The Swamping Catalyst Effect. II. Nuclear Halogenation of Aromatic Aldehydes and Ketones

D. E. Pearson, H. W. Pope, W. W. Hargrove, and W. E. Stamper

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Sufficient aluminum chloride to complex with aromatic carbonyl compounds completely has been found to deactivate the aliphatic side chain toward substitution and to permit nuclear substitution. In this manner, good yields of 3-bromo-, 3-bromo-4-methyl-3,4-dibromo-, 3-bromo-4-tert-butyl-, 3-bromo-4-ethyl-, and 3,3'-dibromo-4-methylacetophenones and of 3-bromobenzaldehyde, 3-bromo-4-toluic acid, 3-bromopropiophenone, and 3,3'-dibromobenzophenone have been obtained. Good yields of chloroaldehydes and ketones, including tetrachloroacetophenones, and fair yields of iodoketones have been obtained by this method using the reagents chlorine and iodine monochloride, respectively. No other catalyst has been found to function in the same manner as aluminum chloride or bromide.

The purpose of this paper is to report the scope of the swamping catalyst effect. We have found that, if sufficient catalyst is used to complex completely the halogen and accelerate the rate of reaction, has been called the swamping catalyst effect. The swamping catalyst effect with acetophenone and bromine yielded 60% (now raised to 70%) of 3-bromobenzaldehyde with no trace whatever of phenacetyl bromide as communicated previously. A small amount of tar, dibrominated ketone, and phenacyl bromide as communicated previously. A small amount of tar, dibrominated ketone, and starting material accompanied the bromoketone.

The preparation of phenacyl bromide from aceto-phenone and bromine in the presence of catalytic amounts of aluminum chloride is a well known procedure. We have found that, if sufficient catalyst is used to complex completely the carbonyl compound without solvent and to activate the halogen, side-chain halogenation is suppressed completely and nuclear halogenation takes place. The result brought about by the large excess of catalyst used, of necessity one equivalent to complex the carbonyl compound and of desirability an extra equivalent to complex the halogen and accelerate the rate of reaction, has been called the swamping catalyst effect. The swamping catalyst effect with acetophenone and bromine yielded 60% (now raised to 70%) of 3-bromobenzaldehyde with no trace whatever of phenacetyl bromide as communicated previously. A small amount of tar, dibrominated ketone, and starting material accompanied the bromoketone.

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A brief history of halogenation of aromatic carbonyl compounds is pertinent. Emmending and Engler in 1871 mixed equimolecular quantities of bromine and acetophenone at room temperature and claimed that the lachrymatory, crystalline and oily portions obtained from the mixture could be oxidized in part to a bromobenzoic acid. No one has ever been able to substantiate this claim. Hunnius showed that the product was actually phenacetyl bromide, later confirmed by other workers. Previous to this work Graebe had shown that only phenacetyl chloride was obtained by introducing chlorine into boiling acetophenone. Even benzophenone, which has no aliphatic side-chain to be substituted, does not seem to lend itself well to halogenation. No other nuclear halogenations of simple aromatic ketones, containing groups of less activating power than hydroxyl or amino groups, have been found in the literature. Of course, the latter groups do activate sufficiently to permit nuclear substitution. Buu-Hoi, for example, found that side-chain bromination of 2- and 4-hydroxyacetophenones took place with bromine in glacial acetic acid and nuclear bromination in aqueous acetic acid.

The nuclear halogenation of aromatic aldehydes is more common, although here again side-chain halogenation leading to benzoyl chlorides can take place if no catalyst is used. For example nuclear chlorination of benzaldehyde, yielding a mixture of chlorinated benzaldehydes, occurred in the presence of antimony chloride and iodine. Also, 3-iodobenzaldehyde was made in 30% yield by bringing together benzaldehyde, iodine, and silver nitrate in 90 percent aqueous sulfuric acid. In this concentration of sulfuric acid benzaldehyde is no doubt protonated since it is probably more basic than acetophenone, and the silver ion and iodine mixture is no doubt a source of strong electrophilic reagent.
the reaction thus serving as an example of the swamping catalyst effect. In summary, no examples of aromatic substitution of ketones of the simple acetophenone type have been found. Several examples of aromatic substitution of benzaldehyde have been found, using silver sulfate as a catalyst in cases where yields were satisfactory. The need for a reagent of general applicability to bring about nuclear substitution of carbonyl compounds becomes apparent when it is noted in the next section that so many rather simple compounds, like 3-iodo-4-methylacetophenone, have been made for the first time.

The best conditions for the swamping catalyst effect were developed in the preparation of 3-bromoacetophenone. The success of the preparation depended upon three important factors: (1) the ketone must be complexed rapidly and completely with aluminum chloride before the addition of bromine; (2) no solvent is used; (3) the complex must be molten enough to be stirred during the addition of bromine. In addition, sufficient aluminum chloride to complex the bromine was found to accelerate the rate of reaction considerably. Thus, most of the other reactions were investigated under conditions where one equivalent of carbonyl compound was added to 2.5 equivalents of aluminum chloride where 1.1 equivalents of bromine were added to the molten complex maintained at temperatures between 25–100°. Within the limitations of temperature imposed by fluidity and decomposition, however, the preparations of haloaldehydes were extremely satisfactory considering our initial pessimism.

