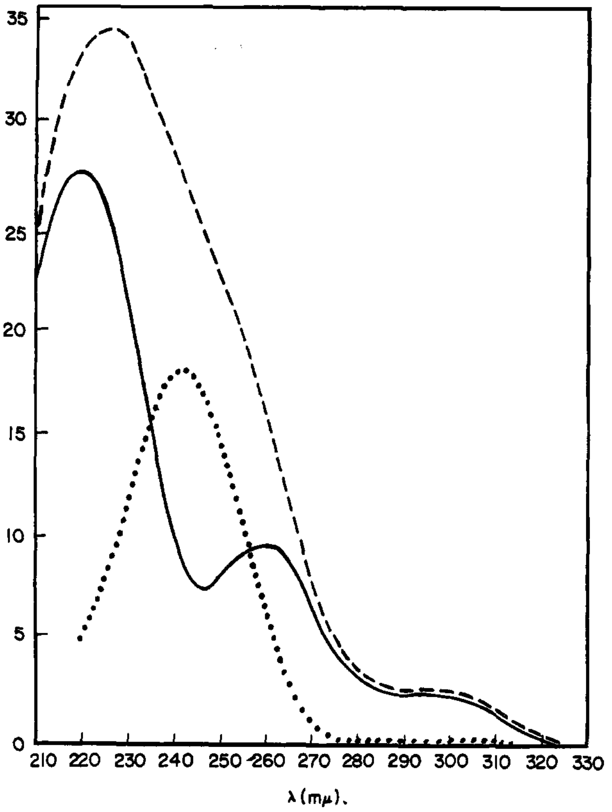

Fig. 2.—Absorption spectra of dimethyl 4′-hydroxy-(16,17-butanoandrosta-1′,3′,4,16-tetraene)-3-one-1′,2′-dicarboxylate (V), – – – –; dimethyl 3β,4′-dihydroxy-(16,17-butanoandrosta 1′,3′,5,16-tetraene)-1′,2′-dicarboxylate (IV), ———; V, run against IV as a "blank", ...

(methyl esters). A sample was recrystallized from isopropyl alcohol giving colorless plates, m.p. 125–130°, with evolution of gas; $[\alpha]_{\text{D}}$ −88°; $\nu_{\max}$ 1760 (phenolic acetate), 1735–1720 (3-acetate and methyl esters), 1583 (aromatic), and 3600 cm.$^{-1}$ (weak, isopropyl alcohol of crystallization).

Anal. Calcd. for $C_{31}H_{38}O_8 \cdot 0.5\ C_3H_8O$: C, 68.64; H, 7.45. Found: C, 68.77; H, 7.49.

B. Chloranil Method.—The amorphous C-16 epimer mixture remaining after crystallization of adduct II (see preceding) was freed carefully of solvent by conversion to a dry foam and warming *in vacuo*. A 9.80-g. sample of this material and 5.0 g. of chloranil were dissolved in 150 ml. of dry, redistilled chlorobenzene and heated under reflux for 16 hr. Solvent was then removed at reduced pressure; residue was taken up in benzene, washed with saturated aqueous sulfur dioxide, then with cold dilute sodium hydroxide, and finally with water until neutral. Dried (magnesium sulfate) benzene solution was decolorized by passage through 100 g. of Florisil. Benzene eluates were combined, concentrated, and the residue crystallized from isopropyl alcohol, yielding 5.72 g. (56%) of plates, m.p. 124–128° dec., identical with the aromatization product III prepared as described previously.

