[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

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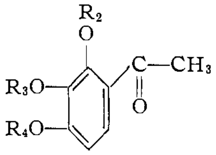
Five 2-hydroxy-3,4-dialkoxyacetophenones were cleaved with hydrogen bromide–acetic acid at room temperature. It has been demonstrated that the 3-alkoxy group (*meta*) is cleaved and not the 4-alkoxy group (*para*) as has been claimed for aluminum chloride–ether cleavage. An influence of the 4-alkoxy 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-methoxyacetophenones[1] 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 reported[3] to be the result when I is cleaved by aluminum chloride. Moreover, it is stated[3] 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.



R otherwise = H

I, R_2, R_3, R_4 = CH_3
II, R_3, R_4 = CH_3
III, R_4 = CH_3
IV, R_3 = CH_3
V, R_2, R_3 = C_2H_5; R_4 = CH_3
VI, R_2, R_4 = C_2H_5; R_3 = CH_3
VII, R_3 = C_2H_5; R_2, R_4 = CH_3
VIII, R_2, R_3, R_4 = C_2H_5
IX, R_3, R_4 = C_2H_5

(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 reported[4] 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 monocleaved 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.

Experimental[6]

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

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(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).

(5) 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

TABLE I

Polyalkoxyacetophenone[a]	Moles acylated	Yield, %	B.p., °C. (mm.)	Corresponding 2-hydroxypoly-alkoxyacetophenone[1] Yield, %	M.p., °C.
2,3,4,6-$(CH_3O)_4$	0.046	81[b]	172–186(17) M.p. 49–52	58	103–107[c]
2,4-$(CH_3O)_2$-3-C_2H_5O	.0824	54.3	M.p. *ca.* 23–25[d]	71	49–52
2,3-$(C_2H_5O)_2$-4-CH_3O	....	85[e]	118 (0.85)	75	50–56[f]
2,4-$(C_2H_5O)_2$-3-CH_3O	.03	84	111 (0.4–0.32)[g]	..	......
2,3,4-$(C_2H_5O)_3$	.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 $C_{22}H_{28}O_8$: 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°.[3] [d] Distilled at high vacuum and a center cut taken for analysis. *Anal.* Calcd. for $C_{12}H_{16}O_4$: 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 $C_{13}H_{19}O_4N_3$: 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 $C_{13}H_{18}O_4$: 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 $C_{13}H_{19}O_4N$: 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°). Reported[4] m.p. 75° (cor.). *Anal.* Calcd. for $C_{12}H_{16}O_5$: 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 $C_{11}H_{14}O_4$: 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 $C_{13}H_{18}O_4$: 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.) (sublimer temperature) melted at 102.8–105.6° (cor.). *Anal.* Calcd. for $C_{13}H_{19}O_4N$: 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 $C_{12}H_{16}O_5$: 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 $C_{14}H_{21}O_4N$: C, 62.90; H, 7.92. Found: C, 63.09; H, 8.10. [i] After sublimation at 125–145° (0.14 mm.) (sublimer temperature) and two crystallizations from cyclohexane, colorless short thin prisms, m.p. 51.4–52.4° (cor.), were obtained. *Anal.* Calcd. for $C_{12}H_{16}O_4$: 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 $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.84; H, 6.34.

TABLE II

2-Hydroxypolyalkoxy-acetophenone	Corresponding 2,3-dihydroxy compound[a] m.p., °C.	Yield, % (moles used)	
3,4-$(CH_3O)_2$[b]	126–130	46[c]	(0.05)
3,4,6-$(CH_3O)_8$	146–154	42[d]	(.01)
3-C_2H_5O-4-CH_3O	122–126	22[e]	(.005)
[2,4-$(C_2H_5O)_2$-3-CH_3O][f]	99–104	43[g]	(.01)
3,4-$(C_2H_5O)_2$	94–102	20[h]	(.01)
3-CH_3O	.....	14.4[i]	(.01)
4-CH_3O	.....	9.6[j]	(.01)
4,6-$(CH_3O)_2$	.....	0[k]	(.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 acid[3] 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 $C_{10}H_{11}O_6N$: 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 $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.80; H, 5.76. Reported 127–128°,[2a] 132°.[2c] The diacetate melted at 148–149.5°; reported m.p. 150–151°.[2a] The dibenzoate melted at 184–186°; reported m.p. 185–186°.[2a] A run on 0.143 mole of I gave 54.7% of III, m.p. 125–130°. [d] After one crystallization from benzene. [e] After one crystallization from benzene. Not depressed on melting with previously obtained III. [f] Lack of material prevented the use of the 2-hydroxy compound. [g] 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. [h] 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 $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.61; H, 6.51. [i] 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°. [j] Yield by difference based on recovered starting material, m.p. 45–48°. [k] 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°.[7]

Anal. Calcd. for $C_9H_8O_5$: 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 $C_{10}H_{14}O_3$: 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 $C_{10}H_{14}O_3$: 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 $C_{17}H_{17}O_6N$: C, 61.62; H, 5.17. Found: C, 61.89; H, 5.24.

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(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*-Hydroxybenzaldehyde[1]

BY WESLEY J. DALE AND HENRY E. HENNIS

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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*-propenylphenol[2] 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 Kohn[4] 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–

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[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).