The preparation of 3,3′-dibromobenzophenone in 35% yield may seem unsatisfactory, but it is the best yield by direct halogenation recorded in the literature.11 The difficulty was the separation of other brominated ketones. Our work suggested that the preparation of 3-bromobenzophenone was not satisfactory and perhaps not even feasible by this method.

**Chlorination.** Two main differences exist between chlorination and bromination in swamping catalyst experiments. First, chlorine, being a gas, must be fed into the system over a longer period of time to avoid its loss with the effluent gases. Second, the reactivity of chlorine is much greater, thus giving less product control but also permitting the introduction of up to four chlorine atoms. The experiments with acetophenone were run with such quantities of chlorine as to give mono-, di-, tri-, and polychlorination. The products from each of these runs are listed in Table II.

The poor yield in dibromination of acetophenone was caused by difficulty of separation of other bromoketones present. On the other hand, the yield of 3,5-dibromo-4-methylacetophenone from dibromination of 4-methylacetophenone was good. These facts suggested that the orientation of the second bromine atom entering acetophenone was not well controlled. The presence of a 4-methyl group was sufficient to alter a mixed orientation to one where the second bromine atom entered meta to the ketone group. We shall see a similar behavior in chlorination.

The bromination of benzaldehyde was undertaken with some trepidation since several papers suggested that aluminum chloride brought about decarbonylation or other profound changes at temperatures as low as 60°. The complex of benzaldehyde and aluminum chloride indeed was harder to make: it seemed higher melting than that of acetophenone, and it gave very poor yields if the temperature was higher than about 100°. Within the limitations of temperature imposed by fluidity and decomposition, however, the preparations of haloaldehydes were extremely satisfactory considering our initial pessimism.

**Bromination.** Two main differences exist between chlorination and bromination in swamping catalyst experiments. First, chlorine, being a gas, must be fed into the system over a longer period of time to avoid its loss with the effluent gases. Second, the reactivity of chlorine is much greater, thus giving less product control but also permitting the introduction of up to four chlorine atoms. The experiments with acetophenone were run with such quantities of chlorine as to give mono-, di-, tri-, and polychlorination. The products from each of these runs are listed in Table II.

The results in Table II suggest that the chlorine atoms enter in the following sequence:

In addition to the above chlorinations the following preparations were made. (1) 3,5-Dichloro-4-methylacetophenone, 15% yield, a new compound. The yield was not maximum and could perhaps be improved by taking more care to keep the complex molten. Trace amounts of hexachlorobenzene were also found which is not unusual in chlorination processes. 26

(2) 2,3,5,6-Tetrachloro-4-methylacetophenone, 67% yield, a new compound.

(3) 3-Chlorobenzaldehyde, 43% conversion, 59% yield.

**Iodination**. Although iodine cannot be made to substitute in swamping catalyst experiments, iodine monochloride was found to give halogenated products with acetophenone. Unfortunately, both 3-iodoacetophenone (15%) and 3-chloroacetophenone (47%) were formed simultaneously. We suspected that aluminum chloride brought about isomerization of iodine monochloride to unreactive iodine and to chlorine. The following facts more or less confirmed this suspicion: iodine monochloride pre-equilibrated with aluminum chloride gave only 6% of 3-iodoacetophenone and 32% of 3-chloroacetophenone, and the more reactive 4-methylacetophenone gave a higher yield of 3-iodoketone, 36%, and a lower yield of 3-chloroketone, 25%. Despite the fact that mixtures of iodo- and chloroketones are obtained, the swamping catalyst method with iodine monochloride is so simple and the separation of the ketones is so easy that this process is the method of choice for synthesis of m-iodo ketones.

**Search for other catalysts**. The most surprising aspect of the swamping catalyst experiments is that aluminum chloride (or bromide) is the only catalyst which seems to be effective in bromination of aldehydes and ketones. 26a Sulfuric acid either alone or mixed with aluminum chloride gave lachrymatory products. Chlorosulfonic acid gave a sulfonated ketone. Boron trifluoride proved very difficult to handle and impossible to keep in excess, as is necessary for successful bromination. 26b Boron trifluoride gave a solid complex with acetophenone which could be stirred readily in excess boron trifluoride. Nevertheless, only lachrymatory substances were isolated after bromination. Benzaldehyde, the stannic chloride complex of which was suspended in excess stannic chloride, gave no chlorinated product after chlorination. 27

From the negative results of these experiments we are almost forced to believe that the action of

[Diagram of molecular structures]