Dimethyl 3β,4′-Dihydroxy(16,17-butanoandrosta-1′,3′,5,16-tetraene)-1′,2′-dicarboxylate (IV).—The aromatization product III (34.3 g.) was dissolved in 1300 ml. of methanol (freshly distilled from magnesium methoxide) containing sodium methoxide (from 3.57 g. of sodium). The solution was allowed to stand at 25° for 54 hr. under a nitrogen atmosphere. A 10-ml. portion of glacial acetic acid was then added followed by 200 ml. of water. About 1 l. of solvent was then removed at reduced pressure leaving a colorless crystalline sludge. The solid was collected and washed with 50% methanol–water; drying overnight at 50° *in vacuo* gave 21.0 (77%) of phenolic product, m.p. 250–255°. A sample of this material, further purified by two recrystallizations from acetone, had m.p. 258–261°, $[\alpha]_{\text{D}}^{\text{CHCl}_3}$ −107°; $\nu_{\max}^{\text{Nujol}}$ 3460 (3-OH), 3150 (phenolic OH), 1720 and 1702 cm.$^{-1}$ (methyl esters); $\lambda\lambda_{\max}^{\text{CH}_3\text{OH}}$ 219 (30,800), 258 (10,300), 294 mμ (inflection, ε 2810); $\lambda\lambda_{\max}^{1\,N\ \text{NaOCH}_3}$ 244 (22,600), 306 mμ (ε 11,000).

Anal. Calcd. for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.16; H, 7.64.

Dimethyl 4′-Hydroxy-(16,17-butanoandrosta-1′,3′,4,16-tetraene)-3-one-1′2′-dicarboxylate (V).—A solution of 5.0 g. of the 3-alcohol IV and 50 ml. of cyclohexanone in 200 ml. of dry toluene was distilled until about 10 ml. of solvent was collected. A solution of 5.0 g. of aluminum isopropoxide in 50 ml. of toluene was added and the reaction mixture heated under reflux in a nitrogen atmosphere for 2 hr. About 100 ml. of toluene was then removed by distillation. The cooled reaction mixture was treated with ice (*ca.* 100 g.) and 150 ml. of cold 5% hydrochloric acid. The precipitated product was found to be very poorly soluble in the common organic solvents but could be extracted with three 200-ml. portions of 10% isopropyl alcohol in chloroform. The combined organic extracts were washed with dilute sodium bicarbonate, then water, and dried over sodium sulfate. The solution was concentrated, diluted with hot hexane, and the crystalline product collected. The conjugated ketone V (4.40 g., 88%) had m.p. 315–317°. The material was inserted in a Soxhlet thimble and continuously extracted with the solvent mixture toluene–chloroform–isopropyl alcohol (3:1:1); this resulted in recrystallization but caused no change in melting point. The product had $[\alpha]_{\text{D}}^{\text{pyridine}}$ −25°; $\nu_{\max}^{\text{Nujol}}$ 1695 (conj. ketone), 1720 and 1730 (ester), and 3350 cm.$^{-1}$ (phenolic OH); $\lambda_{\max}^{\text{CH}_3\text{OH}}$ 224 (35,900), 294 mμ (inflection, ε 2770); λλ 1$_{\max}^{1\,N\ \text{NaOCH}_3}$ 244 (38,300), and 306 mμ (ε 11,400). An ultraviolet spectrum of the conjugated ketone V was rerun in methanol using a solution of the 3-hydroxy compound IV (in identical concentration) as a "blank." The resulting tracing showed a single maximum at 241 mμ (ε 15,000).

Anal. Calcd. for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.40; H, 7.19.

Synthesis of Compounds Containing Carbon–Mercury and Carbon–Tin Bonds[1,2]

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The attempted preparation of compounds containing both carbon–tin and carbon–mercury bonds was reported in 1926.[3] Later investigation of the reaction indicated a stepwise degradation of the aryl or alkyl tin compound by the monosubstituted or inorganic mercury compound.[4] In the present investigation, the degradation of the substituted tin compounds was prevented by using disubstituted mercurials. This paper describes the synthesis of the tributyltin salt of

TABLE I

TRISUBSTITUTED TIN HALO ESTERS

Compound	M.p., °C.	Calcd. Sn	Found Sn	Yield,[a] %
Tri-*n*-butyl iodoacetate	68	25.1	25.5	50–60
Tri-*n*-propyltin iodoacetate	75	29.5	29.7	50–60
Tri-*n*-butyltin iodopropionate	61	24.3	24.3	50–60
Tri-*n*-butyltin bromoacetate	64	27.8	29.0	50–60
Tri-*n*-propyltin bromoacetate	73	30.8	30.9	50–60

[a] Crystallized from petroleum ether.

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(1) Portions of this work were reported at the Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June, 1962. Scientific paper no. 2280, Washington Agricultural Experiment Stations, Pullman, Wash. Project 1525.

