Summary

1. The monophenyl and monomethyl esters of α-phenyl-β-bromo-β-p-chlorobenzoylethyl-phosphonic acid have been prepared and their behaviors in alkaline solution studied.

2. The two stereo-isomeric bromomonophenyl esters form stable sodium salts but are decomposed in alkaline solution with the formation of an unsaturated ketone and the elimination of the bromine atom and the phosphonic acid group from the molecule. The speed of the decomposition is proportional to the hydroxyl-ion concentration. The reaction does not proceed through an initial hydrolysis of the ester group since the hydrolysis of the unbrominated ester is relatively a very slow reaction. The rate of decomposition of one of the stereo-isomers of α-phenyl-β-bromo-β-benzoylethylphenyl-phosphonic acid is also proportional to the hydroxyl-ion concentration.

3. The bromomonomethyl ester is stable in neutral solutions but easily loses the bromine atom in alkaline solution, although the phosphonic acid group is not removed in this reaction. The product is probably an unsaturated or hydroxy phosphonic acid.

4. These facts cannot be explained in terms of a mechanism involving the intermediate formation of a β-phostone. It is suggested that the first step is the interaction of the organic molecule and the hydroxyl ion with the formation of an unstable ionized hydroxyl compound. The decomposition of this intermediate compound could take place in several ways corresponding to the several products obtained by the action of alkalies on different types of bromophosphonic acids.

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THE ADDITION REACTIONS OF CERTAIN PENTADIENONES
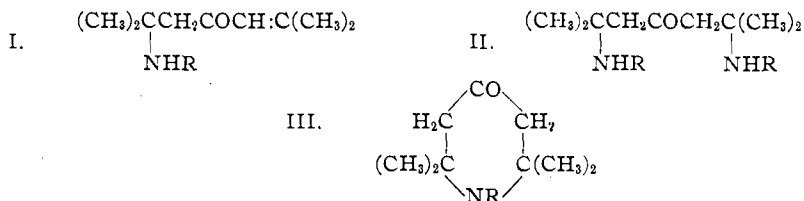
BY E. P. KOHLER AND R. W. HELMKAMP

The addition reactions of pentadienones of the type represented by phorone and dibenzal-acetone have been the subject of many investigations. As a result it is known that under the influence of basic condensing agents these ketones combine with a great variety of substances that have reactive hydrogen. The mode of addition is in all cases the same but the ease of addition depends upon the character of the groups in the β-position, and when these groups are aromatic it is affected to a quite remarkable degree by substitution in the nucleus. Thus Vorländer,[1] using an equivalent of sodium alcoholate, was able to add malonic ester to phorone but failed to get definite products with dibenzal-acetone, and

[1] Vorländer, Ann., 304, 1 (1899).

Borsche[2] using piperidine found it impossible to add aceto-acetic ester to dianisal-acetone, tetramethyldiamido dibenzal-acetone and dicinnamal-acetone, under conditions under which it added to dibenzal-acetone with the greatest ease.

Another peculiarity that has been observed in the addition reactions of these doubly unsaturated ketones is that it is generally much more difficult to add two than one molecule of any substance to one of the ketone.   Indeed in many cases it has been found quite impossible to add more than one molecule even though the product is still an α, β-unsaturated ketone and as such readily combines with bromine and reduces permanganate.   Kohler and Reimer,[3] for example, found that while dibenzal-acetone combines very readily with sulfinic acids, it is impossible to add more than one molecule.   Similarly, Borsche[2] met with no difficulty in adding malonic ester to dibenzal-acetone in the presence of piperidine, but no matter how large the excess of malonic ester, he could isolate only the product that contained one molecule of ester to one of ketone.   Conant, Bump and Holt,[4] using phosphorus trichloride, a reagent of an entirely different type, likewise found it impossible to isolate a product containing more than one molecule to one of dibenzal-acetone.

The cases cited seem to indicate a decided hindrance to the addition of more than one molecule of a substance to the aromatic dienones. Whether this hindrance also operates to prevent the saturation of the ketone by intramolecular condensation to a cyclohexanone derivative is not clear from the published facts.   Thus while ammonia and amines combine with phorone to form all possible types of addition products, only the substance corresponding to Type II has been obtained by adding malonic ester to this ketone, and only substances of Type I by adding malonic and aceto-acetic ester to dibenzal-acetone.   Cyclohexanone derivatives of Type III have, heretofore, been obtained only with ammonia and its derivatives.

