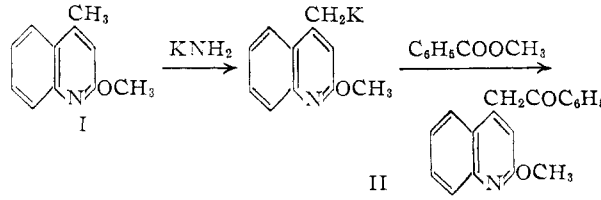
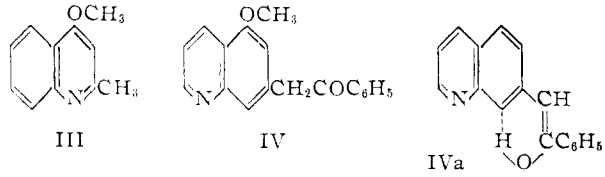
means of potassium amide without displacing the methoxy group to form II. This was accomplished employing essentially the conditions used previously with lepidine and quinaldine.[3]



Similarly 4-methoxyquinaldine (III) was benzoylated to form IV. Whereas II is nearly colorless, IV is bright yellow. This suggests that the latter compound exists at least partly in the enol structure which would presumably be stabilized by hydrogen bonding (IVa). In agreement with this, the hydrochloride of IV is colorless. Levine[4] has proposed the corresponding structure for the copper chelate of 2-phenacylpyridine.



The yields in these acylations were 37 and 48%, respectively, and are probably not the maximum obtainable. At least there was no indication that the methoxy group was displaced by the amide ion to form the corresponding amine under the conditions employed. Moreover, III was largely recovered after standing an hour with excess potassium amide in liquid ammonia. 4-Chloroquinaldine, on the other hand, produced tars under similar conditions.

Experimental[5]

2-Methoxy-4-phenacylquinoline (II).—2-Methoxylepidine[6] (I) (1.73 g., 0.01 mole) in dry ether was added to a solution of 0.026 mole of potassium amide in liquid ammonia prepared from 1.01 g. (0.026 mole) of potassium. Methyl benzoate (3.53 g., 0.026 mole) in ether was added, and the mixture stirred for an hour. After removing the ammonia on a water-bath, the resulting ether suspension was refluxed for 1 hour (5 hours refluxing did not improve the yield). Wet ether was added followed by water, and the ether layer extracted with 6 *N* hydrochloric acid. The acid solution, which sometimes contained a precipitate of the amine hydrochloride, was washed with ether, and then neutralized with sodium bicarbonate. The precipitated amine was extracted with ether. After drying, the ether was removed, and the residue recrystallized from ether yielding 0.82 g. of colorless needles of 2-methoxy-4-phenacylquinoline (II), m.p. 124–125.5°. More (0.20 g.) of this compound, m.p. 120–122°, was isolated from the filtrate; total yield 37%. A sample, recrystallized from ethanol, melted at 124.5–125.5°.

Anal. Calcd. for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.99; H, 5.60; N, 5.36.

2-Phenacyl-4-methoxyquinoline (IV).—4-Methoxyquinaldine[7] (III) was benzoylated as described above for 2-methoxylepidine. After the removal of the ammonia, the ether solution was refluxed for 6 hours, and the product recrystallized from ethanol giving 1.09 g. of bright yellow needles of 2-phenacyl-4-methoxyquinoline (IV), m.p. 129–131°. More (0.23 g.) of this product, m.p. 127–130°, was isolated from the filtrate; total yield 48%. A sample, recrystallized from ethanol, melted at 132–133°.

Anal. Calcd. for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.19; H, 5.24; N, 5.35.

The dinitrophenylhydrazone of IV (orange needles), recrystallized from ethanol, melted at 224°.

Anal. Calcd. for $C_{24}H_{19}N_5O_5$: N, 15.31. Found: N, 15.04.

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(3) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2023 (1949).

(4) N. N. Goldberg, L. B. Barkley and Robert Levine, *ibid.*, **73**, 4301 (1951).

(5) Melting points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(6) L. Knorr, *Ann.*, **236**, 100 (1886).

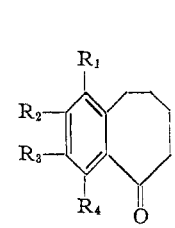
(7) M. Conrad and L. Limpach, *Ber.*, **20**, 954 (1887).

