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

Boron Trifluoride-Catalyzed Acetylation of Methoxyhydroxybenzenes¹

W. J. HORTON AND MASON G. STOUT²

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Mono- or diacetylation of some methoxyhydroxybenzenes and their esters was found dependent on (1) the presence or absence of acetic anhydride in the solvent acetic acid and (2) the availability of two unsubstituted positions *ortho* to a free hydroxyl or ester group. 2,4-Dinitrophenyl ethers, like methyl ethers, monoacetylate with selective cleavage of the methoxyl *ortho* to the acetyl group.

The reaction of 1,2,3,5-tetramethoxybenzene (I) in acetic acid-acetic anhydride which was nearly saturated with boron trifluoride and held below 30° gave 2-hydroxy-3,4,6-trimethoxyacetophenone (II) in excellent yield (Table I). This acetylation with selective cleavage of a methoxyl group ortho to the acetyl group conveniently replaces the twostep acetylation with polyphosphoric acid³ followed by cleavage with hydrogen bromide in acetic acid.^{4,5}



The boron trifluoride-catalyzed acetylation of compounds related to I but containing free phenolic groups gave mono-C-acetyl or di-C-acetyl products depending on the location of the free hydroxyl group and on whether or not acetic anhydride was used in the reaction. The following general statements summarize the reactions, both those in the literature and those now newly reported.

A. Diacetylation of the benzenoid ring occurs (at 30°) if the initial compound contains two unsubstituted positions *ortho* to a free hydroxyl group (or the corresponding acetate or benzoate) and provided also that *acetic anhydride*-acetic acid is used. In acetic acid alone, only one acetyl group enters the ring. Acetyl or benzoyl derivatives of the free phenolic group do not impede diacetylation if vacant *ortho* positions are available: 2,4-dinitrophenyl ethers of the free phenol do limit the reaction to monoacetylation and constitute a useful

blocking group which may subsequently be removed.

B. The formation of a boron complex (III) preserves a free hydroxyl group ortho to each C-acetyl group introduced. Otherwise, initially free hydroxyls (and O-benzoyl derivatives) are converted to O-acetyl compounds.⁶

C. Complex formation as in III prevents cleavage of the methoxyl at the other position *ortho* to the acetyl even though this methoxyl is buttressed by an adjacent methoxyl group.⁴

Antiarol⁷ (IV), its benzoate, or the isopropyl ether (Table I) produced a di-C-acetyl compound (X) in acetic anhydride-acetic acid. The 2,4-dinitrophenyl ether of antiarol, under conditions identical to those used on antiarol, gave a mono-C-acetyl derivative (VII);⁸ the course of this reaction, as for I, illustrates the requirement of a free hydroxyl group for di-C-acetylation.



The boron trifluoride-catalyzed acetylation of 2,4,6-trimethoxyphenol⁹ (V), as benzoate or acetate, indicates that a free phenol or phenol ester group is not sufficient to cause diacetylation in acetic acid with or without acetic anhydride. With both of these compounds, a mono-C-acetyl compound (VI) was obtained¹⁰; this was converted to known 2,3-dihydroxy-4,6-dimethoxyacetophenone.⁵

⁽¹⁾ This investigation was supported by a Public Health Service Grant CY-4817 from the National Cancer Institute, Public Health Service.

⁽²⁾ A part of the Doctoral dissertation of M. G. Stout.

⁽³⁾ P. D. Gardner, J. Am. Chem. Soc., 76, 4550 (1954);
H. R. Snyder and R. W. Roeske, J. Am. Chem. Soc., 74, 5820 (1952).

⁽⁴⁾ W. J. Horton and J. T. Spence, J. Am. Chem. Soc., 77, 2894 (1955); 80, 2453 (1958).

⁽⁵⁾ P. D. Gardner, W. J. Horton, and R. E. Pincock, J. Am. Chem. Soc., 78, 2541 (1956).

⁽⁶⁾ Acetylation of 2,6-dimethoxyphenol gave 2-hydroxy-3-acetoxy-4-methoxyacetophenone. W. J. Horton and M. G. Stout, J. Org. Chem., 26, 1221 (1961).

