[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, No. 415]

THE RELATION BETWEEN MOLECULAR STRUCTURE AND ODOR IN TRI-SUBSTITUTED BENZENES. I. DERIVATIVES OF PARA-METHOXY-ACETOPHENONE

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Introductory

So many well-known perfume substances among the tri-substituted benzenes possess the 1,3,4 arrangement that this has been called by Georg Cohn the "ideal configuration." Borneol, menthol, carone, fenchone, thujone, menthone, pulegone, camphor, carvacrol, thymol, eugenol, isoeugenol, safrol, piperonal, vanillin, acetovanillone, certain of the synthetic musks, and many others might be cited as illustrations of the fact that such an arrangement of the osmophore groups is of remarkably frequent occurrence in compounds possessing strong, agreeable odors.

In following this observation further, we have investigated various derivatives of *p*-methoxy-acetophenone, a substance which itself has a fine floral odor, and whose *m*-hydroxy derivative (2-hydroxy-4-methoxy-acetophenone), also known as peonol, occurs in the roots of the tree peony (*Paeonia moutan*) and has been employed in the perfume industry on account of its pleasant aroma.

Our purpose was to throw some additional light upon the connection between odor and structure in compounds of this type, by preparing new 1,3,4 derivatives and noting their odor.

One of the products we had in mind was the isomer of peonol, iso-acetovanillone (3-hydroxy-4-methoxy-acetophenone), but while our experiments were in progress, the article by Schneider and Kraft[1] appeared, describing the preparation of this compound by the action of sulfo-acetic acid upon guaiacol. As the authors make no mention of its possessing any noteworthy odor, the inference is that it has none.

The following derivatives of 4-methoxy-acetophenone were synthesized carrying an additional osmophore group adjacent to the methoxy: 3-nitro, 3-amino, 3-iodo, 3-cyano and 3-azido. Of these, all but the nitro derivative are new. All proved to be practically odorless.

In addition to the above, other new derivatives, carrying non-osmophores in Position 3, were prepared in the course of the investigation, as follows: aceto-amino, iodochloride, iodoso, *p*-nitrobenzalamino, sodium sulfonate, diazo perbromide, diazo-amino, amino-azo and 4-hydroxy-3-iodoso-acetophenone. These likewise were odorless, as might have been expected on account of their nonvolatility.

A tri-substituted benzene containing 3 osmophore groups in 1,3,4 re-

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[1] Schneider and Kraft, *Ber.*, **55B**, 1892 (1922).

lation, therefore, is not because of that reason a perfume, even though its physical constants, such as boiling point, solubilities, etc., may be favorable. The connection between odor and constitution is not so simple then, and other factors must be involved which we hope may be discovered by a continuation of this investigation.

While *p*-methoxy-acetophenone itself is very stable and can be distilled at 258° without decomposition, its derivatives noted above are much more sensitive to the action of heat, especially in the presence of acid or alkali, and tarry by-products often seriously diminished the yields.

In carrying out reactions upon groups *ortho* to the methoxy, we encountered the well-known obstacle of steric hindrance.[2,3,4] Thus, it was found impossible to hydrolyze the 3-cyano derivative to the corresponding amide or acid, or to obtain therefrom an imino ester; nor could we convert the 3-amino derivative into the phenol.

Many years ago, Victor Meyer[5] pointed out that the hindering effect of the interfering group increased with its molecular weight. Our own observations lead us to suggest the following supplementary hypotheses.

1. The hindering effect of an interfering group diminishes as the molecular weight of the reacting group in the *ortho* position increases.

2. The hindering effect of an interfering group diminishes as the molecular weight of the foreign reacting molecule increases.

These tentative hypotheses are based upon the simple physical considerations of mass and inertia and are, of course, of a qualitative nature only. None the less, they may prove of service to others, as they have to us.

As an illustration of Hypothesis 1, the formation of the azido derivative from the diazo perbromide and ammonia may be cited. The methoxy group, with a molecular weight of 31, is crowded out to such an extent by the heavy diazo perbromide group (molecular weight, 268), that the azido compound is formed practically instantaneously in excellent yield, although the foreign attacking molecule has a molecular weight of only 17.

In confirmation of the second hypothesis are the failures to hydrolyze the cyano derivative by water or hydrogen dioxide, or to change it to an imino ester by anhydrous methyl alcohol and hydrogen chloride, and the inability to hydrolyze the diazonium chloride. In all these cases, the molecular weight of the reacting group was not far from that of the interfering one (methoxyl). On the other hand, reactions involving heavier foreign molecules were particularly satisfactory; as, for example, those with hydrogen iodide, tin, copper, potassium cyanide, and those participating in the formation of Schiff bases or diazo-amino derivatives.

