methyl phosphite in 20 mL of toluene was heated at reflux under nitrogen for 3 h. After concentration, the residue was chromatographed on silica with the elution of benzene to give 1.35 g of orange liquid, whose spectral data were all identical with the authentic sample **15**.[13]

Reduction by Raney Nickel. To a suspended solution of 10–15 g of Raney nickel (W-2 type) in 50 mL of ethanol was added a solution containing phosphonic esters **5–10** (1.5–2.0 g in 5 mL of ethanol). The reaction mixture was heated at reflux for 20 h. After filtration of nickel, the filtrate was concentrated and the residue was distilled to afford cycloalkanephosphonic esters **16–18**. The yields were summarized in Table II.

Registry No.—**1**, 2720-41-4; **8a**, 65392-38-3; **11a**, 55499-42-8; **11b**, 65392-39-4; **14**, 10181-56-3; **15**, 10181-61-0; 1-morpholinocycloheptene, 7182-08-3.

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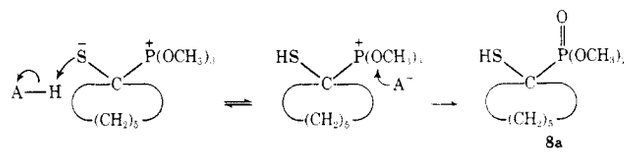
(18) When the other solvents having an active hydrogen were used in the reaction of cyclohexanedithiol with trimethyl phosphite, **8a** was also obtained in considerable yields [**7a**, 33.3%, and **8a**, 50.3% (isobutyl alcohol); **7a**, 36.8%, and **8a**, 33.8% (acetonitrile); **7a**, 29.4%, and **8a**, 35.6% (propionitrile)]. The favorable formation of **8a** might possibly be explained by the following reaction scheme.



Facile and Selective Chlorination–Cleavage of Some Cyclanones and Cyclanols with the CCl_4–KOH–*t*-BuOH Reagent. In Situ Conversion of Estrones and Estradiols into Dichlorodoisynolic Acids[1a]

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Studies of the reactions of ketones and alcohols with CCl_4–KOH–*t*-BuOH have been extended to include cyclanones and cyclanols represented by a series of estrogens. With this reagent estrone (**1**) and estrone 3-methyl ether (**4**) were rapidly and selectively converted into the corresponding 16,16-dichlorodoisynolic acids (**3**, **6**). The in situ reaction pathway consists of D-ring *gem*-α-dichlorination followed by ring cleavage. Similar treatment of estradiol (**2**) and estradiol 3-methyl ether (**5**) also provided these respective products, but at much slower rates because the initial slow oxidation step is rate determining. However, because this step involves a free-radical chain mechanism initiated by dioxygen, the conversion of **5** was greatly accelerated when contact with air was unrestricted. Reaction of **2** could not be accelerated this way because its phenolic moiety functions as a built-in inhibitor of this oxidation process.

In the course of our recent investigations of the reactions of ketones and alcohols with CCl_4-powdered KOH–*t*-BuOH, the use of estrones and estradiols as substrates was considered a valuable excursion because they represent a common class of cyclanones and cyclanols, respectively (Scheme I). It was already recognized that ketones possessing α-H's are easily α chlorinated with this reagent; rapid subsequent reactions, however, generally lead to the formation of a variety of products.[2-6] While ketones whose carbonyl function is sterically hindered, e.g., mesityl alkyl ketones, are still quite easily converted into α-chlorinated ketones, the latter do not undergo further reaction.[7] Secondary alcohols are initially oxidized with this reagent into ketones which, as already indicated, are α chlorinated in this medium.[2,5,6,8] Sterically hindered alcohols, e.g., neopentyl alcohol and di-*tert*-butylcarbinol, react slowly or not at all with this reagent at moderate temperatures.[2,6,8]

Results

Estrone (**1**) and estrone 3-methyl ether (**4**) are ketones whose carbonyl is hindered from attack mainly on one face. This degree of steric hindrance in **1** and **4** prevented neither the formation nor subsequent reaction of their α-chlorinated derivatives. Thus, both ketones underwent facile conversion with CCl_4–KOH–*t*-BuOH at 25 °C into the *gem*-α-dichloro ketones (**1a**, **4a**) which, however, could not be detected per se because they were rapidly cleaved into 16,16-dichlorodoisynolic acid (**3**) and 16,16-dichlorodoisynolic acid 3-methyl ether (**6**), respectively. Neither product has previously been reported. Within 1 h at room temperature **4** was converted into **6** in 75–80% yield; the white crystalline product, mp 157–158 °C, was analytically pure. The phenolic ketone **1**, similarly treated for 1.5 h, was converted into **3** in yields estimated to be at least 90%; however, the crystalline product, mp 155–157 °C, in this case was contaminated with material suspected to