⁽⁷⁾ Previously reported to yield the 2-acetyl derivative (XI) with boron trifluoride-acetic acid. K. Venkataraman, *Current Sci. (India)*, 23, 220 (1954).

⁽⁸⁾ Subsequent removal of the 2,4-dinitrophenyl group gave 2,6-dihydroxy-3,4-dimethoxyacetophenone and suggests this pathway as a general synthesis of 2,6-dihydroxyacetoxyphenones.

⁽⁹⁾ W. J. Horton and E. G. Paul, J. Org. Chem., 24, 2000 (1959); footnote 12.

⁽¹⁰⁾ Cf. the acetylation of 2,6-dimethoxyphenol, ref. 6.

Starting		Yield.		Anal. Sample. ^b	Caled.	Found			
(Moles Used)	Producta	%	М.Р.	M.P.	for	С	H	C	Н
I ^c (0.0506)	II	74	110-116	d II-benzyl ether 91.0-93.2 II-benzoate 124-125*	$C_{18}H_{20}O_5$	68.34	6.37	68.54	6.71
$ \begin{array}{c} \mathbf{I}^{f}(0.055) \\ \mathbf{II-benzoate}^{f} \\ (0.02) \end{array} $	II II	81 80	$109-114^{d}$ $107-114^{d}$						
IV [¢] (0.055) IV ^f (0.055)	X XI	$\begin{array}{c} 100 \\ 64 \end{array}$	i	93.5-94.5" XI-benzoate 86.5-87.5 ⁱ					
IV-benzoate ^c	х	80	81-86	Methanol-water 93.0-93.8 ^g X-dibenzoate	$C_{12}H_{14}O_6$	56.69	5.55	56.97	5.55
IV-isopropyl ether ^c (0.0044)	х	27	75-83	153.5-154.4 $93.5-94.5^{h}$	U ₂₆ H ₂₂ U ₈	07.52	4.80	07.25	4.84
IV-2,4-dinitro- phenyl ether	VII	97	163–165	Ethanol 165.0–166.4 VII-benzoate methanol	$C_{16}H_{14}O_9N_2$	50.80	3.73	50.89	3.75
V-benzoate ^c	VI	62	140-168	128.5-129.5 Ethyl acetate	$C_{23}H_{18}O_{10}N_2$	57.26	3.76	57.29 57.20	3.86
(0.02) V-benzoate ^f (0.01)	VI	73	$168 - 176^{k}$	178.0-181.0	012111406	50.03	0,00	07.20	0.02
V-acetate ^c (0.01)	VI	79	175–180 ¹						
2,6-Dimethoxy- hydroquinone diacetate ^e (0 0354)	VIII	60	97–103	Ethanol 98.5–100.2	${\rm C}_{13}{\rm H}_{14}{\rm O}_7$	55.32	5.00	55.68	5.03
2,5-Dimethoxy- hydroquinone diacetate ^f	IX	86	105–111						
XII ⁷ (0.0028) 1,2,4-Trimeth- oxy-5-bromo- benzene (0.05)	IX 2,2',4,4',5,5'- Hexameth- oxybi- phenyl	72 40	96.5–110 173–178	$107.5-110.5^{m}$ $178.8-179.9^{n}$	$C_{18}H_{22}O_6$	64.65	6.63	64.78	6.60
1,2,3,5-Tetra- methoxy-4- bromoben- zene (0.05)	2,4,5,6-Tetra- methoxy- 1,3-dibromo- benzene and	12	69-71.5	Methanol-water 68.9-70.1	${ m C_{10}H_{12}O_4Br_2}$	33.73	3.40	33.65	3.45
	11	23	$108 - 112^{\circ}$						