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[2] Biginelli, *Gazz. chim. ital.*, **27,** 347 (1897).

[3] Cain and Nicoll, *J. Chem. Soc.*, **81,** 1440 (1902).

[4] Cain, *ibid.*, **83,** 688 (1903).

[5] Meyer, *Ber.*, **28,** 1260 (1895).

Experimental Part

The *p*-methoxy-acetophenone used in these experiments was prepared from anisole by a combination of the methods of Gattermann, Ehrhardt and Maisch[6] and of Charon and Zamanos.[7] The yield of pure product (m. p., 38–39°) was 61%. Charon and Zamanos report that their yields were those calculated. We were not so successful, as some unsymmetrical bis(*p*-anisyl)ethylene, small amounts of other products and considerable tar were always formed, although the acetyl chloride was added very slowly (2 hours) and the temperature was maintained below 10°. When petroleum ether was employed as solvent, in place of carbon disulfide, the yield was only 8%. With excess anisole as solvent, the yield was 30%, calculated to the anisole consumed in the reaction.

***p*-Methoxy-acetophenone Sodium Sulfonate.**—*p*-Methoxy-acetophenone is not attacked by 95% sulfuric acid at 80°. Even fuming acid containing 15% of sulfur trioxide attacks it but slightly at laboratory temperature. It can be satisfactorily sulfonated, however, by great excess of stronger acid.

One hundred g. of fuming sulfuric acid containing 30% of sulfur trioxide was cooled to 5° and 25 g. of *p*-methoxy-acetophenone was added very slowly (30 minutes) with efficient stirring. After all the *p*-methoxy-acetophenone had been added, the stirring was continued for another half hour at low temperature, and the mixture then poured into 5 times its volume of ice-cold saturated salt solution. The sodium sulfonate soon began to separate, and after 20 minutes' further stirring the voluminous precipitate was filtered out; yield, nearly that calculated.

The salt formed large, snow-white, fatty leaflets, that turned pink when exposed to direct sunlight while still moist. Both the salt and the free acid were easily soluble in water.

Analysis. Calc. for $C_9H_9O_5SNa$: S, 12.69. Found: 12.82.

Fusion of this sodium salt for 3 minutes with a low-melting mixture of sodium and potassium hydroxides completely destroyed it. The insignificant amount of phenolic product appeared to be mainly a catechol derivative, since with ferric chloride solution it gave immediately a deep green, turning red upon the addition of sodium carbonate. Evidently, the ether linkage was also ruptured in the fusion.

METHYL ESTER.—This was a colorless liquid prepared from the sodium sulfonate and dimethyl sulfate.

3-Nitro-4-methoxy-acetophenone has been described already by Stockhausen and Gattermann,[8] who obtained it from *o*-nitro-anisole by the Friedel-Crafts reaction. Their yield was less than 9%. We find that high yields may be secured by the direct nitration of *p*-methoxy-acetophenone.

Fifty g. of *p*-methoxy-acetophenone was dissolved in 200 cc. of concd. sulfuric acid at laboratory temperature and the solution cooled to 0°. This solution was nitrated by the gradual (1 hour) addition of an ice-cold mixture of concd. nitric acid (containing $^1/_3$ mole of nitric acid) with an equal volume of concd. sulfuric acid. Stirring was continued for 15 minutes after the addition of the mixed acids, and the solution was then poured into a liter of ice water. After standing for an hour, the precipitated nitro derivative was collected and crystallized from alcohol; yield, 95%. It formed slender, lemon-yellow, odorless needles; m. p., 99.5° (corr.). Stockhausen and Gattermann found this same melting point for their product.

Although it has been observed that *o*-methoxynitro derivatives are not readily reduced to the corresponding hydrazo compounds, the reaction was attempted with the

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[6] Gattermann, Ehrhardt and Maisch, *Ber.*, **23,** 1201 (1890).

[7] Charon and Zamanos, *Compt. rend.*, **133,** 741 (1900).

[8] Stockhausen and Gattermann, *Ber.*, **25,** 3521 (1892).

above nitromethoxy-acetophenone, following the procedure of Starke.[9] Only tarry products resulted, nor could any benzidine derivative be isolated after treatment of the crude reaction product with concd. hydrochloric acid.

3-Amino-4-methoxy-acetophenone was prepared by reducing the above nitro derivative with tin and hydrochloric acid; yield, 74%. It crystallized from alcohol in large, flat, colorless, odorless hexagonal prisms; m. p., 102° (corr.); it was easily soluble in benzene, and moderately soluble in ether.