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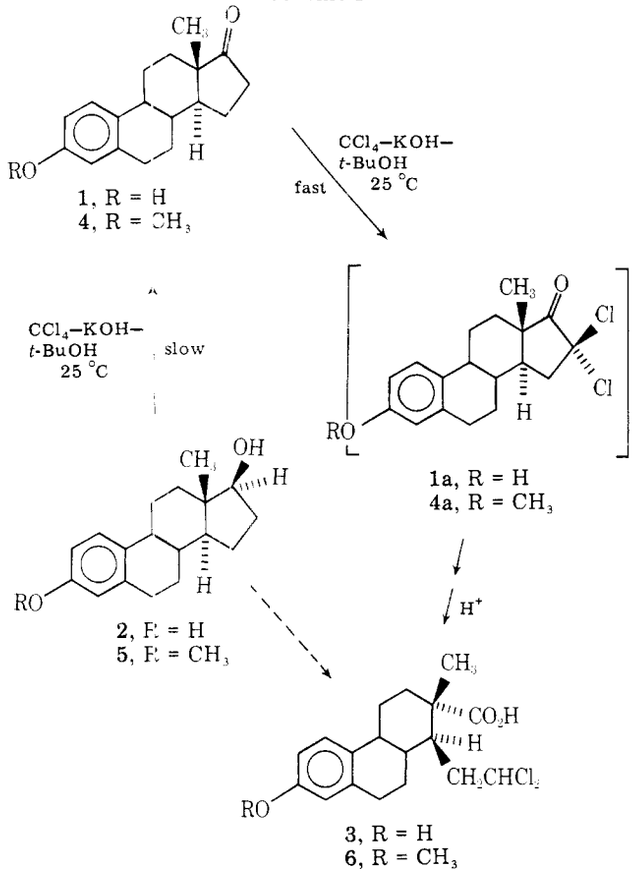
Scheme I

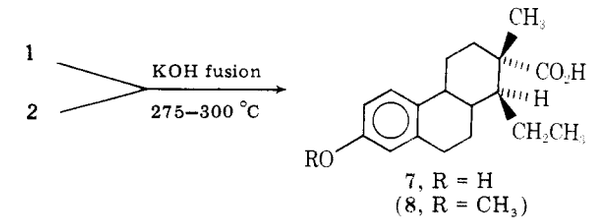


be the 2-aldehyde and 2-carboxylic acid derivatives of **3**. These reactions of both **1** and **4** were conducted in systems continuously flushed with nitrogen or with air. However, little if any variation in reaction rate or product composition could be discerned in either case.

Estradiol (**2**) and estradiol 3-methyl ether (**5**) are secondary alcohols whose carbinol OH, but not α-H, is hindered. These steroidal alcohols slowly underwent reaction with CCl_4–KOH–*t*-BuOH, first being converted into the corresponding estrones, **1** and **4**, and then into the respective dichlorodoisynolic acids, **3** and **6**. After being treated under nitrogen for 5 h at 25 °C, the 3-methoxy alcohol (**5**) was recovered to the extent of 84% and **6** was isolated in 14% yield. Based on consumed substrate, however, the conversion was close to 87%, which suggested that this transformation could be improved by enhancing the rate of the initial, slow oxidation step.[3,6,8] Such a modification was easily effected by carrying out the reaction in a system open to air; after 5 h at 25 °C these reactions provided **6** in yields averaging 30%, and unchanged **5** was recovered to the extent of 50–60%. The phenolic alcohol **2** provided results surprisingly different from those of its methoxy counterpart. Thus, **2** not only was considerably less reactive, but its reactivity was not enhanced by the presence of dioxygen; less than 10% of **2** was consumed during 5 h at 25 °C in reactions maintained under nitrogen *or* open to air.

The facile D-ring cleavage effected in these reactions via the *gem*-α-dichloroestrone intermediates (**1a, 4a**) is quite striking in light of the fact that estrone and estradiol themselves are rather resistant to base-induced cleavage. As illustrated in Scheme II, fusion with KOH is required to convert these estrogens into doisynolic acid (**7**).[9–11] Moreover, as a result of this vigorous process, yields are minimal, chiral modification can accompany the cleavage, and 3-methoxy substrates undergo conversion into 3-hydroxy products (when 3-methoxy products are desired, methylation is generally

