The tube was placed in a water-bath at 100° and observations made every two or three minutes. With every arsonic acid examined a characteristic precipitate of the corresponding arseno compound (with perhaps some arsine oxide) was obtained within twenty minutes. When a solution of arsenic trioxide in dilute hydrochloric acid was treated with hypophosphorous acid under these conditions, no precipitate was obtained. Table I summarizes the results obtained in testing a series of arsonic acids. In two cases it was found more satisfactory to dissolve the arsonic acid in hypophosphorous acid and omit the water.

TABLE I

ACTION OF HYPOPHOSPHOROUS ACID

Arsonic acid	Solvent	Minutes for reduction	Color of precipitate
1 *p*-Hydroxyphenylarsonic acid	H_2O	4	Red
2 Phenylarsonic acid	H_2O	1	White
3 Mono-sodium salt of *p*-arsonophenoxyethanol	H_2O	1	Pale yellow
4 *p*-Arsanilic acid	(a) H_2O	19	Red
	(b) H_3PO_2	13	Solid red mass
5 Tryparsamide	H_3PO_2	2	Red
6 3-Nitro-4-aminophenylarsonic acid	H_2O	2	Golden-yellow

Summary

1. A rapid qualitative test of arsonation for aromatic compounds has been suggested.

2. A new type of arsonic acid, the arsonated aromatic aldehyde, has been developed.

3. The preparation of three arsonated aromatic aldehydes, 3-nitro-4-arsonobenzaldehyde, *m*-arsonobenzaldehyde and *p*-arsonobenzaldehyde has been described. *p*-Arsonobenzaldehyde was prepared by a new and independent synthetic method.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE REACTION BETWEEN HIGHLY PHENYLATED COMPOUNDS AND ORGANIC MAGNESIUM COMPOUNDS

BY E. P. KOHLER AND E. M. NYGAARD

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A study of the reaction between α,β-unsaturated ketones and organic magnesium compounds, made many years ago, included every member except the last of a series beginning with acrolein and ending with its most highly phenylated substitution product, tetraphenyl propenone. In view of the increasing interest in highly phenylated compounds and especially of our own results with highly phenylated unsaturated nitro compounds, it was desirable to complete the study of this series.

We have, therefore, investigated the behavior of the completely phenylated unsaturated ketone I both toward methyl magnesium iodide and toward phenyl magnesium bromide. And since the results were rather surprising, we also included in the investigation the behavior of the corresponding saturated ketone, α,β,β-triphenylpropiophenone, II.

$$\underset{\text{I}}{(C_6H_5)_2C{=}C(C_6H_5)COC_6H_5} \qquad \underset{\text{II}}{(C_6H_5)_2CHCH(C_6H_5)COC_6H_5}$$

We found that the saturated ketone reacts much more readily than we had anticipated, both with methyl magnesium iodide and with phenyl magnesium bromide. Indeed the reaction with methyl magnesium iodide proceeds rapidly in ethereal solution at the ordinary temperature, and the yield of the tertiary alcohol to be expected is practically quantitative. The structure of the product was established by treating it with a dehydrating agent and ozonizing the resultant hydrocarbon. The oxidation product was the original ketone

$$\underset{\text{II}}{(C_6H_5)_2CHCH(C_6H_5)COC_6H_5} \longrightarrow \underset{\text{III}}{(C_6H_5)_2CHCH(C_6H_5)C(CH_3)(C_6H_5)OH} \longrightarrow$$

$$(C_6H_5)_2CHCH(C_6H_5)C(C_6H_5){=}CH_2 \longrightarrow \underset{\text{IV}}{(C_6H_5)_2CHCH(C_6H_5)COC_6H_5}$$

With phenyl magnesium bromide the saturated ketone reacts less readily, but this reaction can likewise be completed in ether, at the ordinary temperature. In this case also the principal product is the tertiary alcohol but the yield is not nearly so good, doubtless because of the ease with which the highly phenylated carbinols undergo cleavage to a mixture of simpler products. The proof of the structure of the Grignard product was obtained by oxidation. The carbinol was readily oxidized by chromic acid in glacial acetic acid, and yielded two moles of benzophenone to one of benzoic acid.

$$\text{II} \longrightarrow \underset{\text{V}}{(C_6H_5)_2CHCH(C_6H_5)C(C_6H_5)_2OH} \longrightarrow 2(C_6H_5)_2CO + C_6H_5CO_2H$$

In sharp contrast with the saturated ketone, the corresponding unsaturated compound does not react at all with either of the Grignard reagents at the ordinary temperature, and it was recovered even after prolonged boiling. In order to secure any reaction it was necessary to replace most of the ether with benzene and operate at a higher temperature.

