton adjacent to the C-3 carbonyl group by the direct oxymercuration of α,β-unsaturated ketones.

Results and Discussion

Oxymercuration of α,β-Unsaturated Ketones and Alcohols.—Methoxymercuration of *trans*-benzalacetophenone (**3**) with mercuric acetate in methanol at room temperature gave α-acetoxymercuri-β-methoxy-β-phenylpropiophenone (**4**) (Scheme I).[7] On the assumption that the oxymercuration of an unstrained olefin such as **3** [as well as *trans*-benzalacetone (**5**) and cinnamyl alcohol (**6**) below] is preferably trans,[8] the nmr spectrum of the crude reaction product indicated that it contained 81% of the erythro (**4a**) and 19% of the threo (**4b**) isomer. Recrystallization of the crude product gave **4a** with the same sharp melting point as the compound described by Middleton.[7]

SCHEME I



Treatment of *trans*-benzalacetone (**5**) with mercuric acetate in methanol at room temperature gave 3-acetoxymercuri-4-methoxy-4-phenyl-2-butanone (**7**) (Scheme I). The nmr spectrum of the crude product indicated that the erythro (**7a**) and threo (**7b**) isomers are formed in the ratio of 85:15, respectively. The crude reaction product was further characterized by replacement of the acetoxymercuri group with bromine and with iodine.[9,10] *erythro*-3-Bromo- and -3-iodo-4-methoxy-4-phenyl-2-butanone (**8a** and **9a**) and the respective threo isomers (**8b** and **9b**) were formed, but

(1) Supported by the Agency for International Development under Contract AID/csd 2491 administered by the Population Council; presented at the 24th Southeastern Regional Meeting of the American Chemical Society, Birmingham, Ala., Nov 1972, Abstract 300.

(2) Supported by National Institutes of Health Grant HD-05797.

(3) M. R. Sherman, P. L. Corvol, and B. W. O'Malley, *J. Biol. Chem.*, **245**, 6085 (1970).

(4) C.-C. Chin and J. C. Warren, *ibid.*, **243**, 5056 (1968).

(5) T. G. Muldoon and J. C. Warren, *ibid.*, **244**, 5430 (1969).

(6) T. G. Muldoon, *Biochemistry*, **10**, 3780 (1971).

(7) E. B. Middleton, *J. Amer. Chem. Soc.*, **45**, 2763 (1923).

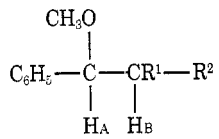
(8) W. Kitching, *Organometal. Chem. Rev.*, **3**, Part A, 61 (1968).

(9) F. R. Jensen and L. H. Gale, *J. Amer. Chem. Soc.*, **82**, 148 (1960).

(10) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, pp 77–86.

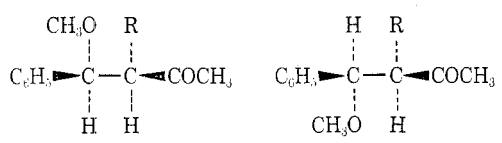
TABLE I

NMR DATA FOR OXYMERCURI AND OXYHALO COMPOUNDS IN DEUTERIOCHLOROFORM[a]



Compd	R^1	R^2	Configuration	δ_{H_A}[b]	δ_{H_B}[b]	J_{AB}, Hz	δ_{OCH_3}[c]	R^2, δ_{CH}[c]
4a	HgOAc	COC_6H_5	Erythro	5.20	4.62	7.0	3.32	
4b	HgOAc	COC_6H_5	Threo	5.25	4.79	9.5	3.21	
7a	HgOAc	$COCH_3$	Erythro	4.93	3.83	6.5	3.25	2.04
7b	HgOAc	$COCH_3$	Threo	*d*	*d*	*d*	3.17	2.29
8a	Br	$COCH_3$	Erythro[e]	4.57	4.46	8.0	3.27	2.15
8b	Br	$COCH_3$	Threo[e]	4.55	4.27	9.5	3.13	2.33
9a	I	$COCH_3$	Erythro[e]	4.76	4.41	9.5	3.22	2.11
9b	I	$COCH_3$	Threo[e]	4.69	4.42	10.5	3.19	2.44
10b	HgCl	CH_2OH	Erythro	4.71	3.34[f]	7.5	3.26	
11[g]	HgBr	COC_6H_5	*h*	5.35	4.60	*i*	*i*	*i*
12[g]	HgBr	CO_2CH_3	*h*	5.00	3.65	*i*	*i*	*i*

[a] Chemical shift (δ) in parts per million downfield from TMS. Measured at 60 MHz at about 35°. [b] Doublet or as noted otherwise. [c] Singlet. [d] Too weak to observe. [e] Tentative assignment. [f] Center of multiplet, 3.21–3.50 ppm. [g] From ref 11. [h] Not assigned. [i] Not reported.



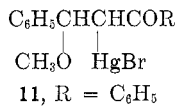
8a, R = Br
9a, R = I

8b, R = Br
9b, R = I

in each case, only one isomer was isolated and this is tentatively assigned the threo configuration (**8b** and **9b**).

Cinnamyl alcohol (**6**) was also methoxymercurated (Scheme I). The crude product was characterized as 2-chloromercuri-3-methoxy-3-phenyl-1-propanol (**10b**). Its nmr spectrum indicates that mainly the erythro isomer (**10a**) is formed in the reaction.