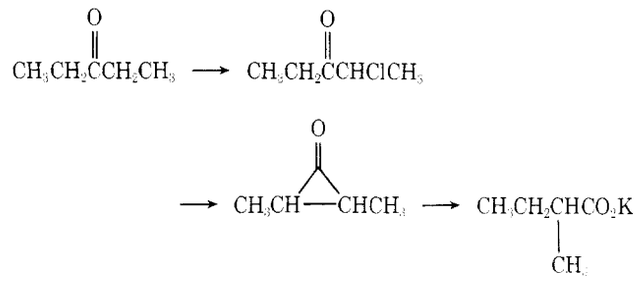
Scheme II



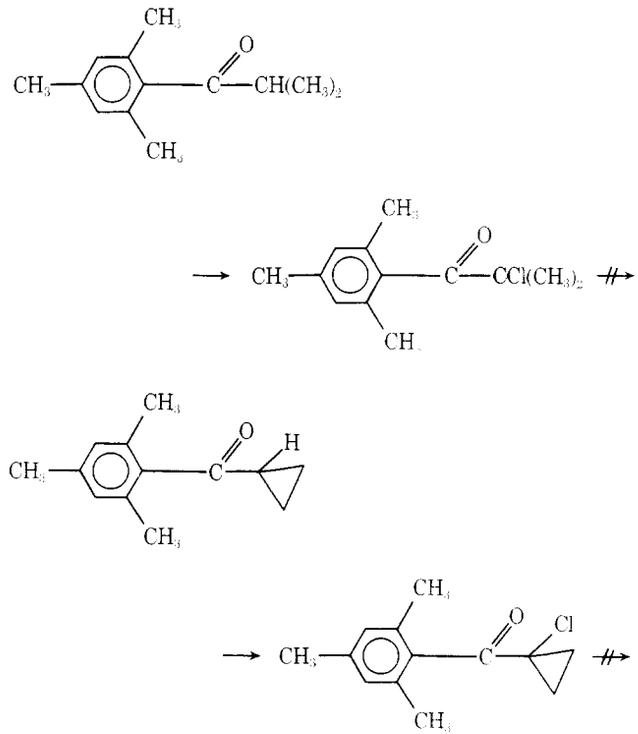
performed *after* the cleavage acids are isolated from the KOH fusion mixtures).[11,12] By comparison, the conversions of the 3-methoxy substrates **4** and **5** into **6** with CCl_4–KOH–*t*-BuOH were carried out at 25 °C, the methoxy group was retained, and chirality was preserved.

Discussion

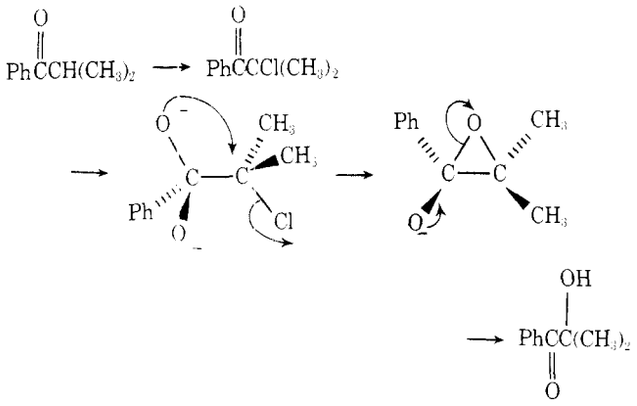
Cyclanones 1 and 4. We have found that in their reactions with CCl_4–KOH–*t*-BuOH, ketones generally fall into four categories:[2–7] (**a**) those having α- and α'-H's, whose α-chloro derivative is formed but rapidly undergoes Favorskii rearrangement, e.g.,



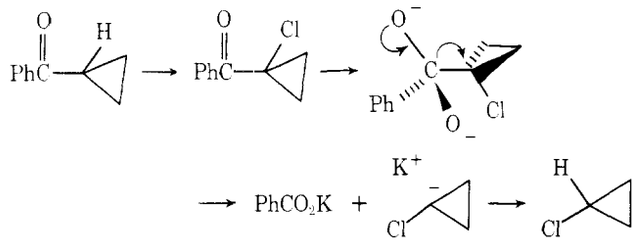
(**b**) those having an α-H but no α'-H and a sterically blocked carbonyl, whose α-chloro derivative is formed and is resistant to further reaction, e.g.,



(**c**) those having an α-H but no α'-H, whose α-chloro derivative is formed but is rapidly converted into the α-hydroxy derivative, e.g.,



(d) Those having an α-H but no α′-H, whose α-chloro derivative is formed but undergoes cleavage, e.g.,



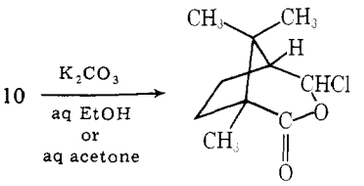
Cyclanones 1 and 4 possess α-H's but no α′-H. Thus, the α-chlorination–Favorskii rearrangement of category a, which is most commonly observed with ketones treated with this reagent, cannot be considered in the cases of 1 and 4.

While molecular models suggest that the carbonyl of these rigid, trans-fused α-methyl ketones may be considerably hindered from attack, steric hindrance of the degree illustrated in category b evidently is not exhibited by 1 and 4 whose α-chloro derivatives underwent rapid transformation.

