

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

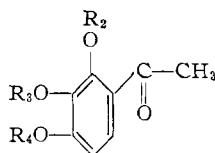
Cleavage of Polyalkoxyacetophenones with Hydrogen Bromide-Acetic Acid

BY PETE D. GARDNER, W. J. HORTON AND R. E. PINCOCK

RECEIVED JANUARY 16, 1956

Five 2-hydroxy-3,4-dialkoxyacetophenones were cleaved with hydrogen bromide-acetic acid at room temperature. It has been demonstrated that the 3-alkoxy group (*meta*) is cleaved and not the 4-alkoxy group (*para*) as has been claimed for aluminum chloride-ether cleavage. An influence of the 4-alkoxy group in promoting the above cleavage seems likely.

Consideration of the accelerating effect of the 3-methoxyl group in the hydrogen bromide-acetic acid cleavage of 2,3-dimethoxyacetophenones to yield 2-hydroxy-3-methoxyacetophenones¹ suggested the investigation of the cleavage of 2-hydroxy-3,4-dimethoxyacetophenone (II) to determine whether the 4-methoxyl group would similarly expedite the removal of the adjacent 3-methoxyl group. The product obtained after 24 hr. at room temperature was identical to the compound given the structure III.² However, the alternate cleavage product IV is reported³ to be the result when



R otherw ise = H

- | | |
|---|---|
| I, R ₂ , R ₃ , R ₄ = CH ₃ | V, R ₂ , R ₃ = C ₂ H ₅ ; R ₄ = CH ₃ |
| II, R ₃ , R ₄ = CH ₃ | VI, R ₂ , R ₄ = C ₂ H ₅ ; R ₃ = CH ₃ |
| III, R ₄ = CH ₃ | VII, R ₃ = C ₂ H ₅ ; R ₂ , R ₄ = CH ₃ |
| IV, R ₃ = CH ₃ | VIII, R ₂ , R ₃ , R ₄ = C ₂ H ₅ |
| | IX, R ₃ , R ₄ = C ₂ H ₅ |

I is cleaved by aluminum chloride. Moreover, it is stated³ that the methoxy groups cleaved are those *ortho*, followed by the group *para* to the carbonyl group in aryl ketones. It was felt necessary, therefore, to rigorously establish the structure of the material which we obtained. The following evidence indicates that the 3-methoxyl group (*meta*) is cleaved and not the 4-methoxyl group.

(1) The cleavage product III gave V when treated with ethyl sulfate. Oxidation of V gave an acid with a melting point identical to that reported⁴ for 2,3-diethoxy-4-methoxybenzoic acid. The possibility of fortuitous agreement of the melting point was eliminated by the preparation of the unknown 2,4-diethoxy-3-methoxybenzoic acid which had a different melting point and depressed the melting point of the known benzoic acid. The oximes of V and VI were different as evidenced by mixed melting point determination.

(2) The polyalkoxyacetophenones VI and VII have dissimilar alkoxy groups in the 3- and 4-positions. Hence the analysis of the product after cleavage distinguishes between cleavage in the 3- or in the 4-position. These acetophenones (VI and VII) were prepared and the *ortho*-alkoxy group was first removed.¹ Further cleavage of these mono-

cleaved materials produced in each case the 2,3-dihydroxy-4-alkoxy compound. To supplement the analytical data, the 2,3-dihydroxy-4-methoxy (or ethoxy)-acetophenones were found to be identical to cleavage products from II or from IX, respectively.

(3) 2-Hydroxy-4-methoxy- and 2-hydroxy-4,6-dimethoxyacetophenones,⁵ which contain a 4-methoxyl but no 3-methoxyl group, were submitted to cleavage under the conditions used above. The compounds were recovered in yields of 90 and 100%, respectively, indicating the stability of *para*-methoxyl groups under these conditions.

In the attempt to demonstrate the influence of the 4-alkoxyl group on the reaction at the adjacent 3-alkoxyl group, it was felt desirable to compare the 2-hydroxyl compounds, thus eliminating differences due to the initial splitting of the 2-alkoxyl group. The preparation of the polyalkoxyacetophenones and their reaction to give the related 2-hydroxy compounds are given in Table I. The yields in the reaction at the 2-position are consistent with previous work.¹

The 2-hydroxypolyalkoxyacetophenones were allowed to stand at room temperature in *ca.* 6% hydrogen bromide-acetic acid for 24 hr. The data are collected in Table II. In five cases, a 4-alkoxy group was present and a 2,3-dihydroxy compound could be isolated. In the case of 2-hydroxy-3-methoxyacetophenone, the only control compound available, 2,3-dihydroxyacetophenone was not found and the unreacted compound was recovered in 85.6% yield excluding an additional 7.9% yield of low melting solid. It would therefore appear likely that a 4-alkoxy group assists the removal of a 3-alkoxy group when hydrogen bromide-acetic acid is used.