 TABLE I

 Data on Boron Trifluoride-Catalyzed Acetylations

^a All in boron trifluoride-acetic acid at 30° (max.) followed by standing overnight. ^b Corrected. ^c In acetic acid-acetic anhydride. ^d Mixture with authentic material melted undepressed, ref. 5. ^e Reported m.p. 120–121°, G. Bargellini, *Gazz. chim. ital.*, **41**, 1 (1911). ^f In acetic acid. ^g Reported m.p. 93°, ref. 14c. ^h Same when mixed with material from the benzoate. ⁱ Reported as a bright yellow oil, b.p. 184–186° (27 mm.), W. Baker, *J. Chem. Soc.*, 668 (1941), and ref. 18. Converted directly to the benzoate. ⁱ Reported m.p. 87–88°, ref. 18. ^k From ethyl acetate-alcohol, m.p. 171.5–178°, undepressed when mixed with analytically pure material above. ^m Undepressed on admixture with IX made from 2,6-dimethoxyhydroquinone diacetate. ⁿ λ_{max}^{alc} 298 m μ (ϵ 12,700); reported m.p. 176–177°, λ_{max}^{alc} 298 m μ (log ϵ 4.06); W. I. Taylor, *J. Chem. Soc.*, 3636 (1954).

Benzoylation of VI in alkali gave directly the dibenzoate.

Results obtained on boron trifluoride-catalyzed acetylation of 2,6-dimethoxyhydroquinone diacetate were consistent with the above. In acetic acid-acetic anhydride, a di-C-acetyl compound (VIII) was obtained which also contained an *O*acetyl group, removed by gentle hydrolysis. In the absence of acetic anhydride, an O-acetyl compound (IX) was obtained which gave 2,4-dimethoxy-3,6-dihydroxyacetophenone, identical to material prepared *via* the Fries rearrangement of 2,6-dimethoxyhydroquinone diacetate.¹¹

(11) F. Mauthner, J. prakt. Chem., 147, 287 (1937).



To test the suggestion that acetic anhydride functions in di-C-acetylation by breaking the boron trifluoride complex to form an O-acetate and a boron trifluoride-catalyzed Fries rearrangement then ensues, the supposed O-diacetyl intermediate (XII) was submitted to the same reaction conditions with omission of the acetic anhydride. No diacetylation was found. It therefore seems likely that di-Cacetylation is due to the greater electrophilic demands of an acetic anhydride-boron trifluoride attacking complex in contrast to that formed from acetic acid-boron trifluoride.

The above results confirm, for the most part, the extensive study of boron trifluoride-catalyzed acetylation of phloroglucinol and its derivatives.¹²

When an attempt was made to acetylate 1,2,4trimethoxy-5-bromobenzene under our conditions, the product isolated was 2,2',4,4',5,5'-hexamethoxybiphenyl.¹³ However, 1,2,3,5-tetramethoxy-4bromobenzene gave 1,3,4,5-tetramethoxy-2,6-dibromobenzene and II.

The 2,6-dihydroxy-3,4-dimethoxyacetophenone, m.p. 135.6-135.9°, obtained by removal of the 2,4dinitrophenyl group from VII did not have the melting point previously reported for this compound.¹⁴ We therefore converted the 2,6-dihydroxy compound to a monobenzyl derivative which gave on methylation 2,3,4-trimethoxy-6-benzyloxyacetophenone identical to the benzyl ether, m.p. 41.8-42.6°,¹⁵ prepared from XI. The previous reports on 2,6-dihydroxy-3,4-dimethoxyacetophenone are therefore erroneous.

EXPERIMENTAL¹⁶

General procedure. The acetylation procedure using boron trifluoride-acetic acid-acetic anhydride has been described.⁶

(12) F. M. Dean and A. Robertson, J. Chem. Soc., 1241 (1953).

(13) Reported as a product of the action of boron trifluoride etherate on 1,2,4-trimethoxy-5-iodobenzene. H. Meerwein, P. Hofmann, and F. Schill, J. prakt. Chem., 154, 266 (1940).