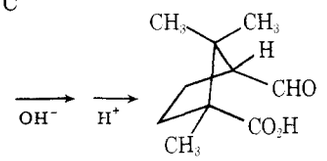
Unhindered ketones possessing only α-H's are usually converted with this reagent into α-chlorinated ketones which undergo either α hydroxylation, category c, or cleavage, category d. These two pathways are not generally competitive; α-hydroxy ketones are usually formed exclusively. However, this α-hydroxylation reaction proceeds via an epoxide intermediate whose formation requires 1,3 elimination of Cl^- from a transition characteristic of S_N2 displacement reactions. When such a transition is not easily attained, the generally disfavored cleavage pathway may be followed, often exclusively as illustrated in the example of α-chlorocyclopropyl phenyl ketone. The unusual stability of the 1-chlorocyclopropyl anion,[13] augmented by the reduced ring strain in cyclopropanes which may be effected by metallation,[14] are factors which would accelerate the cleavage reaction in this example.

Similarly, α hydroxylation of α-chlorinated 1 and 4 is disfavored; in these rigid cyclic structures the transitional antiperiplanar geometry, required for displacement of Cl^- leading to epoxide formation, is not easily accommodated. Moreover, cleavage of these monochlorinated cyclopentanones is relatively slow, and in these systems gem dichlorination can and does occur rapidly. The *gem*-α-dichlorocyclanones **1a** and **4a**, therefore, are formed. They cannot be isolated, however, because they undergo cleavage at a rate which is apparently accelerated by the formation of stabilized α,α-dichlorocarbanions and by the concomitant alleviation of ring strain and unfavorable vicinal interactions between the *gem*-dichloro substituents and *gem*-dioxyanions. In these reactions, then, 1 and 4 follow the pathway first observed with camphor (**9**).[2,4,6] Similar facile base-induced cleavage of *gem*-α-dichlorocyclobutanones has been reported.[15] The dichlorination–cleavage pathway followed by cyclanones **1**, **4**, and **9** is illustrated in Scheme III.

As illustrated in Scheme III, dichlorination–cleavage of **9** into the dichlorocyclopentanoic acid **10** with this reagent proceeds with little if any epimerization of the two chiral centers.[4] Thus, the fact that the dichloromethyl and carboxyl substituents of **10** are in a cis juxtaposition was demonstrated by the conversion of this acid into the chlorolactone **11** (α-chloro-α-campholide) and then into the known product, **12** (camphoric acid *sec*-semialdehyde).[16]



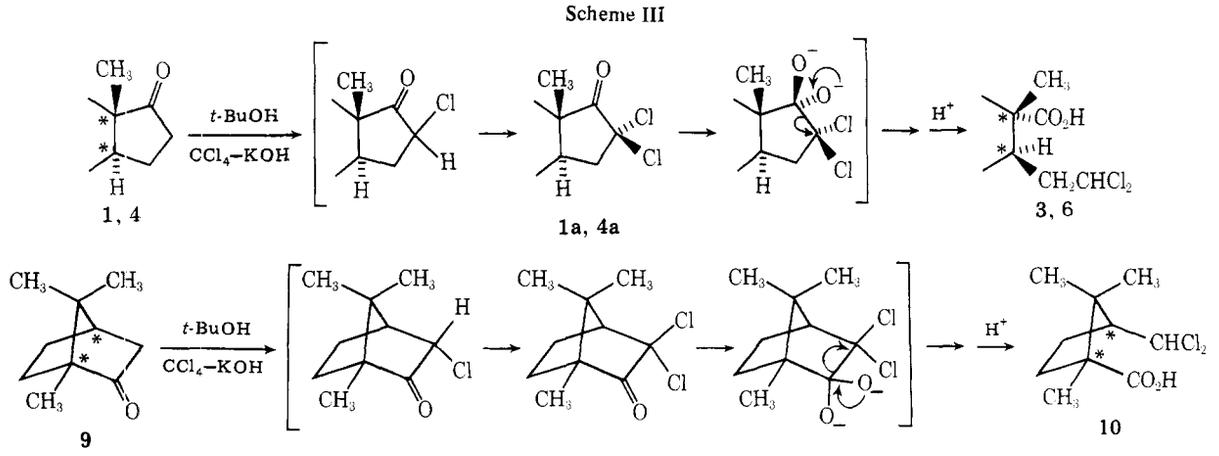
11
mp 135 °C



12
mp 126 °C

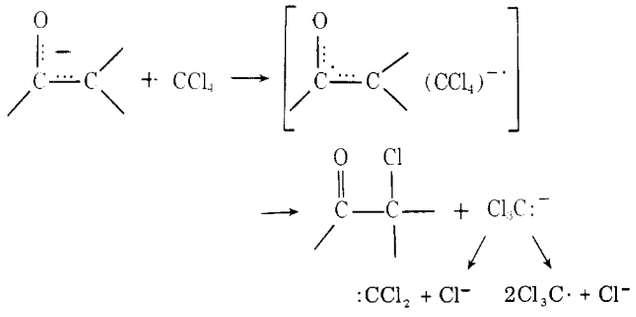
Likewise, 1 and 4 apparently underwent dichlorination–cleavage with this reagent without suffering epimerization of the corresponding chiral centers. In each case the NMR spectrum of the cleavage product exhibited only one sharp singlet representing the methyl on the cyclohexanoic acid ring. Moreover, in those instances where the reactions were quenched prior to completion, the recovered ketone was identical to the original substrate (IR, NMR, mmp).

