TABLE I

| | | Chemotherapy | | | |
|---|---|---|---|---|---|
| | | β-Strep. hemolyt. salivarius[b] | | Pneumococcus[c] | |
| Compound | $LD_{50}$-oral[a] mg./mouse | M. E. D.[d] × days mg./M./day | % Survival 14 days | mg./M./day × 3 days | % Survival 7 days |
| 4,4'-Diaminodiphenylsulfone | 12.6 | 0.25 | 80 | 2.5 | 80 |
| disodium didextrosesulfonate[e] | 130 | 2.8 | 90 | 10.0 | 56 |
| disodium diformaldehydesulfoxylate[f] | 250 | 10.0 | 90 | .. | .. |
| 4,4'-bis-Triazodiphenylsulfone | 250 | 0.5 | 83 | 20.0 | 13 |
| 4-Amino-4'-triazodiphenylsulfone | 21.4 | 0.5 | 90 | 5.0 | 12 |
| 2-Sulfamyl-4,4'-bis-triazodiphenylsulfone | >500 | 2.5 | 83 | 20.0 | 0 |

[a] Calcd. by the method of Dragstedt, *J. Pharmacol.*, **32**, 217 (1927–1928). [b] Lancefield's Group A, 01625. [c] Type I, 02444. [d] M. E. D. = mininal effective dose permitting survival of 80 to 90% of mice. [e] Promin. [f] Diamidin, Diasone.

once daily for three days when infected with streptococci. The animals were observed for twenty-eight days; however, the comparison of compounds was made on the basis of fourteen and seven day survival rates, respectively. Except for 4,4'-diaminodiphenylsulfone, the results tabulated in Table I are based on one or two routine tests for each compound, using ten to fifteen animals per dose level. Diaminodiphenylsulfone was used as a reference standard in all tests and the values given are the statistical average of all tests. Only those minimal doses which achieved comparable therapy are reported. The oral $LD_{50}$ in mice was also determined for each compound.

The activities of the triazo compounds against mouse streptotoccal infections resembled those of the analogous aminosulfones but the pneumococcal activities were much less. 4,4'-bis-Triazodiphenylsulfone was of greatest interest. The acute toxicity of the triazo compound given orally in mice was much less than that of the analogous amino compound, yet the minimal dose of triazosulfone to achieve comparable therapy was only twice that required for the aminosulfone. Furthermore, no free or hydrolyzable amine could be detected in the blood of mice given up to 10 mg./mouse of 4,4'-bis-triazodiphenylsulfone orally, while the minimum oral therapeutic dose of 4,4'-diaminodiphenylsulfone (0.25 mg./mouse) gave demonstrable blood levels, indicating that conversion of any triazo group to amino *in vivo* was of a very low order.

## Summary

1. Four new triazodiphenylsulfones are described. These compounds had antistreptococcal activity in mice comparable to that of the corresponding aminodiphenylsulfones.

2. 4,4'-bis-Triazodiphenylsulfone, although absorbed orally in sufficient amounts to achieve demonstrable antistreptococcal activity, was not converted *in vivo* to an amino compound in detectable amounts. It is possible that the activity of this compound functions through a different mechanism than that common to sulfa drugs in general.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

# Reactions of Atoms and Free Radicals in Solution. XIII. The Reactions of Diacetyl Peroxide with Aliphatic Ketones. A New Synthesis of 1,4-Diketones

BY M. S. KHARASCH, HENRY C. MCBAY AND W. H. URRY

Attention has been called[1] to the fact that the free primary or secondary alkyl radicals (formed by the decomposition of the diacyl peroxides of low molecular weight) remove hydrogen atoms from solvents to form new free radicals. The relations between the structure and the properties of the new free radicals thus formed are of considerable interest. A good deal of information regarding the behavior of the free radicals formed by the removal of hydrogen atoms from acids,[1] esters,[2] nitriles,[3] acid halides,[2] alkylbenzenes and ring-substituted alkylbenzenes[4] has already been recorded. The present paper deals with the reactions of the free radicals formed by the removal of hydrogen atoms from aliphatic and aryl-substituted aliphatic ketones.

## Discussion

The products and the yields of such products obtained by the decomposition of diacetyl peroxide in aliphatic ketones, can be best explained by assuming that the free methyl radical, formed by the decomposition of the diacetyl peroxide, abstracts an *alpha* hydrogen atom from the ketone molecule, and that the new free radical, thus formed, dimerizes.

$$(1)\quad \underset{(A)}{RR'CHCOCHRR'} + H_3C\cdot \longrightarrow \underset{(B)}{RR'COCHRR'}$$

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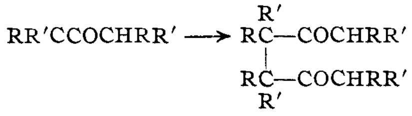
(1) Kharasch and Gladstone, THIS JOURNAL, **65**, 15 (1943).

(2) Kharasch, Jensen and Urry, *J. Org. Chem.*, **10**, 386 (1945).

(3) Kharasch, Smith and Urry, unpublished work.