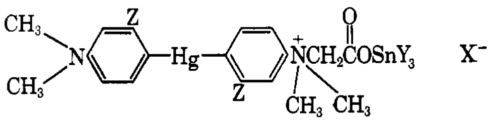
(2) Supported in part by medical and biological research funds, initiative 171, State of Washington.

(3) R. F. Chambers and P. C. Scherer, *J. Am. Chem. Soc.*, **48**, 1054 (1926).

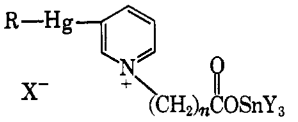
(4) A. N. Nesmeyanov and K. H. Kocheshkov, *Ber.*, **67**, 317 (1934).

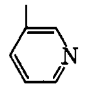
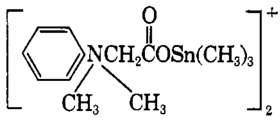
TABLE II

QUATERNARY AMMONIUM COMPOUNDS



X	Y	Z	M.p., °C.[a]	Calcd. Hg	Calcd. Sn	Calcd. I	Found Hg[b]	Found Sn[c]	Found I[d]	Yield. %
I	n-C_4H_9	H	168–170	21.9	13.0	13.9	21.6	12.7	13.8	52
Br	n-C_4H_9	H	155–157	23.1	13.7	..	23.1	13.3	..	72
I	n-C_4H_9	CH_3	145–148	21.3	12.6	..	20.8	12.3	..	84
I	n-C_4H_9	Cl	161	20.4	12.0	..	20.6	11.8	..	50
I	n-C_3H_7	H	168	23.0	13.6	..	22.6	13.2	..	51
Br	n-C_3H_7	H	165	24.3	14.4	..	23.6	14.3	..	70



X	Y	n	R	M.p., °C.	Calcd. Hg	Calcd. Sn	Calcd. I	Found Hg[b]	Found Sn[c]	Found I[d]	Yield, %
I	n-C_4H_9	1		110–112	24.2	14.3	..	23.9	14.7	..	75
I	n-C_3H_7	1	same	124	25.4	15.1	..	24.8	15.5	..	75
I	n-C_4H_9	2	same	137	23.8	14.1	..	23.7	13.6	..	71
I	n-C_4H_9	1		120	24.2	14.3	..	24.5	14.5	..	65
Hg  I_2^-				143	..	20.9	22.3	..	21.0	22.3	87

[a] Uncorrected, with decomposition. [b] Using Whitton's apparatus. [c] Kochesckov's procedure (K. A. Kochesckov, "Investigation in the Field of Organotin Chemistry," J. G. A. Luijten and G. J. M. vander Kerk, Ed., Tin Research Institute, Middlesex, England, 1955, p. 83). [d] Fusion with sodium hydroxide and sodium carbonate followed by Winkler's titration (L. W. Winkler, "Volumetric Analysis," Vol. 3, I. M. Kolthoff and R. Belcher, Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 247).

(carboxymethyl) [p-(p-dimethylaminophenylmercuri)-phenyl]dimethylammonium iodide (1) and related compounds.

Experimental

Table I lists trisubstituted tin halo esters prepared by heating the organic tin oxide or hydroxide[5] with the calculated amount of iodoacetic acid, β-iodopropionic acid, or bromoacetic acid.[6,7]

Mercuribis-4-dimethylaniline and derivatives,[8] mercuribis-3-pyridine,[9] and 3-pyridylmercuribenzene[10] were prepared by known procedures.

Synthesis of I and other compounds (Table II) resulted when the calculated amount of mercuribis-4-dimethylaniline or other base and a slight excess of a trisubstituted tin halo ester were heated with stirring to 110° for 15 min. in a beaker in an oil bath. The mixture quickly melted, then set to a paste. After cooling, the pasty mass was transferred to a small mortar and ground with diethyl ether. The somewhat granular material was transferred to a paper thimble in an ASTM Method D147 extraction apparatus; more ether was added; and extraction was continued for at least 4 hr. An insoluble yellow powder remained in the thimble. Other compounds were prepared in exactly the same manner, except that heating was limited to 70° for 10 min. with mercuribis-3-pyridine or 3-pyridylmercuribenzene. Heating the compounds with solvents for recrystallization resulted in the formation of gum. However, near saturated solutions of I in butyrolactone or dimethyl sulfoxide, on dilution with water, yielded a product with unchanged melting point and mercury analysis.

