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REACTIONS OF ACID ANHYDRIDES—I

REACTIONS OF KETONES WITH TRICHLOROACETIC ANHYDRIDE

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Abstract—The reactions of saturated and unsaturated ketones with trichloroacetic anhydride both alone and in the presence of trichloroacetic and *p*-toluenesulphonic acids were studied.

Treatment of pentan-3-one (**1**), cyclobutanone (**2**), cyclohexanone (**3**), nor-camphor (**4**), 17β-acetoxy-5α-androstan-3-one (**5a**) 17β-acetoxy-5β-androstan-3-one (**6a**) and cyclohexen-2-one (**25**) with trichloroacetic anhydride resulted in the corresponding *geminal* bis-trichloroacetates **7**, **8**, **9**, **10**, **11**, **12** and **26**. The presence of trichloroacetic acid decreases the rate of the conversion of these ketones to the *geminal* bis-trichloroacetates.

Testosterone acetate (**28a**), acetophenone (**31**) and the steroidal dimethylketone **21a**, gave, on treatment with trichloroacetic anhydride, the corresponding enol trichloroacetates **30**, **33** and **23**. Camphor (**17**) resulted in a rearrangement product, the 1-trichloroacetoxy-camphene **19a**. In the presence of trichloroacetic acid, the dimethylketone **21a** gave in addition to **23** the aromatization product, **24a** and camphor **17** gave in addition to **19a** the 2β,4-bis-trichloroacetoxy-bornane **20a**.

Trichloroacetic anhydride in the presence of *p*-toluenesulphonic acid converted ketones **1**, **3**, **5a** and **6a**, as well as the *geminal* bis-trichloroacetates **7**, **9**, **11** and **12**, to the corresponding enol trichloroacetates **13**, **14**, **15** and **16**.

The spectral properties of the *geminal* bis-trichloroacetates and enol trichloroacetates are discussed.

The reactivities of the various ketones towards trichloroacetic anhydride were compared, and the mechanism of formation of *gem* diesters and enol esters is proposed. It is suggested that the *gem* diesters are invariably intermediates in the conversion of the ketones to the enol esters.

IT IS well known that aldehydes react with anhydrides of carboxylic acids on acid[1] or basic[2] catalysis to give *gem* diesters. On the other hand, ketones are transformed under similar conditions to enol esters. It was, however, reported[3] that the reaction of cyclohexanone, acetic anhydride and sulphuric acid gave a *gem* diacetate as a minor product in addition to the enol acetate. This *gem* diacetate was further transformed to the corresponding enol acetate on prolonged treatment with the same reagents. Such a result suggests, that *gem* diesters may be the primary products in the reactions of ketones with anhydrides.

We have found, that ketones, on treatment with trichloroacetic anhydride, are converted to the analogous *gem* bis-trichloroacetates. The *gem* diesters were readily isolated and characterized by their analytical and physical properties.

Pentan-3-one (**1**) cyclobutanone (**2**), cyclohexanone (**3**) norcamphor (**4**) and the steroidal ketones: 17β-acetoxy-5α-androstan-3-one (**5a**) and 17β-acetoxy-5β-androstan-3-one (**6a**) were transformed on treatment with trichloroacetic anhydride at

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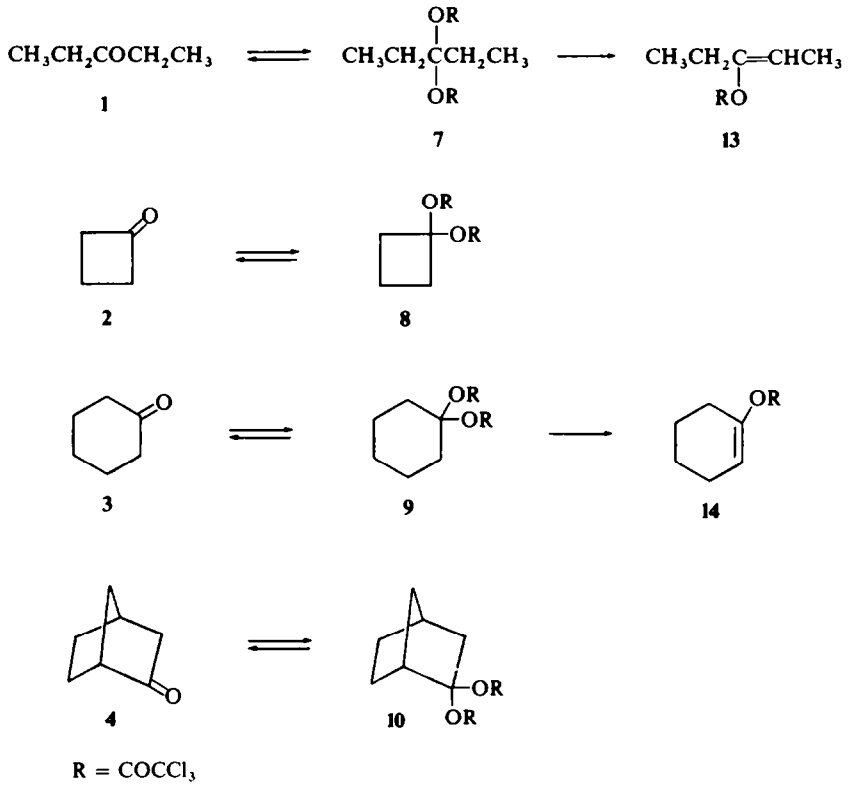
CHART I



R = $COCCl_3$

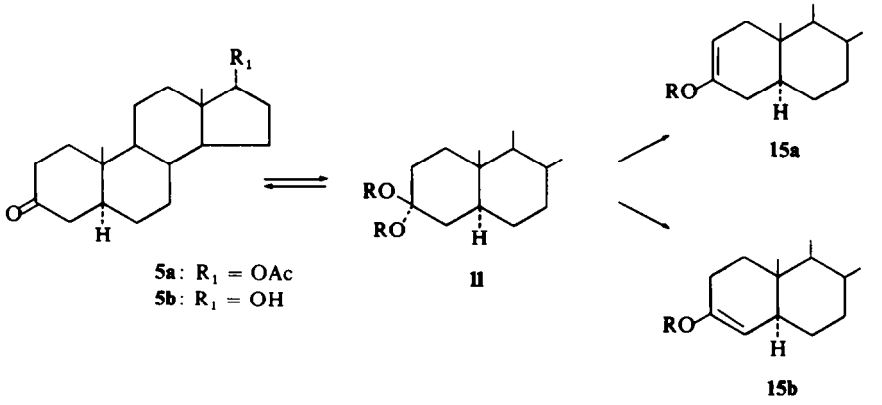
90–100° to the corresponding *gem* bis-trichloroacetates **7**, **8**, **9**, **10**, **11** and **12**. These *gem* diesters were the only products isolated from these reactions apart from unreacted ketones.

The steroidal *gem* diesters **11** and **12** were hydrolyzed to their corresponding ketones **5b** and **6b** in aqueous alcohol in the presence of acid, and **12** resulted in the ketone **6a** on heating with anhydrous dimethylformamide.

Bis-trichloroacetates **7**, **8**, **9**, **10**, **11** and **12** were also formed with the ketones **1**, **2**, **3**, **4**, **5a** and **6a** when treated with trichloroacetic anhydride in the presence of trichloroacetic acid. A decrease in the reaction rate was however observed in the presence of the acid. (Table 1).

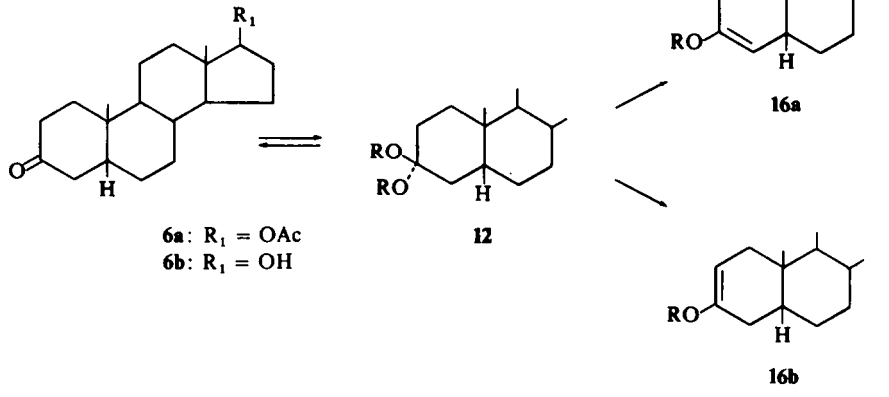
In a parallel series of experiments cyclohexanone (**3**) was treated with the anhydride, both alone and in the presence of ca. 20% trichloroacetic acid. The percentage yields of the product formed were determined by integration of the appropriate signals in the NMR spectra of the reaction mixtures. The results summarized in Table 1 show that presence of the acid lowers the rate of anhydride addition—presumably the carbonyl in its protonated form does not react with anhydride.