The structure of erythro-α-acetoxymercuri-β-methoxy-β-phenylpropiophenone (**4a**) was established directly by Middleton.[7] The assignment of the structures to the other mercuration (**4b**, **7**, and **10**) and halogenation (**8** and **9**) products are made by comparison of their respective nmr spectra with that of **4a** (Table I). The assigned chemical shifts for **4**, **7**, and **10** are in accord with those reported[11] for α-bromomercuri-β-methoxy-β-phenylpropiophenone (**11**) and methyl α-bromomercuri-β-methoxy-β-phenylpropionate (**12**) (Table I). The coupling between the chiral protons in **11** and **12** was not reported and the configurations of these two compounds were not assigned.[11]



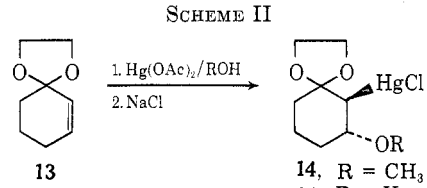
11, R = C_6H_5
12, R = OCH_3

The nmr spectra of the halogenation products of **7a** show a shift to lower field for the high-field chiral proton signal. This confirms our assignments of the low-field and high-field signals of **7a** (Table I). Since the preferred conformation of erythro and threo isomers of **8** and **9** could not be predicted,[12] comparisons of the chemical shifts and coupling constants of the chiral protons and the chemical shifts of the methyl protons in the spectra of *erythro*- and *threo*-**8** and -**9** with *erythro*- and *threo*-**7** were used to tentatively assign the configurations of the isomers of **8** and **9**.

Oxymercuration of 2-cyclohexenone in methanol and in tetrahydrofuran (THF)–water[13] was unsuccessful. In THF–water, 2-cyclohexenone apparently reacts, as evidenced by the typical precipitation and color changes reported for this type of reaction.[13] The product did not have the expected properties of an α-mercuri ketone and remains unidentified.

Methoxy- and hydroxymercuration of 2-cyclohexenone ethylene ketal (**13**) at room temperature gave *trans*-2-chloromercuri-3-methoxycyclohexanone ethylene ketal (**14**) and *trans*-2-chloromercuri-3-hydroxycyclohexanone ethylene ketal (**15**), respectively (Scheme II). Treatment of either ketal with aqueous acid

SCHEME II



13

14, R = CH_3
15, R = H

caused hydrolysis of the ketal blocking group, but returned only 2-cyclohexenone.

The structure and configuration of **14** and **15** were assigned on the basis of their nmr spectra. The constant for the coupling between the two chiral protons (10.5–12.0 Hz) shows them to be diaxial.[14] The signal for the C-2 proton in the nmr spectra of **14** and **15** is a doublet at 2.66 and 2.71 ppm, respectively. The multiplet due to the C-3 proton in each is at a substantially different chemical shift, 3.23–3.60 ppm for **14** and 3.78–4.36 ppm for **15**, and thus the structures of **14** and **15** are as assigned.

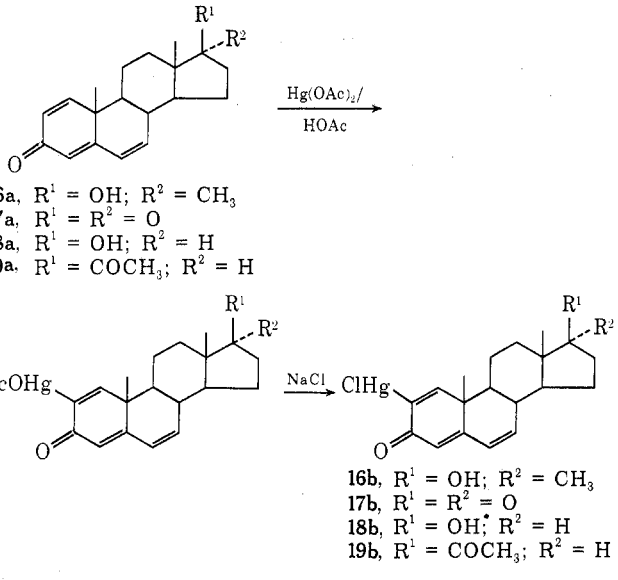
Oxymercuration of Steroids.—Using the same reactions as discussed above for methoxy- and hydroxy-

(11) A. J. Bloodworth and R. J. Bunce, *J. Chem. Soc. C*, 1453 (1971).
(12) C. A. Kingsbury and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967).
(13) H. C. Brown and P. J. Geoghegan, Jr., *ibid.*, **35**, 1844 (1970).
(14) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

mercuration, progesterone (1) and its bis ethylene ketal were unreactive at room temperature even on the addition to the former reaction of a catalytic amount of perchloric acid. Similarly, 1,4-androstadien-17β-ol-3-one, 5α-androst-1-ene-3,17-dione, 5-pregnen-3β-ol-20-one, and 5-androstene-3β,17β-diol 17-benzoate were unreactive. Attempts to force reaction with progesterone (1) were unsuccessful in that heating a mixture of 1 and mercuric acetate in methanol and in methanol with added perchloric acid resulted in the precipitation of a large quantity of mercurous acetate, presumably owing to oxidation of progesterone by mercuric acetate. Precipitation of a large amount of mercurous acetate also occurs when 4-androstene-3,17-dione is boiled with mercuric acetate in acetic acid.