The assistance of grants from the National Science Foundation and from the University Research Committee is gratefully acknowledged.

Experimental⁶

Preparation of Polyalkoxybenzenes. (a).—1,2,3,5-Tetramethoxybenzene was prepared as described³ and melted at 38–40°; reported 47°. The acetophenone from this material when oxidized with alcohol and 35% nitric acid analogous to the oxidation of 1,2,3-trimethoxybenzene³ gave 2-hydroxy-6-methoxy-3-acetylbenzoquinone; m.p. 154–155°

(3) The recovery of the phloracetophenone derivative after 24 hr., without cleavage of the 6-methoxyl group, indicates that the chelation proposed by Hughes for the splitting of *ortho*-alkoxyaryl ketones cannot take place in this case. The carbonyl group is not available for chelate formation due to hydrogen bonding with the *ortho*-hydroxyl hydrogen. This chelate must be unopened during the course of the reaction. 2,4,6-Trimethoxyacetophenone is mono-cleaved in 83% yield after 24 hr. G. K. Hughes, N. K. Matheson, A. T. Norman and E. Ritchie *Australian J. Sci. Research, Ser. A.*, **5**, 206 (1952).

(6) Melting points of analyzed compounds are corrected

- (1) W. J. Horton and J. T. Spence, *THIS JOURNAL*, **77**, 2894 (1955).
 (2) (a) Ishwar-Dass, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **37A**, 599 (1953); (b) N. Mauthner, *J. prakt. Chem.*, **150**, 257 (1938); (c) W. Baker, E. H. T. Jukes and C. A. Subrahmanyam, *J. Chem. Soc.*, 1681 (1934).
 (3) W. Baker, *ibid.*, 662 (1941).
 (4) F. Wessely and K. Sturm, *Ber.*, **62B**, 119 (1929).

TABLE I

Polyalkoxyacetophenone ^a	Moles acylated	Yield, %	B.p., °C. (mm.)	Corresponding 2-hydroxypolyalkoxyacetophenone ¹ Yield, %	M.p., °C.
2,3,4,6-(CH ₃ O) ₄	0.046	81 ^b	172-186(17) M.p. 49-52	58	103-107 ^c
2,4-(CH ₃ O) ₂ -3-C ₂ H ₅ O	.0824	54.3	M.p. ca. 23-25 ^d	71	49-52
2,3-(C ₂ H ₅ O) ₂ -4-CH ₃ O	85 ^e	118 (0.85)	75	50-56 ^f
2,4-(C ₂ H ₅ O) ₂ -3-CH ₃ O	.03	84	111 (0.4-0.32) ^g
2,3,4-(C ₂ H ₅ O) ₃	.1	86.6	100-110 (0.20) ^h	42	49-55 ⁱ