CHART II



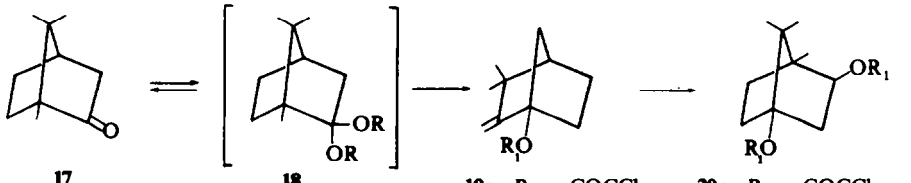
5a: R_1 = OAc
5b: R_1 = OH

11



6a: R_1 = OAc
6b: R_1 = OH

12



17

18

19a: R_1 = $COCCl_3$
19b: R_1 = H

20a: R_1 = $COCCl_3$
20b: R_1 = H

R = $COCCl_3$

TABLE 1. COMPARISON OF RATES OF REACTIONS OF KETONES WITH TRICHLOROACETIC ANHYDRIDE AND IN THE PRESENCE OF TRICHLOROACETIC ACID

Reactant[a]	Product	Reagent	Reaction half time
Cyclohexanone (3)	*Gem* diester 9	$(CCl_3CO)_2O$	1½ hr[b]
	Gem diester 9	$(CCl_3CO)_2O + CCl_3COOH$	3 hr[b]
Cyclohex-2-enone (25)	*Gem* diester 26	$(CCl_3CO)_2O$	10 min[b]
	Gem diester 26	$(CCl_3CO)_2O + CCl_3COOH$	15 min[b]
Testosterone acetate (28a)	Dienol ester 30	$(CCl_3CO)_2O$	1½ hr[c]
	Dienol ester 30	$(CCl_3CO)_2O + CCl_3COOH$	3 hr[c]
	Dienol ester 30	$(CCl_3CO)_2O + CCl_3COOH + CCl_3COONa$	1½ hr[c]

[a] 1·0 molar solution: [b] at 105–110°: [c] at 25°.

The readily enolizable ketones **1**, **3**, **5a**, and **6a** gave when treated with trichloroacetic anhydride in the presence of *p*-toluenesulphonic acid at 125–135° enol trichloroacetates. Thus the symmetrically substituted ketones **1** and **3** were converted to the enol trichloroacetates **13** and **14**, and the unsymmetrically substituted ketones **5a** and **6a** gave mixtures of the two positional double bond isomers **15a** + **15b**. and **16a** + **16b** respectively. The ratio of **15a** and **15b**, and **16a** and **16b** was after 60 min of reaction 3:1 and 4:1 respectively. Prolonged treatment with the same reagent at the same temperature equilibrated these mixtures to give the thermodynamically more stable isomers **15a** and **16a** in a proportion exceeding 90%.

On the other hand cyclobutanone (**2**) and norcamphor (**4**), enolizable only with difficulty did not give the corresponding enol esters.

It was found that the presence of a strong acid (*p*-toluenesulphonic acid) and higher temperatures (125–135°) are necessary for the formation of these enol trichloroacetates. When the steroidal ketone **5a** was treated with trichloroacetic anhydride in the presence of *p*-toluenesulphonic acid at 90–100°, or in the presence of trichloroacetic acid at 125–135°, the *gem* bis-trichloroacetate **11** was obtained, and not the enol esters **15**. The latter were formed only when the reaction was carried out in the presence of *p*-toluenesulphonic acid at 125–135°.

The enol trichloroacetates are more readily solvolysed under basic catalysis than the corresponding enol acetates. Even commercial spectroscopic methanol, which is very slightly basic, converted the enol trichloroacetates **15a** and **15b** to the parent ketone **5a**. This enhanced reactivity towards bases is due to the strong inductive effect of the trichloromethyl group, rendering the CO carbon a stronger electrophile.

The *gem* diesters **7**, **9**, **11** and **12** reacted with trichloroacetic anhydride and *p*-toluenesulphonic acid at 125–135° in the same way as the corresponding ketones, resulting in the enol trichloroacetates **13**, **14**, **15** and **16**. The ratio of the positional double bond isomeric enol trichloroacetates **15a** + **b** and **16a** + **b**, obtained from the *gem* diesters **11** and **12**, were almost the same as those obtained directly from the corresponding ketones **5a** and **6a**.

We have also found, that the *gem* diesters **7**, **9** and **11** are converted much faster to

the enol esters **13**, **14** and **15** than their parent ketones **1**, **3** and **5** (Table 2), thus indicating the intermediacy of the former compounds in the conversion of the ketones to the enol trichloroacetates.

TABLE 2. RATES OF FORMATION OF ENOL TRICHLOROACETATES IN THE PRESENCE OF P. TOLUENESULPHONIC ACID AT 130°.

Reactant	Product	Concentration of reactant moles/l	Concentration of *p*-toluenesulphonic acid, moles/l	Reaction half time
Pentan-3-one (**1**)	enol ester **13**	0·2	0·1	>1½ hr
Gem-diester **7**	enol ester **13**	0·2	0·1	10 min
Cyclohexanone (**3**)	enol ester **14**	0·2	0·1	1½ hr
		0·5	0·16	1¾ hr
gem-diester **9**	enol ester **14**	0·2	0·1	½ hr
		1·2	0·6	7 min
Cyclohex-2-enone (**25**)	dienol ester **27**	0·5	0·16	1 hr
gem-Diester **26**	dienol ester **27**	1·2	0·6	<5 min
17β-Acetoxy-5α-androstane-3-one (**5a**)	enol ester **15**	0·65	0·5	½ hr
gem-Diester **11**	enol ester **15**	0·65	0·5	<5 min

Enol trichloroacetates **15**, accompanied by the ketone **5a**, were also formed on pyrolysis of the solid *gem* diester **11** at 185°. This decomposition is likely to proceed through a cyclic transition state, as proposed for the analogous reactions of diacetates derived from aldehydes.[4]

1,1′-bis-trichloroacetoxy-cyclobutane (**8**) and 2,2′-bis-trichloroacetoxynorcamphor (**10**) were not converted to the corresponding enol trichloroacetate when treated with trichloroacetic anhydride and *p*-toluenesulphonic acid at 125–135°. The stability of the diesters **8** and **10** towards elimination of trichloroacetic acid is due to the strain present in the cyclobutene and bicyclo[2.2.1]heptene systems.

Although norcamphor (**4**) reacted as expected with trichloroacetic anhydride, D-camphor (**17**) under similar conditions gave a rearranged product, 1-trichloroacetoxycamphene (**19a**). Base catalysed hydrolysis of the camphene ester **19a** resulted in the known 1-hydroxycamphene **19b** which gave a similar NMR spectrum to the former compound. The isolated alcohol **19b** was optically active, although its optical rotation was somewhat lower than that reported[5a] ($[\alpha]_D$ +22·5° instead of $[\alpha]_D$ +29·5°).

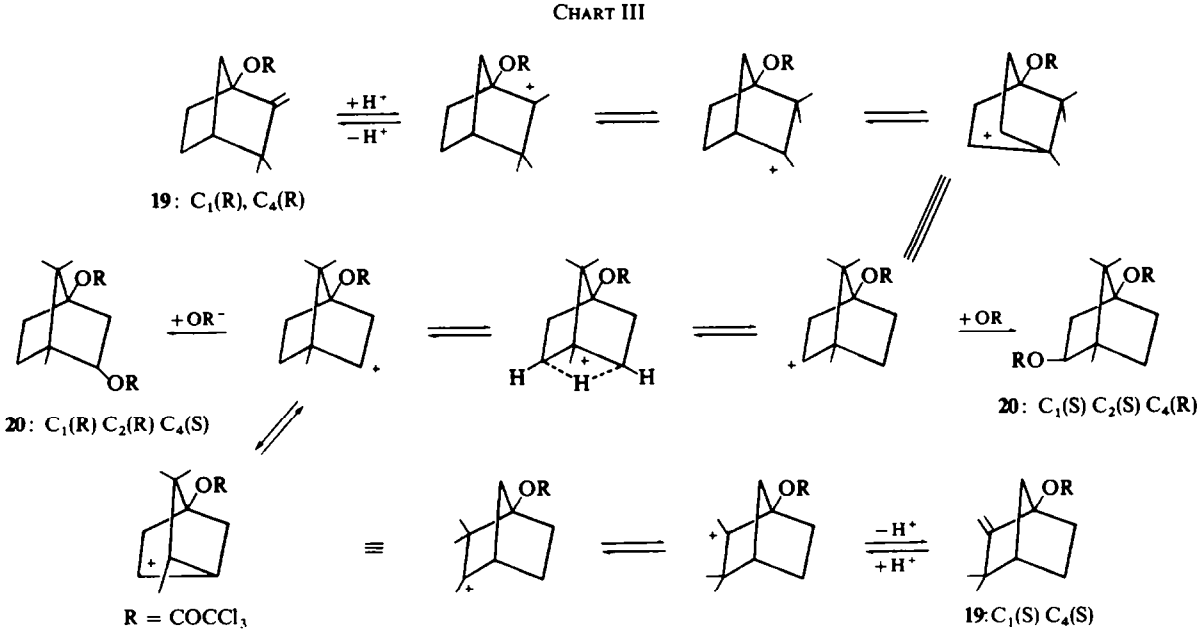
It is conceivable that the primary product in the reaction of D-camphor **17** with trichloroacetic anhydride is the 2,2′-bis-trichloroacetoxybornane (**18**), which eliminates trichloroacetic acid while rearranging to the camphene derivative **19a**. The analogous rearrangement of 2,2′-dichlorobornane to the 1-chlorocamphene is well known.[6] The observed elimination of trichloroacetic acid from the diester is probably catalysed by minute amounts of acid, which may be formed in the reaction mixture.

The liberated trichloroacetic acid autocatalyses the further decomposition of the diester to the camphene derivative **19a**.