Substitution of Mercury at C-2 in the Steroid Nucleus.—The ready oxidation of progesterone (1) by mercuric acetate in boiling acetic acid is probably related to dehydrogenation reactions by mercuric acetate under similar conditions.[15] It may be assumed that, if an unsaturated steroidal ketone does not have an easily abstractable allylic hydrogen atom, the steroid would be resistant to oxidation on heating with mercuric acetate in acetic acid, and an oxymercury adduct, similar to **4** and **7**, might be obtained. This argument may be used to explain a reaction recently reported by Kocor and Gumulka.[16,17] In an attempt to oxidize 17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16a**), they obtained 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16b**) (Scheme III). The

SCHEME III



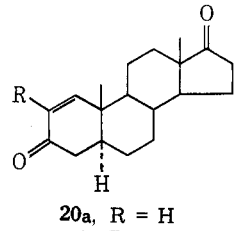
16a, R^1 = OH; R^2 = CH_3
17a, R^1 = R^2 = O
18a, R^1 = OH; R^2 = H
19a, R^1 = $COCH_3$; R^2 = H

16b, R^1 = OH; R^2 = CH_3
17b, R^1 = R^2 = O
18b, R^1 = OH; R^2 = H
19b, R^1 = $COCH_3$; R^2 = H

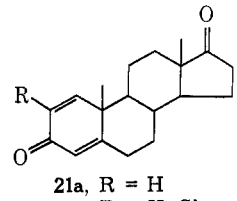
steroid **16a** is resistant to oxidation, since the allylic hydrogen at C-8 is not easily abstracted.[18]

As suggested by this reasoning, a series of steroids containing the 1,4,6-trien-3-one system (**17a–19a**) was mixed with mercuric acetate in boiling acetic acid. After reaction, the products were treated with sodium chloride, and 2-chloromercuri-1,4,6-androstatriene-3,17-dione (**17b**), 2-chloromercuri-1,4,6-androstatrien-17β-ol-3-one (**18b**), and 2-chloromercuri-1,4,6-pregnatriene-3,20-dione (**19b**) were obtained. Similarly, 2-chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**16b**) was also prepared from **16a**. In none of these reactions was mercurous acetate formed in any appreciable amount.

During the course of reaction of **16a–19a** with mercuric acetate, it is possible to follow the conversion of the steroidal substrate to the 2-acetoxymercuri derivative using nmr spectroscopy. In the substrate spectrum, the doublet at 7.1 ppm (J = 10.0 Hz) is assigned to the proton at C-1. On mercuration at C-2, this doublet collapses to a singlet and is shifted to a slightly lower field. Using this technique, it was found that, while **16a–18a** react very readily with an equivalent amount of mercuric acetate (50% conversion in 15 min at 118°), a comparable conversion of **19a** in 15 min requires a 4-equiv excess of mercuric acetate. The reactivity of 5α-androst-1-ene-3,17-dione (**20a**) is also less than that of **16a–18a** and a 50% conversion to 2-acetoxymercuri-5α-androst-1-ene-3,17-dione required a reaction time of 24 hr with a 4-equiv excess of mercuric acetate. 2-Chloromercuri-5α-androst-1-ene-3,17-dione (**20b**) was prepared using these reaction conditions.



20a, R = H
b, R = HgCl



21a, R = H
b, R = HgCl

The 1,4-dien-3-one and 4,6-dien-3-one systems are also resistant to oxidation by mercuric acetate in boiling acetic acid. Using a 4-equiv excess of mercuric acetate, 1,4-androstadiene-3,17-dione (**21a**) was converted to its 2-acetoxymercuri derivative and 2-chloromercuri-1,4-androstadiene-3,17-dione (**21b**) was isolated. A 50% conversion required a reaction time of 6 hr. Similar attempts to mercurate 1,4-androstadien-17β-ol-3-one, 1,4-pregnadiene-3,20-dione, and 4,6-pregnadiene-3,20-dione were unsuccessful. In none of these reactions was more than a trace of mercurous acetate produced.

The structure of each of the 2-chloromercuri steroids, **16b–21b**, was established by combustion analysis and a variety of spectral measurements. All show a strong absorption band at 1610–1640 cm^{-1}, shifted 15–35 cm^{-1} bathochromically from 1640–1665 cm^{-1} for the unmercurated steroid. Contrary to the report by Kocor and Gumulka[16,17] there is no absorption band in the ir spectra of **16b** in the region 1650–1750 cm^{-1}. The nmr spectra of the mercurated steroids showed predictable differences from those of the parent steroids. Finally, the mass spectrum of each of the 2-chloromercuri steroids showed molecular ions and daughter fragments of the expected mercury isotope pattern.[19] The interpretation of the fragmentations is simplified by this characteristic pattern and is in accord with the assigned structures.

(15) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 644–646.
(16) M. Kocor and M. Gumulka, *Tetrahedron Lett.*, 3067 (1969).
(17) M. Kocor and M. Gumulka, *Rocz. Chem.*, **45**, 1003 (1971).
(18) R. H. Shapiro and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2825 (1964).
(19) "Handbook of Chemistry and Physics," 43rd ed, C. D. Hodgman, R. C. Weast, R. S. Shankland, and S. M. Selby, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1962, pp 493–494.