(4) Kharasch, McBay and Urry, *J. Org. Chem.*, **10**, 401 (1945).

(2) 

$$RR'CCOCHRR' \longrightarrow \begin{array}{l} \;\;R' \\ RC\text{—}COCHRR' \\ \;\;| \\ RC\text{—}COCHRR' \\ \;\;R' \end{array}$$

(C)

R is an alkyl radical, an aryl radical, or a hydrogen atom, and R' is an alkyl or an aryl radical. Furthermore, since the "dimer" (C) contains hydrogen atoms (secondary or tertiary) susceptible to attack by free methyl radicals, it is to be expected that "trimers" (formed by a combination of the free radical (B) and the free radical produced by removal of a hydrogen atom from (C)) and "tetramers" (formed by the combination of two free radicals produced by removal of a hydrogen atom from (C)) should occur among the reaction products. In most of the reactions studied, both of these types of reaction product were isolated. The yields of the "dimers," "trimers" and "tetramers" are strongly influenced by the molecular ratio of ketone to peroxide. When this ratio is very high (*e. g.*, 10:1), the "dimer" predominates. With lower ratios (*e. g.*, 3:1) the yields of the "trimers" and "tetramers" are fairly high. These findings illustrate the selective action of free methyl radicals to which attention has been called in previous articles. In closely related series of compounds, the ease of removal of hydrogen atoms by free methyl radicals follows the order tertiary > secondary > primary. If the radical R in compound (A) is a hydrogen atom (that is, if the compound is $R'CH_2COCH_2R'$), then its "dimer" (C), because it contains tertiary hydrogen atoms, should have a strong tendency to form "trimers" and "tetramers." A large ratio of ketone to diacetyl peroxide would therefore be required to ensure the formation of an appreciable quantity of the "dimer" (C).

Furthermore, the selective action of free methyl radicals in removing secondary or tertiary rather than primary hydrogen atoms is well illustrated by the products formed from the action of free methyl radicals on the following ketones: butanone, 3-methylbutanone, 2,4-dimethyl-3-pentanone, 2,6-dimethyl-4-heptanone, 1-phenylpropanone, methyl acetoacetate, and 3,3-dimethylbutanone. No evidence of attack on primary hydrogen atoms was found in any of these compounds (except in the case of 3,3-dimethylbutanone). It should, however, be stated that, with the methods used, even careful examination of the reaction products may have failed to detect small quantities of the substances formed by removal of primary hydrogen atoms. To settle this point another experimental procedure is needed. It is proposed to study the comparative reactivity of primary, secondary, and tertiary hydrogen atoms by labeling one of the hydrogen atoms, that is, by replacing it by a deuterium atom and determining the amounts of $CH_4$ and $CH_3D$ formed.

The products formed by the decomposition of diacetyl peroxide in various ketones are indicated in Table I.

Whenever the 1,4-diketones ("dimers"), formed by the decomposition of diacetyl peroxide in ketones, were new compounds, their structure was established by conventional methods. The experimental part of this paper should be consulted for the procedures used in individual cases. This part also contains a full list of the gaseous and other products (methane, carbon dioxide, methyl acetate) formed from the diacetyl peroxide when that compound is decomposed in aliphatic ketones. Since these products are the same as those formed when diacetyl peroxide is decomposed in other solvents (acids, esters, nitriles, etc.), the mechanism of their formation is presumably the one discussed in previous articles.

"Dimers" (1,4-diketones), "trimers" (triketones), and "tetramers" (tetraketones) are formed by the action of a diacyl peroxide on ketones whenever the ketones are either aliphatic or of the type Aryl-CHR-CO-Alkyl, (in which R is a hydrogen atom or an alkyl group); they are not formed from ketones in which an aryl group is directly attached to a carbonyl group. Thus, no polymers of low molecular weight, but only higher polymers were formed when acetophenone, propiophenone, or phenyl isopropyl ketone was treated with diacetyl peroxide. Furthermore, judging by the nature of the gaseous products produced in these

TABLE I

DECOMPOSITION OF DIACETYL PEROXIDE IN KETONES

| | Ketone | Major reaction product | Other products |
|---|---|---|---|
| 1 | Butanone | 3,4-Dimethyl-2,5-hexanedione | Heavy oil, probably "trimer" and "tetramer" |
| 2 | 3-Methylbutanone | 3,3,4,4-Tetramethyl-2,5-hexanedione | "Trimer" and some higher polymer |
| 3 | 2,4-Dimethyl-3-pentanone | 2,4,4,5,5,7-Hexamethyl-3,6-octanedione | "Trimer" and some higher polymer |
| 4 | 2,6-Dimethyl-4-heptanone | 2,9-Dimethyl-5,6-diisopropyl-4,7-decanedione (*meso* and racemic) | Some "trimer" |
| 5 | 1-Phenylpropanone | 3,4-Diphenyl-2,5-hexanedione (*meso* and racemic) | Some polymer |
| 6 | 2,4-Pentanedione | *sym*-Tetraacetylethane | Some polymer |
| 7 | 2,5-Hexanedione | | Mostly "trimer" and "pentamer" |
| 8 | 3,3-Dimethylbutanone | 2,2,7,7-Tetramethyl-3,6-octanedione (about 15%) | "Tetramer" and polymer |
| 9 | Cyclohexanone | 2,2'-Dioxobicyclohexyl (*meso* and racemic) | High polymer |

reactions (high carbon dioxide to methane ratio), it is probable that some of the free methyl radicals attach themselves to the benzene ring. If such is the fact the benzene ring must be greatly activated by the adjacent carbonyl group, for in the ketones mentioned, it competes successfully for free methyl radicals with such active atoms as the secondary and tertiary hydrogen atoms in the alkyl groups of propiophenone and phenyl isopropyl ketone, respectively. Further examination of such ketones is in progress.