When D-camphor (**17**) was treated with anhydride in the presence of trichloroacetic acid two products were isolated. One was identical to the camphene derivative **19a** obtained in the reaction with trichloroacetic anhydride alone, except for its lower rotation ($[\alpha]_D$ +7° instead of $[\alpha]_D$ +16·3°). To the second one we assigned the structure of the 2β,4-bis-trichloroacetoxybornane **20a**. Its NMR spectrum was characteristic for the bornane skeleton substituted at the *exo*-C2 position (three singlets for the Me protons, an AMX quartet J_{AM} = 8 c/s J_{AX} = 3 c/s for the *endo*-C2 proton and a second AMX quartet J_{MX} 13 c/s, J_{MA} = 8 c/s for the *endo*-C3 proton)

Basic hydrolysis of the bis-trichloroacetate **20a** resulted in 2β,4-dihydroxybornane **20b**, which shows a similar NMR pattern to the former diester. Both **20a** and **20b** were optically active.

CHART III

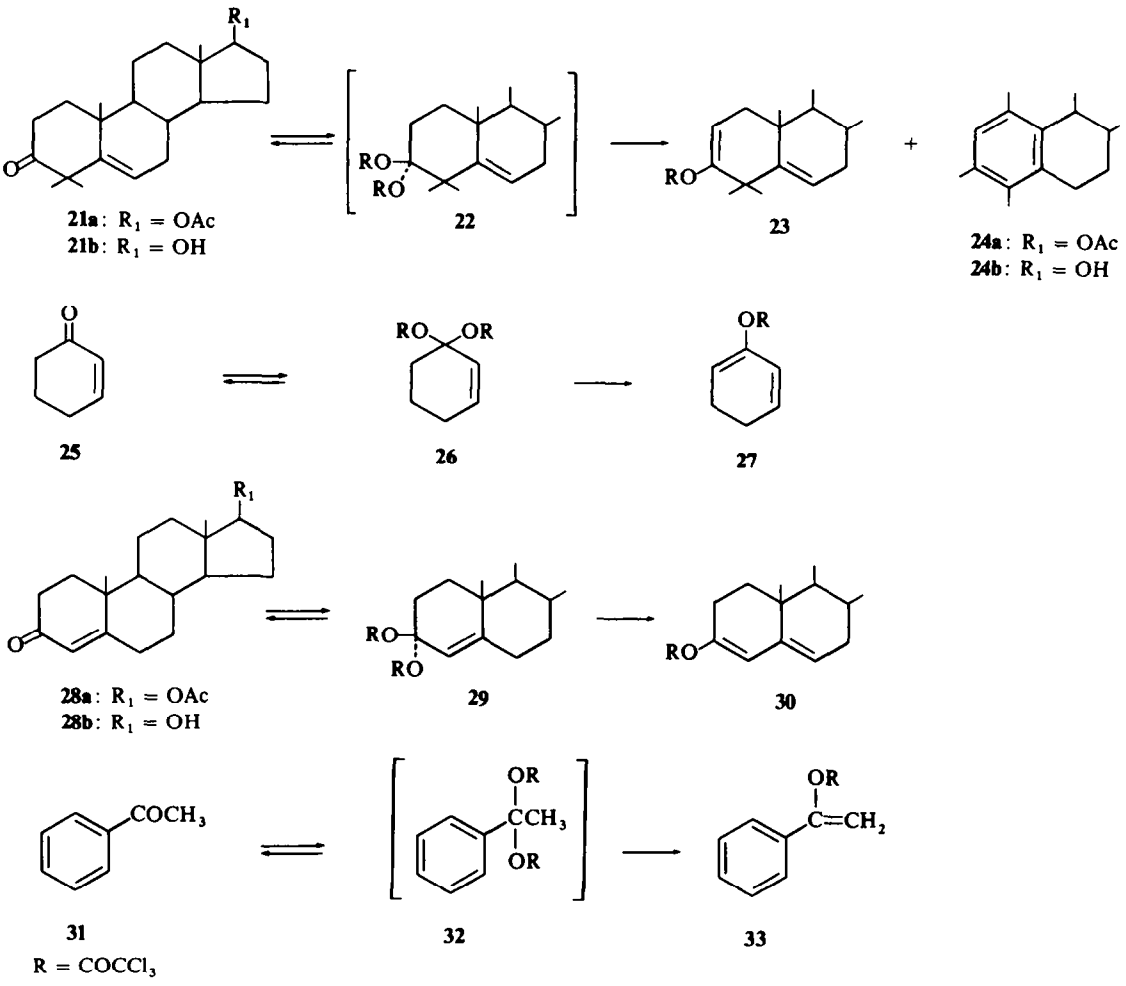


Formation of the bornane derivative **20a** may be explained by consecutive Nametkin and Wagner–Meerwein rearrangements of the protonated camphene ester **19a** (Chart III). An analogous scheme was previously postulated for the rearrangement of 2,2′-disubstituted bornane derivatives.[7] The lower rotation of the camphene derivative **19a** isolated from this reaction may be due to its partial racemation. We assume that a 1:3 hydride shift occurring in the bornane cation is responsible for the partial racemation of both the camphene derivative **19a** and the bornane derivative **20a** (Chart III).

Another sterically hindered ketone, 17β-acetoxy-4,4-dimethylandrost-5-en-3-one **21a**, reacted only slowly with trichloroacetic anhydride and after prolonged heating most of the starting material was recovered unchanged. The only product isolated

from this reaction was the enol ester **23**, which regenerated the parent ketone **21b** on treatment with basic aqueous methanol.

CHART IV



21a: R_1 = OAc
21b: R_1 = OH

22

23

24a: R_1 = OAc
24b: R_1 = OH

25

26

27

28a: R_1 = OAc
28b: R_1 = OH

29

30

31
R = $COCCl_3$

32

33

In this case the formation of the geminal diester **22** is also likely to precede that of the enol ester **23**, although its presence in the reaction mixture could not be observed. The low conversion of the ketone **21a** in this reaction reflects the considerable steric interference in the vicinity of the CO group to the approach of the reagent.

Treatment of the 4,4-dimethylandrostane derivative **21a** with trichloroacetic anhydride and trichloroacetic acid resulted in the formation of a benzenoid compound in addition to the enol-ester **23**. Since 4,4-dimethyl-cholest-5-en-3-one is known to give with strong acids 1,3,4-trimethyl-19-nor-cholesta-1,3,5(10)-triene,[8] we postulated an analogous structure **24a** for the isolated aromatic compound. The spectroscopic

properties of **24a**, as well as those of its hydrolysis product **24b** were compatible with the given structure and were also in good agreement with the data reported for the analogous compound in the cholestane series.[8] It is likely that protonation of the ketone by the acid leads to the aromatization product **24a**. This protonation occurs competitively with the attack of the anhydride leading to the enol ester **23**.

Cyclohex-2-enone **25** was heated with trichloroacetic anhydride and the course of the reaction followed by NMR. After 15 minutes new signals appeared in the vinylic region which intensities increased on additional heating. These resonance lines were assigned to the *gem* diester **26**, produced in a high yield as estimated from the NMR spectrum. In the case of cyclohex-2-enone (**25**) the rate of addition of trichloroacetic anhydride is also decreased in the presence of trichloroacetic acid as may be seen from Table 1. In the presence of *p*-toluenesulphonic acid, trichloroacetic anhydride converts cyclohexenone (**25**) into 2-trichloroacetoxy-cyclohexa-1,3-diene, (**27**).

The α,β-unsaturated ketone, testosterone acetate **28a**, reacted very rapidly with trichloroacetic anhydride when heated at 90–100°. The product isolated was the dienol trichloroacetate **30**, which was characterized by its physical properties and by regeneration of testosterone **28b** on basic hydrolysis. Moreover, testosterone acetate **28a** reacted with trichloroacetic anhydride even at room temperature. The progress of this reaction was followed by recording the NMR spectra of the reaction mixtures after various time intervals. An almost instantaneous change was observed in the NMR spectrum, where new peaks in both vinylic and Me region appeared (Fig. 1).

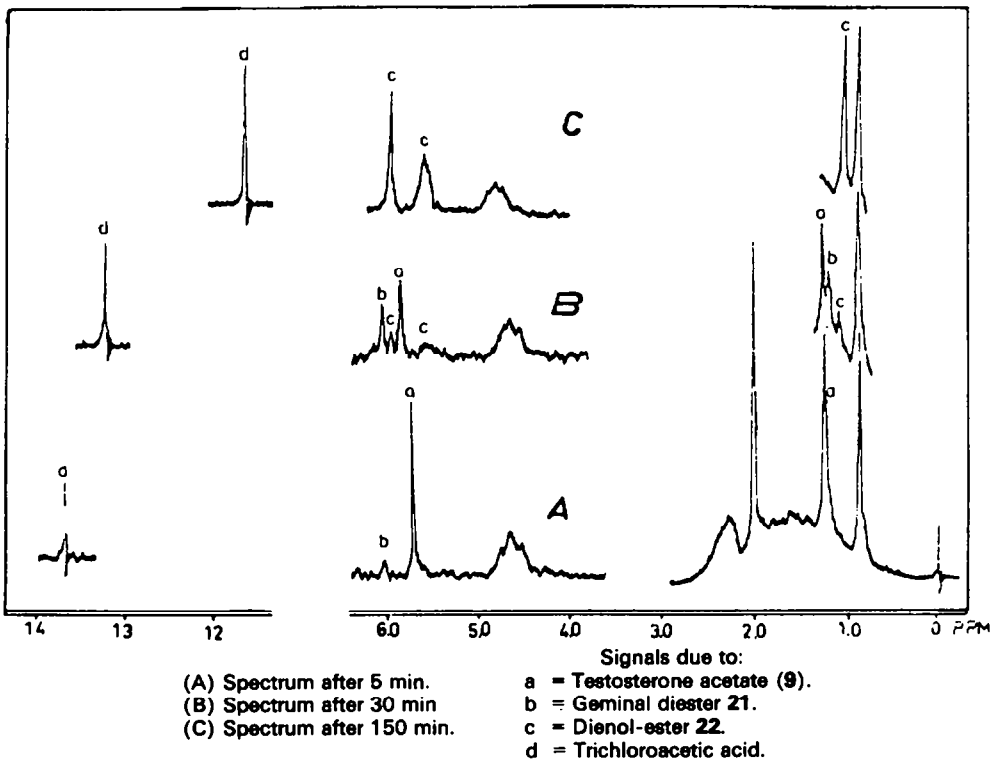


FIG. 1 NMR Spectra of Testosterone acetate (9) in Trichloroacetic Anhydride.