TABLE II

RATE OF REACTION OF STEROIDAL UNSATURATED KETONES WITH MERCURIC ACETATE IN ACETIC ACID-d_4 AT 87°[a]

Steroid substrate	Initial concentrations: Steroid, mol l.$^{-1}$	Mercuric acetate, mol l.$^{-1}$	Rate constant[b] $k \times 10^2$, l. mol^{-1} min^{-1}
1,4,6-Androstatriene-3,17-dione (**17a**)	0.50	0.50	1.50[c] ± 0.06[d]
	0.50	0.25	1.42[e] ± 0.01
	0.25	0.50	1.46 ± 0.002
	0.10	0.50	1.49 ± 0.01
	0.050	0.50	1.50 ± 0.007
1,4,6-Pregnatriene-3,20-dione (**19a**)	0.50	0.50	1.18[f] ± 0.001
	0.25	0.50	1.16[e] ± 0.000
	0.10	0.50	1.53 ± 0.000

[a] Temperature ±3°. [b] Unless noted otherwise, based on data up to 75% substrate conversion. [c] Based on data up to 50% substrate conversion. [d] Standard deviation from least squares fit. [e] Based on data up to 18% substrate conversion. [f] Based on data up to 25% substrate conversion.

Kinetics and Mechanism for Steroid Mercuration.—The rate of reaction of 1,4,6-androstatriene-3,17-dione (**17a**) and 1,4,6-pregnatriene-3,20-dione (**19a**) with mercuric acetate were studied quantitatively at 87° in a nmr spectrometer. The solvent was acetic acid-d_4. The chemical shifts of the C-1 proton signal in the spectrum of the substrate and of the product were used to follow the course of the reaction with time. Although it has been shown[20] that mercuric acetate reacts with acetic acid, the pseudo-first-order rate constant for this process (4.8×10^{-4} min^{-1} at 90.5° and 6.2×10^{-5} min^{-1} at 70.2°) precludes its interference with these present rate measurements. Since in none of the nmr spectra was there any evidence detected for polymercuration of the steroids, it is also assumed that the amount of mercuric acetate at any stage in the reaction can be calculated from its initial concentration and the amount of product formed.

The rate constants shown in Table II were calculated in the usual way.[21] As seen in Table II, the rate for reaction of **17a** is constant over a considerable concentration range of **17a**. When the initial concentration of **17a** is equal to or larger than the initial concentration of mercuric acetate, the rate constant decreases rapidly after some reaction has occurred (Figure 1). For calculation of these rate constants, data up to 50 and 18% substrate conversion, respectively, were used. When the initial concentration of **17a** was smaller than that of mercuric acetate, data up to 75% conversion of **17a** were used. The decrease in rate constant with reaction is even more pronounced in the case of 1,4,6-pregnatriene-3,20-dione (**19a**), and the kinetic data are not too compelling for a second-order reaction. However, it is considered that the reaction is approximately second order and is being complicated by a side reaction. For high initial concentrations of **19a**, the rate constant is somewhat low, but with a four molar excess of mercuric acetate it is essentially the same as that of **17a** (Table II and Figure 1).

The rate of reaction of 1,4-androstadiene-3,17-dione (**21a**) with mercuric acetate in acetic acid-d_4 at 87° is too slow to measure. Using 0.10 *M* **21a** and 0.50 *M* mercuric acetate, there was no detectable reaction after 180 min. With the same conditions, 73% of **17a** was converted to 2-acetoxymercuri-1,4,6-androstatriene-3,17-dione.

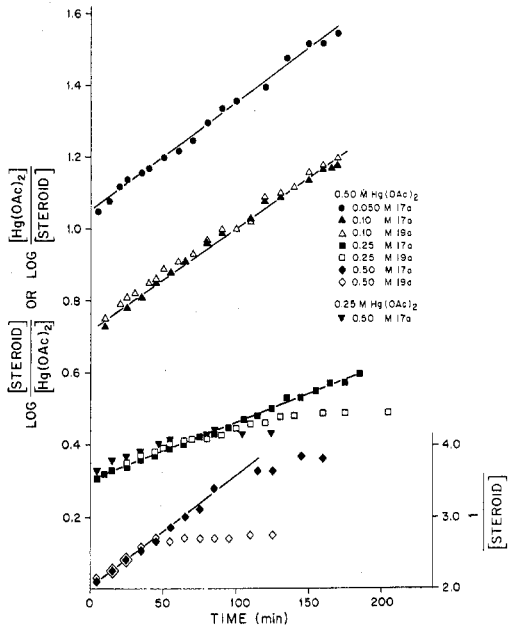
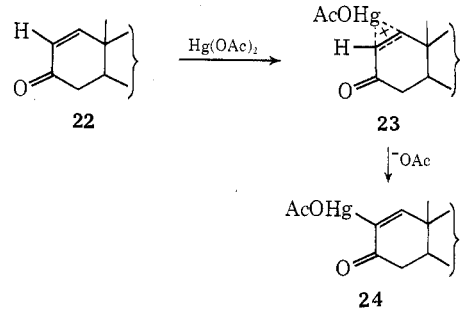


Figure 1.—Comparison of rate data for the mercuration of 1,4,6-androstatriene-3,17-dione (**17a**) and 1,4,6-pregnatriene-3,20-dione (**19a**) with mercuric acetate in acetic acid-d_4 at 87°. Lines are drawn through the data obtained for **17a** when its initial concentration (shown on the figure) is equal to or less than that of mercuric acetate.

All attempts to detect a mercuric acetate adduct, similar to **4** and **7**, were unsuccessful. When 1,4,6-androstatriene-3,17-dione (**17a**) was allowed to stand with mercuric acetate in acetic acid at room temperature for 70 hr, a 17% conversion to the 2-acetoxymercuri derivative resulted, but no trace of a mercuric acetate adduct could be observed. When methanol was the solvent no reaction occurred. After this latter mixture was boiled for 1 hr, only **17a** was isolated. When mercuric perchlorate in acetic acid[22] was used with **17a** at room temperature a 50% conversion to the 2-acetoxymercuri derivative was detected in 20 hr. Again no intermediate adduct was detected.