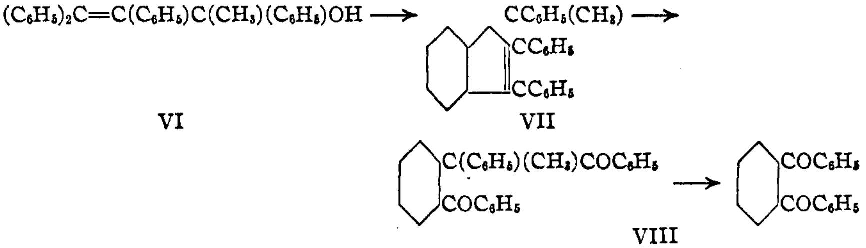
The reaction between the unsaturated ketone and methyl magnesium iodide gave two solid products and a small quantity of oil. The composition of the principal product indicates that it is formed as a result of the addition of one molecule of methyl magnesium iodide to the unsaturated ketone. The second product, always formed only in relatively small quantities, is a hydrocarbon which is doubtless formed from the primary product by loss of water.

A quantitative examination of the behavior of the primary product toward methyl magnesium iodide showed that it reacts with only one mole of the reagent and liberates one mole of gas; it therefore probably is a hydroxyl compound. It reacts with ozone and is in part converted into a peroxide, and in part oxidized to benzophenone and other products. These transformations indicate that the substance is a tertiary alcohol formed by addition to the carbonyl group. The results are, however, not quite conclusive because it was impossible to prove the presence of methyl benzoin in the ozonization products.

$$\underset{\text{I}}{(C_6H_5)_2C{=}C(C_6H_5)COC_6H_5} \longrightarrow \underset{\text{VI}}{(C_6H_5)_2C{=}C(C_6H_5)C(C_6H_5)(CH_3)OH} \longrightarrow$$

$$(C_6H_5)_2CO + C_6H_5COC(C_6H_5)(CH_3)OH$$

More definite proof of the structure of the substance was obtained by studying the hydrocarbon that is formed in the same reaction. This hydrocarbon can be obtained at will by heating the primary product with acetic anhydride and sodium acetate. When it is gently oxidized with chromic acid, it first combines with two atoms of oxygen and forms a diketone and when this diketone is oxidized more intensively it passes into ortho dibenzoyl benzene. The hydrocarbon is, therefore, methyl triphenyl indene and the primary product must be the carbinol, VI.



VI VII VIII

It proved to be far more difficult to establish the course of the reaction with phenyl magnesium bromide because, although the conditions under which the experiments were conducted were varied in every conceivable manner, the almost invariable result was a mixture of heavy oils from which but little solid product could be extracted. It was not until we adopted the device of decomposing the magnesium compound with acid at the lowest possible temperature and subjecting the product to the action of air or oxygen that we began to get solids in sufficient quantity for examination.

It is known from earlier experiments,[1] that when the enolic modifications which are obtained by 1,4-addition to such unsaturated ketones as contain a hydrocarbon residue in the α-position are exposed to oxygen they form peroxides. This procedure in our case likewise resulted in the addition of a molecule of oxygen but surprisingly enough the product had a deep yellow color. We were therefore confronted with the fact that we had started with a colorless unsaturated compound, added first the equivalent of a

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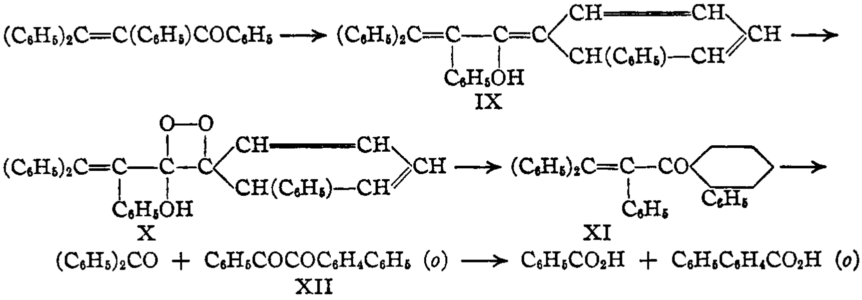
[1] Kohler, *Am. Chem. J.*, 36, 181 (1906).

molecule of benzene and then a molecule of oxygen, and had ended with a deep yellow product which to all appearances was more highly unsaturated than our original substance. The conclusion appeared inevitable that a benzene ring had become involved in the reaction. The transformations of the product confirmed this conclusion.

When the yellow peroxide was treated with cold sodium methylate, which usually cleaves these enolic peroxides, it lost oxygen and water and passed into a new yellow compound which had the composition $C_{33}H_{24}O$. This new yellow compound was subjected to the action of ozone, which, as usual, added two atoms of oxygen and gave two products—benzophenone and a third yellow substance with the composition $C_{20}H_{14}O_2$.