Analysis. Calc. for $C_9H_{11}O_2N$: C, 65.45; H, 6.67. Found: C, 65.68; H, 6.77.

ACETYL DERIVATIVE.—This was obtained by dissolving the amine in a slight excess of acetic anhydride and allowing the solution to stand for 2 or 3 days. It crystallized in colorless, rhombic prisms; m. p., 122.5° (corr.).

Analysis. Calc. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.33. Found: C, 63.68; H, 6.25.

Boiled with water, it was partially hydrolyzed. On crystallization from water, therefore, it showed a lower melting point, due to contamination with the free amine.

BENZAL DERIVATIVE.—This was a sirupy substance that solidified only after long standing. When warmed slightly, it reverted to the sirupy form.

p-NITROBENZAL DERIVATIVE.—This was obtained when the amine and *p*-nitrobenzaldehyde were heated at 110° for 15 hours.

Although a solid at laboratory temperatures, this product was not a crystalloid but a supercooled liquid. At room temperature, it was hard and brittle, but softened above 135° and was completely melted at 160°. The color ranged from deep red to yellow, depending upon the degree of subdivision of the solid. It was purified by dissolving it in boiling alcohol, in which it is but moderately soluble, and on cooling it separated in small droplets which soon solidified.

Analysis. Calc. for $C_{16}H_{14}O_4N_2$: C, 64.43; H, 4.70. Found: C, 64.18; H, 4.69.

Attempts to obtain the phenylhydrazine from the amine failed, in part due probably to intermolecular condensations of hydrazine and acetyl groups with formation of complex hydrazone types, leading finally to tars.

Similar lack of success attended our experiments for the production of a quinoline from the amine. Arsenic acid[10] was used as the oxidizing agent, but the yield of the quinoline was exceedingly poor, and tars were the main products.

Before the publication of the article by Schneider and Kraft[1] reporting the preparation of iso-acetovanillone from guaiacol, we had made a number of futile attempts to produce the same compound from the above amine. The diazonium salt was boiled in aqueous solution, it was dropped cold into a mixture of sulfuric acid and sodium hydrogen sulfate at 140° and at 160°,[11] and it was added to a boiling solution of equal parts by weight of copper sulfate and water;[12] but no iso-acetovanillone was isolated in any of these experiments, only tarry substances being formed.

3-Iodo-4-methoxy-acetophenone, prepared from the amino derivative, through the diazo reaction, was purified by repeated crystallization from 50% acetic acid, after decantation from tarry by-products; yield, 55%. It was obtained as yellow, feathery, odorless needles, m. p., 103.6° (corr.), that rapidly became brownish in the light and were easily soluble in alcohol, chloroform, ether or glacial acetic acid.

Analysis. Calc. for $C_9H_9O_2I$: C, 39.13; H, 3.26. Found: C, 39.29; H, 3.36.

When it was boiled for several hours with alcoholic potassium hydroxide solution, no phenol was formed.

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[9] Starke, *J. prakt. Chem.* [2] **59,** 210 (1889).

[10] Kueppel, *Ber.*, **29,** 704 (1896).

[11] Ger. pat., 95,339; *Winther,* **I,** 216.

[12] Ger. pat., 167,211; *ibid.*, **I,** 211.

3-Iodochloride-4-methoxy-acetophenone, $(ICl_2)(CH_3O)C_6H_3COCH_3$.—When the iodo derivative was dissolved in chloroform and the solution saturated with dry chlorine, an unstable iodochloride was obtained in fine, bright yellow crystals.

This compound lost its chlorine so easily that it could not be obtained pure. In a closed vessel, the chlorine liberated displaced hydrogen of the molecule, and the only gas then found present was hydrogen chloride. The result was a mixture of products, which is now awaiting further examination, and which probably contains some of its chlorine in Position 6.

3-Iodoso-4-methoxy-acetophenone.—The freshly precipitated iodochloride was treated with 5 *M* potassium hydroxide solution. The product was a grayish white, putty-like, amorphous mass that decomposed suddenly when heated. Efforts to purify it by crystallization from various solvents were unavailing, as it always separated in a slimy, amorphous form.

3-Iodoso-4-hydroxy-acetophenone.—In the preparation of the above iodosomethoxy derivative, the clear alkaline filtrate was made acid by passing into it a current of sulfur dioxide. A precipitate resulted that was believed at first to be the iodonium iodide,[13] an assumption which was shown to be untenable because of the ready solubility of the substance in dil. aqueous alkali and the analytical results. The precipitation of the compound from its alkaline solution by sulfur dioxide also indicated the presence of a phenolic hydroxyl group, presumably formed by the action of the strong alkali used in attacking the iodochloride, the ether being saponified thereby, due to the acid groups *ortho* and *para* to it.