## Experimental

The general method for the preparation, isolation, analysis and decomposition of diacetyl peroxide in organic solvents is described in previous articles of this series.

**I. The Decomposition of Diacetyl Peroxides in Organic Solvents. A. The Preparation of 3,4-Dimethyl-2,5-hexanedione, $[CH_3(CH_3CO)CH]_2$.**—Diacetyl peroxide (61.0 g., 0.517 mole) was dissolved in butanone (129 g., 1.79 mole), and this solution was introduced into butanone (159 g., 2.21 moles) heated to 75°. Carbon dioxide (34.76 g., 0.79 mole), methane, (14 liters, S. C., 0.62 mole, mol. wt. 16.95), and methyl acetate (6.09 g., 0.08 mole, b. p. 56–7°) were collected and identified in the usual manner.

The first fraction obtained when the contents of the reaction flask were distilled was unchanged butanone (237.0 g., 3.30 moles, b. p. 78.5°, $n^{20}D$ 1.3800). The second fraction was collected at 57° (1 mm.) (38.3 g.). The residue in the flask weighed 4 g. The second fraction was then fractionated through a 10-plate column, and the fraction boiling at 92° (30 mm.) ($n^{20}D$ 1.4330) was collected.

*Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.44; H, 9.56.

The analysis and the observation that the compound gave positive ferric chloride and iodoform tests suggested that the substance was the expected 3,4-dimethyl-2,5-hexanedione. The structure of the compound was established in the following manner. (a) When a sample of the presumed diketone was treated with an excess of sodium hypobromite a nearly quantitative yield of $\alpha,\alpha'$-dimethylsuccinic acid (*meso* and racemic) was obtained. The melting point of the *meso* dimethylsuccinic acid thus obtained was 206°. The recorded melting point of this acid is 209°. (b) The compound when heated with ammonium hydroxide and methyl alcohol gave 2,3,4,5-tetramethylpyrrole, which upon crystallization from methyl alcohol melted at 110°. The recorded melting point of 2,3,4,5-tetramethylpyrrole is 114°.[5] (c) The compound when treated with phenylhydrazine in ethyl alcohol gave a pyridazine derivative which melted at 127–128°. The recorded melting point for this pyridazine derivative is 130°.

*Anal.* Calcd. for $C_{14}H_{18}N_2$: N, 13.1. Found: N, 12.6.

**B. The Preparation of 3,3,4,4-Tetramethyl-2,5-hexanedione, $[CH_3CO(CH_3)_2C]_2$.**—Diacetyl peroxide (67.0 g., 0.57 mole) was dissolved in 3-methylbutanone (260 g., 3.0 moles), and this solution was introduced into 3-methylbutanone (131.0 g., 1.52 mole) heated to the boiling point of the solvent (93°). Carbon dioxide (42.25 g., 0.96 mole), methane (18.2 liters, S. C., 0.81 mole; mol. wt. 18.4), and methyl acetate (1.6 g., 0.02 mole, b. p. 57°) were collected and identified in the usual manner.

The unchanged ketone (333 g.) was recovered by distillation at ordinary pressure. The residue (64 g.) was distilled at 0.5 mm. pressure. The following fractions were collected: Fraction 1: b. p. 40° (0.5 mm.), $n^{20}D$ 1.4522, colorless oil, 23 g.; Fraction 2: b. p. 40–55° (0.5 mm.), $n^{20}D$ 1.4559, 9 g.; Fraction 3: b. p. 103–125 (0.5 mm.); $n^{20}D$ 1.4713, pale yellow sirup, 6.5 g. The residue weighed 7.0 g.

**Fraction 1.**—This material was shown to be the "dimer" of 3-methylbutanone (3,3,4,4-tetramethyl-3,5-hexanedione) by analysis and by the fact that it reacts with sodium hypobromite to give tetramethylsuccinic acid.

*Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65; mol. wt., 170. Found: C, 70.94; H, 10.34; mol. wt., 179.

Fraction 1 ("the dimer") (9 g.) was treated with the calculated amount of sodium hypobromite. The white solid which separated (9 g.) was crystallized from methyl alcohol. Beautiful white needles of a compound which melted at 117° were thus obtained. The compound contained bromine and was undoubtedly the tetrabromo derivative of the "dimer" (3,3,4,4-tetramethyl-2,5-hexanedione).