This structure explains the stoichiometry of the reaction, the deactivation of the methyl group toward side-chain substitution through preferential coordination of the carbonyl carbon with the chlorine atom in the catalyst, the weakening of the carbonyl double-bonded structure, and inability of protonic acids to catalyze this reaction. Perhaps this structure also explains why boron trihalides are ineffective catalysts because the small size of the boron atom precludes its inclusion in an eight-membered ring complex. With side-chain bromination suppressed in the aluminum chloride complex, nuclear bromination can now take place. The nucleus of aluminum chloride (or antimony pentachloride) is specific. In any specific catalytic effect of this nature, a cyclic electron shift mechanism is to be suspected, and one can be visualized in which both bromine and the ketone are complexed in the aluminum chloride dimer in such a way as to bring the bromine atom over the face of the benzene ring and in the vicinity of the π-electron cloud. We have rejected this possibility, however, since the swamping catalyst effect takes place with an aluminum chloride-ketone ratio of 1, not the ratio 2 to be expected for the dimer of aluminum chloride. Furthermore, the orientation, predominantly meta but occasionally ortho, or para, is not truly specific. We are more inclined to believe tentatively that the main function of the aluminum chloride is to block side-chain halogenation by forming a *very stable* hybrid complex of a dimeric, cyclic nature. 26


(26) (a) In later experiments, antimony pentachloride has been found to yield 3-chloroacetophenone upon chlorination of acetophenone. The yield, however, is lower than with aluminum chloride. (b) Liquid hydrogen fluoride, either by itself or mixed with boron trifluoride, was unsuccessful as a catalyst in the chlorination of acetophenone.

(27) In all of these negative experiments, a few per cent, but no more, of nuclear-halogenated carbonyl compounds may have escaped detection.


(29) The nucleus in the complex also may be more susceptible to substitution than the nucleus in the free ketone because of the loss of contribution of canonical forms such as \[
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representing the free ketone. These forms deactivate the hybrid of the free ketone toward aromatic substitution.


acetoephone must be substitutable for to
we know that it is easily nitrat to yield 3-nitro-
acetoephone. Thus, our tentative theory requires
complete and perhaps specific complex formation
between ketone and Lewis acid, presently found
only with the catalysts, anhydrous aluminum chlor-
ide or bromide and antimony pentachloride.19,25a
The theory also suggests that an extra mole of cata-
lyst is desirable to increase the activity of the at-
tacking reagent. A mixture of halogen and alumi-
nium chloride should by all means give rise to a
transition complex in which the bond-breaking pro-
cess of bromine is well advanced:

\[ \text{AR: H} \quad \xrightarrow{\text{Br: Br}} \quad \text{AlCl}_3 \]

thus making bromine a more active substituting
agent as is noted in the acceleration of the rate of
bromination when larger excesses of catalyst are
used. All the experimental evidence obtained to date
supports the tentative theory. It remains to be seen
whether future evidence shows it to be the right
theory. A reaction of such relatively narrow scope
perhaps does not seem worthy of labelling with a
new name, the swamping catalyst effect. We have
reason to believe that the scope is in reality much
greater than described here. For example, we have
been able to obtain good yields of 3-bromo- and
2,5-dibromobenzonitrile by bromination of benzo-
nitrile. We have also under study the effect of sub-
stituting agents other than halogens. These experi-
ments will be described in a later paper.

EXPERIMENTAL

All melting points are corrected and boiling points uncor-
corrected. Analyses were by Gulfnorth Laboratories, Knoxville,
Tenn. Greater detail of experimental work is to be found in
the thesis of H. W. Pope3 and the forthcoming these of
W. W. Hargrove and W. E. Stamper. Hexane refers to
petroleum ether, b.p. 69-70°, and pentane to petroleum ether
b.p. 35-60°. Oximes35 and 2,4-dinitrophenylhydrazones36
were made by published methods.

General procedure exemplified by preparation of 3-bromo-
acetoephone. The apparatus was usually a 1-liter, three
necked, standard tared, round bottomed flask equipped
with condenser, dropping funnel, and glass stirrer terminat-
ing in a stiff, crescent a-shaped Teflon paddle. Occasionally
a Tru-Bore stirrer and a pressure-equalizer dropping fun-
el were used. The hydrogen bromide gas evolved through the
condenser was led to the sink by means of rubber tubing. A
motor with good torque (Sargent Cone Drive or Waco)
was used to provide stirring. The assembled apparatus,
protected from moisture by means of drying tubes in the
condenser and funnel, was pre-dried by passing a slow
stream of air through entire apparatus while each section
was warmed with a soft flame. The condenser jacket
was not filled with water until the drying process was complete.

The catalyst was dispensed very conveniently by adding
rapidly the entire contents of a 4-oz. bottle of Baker and
Adamson, Anhydrous Aluminum Chloride, Resublimed. About 110 g. (0.523 mole) to 112 g. (0.84 mole) was delivered
to the flask in this manner. The catalyst was quite free-
flowing and could be stirred. Acetophenone (40.4 g., 0.336
mole) was added in a slow stream from the dropping funnel
to the stirred solid over a period of 10-15 min. Considerable
heat was evolved and, if the drops of ketone were not dis-
persed, darkening or charring occurred. At about the half-
way point of addition the solid became a viscous, ball-like
mass which was difficult to stir. It was necessary on occasion
to turn the stirrer by hand at this point. More rapid addi-
tion of ketone also aided stirring but not so rapidly as to
produce an unduly high temperature. Near the end of the
addition, the mass became molten and could be stirred
easily. No heat or cooling was applied. At the end of a
successful addition the mixture was molten, quite warm but
below 100°, and tan to clear brown in color. In the event
that the complex was higher melting than that of aluminum
chloride-acetophenone, the aluminum chloride was heated
before the addition of the ketone, and a minimum tempera-
ture maintained to keep the complex molten. A molten
mixture was essential to the success of all halogenation
reactions. Some of the remarks above are matters of con-
venience rather than of necessity.