Approximate solubility of several of the compounds was determined by machine shaking with the solvent at room temperature for 16 to 24 hr. After filtration, the solution was analyzed for mercury.[11] The compounds prepared were rather insoluble; the water solubility tended to be the reverse of alcohol solubility (Table III). The alcoholic solutions of mercuribis-3-pyridine quaternary ammonium compounds frequently precipitated on standing. When sufficient material was available, the mercury analysis of the precipitate and the original material was the same. One per cent aqueous sodium sulfide caused no separation of black mercuric sulfide on standing a week with satu-

TABLE III

APPROXIMATE SOLUBILITY IN MG./ML. OF REPRESENTATIVE COMPOUNDS

Compound	Solvent Water	Solvent Ethanol
I[a]	3.3	8.3
II[b]	28.6	1.2
III[c]	8.4	5.3
IV[d]	1.8	0.4

[a] Tri-n-butyltin salt of (carboxymethyl)[p-(p-dimethylaminophenylmercuri)phenyl]dimethylammonium iodide. [b] Tri-n-butyltin salt of 1-(carboxymethyl)-3-(3-pyridylmercuri)pyridinium iodide. [c] Tri-n-butyltin salt of 1-(carboxymethyl)-3-(phenylmercuri)pyridinium iodide. [d] Bis(trimethyltin) salt of (mercuridi-p-phenylene)bis[(carboxymethyl)dimethylammonium iodide].

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(5) The trisubstituted tin bases were furnished by R. J. Zedler of the Metal and Thermit Corporation, New York, N. Y.

(6) G. S. Sasin, *J. Org. Chem.*, **18**, 1142 (1953).

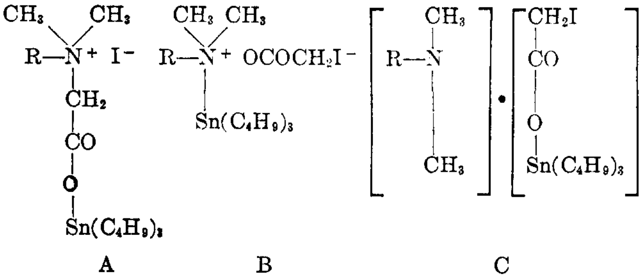
(7) H. H. Anderson, *ibid.*, **22**, 147 (1957).

(8) F. C. Whitmore, "Organic Compounds of Mercury," Chemical Catalogue Company, New York, N. Y., 1921, p. 365.

(9) C. D. Hurd and C. J. Morrissey, *J. Am. Chem. Soc.*, **77**, 4658 (1955).

(10) A. N. Nesmeyanov and I. F. Lutsenko, *J. Gen. Chem. USSR.*, **11**, 382 (1941).

(11) V. L. Miller and F. Swanberg, Jr., *Anal. Chem.*, **29**, 391 (1957).



R = mercurated base

Fig. 1.—Possible structural formulas.

rated aqueous I or IV but II precipitated mercuric sulfide, instantly, and III on standing 12 to 24 hr.

Trimethyltin iodoacetate reacted with both dimethylamino groups of mercuribisdimethylaniline. The other tin halo esters combined with only one. Several attempts to add a second tri-*n*-butyl- or propyltin halo ester or methyl iodide failed.

The compounds prepared are believed to be the iodide of the quaternary ammonium base (Fig. 1A). Figure 1B represents a substituted acetate of the quaternary ammonium base. Figure 1C represents the addition of the tri-*n*-butyltin iodoacetate as a double salt of a tertiary base as suggested by Kraus and Greer[12] for the addition of trimethyltin salts to bases such as pyridine or aniline. The latter two compounds should be obtainable with esters or salts other than the bromoacetic or iodoacetic ester. However, when the chloroacetate, acetate, or iodide reacted at 100° with mercuribis-4-dimethylaniline, the only identifiable compounds obtained were the starting materials. Feigl's test[13] for iodide was positive. It is recognized that no rigorous proof of the proposed structure of I and analogous products has been possible; however, it does seem that the fact that several similar pairs of compounds do react to yield products with compositions which indicate that corresponding types of reactions must have occurred in the several instances gives substantial justification to the proposed structure.