I.
$$(CH_3)_2CCH_2COCH:C(CH_3)_2$$
$$\overset{|}{NHR}$$

II.
$$(CH_3)_2CCH_2COCH_2C(CH_3)_2$$
$$\overset{|}{NHR} \qquad \overset{|}{NHR}$$

III.
$$\begin{array}{c} CO \\ H_2C \qquad CH_2 \\ | \qquad | \\ (CH_3)_2C \qquad C(CH_3)_2 \\ NR \end{array}$$
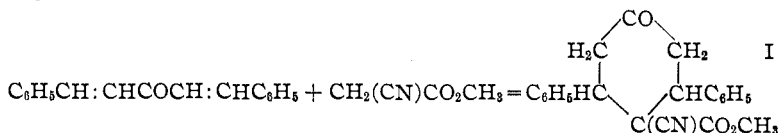
Our results with dibenzal-acetone and methyl cyano-acetate indicate that there is no hindrance whatsoever to the formation of cyclohexanone derivatives.   In the presence of a small quantity of sodium methylate

[2] Borsche, *Ann.*, **375**, 145 (1910).

[3] Kohler and Reimer, *Am. Chem. J.*, **31**, 163 (1904).

[4] Conant, Bump and Holt, THIS JOURNAL, **43**, 1677 (1921).

or sodium hydroxide the two substances react rapidly in accordance with
the equation

$$C_6H_5CH:CHCOCH:CHC_6H_5 + CH_2(CN)CO_2CH_3 = C_6H_5HC\begin{matrix} CO \\ H_2C \quad CH_2 \\ CHC_6H_5 \\ C(CN)CO_2CH_3 \end{matrix} \quad I$$

No unsaturated open-chained ketone of Type I could be found in the
product and no saturated compound of Type II was formed even when
the ester was used in great excess.

Our experiments also fail to disclose any such marked difference in the
activity of dibenzal-acetone and dianisal-acetone as is implied by the
results obtained by Borsche with aceto-acetic ester and piperidine. When
a small amount of sodium methylate solution is added to a suspension
of dianisal-acetone in methyl alcohol containing methyl cyano-acetate
somewhat in excess of one equivalent, the ketone, which is very sparingly
soluble in methyl alcohol, dissolves readily on vigorously shaking the
mixture. Almost immediately the cyclohexanone derivative begins to
crystallize from the solution.

It is not a difficult matter to differentiate between these cyclohexanone
derivatives and open-chained addition products of Types I and II; they
do not, like the former, reduce permanganate and they differ from the
latter in composition. They have an active carbonyl group, hence are
extracted from ethereal solution by sodium bisulfite and form acetals
with surprising ease.

Experimental Part

Dibenzal-acetone and Methyl Cyano-acetate

The condensation may be brought about either with sodium methylate
or with sodium hydroxide. The cyclohexanone derivative which results
is capable of existing in stereoisomeric forms, and the one which is at
first obtained is readily transformed by means of a small amount of sodium
hydroxide into a form more stable toward alkali.

Condensation with Sodium Methylate.—A few drops of a sodium methylate solution
were added to a hot saturated solution of dibenzal-acetone in methyl alcohol containing
a little more than one equivalent of methyl cyano-acetate. The mixture on cooling
completely solidified. The solid was recrystallized from methyl alcohol, from which
it separated as a woolly mass of fine, white filaments; m. p.,137–138°.

Analyses. Calc. for $C_{21}H_{19}O_3N$: C, 75.7; H, 5.8. Found: C, 75.5; H, 5.8.

Methyl 1-Cyano-2,6-diphenyl-4-keto-cyclohexanoate, (I) dissolves readily in
chloroform, acetone, and benzene, moderately in carbon tetra-chloride, sparingly in ether
and cold methyl alcohol. It does not reduce a solution of permanganate in acetone.

Condensation with Sodium Hydroxide.—This condensation is a good illustration
of the remarkable ease with which these addition reactions take place. When aqueous
sodium hydroxide is added to a suspension of dibenzal-acetone in a cold methyl alcoholic

solution containing methyl cyano-acetate somewhat in excess of one equivalent, the liquid warms at once, and the ketone, which is quite sparingly soluble in cold methyl alcohol, disappears in a very short time. This solution, on immediate cooling under the tap, quickly deposits the cyclohexanone derivative that has just been described. When this is allowed to remain in contact with the alkaline liquid, it begins to redissolve, and when the solution becomes clear it contains only an isomeric cyclohexanone derivative. A very satisfactory procedure for getting this product is as follows.