Bromine (94.4 g., 0.405 mole) was added dropwise to the
stirred, molten mass over a period of about 20 min. The rate
of addition was regulated by the rate of evolution of hydro-
gen bromide. About one hour after the completion of the
addition of bromine, the stirred mass solidified. The solid
complex was then (or the next day) carefully dropped por-
tionwise into a 2-l. beaker containing cracked ice and
100 ml. of concentrated hydrochloric acid while the ice was
hand stirred vigorously. The acid was found to be quite
necessary, for if it were omitted, separation of ether-water
layers became difficult because of the effect of small amounts
of insoluble aluminum salts. The dark colored oil at the
bottom of the beaker was extracted with ether; the ether
solution was washed consecutively with water and with
sodium bicarbonate solution and dried with anhydrous
sodium sulfate. After removal of the ether, the oil was
stripped from a few grams of heavy residue by distillation
from a short necked flask at 1 mm. pressure. The distillate
was separated by fractionation in a 200 X 15 mm. column
filled with carborundum or Helipak filling. The combined
middle fractions were 3-bromooacetophenone, b.p. 101-
75-76° at 0.5 mm., n" 1.5740, m.p. 7-8°; oxime m.p.
100-101°; reported n" 1.5755; reported m.p. 7-8°.

Further comments about the bromination of acetoephone.
When the reaction mixture was maintained at 80-85°
during addition of bromine rather than at room tempera-
ture or slightly higher, the yield of 3-bromooacetophenone
was 73.5% rather than 71%. This experiment suggested that
the temperature of reaction for this preparation was not critical.

Three runs were made under the same conditions (except
those mentioned) to test the effect of mole ratio of catalyst.
The results were as follows:

<table>
<thead>
<tr>
<th>Run</th>
<th>AlCl₃</th>
<th>C₆H₅COCH₃</th>
<th>Br₂</th>
<th>Time, Min.</th>
<th>Yield, %</th>
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<td>69</td>
<td>60</td>
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<td>2</td>
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<td>3</td>
<td>1.2</td>
<td>1</td>
<td>1</td>
<td>180</td>
<td>63</td>
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Although the third run appeared to be superior, the rate of substitution was perceptibly slower. On the basis of these experiments, the mole ratio AlCl₃ 2.5, ketone 1.0, and bromine 1.1 was used for most other experiments unless otherwise specified.

General procedure for preparation of β-chlorocacetophenone. In place of the separatory funnel in the apparatus just described, an inlet tube for chlorine was inserted in the three necked flask so that the gas could be introduced under the surface of the molten complex. The complex of acetophenone and aluminum chloride was made in the same quantity as described above. In the meantime, 19.5 ml. of chlorine was condensed in a trap cooled with Dry Ice and acetone. The weight of this volume of chlorine was assumed to be 30 g., 0.42 mole. The gas was bubbled through concentrated sulfuric acid into the stirred complex, the rate being controlled by gradually lowering the Dry Ice container surrounding the liquid chlorine trap. Evolution of hydrogen chloride was noticeable; the internal temperature of reaction mixture rose to about 45°; the color changed from light brown to deep red-brown. The addition of chlorine was complete in 5 hr. and the stirring continued for at least another hour. The reaction mixture was handled from here in the same manner just described, and the separation by fractionation yielded 5.2 g. of acetophenone and 38.8 g., 60% of 3-chlorocacetophenone: b.p. 61–63° at 0.5 mm., nD₂ 1.5480, oxime m.p. 87.5–88.5°, reported as 88°.

3-Bromophenone. The yield was 60% of white, small plates, once recrystallized from hexane: m.p. 40–41°; semicarbazone m.p. 181–182°; reported 182–183°.

3-Bromo-α-nitrocacetophenone. The yield was 56% of white plates, once recrystallized from petroleum ether, m.p. 42–43°, reported m.p. 43°; oxime m.p. 94–95°; reported m.p. 94.5–95.5°.

3,4-Dibromo-α-acetophenone. This compound was made from β-bromocacetophenone. The bromination rate was considerably slower than that of acetophenone. The complex in contact with bromine was allowed to stir for 24 hr. at room temperature. A higher temperature may have improved the yield. The yield was 55% of white, thick needles, once recrystallized from hexane: m.p. 90–91°, reported m.p. 90–92°; oxime m.p. 116–117°, 3,4-Dibromobenzonitrile acid made from the ketone by hypobromite oxidation had a m.p. 235–236°, reported m.p. 235–236°.