Inasmuch as a yellow compound that is formed by ozonization is most likely to be an α-diketone, we treated this yellow ozonization product with ortho phenylene diamine and found that it readily formed a glyoxaline derivative. Ortho diketones are most cleanly oxidized with alkaline hydrogen peroxide, which cleaves them between the two carbonyl groups. With this reagent our third yellow product gave, quantitatively, benzoic and ortho phenyl benzoic acids.

The organic degradation products of our peroxide are, therefore, benzophenone, benzoic acid and ortho phenyl benzoic acid. The ortho phenyl benzoic acid proves that one of the phenyl groups participates in the reaction, and when all the degradation products are reassembled in their proper order they show quite conclusively which of the phenyl groups is involved, the long series of transformations being represented as follows


IX

X

XI

$$(C_6H_5)_2CO + C_6H_5COCOC_6H_4C_6H_5\ (o) \longrightarrow C_6H_5CO_2H + C_6H_5C_6H_4CO_2H\ (o)$$

XII

In addition to the 1,4-addition product IX, there is formed a relatively small quantity of an unstable colorless compound. This substance liberates gas from methyl magnesium iodide and is capable of forming an acetate. Since it is colorless it cannot be the enol IX, but it might be either a rearrangement product of the enol (XIV) or the 1,2-addition product (XV)

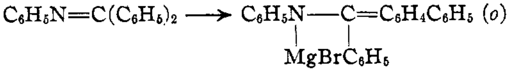
$$(C_6H_5)_2C{=}C(C_6H_5)CHOHC_6H_4C_6H_5\ (o) \qquad (C_6H_5)_2C{=}C(C_6H_5)C(C_6H_5)_2OH$$

XIV XV

In order to distinguish between these two possible formulas we oxidized the acetate and found that one mole of the substance gives one mole of benzoic acid and two moles of benzophenone, proving that the substance must be the 1,2-addition product. Our total yield of definite products is unsatisfactory; at best, we account for only 70% of the unsaturated ketone. But whether this low yield is due to the formation of other substances or the difficulty of isolating these unstable compounds we have been unable to ascertain.

Taken in their entirety, our results show that the most highly phenylated α,β-unsaturated ketone, like most other members of the series, is capable of forming both 1,2- and 1,4-addition products with organic magnesium compounds. Here, however, the resemblance ceases. In all other cases in which both types of addition occur, the relative quantity of the 1,4-addition product is always larger with alkyl than with aryl magnesium compounds. In our case these relations are completely reversed. Methyl magnesium bromide gives no 1,4-addition product, phenyl magnesium bromide but little of the 1,2-product.

A much more interesting difference, however, is represented by the fact that it is not, as in the case of all other members of this series, the ethylenic system but a phenyl group that is involved in 1,4-addition. The first—and only other—case of an addition of this type was reported last year. The two cases are not dissimilar. Gilman and his co-workers[2] found that benzophenone anil reacts with phenyl magnesium bromide only at a relatively high temperature, and that the reaction then consists in 1,4-addition and involves one of the phenyl groups



$$C_6H_5N{=}C(C_6H_5)_2 \longrightarrow C_6H_5\underset{\displaystyle MgBr}{\underset{|}{N}}{-\!-}\underset{\displaystyle C_6H_5}{\underset{|}{C}}{=}C_6H_4C_6H_5\ (o)$$

These two cases serve to diminish to some extent the difference between aromatic and ethylenic systems. It is clear that a phenyl group will participate in a reaction involving 1,4-addition when the hindrance to every other reaction is sufficiently great. It is far from clear, however, why there should be so much more hindrance to 1,2-addition in the unsaturated than in the saturated ketone.

Experimental Part

I. Preparation of Materials

No better methods were found for preparing either the saturated or the unsaturated ketones, but the yields have been improved greatly by modifying the procedure at nearly every stage. The steps involved in the preparation of the saturated ketone are shown in the following series of formulas

$$C_6H_5CHOHCOC_6H_5 \longrightarrow C_6H_5CH_2COC_6H_5 \longrightarrow C_6H_5CHClCH(C_6H_5)COC_6H_5 \longrightarrow$$
$$C_6H_5CH{=}C(C_6H_5)COC_6H_5 \longrightarrow (C_6H_5)_2CHCH(C_6H_5)COC_6H_5$$

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[2] Gilman, Kirby and Kinney, This Journal, **51**, 2252 (1929).