These were attributed to an intermediate product, since their intensities reached a maximum value after ca. 30 min and then gradually decreased. We assigned to this intermediate the structure of the *gem* diester **29**. The resonance lines of the final product, the dienol trichloroacetate **30**, intensified as the intensities of the signals due to the starting material diminished further, while shifting to the lower field.† After $2\frac{1}{2}$ hr the NMR spectrum showed only signals due to the dienol ester **30** and a low field proton,‡ assigned to the trichloroacetic acid liberated during the reaction.

Testosterone acetate **28a** was then treated with trichloroacetic anhydride in the presence of minute amounts of triethylamine. The NMR spectra, recorded during the course of the reaction, showed the appearance of the signals due to the intermediate **29**, but the signals of the dienol ester **30** were absent. Addition of small amounts of trichloroacetic acid however caused an intermediate change: the signals due to the intermediate **29** decreased in intensity, and after ca. 10 min only the signals of the starting material **28a** and of the final product **30** could be seen.

These results strongly indicate that the primary product of the reaction, the *gem* diester **29**, undergoes acid catalyzed elimination. This step is initiated by catalytic amounts of trichloroacetic acid present in the reaction mixture. The triethylamine neutralizes the acid and thus prevents decomposition of the diester **29** to the dienol ester **30**.

No formation of *gem* diester **29** was observed when testosterone acetate **28a** was treated at room temperature with trichloroacetic anhydride in the presence of trichloroacetic acid. The NMR spectra, recorded during the course of the reaction, showed solely the appearance of signals due to the dienol trichloroacetate **30**, which was subsequently isolated.

The overall rate of the formation of the dienol ester **30** in the presence of trichloroacetic acid was also found to be lower than in its absence, (Table 1). It is plausible that the acid present lowers the rate of formation of the primary product, the *gem* diester **29** by protonation of the carbonyl group. Addition of sodium trichloroacetate to the reaction mixture, however, enhanced the rate of the formation of the dienol ester **30** (Table 1). This may be explained by the decrease in the ionization of the trichloroacetic acid in the presence of its sodium salt.

Trichloroacetic anhydride, at 95–100°, converted acetophenone (**31**) to the corresponding enol trichloroacetate **33**. This reaction was followed by NMR measurements: the new signals observed were assigned to the vinylic protons of the enol

† The shift in the position of the vinylic proton at C4 of the ketone **28a** arises from protonation of the carbonyl group by the liberated acid. At the beginning of the reaction the concentration of the trichloroacetic acid is negligible and the chemical shift observed is very close to that found in neutral solvents. While the reaction is proceeding, the concentration of the acid increases resulting in increasing number of protonated steroidal molecules. Since a rapid exchange occurs between the protonated and nonprotonated species, the observed resonance line shifts to lower fields. Shifts to lower fields, but of smaller magnitude, were observed also for the C17-acetoxy- and the C19-methyl proton signals.

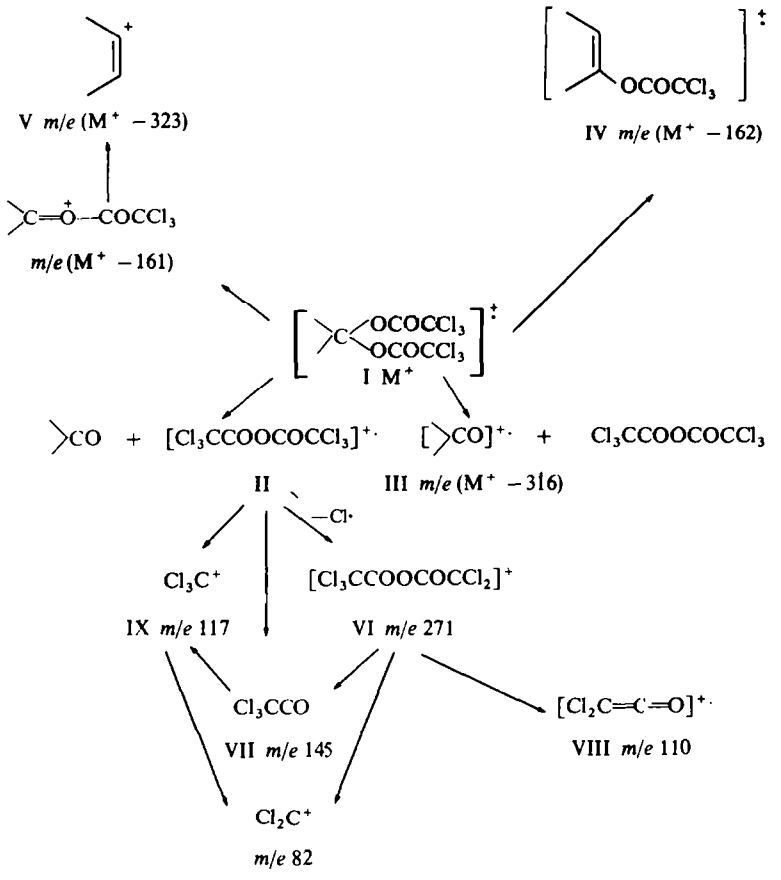
‡ The rapid exchange of the acidic proton between the trichloroacetate ion and the ketonic oxygen atom of the steroidal molecule is responsible for its comparatively low field signal (δ 13·7 ppm) at the beginning of the reaction. Since the proton signal of the trichloroacetic acid in trichloroacetic anhydride at similar concentration was observed at higher field (δ 10·33 ppm), most of the acidic proton must be located at the carbonyl oxygen of the steroid. With the progress of the reaction, the concentration of the trichloroacetic acid increases while that of the starting ketone decreases, resulting in a shift of the acid proton signal to lower field (Fig. 1). The signals of the protons of protonated carbonyl compounds have been reported to appear between δ 13·5–15·0 ppm in $HOSO_2F$—SO_2—SbF_5 system.[9]

TABLE 3. SPECTRAL PROPERTIES OF *gem* BIS TRICHLOROACETATES

Compound	UV[a]	IR[b] cm^{-1}		NMR[c,d] δ ppm		
	ε at 220 mμ	ν(C=O)	ν(C—O—C), ν(O—C—O)	$-CH_2-C(=O)-O$	$CH_2 \cdot CH_2$ $C(=O)-O$	CH_3 at C10
7	675	1770	1250, 1210, 1150, 1115, 975	2·5 (q, J = 8 c/s)	1·05 (t, J = 8 c/s)	
8	650	1770	1265, 1230, 1190, 1135, 950	2·90 (m)	2·10 (m)	
9	800	1770	1230, 1200, 1140, 1060, 960	2·45 (m)	1·25 (m)	
11	560	1770 1735 (OAc)	1250, 1215, 1030, 965			0·9 (s)
12	675	1770 1735 (OAc)	1250, 1210, 1170, 1050, 965			1·0 (s)

[a] In ethanol. [b] **7**, **8**, **9** in neat film; **11**, **12** in KBr. [c] In $CDCl_3$. [d] s = singlet, t = triplet, q = quartet, m = multiplet.

CHART V



I, II were not observed in **7**, **8**, **9**
III was not observed in **7**
IV, V were not observed in **8**

trichloroacetate **33**. No resonance lines attributable to an intermediate *gem* bis-trichloroacetate **32** could be seen in the spectrum.

Spectral properties of gem *bis-trichloroacetates and of enol trichloroacetates*

In the UV spectra of all the *gem* bis-trichloroacetates (Table 3) only end-absorptions (ε 500–800 at 220 mμ) were observed. Addition of small amounts of aqueous sodium hydroxide to the ethanolic solutions of the diesters **7**, **8** and **9** gave rise to a new absorption max at about 280 mμ, attributed to the parent ketones formed by hydrolysis. The *gem* bis-trichloroacetates show in their IR spectra (Table 3) strong absorption at 1770 cm^{-1} and several bands between 950–750 cm^{-1}. These bands are attributed to C=O and C—Cl stretching vibrations. The *gem* bis-trichloroacetates differ from the corresponding mono-trichloroacetates having multiple bands in the

1265–950 cm^{-1} region, due to the C—O—C—O—C stretching modes, instead of two bands characteristic of the C—O—C vibrations observed in mono-esters.[10]

The NMR spectra of the diesters (Table 3) show the same pattern as the corresponding ketones. Thus the α-protons in both systems have similar chemical shifts. The low field values of the α-protons in the *gem* diesters result from the additive inductive effect of the two trichloroacetoxy groups.

A generalized mass spectral fragmentation scheme for all the *gem* diesters investigated is illustrated on the Chart V. However not all mass peaks were observed for each diester (see footnote, Chart V).