Attempted dibromination of acetophenone. The mole ratio was ketone 1, bromine 2.1, and aluminum chloride 3.1. The temperature of the mixture was maintained at 80–85° during the addition of bromine. From 0.27 mole of acetophenone, 57.6 g. of a crude oil was obtained which by further fractionation and by freezing. This ketone was oxidized to 2,5-dibromobenzoic acid, m.p. 156–157°, reported m.p. 156°. Attempts to dibromate acetophenone at room temperature led to complexes which could not be stirred and subsequently to mixtures of 3-bromo- and 2,5-dibromocacetophenone and some labratory material assumed to be phenacyl bromide.

Attempted monobromination of 3-methylacetophenone. A mixture of brominated ketones was obtained, b.p. 94–117° at 2 mm., nD₂ 1.5622–1.5731 which could not be separated in the Kelpak column used for other separations.

3,5-Dibromo-α-acetophenone. The ratio of reagents was ketone 1, bromine 2.1, and aluminum chloride 3.1. The crude solid, obtained from this reaction, b.p. 109–140° at 0.5 mm., was recrystallized from hexane: white needles, m.p. 97%, m.p. 102.5–103.5°.

Anal. Calcd. for C₆H₅Br₂O: Br, 54.62. Found: Br, 54.65. The ketone was converted to 3,5-Dibromo-4-toluic acid by hypobromite oxidation, m.p. 235–236°, reported m.p. 235–236°.

3,5-Dibromobenzonitrile. The molar quantities were benzophenone 0.05 mole, aluminum chloride 0.11 mole, and bromine 0.11 mole. Bromine was added dropwise to the yellow-green fluid complex over a period of 0.5–2 hr. while the temperature was maintained near 25° by intermittent refrigeration.


(96) L. Vecchiotto, Gazz. chim. ital., 58, 181 (1928).
cooling. At the completion of the addition of bromine the mixture was warmed by means of a water-bath to 70° and held there for an hour or two. The mixture became a thick orange to brown colored paste on cooling to room temperature. The paste was poured into ice and water, an equal volume of concentrated hydrochloric acid added, and the mixture digested by refluxing for a hour. On being cooled, the crude solid was removed by filtration, thoroughly washed with water and aqueous sodium bicarbonate, and recrystallized from ethanol. The yield was 5-6 g., 30-35% of white plates, m.p. 137-140°. Further recrystallization gave small needles, m.p. 138-140°, reported m.p. 140° and 141°. Attempts to prepare 3-bromobenzophenone in good yield were unsuccessful. Bromination at higher temperatures than those reported above led to resinous products. The above preparation of 3,3'-dibromobenzophenone is evidently superior to any other method of direct bromination, although the preparation of 3-chlorobenzophenone by electrochemical generation of chlorine has been reported. The product, however, was not well characterized.

3-Chlorobenzaldehyde. The benzaldehyde-aluminum chloride complex was maintained at 76-85°, by regulating first the rate of addition of benzaldehyde to aluminum chloride (25 min.) and then the rate of addition of chlorine (150 min.). At the end of the addition, the mixture was maintained at 80° by means of an oil bath and stirred for 3 more hours. The complex was decomposed in the usual manner, and 3-chlorobenzaldehyde was obtained: b.p. 93-96° at 15 mm., 31.0 g., 43% conversion, 59% yield; m.p. of phenylhydrazones 133-135°, reported m.p. 134-135°; m.p. of semicarbazone 227-228°, reported 228°; m.p. of 3-chlorobenzoic acid 155-156°, reported 156.5°. The refractive indices of various fractions were not taken because of ease of air-oxidation of the aldehyde.

Dichlorination of acetoephone. The ratio of reagents was aluminum chloride 2, chloroform 2.3, and ketone 1. The complex was maintained at 50° by means of a Glaessl heater and at a somewhat higher temperature toward the end of the addition of chlorine. The addition was complete in 12 hr. If the rate of addition were made faster, some chlorine gas tended to escape in effluent gases. By means of fractional distillation in a Helipak column, 2,5-dichloroacetophenone was obtained in 43% yield; b.p. 71-72.5° at 2 mm., nD 1.5596, oxime m.p. 127-130°, rearranged to 2,5-dichloroacetanilide, m.p. 133-133.5°; reported m.p. 134-135° and of 2,5-dichloroacetanilide 133°. Apparently, no other dichloro isomer was formed as judged from b.p. and refractive indices, although some crude mono- and trichlorinated compounds were isolated.