For the reduction of benzoin to desoxybenzoin we used zinc and glacial acetic acid as recommended by Sudborough,[3] but by introducing an effective mechanical stirrer and by raising the temperature from that of the steam-bath to that of the boiling point of the liquid we not only greatly decreased the time of heating but improved the yield as well. The success of this method depends almost entirely on the quality of the zinc dust. With the finely powdered zinc which is frequently sold as zinc dust the yield is small. Instead of separating a part of the product by crystallization we found it advantageous to subject the entire product to distillation under diminished pressure.

Desoxybenzoin.—Two lots, each of 346 g. of benzoin, 600 g. of glacial acetic acid and 105 g. of zinc dust contained in a flask provided with a mechanical stirrer and an air condenser, were heated in an oil-bath at the boiling point of the liquid until a sample no longer gave a flocculent precipitate when it was dropped into water (four to five hours). The benzoin was first dissolved in the acid heated to about 115°, then the zinc dust was added as rapidly as possible without causing frothing, and finally the temperature was raised to the boiling point.

The solution was poured into hot water, the mixture boiled until the oil collected on the bottom, then cooled and filtered. The solid was washed with water and dissolved in alcohol. After removal of the zinc, the alcoholic solution was distilled under ordinary pressure until free from alcohol, then fractionated under diminished pressure. The yield was 534 g. of desoxybenzoin, equal to 82%.

β-Chloro Benzyl Desoxybenzoin.—The desoxybenzoin obtained in the preceding experiment was dissolved in 350 g. of benzaldehyde, the solution cooled in a freezing mixture, and saturated with hydrogen chloride which was passed into it for seven to eight hours. After standing overnight the resulting solid cake was broken up under alcohol, washed—first with alcohol, then with ether—and dried. The yield was 622 g. of chloro compound from 534 g. of desoxybenzoin, equal to 71%.

Benzal Desoxybenzoin.—A suspension of 250 g. of *p*-chloro benzyl desoxybenzoin, 200 g. of fused potassium acetate and 65 g. of dry sodium carbonate in one liter of methyl alcohol was boiled with constant vigorous mechanical stirring for three hours, then cooled and filtered. The solid was washed with sufficient water to remove inorganic salts completely. Its melting point was 100°, only 1° below that of the pure substance, which was obtained by one crystallization from ether. The yield is 180 g.—equivalent to 81%.

The Saturated Ketone (II).—To a solution of phenyl magnesium bromide prepared from 10 g. of magnesium, 50 g. of finely ground benzal desoxybenzoin was added as fast as it dissolved. The mixture was heated for a short time, then cooled and decomposed with ammonium chloride and ammonia in the usual manner. It yielded 61 g. of pure ketone equivalent to 95.8%.

The saturated ketone cannot be brominated. The route to the unsaturated ketone, therefore, follows the course

$$C_6H_5CH{=}C(C_6H_5)COC_6H_5 \longrightarrow (C_6H_5)_2CHC(C_6H_5){=}C(OMgBr)C_6H_5 \longrightarrow$$
$$(C_6H_5)_2CHC(C_6H_5)BrCOC_6H_5 \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)COC_6H_5$$

For the purpose of preparing the α-bromo compound, 100 g. of finely ground benzal desoxybenzoin was added to a solution of phenyl magnesium bromide made from 20 g. of magnesium. The mixture was heated for a short time, then cooled in a freezing mix-

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[3] Sudborough, *J. Chem. Soc.*, **71**, 219 (1897).

ture. To it was added, with constant stirring and very slowly, to avoid local rise in temperature, 120 g. of bromine which had been dried over phosphorus pentoxide. The mixture was poured into ice and hydrochloric acid and shaken until solid began to separate. The ethereal layer was then diluted with petroleum ether. The resulting solid was washed with water, a mixture of ether and petroleum ether and finally petroleum ether alone. The yield of α-bromo compound was 133 g., equivalent to 87%.

The Unsaturated Ketone.—A suspension of 130 g. of the α-bromo compound and an equal weight of potassium acetate in 650 g. of dry ethyl alcohol was boiled for two hours with sufficiently rapid stirring to prevent bumping. Most of the unsaturated ketone separates on cooling, mixed with potassium chloride. After washing and drying it is sufficiently pure for most purposes. The remainder of the product is obtained by distilling off most of the alcohol, diluting the residue with water and extracting with ether. This is less pure and needs to be recrystallized from chloroform and alcohol. The yield was 94.5 g., equal to 89%.

II. Experiments with the Saturated Ketone

2,3,4,4,-Tetraphenyl Butanol-2 (III).—Fifteen grams of the finely ground saturated ketone was added to a solution of phenyl magnesium bromide made from 4 g. of magnesium. There was no perceptible warming and no change in color but the solid gradually dissolved. After remaining for two hours at the ordinary temperature, the clear solution was decomposed with iced ammonium chloride in the usual manner. The washed and dried ethereal layer, on evaporation, left a solid. This was recrystallized from methyl alcohol. The yield was 12.5 g. of pure product and 2 g. of material, largely composed of the same substance as the principal product.