Scheme III



There seemed to be little difference between the reactivities of estrones 1 and 4; the conversion of each proceeded to the extent of at least 80% within about 1 h at 25 °C. Furthermore, neither reaction exhibited much sensitivity to dioxygen, so that it mattered little if these reactions were carried out under a blanket of nitrogen or in a system open to air. These results are consistent with data suggesting that α chlorination of ketones with this reagent involves the reaction of enolate anions with CCl_4 in a discrete electron transfer/chlorine atom transfer step proceeding through a radical/anion–radical pair (RARP) mechanism, which is neither a radical chain process nor one that requires initiation by dioxygen.[6,17]

As shown in the equation, the coformation of $Cl_3C:^-$ in the chlorination step leads to the generation of $:CCl_2$ as well as $\cdot CCl_3$.[2,6,17] Under the reaction conditions neither of these species is reactive with the 3-methoxy ketone (4) or its product (6); the latter, therefore, was formed and isolated in a high state of purity. Phenoxides, however, are quite reactive with $:CCl_2$ and with $\cdot CCl_3$–CCl_4 under these conditions.[6,17,18] It was

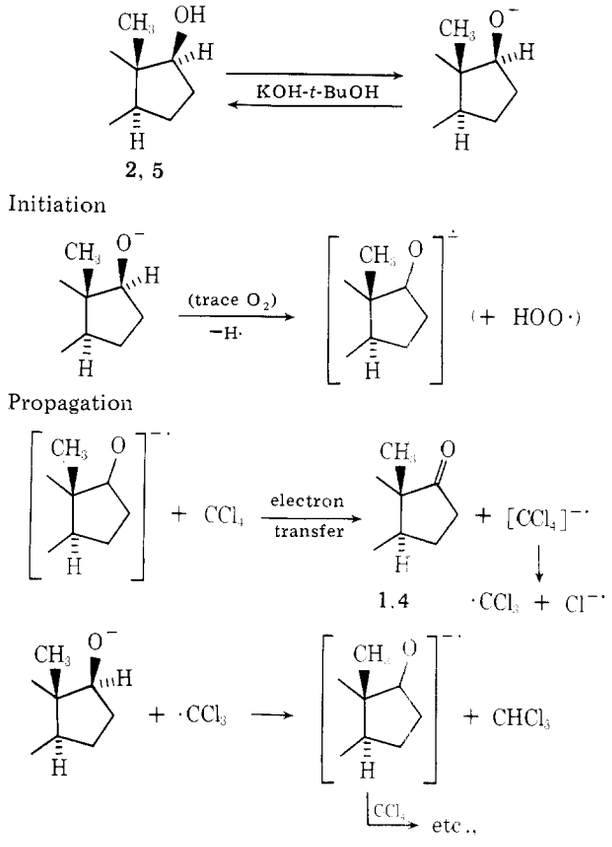


not suprising, then, that the conversion of the phenolic ketone (1) into 3 was accompanied by the formation of small amounts of by-products spectrally characteristic of the 2-aldehyde and 2-carboxylic acid derivatives of 3 which might be expected from these minor secondary reactions.

Cyclanols 2 and 5. Alcohols 2 and 5 underwent reaction with CCl_4–KOH–*t*-BuOH quite slowly relative to the reactions of the corresponding ketones, 1 and 4, with this reagent. This result is reasonable because in these in situ transformations of the alcohols in the initial step, oxidation to ketones, is low with this reagent and, therefore, is rate determining.[3,5,6,8] Steric hindrance may be a factor retarding the rate of these oxidations. Thus, neopentyl alcohol reacts with this reagent at a respectable rate only when the mixture is warmed,[2,3] and isopropyl alcohol reacts faster than di-*tert*-butylcarbinol which exhibits no reactivity even at elevated temperatures.[3] On the other hand, phenylcarbinols are especially reactive, even when hindered (e.g., benzhydrol). There is sufficient evidence now to indicate that alcohols, via their oxyanions/oxyanion radicals, undergo a free-radical chain reaction with CCl_4, a process responsible for their oxidation with this reagent.[6,8] The oxidation of cyclanols 2 and 5 into cyclanones 1 and 4 by this pathway is illustrated in Scheme IV. The fact that these carbinols are relatively hindered and that neither their oxyanions nor oxyanion radicals are especially stabilized may reinforce each other in retarding the rate of these oxidations by this process.