Dichlorination of 4-methylacetoephone. The ratio of reagents was ketone 1, aluminum chloride 2.5, and chloroform 2. The mixture was maintained at 55° throughout the 4-hr. period of addition of chlorine. This temperature probably was not quite high enough to give complete mixing and a maximum yield. The chlorinated complex was difficult to remove from the flask. The slurry of ice and hydrochloric acid therefore was added all at once to the chilled flask containing the complex. If only a small portion of ice were added, strong local heating occurred at the interface of complex and water. The complex was usually decomposed after standing in contact with water overnight and after some stirring the next day. This reverse method of decomposition was used whenever the complex was too difficult to remove from flask. The crude product was stripped from the tar and fractionated in the usual manner. 3-Chloro-4-methylacetophenone (b.p. 88-107° at 3 mm., 7.2 g., 13%, m.p. 45-46° after recrystallization from pentane, reported m.p. the same), 3,5-dichloro-4-methylacetophenone (b.p. 108-111° at 3 mm., 8.3 g., 15%, m.p. 66-67°; oxidized to acid, m.p. 191-192°, neutral equivalent 204, calculated 205; oxime m.p. 185.5-186° which was rearranged to 3,5-dichloro-4-acetolactimide m.p. 220-221°, reported m.p. 220°, and trace amounts of hexachlorobenzene, m.p. 230°, were obtained. The latter was separated by its ready elution from an aluminum column. The remainder of the product was a solid of wide m.p. range.

Trichlorination of acetoephone. The mole ratio was ketone 1, aluminum chloride 2.5, and chlorine 3. The temperature of mixture was maintained at about 40° throughout the 9 hr. required for the addition of chlorine. The complex was decomposed by adding the slurry of ice and acid to the flask as described in previous section. The crude oil, stripped from the small amount of residue was separated by means of a Todd column, monoi spiral, 5/1 reflux ratio into the following compounds: Crude 2,5-dichloroacetophenone: 11 g., 17%, nD 1.5992-1.6002.

Crude 2,3,5-trichloroacetophenone: 20.5 g., 38% crude yield, recrystallized to constant refractive index, b.p. 132° at 7 mm., nD 1.5720.

Anal. Caled. for C8H4Cl3O: C, 47.5. Found: C, 47.3.

The ketone was oxidized with sodium hypobromite to 2,3,5,6-tetrachlorobenzoic acid; m.p. 102.5-103°, neutral equivalent 225, reported m.p. 168°, theoretical neutral equivalent 223.5. The oxime, m.p. 143-145°, was rearranged to phosgene in polyphosphoric acid to 2,3,5-trichloroacetanilide, m.p. 173°. 2,3,5,6-Tetrachloracetophenone. This isomer was separated from the 2,3,5,4 isomer by its lower b.p. (ca. 160° at 5 mm.) in the Todd still and by its difference in crystal habit (rhombic plates from aqueous ethanol which could be hand-picked). The yield of 2,3,5,6-tetrachloracetophenone was 22°, m.p. 61.5-62.5°.


The ketone failed to form an oxime and a 2,4-dinitrophenylhydrazine by the usual methods and failed also to form the corresponding acid by hypobromite oxidation. However, it was converted to 2,3,5,6-tetrachlorobenzoic acid by means of oxidation in pyridine-water-potassium permanganate solution; m.p. 181.5-182° after two recrystallizations from water; calcd. neutral equivalent 257.3; found, 255. The ketone was also cleaved to 1,2,4,5-tetrachlorobenzene, m.p. and mixed m.p. with authentic sample, 139-139.5° by means of 50% potassium hydroxide in aqueous alcohol after the method of Lock. 2,3,5,6-Tetrachloracetophenone. This ketone was higher boiling than the 2,3,5,6-isomer (b.p. ca. 138° at 5 mm.) and was recrystallized from pentane: 5% yield of colorless needles, m.p. 74-75°.

Anal. Caled. for C8H4Cl4O: C, 55.0. Found: C, 54.60.

The ketone was converted by potassium permanganate in aqueous pyridine to 2,3,4,5-tetrachlorobenzoic acid; m.p. and reported m.p. 194-194.5°, neutral equivalent 266.5, calcd. 257.9. Huntress reports the m.p. as 186°. The oxime, m.p. 172-174°, was rearranged in polyphosphoric acid to 2,3,4,5-tetrachloracetanilide, m.p. 165-166°, reported m.p. 160-162°. Further statements are made about the two tetrachloro ketones in the following two sections.

Zekasian chlorination of acetoephone. The mole ratio was ketone 1, aluminum chloride 2, and excess chlorine led directly from the tank to the reaction mixture. The mixture was maintained at 50° during the period of addition, 18 hr. The complex solidified before the addition of chlorine was complete. The crude product was distilled under vacuum with separation into a liquid fraction, b.p. 107-111° at 1 mm., consisting mostly of di- and trichlorinated ketones, and a solid fraction, b.p. 112-115° at 1 mm., consisting of a mix-
tecture of tetrachloro ketones was treated with 2,4-dinitrophenylhydrazine in acidic aqueous ethanol, and the 2,4-dinitrophenylhydrazone of the concentrate with Noit, and recrystallization: white plates, m.p. 60-62°, 57 g., 54%. No pentachloroacetophenone was detected.