Anal. Calcd. for $C_{28}H_{26}O$: C, 88.8; H, 6.9. Found: 88.4; H, 7.0.

The carbinol is readily soluble in all common organic solvents except petroleum ether. It crystallizes in long, flat needles and melts at 140°. It appears to be stable in the air but its melting point gradually drops when it is kept over sulfuric acid in a vacuum desiccator.

2,3,4,4-Tetraphenyl Butene (IV).—A solution of one gram of the hydroxyl compound in the requisite quantity of glacial acetic acid containing two drops of sulfuric acid was set aside for twelve hours. It deposited 0.71 g. of a colorless solid and when the acid was pumped off it left 0.2 g. more of the same substance. The substance is quite readily soluble in all common organic solvents including petroleum ether. It was recrystallized from methyl alcohol, from which it separated in needles melting at 104–106°.

Anal. Calcd. for $C_{28}H_{24}$: C, 93.3; H, 6.7. Found: C, 93.2; H, 6.9.

Ozonization.—A current of ozonized oxygen containing about 6% of ozone was passed through a solution of 2 g. of the hydrocarbon in ethyl bromide for two hours. A considerable quantity of a crystalline solid separated from the solution during the passage of the ozone and more of the same substance was obtained when the ozonized solution was manipulated in the usual manner. The solid had the melting point of the saturated ketone—tetraphenyl propanone—and it caused no depression of the melting point when it was mixed with this ketone. The saturated ketone was likewise obtained when the hydrocarbon was oxidized with permanganate.

1,1,2,3,3-Pentaphenyl Propanol-1 (V).—A solution of 5 g. of the saturated ketone in dry benzene was added to a solution of phenyl magnesium bromide which had been made from 1.4 g. of magnesium and cooled in a freezing mixture. After the addition, the solution was stirred at the ordinary temperature for an hour. A test made at this time still showed much unchanged ketone. The mixture was therefore set aside for seven hours, then decomposed with iced acid in the usual manner. In addition to much oil, it gave 3.0 g. of a solid melting at 158–159°—a yield of about 33%.

All attempts to reduce the quantity of oil and increase the yield of the solid carbinol were unsuccessful. Lowering the temperature and stopping the reaction sooner resulted in mixtures of products and unchanged substance which were difficult to handle, and decomposing with ice and ammonium chloride in place of hydrochloric acid had no effect on the yield.

The solid product was purified by crystallizing it from methyl alcohol, from which it separates in the form of small white prisms melting at 159°.

Anal. Calcd. for $C_{33}H_{28}O$: C, 90.0; H, 6.4. Found: C, 89.5; H, 6.8.

A test by the Zeisel method showed that the substance has no alkoxyl group, and a quantitative examination of its reaction with a solution of methyl magnesium iodide in iso-amyl ether showed that it reacts with one mole of the reagent and liberates one mole of gas.

Oxidation.—All attempts to eliminate water from the hydroxyl compound led to unmanageable oils. The compound was therefore oxidized with excess of chromic acid in hot glacial acetic acid. To this end one gram of the substance in glacial acetic acid was treated with excess of chromic acid and heated on a steam-bath for two hours. It yielded 0.73 g of benzophenone and 0.16 g. of benzoic acid, instead of 0.83 g. of the former, 0.2 g. of the latter assuming that one mole of substance gives two moles of the ketone and one mole of the acid.

III. Experiments with the Unsaturated Ketone

A. Reaction with Methyl Magnesium Iodide

The reaction between methyl magnesium iodide and the unsaturated ketone was carried out a great many times. In the early experiments we became convinced that the reaction would not run in ether alone, no matter how prolonged the boiling. We then turned to benzene and found that the minimum temperature at which the reaction would run at an appreciable rate was about 50°.

In subsequent experiments, therefore, we used four equivalents of the reagent, replaced the ether with benzene, heated for periods ranging between forty minutes and ten hours and decomposed sometimes with ice and acid, sometimes with ice and ammonium chloride. The yields of carbinol varied from 53.6 to 63.4%. In addition to the carbinol the product usually contained small quantities of its dehydration product—methyl triphenyl indene. No evidence was found for any 1,4-addition product. The lack of color showed conclusively that no phenyl group was involved in the reaction, and the inability to obtain a peroxide was good even if inconclusive evidence that no other type of 1,4-addition had occurred.