All of these results suggest that the reaction proceeds by the sequence shown in Scheme IV. Attack of the acetoxymercuri ion at the α side of the C-1 double bond of **22** gives **23**. The proton at C-2 is abstracted and **24** is formed. A similar course for the mercuration of

SCHEME IV



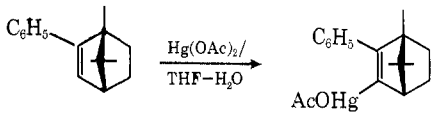
22 **23** **24**

(20) H. C. Brown and C. W. McGary, Jr., *J. Amer. Chem. Soc.*, **77**, 2306 (1955).

(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, pp 12–19.

(22) A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745 (1967).

SCHEME V



other sterically hindered carbon–carbon double bonds has been reported,[23,24] an example of which is shown in Scheme V.

The order of reactivity 1,4,6-trien-3-one > 1,4-dien-3-one > 1-en-3-one and the accelerated rate using mercuric perchlorate in acetic acid does not distinguish between the formation of the intermediate **23** or the abstraction of the C-2 proton of **23** as the rate-limiting step.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Optical rotations were measured using a visual polarimeter and 1-dm sample tubes. Ir spectra were obtained with a Beckman Model IR-10 spectrophotometer and were measured as potassium bromide pellets. Reported nmr spectra were obtained as solutions in deuteriochloroform with a Varian Model A-60 or Model XL-100-15 operating at 60 or 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield with tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are estimated to ± 0.5 Hz. Reaction rates were determined on the XL-100-15 nmr spectrometer by measurement and comparison of the relative intensities of the signals for the C-1 proton of the substrate and product. Acetic acid-d_4 was used as solvent in these determinations and the deuterium lock mode of the spectrometer was locked to the CD_3 peak of the solvent. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Molecular weights were determined with an LKB Type 9000 mass spectrometer using an ionizing voltage of 70 eV. As indicated, the reported molecular ions (M^+) are those corresponding to the most abundant isotope of mercury (^{202}Hg).[18]

Preparation of 2-Chloromercuri Steroids.—A solution of the steroid in boiling glacial acetic acid was mixed with a solution of mercuric acetate also in boiling glacial acetic acid. In each case, after reaction, the cooled mixture was diluted with excess saturated aqueous sodium chloride. The mercurated steroids were extremely difficult to purify since even after purification they tended to form gums. They also appeared to have a high affinity for solvents, as indicated by the nmr spectra of purified compounds which showed additional protons characteristic of the solvent used. It is for these reasons that, although conversion to the mercurated steroid was high, the isolated yield of pure mercurated compound in some cases was low. Repeated recrystallizations or precipitations were performed at the expense of yield in order to achieve high purity.

α-Acetoxymercuri-β-methoxy-β-phenylpropiophenone (4).—A solution of *trans*-benzalacetophenone (**3**) (5.00 g, 24.0 mmol) and mercuric acetate (7.60 g, 23.8 mmol) in methanol (80 ml) was allowed to stand at room temperature for 2 days. Complete evaporation of the solvent gave a mixture of 81% *erythro*-**4** (**4a**) and 19% *threo*-**4** (**4b**): nmr see Table I and δ 7.2–8.0 ppm (m, 10, aromatic H). Recrystallization of the solid mixture from methanol gave **4a** (8.9 g, 74%) as white needles: mp 115–116° (lit.[7] mp 115°); nmr see Table I and δ 7.2–8.0 ppm (m, 10, aromatic H).

3-Acetoxymercuri-4-methoxy-4-phenyl-2-butanone (7).—A solution of *trans*-benzalacetone (**5**) (25.0 g, 0.171 mol) and mercuric acetate (54.5 g, 0.171 mol) in methanol (250 ml) was allowed to stand at room temperature for 17 days, during which a solid precipitated (49.3 g, 66%). This solid was a mixture of 85% *erythro*-**7** (**7a**) and 15% *threo*-**7** (**7b**): mp 112–115°; nmr Table I and δ 7.34 ppm (s, 5, aromatic H).

3-Bromo-4-methoxy-4-phenyl-2-butanone (8).—Bromine (7.4 g, 0.046 mol) was added to a stirred suspension of 3-acetoxymercuri-4-methoxy-4-methyl-2-butanone, 85% erythro (**7a**) and 15% threo (**7b**) isomer (20.0 g, 0.0458 mol) in methanol (500 ml). After 1 hr the solution was clear, and the solvent was evaporated. The residue was dissolved in ether, and the solution was washed with aqueous sodium bromide and then with water. After drying, the ether solution was evaporated, and distillation of the residue gave a mixture of *erythro*-**8** (**8a**) and *threo*-**8** (**8b**) (9.0 g, 77%) as an oil, bp 84–99° (0.35 mm). A portion of this oil (5.24 g) was chromatographed on silica gel (175 g). Elution with heptane–carbon tetrachloride gave pure **8b** (1.88 g, 28%), recrystallized from petroleum ether (bp 30–60°): mp 68–69°; nmr see Table I and δ 7.38 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.09; Br, 31.08. Found: C, 51.12; H, 5.15; Br, 31.35.

The later fractions were mixtures of **8a** and **8b**. That containing 83% **8a** afforded its nmr spectrum, Table I and 7.33 ppm (s, 5, aromatic H).