^a Prepared from polyalkoxybenzene, acetic acid and polyphosphoric acid according to P. D. Gardner, *THIS JOURNAL*, 76, 4550 (1954). The temperature was 60-65° for 2.5 hr. in each case. ^b In another run 1,1-bis-(2,3,4,6-tetramethoxyphenyl)-ethylene was obtained in 20% yield after crystallization from ethanol; m.p. 122-132°. It was also prepared (15%) from 2,3,4,6-tetramethoxyacetophenone and the tetramethoxybenzene in polyphosphoric acid for 2.5 hr. at 60°. The product was negative to 2,4-dinitrophenylhydrazine or ferric chloride and insoluble in 40% sodium hydroxide. From ethanol it melted at 151.5-152.5° (cor.). *Anal.* Calcd. for C₂₂H₂₈O₈: C, 62.84; H, 6.71. Found: C, 62.49; H, 6.70. ^c Reported, m.p. 112-113°, G. Bargellini and S. M. Zoras, *Gazz. chim. ital.*, 64, 192 (1934); m.p. 103-104°. ^d Distilled at high vacuum and a center cut taken for analysis. *Anal.* Calcd. for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.36; H, 7.49. The semicarbazone from benzene-petroleum ether (60-71°) melted at 161.8-163° (cor.). *Anal.* Calcd. for C₁₃H₁₉O₄N₃: C, 55.50; H, 6.81. Found: C, 55.51; H, 6.65. ^e By ethylation of 2-hydroxy-3-ethoxy-4-methoxyacetophenone. *Anal.* Calcd. for C₁₃H₁₉O₄: C, 65.53; H, 7.61. Found: C, 65.56; H, 7.63. The oxime melted at 85-87° and did not depress the melting point of the oxime of material prepared by ethylation of 2,3-dihydroxy-4-methoxyacetophenone. The latter oxime recrystallized from petroleum ether (60-71°) melted at 87.5-88° (cor.). *Anal.* Calcd. for C₁₃H₁₉O₄N: C, 61.64; H, 7.56. Found: C, 62.16; H, 7.76. Permanganate oxidation of V gave 2,3-diethoxy-4-methoxybenzoic acid, m.p. 75.4-76.5° (cor.) after crystallization from ethyl acetate-petroleum ether (60-71°). Reported⁴ m.p. 75° (cor.). *Anal.* Calcd. for C₁₂H₁₆O₅: C, 59.99; H, 6.71. Found: C, 60.06; H, 6.64. ^f Material crystallized from aqueous ethanol and sublimed melted at 57.8-58.5° (cor.). *Anal.* Calcd. for C₁₁H₁₄O₄: C, 62.84; H, 6.71. Found: C, 63.17; H, 6.83. ^g On redistillation, a center cut boiled at 106-107° (0.30 mm.). *Anal.* Calcd. for C₁₃H₁₈O₄: C, 65.53; H, 7.61. Found: C, 66.06; H, 7.75. The oxime from cyclohexane-petroleum ether (60-71°) and finally sublimed at 83° (0.17 mm.) (sublimation temperature) melted at 102.8-105.6° (cor.). *Anal.* Calcd. for C₁₃H₁₉O₄N: C, 61.64; H, 7.56. Found: C, 61.83; H, 7.38. Permanganate oxidation of VI gave 2,4-diethoxy-3-methoxybenzoic acid which was sublimed at 80-100° (0.19 mm.) (bath temperature) and then melted at 88.4-89.4° (cor.). *Anal.* Calcd. for C₁₂H₁₆O₅: C, 59.99; H, 6.71. Found: C, 60.38; H, 6.70. Mixed with 2,3-diethoxy-4-methoxybenzoic acid, m.p. 59-77°. ^h Redistillation produced a colorless cut b.p. 100° (0.14 mm.) which repeatedly gave unsatisfactory analyses. The oxime, sublimed at 0.2 mm. and crystallized from cyclohexane melted at 91.6-92.2° (cor.). *Anal.* Calcd. for C₁₄H₂₀O₄N: C, 62.90; H, 7.92. Found: C, 63.09; H, 8.10. ⁱ After sublimation at 125-145° (0.14 mm.) (sublimation temperature) and two crystallizations from cyclohexane, colorless short thin prisms, m.p. 51.4-52.4° (cor.), were obtained. *Anal.* Calcd. for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found: C, 64.54; H, 7.31. The benzoate after purification from cyclohexane formed pale yellow long rods, m.p. 69.4-71° (cor.). *Anal.* Calcd. for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.84; H, 6.34.

TABLE II

2-Hydroxypolyalkoxyacetophenone	Corresponding 2,3-dihydroxy compound ^a m.p., °C.	Yield, % (moles used)
3,4-(CH ₃ O) ₂ ^b	126-130	46 ^c (0.05)
3,4,6-(CH ₃ O) ₃	146-154	42 ^d (0.01)
3-C ₂ H ₅ O-4-CH ₃ O	122-126	22 ^e (0.005)
[2,4-(C ₂ H ₅ O) ₂ -3-CH ₃ O] ^f	99-104	43 ^g (0.01)
3,4-(C ₂ H ₅ O) ₂	94-102	20 ^h (0.01)
3-CH ₃ O	14.4 ⁱ (0.01)
4-CH ₃ O	9.6 ^j (0.01)
4,6-(CH ₃ O) ₂	0 ^k (0.02)

