The Reactions of Diphenylphosphine with α-Substituted Ketones. A New Dehalogenation and Demesylation Procedure[1]

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Diphenylphosphine converts acyclic α-halo ketones and α-mesyloxyketones into the dehalogenated or demesylated ketone, respectively. Reaction with cyclohexanone, α-chlorocyclohexanone, or α-mesyloxycyclohexanone gives the corresponding carbonyl adduct, an α-hydroxydiphenylphosphine, which is isolated as the phosphine oxide. The debromination reaction exhibits a moderate and negative Hammett ρ value. The reaction of diphenylphosphine with α-bromoacetophenone or with 2,4,6-trimethyl-α-bromoacetophenone, a hindered carbonyl case, proceeds at about the same rate. These facts, as well as other data which are given, suggest that the dehalogenation reactions proceed *via* nucleophilic displacement on halogen by phosphorus with transfer of an incipient proton to carbonyl oxygen. Other mechanistic pathways and the scope of the reactions of carbonyl compounds with diphenylphosphine are discussed.

We[3,4] and others[5,6] have shown that α-bromo ketones are debrominated with triphenylphosphine in the presence of hydroxylic solvents such as alcohols, water, or acetic acid. This behavior is in contrast to the reactions of triphenylphosphine with α-chloro ketones[7] or with α-mesyloxy ketones[8] which usually give ketophosphonium salts in either nonhydroxylic or hydroxylic solvents. Several α-chloro ketones give enol phosphonium salts with triphenylphosphine in aprotic solvents.[8] These systems yield the dehalogenated ketone if the reaction is performed in the presence of an alcohol since enol phosphonium salts are readily solvolyzed by alcohols or water.[8,9]

We have sought organophosphorus reagents which would generally cause the removal of groups adjacent to a carbonyl. Such reagents might prove to be useful in organic synthesis and they should aid us in our continuing study of the modes and sites of reaction of nucleophiles with α-halo ketones and with other activated carbonyl compounds.

We now report our results on the reactions of diphenylphosphine with α-halo ketones, α-mesyloxy ketones, and other carbonyl species.

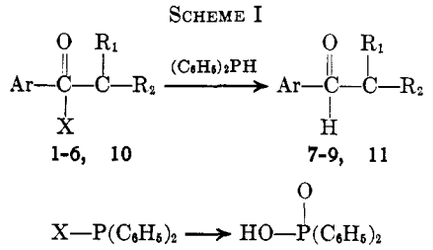
Results and Discussion

The Reactions of Diphenylphosphine with α-Halo Ketones.—Diphenylphosphine (DPP) reacts with a number of acyclic α-chloro or α-bromo ketones to give the dehalogenated ketone and halodiphenylphosphine, in good yield (Table I, Scheme I). In most of the reactions, the halodiphenylphosphine was allowed to hydrolyze and oxidize to diphenylphosphinic acid by exposure to the atmosphere.[10]

In contrast to the dehalogenation of acyclic ketones, DPP adds to the carbonyl group of 2-chlorocyclohexanone (**12**) to give 1-hydroxy-1-diphenylphosphinoxy-2-chlorocyclohexane (**15**) (Scheme II). A mixture of *cis* and *trans* isomers for **15** is indicated by the presence of two hydroxyl peaks (30:70) in the nmr spectrum. The stereochemistry of the isomers has not been determined. A similar adduct, **17**, is obtained with cyclohexanone (**14**). Primary and secondary phosphines have been previously shown to react with a variety of carbonyl compounds to give carbonyl adducts.[11a] It is not surprising that addition to cyclohexanone carbonyl, a most reactive carbonyl in addition reactions,[12] occurs more rapidly than do other processes such as dehalogenation.

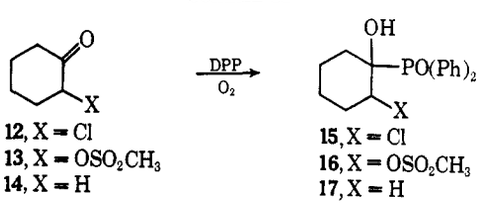
The reactions of 2-bromocyclohexanone and 2-chlorocyclopentanone with DPP give ill-defined products involving little if any dehalogenation. The debromination of diethyl bromomalonate with DPP, as with bromoacetophenone (**1**), proceeds rapidly at room temperature. Benzyl bromide reacts with DPP to give an unidentified product but no toluene. Competition experiments show that the bromoacetophenone 1/bro-

SCHEME I



Halo ketone	X = Br	X = Cl	Ketone
Ar = C_6H_5, $R_1 = R_2 = H$	1	4	7
Ar = C_6H_5, $R_1 = CH_3$, $R_2 = H$	2	5	8
Ar = C_6H_5, $R_1 = R_2 = CH_3$	3	6	9
Ar = 2,4,6-tri-$CH_3C_6H_2$, $R_1 = R_2 = H$	10		11

SCHEME II



12, X = Cl
13, X = OSO_2CH_3
14, X = H

15, X = Cl
16, X = OSO_2CH_3
17, X = H

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(3) (a) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, 471 (1962); (b) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963).

(4) I. J. Borowitz, K. C. Kirby, Jr., and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(5) H. Hoffman and H. J. Diehr, *Tetrahedron Lett.*, 583 (1962).

(6) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

(7) K. C. Kirby, Jr., unpublished results. See also ref 4.