3-Iodo-4-methoxy-4-phenyl-2-butanone (9).—Iodine (6.0 g, 0.024 mol) was added to a stirred suspension of 3-acetoxymercuri-4-methoxy-4-methyl-2-butanone, 85% erythro (**7a**) and 15% threo (**7b**) isomer (10.0 g, 0.0229 mol). After 20 min, the solvent was evaporated and the residue was dissolved in ether. The ethereal solution was washed successively with 10% aqueous sodium bisulfite, aqueous potassium iodide, and water. After drying, evaporation of the ether gave a mixture of 40% *erythro*-**9** (**9a**) and 60% *threo*-**9** (**9b**) as an oil, nmr Table I and δ 7.31 and 7.36 ppm (two s, total 5 protons, aromatic H for **9a** and **9b**, respectively). Crystallization from petroleum ether gave **9b** (1.78 g, 26%) as white needles: mp 80–81°; nmr Table I and δ 7.36 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{10}H_{13}IO_2$: C, 43.45; H, 4.31; I, 41.72. Found: C, 43.21; H. 4.28; I, 41.63.

***erythro*-2-Chloromercuri-3-methoxy-3-phenyl-1-propanol (10b).**—A solution of cinnamyl alcohol (5.00 g, 37.3 mmol) and mercuric acetate (12.0 g, 37.7 mmol) in methanol (100 ml) was allowed to stand at room temperature for 36 hr, after which the sodium hydroxide test for mercuric ion was negative. The solution was filtered and its volume was reduced to 50 ml by evaporation. Addition of saturated aqueous sodium chloride (50 ml) caused the precipitation of a white solid (14.6 g), mp 115–120°. Recrystallization of this solid from methanol–water and then chloroform gave **10b** (9.9 g, 66%) as white plates: mp 121–122°; nmr Table I and δ 2.5 (s, 1, OH), 3.84–3.98 (m, 2, CH_2OH), and 7.42 ppm (s, 5, aromatic H).

Anal. Calcd for $C_{10}H_{13}ClHgO_2$: C, 29.93; H, 3.27; Hg, 49.99. Found: C, 29.83; H, 3.35; Hg, 50.19.

***trans*-2-Chloromercuri-3-methoxycyclohexanone Ethylene Ketal (14).**—2-Cyclohexenone ethylene ketal[25] (**13**), bp 87–90° (25 mm) [lit.[25] bp 86.5–88.5° (23 mm)] (0.650 g, 4.64 mmol), was added to a stirred slurry of mercuric acetate (1.48 g, 4.64 mmol) in methanol (5 ml). After stirring for 5 min, the mixture was diluted with saturated aqueous sodium chloride, causing precipitation of **14** as a white solid (1.47 g, 78%), mp 115–120°. Recrystallization of this solid from methanol containing a trace of triethylamine gave **14** (0.750 g, 40%) as white needles: mp 117–118°; nmr δ 2.66 (d, 1, J = 12.0 Hz, ClHgCH), 3.40 (s, 3, $COCH_3$), 3.23–3.60 (m, 1, CH_3OCH), and 4.04 ppm (s, 4, OCH_2CH_2O).

Anal. Calcd for $C_9H_{15}ClHgO_3$: C, 26.54; H, 3.71; Cl, 8.71; Hg, 49.25. Found: C, 26.47; H, 3.68; Cl, 8.53; Hg, 49.05.

***trans*-2-Chloromercuri-3-hydroxycyclohexanone Ethylene Ketal (15).**—2-Cyclohexenone ethylene ketal[25] (**13**) (7.00 g, 49.9 mmol) was added to a solution of mercuric acetate (18.0 g, 56.5 mmol) in tetrahydrofuran (70 ml) and water (70 ml). The yellow color of the solution disappeared after 37 sec, and after 7 min, saturated aqueous sodium chloride (25 ml) was added. The oil which separated was extracted into chloroform. This solution was dried, and the chloroform was evaporated. Crystallization of the residue from benzene gave **15** (12.2 g, 62%) as white needles: mp 137–138°; nmr δ 2.71 (d, 1, J = 10.5 Hz, ClHgCH), 3.06 (s, 1, OH, disappeared on addition of D_2O), 4.05 (s, 4, OCH_2CH_2O), and 3.68–4.36 ppm (m, 1, HOCH).

Anal. Calcd for $C_8H_{13}ClHgO_3$: C, 24.43; H, 3.33; Cl, 9.02; Hg, 51.01. Found: C, 24.38; H, 3.13; Cl, 8.99; Hg, 51.19.

2-Chloromercuri-17α-methyl-1,4,6-androstatrien-17β-ol-3-one (16b).—17α-Methyl-1,4,6-androstatrien-17β-ol-3-one (**16a**), mp

(23) J. M. Coxon, M. P. Hartshorn, and A. J. Lewis, *Tetrahedron Lett.*, 3521 (1969).

(24) V. I. Sokolov, V. V. Bashilov, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **188**, 127 (1969); *Chem. Abstr.*, **72**, 3549h (1970).