Three cc. of 10% aqueous sodium hydroxide and 6.5 cc. of methyl cyano-acetate are added to 15 g. of dibenzal-acetone suspended in 200 cc. of methyl alcohol. The mixture becomes warm and solution is complete in about a minute. The solution is cooled under the tap, whereupon it is transformed through the separation of the white condensation product into a semi-solid mass. The addition of 50 cc. of methyl alcohol facilitates the shaking of the mixture. It is shaken on the machine until all of the solid has redissolved—from one and a half to two hours—and the solvent then evaporated in a draft, distilled under diminished pressure, or neutralized with acetic acid and distilled under ordinary pressure. Hydrochloric acid must not be used for neutralizing the base because in the presence of the alcohol this acid induces the formation of acetals. The oily residue, left after removing the alcohol as completely as possible, is dissolved in ether, the ethereal solution washed with water, dried and concentrated. The ether deposits the new product in stout prisms which after recrystallization from ether or, better, from mixtures of ether and petroleum ether melt at 146°. The yield is 15.5 g., or about 72%.

Analyses. Calc. for $C_{21}H_{19}O_3N$: C, 75.7; H, 5.8. Found: C, 75.3; H, 5.8.

Although this substance has a higher melting point than its isomer, it is much more readily soluble in the ordinary solvents and, therefore, better adapted for transformation. It does not reduce permanganate.

The Bisulfite Addition Product.—The cyclohexanone derivative (146°) is completely extracted from an ethereal solution when this is shaken with a saturated aqueous solution of sodium bisulfite. The addition product appears as a liquid layer between the two solutions and as a sticky film adhering to the glass walls of the container. Although it was not obtained in a form suitable for analysis, there is no doubt as to the nature of the substance. It is readily and completely soluble in water, and when sodium carbonate is added to the clear water solution it reprecipitates the condensation product.

The Oxime.—Solutions of 3.2 g. of hydroxylamine hydrochloride and 5.5 g. of sodium hydroxide, each in 10 cc. of water, were added to a solution of 5 g. of the condensation product (146°) in 175 cc. of methyl alcohol. The mixture was allowed to stand at a temperature near the freezing point for three days, then evaporated in a draft and finally diluted with water. This precipitated a solid which was freed from inorganic material by solution in ether and, after removal of the ether, purified by recrystallization from methyl alcohol; yield, 5 g.

Analysis. Calc. for $C_{21}H_{20}O_3N_2$: N, 8.1. Found: 8.3.

The oxime is moderately soluble in ether and in methyl alcohol; it crystallizes in glistening white plates, and melts at 190°.

Acetal Formation.—The condensation products form acetals with quite unexpected ease doubtless, in part at least, because the acetals are solids that are sparingly soluble in the alcohols. The ease of formation of these compounds first became evident in a condensation experiment with methyl cyano-acetate and dianisal-acetone when, instead of using acetic acid to neutralize the catalyst as had been done in some previous experiments with dibenzal-acetone, a small amount of hydrochloric acid was employed for this purpose. The methyl acetal of the condensation product from dibenzal-acetone was subsequently made by passing dry hydrogen chloride into a solution of 4 g. of the

cyclohexanone derivative (146°) in 50 cc. of dry methyl alcohol cooled by ice water. The white solid began to separate after a minute, but the current of gas was continued for an additional two minutes. The mixture was set aside for 15 minutes, then filtered and the solid washed with a little methyl alcohol. This left 4.3 g. of solid melting at 172–174°. After a few recrystallizations of the substance from a mixture of chloroform and methyl alcohol the melting point became constant at 181°.

Analyses. Calc. for $C_{23}H_{25}O_4N$: C, 72.8; H, 6.6. Found: C, 73.1; H, 6.6.

THE METHYL ACETAL.—The methyl acetal is sparingly soluble in methyl alcohol, readily soluble in chloroform. It crystallizes in long, lustrous prisms.
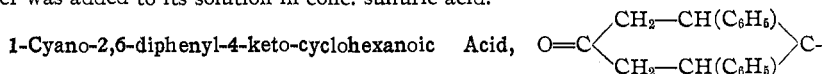
THE ETHYL ACETAL.—The ethyl acetal was first made like the corresponding methyl compound and its character was confirmed by also preparing it by Claisen's method of making ketone acetals. For this purpose a solution of 2 g. of the condensation product (146°), 1.5 g. of ethyl orthoformate, and a trace of ammonium chloride in 50 cc. of dry ethyl alcohol was boiled for about an hour, concentrated to a third of its volume and allowed to cool. The solid that separated was found to be identical with that formed by using hydrogen chloride. The acetal was purified by recrystallization from alcohol.

Analyses. Calc. for $C_{25}H_{29}O_4N$: C, 73.7; H, 7.2. Found: C, 73.9; H, 7.3.