(14) (a) G. Bargellini and L. Bini, Atti accad. Lincei., 19, II, 595 (1910); Chem. Abstr., 5, 1279 (1911). No melting point given. (b) M. Nierenstein, J. Chem. Soc., 111, 4 (1917); m.p. 166°. (c) E. Chapman, A. G. Perkin, and R. Robinson, J. Chem. Soc., 3015 (1927); m.p. 161°. These compounds could be 3,6-dihydroxy-2,4-dimethoxyacetophenone, m.p. 162°. A. Oliverio and G. Bargellini, Gazz. chim. ital., 78, 372 (1948).

(15) The isomeric benzyl ether (from II) melted at 91.0-93.2°.

(16) Melting points of analytically pure materials are corrected.

In the indicated cases (Table I), acetic anhydride was omitted; the procedure otherwise was identical.

Antiarol derivatives. Antiarol,¹⁴⁰ (IV) m.p. 149–150°, (20 g.) and 24 g. of recrystallized 2,4-dinitrochlorobenzene in 100 ml. of anhydrous pyridine was allowed to stand for 14.5 hr. and then heated in a boiling water bath for 3 hr. On dilution with water and cooling, 31 g. (83%) of the 2,4dinitrophenyl ether of antiarol m.p. 143.5–144.5° was obtained. The sample of ether for analysis was crystallized from methanol, m.p. 144.8–145.6°.

Anal. Calcd. for C15H14O8N2: C, 51.43: H, 4.03. Found: C, 51.41; H, 4.04.

Catalytic reduction of the dinitrophenyl ether (0.5 g.) in alcoholic solution over 50 mg. of platinum oxide at room temperature gave the 2,4-diaminophenyl ether of anliarol which melted, after repeated crystallization from benzene, at 154.6-155.3°.

Anal. Calcd. for $C_{16}H_{18}O_4N_2$: C, 62.05; H, 6.25. Found: C, 62.11; H, 6.28.

Antiarol isopropyl ether was prepared by refluxing 30 g. of antiarol, 110 g. of anhydrous potassium carbonate, 34 ml. of diisopropyl sulfate,¹⁷ and 350 ml. of anhydrous acetone for 10 hr. After the usual isolation process, distillation gave 32.2 g. (87%) of the ether, b.p. $131-134^{\circ}$ (3 mm.). The sample for analysis boiled at $95-97^{\circ}$ (0.6 mm.).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.85; H, 8.00.

Antiarol benzoate. From 10 g. of antiarol and 7 ml. of benzoyl chloride in 60 ml. of pyridine with 20 min. heating on the steam bath, 15.6 g. (100%) of the benzoate was obtained, m.p. 115–116°. The sample for analysis recrystallized from methanol, melted at 115.0–116.5°.

Anal. Calcd. for $C_{16}H_{10}O_{6}$: C, 66.65; H, 5.60. Found: C, C, 66.95; H, 5.65.

2,6-Dihydroxy-3,4-dimethoxyacetophenone. A solution of 15 g. of VII in 30 ml. of piperidine was heated on the steam bath for 15 min. The solution was then diluted with 75 ml. of water, cooled, and filtered from the sticky residue of dinitrophenylpiperidine. By acidification of the filtrate a solid was obtained whose ether solution, by extraction with 5% sodium hydroxide, gave 6.40 g. (76%) of a red solid, m.p. 127-134°. Material recrystallized from cyclohexane and sublimed melted at 135.6-135.9°. With alcoholic ferric chloride a grey-black color turning red on dilution was obtained.

Anal. Čaled. for C10H12O5: C, 56.60; H, 5.70. Found: C, 56.82; H, 5.74.

The same compound was produced by hydrogen bromideacetic acid cleavage⁴ of 2,3,4-trimethoxy-6-isopropoxyand 2,3,4-trimethoxy-6-hydroxyacetophenone, both in 23% yield.

The *dibenzoate* melted at 96.0–97.2° after extensive crystallization from aqueous methanol and from cyclohexane.

Anal. Calcd. for C24H20O7: C, 68.56; H, 4.80. Found: C, 68.40; H, 4.90.