2,3,4,4-Tetraphenyl Butenol-2 (VI).—A solution of 10 g. of the unsaturated ketone in 60 cc. of dry benzene was added rapidly to a solution of methyl magnesium iodide which had been prepared in an atmosphere of dry nitrogen from 2.72 g. of magnesium. The mixture was heated to 60° for ten hours while a current of dry nitrogen was passed through the apparatus. After decomposing the magnesium compounds with ice and ammonium chloride in the usual manner, the benzene–ether layer was washed, dried and evaporated in a current of dry air. It deposited a solid which after washing with petroleum ether melted at 96.5°, therefore was pure carbinol. The petroleum ether washings yielded 0.8 g. of methyl triphenyl indene. The rest was oil.

The carbinol dissolves freely in all common organic solvents except petroleum ether. It crystallizes well from ether and petroleum ether and it can also be recrystallized from methyl alcohol and water. It separated in white plates and melts at 96.5°.

Anal. Calcd. for $C_{28}H_{24}O$: C, 89.4; H, 6.4. Found: C, 89.5; H, 6.7.

Proof of Hydroxyl Group.—One mole of the substance reacted with one mole of methyl magnesium iodide and liberated one mole of methane.

Proof of Double Linkage.—The carbinol was ozonized in ethyl bromide with ozonized oxygen containing 6% ozone. The product, decomposed with ice in the usual manner, and then set aside, slowly deposited a small quantity of solid. After recrystallization from alcohol the solid melted with decomposition at about 148°. Its composition corresponds to that of a peroxide of the carbinol and it flashed when it was heated rapidly.

Anal. Calcd. for $C_{28}H_{24}O{\cdot}O_2$: C, 82.4; H, 5.9. Found: C, 82.3; H, 6.0.

The oil that was left after the removal of the peroxide was distilled with steam. The oil in the distillate formed an oxime which melted at 141° and a phenylhydrazone melting at 138°, therefore was benzophenone.

Conversion into Methyl Triphenyl Indene.—A solution of one gram of the carbinol and the same quantity of sodium acetate in acetic anhydride was boiled for five hours, then poured into water and made alkaline with excess of sodium carbonate. The alkaline solution was extracted with ether, the ethereal layer washed, dried and evaporated. It left a solid which after washing with a little ether proved to be pure methyl triphenyl indene. The yield was 0.67 g.

Methyl Triphenyl Indene (VII).—The indene derivative, as has been shown, can be obtained in an excellent yield by heating the carbinol with a suitable condensing agent. It was generally obtained in small quantities as a by-product of the Grignard reaction. In one experiment, 50 g. of the ketone gave 12 g. of the pure indene derivative. Whether this uncommonly large yield was formed during the reaction or during the decomposition of the magnesium derivatives with hydrochloric acid could not be ascertained because we were unable to duplicate the result. The indene crystallizes from absolute ethyl alcohol in the form of prisms melting at 118°.

Anal. Calcd. for $C_{28}H_{22}$: C, 93.9; H, 6.2; mol. wt., 358. Found: C, 93.8; H, 6.2; mol. wt., 320.

Oxidation: α,α,α-Benzoyl-methyl-phenyl-ortho-tolyl Phenyl Ketone (VIII).—A solution of 1.5 g. of the hydrocarbon and 1.2 g. of chromic acid in glacial acetic acid was warmed until oxidation began at 50–60°. The temperature was held at this point for fifteen minutes. The solution was then diluted with water and extracted with ether. The washed and dried ethereal solution was concentrated and diluted with petroleum ether, whereupon it deposited a solid. The solid was recrystallized from anhydrous ether, from which it separated in white prisms melting at 182°.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.2; H, 5.6. Found: C, 86.4; H, 5.2.

Ortho Dibenzoyl Benzene.—The oily mother liquors from the diketone were oxidized with a larger quantity of chromic acid. The principal product was *o*-dibenzoyl benzene, which was identified by comparison with a sample on hand. Ortho dibenzoyl benzene was also one of the products formed when the oily by-products of the Grignard reaction were oxidized with excess of chromic acid.

B. Reaction with Phenyl Magnesium Bromide

A series of preliminary experiments showed that the unsaturated ketone does not react with phenyl magnesium bromide in boiling ether and that when the reaction was carried out in boiling benzene no solid products could be isolated. We used, therefore, a large excess of the reagent—usually four equivalents—and operated at temperatures between 45–60°. The procedure most favorable for securing the peroxide was the least favorable for isolating the unstable 1,2-addition product. Moreover, the acetate of the 1,2-addition product was most easily obtained directly from the magnesium derivative

$$(C_6H_5)_2C{=}C(C_6H_5)COC_6H_5 \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)C(C_6H_5)_2OMgBr \longrightarrow$$
$$(C_6H_5)_2C{=}C(C_6H_5)C(C_6H_5)_2OCOCH_3$$

The Peroxide (X).—A solution of 15 g. of the ketone in 90 cc. of benzene was added drop by drop to an ethereal solution of phenyl magnesium bromide that was made from 4.08 g. of magnesium. Each drop of the solution produced a momentary red color, which turned to yellow, but by the time all of the ketone had been added, the color of the solution was dark red to brown. Ether was boiled off until the boiling point of the solution reached 50–52°.