^a All products gave strong positive Tollens tests. All were obtained by reaction with ca. 6% hydrogen bromide-acetic acid for 24 hr. at room temperature. ^b An attempt to prepare the quinone with alcohol-nitric acid⁸ gave (32.5%) of 5-nitro-2-hydroxy-3,4-dimethoxyacetophenone, long yellow needles from ethanol; m.p. 83-83.8° (cor.). *Anal.* Calcd. for C₁₀H₁₁O₅N: C, 49.79; H, 4.60. Found: C, 50.21; H, 4.49. The compound gave a red color with alcoholic ferric chloride and was soluble in 5% sodium bicarbonate. ^c For analysis, m.p. 131-132.5° (cor.). *Anal.* Calcd. for C₉H₁₀O₄: C, 59.34; H, 5.53. Found: C, 59.80; H, 5.76. Reported 127-128°, 132°. ^d The diacetate melted at 148-149.5°; reported m.p. 150-151°. ^e The dibenzoate melted at 184-186°; reported m.p. 185-186°. ^f A run on 0.143 mole of I gave 54.7% of III, m.p. 125-130°. ^g After one crystallization from benzene. ^h After one crystallization from benzene. Not depressed on melting with previously obtained III. ⁱ Lack of material prevented the use of the 2-hydroxy compound. ^j After one crystallization from cyclohexane. Melts undepressed when mixed with 2,3-dihydroxy-4-ethoxyacetophenone obtained below. Melts at 88-118° when mixed with III. ^k After crystallization from benzene-cyclohexane. For analysis, m.p. 102.2-103.2° (cor.). Reported for a monoethyl ether of gallacetophenone, m.p. 102°. A. G. Perkin and C. R. Wilson, *J. Chem. Soc.*, 83, 132 (1903). *Anal.* Calcd. for C₁₀H₁₂O₄:

C, 61.21; H, 6.17. Found: C, 61.61; H, 6.51. ⁴ Yield by difference based on recovery of unreacted compound, m.p. 44-49°. This value is high. An additional 7.9% was recovered by vacuum distillation of the residue and treatment of the distillate with ice cold 5% sodium carbonate which gave crystals, m.p. 34-47°. ⁵ Yield by difference based on recovered starting material, m.p. 45-48°. ⁶ Recovered starting compound in two crops, m.p. 79-83°, 75-80°, in quantitative yield.

after crystallization from ethyl acetate; reported m.p. 158-160°.

Anal. Calcd. for C₉H₈O₅: C, 55.11; H, 4.11. Found: C, 55.24; H, 4.57.

(b).—1,3-Dimethoxy-2-ethoxybenzene resulted (50%) from the ethylation of 2,6-dimethoxyphenol. The compound distilled at 133° (17 mm.) and a redistilled center cut was taken at 80° (0.7 mm.).

Anal. Calcd. for C₁₀H₁₄O₃: C, 65.91; H, 7.74. Found: C, 66.16; H, 7.83.

(c).—2,6-Diethoxyphenol was prepared from 1,2,3-triethoxybenzene in a manner analogous to that used for 2,6-dimethoxyphenol.⁸ From 31.5 g. of the triethoxybenzene, 18.6 g. (68.2%) of light yellow solid, b.p. 90-82° (0.37-0.17 mm.), m.p. 59-62.5°, was obtained. By repeated crystallization from cyclohexane and from dilute methanol long thin prisms, m.p. 60.6-62°, were obtained. The compound gave a dark green ferric chloride test which soon changed to orange on standing.

Anal. Calcd. for C₁₀H₁₄O₄: C, 65.91; H, 7.74. Found: C, 65.32; H, 7.87.

The benzoate could not be crystallized. The *p*-nitrobenzoate, crystallized four times from ethanol, formed colorless plates, m.p. 99.8-101.8°.

Anal. Calcd. for C₁₇H₁₇O₆N: C, 61.62; H, 5.17. Found: C, 61.89; H, 5.24.

(7) G. S. K. Rao, K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 27A, 245 (1948).

(8) C. D. Hurd and H. E. Winberg, *THIS JOURNAL*, 64, 2085 (1942).

Methylation of 2,6-diethoxyphenol with methyl sulfate gave 1,3-diethoxy-2-methoxybenzene (77%), b.p. 168–174° (84 mm.). On redistillation the middle colorless fraction boiled at 145–146° (34 mm.).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.75; H, 8.28.

2,3-Dihydroxy-4,6-dimethoxyacetophenone.—The following is typical of the method used to prepare the 2,3-dihydroxyacetophenones in Table II. A solution of 2.66 g. of 2-hydroxy-3,4,6-trimethoxyacetophenone, m.p. 108–112°, in 37.5 ml. of acetic acid was combined with 7.5 ml. of 30% hydrogen bromide–acetic acid and allowed to stand at room temperature for 24 hr. The solution was treated at 0° with

160 ml. of 10% sodium hydroxide and extracted four or five times (or continuously in an extractor) with ether. Evaporation of the ether gave crystals which were then recrystallized from benzene, 0.9 g. (42%), m.p. 146–154°. Further purification brought the melting point to 165.2–166.5°. The compound gave a black color with ferric chloride and depressed the melting point of 2,3,6-trihydroxy-4-methoxyacetophenone which was prepared by reduction of the quinone above.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.96; H, 5.71.