The 6-benzyl derivative was prepared by addition of the 2,6dihydroxy compound (2.46 g.) to a solution of 0.273 g. of sodium in 10 ml. of methanol. After addition of 0.1 g. of sodium iodide and 1.42 ml. of benzyl chloride, the solution was refluxed for 5 hr. and allowed to stand overnight. Isolation required distillation of the acetone, extraction with ether, and washing with 10% aqueous sodium hydroxide to give, after crystallization from cyclohexanebenzene, 1.14 g. of product, m.p. 103-128°. Further crystallization brought the melting point to 137.2-137.8°. The compound gave a dark greenish-brown ferric chloride test.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 67.54; H, 6.00. Found: C, 67.74; H, 6.12.

2,3,4-Trimethoxy-6-benzyloxyacetophenone. (a) From 2hydroxy-3,4-dimethoxy-6-benzyloxyacetophenone. The benzyl ether (0.67 g.) on refluxing for 10 hr. with 2.5 ml. of methyl sulfate and 1.5 g. of potassium carbonate in 21 ml. of ace-

(17) T. B. Dorris and F. J. Sowa, J. Am. Chem. Soc., 60, 358 (1938).

tone gave 0.73 g. of colorless oil which eventually crystallized, m.p. 38-40°. From petroleum ether (b.p. $30-60^{\circ}$) square crystals, m.p. $41.5-43^{\circ}$, were obtained. The ferric chloride test was negative. A mixture with the material from (b) below melted at $42-43^{\circ}$.

Anal. Caled. for C₁₈H₂₀O₅: C, 68.34; H, 6.37. Found: C, 68.23; H, 6.47.

(b) From XI. Benzylation of 2.0 g. of 6-hydroxy-2,3,4-trimethoxyacetophenone, m.p. $39-44^{\circ}$, as above gave 2.03 g. m.p. $40-45^{\circ}$. Twice crystallized material (benzene-petroleum ether, b.p. $30-60^{\circ}$) melted at $42-43^{\circ}$ but melted at room temperature when mixed with XI.

2,4,6-Trimethoxyphenyl 2,4-dinitrophenyl ether. (a) The phenol⁹ (m.p. 60-64°, 1.25 g.) was allowed to stand overnight with 1.38 g. of 2,4-dinitrochlorobenzene in 6.5 ml. of pyridine followed by heating for 2 hr. on the steam bath. On addition of 30 ml. of water 2.07 g. of light yellow material, m.p. 149-155°, was obtained. Crystallization from ethanol brought the melting point to 153-157.5°. (b) Dinitrochlorobenzene with 2,6-dimethoxyhydroquinone (2.55 g.) as above gave 1.82 g. (36%) of the *bisdinitrophenyl ether*, canary yellow crystals, m.p. 220-225°, insoluble in 10% sodium hydroxide and in hot benzene-alcohol. After five crystallizations from acetic acid-dimethylformamide, these melted at 227.7-229.7°.

Anal. Calcd. for $C_{20}H_{14}O_{12}N_4$: C, 47.82; H, 2.81. Found: C, 47.46; H, 2.91.

Concentration of the benzene-alcohol extract of the bisether gave a residue soluble in dilute sodium hydroxide. Filtration and acidification of the alkaline solution followed by crystallization from aqueous ethanol gave a dark yellow solid (1.32 g.), m.p. 141-146° (gas evol.). Extensive purification from benzene-cyclohexane produced 3,5-dimethoxy-4-(2,4-dinitrophenoxy)phenol as golden yellow crystals, m.p. 147.6-149.5° (dec. with gas evol).

Anal. Calcd. for C₁₄H₁₂O₈N₂: C, 50.00; H, 3.60. Found: C, 50.46; H, 3.80.

Methylation of 0.84 g. of the mono-dinitrophenyl ether (m.p. 141-146°) in 4% sodium hydroxide with 4.2 ml. of methyl sulfate gave a solid, m.p. 149-170° after crystallization from benzene-cyclohexane. This formed long yellow prisms after crystallization from alcohol, m.p. 154.8-156.8°. The mixture with the dinitrophenyl ether of antiarol melted at 123-140°, but that with material made by method (a) melted at 153-156°.