*Anal.* Calcd. for $C_{10}H_{14}O_2Br_4$: Br, 65.79. Found: Br, 65.71.

The appearance of this type of bromo derivative when a hindered methyl ketone is treated with sodium hypobromite has been noted previously.[6]

The hypobromite oxidation was repeated using 0.5 mole of sodium hypobromite in 300 cc. of solution and 2.5 g. (0.015 mole) of the diketone. The reaction mixture was stirred for twenty-four hours at room temperature, and eight hours at 60–80°. The reaction mixture gave 2.0 g. of the tetrabromide (m. p. 113–15°) described in the preceding paragraph, and 0.25 g. of an acid which, upon recrystallization from water, melted at 200°. The melting point of this acid was not depressed by mixture with an authentic sample of tetramethylsuccinic acid. Reflux of the tetrabromoderivative of the diketone (1 g.) in a 20% solution of potassium hydroxide in ethylene glycol for five hours and subsequent acidification gave a small quantity of tetramethylsuccinic acid.

**Fraction 2.**—This material is probably a mixture of the "dimer" and small amounts of the "trimer."

**Fraction 3.**—This material is mostly the "trimer" (mol. wt. 280; calcd. mol. wt. 255) contaminated with small amounts of the "tetramer." The structure of this compound was not established, but, on the basis of previous experience in this field, we favor the structure assigned to the "trimer" in the theoretical part.

**C. The Preparation of 2,4,4,5,5,7-Hexamethyl-3,6-octanedione, $[i\text{-}C_3H_7CO(CH_3)_2C]_2$.** Diacetyl peroxide (64.5 g., 0.546 mole) was dissolved in 230.5 g., 2.0 moles, of 2,4-dimethyl-3-pentanone, and this solution was added to the ketone (312.5 g., 2.74 moles) heated to 135°. Carbon dioxide (40.4 g., 0.92 mole), methane (16.34 liters, S. C., 0.73 mole, mol. wt. 17.0), and methyl acetate (2.7 g., 0.036 mole, b. p. 56.5–57°; $n^{20}D$ 1.3599) were collected and identified in the usual manner.

The unchanged ketone (477 g.) was recovered by distillation at reduced pressure (40° (35 mm.)). The straw-colored residue (62.5 g.) was fractionated at a pressure of 1.5 mm. through a six-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 75–77° (1.5 mm.), $n^{20}D$ 1.4520, 30 g.; Fraction 2: b. p. 77–85° (1.5 mm.), $n^{20}D$ 1.4583, 8 g.; Fraction 3: b. p. 100–140° (1.5 mm.), $n^{20}D$ 1.4694, 10 g. The residue weighed 5 g.

**Fraction 1.**—This material was shown to be the "dimer" of 2,4-dimethyl-3-pentanone (2,4,4,5,5,7-hexamethyl-3,6-octanedione) by analysis and by the fact that it gave upon oxidation tetramethylsuccinic acid and acetone.

*Anal.* Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58; mol. wt., 226. Found: C, 74.54; H, 11.79; mol. wt., 229.

Two grams of Fraction 1 ("dimer") was added at 0° to 100 cc. of glacial acetic acid containing 8 g. of chromic anhydride. The mixture was kept at 0° for five hours, at the end of which time it was heated to 100° and kept at that temperature for one hour. The reaction mixture was then cooled, diluted with 900 cc. of water, and the whole was extracted with 200 cc. of ether. The ether extraction was repeated five times, and the ether extracts

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(5) Ciamician and Silber, *Ber.*, **45**, 1542 (1912); Démètre-Vladesco, *Bull. soc. chim.*, [3] **6**, 807 (1891).

(6) Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

were combined. The ether extract was then shaken three times with a dilute solution of sodium hydroxide (20 cc. of 2% sodium hydroxide), and the alkaline extracts were combined. Upon acidification with hydrochloric acid 0.8 g. of a solid separated. When crystallized from hot water the material melted at 201°, and its melting point was not depressed by the addition of an authentic sample of tetramethylsuccinic acid.

The original aqueous solution (from which the tetramethylsuccinic acid was removed by extraction with ether) was distilled. The first 75 cc. of the distillate was collected and tested for acetone, the other expected oxidation product of the "dimer." The solution in fact gave with 2,4-dinitrophenylhydrazine a yellow crystalline product which did not depress the melting point of a known sample of the 2,4-dinitrophenylhydrazone of acetone.

**D. The Preparation of 2,9-Dimethyl-5,6-diisopropyl-4,7-decanedione, $[i\text{-}C_3H_7(i\text{-}C_3H_7CH_2CO)CH]_2$.**—Diacetyl peroxide (31.0 g., 0.26 mole) was dissolved in 2,6-dimethyl-4-heptanone (230.0 g., 1.62 mole), and this solution was introduced into the ketone (48.0 g., 0.34 mole) heated to 115°. Carbon dioxide (20.7 g., 0.47 mole), methane (9.0 liters, S. C., 0.40 mole, mol. wt. 17.69), and methyl acetate (2.0 g., 0.027 mole, $n^{20}D$ 1.3614) were collected and identified in the usual manner.