These radical-chain oxidations are initiated by dioxygen and propagated by $\cdot CCl_3$ which is subsequently generated. The number of propagating chains in such a process is closely related to the amount of dioxygen available. Consistent with this mechanism, therefore, is the fact that the reaction of methoxy alcohol 5 (25 °C, 5 h) proceeded much faster in an atmosphere of air (44% reaction) than in an atmosphere of nitrogen (16% reaction). Less obvious, but also consistent with this mechanism, is the fact that *phenolic* alcohol 2 was considerably *less* reactive than its methoxy alcohol counterpart and that its reactivity was indifferent to the amount of dioxygen present,

Scheme IV



viz., less than 10% of 2 underwent reaction during treatment for 5 h at 25 °C in a system maintained under nitrogen *or* open to air. In these reactions a phenolic moiety is essentially all in the form of its phenoxy anion, a function known to inhibit autoxidation and free-radical chain reactions.[19] Moreover, we have found that $\cdot CCl_3$ in CCl_4 solution undergoes a radical-chain addition reaction with a variety of phenoxy anions,[6,17,18] a reaction which would interfere with other chain reactions propagated with $\cdot CCl_3$. The oxidation of 2, therefore, suffers inhibition by these processes because its phenolic moiety functions as a "built-in" inhibitor.

A comparison of the reactions and reactivity of the CCl_4–KOH–*t*-BuOH reagent with those of alkaline potassium hypochlorite revealed that these two reagents perform differently.[2,3,5] Thus, while camphor is easily α,α dichlorinated with the CCl_4 reagent (vide supra), it is completely recovered, unchanged, when refluxed for 6 h with 1*N* KOH–1*N* KOCl in aqueous dioxane (even though its enolate anion is formed under these conditions).[20] Moreover, while phenolic carbinols are oxidized to the *corresponding* phenolic aldehydes or ketones with the CCl_4 reagent, they primarily undergo ring polychlorination when treated with alkaline hypochlorite.[21] These results indicate that the selective dichlorination–cleavage reactions of the cyclanone and cyclanol systems described here cannot be carried out successfully with alkaline hypochlorite.

Bioassay

Doisynolic acid (7) and its methyl ether (8) are reported to exhibit estrogenic activity in rats equal to or greater than that of estrone itself.[22] Halogenation of a steroid may enhance, reduce, or change the nature of its activity depending on the steroidal structure, the position of substitution, and the stereochemistry associated with the substitution.[23] The effect of 16,16-dichloro substitution on the activity of 8 was found to be interesting in several aspects. Thus, 6 exhibited estro-

genic *and* anti-estrogenic activity in the mouse-uterine weight assay when tested at the standard screening dosage level of 25 mg/kg. At the reduced dosage level of 8 mg/kg, however, estrogenic activity was maintained but anti-estrogenic activity no longer was exhibited.[24]

Experimental Section

Commercial-grade KOH pellets (85%) were freshly powdered (mortar and pestle) and used immediately. Both CCl_4 and *t*-BuOH were spectroquality. All TLC's were developed with benzene–EtOAc (7:3, v/v), sprayed with 50% H_2SO_4, then heated at 100 °C. NMR spectra were taken on a Varian A-56/60 spectrometer; IR spectra were taken on Beckman IR-5A or IR-10 spectrophotometers; pK_a and neutralization equivalent measurements were determined on a Corning Model 12 pH meter, and melting points were determined on a Thomas–Hoover capillary melting point apparatus and are not corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

16,16-Dichlorodoisynolic Acid 3-Methyl Ether (6). (a) From Estrone 3-Methyl Ether (4). A solution of 570 mg (2.00 mmol) of estrone 3-methyl ether (**4**; mp 170–171 °C [from MeOH], prepared by the Jones oxidation of estradiol 3-methyl ether [**5**; G. D. Searle and Co.]) in 30 mL of CCl_4 was added to a mixture of 4 g of well-powdered KOH and 16 mL of *t*-BuOH magnetically stirred and maintained under N_2. The reaction was immediately exothermic and the colorless mixture became yellow, gradually deepening to orange. Within 10 min the temperature of the mixture fell to 25 °C and remained constant. After 1 h the mixture was poured into ice–water and extracted several times with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving 100 mg of a viscous oil containing at least five components (TLC) which were not characterized. The aqueous layer and water washings were combined, acidified (HCl) to pH <1, and extracted several times with ether. The combined extracts were washed with aqueous $NaHCO_3$ (vide infra), dried ($MgSO_4$), and evaporated leaving 550 mg (1.48 mmol, 74%) of a crystalline solid, mp 147–148 °C, whose TLC exhibited one major green spot and four barely detectable other spots. Trituration with and recrystallization from ether provided white crystals (TLC pure, one green spot): mp 157–158 °C; NMR ($CDCl_3$) δ 1.15 (s, 3, CCH_3), 3.77 (s, 3, OCH_3), 5.82 (t, J = 6 Hz, 1, $CHCl_2$), 6.53 (d, J = 3 Hz, 1, C-4 H), 6.61 (split d, J = 8 Hz, 3 Hz, 1, C-2 H), 7.08 (d, J = 8 Hz, 1, C-1 H), and 10.92 (s, 1, CO_2H); IR (Nujol) ν 3333–2250 (broad, OH), 1681 (intense, CO_2H), 1282 (v str, OC–O), 737 and 727 cm^{-1} (med, Cl–C–Cl); pK_a 6.65 (in 48% EtOH, 25 °C; average of several values determined with 4.9×10^{-4} M solutions titrated with 10^{-2} N NaOH);[25] neutralization equivalent Calcd for $C_{19}H_{24}O_3Cl_2$: 371. Found: 360 ± 3.