(8) P. Rusek, Ph.D. Thesis, Yeshiva University, New York, N. Y., 1968.

(9) R. D. Partos and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 5068 (1965).

(10) "Methoden Der Organischen Chemie," Houben-Weyl, K. Sasse, Ed., G. Thieme Verlag, Stuttgart, 1963, Vol. 12/1, p 69.

(11) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965: (a) p 201; (b) p 33.

(12) H. C. Brown and K. Ichikawa, *Tetrahedron Lett.*, No. 1, 221 (1957).

TABLE I

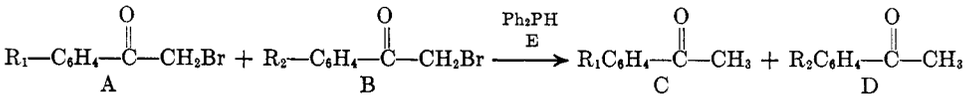
THE REACTIONS OF DIPHENYLPHOSPHINE WITH α-HALOCARBONYL COMPOUNDS

α-Halocarbonyl compound	Reaction conditions	Time	Product	Yield, %
α-Bromoacetophenone[a]	C_6H_6, reflux	2 hr	Acetophenone	100[b]
α-Bromoacetophenone[a]	CCl_4[d]	10 min	Acetophenone	100[c]
α-Bromopropiophenone	CCl_4[d]	10 min	Propiophenone	100[c]
α-Chloropropiophenone	C_6H_6, reflux	7 days	Propiophenone	62[e]
α-Bromoisobutyrophenone	CCl_4[d]	16 hr	Isobutyrophenone	100[c]
α-Chloroisobutyrophenone	neat, 95–100°	6 days	Isobutyrophenone	72[c]
Diethyl bromomalonate	CCl_4[d]	20 min	Diethyl malonate	100[c]
p-Methoxy-α-bromoacetophenone	CCl_4[d]	20 min	*p*-Methoxyacetophenone	100[c]
p-Bromo-α-bromoacetophenone	CCl_4[d]	20 min	*p*-Bromoacetophenone	100[c]
2,4,6-Trimethyl-α-bromoacetophenone	CCl_4[d]	20 min	2,4,6-Trimethylacetophenone	100[c]

[a] Similar result in CCl_4 with collidine (0.2 equiv) present. [b] Isolated yield, by vpc analysis. [c] Not isolated from reaction in nmr tube. [d] At room temperature. [e] Isolated yield.

TABLE II

COMPETITION DEBROMINATIONS OF α-BROMO KETONES WITH DIPHENYLPHOSPHINE



Initial moles A = B = E	R_1	R_2	Final nmr area Ratio	Final nmr area B/A	Final nmr area Ratio	Final nmr area C/D	Average ratio	$\frac{k_2A}{k_2(B)}$
0.0054	*p*-CH_3O	*p*-Br	2.23[a]	2.11[b]	2.21[a]	2.35[b]	2.22	3.14
0.0072	*p*-CH_3O	H	...		1.59[a]	1.57[b]	1.50	1.79
0.0122	*p*-CH_3O	H	1.12[a,c]		1.35[a]	1.49[b]	1.50	1.79
0.0102	H	*p*-Br	...		1.14[a]		1.20	0.69
0.0150	H	*p*-Br	...		1.26[a]		1.20	0.69

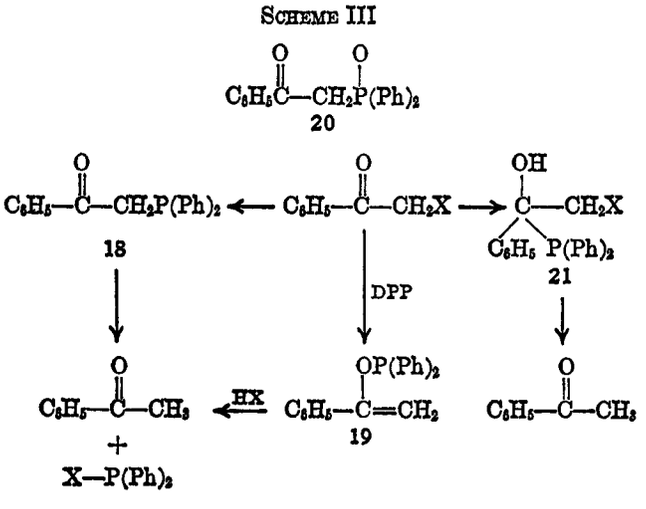
[a] Area calculated by triangulation of nmr peaks. [b] Area calculated by planimeter measurement of nmr peaks. [c] Value not used in relative rate calculation. Calculated ρ from three-point graph (CH_3O/H, H, H/Br) = −0.74. Calculated ρ from above ratios = −0.76.

mopropiophenone **2** reaction rate ratio with DPP is *ca.* 15 while the bromopropiophenone **2**/bromoisobutyrophenone **3** rate ratio is *ca.* 7.0. The α-bromoacetophenone **1**/trimethyl-α-bromo-acetophenone **10** reaction ratio is 5.3. The bromoacetophenone/chloroacetophenone rate ratio is greater than 162:1. This is based on the observed ratio of **1**/**4** of 162 with triphenylphosphine,[13] and the fact that triphenylphosphine reacts more rapidly than does DPP with **1** while DPP is faster than triphenylphosphine in reaction with **4** (see Experimental Section).