When freshly prepared the acetal melts at 151–152°. The melting point soon begins to drop, however, and by the following day may be as low as 135–145°. After one re-crystallization from alcohol the substance melts again at 151–152°.

Bromination.—Wallach[5] found that it was possible to get very definite dibromo sub-stitution products of cyclohexanone and its simpler alkyl derivatives by brominating in cold glacial acetic acid. Our condensation products reacted with bromine very readily under these conditions, but the results were far from definite. The slow addition of about two molecular equivalents of bromine to the cyclohexanone derivative (146°) suspended in cold glacial acetic acid, resulted in a mixture of brominated products which melted with decomposition. Analyses showed, even after repeated recrystallization of the material, a bromine content 1–2% higher than that required by the dibromo com-pound.

Hydrolysis.—The cyanogen group in the cyclohexanone derivative, as in most tertiary nitriles, resists hydrolysis. The substance was recovered without change when water was added to its solution in conc. sulfuric acid.

1-Cyano-2,6-diphenyl-4-keto-cyclohexanoic Acid, $O = C \underset{CH_2-CH(C_6H_5)}{\overset{CH_2-CH(C_6H_5)}{\diagup \diagdown}} C-$

(CN)CO_2H.—The ester group, in the condensation product, is hydrolyzed with ease. Thus when 60 cc. of a methyl alcohol solution of potassium hydroxide (300 g. per liter) was added to 25 g. of the substance (146°), which was suspended in 100 cc. of methyl alcohol, it dissolved immediately with appreciable evolution of heat. The solution turned red overnight. Most of the alcohol was evaporated in a current of air, the residue diluted with water and the mixture extracted with ether. This removed 2.7 g. of un-changed ketone. The aqueous layer, when treated in the usual way yielded 15.8 g. of pure acid. The acid can be purified by drying it in ethereal solution, evaporating the ether, and cautiously adding petroleum ether to a solution of the dry residue in acetone. From this mixture it separates in needles when it is precipitated rapidly, and in large colorless prisms when the mixed solvents are allowed to evaporate slowly. The acid when thus purified contains a molecule of acetone.

Analyses. Calc. for $C_{20}H_{17}O_3NC_3H_6O$: C, 73.2; H, 6.2. Found: C, 73.1; H, 6.2.

The presence of the acetone was established by heating the substance to about 165°
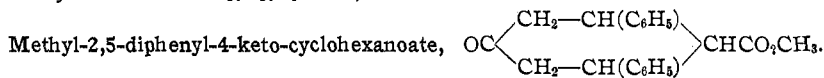
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⁵ Wallach, *Ann.*, **414**, 271 (1918).

in a small distilling flask; the vapor was removed by suction and condensed. The liquid thus obtained was identified by its odor, an iodoform test, and condensation to dibenzalacetone. In order to prove that the hydrolysis of the ester group was the only change brought about by the alkali, the acid was re-esterified by way of the silver salt and methyl iodide.

3-5-Diphenyl-4-cyano-cyclohexanone-1.—When the cyano acid is heated it first loses its acetone of crystallization, then melts and decomposes with loss of carbon dioxide at about 185°. Ten g. of acid was heated to remove the acetone of crystallization and then for 20 minutes at 180–190°, the light brown melt dissolved in alcohol, and the solution allowed to evaporate spontaneously. It ultimately left a mixture of solid and oil that yielded about 4 g. of solid. This was purified by recrystallization from alcohol, from which it separated in prisms melting at 81–83°.

Analyses. Calc. for $C_{19}H_{17}ON$: C, 82.9; H, 6.2. Found: C, 82.8; H, 6.3.

SEMICARBAZONE.—As a little difficulty was at first experienced in getting the product from the heating of the acid to crystallize, the formation of the ketone just described was at first established by the preparation of the semicarbazone from the melt as such. This compound was obtained in the usual way and purified by recrystallization from boiling alcohol. It separated in minute prisms and melted, with decomposition, at 194–196°.

Analysis. Calc. for $C_{20}H_{20}O_4N$: N, 16.9. Found: 17.4.

Methyl-2,5-diphenyl-4-keto-cyclohexanoate, $OC\begin{array}{c}CH_2—CH(C_6H_5)\\CH_2—CH(C_6H_5)\end{array}CHCO_2CH_3.$
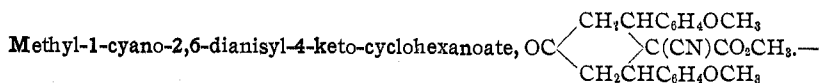
—A solution of 3 g. of the nitrile in 50 cc. of dry methyl alcohol was saturated with hydrogen chloride, allowed to stand overnight and then boiled for six hours. After the alcohol was distilled, a thick oil remained which was dissolved in ether. The ethereal solution was freed from acid, dried and allowed to evaporate. The resulting solid was purified by recrystallization from methyl alcohol. It separated in prisms that melted at 104.5–106°.