The unchanged ketone (232 g.) was removed at reduced pressure (b. p. 30° (1 mm.)), and the residue (48 g.) was distilled through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 95–97° (1.5 mm.), $n^{20}D$ 1.4430, clear oil, 8 g.; Fraction 2: b. p. 98–110° (1.5 mm.), mixture of crystals and an oil, 3 g.; Fraction 3: b. p. 110–114° (1.5 mm.), white crystalline material, 9 g.; Fraction 4: b. p. 114–24° (1 mm.), yellow oil, 4 g. The residue ($n^{20}D$ 1.4705) weighed 7 g.

The solid material which comprises Fraction 3 crystallizes from methyl alcohol in long white needles which melt at 87–90°. This material and the substance of Fraction 1, which is an oil, are assumed to be the *meso* and racemic forms of the "dimer" of 2,6-dimethyl-4-heptanone, namely, 2,9-dimethyl-5,6-diisopropyl-4,7-decanedione. The evidence for this assumption is based upon the difference in their boiling points, the fact that one of the isomers is a solid and the other a liquid (which resisted all our efforts to transform it into a solid), their identical analyses for carbon and hydrogen, their almost identical molecular weights, and the fact that an alcoholic solution of the liquid material of Fraction 1 could be transformed by sodium ethoxide into the solid material (m. p. 87–90°) of Fraction 3. (Note that these substances contain enolizable hydrogen atoms on the carbon atoms adjacent to the carboxyl groups.)

*Anal.* Calcd. for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13; mol. wt., 282. Found: (solid, m. p. 87–90°) C, 76.45; H, 11.53; mol. wt., 292. (Fraction 1) C, 76.32; H, 11.41; mol. wt. 300.

Fraction 2 is probably a mixture of the two stereoisomers of Fractions 1 and 3. The residue is a tan-yellow sirup. The molecular weight of this material is 466. It is probably a "trimer" (mol. wt. 432) admixed with some of the "tetramer."

**E. The Preparation of 3,4-Diphenyl-2,4-hexanedione, $[CH_3CO(C_6H_5)CH]_2$.**—Diacetyl peroxide (19.6 g., 0.17 mole) was dissolved in 1-phenylpropanone (69.4 g., 0.52 mole) and this solution was introduced dropwise into the ketone (40 g., 0.3 mole) heated to 125–30°. Carbon dioxide (11.7 g., 0.27 mole), methane (4.79 liters, S. C.; 0.21 mole; mol. wt. 18.4), and methyl acetate (2.0 g., 0.03 mole; b. p. 56.5°; $n^{20}D$ 1.3615) were collected and identified in the usual manner.

The reaction mixture, upon standing overnight, deposited white crystals. These were collected on a filter. They weighed 6.5 g. When crystallized from a mixture of methyl and ethyl alcohols they melted at 201–202°. This material is quite insoluble in methyl alcohol.

The filtrate obtained when the reaction mixture was freed of the solid material was subjected to distillation at reduced pressure (5–6 mm.), and the unchanged ketone (86 g., 0.638 mole) thus recovered. The residue in the flask when allowed to stand overnight deposited some crystals. These were collected on a filter (6.0 g.). This material when crystallized first from methanol, in which it is very soluble, and then from ligroin, melted at 98–100°.

It is submitted that the compound which melts at 201–202°, and the compound which melts at 98–100°, are stereoisomers (*meso* and racemic, respectively) of 3,4-diphenyl-2,5-hexanedione. The evidence is based upon analyses, oxidation of the material to *sym*-diphenylsuccinic acid, and the fact that both materials when treated with aniline gave the identical substituted pyrrole.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: (solid m. p. 201–202°) C, 81.37; H, 6.88 (solid m. p. 98–100°) C, 80.93; H, 6.56.

The high-melting material (201°) when treated with sodium hypobromite gave a solid which upon crystallization from water melted at 253°. The melting point of this material was not depressed when mixed with an authentic sample of *meso* diphenylsuccinic acid.

The high-melting and the low-melting forms of the 3,4-diphenyl-2,5-hexanedione were converted to the same pyrrole (m. p. 135°) when treated with aniline. The procedure employed was as follows. About 0.7 g. of the material was dissolved in 20 cc. of glacial acetic acid to which 0.5 g. of aniline had been added. The mixture was refluxed for six hours and then allowed to cool. About 200 cc. of water was then added, and the whole was extracted with ether. The ethereal solution upon evaporation gave a solid which upon crystallization from methyl alcohol separated in the form of pale straw-colored needles which melted at 133–135°. Furthermore, no depression in the melting point was noted, when the pyrroles from the two compounds were mixed. For analysis the 1,3,4-triphenyl-2,5-dimethylpyrrole was further purified by sublimation. The melting point of the sublimed material was 135°.

*Anal.* Calcd. for $C_{24}H_{21}N$: C, 89.12; H, 6.55; N, 4.33. Found: C, 88.95; H, 6.32; N, 4.44.