Comparison of the relative reactivities of **1** with its *p*-methoxy and *p*-bromo derivatives, by competition experiments, indicates that the debromination of bromoacetophenones with DPP (Table II) exhibits a moderate and negative Hammett ρ value (*ca.* −0.74). The debromination of **1** with DPP is not affected by the initial presence of collidine, *i.e.*, the dehalogenation is presumably not acid catalyzed. This result is in contrast to the debromination of **1** or **2** with triphenylphosphine and ethanol. Our kinetic studies show that these dehalogenation reactions are acid catalyzed. They are furthermore greatly inhibited by the initial presence of triethylamine which removes free acid.[14]

There are several pathways, *a priori*, for the DPP dehalogenation reactions. Thus one might have postulated initial reaction of an α-halo ketone with DPP to give the corresponding ketophosphine, such as **18**, or the enol phosphine, such as **19**, *via* one of several pathways (Scheme III).

SCHEME III



The dephosphorylation of **18** or **19** would then have to be postulated to occur, perhaps with the aid of hydrogen halide. The dehalogenations occur in the absence of acid (note no effect by collidine). Furthermore, **18** is a known species which is stable to methanesulfonic acid[8] and is stable enough in neutral pH solution to be air oxidized to **20**.[15] This data and the observed similar reaction rates of **1** and **10**, which has a hindered

(13) I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967).

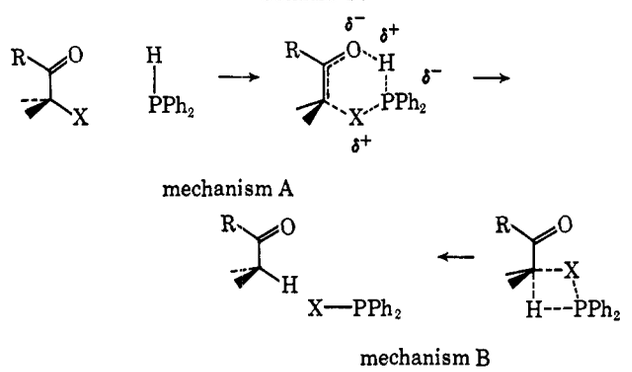
(14) The effect of triethylamine in curbing the debromination of α-bromoacetophenones by triphenylphosphine–alcohol, and thereby allowing ketophosphonium salt formation to occur, has been noted by K. Fukui, R. Sudo, M. Masaki, and M. Ohta, *ibid.*, **33**, 3504 (1968). These authors have ascribed their observations to a catalysis of ketophosphonium salt formation by the amine. We have shown kinetically that there is no such catalysis and we believe that the true function of the triethylamine is to prevent the acid-catalyzed debromination reaction.

(15) G. Burchman Borowitz and M. Saunders, *Tetrahedron Lett.*, 8 (1959).

carbonyl, eliminate rate-determining SN2 processes from consideration.[16] The intermediacy of hydroxyphosphines, such as **21**, can also be dismissed on the basis of the similar reactivities of **1** and **10** and the fact that no reasonable pathway exists for the further conversion of species such as **21** into the dehalogenated ketone. Finally, the observed negative ρ value is not explained by any of these pathways.

We believe that our data is best explained by mechanism A (Scheme IV), a six-centered transition state featuring attack on "soft" halogen by "soft" phosphorus and a transfer of an incipient "hard" proton to "hard" oxygen.[17]

SCHEME IV



This pathway accounts for the negative ρ value since there is a stabilization of positive charge on oxygen in the postulated transition state, and it accounts for the relatively small rate ratios for the primary, secondary, and tertiary α-bromo ketones, **1:2:3**. These ratios are quite smaller than those found in normal solvolysis at carbon.[18] Nucleophilic displacement at carbon, a "hard" center, should be more subject to steric factors than displacement at bromine, a polarizable or "soft" center. The great reactivity of an α-bromo ketone when compared with an α-chloro ketone (more stabilization for displacement of "positive" bromine than chlorine) and the relatively high reactivity of **10** (the hindered carbonyl is not involved in halogen attack) are also well explained by mechanism A.

A four-centered pathway (mechanism B) does not explain the apparent need for a carbonyl in the dehalogenation reactions. It is also anticipated that steric requirements for this pathway would be greater than for mechanism A. Therefore mechanism B is considered to be a less likely possibility.

The Reaction of Diphenylphosphine with α-Mesyloxy Ketones.—We have synthesized a number of α-mesyloxy ketones by the reaction of α-bromo ketones with silver mesylate (Table III). We have also converted several α-hydroxy ketones, such as 2-hydroxycyclohexanone or benzoin, into the mesyloxy ketone with methanesulfonyl chloride and triethylamine. Mesylate formation under these conditions has been shown to involve the intermediacy of sulfene.[19] It has been more satisfactory than the formation of the corresponding α-tosyloxy ketone,[20] in our hands.

As indicated in Table IV, several acyclic α-mesyloxy ketones are demesylated by DPP. These reactions proceed more slowly than do the corresponding dehalogenation reactions. Ostensibly we might convert α-hydroxy ketones (acyloins) into the parent ketone *via* the intermediacy of mesyloxy ketones. 2-Mesyloxycyclohexanone (**13**) (Scheme II), however, gives the carbonyl adduct **16** and no cyclohexanone. In contrast to the infrared spectra of **15** and **17**, which show free and bonded OH absorption, the spectrum of **16** reveals only hydrogen-bonded OH absorption. This may be due to interaction of the hydroxyl group with the adjacent mesyloxy group, and it suggests a predominance of that isomer of **16** wherein the groups are *cis* oriented. Unfortunately, the limited solubility of **16** and its apparent decomposition in solution precluded nmr studies. 2-Mesyloxycyclodecanone gives no reaction with DPP while 2-mesyloxycyclododecanone is converted into cyclododecanone in 12% yield. Attempts to make these alicyclic demesylations more synthetically feasible are in progress.