(25) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

136–138° (lit.[26] mp 139–140°), nmr δ 1.00 (s, 3, C-18 H), 1.23 (s, 6, C-17 CH_3 and C-19 H), 2.30 (b s, 1, OH, disappeared on addition of D_2O), 5.92–6.36 (m, 4, C-2, C-4, C-6, and C-7 H), and 7.08 ppm (d, 1, J = 10.0 Hz, C-1 H), prepared from 17α-methyl-5-androstene-3β,17β-diol[27] by dehydrogenation[28] (0.813 g, 2.72 mmol), and mercuric acetate (4.00 g, 12.6 mmol) in acetic acid (20 ml) were heated for 15 min. Dilution of the reaction mixture with saturated aqueous sodium chloride (250 ml) precipitated a yellow solid. The solid was thoroughly washed with water, and crystallization from 95% ethanol gave a yellow microcrystalline first crop (0.574 g, 40%), mp 193–195° dec, and a white, powdery second crop (0.090 g, 6%), mp 183–185° dec. Two recrystallizations of the combined crops from 95% ethanol gave **16b** (0.370 g, 25%) as pale yellow microcrystals: mp 180–181° dec (lit.[15] mp 155–162°); ir 1585 (C=C) and 1612 cm^{-1} (C=O); nmr δ 1.00 (s, 3, C-18 H), 1.06 and 1.11 (two s, 3 and 3, C-17 CH_3 and C-19 H), 2.97 (s, 1, OH, disappeared on addition of D_2O), 6.0–6.3 (m, 3, C-4, C-6, and C-7 H), and 7.29 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{20}H_{25}ClHgO_2$: C, 45.03; H, 4.72; Cl, 6.65; Hg, 37.60; mol wt ($C_{20}H_{25}Cl^{202}HgO_2$), 534. Found: C, 44.95; H, 5.18; Cl, 6.65; Hg, 38.07; mol wt, 534 (M^+).

2-Chloromercuri-1,4,6-androstatriene-3,17-dione (17b).—1,4,6-Androstatriene-3,17-dione[27] (**17a**) (5.00 g, 17.7 mmol) and mercuric acetate (13.00 g, 40.8 mmol) in acetic acid were heated for 30 min. Dilution of the reaction mixture with water (250 ml) containing sodium chloride (15 g) precipitated a solid which was washed with water. Trituration of the solid with acetone (50 ml) left a white powder (5.00 g), mp 230–240° dec. On standing the acetone solution deposited crystals of **17b** (0.329 g, 3.6%), mp 280–285° dec. The residue from the trituration was extracted with hot acetone (400 ml) and the hot acetone solution was combined with the acetone mother liquors obtained earlier. This solution was evaporated to one-sixth (75 ml) its original volume. Dilution with *n*-hexane (100 ml) caused the precipitation of a white powder (3.80 g), mp 180–240° dec. Crystallization of this solid from acetone gave **17b** (0.867 g, 9.5%) as white needles: mp 280–285° dec; $[\alpha]^{25}D$ +27° (*c* 0.84, $CHCl_3$); ir 1615 (conjugated C=O) and 1715 cm^{-1} (C=O); nmr δ 1.03 (s, 3, C-18 H), 1.30 (s, 3, C-19 H), 6.05–6.45 (m, 3, C-4, C-6, C-7 H), 7.28 (s, 1, C-1 H), and 7.28 ppm (d, ~0.2, J = 280 Hz, C-1 H coupled to ^{199}Hg).

Anal. Calcd for $C_{19}H_{21}ClHgO_2$: C, 44.10; H, 4.09; Cl, 6.85; Hg, 38.77; mol wt ($C_{19}H_{21}Cl^{202}HgO_2$), 518. Found: C, 43.80; H, 4.26; Cl, 6.87; Hg, 38.81; mol wt, 518 (M^+).

2-Chloromercuri-1,4,6-androstatrien-17β-ol-3-one (18b).—1,4,6-Androstatrien-17β-ol-3-one[27] (**18a**) (1.00 g, 3.52 mmol) and mercuric acetate (5.00 g, 15.7 mmol) in acetic acid (20 ml) were heated for 10 min. Dilution with saturated aqueous sodium chloride (100 ml) precipitated a solid (1.64 g) which was 70% pure **18b** (nmr). Crystallization of this solid followed by four recrystallizations from chloroform–ether gave **18b** (0.032 g, 1.7%) as pale yellow microcrystals: mp 189–192° dec; ir 1620 (C=O) and 3440 cm^{-1} (OH); nmr δ 0.90 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 2.70 (s, 1, OH), 3.64 (m, 1, HOC**H**), 5.87–6.34 (m, 3, C-4, C-6, and C-7 H), and 7.27 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{23}ClHgO_2 \cdot 1.2CHCl_3$:[29] C, 36.61; H, 3.68; mol wt ($C_{19}H_{23}Cl^{202}HgO_2$), 520. Found: C, 36.27; H, 3.62; mol wt, 520 (M^+).