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[12] C. A. Kraus and W. N. Greer, *J. Am. Chem. Soc.*, **45**, 3708 (1923).

[13] F. Feigl, "Spot Tests, Inorganic Applications," Elsevier Publishing Company, Amsterdam, 1954, p. 248.

Temperature Dependence of Stereochemistry of Complex Metal Hydride Reductions

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Although appreciable attention recently has been focused on the effect of solvent and reagent composition on the stereochemistry of reduction by complex metal hydrides,[1] little data appear in the literature on temperature effects on stereochemistry when other variables are held constant. Vail and Wheeler[2] have recently observed minor changes in the relative amounts of 3α- and 3β-cholestanols when reductions of 3-cholestanone were performed with various reducing agents and solvents at several temperatures. The general trend was toward increasing amounts of axial alcohol at higher temperature.[2] We wish to report results on the temperature dependence of product stereochemistry, utilizing conformationally pure ketones, in which case increased temperature may result in either an increase or decrease in the relative amount of axial alcohol, although both cases actually involve greater proportions of the major product at low temperature (an enthalpy effect).

The table shows some typical results of reduction of 3,3,5-trimethylcyclohexanone (I) (a hindered ketone) and 4-*t*-butylcyclohexanone (II) (an unhindered ketone) by excess lithium aluminum hydride and sodium borohydride (>one mole of reducing agent/mole of ketone) in various solvents, each combination of reagent and solvent being studied at several temperatures. The molar ratios of the complex metal hydride to the ketone were not kept constant, but it is felt that this has no effect on the stereochemistry since Haubenstock and Eliel[1] have shown that the stereochemistry of reductions of 3,3,5-trimethylcyclohexanone with lithium aluminum hydride in either diethyl ether or tetrahydrofuran is independent of the proportion of reactants and order of addition. Entries 5a–d likewise show that this also applies in pyridine. Eliel and Haubenstock have also shown that the relative proportion of ketone and reducing agent does not affect the stereochemical result in the reductions with sodium borohydride. It can be seen that I gives substantially greater amounts of axial alcohol (the major product) at lower temperatures, whereas there is a slight decrease in per cent axial (the minor product) when reduction of II is performed at lower temperatures, as was observed with 3-cholestanone.[2] These data are rationalizable according to the earlier views of Dauben, Fonken, and Noyce[3] on "steric approach control" and "product development control" and by assuming that the transition state for reduction of unhindered ketones (*e.g.*, II) does *not* resemble reactants but is well along the reaction coordinate toward product,[4] thus leading mainly to equatorial alcohol. This latter view is supported by several recent studies of borohydride reduction of unhindered ketones where linear-free energy relationships are obeyed[5,6] with highly positive ρ values being observed (+2.6 for *p*-substituted acetophenones[5] and +2.65 for 2- and 3-substituted fluorenones[6]). Hindered ketones, on the other hand, reach the transition state earlier ("steric approach control"), thus leading to a predominance of *exo*-attack.

The present work provides further examples of the effect of temperature and solvent on the stereochemistry of reduction of cyclic ketones. A practical aspect of the data is the indication that greatest stereoselectivity in the reduction of hindered ketones to axial alcohols can be achieved in good solvating media[1] at low temperature.

Experimental

In all the complex metal hydride reductions the ketone (approximately 7 mmoles) was dissolved in 25 ml. of the indicated solvent (Table I), protected from the atmosphere, and cooled in a bath to the desired temperature. A molar excess of the complex metal hydride was then added in powdered form to the system and stirred for 15–30 min. with a magnetic stirrer, except for the sodium borohydride reductions in isopropyl alcohol which were stirred approximately 48 hr.

All reductions run at 0° or higher were essentially complete in the reduction period (less than 1% unchanged ketone),

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[1] H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).

[2] O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

[3] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

[4] M. G. Coombe and H. B. Henbest, *Tetrahedron Letters*, 404 (1961).

[5] H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962).

[6] G. G. Smith and R. P. Bayer, *Tetrahedron*, **18**, 323 (1962).