Anal. Calcd. for C₁₈H₁₄O₄N₂: C, 51.43; H, 4.03. Found: C, 51.66; H, 4.14.

2,4,6-Trimethoxyphenyl acetate after extensive recrystallization from alcohol melted at $99.0-100.6^{\circ}$.

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 58.40; H, 6.24. Found: C, 58.29; H, 6.32.

2,6-Dimethoxyhydroquinone derivatives. The Fries rearrangement¹¹ of 2,6-dimethoxyhydroquinone diacetate provided an authentic sample of 3,6-dihydroxy-2,4-dimethoxyacetophenone, m.p. 154-163°; reported¹¹ m.p. 162-163°. The acetophenone dibenzoate was prepared by means of benzoyl chloride and sodium hydroxide and formed short stout colorless prisms after extensive recrystallization from alcohol-ethyl acetate, m.p. 152.6-154.3°; reported m.p. 153-154°.18

Anal. Calcd. for $C_{24}H_{20}O_7$: C, 68.56; H, 4.80. Found: C, 68.77; H, 4.80.

On gentle hydrolysis of IX in 10% hydrochloric acidethanol (1:2) with refluxing for 2 hr., 3,6-dihydroxy-2,4dimethoxyacetophenone, m.p. 162-162.5° was obtained which did not depress the melting point of the Fries product above. Further, IX was converted directly via benzoyl chloride and base to acetophenone dibenzoate, m.p. 149.5-152°, which melted at 150-154.5° when mixed with the analytically pure acetophenone dibenzoate above.

The *diacetate* of IX was prepared in pyridine with acetic anhydride. Extensive purification from benzene-cyclohexane and from aqueous alcohol gave XII which half melted at 100.6° and then melted at 106.0-107.1°.

Anal. Calcd. for C₁₄H₁₆O₇: C, 56.75; H, 5.49. Found: C, 56.81; H, 5.49.

The di-C-acetyl compound from 2,6-dimethoxyhydroquinone diacetate, boron trifluoride, and acetic anhydride. One gram of 5 - acetoxy - 1,3 - diacetyl - 2,4 - dihydroxy - 6 - methoxybenzene (VIII) was refluxed for 2 hr. with 20 ml. of 6N hydrochloric acid and 20 ml. of alcohol. On cooling and filtering, 0.74 g. (87%) of 1,3-diacetyl-2,4,5-trihydroxy-6-methoxybenzene was obtained. After repeated recrystallization from ethanol, long thick pointed lemon yellow prisms were obtained, m.p. 145.5-147.9°. These gave a very dark red color with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; 5.04. Found: C, 55.24; H, 5.14.

2,3-Dihydroxy-4,6-dimethoxyacetophenone. On hydrolysis of 1.0 g. of VI (from the benzoate of V, boron trifluoride, and acetic anhydride) by the above procedure, 2,3-dihydroxy-4,6-dimethoxyacetophenone (0.77 g., 92%), m.p. 160-163.5°, was obtained. The material melted at 160-165° after crystallization from ethyl acetate and at 161-165.5° when mixed with known material.⁵

The *dibenzoate* made with benzoyl chloride and pyridine, after five crystallizations from alcohol, melted at 185.0-188.0° and gave a negative ferric chloride test.

Anal. Caled. for C₂₄H₂₀O₇: C, 68.56; H, 4.80. Found: C, 68.71; H, 4.98.

The dibenzoate prepared directly from VI with benzoyl chloride and aqueous alkali melted at 177-185.5° and when mixed with analytically pure material at 180-184.5°.

The *diacetate* prepared from VI melted at 137.2-138.4° after crystallization from benzene-cyclohexane.

Anal. Caled. for C14H16O7: C, 58.07; H, 5.57. Found: C, 57.20; H, 5.42.

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SALT LAKE CITY 12, UTAH

(18) V. D. N. Sastri and T. R. Seshadri, Proc. Indian Acad. Sci., 23A, 262 (1946).