The Reaction of Hydrogen Bromide–Acetic Acid on *o*-Alkoxyacetophenones

BY W. J. HORTON AND JACK T. SPENCE

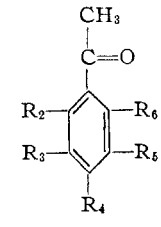
RECEIVED DECEMBER 4, 1954

The cleavage of the 4-methoxy group of 2,3,4-trimethoxybenzosuberone[1] (Ia) in hydrogen bromide–acetic acid at room temperature has been extended to 1,4-dimethoxy- (Ib) and 1,2,3,4-tetramethoxybenzosuberone (Ic). Only Ic seemed to show the behavior of the original Ia. These exploratory experiments suggested that the adjacent 3-methoxy group in Ia and Ic was responsible for the high yield of cleavage product under these mild conditions.



Ia, R_2, R_3, R_4 = OCH_3
Ib, R_1, R_4 = OCH_3
Ic, R_1, R_2, R_3, R_4 = OCH_3

R otherwise = H



IIa, R_2, R_3 = OCH_3
IIb, R_2, R_3, R_4 = OCH_3
IIc, R_2, R_4, R_5 = OCH_3
IId, R_2, R_4, R_6 = OCH_3
IIe, R_2, R_4 = OCH_3
IIf, R_2, R_5 = OCH_3
IIg, R_3, R_4 = OCH_3
IIh, R_2 = OC_2H_5; R_3 = OCH_3
IIi, R_2 = OC_2H_5; R_3, R_4 = OCH_3

We have investigated this matter in the more easily available methoxy- and ethoxyacetophenones (Table I). Column 5 gives the yields of the corresponding 2-hydroxyacetophenones after 4.5 hours in *ca.* 6% hydrogen bromide–acetic acid at room temperature. Only those compounds (IIa, IIb, IIh, IIi) containing a *3-methoxy group* gave high yields. 2,4,6-Trimethoxyacetophenone (IId) apparently has the advantage of two methoxy groups *ortho* to the acetyl group. The case IIf indicates that a 5-methoxy (*para* to the cleavable group) is not as effective as the (*ortho*) 3-methoxy substituent. Hence the spacial position of the 3-methoxy group relative to the group cleaved, rather than an inductive effect due to salt formation, would seem to be responsible for the high rate of cleavage.

In columns 2 and 3, Table I, the yields of acetophenones from appropriate methoxybenzenes, ace-

(1) P. D. Gardner and W. J. Horton, *J. Org. Chem.*, **19**, 213 (1954).

TABLE I

1	2	3	4	5		
Acetophenone	Yield of acylation (moles of methoxybenzene employed), %	Reacn. temp., °C. (reacn. time, hr.)	M.p. or b.p. (mm.), °C.	Yield[a] of corresponding 2-hydroxyacetophenone, %	M.p. of cleavage product, °C.	M.p. of acetate, °C.
2,3,4-$(CH_3O)_3$-	96 (0.2)	60 (2.5)	170–178 (17)	71.3[b]	65.5–71.5[c]	[c]
2,3-$(CH_3O)_2$-	.....[d]	.....	150–153 (20)	70	29–51.5[e]	44.5–46.5[e]
2,4,5-$(CH_3O)_3$-	84.5 (0.02)	45 (2.5)	96–100	[f]	.....	.....
2,4,6-$(CH_3O)_3$-	57 (0.02)	60 (2.5)	93.5–104	27	79–82[g]	105–108[g]
2,4-$(CH_3O)_2$-	98.4 (0.1)	60 (2.5)	37–41.5	8.7	41–50[h]	43–46[h]
2,5-$(CH_3O)_2$-	45.5 (0.1)	85 (0.75)	149–154 (8)	6	46–47[i]	60–62[i]
3,4,5-$(CH_3O)_3$-	.....[d]	.....	78–81.5	8.7	122–148[j]	.....
3,4-$(CH_3O)_2$-	83 (0.2)	60 (2.5)	160–164 (7.5)	0	.....	.....
2-C_2H_5O-3-CH_3O-	.....	.....	163–166 (34)	58	48–53.5	
2-C_2H_5O-3,4-$(CH_3O)_2$-	.....	.....	177–183 (25)	71	66.5–73	