Anal. Calcd for $C_{19}H_{24}O_3Cl_2$: C, 61.46; H, 6.52; Cl, 19.10. Found: C, 61.53; H, 6.63; Cl, 19.04.

The aqueous $NaHCO_3$ washings were combined, acidified (HCl) to pH <1, and extracted several times with ether; the combined ethereal extracts were dried ($MgSO_4$) and evaporated to provide 50 mg of crystalline material (mp 68–135 °C) about one-half of which was **6** (TLC, IR).[26] Including this additional amount the total yield approached 78%. Several preparations carried out under similar conditions provided almost identical results. In addition, two runs carried out in systems opened to air (25 °C, 1 h) afforded yields of about 75%. The same sample of recrystallized product did not always exhibit the same mp, which ranged from 157–158 °C (most frequently) to 164–166 °C.

(b) From Estradiol 3-Methyl Ether (5). To a stirred solution of 572 mg (2.00 mmol) of estradiol 3-methyl ether (**5**; Searle, mp 118–120 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH, maintained under N_2, was added 4.0 g of well-powdered KOH in one portion. The stirred mixture exhibited only a very small exotherm and became slightly yellow. Stirring was continued for 5 h (25 °C) after which time the pale yellow mixture was added to ice–water and extracted several times with ether. The combined ethereal extracts were dried ($MgSO_4$) and evaporated leaving 480 mg (1.68 mmol, 84%) of recovered **5** (IR, mp, mmp). The aqueous residue was acidified (HCl) to pH <1 and extracted with ether, and the extracts were washed with aqueous $NaHCO_3$. The ethereal layer was dried ($MgSO_4$) and evaporated to provide 100 mg (0.27 mmol, 13.5%) of crude product, mp 149–156 °C; IR and NMR spectra were identical to those of the product prepared in (a). The aqueous $NaHCO_3$ washings were acidified to pH <1 with HCl and extracted with ether, and the extracts were dried ($MgSO_4$) and evaporated; only a few milligrams of material were obtained from this fraction.[26]

When this reaction was carried out similarly (25 °C, 5 h) but in a vessel opened to air the yield was improved considerably, to about 30%, while correspondingly less starting material (50–60%) was recovered.

16,16-Dichlorodoisynolic Acid (3). (a) From Estrone (1). To a vigorously stirred solution of 540 mg (2.00 mmol) of estrone (**1**; Upjohn, mp 253–258 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH maintained under N_2 was added 4.0 g of well-powdered KOH in one portion. The mixture immediately became quite warm and attained a reddish brown coloration. The exotherm soon subsided and the mixture, at 25 °C, was stirred for a total of 1.5 h and then poured into ice–water. The mixture was acidified (HCl) to pH <1 and extracted with ether, several drops of 2-octanol being added to break the thick emulsion which formed during the extraction. The combined ethereal extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated, leaving 430 mg of solid material whose NMR spectrum ($CDCl_3$–acetone-d_6: δ 1.23 (s, CCH_3), 5.92 (t, J = 6 Hz, $CHCl_2$)) was characteristically similar to that of **6** but, in addition, exhibited small changes in the aromatic H pattern; likewise, its IR spectrum (Nujol: ν 3400 (Ar–OH), 3200–2450 (broad, CO_2H), 1681 (str, CO_2H), 1282 (med, OC–O), and 727 cm^{-1} (med, Cl–C–Cl)) reflected the pattern of that exhibited by **6**. The combined aqueous $NaHCO_3$ washings were acidified with HCl to pH <1 and extracted with ether; evaporation of the dried extracts provided a solid, 270 mg (after being washed with pentane), whose NMR and IR spectra were very similar to those just described.[26] The absence of starting material was evidenced by the NMR spectra of the two fractions. While the total weight of product, 700 mg, represented a yield of 98%, this material was impure **3**; the presence of the 2-aldehyde and 2-carboxylic acid derivatives of **3** was suggested by the NMR spectrum (δ 7.52 (m, Ar–H ortho to CHO or CO_2H), and 10.40 (s, O=CH or CO_2H)).

This reaction (with 270 mg [1.00 mmol] of **1**, 15 mL of CCl_4, 10 mL of *t*-BuOH, and 2.0 g of powdered KOH) was repeated but in a system opened to air. After 1.5 h at 25 °C the mixture was quenched with ice–water and extracted with CCl_4 three times. The residual aqueous layer was acidified with HCl to pH <1 and the precipitated solid material was separated by filtration, washed with water, and dried in vacuo (25 °C, 16 h), providing 430 mg of a crystalline solid, mp 155–157 °C. Its IR and NMR spectra were almost identical to those described above, indicating the absence of **1**, but suggesting the presence of somewhat more aldehyde contaminent. No further attempt was made to purify **3** prepared in these reactions.