Besides the *meso* and racemic forms of 3,4-diphenyl-2,5-hexanedione there is formed a sirupy polymer. The weight of the polymer is about equal to the weight of the two stereoisomers. All efforts to obtain a crystalline material from the sirupy polymer have been unsuccessful.

**F. Preparation of *sym*-Tetraacetylethane, $[(CH_3CO)_2\text{-}CH]_2$.**—Diacetyl peroxide (65.0 g., 0.55 mole) was dissolved in 2,4-pentanedione (229.0 g., 2.29 moles) and this solution was introduced into the diketone (191.0 g., 1.91 mole) heated to 125°. Carbon dioxide (35.80 g., 0.81 mole), methane (14.75 liters S. C., 0.66 mole, mol. wt. 17.0), and methyl acetate (4.0 g., 0.05 mole; b. p. 55–6°; $n^{20}D$ 1.3605) were collected and identified in the usual manner.

The unchanged diketone (350 g.) was removed at reduced pressure (about 25 mm.). When the residue (64 g.) was allowed to stand overnight a solid separated. This was collected on a filter, and the filtrate ("A") was reserved for further treatment. The solid material when crystallized from ethyl alcohol melted at 189–191°. The melting point of tetraacetylethane, as recorded in the literature, is 189 or 191°. The identity of the 189–191° melting material, obtained in this reaction, was further confirmed by the fact that the melting points of its furan and pyrrole derivatives corresponded with those described in the literature.

The filtrate "A" began to decompose when an attempt was made to distill it in a molecular still. Its average molecular weight as determined in carbon tetrachloride was 326.

**G. Preparation of 2,2,7,7-Tetramethyl-3,6-octanedione, $t\text{-}(C_4H_9COCH_2)_2$.**—Diacetyl peroxide (59.5 g., 0.50 mole) was dissolved in 3,3-dimethylbutanone (316.0 g., 3.16 moles), and this solution was introduced into the ketone (58.0 g., 0.58 mole) heated to 104°. Carbon dioxide (37.9 g., 0.86 mole), methane (16.52 liters, S. C., 0.74 mole; mol. wt. 17.12), and methyl acetate (1.2 g., 0.016 mole) were collected and identified in the usual manner.

The unchanged ketone (330 g.) was recovered from the reaction mixture at reduced pressure (35 mm.), and the residue remaining in the distilling flask (44 g. of a yellow oil) was distilled at reduced pressure through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 55–60° (0.5 mm.), $n^{20}D$ 1.4400, colorless oil, 6.5 g.; Fraction 2: 60–115° (0.5 mm.), $n^{20}D$ 1.4545, mol. wt. 258, 7.5 g.; residue: red sirup, mol. wt. 347, 20 g.

Fraction 1 was shown to be the expected "dimer," 2,2,7,7-tetramethyl-3,6-octanedione, by its reactions and analyses.

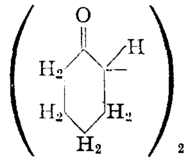
*Anal.* Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; mol. wt., 198. Found: C, 73.67; H, 11.09; mol. wt., 199.

The "dimer" when treated with a methyl alcohol solution of ammonium hydroxide and allowed to stand for several days gave an oil. This oil gave a positive pyrrole test with a pine splint. Furthermore, the "dimer" gave no iodoform when treated with iodine and a base.

The "dimer" (Fraction 1) (1.5 g.) when treated with phenylhydrazine (1.0 g.) and heated for several hours at 120° gave compound which upon crystallization from alcohol melted at 144–147°. This white crystalline compound is probably the di-phenylhydrazone of 2,2,7,7-tetramethyl-3,6-octanedione.

*Anal.* Calcd. for $C_{24}H_{34}N_4$: N, 14.83. Found: N, 14.73.

As would be expected from the considerations discussed in the theoretical part, the "dimer" should be more readily attacked than the starting material since it contains secondary hydrogen atoms, while the hydrogen atoms in the original ketone are all primary. The low yield of the "dimer" is thus readily explained. Furthermore, it follows that Fraction 2 contains some dimer and some higher polymer, while the residue is probably a "tetramer" contaminated with some "dimer." No work was done with these higher condensation products.

**H. Preparation of**  **2,2′-Dioxobicyclohexyl.**—Diacetyl peroxide (46.0 g., 0.39 mole) was dissolved in cyclohexanone (404.5 g., 4.13 moles), and this solution was introduced into the ketone (274.5 g., 2.80 moles) heated to 130°. Carbon dioxide (25.3 g., 0.57 mole), methane (10.71 liters, S. C., 0.48 mole; mol. wt. 17.79), and methyl acetate (3.4 g., 0.04 mole, b. p. 55.5–56°, $n^{20}D$ 1.3599) were collected and identified in the usual manner.

The unchanged cyclohexanone (6.22 g., 6.25 moles) was recovered from the reaction mixture by distillation at reduced pressure (1 mm.). The residue remaining in the flask (47 g.) was distilled at reduced pressure through a 6-inch Vigreux column. The following fractions were collected: Fraction 1: b. p. 114–117° (1 mm.), $n^{20}D$ 1.4958, orange oil which darkens on standing in air, 15 g; residue, dark-red glassy material, mol. wt. 605, 13 g.