From 50% alcohol, the compound crystallized in long, pale yellow needles, that melted without decomposition at 243° when carefully heated, but decomposed suddenly when heated rapidly. It was easily soluble in alcohol or benzene, and moderately soluble in ether.

Analysis. Calc. for $C_8H_7O_3I$: C, 34.55; H, 2.54. Found: C, 33.58, 34.26; H, 2.62, 2.68.

3-Cyano-4-methoxy-acetophenone (3-Acetyl-6-methoxy-benzonitrile) was prepared from the amine by the usual Sandmeyer method; yield, 70%.

The product crystallized from alcohol in fine, pale yellow, odorless needles, m. p. 159.5° (corr.), that soon changed to a light orange-yellow color. It was moderately soluble in alcohol or ether, and dissolved readily in benzene.

Analysis. Calc. for $C_{10}H_9O_2N$: C, 68.55; H, 5.18. Found: C, 68.35; H, 5.27.

An attempt to prepare the amide from this nitrile by the action of alkaline hydrogen dioxide[14] proved unsuccessful, the nitrile being recovered unchanged.

Efforts to saponify the nitrile to the corresponding acid were almost equally disappointing. Heating it with 70% sulfuric acid for several hours gave mainly tarry products, but a very small amount of a carboxylic acid was isolated, insufficient for purification, which melted with decomposition at 255°. Boiling the nitrile with concd. hydrochloric acid for 10 hours, heating it with 5 *M* potassium hydroxide solution for several hours, or fusing the sodium sulfonate with sodium formate, alike failed to yield the acid sought and gave only decomposition products.

Experiments were also conducted for the conversion of the nitrile into the imino ester by the action of dry hydrogen chloride and anhydrous methyl alcohol, but no reaction occurred, and the nitrile was recovered unaltered.

2-Methoxy-5-acetyl-diazobenzene Perbromide was precipitated at once when the calculated amount of bromine dissolved in hydrobromic acid was added to the diazonium chloride; yield, nearly that calculated.

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[13] V. Meyer, *Ber.*, **27**, 1592 (1894).

[14] Radziszewski, *ibid.*, **18**, 355 (1885).

The compound formed pale yellow, flat needles (from cold alcohol), m. p., 68–70°, that decomposed on standing or on heating them with alcohol.

2-Methoxy-5-acetyl-azidobenzene, $(CH_3O)(CH_3CO)C_6N_3.N_3$.—Ammonium hydroxide solution was added with vigorous stirring to a fine suspension of the diazo perbromide in water.[15] The azido compound was precipitated instantly as a mahogany-red mass which, after decolorization and recrystallization from dil. alcohol, was obtained in long, delicate needles of a peculiar faint pinkish buff color that darkened on standing and melted with decomposition at 87° (corr.). When heated rapidly, the substance exploded slightly above its melting point. It was freely soluble in alcohol or benzene, and also dissolved easily in ether; yield, 75%.

Analysis. Calc. for $C_9H_9O_2N_3$: C, 56.53; H, 4.74. Found: C, 56.33; H, 4.65.

The method of Culmann and Gasiorowski[16] for the synthesis of azidobenzenes by the action of hydrochloric acid and stannous chloride upon the diazonium chloride was tried and found to be unsuitable for the production of this azide.

Griess[17] has shown that certain azidobenzenes with a free *para* position rearrange to *p*-aminophenols when heated with 50% sulfuric acid. The azido derivative of *p*-methoxy-acetophenone described above, however, decomposed to a tar after only 15 minutes' heating with 25% acid.

2,2′-Dimethoxy-5,5′-diacetyl-diazo-aminobenzene, $(CH_3O)(CH_3CO)C_6H_3.N:N.NH.C_6H_3(COCH_3)(OCH_3)$.—Ten g. of the 3-amino-4-methoxy-acetophenone was dissolved in 50 cc. of water and 20 g. of concd. hydrochloric acid, and the solution was well cooled and diazotized with the exact amount of sodium nitrite. To this diazo solution was added a solution of 10 g. of the same amine in 20 cc. of water and 6 g. of concd. hydrochloric acid, followed by a saturated aqueous solution of 35 g. of potassium acetate. The diazo-amino compound precipitated immediately. It was purified by boiling it in alcoholic solution with a decolorizing carbon, filtering the solution while it was still boiling hot, cooling quickly in an ice pack and filtering it promptly with suction. When the pale yellow solution was allowed to cool slowly, orange-colored needles formed that were contaminated with the isomeric amino-azo derivative described below; yield, 95%.