In contrast to the above results, α-hydroxyacetophenone, benzoin, α-acetoxydeoxybenzoin, and α-phenylphenacyltriphenylphosphonium mesylate[8] do not react with DPP. Neither carbonyl addition nor removal of the group adjacent to the carbonyl is observed. Interestingly, a mesyloxy group adjacent to a ketone can be removed but not a similarly situated acetoxy group. The paucity of our data on the demesylations makes speculation as to the mechanistic pathway involved rather risky. A pathway similar to mechanism A above, involving attack by DPP at alkyl oxygen, may be involved.[21]

In summary, diphenylphosphine shows promise as a reagent for the selective removal of certain groups adjacent to a carbonyl. Addition to carbonyl is observed as an alternative process only in cyclohexyl cases.[22]

Experimental Section[23]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions were usually conducted under an atmosphere of nitrogen to prevent air oxidation of DPP. Organic solutions were dried over magnesium sulfate.

α-Bromoacetophenone and α-chloroacetophenone (J. T. Baker) were recrystallized from absolute diethyl ether to mp 49–50° and 53–54°, respectively. Cyclohexanone (J. T. Baker) was distilled prior to use, bp 154–156°. α-Bromopropiophenone, α-bromoisobutyrophenone, diethyl α-bromomalonate, and benzyl bromide (Aldrich) were used without further purification. α-Chlorocyclohexanone and α-chlorocyclopentanone (Aldrich) were redistilled before use. *p*-Nitro-α-bromoacetophenone, *p*-methoxy-α-bromoacetophenone, *p*-bromo-α-bromoacetophenone, and

(16) The 2,4,6-trimethyl-α-bromoacetophenone system reacts quite slowly in SN2 displacements. See R. G. Pearson, S. H. Langer, F. W. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, **74**, 5130 (1952).

(17) (a) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967); (b) B. Saville, *Angew. Chem. Intern. Ed. Engl.*, **6**, 928 (1967).

(18) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, Inc., New York, N. Y., 1962, pp 11–20.

(19) (a) J. F. King and A. Durst, *J. Amer. Chem. Soc.*, **86**, 287 (1964); (b) W. E. Truce, R. W. Campbell, and J. R. Norell, *ibid.*, **86**, 288 (1964).

(20) P. S. Wharton, S. Dunny, and L. Soto Krebs, *J. Org. Chem.*, **29**, 958 (1964).

(21) Diphenylphosphinic acid is also isolated in these reactions, perhaps *via* the intermediacy of mesyloxydiphenylphosphine. Further research on these reactions is in progress.

(22) Our carbonyl adducts are clearly not phosphinites; *i.e.*, we do not obtain addition of diphenylphosphine to carbonyl oxygen. The latter pathway has been found in the reactions of diphenyl- or dicyclohexylphosphine with hexafluoroacetone: R. F. Stockel, *Chem. Commun.*, 1594 (1968).

(23) The instrumental and other techniques used have been recorded previously.[4]

TABLE III

THE SYNTHESIS AND PROPERTIES OF α-MESYLOXY KETONES

Mesyloxy ketone, method	Registry no.	Starting compound, time	Yield, %	Properties of mesyloxy ketones: Mp, °C	Ir (CH_2Cl_2), μ	Nmr ($CDCl_3$), τ
α-Mesyloxyacetophenone[a]	20187-61-5	α-Bromoacetophenone, 24 hr	88	78.0–79.5	5.91 (C=O), 7.41, 8.50 (OSO_2CH_3)	6.78 (s, 3, OSO_2CH_3), 4.50 (s, 2, CH_2C=O), 2.00–2.80 (m, 5, phenyl H)
α-Mesyloxyacetophenone[b]		α-Hydroxyacetophenone	65	77–78		
α-Mesyloxypropiophenone[a]	20187-62-6	α-Bromopropiophenone, 30 days	77	67.0–68.0	5.90, 7.41, 8.50	8.40 (d, 3, C—CH_3), 6.90 (s, 3, OSO_2CH_3), 3.95 (quart, 1, CH), 1.9–2.6 (m, 5, phenyl H)
α-Mesyloxyisobutyrophenone[a]	17231-17-3	α-Bromoisobutyrophenone, 30 days	68	90.0–91.0	5.92, 7.5, 8.5	8.13 (s, 6, C—CH_3), 7.17 (s, 3, OSO_2 CH_3), 2.0–2.6 (m, 5, phenyl H)
α-Mesyloxycyclohexanone[a]	20187-64-8	α-Bromocyclohexanone, 7 days	88	60–61.5	5.78 (C=O), 7.40, 8.40	7.3–8.6 (m, 8, alicyclic H), 6.83 (s, 3, OSO_2CH_3), 4.80 (m, l, methine H)
α-Mesyloxycyclohexanone[b]		Adipoin	91	60–61.0	Similar	
α-Mesyloxycyclododecanone[a]	3667-85-4	α-Bromocyclododecanone, 4 months	59	109–111	5.80 (C=O), 7.45, 8.50	7.15–9.1 (m, 18, alicyclic H), 7.4 (t, 2, CH_2C=O), 6.85 (s, 3, OSO_2CH_3), 4.90 (t, l, methine H)
2,4,6-Trimethyl-α-mesyloxyacetophenone[a]	20187-66-0	2,4,6-Trimethyl-α-bromoacetophenone, 30 days	51	99–101	5.80 (C=O), 7.39, 8.40	7.8 (s, 6, *o*-CH_3), 7.75 (s, 3, *p*-CH_3), 6.81 (s, 3, OSO_2CH_3), 4.95 (s, 2, CH_2C=O), 3.1 (s, 2, *m*-phenyl H)
α-Mesyloxydesoxybenzoin[b]	19255-01-7	Benzoin	69	120–121	5.89 (C=O), 7.40, 8.50	6.95 (s, 3, OSO_2CH_3), 3.15 (s, 1, methine H), 2.0–2.9 (m, 10, phenyl H)
α-Mesyloxycyclodecanone[b]	20187-68-2	α-Hydroxycyclodecanone	*ca.* 82 (crude)[c]	Oil		6.90 (s, OSO_2CH_3), 7.5–8.6 (m, alicyclic H)[d]