Exhaustive chlorination of p-methylacetophenone. The reaction was carried out as above except that the reaction mixture was maintained at 85° for 5 hr. and then at 95° for 1 hr. The flow-rate of chlorine was increased as the temperature was raised. At the end of the sixth hour, the mixture froze to hard brick-red lumps which stopped the flow of chlorine. Chlorine escaped from the sulfuric acid trap into the hood. The crude solid obtained from the ether extract was stripped from the tar (9 g.) by distillation at 1-mm. pressure. The distillate was solid and weighed 78.4 g. Recrystallization of a small amount from hexane gave crystals of hexachlorobenzene: needles, m.p. 41.5-42°, yellowing slightly on storage for a year in a brown bottle; reported (55) m.p. 44-45°, oxime m.p. 94.5-95.5°, reported (56) m.p. 41.5-42°.

Iodination of acetophenone. Iodine failed to react with acetophenone in the presence of swelling amounts of aluminum chloride. Only acetophenone with a small amount of polymeric material was recovered. Iodine monochloride however, was found to react to give mixtures of 3-chloro- and 3-iodoacetophenones. Iodine monochloride was made by the Inorganic Syntheses method.82 Care was taken to add only small portions of iodine during the earlier stages of addition.83 The molar ratio was ketone 1, AlCl₃ 2.5, I₂ 1.5. The reaction mixture was held at room temperature while iodine monochloride was added dropwise over a period of 70 min. The contents were stirred for several hours longer and then allowed to stand overnight. The ether extract was washed with sodium bisulfite solution in addition to the usual water and sodium bicarbonate washes. The ether residue was separated by fractionation in an 8-in. column filled with Helipak filling at 1.5 mm. Acetophenone (b.p. 82-83° at 1.5 mm, 11.5 g., 28% m.p. 89-91°, 1.5312) and crude 3-chloroacetophenone (b.p. 87-96° at 1.5 mm, m.p. 51.5 g., 52% m.p. 1.5440-1.5490, 22 g., 47%) were separated. The residue was distilled in a short-path apparatus at 1.5 mm., yielding crude 3-iodoacetophenone; b.p. 112-120° at 1.5 mm, m.p. 111 g., 1.6188, 12.5°, 19%. Distillation through a Helipak column promoted decomposition of the iodo ketone. Redistillation of 3-chloroacetophenone gave the pure compound: b.p. 61-63° at 0.5 mm., nD₂ 1.548, oxime m.p. 87.5-88.5°. Slow redistillation of 3-iodoacetophenone from a short-path apparatus at 0.5 mm. gave the pure compound: b.p. 83-85° at 0.5 mm., m.p. 27.5-29.5°, nD₂ 1.620, 1.754, reported as a dark liquid, b.p. 102° at 2 mm. The iodoacetone was quite heat-sensitive, turning yellow when warmed on a porcelain spatula and turning to a liquid on storage for a year in a brown bottle.

The formation of both 3-chloro- and 3-iodoacetophenone from iodine monochloride suggested that the latter was disproportionate by the catalyst to unreactive iodine and chlorine. To check this possibility, iodine monochloride was mixed with an equimolecular portion of aluminum chloride and this mixture introduced proportionwise into the flask containing the ketone-aluminum chloride complex. The yields of ketones of comparable purity to the ordinary runs were 32% 3-chloroacetophenone and 6.5% 3-iodoacetophenone. This result together with the fact that the yield of iodo ketone is greater with more reactive ketones (see next section) strengthens the suggestion that iodine monochloride undergoes disproportionation in the presence of aluminum chloride. Reducing the molar ratio of aluminum chloride, however, reduced the yield of both 3-chloro- and 3-iodoacetophenones. The concentration of a single ketone in a mixture of two ketones could be estimated from the refractive index as shown. The per cent of 3-chloroacetophenone in acetophenone had refractive indices, nD₂ as follows: 100%, 1.5479; 73.1%, 1.5427; 27.6%, 1.5354; 0%, 1.5319. The per cent of 3-iodoacetophenone in 3-chloroacetophenone had refractive indices as follows: 100%, 1.6199; 77.1%, 1.5966; 50.9%, 1.5765.

Iodination of 4-methylacetophenone. The molar ratio was ketone 1, AlCl₃ in chlorine 2, and iodine monochloride 1.2. The reaction mixture was held at 80° ± 2° during the addition of iodine monochloride (30 min.). Some heat of reaction was noticeable. A small amount of iodine sublimed on walls, and evolution of hydrogen chloride was very rapid. The work-up of halogenated ketones was the same as usual except a wash with aqueous sodium bisulfite was done first. The separation of ketones was accomplished by very slow distillation in a 3-in. Vigreux column. Crude 4-methylacetophenone (b.p. 60° at 1 mm., 23 g., 36%, nD₂, 1.5939), crude 3-chloro-4-methylacetophenone (b.p. 72-80° at 1 mm., 18 g., 25%, recrystallized from hexane, m.p. 43-44°, reported (56) m.p. 44-45°, oxime m.p. 44.5-45.5°, reported (56) m.p. 44.5-45°), crude 3-iodo-4-methylacetophenone (b.p. 109° at 1 mm., 41 g., 36%; recrystallization from an equal volume of hexane with seeding gave dense transparent cubes, m.p. 41.5-42°, yellowing slightly on storage for a year in a brown bottle; nD₂ of supercooled liquid 1.017, oxime: needles with yellow-green cast, m.p. 107-107.5°; 2,4-dinitrophenylhydrazone: burnt-orange colored needles from nitrobenzene, m.p. 270-272°, dec.) were obtained.