The spectral properties of enol trichloroacetates are strongly influenced by the inductive effect of the trichloromethyl group. Thus the inductive effect of the trichloromethyl group is reflected in the UV spectrum of the dienol trichloroacetate **30**. Its π–π* absorption (λ 232 mμ) is shifted to shorter wavelength when compared with that of the diene and corresponding dienol acetate (235 and 235·5 μ respectively). This inductive effect opposes the mesomeric one, which is responsible for the bathochromic shift observed in the dienol ether (239 mμ).

The UV spectra of the enol-trichloroacetates show a *characteristic absorption* at 220–230 mμ, appearing as a shoulder (ε 800–1400) on the more intense end-absorption (Table 4). Since neither trichloromethyl ketones, nor alkyl trichloroacetates show an absorption in this region, the observed transition must involve the double bond electrons. A similar band at about 220 mμ appears also in the UV spectra of enol dichloroacetates.†

The C=O and C—O stretching frequencies of enol trichloroacetates are similar to those of alkyl trichloroacetates (the relevant bands in $CCl_3COOC_2H_5$ are at 1770 and 1245 cm^{-1}). This contrasts the substantial influence of the double bond on the C—O stretching modes of enol acetates, resulting in a shift of their C=O absorption to higher frequencies, and that of C—O to lower ones when compared to that of

TABLE 4. SPECTRAL PROPERTIES OF ENOL TRICHLOROACETATES

Compound	UV mμ[a]			IR cm^{-1} [b]			NMR ppm[c]	
	λ_{max}	ε	ε 200 mμ	ν(CO),	ν(C=C)	ν(C—O—C)	C=C—H	Δ[d]
13	220	(880)	(2400)	1768,	1700,	1220, 1165	5·22	0·32
14	225	(1200)	(3000)	1770,	1690,	1220, 1095	5·55	0·35
15a	220	(1200)	(3400)	1775,	1700,	1230, 1150	5·45	0·24
16a	225	(1200)	(3700)	1795,	1700,	1250	5·27	0·27
15b[e]							5·20	0·25
16b[e]							5·45	0·25

[a] in cyclohexane;

[b] **13** and **14** in neat liquid, **15** and **16** in KBr.

[c] in $CDCl_3$.

[d] Δ = differences in the chemical shifts between the vinylic protons of the respective enol trichloracetates and enol acetates (R = OAc).

[e] NMR values taken from mixture of both double bond isomers.

† Enol-dichloroacetates will be described in a later publication.

alkyl acetates.[11] The similarity of the carbonyl stretching frequencies in both enol trichloroacetates and alkyl trichloroacetates indicates the greatly diminished overlap between lone pair oxygen electrons and ethylenic π-electrons in the former compounds.

The vinylic protons in the enol trichloroacetates have chemical shifts of lower field values than the corresponding protons in enol acetates (Table 4). On the other hand, the resonance lines of vinylic protons in enol ethers are known to appear at even higher field than those in enol acetates.[12] The shielding in the enol ethers was explained by delocalization of the lone pair electrons of the ether oxygen over the double bond.[12] The mesomeric effect of the carbonyl group in enol acetates diminishes this delocalization, and the inductive effect of the trichloromethyl group in enol trichloroacetates renders it negligible. Also in the dienol trichloroacetate **30** both vinylic protons, at C4 and C6, are deshielded (5·91 and 5·53 ppm) when compared with the respective protons of the $\Delta^{3,5}$-dienol acetate (5·61 and 5·31 ppm[13]).

All the enol trichloroacetates investigated show in their mass spectra molecular ion peaks, and peaks corresponding to fragments derived from loss of trichloroacetic acid from the molecular ion.

Mechanism of formation of the gem *bis-trichloroacetates and enol trichloroacetate*

It was expected by analogy with other addition reactions of the carbonyl group,[14] that the addition of trichloroacetic anhydride to ketones is also a reversible process. In order to establish this point, the carbonyl oxygen of the steroidal ketone **5a** was labelled with ^{18}O and heated for two different reaction period with trichloroacetic anhydride. After one hour of heating the resulting geminal diester **11** contained 88%, and after 2 hr of heating 66% of the labelled oxygen present in the starting ketone **5a** (as determined by mass spectrometry), effectively demonstrating the reversibility of the addition reaction.

The following sequence of decreasing reactivity of the ketones towards trichloroacetic anhydride was observed:† testosterone acetate **28a** > cyclohex-2-enone **25** > 17β-acetoxy-5α-androstan-3-one **5a** > cyclohexanone **3** > cyclobutanone **2** > pentan-3-one **1** > acetophenone **31** > D-camphor 17β-acetoxy-4,4-dimethyl androst-5-en-3-one **21a**.

This sequence generally resembles that observed in other non-catalysed additions to the CO group, e.g. in additions of water and semicarbazide.[14–16]

The main factors which influence the rates of such additions are the entropy and the steric effects in the transition state. Both factors may thus be responsible for the high reactivity of the two α,β-unsaturated ketones **28a** and **25**, in comparison with the saturated ones **5a** and **3**. Since the α,β-unsaturated ketones possess a lesser degree of freedom than the saturated analogs, they lose less entropy in passing from the ground state to the bulky transition state. In addition, the α,β-unsaturated ketones have a smaller number of non-bonded interactions in the transition state than the saturated ketones which also increases the rate of the addition reaction.

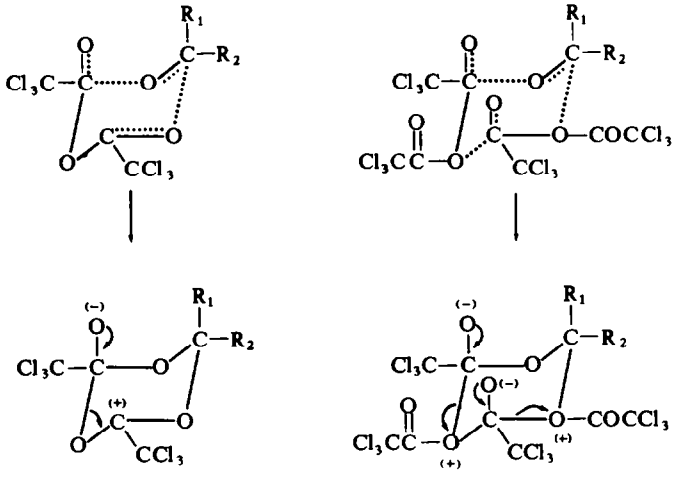
† The reactivities of the ketones **1**, **2**, **3** and **25** were compared using the nmr technique and that of **5a** by a preparative scale experiment. Since **17**, **21a**, **28a** and **31** were converted to secondary products under the reaction conditions used, their reactivities towards $(CCl_3CO)_2O$ were roughly estimated by the rate of formation of these products using nmr technique for all but the second one for which a preparative scale experiment was needed. However, these methods were not suitable for determination of kinetic data.

The entropy may furthermore be responsible for the increased rates of the fused ketone **28a** when compared with the monocyclic ketone, **25**, and the reduced reactivity of the acyclic ketone **1**.

On the other hand, the steric effect contributes to the comparative inertness of camphor **17** and the steroidal dimethyl ketone **21a**. Two further factors which may influence the reaction rates of the cyclic ketones is their tendency to pass from trigonal to a tetrahedral ring carbon, and the basicity of the carbonyl oxygen. The comparatively low basicity of cyclobutanone **2** may thus be the reason for its unexpectedly low rate of addition.

The formation of geminal bis-trichloroacetates from the reaction of ketones with trichloroacetic anhydride might involve a dipolar concerted addition of one molecule trichloroacetic anhydride to the carbonyl function (bimolecular reaction) leading to a 6-centered transition state. This transition state, which may assume chair geometry, subsequently collapses to give the *gem* diester (Chart VI). An alternative mechanism

CHART VI



might involve a concerted addition of two molecules trichloroacetic anhydride to the CO chromophore (termolecular reaction) leading also the a 6-centered transition state. A similar mechanism has previously been suggested for the addition of water to carbonyl groups.[14, 15]

As pointed out above, the *gem* diesters may eliminate trichloroacetic acid in acid catalysed reaction. Since the positive charge developed in the transition state is destabilized by the high electron withdrawing effect of the trichloroacetoxy group a comparatively high energy of activation is required for this elimination of trichloroacetic acid. A decrease in the energy of activation will thus be expected, whenever a participation of electrons, whether π or σ, will tend to stabilize the positive charge in the transition state.

This expectation was realized when the relative rate of the formation of dienol ester **27** was found to be faster than that of the enol esters **14** (Table 2). More striking is the very rapid conversion of the steroidal unsaturated *gem* diester **29** to the dienol ester

30, which occurs readily at room temperature in the presence of traces of trichloroacetic acid. In this case the formation of an extended overlapping π system in the transition state seems to diminish the energy of activation.

The fact, that no formation of *gem* diesters was observed on treatment of the 4,4-dimethyl-androstane derivative **21a** or the D-camphor **17** with trichloroacetic anhydride may be attributed to the rapid decomposition of these *gem* bis-trichloroacetates. Both the release of steric compression and the electronic factors may be responsible for the high reactivity of these *gem* diesters. Thus, participation of the π-electrons at C5–C6 may enhance the rate of the formation of the enol ester **23**, and participation of the σ-electrons at C6–C1 that of the camphene derivative **19a**.

EXPERIMENTAL

All mps were taken in capillaries and are uncorrected. UV spectra were determined on a Cary 14 spectrophotometer and the IR spectra on a Perkin–Elmer Infracord. The NMR spectra were recorded on a Varian A-60 spectrometer, using TMS as internal standard. The mass spectra were measured with an Atlas CH-4-instrument.