[a] From the reaction with silver mesylate in acetonitrile. [b] From the reaction with methanesulfonyl chloride and triethylamine. [c] Crude compounds shows presence of small amount of starting material as well as product (tlc, nmr). [d] Integrated areas only approximately correct.

TABLE IV

THE REACTIONS OF DIPHENYLPHOSPHINE WITH α-MESYLOXY KETONES AND WITH OTHER KETONES

Ketone	Reactions conditions	Time, days	Products	Yield, %
α-Mesyloxyacetophenone	C_6H_6, reflux	4	Acetophenone	43
			Diphenylphosphinic Acid	100
α-Mesyloxyisobutyrophenone	C_6H_6, reflux	14	Isobutyrophenone	51
α-Mesyloxybenzylphenyl ketone	C_6H_6, reflux	6	Deoxybenzoin	70
α-Mesyloxycyclodecanone	Glyme, reflux	30	No reaction	
α-Mesyloxycyclododecanone	C_6H_6, reflux	35	Cyclododecanone	12
α-Hydroxyacetophenone	C_6H_6, reflux	4	No reaction	(recovery 100%)
Benzoin	C_6H_6, reflux	4	No reaction	(recovery 100%)
α-Acetoxybenzylphenyl ketone	C_6H_6, reflux	5	No reaction	(recovery 86%)
α-Phenylphenacyl triphenylphosphonium mesylate	C_6H_6, reflux	10	No reaction	(recovery 83%)

α-bromocyclohexanone were prepared as previously reported[13] or purchased commercially. 2,4,6-Trimethyl-α-bromoacetophenone was prepared by the bromination of 2,4,6-trimethylacetophenone in 51% yield, mp 53–54.5° (lit.[16] mp 54°).

α,α-Dibromoacetophenone was synthesized by the bromination of acetophenone in 80% yield, mp 33–35° (lit.[24] mp 35–36°). α-Bromocyclododecanone was prepared by the chromic acid oxidation of *trans*-2-bromo-1-hydroxycyclododecane, itself synthesized by the addition of hydrogen bromide to epoxycyclododecane (Aldrich) in 52% yield.[25]

α-Chloropropiophenone and α-chloroisobutyrophenone were prepared as previously described.[26] Diphenylphosphine was synthesized from the reduction of chlorodiphenylphosphine with lithium aluminum hydride[27] in 72% yield, bp 112–115° (0.5 mm). It was stored at 0–5°.

α-Mesyloxyacetophenone.—The following procedure is a general one for the conversion of α-bromo ketones to α-mesyloxy ketones. A mixture of α-bromoacetophenone (10.0 g, 0.0502 mol) and silver mesylate (10.0 g, 0.0502 mol) in acetonitrile (250 ml) was stirred for 24 hr in a 500 ml flask covered with aluminum foil. The solvent was then removed *in vacuo* and the resultant solid was slurried in hot benzene (250 ml). Filtration of silver bromide, evaporation of the solvent *in vacuo*, and recrystallization of the resultant solid from CCl_4 gave α-mesyloxyacetophenone (9.16 g, 0.045 mol, 88%). Spectral data for this compound as well as for other mesyloxy ketones is given in Table III. Analytical data for the α-mesyloxy ketones follows.

(24) F. Krohnke, *Chem. Ber.*, **83**, 53 (1950).

(25) L. I. Zakharkin and V. V. Kornevsi, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1817 (1962); *Chem. Abstr.*, **58**, 7841d (1963).

(26) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(27) W. Kuchen and H. Buchwald, *Angew. Chem.*, **68**, 791 (1956).

Anal. Calcd for $C_9H_{10}O_4S$ (α-mesyloxyacetophenone): C, 50.46; H, 4.70; S, 14.96. Found: C, 50.20; H, 4.68; S, 14.96.

α-Mesyloxypropiophenone was recrystallized from cyclohexane.

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.61; H, 5.29; S, 14.05. Found: C, 52.70; H, 5.35; S, 14.29.

α-Mesyloxyisobutyrophenone was recrystallized from cyclohexane.

Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; S, 13.23. Found: C, 54.70; H, 5.80; S, 13.16.