With more precise fractionation, greater amounts of each ketone probably could be obtained; intermediate fractions were not counted in % yield. A run was also made in which the reaction mixture was maintained at room temperature. The yields of ketones comparable in purity to first run were as follows: 18% recovered 4-methylacetophenone, 32% 3-chloro-4-methylacetophenone, and 25% 3-iodo-4-methylacetophenone.

Aluminum bromide as a catalyst. 3-Bromacetophenone was obtained in 77% yield, b.p. 80° at 0.5 mm., nD₂ 1.5729 by using anhydrous aluminum bromide (Fluka) in place of aluminum chloride.

Attempted use of sulfuric acid. Acetophenone (24 g.) was added dropwise to 100% sulfuric acid (55 ml.) held at ice temperature. Bromine (34 g.) was then added and the
mixture allowed to come to room temperature during the next 6 hr. Bromine was found to be insoluble in sulfuric acid. The mixture was quenched in crushed ice and worked up in the usual manner. The lachrymatory oil was treated with diethylamine in ether by the method of Lutz\textsuperscript{4} to remove phenacyl bromide. After this treatment, only a small amount of acetophenone (b.p. less than 62° at 1 mm.) was obtained.

A mixture of sulfuric acid (184 g.) and anhydrous aluminum chloride (45.7 g.) was also used as a catalyst. The mixture evolved hydrogen chloride and became solid. An additional 100 ml. of sulfuric acid was added to make the system fluid. Acetophenone (40.4 g.) was added dropwise forming a yellow orange complex. Bromine (53.7 g.) was added with stirring over a one hour period and this mixture was allowed to stir overnight. Phenacyl bromide, b.p. 71-73° at 1.5 mm., 30.5 g., 45%, was obtained as a semi-solid and greenish black in color. The heat of reaction seemed comparable to that of benzaldehyde and acid chloride. Chlorine (438 g., 0.49 mole) was bubbled through the mixture over a period of 3 hr. After the usual isolation, benzaldehyde (b.p. 69° at 15 mm., 37 g., 71%) was first removed leaving a semisolid residue (3 g.) in still pot. The residue was oxidized in quantitative yield to benzoic acid, m.p. and mixed m.p. 122°.

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NASHVILLE, TENN.

[CONTRIBUTION FROM UNIVERSITY COLLEGE FOR GIRLS, EIN SHAMS UNIVERSITY, AND SCHOOL OF PHARMACY, LONDON UNIVERSITY]

**Synthesis of Decahydro-5,6-benzindan-1-yl Acetoxymethyl Ketone and 1-Acetoxydecahydro-4,5-benzindan-1-yl Methyl Ketone**

A. M. EL-ABBADY\textsuperscript{1}

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Decahydro-5,6-benzindan-1-yl acetoxymethyl ketone and 1-acetoxydecahydro-4,5-benzindan-1-yl methyl ketone were synthesized from 1-carbethoxy-4,5,6,7,1',2',3',4'-octahydro-5,6-benzindan-3-one and decahydro-4,5-benzindan-1-one, respectively. These compounds are of interest as analogs of adrenal cortical hormones.

Adrenal cortical hormones usually have a —CO-CH\textsubscript{2}R side chain and an R' group (where R and R' = H or OH) attached to the carbon atom at position 17 in the cyclopentanoperhydrophenanthrene nucleus. Moreover, the presence of cortical activity has been demonstrated in perhydropyridan-1-yl hydroxymethyl ketone\textsuperscript{6} in the life maintenance test. In view of these observations and because the optimum skeleton upon which to attach the side chain has not been determined, it was decided to attempt the preparation of such derivatives of decahydrobenzindans which may be regarded as analogs of the cyclopentanoperhydrophenanthrene nucleus. Thus, decahydro-5,6-benzindan-1-yl acetoxymethyl ketone and 1-acetoxy-decahydro-4,5-benzindan-1-yl methyl ketone were synthesized according to the following scheme.

Clemmensen reduction of 1-carbethoxy-4,5,6,7,1',2',3',4'-octahydro-5,6-benzindan-3-one\textsuperscript{6} II gave mainly an unsaturated ester tentatively assigned the constitution III. A trace of another product was also isolated and shown to be the paraconic acid X. With regard to the absorption properties of the unsaturated ester III, attention was drawn to the investigation of Ungnade and Ortega,\textsuperscript{1} which has established that \(\alpha,\beta\)-unsaturated acids or esters in alcoholic solution show a distinct maximum in the region between 210-225 \(\mu\)m (\(E = 9000\)).

\textsuperscript{1}Chemistry Department, University College for Girls, Ein Shams University, Cairo, Egypt.