Preparation of gem *bis-trichloroacetates* **7**, **8**, **9**, **10**, **11** *and* **12**

General procedure. Molar solns of ketone in acid free trichloroacetic anhydride were heated from 1–7 hr in an oil bath at 90–100°. (The acid free anhydride was prepared from trichloroacetic acid by heating with P_2O_5 and subsequent distillation under reduced press, or by similar purification of commercially available anhydride). The reaction mixtures were cooled and then poured into 5% $NaHCO_3$ aq. The mixtures were stirred until the evolution of CO_2 subsided, extracted with ether, washed with water and dried. The bis-trichloroacetates were isolated either directly by crystallization or distillation under reduced press. In one case (compound **12**) chromatography on silicagel was necessary to obtain pure product.

Similarly, the ketones **1–6** were converted to the bis-trichloroacetates when treated with trichloroacetic anhydride containing ca. 25% of the trichloroacetic acid. The yields were the same as with free anhydride, but the reaction times were longer.

3,3'-*Bis-trichloroacetoxy-pentane* **7**. Pentan-3-one (**1**), 400 mg, was heated for 7 hr with trichloroacetic anhydride. The crude product was distilled under reduced press to give 100 mg (6%) of **7**; b.p. 88–90° (0·001 mm); mass spectrum *m/e* 363, 271, 231, 230, 145, 117, 110, 82, 69, 57, 29.

1,1'-*Bis-trichloroacetoxy-cyclobutane* **8**. Cyclobutanone (**2**), 2·1 g, was heated for 4 hr with trichloroacetic anhydride. Distillation of the crude product under reduced press furnished 1·0 g (9%) of **8**, b.p. 84–86° (0·001 mm); n_D^{23} 1·4882; mass spectrum *m/e* 281, 259, 231, 214, 187, 145, 117, 110, 82, 70, 42.

1,1'-*Bis-trichloroacetoxy-cyclohexane* **9**. Cyclohexanone (**3**), 2·95 g, was heated for 3 hr with 30 ml trichloroacetic anhydride to give 1·5 g (13%) of **9**. It was distilled at 110–112° (0·05 mm); n_D^{23} 1·4975; mass spectrum *m/e* 369, 271, 243, 242, 207, 145, 117, 110, 98, 97, 81.

2,2'-*Bis-trichloroacetoxy-norbornane* **10**. Norbornanone (**4**), 1·1 g, was heated for 4½ hr with 9 ml trichloroacetic anhydride. The material was extracted with ether and chromatographed on silica. Elution with pentane–ether (99:1) gave 1·56 g of **10**; m.p. 96–98° (after crystallization from pentane); UV (EtOH) λ_{max} 230 mμ (sh, ε 370); IR (KBr) 1770, 1250, 1150, 1080 and 965 cm^{-1}; NMR ($CDCl_3$) δ 3·36 (m, 1), 2·48 (m, 1), 2·25 (m, 1), 2·00 (m, 1) and 1·62 ppm (m, 6). (Found: C, 31·53; H, 2·47; Cl, 50·46. Calcd. for $C_{11}H_{10}O_4Cl_6$: C, 31·54; H, 2·41; Cl, 50·78%).

17β-*Acetoxy*-3,3'-*bis-trichloroacetoxy*-5α-androstane **11**. Compound **5a**, 500 mg, was heated for 1 hr with trichloroacetic anhydride. Recrystallization of the crude reaction product from ether–pentane furnished 430 mg (45%) of **11**; m.p. 207–209°; mass spectrum *m/e* 638, 578, 477, 476, 416, 332, 331, 314, 272. (Found: C, 47·72; H, 5·10; Cl, 33·21. Calcd. for $C_{25}H_{32}O_6Cl_6$: C, 46·82; H, 5·03; Cl, 33·18%).

17β-*Acetoxy*-3,3'-*bis-trichloroacetoxy*-5β-androstane **12**. Compound **6a**, 1·0 g, was heated with trichloroacetic anhydride for 1 hr. Chromatography of the crude reaction product on silicagel and elution with ether–pentane (1:9) yielded 135 mg (9%) of **12**, which was recrystallized from ether–pentane; m.p. 172–174°; mass spectrum *m/e* 578, 563, 543, 477, 476, 461, 441, 416, 332, 331, 314. (Found: C, 46·93; H, 5·16; Cl, 33·38. Calcd. for $C_{25}H_{32}O_6Cl_6$: C, 46·82; H, 5·03; Cl, 33·18%).

Preparation of enol-trichloroacetates **13**, **14**, **15** and **16**

General procedure. 10 ml of molar solns of ketone in trichloroacetic anhydride were treated with 0·6–1·0 g *p*-toluenesulphonic acid and heated for 1 hr at 125–135°. The reaction mixtures were cooled to room temp and then poured into 150 ml of 5% $NaHCO_3$ aq. The mixtures were stirred until the evolution of CO_2 subsided, extracted with ether, washed with water, dried and the ether evaporated. The enol trichloroacetates were isolated either directly by crystallization or by distillation under reduced press. In few cases chromatography on silicagel was necessary to obtain pure products.

3-*Trichloroacetoxypent-2-ene* (**13**). Pentan-3-one (**1**), 8·0 g, was treated with *p*-toluenesulphonic acid and trichloroacetic anhydride to give after distillation of the crude reaction product under reduced press 3·28 g (15·5%) enol ester **13**. b.p. 103–105° (22 mm): n_D^{19} 1·464: NMR ($CDCl_3$) δ 5·22 (q, 1, J = 7·5 c/s, C=C<u>H</u>); 2·3 (m, 2, C=C<u>H</u>$_2$), 1·6 (sextet, 3 C=CC<u>H</u>$_3$), 1·09 (t, 3, C=CCH$_2$C<u>H</u>$_3$); mass spectrum *m/e* 230, 117, 69, 68, 57, 29. (Found: C, 36·87; H, 3·87; Cl, 45·40. Calcd. for $C_7H_9O_2Cl_3$: C, 36·31; H, 3·92; Cl, 45·95%).

1-*Trichloroacetoxy-cyclohex-1-ene* (**14**). Cyclohexanone (**3**), 8·0 g, was treated with trichloroacetic anhydride in the presence of *p*-toluenesulphonic acid. Distillation of the crude readtion product yielded 8·05 g (40%) enol ester **14**. b.p. 53–56° (0·11 mm); n_D^{19} 1·496; NMR ($CDCl_3$) δ 5·55 (m, 1, C=C<u>H</u>), 2·15 (m, 4, C=CC<u>H</u>$_2$), 1·7 m, (C=CCH$_2$C<u>H</u>$_2$); mass spectrum *m/e* 242, 117, 97, 80, 79, 69, 55. (Found: C, 40·69; H, 3·78. Calcd. for $C_8H_9O_2Cl_3$: C, 39·45; H, 3·72%).

17β-*Acetoxy-3-trichloroacetoxy-5α-androst-2-ene* (**15a**) *and* 17β-*acetoxy-3-trichloroacetoxy-5α-androst-3-ene* (**15b**). Compound **5a**, 1·0 g, was heated with trichloroacetic anhydride in the presence of *p*-toluenesulphonic acid. Extraction with ether followed by recrystallization from ether–pentane yielded 745 mg (51%) of a mixture, containing 75% **15a** and 25% **15b**, as determined by NMR spectroscopy, m.p. 169–171°; UV max (EtOH) 220 mμ (ε 1200), shoulder: IR (KBr) 1775 cm^{-1} (trichloroacetoxy C=O), 1700 cm^{-1} (C=C), 1230 cm^{-1} and 1150 cm^{-1} (trichloroacetoxy C—O—C); NMR ($CDCl_3$) δ 5·50 (m, 0·75, C=C<u>H</u> at C2 of **15a**), 5·25 (s, 0·25, C=C<u>H</u> at C4 of **15b**), 0·88 (s, 3, C<u>H</u>$_3$ at C10), 0·80 (s, 3, C<u>H</u>$_3$ at C13); mass spectrum *m/e* 476, 416, 331, 314, 262, 202. (Found: C, 57·66; H, 6·44; Cl, 22·31. Calcd. for $C_{23}H_{31}O_4Cl_3$: C, 57·81; H, 6·54; Cl, 22·26%).

17β-*Acetoxy-3-trichloroacetoxy-5β-androst-3-ene* (**16a**) and 17β-*acetoxy-3-trichloroacetoxy-5β-androst-2-ene* (**16b**). Compound **6a**, 3·0 g, was treated with *p*-toluenesulphonic acid and trichloroacetic anhydride. Extraction with ether followed by chromatography on silicagel and elution with ether–pentane (1:9) gave 1·32 g (31%) of a mixture, consisting of 80% **16a** and 20% **16b**, as determined by NMR spectroscopy. The mixture was recrystallized from ether–pentane, m.p. 90–93°; NMR ($CDCl_3$) δ 5·45 (m, 0·2, C=C<u>H</u> at C2 of **16b**), 5·27 (s, 0·8, C=C<u>H</u> at C4 of **16a**), 1·01 (s, 3, C<u>H</u>$_3$ at C10), 0·8 (s, 3, C<u>H</u>$_3$ at C13); mass spectrum *m/e* 476, 416, 331, 314, 262, 202. (Found: C, 57·91; H, 6·68; Cl, 22·23. Calcd. for $C_{23}H_{31}O_4Cl_3$: C, 57·81; H, 6·54; Cl, 22·26%).