After the solution had been boiled at 50–52° for an hour, it was cooled and poured into iced hydrochloric acid contained in a separating funnel. The mixture was shaken vigorously, the acid layer drawn off and the ethereal layer rapidly washed with ice water. The washed ethereal solution was then transferred to a suction flask which was cooled with ice while a rapid current of air was drawn through it. A yellow precipitate soon began to separate. This was collected on a filter when the solution became too thick; a second crop was obtained by diluting the oily residue with ether and repeating the operation, and a third by treating the oil with ether and petroleum ether. The total yield was 7.3 g., equivalent to 37.3%.

The peroxide was recrystallized from ether, from methyl alcohol, and from chloroform, but it is doubtful that this increased its purity. Its melting point varied with the mode of heating, the highest being 186.5°.

Anal. Calcd. for $C_{33}H_{26}O_3$: C, 84.3; H, 5.5. Found: C, 84.0; H, 6.0.

In the machine one mole of the compound consumed three moles of methyl magnesium iodide and liberated one mole of gas. The peroxide crystallizes in long yellow prisms.

Ozonization.—The peroxide was oxidized with ozone in the usual manner but the results were not very instructive. It gave a considerable quantity of benzophenone, showing that the ethylene linkage was intact but, as was to be expected, the remainder of the molecule was converted into highly colored oils from which only benzoic acid could be isolated.

Reaction with Sodium Methylate. The Unsaturated Ketone (XI).—When the peroxide is added to a concentrated solution of sodium methylate in methyl alcohol it dissolves in part and forms a brilliant red solution, but the ketone begins to separate before solution is complete. The reaction appears to be complete in an hour, but the mixture was usually set aside overnight. Thus 2.5 g. of the finely ground peroxide was added to 20 cc. of 10% sodium methylate. The mixture was set aside for fifteen hours, then diluted with water and extracted with ether. The washed and dried yellow ethereal solution, on evaporation, deposited 2.45 g. of crude product. This was washed with methyl alcohol and further purified by recrystallization from the same medium. The yield of pure ketone was 1.6 g., equivalent to 69%.

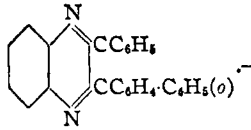
Anal. Calcd. for $C_{33}H_{24}O$: C, 90.8; H, 5.5; mol. wt., 436. Found: C, 90.9; H, 5.6; mol. wt., 412.

The color of the ketone is a lighter yellow than that of the peroxide. It crystallizes in long plates and melts at 138°.

Ozonization: Ortho Phenyl Benzil (XII).—A current of ozonized oxygen containing about 6% of ozone was passed through a solution of one gram of the ketone in ethyl bromide for one and one-half hours. The ozonide was decomposed in the usual manner and the solvent removed. The residue was an oil which partially solidified when it was rubbed with alcohol. The resulting solid was recrystallized from alcohol, from which it separated in pale yellow plates melting at 80°.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. Found: C, 83.5; H, 5.3.

The filtrate from the diketone was distilled with steam and the distillate extracted with ether. The ethereal solution contained benzophenone, which was identified by converting it into phenylhydrazone and comparing this with a sample on hand.

The Glyoxaline Derivative, 

.—An alcoholic solution of 0.1 g. of the diketone, 0.09 g. of ortho phenylene diamine hydrochloride and an equivalent quantity of sodium acetate was boiled for a short time, then diluted with water and extracted with ether. The ethereal extract was freed from excess of the diamine by shaking with dilute acid, then washed, dried and evaporated. It deposited a colorless solid. The solid was recrystallized from alcohol, which deposited it in large square plates which melted at 163°.

Anal. Calcd. for $C_{26}H_{18}N_2$: C, 87.1; H, 5.0. Found: C, 86.6; H, 5.1.

Oxidation of the Diketone: Ortho Phenyl Benzoic Acid.—A solution of 0.2 g. of the diketone in methyl alcohol was treated first with excess of 15% hydrogen peroxide, then with excess of 10% sodium hydroxide. It soon became colorless. It was then heated to remove the methyl alcohol, and acidified. From the acid solution ether extracted 0.23 g. of a mixture of acids which could not be separated by steam distillation, but which was readily separated by sublimation. The sublimate was benzoic acid. The residue (0.15 g.) melted at 113°. It was identified as ortho phenyl benzoic acid by comparison with a sample of this acid which was obtained by fusing fluorenone with potassium hydroxide.