The pure product formed small, pale yellow needles, m. p. 178° (corr.), but was sparingly soluble in boiling alcohol and nearly insoluble in cold.

Analysis. Calc. for $C_{18}H_{19}O_4N_3$: C, 63.34; H, 5.57. Found: C, 63.10; H, 5.46.

2,2′-Dimethoxy-5,5′-diacetyl-4-amino-azobenzene.—The diazo-amino derivative was suspended in water and an equivalent amount of hydrochloric acid[18] added. After standing at laboratory temperature for 3 days, the mixture had changed mainly to tarry products and only a small amount of the aminoazo derivative was secured. It formed dark red microscopic crystals (from 50% alcohol), m. p. 198–200° (corr.), and proved to be an extremely feeble base, being insoluble in 10 *M* hydrochloric acid, but soluble in 13 *M* with a greenish blue color.

Analysis. Calc. for $C_{18}H_{19}O_4N_3$: C, 63.34; H, 5.57. Found: C, 63.18; H, 5.44.

Summary

1. Tri-substituted benzenes carrying osmophores in 1,3,4 arrangement are not always odorous, even when sufficiently volatile.

2. Although 4-methoxy-acetophenone is itself a perfume substance

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[15] Griess, *Ann.*, **137,** 68 (1866).

[16] Culmann and Gasiorowski, *J. prakt. Chem.*, [2] **40,** 99 (1889).

[17] Griess, *Ber.*, **27,** 313 (1894).

[18] Friswell and Green, *J. Chem. Soc.*, **47,** 920 (1885).

the introduction of the osmophores NO_2, NH_2, N_3 or CN, in Position 3 results in odorless products.

3. Certain new hypotheses are advanced concerning steric hindrance.

4. The following new compounds are described: the 3-sulfo, 3-amino, 3-acetamino, 3-*p*-nitrobenzalamino, 3-iodo, 3-iodochloride, 3-iodoso and 3-cyano derivatives of 4-methoxy-acetophenone; and from the 3-amino, the corresponding diazo perbromide, azido, diazo-amino and amino-azo derivatives; also the 3-iodoso-4-hydroxy-acetophenone.

5. Some improved methods of preparation have been developed for compounds previously known.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE KETENIC DECOMPOSITION OF METHYLETHYL KETONE

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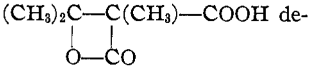
It has recently been demonstrated that ketene can be prepared in excellent yields[1] merely by heating acetone vapors in a suitable apparatus. With this in view, methylethyl ketone was put to the same test. It can evidently decompose in two ways: $CH_3–CO–C_2H_5 \longrightarrow CH_2:CO + C_2H_6$; or $CH_3–CH_2–CO–CH_3 \longrightarrow CH_3–CH:CO + CH_4$. If ketene were formed, it would not be a profitable process unless the yield were better than that obtained in the decomposition of acetone.[2] However, if methyl ketene were formed, the reaction would be one of great interest regardless of the yield, inasmuch as methyl ketene is unusually difficult to prepare.

The literature that deals with methyl ketene is very limited. Staudinger[3] prepared it in ethereal solution in 6 to 8% yield from α-bromopropionyl bromide and zinc shavings. No other positive statements are on record, although a few negative items bear witness to the difficulty of its isolation. One such is given by Ott.[4] In his discussion of the ketonic decomposition of β-lactones, he observed that  $\begin{array}{l}(CH_3)_2C—C(CH_3)—COOH\\ \qquad\ \ |\quad\ |\\ \qquad\ O—CO\end{array}$ decomposed at 110–113° into acetone, carbon suboxide, and an oil in approximately 80–

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[1] Hurd and Cochran, THIS JOURNAL, **45**, 515 (1923). A repetition of the experiment was made in this Laboratory by Mr. J. W. Kern who obtained 18.5 g. of purified acetanilide from 28 g. of unrecovered acetone, a yield of 28.3%, in contrast to the yield of 17.5% reported in the original article. The only change in the apparatus was the use of tight-fitting rubber stoppers in place of corks, wherever possible; where corks were used they were well softened and painted with water glass inside and outside 1 day before use. As in the original report, the gas burners were giving their full blast. It is now thought that the temperature 600°, which was originally reported, is somewhat lower than the true temperature of the furnace.

[2] Methylethyl ketone is nearly as inexpensive as acetone.

[3] Staudinger, *Ber.*, **44**, 535, 541 (1911).

[4] Ott, *Ann.*, **401**, 159 (1914).