[a] All on 0.01–0.02 mole at room temperature for 4.5 hours. [b] After 6.5 hours at room temperature and distillation of the solvent at 25 mm., 91.2% yield on 0.167 mole, b.p. 124–117° (0.75–0.3 mm.), m.p. 61–70°. [c] Reported m.p. 75–77°; W. Baker, *et al.*, *J. Chem. Soc.*, 1683 (1934). The phenylhydrazone melted at 170–174°; reported m.p. 171°: W. H. Perkin and C. Weizmann, *ibid.*, 89, 1655 (1906). [d] From the corresponding benzoyl chloride by the method of A. L. Wilds and L. W. Beck, THIS JOURNAL, **66**, 1692 (1944). [e] Reported m.p. 53–54°: ref. 6. The acetate formed colorless thin plates from petroleum ether (60–71°). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.40; H, 5.86. The benzoate formed short rectangular prisms from dilute ethanol; m.p. 90–92°. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.94; H, 5.49. [f] Yellow-green crystals (82%) of the unstable hydrobromide of IIc, m.p. 118–123° dec., separated at once from the hydrogen bromide–acetic acid solution. Material washed with acetone was titrated; neut. equiv. calcd. for $C_{11}H_{14}O_4$·HBr 291.2, found 291.6. [g] Reported m.p. 86–87°: H. F. Dean and M. Nierenstein, THIS JOURNAL, **47**, 1679 (1925); the acetate, m.p. 107°: S. v. Kostanecki and J. Tambor, *Ber.*, **32**, 2262 (1899). [h] From methanol, m.p. 45.5–51°, liquid when mixed with IIe; reported m.p. 51.3°: P. Pfeiffer and L. Wang, *Z. angew. Chem.*, **40**, 990 (1927). Reported for the acetate m.p. 46–47°; H. Lindemann, *et al.*, *Ann.*, **456**, 308 (1927). [i] Reported m.p. 48–50°; G. N. Vyas and N. M. Shah, *Org. Syntheses*, **31**, 90 (1951). The acetate was evaporatively distilled *in vacuo* and crystallized from petroleum ether (30–60°). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.51; H, 5.95. [j] Not identified.

tic acid and polyphosphoric acid[2] are given together with the reaction conditions used. 1,2,3,4-Tetramethoxybenzene could not be acetylated with this reagent.

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

Experimental[3]

1,2,3,4-Tetramethoxybenzosuberone (Ic).—2,3-Dimethoxy-4-hydroxybenzosuberone[1] was treated with diazotized sulfanilic acid[4] and the red dye was reduced with sodium hydrosulfite to **1-amino-2,3-dimethoxy-4-hydroxybenzosuberone** (32%), m.p. 72.5–78°. After five crystallizations from aqueous methanol it formed golden long thin rods, m.p. 76–78.5°.

Anal. Calcd. for $C_{13}H_{17}O_4N$: C, 62.13; H, 6.82. Found: C, 61.85; H, 6.81.

The N-acetyl derivative melted at 144–145° after repeated recrystallization from dilute methanol. The compound was soluble in dilute potassium hydroxide, insoluble in 5% hydrochloric acid and gave a deep purple ferric chloride test.

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53. Found: C, 62.05; H, 6.65.

Oxidation[5] of the aminophenol gave the **quinone.** By decantation of a hot cyclohexane solution from insoluble matter bright red crystals (38%), m.p. 76–83.5°, were obtained pure enough for rapid reduction over platinum. Four crystallizations of the **quinone** from cyclohexane gave bright red crystals, m.p. 79–81°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.34; H, 5.70.

Catalytic hydrogenation at room temperature over platinum gave **1,4-dihydroxy-2,3-dimethoxybenzosuberone** (84%), m.p. 113–134°. Purification from cyclohexane gave long thin canary-yellow prisms, m.p. 130.5–134°, which produced a deep green color with ferric chloride.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.17; H, 6.55.

The hydroquinone in 10% sodium hydroxide was treated with dimethyl sulfate to yield Ic (70%), m.p. 76.5–80°. After sublimation at 110–120° (bath temperature) (0.3 mm.) and crystallization from dilute ethanol and from cyclohexane, microscopic flat prisms, m.p. 85–88°, negative to ferric chloride, were obtained.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.17; H, 7.06.

Hydrogen bromide–acetic acid[1] on Ic gave (75%) an orange oil soluble in 5% sodium hydroxide. The compound gave a strong black ferric chloride test but resisted crystallization. An attempt to prepare the acetate produced a colorless oil insoluble in 10% sodium hydroxide which failed to crystallize after evaporative distillation at 140–145° (bath temperature) (0.13 mm.).

2-Ethoxy-3-methoxyacetophenone (IIh).—The cleavage product from IIa with diethyl sulfate gave IIh (90%). The colorless oil for analysis boiled at 93° (0.75 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.35; H, 7.34.

The phenylhydrazone formed long thin needles from ethanol, m.p. 113–114°, but soon turned reddish-brown in air. **The *p*-nitrophenylhydrazone** formed golden yellow short thin prisms from ethanol, m.p. 91–93°.