Reactions of the bis-trichloroacetates **11** *and* **12**

Hydrolysis of **11**. A soln of **11** (117 mg) in 27 ml EtOH and 3 ml of 10% HCl aq was refluxed for 2 hr. Evaporation of the EtOH, subsequent extraction with ether and recrystallization from ether–pentane gave **5b**, m.p. 180–182°.

Hydrolysis of **12**. A soln of **12**, 150 mg, in 50 ml MeOH and 5 ml of 10% HCl aq was refluxed for 2 hr. The material was isolated from ether and recrystallized from ether to give **6b**, m.p. 139–141°, which was identical with an authentic sample.

Treatment of **12** *with dimethyl formamide.* A soln of *geminal* **12**, 100 mg, in 10 ml dry DMF was heated for 1 hr at 120–130°. The mixture was diluted with ether, washed with water, dried and evaporated. The residue, 78 mg, was chromatographed on silicagel to give **6a** m.p. 145–147° (after recrystallization from ether), which was identical with an authentic sample.

Conversion of **11** *to enol trichloroacetates* **15a** + **15b**. A soln of 250 mg of **11** in 0·75 ml trichloroacetic anhydride was treated with 50 mg *p*-toluenesulphonic acid. This soln was heated for 15 min at 125–135°. Isolation of the product by extraction with ether followed by crystallization from ether–pentane gave 135 mg (72%) of a mixture, m.p. 169–171°, containing 75% **15a** and 25% **15b**.

Conversion of **12** *to enol trichloroacetates* **16a** + **16b**. A soln of 150 mg of **12** in 0·45 ml trichloroacetic anhydride was heated for 15 min at 125–135° in the presence of 45 mg *p*-toluenesulphonic acid. The reaction products were isolated by extraction with ether and chromatography on silicagel. Elution with ether–pentane (5:95) yielded 25 mg (22%) of enoltrichloroacetate, consisting of about 80% **16a** and 20% **16b**, m.p. 90–93°. Further elution with ether–pentane (2:8) gave 28 mg (36%) of **6a**.

Pyrolysis of **11**. Diester **11**, 440 mg, was heated at 185° for 30 min at high vacuum (1·5 mm), and the resulting material chromatographed on silicagel. Elution with ether–pentane (5:95) gave 30 mg (28%) of a crystalline mixture, m.p. 169–171° (after recrystallization from ether–pentane). It consisted of 75% **15a** and of 25% **16b** according to NMR spectrum. Elution with ether–pentane (2:8) furnished 44 mg (52%) of **5a**, m.p. 159–160°, which was identical with an authentic sample.

Reaction of enol trichloroacetates **15** *and* **16**

Hydrolysis of **15a** + **15b**. A soln of **15a** + **15b**, 70 mg, in 30 ml methanol (BDH, special for spectroscopy), was heated for 1 hr under reflux. Evaporation of the solvent under reduced press gave **5a**, as shown by TLC and NMR spectroscopy. It was recrystallized from ether–pentane, m.p. 157–159°.

Hydrolysis of **16a** + **16b**. A soln of **16a** + **16b**, 100 mg, in 50 ml MeOH and 5 ml of 10% HCl aq were heated under reflux for 2 hr. After evaporation of the MeOH under reduced press the aqueous mixture was extracted with ether, washed with water, dried and the ether evaporated. Recrystallization of the residue gave crystalline **6b**, m.p. 139–141°, which was identical with an authentic sample.

Equilibration of **15a** *and* **15b**. A mixture of isomeric enol trichloroacetates, 7·0 g, (containing 75% of **15a** and 25% of **15b**) was treated for 24 hr at 120–130° with 21 ml trichloroacetic anhydride in the presence of 2·1 mg *p*-toluenesulphonic acid. The product was isolated by extraction with ether and chromatography on silicagel. Elution with ether–pentane (1:99) gave 877 mg (13%) of material, m.p. 169–171°, which contained 95% of **15a** and 5% of **15b** as determined by NMR spectroscopy.

Reaction of D-*camphor* **17** *with trichloroacetic anhydride*

A soln of **17**, 1·5 g, in 9 ml trichloroacetic anhydride was heated for 4·5 hr in an oil bath at 110–120°. The product was isolated from ether and chromatographed on silicagel. Elution with pentane gave 610 mg (21%) **19a**, which was further purified by distillation. b.p. 178–179° (40 mm); $[\alpha]_D^{25}$ +16·35° in benzene); IR (neat) 1770 cm^{-1} (ester C=O), 1660 cm^{-1} (C=C), 1250 cm^{-1} and 1070 cm^{-1} (ester C—O—C), 890 cm^{-1} (C=CH); NMR ($CDCl_3$) δ 4·9 (s, 1, C=C<u>H</u>), 4·72 (s, 1, C=C<u>H</u>), 1·13 (s, 6, C(C<u>H</u>$_3$)$_2$); mass spectrum *m/e* 296, 253, 135, 134, 119, 92, 91. (Found: C, 49·22; H, 5·12. Calcd. for $C_{12}H_{15}O_2Cl_3$: C, 48·50; H, 5·08%). Further elution with ether–pentane (5:95) furnished 755 mg (51%) **17**.

Reaction of D-*camphor* **17** *with trichloroacetic anhydride and trichloroacetic acid.*

A soln of 5·0 g of **17** in 24 ml trichloroacetic anhydride and 6 ml trichloroacetic acid was heated for 4·5 hr at 110–120°. The reaction mixture was poured into cold 5% $NaHCO_3$ and extracted with ether. The ether residue was chromatographed on silicagel. Elution with pentane furnished 1·85 g (19%) **19a** which was further purified by distillation (b.p. 178–179°/40 mm): $[\alpha]_D^{25}$ +7·05° (in benzene), identified by comparison with an authentic sample. Elution with pentane–ether (99:1) gave 750 mg (5%) **20a**, which was recrystallized from ether pentane; m.p. 99–102°; $[\alpha]_D^{25}$ +12·3° (in benzene); IR (KBr) 1770 cm^{-1} (ester C=O), 1250 cm^{-1} (ester C—O—C); NMR ($CDCl_3$) δ 4·92 (q, J_{AM} = 8 c/s, J_{AX} = 3 c/s, 1, C2-*endo* proton), 2·95 (q, J_{MA} = 8 c/s, J_{MX} = 13 c/s, 1, C3-*endo* proton), 1·14 (s, 3, C<u>H</u>$_3$ at C1), 0·98 and 1·00 ppm (two s, 3 each, C<u>H</u>$_3$ at C7); mass spectrum *m/e* 458, 423, 297, 296, 255, 135, 134, 117. (Found: C, 36·77; H, 3·26. Calcd. for $C_{14}H_{16}O_4Cl_6$: C. 36·47; H. 3·50%). Elution with pentane–ether (9:1) furnished 2·68 g (54%) **17**.

Hydrolysis of 1-*trichloroacetoxy-amphene* (**19a**). A soln of ester **19**, 180 mg, in 8 ml MeOH and 0·01 ml of 10% NaOH aq was stirred overnight at room temp. The product was isolated from ether and chromatographed on silicagel. Elution with ether–pentane (2:98) gave **19b**, m.p. 69–74°; $[\alpha]_D^{25}$ +22·5° (in benzene); IR (KBr) 3330 cm^{-1} (OH), 1660 cm^{-1} (C=C), 885 cm^{-1} (C=CH); NMR ($CDCl_3$) δ 4·87 (s, 1, C=C<u>H</u>), 4·64 (s, 1, C=C<u>H</u>), 1·08 (s, 6, C(C<u>H</u>$_3$)$_2$); mass spectrum *m/e* 152, 109, 69 (lit[7] m.p. 74°, $[\alpha]_D$ +29·5°).

Hydrolysis of 2β,4-*bis-trichloroacetoxybornane* (**20a**). Diester **20a**, 350 mg, was dissolved in 30 ml MeOH and 1 ml of 10% NaOH aq and stirred overnight at room temp. The soln was then diluted with ether, washed with water, dried and the solvent evaporated under reduced press. Recrystallization of the residue from ether gave analytically pure **20b**; subl. over 215°; $[\alpha]_D^{25}$ +14·05 (in EtOH); IR (KBr) 3330 cm^{-1} (OH); NMR ($CDCl_3$) δ 3·72 (m, 1, C2-*endo*-proton), 1·85 (m, 1, C3-*endo*-proton), 1·00 (s, 3, CH_3 at C1), 0·92 (s, 3, C<u>H</u>$_3$ at C7), 0·80 (s, 3, C<u>H</u>$_3$ at C7); mass spectrum *m/e* 170, 152, 137. Found: C, 70·06; H, 10·31. Calcd. for $C_{10}H_{18}O_2$: C, 70·54; H, 10·66%).

Conversion of **19a** *to* **20a**. Ester **19a**, 500 mg, was heated for 4½ hr at 120° with 1·5 ml trichloroacetic anhydride, which contained about 20% trichloroacetic acid. Extraction with ether and subsequent chromatography yielded 173 mg (35%) **19a** and 108 mg (14%) **20a** m.p. 99–102°.

Reaction of 17β-*acetoxy*-4,4-*dimethylandrost*-5-*en*-3-*one* (**21a**) with trichloroacetic anhydride.