Triphenylvinyl Diphenyl Carbinol (XV).—A solution of 10 g. of the ketone was added in the usual manner to a solution of phenyl magnesium bromide made from 2.7 g. of magnesium. The mixture was heated to 60° for two hours, then decomposed with iced hydrochloric acid. The ethereal layer was washed, dried and then evaporated in a draught. It first deposited the yellow peroxide, and later a colorless solid which was purified by recrystallization from ether–petroleum ether; yield, 12%.

Anal. Calcd. for $C_{33}H_{26}O$: C, 90.4; H, 5.9. Found: C, 90.1; H, 6.0.

The carbinol is sparingly soluble in alcohol, moderately soluble in ether. It crystallizes in thin white plates. It melts with decomposition, and the melting point varies with the rate of heating. The highest melting point observed was 169°. Even the purest samples slowly change at the ordinary temperature, turning ultimately into brown viscous oils, but it can be kept apparently without change at 0°.

The Acetate (XVI).—The acetate was first obtained by boiling a solution of the carbinol for seventeen hours with acetyl chloride and then distilling off the excess of the chloride. It is made much more easily directly from the magnesium derivative of the carbinol. Thus a solution of 25 g. of the ketone in benzene was added to an ethereal solution of phenyl magnesium bromide which contained 6.8 g. of magnesium. The mixture was kept for one hour at 50°, then cooled in a freezing mixture. Into the cooled solution was dropped a mixture of 33 g. of acetyl chloride and twice its volume of absolute ether. The brilliant red solution was allowed to reach the temperature of the room, then decomposed with ice and acid in the usual manner.

The ethereal layer was thoroughly washed with water, dried and concentrated. It yielded 10.6 g. of the same acetate that had been obtained from the carbinol. It was purified by recrystallization from chloroform and ether.

Anal. Calcd. for $C_{35}H_{28}O_2$: C, 87.5; H, 5.8. Found: C, 87.5; H, 6.2.

The acetate is readily soluble in benzene and in chloroform, very sparingly soluble in ether and in alcohol. It crystallizes in colorless plates and melts at 218°.

Oxidation.—A solution of one gram of the acetate and an equal weight of chromic acid in glacial acetic acid was heated on a steam-bath for about an hour, then cooled and diluted with ice and ether. The ethereal layer was shaken with sodium carbonate, which extracted benzoic acid, then dried and evaporated. The residue when distilled with steam yielded 0.61 g. of pure benzophenone.

Summary

When tetraphenyl propenone reacts with phenyl magnesium bromide, the principal product is a diphenyl derivative which is formed by 1,4-addition to the system $-CO-C_6H_5$.

Converse Memorial Laboratory
Cambridge, Massachusetts

[Contribution from the Department of Chemistry, Yale University]

THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. V

By W. S. Hinegardner[1] and T. B. Johnson

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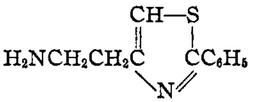
In Paper IV of this series, Hinegardner and Johnson[2] have described the synthesis of 2-phenylthiazole-4-ethylamine, expressed structurally by formula I. This is a representative of a new type of aliphatic amines in which the thiazole nucleus has been substituted for a methylene *radical* in γ-phenylpropylamine. It is a bridged thiazole compound of pharmacological interest and is only one of a series of compounds of its type which may be prepared by our method of synthesis. In this paper we describe a series of intermediate compounds which have been prepared in the development of a practical synthesis of 2-*p*-hydroxyphenylthiazole-4-ethylamine, XIV. This latter amine bears the same relationship to tyramine III as the thiazole amine I does to phenylethylamine II. It is a very potent substance biologically and its pharmacological activity is being investigated.



I

$C_6H_5CH_2CH_2NH_2$

II

$HOC_6H_4CH_2CH_2NH_2$

III

The starting points for our research were *sym.*-dichloro-acetone and the thioamide of anisic acid. These interact smoothly when warmed together in alcoholic solution, giving an excellent yield of the primary halide IV. Utilizing then the same technique as was described in our previous paper[2] for the preparation of the amine I, the various transformations recorded in Table I have been carried through successfully, leading up to the desired amine, XIV. The experimental data establishing the constitution and chemical identity of these various thiazoles are recorded in Table II.

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[1] Metz Research Fellow in Organic Chemistry, 1928–1929.

[2] Hinegardner and Johnson, This Journal, 52, 3724 (1930).