Anal. Calcd. for $C_{17}H_{19}O_4N_3$: C, 61.99; H, 5.82. Found: C, 61.45; H, 5.93.

Permanganate oxidation of IIh gave 2-ethoxy-3-methoxybenzoic acid, m.p. 49–52°, reported[6] m.p. 52–53°. **2-Ethoxy-3-methoxybenzamide** formed as long thin prisms from cyclohexane, melted at 119–121°.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71. Found: C, 61.73; H, 6.65.

2-Ethoxy-3,4-dimethoxyacetophenone (IIi).—Analogous to the above, IIi was obtained from the cleavage product of IIb in 93% yield. For analysis a cut b.p. 113° (0.55 mm.) was collected.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.58; H, 7.06.

(2) P. D. Gardner, THIS JOURNAL, **76**, 4550 (1954). We wish to thank Dr. Gardner for communications prior to publication of this work.

(3) Melting points are uncorrected.

(4) L. C. Anderson and W. E. Bachmann, "A Manual for the Organic Chemistry Laboratory," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 124–127.

(5) E. Grandmougin and O. Michel, *Ber.*, **25**, 982 (1892).

(6) T. Reichstein, *Helv. Chim. Acta*, **10**, 396 (1927).

The *p*-nitrophenylhydrazone appeared as golden yellow needles from alcohol; m.p. 172.5–175°.

Anal. Calcd. for $C_{18}H_{21}O_5N_3$: C, 60.16; H, 5.89. Found: C, 59.68; H, 6.01.

Permanganate oxidation of IIi gave **2-ethoxy-3,4-dimethoxybenzoic acid** as colorless fine thin prisms from cyclohexane; m.p. 77.5–80.5°.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.32; H, 6.26.

The amide, sublimed at 150° (bath temperature) (0.05 mm.), melted at 100–103°.

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.56; H, 6.71. Found: C, 58.43; H, 6.59.

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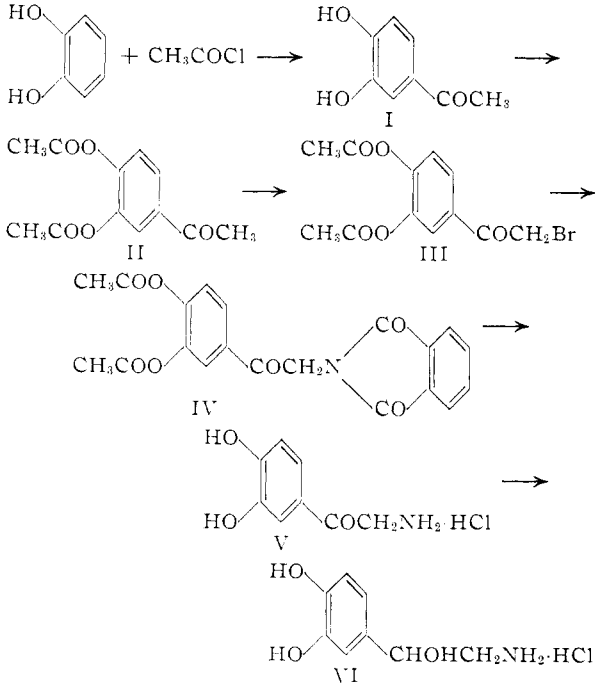
A New Synthesis of *dl*-Arterenol[1]

BY DAVID R. HOWTON, JAMES F. MEAD AND WILLIAM G. CLARK

RECEIVED AUGUST 20, 1954

In order to implement the preparation of α-C^{14}-*dl*-arterenol,[2] a new synthesis of this important pressor substance has been devised which avoids oxidative losses (or the rather elaborate precautions necessary to prevent them) by employing intermediates in which the sensitive 3,4-dihydroxyphenyl moiety is protected by acetylation. The steps involved in the procedure are outlined below (in practice, neither I nor V was isolated).



On a 5–10 mM. scale, the procedure diagrammed above and described in detail below gave *dl*-arterenol as the hydrochloride (VI) in 6–15% over-all yield based on sodium acetate (*cf.* 5% on the same basis obtained[4] by the older method[3]).

Experimental

All melting points are corrected. Microanalyses were performed by Dr. A. Elek of the Elek Microanalytical Laboratories, Los Angeles.