Ketone **21a**, 620 mg, was heated for 24 hr with 2 ml trichloroacetic anhydride at 110–120°. The product was isolated from ether and chromatographed on silicagel. Elution with ether–pentane (5:95) yielded 16 mg (7%) **23**, m.p. 140–142° (recrystallized from ether–pentane); IR KBr) 1770 cm^{-1} (ester C=O), 1715 cm^{-1} (C=C), 1230 cm^{-1} and 1150 cm^{-1} (ester C—O—C); NMR ($CDCl_3$) δ 5·60 (m, 2, C=C<u>H</u> and C<u>H</u>OAc), 1·25 and 1·23 (both s, 3, C<u>H</u>$_3$ at C4), 1·16 (s, 3, C<u>H</u>$_3$ at C10); mass spectrum *m/e* 502, 487, 427, 340, 325, 117. (Found: C, 59·92; H, 6·50; Cl, 20·81. Calcd. for $C_{25}H_{33}O_4Cl_3$: C, 59·59; H, 6·60; Cl, 21·11%). Further elution with ether–pentane (1:9) gave 374 mg (61%) **21a**.

Reaction of **21a** *with trichloroacetic anhydride and trichloroacetic acid*

A soln of 1·0 g of **21a** in 2·4 ml trichloroacetic anhydride and 0·6 ml trichloroacetic acid was heated for 24 hr at 110–120°. The reaction mixture was then poured into cold $NaHCO_3$aq and extracted with ether. Subsequent chromatography of the ether extract on silicagel and elution with ether–pentane (5:95) yielded 43 mg (5%) of oily **24a**; IR ($CHCl_3$) 1735 cm^{-1} (acetoxy C=O), 1250 cm^{-1} (acetoxy C—O—C), 865 cm^{-1} (CH out of plane deformation); NMR ($CDCl_3$) δ 6·8 (s, 1, phenyl <u>H</u>), 2.3 (s, 3, phenyl C<u>H</u>$_3$), 2·23 (s, 3, phenyl C<u>H</u>$_3$) 2·1 (s, 3, phenyl C<u>H</u>$_3$) 2·03 (s, 3, OCOC<u>H</u>$_3$), 0·8 (s, 3, C<u>H</u>$_3$ at C13); UV max (cyclohexane) 270 mμ (ε 378). Further elution with ether–pentane (5:95) furnished 115 mg (8%) **23**, m.p. 140–142°, elution with ether–pentane (1:9) 408 mg (41%) starting material **21a**.

Hydrolysis of **24a**. A soln of **24a**, 40 mg, in 19 ml MeOH and 1 ml of 10% NaOH was heated for 2 hr under reflux. Isolation with ether gave 28 mg **24b**; IR (KBr) 3400 cm^{-1} (OH), 1650–1550 cm^{-1} (weak bands, phenyl), 860 cm^{-1} (CH out of plane deformation); NMR ($CDCl_3$ δ 6·83 (s, 1, phenyl <u>H</u>), 2·3 (s, 3, phenyl C<u>H</u>$_3$), 2·20 (s, 3, phenyl C<u>H</u>$_3$), 2·1 (s, 3, phenyl C<u>H</u>$_3$), 0·80 (s, 3, C<u>H</u>$_3$ at C13); UV max (EtOH) 271 mμ (ε 446); mass spectrum *m/e* 298, 283, 280, 265.

Hydrolysis of **23**. A soln of **23**, 45 mg, in 20 ml MeOH and 5 ml of 10% NaOH was refluxed for 2 hr. Evaporation of the MeOH followed by extraction with ether gave after recrystallization from ether–pentane **21a**, m.p. 192–194°, which was identical with an authentic sample.

Reaction of testosterone **28a** *with trichloroacetic anhydride*

(a) Testosterone acetate (**28a**), 1·0 g, was treated with 0·58 ml trichloroacetic anhydride and heated at 90°. After ca 5 min the ketone had dissolved. The mixture was heated for another 5 min at 90°, where upon the melt solidified. Filtration and crystallization from ether–pentane yielded 720 mg (46·5%) **30**, m.p. 169–173°; IR (KBr) 1775 cm^{-1} (enol ester C=O), 1230 cm^{-1} (enol ester C—O—C), 1090 cm^{-1} (enol ester C—O—C); NMR ($CDCl_3$) δ 5·91 (d, J = 1·5 c/s, 1, C=C<u>H</u> at C4), 5·53 (m, 1, C=C<u>H</u> at C6), 1·03 ppm (s, 3, C<u>H</u>$_3$ at C10); UV max (EtOH) 232 mμ (ε 16,700). (Found: C, 58·05; H, 6·14; Cl, 22·35. Calcd. for $C_{23}H_{29}O_4Cl_3$: C, 58·05; H, 6·14; Cl, 22·46%).

(b) A soln of **28a**, 1·0 g, in 5 ml trichloroacetic anhydride was kept at room temp for 6 hr, then it was evaporated to dryness in high vacuum and the solid recrystallized from ether–pentane to give 800 mg **30**, m.p. 169–173°.

(c) A soln of **28a**, 1·0 g, in 12 ml of trichloroacetic anhydride and 0·3 ml trichloroacetic acid was kept for 3 hr at room temp. The product (0·8 g) isolated from ether had m.p. 169–173° and was identified as **30**.

Hydrolysis of **30**. A soln of 100 mg **30** in 50 ml MeOH and 5 ml 10% NaOH aq was heated for 2 hr under reflux. Evaporation of the MeOH under reduced press followed by extraction of the residue with ether gave **28b**, m.p. 155–156°, identified by comparison with an authentic sample.

Preparation of 17β-*acetoxy*-5α-*androstan*-3(^{18}O)-*one* (**5a**)

A soln of 1·0 g of **5b** in 20 ml absolute benzene was treated with 1·5 ml $H_2{}^{18}O$ (cont. 80% ^{18}O) and 0·02 ml conc H_2SO_4. The mixture was heated under reflux for 3 days, followed by removal of the water by azeotropic distillation and evaporation of the benzene. The residue was acetylated with 5 ml Ac_2O and 5 ml pyridine at room temp overnight. Evaporation to dryness under reduced press (0·005 mm) and recrystallization from ether–pentane yielded labelled ketone **5a**, m.p. 154–156°C; IR (KBr) 1715 cm^{-1} (ketone C=^{16}O), 1680 cm^{-1} (ketone C=^{18}O), mass spectrum *m/e* (rel. intensities of molecular ion peaks), 334 (100), 332 (47). These values correspond to 68% ^{18}O in the ketone.

Preparation of ^{18}O *labelled* 17β-*acetoxy*-3,3′-*bis*-*trichloroacetoxy*-5α-*androstane* (**11**)

(a) Compound **5a**, 100 mg, (containing 68% of ^{18}O) was heated for 1 hr at 90–100° with 0·3 ml trichloroacetic anhydride. The product was isolated from ether and recrystallized from ether–pentane to give 30 mg

of **11**, m.p. 205–207°. Mass spectrum *m/e* (rel. intensity) 578 (23), 580 (77), 582 (100), 584 (73), 586 (27). These values correspond to 60% ^{18}O in the diester.

(b) Compound **5a** (100 mg, (containing 68% of ^{18}O) was heated for 2 hr at 90–100° with 0·3 ml trichloroacetic anhydride. Isolation as described under (a) gave 50 mg **11**, m.p. 205–207°. Mass spectrum *m/e* (rel. intensity) 578 (32), 580 (84), 582 (100), 584 (58), 586 (21). These values correspond to 45% ^{18}O in the diester **11**.

NMR measurements of reactions of ketones with trichloroacetic anhydride

Molar solns of ketones in trichloroacetic anhydride alone and in trichloroacetic anhydride containing 20% trichloroacetic acid were heated at 95–100° in NMR tubes, and the NMR spectra of these reaction mixtures were recorded after various periods.

The yields of the reaction products were determined by integration of the appropriate proton signals of the reactants and the products. Tetramethylsilane was used as external standard.

The following signals were used for the ketones: **1** at 2·40 and 0·98; **2** at 3·00, **3** at 2·30 and 1·80; **17** at 0·83; **25** at 5·91; **28a** at 5·68 and 1·21 and **31** at 2·68 ppm. For the diesters: **7** at 2·45 and 1·03; **8** at 2·95; **9** at 2·48 and 1·70; **19a** at 4·82 and 4·74; **26** at 5·88 and 5·62; **29** at 6·00 and 1·17; **30** at 5·90 and 5·59 and **33** at 5·59 ppm.

The results of the reactivity measurements are summarized in Table 5.

TABLE 5. COMPARISON OF RATES OF REACTIONS OF KETONES WITH TRICHLOROACETIC ANHYDRIDE[a]

Reactant	Product	Reaction temp	Reaction time	Percentage of product	Reaction half time
Pentan-3-one (**1**)	*gem* diester **7**	95–100°	3 hr	35	
			6 hr	45	10 hr
			15 hr	50	
Cyclobutanone (**2**)	*gem* diester **8**	95–100°	3 hr	50	
			6 hr	60	3 hr
			15 hr	70	
Cyclohexanone (**3**)	*gem* diester **9**	95–100°	30 min	25	
			3 hr	70	1½ hr
			15 hr	80	
D-camphor (**17**)	camphene ester **19a**	110–120°	5 hr	12	
			24 hr	17	>24 hr
Cyclohex-2-enone (**25**)	*gem* diester **26**	95–100°	15 min	60	>15 min
			30 min	22	
Testosterone acetate (**28a**)[b]	*gem* diester **29**	25°	15 min	30	
			30 min	58	25 min
			45 min	70	
			60 min	74	
Acetophenone (**31**)	enol ester **33**	95–100°	3 hr	24	
			6 hr	50	6 hr
			15 hr	51	

[a] see footnote ‡ on page 1687 of the text.

[b] In the presence of Et_3N.

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