(b) From Estradiol (2). To a vigorously stirred solution of 544 mg (2.00 mmol) of estradiol (**2** [17β]; Schering, mp 174–175 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH maintained under N_2 was added 4.0 g of powdered KOH. The colorless mixture became light orange immediately on contact with the KOH, although no exotherm was evident. After being stirred for 5 h at 25 °C the mixture was poured into ice–water and extracted several times with CCl_4, and the aqueous residue was acidified to pH <1 with HCl which provided a mass of precipitated crystals. This mixture was extracted with ether and the combined extracts were dried ($MgSO_4$) and evaporated to leave 560 mg of a solid composed of (IR, NMR) at least 90% of recovered **2** and less than 10% of **3** (the characteristic CO_2H bands and the CCH_3 singlet of the latter were barely discernable in these spectra).

The same reaction was carried out but in a system opened to air, again for 5 h at 25 °C. The mixture seemed to be somewhat deeper orange-brown than that noted above, but similar workup provided about the same amount of solid whose spectra were almost identical to those described above; again, about 90% of **2** was recovered and no more than 10% of **3** was detected.

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Registry No.—**1**, 53-16-7; **2**, 50-28-2; **3**, 65311-07-1; **3** 2-aldehyde derivative, 65311-08-2; **3** 2-carboxylic-acid derivative, 65311-09-3; **4**, 1624-62-0; **5**, 1035-77-4; **6**, 65311-10-6.

References and Notes

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(24) The assays of **6** were carried out at G. D. Searle and Co. We are grateful to Dr. Kurt Rorig for this service and for providing us with these results.
(25) The related dichloromethylcyclopentanecarboxylic acid (**10**), similarly derived from camphor, exhibited pK_a values of 6.25 in 50% EtOH and 5.30 in water (25 °C).[16]
(26) Evidently **6**, because of its high molecular weight and nonphenolic character, is not very polar and therefore is not readily neutralized in ethereal solution by treatment with aqueous $NaHCO_3$. The corresponding phenolic carboxylic acid (**3**) under the same conditions is more readily neutralized.

Identity of the Stereochemistry of Dinosterol and Gorgosterol Side Chain[1]

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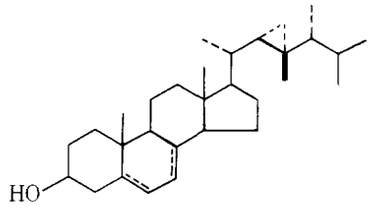
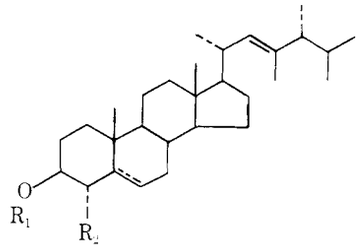
The structure of dinosterol, a peculiar sterol isolated from the dinoflagellate *Gonyaulax tamarensis*, was confirmed by x-ray crystallography. The proven identity of the stereochemistry of the side chain provided further support for the suspected close biogenetic relationship of dinosterol with gorgosterol and acanthasterol.

A difficult but intriguing problem in the study of marine animal constituents is the metabolite transfer inherent in the marine food chain and symbiosis. More often than not, it is difficult to determine whether an isolated compound is biosynthesized by the organism itself or is of dietary origin, either intact or partially transformed. A most intriguing example is gorgosterol **1** and its derivatives isolated from soft coral or gorgonians.[4] Their structures are unique not only for the presence of a cyclopropane ring but also for the unprecedented C-23 alkylated side chain. The abnormal side chain seems to be formed by methylation at C-24 followed by a second methylation at Δ^{22} and a third alkylation leading to the cyclopropane ring (Scheme I). In fact, Kanazawa et al.[5] isolated from a soft coral, *Sarcophyta elegans*, 23ξ,24ξ-dimethylcholesta-5,22-dien-3β-ol (**2**) which fits well into this scheme. A double bond isomer of gorgosterol, acanthasterol (**3**), was also isolated from the crown-of-thorns starfish, *Acanthaster planci*.[6] Since starfish are known to transform exogenous Δ^5 sterols to Δ^7 sterols,[7] it was immediately speculated that acanthasterol was of dietary origin. Indeed the crown-of-thorns starfish is known to feed on soft corals. As to the origin of gorgosterol in soft corals, Ciereszko et al.[8] already speculated that it might have come from symbiotic dinoflagellates, *Zooxanthellae*, which sometimes constitute a substantial part of the total body weight. The extract of the washed-out zooxanthellae was found to give a mass spectrum peak *m/e* 426 corresponding to gorgosterol. It was also noticed



1 Δ^5
3 Δ^7



2 Δ^5, R_1, R_2 = H
4 5α, R_1 = H; R_2 = CH_3
5 R_1 = *p*-I-C_6H_5CO; R_2 = CH_3

that the anaerobically kept zooxanthellae gave a *m/e* 428 peak of "dihydrogorgosterol".[8]

In view of the above-mentioned observation and the fact

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