SALT LAKE CITY 12, UTAH

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

The Anomalous Reaction of Methylmagnesium Iodide with the Tosylate of *p*-Hydroxybenzaldehyde¹

BY WESLEY J. DALE AND HENRY E. HENNIS

RECEIVED NOVEMBER 28, 1955

The addition of methylmagnesium iodide to the tosylate of *p*-hydroxybenzaldehyde did not give the expected product, *p*-vinylphenyl tosylate; rather, *p*-isopropenylphenyl tosylate was obtained in 52% yield. The structure of the anomalous product was determined by an independent synthesis. It is postulated that a small amount of the normal Grignard complex, in the presence of an excess of the aldehyde, serves as a Tischenko catalyst to form the ditosylate of *p*-hydroxybenzyl *p*-hydroxybenzoate. Reaction of this ester with methylmagnesium iodide, followed by dehydration of the resulting tertiary carbinol, gives *p*-isopropenylphenyl tosylate.

In a study concerning the preparation of various esters of *p*-vinylphenol, addition of methylmagnesium iodide to the tosylate of *p*-hydroxybenzaldehyde (I) via the inverse technique did not yield the expected product, *p*-vinylphenyl tosylate. Instead, a brown oil was obtained which could not be induced to crystallize from a variety of solvents tried, but which gave, upon distillation *in vacuo*, a single white solid III having the composition of a homolog of *p*-vinylphenyl tosylate.

The structure of this unexpected product was determined by the reactions shown below (I–VII). Compound III added bromine readily but failed to give a crystalline bromine derivative. When III was saponified and the basic hydrolysis mixture was carbonated, a white crystalline solid IV separated whose physical properties did not resemble those of either *p*-propenylphenol² or *p*-allylphenol.³ Since IV was not very stable and became yellow on contact with air, it was converted to its benzoate derivative V whose composition again indicated that the parent phenol was a homolog of *p*-vinylphenol. It was apparent that III was the tosylate of *p*-isopropenylphenol. An authentic sample of III was prepared by the reaction of methylmagnesium iodide with *p*-carboethoxyphenyl tosylate (VI). The product of this reaction possessed physical properties identical to those of III obtained from I and the mixed melting point of III with authentic *p*-isopropenylphenyl tosylate was not depressed. When a sample of authentic *p*-isopropenylphenyl tosylate was converted to its benzoate without isolation of the intermediate phenol, the melting point of the product was identical to that

of V obtained from the anomalous reaction and the mixed melting point with V was not depressed. Further, authentic III, like the product obtained from I, absorbed bromine but also failed to give a solid bromine derivative.

It seemed most likely that the anomalous compound III was obtained from the dehydration of a tertiary alcohol which could result from the reaction of the Grignard reagent with a ketone, such as the tosylate of *p*-hydroxyacetophenone, or with some ester of the tosylate of *p*-hydroxybenzoic acid. The possibility was first examined that a substituted acetophenone was the precursor of *p*-isopropenylphenyl tosylate, although no evidence of the presence of even a trace of ketone was detected in the product of the anomalous reaction. When methylmagnesium iodide was added to *p*-acetylphenyl tosylate under the conditions of the original Grignard reaction, no distillable products were obtained and, in another experiment, the only volatile product obtained was unreacted *p*-acetylphenyl tosylate (15% recovery). It was concluded that even if *p*-acetylphenyl tosylate had been generated in the original reaction mixture, its reaction with methylmagnesium iodide would not lead to the formation of *p*-isopropenylphenyl tosylate under the conditions of our experiments.

An ester therefore appeared to be the more probable precursor, especially since Franke and Kohn⁴ obtained an ester, hydroxypivalyl hydroxypivalate, from the reaction of hydroxypivalaldehyde with ethylmagnesium bromide. The most plausible explanation for the origin of III therefore seems to be that a Tischenko type of reaction is involved once a Grignard complex is formed; the over-all reaction can thus be imagined to proceed through the series of transformations shown below (VIII–

(1) Abstracted from a portion of a thesis to be submitted by H. E. H. to the Graduate School of the University of Missouri in partial fulfillment of the requirements for the Ph.D. degree.

(2) R. Stoermer and B. Kahlert, *Ber.*, **34**, 1812 (1901).

(3) J. F. Eykman, *ibid.*, **22**, 2736 (1889).

(4) A. Franke and M. Kohn, *Monatsh.*, **25**, 865 (1904).