α-Mesyloxydeoxybenzoin was recrystallized from ethyl acetate and cyclohexane.

Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.06; H, 4.85; S, 11.04. Found: C, 62.18; H, 5.00; S, 10.91.

α-Mesyloxycyclohexanone was recrystallized from cyclohexane.

Anal. Calcd for $C_7H_{12}O_4S$: C, 43.74; H, 6.29; S, 16.68. Found: C, 43.92; H, 6.21; S, 16.73.

α-Mesyloxycyclododecanone was recrystallized from methanol.

Anal. Calcd for $C_{13}H_{24}O_4S$: C, 56.49; H, 8.75; S, 11.60. Found: C, 56.57; H, 8.59; S, 11.57.

The following α-bromo ketones failed to be converted into α-mesyloxy ketones upon treatment with silver mesylate in acetonitrile (after the indicated time length): α-bromocamphor (16 weeks) and 2-bromodimedone (after 11 weeks).

The Conversion of α-Hydroxy Ketones into α-Mesyloxy Ketones.—The following procedure for the synthesis of α-mesyloxybenzylphenyl ketone was used for the conversion of α-hydroxy ketones into the corresponding mesyloxy ketones. Methanesulfonyl chloride (2.15 g, 0.0189 mol) in dry benzene (40 ml) was added dropwise with stirring over a 1-hr period to a mixture of benzoin (4.0 g, 0.0189 mol) and triethylamine (3.82 g, 0.0478 mol) in benzene (20 ml). After the mixture was stirred for an additional hour, triethylamine hydrochloride was filtered off, and the organic layer was washed with water, dried, evaporated *in vacuo*, and recrystallized from EtOAc–cyclohexane to give α-mesyloxybenzylphenyl ketone (3.80 g, 0.0131 mol, 69%). Other data for this compound and related syntheses are given in Table III.

The Reactions of α-Halo Ketones with Diphenylphosphine.—The following is a general procedure. To diphenylphosphine (0.450 g, 0.00242 mol) in a 5-mm nmr tube was added α-bromoacetophenone (0.481 g, 0.00242 mol) in CCl_4 (1 ml), causing an exothermic reaction. After 10 min, reaction was complete; nmr τ 7.70 (s, 3, $CH_3C{=}O$) and 2.0–3.0 (m, 5, phenyl H) indicated quantitative conversion into acetophenone, no absorption at 5.8 (s, 2, CH_2Br) indicated the absence of α-bromoacetophenone. In a similar experiment, ^{31}P nmr indicated only a sharp singlet at −72 ppm (relative to H_3PO_4) for bromodiphenylphosphine.[28]

Other examples are given in Table I. The reaction of *p*-nitro-α-bromoacetophenone with DPP was very exothermic and was accompanied by the formation of a deep red color and a reddish brown solid which was not readily characterized. A similar reaction occurred between DPP and *p*-nitroacetophenone.

The reaction of DPP with α-bromocyclohexanone was done in benzene, diethyl ether, ethyl acetate, glyme, and methanol at room temperature and at reflux. Oils were generally obtained which could be separated into diphenylphosphinic acid (identified by ir, tlc) and viscous hydrocarbons (alicyclic H by nmr). When the reaction was followed by ir (CH_2Cl_2), the 5.85-μ peak of α-bromocyclohexanone disappeared within several min at room temperature. The reaction of DPP with α-chlorocyclopentanone occurred rapidly to give unknown products and no cyclopentanone. The reaction of DPP (1 equiv) with α,α-dibromoacetophenone led to a mixture of acetophenone, α-bromoacetophenone, and α,α-dibromoacetophenone. A preferential removal of one bromine was not observed.

The Reaction of Benzyl Bromide with Diphenylphosphine.—Benzyl bromide (0.316 g, 0.00186 mol) in CCl_4 (1 ml) was added to DPP (0.323 g, 0.00173 mol) in an nmr tube. Little or no immediate reaction occurred. After 15 hr a white solid was present and the nmr spectrum had absorption at τ 2.4–3.0 (aromatic H) but no methyl group absorption; *i.e.*, toluene was absent. The solid was not characterized.

(28) (a) Kindly performed by Dr. Dorothy Denney, Rutgers University, on a Varian HA-100 nmr spectrometer at 40 MHz; (b) L. Maier, *Helv. Chim. Acta*, **46**, 2026 (1963).

1-Hydroxy-1-diphenylphosphinoxy-2-chlorocyclohexane.—A mixture of DPP (2.21 g, 0.0119 mol) and α-chlorocyclohexanone (1.565 g, 0.0117 mol) in benzene (30 ml) was heated at reflux for 12 hr. White solid was formed. Upon exposure to the air more slowly precipitated to give 1-hydroxy-1-diphenylphosphinoxy-2-chlorohexane (**15**, 2.756 g, 0.00825 mol, 71%): mp 158–160° (recrystallization from toluene); ir ($CHCl_3$) 2.78, 3.0, 3.4, 6.95, 8.3, 8.55, 8.75, 8.95 μ; ir (KBr) 3.18 μ (H-bonded OH); mass spectrum (70 eV)[29] *m/e* (rel intensity, assignment) 334 (w, $M\cdot^+$), 316 (w, $M\cdot^+ - H_2O$), 298 (w, $M\cdot^+ - H^{35}Cl$), 201 (vs, $Ph_2PO\cdot^+$), 202 (s, $Ph_2POH\cdot^+$), 132 (s, $C_6H_9OCl\cdot^+$), 124 (s, $PhPO\cdot^+$), 97 (s, $C_6H_9O\cdot^+$), 88 (s, $C_4H_5Cl\cdot^+$), as well as the corresponding peaks for ^{37}Cl isomers for Cl-containing fragments; nmr ($CDCl_3$),[30] τ 2.50 (m, 10, aryl H), 5.70 [m, 1, C(Cl)H], 5.95 (s, 0.3, OH), 6.90 (s, 0.7, OH), 8.20 (m, 8, alicyclic H); OH peaks were exchanged with D_2O.