The analysis and molecular weight of Fraction 1 show it to be the "dimer" of cyclohexanone.

*Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt., 194. Found: C, 74.42; H, 9.21; mol. wt., 215.

If the "dimer" of cyclohexanone is 2,2′-dioxobicyclohexyl, then the compound should exist in two stereoisomeric forms. As a matter of fact, Fraction 1 upon standing deposited a crystalline material which upon crystallization from low-boiling (60°) ligroin melted at 70–71°. This melting point is that recorded by Plant[7] for 2,2′-dioxobicyclohexyl.

To confirm the structure of the solid from Fraction 1, it was converted to the 9-methyloctahydrocarbazole by heating it with methylamine in acetic acid. The melting point of the compound thus obtained was 94–95°. The recorded melting point of 9-methyloctahydrocarbazole is 94–95°.

As indicated, the residue left in the flask was a dark-red glassy material. Its high molecular weight (605) indicated that it is either a "hexamer" of cyclohexanone or a mixture of a very high molecular weight material with some materials of lower molecular weight. No further work was done with this polymer.

**Decomposition of Diacetyl Peroxide in 2,5-Hexanedione.**—Diacetyl peroxide (56.0 g., 0.47 mole) was dissolved in 2,5-hexanedione (273 g., 2.39 moles), and this solution was introduced into the diketone (297.5 g., 2.61 moles) heated to 145°. Carbon dioxide (34.08 g., 0.77 mole), methane, (14.47 liters, S. C., 0.64 mole; mol. wt. 17.56), and methyl acetate (5.5 g., 0.07 mole, b. p. 56°) were collected and identified in the usual manner.

The unchanged diketone (495 g.) was recovered by distillation at reduced pressure. The reddish-brown oil (72 g.) was distilled through a 6-inch Vigreux column, and the following fractions were collected: Fraction 1: b. p. 35–55 (1 mm.), 5 g.; Fraction 2: b. p. 145–155° (1 mm.), 38 g.; residue, dark-red gummy material.

Fraction 1 is the unchanged diketone.

From the molecular weight of Fraction 2 (330) it would appear that this substance is a "trimer" of the diketone (calcd. mol. wt. 338). The residue had a molecular weight of 552. The calculated molecular weight for a "pentamer" of the diketone is 562. No further chemical work was done with either Fraction 2 or the residue.

**Decomposition of Diacetyl Peroxide in Acetophenone.**—Diacetyl peroxide (70.0 g., 0.60 mole) was dissolved in 183 g., 1.52 mole, of acetophenone, and this solution was introduced dropwise into acetophenone (152.3 g., 1.26 mole) heated to 125°. Carbon dioxide (41.47 g., 0.94 mole), methane (8.57 liters, S. C.; 0.382 mole; mol. wt. 16.43), and methyl acetate (7.4 g., 0.10 mole, b. p. 58°, $n^{20}D$ 1.3620) were collected and identified in the usual manner. Note, however, that the amount of methane formed is about one-half of the amount formed when diacetyl peroxide is decomposed in ketones in which the carbonyl group is not adjacent to a benzene ring.

The unchanged acetophenone (300 g.) was recovered from the reaction mixture by distillation at low pressure. The residue (35 g.) was a dark red-brown gummy substance. The molecular weight of the residue was 648.

**Decomposition of Diacetyl Peroxide in Propiophenone.**—Diacetyl peroxide (57.8 g., 0.49 mole) was dissolved in propiophenone (187.5 g., 1.40 mole), and this solution was introduced into propiophenone (164.5 g., 1.22 mole) heated to 115°. Carbon dioxide (31.56 g., 0.717 mole), methane (10.44 liters, S. C., 0.466 mole, mol. wt. 16.38) and methyl acetate (5.4 g., 0.08 mole, b. p. 56–57°) were collected and identified in the usual manner.

The unchanged propiophenone (301 g.) was removed from the reaction mixture by distillation at reduced pressure. The residue (50 g.) was an orange-colored semi-solid resin. The molecular weight of this material (in carbon tetrachloride) was 389.

**The Decomposition of Diacetyl Peroxide in Phenyl Isopropyl Ketone.**—Diacetyl peroxide (72.0 g., 0.61 mole) was dissolved in phenyl isopropyl ketone (140.0 g., 0.946 mole), and this solution was introduced dropwise beneath the surface of phenyl isopropyl ketone (75.0 g., 0.51 mole) heated to 115°. Carbon dioxide (40.05 g., 0.91 mole), methane (11.41 liters, S. C., 0.509 mole, mol. wt. 22.4), and methyl acetate (11.0 g., 0.15 mole, b. p. 55–56.4°; $n^{20}D$ 1.3610) were collected and identified in the usual manner.

The unchanged phenyl isopropyl ketone (171 g.) was recovered from the reaction mixture by distillation at reduced pressure. The residue (44 g.) remaining in the flask was an orange-red sirupy material which could not be crystallized. The molecular weight of this material (in carbon tetrachloride) was 784.