3,4-Dihydroxyacetophenone (I) was prepared by a modification of the procedure of Miller, *et al.*[5] After standing at room temperature for 15 minutes, a mixture of 0.70 g. (6.4 mM.) of catechol and 2.55 g. (19.1 mM.) of anhydrous aluminum chloride in 7.5 ml. of carbon disulfide was heated for one hour at 40°; 0.50 g. (6.8 mM.) of acetyl chloride[6] then was added dropwise. The mixture next was heated to about 70°, the carbon disulfide being permitted to distil out, and finally to 140°, where it was maintained for 3.5 hours. The resulting buff or light-brown solid then was cooled in ice, treated with ice and 20 ml. of 3 *N* HCl and shaken vigorously with 5 ml. of ice-cold ethyl acetate until the solid reaction product dissolved completely. Two additional 5-ml. ethyl acetate extracts were combined with the first and washed with two 1-ml. portions of water (excess water is to be avoided since I has a moderate water solubility); the crude dihydroxyacetophenone was acetylated directly (see below). Samples of I isolated at this point in earlier experiments and recrystallized from benzene melted higher (119.2–119.7°) than has been reported previously (lit. 116°,[8] 115–116°,[9] 114–115°[10]). Use of ethyl acetate instead of butanol[5] as an extracting solvent for I is not only dictated by the conditions of the acetylation reaction (see below), but also is preferred if I is to be isolated; butanol is difficult to remove completely and the persistence of even small amounts affects the crystallizing power of the product adversely.

3,4-Diacetoxyacetophenone (II).—The ethyl acetate extracts of I obtained above were carefully floated on an ice-cold solution of 1.66 g. of potassium hydroxide pellets in 24 ml. of water and 2.07 g. of acetic anhydride was added to the upper phase. (The anhydride employed had been shown[11] previously to contain about 34% acetic acid by weight; the amount of KOH used was adjusted to provide a 10% excess over that required to neutralize any acetic acid in the acetic anhydride and to complete the acetylation.) After adding a few pieces of ice, the mixture was shaken vigorously; initially dark green, it soon turned pale brown, indicating completion of the desired acetylation. The ethyl acetate phase was washed with 5% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated to give 1.335 g. of yellow-brown solid residue. II was obtained best from this material by dissolving in a little benzene, evaporating on a steam-bath, and rapidly diluting the residual oil with 4 ml. of boiling isopropyl ether; on cooling and standing, beautiful clusters of near-colorless slats emerged, weighing 0.605 g. (40.3% from catechol; other experiments run in apparently identical manner gave yields varying between this figure and 22.1%) and melting at 87.8–88.2° (lit. 84–85°,[10] 91°,[12] 86°[13]). Further processing of the mother liquors yielded 0.39 g. of crude catechol diacetate, but no appreciable additional amounts of II.

3,4-Diacetoxy-α-bromoacetophenone (III) was prepared by blowing bromine vapors with nitrogen into a concen-

(1) Supported by Grant No. 9, 1951–1952, from the Los Angeles County Heart Association to W. G. C. Grateful acknowledgment also is made to the Atomic Energy Commission for the 200 mc. of $BaC^{14}O_3$, contributed under the free distribution cancer plan, authorization No. 11260, Nov. 6, 1951.

(2) Synthesis of this radioactive substance by known procedures[3] was reported[4] during completion of the work presently described.

(3) W. Langenbeck and F. Fischer, *Pharmazie*, **5**, 56 (1950).

(4) R. W. Schayer, THIS JOURNAL, **75**, 1757 (1953).

(5) E. Miller, W. H. Hartung, H. J. Rock and F. S. Crossley, *ibid.*, **60**, 7 (1938).

(6) Radioactive acetyl chloride was prepared by the action of benzoyl chloride on sodium 1-C^{14}-acetate, prepared in turn from $BaC^{14}O_3$ by the procedure of Spector.[7]

(7) *Cf.* H. J. Strecker and L. B. Spector, cited in Calvin, *et al.*, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 176–177.

(8) V. S. Dzierzgovski, *J. Russ. Phys. Chem. Soc.*, **25**, 157 (1893).

(9) E. Clemmensen, *Ber.*, **47**, 56 (1914).

(10) L. S. Birnbaum and G. Powell, *J. Org. Chem.*, **4**, 139 (1939).

(11) L. F. Fieser, "Experiments in Organic Chemistry," Part II, Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 380. In determining amounts of acetic acid in samples of acetic anhydride, ethyl bis-(2,4-dinitrophenyl)-acetate is employed as indicator, since phenolic indicators are acetylated rapidly and thus rendered nonfunctional under these conditions.

(12) P. W. Neber, A. Burgard and W. Thier, *Ann.*, **526**, 277 (1936).

(13) C. Schöpf, E. Brass, E. Jacobi, W. Jorde, W. Mocnik, L. Neuroth anh W. Salzer, *ibid.*, **544**, 30 (1940).