Anal. Calcd for $C_{18}H_{20}O_2ClP$: C, 64.57; H, 6.02; Cl, 10.58; P, 9.26. Found: C, 64.43; H, 6.14; Cl, 10.78; P, 8.99.

Attempts to dehydrate **15** with *p*-toluenesulfonic acid in benzene at reflux with azeotropic removal of water gave only starting material.

1-Hydroxy-1-diphenylphosphinoxycyclohexane.—Similar reaction of DPP with cyclohexanone (0.0165 mol each) in benzene at reflux for 20 hr gave 1-hydroxy-1-diphenylphosphinoxycyclohexane (2.97 g, 0.0099 mol, 60%): mp 159–161° (recrystallized from toluene); ir ($CHCl_3$), 2.78, 3.0 (broad), 3.40 (s), 6.95 (ms), 8.51 (s), 8.71 (s), 9.96 (s), 10.35 (m), μ; ir (KBr) 3.15 μ (H-bonded OH); nmr ($CDCl_3$)[30] τ 1.98 (m, 4, *o*-aryl H), 2.45 (m, 6, *m,p*-aryl H), 6.72 (s, 1, OH), 8.28 (m, 10, alicyclic H).

Anal. Calcd for $C_{18}H_{21}O_2P$: C, 72.06; H, 7.00; P, 10.35. Found: C, 72.08; H, 7.04; P, 10.07.

Relative Rates of Debromination of α-Bromo Ketones by Competition Experiments.—DPP was weighed into a 5-mm nmr tube. One equivalent of each of two α-bromo ketones was combined, dissolved in CCl_4, and added to the nmr tube. Reactions involving bromoacetophenones or bromopropiophenone were essentially instantaneous. Nmr spectra of the methylene groups of the unreacted bromoacetophenones and the methyl groups of the dehalogenated acetophenones were cleanly separated at a 50-Hz sweep width. The relative areas of the starting bromo ketones and of the product ketones were thus obtained (Table II), the average ratios were taken, and these were used to calculate relative reaction rates by use of the following equation.[31] Second-order rate relationships were assumed for the debromination reactions. For other competition reactions, the relative areas used were obtained as follows.

$$\frac{k_2\,(\mathrm{B})}{k_2\,(\mathrm{A})} = \frac{\log\,[\mathrm{B}]_f/[\mathrm{B}]_i}{\log\,[\mathrm{A}]_f/[\mathrm{A}]_i}$$

Competition Reaction between α-Bromoacetophenone and α-Bromopropiophenone with DPP.—A mixture of **1** and **2** (0.00197 mol each) in CCl_4 was added to DPP (0.00197 mol) to give complete reaction of DPP after several minutes: nmr integrated area ratio of propiophenone to α-bromopropiophenone was 1:6.7; *i.e.*, 0.00025 mol of **1** and 0.00172 mol of **2** was left. The relative rate ratio for **1**:**2** is 15.4.

Other Competition Experiments.—The competition reaction of α-bromopropiophenone (**2**) and α-bromoisobutyrophenone (**3**) with DPP (0.00197 mol each) gave an area ratio (nmr) of isobutyrophenone to **3** of 1:3.8 upon completion. The relative rate ratio for **2**/**3** is 6.8. A similar competition reaction between **1** and 2,4,6-trimethyl-α-bromoacetophenone (**10**) for DPP (0.000555 mol each) gave an area ratio (nmr) of **1**/**10** of 1:3.22 upon completion. The relative rate ratio for **1**/**10** is 5.3. The competition of **1** with α-chloroacetophenone (**4**) for DPP resulted in complete reaction of **1** and no reaction of **4**; *i.e.*, the relative rate ratio for **1**/**4** is large (see Discussion). Previously, less accurate competition experiments had shown that (a) DPP reacts more rapidly than does triphenylphosphine with **1** since at least 80% of the triphenylphosphine is left, none of the DPP is left, and no phenacyltriphenylphosphonium bromide is formed; (b) triphenylphosphine reacts more rapidly than does DPP with **4**

(29) Done at Mellon Institute on a MS-9 mass spectrometer.

(30) The nmr spectrum was obtained with the aid of the Varian C-1024 time averaging computer.

(31) G. Russell in "Technique of Organic Chemistry," Vol. VIII, part I, 2nd ed, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961.

since 64% phenacyltriphenylphosphonium chloride is formed and no triphenylphosphine is left, but diphenylphosphine is left.

Attempts to Derivatize Bromo- or Chlorodiphenylphosphine from Dehalogenation Reactions.—Reaction of two equivalents of DPP with one equivalent of 1 led to acetophenone and diphenylphosphinic acid but no tetraphenyldiphosphine or the corresponding dioxide.[11b] In other experiments involving either bromodiphenylphosphine (from 1) or chlorodiphenylphosphine (from 4), addition of aniline or *t*-butylamine led to mixtures possibly containing anilino- or *t*-butylaminodiphenylphosphine. The products could not be purified to analytical purity and these experiments were abandoned.