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(7) Plant, *J. Chem. Soc.*, 1595 (1930).

## Summary

1. A new method for the preparation of 1,4-diketones is described.
2. A number of new 1,4-diketones have been prepared and characterized.
3. The mechanism of the formation of the 1,4-diketones is discussed.

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# NOTES

## Studies on the Mechanism of the Sulfonation of Aromatic Amines. III. Rearrangement of Barium Phenylsulfamate

BY ELLIOT R. ALEXANDER

In earlier communications, it has been shown that freezing point data and kinetic data[1] support a bimolecular mechanism for the sulfonation of aromatic amines rather than an intramolecular rearrangement of phenylsulfamic acid which has been postulated as an intermediate. There is one fact, however, that appears to be an anomaly: The dihydrate of barium phenylsulfamate can be transformed into sulfamic acid on heating at 180°.[2] It therefore seemed advisable to repeat Bamberger's experiments with carefully purified materials and to determine whether the reaction would proceed with the anhydrous salt.

On heating the dihydrate of barium phenylsulfamate in a closed vessel four and one-half hours at 175–185°, sulfonation of the aromatic nucleus was indeed found to have occurred to the extent of 26%. When the reaction was carried out with *anhydrous* barium sulfamate, however, no sulfonation occurred.

While these facts do not necessarily preclude an intramolecular rearrangement of the hydrate (since the water of hydration might have weakened and labilized certain bonds in the molecule permitting rearrangements which would not be possible in the anhydrous material), nevertheless it is interesting that this reaction is not characteristic of the anhydrous salt.

### Experimental

**Rearrangement of the Dihydrate of Barium Phenylsulfamate.**—Barium phenylsulfamate dihydrate[3] (5.0 g., 0.00965 mole) was crushed into a fine powder and heated for four and one-half hours at 175–185° in a stoppered round-bottomed flask partially immersed in a metal heating bath. At the beginning of the heating moisture could be seen to condense on the cooler portion of the flask. As heating was continued the solid became streaked with purple but did not melt. After the heating period was completed, the flask was cooled and a mixture of 15 ml. of concentrated hydrochloric acid in 100 ml. of water was added. This mixture was digested fifteen minutes on a steam-bath and attached to a Kjeldahl apparatus. The solution was then made basic with sodium hydroxide solution and steam distilled quantitatively into 10 ml. of concentrated hydrochloric acid and 25 ml. of distilled water. The aromatic amine content of the distillate and the non-volatile portion was determined by titrating with standard sodium nitrite solution.[4] The steam-volatile portion required 28.91 ml. of 0.484 *N* sodium nitrite solution (72.6%) while the non-volatile portion required 10.38 ml. (26.1%).

**Attempted Rearrangement of Anhydrous Barium Phenylsulfamate.**—Anhydrous barium phenylsulfamate was prepared by drying the dihydrate for eight hours at 100° and 1 mm. It was analyzed by titration with sodium nitrite solution.[4]

*Anal.* Calcd. for $C_{12}H_{12}N_2S_2O_6Ba$: $NH_2$, 6.58. Found: $NH_2$, 6.55.

This salt (5.0 g., 0.00104 mole) was treated exactly as described above. Three drops of the sodium nitrite solution was required for the non-volatile portion while 42.87 ml. (99.6%) was required for the portion volatile with steam.

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[1] Alexander, THIS JOURNAL, **68**, 969 (1946); **69**, 1599 (1947).

[2] Bamberger and Hinderman, *Ber.*, **30**, 655 (1897).

[3] Traube, *ibid.*, **23**, 1654 (1890).

[4] Kolthoff and Stenger, "Volumetric Analysis," Interscience Publishers, Inc., New York, N. Y., 1942, p. 240.

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## The Preparation of 2-Amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine

BY R. B. ANGIER, J. H. MOWAT, J. H. BOOTHE, C. W. WALLER, J. SEMB, B. L. HUTCHINGS, E. L. R. STOKSTAD AND Y. SUBBAROW

In connection with the investigation of the synthesis of pteroylglutamic acid[1] the compound, 2-amino-4-hydroxy-6-keto-5,5-dichlorodihydropyrimidine (III), became of some interest. The corresponding 2,4-dihydroxy-6-keto-5,5-dichlorodihydropyrimidine (IV) has been prepared by several methods[2,3,4] including the direct chlorination of barbituric acid (II) in water solution.[4] Several attempts to chlorinate 2-amino-4,6-dihydroxypyrimidine (I) by the use of chlorine in a water solution were unsuccessful. A good deal of decomposition occurred and the small yield of product usually obtained was apparently a mixture of the starting material and the monochloro and dichloro substitution products. When a potassium chlorate and hydrochloric acid mixture was used as a chlorinating agent a reasonably pure

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[1] Waller, *et al.*, THIS JOURNAL, **70**, 19 (1947).

[2] Behrend, *Ann.*, **236**, 64 (1886).

[3] Blitz and Hamburger, *Ber.*, **49**, 639 (1916).

[4] Bock, *ibid.*, **56B**, 1222 (1923).