2-Chloromercuri-1,4,6-pregnatriene-3,20-dione (19b).—1,4,6-Pregnatriene-3,20-dione (**19a**), mp 148–149 (lit.[30] mp 150–152°), nmr δ 0.76 (s, 3, C-18 H), 1.22 (s, 3, C-19 H), 2.16 (s, 3, C-21 H), 5.91–6.37 (m, 4, C-2, C-4, C-6, and C-7 H), and 7.08 ppm (d, 1, J = 10.0 Hz, C-1 H), prepared from 5-pregnen-3β-ol-20-one[27] by dehydrogenation[28] (4.40 g, 14.2 mmol), and mercuric acetate (22.0 g, 69.0 mmol) in acetic acid (40 ml) were heated for 30 min. Dilution with saturated aqueous sodium chloride precipitated a solid. The solid was washed with water and then extracted into chloroform. The chloroform solution was washed with saturated aqueous sodium chloride and dried. Evaporation of the chloroform left a yellow gum (4.40 g) which was at least 80% **19b** (nmr). The gum was dissolved in acetone and then poured into saturated aqueous sodium chloride. The precipitated oil was extracted into chloroform and this solution was dried. Evaporation of chloroform left a gum which on heating in 95% ethanol gave **19b** (2.5 g, 32%), mp (135° softens) 150° dec. This was difficult to crystallize and readily formed a gum on warming in a solvent. An analytical sample was obtained by heating a suspension of the solid in ethanol for a few minutes, allowing the mixture to cool to 50°, decantation of the ethanolic solution from any gummy residue, and then allowing crystallization to proceed at 0° for 24 hr. Two repetitions of this procedure gave **19b** (0.51 g, 6.6%) as off-white microcrystals: mp (shrinks 137°) 145–150° dec; $[\alpha]^{25}D$ +58° (*c* 1.0, $CHCl_3$); ir 1620 (conjugated C=O), 1680 cm^{-1} (C=O); nmr δ 0.77 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 2.18 (s, 3, C-21 H), 5.94–6.36 (m, 3, C-4, C-6, and C-7 H), and 7.28 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{21}H_{25}ClHgO_2$: C, 46.24; H, 4.62; Cl, 6.50; Hg, 36.78; mol wt ($C_{21}H_{25}Cl^{202}HgO_2$), 546. Found: C, 46.02; H, 4.88; Cl, 6.66; Hg, 36.53; mol wt, 546 (M^+).

2-Chloromercuri-5α-androst-1-ene-3,17-dione (20b).—5α-Androst-1-ene-3,17-dione[31] (**20a**) (0.200 g, 0.698 mmol) and mercuric acetate (1.00 g, 3.14 mmol) in acetic acid (5.0 ml) were heated for 24 hr. Dilution of the reaction mixture with saturated aqueous sodium chloride (50 ml) precipitated a gummy solid, which was extracted into chloroform. This solution was washed with water until the wash water was neutral. Evaporation of the dried chloroform solution left a gum which on trituration with ether gave a white solid (0.100 g), over 90% pure **20b** (nmr). Crystallization of this solid from chloroform–ether followed by three recrystallizations from the same solvents gave **20b** (0.040 g, 12%) as white microcrystals but containing chloroform:[29] mp 180° dec; ir 1640 (conjugated C=O) and 1730 cm^{-1} (C=O); nmr δ 0.92 (s, 3, C-18 H), 1.08 (s, 3, C-19 H), and 7.25 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{25}ClHgO_2 \cdot CHCl_3$:[29] C, 37.48; H, 4.09; mol wt ($C_{19}H_{25}Cl^{202}HgO_2$), 522. Found: C, 37.80; H, 3.97; mol wt, 522 (M^+).

2-Chloromercuri-1,4-androstadiene-3,17-dione (21b).—1,4-Androstadiene-3,17-dione[27] (**21a**) (2.00 g, 7.03 mmol) and mercuric acetate (10.0 g, 31.4 mmol) in acetic acid (125 ml) were heated for 6 hr. Dilution with saturated aqueous sodium chloride gave a yellow precipitate (0.440 g). This solid was a 1:1 mixture of **21a** and **21b** (nmr). The aqueous filtrate was thoroughly extracted with chloroform, and the chloroform solution was washed with water until neutral. Evaporation of the dried solution left a yellow oil (1.80 g) with a nmr spectrum identical with that of **21a**. The solid (0.440 g) was dissolved in chloroform and **21b** was precipitated by the careful addition of *n*-hexane. Reprecipitation on cooling from hot 95% ethanol gave **21b** (0.16 g, 44%) as a white, amorphous solid: mp 282–283° dec; ir 1640 (conjugated C=O) and 1725 cm^{-1} (C=O); nmr δ 0.94 (s, 3, C-18 H), 1.31 (s, 3, C-19 H), 6.20 (s, 1, C-4 H), and 7.17 ppm (s, 1, C-1 H).

Anal. Calcd for $C_{19}H_{23}ClHgO_2$: C, 43.93; H, 4.46; Cl, 6.83; Hg, 38.92; mol wt ($C_{19}H_{23}Cl^{202}HgO_2$), 520. Found: C, 43.72; H, 4.16; Cl, 6.52; Hg, 38.90; mol wt, 520 (M^+).

Registry No.—**4a**, 36794-15-7; **4b**, 36794-16-8; **7a**, 36794-17-9; **7b**, 36794-18-0; **8a**, 36794-19-1; **8b**, 36794-20-4; **9a**, 36794-21-5; **9b**, 36794-22-6; **10b**, 36794-23-7; **14**, 36794-24-8; **15**, 36794-25-9; **16a**, 28816-02-6; **16b**, 24272-44-4; **17a**, 633-35-2; **17b**, 36794-29-3; **18b**, 36794-30-6; **19a**, 4192-93-2; **19b**, 36794-32-8; **20b**, 36794-33-9; **21a**, 897-06-3; **21b**, 36794-35-1.

(26) G. O. Weston, D. Burn, D. N. Kirk, and V. Petrow, British Patent 854,343 (1960); *Chem. Abstr.*, **55**, 18813f (1961).

(27) Purchased from Searle Chemicals, Inc., Chicago, Ill., and used without further purification.

(28) A. B. Turner, *Chem. Commun.*, 845 (1966).

(29) Inclusion of chloroform was indicated by enhancement of the chloroform signal in the nmr spectrum of this sample in deuteriochloroform.

(30) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

(31) Purchased from Steroloids, Inc., Pauling, N. Y., and used without further purification.