The Reactions of α-Mesyloxy Ketones and Other Ketones with Diphenylphosphine.—The following serves as a general procedure with minor variations and other data given in Table IV. A mixture of α-mesyloxyacetophenone and DPP (0.0233 mol each) was heated at reflux in benzene for 240 hr under nitrogen and then left exposed to the air for 72 hr. Diphenylphosphinic acid, mp 193.0–196.0°, was removed by filtration and the residual solution was chromatographed through silica gel (20 g). Elution with benzene gave acetophenone (1.21 g, 0.0101 mol, 43%): ir (CH_2Cl_2) and nmr ($CDCl_3$) identical with a genuine sample's.

1-Hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane.—A mixture of α-mesyloxycyclohexanone (2.0 g, 0.010 mol) and DPP (2.32 g, 0.0125 mol) in benzene (5 ml) was stirred at room temperature for 168 hr. After removal of the solvent *in vacuo*, the resultant solid was dissolved in CH_2Cl_2 (25 ml) and washed with 5 *N* NaOH. The organic layer was dried and evaporated *in vacuo* to give 1-hydroxy-1-diphenylphosphinoxy-2-mesyloxycyclohexane (3.41 g, 0.00855 mol, 83.5%) after recrystallization from $CHCl_3$ (25 ml)–CH_3OH (3 drops): mp 147–148°; ir (CH_2Cl_2) 3.1–3.8 (broad), 7.3–7.7 (mesylate), 8.3–8.8 (mesylate), 10.2, 10.4, 10.7 μ.

Anal. Calcd for $C_{19}H_{23}O_5SP$: C, 57.85; H, 5.87; P, 7.85. Found: C, 57.60; H, 5.82; P, 7.93.

Registry No.—DPP, 829-85-6; **15**, 20187-69-3; **16**, 20187-70-6; **17**, 20187-71-7.

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Nor Steroids. VIII. Partial Synthesis and Chemical Studies of A-Nor Bile Acids[1,2]

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Methyl 3-keto-A-norcholanate (6) was reduced with several reagents to give the 3α- and 3β-hydroxy-A-nor compounds, with the former isomer predominating. The structural assignments were made on the basis of the nmr spectra and comparison with known model compounds. Similar studies were made with methyl 3,12-diketo-A-norcholanate (12a) to give A-nordeoxycholic acids. The benzilic acid rearrangement of methyl 3-hydroxy-4-keto-12α-acetoxy-5α-chol-2-enate (16) and lead tetraacetate cleavage of the product gave methyl 3-keto-12α-hydroxy-A-norcholanate (15a).

Despite a considerable amount of interest in recent years in the partial synthesis of ring-nor steroids and their biological activity, little work has been reported in the bile acid series. Many years ago Windaus[4] pyrolyzed 2,3- and 3,4-secocholanic acid dioic acid to 2-keto- and 3-keto-A-norcholanic acid, respectively. He also[5] prepared 2,6-diketo-A-norcholanic acid by the pyrolysis of 2,3-seco-6-ketocholane-2,3,24-trioic acid. Wieland[6] obtained 2,12-diketo-A-norcholanic acid and 3,12-diketo-A-norcholanic acid by pyrolysis of the corresponding secodeoxycholic acids. No reports could be found of the reduction of any of these keto compounds to the corresponding A-nor bile acids. The present work was undertaken to accomplish this and to explore further the chemistry of the A-nor compounds.

In order to gain some understanding of the stereochemical behavior of several common reducing agents toward the cholanic acid molecule, lithium aluminum hydride and sodium borohydride were used to reduce the 3-carbonyl group of 3-ketocholanic acid (1) in the six-membered A-ring series. Lithium aluminum hydride gave 12% of 3β-hydroxycholan-24-ol (2)[7] and 88% of 3α-hydroxycholan-24-ol (3),[8] both previously prepared by different routes. Sodium borohydride gave, after esterification of the reduction product, 10% of methyl 3β-hydroxycholanate (4) and 90% of methyl 3α-hydroxycholanate (5). (The above percentages are relative figures, not yields.) The upper, or β side of the molecule must therefore be less hindered, allowing easier approach of the hydride to the carbonyl group.

Methyl 3-keto-A-norcholanate (6) was studied next. It is interesting to note that the A-nor ketone has a deshielding effect on the C-19 methyl protons, δ 1.16, compared to the six-membered keto compound, δ 1.03. Reduction of the A-nor ketone with sodium borohydride gave 75% of the 3α-hydroxy compound **7a** and 25% of the 3β isomer **8a**. Reduction with lithium aluminum hydride gave a ratio of 54% of 3α-hydroxy-A-norcholan-24-ol (9) to 46% of 3β-hydroxy-A-norcholan-24-ol (**10**). Reduction with lithium borohydride gave a ratio of 62% of the 3α-hydroxy compound **7a** and 38% of the 3β compound **8a**. Reduction with lithium in liquid ammonia gave a ratio of 51% of the 3α-hydroxy compound **7a** and 49% of the 3β compound **8a**.

(1) For the previous paper in the series, see H. R. Nace and G. A. Crosby, *J. Org. Chem.*, **33**, 834 (1968).

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(3) Abstracted from the Ph.D. Thesis of E. M. H., Brown University, 1966.

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