Analyses. Calc. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.9; H, 6.6.

Dianisal-acetone and Methyl Cyano-acetate

As stated in the introduction there is no indication that the ease of condensation with cyano-acetic esters to form cyclic compounds is markedly different with dianisal-acetone than with dibenzal-acetone. A little sodium methylate solution suffices to induce reaction, which takes place readily even at room temperature. In the case of the dianisal-acetone the product is evidently a mixture of stereomeric cyclohexanone derivatives.

Thus when a suspension of the ketone in cold methyl alcohol containing methyl cyano-acetate in slight excess, was treated with a small amount of sodium methylate, the sparingly soluble ketone readily dissolved on shaking, whereupon the condensation product immediately began to crystallize from solution. This product after recrystallization from methyl alcohol, from which it separated in fine tufts, melted at 156–159° and the melting point was not materially changed by subsequent recrystallization from this solvent. Some of the same crude material, however, after being recrystallized from carbon tetrachloride melted at 166–167.5°. The product which resulted from carrying out the condensation in hot methyl alcohol and allowing the solution to cool, showed a similar melting-point behavior. In order to avoid a tedious separation of isomers, the product was turned into the alkali-stable form by boiling it with a small quantity of sodium methylate.

Methyl-1-cyano-2,6-dianisyl-4-keto-cyclohexanoate, $OC\begin{matrix} CH_3CHC_6H_4OCH_3 \\ \diagdown \\ CH_2CHC_6H_4OCH_3 \end{matrix} C(CN)CO_2CH_3.-$

When a methyl alcohol suspension of the condensation product first obtained from dianisal-acetone and methyl cyano-acetate was heated with a little sodium methylate, the more stable form began to separate from the boiling solution. After the mixture had boiled for ten minutes it was allowed to cool and then filtered. The product was purified by recrystallization from boiling methyl alcohol and then from acetone and petroleum ether. It crystallizes in fine, white needles and melts at 208–209°. It is sparingly soluble in hot methyl alcohol and readily soluble in chloroform and in acetone. The structure of this product is established by its indifference to permanganate and by the ease with which it forms an acetal.

Analyses. Calc. for $C_{23}H_{23}O_5N$: C, 70.2; H, 5.9. Found: C, 70.1; H, 5.9.

THE METHYL ACETAL.—A current of hydrogen chloride was passed for about a minute into 75 cc. of dry methyl alcohol holding 1 g. of the cyclohexanone derivative in suspension. The flask was shaken, occasionally, for an hour during which the acetal separated as the ketone dissolved, suspended solid being present throughout the operation. The product was recrystallized from methyl alcohol from which it separated in fine needles melting at 175.5–176°. The same substance was obtained when a solution of the ketone and ester was first boiled with a little sodium methylate, then acidified with hydrochloric acid and concentrated by distilling a part of the alcohol.

Analyses. Calc. for $C_{25}H_{29}O_6N$: C, 68.3; H, 6.7. Found: C, 68.2; H, 6.7.

The Ethyl Acetal of the Condensation Product with Ethyl Cyano-acetate.—The formation of this substance shows that the condensations which have been described are not due to any peculiarity of methyl esters. It was obtained by boiling for half an hour a solution containing 6 g. of dianisal-acetone and 2.4 cc. of ethyl cyano-acetate in 150 cc. of ethyl alcohol with enough sodium ethylate to produce definite alkalinity. The mixture was then acidified with hydrochloric acid, most of the alcohol removed and the product isolated in the usual manner. After recrystallization from alcohol, from which it separated in needles, the product melted at 132–134°.

Analyses. Calc. for $C_{28}H_{35}O_6N$: C, 69.8; H, 7.3. Found: C, 70.0; H, 7.3.

Summary

1. In the presence of a trace of sodium alcoholate the esters of cyano-acetic acid combine very rapidly with dibenzal and dianisal-acetone. The products are cyclohexanone derivatives.

2. There is evidently no hindrance to the closing of the cyclohexanone ring, for no unsaturated open-chained compounds could be detected, no matter how soon the reaction was stopped.

3. The closing of the ring takes place much more rapidly than the addition of a second molecule of cyano-acetic ester; no saturated open-chained addition product could be detected even when the ester was used in large excess.

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